Review

Diabetes
Advances in Diagnosis and Treatment

David M. Nathan, MD

IMPORTANCE Chronic diseases have overtaken acute diseases, such as infections, as the major cause of premature mortality worldwide. Diabetes mellitus, a chronic degenerative metabolic disease, has reached epidemic proportions in the past 30 years, with worldwide prevalence approaching 400 million people.

OBSERVATIONS AND ADVANCES The epidemic is largely secondary to an increasing sedentary lifestyle and highly prevalent overweight and obesity contributing to the development of type 2 diabetes. Clinical research efforts have developed and demonstrated effective strategies for prevention, and the annual incidence of diabetes in the United States may be decreasing for the first time in 3 decades. The long-term complications of diabetes cause severe morbidity and mortality. Here too the means of reducing the burden of microvascular and cardiovascular disease have been proved.

CONCLUSIONS AND RELEVANCE Improved glycemic control and better management of other identified risk factors for the complications of diabetes and more effective treatment of cardiovascular disease and microvascular complications have resulted in a more optimistic outlook for people with diabetes. This review focuses on recent advances in diagnosis and management and the remaining challenges in the prevention and treatment of diabetes mellitus.

JAMA. 2015;314(10):1052-1062. doi:10.1001/jama.2015.9536

Related article page 1021

CME Quiz at jamanetworkcme.com and CME Questions page 1068

Author Affiliation: Diabetes Center, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

Corresponding Author: David M. Nathan, MD, Diabetes Center, Massachusetts General Hospital, Harvard Medical School, 50 Staniford St, Ste 340, Boston, MA 02114 (dnathan@MGH.Harvard.edu).

Section Editors: Edward Livingston, MD, Deputy Editor, and Mary McGrae McDermott, MD, Senior Editor.

The diabetes epidemic of the late 20th and 21st centuries, related to a combination of social, behavioral, in utero, and genetic factors, is one of the greatest current public health challenges. Although type 1 diabetes has slowly increased in incidence,[1] it accounts for less than 5% of the US diabetes population. Type 2 diabetes makes up the vast majority of cases worldwide. Twenty-eight million people in the United States have type 2 diabetes, and more than 80 million people are considered to be at high risk of developing it, a state called *prediabetes*.[2] Worldwide, more than 350 million people are estimated to have type 2 diabetes.[3]

Diabetes, a chronic degenerative disease, results in relatively specific long-term complications affecting the eyes, kidneys, and peripheral and autonomic nervous systems,[4] accounting for more adult cases of vision loss, end-stage kidney disease, and amputations than any other disease.[5] In addition, both type 1 and type 2 diabetes increase the risk of cardiovascular disease (CVD) 2- to 5-fold.[6] In the past decade, an increased risk of some cancers, including pancreatic, liver, colorectal, endometrial, and breast, has been added to the traditional vascular complications of diabetes.[7] The economic burden of diabetes and prediabetes, estimated in the United States to total $322 billion annually,[8] results largely from the cost of complications,[9] although recently the costs of medications and monitoring have contributed an increasing proportion of total costs.

This Review focuses on the diagnostic, prevention, and intervention methods that have been developed and introduced in the past 5 to 10 years. These developments are reviewed in the context of the current epidemic of prediabetes and type 2 diabetes and the overarching need to identify these dysglycemic states and intervene as early as possible in order to maximize prevention and the beneficial effects of intervention.

Advances in Diagnosis

Advances in the Measurement of Glycemia

Although diabetes has numerous associated metabolic disturbances, diagnosis and management have historically relied on measures of circulating glucose in whole blood, plasma, or serum and, more recently, in capillary blood glucose or interstitial fluid.[10] Self-monitoring to measure ambient glucose levels in capillary samples obtained by fingerstick, although no longer a new method, revolutionized the treatment of type 1 diabetes and has contributed to the management of type 2 diabetes. The enzymatic methods on which these assays rely have not changed, but the devices have become progressively smaller, faster, and more accurate, although not all meters, including devices approved by the US Food and Drug Administration (FDA), perform at an acceptable level.[11]

Table 1. Diagnosis of Type 2 Diabetes and Prediabetes in Nonpregnant Adults[a]

	Glucose Measuring Method, mg/dL[b]		
	Fasting	Oral Glucose Tolerance Test	Hemoglobin A_{1c}
Diagnostic cut points			
Prediabetes	110-125	140-199	5.7-6.4
Diabetes	≥126	≥200	≥6.5
Evaluation of methods			
Advantage	Easy, inexpensive measurement	As a metabolic stress test, may be most sensitive	Convenient, best measure of chronic glycemia, more closely associated with risk of complications, and less biologic variability than glucose-based tests; needed for management at diabetes onset
Disadvantage	Relatively insensitive, fluctuates, is affected by stress, and requires overnight fast	Inconvenient, time-consuming, and expensive	More expensive than fasting glucose, may be less sensitive than oral glucose tolerance test, and cannot be performed in setting of alterations in red blood cell turnover and with some hemoglobinopathies[c]

[a] Based on American Diabetes Association recommendations.[18] See recommendations for target populations and frequency of screening. Owing to variability, diagnoses based on glucose levels require confirmation on a separate day; confirmation of HbA_{1c}-based diagnosis is also recommended but, in the author's opinion, is unnecessary.

[b] Plasma glucose levels. Fasting blood sample is obtained after an overnight fast of at least 8 hours; OGTT, 75-g oral glucose tolerance test with samples obtained fasting and 2 hours after glucose ingestion.

[c] The National Glycohemoglobin Standardization Program provides a detailed list of the hemoglobinopathies that may interfere with specific assays at http://www.ngsp.org.

The newest method of measuring glucose levels, continuous glucose monitoring, uses an indwelling catheter that is inserted into the subcutis by the patient and changed every 3 to 7 days.[12] Continuous glucose monitoring devices "sip" fluid from the interstitial space and measure glucose levels every 2 to 5 minutes. Interstitial levels generally reflect venous blood or capillary levels, with some differences in equilibration when glucose levels are changing rapidly after meals.[13] Each new generation of these devices has provided increasingly accurate measurements.[14] Continuous glucose monitoring has been used to manage type 1 diabetes and is an integral element in the development of the artificial pancreas. It currently has little if any proved role in type 2 diabetes.

Chronic levels of glycemia have been assessed with glycated protein assays, most often glycated hemoglobin A_{1c} (HbA_{1c}), for 30 years.[15] These assays reflect mean glucose levels integrated over the lifespan of the protein. The HbA_{1c} assays are now standardized[16] and are a reliable index of average glucose levels over the preceding 8 to 12 weeks.[17]

Advances in Diagnosis

The usual clinical presentation of type 1 diabetes, with relatively acute, severe hyperglycemia resulting in polyuria, polydipsia, weight loss, and potentially ketoacidosis, should not escape clinical notice. Diagnosis does not usually require glucose cut points. On the other hand, the more insidious onset of type 2 diabetes, with glucose levels that increase slowly and are often asymptomatic, requires diagnostic cut points to identify persons needing treatment as well as those at high risk of developing type 2 diabetes for the purpose of targeted prevention.

Historically, glucose levels measured in the fasting state or after an oral glucose tolerance test, which is a metabolic stress test, have been used to diagnose type 2 diabetes and identify persons at high risk (**Table 1**). The glucose levels chosen to diagnose diabetes are based on their association with risk of developing retinopathy.[19] More recently, HbA_{1c} levels have been recommended for diagnosis of diabetes and prediabetes.[19] The decision to use HbA_{1c} concentration was based on improvements in the precision and standardization of the assay; the recognition that chronic glycemia was at least as closely related to risk of diabetic complications as glucose levels, which fluctuate constantly; and the relative ease of obtaining samples for HbA_{1c}, which require neither timed samples nor an oral glucose tolerance test. Because the measures of acute glucose levels, either fasting or after a glucose challenge, and measures of chronic glycemia reflect different metabolic phenomena, many studies comparing their diagnostic capabilities have shown that the different tests identify somewhat different populations as having diabetes. Nevertheless, each of the tests identifies patients who are at risk of developing microvascular complications and, depending on availability and other patient factors (Table 1), either fasting, 2-hour post–oral glucose tolerance test glucose levels or HbA_{1c} levels can be used for diagnosis. The populations recommended for screening for type 2 diabetes and screening frequency are generally selected to make screening efficient and have not changed for more than a decade.[18] Factors that are associated with higher risk of type 2 diabetes include being 45 years or older; having a body mass index (calculated as weight in kilograms divided by height in meters squared) of 25 or higher; not being physically active; having a prior history of gestational diabetes; having hypertension, dyslipidemia, or cardiovascular disease; having a first-degree family member with diabetes; being African American, Latino, American Indian, Asian American, or Pacific Islander; or having tested positive for prediabetes (Table 1).[18]

Genetics and Metabolomics

Type 1 and type 2 diabetes are polygenetic. Almost 100 genes or genetic regions have been implicated in type 2 diabetes. Most of the genes identified by genome-wide association studies confer a small risk of diabetes, with the genes conveying greatest risk increasing risk by approximately 25% to 40% in the homozygous state.[20] Fewer genes have been shown to underlie type 1 diabetes; most are related to autoimmunity.[21]

The genetic risk for type 2 diabetes is largely expressed in the setting of environmental factors such as obesity and sedentary

lifestyle.[22] Because there has been no change in the human genome during the past 50 years when the diabetes epidemic has occurred, the cause of the epidemic is largely environmental.

Whether new knowledge of genetic risk factors will add to the identification of persons at high risk is unclear. Studies that have examined the role of genetic profiles in the identification of high-risk individuals have not shown a significant added benefit compared with the use of easily measured demographic and clinical factors such as age, family history of diabetes, body mass index, systolic blood pressure, and fasting glucose and lipid levels.[23] In the future, genotyping may play a useful role differentiating subtypes of diabetes with different pathophysiological mechanisms and may help to individualize the treatment of type 2 diabetes by identifying persons more likely to respond to specific treatments.[24]

Metabolomic analyses of blood have also identified profiles of amino acids that identify persons at high risk of developing diabetes.[25] The specificity and predictive value of these metabolic fingerprints and their clinical utility have not been established, but they may complement genetic markers.[26]

Advances in Prevention

Type 1 Diabetes

Clinical studies examining the potential of preventing or delaying autoimmune type 1 diabetes have focused on immune manipulation in high-risk populations. Many prevention studies have included patients with recent-onset type 1 diabetes, for example, within 6 weeks of clinical presentation when an estimated 80% to 90% of the β-cell mass has already been destroyed.[27] Rather than addressing true prevention, such studies examine whether further islet destruction can be slowed or stopped. Studies with various immune modulations have demonstrated a slowing of β-cell destruction with preservation of some insulin secretion[28-30]; however, the modest 6- to 12-month reductions in insulin requirements are of questionable clinical benefit, especially balanced against the risks of the interventions.

The only large-scale studies of type 1 diabetes prevention in moderate- to high-risk populations—defined by the presence of a family history of type 1 diabetes, autoantibodies, and reduced insulin secretion but still with normoglycemia—were the European Nicotinamide Diabetes Intervention (ENDIT) study[31] and Diabetes Prevention Trial 1 (DPT-1).[32] The ENDIT study examined nicotinamide, and DPT-1 used intermittent intravenous insulin therapy and daily low dose subcutaneous insulin or oral insulin as potential immunomodulation and to spare β-cell activity. None of these interventions reduced or stopped the development of diabetes.[31-33]

Type 2 Diabetes

The worldwide epidemic of type 2 diabetes has prompted many prevention studies. Clinical trials, including the US Diabetes Prevention Program (DPP), have demonstrated effective means of preventing or delaying diabetes onset.[34-38] Lifestyle interventions that address the risk factors of obesity and sedentary activity reduce the development of diabetes by as much as 58%.[34,36] In addition, lifestyle programs reduce CVD risk factors and the need for blood pressure and lipid-lowering medicines.[35] Metformin,[34] acarbose,[37] and thiazolidinediones[38] have also been shown to reduce the development of diabetes. Only lifestyle intervention and metformin, which is not currently labeled for prevention, have been recommended based on their risk-benefit ratio.[18] Metformin is particularly effective in persons younger than 60 years and with a body mass index of 35 or higher.[34] Numerous lifestyle translation projects have been initiated,[39] and proposed US legislation to support the National Diabetes Prevention Program has bipartisan and bicameral support.[40] For the first time in 30 years, the annual incidence rates of type 2 diabetes in the United States appear to be decreasing.[41]

Advances in Management

The management strategy for the 29 million persons in the United States with either type 1 or 2 diabetes aims at achieving long-term glycemic control, which has been shown to be safe and to reduce the risk of microvascular disease over time (**Table 2**).[42,47-50,52,56] Control of hyperglycemia has long-lasting effects that persist beyond the period of glycemic control, termed *metabolic memory*[57] or *legacy effect*.[48] In type 1 diabetes, intensive metabolic control also reduces the risk of CVD[45]; however, the role of intensive glycemic therapy on CVD in type 2 diabetes remains less certain.[58] Two clinical trials with long-term follow-up have shown a 15% to 17% reduction in CVD with intensive glycemic therapy,[48,55] whereas others have shown no benefit[52] or harm.[51] Although this Review focuses on glycemic management, treatment of hypertension, and hyperlipidemia has a greater influence on mortality than control of glycemia among those with type 2 diabetes. For both type 1 and type 2 diabetes, smoking cessation and weight management are of major importance.

Based on the Diabetes Control and Complications Trial (DCCT)[42,56] and United Kingdom Prospective Diabetes Study (UKPDS)[47,48] results and balancing long-term benefits and risks, the accepted metabolic goal for most people is an HbA_{1c} level of less than 7%.[18] Interventions to achieve this goal, commonly called intensive therapy, should be implemented as soon in the course of diabetes as possible. Patients who have projected lifespans that are too brief (eg, <5-10 years) to benefit from intensive therapy or who are at heightened risk from the hypoglycemic risks of the therapy, such as injury in patients engaged in potentially hazardous occupations, cases where risks outweigh benefits, should have their metabolic goals relaxed.[18] The glucose levels necessary to achieve specific HbA_{1c} levels have recently been determined based on empirical data (**Table 3**).[59]

Type 1 Diabetes

The modern-day goal of intensive therapy is to provide as much physiological replacement of insulin as possible, aiming to maintain HbA_{1c} levels of less than 7%. Insulin formulations and the means of administering them have evolved substantially since insulin's introduction in 1922. Insulin analogs have been developed to provide varying onsets and durations of biological activity (**Figure 1**).[60] Multidose insulin regimens, with at least 3 daily injections, are facilitated with insulin pens and pumps. Basal insulin delivery and prandial boluses, each contributing approximately 50% of total daily insulin, need to be coordinated (**Figure 2**). Owing to its complexity and reliance on devices, clinical care for most patients with type 1 diabetes is ideally provided by specialists (endocrinologists and diabetologists) with a team approach including nurse educators, dietitians, ophthalmologists, and other clinicians, such as podiatrists, cardiologists, nephrologists, and neurologists, as needed.

Table 2. Risk Reductions in Diabetes Complications With Intensive Therapy Compared With Conventional Therapy in Type 1 Diabetes (DCCT and DCCT/EDIC) and in Type 2 Diabetes (All Other Studies)

Source	Mean Duration of Follow-up, y	Difference in Mean HbA_{1c} Between Intensive vs Conventional Therapy, %[a] (Intensive vs Conventional)	Clinical Outcomes	Hazard Ratio Intensive vs Conventional Therapy (95% CI)[a]
Type 1 diabetes				
DCCT,[42] 1993	6.5	2.0 (~7 vs 9)	Retinopathy development	0.24 (0.15-0.38)
			Retinopathy progression	0.46 (0.34-0.61)
			Microalbuminuria[b]	
			Neuropathy[b]	0.43 (0.27-0.71)
EDIC,[43] 2015	23	0.1 (NS) (~7.9 vs 8.0)[c]	Ocular surgery[d]	0.63 (0.45-0.88)
EDIC,[44] 2014	22	0.1 (NS)[c]	eGFR <60 mL/min/1.73 m^2	0.50 (0.31-0.82)
EDIC,[45] 2005	17	0.1 (NS)[c]	MACE	0.43 (0.21-0.88)
EDIC,[46] 2015	27	0.1 (NS)[c]	Mortality	0.67 (0.46-0.99)
Type 2 diabetes				
UKPDS,[47]1998	10	0.9 (7 vs 7.9)	Advanced microvascular[e]	0.75 (0.60-0.93)
			Myocardial infarction	0.84 (0.71-1.0)
UKPDS-follow-up,[48] 2008	20	<0.1 (NS) (~8.0)[c]	Advanced microvascular[e]	0.76 (0.64-0.89)
			Myocardial infarction	0.85 (0.74-0.97)
Kumamoto et al,[49] 1995	6	2.3 (7.1 vs 9.4)	Retinopathy	0.31 (0.13-0.76)
			Microalbuminuria	0.30 (0.11-0.86)
ACCORD,[50] 2010	3.5	1.1 (6.4 vs 7.5)	Microalbuminuria	0.81 (0.70-0.94)
ACCORD,[51]2008			MACE	0.90 (0.78-1.04)
			Mortality	1.22 (1.01-1.46)
ADVANCE,[52] 2008	5.0	0.67 (~6.5 vs 7.3)	MACE	0.94 (0.84-1.06)
			Advanced microvascular[e]	0.86 (0.77-0.97)
ADVANCE-follow-up,[53] 2014	9.9	0.08 (NS) (~7.2 vs 7.4)[c]	MACE	1.0 (0.92-1.08)
VADT,[54] 2009	5.6	1.5 (6.9 vs 8.4)	Major CVD[f]	0.88 (0.74-1.05)
VADT-follow-up,[55] 2015	9.8	0.2-0.3[c]	Major CVD	0.83 (0.70-0.99)

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes Study; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications study; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; MACE, major atherosclerotic cardiovascular events, including myocardial infarctions and stroke and cardiovascular deaths; NS, nonsignificant; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Administration Diabetes Trial.

[a] Intensive therapy aims to achieve near-normal glycemia.

[b] Microalbuminuria and neuropathy in secondary intervention cohort.

[c] Separation in HbA_{1c} levels achieved during original trial dissipated during observational follow-up. Persistent effects of original separation of glycemia on long-term complications consistent with metabolic memory effect.

[d] Diabetes-related ocular surgery included cataract extraction; vitrectomy or retinal detachment surgery; glaucoma-related surgery (including laser treatment, filtering surgery, cyclocryotherapy, and other operative procedures to lower intraocular pressure); cornea-related or lens-related surgery; or enucleation.

[e] *Advanced microvascular outcomes* defined in UKPDS as retinopathy requiring photocoagulation, vitreous hemorrhage, or fatal or nonfatal renal failure and in ADVANCE as new or worsening nephropathy (ie, *development of macroalbuminuria*, defined as a urinary albumin:creatinine ratio of more than 300 µg of albumin per milligram of creatinine [33.9 mg/mmol], or doubling of the serum creatinine level to at least 200 µmol/L [2.26 mg/dL], need for renal-replacement therapy, or death due to renal disease) or retinopathy (ie, development of proliferative retinopathy, macular edema or diabetes-related blindness, or the use of retinal photocoagulation therapy).

[f] Major CVD includes MACE plus new or worsening congestive heart failure or amputation.

Table 3. Levels of Mean Glucose Associated With Specified Hemoglobin A_{1c} Levels[a]

	Mean (95% CI), mg/dL			
	Fasting Glucose	Before Meal[b]	After Meal	Before Bed
HbA_{1c}, %				
5.5-6.49	122 (117-127)	118 (115-121)	144 (139-148)	136 (131-141)
6.5-6.99	142 (135-150)	139 (134-144)	164 (159-169)	153 (145-161)
7.0-7.49	152 (143-162)	152 (147-157)	176 (170-183)	177 (166-188)
7.5-7.99	167 (157-177)	155 (148-161)	189 (180-197)	175 (163-188)
8.0-8.5	178 (164-192)	179 (167-191)	206 (195-217)	222 (197-248)

Abbreviation: HbA1c, hemoglobin A_{1c}.

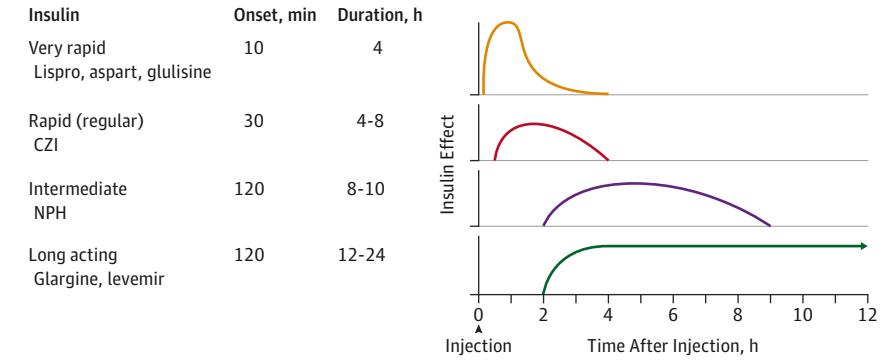
[a] Results were derived from 378 (237 with type 1 and 141 with type 2 diabetes) members of the study for which more than 25 000 fingerstick tests were performed in the 3 months prior to HbA_{1c} measurements. Averages are for combined type 1 and type 2 diabetic patients. Adapted from Wei et al.[59]

[b] Includes fasting values.

Basal Insulin

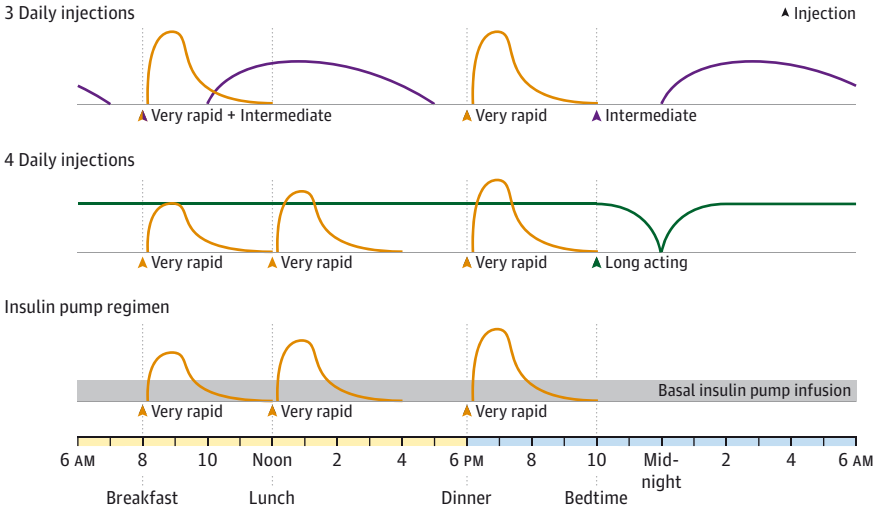
Basal insulin is designed to provide enough insulin to maintain near-normal glucose levels overnight and when patients are not eating. It can be provided with intermediate-acting neutral protamine Hagedorn (NPH) insulin, which patients usually take in the morning and at bedtime, or provided with very long-acting insu-

Figure 1. Insulin Activity Profiles



Inhaled insulin (profile not shown) is most similar to subcutaneous very rapid-acting insulin in onset and duration. CZI indicates crystalline zinc insulin; NPH, neutral protamine Hagedorn.

Figure 2. Three Examples of Insulin Regimens for Type 1 Diabetes



The preprandial boluses can be administered with conventional injections or by pump. The injection of intermediate and rapid-acting insulins in the morning can be administered separately or mixed in a single syringe. The basal insulin can be administered as a single injection of a long-acting insulin, usually injected at bedtime, but can be given in morning, or as a basal rate of very-rapid acting insulin by pump infusion, as indicated.

lins such as glargine or levemir, the latter of which often requires twice daily administration.[61,62] Basal insulin doses are usually determined based on fasting-fingerstick glucose levels. Meta-analysis of clinical trials investigating type 1 diabetes have shown that glargine insulin is associated with minimally lower HbA_{1c} levels (<0.1 percentage point) than NPH with somewhat lower risk of nocturnal and severe hypoglycemia, defined as episodes needing assistance.[63] Whether these modest advantages are worth the substantially greater costs of the long-acting analogs is not clear. Newer long-acting insulins such as degludec,[64] recently submitted for approval, and the recently approved U-300 glargine have been created to provide even longer duration and more stable profiles, and more concentrated insulin to facilitate treatment with higher doses, respectively. The available data support noninferiority[64] with regard to glycemic control, but no obvious advantages. The high costs of these new basal insulins will remain a substantial barrier to their use.

Insulin pumps administer rapid (regular) or, preferably, very rapid-acting insulin analogs continuously to provide basal insulin for type 1 diabetes (Figure 2). One of the putative advantages of insulin pump therapy is the consistency of delivery, with the depth and location of insulin identical for each catheter, usually changed every 3 days. In addition, basal rate delivery can be adjusted as often as needed to match insulin needs during the day; however, insulin pumps carry the risk of rapid deterioration of metabolic control, including ketoacidosis, if the continuous infusion is intentionally or accidentally interrupted for more than 4 to 6 hours.

Preprandial Insulin

Preprandial boluses, administered with injections or pump, are directed at limiting the glucose excursions that otherwise occur after meals and snacks (Figure 2). Doses are adjusted based on meal size and composition, anticipated activity levels, and ambient glucose levels, the latter measured with fingerstick capillary tests or with continuous glucose monitoring. Self-monitoring usually needs to be performed before meals and bedtime, and often more frequently, in order to guide the choice of bolus doses.

The timing of the preprandial bolus is designed so the peak insulin effect matches the absorption of ingested carbohydrate and the resultant glucose peaks that occur. Rapid-acting (regular) insulin, with an onset of action in 30 to 45 minutes and a peak effect approximately 120 minutes after injection, should be given 30

to 45 minutes before the meal. The newer, very rapid-acting analogs, all of which have a substantially more rapid onset and shorter duration of activity than regular insulin[60] (Figure 1), can be given at the time of the meal, and are therefore more convenient. Meta-analyses of the clinical trials with regular compared with very rapid-acting analogs reveal inconsistent results. However, in general the very rapid-acting insulin analogs are associated with only a marginally lower HbA_{1c} (by ~ 0.09%), and 20% and 49% lower risks of severe and nocturnal hypoglycemia, respectively.[65] Putative benefits with regard to quality of life and patient satisfaction have been inconsistent across studies.

Overall, insulin pumps may provide marginally lower HbA_{1c} levels than multiple daily injection regimens[66] and improved quality of life.[66,67] However, their modest benefits with regard to flexibility of dosing pale next to the importance of patient preference. Because the patients need to live with their insulin delivery 24 hours a day, their enthusiasm for either a multiple injection regimen vs pump therapy must be considered.

The newest mode of delivering preprandial boluses is inhaled insulin. The first inhaled insulin and inhaler were approved and brought to market in 2006.[68] They were removed from the US market within about a year because of poor sales. A new inhaled insulin and inhaler were approved in 2014.[69] The inhaled insulins have a profile that is similar to the very rapid-acting analogs (Figure 1). Doses are administered in 4- to 8-unit increments. They have been shown to achieve noninferior HbA_{1c} results as injected regimens but have not achieved levels less than 7%, even in short-term studies.[68,69] Periodic testing of pulmonary function is required.

The clinical role of continuous glucose monitoring, which provides continuous information regarding ambient glucose levels and has alarms that can warn patients of current or impending hypoglycemia, for example, during sleep, is under active investigation. The clinical trials, in the setting of insulin pump or multiple daily injection therapy, have demonstrated that it works best when used consistently.[70] The major hope that continuous glucose monitoring would reduce the threat of hypoglycemia and improve quality of life has not been demonstrated consistently.[70-72]

Newer insulin pumps feature integrated continuous glucose monitoring, with the results telemetered to the pump and shown on the pump display. It is not clear whether this feature improves glycemic management. Patients need to be reminded that continuous glucose monitoring provides continuous feedback but does not automatically adjust their insulin doses. Intensive therapy in type 1 diabetes still relies on the patient integrating a large number of factors in order to decide how much insulin to administer to achieve desirable hour-to-hour and chronic levels of glycemia safely.

Although the role of continuous glucose monitoring in the routine management of type 1 diabetes is unclear, it is a critical element in the development of the artificial or bionic pancreas. The first FDA-approved step in the development of automated delivery is an automatic shut-off feature that suspends insulin pump delivery when glucose levels fall below a stipulated level.[73] True artificial pancreases use computer algorithms and continuous monitoring results to determine insulin and, in some devices, glucagon delivery with pumps.[74-76] Early studies conducted in inpatient clinical research centers[74] have advanced to outpatient studies that have shown improved glycemia with reduced frequency of hypoglycemia and without the burden of self-care usually necessary to achieve goal glycemia.[75,76] Further development of these devices will be the next transformative step in the treatment of type 1 diabetes.

Whole-organ pancreas or islet transplants, which can restore normoglycemia, at least transiently, require surgical or radiologic interventions, respectively, and immunosuppressive therapy. These requirements, compounded by the limited availability of donor pancreases, currently limit their potential application. Pancreas transplants, usually performed at the time of kidney transplant, result in a "glycemic cure" of type 1 diabetes in approximately 90% of recipients with 72% still not requiring insulin and with normal HbA_{1c} levels 5 years after the transplant.[77] Islet transplants, which remain experimental, result in glycemic cure in 66% at 1 year, but more than 50% of recipients require exogenous insulin within 3 years.[78]

Type 2 Diabetes

In the past 20 years, the number of classes of glucose-lowering medicines has more than tripled, with 1 to 5 drugs in each class. The increased complexity of type 2 diabetes care has prompted the development of guidelines and algorithms to help primary care clinicians.[79-81] Some of the guidelines have included relatively prescriptive recommendations and incorporated cost as an important element in decision making,[79] whereas others have been less proscriptive, providing the characteristics of the numerous agents and leaving the choice of therapy up to the clinician.[80,81] Although substantial emphasis has been placed recently on "individualization" of therapy, there is a paucity of data available to guide the choice of drugs. The vast majority of patients with type 2 diabetes are treated as if they have the same underlying pathophysiology, despite the increasing appreciation that type 2 diabetes is highly heterogeneous, changes over time, and has inconsistent patient responses to different medications.[82] The ongoing Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) study is the first comprehensive comparative effectiveness study to examine the major classes of glucose-lowering medications, when added to metformin, in a head-to-head comparison.[83] Until GRADE's results are available, clinicians must make best-guess choices based on an inadequate evidence base.

Although care for type 2 diabetes can be as complex as that for type 1 diabetes and also requires a team approach, the vast majority of clinical care for type 2 diabetes is provided by nonspecialists, in part because the sheer number of patients cannot be accommodated by the small population of diabetes experts. Referral to a specialist should be considered when the complexity of care exceeds the capacity of the primary care setting. This often occurs when teaching and supervising insulin therapy is required or when complications, such as kidney or heart disease, further complicate management.

The desire to maintain HbA_{1c} levels that are less than 7% in many patients and the progressive metabolic dysfunction of type 2 diabetes predictably result in the need for increasingly complex medication regimens over time. A lifestyle intervention directed at weight loss and increased physical activity, similar to the one used successfully in the Diabetes Prevention Program,[34] has been shown to ameliorate hyperglycemia and the need for medications in established type 2 diabetes.[84]

The medications most commonly used to treat type 2 diabetes are shown in **Table 4**. All of the medicines in use have advantages and disadvantages that need to be considered within and between

Table 4. Medicines Used Most Commonly to Treat Type 2 Diabetes[a]

Drug Classes and Medicines in Class Available in United States	Usual Absolute HbA_{1c} Lowering, %	Major Adverse Effects	Adverse Effects	Added Benefits	Comments	Cost for 30 Days (Typical Dose, as Indicated), US $[b]
Metformin[c]	~1.0-1.5	Lactic acidosis (<3/100 000)	Soft bowel movement, diarrhea	No hypoglycemia, 1-2 kg weight loss	Unsafe with GFR<30 mL/min because of risk of lactic acidosis	87 (2000 mg/d)[d]
Basal insulin	>1.5	Hypoglycemia	Weight gain	Most potent	1Vial ≈ 35U/d	
NPH				Can be mixed with bolus insulins	2 Daily injections may be necessary	132 Per vial[d]
Glargine				Once daily	Cannot be mixed with bolus insulins	298 Per vial
Levemir					2 Daily injections may be necessary	298 Per vial
Bolus insulin	>1.5	Hypoglycemia	Weight gain		Usually combined with basal insulin	
Regular (CZI)					Administer 30-45 min before meal	132 Per vial[d]
Very-rapid acting (lispro, aspart, glulisine)				Timing more convenient than regular	Administer immediately before meal	243 For lispro per vial
Sulfonylurea (glyburide, glipizide, glimepiride)[c,e]	~1.0-1.5	Hypoglycemia	Weight gain		Prefer shorter-duration agents (eg, glimepiride of glipizide) with lower risk of hypoglycemia	53 For glimepiride (2 mg/d) 46 for glipizide (10 mg 2/d)[d]
Meglitinides (repaglinide, nateglinide)[c,e]	~1.0	Hypoglycemia	Weight gain	Repaglinide safe in patients with renal failure	Similar mechanism of action as sulfonylureas	61 For repaglinide (1 mg 3/d)
Thiazolidinedione (rosiglitazone, pioglitazone)[c,e]	~1.0		Fluid retention, heart failure, bone loss		Concerns regarding risk of CVD and bladder cancer have been investigated	322 For brand pioglitazone (30 mg per d)
α-Glucosidase inhibitors (acarbose, miglitol)[c]	~0.8		Flatulence, diarrhea		Most effective with high-carbohydrate diets, but not well tolerated by many patients	88 For acarbose (three 50-mg/d tablets)
GLP-1 receptor agonists (exenatide, liraglutide, dulaglutide, albiglutide)	~1.0		Nausea, vomiting, diarrhea	Weight loss (~2-3 kg)	Injected 2/d, daily, or potentially weekly, depending on medicine; no CVD benefit shown	769 For liraglutide (1.8 mg/d)
DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)[c]	~0.6-0.8	Increased risk of CHF with saxagliptin and perhaps with alogliptin	May increase frequency of upper respiratory infections	Weight neutral	Sitagliptin, saxagliptin and alogliptin require adjustment for reduced renal function. No CVD benefit shown.	397 For sitagliptin (100 mg/d)
SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)	~0.6-0.8	May increase risk of DKA if used (off-label in type 1 or in type 2)	Genitourinary yeast and urinary tract infections	2-3 mm Hg decrease in BP		412 For dapagliflozin (10 mg/d)

Abbreviations: BP, blood pressure; CHF, congestive heart failure; CVD, cardiovascular disease; CZI, crystaline zinc insulin; DKA, diabetic ketoacidosis; DPP, dipetidyl peptidase; GFR, glomerular filtration rate; GLP, glucagonlike peptide; HbA_{1c}, hemoglobin A_{1c}; NPH, neutral protamine Hagedorn; SGLT, sodium-glucose transport protein.

[a] In general, although there are slight differences in glycemia-lowering effectiveness among the members of the class, they are more similar than not. The adverse effect profiles are also similar within classes. The major distinction among individual drugs within classes are frequency of administration and need to adjust based on renal impairment.

[b] Typical wholesale cost for average or usual dose, as indicated, every 30 days.

[c] Available as combination pill with metformin.

[d] Metformin and sulfonylureas are available for $4 a month, and NPH and regular for approximately $25 per vial at discount store pharmacies.

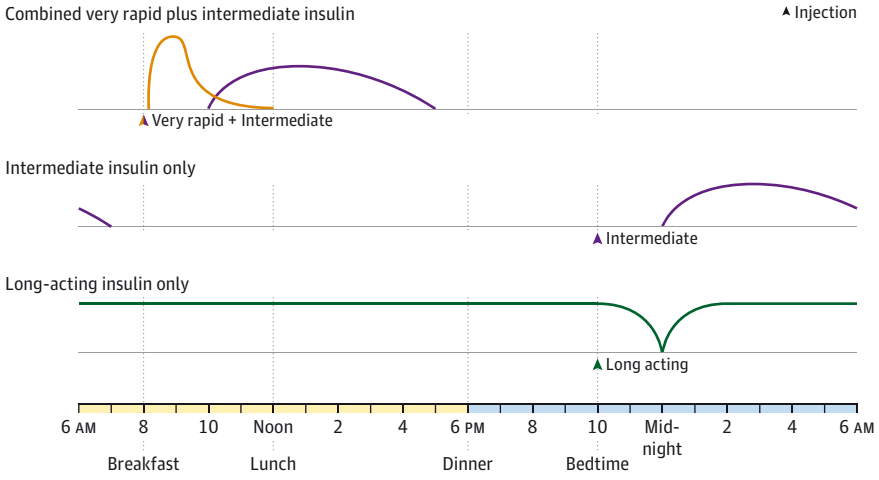
[e] Available as generic in the United States.

medicines. Regardless of medication chosen, there is good support for early and aggressive treatment, aimed at improving glycemia before β-cell function wanes further.[85] Aggressive therapy, most often with insulin, has been shown to improve insulin secretion and can result in a respite from the need for medicinal treatment for several years.[86]

The first medicine used is usually metformin. Based on its efficacy in lowering glycemia, long history of use, demonstrated safety and tolerability, and other characteristics including the absence of hypoglycemia, associated weight loss, and low cost, metformin is the consensus choice as the first medicine that should be used to treat type 2 diabetes.[18,79-81] Although most experts agree with this choice, there is, in fact, little compelling direct evidence that supports metformin as the first choice compared with other available medicines. In China, for example, the α-glucosidase inhibitors, which are particularly effective among patients who consume high-carbohydrate diets, are used commonly as the first choice for treatment.[87] Starting metformin at or near the time of diagnosis, contemporaneously with lifestyle intervention aimed at weight loss, is recommended.[79-81] Metformin is usually continued through the treatment course of type 2 diabetes, assuming that contraindications or intolerance does not develop.

The choice of a second medication to add to metformin, which is often required to maintain HbA_{1c} levels at target, is more uncer-

Figure 3. Three Examples of Single Injection Regimens for Type 2 Diabetes



tain. Few comparative effectiveness studies have been performed. Those that have been completed are relatively short-term, usually 6 to 12 months, which is inadequate for drugs that are usually taken for many years, if not decades. Moreover, clinical studies of more recently developed medications have often been performed in study cohorts with recent-onset disease and lower starting HbA_{1c} levels than the studies of older medications. Thus, a direct comparison of older and newer studies and the relative effectiveness of medications to lower glycemia is difficult. Finally, the FDA requires only a modest reduction in HbA_{1c} levels (≥0.5%) for new drug approval, rather than a demonstration of reduced risk of complications (which has been shown specifically only for insulin and sulfonylureas and, arguably, for metformin).[42,47,49] This relatively low bar for demonstrating glucose-lowering efficacy has facilitated the development and approval of numerous new, relatively weak glucose-lowering classes and drugs, some of which have had safety issues discovered during their widespread use. The FDA has mandated postmarketing studies of new diabetes drugs to evaluate their cardiovascular safety.

In the setting of the inadequate evidence base noted above, clinicians still need to choose the second agent to be added to lifestyle interventions and metformin. The choice should be based on the ability to lower HbA_{1c} to less than 7%, the current goal for treating diabetes. The demonstrated longevity of the drug's glucose-lowering effect, safety, adverse effects, tolerability, and patient acceptance are other important considerations. Finally, the relative cost of these medications needs to be considered, especially in the middle- and low-income countries that are increasingly bearing the human and economic burden of the diabetes epidemic. All of the glucose-lowering medications have advantages and disadvantages. Their value added and value subtracted are delineated in Table 4.

The 2 oldest medications used to treat type 2 diabetes are insulin and the sulfonylureas. Most of the long-term data regarding the beneficial effects of glycemic control on complications have been generated with these two classes of drugs[47,49] and they are acknowledged to be among the most powerful classes of glucose-lowering medications (Table 4). Insulin is often reserved as the drug of last resort; however, owing to its ability to control all levels of glycemia predictably, its ability to induce remissions[86] and its long track-record, insulin should be considered earlier in the treatment course of type 2 diabetes.[80] Although the risk of severe hypoglycemia with insulin needs to be considered, the rates of such episodes are far lower in type 2 diabetes than in type 1 diabetes. Simple, single, daily injection regimens (**Figure 3**) often suffice and should be adequate to achieve goal glycemia in many patients, especially early in their clinical course. The other, newer medication classes follow.

Thiazolidinediones

The thiazolidinediones or TZDs activate the nuclear superfamily of peroxisome proliferator-activated receptors (predominantly gamma).[88] They were introduced first with troglitazone which was withdrawn owing to relatively rare (≈ 1/20 000 patients), but severe, liver failure. Although the next 2 TZDs, rosiglitazone and pioglitazone, were not associated with liver problems, rosiglitazone was associated with an increase in CVD risk[89] and pioglitazone with increased bladder cancer risk,[90] although a recent analysis suggests that the risk is unlikely.[91] The concern regarding the putative increased risks of the 2 agents, despite evidence that may belie those risks,[92,93] has led to a substantial reduction in their use, especially rosiglitazone. The TZDs' shared and uncontested adverse effects, including fluid retention, congestive heart failure, and bone loss, also limit their use.

Glucagonlike Peptide–Based Therapy

The discovery of the potentially beneficial effects of the naturally occurring gut peptide glucagonlike peptide 1 (GLP-1), including glucose-dependent insulin secretion, glucagon suppression, and slowed gastric emptying,[94] resulted in substantial efforts to develop analogs that would resist rapid in vivo degradation by dipeptidyl peptidase 4. The available injectable GLP-1 receptor agonists lower HbA_{1c} levels by approximately 1% when added to metformin.[94] The value-added of the GLP-1 agonists includes an absence of hypoglycemia and weight loss of 2 to 3 kg vs a 2 to 3 kg weight gain with insulin.[95] Balanced against these benefits is the need for injections, the limited period of clinical studies, a high rate of nausea, vom-

iting, and diarrhea, especially during initial treatment, and their cost (Table 4). Some fraction of the weight loss is attributable to the adverse gastrointestinal tract effects. Determining which patients would have a desirable response to GLP agonist therapy, with weight loss and acceptable control of glycemia, and which would have inadequate HbA_{1c} levels and gastrointestinal symptoms is not currently possible. Concerns regarding an increased risk of pancreatitis and pancreas cancer have been raised, although compelling evidence remains elusive.[96,97]

Dipeptidyl Peptidase 4 Inhibitors

The inhibition of dipeptidyl peptidase 4 (DPP-4) increases endogenous GLP-1 levels, although not to the levels achieved with GLP-1 agonist injections. They also reduce glucagon and increase gastric inhibitory polypeptide levels, but only lower HbA_{1c} levels by 0.6% to 0.8%.[98] Despite relatively modest glycemia-lowering and high costs, DPP-4 inhibitors have become some of the most popular agents in use, perhaps because they are weight neutral, not associated with hypoglycemia or other clinically worrisome adverse effects, and require titration only for reduced renal function (sitagliptin, saxagliptin, and alogliptin, but not linagliptin). None of the DPP-4 inhibitors have been shown to increase CVD, other than an increased risk of hospitalized congestive heart failure with saxagliptin.[99] No benefit with regard to CVD has been demonstrated.[99,100]

Sodium-Glucose Transport Protein 2

Sodium-glucose transport protein 2 (SGLT-2) inhibitors are the newest approved class of glucose-lowering drugs. These drugs increase glycosuria by blocking glucose reabsorption in the proximal renal tubule.[101] Their glucose-lowering effect is limited by the amount of glucose delivered to the proximal tubule and the extent of inhibition of glucose reabsorption. Predictably, they are relatively weak, lowering HbA_{1c} levels by 0.6% to 0.8%.[101] The SGLT-2 inhibitors do not cause hypoglycemia, are generally weight neutral, and may have the benefit of a small reduction in blood pressure. Although they apparently do not cause enough of an osmotic diuresis to result in overt dehydration, the SGLT-2 inhibitors are associated with a 2-fold increase in mycotic genitourinary infections and urinary tract infections. They also may predispose patients with type 2 diabetes and with off-label use in type 1 diabetes to develop ketoacidosis.[102]

Conclusions

Although the epidemic of type 2 diabetes has increased the societal burden and costs of diabetes and its care, the outlook for the individual with prediabetes or diabetes has improved. Programs that focus on ameliorating the major environmental risk factors underlying the current type 2 diabetes epidemic have been developed but need to be implemented more widely. For patients with type 1 diabetes and the many patients who still develop type 2 diabetes, risk factor reduction is increasingly widespread.[103] Rates of renal disease and CVD in the diabetic population have been reduced substantially in the past decade.[104]

The expectations for a long and healthy lifespan for the individual who develops diabetes have never been higher. From a societal perspective, the ongoing epidemic threatens to swamp these individual improvements. The major challenges from the individual and societal perspective are to make primary prevention and secondary intervention as effective, widely available, and affordable as possible.

ARTICLE INFORMATION

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

REFERENCES

1. Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltész G; EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20. *Lancet*. 2009;373(9680):2027-2033.

2. Centers for Disease Control and Prevention. National diabetes statistics report, 2014. http://www.cdc.gov/diabetes/data/statistics/2014StatisticsReport.html. Accessed January 5, 2015.

3. International Diabetes Federation. *IDF Diabetes Atlas*. 6th ed. Brussels, Belgium: International Diabetes Federation; 2013.

4. Nathan DM. Long-term complications of diabetes mellitus. *N Engl J Med*. 1993;328(23):1676-1685.

5. *National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States, 2011*. Atlanta, GA: Dept of Health and Human Services, Centers for Control and Prevention; 2011.

6. Preis SR, Hwang SJ, Coady S, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. *Circulation*. 2009;119(13):1728-1735.

7. Harding JL, Shaw JE, Peeters A, Cartensen B, Magliano DJ. Cancer risk among people with type 1 and type 2 diabetes. *Diabetes Care*. 2015;38(2):264-270.

8. Dall TM, Yang W, Halder P, et al. The economic burden of elevated blood glucose levels in 2012. *Diabetes Care*. 2014;37(12):3172-3179.

9. American Diabetes Association. Economic costs of diabetes in the US in 2012. *Diabetes Care*. 2013;36(4):1033-1046.

10. Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan DM, Peterson CM. Technical review on tests of metabolic status to monitor diabetes mellitus. *Diabetes Care*. 1995;18:896-909.

11. Klonoff DC, Prahalad P. Performance of cleared blood glucose monitors. *J Diab Sci Technol*. 2015;9(4):895-910.

12. Lodwig V, Kulzer B, Schnell O, Heinemann L. Current trends in continuous glucose monitoring. *J Diabetes Sci Technol*. 2014;8(2):390-396.

13. Basu A, Dube S, Veettil S, et al. Time lag of glucose from intravascular to interstitial compartment in type 1 diabetes. *J Diabetes Sci Technol*. 2015;9(1):63-68.

14. Damiano ER, McKeon K, El-Khatib FH, Zheng H, Nathan DM, Russell SJ. A comparative effectiveness analysis of three continuous glucose monitors. *J Diabetes Sci Technol*. 2014;8(4):699-708.

15. Nathan DM, Singer DE, Hurxthal K, Goodson JD. The clinical information value of the glycosylated hemoglobin assay. *N Engl J Med*. 1984;310(6):341-346.

16. Little RR, Rohlfing CL, Sacks DB; National Glycohemoglobin Standardization Program (NGSP) Steering Committee. Status of hemoglobin A_{1c} measurement and goals for improvement. *Clin Chem*. 2011;57(2):205-214.

17. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ; A_{1c}-Derived Average Glucose Study Group. Translating the A_{1C} assay into estimated average glucose values. *Diabetes Care*. 2008;31(8):1473-1478.

18. American Diabetes Association. Standards of medical care in diabetes—2015. *Diabetes Care*. 2015;38(suppl 1):S1-S93.

19. Nathan DM, Balkau B, Bonora E, et al; International Expert Committee. International Expert Committee report on the role of the A_{1C} assay in the diagnosis of diabetes. *Diabetes Care*. 2009;32(7):1327-1334.

20. Bonnefond A, Froguel P. Rare and common genetic events in type 2 diabetes. *Cell Metab*. 2015; 21(3):357-368.

21. Barrett JC, Clayton DG, Concannon P, et al; Type 1 Diabetes Genetics Consortium. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. *Nat Genet*. 2009;41(6):703-707.

22. Hivert MF, Jablonski KA, Perreault L, et al; DIAGRAM Consortium; Diabetes Prevention Program Research Group. Updated genetic score based on 34 confirmed type 2 diabetes Loci is associated with diabetes incidence and regression to normoglycemia in the diabetes prevention program. *Diabetes*. 2011;60(4):1340-1348.

23. Meigs JB, Shrader P, Sullivan LM, et al. Genotype score in addition to common risk factors for prediction of type 2 diabetes. *N Engl J Med*. 2008;359(21):2208-2219.

24. Segrè AV, Wei N. Altshuler D, Florez JC; DIAGRAM Consortium; MAGIC Investigators. Pathways targeted by anti-diabetes drugs are enriched for multiple genes associated with type 2 diabetes risk. *Diabetes*. 2015;64:1470-1483.

25. Wang TJ, Larson MG, Vasan RS, et al. Metabolite profiles and the risk of developing diabetes. *Nat Med*. 2011;17(4):448-453.

26. Walford GA, Porneala BC, Dauriz M, et al. Metabolite traits and genetic risk provide complementary information for the prediction of future type 2 diabetes. *Diabetes Care*. 2014;37(9): 2508-2514.

27. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. *Lancet*. 2014;383(9911):69-82.

28. Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. *Nature*. 2010;464(7293):1293-1300.

29. Hagopian W, Ferry RJ Jr, Sherry N, et al; Protégé Trial Investigators. Teplizumab preserves C-peptide in recent-onset type 1 diabetes. *Diabetes*. 2013;62(11):3901-3908.

30. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, et al; Type 1 Diabetes TrialNet Anti-CD20 Study Group. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. *N Engl J Med*. 2009;361(22):2143-2152.

31. Gale EA, Bingley PJ, Emmett CL, Collier T. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. *Lancet*. 2004;363(9413):925-931.

32. Diabetes Prevention Trial—Type 1 Diabetes Study Group. Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med*. 2002;346(22):1685-1691.

33. Skyler JS, Krischer JP, Wolfsdorf J, et al. Effects of oral insulin in relatives of patients with type 1 diabetes: the Diabetes Prevention Trial—Type 1. *Diabetes Care*. 2005;28(5):1068-1076.

34. Knowler WC, Barrett-Connor E, Fowler SE, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403.

35. Knowler WC, Fowler SE, Hamman RF, et al; Diabetes Prevention Program Research Group. 10-Year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009;374(9702):1677-1686.

36. Tuomilehto J, Lindström J, Eriksson JG, et al; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344(18):1343-1350.

37. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus. *Lancet*. 2002;359(9323):2072-2077.

38. Gerstein HC, Yusuf S, Bosch J, et al; DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet*. 2006;368(9541):1096-1105.

39. Whittemore R. A systematic review of the translational research on the Diabetes Prevention Program. *Transl Behav Med*. 2011;1(3):480-491.

40. Medicare Diabetes Prevention Act of 2015. S 1131/HR 2102. https://www.govtrack.us/congress/bills/114/s1131. Accessed August 14, 2015.

41. Geiss LS, Wang J, Cheng YJ, et al. Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980-2012. *JAMA*. 2014;312(12):1218-1226.

42. Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):978-986.

43. Aiello LP, Sun W, Das A, et al; DCCT/EDIC Research Group. Intensive diabetes therapy and ocular surgery in type 1 diabetes. *N Engl J Med*. 2015;372(18):1722-1733.

44. DCCT/EDIC Research Group. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med*. 2011;365(25):2336-2366.

45. Nathan DM, Cleary PA, Backlund J-YC, et al. Intensive diabetes treatment and cardiovascular disease in type 1 diabetes mellitus. *N Engl J Med*. 2005;353:2643-2653.

46. Orchard TJ, Nathan DM, Zinman B, et al; Writing Group for the DCCT/EDIC Research Group. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. *JAMA*. 2015;313(1):45-53.

47. 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(9131):837-853.

48. 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 (15):1577-1589.

49. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract*. 1995;28(2):103-117.

50. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomized trial. *Lancet*. 2010;376(9739):419-430.

51. Gerstein HC, Miller ME, Byington RP, et al; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24): 2545-2559.

52. Patel A, MacMahon S, Chalmers J, et al; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24): 2560-2572.

53. Zoungas S, Chalmers J, Neal B, et al; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med*. 2014;371(15):1392-1406.

54. 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(2):129-139.

55. 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(23):2197-2206.

56. Nathan DM, Bayless M, Cleary P, et al; DCCT/EDIC Research Group. Diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years. *Diabetes*. 2013;62(12):3976-3986.

57. Lachin JM, Genuth S, Cleary P, Davis MD, Nathan DM; The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med*. 2000;342(6):381-389.

58. Skyler JS, Bergenstal R, Bonow RO, et al; American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events. *Diabetes Care*. 2009;32(1):187-192.

59. Wei N, Zheng H, Nathan DM. Empirically establishing blood glucose targets to achieve HbA_{1c} goals. *Diabetes Care*. 2014;37(4):1048-1051.

60. Hirsch IB. Insulin analogues. *N Engl J Med*. 2005; 352(2):174-183.

61. Tricco AC, Ashoor HM, Antony J, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes. *BMJ*. 2014;349:5459.

62. Porcellati F, Rossetti P, Busciantella NR, et al. Comparison of pharmacokinetics and dynamics of the long-acting insulin analogs glargine and detemir at steady state in type 1 diabetes. *Diabetes Care*. 2007;30(10):2447-2452.

63. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues vs NPH human insulin in type 1 diabetes. *Diabetes Obes Metab*. 2009;11(4):372-378.

64. Heller S, Buse J, Fisher M, et al. Insulin degludec, an ultra-long acting basal insulin vs insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1). *Lancet*. 2012;379:1489-1497.

65. Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus. *CMAJ*. 2009;180 (4):385-397.

66. Yeh HC, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus. *Ann Intern Med*. 2012;157(5):336-347.

67. Bolli GB, Kerr D, Thomas R, et al. Comparison of a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) in type 1 diabetes. *Diabetes Care*. 2009;32(7):1170-1176.

68. Ceglia L, Lau J, Pittas AG. Efficacy and safety of inhaled insulin therapy in adults with diabetes mellitus. *Ann Intern Med*. 2006;145(9):665-675.

69. FDA briefing document Endocrinologic and Metabolic Drugs Advisory committee meeting: April 1, 2014, 8:00 AM to 5:00 PM. http://www.fda.gov/downloads/Advisorycommittees/Committeesmeetingmaterials/Drugs/EndocrinologicandMetabolicDrugsAdvsoryCommittee/UCM390864.pdf. Accessed March 7, 2015.

70. Tamborlane WV, Beck RW, Bode BW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med*. 2008; 359(14):1464-1476.

71. Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose. *BMJ*. 2011;343:d3805.

72. Beck RW, Lawrence JM, Laffel L, et al. Quality-of-life measures in children and adults with type 1 diabetes. *Diabetes Care*. 2010;33(10):2175-2177.

73. Bergenstal RM, Klonoff DC, Garg SK, et al. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med*. 2013;369 (3):224-232.

74. El-Khatib FH, Russell SJ, Nathan DM, Sutherlin RG, Damiano ER. A bihormonal closed-loop artificial pancreas for type 1 diabetes. *Sci Transl Med*. 2010;2 (27):27ra27.

75. Haidar A, Legault L, Messier V, Mitre TM, Leroux C, Rabasa-Lhoret R. Comparison of dual-hormone artificial pancreas, single-hormone artificial pancreas, and conventional insulin pump therapy for glycaemic control in patients with type 1 diabetes. *Lancet Diabetes Endocrinol*. 2015;3(1):17-26.

76. Russell SJ, El-Khatib FH, Sinha M, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. *N Engl J Med*. 2014;371(4):313-325.

77. Gruessner AC, Sutherland DER, Gruessner RW. Long-term outcome after pancreas transplantation. *Curr Opin Organ Transplant*. 2012;17(1):100-105.

78. Barton FB, Rickels MR, Alejandro R, et al. Improvement in outcomes of clinical islet transplantation: 1999-2010. *Diabetes Care*. 2012;35 (7):1436-1445.

79. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes*. 2013;37(suppl 1):S61-S68.

80. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Medical management of hyperglycemia in type 2 diabetes. *Diabetelogia*. 2009;52(1):17-30.

81. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach. *Diabetes Care*. 2015;38(1):140-149.

82. Smith RJ, Nathan DM, Arslanian SA, Groop L, Rizza RA, Rotter JI. Individualizing therapies in type 2 diabetes mellitus based on patient characteristics. *J Clin Endocrinol Metab*. 2010;95(4):1566-1574.

83. Nathan DM, Buse JB, Kahn SE, et al; GRADE Study Research Group. Rationale and design of the glycemia reduction approaches in diabetes. *Diabetes Care*. 2013;36(8):2254-2261.

84. Wing RR, Bolin P, Brancati FL, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013; 369(2):145-154.

85. Colagiuri S, Cull CA, Holman RR; UKPDS Group. Are lower fasting plasma glucose levels at diagnosis of type 2 diabetes associated with improved outcomes?. *Diabetes Care*. 2002;25(8):1410-1417.

86. Hu Y, Li L, Xu Y, et al. Short-term intensive therapy in newly diagnosed type 2 diabetes partially restores both insulin sensitivity and β-cell function in subjects with long-term remission. *Diabetes Care*. 2011;34(8):1848-1853.

87. Ji L, Lu J, Weng J, et al. China type 2 diabetes treatment status survey of treatment pattern of oral drugs users 2. *J Diabetes*. 2015;7(2):166-173.

88. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med*. 2004;351:1106.

89. Nissen SE, Wolski K. Rosiglitazone revisited. *Arch Intern Med*. 2010;170(14):1191-1201.

90. Lewis JD, Ferrara A, Peng T, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone. *Diabetes Care*. 2011;34(4):916-922.

91. Lewis JD, Habel LA, Quesenberry CP, et al. Pioglitazone use and risk of bladder cancer and other common cancers in persons with diabetes. *JAMA*. 2015;314(3):265-277.

92. US Food and Drug Administration. FDA requires removal of some prescribing and and dispensing restrictions for rosiglitazone-containing diabetes medicines. http://www.fda.gov/Drugs/DrugSafety/ucm376389.htm. Accessed July 2, 2015.

93. Levin D, Bell S, Sund R, et al. Pioglitazone and bladder cancer risk. *Diabetologia*. 2015;58(3):493-504.

94. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2011;(10):CD006423.

95. Bunck MC, Diamant M, Cornér A, et al. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients. *Diabetes Care*. 2009;32(5):762-768.

96. Li L, Shen J, Bala MM, et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus. *BMJ*. 2014;348:g2366.

97. Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs—FDA and EMA assessment. *N Engl J Med*. 2014;370(9):794-797.

98. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes. *JAMA*. 2007; 298(2):194-206.

99. 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(14):1317-1326.

100. 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(3):232-242.

101. Zhang Q, Dou J, Lu J. Combinational therapy with metformin and sodium-glucose cotransporter inhibitors in management of type 2 diabetes. *Diabetes Res Clin Pract*. 2014;105(3):313-321.

102. Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. *J Clin Endo Metab*. 2015;100(8):2849-2852.

103. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in US diabetes care, 1999-2010. *N Engl J Med*. 2013; 368(17):1613-1624.

104. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990-2010. *N Engl J Med*. 2014;370(16):1514-1523.