MANAGEMENT OF TYPE 2 DIABETES: SELECTING AMONGST AVAILABLE PHARMACOLOGICAL AGENTS

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ABSTRACT

In the early 1990's, clinicians' choices for pharmacological management of type 2 diabetes were limited to insulin, sulfonylureas, and metformin. Since then, multiple classes of agents have been discovered, approved, and put into clinical use. Through a series of cardiovascular outcome trials and other clinical trials, some classes of agents have been found to have benefits on atherosclerotic cardiovascular disease, congestive heart failure, and chronic kidney disease, sometimes independent of glycemic control. As a result, diabetes management has shifted away from a "one size fits all" care to an individualized approach for each patient. Important factors to consider include efficacy, cost, side effects, adherence and treatment burden, comorbidities, mechanisms of action, and non-glycemic effects on atherosclerotic cardiovascular disease, congestive heart failure, and chronic kidney disease. The goal of this chapter is to discuss an approach to pharmacological management that reviews current guidelines, discusses choosing appropriate glycemic targets, and presents the rationale for choosing certain medications in different situations.

INTRODUCTION

Foundational to the treatment of type 2 diabetes is glucose control. Diabetes increases the risk of microvascular and macrovascular complications, as well as mortality, morbidity, and healthcare costs. While lifestyle interventions are the basis for glucose control, most people will eventually need one or more pharmacologic treatments. This is because type 2 diabetes is a disease characterized by progressive beta-cell loss and dysfunction, leading to deterioration of metabolic control over time. Because of the growth in the number of antihyperglycemic agents in recent years, there are now more choices than ever in terms of how to achieve glucose control. Agents should be chosen with a goal of achieving glucose control, reducing risk of microvascular and macrovascular disease, and minimizing treatment burden (1-8)

SELECTION OF GLYCEMIC TARGETS

The first step in the approach to glycemic control in type 2 diabetes is the selection of an appropriate glycemic target. Glycemic control can be measured in a variety of ways, including hemoglobin A1c, self-monitoring of blood glucose (SMBG), and continuous glucose monitoring. Continuous glucose monitoring (CGM) makes available a range of metrics, including time in target, percent of time with hypoglycemia, percent of time with hyperglycemia, and glucose variability (as determined by standard deviation or coefficient of variation). Hemoglobin A1c has traditionally been the metric used in clinical trials. However, there is increasing interest in the use of time in range from CGM, as it is not subject to the same measurement limitations as hemoglobin A1c, responds more quickly to changes in glucose, and better reflects glucose variability (4, 6, 9, 10). Note that the hemoglobin A1c may not be accurate in conditions in which there is altered red blood cell turnover or in the presence of some hemoglobin variants. Further details can be found in the Endotext chapter (Monitoring Techniques- Continuous Glucose Monitoring, Mobile Technology, Biomarkers of Glycemic Control (11)).

Professional societies such as the American Diabetes Association (ADA) and the American Association of Clinical Endocrinology (AACE) differ somewhat on their recommendations for glycemic targets. However, the tenant of individualization of glycemic targets is central to both of their recommended approaches. The ADA recommendations are shown in Table 1, and were modified to include time in range targets from CGMs in 2021 (4, 12). In contrast, the AACE clinical guidelines state that "An A1c of $\leq$ 6.5% (48 mmol/mol) is considered optimal if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time." (1)

Table 1. Glycemic Target Recommendations from the American Diabetes Association 2021 Standards of Medical Care in Diabetes
An A1c goal for many nonpregnant adults of <7% without significant hypoglycemia is appropriate.
If using ambulatory glucose profile/glucose management indicator to assess glycemia, a parallel goal for many non-pregnant adults is time in range of >70% with time below range <4% and time <54 mg/dL <1%.
On the basis of provider judgement and patient preference, achievement of lower A1c levels than the goal of 7% may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment.
Less stringent A1c goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits.

Adapted from American Diabetes Association (4).

The differing recommendations of the ADA and AACE are based, in part, on considerations and interpretations of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation), ACCORD (Action to Control Cardiovascular Risk in Diabetes), and VADT

(Veterans Affairs Diabetes Trial) trials. A discussion of these trials is outside the scope of this chapter, but excellent summaries can be found elsewhere (1, 4, 13-17).

The primary risk of lower glycemic targets is hypoglycemia. In general, rates of hypoglycemia are unappreciated (18). A meta-analysis has found that among individuals with type 2 diabetes on insulin, the average incidence of hypoglycemia is 23 mild or moderate events and 1 severe episode annually (19). In 2015, there were 235,000 emergency room visits in the U.S. for hypoglycemia among adults with type 2 diabetes. This corresponds to a rate of 10.2 per 1,000 adults with diabetes (20). Hypoglycemia is associated with significant morbidity, mortality, and decreased quality of life. For example, among Medicare beneficiaries in 2010, hospitalizations for hypoglycemia were associated with an adjusted 30-day readmission rate of 18.1% and 30-day mortality rate of 5% (21). The use of glucose lowering drugs with a low potential for hypoglycemia allows one to safely achieve lower glycemic targets.

Other risks of lower glycemic targets include increased burden of treatment, polypharmacy, cost, and side effects from particular medications (weight gain, pancreatitis, etc.). Lower glucose targets early in the course of the disease can have a favorable legacy effect which can last for years later. Conversely, individuals with multiple comorbidities and complications from diabetes show less benefit from lower glucose targets. Factors to consider in the individualization of glycemic targets are shown in Table 2 (4).

Table 2. Factors Guiding Individualization of Glycemic Targets

Favoring lower glucose targets	Favoring higher glucose targets
Low risks associated with hypoglycemia and other drug adverse effects	High risks associated with hypoglycemia and other drug adverse effects
Newly diagnosed	Long standing diabetes
Long life expectancy	Short life expectancy
No important comorbidities	Many comorbidities
No vascular complications	Severe vascular complications
Highly motivated patient with excellent self-care capabilities	Patient preference for less burdensome therapy
Available resources and support system	Limited resources and support system

Adapted from American Diabetes Association (4).

For most patients, an A1c goal of <7% will be appropriate. However, for older patients with multiple comorbidities, an A1c goal of 8-8.5% is more appropriate, and will minimize risks of hypoglycemia, increased treatment burden, and potential side effects. Major exceptions to this goal would be patients with a short life expectancy for any reason (severe comorbidities, very old age, etc.) in which the risks of tight control outweigh the long-term benefits in reduction of complications that may never be realized. In these populations, the goal is to avoid hypoglycemia and symptomatic hyperglycemia (4, 6).

GENERAL PRINCIPLES

Table 3 outlines basic principles of type 2 diabetes management, as formulated by the AACE and the American College of Endocrinology.

Table 3. Principles of Type 2 Diabetes Management
Lifestyle modification underlies all therapy (e.g., weight control, physical activity, sleep, etc.)
Avoid hypoglycemia
Avoid weight gain
Individualize all glycemic targets
Optimal A1c is $\leq$6.5% or as close to normal as is safe and achievable
Therapy choices are patient centric based on A1c at presentation and shared decision-making
Choice of therapy reflects presence of atherosclerotic cardiovascular disease, congestive heart failure, and renal status
Comorbidities must be managed for comprehensive care
Get to goal as soon as possible – adjust at $\leq$ 3 months until at goal
Choice of therapy includes ease of use and affordability
Continuous glucose monitoring is highly recommended, as available, to assist patients in reaching goals safely

Adapted from the American Association of Clinical Endocrinology and the American College of Endocrinology (1).

Specific medication choices should be tailored to the needs of the individual patient. Important factors to consider include initial A1c, duration of diabetes, comorbidities, cardiac, cerebrovascular and renal status, cost, risk of hypoglycemia, available social supports, and patient preference.

Classes of Antihyperglycemic Medications

The number of classes of diabetes medications available have increased greatly since the 1990's, as shown in Figure 1. In 2022 a new type of incretin was added to the antihyperglycemic armamentarium – a combined GIP/GLP-1 receptor agonist (22-26). A thorough discussion of the available medication types can be found in other Endotext chapters, including Oral and Injectable (Non-Insulin) Pharmacologic Agents for Treatment of Type 2 Diabetes and Insulin – Pharmacotherapy, Therapeutic Regimens and Principles of Intensive Insulin Therapy (27, 28).

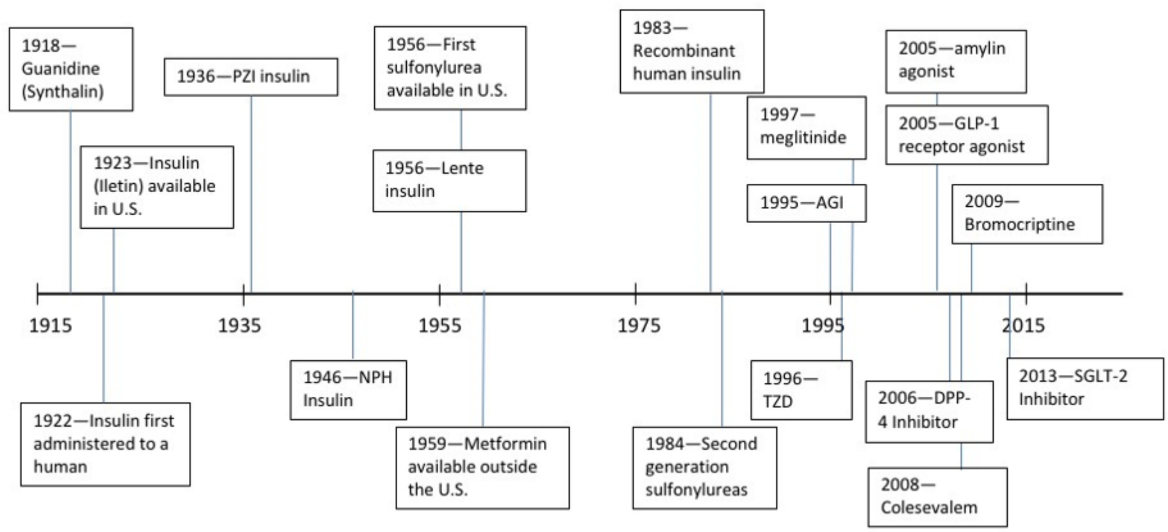

Figure 1. The History of Antihyperglycemic Agents. Figure adapted from White (29).

It is recognized that diabetes effects many organ systems throughout the body. Because of the multiple abnormal pathways, different medications can target different defects, and therefore work in a complementary fashion (see Table 4). Understanding has grown from the original "terrible triumvirate" with abnormalities of the beta cell (reduced insulin secretion), the liver (increased endogenous glucose production) and the peripheral insulin resistance. Overtime there was recognition of the "ominous octet", and now there is understanding of even more pathways/defects (30-32). Characteristics of the most commonly used medications are shown in Tables 5 and 6.

Table 4. Pathways in the Treatment of Type 2 Diabetes		
Pathway	**Defect**	**Medication classes**
Beta cell dysfunction	Decreased beta cell function and mass	Incretins, sulfonylureas, meglitinides
Incretin effect	Decrease in the incretin effect	Incretins
Alpha cells	Increase in glucagon	Incretins, pramlintide
Adipose tissue	Insulin resistance, increased lipolysis	Metformin, thiazolidinediones
Muscle	Insulin resistance, decreased peripheral glucose uptake	Metformin, thiazolidinediones
Liver	Insulin resistance, increased glucose production	Metformin, thiazolidinediones
Brain	Increased appetite, decreased morning dopamine surge, increased sympathetic tone	Incretins, dopamine agonists, appetite suppressants
Colon/biome	Abnormal microbiome, possible decreased GLP-1 secretion	Probiotics, incretins, metformin
Immune dysregulation/inflammation		Incretins, anti-inflammatories, immune modulators
Stomach/small intestine	Increased rise of glucose absorption	Incretins, pramlintide, alpha glucosidase inhibitors
Kidney	Increased glucose reabsorption	SGLT-2 inhibitors

GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium-glucose co-transporter 2. Adapted from Schwartz (32).

Table 5. Antihyperglycemic Agents and Mechanisms of Action	
Class	**Primary Mechanism of Action**
α-Glucosidase inhibitors	Delay carbohydrate absorption from intestine
Amylin analogue	Decrease glucagon secretion Slow gastric emptying Increase satiety
Biguanide	Decrease hepatic glucose production Increase glucose uptake in muscle
Bile acid sequestrant	Decrease hepatic glucose production? Increase incretin levels?
DPP-4 inhibitors	Increase glucose-dependent insulin secretion Decrease glucagon secretion
Dopamine-2 agonist	Activates dopaminergic receptors
Meglitinides	Increase insulin secretion
GLP-1 receptor agonists / combined GIP and GLP-1 receptor agonists	Increase glucose-dependent insulin secretion Decrease glucose secretion Slow gastric emptying Increase satiety
SGLT-2 inhibitors	Increase urinary excretion of glucose
Sulfonylureas	Increase insulin secretion
Thiazolidinediones	Increase glucose uptake in muscle and fat Decrease hepatic glucose production

DDP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium-glucose co-transporter 2. Adapted from AACE 2015 and slideshow (2, 33)

Table 6. Characteristics of Commonly Used Antihyperglycemic Medication Classes						
Drugs	**Ability to Lower Glucose**	**Risk of Hypoglycemia**	**Weight Change**	**Effect on ASCVD**	**Effect on CHF**	**Effect on Renal Disease**
2nd generation SU	High	Yes	Increase	Neutral	Neutral	Neutral
Metformin	High	No	Neutral-modest weight loss	Potential benefit	Neutral	Neutral
TZDs	High	No	Increase	Potential benefit (pioglitazone)	Increased	Neutral
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential increase (saxagliptin, alogliptin)	Neutral
SGLT-2 inhibitors	Intermediate	No	Decrease	Potential benefit	Benefit	Benefit – reduced progression of renal failure
GLP-1 receptor agonists	High	No	Decrease	Benefit	Neutral-Potential Benefit	Benefit-decreased proteinuria

DDP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium-glucose co-transporter 2; SU = sulfonylurea; TZD = thiazolidinediones. Adapted from American Diabetes Association and Endotext Chapter Pharmacological Agents for the Treatment of Type 2 Diabetes (5, 27)

Therapeutic Inertia

Reassessment of patient's achievement of their glycemic goals as well as the appropriateness of these goals at regular intervals is necessary. In diabetes, therapeutic inertia can include both the failure to advance or to de-intensify treatment when appropriate to do so. Failure to escalate therapy when appropriate is associated with worse microvascular and macrovascular outcomes and higher health costs (34, 35). Furthermore, several studies have shown that achieving A1c targets early in the course of the disease is associated with maintaining lower A1c levels for longer (35-37). Delays in appropriate deintensification of therapy is also a widespread problem (35, 38, 39). A number of factors contribute to therapeutic inertia, many of which can be classified as patient-related factors, physician-related factors, and health care system factors (see Table 7) (40). In addition, societal level factors, such as health care payment models, society inequity, and social determinants of health care contribute to therapeutic inertia.

Table 7. Factors Contributing to Therapeutic Inertia in Diabetes Care		
Patient-related	**Physician-related**	**Healthcare system-related**
Denial of disease	Time constraints	No clinical guidelines
Lack of awareness of progressive nature of disease leading to feeling of "failure"	Lack of support	No disease registry
Lack of awareness of implications of poor glycemic control	Concerns over costs of treatment and testing	No visit planning
Fear of side effects (hypoglycemia, weight gain)	Reactive rather than proactive care	No active outreach to patients
Concerns over ability to manage more complicated treatment regimens	Underestimation of patient's needs	No decision support
Too many medications	Lack of information/understanding of new treatment options	No team approach to care
Treatment costs	Lack of information on side effects/fear of causing harm	Poor communication between physician and staff
Poor communication with physician	Lack of clear guidance on individualizing treatment	
Lack of support	Concern over patient's ability to manage for complicated treatment regimens	
Lack of trust in physician	Concerns over patient adherence	

Adapted from Okemah (40).

ALGORITHM FOR ANTIHYPERGLYCEMIC MEDICATIONS

There are a number of algorithms available to guide the choice of antihyperglycemic medications for type 2 diabetes. These include algorithms from the American Diabetes Association, the American Association of Clinical Endocrinology and American College of Endocrinology, and the European Society of Cardiology and the European Association for the Study of Diabetes, among others. While these differ in the details, they share a similar approach (1-3, 5, 28, 41, 42). The cornerstone of treatment of type 2 diabetes is comprehensive lifestyle education. This includes diabetes self-management education and support (DSMES), medical nutrition therapy, routine physical activity, smoking cessation counseling, and psychosocial care. DSMES has been shown to result in improved quality of life, reduced all-cause mortality risk, and health care costs (43-49). Specific lifestyle goals, if possible, include at least 150 minutes of moderate exercise per week and a reduction in body weight by 5-10% (1, 49). Weight loss in type 2 diabetes can improve glycemic control, result in diabetes remission, and cause improvements in blood pressure, lipids, hepatic steatosis, obstructive sleep apnea, osteoarthritis, and renal function (1, 2, 50-53).

Initiating Treatment

For individuals requiring pharmacologic treatment, monotherapy is a reasonable approach for patients whose A1c is close to goal. Historically, metformin has been recommended as the first line agent, unless there are contraindications. However, in light of the growing evidence supporting use of GLP-1 receptor agonists and/or SGLT-2 inhibitors to decrease atherosclerotic cardiovascular disease (ASCVD), heart failure, and/or chronic kidney disease, there has been movement to consider use of these agents before metformin (1, 5, 42). In 2022, the ADA modified its previous recommendations that metformin be used as a first line agent in the absence of contraindications (54). The ADA now recommends that "First-line therapy depends on comorbidities, patient-centered treatment factors, and management needs and generally includes metformin and comprehensive lifestyle modification…. Other medications (glucagon-like peptide 1 receptor agonists, sodium-glucose cotransporter 2 inhibitors), with or without metformin based on glycemic needs, are appropriate initial therapy for individuals with type 2 diabetes with or at high risk for atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease" (5). AACE recommends that "The choice of diabetes therapies must be individualized based on attributes specific to both patients and the medications themselves…. The choice of therapy depends on the patients cardiac, cerebrovascular, and renal status" (1). Thus, the ADA and AACE are now in agreement that GLP-1 receptor agonists and SGLT-2 inhibitors should be considered as first line agents in certain patients (1, 5). Of note, use of these agents as first line treatment can often still be limited by cost and insurance coverage considerations.

Combination Therapy

Many patients will require combination treatment. Initial combination treatment should be considered in individuals with an elevated A1c. AACE recommends initial combination treatment for A1c > 7.5%, while the ADA recommends initial combination treatment for patients with A1c 1.5-2% above their glycemic target (1, 5). For individuals with A1c > 9-10% with symptoms of hyperglycemia or catabolism, insulin therapy should be the initial treatment. For individuals with A1c > 9-

10% without symptoms, initial treatment with dual or triple therapy without insulin can be considered, although insulin is often needed. Generally, medications are added, instead of substituting medications. This is because of the progressive nature of diabetes, and because medications can be chosen that act in complementary manners. Important exceptions to this is that incretin agents should not be combined (i.e. DDP-4 inhibitors and GLP-1 receptor agonists), and that sulfonylureas and meglitinide are typically stopped when prandial insulin is initiated.

DURABILITY

The natural history of type 2 diabetes is one of progressive beta cell failure that leads to the need to intensify a medical regimen over time. This generally means starting with one medication and adding others as needed to meet glycemic goals. Some medications are able to maintain glycemic control for longer than others, and thus have a more favorable effect on the natural history of diabetes, likely by successfully modifying and improving the underlying abnormal physiology.

In general, sulfonylureas have been found to be less durable than other diabetes medications. For example, in the A Diabetes Outcome Progression Trial (ADOPT), among patients with newly diagnosed diabetes, the 5-year failure rate for sulfonylureas was 15% for rosiglitazone, 21% for metformin, and 34% for glyburide (55). While sulfonylureas are able to affect an increase in insulin production, they are unable to correct the underlying beta cell dysfunction.

Metformin

Metformin is traditionally considered the first line agent due to low risk of hypoglycemia, good antihyperglycemic efficacy, ability to promote weight loss, and cost. Compared to sulfonylureas, its effects tend to be more durable, and there is stronger data supporting its cardiovascular safety (56). Metformin commonly causes gastrointestinal side effects, which can often be minimized by starting at a low dose and gradually titrating and using extended release formulations (57). While the maximum dose is 850 mg three times a day, most people do not titrate past 1000 mg twice a day. Metformin is associated with an increased risk of lactic acidosis, and should not be used in individuals at increased risk of lactic acidosis, such as in chronic kidney disease or hepatic disease. While metformin used to have contraindications based on creatinine levels, in 2016 the FDA changed these recommendations (58). Current renal dosing guidance is shown in Table 8 (1, 5, 59-62). Metformin can also lead to vitamin B12 malabsorption and/or deficiency, which can lead to anemia and peripheral neuropathy, and so B12 levels should be monitored periodically (63).

Table 8. Metformin Dosing Recommendations	
eGFR (mL/min/1.73 m^2)	**Recommendation**
> 60	No adjustments Monitor annually
45-60	No adjustments Monitor every 3-6 months
30-45	Initiation generally not recommended, but can be considered Continuation of therapy: maximum dose of 500 mg twice a day
< 30	Contraindicated

eGFR = estimated glomerular filtration rate. Adapted from multiple sources (1, 5, 59-62).

Patients with ASCVD, Congestive Heart Failure, or Chronic Kidney Disease

For patients with high-risk or established ASCVD, heart failure, or chronic kidney disease, GLP-1 receptor agonists and SGLT-2 inhibitors should be considered independent of baseline A1c, individualized A1c target, or metformin use. As described in Endotext chapter Pharmacological Agents for the Treatment of Type 2 Diabetes, the GLP-1 receptor agonists dulaglutide, liraglutide, and semaglutide have been shown to reduce cardiovascular events in individuals at high-risk or with established ASCVD (1, 5, 27, 64-66). In secondary analysis, improvement in renal outcomes were also seen in prespecified secondary outcomes in these trials (LEADER, SUSTAIN-6, and REWIND) (64-66). Markers of high-risk of ASCVD can include patients 55 years or older with coronary, carotid, or lower-extremity artery stenosis of >50% or left ventricular hypertrophy (5). Contraindications to the use of GLP-1 receptor agonists include history of pancreatitis and a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia 2A or 2B. Some agents (exenatide, lixisenatide) are not approved in the setting of chronic kidney disease. Increase in the progression of retinopathy was seen in the pivotal trial of semaglutide, but it is unclear whether that was an effect specific to the medication or a consequence of the rapid glucose lowering (65). Tirzepatide is a novel combined GIP and GLP-1 receptor agonist which has showed substantial A1c lowering and weight loss (22-26). The tirzepatide cardiovascular disease outcome trials are still ongoing.

SGLT-2 inhibitors have been shown to reduce diabetic kidney disease progression, hospitalizations for heart failure, and ASCVD (5, 7, 8, 67-82). See in Endotext chapter Pharmacological Agents for the Treatment of Type 2 Diabetes for additional details (27). SGLT-2 inhibitors with benefits on progression of diabetic kidney disease include canagliflozin, empagliflozin, and dapagliflozin. SGLT-2 inhibitors with proven effects on ASCVD include empagliflozin and canagliflozin. SGLT-2 inhibitors with proven effects on heart failure include empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin. SGLT-2 inhibitors are contraindicated in patients with a history of or increased risk of diabetic ketoacidosis, due to increased risk of euglycemic diabetic ketoacidosis with these agents. In addition, they should be used caution in individuals with frequent bacterial urinary tract infections or genitourinary yeast infections, high risk for fractures and falls, foot ulceration, or other factors predisposing to diabetic ketoacidosis.

An area of ongoing discussion is the use of SGLT-2 inhibitors in individuals who already have advanced chronic kidney disease. At estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73m^2, SGLT-2 inhibitors are unlikely to result in substantial glucose lowering. However, they have been shown to have beneficial effects on delaying the progression of chronic kidney disease in patients with eGFRs down to 25 mL/min/1.73 m^2 (7). Patients with advanced chronic kidney disease on SGLT-2 inhibitors must be monitored closely, and counselled to maintain adequate fluid intake and avoid hypoglycemia.

Thus, for individuals with established ASCVD or at high risk for ASCVD, either a GLP-1 receptor agonist with proven cardiovascular disease benefits (dulaglutide, liraglutide, semaglutide) or an SGLT-2 inhibitor with proven cardiovascular disease benefit (empagliflozin, canagliflozin) should be strongly considered, potentially as a first line agent. For patients with heart failure, a SGLT-2 inhibitor with a proven benefit for heart failure hospitalizations should be considered, potentially as a first line agent. For patients with chronic kidney disease and albuminuria, a SGLT-2 inhibitor should be strongly considered regardless of glycemic control. If SGLT-2 inhibitors are not tolerated or are contraindicated, a GLP-1 receptor agonist can be considered. For patients with chronic kidney disease without albuminuria, either a GLP-1 receptor agonist with proven cardiovascular disease benefit or a SGLT-2 inhibitor with proven cardiovascular disease benefit can be considered. In addition, combination therapy with GLP-1 receptor agonist and SGLT-2 inhibitor likely has synergistic effects on glucose lowering and CVD prevention, and thus should be considered (8, 83).

Note that some SGLT-2 inhibitors and GLP-1 receptor agonists have indications for individuals without diabetes (see Table 9).

Table 9. Antihyperglycemic Medications with Indications in Individuals Without Diabet	
Medication	**Indication**
Liraglutide (Saxenda)	As an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of 30 kg/m^2 or greater or BMI of 27 kg/m^2 and at least one weight-related comorbid condition (e.g. hypertension, type 2 diabetes mellitus, dyslipidemia) (84)
Semaglutide (Wegovy)	As an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of 30 kg/m^2 or greater or BMI of 27 kg/m^2 and at least one weight-related comorbid condition (e.g. hypertension, type 2 diabetes mellitus, dyslipidemia) (85)
Dapagliflozin (Farxiga)	Reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV) (86)
Dapagliflozin (Farxiga)	Reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease at risk for progression (86)
Empagliflozin (Jardiance)	Reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure and reduced ejection fraction (87)

BMI = body mass index; eGFR = estimated glomerular filtration rate; NYHA = New York Heart Association.

Patients at Risk for Hypoglycemia

While hypoglycemia should be avoided for all patients, it is especially important in patients with hypoglycemia unawareness, in older patients, and in patients with multiple comorbidities or diabetes complications. Medications with a higher risk of hypoglycemia should be avoided in these patients, and include sulfonylureas, meglitinides, and insulin. Medications to consider with a low risk of hypoglycemia include metformin, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, or thiazolidinediones.

If a sulfonylurea must be added, a later generation agent should be chosen. Meglitinides also can be considered in some patients, and generally have a lower risk of hypoglycemia (and also less A1c lowering potential) than sulfonylureas. Basal insulins with lower risk of hypoglycemia can also be chosen. The risk of hypoglycemia is lowest for degludec and glargine U-300, followed by glargine U-100 and detemir, with the highest risk of hypoglycemia with Neutral Protamine Hagedorn (NPH) insulin (5).

Patients with Compelling Need for Weight Loss

Most patients with diabetes have obesity or overweight, and thus benefit from medications that promote weight loss. Two of the pillars of the AACE's treatment approach to individuals with diabetes are lifestyle modifications including weight control, and avoiding weight gain. Both GLP-1 receptor agonists and SGLT-2 inhibitors can result in weight loss, although effects are generally greater for GLP-1 receptor agonists (5, 52). Liraglutide and semaglutide also have separate indications for weight loss regardless of diabetes status. In general, the degree of weight loss for semaglutide and liraglutide is greater than that of dulaglitude, which is greater than that of exenatide (5, 52). The combined GIP and GLP-1 agonist tirzepatide has shown even greater weight loss than that for GLP-1 receptor agonists (23, 25). In contrast, medications such as sulfonylureas, thiazolidinediones, and insulin tend to lead to weight gain (1, 5).

Patients Where Cost is an Issue

For many patients, cost can be a substantial barrier to care. Many patients are uninsured or underinsured. One in four patients on insulin report rationing their insulin doses due to cost (88). Patients should be asked about barriers to care. Often medication assistance programs and rebate programs can be used to decrease or eliminate the cost burden for patients. If these approaches are not successful, medications should be chosen keeping in mind the out-of-pocket cost for the patient. The cheapest medications are metformin, sulfonylureas, and thiazolidinediones. The typical approach, unless there are contraindications, is to start with metformin, then if additional agents are necessary to add sulfonylureas and then thiazolidinediones. If additional agents are needed, insulin can be added. Human insulins (regular, NPH) are cheaper than analogue insulins, and are discussed in the Insulin Therapy section.

Insulin Therapy

For individuals with A1c > 9-10% with symptoms of hyperglycemia or catabolism, insulin therapy should be the initial treatment. Once the initial glucotoxicity has resolved, some individuals will be able to stop insulin, especially if they are able to make lifestyle modifications and achieve weight loss.

Individuals who are on maximal non-insulin therapy and still not at their goal A1c should have insulin initiated. Insulin should not be presented as a "threat" to patients. The natural history of type 2 diabetes should be discussed with patients, so that they understand that escalation of therapy and/or initiation of insulin are common, and do not represent a "failure" on the patient's part.

If individuals are not already taking a GLP-1 receptor agonist, it should be considered prior to starting insulin. There are a number of insulin titration regimens that can be followed (1, 5). If cost is an issue, NPH and Regular insulin can be used. In patients with type 2 diabetes, insulin analogues do not always have a major advantage over human insulin products. Most studies comparing analogue insulins to human insulin products have not shown an improvement in glycemic control or reduced risk of severe hypoglycemia, although they do show reduced risk of overall and nocturnal hypoglycemia (89, 90).

A number of algorithms are available for insulin initiation and titration (1, 5). The key is to continue to adjust the insulin doses until the patient achieves their glycemic target. Typically, the patient is first started on basal insulin, and then the dose is gradually increased. The appropriateness of their preexisting diabetes medications should be evaluated when basal insulin is started. Most medications can be continued, but consideration can be given to stopping medications without cardiovascular, congestive heart failure, or renal benefit. Patients should be regularly assessed for "overbasalization." Signs of overbasalization are shown in Table 10.

Table 10. Signs of Overbasalization
Basal dose > 0.5 IU/kg
Elevated bedtime-morning differential ($\geq$ 50 mg/dL)
Elevated post-preprandial differential
Hypoglycemia
High glucose variability

Adapted from American Diabetes Association (5)

At that point, prandial insulin should be initiated. If patients have a meal that is substantially larger than others (typically supper), prandial insulin can be started at the largest meal, and then additional doses added as needed. Most individuals with type 2 diabetes use a fixed prandial dose for meals, or a fixed dose with a correctional scale. However, individuals with highly variable meals or minimal insulin reserve (as assessed with a c-peptide measurement), using a carbohydrate to insulin ratio (as is done in type 1 diabetes) can be helpful. As with the initiation of basal insulin, when prandial insulin is initiated the patient's preexisting diabetes regimen should be evaluated. In particular, sulfonylureas and meglitinides should be stopped when prandial insulin is added.

For patients where cost is an issue, human insulins can be more affordable than analogue insulins. In general, insulin doses should be decreased by 20% when switching from analogue insulin to human insulin in order to minimize the risk of hypoglycemia (89, 90).

The volume of insulin that can absorbed at a given time and given site can be a factor limiting insulin titration, especially as patients get to higher doses. For patients on over 200 units of insulin a day, switching to concentrated insulin formulations should be considered. In the past, U-500 regular insulin was the only option available. It has dose dependent pharmacokinetics, typically intermediate between regular and NPH insulin. In more recent years, U-200 degludec, U-300 glargine, and U-200 lispro have become available, and are often easier to use than U-500 regular insulin. While U-500 is available in vials and pens, if at all possible pens should be used, in order to reduce the chance of dosing errors.

Some individuals with type 2 diabetes on basal-bolus insulin regimens can benefit from an insulin pump (91, 92). Insurance coverage for insulin pumps for people with type 2 diabetes varies. When coupled with a CGM, some pumps allow for hybrid closed loop dosing, in which insulin doses are adjusted automatically based on current glucose values from the CGM.

CONCLUSION

Pharmacologic management of type 2 diabetes requires an individualized approach that weighs important factors such as efficacy, cost, side effects, adherence and treatment burden, comorbidities, mechanisms of action, and non-glycemic effects. Appropriate selection of medication can not only result in improved glucose control, but also have favorable effects on obesity, atherosclerotic cardiovascular disease, congestive heart failure, and chronic kidney disease.

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E. Schroeder has no conflicts of interest to disclose.

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