

# Current State of Type 2 Diabetes Management

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## Abstract

Type 2 diabetes mellitus (T2DM) and its associated comorbidities are a major public health issue in the United States. Although a sizable pharmacotherapeutic armamentarium exists to combat this disease and several sources have published evidence-based management guidelines, the management of patients with T2DM remains complex and suboptimal. Currently available medications target various organs in an attempt to normalize hyperglycemia; however, newer agents targeting additional organ systems are in development. Among these, a class of medications that inhibit the sodium glucose cotransporter 2 (SGLT2) in the kidney show promise in their ability to decrease glucose reabsorption and increase glucose excretion. In particular, one of these compounds, canagliflozin, recently was approved by the US Food and Drug Administration. Despite such advances, the natural course of T2DM often eventually leads to the initiation of insulin therapy. A working knowledge of management guidelines, particularly concerning when and how to initiate monotherapies, combination therapies, and complex insulin regimens, is essential for optimal patient management. Insulin therapies should mimic normal physiologic levels of insulin through the use of both basal and bolus insulin analogues. Recognition of the various factors influencing therapeutic choices is also critical for improved patient management.

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For author information and disclosures, see end of text.

**T**ype 2 diabetes mellitus (T2DM), which accounts for approximately 90% to 95% of those with diabetes mellitus (DM), is primarily due to insulin resistance and relative insulin deficiency.<sup>1,2</sup> According to data collected by the Centers for Disease Control and Prevention (CDC) in 2010, a total of 25.8 million people, or 8.3% of the US population, are estimated to have DM.<sup>3</sup> This figure reflects both diagnosed (18.8 million) and undiagnosed (7.0 million) cases.<sup>3</sup> Furthermore, 79 million adults over age 20 years were found to have “prediabetes,” a condition marked by levels of blood glucose or glycated hemoglobin (A1C) that are above normal ranges, but not high enough to be classified as T2DM.<sup>3</sup> Additional CDC statistics indicate that DM is associated with significant morbidity and mortality. For example, the risk for death among people with T2DM is about twice that of people of similar age without T2DM, and T2DM is the seventh-leading cause of death in the United States.<sup>3</sup> Furthermore, T2DM is the leading cause of kidney failure, nontraumatic lower-limb amputations, and new cases of blindness among adults in the United States, and is a major cause of heart disease and stroke.<sup>3</sup>

## Evidence That T2DM Is Treated Suboptimally

The American Diabetes Association (ADA) has published recommendations for glycemic, blood pressure (BP), and lipid control for adults with T2DM in its annual Standards of Medical Care publication.<sup>4</sup> The ADA recommends that A1C should be less than 7%, although more or less stringent glycemic goals may be appropriate for individual patients. In addition, goals should be individualized based on the duration of DM, patient age and life expectancy, comorbid conditions, known cardiovascular disease (CVD) or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. BP should be less than 140/80 mm Hg; however, higher or lower systolic blood pressure targets may be appropriate based on patient characteristics and response to therapy. Regarding lipids, low-density lipoprotein cholesterol (LDL-C) should be less than 100 mg/dL (<2.6 mmol/L) and a lower goal of less than 70 mg/dL (<1.8 mmol/L) is recommended for individuals with overt CVD, with the use of a high dose of statin as an option.<sup>4</sup> Data collected from the National Health and Nutrition Examination Survey

■ **Table.** Medications Used in the Management of Type 2 Diabetes

Drug Class	Description/Effects
<b>Sulfonylureas (glipizide, glyburide, glimepiride)</b>	Oldest class High risk of hypoglycemia (especially glyburide) Weight gain common Less likely to maintain glycemic control as monotherapy
<b>Meglitinides (nateglinide, repaglinide)</b>	Moderate risk of hypoglycemia Some weight gain Short acting, take 3 times a day with meals
<b>Metformin</b>	Long experience GI intolerance Very rare lactic acidosis (susceptible patients); cannot use if ↓GFR Weight neutral Generally recommend as first-line oral agent, if tolerated
<b>Thiazolidinediones (rosiglitazone, pioglitazone)</b>	Can cause fluid retention, worsen CHF Weight gain common Fractures increased (distal arm and foot) Bladder cancer
<b>Disaccharidase inhibitors (acarbose, miglitol)</b>	Cause increase in intestinal gas—poorly tolerated
<b>Glucagon-like peptide 1 (GLP-1) receptor agonists (exenatide, liraglutide)</b>	Can be used with other agents, including insulin Weight loss can be substantial
<b>Dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, saxagliptin, linagliptin)</b>	Not associated with weight gain. Well tolerated, with few adverse effects Doses adjusted for renal insufficiency for sitagliptin and saxagliptin but not necessary for linagliptin Efficacious when used in combination with other oral antidiabetic agents

CHF indicates congestive heart failure; GFR, glomerular filtration rate; GI, gastrointestinal.

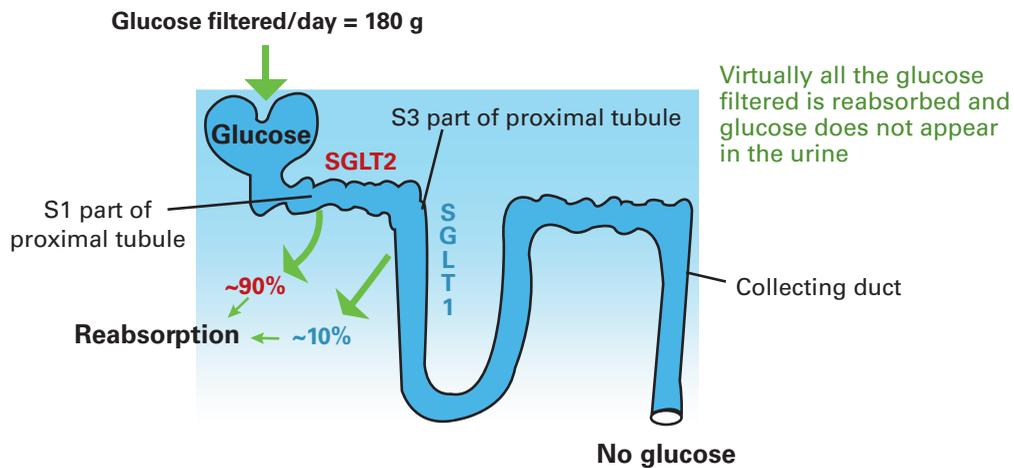
(NHANES) from 2003 to 2006 demonstrated a clear lack of adherence to these recommendations, with 57.1% of participants reaching the recommended A1C goal, 45.5% reaching the recommended blood pressure goal, 46.5% reaching the recommended LDL-C goal, and only 12.2% meeting all 3 goals.<sup>5</sup> Additionally, a CDC analysis of NHANES data from 2007 to 2010 showed that 16% of those with diagnosed DM were not receiving any pharmacotherapy for the disease.<sup>3</sup> An additional analysis of NHANES data from 2007 to 2010 reported the proportion of diabetic patients with A1C values over 9% as a function of source of care and insurance status.<sup>6</sup> Study results regarding source of care revealed that patients receiving care outside of a hospital, clinic, or physician's office had the highest adjusted prevalence, slightly above 20%, and insurance data indicated that the uninsured had the highest adjusted prevalence, slightly below 30%, compared with those on Medicare, or with public or private insurance.<sup>6</sup> It should be noted that most of the source of care and insurance status categories showed adjusted prevalences of approximately 10% or greater; however, among the privately insured, 7.2% had an A1C over 9%.<sup>6</sup> Based on these data, it seems clear that T2DM is treated suboptimally; however, the question remains as to why this is the case. Several barriers to effective DM control have been postulated, including clinical inertia,

financial issues, cultural issues, adverse effects associated with oral agents, the reality that targets of treatment require careful adjustment in each individual patient, and issues pertaining to the use of insulin such as fear of injections, fear of hypoglycemia, and the complexity of management.

### Diabetes Management

There are several classes of therapeutic agents available to treat T2DM (Table)<sup>7-10</sup> and each agent acts on different pathways to control hyperglycemia.<sup>11,12</sup> For example, sulfonylureas act in the pancreas, stimulating insulin release by binding to the sulfonylurea receptors on  $\beta$ -cell membranes.<sup>11</sup> Meglitinides, another class of short-acting insulin secretagogues, are used to control postprandial hyperglycemia and also act in the pancreas, stimulating insulin release by binding to several sites on  $\beta$  cells.<sup>11</sup> Thiazolidinediones (TZDs) are selective peroxisome proliferator-activated receptor gamma agonists that work in muscle and can also exert effects in the liver and adipose tissue and act by reducing insulin resistance and decreasing hepatic glucose output.<sup>11,12</sup> Alpha-glucosidase inhibitors lower postprandial blood glucose concentrations by inhibiting disaccharidase enzymes in the gut, thereby delaying carbohydrate absorption and retarding glucose entry into the systemic circulation.<sup>11</sup> Biguanides (metformin) act

■ **Figure 1.** Renal Handling of Glucose in Individuals Without Diabetes<sup>19,20</sup>



SGLT indicates sodium-glucose cotransporter. SGLT2 in the kidney plays a critical role in the reabsorption of glucose. Each day, 180 g of plasma glucose are filtered by the kidney and virtually all is reabsorbed into plasma in the proximal tubules. In healthy individuals, virtually all the glucose filtered is reabsorbed and glucose does not appear in the urine.

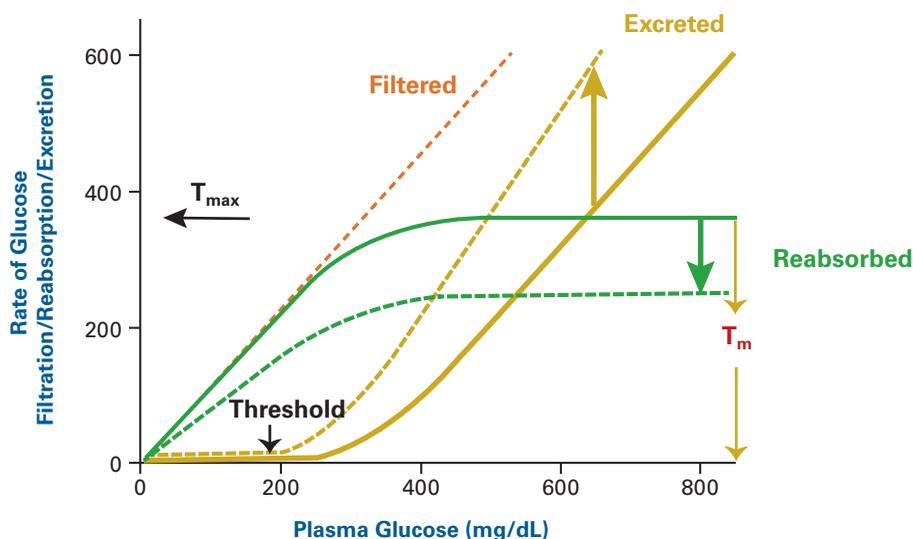
predominantly by reducing hepatic glucose production.<sup>7</sup> Metformin also enhances insulin sensitivity in muscle and decreases intestinal absorption of glucose.<sup>7,11,13,14</sup> Based on their different mechanisms of action, these drugs may be used in combination. The dipeptidyl peptidase-4 (DPP-4) inhibitors prevent the enzyme DPP-4 from degrading and inactivating glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide, incretin hormones that are produced in the gut and help regulate insulin production and secretion.<sup>15</sup> This glucose-dependent mechanism targets 2 key defects: insulin release and hepatic glucose production (via reduced glucagon production). Although some concern has been expressed regarding the use of DPP-4 inhibitors and the development of pancreatitis, a retrospective cohort study of a large medical and pharmacy claims database that analyzed data from 786,656 patients using Cox proportional hazard models demonstrated an increased incidence of acute pancreatitis in diabetic versus nondiabetic patients; however no association was found between the use of the DPP-4 inhibitors, exenatide or sitagliptin, and acute pancreatitis.<sup>16</sup> Exenatide and liraglutide are injectable GLP-1 receptor agonists that exert their antihyperglycemic effects through increasing insulin secretion, inhibiting glucagon secretion, and reducing appetite.<sup>17</sup>

**Emerging Novel Therapeutic Class of Antidiabetic Drugs: Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors**

In a review, published in 2012, of novel pharmacologic approaches to the treatment of T2DM, Verspohl reviewed

the reasons why new agents are being actively pursued and explained that nearly 1000 compounds have been described, approximately 180 of which are already in clinical studies in the United States.<sup>18</sup> Some of these compounds in development would exert an antidiabetic effect by inhibiting the sodium glucose cotransporter 2 (SGLT2) in the kidney, which plays a critical role in the reabsorption of glucose (Figure 1). Each day, 180 g of plasma glucose are filtered by the kidney and virtually all is reabsorbed into plasma in the proximal tubules.<sup>19,21</sup> In healthy individuals, virtually all the glucose filtered is reabsorbed and glucose does not appear in the urine. However, glucose starts appearing in urine once levels exceed the maximum capacity ( $T_m$ ) of the carrier protein, usually corresponding to a plasma glucose level of approximately 200 mg/dL.<sup>21</sup> Hyperglycemia results in hyperfiltration of glucose in the kidney in patients with DM, which in turn leads to increased luminal glucose that exceeds the maximum reabsorption rate, resulting in glucosuria (Figure 2).<sup>21,22</sup> SGLT2 inhibitors can act in the kidney to decrease reabsorption and increase excretion of glucose (Figure 2).<sup>21,22</sup> One of these SGLT2 inhibitors, canagliflozin, has recently been approved by the US Food and Drug Administration. In a 26-week, randomized, double-blind, placebo-controlled, phase 3 trial, 584 adult subjects with T2DM who were inadequately controlled with diet and exercise received canagliflozin 100 or 300 mg or placebo once daily.<sup>23</sup> At week 26, canagliflozin 100 and 300 mg (compared with placebo) significantly reduced A1C from baseline (-0.77, -1.03, and 0.14%, respectively;  $P < .001$  for both). Additionally, both canagliflozin doses significantly

■ **Figure 2.** Renal Glucose Handling<sup>21,22</sup>



$T_m$  indicates maximum capacity;  $T_{max}$ , time to maximum plasma concentration.

The threshold  $T_{m(\text{glucose})}$  represents the maximal resorptive capacity of the proximal tubule. Glucose starts appearing in urine once levels exceed the  $T_m$  of the carrier protein, usually corresponding to a plasma glucose level of approximately 200 mg/dL. Hyperglycemia results in hyperfiltration of glucose in the kidney in patients with diabetes mellitus which in turn leads to increased luminal glucose that exceeds the maximum reabsorption rate, resulting in glucosuria. Sodium-glucose cotransporter 2 inhibitors can act in the kidney to decrease reabsorption and increase excretion of glucose.

Adapted from Marsenic O. *Am J Kidney Dis.* 2009;53:875-883 and Silverman M, Turner RJ. In: Windhager EE, ed. *Handbook of Physiology: Renal Physiology.* New York: Oxford University Press; 1992:2017-2038.

decreased body weight ( $P < .001$  for both). Regarding safety results, the overall incidences of adverse events (AEs) were modestly higher with canagliflozin versus placebo. Low and similar rates of serious AEs and AE-related discontinuations were reported across groups. In addition, the incidences of genital mycotic infections, urinary tract infections, and osmotic diuresis-related AEs were higher with canagliflozin, although these led to few discontinuations. Lastly, the incidence of hypoglycemia was low across groups. The study authors concluded that treatment with canagliflozin improved glycemic control, reduced body weight, and was generally well tolerated in subjects with T2DM inadequately controlled with diet and exercise.<sup>23</sup> Canagliflozin, as a monotherapy, has A1C-lowering abilities of 0.77 to 1.03 percentage points depending on dose.<sup>23</sup>

### Natural History of T2DM

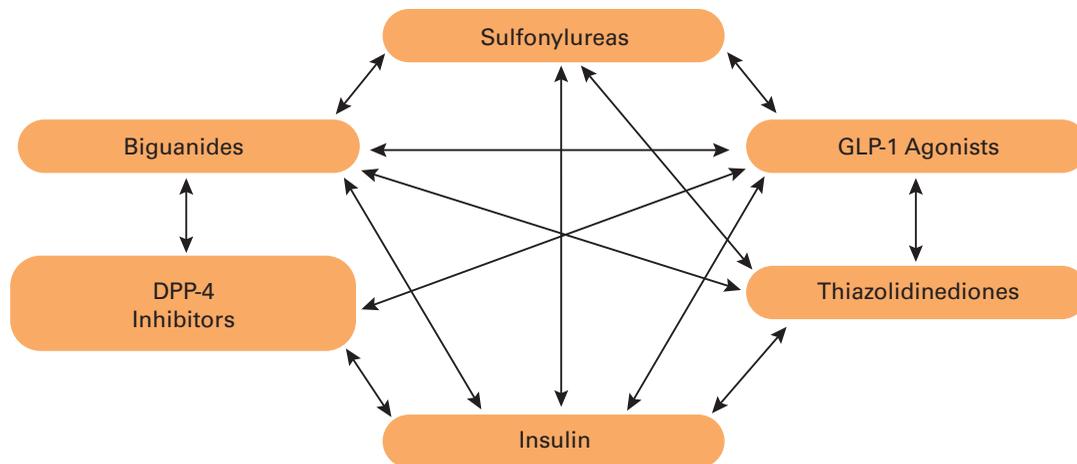
Before the manifestation of the metabolic defects that lead to T2DM, fasting and postprandial insulin levels are similar and constant. In the majority of patients in whom T2DM develops, increasing insulin resistance leads to compensatory increases in circulating insulin which prevent an increase in glucose levels. As time progresses, the insulin resistance reaches a peak and stabilizes, while the compensatory increase in insulin continues to prevent fasting glucose

levels from becoming abnormal. However, at some point, either because of early  $\beta$ -cell dysfunction or because of a natural limit of  $\beta$ -cell capacity, challenge of this delicate balance with a glucose load may demonstrate that, although fasting glucose levels remain normal, postprandial glucose levels become abnormal as a limitation in insulin response is reached. Following the onset of  $\beta$ -cell dysfunction, insulin levels can no longer keep up in overcoming the insulin resistance, and fasting and postprandial glucose levels increase progressively over time.<sup>24</sup> Based on this pattern, there may be a need to add additional drugs or change to insulin to achieve adequate glycemic control with longer duration of T2DM.

### Treatment Guidelines

Multiple T2DM evidence-based clinical practice guidelines or consensus statements describe appropriate goals and treatment options for the management of hyperglycemia. Such documents have been developed by the ADA,<sup>4</sup> ADA/European Association for the Study of Diabetes (EASD),<sup>25</sup> American Association of Clinical Endocrinologists,<sup>26</sup> and the American College of Physicians.<sup>27</sup> The ADA/EASD practice guideline<sup>25</sup> recommends an individualized, patient-centered approach to A1C goal setting and states that an A1C less than 7% is appropriate for the majority of T2DM patients. The more stringent A1C goal of less than 6.5%

■ **Figure 3.** Combination Therapy for Type 2 Diabetes Mellitus<sup>78</sup>



DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1. Pharmacotherapy for the treatment of type 2 diabetes mellitus would ideally combine 2 drugs with 2 different mechanisms of action, eg, a drug that stimulates insulin secretion and a drug that improves insulin sensitivity. Some of the most popular combinations are a sulfonylurea with metformin, metformin with a thiazolidinedione, and a sulfonylurea with a thiazolidinedione.

has been recommended for younger patients and those who have had T2DM for only a short time, have no significant CVD, and for whom significant hypoglycemia is not a risk. Additionally, a more aggressive, tailored, upfront approach to the treatment of T2DM to help patients reach stringent goals more quickly in order to prevent the development of micro- and macrovascular complications is recommended. At the time of diagnosis, metformin and lifestyle interventions are recommended unless specifically contraindicated. In highly symptomatic patients or those with markedly elevated blood glucose levels (300-350 mg/dL), consideration of insulin therapy is recommended at the outset, with or without additional agents. Furthermore, addition of a second oral agent, a glucagon-like peptide-1 receptor agonist, or insulin is recommended if A1C targets are not achieved within the first 3 to 6 months. The goal of combination therapy is to combine the effects of 2 or more drugs to reach the desired A1C level. Ideally, one would combine 2 drugs with 2 different mechanisms of action, for example, a drug that stimulates insulin secretion and a drug that improves insulin sensitivity (Figure 3). Some of the most popular combinations are a sulfonylurea with metformin, metformin with a thiazolidinedione, and a sulfonylurea with a thiazolidinedione. Three-drug combinations or more complex insulin regimens consisting of multiple daily doses are also recommended for patients who do not achieve target goals on 2-drug therapy.<sup>25</sup>

**Role of Insulin**

Insulin therapy in T2DM is indicated for patients with significant hyperglycemia at presentation; hyperglycemia

despite maximal doses of oral agents; decompensation due to acute injury, stress, or infection; severe hyperglycemia with ketonemia and/or ketonuria; or uncontrolled weight loss.<sup>25</sup> Additionally, insulin is indicated for those patients who are undergoing surgery, are pregnant, or have an allergy or serious reaction to oral agents.<sup>26</sup> When insulin therapy is initiated, it is important to be mindful of the basal/bolus concept. Basal insulin suppresses glucose production between meals and overnight, provides nearly constant levels, and should account for about 50% of daily needs. Bolus insulin should be used at mealtimes (prandially) to limit hyperglycemia after meals. An immediate rise and sharp peak occurs at 1 hour with the rapid-acting analogue insulins.<sup>28</sup> Therefore, bolus insulin should account for 10% to 20% of the total daily insulin requirement at each meal. Upon starting basal insulin therapy, patients should be continued on oral agent(s) at the same dosage with the intention of eventual dose reductions. A single evening insulin dose (around 10 U) should be added to the patient’s regimen, usually either glargine or detemir; neutral protamine Hagedorn insulin may also be used. Dosages can be adjusted by patients through the use of self-monitoring of blood glucose (SMBG) and increases should be made weekly as needed. For example, an increase of 4 U is appropriate if fasting blood glucose (FBG) levels are over 140 mg/dL, and an increase of 2 U is appropriate if FBG levels are between 120 and 140 mg/dL. Based on the author’s clinical experience, treatment should continue such that an FBG target of 100 to 120 mg/dL is reached. Advancing from basal to basal/bolus insulin is indicated for patients when FBG levels are acceptable but A1C remains over 7% and/or SMBG before dinner remains

over 180 mg/dL. Usually, mealtime regular or lispro/aspart/glulisine insulin injections are added to once-daily glargine/detemir. Regarding oral agent usage, sulfonylureas are usually stopped, but metformin can be continued for weight control and TZDs can be continued for glycemic stability (unless the patient has cardiovascular risk factors). Ideally, insulin treatment should mimic physiologic insulin levels; several insulin analogues with pharmacodynamic profiles that more closely mimic prandial and basal insulin profiles have been developed over the past 15 years.<sup>28,29</sup>

### Factors Influencing Therapeutic Choices

A variety of factors should be considered when making therapeutic choices for patients with T2DM. Medical needs and treatment goals such as A1C level and distance from target, postprandial glycemia, and costs (immediate vs long-term savings from decreased complications) should be taken into account. In addition, safety issues, particularly with regard to hypoglycemia, are important. Furthermore, the need for flexibility in the treatment program is essential. Several patient characteristics should be taken into account with respect to insulin use, including intellect and judgment, psychosocial and cultural considerations, and physical capabilities and limitations; other medical conditions and issues relating to the use of other noninsulin medications also require careful attention. Lastly, it is reasonable to set less intensive target goals for patients with advanced DM complications, life-limiting comorbid illness, or cognitive or functional impairment.

### Summary

T2DM is a progressive, life-threatening disease characterized by the dysregulation of glucose homeostasis, resulting in hyperglycemia. There is ample evidence that patients are being treated suboptimally despite an array of treatment options and guideline recommendations. Agents that act on organs not traditionally targeted, such as SGLT2 inhibitors, may represent a new approach to treatment. The role of insulin is also critically important and knowledge of when and how to use insulin can impact the quality of patient care.

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**Authorship information:** Concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

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## REFERENCES

1. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications: part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med.* 1998;15(7):539-553.
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2010;33(suppl 1):S62-S69.
3. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2011.
4. American Diabetes Association. Standards of medical care in diabetes—2013. *Diabetes Care.* 2013;36(suppl 1):S11-S66.
5. Cheung BM, Ong KL, Cherny SS, Sham PC, Tso AW, Lam KS. Diabetes prevalence and therapeutic target achievement in the United States, 1999 to 2006. *Am J Med.* 2009;122(5):443-453.
6. Ali MK, McKeever Bullard K, Imperatore G, Barker L, Gregg EW; Centers for Disease Control and Prevention (CDC). Characteristics associated with poor glycemic control among adults with self-reported diagnosed diabetes—National Health and Nutrition Examination Survey, United States, 2007-2010. *MMWR Morb Mortal Wkly Rep.* 2012;61(suppl):32-37.
7. Krentz AJ, Bailey CJ. Oral antidiabetic agents: current role in type 2 diabetes mellitus. *Drugs.* 2005;65(3):385-411.
8. Kimmel B, Inzucchi SE. Oral agents for type 2 diabetes: an update. *Clinical Diabetes.* 2005;23(2):64-76.
9. Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE; Sitagliptin Study 021 Group. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care.* 2006;29(12):2632-2637.
10. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G; Sitagliptin Study 020 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care.* 2006;29(12):2638-2643.
11. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med.* 1999;131(4):281-303.
12. Actos [package insert]. Lincolnshire, IL: Takeda Pharmaceuticals America, Inc; 2011.
13. Buse JB, Polonsky KS, Burant CF. Type 2 diabetes mellitus. In: Larsen PR et al, eds. *Williams Textbook of Endocrinology*. 10th ed. Philadelphia, PA: WB Saunders; 2003:1427-1483.
14. Glucophage [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2008.
15. Herman GA, Bergman A, Stevens C, et al. Effect of single oral doses of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on incretin and plasma glucose levels after an oral glucose tolerance test in patient with type 2 diabetes. *J Clin Endocrinol Metab.* 2006;91(11):4612-4619.
16. Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. *Diabetes Care.* 2010;33(11):2349-2354.
17. Eckerle Mize DL, Salehi M. The place of GLP-1-based therapy in diabetes management: differences between DPP-4 inhibitors and GLP-1 receptor agonists. *Curr Diab Rep.* 2013;13(3):307-318

## Reports

18. Verspohl EJ. Novel pharmacological approaches to the treatment of type 2 diabetes. *Pharmacol Rev.* 2012;64(2):188-237.
19. Wright EM, Turk E. The sodium/glucose cotransport family SLC5. *Pflugers Arch.* 2004;447:510-518.
20. Thorens B. Glucose transporters in the regulation of intestinal, renal, and liver glucose fluxes. *Am J Physiol.* 1996;270(4, pt 1):G541-G553.
21. Marsenic O. Glucose control by the kidney: an emerging target in diabetes. *Am J Kidney Dis.* 2009;53:875-883.
22. Silverman M, Turner RJ. Glucose transport in the renal proximal tubule. In: Windhager EE, ed. *Handbook of Physiology: Renal Physiology.* New York, NY: Oxford University Press; 1992:2017-2038.
23. Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab.* 2013;15(4):372-382.
24. Kendall DM, Cuddihy RM, Bergenstal RM. Clinical application of incretin-based therapy: therapeutic potential, patient selection and clinical use. *Am J Med.* 2009;122(6 suppl):S37-S50.
25. Inzucchi SE, Bergenstal RM, Buse JB, et al; American Diabetes Association; European Association for the Study of Diabetes. 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). *Diabetes Care.* 2012;35(6):1364-1379.
26. Handelsman Y, Mechanick JI, Blonde L, et al; AACE Task Force for Developing a Diabetes Comprehensive Care Plan. American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan: executive summary. *Endocr Pract.* 2011;17(2):287-302.
27. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2012;156(3):218-231.
28. Hirsch IB. Insulin analogues. *N Engl J Med.* 2005;352(2):174-183.
29. Rachmiel M, Perlman K, Daneman D. Insulin analogues in children and teens with type 1 diabetes: advantages and caveats. *Pediatr Clin North Am.* 2005;52(6):1651-1675.