REPORT

Economic Impact of and Treatment Options for Type 2 Diabetes

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ABSTRACT

Diabetes and its various comorbidities are responsible for a substantial societal financial burden. Healthcare and managed care providers must take responsibility for and address the high healthcare costs attributed to diabetes care. They can work together to improve diabetes-related patient care and reduce costs. Newer therapeutic agents and those used as combination therapy may decrease direct costs by improving glycemic control and preventing negative outcomes associated with diabetes comorbidities. Additional diabetes education, increased time to review medication adherence and diabetes monitoring, and having affordable care are all necessary to improve the care of individuals with diabetes.

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For author information and disclosures, see end of text.

The prevalence of diabetes continues to increase as more Americans live longer and the prevalence of obesity increases. As the prevalence and the associated costs of diabetes care increase, so does the national burden of this disease. Notably, of the 30.3 million Americans diagnosed with diabetes in 2015, an estimated 7.3 million were undiagnosed, despite the wide variety of agents currently available for the treatment and management of this disease.[1] Several older diabetes therapies are guideline-supported, first-line options typically covered by prescription insurance with a low patient co-pay. However, there is still a huge, unmet need to appropriately use these agents for optimal patient care. Newer therapeutic agents may increase the number of patients achieving glycemic goals, which should reduce diabetes-related complications and thereby reduce the direct and indirect costs of care.

Economic Burden and Impact of Diabetes

The cost of treating diabetes in the United States increased from $174 billion in 2007 to $245 billion in 2012, or 41% over 5 years.[2] Of this increase, 27% is attributed to the higher prevalence of diagnosed diabetes and 14% to the rising costs of diabetes care.[2,3] The 2012 costs include $176 billion in direct medical costs and $69 billion in reduced productivity. Hospital inpatient care (43% of all medical costs) and prescription medications to treat complications of diabetes (18%) were the 2 largest direct costs.[4] Medication costs are an estimated 2.3 times higher for those with diabetes compared with those without diabetes. Indirect costs for those who are employed were increased absenteeism ($5 billion) and reduced productivity while at work ($20.8 billion). For those not working, indirect costs included reduced productivity ($2.7 billion), inability to work due to disease-related disability ($21.6 billion), and lost productive capacity because of early mortality ($18.5 billion).[2] In the United States, the majority (62%) of diabetes medical costs are covered by Medicare, Medicaid, and the military, while private insurance covers about one-third; 3.2% of diabetes costs are paid by the uninsured.[4]

Another consideration is the cost associated with people who have yet to be diagnosed. The estimated burden of undiagnosed diabetes

in 2007 was $18 billion.[5] In 2012, costs associated with elevated blood glucose levels for undiagnosed diabetes were estimated to be $33 billion.[6] Between 2007 and 2012, this national cost burden for undiagnosed diabetes had increased by 82%.

Achieving and maintaining goal glycated hemoglobin (A1C) values has been shown to prevent and delay diabetes-related complications and to decrease direct medical costs.[7,8] For example, in a nested case-control study of Kaiser Permanente Southern California members, those with an average A1C >8% were 16% more likely to experience a cardiovascular (CV) event than those with an A1C of 6% to 8% (P <.0001). However, A1C that is too low can also be problematic; patients with an A1C ≤6% were 20% more likely to experience a CV event (P <.0001).[7] This outcome further demonstrates the importance of helping patients achieve personalized glycemic control without hypoglycemia. Two additional studies of note: a cohort study of claims data from a large health maintenance organization found that an A1C decrease of 1% or more was associated with lower total healthcare costs ($685-$950 less per year) than those without an improvement in the A1C value,[9] and a retrospective analysis from a large US health plan showed that a 1% increase in A1C was associated with a 7% increase in healthcare costs over the next 3 years.[10]

To halt the diabetes epidemic, healthcare and managed care providers must work together to improve patient care outcomes, medication adherence, and access to care, especially to help identify undiagnosed diabetes.

Call for Action

The personal impact associated with diabetes is great and has a rigorous daily toll: monitoring of diet and blood glucose, medication adjustments, and fear and/or presence of life-altering acute and chronic complications.[11] Healthcare and managed care providers must take responsibility for and address high healthcare costs at the public level and, at the personal level, the lost productivity, mortality, and morbidity attributed to diabetes care.[11]

Coupling personalized clinical care with real-time, patient-specific diabetes education leads to improved glycemic control in a short time and produces cost savings.[8,12] Effectively communicating with patients and empowering them as decision makers about their own care has been successful and is a key to change. In addition, more time spent with patients allows for discussion of how medications work to improve their diabetes and how the synergistic relationship with diet and exercise improves outcomes.

With the increased economic and personal costs of uncontrolled hyperglycemia and poor glycemic control, achieving A1C goals and making medications and clinical care more affordable to all is necessary. This will likely require a shift in the way we currently provide diabetes care, moving toward a more team-based and patient-centered approach. A growing trend is to provide collaborative care to patients with diabetes. A team can consist of physicians, pharmacists, nurse practitioners, physician assistants, dietitians, certified diabetes educators (CDEs), medical assistants, and social workers to provide patient-centered care, and treatment decisions are determined with active participation by the patient. A collaborative practice agreement allows pharmacists to provide direct care to patients and make therapy changes within scope of practice and agreement guidelines. This method also frees up primary care providers (PCPs) to focus on other chronic diseases, thus potentially improving overall care and patient satisfaction.

Treatment Challenges: Need for Additional Data

To achieve this collaborative care and patient-centered approach, it is crucial to understand the various treatment challenges (ie, areas in diabetes care that are currently lacking or missing). Several that are relevant to the managed care perspective are briefly discussed below.

Lack of Comparative Effectiveness Data

Clinical trials directly comparing clinical outcomes of diabetes medications are lacking.[13] Not having comparative effectiveness data makes drug therapy decisions challenging for prescribers and managed care decision makers. Conducting these trials can be difficult because of the number of different therapies available, interpatient variability, multiple second- and third-line options, and the rapidly developing diabetes marketplace. A potential recommendation to close this gap is for the FDA approval process to require head-to-head comparison trials based on guideline-recommended treatment combinations for all investigational diabetes medications.[13]

Need for Patient-Reported Outcomes Data

Diabetes clinical trials assessing patient-reported outcomes (PROs) are lacking.[13] These measures provide valuable information regarding the patient's perspective on the benefits and adverse events of real-world medication use (eg, impact on physical, mental, and social well-being). Encouraging manufacturers and others who are conducting large-scale clinical trials to use a standard set of PROs for diabetes medications would facilitate comparison of these important outcomes. The National Institutes of Health's Patient-Reported Outcomes Measurement Information System (PROMIS) program could serve as a model.[13,14] PROMIS is a rigorously tested measurement tool that uses advanced information technology and psychometrics, as well as qualitative, cognitive, and health survey research techniques, to measure PROs.[14]

Time and Compensation for Alternative Care Delivery Models

Patients with diabetes who were managed in a collaborative practice model and who received additional time beyond usual care to receive patient education and clinical care led to significant positive

outcomes and cost avoidance.[8] The collaborative practice model consisted of an endocrinologist and pharmacist-CDE. Compared with usual PCP visits, the pharmacist spent more time (60 minutes) with patients. Cost-effectiveness was demonstrated from the clinic, health system, and payer perspectives. At 6 months, mean A1C significantly improved in the intervention group compared with the usual care (PCP) group (2.4 ± 2.1 vs -0.8 ± 1.7, respectively; $P < .001$).[12] Significantly more patients met A1C goals (at 3 and 6 months) in the intervention group compared with control-group patients. This model is unique and promising because there was a limited time-intense pharmacist intervention phase (mean of 3 visits within 6 months) and then the patient was discharged back to their PCP for ongoing care. This demonstrated that substantial clinical improvements can be observed in a short period of time and at a limited cost.[8] Despite these positive outcomes, this practice model is not commonly used and would likely not be covered by health insurance unless "incident to" or medication therapy management billing codes are used.

Knowledge of Diabetes Medication Use and Outcomes in Different Races and Ethnicities

Certain medications, such as sulfonylureas, miglitol, metformin, and rosiglitazone, have been evaluated in African American, Hispanic, and Asian populations.[15] However, studies are lacking for other, newer diabetes medications in nonwhite races/ethnicities. These studies are needed to determine if efficacy, adverse effects (AEs), or usage vary based on the individual's race/ethnicity.

Patient and Provider Barriers for the Appropriate Treatment of Diabetes

In addition to lack of existing data, there are numerous patient and provider barriers to achieving treatment goals in diabetes care. In this section, potential barriers from the managed care perspective, such as clinical inertia, limited access, and medication nonadherence, are briefly detailed.

Clinical Inertia

Recent data show that A1C values are not at recommended target levels in 40% to 60% of people with diabetes.[16] This occurs across geographic regions and in high- and low-income countries. Clinical inertia occurs when intensification of diabetes treatment stalls because of patient nonadherence and provider factors.[17,18] It is believed to occur in up to 50% of patients with diabetes.[16] Delays in treatment intensification can allow disease progression and the development of comorbidities that increase healthcare costs and reduce quality of life. Individuals with diabetes are at considerable risk for clinical inertia because of the need for dramatic lifestyle changes and because of the risks (such as hypoglycemia and weight gain) associated with therapy intensification.[17,19] The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) 2017 guidelines support the addition of insulin to reduce substantially elevated A1C levels (A1C >10%) in symptomatic patients, or if patients are already receiving 2 oral agents and not achieving glycemic goals.[20,21] However, on average, it takes 7 years after diagnosis for prescribers to add insulin to a patient's treatment regimen.[18] Clinical inertia occurs when prescribers have low expectations of patients' ability to make the needed dramatic lifestyle changes and will instead allow patients to endure extended periods of mild hyperglycemia to avoid hypoglycemia. It can take 3 years or longer to initiate or intensify glucose-lowering therapy.[16] Overcoming clinical inertia involves provider and patient education as well as close patient follow-up to minimize AEs and make changes to medication therapy as quickly as possible. It is recommended that therapy be evaluated every 3 months until the patient is stable and target levels set for the patient are achieved.[21]

Limited Access to Medical Care and Medications

Approximately 30% of adults with diabetes remain undiagnosed, likely because of limited access to medical care.[22] Compared with adults with a diabetes diagnosis, adults whose diabetes has not been diagnosed have lower A1C levels, but are less likely to receive statins and have an increased risk for future complications.

For those who are diagnosed, access to newer medications may be reduced by placement on higher formulary tiers with higher co-pays or no coverage offered by the prescription insurance provider. A value-based benefit design that reduced diabetes medication co-pays by 36% was shown to affect access by decreasing medication nonadherence by 30%.[5] Creative benefit designs such as this, coupled with public and patient education as well as health policy efforts, are needed to make these services affordable to all.

Medication Nonadherence

Medication nonadherence costs associated with medication-related hospital admissions were estimated to be $100 billion annually more than 10 years ago; nonadherence is linked with increased adverse clinical outcomes and mortality.[23] Medication nonadherence is associated with increased medication regimen complexity, multiple comorbidities, high medication cost, lack of patient understanding and engagement, and a poor relationship with providers.[13] About 30% of prescriptions for diabetes medications are never filled. Of those that are filled, even fewer are taken or refilled as prescribed. Commonly, poor outcomes in individuals with type 2 diabetes (T2D) are because of medication nonadherence.[24,25]

A1C As a Target Goal

It is important to address these barriers to appropriately meet treatment goals, including achieving target A1C values. A1C measurements

TABLE 1. Guideline-Recommended Glycemic Targets[20,21]

Glycemic Target	ADA/EASD Goal	AACE/ACE Goal
A1C	<7% with individualization[a]	≤6.5% if no concurrent serious illness and not at risk for hypoglycemia >6.5% if concurrent serious illness and at risk for hypoglycemia
Preprandial glucose (mg/dL)	80-130	≤110
Postprandial glucose (mg/dL)	<180	≤140

A1C indicates glycated hemoglobin; AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes.
[a]ADA A1C goal individualization includes tighter targets (6.0%-6.5%) for younger, healthier patients and less stringent targets (7.5%-8.0% or higher) for older patients with comorbidities who are prone to hypoglycemia.

are used to diagnose and make treatment decisions for patients with diabetes.[26] The A1C value reflects a weighted average of blood glucose concentrations over the previous 2 to 3 months; it does not require fasting and can be tested at any time of day. Recommended glycemic targets, including A1C, are described in **Table 1**.[20,21]

The ADA recommends checking A1C levels at least twice a year for those who are meeting treatment goals and have stable blood glucose levels.[20] A1C can be checked in a healthcare provider's office using a point-of-care (POC) device. While POC testing is not as accurate as a laboratory test, POC A1C testing is a convenient way to assess long-term blood glucose control. The estimated average glucose (eAG) can be calculated from the A1C. The eAG value helps associate the A1C value to daily blood glucose levels. An A1C of 7% is comparable with an eAG of 154 mg/dL and an A1C of 8% is comparable with an eAG of 183 mg/dL.[27] Dramatic changes in blood glucose levels over the past few months are detected in the A1C test result, but the A1C does not provide insight into sudden, temporary increases or decreases in blood glucose levels. Blood glucose levels within the past 30 days have a greater effect on the A1C reading than those in preceding months. Because the A1C test is an indirect measure of the average blood glucose concentration, its use is limited in conditions that affect red blood cell turnover. For example, chronic kidney disease, hemolysis, blood loss, and hemoglobin variants may alter the A1C, and such factors should be suspected when the A1C value is not consistent with the patient's self-monitored blood glucose levels.[20]

Overview of Medication Treatment Options

In addition to lifestyle management as a means of controlling A1C, various agents are available for diabetes management. While some have been available for decades, several new agents and combinations are on the market, and recent data exist regarding many commonly used agents. The following is a brief review of the different diabetic agents available, their roles in therapy, and updates to current treatment guidelines.

Evidence-Based Care

The ADA and AACE/ACE released diabetes treatment guidelines in 2017.[20,21] The ADA guidelines provide recommendations for all individuals with diabetes, while the AACE/ACE guidelines focus on T2D management. Both sets emphasize lifestyle changes and obesity management to prevent and manage T2D.

Diabetes care should be patient centered. To individualize therapy, clinicians should consider treatment efficacy, hypoglycemia risk, weight effects, AEs, cost, glycemic target, complications, and patient preferences, especially when selecting medications and A1C goals. Some patients may require a higher (less aggressive) A1C goal. In general, AACE/ACE guidelines recommend an A1C level below 6.5%; ADA recommends an A1C less than 7%. However, both sets of guidelines allow for higher A1C goals depending on patient characteristics and risk for complications.[20,21]

All patients should receive education about lifestyle management (nutrition, sleep, exercise, and tobacco cessation) as the foundation for treatment.[20,21] Frequent monitoring of blood glucose, body weight, blood pressure, and cholesterol levels is vital to direct therapy and to minimize clinical inertia. Unless contraindicated, most patients should receive metformin as first-line treatment, per the ADA guidelines, if A1C is less than 9%; if 9% or higher, 2 agents should be initiated. The AACE/ACE guidelines allow a range of first-line monotherapy options (**Figure 1**[20] and **Figure 2**[21]).[20,21] Available diabetes medications have different and sometimes complementary mechanisms of action. Most patients will eventually require combination therapy. Using certain combinations takes advantage of complementary glycemic effects and can offset certain AEs. Details on the recommendations are found in the published guidelines. The common diabetes drug classes recommended in the guidelines are briefly described below and individual agents are listed in **Table 2**.[20,21]

Role of Diabetes Therapeutic Agents

Fortunately, several classes of diabetic agents are now available. These classes are unique and target various organs and defective functions that occur with T2D. Many of these agents have been available for use for many years, but brief overviews and updates of these medication classes are provided below.

Sulfonylureas (SUs) include glyburide, glipizide, and glimepiride.[20,21] SUs stimulate insulin secretion from the pancreas by blocking ATP-sensitive potassium (KATP) channels. These are commonly used as second-line agents and in combination with metformin because of low costs and evidence-based data to support use. However, SUs are associated with hypoglycemia and

FIGURE 1. Antihyperglycemic Therapy in Type 2 Diabetes: General Recommendations from the ADA[20,a]

Start with Monotherapy unless:

A1C is ≥ 9%, consider **Dual Therapy**.

A1C is ≥ 10%, blood glucose is ≥ 300 mg/dL, or patient is markedly symptomatic, consider **Combination Injectable Therapy**.

Monotherapy	**Metformin**	**Lifestyle Management**
EFFICACY	high	
HYPO RISK	low risk	
WEIGHT	neutral/loss	
ADVERSE EFFECTS	GI/lactic acidosis	
COSTS	low	

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

Dual Therapy — **Metformin +** — **Lifestyle Management**

	Sulfonylurea	**Thiazolidinedione**	**DPP-4 Inhibitor**	**SGLT-2 Inhibitor**	**GLP-1 Receptor Agonist**	**Insulin (basal)**
EFFICACY	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
ADVERSE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

Triple Therapy — **Metformin +** — **Lifestyle Management**

Sulfonylurea +		**Thiazolidinedione +**		**DPP-4 Inhibitor+**		**SGLT-2 Inhibitor+**		**GLP-1 Receptor Agonist +**		**Insulin (basal) +**
TZD		SU		SU		SU		SU		TZD
or DPP-4-i	or	DPP-4-i	or	TZD	or	TZD	or	TZD	or	DPP-4-i
or SGLT-2-i	or	SGLT-2-i	or	SGLT-2-i	or	DPP-4-i	or	SGLT-2-i	or	SGLT-2-i
or GLP-1 RA	or	GLP-1 RA	or	Insulin[b]	or	GLP-1 RA	or	Insulin[b]	or	GLP-1 RA
or Insulin[b]	or	Insulin[b]			or	Insulin[b]				

If A1C target not achieved after approximately 3 months of triple therapy and patient 1) on oral combination, move to basal insulin or GLP-1 RA, 2) on GLP-1 RA, add basal insulin, or 3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (ie, adding a fourth antihyperglycemic agent).

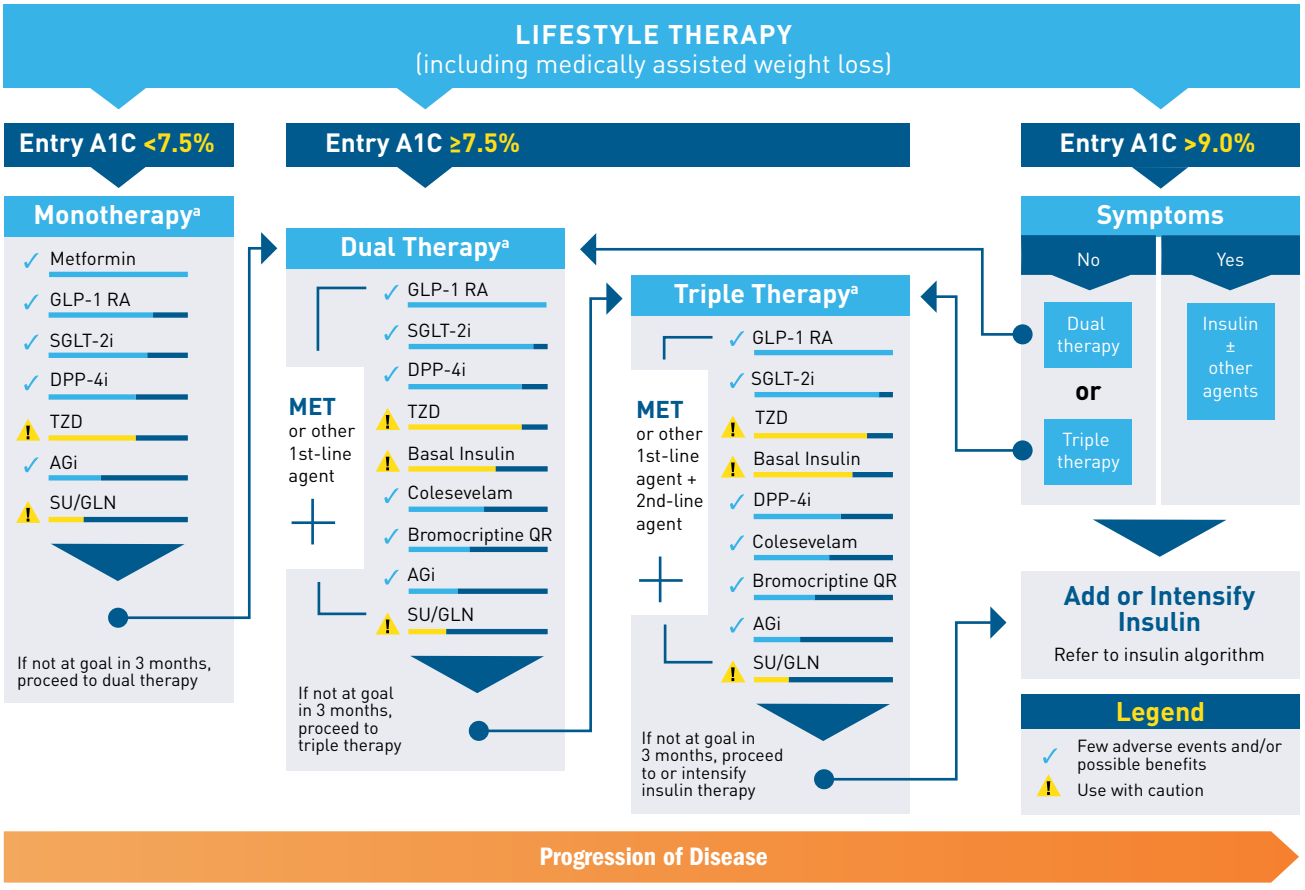
Combination Injectable Therapy

A1C indicates glycated hemoglobin; ADA, American Diabetes Association; DPP-4-i, DPP-4 inhibitor; fxs, fractures; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GU, genitourinary; HF, heart failure; Hypo, hypoglycemia; NPH, neutral protamine Hagedorn; SGLT-2-i, SGLT-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

[a]The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic therapy for patients with type 2 diabetes are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances).

[b]Usually a basal insulin (NPH, glargine, detemir, degludec).

FIGURE 2. AACE/ACE Glycemic Control Algorithm[21]



A1C indicates glycated hemoglobin; AACE/ACE, American Association of Clinical Endocrinologists/American College of Endocrinology; AGi, alpha-glucosidase inhibitor; DPP-4-i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; Met, metformin; SU/GLN, sulfonylurea/glinide; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione.

[a]Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation.

weight gain, and lose effectiveness over time because of the natural progression of diabetes.[20,21]

Biguanides are a class of diabetes drugs that includes 1 agent: metformin.[20,21] One of the best studied diabetes medications, metformin is associated with positive macrovascular outcomes and is typically first-line therapy for T2D unless contraindications exist. In addition, metformin has a high-efficacy, low-AE profile, usually results in modest weight loss, and is inexpensive. It decreases hepatic glucose production and improves insulin sensitivity via activation of adenosine monophosphate-activated protein kinase and other cellular mechanisms. Unless combined with another hypoglycemia-causing agent, metformin does not cause hypoglycemia. Lactic acidosis is very rare and generally occurs in patients with active congestive heart failure (CHF) and poor renal function. Avoid use if glomerular filtration rate is less than 30 mL/min/1.73 m^2. With long-term metformin use, vitamin B_{12} deficiency may occur; periodic monitoring of vitamin B_{12} levels should be considered, particularly if anemia or peripheral neuropathy is present.[20,21] Annual complete blood count with mean corpuscular volume may be more economical for screening vitamin B_{12} deficiency.

Meglitinides, including nateglinide and repaglinide, are noninsulin secretagogues. These medications stimulate insulin secretion by blocking KATP channels.[20] They have a shorter half-life than SUs and, to avoid hypoglycemia, may be useful when patients skip meals.

Alpha-glucosidase inhibitors include acarbose and miglitol. Postprandial blood glucose levels decrease with the inhibition of intestinal alpha-glucosidase, which decreases carbohydrate digestion and absorption.[20] These drugs reduce postprandial glucose concentrations but are limited by their gastrointestinal AE profile, with 70% of patients experiencing flatulence.

TABLE 2. FDA-Approved Diabetes Medications[20,21]

Oral	Injectable	Inhaled
• Sulfonylureas › Glipizide (Glucotrol), glimepiride (Amaryl), glyburide (Diabeta) • Biguanide › Metformin (Glucophage) • Non-sulfonylurea insulin secretagogues › Repaglinide (Prandin), nateglinide (Starlix) • Alpha-glucosidase inhibitors › Acarbose (Precose), miglitol (Glyset) • Thiazolidinediones › Rosiglitazone (Avandia), pioglitazone (Actos) • DPP-4 inhibitors › Sitagliptin (Januvia) › Saxagliptin (Onglyza) › Linagliptin (Tradjenta) › Alogliptin (Nesina) • SGLT-2 inhibitors › Canagliflozin (Invokana) › Dapagliflozin (Farxiga) › Empagliflozin (Jardiance)	• Insulin › Rapid-acting ▪ Insulin lispro (Humalog; U100 & U200), aspart (NovoLog), glulisine (Apidra) › Short-acting ▪ Regular insulin (Humulin R, Novolin R) › Intermediate-acting ▪ NPH (Humulin N, Novolin N) › Long-acting ▪ Insulin detemir (Levemir) ▪ Insulin glargine (Lantus; UlOO & U300) ▪ Insulin degludec (Tresiba; UlOO & U200) • Amylin analog › Pramlintide (Symlin) • GLP-1 receptor agonist (incretin mimetic) › Exenatide (Byetta), liraglutide (Victoza), lixisenatide (Adlyxin) • GLP-1 receptor agonist ONCE WEEKLY › Exenatide (Bydureon) › Albiglutide (Tanzeum) › Dulaglutide (Trulicity)	• Insulin powder › Rapid-acting (Afrezza)

DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; NPH, neutral protamine Hagedorn; SGLT-2, sodium-glucose cotransporter-2.

Thiazolidinediones (TZDs) include pioglitazone and rosiglitazone.[20,21] TZDs are peroxisome proliferator-activated receptor gamma receptor agonists that increase insulin sensitivity and increase glucose uptake in various tissues.[20,21] Pioglitazone has been linked to bladder cancer and should not be used in patients with a personal or family history of bladder cancer. This class of drugs should also not be used in patients with osteoporosis or CHF.

Dipeptidyl peptidase-4 (DPP-4) inhibitors include sitagliptin, saxagliptin, linagliptin, and alogliptin.[20,21] Insulin secretion is increased with the inhibition of DPP, which increases incretin (eg, glucagon-like peptide-1 [GLP-1] and gastric inhibitory polypeptide) levels and mildly decreases postprandial blood glucose levels.[20] With the exception of linagliptin, all must be dosed based on a patient's renal function. Saxagliptin and alogliptin have been associated with CHF exacerbations and should not be used in patients with CHF.

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors include canagliflozin, dapagliflozin, and empagliflozin. Blood glucose decreases with the inhibition of SGLT-2 in the proximal renal tubule, which blocks glucose reabsorption and leads to the elimination of glucose in the urine.[20,21] The FDA approved empagliflozin to reduce CV death in adults with T2D, as it has also been shown to reduce CV and all-cause mortality. The EMPA-REG OUTCOME study found that patients with T2D and a high risk of CV disease experienced significantly fewer negative CV events with empagliflozin plus standard of care compared with placebo plus standard of care.[28] The CV benefits of other SGLT-2 inhibitors are under investigation.[20] Canagliflozin has been reported to cause osteoporosis, increased amputation risk, and diabetic ketoacidosis.

Insulin products activate insulin receptors and are formulated as rapid-acting, short-acting, intermediate-acting, and long-acting. All come in insulin analogue formulations except for short- and intermediate-acting insulins (regular and neutral protamine Hagedorn [NPH], respectively). Intermediate- and long-acting insulins are considered basal insulin (includes NPH, glargine, detemir, and degludec), which controls fasting blood glucose, while bolus insulin (includes rapid- and short-acting) controls postprandial blood glucose.[20,21] Insulin is most commonly associated with hypoglycemia and weight gain. Hypoglycemia can be severe and result in death; however, careful glucose monitoring and education can prevent this from occurring. ADA guidelines recommend beginning insulin in patients with T2D who are on metformin but not achieving glycemic goals.[20] Inhaled insulin is a rapid-acting insulin for prandial use only; it has a more limited dosing range than insulin analogues. Inhaled insulin should not be used in individuals with chronic lung disease (eg, asthma or chronic obstructive pulmonary disease) or those who currently smoke or recently stopped smoking. All patients taking inhaled insulin should undergo forced expiratory volume spirometry testing to identify potential lung disease before and after beginning therapy.[20]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) include exenatide, liraglutide, albiglutide, dulaglutide, and lixisenatide. GLP-1 RAs activate GLP-1 receptors and increase glucose-dependent

insulin secretion (resulting in reduced hypoglycemia risk), decrease glucagon secretion, and delay gastric emptying.[20,21] GLP-1 RAs curtail postprandial glucose spikes and are associated with weight loss. Because this class stimulates insulin release, it may reduce the amount of exogenous insulin required when given concurrently with insulin. These agents are contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2, which are rare cancers. For patients with long-term, poorly controlled T2D and CV disease, as demonstrated in the LEADER trial, liraglutide could be used, as it reduces CV and all-cause mortality in combination with standard of care.[29] The CV benefits of other agents in this drug class are being investigated.[20]

At diagnosis, the patient's A1C level dictates which and how many medications should be initiated.[20,21] If A1C is at 9.0% or above, 2 medications should be started.[20] Combination injectable therapy should be initiated for those with an A1C greater than 10% or a blood glucose level of 300 mg/dL or more, or if markedly symptomatic.[20] Per the AACE/ACE guidelines, combination therapy should begin when A1C is 7.5% or higher; 3 medications should be started for those patients with A1C of 9.0% or higher.[21] Cost-effectiveness analyses indicate that some newer agents are of relatively lower clinical utility based on high cost and moderate glucose lowering.[20] In addition, patients should eat a diet high in fiber, whole grains, low-fat proteins, and fresh vegetables and fruit; they should also begin and adhere to a healthy activity program of 150 or more minutes per week.

Newer Diabetes Therapies

Several newer diabetes therapies have recently become FDA approved; these include high-concentration insulins, a biosimilar insulin analogue, and GLP-1 receptor agonist pumps and implants.

High-Concentration Basal Insulin

U200 degludec and U300 glargine respectively, are 2 and 3 times as concentrated as their U100 formulations.[20] These products have different pharmacokinetic and pharmacodynamic effects, including a longer duration of action and peakless effect.[20,30] Noninferiority studies found that while A1C reduction with degludec U200 and glargine U300 is similar to that of insulin glargine U100, less nocturnal hypoglycemia occurs.[30] Concentrated basal insulins appear to reduce intrapatient variability and may minimize injection burden, which could improve adherence for patients requiring large daily insulin doses.[20,30] Understanding the pharmacokinetic and pharmacodynamic properties of these concentrated insulin formulations is important for safe dosing and use. To reduce hypoglycemia risk, these concentrated formulations come in easy-to-use insulin pens with built-in dosing conversions so the patient can use the same dose as the U100 product. Insulin degludec also comes in a 70/30 combination with rapid-acting aspart.[31] A concentrated formulation of the rapid-acting insulin lispro, U200, is also available for patients requiring larger preprandial doses. U500 regular insulin was previously only available as a vial, but now is available as a pen.[20] All the other concentrated insulins are only available as prefilled pens to minimize the potential for dosing errors.

Biosimilar Insulin Analogues

A biosimilar product is a copy of a biological molecule that is already FDA approved.[32] The copy is very similar, but is not identical, because the manufacturing process uses organisms (typically, genetically modified bacteria or yeast), incubation technologies, and other proprietary processes. Therefore, minor changes can occur even within lots of the original product, and between the original and biosimilar products. Insulin is manufactured by a few companies, each manufacturing their specific patented formulation. With advances in the production of recombinant proteins, it is much less expensive to manufacture insulin. For many insulins, patents have expired and new "follow on" legislation has encouraged many manufacturers all over the world to pursue creating biosimilar insulin products.[32]

The FDA has established an abbreviated approval pathway for biosimilars under the Federal Food, Drug, and Cosmetic Act.[33] A 505(b)(2) application is submitted that relies on the original product's data to support approval. The manufacturer of the new product must demonstrate that the copy is sufficiently similar to the original and provide copy-specific data to establish safety and efficacy for the approved uses. Currently, at least 6 companies are developing biosimilar insulin products.[32] Although not approved by the FDA as a biosimilar for regulatory reasons, insulin glargine injection (Basaglar) is the first "follow on" long-acting human insulin analogue.[33] Two clinical trials enrolling 534 and 744 patients with type 1 and type 2 diabetes, respectively, were conducted to provide the data to meet approval requirements.

As with generic products, biosimilar products are expected to be less expensive than the original products. However, price reductions may be limited because of high investment costs associated with development and approval.[32] Also, postmarketing programs and the high cost to manufacture and distribute insulin will likely limit price reductions for biosimilar insulin products. Despite this, it is believed that even a small decrease in price will have a beneficial effect.[32]

Novel Pumps

GLP-1 Receptor Agonist Pump

ITCA 650 is an osmotic mini-pump, subcutaneously implanted, that consistently and continuously delivers exenatide.[34] Patients using the ITCA 650 60 mcg had statistically significantly greater reductions in A1C (–1.5% vs –0.8%; P <.001) and weight (–4.0 kg [8.8 lb] vs –1.3 kg [2.8 lb]; P <.001) compared with sitagliptin 100 mg, respectively. Also, more patients treated with ITCA 650 60 mcg

achieved an A1C target of <7.0% than those receiving sitagliptin (61% vs 42%, respectively; P <.001).[34] In the FREEDOM-CVO trial, more than 4000 people with T2D received ITCA 650 or a placebo (plus other diabetes medications).[35] ITCA 650 was found to be noninferior to placebo and did not have any negative CV effects. This device will improve medication adherence and increase patient convenience by avoiding daily or weekly injections. The FDA approved a New Drug Application for ITCA 650 in February 2017, and the approval process outcome is expected by late 2017.[35]

Novel Diabetes Medication Combinations

Several novel diabetes combinations are under investigation. Insulin/GLP-1 RA and SGLT-2 inhibitor/DPP-4 inhibitor combinations are briefly described here and in more detail in "Overview of the Cardiovascular Benefit With Diabetic Agents and Novel Combination Products for Type 2 Diabetes. "

Insulin/GLP-1 RA Combinations

Two new insulin/GLP-1 RA combinations, insulin degludec/liraglutide and insulin glargine/lixisenatide, are now available. Results from the DUAL trials and LixiLan trials suggest greater A1C reductions, less weight gain or weight loss, and lower rates of hypoglycemia with these combination medications versus comparators.[36,37] Pen administration may also improve adherence and dosing accuracy.

SGLT-2 Inhibitor/DPP-4 Inhibitor Combinations

Empagliflozin/linagliptin combination tablet was approved in 2015. This fixed-dose combination contains 10 or 25 mg of empagliflozin and 5 mg of linagliptin.[38] Dapagliflozin 10 mg/saxagliptin 5 mg was FDA approved in early 2017 as a once-daily oral combination tablet. Combination products may improve medication adherence and patient convenience due to reduced medication regimen complexity and pill burden.[38]

Conclusion

Despite substantial advances in care, 33% to 49% of individuals with T2D miss glycemic, blood pressure, or cholesterol targets. Only 14% meet all 3 goals in addition to not smoking.[20] Data indicate that previously noted improvements in CV risk-factor control (especially tobacco use) may be declining.[39] Young adults and individuals with several comorbidities and other barriers, such as financial or social issues, and/or poor English proficiency, are less likely to achieve these goals. Data suggest that system-level changes are still necessary for all patients to receive adequate care.[20]

Importantly, certain newer agents can improve CV outcomes as well as glycemic control, and when available as a combination product, may also improve adherence. Some agents may worsen heart failure, a common comorbidity seen in patients with T2D.[20] While newly approved products tend to be more expensive than those already on the market (especially if available as a generic), cost benefits may be found with the prevention of CV disease and more than offset the additional product costs.

Diabetes imposes a substantial financial burden on society. Healthcare and managed care providers can work together to improve diabetes-related patient care and reduce healthcare costs. Newer therapeutic agents, and certain agents used in combination, may reduce direct costs by improving glycemic control and preventing negative outcomes associated with diabetes comorbidities. Patients will benefit from additional diabetes education, increased time to understand medication adherence and diabetes monitoring, and having affordable care. ■

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