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Diabetes Management Today

Issues in achieving glycemic goals

The role of HbA1c

Antihyperglycemic drugs and cardiovascular outcomes

Newer oral and noninsulin therapies

New insulin preparations

Inpatient hyperglycemia management

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Diabetes management today: Issues in achieving glycemic goals

In the years since the discovery of insulin in 1921, our understanding of diabetes and the development of treatments have greatly improved the lives of patients with diabetes. These advances have not yet led us to a cure. In fact, the percentage of the US population diagnosed with diabetes continues to rise.

In 2001, it was projected that nearly 20 million Americans would have diabetes by 2025.[1] But in 2015, 29 million Americans had been diagnosed with diabetes, exceeding the 2001 projection by 9 million. Newer projections are sobering—the prevalence of diabetes is estimated to increase from 9.3% of the population in 2012 to between 21% and 30% by 2050.[2]

As a result, most healthcare providers will face patients with diabetes or at risk for diabetes. Patients with diabetes today differ from those in the past in that increasing numbers of them are insulin resistant with impaired insulin secretion. Elements of metabolic syndrome including obesity, hypertension, high triglyceride levels, and low high-density lipoprotein levels increase the risk of diabetes and cardiovascular disease.

With the medications and treatments available today, how well are we practitioners doing in managing hyperglycemia? National Health and Nutrition Examination Survey data from 2005 to 2010 show that among patients taking diabetes medication, only 55% had controlled hemoglobin A1c (HbA1c) levels.[3] The role of HbA1c in the assessment and management of patients with diabetes is discussed in this supplement by Marie E. McDonnell, MD, and Courtney Nagel Sandler, MD. Though an essential tool in blood glucose control, appropriate HbA1c target levels and reliability vary among patients. Interpretation of HbA1c may be difficult in some patients, and HbA1c levels should be tailored by balancing risks and benefits.

Diabetes management is complicated by the existence of comorbid cardiovascular disease. While a number of studies link intense glycemic control to improved cardiovascular outcomes in patients with diabetes, other studies have demonstrated higher morbidity and mortality associated with antihyperglycemic drugs. Om P. Ganda, MD, reviews the sometimes perplexing and confusing research on the effect of glucose-lowering drugs on cardiovascular outcomes, including results from a recently completed trial evaluating empagliflozin.

Further reflecting the complexity of the biologic mechanisms associated with treating diabetes, today we have 12 classes of drugs approved by the US Food and Drug Administration (FDA) for diabetes compared with the two classes (insulin and sulfonylureas) available in the 1980s. In the last decade, the FDA approved 14 noninsulin drugs in 5 classes. In this supplement, Kathie L. Hermayer, MD, MS, and Andrew Dake, MD, discuss the various noninsulin therapies and their use in achieving the balance of blood glucose control and reduced adverse events and hypoglycemia in patients with type 2 diabetes.

For patients with profound insulin deficiency, insulin remains the most important therapeutic option. Insulin is available in four general classes: rapid-, short-, intermediate-, and long-acting (and in premixed variations). The latest in insulin formulations include ultra-long-act-

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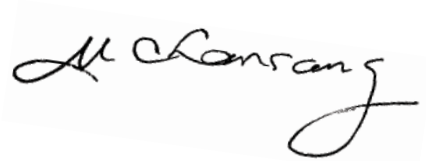
ing insulin, new concentrated insulin (glargine U-300 and lispro U-200), and inhaled insulin. A primer on these new insulin preparations and how they fit into clinical practice is provided by Luigi Meneghini, MD, MBA.

Finally, despite the availability of new medications for outpatient management of patients with diabetes, inpatient care represents the largest proportion of healthcare dollars spent on these patients. In inpatients, hyperglycemia is associated with a higher risk of complications, higher utilization of healthcare resources, and increased mortality rates. Guillermo E. Umpierrez, MD, CDE, and I outline best practices to achieve glycemic control and avoid hypoglycemia in critically and noncritically ill inpatients.

The growing number of patients with diabetes and the variety of therapeutic options available present physicians with many considerations in achieving glycemic goals. With great enthusiasm, I invite you to read this supplement on diabetes and hope you find it worthwhile and useful in elucidating issues in the management of diabetes today.

REFERENCES

1. **Boyle JP, Honeycutt AA, Narayan KM, et al.** Projection of diabetes burden through 2050: impact of changing demography and disease prevalence in the U.S. Diabetes Care 2001; 24:1936–1940.
2. **Boyle JP, Thompson TJ, Gregg EW, Baker LE, Williamson DF.** Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr 2010; 8:29.
3. **Selvin E, Parrinello CM, Sacks DB, Coresh J.** Trends in prevalence and control of diabetes in the United States, 1988-1994 and 1999-2010. Ann Intern Med 2014; 160:517–525.



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The role of hemoglobin A1c in the assessment of diabetes and cardiovascular risk

ABSTRACT

Hemoglobin A1c (HbA1c) is a widely used tool for diagnosing, screening, and managing patients with diabetes; however, proper application and interpretation of the HbA1c test is crucial to master for accurate assessment of patients. It also has become the standard test in population-based studies for evaluating the relationship between glycemic control and cardiovascular risk. Results from large clinical trials support the modern perspective that the HbA1c target should be personalized according to the risks and benefits of glycemic control. This likely is most important in patients with diabetes and elevated cardiovascular risk in whom achieving low HbA1c levels early in the natural history may be the most beneficial.

KEY POINTS

An HbA1c level ≥ 6.5% is the diagnostic cutoff used for diabetes diagnosis; patients with prediabetes have HbA1c values of 5.7% to 6.4%.

HbA1c is formed by the glycation of hemoglobin, thus HbA1c may be difficult to interpret in patients with medical disorders affecting red blood cell survival or glycosylation.

The use of HbA1c monitoring to manage patients with diabetes should include target levels that are tailored according to the risks and benefits of glycemic control, especially cardiovascular risks.

Although commonly used by population studies as a risk indicator for diabetes and cardiovascular complications, HbA1c may misrepresent the glycemic "big picture."

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Since its widespread introduction into routine clinical practice nearly 2 decades ago, hemoglobin A1c (HbA1c) measurement has become an integral tool for the diagnosis and management of diabetes mellitus. It is frequently used in both the care of individuals and in landmark population-based clinical trials. It also serves as a surrogate marker of glycemic control and is a key risk indicator for diabetes-associated microvascular and macrovascular complications and mortality.

With so much importance placed on one laboratory value, it is imperative to remember that the test is imperfect, with pitfalls both in accuracy and interpretation. The purpose of this review is to provide a broad understanding of HbA1c and how it can be optimally applied to patient management and the assessment of diabetes and cardiovascular (CV) risk.

HbA1c TESTING, BACKGROUND

HbA1c was first discovered in 1955, but elevated HbA1c levels in diabetes patients were not noted until 1968.[1] Another 8 years passed before HbA1c was correlated with blood glucose values in hospitalized patients with diabetes and was proposed for monitoring glycemia.[2]

Biochemically, HbA1c forms through a nonenzymatic reaction in which glucose attaches to the valine amino terminal of one or both beta chains of hemoglobin A. This compound can be separated out from nonglycated hemoglobin and from other glycated hemoglobin molecules through various methods, such as high performance liquid chromatography or immunoassay.[3]

During the first few years of clinical use, HbA1c measures were inconsistent. The publication of the Diabetes Control and Complications Trial (DCCT) in 1993[3] made the importance of precise HbA1c measurement apparent. This study found that the approximate 2% difference in HbA1c between standard- and intensive-insulin therapy groups resulted in dramatically reduced risk of microvascular disease

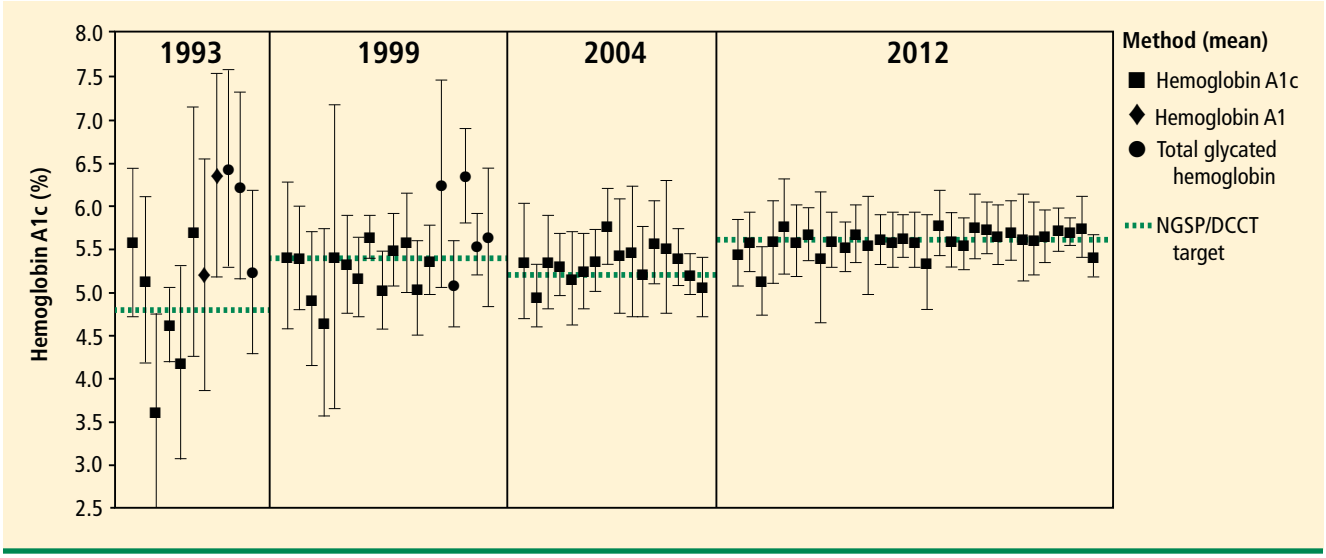

FIGURE 1. Enhanced reproducibility of hemoglobin A1c over time.[7] Shown as mean (± 2 standard deviations) of methods compared with NGSP/DCCT target in 1993, 1999, 2004, and 2012. DCCT = Diabetes Control and Complications Trial; NGSP = National Glycohemoglobin Standardization Program

in patients with type 1 diabetes. The continuation of the DCCT, the Epidemiology of Diabetes Interventions and Complications trial,[4] and a study of patients with type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS),[5] further supported the relationship between sustaining a lower average HbA1c over time and improved patient outcomes, including CV events and mortality. Given the implications of small changes in HbA1c on morbidity, the need to reduce error margins in measurement became apparent.

The NGSP (formerly the National Glycohemoglobin Standardization Program) was founded in 1996 to regulate HbA1c measurements to DCCT standards.[6] This program, now international in scope through involvement with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), calibrates HbA1c measurements by outside laboratories and manufacturers to reference standards. Laboratories and manufacturers that measure HbA1c certify through IFCC/NGSP and participate in yearly surveys to ensure inter-laboratory reproducibility. Through this successful program, standardization and accuracy of HbA1c measurements greatly improved from 1993 to 2012 (**Figure 1**).[1,6,7] Largely owing to this fact, HbA1c was approved as a diagnostic tool by the American Diabetes Association (ADA) in 2009;[8] the test has become a key measure for diagnosing, screening, and monitoring diabetes.

The HbA1c level is affected by the blood glucose concentration, the duration of red blood cell (RBC) exposure to varying concentrations, and RBC quantity. HbA1c most accurately reflects the previous 2 to 3 months of glycemic control in the setting of the usual RBC life span of 120 days.[9] As a relatively long-term indicator of glycemic control, it may not accurately represent acute improvements or deteriorations in glycemia. Recent factors affecting glycemia must be considered, as HbA1c represents a weighted average glucose with 50% contribution from the preceding month.[10]

HbA1c must be interpreted with caution. In nonpregnant adults, HbA1c is often falsely low in conditions that reduce the number of glycosylated RBCs, such as hemolysis, splenomegaly, chronic kidney disease, cirrhosis, hemorrhage, blood transfusions, use of erythropoiesis-stimulating agents, and certain hemoglobinopathies (ie, HbS, HbC, HbF). Alternately, HbA1c is elevated in other hemoglobinopathies and in conditions that result in decreased RBC turnover such as iron or vitamin B12-deficiency anemia.[11–13]

The 2008 A1c-Derived Average Glucose study group (507 participants from 10 international centers) used linear regression analysis to correlate HbA1c drawn every 3 months with average blood glucose readings taken during those 3 months. Results from participants without diabetes were compared with patients with type 1 or type 2 diabetes.[14] The resulting

TABLE 1
Hemoglobin A1c (HbA1c) and corresponding estimated average glucose

HbA1c (%)	Mean plasma glucose (mg/dL)	IFCC units (mmol/mol)
6	126	42
6.5	141	48
7	154	53
7.5	169	59
8	183	64
8.5	198	69
9	212	75
9.5	226	80
10	240	86
11	269	97
12	298	108

IFCC = International Federation of Clinical Chemistry and Laboratory Medicine.

significant correlation between HbA1c and average blood glucose readings (coefficient of determination 0.84, P <.0001) became the standard for estimating glycemia from HbA1c (**Table 1**).

DIAGNOSIS, SCREENING FOR DIABETES

HbA1c was accepted by the ADA as a diagnostic test for diabetes in 2009[4] and the World Health Organization (WHO) in 2011,[13] although the WHO recommended alternate methods for diagnosis given concerns about test availability, cost, and accuracy in the developing world.[15]

Advantages to HbA1c use in diagnosis include standardization of measurement, convenience as a single blood-draw that does not require fasting, minimal day-to-day variability, and preanalytic sample stability. Although point-of-care testing for HbA1c is widely available, it is not recommended for diagnostic use because these assays are generally not IFCC/NGSP certified and do not undergo the same proficiency testing as laboratory samples.[12,16]

The 1997 Expert Committee on the Diagnosis and Classification of Diabetes Mellitus[17] encouraged that diagnosis be based on the glycemic level at which microvascular complications develop. Using fasting plasma glucose (FPG), 2-hour postprandial plasma glucose, and funduscopic data from several large epidemiologic studies, the committee established that increased risk of diabetic retinopathy occurs at

TABLE 2
Criteria for the diagnosis of diabetes

Measurement	ADA 2015 diagnostic values
Hemoglobin A1c	≥ 6.5% (48 mmol/mol)
Fasting plasma glucose	≥ 126 mg/dL (7.0 mmol/L)
2-Hour postprandial plasma glucose	≥ 200 mg/dL (11.1 mmol/L)

ADA = American Diabetes Association.

Based on information in American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In: Standards of Medical Care in Diabetes—2015. Diabetes Care 2015; 38(suppl 1):S8–S16.

FPG levels greater than or equal to 126 mg/dL (7.0 mmol/L). Subsequent studies analyzed sensitivity and specificity correlations between FPG levels above 126 mg/dL and HbA1c in an effort to define cutoffs for HbA1c as a diagnostic tool; however, their results lacked clear clinical relevance.[18–20]

In 2003, the DETECT-2 trial analyzed HbA1c levels in more than 28,000 participants to determine HbA1c diagnostic definitions based on microvascular complications.[21] Evaluating HbA1c in 0.5% increments, investigators found that the incidence of diabetic retinopathy rose above baseline at HbA1c of 6.5%, the now accepted diagnostic value. It is important to note that this cutoff makes HbA1c less sensitive than other diagnostic indicators, which if applied to the same number of individuals, would result in up to one-third more patients diagnosed with diabetes. However, the lower sensitivity is balanced by higher screening rates given HbA1c accessibility.[16]

Diabetes can be diagnosed according to the criteria in **Table 2**, using venous plasma samples for HbA1c and glucose measurements. FPG assessment, both alone and as part of a 2-hour oral glucose tolerance test (OGTT), requires a minimum 8-hour fast. Although it is more cumbersome for both patients and practitioners, the 2-hour OGTT remains the technical standard diagnostic test for diabetes. It can formally identify patients with impaired fasting glucose and impaired glucose tolerance, which are markers of impaired beta cell function and future progression to frank diabetes mellitus.

In the presence of clear symptoms of hyperglycemia such as blurry vision, polyuria, polydipsia, weight loss, and a random plasma glucose value ≥ 200 mg/dL (11.1 mmol/L), a single laboratory measurement fit-

TABLE 3
Diabetes risk criteria for screening nonpregnant adults

Age ≥ 45

BMI ≥ 25 kg/m^2 or ≥ 23 kg/m^2 in Asian populations

First-degree relative with diabetes

High-risk race/ethnicity (African American, Latino, Native American, Asian, Pacific Islander)

Women with history of gestational diabetes mellitus or who delivered a baby weighing > 9 lb (4 kg)

Hypertension (≥ 140/90 mm Hg or on therapy for hypertension)

Dyslipidemia: HDL cholesterol < 35 mg/dL (0.90 mmol/L), triglyceride > 250 mg/dL (2.82 mmol/L), or both

Women with polycystic ovary syndrome

Prior history of HbA1c ≥ 5.7%, IGT, or IFG

Acanthosis nigricans, severe obesity, or other conditions associated with insulin resistance

History of cardiovascular disease

Physical inactivity

BMI = body mass index; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; IFG = impaired fasting glucose; IGT = impaired glucose tolerance.

Based on information in American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In: Standards of Medical Care in Diabetes—2015. Diabetes Care 2015; 38(suppl 1):S8–S16.

TABLE 4
Criteria for identifying prediabetes

Measurement	ADA 2015 criteria[16]	WHO 2006/2011 criteria[13,15]
Hemoglobin A1c	5.7%–6.4% (39–46 mmol/mol)	6.0%–6.5% (42–48 mmol/mol)
Fasting plasma glucose	100–125 mg/dL (5.6–6.9 mmol/L)	110–125 mg/dL (6.1–6.9 mmol/L)
2-Hour postprandial plasma glucose	140–199 mg/dL (7.8–11.0 mmol/L)	140–200 mg/dL (7.8–11.1 mmol/L)

ADA = American Diabetes Association; WHO = World Health Organization.

ting any of the three diagnostic criteria confirms the diagnosis of diabetes. In the absence of these symptoms, one positive test must be repeated and remain positive in order to confirm diabetes. As an alternative to repeating the original diagnostic test, two of the three criteria may be positive at any one time to make the diagnosis.[13,16]

Routine screening for diabetes using HbA1c should be based on risk in the absence of symptoms (**Table 3**). The ADA recommends screening at 3-year intervals if an initial screen is within normal limits or yearly in individuals with prediabetes or a change in risk status.[16] Screening also is recommended for patients on medications that increase the risk of hyperglycemia (eg, glucocorticoids, thiazides, and atypical antipsychotics).

Individuals with prediabetes are identified as having impaired fasting glucose and impaired glucose tolerance based on 2-hour OGTT, FPG, or HbA1c (**Table 4**). Those with HbA1c values 6.00% to 6.49% are considered by the ADA and WHO to have the highest risk of developing diabetes.[13,15,16] This range is based primarily on a 2010 systematic review[22] evaluating the relationship between HbA1c and progression to diabetes in studies involving more than 44,000 participants. Patients with HbA1c of 6.0% or above had a 5-year risk of progression to diabetes between 25% and 50%, 20 times higher than those with HbA1c less than 5%.[22] The ADA-defined lower limit for diagnosing prediabetes (HbA1c ≥ 5.7%) is based on a 2011 analysis of National Health and Nutrition Examination Survey data.[23] In that study, adults with HbA1c levels at or above 5.7% were at similar risk of developing frank type 2 diabetes and CV disease (41.3% over 7.5 years and 13.3% over 10 years, respectively) as the 3,234 participants in the Diabetes Prevention Program, a prospective, population-based study evaluating the risk of incident diabetes.[23,24]

MONITORING PATIENTS WITH DIABETES

HbA1c should be performed every 3 months in patients with known diabetes and can be spaced to twice yearly in patients meeting treatment goals on stable therapy.

While not recommended for diagnosis, point-of-care testing of HbA1c has been endorsed by the ADA for monitoring patients with diabetes. Studies have shown that a higher percentage of patients achieve HbA1c targets with treatment adjustment based on point-of-care testing of HbA1c at the time of visit vs usual laboratory monitoring.[16,25]

Goal HbA1c levels in patients with diabetes should be patient-tailored, as outlined in **Figure 2**. For example, stricter control with HbA1c (≤ 6.5%) may be desired in a young, otherwise healthy individual, whereas an HbA1c of 8% may be appropriate in a patient with multiple comorbidities.[26]

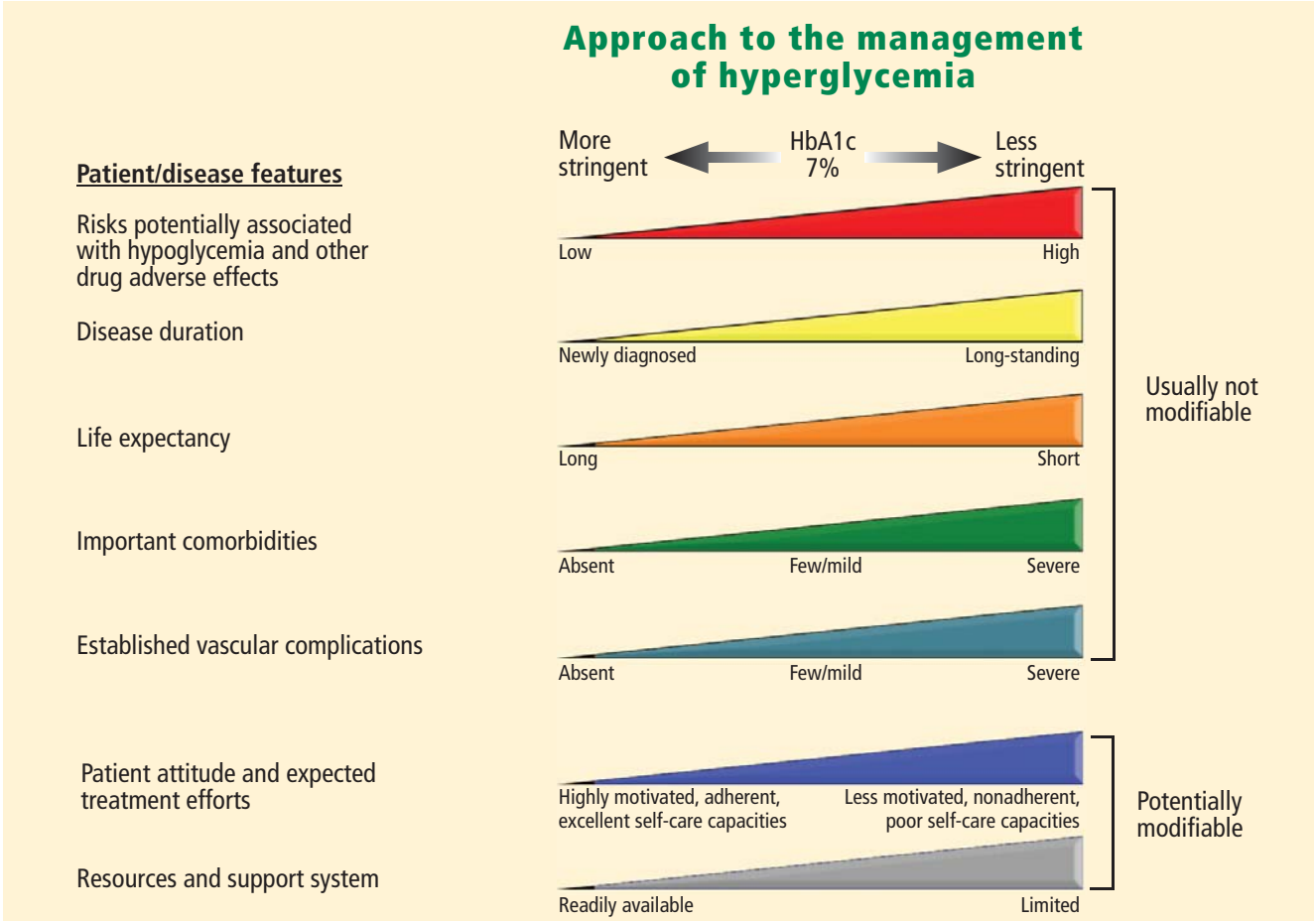

FIGURE 2. Schematic for setting hemoglobin A1c (HbA1c) goals according to a patient-tailored approach.

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HbA1c AND CARDIOVASCULAR RISK

HbA1c has been established as a strong predictor of CV events and mortality in patients with diabetes despite the absence of firm evidence that glycemic control modifies this risk substantially over time.[27] Results from the UKPDS and DCCT trials lend strong support to the hypothesis that glycemic control early in the course of disease provides preventive benefit.[3–5] In contrast, three major trials that enrolled older patients at higher baseline risk showed no mortality or CV benefit of tighter glycemic control.[28–30] One of these, the Action to Control Cardiovascular Risk in Diabetes trial,[28] found increased mortality risk in the intensive glycemic-control arm among those who did not achieve the HbA1c target, illustrating the complexity of interpreting HbA1c in clinical practice.

While HbA1c may predict the risk of mortality and CV events in diabetes populations, it is unlikely to be a strong predictor in patients without established diabetes. Analysis of data from the Emerging Risk Factors Collaboration indicates that below the HbA1c diagnostic threshold of diabetes (< 6.5%), HbA1c is less predictive than stronger risk factors such as lipids.[31] In this retrospective analysis, which included a cohort of more than 200,000 individuals without diabetes, the risk model to predict CV events was not enhanced significantly by the addition of HbA1c information.

MISREPRESENTING THE GLYCEMIC 'BIG PICTURE'

Aside from the previously discussed medical conditions that may affect HbA1c accuracy, other factors may complicate HbA1c interpretation. Recent studies raised concern about the generalizability of

HbA1c across racial and ethnic groups. A 2010 study of non-Hispanic black and white participants without diabetes revealed that black participants had higher HbA1c levels across the glycemic continuum.[32] In the past, concern was raised that these HbA1c elevations were related simply to poorer glycemic management and healthcare disparities. However, a study using data from the Diabetes Prevention Program compared HbA1c in five racial and ethnic groups and found that racial and ethnic minorities had higher HbA1c levels after adjusting for demographics, socioeconomics, and anthropometrics.[33] This suggests that racial-genetic differences in RBC survival or glycation of hemoglobin may affect HbA1c. These studies did not assess for the presence of hemoglobinopathies despite higher prevalence in certain ethnic groups.

One critique of the HbA1c assay is that HbA1c does not reflect glycemic variability. A 2007 study analyzing DCCT data found that participants with similar HbA1c levels had dissimilar mean plasma glucose (MPG) levels and glucose variability (standard deviation of MPG).[34] The authors provided an example of two patients with identical HbA1c and MPG but disparate glucose variability. The patient with higher glucose variability had a 35% to 45% excess risk of hypoglycemia. Failure of HbA1c to clearly define those at risk for frequent hypoglycemic events is problematic, since hypoglycemia is an identified risk factor for CV disease and morbidity.[35,36] Of perhaps greatest concern is that an elevated HbA1c may be a common presentation of variability in the elderly. One study showed that more than 60% of elderly patients taking insulin with an average HbA1c above 8% had several hypoglycemic events per week, and based on elevated HbA1c, they may be advised to increase insulin dosing.[37]

Glucose variability itself, including wide postprandial excursions, may be a risk factor for CV disease. The recent FLAT-SUGAR trial used HbA1c and continuous glucose monitoring to assess glycemic control and CV risk markers in participants on basal-bolus insulin therapy plus metformin versus subjects on basal insulin, metformin, and a GLP-1 agonist intended to reduce postprandial glucose excursions.[38] Although groups achieved similar target HbA1c levels, the intervention group had fewer glycemic excursions as well as reductions in some CV risk markers.

Alternatives to HbA1c are available for monitoring glycemic control. The monosaccharide 1,5-anhydroglucitol, a short-term marker of glycemia, competes with glucose for reabsorption in the kidney. In patients with normal renal function, low serum levels represent short-term hyperglycemia. Fructosamine and glycated albumin, formed by the glycation of proteins, reflect glycemia over the 2- to 4-week protein half-life.[39] Fructosamine measurement is confounded by the presence of low molecular weight substances such as bilirubin and uric acid; therefore, it may not be useful in medically complex patients. Glycated albumin is not affected by these substances; it may also be useful in patients in whom variations in RBC survival make HbA1c unreliable.[11,40] Despite the growing body of research about their usefulness, these tests lack the stringent standardization of HbA1c and have not been vetted for use in large clinical trials. Thus, their use in routine clinical practice remains controversial.

CONCLUSION

The focus on HbA1c during the last 40 years has resulted in enhanced test accuracy, availability, and use among patients and providers in the care of diabetes. Because HbA1c has become the standard in how population-based studies evaluate the effects of glycemic control on disease progression and complications, it serves as the basis for guidelines that address diabetes and CV risk definition and management. Although HbA1c may seem familiar, there is much not known about test interpretation and how it may actually miss the mark. As HbA1c use continues, these concerns need to be clarified to optimize the screening, diagnosis, and care of patients with diabetes and CV disease.

REFERENCES

1. **Little RR, Rohlfing CL.** The long and winding road to optimal HbA1c measurement. Clin Chim Acta 2013; 418:63–71.
2. **Koenig RJ, Peterson CM, Jones RL, Saudek C, Lehrman M, Cerami A.** Correlation of glucose regulation and hemoglobin A1c in diabetes mellitus. N Engl J Med 1976; 295:417–420.
3. **The Diabetes Control and Complications Trial Research Group.** The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329:977–986.
4. **Nathan DM, Cleary PA, Backlund JY; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group.** Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005; 353:2643–2653.
5. **UK Prospective Diabetes Study (UKPDS) Group.** Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352:837–853.
6. **National Glycohemoglobin Standardization Program.** About the NGSP: background. NGSP website. http://www.ngsp.org/bground.asp. Published 2010. Accessed March 15, 2016.
7. **Little RR, Rohlfing CL, Sacks DB; National Glycohemoglobin Standardization Program (NGSP) Steering Committee.** Status of hemoglobin A1c measurement and goals for improvement: from chaos to order for improving diabetes care. Clin Chem 2011; 57:205–214.

8. **Cox ME, Edelman D.** Tests for screening and diagnosis of type 2 diabetes. Clinical Diabetes 2009; 27:132–138.
9. **American Diabetes Association.** Tests of glycemia in diabetes. Diabetes Care 2004; 27(suppl 1):S91–S93.
10. **Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE.** Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. Diabetes Care 2002; 25:275–278.
11. **Koga M.** Glycated albumin: clinical usefulness. Clin Chim Acta 2014; 433:96–104.
12. **International Expert Committee.** International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes. Diabetes Care 2009; 32:1327–1334.
13. **World Health Organization.** Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Abbreviated report of a WHO consultation. World Health Organization website. http://www.who.int/diabetes/publications/report-hba1c_2011.pdf. Published 2011. Accessed March 15, 2016.
14. **Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ; A1c-Derived Average Glucose Study Group.** Translating the A1c assay into estimated average glucose values. Diabetes Care 2008; 31:1473–1478.
15. **World Health Organization.** Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. World Health Organization website. http://apps.who.int/iris/bitstream/10665/43588/1/9241594934_eng.pdf. Published 2006. Accessed March 15, 2016.
16. **American Diabetes Association.** Classification and diagnosis of diabetes. Sec 2. In: Standards of Medical Care in Diabetes—2015. Diabetes Care 2015; 38(suppl 1):S8–S16.
17. **The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.** Report of the Expert Committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 1997; 20:1183–1197.
18. **Buell C, Kermah D, Davidson MB.** Utility of A1c for diabetes screening in the 1999-2004 NHANES population. Diabetes Care 2007; 30:2233–2235.
19. **Bennett CM, Guo M, Dharmage SC.** HbA(1c) as a screening tool for detection of type 2 diabetes: a systematic review. Diabet Med 2007; 24:333–343.
20. **Rohlfing CL, Little RR, Wiedmeyer HM, et al.** Use of GHb (HbA1c) in screening for undiagnosed diabetes in the U.S. population. Diabetes Care 2000; 23:187–191.
21. **Colagiuri S, Lee CM, Wong TY; DETECT-2 Collaboration Writing Group.** Glycemic thresholds for diabetes-specific retinopathy: implications for diagnostic criteria for diabetes. Diabetes Care 2011; 34:145–150.
22. **Zhang X, Gregg EW, Williamson DF, et al.** A1c level and future risk of diabetes: a systematic review. Diabetes Care 2010; 33:1665–1673.
23. **Ackermann RT, Cheng YJ, Williamson DF, Gregg EW.** Identifying adults at high risk for diabetes and cardiovascular disease using hemoglobin A1c National Health and Nutrition Examination Survey 2005-2006. Am J Prev Med 2011; 40:11–17.
24. **Knowler WC, Barrett-Connor E, Fowler SE; Diabetes Prevention Program Research Group.** Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346:393–403.
25. **Kennedy L, Herman WH, Strange P, Harris A; GOAL A1C Team.** Impact of active versus usual algorithmic titration of basal insulin and point-of-care versus laboratory measurement of HbA1c on glycemic control in patients with type 2 diabetes: the Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1c) trial. Diabetes Care 2006; 29:1–8.
26. **Inzucchi SE, Bergenstal RM, Buse JB, et al.** Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38:140–149.
27. **Khaw KT.** Elevated HbA1c level: a risk factor for cardiovascular disease mortality in patients with chronic heart failure? Nat Clin Pract Endocrinol Metab 2009; 5:130–131.
28. **Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC, Miller ME, Byington RP, et al.** Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358:2545–2559.
29. **ADVANCE Collaborative Group; Patel A, MacMahon S, Chalmers J, et al.** Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358:2560–5572.
30. **Duckworth W, Abraira C, Moritz T, et al; VADT Investigators.** Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009; 360:129–139.
31. **Emerging Risk Factors Collaboration; Di Angelantonio E, Gao P, Kahn H, et al.** Glycated hemoglobin measurement and prediction of cardiovascular disease. JAMA 2014; 311:1225–1233.
32. **Ziemer DC, Kolm P, Weintraub WS, et al.** Glucose-independent, black-white differences in hemoglobin A1c levels: a cross-sectional analysis of 2 studies. Ann Intern Med 2010; 152:770–777.
33. **Herman WH, Ma Y, Uwaifo G, et al; Diabetes Prevention Program Research Group.** Differences in A1c by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. Diabetes Care 2007; 30:2543–2457.
34. **Kilpatrick ES, Rigby AS, Good K, Atkin SL.** Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes. Diabetologia 2007; 50:2553–2561.
35. **Khunti K, Davies M, Majeed A, Thorsted BL, Wolden ML, Paul SK.** Hypoglycemia and risk of cardiovascular disease and all-cause mortality in insulin-treated people with type 1 and type 2 diabetes: a cohort study. Diabetes Care 2015; 38:316–322.
36. **Krinsley JS, Schultz MJ, Sprong PE, et al.** Mild hypoglycemia is independently associated with increased mortality in the critically ill. Crit Care 2011; 15:R173.
37. **Munshi MN, Segal AR, Suhl E, et al.** Frequent hypoglycemia among elderly patients with poor glycemic control. Arch Intern Med 2011; 171:362–364.
38. **Hirsch IB, Probstfield JL, Davis BR, et al.** Glucose variability in type 2 diabetes: the initial results of the FLAT-SUGAR trial. Diabetes 2015; 64(suppl 1): A100. Abstract 385-OR.
39. **Kim KJ, Lee BW.** The roles of glycated albumin as intermediate glycation index and pathogenic protein. Diabetes Metab J 2012; 36:98–107.
40. **Klonoff DC.** Serum fructosamine as a screening test for type 2 diabetes. Diabetes Technol Ther 2000; 2:537–539.

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Antihyperglycemic drugs and cardiovascular outcomes in type 2 diabetes

ABSTRACT

In patients with diabetes, a complex and controversial relationship exists between intensive glycemic control and cardiovascular (CV) outcomes. Although the value of glucose-lowering agents in preventing microvascular complications associated with diabetes has been established, along with reductions in ischemic coronary events, active treatment in one major glycemic-control trial resulted in an unexplained increase in CV-associated mortality and total deaths compared with controls. Questions of CV safety with specific glucose-lowering agents along with the mechanisms underlying their effects on CV events have not been fully answered, underscoring the need for additional well-designed, long-term randomized controlled trials (RCTs) to prove their CV safety vs an active comparator. The CV benefits of one sodium-glucose cotransporter-2 inhibitor reported in an RCT await confirmation in ongoing trials.

KEY POINTS

Long-term randomized controlled trials have established the value of intensive glycemic control in reducing CV outcomes in patients with type 2 but only after many years of follow-up.

Despite reductions in ischemic coronary events, some clinical trials have reported unexplained increases in CV-associated mortality and total deaths in patients receiving intensive glycemic control.

Trials reporting the impact of specific glucose-lowering agents on CV events have reported perplexing, sometimes contradictory results, underscoring the need for additional trials.

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The essential value of glycemic control in preventing microvascular and neuropathic complications was established in the Diabetes Control and Complications Trial (DCCT)[1] and the United Kingdom Prospective Diabetes Study (UKPDS),[2] conducted in patients with type 1 and type 2 diabetes, respectively. However, it took another 10 or more years of observational follow-up of those cohorts to demonstrate statistically significant atherosclerotic cardiovascular (CV) disease benefits resulting from the intensive glycemic control achieved during those trials, as reported in the DCCT-Epidemiology of Diabetes Interventions and Complications (EDIC)[3] and the UKPDS follow-up studies.[4] Overall, it took more than 20 years of observational follow-up of the original intensive glucose-treatment cohort of DCCT/EDIC to show a significant decline in total deaths compared with the conventional treatment cohort.[5]

In patients with type 2 diabetes, the relationship between intensive glycemic control and CV benefits is somewhat controversial, particularly in view of negative CV outcomes from several long-term clinical trials in subjects older than the UKPDS subjects and with longer duration of diabetes:

- ACCORD trial (Action to Control Cardiovascular Risk in Diabetes)[6,7]
- ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation)[8,9]
- VADT: (Veteran Affairs Diabetes Trial).[10,11]

The controversy was spurred by an unexplained increase in total deaths in ACCORD,[6,7] despite a reduction in ischemic coronary events. In the VADT,[10,11] a significant decline was reported for major CV events, but not total deaths, after a median of 9.8 years of observational follow-up.[11] In the ADVANCE cohort,[8,9] a reduction in total deaths or CV events was not seen after 5.4 years of additional follow-up.[9] Some of these differences in outcomes between the UKPDS and these other long-term trials may well reflect the younger aged and the newly diagnosed

TABLE 1
Randomized controlled trials of antihyperglycemic agents in patients with type 2 diabetes or impaired glucose tolerance

Drug class	Agent (trial)
Sulfonylureas	Various (UKPDS)[2,4]
Biguanides	Metformin (UKPDS)[15]
Meglitinides	Nateglinide (NAVIGATOR)[21]
Alpha-glucosidase inhibitors	Acarbose (STOP-NIDDM)[22,23]
Thiazolidinediones	Pioglitazone (PROactive)[26] Rosiglitazone (RECORD)[13] Rosiglitazone (BARI 2D)[28]
Dopaminergic agents	Bromocriptine quick-release (Cycloset Safety Trial)[29]
DPP-4 inhibitors	Alogliptin (EXAMINE)[30,34] Saxagliptin (SAVOR-TIMI 53)[31,33] Sitagliptin (TECOS)[32]
GLP-1 receptor agonists	Lixisenatide (ELIXA)[40]
SGLT-2 inhibitors	(EMPA-REG OUTCOME trial)[43]
Insulin	(DIGAMI-1, DIGAMI-2)[44–46] (HI-5)[47] Prandial vs basal insulin (HEART2D)[48,49] Basal insulin (ORIGIN)[50]

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose cotransporter-2.

patients in the UKPDS population, and differences in specific glucose-lowering strategies. Nevertheless, this remains an unsettled issue.

CV OUTCOMES WITH SPECIFIC ANTIHYPERGLYCEMIC AGENTS

Another poorly understood question relates to the impact of specific glucose-lowering agents on CV events, regardless of the glucose control. **Table 1** lists the studies of the currently available agents. Studies such as the UKPDS have investigated the question of intensive hyperglycemia control compared with standard, less intensive control.

The question of CV safety with glucose-lowering agents was highlighted in a 2007 meta-analysis of 42 short-term studies with rosiglitazone that reported significantly worse myocardial infarction (MI) risks along with increased mortality from all CV causes that was borderline significant (P = .06).[12] This finding, however, was not confirmed in the only randomized controlled trial (RCT) completed with rosiglitazone.[13] The controversy led the US Food and Drug Administration (FDA) to issue a 2008 guidance statement recommending that all new diabetes drugs undergo a long-term, noninferiority RCT to prove their CV safety vs an active comparator.[14] Before the FDA mandate, few clinical trials had addressed the long-term effects of glucose-lowering drugs on CV outcomes in patients with type 2 diabetes.

In the UKPDS, the only primary prevention trial thus far, investigators used first-generation sulfonylureas (glyburide and chlorpropamide) with or without insulin as the intensive control strategy in 3,867 patients newly diagnosed with type 2 diabetes.[2] After a median follow-up of 10 years, the active treatment group had a borderline benefit in fatal and nonfatal MI (16% reduction in relative risk for MI; P = .052) compared with the nondrug treatment.

Additionally, a small subgroup of overweight patients in the UKPDS who were randomized to metformin (N = 342) had 36% (P = .010) lower risk of all-cause mortality and 39% (P = .011) lower risk of MI compared with conventional treatment.[15] This benefit occurred despite a more modest hemoglobin A1c (HbA1c) reduction (0.6%) in the metformin group than in the entire UKPDS trial (0.9%).

The mechanism underlying these impressive CV benefits remains unclear in view of the nonglucose effects of metformin, such as lack of weight gain. Metformin also has been reported to reduce generation of advanced glycosylation end products and oxidative damage to apolipoprotein B100 in patients with type 2 diabetes.[16]

One curious but unexplained finding in the UKPDS was an increase in both diabetes-related deaths (relative risk [RR], 1.96; P = .039) and total deaths (RR, 1.60; P = .04) in a subgroup of 268 patients in whom metformin was added to sulfonylurea therapy; however, the number of total deaths was relatively small, 47 deaths in the metformin added group and 31 deaths in the sulfonylurea group.[15] Because of the absence of proven CV benefits with any other diabetes drug thus far, metformin is generally the preferred initial drug in all treatment guidelines.

The relative effects of metformin and sulfonylureas when used as the initial monotherapy regimen have been studied in several large observational studies.[17–20] In general, there appears to be a consistent pattern of significantly increased CV events and total mortality—by 20% to 50%—in those treated with sulfonylureas, with or without prior CV disease. However, these analyses were not based on RCTs.

In two RCTs—NAVIGATOR Study Group[21] and STOP-NIDDM Trial[22]—patients with impaired

glucose tolerance were recruited with the primary aim of preventing progression to diabetes. In the NAVIGATOR trial, the short-acting insulin secretagogue nateglinide did not reduce CV events or the progression to diabetes.[21] In the other study, acarbose, an alpha-glucosidase inhibitor, significantly reduced CV events (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.28–0.85; $P = .03$)[22] and also prevented progression to diabetes. ($P < .002$).[23] Although the number of CV events in that 3-year study was small, a meta-analyses of seven studies using acarbose therapy in patients with diabetes also found a significant reduction in composite CV events (HR, 0.65; $P < .007$), including MIs.[24] A long-term, much larger RCT with acarbose is in progress.[25]

Following the demonstration of strikingly protective effects of metformin on CV events in the UKPDS,[16] two major trials of thiazolidinediones (TZDs) investigated the effects of insulin sensitization on CV events.[13,26] Pioglitazone in patients with long duration type 2 diabetes mellitus and pre-existing CV disease was reported to marginally reduce major CV outcomes (HR, 0.84; 95% CI, 0.72–98; $P < .03$),[26] whereas rosiglitazone in patients with a shorter duration of diabetes was found to be noninferior to the control group.[13] In both trials, however, there was a twofold increased risk for hospitalization for heart failure and increased risk for bone fractures in women,[13,26] but without an increased risk for mortality.[27] Furthermore, in the BARI 2D trial in patients with diabetes and established CV disease, adding rosiglitazone did not significantly reduce propensity-matched CV outcomes, compared with insulin secretagogues or insulin.[28] Thus, while TZDs appear to have no major adverse effects on CV outcomes, the other associated adverse effects limit their use.

In a 1-year study of the efficacy and CV safety of the dopaminergic agent quick-release bromocriptine, an FDA-approved drug for diabetes, there was a marked decrease in incidence of composite CV end points (HR, 0.60; 95% CI, 0.37–0.96).[29] However, there also was a 47% dropout rate and a small number of total events; thus, the implications remain inconclusive.

Incretin-mimetic agents and CV outcomes

Following the FDA guidance,[14] all newer agents, including incretin-mimetic agents (dipeptidyl peptidase-4 [DPP-4] inhibitors and glucagon-like peptide-1 [GLP-1] receptor agonists) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors have been undergoing well-designed, long-term, noninferiority trials with the comparison group receiving the standard of diabetes and CV care. The goal of these trials, unlike that of most of the studies discussed in this article, was to investigate the safety of individual agents rather than different levels of glycemic control.

Since 2013, such trials with three of the available DPP-4 inhibitors have been completed (**Table 2**).[30–34] Each trial was conducted in patients with pre-existing CV disease or high risk of it. The mean duration of follow-up in these trials was 1.5 to 3.0 years. There were significant, but only marginal, differences in HbA1c compared with the control groups receiving standard care. In each trial, the primary CV end points showed noninferiority, thus documenting their CV safety. One important difference in secondary end points was a significant increase in hospitalization rates for heart failure with saxagliptin[31,33] that was not observed in the trials with alogliptin[30,34] or sitagliptin.[32] Another secondary end point—hospitalization for heart failure plus CV mortality—also was not increased in the alogliptin[34] and sitagliptin[32] trials (rates not reported for saxagliptin); however, there was no increase in total deaths from any cause in these trials.

The mechanisms underlying the increased rates of heart failure with saxagliptin are unclear. The baseline characteristics of patients in these three trials were similar (**Table 2**). Patients with type 2 diabetes have higher rates of heart failure in general, but the effects of concomitant drug therapy on risk of heart failure, other than with TZDs, have not been well studied. In an extensive meta-analysis of 84 RTCs of various durations, the overall risk (OR) of heart failure was higher in patients treated with DPP-4 inhibitors than in those treated with placebo or active comparators (OR, 1.19; 95% CI, 1.03–1.37; $P = .015$), suggesting that DPP-4 inhibitors as a class could be associated with an increased risk of heart failure.[35] A case-control study, however, found no increase in rates of heart failure with DPP-4 inhibitors, although there were very few patients on saxagliptin.[36] Yet another large retrospective, propensity-adjusted observational analysis of more than 112,000 patients, which compared those on saxagliptin and sitagliptin, reported no difference in rates of heart failure; however, the median follow-up period was less than 6 months.[37]

In comparative observational analyses,[18,37,38] the risks of heart failure with TZDs and sulfonylureas were increased, compared with DPP-4 inhibitors, particularly with TZDs. On the other hand, a large population-based analysis from Italy found that DPP-4 inhibitors were associated with a propensity-matched 36% lower rate of hospitalization for heart failure compared with sulfonylureas.[39] These data point to a need for more

TABLE 2
DPP-4 inhibitors: Patient characteristics and outcomes in randomized controlled trials

Patient characteristics	Drug (trial) Alogliptin (EXAMINE)[30,34]	Saxagliptin (SAVOR- TIMI-53)[31,33]	Sitagliptin (TECOS)[32]
N	5,380	16,492	14,671
Age (mean or median)	61.0	65.1	65.4
Gender (male/female), %	68/32	67/33	71/29
BMI (mean or median)	28.7	31.1	30.2
DM duration (mean or median), yrs	7.2	10.3	11.6
Median study follow-up, yrs	1.5	2.1	3.0
HbA1c at baseline, mean % ± SD	8.0 ±1.1	8.0 ±1.4	7.2 ±0.5
Decrease in HbA1c during trial, mean	0.36%	0.20%	0.29%
Presentation at baseline	Acute coronary syndrome	CVD or multiple risk factors	CVD
Heart failure at baseline (%)	28	13	18
Outcomes			
Primary CV end point; HR (95% CI)	0.96 (≤ 1.16)	1.00 (0.89–1.12)	0.98 (0.89–1.08)
Death from any cause; HR (95% CI)	0.88 (0.71–1.09)	1.11 (0.96–1.27)	1.01 (0.90–1.14)
Death from CV causes; HR (95% CI)	0.85 (0.66–1.10)	1.03 (0.87–1.22)	1.03 (0.89–1.19)
Hospitalization for heart failure; HR (95% CI)	1.07 (0.79–1.46)	1.27 (1.07–1.51)	0.98 (0.81–1.19)
Death from CV causes + hospitalization for heart failure; HR (95% CI)	1.00 (0.82–1.21)	Not reported	1.01 (0.88–1.16

BMI = body mass index; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; DM = diabetes mellitus; HbA1c = hemoglobin A1c; HR = hazard ratio; SD = standard deviation.

well-designed comparative studies to investigate valid differences between drugs in this class.

In the only GLP-1 receptor agonist trial completed thus far, ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome), there were no differences in primary and major secondary CV outcomes in 6,068 very high-risk patients randomized to lixisenatide or placebo after a 25-month follow-up (HR, 1.02; 95%, CI, 0.89–1.17).[40] Moreover, the hospitalization rates for heart failure were not increased (HR, 0.96; 95% CI, 0.75–1.23). The earlier meta-analyses of short-term studies with DPP-4 inhibitors reporting significant reductions in CV events[41,42] also underscore the need for well-designed long-term RCTs to accurately interpret drug effects.

SGLT-2 inhibitors and CV outcomes

The first CV outcome RCT with the SGLT-2 inhibitor empagliflozin, the EMPA-REG OUTCOME trial,[43] was recently reported. Of great importance in this 7,020-patient trial comparing empagliflozin with placebo were the following results:

- 14% reduction in the primary end point (composite of death from CV causes, nonfatal MI, or nonfatal stroke) ($P = .04$)
- 32% reduction in all-cause deaths ($P < .001$)
- 35% reduction in hospitalization for heart failure ($P = .002$).

The mechanism underlying these impressive benefits is not known, although there were modest reductions in HbA1c levels, body weight (~2 kg), waist circumference (~2 cm), and systolic blood pressure (~4 mm Hg) with empagliflozin. The main adverse effects were related to a 3 to 4 times increased incidence of genital infections. Trials with other agents in this class are currently ongoing.

Insulin and CV outcomes

The UKPDS trial is the only primary prevention trial that provided evidence of significant benefits from intensive glucose control (with insulin, with or without sulfonylurea therapy) on CV outcomes and mortality, but only after 10 additional years of follow-up after the end of the trial.[4] A few other trials have investi-

gated the long-term effects of insulin compared with conventional therapy in patients with CV disease.

The DIGAMI-1 (Diabetes Insulin-Glucose in Acute Myocardial Infarction) was a RCT conducted between 1990 and 1993 in 620 patients with type 2 diabetes and acute MI randomized to short-term, intensive insulin-based glucose therapy or to conventional glucose-lowering therapy.[44] Results showed the intensive treatment group had an 11% decrease in mortality rate at 3.4 years. A 20-year follow-up reassessment showed the overall survival was improved by a mean of 2.3 years at 8 years, particularly in those at lower risk at baseline.[45] However, none of these patients were on statin therapy at baseline; thus, the implications of that study with current standards of care are quite uncertain. Subsequent studies—DIGAMI-2 (N = 1,253)[46] and the HI-5 (Hyperglycemia: Intensive Insulin Infusion in Infarction) study (N = 240),[47] both investigating the effects of intensive insulin therapy in patients with type 2 diabetes and MI—showed no significant effects on mortality in patients at 1 year (DIGAMI-2) and 6 months (HI-5).

The HEART2D trial (Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus), an RCT of 1,115 post-MI patients, investigated the effects of targeting prandial insulin compared with basal insulin. During a mean follow-up of 2.7 years, there were no between-group differences in CV outcomes (HR, 0.98; 95% CI, 0.8–1.21) or glycemic control.[48] Also, there was no impact of glycemic variability.[49] Finally, the ORIGIN trial (Outcome Reduction With an Initial Glargine Intervention), an RCT of more than 12,000 patients at high risk for CV disease but with relatively recent onset of either type 2 diabetes or prediabetes, randomized patients to basal insulin glargine or noninsulin treatments.[50] The baseline HbA1c was relatively low at 6.4%, but it significantly declined by 0.3% by the end of trial, compared with the control group. There was no effect on CV outcomes (HR, 1.02; 95% CI, 0.94–1.11) after a median follow-up of 6.2 years.

However, it remains a perplexing question regarding whether long-term treatment with increasing insulin dosages in a subset of obese patients with poorly controlled type 2 diabetes and increasing insulin resistance could be potentially harmful to the CV system.[51]

CONCLUSION

The long-term RCTs with antihyperglycemic agents, including DCCT/EDIC in type 1 diabetes and UKPDS, ACCORD, and VADT in type 2 diabetes, with the exception of ADVANCE, have established the value of intensive glycemic control in reducing CV outcomes but only after many years of follow-up. However, the effects of intensive glycemic control on CV disease in type 2 diabetes are inconsistent, with only the primary prevention cohorts of UKPDS showing significant effects on mortality after prolonged follow-up. This is in contrast to the positive effects of statins in relatively short-term trials.

While it is difficult to interpret the CV results of specific drugs from the degree of glycemic control, it is reassuring that the large RCTs with several individual agents, including TZDs (both pioglitazone and rosiglitazone), several DPP-4 inhibitors, and one GLP-1 receptor agonist, have demonstrated no appreciable harm. The increase in the secondary outcome of heart failure but with no increase in mortality observed with saxagliptin requires further mechanistic studies while awaiting the results of other ongoing trials with newer agents including other incretin-based drugs and SGLT-2 inhibitors.

With SGLT-2 inhibitors, the recently published results of the empagliflozin trail (EMPA-REG OUTCOME trial) with type 2 diabetes revealed a significant reduction in CV end points and mortality. Before those data were published, metformin was the only antihyperglycemic drug that had shown a significant effect on CV events and mortality, but it was studied in only a small subgroup of the UKPDS cohort, and there are no RCTs of the relative impact of metformin or other agents as compared to sulfonylureas. The results of ongoing CV trials with SGLT-2 inhibitors are eagerly awaited.

REFERENCES

1. **The Diabetes Control and Complications Trial Research Group.** The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329:977–986.
2. **UK Prospective Diabetes Study (UKPDS) Group.** Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352:837–853.
3. **Nathan DM, Cleary PA, Backlund JY, et al; for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group.** Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005; 353: 2643–2653.
4. **Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA.** 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359:1577–1589.
5. **Writing Group for the DCCT/EDIC Research Group; Orchard TJ, Nathan DM, Zinman B, et al.** Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. JAMA 2015; 313:45–53.
6. **Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC, Miller ME, Byington RP, et al.** Effects of

intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358:2545–2559.
7. **Gerstein HC, Miller ME, Ismail-Beigi F, et al.** Effects of intensive glycaemic control on ischaemic heart disease: analysis of data from the randomised, controlled ACCORD trial. Lancet 2014; 384: 1936–1941.
8. **The ADVANCE Collaborative Group; Patel A, MacMahon S, Chalmers J, et al.** Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358:2560–2572.
9. **Zoungas S, Chalmers J, Neal B, et al; ADAVNCE-ON Collaborative Group.** Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014; 371:1392–1406.
10. **Duckworth W, Abraira C, Moritz T, et al.** Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009; 360:129–139.
11. **Hayward RA, Reaven PD, Wiitala WL et al; VADT Investigators.** Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015; 372:2197–2206.
12. **Nissen SE, Wolski K.** Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007; 356:2457–2471.
13. **Home PD, Pocock SJ, Beck-Nielsen H, et al; RECORD Study Team.** Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 2009; 373:2125–2135.
14. **US Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER).** Guidance for Industry. Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. December 2008. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf. Accessed March 15, 2016.
15. **UK Prospective Diabetes Study (UKPDS) Group.** Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352:854–865.
16. **Rabbani N, Chittari MV, Bodmer CW, Zehnder D, Ceriello A, Thornalley PJ.** Increased glycation and oxidative damage to apolipoprotein B100 of LDL cholesterol in patients with type 2 diabetes and effect of metformin. Diabetes 2010; 59:1038–1045.
17. **Tzoulaki I, Molokhia M, Curcin V, et al.** Risk of cardiovascular disease and all-cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ 2009; 339:b4731.
18. **Roumie CL, Hung AM, Greevy RA, et al.** Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. Ann Intern Med 2012; 157:601–610.
19. **Morgan CL, Poole CD, Evans M, Barnett AH, Jenkins-Jones S, Currie CJ.** What next after metformin? A retrospective evaluation of the outcome of second-line, glucose-lowering therapies in people with type 2 diabetes. J Clin Endocrinol Metab 2012; 97:4605–4612.
20. **Li Y, Hu Y, Ley SH, Rajpathak S, Hu FB.** Sulfonylurea use and incident cardiovascular disease among patients with type 2 diabetes: prospective cohort study among women. Diabetes Care 2014; 37:3106–3113.
21. **The NAVIGATOR Study Group, Holman RR, Haffner SM, McMurray JJ, et al.** Effect of nateglinide on the incidence of diabetes and cardiovascular events. N Engl J Med 2010; 362:1463–1476.
22. **Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group.** Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA 2003; 290:486–494.
23. **Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trail Research Group.** Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet 2002; 359:2072–2077.
24. **Hanefeld M, Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Rupp M.** Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. Eur Heart J 2004; 25:10–16.
25. **Holman RR, Bethel MA, Chan JC, et al; ACE Study Group.** Rationale for the design of the Acarbose Cardiovascular Event (ACE) trial. Am Heart J 2014; 168:23–29. Epub ahead of print April 5, 2014. doi:10.1016/j.ahj.2014.03.021
26. **Dormandy JA, Charbonnel B, Eckland DJ, et al; PROactive Investigators.** Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (PROspective pioglitazone clinical trial in macrovascular events): a randomised controlled trial. Lancet 2005; 366:1279–1289.
27. **Lago RM, Singh PP, Nesto RW.** Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomized clinical trials. Lancet 2007; 370:1129–1136.
28. **Bach RG, Brooks MM, Lombardero M, et al; BARI 2D Investigators.** Rosiglitazone and outcomes for patients with diabetes mellitus and coronary artery disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. Circulation 2013; 128:785–794.
29. **Gaziano JM, Cincotta AH, O'Connor CM, et al.** Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. Diabetes Care 2010; 33:1503–1508.
30. **White WB, Cannon CP, Heller SR, et al; EXAMINE Investigators.** Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013; 369:1327–1335.
31. **Scirica BM, Bhatt DL, Braunwald E, et al; SAVOR-TIMI 53 Steering Committee and Investigators.** Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013; 369:1317–1326.
32. **Green JB, Bethel MA, Armstrong PW, et al; TECOS Study Group.** Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015; 373:232–242.
33. **Scirica BM, Braunwald E, Raz I, et al; SAVOR-TIMI 53 Steering Committee and Investigators.** Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation 2014; 130:1579–1588.
34. **Zannad F, Cannon CP, Cushman WC, EXAMINE Investigators.** Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet 2015; 385:2067–2076.
35. **Monami M, Dicembrini I, Mannucci E.** Dipeptidyl peptidase-4 inhibitors and heart failure: a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis 2014; 24:689–697.
36. **Yu OH, Filion KB, Azoulay L, Patenaude V, Majdan A, Suissa S.** Incretin-based drugs and the risk of congestive heart failure. Diabetes Care 2015; 38:277–284.
37. **Fu AZ, Johnston SS, Ghannam A, et al.** Association between hospitalization for heart failure and dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes: an observational study. Diabetes Care 2016 [epub ahead of print].
38. **Gilbert RE, Krum H.** Heart failure in diabetes: effects of antihyperglycaemic drug therapy. Lancet 2015; 385:2107–2117.
39. **Fadini GP, Avagaro A, Degli Esposti L, et al; OsMed Health-DB Network.** Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications: a retrospective registry study on 127,555 patients from the Nationwide OsMed Health-DB Database. Eur Heart J 2015; 36:2454–2462.
40. **Pfeffer MA, Claggett B, Diaz R, et al.** Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015; 373:2247–2257.
41. **Patil HR, Al Badarin FJ, Al Shami HA, et al.** Meta-analysis of effect of dipeptidyl peptidase-4 inhibitors on cardiovascular risk in type 2 diabetes mellitus. Am J Cardiol 2012; 110:826–833.
42. **Monami M, Ahren B, Dicembrini I, Mannucci E.** Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2013; 15:112–120.

43. **Zinamn B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators.** Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373:2117–2128.
44. **Malmberg K, Ryden L, Efendic S, et al.** Randomised trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol 1995; 26: 57–65.
45. **Ritsinger V, Malmberg K, Martensson A, Ryden L, Wedel H, Norhammar A.** Intensified insulin-based glycaemic control after myocardial infarction: mortality during 20 year follow-up of the randomised Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI 1) trial. Lancet Diabetes Endocrinol 2014; 2:627–633.
46. **Malmberg K, Ryden L, Wedel H, et al; DIGAMI 2 Investigators.** Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J 2005; 26:650–661.
47. **Cheung NW, Wong VW, McLean M.** The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. Diabetes Care 2006; 29:765–770.
48. **Raz I, Wilson PW, Strojek K, et al.** Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: the HEART2D trial. Diabetes Care 2009; 32:381–386.
49. **Siegelaar SE, Kerr L, Jacober SJ, Devries JH.** A decrease in glucose variability does not reduce cardiovascular event rates in type 2 diabetic patients after acute myocardial infarction: a reanalysis of the HEART2D study. Diabetes Care 2011; 34:855–857.
50. **ORIGIN Trial Investigators; Gerstein HC, Bosch J, Dagenais GR, et al.** Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012; 367:319–328.
51. **Nolan CJ, Ruderman NB, Kahn SE, et al.** Insulin resistance as a physiological defense against metabolic stress: implications for the management of subsets of type 2 diabetes. Diabetes 2015; 64:673–686.

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Newer oral and noninsulin therapies to treat type 2 diabetes mellitus

ABSTRACT

The pathophysiology of type 2 diabetes mellitus involves several biologic mechanisms and no single medication addresses them all. Most patients require more than one medication to adequately treat their diabetes, needing drugs with unique and complementary mechanisms of action to address and balance insulin and glucagon levels. In the past decade, several therapeutic drug classes have been developed for type 2 diabetes mellitus. Each provides therapeutic options with novel mechanisms of action to help clinicians achieve the goal of glucose homeostasis while controlling adverse events, especially reducing the risk of hypoglycemia.

KEY POINTS

The US Food and Drug Administration has approved 14 noninsulin pharmaceuticals in five drug classes in the past decade for type 2 diabetes therapy.

The noninsulin drug classes of dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, bile acid sequestrants, and dopamine-receptor agonists have different mechanisms of action and therapeutic effects.

Successful management strategies require a balancing of multiple agents to achieve target glucose while avoiding adverse effects.

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Type 2 diabetes mellitus (DM) is caused by hyperglycemia and metabolic alterations due to abnormalities in insulin secretion or insulin action, or both. To achieve desired glycemic targets, different antihyperglycemic drugs are used alone or in combination with other agents, including insulin. First-line options for diabetes treatment are weight loss, lifestyle modification, and metformin. The American Diabetes Association and the European Association for the Study of Diabetes recommend a patient-specific treatment approach to enhance glycemic control while avoiding weight gain and hypoglycemia.[1] This review will focus on the newer oral agents and injectable noninsulin agents that are used to achieve glycemic control. **Table 1** lists the noninsulin drugs approved since 2005.

INCRETIN-BASED THERAPIES

The incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are secreted by the gastrointestinal (GI) tract in response to food intake. Both GLP-1 and GIP stimulate beta cells of the pancreas, which contribute 60% of the insulin secretion after a meal. Type 2 DM is associated with decreased secretion of GLP-1 and lowered responsiveness to GIP. Benefits of the incretin hormones on glycemic control include enhanced satiety, decreased GI motility, increased glucose-dependent insulin secretion, reduced glucagon secretion, and decreased hepatic glucose release.[2] Two incretin-based drug classes are used to treat patients with type 2 DM—oral dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 receptor agonists.

DPP-4 inhibitors

The oral DPP-4 inhibitors block the degradation of the enzyme DPP-4 active site and thus increase the GLP-1 and GIP concentrations by two to three times. Their primary effectiveness centers on controlling insulin and glucagon secretion without increasing weight.

Four DPP-4 inhibitors are approved by the US Food and Drug Administration (FDA) in once-daily oral

formulations: sitagliptin, saxagliptin, linagliptin, and alogliptin. Another DPP-4 inhibitor, vildagliptin, is not licensed in the United States but is approved for use in Europe and Japan.[3] Another DPP-4 inhibitor, teneligliptin, is also marketed in Japan.

The DPP-4 inhibitors are indicated for use as monotherapy or in combination with other agents such as metformin, sulfonylureas, thiazolidinediones, and insulin. Generally, DPP-4 inhibitors do not cause hypoglycemia when used as monotherapy.[1] When adding a DPP-4 inhibitor to a sulfonylurea or insulin, it is recommended to decrease the sulfonylurea or insulin dose to reduce the risk of hypoglycemia. The potential of these agents to lower the hemoglobin A1c (HbA1c) when used as monotherapy and in combination with metformin, sulfonylureas, or thiazolidinediones is 0.3% to 0.71%.[4]

The DPP-4 inhibitors are not known to cause adverse GI effects. Sitagliptin, alogliptin, vildagliptin, and saxagliptin need dosing adjustments for renal insufficiency; however, linagliptin is not renally eliminated and does not require dosing adjustment. Common adverse events (> 5%) are nasopharyngitis, upper-respiratory infection, and headache. Sitagliptin and saxagliptin have been associated with urinary tract infection. Sitagliptin also has been associated with more extremity pain, back pain, and osteoarthritis.[4]

The DPP-4 inhibitors are primarily excreted by the renal or fecal route and, therefore, have few drug interactions. All DPP-4 inhibitors are partially metabolized through cytochrome P450 enzymes, except saxagliptin.[4] Their pharmacokinetic profiles are shown on **Table 2**.

In keeping with the FDA guidelines, sitagliptin, saxagliptin, linagliptin, and alogliptin have been evaluated for cardiovascular (CV) outcomes. The SAVOR-TIMI 53 clinical trial (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53) was a 2-year CV safety and efficacy trial.[5] This trial demonstrated no statistically significant difference in the primary end point as a composite of CV death, myocardial infarction (MI), and ischemic stroke. Additionally, the secondary end points, including hospitalization for unstable angina, coronary revascularization, and heart failure, also did not show significant difference. However, based on a subgroup analysis, there was a statistically significant increase in patients in the saxagliptin group vs the placebo group who were hospitalized for heart failure.

A 2-year trial comparing linagliptin with glimepiride, a second-generation sulfonylurea, showed significantly fewer CV events with linagliptin.[6] This trial found a relative risk reduction of 54% in the end points of CV death, nonfatal MI or stroke, and unstable angina during hospitalization.[4,6] Another trial reviewed the incidence of CV events (CV death, nonfatal MI, and nonfatal stroke) in patients treated with alogliptin, placebo, or comparator antihyperglycemic drugs and found no increased incidence of major adverse CV events vs comparator therapies.[7]

The recently published TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin), reported no increase in major atherosclerotic CV events, no difference in all-cause mortality, and no difference in

TABLE 1
Noninsulin drugs for type 2 diabetes approved by the US Food and Drug Administration since 2005

Drug	Year approved
DPP-4 inhibitors	
Sitagliptin (Januvia)	2006
Saxagliptin (Onglyza)	2009
Linagliptin (Tradjenta)	2011
Alogliptin (Nesina)	2013
GLP-1 receptor agonists	
Short-acting (4–6 hrs)	
Exenatide (Byetta)	2005
Lixisenatide (Lyxumia)	NDA submitted
Intermediate-acting (24 hrs)	
Liraglutide (Victoza)	2010
Long-acting (7 days)	
Exenatide extended-release (Bydureon)	2012
Albiglutide (Tanzeum)	2014
Dulaglutide (Trulicity)	2014
SGLT-2 inhibitors	
Canagliflozin (Invokana)	2013
Dapagliflozin (Farxiga)	2014
Empagliflozin (Jardiance)	2014
Bile acid sequestrant	
Colesevelam (Welchol)	2008
Dopamine-receptor agonist	
Bromocriptine quick-release (Cycloset)	2009

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NDA = new drug application; SGLT-2 = sodium-glucose cotransporter-2.

TABLE 2
Incretins: DPP-4 inhibitors marketed in the United States

Dosing	Sitagliptin (Januvia)	Saxagliptin (Onglyza)	Linagliptin (Tradjenta)	Alogliptin (Nesina)
With or without food	100 mg/day; oral	2.5–5 mg/day; oral	5 mg/day; oral	25 mg/day; oral
Renal dose adjustment	Reduce to 50 mg/day if CrCl 30–50 mL/min; reduce to 25 mg/day if < 30 mL/min or ESRD	Reduce to 2.5 mg/day if CrCl < 50 mL/min or ESRD	Fecal elimination route; no renal adjustment needed	Reduce to 12.5 mg/day if CrCl 30–59 mL/min; reduce to 6.25 mg/day if < 30 mL/min or ESRD
Hepatic dose adjustment	No clinical experience with severe hepatic insufficiency (Child-Pugh score ≥ 9)	None	None	No clinical trials in severe hepatic insufficiency (Child-Pugh grade C)
Elimination half-life	12.4 hours	2.5 hours	> 24 hours	12.5–21.1 hours
Comments	Low risk of hypoglycemia		Long half-life; good choice for patients with chronic kidney disease	Long half-life
	Similar glycemic efficacy as a class: Agents cause modest improvements in glycated hemoglobin levels			
	Overall, well tolerated; insufficient data regarding association with acute pancreatitis			

CrCl = creatinine clearance; DPP-4 = dipeptidyl peptidase-4; ESRD = end-stage renal disease.
Based on information in Tran L, Zielinski A, Roach AH, et al. Pharmacologic treatment of type 2 diabetes: oral medications. Ann Pharmacother 2015; 49:540–556.

heart failure for hospitalization or other adverse events in patients with type 2 DM.[8] Other clinical trials such as the CAROLINA study (linagliptin compared with glimepiride),[9] the EXAMINE study (alogliptin),[10] and the CARMALINA study (linagliptin)[11] are also reviewing the CV safety of DPP-4 inhibitors in the United States.

Concern has been raised about the association between incretin-based therapies and adverse pancreatic effects. CV outcomes trials using saxagliptin and alogliptin found similar rates of pancreatitis and fewer pancreatic cancer cases in comparison with placebo.[5,7,10] TECOS demonstrated that with sitagliptin, acute pancreatitis occurred more in the sitagliptin group, but there was no statistical significance reported. However, pancreatic cancer occurred more in the placebo group, although the difference was not statistically significant.[8] Neither the FDA nor the European Medicines Agency (EMA) has reached a firm conclusion about the possible association between incretin-based therapies and pancreatitis or pancreatic cancer.[12]

GLP-1 agonists

The GLP-1 drugs mimic the action of native GLP-1. Several GLP-1 agents are available in the United States, and several more are in development.[11,13] The drug class is divided into three groups:

- Short-acting (4–6 hours): exenatide, lixisenatide
- Intermediate-acting (24 hours): liraglutide
- Long-acting (7 days): exenatide extended-release (ER), dulaglutide, and albiglutide (semaglutide is in phase 3 study).

The GLP-1 receptor agonists heighten glucose homeostasis by the following mechanisms of action: stimulate insulin secretion, suppress glucagon secretion, directly and indirectly inhibit endogenous glucose production, promote satiety, heighten insulin sensitivity due to weight loss, and slow gastric emptying time. **Table 3** lists dosing and pharmacokinetic profiles for GLP-1 agonists. When GLP-1 agonists are used as monotherapy, the HbA1c is reduced by 0.7% to 1.51%.[13] When GLP-1 agonists are used in combination with metformin, sulfonylureas, thiazolidinediones, or as three-drug therapy with other oral antidiabetic medications, the HbA1c is lowered by 0.4% to 1.9%.[13–17]

A notable advantage of GLP-1 agonists is their effect on weight loss separate from GI side effects. Weight reductions of 0.2 to 3.6 kg in 26 weeks have been seen with the exenatide formulations, liraglutide, albiglutide, and dulaglutide.[13,18] Liraglutide has demonstrated a greater weight reduction than exenatide, exenatide ER, or albiglutide.[13,16,17] There were similar weight reductions of 1.5 kg in 26 weeks in a comparator trial involving liraglutide and dulaglutide (3.6 vs 2.9 kg).[19]

TABLE 3
Incretins: GLP-1 receptor agonists marketed in the United States

	Dosing (subcutaneous)	Renal dosing	Half-life; peak	Side effects
Short-acting (4–6 hours)				
Exenatide (Byetta)	5 µg twice daily; may increase to 10 µg twice daily after 4 weeks; take within 60 minutes of morning and evening meals; at least 6 hours apart	Not recommended if CrCl < 30 mL/min	2.4 hours Peak: 2.1 hours	Weight loss, GI upset
Intermediate-acting (24 hours)				
Liraglutide (Victoza)	Initial: 0.6 mg/day for 7 days Maintenance: 1.2 mg/day; may increase to 1.8 mg/day, if needed Body weight affects dosing: 1.2 mg and 1.8 mg doses provide adequate exposure for body weight ranges between 40–160 kg; has not been studied in body weight > 160 kg	No dose adjustment required but caution needed in patients with renal impairment	~13 hours Peak: 8–12 hours	Weight loss, nausea
Long-acting (7 days)				
Exenatide extended-release (Bydureon)	2 mg once/week	Not recommended if CrCl < 30 mL/min	Not available Peaks: week 2 and week 6–7 (~10 weeks after discontinuation, plasma concentrations fall below minimal detectable levels)	Weight loss, nausea
Albiglutide (Tanzeum)	Initial: 30 mg once/week; may increase to 50 mg once/week, if response inadequate	Not recommended if eGFR < 15 mL/min/1.73 m^2; use with caution in patients with renal impairment	~5 days Peak: 3–5 days	Weight loss, nausea
Dulaglutide (Trulicity)	0.75 mg once/week; may increase to 1.5 mg once/week, if needed Available as prefilled pen or syringe	No dose adjustment required	~5 days Peak: 24–72 hours	Weight loss, nausea

CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1.

Based on information in Tran L, Zielinski A, Roach AH, et al. Pharmacologic treatment of type 2 diabetes: injectable medications. Ann Pharmacother 2015; 49:700–714.

Common adverse effects of the GLP-1 agonists are nausea (8% to 44%), diarrhea (6% to 20%), and vomiting (4% to 18%), which may occur initially and diminish with continued use.[13,14] There have been more GI side effects with liraglutide than with exenatide ER or albiglutide.[20] Increased rates of injection site reactions, such as transient small nodule formations, were seen with exenatide ER (5.4% to 17.6%) and albiglutide, the once-weekly GLP-1 agonist therapies, vs exenatide, liraglutide, and insulin glargine.[13,14] Dulaglutide, another once-weekly GLP-1 agonist, does not have this finding; however, there is enhanced patient satisfaction with the once-weekly preparations in comparison with the twice-daily preparations.[14,16] Patients who received albiglutide have noted hypersensitivity reactions such as pruritus, rash, and dyspnea (10% to 18%).[13] Hypoglycemia is not seen with the GLP-1 agonists, unless they are used in conjunction with a sulfonylurea or insulin.

Exenatide and exenatide ER are excreted by the renal route; therefore, it is not recommended to use these agonists in patients with renal impairment or end-stage renal disease (creatinine clearance [CrCl] < 30 mL/min). Liraglutide is not excreted by the renal route; however, it should be used with caution in patients with renal impairment.[21] No renal dose adjustment is required when using albiglutide or dulaglutide.[21]

Clinical trials have demonstrated the short-term CV outcomes of GLP-1 agonists. The CV benefits include a decrease in blood pressure, reduction of lipid levels, enhanced endothelial function, and improved

TABLE 4
Oral pharmacologic agents for treatment of type 2 diabetes mellitus

Medication	Dosing	Renal dose adjustment	HbA1c reduction; monotherapy	HbA1c reduction; add-on	Hypoglycemia risk; monotherapy
SGLT-2 inhibitors					
Canagliflozin	100 mg once/day; can titrate to 300 mg/day	eGFR 45–60, ≤ 100 mg/day; eGFR < 45, avoid	0.91%–116%	0.37%–0.92%	Low
Dapagliflozin	5 mg once/day; can titrate to 10 mg/day	eGFR < 60, avoid	0.54%–0.66%	0.4%–0.69%	Low
Empagliflozin	10 mg once/day; can titrate to 25 mg/day	eGFR < 45, avoid	0.74%–0.85%	0.38%–0.64%	Low
Bile acid sequestrants					
Colesevelam	3.75 g once/day 1.875 g twice/day	No	0%–0.5%	0.3%–0.5%	Low
Dopamine-receptor agonists					
Bromocriptine quick-release	0.8 mg once/day; titrate by 0.8 mg weekly until 1.6–4.8 mg/day achieved	No	0.55% (single study)	0.4%–0.7%	Low

CV = cardiovascular; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate with units as mL/min/1.72m^2; HbA1c = hemoglobin A1c; LDL = low-density lipoprotein; SGLT-2 = sodium-glucose cotransporter-2.

Based on information in Tran L, Zielinski A, Roach AH, et al. Pharmacologic treatment of type 2 diabetes: oral medications. Ann Pharmacother 2015; 49:540–556.

myocardial function.[13] One meta-analysis reported a tendency for lowering the rate of major CV events, stroke, MI, CV mortality, and all-cause mortality.[22] Several ongoing trials are evaluating the safety of GLP-1 agonists and CV safety: LEADER (liraglutide), EXSCEL (exenatide LR), ELIXA (lixisenatide), SUSTAIN 6 (semaglutide), and REWIND (dulaglutide).[11]

The GLP-1 agonists have been linked to an increased incidence of thyroid cancer. There was a potential increased risk of thyroid cancer in preclinical rodent studies involving liraglutide and exenatide ER, but this risk was not demonstrated for the exenatide twice-daily preparation.[13] The FDA noted that the findings from rodent studies, which demonstrated a possible heightened risk for thyroid cancer, should not be conveyed to the outcomes for humans. Nevertheless, when liraglutide was approved in January 2010, the FDA issued a boxed warning about the risk of thyroid C-cell hyperplasia. The package inserts list a thyroid carcinoma risk for exenatide ER, liraglutide, albiglutide, and dulaglutide in those patients with a personal or family history of medullary thyroid cancer.

There is controversy about the incidence of pancreatitis and pancreatic cancer with the use of the incretin-based therapies. Published studies and case reports seem to support speculation that there is an increased incidence of acute pancreatitis associated with type 2 DM.[21] The FDA and the EMA have independently reviewed postmarketing reports about pancreatitis and pancreatic cancer among more than 28,000 patients who received some form of incretin-based therapy.[12] They independently agreed that a causal association between incretin-based drugs and pancreatitis or pancreatic cancer is inconsistent with the current data.[12] At this time, there is no final conclusion about a causal relationship between the use of incretin-based drugs and possible pancreatitis and pancreatic cancer.

SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS

In 2013, canagliflozin became the first sodium-glucose cotransporter-2 (SGLT-2) inhibitor to be FDA-approved for treating patients with type 2 DM, followed in 2014 by dapagliflozin and empagliflozin. Several other drugs in this class are available outside

Added benefits	Side effects/ disadvantages
Weight loss, decreased blood pressure, works at all stages of type 2 diabetes mellitus	Genitourinary infections, mild increase LDL, volume depletion/ dizziness, transient increase in creatinine, less effective with decreased eGFR, euglycemic DKA
Decreased LDL, weight neutral	Increased triglycerides, constipation, decreased absorption of other medications
Possible decreased CV events, weight neutral	Nausea, headache, diarrhea, fatigue

the US or are currently undergoing clinical development, including ipragliflozin, luseogliflozin, tofogliflozin, and ertugliflozin. Currently, no SGLT-2 inhibitors are FDA-approved for type 1 DM, although they have been used off-label and in trials in this patient population.

These drugs work by targeting the SGLT-2 protein in the kidney. In healthy individuals, 99% of filtered glucose is reabsorbed by the kidney with a filtered load of approximately 180 g/day.[23] Glucosuria occurs with glucose concentrations above this threshold. In patients with type 2 DM, this threshold and the ability to reabsorb glucose is increased, contributing to hyperglycemia.[24] Located in the proximal tubule, the SGLT-2 protein is responsible for 80% to 90% of glucose reabsorption, with SGLT-1 responsible for the other 10% to 20%.[25] Inhibition of SGLT-2 reduces the renal threshold for glucose, thus leading to glucosuria and reduction in serum glucose levels.[24] **Table 4** lists dosing regimens, HbA1c effects, and side-effect profiles for the SGLT-2 inhibitors.

As a monotherapy, SGLT-2 inhibitors significantly reduce HbA1c levels by 0.4% to 1.1% when compared with placebo.[26–28] Reductions may be more significant in patients with HbA1c levels greater than 8.5%, and even more so in patients with HbA1c levels above 10%.[29] When compared with other therapeutic options for type 2 DM, SGLT-2 inhibitors have efficacy similar to metformin, sitagliptin, and glipizide; however, some studies have shown superiority to glimepiride and sitagliptin at reducing HbA1c, depending on the dose and duration of treatment.[26,27]

The SGLT-2 inhibitors do not rely on insulin activity, allowing for their use at any stage of type 2 DM and in combination with other therapies, including insulin. As an add-on medication, SGLT-2 inhibitors reduce HbA1c by 0.5% to 0.7%.[27,28] Given that the mechanism of action depends on the filtered load of glucose, they are less effective in patients with a reduced glomerular filtration rate (GFR).

The SGLT-2 inhibitors have benefits beyond that of glycemic control. Studies report weight loss of 1 to 3 kg, which is maintained up to 104 weeks.[27–31] Sustained weight loss is secondary to glucosuria, which amounts to a caloric loss of 200 to 300 kcal/day.[30] Also, SGLT-2 inhibitors lead to modest reductions in systolic and diastolic blood pressure of approximately 3 to 6 mm Hg and 1 to 2 mm Hg, respectively, due to their diuretic effect.[27,31] The risk of hypoglycemia is low—similar to that of metformin and DPP-4 inhibitors—and only slightly higher than placebo when used as monotherapy.[26,31] When added to sulfonylureas or insulin, however, the risk of hypoglycemia is increased.[26,29]

Meta-analyses of SGLT-2 inhibitors showed rates of death and other serious adverse effects were no different than placebo.[26,27] A 2015 study on the CV safety of empagliflozin showed lower rates of CV death (38% relative risk [RR] reduction), lower rates of hospitalization due to heart failure (35% RR reduction), and lower rates of all-cause mortality (32% RR reduction) when compared with placebo, with no difference in nonfatal stroke and MI.[32] CV safety trials for dapagliflozin and canagliflozin are ongoing, although some trials have shown an increased incidence in CV events in the first 30 days of treatment with canagliflozin.[4]

Common side effects include genital infections, such as vaginitis and balanitis, as well as urinary tract infections. In a 2013 meta-analysis,[27] genital infections carried an odds ratio of 3.5 for SGLT-2 inhibitors compared with placebo, while urinary tract infections carried a 1.34 odds ratio. The increased risk of infection is thought to be secondary to glucosuria combined with immune dysfunction and altered

glycosylation uroepithelium cells.[30]

During clinical trials, more cases of bladder cancer were diagnosed in patients on dapagliflozin than on placebo, leading to a delay in FDA approval. No causal relationship was established, but dapagliflozin is not recommended in patients with active bladder cancer.[30]

Treatment with SGLT-2 inhibitors can lead to a decrease in GFR, likely secondary to the diuretic effect. In patients with GFR greater than 60 mL/min, this decrease is transient. In patients with GFR below 60 mL/min (moderate renal impairment) who were treated with dapagliflozin, GFR did not quite return to baseline, and they did not show an improvement in HbA1c relative to placebo.[33] Canagliflozin at a dose of 300 mg/day caused renal-related adverse events with GFR 45 to 60 mL/min, but a lower dose of 100 mg/day did not.[27] A decrease in GFR also occurred in patients with chronic kidney disease treated with empagliflozin, which returned to baseline after discontinuing the drug.[31] Despite these findings, renal function stabilizes in patients on SGLT-2 inhibitors over time, whereas it continues to decrease with placebo, suggesting there may be a renal protective effect.[30] Their diuretic effect can also lead to volume depletion in patients at risk such as elderly patients or those already taking diuretics.[31]

Some studies have shown mild increases in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels with no change in triglycerides, though long-term effects of this are unknown.[31]

There are case reports of euglycemic diabetic ketoacidosis occurring in patients with type 1 DM and type 2 DM treated with SGLT-2 inhibitors, which led the FDA in May 2015 to issue a warning that SGLT-2 inhibitors may increase the risk of ketoacidosis.[34] There are several possible mechanisms for this increased risk. The SGLT-2 inhibitors may decrease renal clearance of ketones, stimulate glucagon secretion leading to hepatic ketogenesis, or suppress glucose-mediated insulin secretion leading practitioners to decrease insulin doses thus resulting in increased ketone production via lipolysis.[34] More studies are needed, but patients and healthcare providers should be aware of potential euglycemic ketoacidosis associated with SGLT-2-inhibitors, as the lack of hyperglycemia can delay the diagnosis.

BILE ACID SEQUESTRANTS

Bile acid sequestrants have been used for years in hyperlipidemia to reduce LDL concentration; however, colesevelam is the only drug in this class approved (2009) for treating type 2 DM, after studies showed colesevelam improves glycemic control.[35–37] Though several possibilities have been proposed, the precise mechanism of action for lowering blood glucose levels is unknown.[35] Colesevelam is not absorbed systemically and does not affect endogenous insulin levels.[4] **Table 4** lists dosing regimens, HbA1c effects, and side-effect profiles for colesevelam.

As monotherapy, studies have shown varying effectiveness in reducing HbA1c relative to placebo ranging from no statistical difference to 0.54% reduction.[36,37] As an add-on to other diabetic medications, a Cochrane review of six randomized controlled trials showed a decrease in HbA1c by 0.3% to 0.5% and decrease in fasting glucose of 15 mg/dL.[37] Additional benefits of colesevelam include low risk for hypoglycemia, weight neutrality, and reduction in LDL.[4] No serious adverse events or deaths have been associated with colesevelam, including CV events; however, more trials on macrovascular outcomes are needed to clarify its side-effect profile.[35]

Common side effects include constipation, flatulence, and dyspepsia.[35] Colesevelam has shown a statistically significant increase in triglycerides, so its use in patients with triglycerides above 500 mg/dL or with hypertriglyceridemia-induced pancreatitis is contraindicated.[4] Caution should be used prior to starting treatment in patients with triglyceride levels above 200 mg/dL.[35] Colesevelam is contraindicated in patients with a history of small-bowel obstruction, and caution is recommended in patients with decreased gastric motility. This drug may reduce absorption of fat-soluble vitamins and some medications.[4]

Although further research into the long-term effects of colesevelam is needed, its relatively good safety profile makes it a reasonable choice in diabetic patients with hyperlipidemia not controlled with statins.

DOPAMINE-RECEPTOR AGONIST

Bromocriptine, a dopamine-receptor agonist, was FDA-approved for the treatment of Parkinson disease, hyperprolactinemia, and acromegaly in the 1970s. In 2009, a quick-release formulation of bromocriptine (bromocriptine QR) was approved for treatment of type 2 DM. **Table 4** lists dosing regimens, HbA1c effects, and side-effect profiles for bromocriptine.

The precise mechanism of action is unclear, but an American Association of Clinical Endocrinologists expert panel recommendation suggests that it may lower glucose levels by improving hypothalamic-mediated, postprandial insulin sensitivity via increasing morning dopaminergic activity (decreased

in patients with type 2 DM) and by reducing hypothalamic adrenergic tone.[38] It is not currently recommended as monotherapy, although a study of 154 patients showed monotherapy reduced HbA1c by 0.55%.[39] When added to other diabetic medications, it reduced HbA1c by 0.4% to 0.7%.[4,38]

Bromocriptine QR is weight neutral and carries a low risk of hypoglycemia.[4] A safety trial with 3,095 patients showed fewer adverse CV events in patients treated with bromocriptine QR compared with placebo, which may be secondary to reduced sympathetic tone or to reduced systemic inflammation.[40] Some studies have shown reductions in blood pressure, free fatty acid levels, and triglycerides, with no change in LDL or HDL.[38]

Common side effects include nausea, headache, dizziness, diarrhea, and fatigue. Administration is recommended with food to reduce GI side effects. It is contraindicated in women who are nursing and those with syncopal migraines. Furthermore, it may be prudent to avoid this medication in patients with a history of psychosis, those currently treated with dopamine agonists or antagonists, or those at risk for hypotension.[4]

CONCLUSION

The pathophysiology of type 2 DM involves at least seven organs and tissues—the brain, liver, pancreas, intestines, kidneys, fat, and muscle—and no single medication addresses all seven of them. Most patients require more than one medication to adequately treat their diabetes, making availability and development of drugs with unique and complementary mechanisms of action of paramount importance. The medications described here—DPP-4 inhibitors, GLP-1 agonists, SGLT-2 inhibitors, colesevelam, and bromocriptine QR—provide therapeutic options with novel mechanisms of action, all while avoiding weight gain and providing a low risk of hypoglycemia. While not appropriate for every patient, these medications give healthcare providers additional options to individualize treatment and optimize care for patients.

REFERENCES

1. **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; 35:1364–1379.
2. **Cornell S.** Continual evolution of type 2 diabetes: an update on pathophysiology and emerging treatment options. Ther Clin Risk Manag 2015; 11:621–632.
3. **Germino FW.** Noninsulin treatment of type 2 diabetes mellitus in geriatric patients: a review. Clin Ther 2011; 12:1868–1882.
4. **Tran L, Zielinski A, Roach AH, et al.** Pharmacologic treatment of type 2 diabetes: oral medications. Ann Pharmacother 2015; 49:540–556.
5. **Scirica BM, Bhatt DL, Braunwald E, et al; SAVOR-TIMI 53 Steering Committee and Investigators.** Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013; 369:1317–1326.
6. **Gallwitz B, Rosenstock J, Rauch T, et al.** 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomized, double-blind, non-inferiority trial. Lancet 2012; 380:475–483.
7. **White WB, Pratley R, Fleck P, et al.** Cardiovascular safety of the dipeptidyl peptidase-4 inhibitor alogliptin in type 2 diabetes mellitus. Diabetes Obes Metab 2013; 15:668–673.
8. **Green JB, Bethel A, Armstrong PW, et al; TECOS Study Group.** Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015; 373:232–242.
9. **Rosenstock J, Marx N, Kahn SE, et al.** Cardiovascular outcome trials in type 2 diabetes and the sulphonylurea controversy: rationale for the active-comparator CAROLINA trial. Diab Vasc Dis Res 2013; 10:289–301.
10. **White WB, Bakris GL, Bergenstal RM, et al.** EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE): a cardiovascular safety study of the dipeptidyl peptidase 4 inhibitor alogliptin in patients with type 2 diabetes with acute coronary syndrome. Am Heart J 2011; 162:620–626.
11. **Ferrannini E, DeFronzo RA.** Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes. Eur Heart J 2015; 36:2288–2296.
12. **Egan AG, Blind E, Dunder K, et al.** Pancreatic safety of incretin-based drugs – FDA and EMA assessment. N Eng J Med 2014; 370:794–797.
13. **Tran L, Zielinski A, Roach AH, et al.** Pharmacologic treatment of type 2 diabetes: injectable medications. Ann Pharmacother 2015; 49:700–714.
14. **Tella SH, Rendell MS.** Glucagon-like polypeptide agonists in type 2 diabetes mellitus: efficacy and tolerability, a balance. Ther Adv Endocrinol Metab 2015; 6:109–134.
15. **Drucker DJ, Buse JB, Taylor K, et al.** Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomized, open-label, non-inferiority study. Lancet 2008; 372:1240–1250.
16. **Trujillo JM, Nuffer W, Ellis SL.** GLP-1 receptor agonists: a review of head-to-head clinical studies. Ther Adv Endocrinol Metab 2015; 6:19–28.
17. **Harris KB, McCarty DJ.** Efficacy and tolerability of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes mellitus. Ther Adv Endocrinol Metab 2015; 6:3–18.
18. **Vilsboll T, Christensen M, Junker AE, Knop FK, Gludd LL.** Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analysis of randomized controlled trials. BMJ 2012; 344:d7771.
19. **Dungan KM, Povedano ST, Forst T, et al.** Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomized, open-label, phase 3, non-inferiority trial. Lancet 2014; 384:1349–1357.
20. **Pratley RE, Nauck MA, Barnett AH, et al; HARMONY 7 Study Group.** Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomized, open-label, multicenter, non-inferiority phase 3 study. Lancet Diabetes Endocrinol 2014; 2:289–297.
21. **Neumiller JJ.** Incretin-based therapies. Med Clin N Am 2015; 99:107–129.
22. **Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E.** Effects of glucagon-like peptide-1 receptor agonists on cardiovascular risk: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2014; 16:38–47.
23. **Bakris GL, Fonseca VA, Sharma K, Wright EM.** Renal sodium-glucose transport: role in diabetes mellitus and potential clinical

implications. Kidney Int 2009; 75:1272–1277.
24. **Defronzo RA, Hompesch M, Kasichayanula S, et al.** Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. Diabetes Care 2013; 36:3169–3176.
25. **Ghezzi C, Wright EM.** Regulation of the human Na+-dependent glucose cotransporter hSGLT2. Am J Physiol Cell Physiol 2012; 303:C348–C354.
26. **Monami M, Nardini C, Mannucci E.** Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2014; 16:457–466.
27. **Vasilakou D, Karagiannis T, Athanasiadou E, et al.** Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013; 159:262–274.
28. **Yang XP, Lai D, Zhong XY, Shen HP, Huang YL.** Efficacy and safety of canagliflozin in subjects with type 2 diabetes: systematic review and meta-analysis. Eur J Clin Pharmacol 2014; 70:1149–1158.
29. **Dailey G.** Empagliflozin for the treatment of type 2 diabetes mellitus: an overview of safety and efficacy based on phase 3 trials. J Diabetes 2015; 7:448–461.
30. **Peene B, Benhalima K.** Sodium glucose transporter protein 2 inhibitors: focusing on the kidney to treat type 2 diabetes. Ther Adv Endocrinol Metab 2014; 5:124–136.
31. **Vivian EM.** Sodium-glucose co-transporter 2 (SGLT2) inhibitors: a growing class of antidiabetic agents. Drugs Context 2014; 3:212264.
32. **Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators.** Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373:2117–2128.
33. **Hinnen D.** Glucuretic effects and renal safety of dapagliflozin in patients with type 2 diabetes. Ther Adv Endocrinol Metab 2015; 6:92–102.
34. **Taylor SI, Blau JE, Rother KI.** SGLT2 inhibitors may predispose to ketoacidosis. J Clin Endocrinol Metab 2015; 100:2849–2852.
35. **Aggarwal W, Loomba RS, Arora RR.** Efficacy of colesevelam on lowering glycemia and lipids. J Cardiovasc Pharmacol 2012; 59:198–205.
36. **Fonseca VA, Rosenstock J, Wang AC, Truitt KE, Jones MR.** Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. Diabetes Care 2008; 31:1479–1484.
37. **Ooi CP, Loke SC.** Colesevelam for type 2 diabetes mellitus. Cochrane Database Syst Rev 2012; 12:CD009361.
38. **Garber AJ, Blonde L, Bloomgarden ZT, Handelsman Y, Dagogo-Jack S.** The role of bromocriptine-QR in the management of type 2 diabetes expert panel recommendations. Endocr Pract 2013; 19:100–106.
39. **Cincotta AH, Meier AH, Cincotta Jr M.** Bromocriptine improves glycaemic control and serum lipid profile in obese type 2 diabetic subjects: a new approach in the treatment of diabetes. Expert Opin Investig Drugs 1999; 8:1683–1707.
40. **Gaziano JM, Concotta AH, O'Connor CM, et al.** Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. Diabetes Care 2010; 33:1503–1508.

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New insulin preparations: A primer for the clinician

ABSTRACT

The importance of glycemic control in preventing the chronic and devastating complications of diabetes is well established. Insulin administration is an important therapeutic option for managing diabetes, particularly for patients with profound insulin deficiency. Many insulin formulations are on the market, including short-acting insulin analogues, inhaled insulin, concentrated insulin, and basal insulin. Each category has a unique onset, peak, and duration of action. This article reviews the differing pharmacokinetic and pharmacodynamic properties and safety and efficacy data, and discusses the implications for clinical practice.

KEY POINTS

Insulin extracted from an animal pancreas was first administered in 1921; the first insulin analogue was marketed in 1996.

Insulin is considered the therapeutic standard in patients with advanced insulin deficiency.

Types of available insulin products have differing onset, peak, and duration of action ranging from ultra-short-acting to ultra-long-acting.

The US Food and Drug Administration approved an inhaled insulin product in 2014; all other products are administered subcutaneously.

Concentrated insulin preparations provide an alternative for patients requiring consistently high daily doses of insulin.

Dr. Meneghini has reported receipt of consulting/advisory fees from Novo Nordisk and Sanofi-Aventis.

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The first isolation and successful extraction of insulin in 1921 opened an important chapter in the management of diabetes, especially for patients with profound insulin deficiency. At that time, a 14-year-old patient who was dying from type 1 diabetes received the first insulin injection—a canine pancreatic extract. It was a lifesaving treatment. Within a few months of insulin administration, the patient regained weight and health and went on to live another 13 years before succumbing to pneumonia and chronic complications of hyperglycemia.

While the introduction of regular insulin from animal extracts provided lifesaving therapy for patients with type 1 diabetes, it was the introduction of protaminated insulin in 1946 that provided more extended "basal" coverage to taper some of the large glycemic fluctuations that occurred with the administration of regular insulin two to three times daily. The use of a split-mix approach with twice-daily administration of a combination of regular insulin plus either insulin neutral protamine Hagedorn (NPH) or insulin lente provided overall better control with fewer episodes of hypoglycemia or severe hyperglycemia.

Insulin was the first protein to be sequenced (in 1955), and it became the first human protein to be manufactured through human recombinant technology. It was introduced into clinical practice in 1982 as synthetic "human" insulin, with the advantage of being less allergenic than animal insulin preparations. Human insulin eventually replaced all of the animal insulin preparations in the US market.

The pursuit of tight glycemic control as an effective strategy to prevent the chronic and devastating complications of the disease was confirmed in 1993 by publication of the Diabetes Control and Complications Trial (DCCT), which undeniably established the relationship between normalization of glycemia and prevention of microvascular complications in patients with type 1 diabetes.[1] The UK Prospective Diabetes Study, demonstrating a similar relationship in type 2 diabetes, was soon to follow.[2] In both trials,

TABLE 1
Insulin products marketed in the United States

Insulin (Brand)
Rapid-acting
Insulin aspart (NovoLog)
Insulin lispro (Humalog)
Insulin glulisine (Apidra)
Short-acting
Regular insulin (Humulin R, Novolin R/ReliOn R)
Intermediate, basal
NPH insulin (Humulin N, Novolin N/ReliOn N)
Basal analogues
Insulin glargine U-100 (Lantus, Basaglar)
Insulin detemir (Levemir)
Longer-acting basal analogues
Insulin glargine U-300 (Toujeo)
Insulin degludec (Tresiba)
Premixed
75% Insulin lispro protamine/25% insulin lispro (Humalog mix 75/25)
50% Insulin lispro protamine/50% insulin lispro (Humalog mix 50/50)
70% Insulin lispro protamine/30% insulin aspart (Novolog mix 70/30)
70% NPH insulin/30% regular insulin (Humulin, Novolin/ReliOn)
70% Insulin degludec/30% insulin aspart (Ryzodeg 70/30)
Inhaled
Technosphere insulin oral-inhalation system (Afrezza)

NPH = neutral protamine Hagedorn.

TABLE 2
Metabolic control results from meta-analysis of studies comparing short-acting insulin analogues with human regular insulin in patients with type 1 or type 2 diabetes mellitus (DM)

	Patients	
	Type 1 DM	Type 2 DM
HbA1c		
No. studies	22	5
WMD (95% CI)	−0.1%[a] (−0.2 to −0.1)	0.0% (−0.1 to 0.0)
Continuous SC injection subgroup (7 studies)	−0.2%[a] (−0.3 to −0.1)	— —
Multiple dose injections subgroup (15 studies)	−0.1% (−0.1 to 0.0)	— —
Overall hypoglycemia		
No. studies	10	10
WMD mean events/pt/mo (95% CI)	−0.2% (−1.1 to 0.7)	−0.2% (−0.5 to 0.1)
Severe hypoglycemia		
No. studies, 28	Not reported	Not reported
Median events/100 person-years, insulin analogue vs regular insulin	21.8 vs 46.1	0.3 vs 1.4

[a]Statistically significant in favor of insulin analogues vs regular insulin.

CI = confidence interval; SC = subcutaneous; WMD = weighted mean difference.

Based on data in Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database Syst Rev 2006; 19:CD003287.

the follow-up observation periods further underscored the importance of early glycemic control by showing both sustained reductions in microvascular complications (retinopathy, nephropathy, and neuropathy) and statistically significant decreases in the risk of a cardiovascular event.[3,4] Of note, it was the introduction in clinical practice of safer and more user-friendly insulin options that made these gains in glycemic control possible.

With the publication of the DCCT results,[1] physiologic insulin replacement became the therapeutic standard in patients with advanced insulin deficiency, demonstrating that lowering hemoglobin A1c (HbA1c) and mitigating glycemic variability translated into microvascular risk reduction. The use of longer-acting insulin preparations, such as ultralente insulin, and the delivery of the basal component through continuous subcutaneous (SC) insulin infusion using an insulin pump further facilitated achievement of near-normal glycemia.

Insulin products continue to be refined and new formulations and molecular entities developed (**Table 1**). The following sections review the current insulin products, their pharmacologic profiles, and their clinical roles in diabetes practice.

INSULIN ANALOGUES

In 1996, the first short-acting insulin analogue (or insulin-receptor ligand), lispro, was brought to market. In lispro, the penultimate lysine and proline amino acids on the end of the C-terminal of the beta-chain of human insulin are reversed, facilitating faster absorption of the insulin through the greater availability of insulin monomers following SC depot injection.

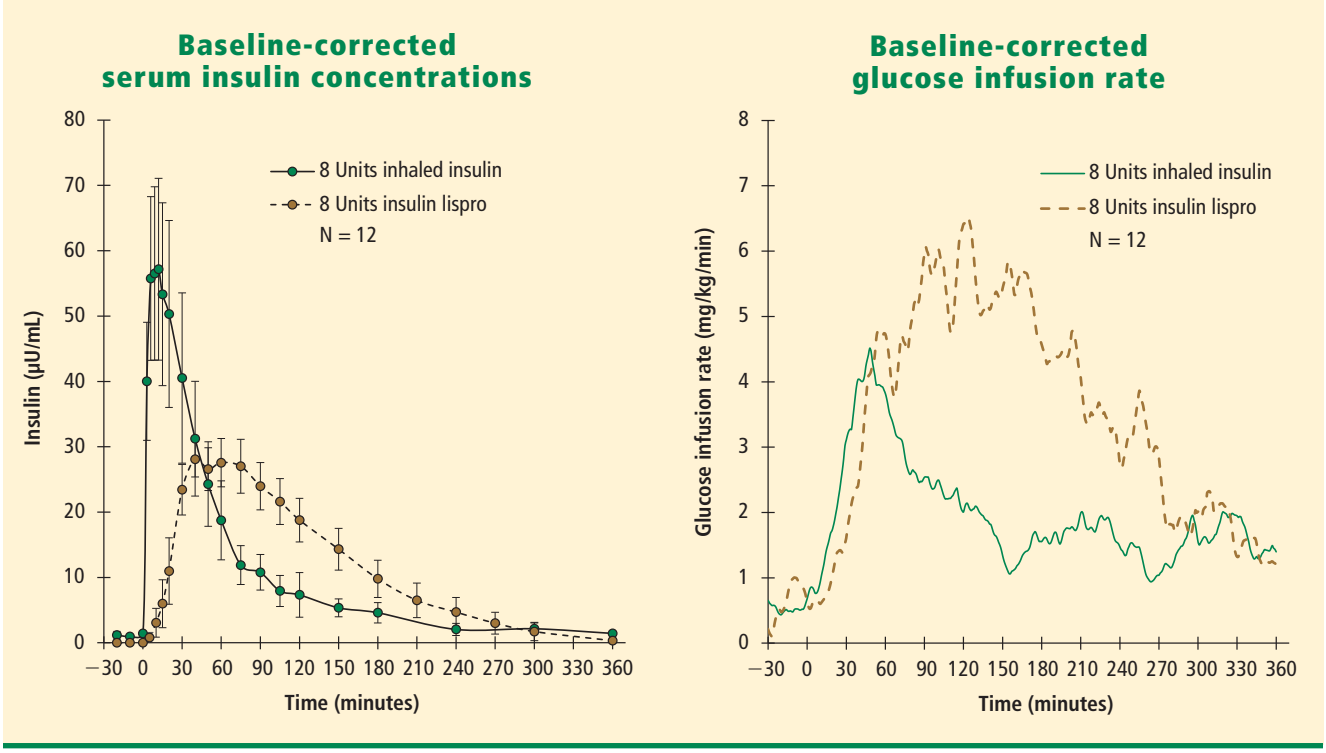

FIGURE 1. Serum insulin concentrations and glucose infusion rate of inhaled insulin for inhaled vs insulin lispro in patients with type 1 diabetes.
Data from Afrezza (insulin human) inhalation powder [package insert]. Danbury, CT: MannKind Corp; 2014.

The three short-acting insulin analogues—lispro, aspart, and glulisine—have similar pharmacokinetic and pharmacodynamic properties, with earlier onset and peak of biologic action, and shorter duration of activity than regular insulin. Potentially, these characteristics should translate into greater administration flexibility (patients can inject anywhere from 20 minutes before to 20 minutes after the start of the meal), better control of postprandial hyperglycemia, and less risk of late prandial hypoglycemia (3 to 6 hours after the meal). In a meta-analysis comparing short-acting analogues with human regular insulin, the most relevant difference reported was a lower risk of severe hypoglycemia with the analogue preparations[5] (**Table 2**). There might be an advantage with regards to bedtime and overnight hypoglycemia when using short-acting analogues, especially if a protaminated insulin is used for overnight basal coverage.[6]

While short-acting analogues have been approved for administration following a meal, postprandial control is clearly better if these preparations are injected prior to the meal, ideally 15 to 20 minutes before, to allow time to enter the circulation.[7] Additionally, the pharmacokinetics and biologic activity of short-acting insulin analogues appear to be very different when administered to obese, insulin-resistant patients with type 2 diabetes, in whom the onset of action is delayed and the biologic activity considerably reduced.[8]

INHALED INSULIN

A recent entry into the short-acting insulin marketplace—Technosphere oral-inhaled insulin (Afrezza)—was US Food and Drug Administration (FDA)-approved in 2014. Inhaled insulin has low bioavailability but is absorbed much more rapidly into the circulation than the current short-acting insulin analogues and has a shorter duration of biologic activity. However, the pharmacodynamics of inhaled insulin, when compared with insulin lispro, show only a slightly faster onset of action and a lower peak of biologic activity[9] (**Figure 1**). Studies comparing the efficacy and safety of inhaled insulin with short-acting analogues or premix insulin have demonstrated equivalent or less effective blood glucose-lowering effect and equivalent or lower risk of hypoglycemia.[10] For example, in trials of aspart insulin in patients with type 1 diabetes, inhaled insulin had statistically less reduction in HbA1c; in only one of the two trials did it show less hypoglycemia risk. Another trial compar-

ing inhaled insulin plus basal insulin to premix aspart 70/30 showed equivalent HbA1c reductions, but less hypoglycemia with inhaled insulin.[10]

Inhaled insulin should not be used by smokers, patients with chronic lung disease (such as asthma and chronic obstructive pulmonary disease), and those with acute episodes of bronchospasm. In patients who have a history of or are at risk for lung cancer, the benefits of using inhaled insulin need to be carefully weighed against the potential risks, especially given the increase in lung cancer events in smokers that was observed with the prior inhaled-insulin preparation Exubera.[11] Baseline and follow-up spirometry needs to be implemented for those using inhaled insulin to exclude clinically significant changes in forced expiratory volume in 1 second. Dosing of inhaled technosphere insulin is done via single-use cartridges of 4-, 8-, or 12-unit composition, making titration of smaller insulin increments more of a challenge. Patient reported outcomes in trials of inhaled insulin report variable effect (equivalent or favorable) on diabetes worries, health-related quality of life, or perceptions of insulin therapy, satisfaction, or preference.[12,13]

CONCENTRATED INSULIN

Concentrated insulin preparations have been available in clinical practice for many years and have been implemented with variable success. For example, Humulin R U-500 is a concentrated human regular insulin product (five times more concentrated than U-100) that has been used in patients requiring consistently high daily doses of insulin (usually > 200 U/day). Nonrandomized studies have shown significant improvement in glycemic control comparing pre- and post-intervention periods in patients switched from U-100 prandial insulin preparations to U-500 regular insulin.[14] Given the slight differences in pharmacodynamic profiles between regular U-100 and U-500 insulin preparations,[15] a randomized controlled trial comparing a U-500 insulin strategy with other currently available alternatives in very insulin-resistant patients will be needed to draw objective conclusions regarding the efficacy and safety of this concentrated insulin preparation.

For patients and providers who opt for a trial of regular U-500 insulin, a number of issues need to be considered to mitigate risks and optimize benefits of using this concentrated insulin. First and foremost is the frequent confusion in the communication between provider, pharmacy, and patient regarding the correct insulin dose to be administered. Because regular U-500 insulin is administered with U-100 insulin syringes, a 1-unit measure of U-500 corresponds to a 5-unit delivery of regular insulin.

To minimize confusion, regular U-500 prescriptions should be made out in volume rather than units, but this difference must be clearly explained to patients to avoid overdosing. For example, 0.01 mL of U-500 equates to 5 units of insulin, but it corresponds to the 1-unit mark of the standard U-100 insulin syringe. Newer concentrated insulin preparations on the market have avoided this confusion by providing measured doses in an insulin pen delivery system. For example, insulin lispro U-200 (Humalog U-200), a twofold concentration of insulin lispro U-100 with similar pharmacodynamics, is only available in a prefilled pen. Using insulin pen technology, a 1-unit dose of insulin actually corresponds to 1 unit of insulin, thereby removing any possible confusion regarding the prescription or administration of the correct insulin dose. Insulin lispro U-200 offers the convenience of holding more insulin per pen; it contains 600 units of insulin per pen compared with 300 units in the lispro U-100 pen.

BASAL INSULIN

Currently available basal insulin preparations include insulin NPH (Humulin N, Novolin N), insulin glargine U-100 (Lantus), insulin detemir (Levemir), and the 2015 FDA-approved formulations insulin glargine U-300 (Toujeo) and insulin degludec (Tresiba). The basal analogues introduced in the year 2000 with glargine U-100 were meant to fill the void left when the long-acting insulin ultralente animal preparations were pulled from the market in the early 1990s. The basal analogues have a longer duration of action than insulin NPH and, more importantly, have more stable and consistent biologic activity over a 24-hour period, resulting in more predictable glycemic levels and a lower risk of hypoglycemia.[16–18]

Three insulin analogue preparations—glargine U-300 and degludec (both FDA-approved) and pegylated lispro (currently in phase 3 trials)—have demonstrated longer protraction of biologic activity than glargine U-100, considered the current technical standard for basal insulin replacement. These three "second-generation" basal insulin analogues have pharmacodynamic activity that extends beyond 24 hours. When compared with glargine U-100 insulin, they exhibited fewer pronounced peaks of biologic activity and less pharmacokinetic variability, with similar glycemic control (as determined by HbA1c) but with an even lower risk of hypoglycemia, especially nocturnal hypoglycemia.[19–21]

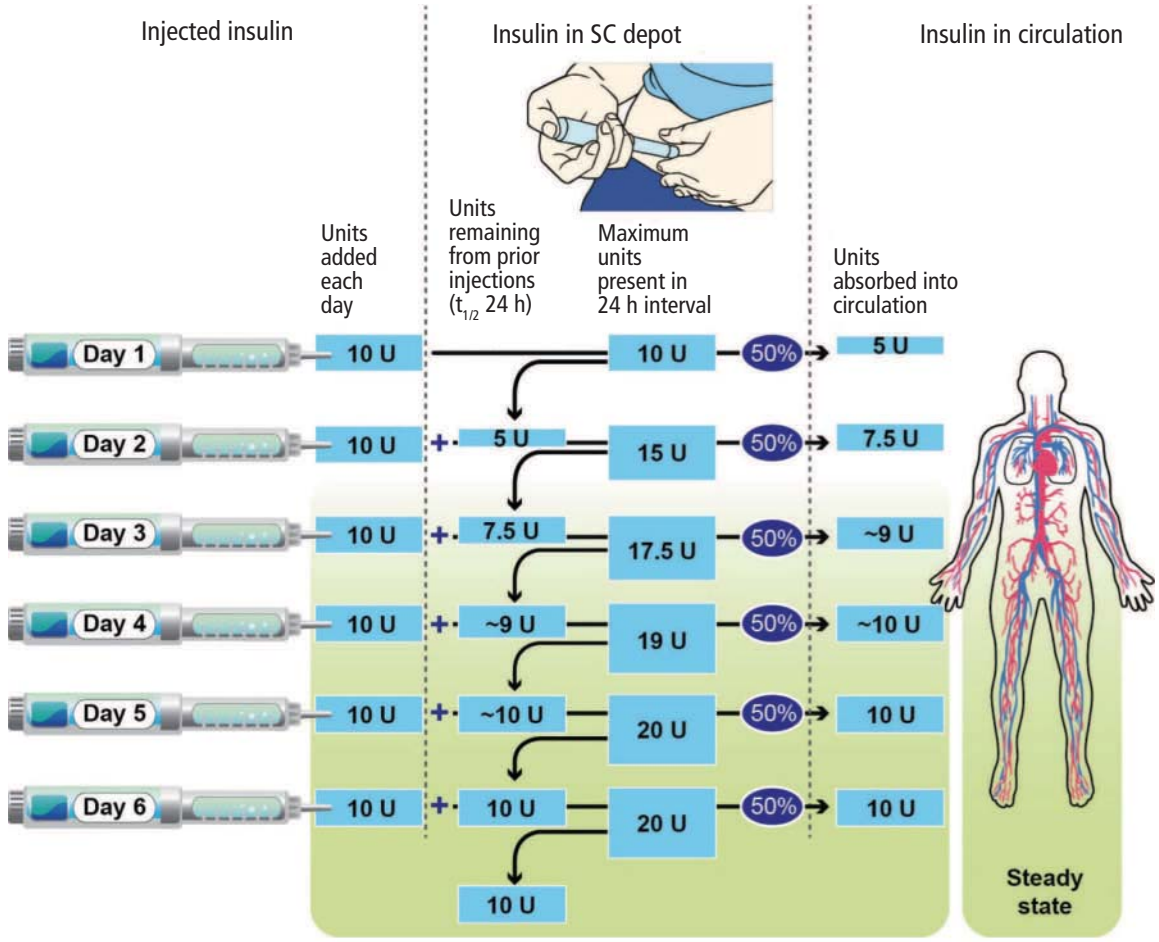

FIGURE 2. Example of time to reach steady state without inappropriate accumulation of basal insulin using a simplified one-compartment model (10 U, with half-life ~24 hours). Because dosing frequency is approximately equal to half-life, insulin only accumulates until steady state is reached, at which time the daily injected dose is balanced by elimination. SC = subcutaneous; $t_{1/2}$ = half-life.

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The extended biologic activity raises concern for potential insulin stacking and subsequent hypoglycemia, which should be easily mitigated by restricting basal insulin dose adjustments to no more frequently than every 3 to 4 days, which corresponds to the time needed for these preparations to reach 90% or more of their effective steady state[22] (**Figure 2**). Indeed, most of the clinical trials comparing these basal insulin preparations with glargine U-100 show a lower risk of hypoglycemia when basal dose adjustments are carried out weekly and no more frequently than every 3 days.[23]

Insulin glargine U-300 is essentially a threefold concentrated preparation of insulin glargine U-100 that results in a two-thirds volume reduction and a one-half reduction in depot surface following SC administration. The reduced depot surface area is presumed to account for much of the protracted absorption of glargine U-300 from the SC tissues. The metabolism and elimination of glargine U-300 is similar to that of the original compound, with formation of two active metabolites: M1 (the principal active moiety) and M2. Biologic steady state is achieved after 4 to 5 days of once-daily injections.[24]

When compared with glargine U-100 in patients with type 1 diabetes, insulin glargine U-300 at doses of 0.4 U/kg produced more stable insulin concentrations and glucose-lowering effect with a longer duration of action at steady state, as reflected by tight glucose control being maintained for about 5 hours longer (median of 30 hours).[25] A meta-analysis of the EDITION I to III clinical trials in patients with type 2 diabetes at various stages of treatment found similar glucose-lowering effects for glargine U-300 compared

with glargine U-100 but a lower rate of nonsevere hypoglycemia.[20] Of note was the need for 10% to 15% more units of insulin for glargine U-300 in these clinical trials. Insulin glargine U-300 is available only in a 1.5 mL disposable prefilled pen, which contains 450 units of insulin. Because the dose counter on the pen window corresponds to the actual number of units of insulin to be injected, no dose recalculation is required by the patient or provider.

Insulin degludec is another ultra-long-acting basal insulin analogue with a half-life at steady state of greater than 25 hours.[26] In comparison, the half-life of insulin glargine U-100 in that same study was reported as 12.1 hours. Further, insulin degludec exhibited flatter and more stable biologic activity, more evenly distributed over the course of a 24-hour period than insulin glargine U-100. The protraction mechanism is based on the formation of long strings of multihexamers, facilitated by a 16-carbon fatty acid chain linked via a glutamic acid spacer to the terminal end of the B-chain of the insulin molecule.[27] In studies of patients with type 2 diabetes at various stages of treatment, insulin degludec also demonstrated lower risk of nonsevere hypoglycemia for an equivalent level of HbA1c control achieved.[19]

The flexibility of administration time for an ultra-long-acting insulin preparation such as degludec was tested by asking patients to alternate the injection of degludec between morning and evening, in effect creating administration intervals of up to 8 to 40 hours.[28] Even within such drastic parameters, the efficacy and safety of insulin degludec were maintained when compared with insulin glargine U-100 injected at the same time of the day every day.

Because of an increase in major adverse cardiovascular events in phase 3 trials, degludec is undergoing a cardiovascular safety trial in patients with type 2 diabetes. The DEVOTE trial, which started in October 2013, will include 7,500 patients and will continue for up to 5 years. Interim results have recently been submitted to the FDA resulting in conditional approval of degludec in the US (Clinical Trials.gov Registration: NCT01959529). Degludec is available in disposable pen or cartridge format in U-100 and U-200 formulations.

COST

These new insulin preparations have introduced clinical options that have efficacy similar to that of available insulin products but, for the most part, have advantages of safety (less risk of nonsevere hypoglycemia) and patient convenience (flexibility in timing of insulin dose administration). While the latter is presumed to improve patient adherence, this has yet to be confirmed. Compared with synthetic human insulin preparations (regular insulin, NPH, and premix 70/30 insulin), which can be obtained in certain pharmacies at a discount (usually around 3 cents per unit of insulin), the currently available insulin analogues are considerably more expensive (around 16 to 27 cents per unit of insulin).

Within the guidelines for initiation and intensification of the insulin regimen using basal insulin formulations, the clinician will need to balance the potential benefits and current costs for the treatment of the individual patient. Clearly, as patients with diabetes are brought closer to their glycemic goals with insulin options, they stand to increasingly benefit from formulations that provide more consistent glycemic response and less risk of hypoglycemia. For those who are unable to afford the higher costs, especially if their glycemic control is far from the desired target, the use of synthetic human insulin formulations may be entirely appropriate. In this era of individualized care and prescriptions, clinicians have a range of insulin treatment options that will facilitate patients reaching appropriate goals.

REFERENCES

1. **The Diabetes Control and Complications Trial Research Group.** The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329:977–986.
2. **UK Prospective Diabetes Study (UKPDS) Group.** Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352:837–853.
3. **Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA.** 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359:1577–1589.
4. **Nathan DM, Cleary PA, Backlund JY, et al; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group.** Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005; 353:2643–2653.
5. **Siebenhofer A, Plank J, Berghold A, et al.** Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database Syst Rev 2006; 19:CD003287.
6. **Gale EA.** A randomized, controlled trial comparing insulin lispro with human soluble insulin in patients with type 1 diabetes on intensified insulin therapy. The UK Trial Group. Diabet Med 2000; 17:209–214.
7. **Cobry E, McFann K, Messer L, et al.** Timing of meal insulin boluses to achieve optimal postprandial glycemic control in patients with type 1 diabetes. Diabetes Technol Ther 2010; 12:173–177.
8. **Gagnon-Auger M, du Souich P, Baillargeon JP, et al.** Dose-dependent delay of the hypoglycemic effect of short-acting insulin analogs in obese subjects with type 2 diabetes: a pharmacokinetic and pharmacodynamic study. Diabetes Care 2010; 33:2502–2507.
9. Afrezza (insulin human) inhalation powder [package insert]. Danbury, CT: MannKind Corp; 2014.
10. **Kugler AJ, Fabbio KL, Pham DQ, Nadeau DA.** Inhaled techno-

sphere insulin: a novel delivery system and formulation for the treatment of types 1 and 2 diabetes mellitus. Pharmacotherapy 2015; 35:298–314.
11. **Kling J.** Inhaled insulin's last gasp? Nat Biotechnol 2008; 26:479–480.
12. **Peyrot M, Rubin RR.** Patient-reported outcomes in adults with type 2 diabetes using mealtime inhaled technosphere insulin and basal insulin versus premixed insulin. Diabetes Technol Ther 2011; 13:1201–1206.
13. **Testa MA, Simonson DC.** Satisfaction and quality of life with premeal inhaled versus injected insulin in adolescents and adults with type 1 diabetes. Diabetes Care 2007; 30:1399–1405.
14. **Reutrakul S, Wroblewski K, Brown RL.** Clinical use of U-500 regular insulin: review and meta-analysis. J Diabetes Sci Technol 2012; 6:412–420.
15. **de la Peña A, Riddle M, Morrow LA, et al.** Pharmacokinetics and pharmacodynamics of high-dose human regular U-500 insulin versus human regular U-100 insulin in healthy obese subjects. Diabetes Care 2011; 34:2496–2501.
16. **Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators.** The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003; 26:3080–3086.
17. **Heise T, Nosek L, Rønn BB, et al.** Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes 2004; 53:1614–1620.
18. **Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B.** Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. Clin Ther 2006; 28:1569–1581.
19. **Einhorn D, Handelsman Y, Bode BW, Endahl LA, Mersebach H, King AB.** Patients achieving good glycemic control (HbA1c <7%) experience a lower rate of hypoglycemia with insulin degludec than with insulin glargine: a meta-analysis of phase 3a trials. Endocr Pract 2015; 21:917–926.
20. **Ritzel R, Roussel R, Bolli GB, et al.** Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. Diabetes Obes Metab 2015; 17:859–867.
21. **Bergenstal RM, Rosenstock J, Arakaki RF, et al.** A randomized, controlled study of once-daily LY2605541, a novel long-acting basal insulin, versus insulin glargine in basal insulin-treated patients with type 2 diabetes. Diabetes Care 2012; 35:2140–2147.
22. **Heise T, Meneghini LF.** Insulin stacking versus therapeutic accumulation: understanding the differences. Endocr Pract 2014; 20:75–83.
23. **Bolli GB, Riddle MC, Bergenstal RM, et al; on behalf of the EDITION 3 study investigators.** New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). Diabetes Obes Metab 2015; 17:386–394.
24. **Steinstraesser A, Schmidt R, Bergmann K, Dahmen R, Becker RH.** Investigational new insulin glargine 300 U/ml has the same metabolism as insulin glargine 100 U/ml. Diabetes Obes Metab 2014; 16:873–876.
25. **Becker RH, Dahmen R, Bergmann K, Lehmann A, Jax T, Heise T.** New insulin glargine 300 units·mL−1 provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 units·mL−1. Diabetes Care 2015; 38:637–643.
26. **Heise T, Hövelmann U, Nosek L, Hermanski L, Bøttcher SG, Haahr H.** Comparison of the pharmacokinetic and pharmacodynamic profiles of insulin degludec and insulin glargine. Expert Opin Drug Metab Toxicol 2015; 11:1193–1201.
27. **Jonassen I, Havelund S, Hoeg-Jensen T, Steensgaard DB, Wahlund PO, Ribel U.** Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. Pharm Res 2012; 29:2104–2114.
28. **Meneghini L, Atkin SL, Gough SC, et al; NN1250-3668 (BEGIN FLEX) Trial Investigators.** The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. Diabetes Care 2013; 36:858–864.

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Inpatient hyperglycemia management: A practical review for primary medical and surgical teams

ABSTRACT

Inpatient hyperglycemia is common and is associated with an increased risk of hospital complications, higher healthcare resource utilization, and higher in-hospital mortality rates. Appropriate glycemic control strategies can reduce these risks, although hypoglycemia is a concern. In *critically ill* patients, intravenous (IV) insulin is most appropriate, with a starting threshold no higher than 180 mg/dL. Once IV insulin is started, the glucose level should be maintained between 140 and 180 mg/dL. In *noncritically ill* patients, basal-bolus regimens with basal, prandial, and correction components are preferred for those with good nutritional intake. In contrast, a single dose of long-acting insulin plus correction insulin is preferred for patients with poor or no oral intake. Measuring hemoglobin A1c at admission is important to assess glycemic control and to tailor the treatment regimen at discharge.

KEY POINTS

Hyperglycemia in hospitalized patients, with or without diabetes, is associated with adverse outcomes.

Measurement of hemoglobin A1c is recommended in all patients at hospital admission.

Insulin administration is the preferred way to control hyperglycemia in hospitalized patients, with a starting threshold below 180 mg/dL then maintaining a level between 140 and 180 mg/dL.

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Hyperglycemia in hospitalized patients, with or without diabetes, is associated with adverse outcomes including increased rates of infection and mortality and longer hospital length of stay.[1–3] The rates of complications and mortality are even higher in hyperglycemic patients without a history of diabetes than in those with diabetes.[1,2] Randomized clinical trials in critically ill and noncritically ill hyperglycemic patients demonstrate that improved glycemic control can reduce hospital complications, systemic infections, and hospitalization cost.[4–6] However, intensive glycemic therapy is associated with increased risk of hypoglycemia, which is independently associated with increased morbidity and mortality in hospitalized patients. The concern about hypoglycemia has led to revised blood glucose target recommendations from professional organizations and a search for alternative treatment options.

This manuscript provides a review of updated recommendations for the management of inpatients with hyperglycemia in the critical care and general medical and surgical settings.

HYPERGLYCEMIA IN CRITICAL CARE SETTINGS

A substantial body of evidence links hyperglycemia in critically ill patients to higher rates of hospital complications, longer hospital stay, higher healthcare resource utilization, and greater hospital mortality.[7,8] Although evidence from several cohort studies and randomized clinical trials suggests that tight glucose control can reduce hospital complications and mortality,[9,10] this target has been difficult to achieve without increasing the risk of severe hypoglycemia. In addition, data from trials using intense glycemic control in patients in the intensive care unit (ICU) have failed to show a significant improvement in mortality and, in some instances, showed increased mortality risk associated with the therapy.[11,12]

The recommended target glucose levels are 140 to 180 mg/dL for most ICU patients.[13] In agreement with this, the recent GLUCO-CABG trial reported no significant differences in the composite end points of complications and death between an intensive glucose target of 100 to 140 mg/dL and a conservative target of 141 to 180 mg/dL after cardiac surgery.[14]

HYPERGLYCEMIA IN NONCRITICAL CARE SETTINGS

In general medical and surgical patients, a strong association has been reported between hyperglycemia and prolonged hospital stay, infection, and disability after hospital discharge.[1,15,16] For example, the risk of postoperative infections in patients undergoing general surgery was estimated to increase by 30% for every 40 mg/dL rise in glucose over normoglycemia (< 110 mg/dL).[16] In general, appropriate glycemic control to maintain recommended glycemic levels in noncritically ill patients can reduce the risks and improve outcomes.

HYPOGLYCEMIA INCIDENCE

Hypoglycemia, defined as glucose less than 70 mg/dL, is a common complication of hyperglycemia treatment.[17] Severe hypoglycemia is defined as glucose less than 40 mg/dL.[18] The incidence of hypoglycemia in ICU trials ranged between 5% and 28%, depending on the intensity of glycemic control,[19] and between 1% and 33% in non-ICU trials using subcutaneous (SC) insulin therapy.[20] The most important hypoglycemia risk factors include older age, kidney failure, change in nutritional intake, interruption of glucose monitoring, previous insulin therapy, and failure to adjust therapy when glucose is trending down or steroid therapy is being tapered.[21,22]

In hospitalized patients with diabetes, hypoglycemia has been associated with poor outcomes, including a 66% increased risk of death within 1 year and 2.8 days longer hospital stay compared with patients without hypoglycemia.[23] Hypoglycemia also has been associated with prolonged QT interval, ischemic electrocardiogram changes, angina, arrhythmias, and sudden death in patients with type 1 diabetes.[24] Despite these observations, other studies have reported that the increased in-hospital mortality rate is limited to patients with spontaneous hypoglycemia rather than drug-associated hypoglycemia,[25] raising the possibility that hypoglycemia may represent a marker of disease burden rather than be a direct cause of death.

INPATIENT ASSESSMENT OF HYPERGLYCEMIA

Clinical guidelines recommend glucose measurement in all patients admitted to the hospital.[13,26] Patients with hyperglycemia (glucose > 140 mg/dL) and patients with a history of diabetes should undergo bedside point-of-care glucose testing before meals and at bedtime. Premeal testing should be done close to the time of the meal tray delivery and no longer than 1 hour before meals. For patients taking nothing by mouth or receiving continuous enteral nutrition, point-of-care testing is recommended every 4 to 6 hours.

Hemoglobin A1c (HbA1c) should be measured in patients with hyperglycemia and in those with diabetes if it has not been performed in the preceding 2 to 3 months. In hyperglycemic patients without a history of diabetes, an HbA1c of 6.5% or greater suggests that diabetes preceded hospitalization. In patients with diabetes, the HbA1c can help assess glycemic control prior to admission and tailor the treatment regimen at discharge.[13,26]

TARGET GLUCOSE LEVELS

Glycemic targets recommended by several organizations are shown in **Table 1**. For critically ill patients, most societies recommend glucose targets below 180 mg/dL, with the lower limit being anywhere from 110 to less than 150 mg/dL.

For patients in non-ICU settings, the Endocrine Society[26] and the American Diabetes Association/American Association of Endocrinologists[13] practice guidelines recommend premeal glucose levels below 140 mg/dL, and below 180 mg/dL if checked randomly. Higher glucose ranges (< 200 mg/dL) may be acceptable in terminally ill patients or in patients with severe comorbidities.[26] Guidelines from the Joint British Diabetes Societies recommend targeting glucose levels between 108 and 180 mg/dL with an acceptable range of between 72 and 216 mg/dL.[27]

INPATIENT MANAGEMENT OF HYPERGLYCEMIA AND DIABETES

Insulin regimens in critical care settings

Insulin administration is the preferred way to control hyperglycemia in hospitalized patients. In critically ill patients, such as those with hypotension requiring pressor support, hyperglycemic crises, sepsis, or shock, insulin is best given via continuous intravenous (IV) infusion. The short half-life of IV insulin (< 15 minutes) allows flexibility in adjusting the infusion rate in the event of unpredicted changes in nutrition or the patient's health. If the glucose level

TABLE 1
Major guidelines for treatment of hyperglycemia in a hospital setting

Organization	Intensive care unit	Non-intensive care unit
American Diabetes Association/ American Association of Endocrinologists[13]	Initiate insulin therapy for persistent hyperglycemia (glucose > 180 mg/dL [10 mmol/L]). **Treatment goal:** For most patients, target a glucose level between 140 and 180 mg/dL. More stringent goals (110–140 mg/dL) may be appropriate for select patients, if achievable without significant risk of hypoglycemia.	No specific guidelines. If treated with insulin, premeal glucose targets should generally be < 140 mg/dL, with random glucose levels < 180 mg/dL.
American College of Physicians[46]	Recommends against intensive insulin therapy in patients with or without diabetes in surgical or medical intensive care. **Treatment goal:** Target glucose level is between 140 and 200 mg/dL in patients with or without diabetes in surgical or medical intensive care.	
Critical Care Society[29]	Glucose level > 150 mg/dL should trigger insulin therapy. **Treatment goal:** Maintain glucose level < 150 mg/dL for most adult patients in intensive care. Maintain glucose level < 180 mg/dL while avoiding hypoglycemia.	
Endocrine Society[26]		Premeal glucose target < 140 mg/dL. Random glucose < 180 mg/dL. A lower target range may be appropriate in patients able to achieve and maintain glycemic control without hypoglycemia. Glucose < 180–200 mg/dL is appropriate in patients with terminal illness or with limited life expectancy or at high risk for hypoglycemia. Adjust antidiabetic therapy when glucose falls < 100 mg/dL to avoid hypoglycemia.
Society of Thoracic Surgeons[28]	**Guidelines specific to adult cardiac surgery.** Continuous insulin infusion preferred over subcutaneous or intermittent intravenous boluses. **Treatment goal:** Recommend glucose < 180 mg/dL during surgery (≤ 110 mg/dL in fasting and premeal states).	
Joint British Diabetes Societies[27]		Target glucose levels in most patients are between 6 and 10 mmol/L (108–180 mg/dL) with an acceptable range of between 4 and 12 mmol/L (72–216 mg/dL).

rises above 180 mg/dL, IV insulin infusion should be started to maintain levels below 180 mg/dL.[13,26,28,29]

A variety of infusion protocols have been shown to be effective in achieving glycemic control with a low rate of hypoglycemia. The ideal protocol should allow flexible rate adjustment taking into account current and previous glucose values as well as changes in infusion rate. Hourly glucose measurements until stable glycemic control is established, followed by point-of-care testing every 1 to 2 hours, is needed to assess response to therapy and prevent hypoglycemia.

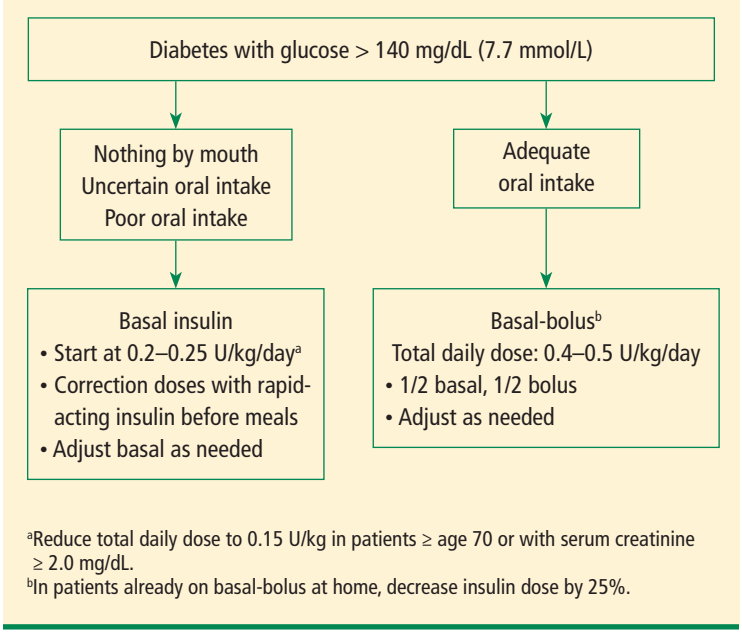

FIGURE 1. Initial insulin treatment for patients with type 2 diabetes in the non-intensive care setting.

Insulin regimens in noncritical care settings

For most patients in a general, non-ICU setting, SC insulin therapy with basal insulin administered once or twice daily, alone or in combination with prandial insulin, is effective and safe.[13] Inhaled insulin is approved by the US Food and Drug Administration, but its use in the hospital has not been studied. The use of sliding-scale insulin is not acceptable as the single regimen in patients with diabetes, as it results in undesirable hypoglycemia and hyperglycemia.[30] **Figure 1** presents an algorithm for selecting initial insulin treatment for patients with type 2 diabetes in the non-ICU setting.

Several SC insulin products are available, each with a different pharmacokinetic profile, as outlined in **Table 2**.[31]

Basal insulin prevents hyperglycemia during fasting states. Basal insulin is usually given as a once- or twice-daily long-acting insulin, such as glargine and detemir insulin. On occasion, twice-daily intermediate-acting insulin (neutral protamine Hagedorn; NPH) is used as a basal insulin.

Prandial insulin, also referred to as *nutritional* or *bolus* insulin, is given before meals as rapid-acting insulin (aspart, lispro, or glulisine) or short-acting insulin (regular) to prevent postmeal hyperglycemia. Rapid-acting insulin is preferred to regular insulin because of the faster onset and shorter duration of action, which may reduce the risk of hypoglycemia.

Correction or supplemental insulin is given to correct hyperglycemia when the glucose is above the goal. The same formulation is given together with prandial insulin.

Total daily dose of insulin is a measure that comprises basal and prandial insulin **Figure 1** lists the recommended total daily dose for different clinical situations and patient populations.

Basal-bolus insulin usually refers to a regimen of long-acting basal insulin plus prandial insulin. In patients with adequate oral intake, the basal-bolus approach is preferred. The RABBIT 2 trial reported that basal-bolus regimens resulted in greater improvement in glucose control than sliding-scale regimens (correction insulin alone without basal or prandial components) in general medicine patients with type 2 diabetes.[32] In general surgery patients, basal-bolus regimens significantly improved glucose control and reduced the numbers of postoperative complications, primarily wound infections compared with sliding-scale regimens.[4]

Multiple doses of NPH and regular insulin were compared with basal-bolus treatment with long-acting and rapid-acting insulin in two controlled trials in medical patients with type 2 diabetes.[20,33] Both studies reported that treatment with NPH and regular insulin resulted in similar improvements in glycemic control and no difference in the rate of hypoglycemic events or in hospital length of stay, compared with basal-bolus insulin. Because NPH has a peak of action approximately 8 to 12 hours after injection, there is a risk of hypoglycemia in patients with poor oral intake.

In hospitalized patients who have reduced total caloric intake due to lack of appetite, acute illness,

TABLE 2
Insulin classes: Onset-of-action profiles

Insulin class	Generic (brand)	Onset	Peak	Duration
Fast- or rapid-acting	Aspart (Novolog)	10–15 min	~60 min	3–4 hrs
	Lispro (Humalog)	10–15 min	~60 min	3–4 hrs
	Glulisine (Apidra)	10–15 min	~60 min	3–4 hrs
Short-acting	Regular insulin (Humulin R, Novolin R/ReliOn R)	30–60 min	2–4 hrs	6–8 hrs
Intermediate-acting	NPH insulin (Humulin N, Novolin N/ReliOn N)	1–2 hrs	3–8 hrs	12–15 hrs
Long-acting	Glargine (Lantus)	2 hrs	No real peak	22–24 hrs
	Glargine (Toujeo)	6 hrs	No real peak	22–24 hrs
	Glargine (Basaglar)[a]	2 hrs	No real peak	24 hrs
	Detemir (Levemir)	3–8 hrs	No real peak	17–24 hrs
	Degludec (Tresiba)	1 hr	No real peak	42 hrs
Premixed	75% Insulin lispro protamine/25% insulin lispro (Humalog mix 75/25)	5–15 min	Dual	10–16 hrs
	50% Insulin lispro protamine/50% insulin lispro (Humalog mix 50/50)	5–15 min	Dual	10–16 hrs
	70% Insulin lispro protamine/30% insulin aspart (Novolog mix 70/30)	5–15 min	Dual	10–16 hrs
	70% NPH insulin/30% regular insulin (Humulin, Novolin/ReliOn)	30–60 min	Dual	10–16 hrs

[a]Approved by the US Food and Drug Administration; scheduled to be marketed December 2016.
NPH = neutral protamine Hagedorn.

medical procedures, or surgical interventions, the Basal Plus trial[34] reported that a single daily dose of glargine plus correction doses of rapid-acting insulin resulted in similar improvement in glycemic control and no difference in the frequency of hypoglycemia compared with a standard basal-bolus regimen. These results indicate that the basal-plus-correction regimen may be preferred for patients with poor or no oral intake, whereas an insulin regimen with basal, nutritional (basal-bolus), and correction components is preferred for patients with good nutritional intake.[35]

SC insulin dosing refers to insulin doses administered subcutaneously calculated based either on weight or on home insulin doses. For insulin-naive patients, the starting total daily dose of insulin can usually be computed as 0.4 to 0.5 U/kg/day. Higher starting doses are associated with greater odds of hypoglycemia than doses lower than 0.2 U/kg/day.[36] In elderly patients and those with impaired renal function, lower initial daily doses (≤ 0.3 U/kg) may reduce the risk of hypoglycemia.[26]

In patients treated with insulin prior to admission, the total daily insulin dose at home can be given as half long-acting basal insulin and half prandial insulin. The dose can be reduced by 20% to 25% to prevent hypoglycemia, particularly in those with poor or uncertain caloric intake.[31]

Noninsulin therapies

The use of oral antidiabetic agents is generally not recommended in hospitalized patients due to the limited data available on their safety and efficacy, frequent contraindications, risk of hypoglycemia, and slow onset of action that may preclude achieving rapid glycemic control and daily dose adjustments. **Table 3** lists the pros and cons of these agents in hospitalized patients.

The safety and efficacy of sitagliptin, a dipeptidyl peptidase-4 inhibitor, for the management of inpatient hyperglycemia was evaluated in a randomized pilot study in patients with type 2 diabetes treated at home with diet, oral antidiabetic agents, or a low daily insulin dose (≤ 0.4 U/kg/day).[37] Patients were randomized to one of two treatments:

- Sitagliptin alone or with low-dose glargine insulin
- Basal-bolus insulin regimen plus supplemental doses of insulin lispro.

TABLE 3
Comparison of medications for the management of hyperglycemia in the hospital setting

Medication	Advantages	Disadvantages
Insulin	Extensive experience with glycemic control Protocols widely available Easy to adjust in the event of hypoglycemia, changes in nutrition, diagnostic procedures, or reduced kidney function	Hypoglycemia Common source of hospital errors Requires injection
GLP-1-based therapy	Good glucose-lowering effect Low risk for hypoglycemia Nonglycemic beneficial effects	Limited data on safety and efficacy Gastrointestinal side effects Injectable
Metformin	Good glucose-lowering effect Low risk for hypoglycemia Inexpensive Oral route	Limited experience Risk of lactic acidosis in patients with impaired kidney function, heart failure, hypoxemia, alcoholism, cirrhosis, contrast exposure, surgery, and shock Gastrointestinal side effects
Sulfonylureas	Good glucose-lowering effect Inexpensive Oral route	Risk for hypoglycemia especially in patients with reduced oral intake or impaired renal function.
Thiazolidinediones	Good glucose-lowering effect Low risk of hypoglycemia Oral route	Slow onset of action Contraindicated in patients with heart failure and hepatic dysfunction Fluid retention
Bromocriptine-quick release	Low risk of hypoglycemia Oral route	No studies in the hospital Risk of hypotension, dizziness
Colesevelam	Low risk of hypoglycemia Oral route	No studies in the hospital Constipation
DPP-4-inhibitors	Modest glucose-lowering effect Low risk of hypoglycemia No major side effects reported in pilot trial Oral route	Limited experience Contraindicated in patients with history of pancreatitis
SGLT-2-inhibitors	Good glucose-lowering effect Low risk of hypoglycemia Oral route	Limited experience Increase risk of urinary and genital tract infections Risk of dehydration, hypotension

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2= sodium-glucose cotransporter-2.

Both treatment regimens resulted in similar improvement in mean daily glucose concentrations. However, patients admitted to the hospital with glucose levels above 180 mg/dL in the sitagliptin group had higher mean daily glucose levels than patients treated with basal-bolus or sitagliptin plus glargine.

Transitioning from IV to SC insulin

When patients in critical care units are ready to be transferred to a general medical floor, appropriate transition from IV insulin to scheduled SC insulin is needed to prevent rebound hyperglycemia. This is imperative in patients with type 1 diabetes in whom just a few hours without insulin can result in diabetic ketoacidosis.

There are three general ways to calculate the SC insulin dose during the transition period. The first two methods are weight-based and based on the home dose, as previously discussed. The third method is to extrapolate from the IV insulin. A common way is to sum up the total IV insulin dose in the past 6 or 8 hours and multiply by 3 or 4, and then reduce by 20% to achieve the basal insulin dose, presuming the patient had no oral intake on the IV insulin infusion. This last method is preferred in hemodynamically stable patients with stable insulin requirements.

If long-acting insulin is chosen as basal insulin, it should be given 2 to 4 hours before discontinuation of the IV insulin infusion. Intermediate-acting insulin should be given 1 to 2 hours before IV insulin discontinuation.

SPECIFIC SITUATIONS AND POPULATIONS

Type 1 diabetes

Patients with type 1 diabetes have minimal to absent pancreatic beta cell function and rely on the exogenous administration of insulin to maintain glucose homeostasis. They have worse glycemic control and higher rates of acute kidney injury than patients with type 2 diabetes; however, the impact of inpatient glycemic control on clinical outcomes has not been determined in patients with type 1 diabetes. Insulin therapy must provide both basal and nutritional components to achieve the target goals. It is important to ask the patient directly to determine the times and doses of prescribed insulin, medication adherence, recent dietary habits (including changes in appetite), and level of physical activity. This information will be used to guide insulin therapy.

A systematic review of 16 clinical studies reported that patients who possess excellent self-management skills can be suitable for successful inpatient diabetes self-management.[38] The American Diabetes Association supports patient self-management of diabetes in the hospital.[39] However, the competence and readiness of each patient with type 1 diabetes need to be carefully determined in an individualized manner. Potential candidates for inpatient self-management are those with unaltered mental status, proven proficient outpatient skills (eg, carbohydrate counting, frequent glucose monitoring, strong knowledge related to the management of insulin pump or injection techniques), and who are tolerating oral intake.

Enteral nutrition and tube feeding

Accidental dislodgement of feeding tubes, temporary discontinuation of nutrition due to nausea or for diagnostic testing, and cycling of enteral nutrition with oral intake in patients with an inconsistent appetite pose unique challenges in the hospital. Although it may be tempting to give basal and nutritional requirements to these patients as a single dose of long-acting insulin, this is not recommended. Low-dose basal insulin plus scheduled doses of short-acting (regular) insulin (every 6 hours) or rapid-acting insulin (every 4 hours) with correction insulin is often used. Some providers prefer giving intermediate-acting (NPH) plus short-acting (regular) insulin every 8 hours or every 12 hours.

It is generally accepted that diabetic enteral formulas that are low in carbohydrate and high in monounsaturated fatty acids are preferable to standard high-carbohydrate formulas in hospitalized patients with diabetes. In a meta-analysis, the postprandial rise in glucose was reduced by 20 to 30 mg/dL with the low-carbohydrate high-fat formulations compared with standard formulations.[40]

Parenteral nutrition

The use of parenteral nutrition has been linked to aggravation of hyperglycemia independent of a history of diabetes as well as a higher risk of complications, infections, sepsis, and death.[41] Regular insulin can be added to the parenteral solution at a starting dose of 0.1 U/g of dextrose in nondiabetic patients and at 0.15 U/g of dextrose in patients with diabetes.[42]

Alternatively, insulin can be given as a continuous IV infusion. Hemodynamically stable patients with mild to moderate hyperglycemia can be managed with basal insulin plus scheduled or as-needed doses of short-acting (regular) insulin every 6 hours. To prevent waste, it is better to underestimate the insulin added to parenteral nutrition so as to avoid having to discontinue it prematurely or add additional glucose.

Glucocorticoids

Glucocorticoids typically raise glucose starting 4 to 6 hours after administration. Low doses of glucocorticoids given in the morning tend to raise the late morning to evening glucose levels without affecting the fasting glucose. In this situation, the patient may

be managed on prandial insulin without long-acting basal insulin or with intermediate-acting insulin given in the morning. Higher glucocorticoid doses may raise fasting glucose levels, in which case basal-bolus insulin would be appropriate, with the basal component comprising about 30% and the bolus about 70% of the daily dose.[26]

Insulin pump

Approximately 400,000 US patients with diabetes use an insulin pump.[43] Successful management of inpatient diabetes with the continuation of insulin pump therapy has been previously demonstrated in select patients. Clear hospital policies, procedures, and physicians' orders with specifics on the type of diet, frequency of point-of-care glucose testing, and insulin doses (ie, basal rates, carbohydrate ratios, and correction formulas) should be in place. An inpatient diabetes specialist should assist with the assessment and management of a patient with an insulin pump.

If pump use is contraindicated (**Table 4**)[44] or if inpatient diabetes resources are not available, discontinuation of insulin pump and transition to a basal-bolus insulin regimen ("pump holiday") may be the safest and most appropriate step. Most patients knowledgeable in insulin pump therapy are able to display in their pump screen the average total daily insulin used for the past few days. Based on this, safe estimations of basal, bolus, and supplemental insulin can be calculated. To avoid severe hyperglycemia or ketoacidosis from lack of basal insulin, it is important to administer the basal insulin component at least 2 hours before disconnecting the insulin pump.

Concentrated insulins

U-500 regular insulin is concentrated insulin that delivers the same amount of units in one-fifth the volume of conventional insulins, which are U-100. Whereas there are 100 units of insulin in 1 mL for conventional insulins, there are 500 units of U-500 regular insulin in 1 mL. Its onset of action is similar to that of regular insulin, and the peak and duration are similar to that of NPH insulin. Concentrated insulin is often administered in the outpatient setting to patients who are insulin resistant and require close to 200 units a day. The U-500 pen device was approved in January 2016 and was projected to be available in April 2016. For now, it can only be procured in the vial form. This causes confusion in its dosing since it is given either with the usual insulin syringes, which are designed for U-100 insulin administration, or a tuberculin syringe, which is not marked in units but in milliliters.

TABLE 4
General contraindications to pump use in the hospital

Altered state of consciousness
Suicidal ideation
Prolonged instability of glucose levels
Diabetic ketoacidosis
Patient or family inability or refusal to participate in own care
Insulin pump malfunction
Lack of appropriate supplies for the insulin pump
Other circumstances as identified by the healthcare provider

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Because of its unique nature and providers' lack of familiarity with U-500, certain institutions have a policy for its use. In many institutions, the doses are confirmed by pharmacy staff and delivered by pharmacy to the patient's medication bin predrawn in a tuberculin syringe.[45] In addition, a study reported that many patients on U-500 at home required significantly lower doses of insulin (average dose of 100 U/day) while hospitalized patients could be managed with conventional insulin formulations.[45]

There are newer concentrated insulins in the market, such as insulin glargine 300 U/mL (Toujeo) and insulin lispro 200 U/mL (Humalog). These insulins, so far, come only in the pen device form and not in vials, obviating the need for dose calculations using a U-100 insulin syringe or tuberculin syringe. The efficacy and safety of these insulin formulations have not been determined in the hospital setting.

Transitioning from home to hospital

Transition to an outpatient setting requires planning and coordination. Although insulin is used in the hospital for most patients with diabetes, many patients do not require insulin after discharge. On the other hand, diabetes regimens sometimes need intensification in other patients. One study showed that patients with acceptable diabetes control (HbA1c < 7.5%) near or on admission could be discharged on their prehospitalization treatment regimen, while those with HbA1c between 7.5% and 9% could be discharged on oral agents plus basal insulin at 50% of the hospital basal dose.[46] Additionally, patients with an HbA1c of 9% to 10% should be discharged

on a basal-bolus regimen or on a combination of oral agents plus basal insulin at 80% of hospital dose, with a reduction in HbA1c seen 12 weeks after discharge.

SUMMARY

Inpatient hyperglycemia is common and is associated with increased risk of hospital complications, higher healthcare resource utilization, and higher rates of in-hospital mortality. In the critically ill, IV insulin is most appropriate, with a starting threshold no higher than 180 mg/dL. Once IV insulin is started, the glucose level should be maintained between 140 and 180 mg/dL.

In noncritically ill patients, a basal-bolus regimen with basal, prandial, and correction components is preferred for patients with good nutritional intake. In contrast, a single dose of long-acting insulin plus correction insulin is preferred for patients with poor or no oral intake. Preliminary data indicate that incretin therapy has the potential to improve glycemic control in patients with mild to moderate hyperglycemia and a low risk of hypoglycemia.

Transition to an outpatient setting requires planning and coordination. Measuring HbA1c at admission is important to assess preadmission glycemic control and to tailor the treatment regimen at discharge. Patients with acceptable diabetes control could be discharged on their prehospitalization treatment regimen. Patients with suboptimal control should have more intensified therapy.

REFERENCES

1. **Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE.** Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab 2002; 87:978–982.
2. **Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML.** Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med 2009; 37:3001–3009.
3. **Kotagal M, Symons RG, Hirsch IB, et al.** Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. Ann Surg 2015; 261:97–103.
4. **Umpierrez GE, Smiley D, Jacobs S, et al.** Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). Diabetes Care 2011; 34:256–261.
5. **Murad MH, Coburn JA, Coto-Yglesias F, et al.** Glycemic control in non-critically ill hospitalized patients: a systematic review and meta-analysis. J Clin Endocrinol Metab 2012; 97:49–58.
6. **Schroeder JE, Liebergall M, Raz I, et al.** Benefits of a simple glycaemic protocol in an orthopaedic surgery ward: a randomized prospective study. Diabetes Metab Res Rev 2012; 28:71–75.
7. **Clement S, Braithwaite SS, Magee MF, et al; American Diabetes Association in Hospitals Writing Committee.** Management of diabetes and hyperglycemia in hospitals. Diabetes Care 2004; 27:553–591.
8. **Inzucchi SE.** Clinical practice: Management of hyperglycemia in the hospital setting. N Engl J Med 2006; 355:1903–1911.
9. **van den Berghe G, Wouters P, Weekers F, et al.** Intensive insulin therapy in the critically ill patients. N Engl J Med 2001; 345:1359–1367.
10. **van den Berghe G, Wilmer A, Hermans G, et al.** Intensive insulin therapy in the medical ICU. N Engl J Med 2006; 354:449–461.
11. **NICE-SUGAR Study Investigators; Finfer S, Chittock DR, Su SY, et al.** Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009; 360:1283–1297.
12. **Griesdale DE, de Souza RJ, van Dam RM, et al.** Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ 2009; 180:821–827.
13. **Moghissi ES, Korytkowski MT, DiNardo M, et al.** American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care 2009; 32:1119–1131.
14. **Umpierrez G, Cardona S, Pasquel F, et al.** Randomized controlled trial of intensive versus conservative glucose control in patients undergoing coronary artery bypass graft surgery: GLUCO-CABG Trial. Diabetes Care 2015; 38:1665–1672.
15. **Montori VM, Bistrian BR, McMahon MM.** Hyperglycemia in acutely ill patients. JAMA 2002; 288:2167–2169.
16. **Ramos M, Khalpey Z, Lipsitz S, et al.** Relationship of perioperative hyperglycemia and postoperative infections in patients who undergo general and vascular surgery. Ann Surg 2008; 248:585–591.
17. **American Diabetes Association.** Standards of medical care in diabetes—2010. Diabetes Care 2010; 33(suppl 1):S11–S61.
18. **Cryer PE, Axelrod L, Grossman AB, et al.** Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009; 94:709–728.
19. **Krikorian A, Ismail-Beigi F, Moghissi ES.** Comparisons of different insulin infusion protocols: a review of recent literature. Current Opin Clin Nutr Metab Care 2010; 13:198–204.
20. **Umpierrez GE, Hor T, Smiley D, et al.** Comparison of inpatient insulin regimens with detemir plus aspart versus neutral protamine hagedorn plus regular in medical patients with type 2 diabetes. J Clin Endocrinol Metab 2009; 94:564–569.
21. **Smith WD, Winterstein AG, Johns T, Rosenberg E, Sauer BC.** Causes of hyperglycemia and hypoglycemia in adult inpatients. Am J Health Syst Pharm 2005; 62:714–719.
22. **Maynard G, Lee J, Phillips G, Fink E, Renvall M.** Improved inpatient use of basal insulin, reduced hypoglycemia, and improved glycemic control: effect of structured subcutaneous insulin orders and an insulin management algorithm. J Hosp Med 2009; 4:3–15.
23. **Turchin A, Matheny ME, Shubina M, Scanlon JV, Greenwood B, Pendergrass ML.** Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. Diabetes Care 2009; 32:1153–1157.
24. **Gill GV, Woodward A, Casson IF, Weston PJ.** Cardiac arrhythmia and nocturnal hypoglycaemia in type 1 diabetes--the 'dead in bed' syndrome revisited. Diabetologia 2009; 52:42–45.
25. **Boucai L, Southern WN, Zonszein J.** Hypoglycemia-associated mortality is not drug-associated but linked to comorbidities. Am J Med 2011; 124:1028–1035.
26. **Umpierrez GE, Hellman R, Korytkowski MT, et al.** Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2012; 97:16–38.
27. **Dhatariya K, Levy N, Kilvert A, et al; Joint British Diabetes Societies.** NHS diabetes guideline for the perioperative management of the adult patient with diabetes. Diabet Med 2012; 29:420–433.
28. **Lazar HL, McDonnell M, Chipkin SR, et al; Society of Thoracic Surgeons Blood Glucose Guideline Task Force.** The Society of Thoracic Surgeons practice guideline series: blood glucose management during adult cardiac surgery. Ann Thorac Surg 2009; 87:663–669.
29. **Jacobi J, Bircher N, Krinsley J, et al.** Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. Crit Care Med 2012; 40:3251–3276.
30. **Hirsch IB.** Sliding scale insulin—time to stop sliding. JAMA 2009; 301:213–214.

31. **Dobri GA, Lansang MC.** How should we manage insulin therapy before surgery? Cleve Clin J Med 2013; 80:702–704.
32. **Umpierrez GE, Smiley D, Zisman A, et al.** Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). Diabetes Care 2007; 30:2181–2186.
33. **Bueno E, Benitez A, Rufinelli JV, et al.** Basal-bolus regimen with insulin analogs versus human insulin in medical patients with type 2 diabetes: a randomized controlled trial in Latin America. Endocr Pract 2015; 21:807–813.
34. **Umpierrez GE, Smiley D, Hermayer K, et al.** Randomized study comparing a basal-bolus with a basal plus correction insulin regimen for the hospital management of medical and surgical patients with type 2 diabetes: basal plus trial. Diabetes Care 2013; 36:2169–2174.
35. **American Diabetes Association.** Standards of medical care in diabetes-2015 abridged for primary care providers. Clin Diabetes 2015; 33:97–111.
36. **Rubin DJ, Rybin D, Doros G, McDonnell ME.** Weight-based, insulin dose-related hypoglycemia in hospitalized patients with diabetes. Diabetes Care 2011; 34:1723–1728.
37. **Umpierrez GE, Gianchandani R, Smiley D, et al.** Safety and efficacy of sitagliptin therapy for the inpatient management of general medicine and surgery patients with type 2 diabetes: a pilot, randomized, controlled study. Diabetes Care 2013; 36:3430–3435.
38. **Munt R, Hutton A.** Type 1 diabetes mellitus (T1DM) self management in hospital; is it possible? A literature review. Contemp Nurse 2012; 40:179–193.
39. **American Diabetes Association.** Diabetes care in the hospital, nursing home, and skilled nursing facility. Diabetes Care 2015; 38(suppl):S80–S85.
40. **Elia M, Ceriello A, Laube H, Sinclair AJ, Engfer M, Stratton RJ.** Enteral nutritional support and use of diabetes-specific formulas for patients with diabetes: a systematic review and meta-analysis. Diabetes Care 2005; 28:2267–2279.
41. **Pasquel FJ, Spiegelman R, McCauley M, et al.** Hyperglycemia during total parenteral nutrition: an important marker of poor outcome and mortality in hospitalized patients. Diabetes Care 2010; 33:739–741.
42. **Umpierrez GE, Spiegelman R, Zhao V, et al.** A double-blind, randomized clinical trial comparing soybean oil-based versus olive oil-based lipid emulsions in adult medical-surgical intensive care unit patients requiring parenteral nutrition. Crit Care Med 2012; 40:1792–1798.
43. **RNCOS Industry Research Solutions.** US to dominate the global insulin pump market—April 28, 2011. www.rncos.com/Press_Releases/US-to-Dominate-the-Global-Insulin-Pump-Market.htm. Accessed March 16, 2016.
44. **Lansang MC, Modic MB, Sauvey R, et al.** Approach to the adult hospitalized patient on an insulin pump. J Hosp Med 2013; 8:721–727.
45. **Tripathy PR, Lansang MC.** U-500 regular insulin use in hospitalized patients. Endocr Pract 2015; 21:54–58.
45. **Umpierrez GE, Reyes D, Smiley D, et al.** Hospital discharge algorithm based on admission HbA1c for the management of patients with type 2 diabetes. Diabetes Care 2014; 37:2934–2939.
46. **Qaseem A, Humphrey LL, Chou R, Snow V, Shekelle P; Clinical Guidelines Committee of the American College of Physicians.** Use of intensive insulin therapy for the management of glycemic control in hospitalized patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2011; 154:260–267.

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