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Clinical Guideline

Hemoglobin A_{1c} Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians

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Description: The American College of Physicians developed this guidance statement to guide clinicians in selecting targets for pharmacologic treatment of type 2 diabetes.

Methods: The National Guideline Clearinghouse and the Guidelines International Network library were searched (May 2017) for national guidelines, published in English, that addressed hemoglobin A_{1c} (HbA_{1c}) targets for treating type 2 diabetes in nonpregnant outpatient adults. The authors identified guidelines from the National Institute for Health and Care Excellence and the Institute for Clinical Systems Improvement. In addition, 4 commonly used guidelines were reviewed, from the American Association of Clinical Endocrinologists and American College of Endocrinology, the American Diabetes Association, the Scottish Intercollegiate Guidelines Network, and the U.S. Department of Veterans Affairs and Department of Defense. The AGREE II (Appraisal of Guidelines for Research and Evaluation II) instrument was used to evaluate the guidelines.

Guidance Statement 1: *Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.*

Guidance Statement 2: *Clinicians should aim to achieve an HbA_{1c} level between 7% and 8% in most patients with type 2 diabetes.*

Guidance Statement 3: *Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA_{1c} levels less than 6.5%.*

Guidance Statement 4: *Clinicians should treat patients with type 2 diabetes to minimize symptoms related to hyperglycemia and avoid targeting an HbA_{1c} level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic conditions (such as dementia, cancer, end-stage kidney disease, or severe chronic obstructive pulmonary disease or congestive heart failure) because the harms outweigh the benefits in this population.*

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Diabetes mellitus is a leading cause of death in the United States and is associated with microvascular and macrovascular complications. Approximately 29.1 million persons, or 9.3% of the U.S. population, have type 2 diabetes (1). In 2012, the total direct and indirect costs associated with diabetes in the United States were $245 billion (1). Markedly elevated glucose levels can result in subacute symptoms, such as polyuria, polydipsia, weight loss, and dehydration. Over time, the metabolic derangements associated with diabetes may lead to vision loss, painful neuropathy or sensory loss, foot ulcers, amputations, myocardial infarctions, strokes, and end-stage renal disease. Lowering blood glucose may decrease risk for complications, but lowering strategies come with harms, patient burden, and costs.

Blood glucose can be measured in various ways, including the hemoglobin A_{1c} (HbA_{1c}; also called glycosylated or glycated hemoglobin) level, which approximates average blood glucose control over about 3 months. As with all laboratory tests, HbA_{1c} measurements are associated with variability (2) and can vary further with race and ethnicity (3–5). Guidelines have historically recommended initiation or intensification of

See also:

Summary for Patients 2

Web-Only
CME/MOC activity

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pharmacologic therapy to achieve specific HbA_{1c} targets, depending on the population in question. The ideal target that optimally balances benefits and harms remains uncertain.

Guidance Statement Focus and Target Population

The purpose of this American College of Physicians (ACP) guidance statement is to critically review the available guidelines from various organizations and the evidence included therein to assist clinicians in making decisions about targets when using pharmacologic therapy in adults with type 2 diabetes. Recent data suggesting that newer agents reduce cardiovascular morbidity and mortality in high-risk patients with type 2 diabetes have prompted calls for a fundamental shift in diabetes management. Some anticipate that treatment decisions will eventually be based more on cardiovascular risk than achievement of specific HbA_{1c} targets, analogous to recent changes in lipid management. However, for the foreseeable future, glycemic targets will continue to influence management decisions by front-line clinicians (6). This statement focuses on the benefits and harms of targeting lower versus higher HbA_{1c} levels and does not cover use of specific medications outside of their use to achieve HbA_{1c} targets. The intended audience is all clinicians, and the target population is nonpregnant adults with type 2 diabetes.

Methods

The Clinical Guidelines Committee (CGC) of ACP develops guidance statements on topics where several conflicting guidelines are available. We provide clinicians with a rigorous review of the guidelines and the evidence they include. We then adopt the clinical recommendations if we agree with their evaluation of benefits and harms or adapt them if changes are needed based on our assessment of the recommendations and evidence.

Data Sources and Guideline Selection

We searched the National Guideline Clearinghouse and the Guidelines International Network library (May 2017) for guidelines on recommended HbA_{1c} targets in the treatment of type 2 diabetes in nonpregnant outpatient adults. We included guidelines that were developed by national organizations, were published in English, and targeted the correct population. We reviewed titles and abstracts and excluded guidelines that were modified or adapted from other organizations or addressed specific populations (such as pregnant women or patients with kidney disease). Our search yielded guidelines from the National Institute for Health and Care Excellence (NICE) (7) and the Institute for Clinical Systems Improvement (ICSI) (8). On the basis of the knowledge and expertise of ACP CGC members, we also selected the following 4 guidelines not identified in either database at the time of the search but commonly used in clinical practice: the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) guideline (9), the American Diabetes Association (ADA) guideline (10), the Scottish Intercollegiate Guidelines Network (SIGN) guideline (11), and the U.S. Department of Veterans Affairs and Department of Defense (VA/DoD) guideline (12).

Quality Assessment

Six coauthors independently reviewed and assessed each guideline using the AGREE II (Appraisal of Guidelines for Research and Evaluation II) instrument (13). This instrument asks 23 questions in the following 6 domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. The authors scored each guideline independently, and the scores were compared (**Appendix Figure** and **Appendix Table 1**, available at Annals.org). Authors then provided a summary determination of whether they "would recommend this guideline for use" by recording "yes," "no," or "yes with modifications."

Peer Review

The draft guidance statement was peer-reviewed through *Annals of Internal Medicine* and was posted online for comments from ACP Regents and Governors, who represent ACP members at the regional level. The final guidance statement incorporated comments from peer reviewers and ACP Regents and Governors.

Public Panel Review

The development of this guidance statement also included perspectives, values, and preferences of 2 CGC members who represent the public and a 7-member public panel.

Summary of Evaluated Guidelines Using the AGREE II Instrument

We reviewed and rated 6 guidelines (AACE/ACE [9], ADA [10], ICSI [8], NICE [7], SIGN [11], and VA/DoD [12]), focusing solely on sections addressing HbA_{1c} targets in patients with type 2 diabetes. **Appendix Table 1** shows the detailed scaled domain scores and average quality ratings for each guideline, and the **Appendix Figure** shows average AGREE II scores for each item in each of the 6 domains. The fundamental difference between high- and low-scoring guidelines was methodology. The 2 lowest-scoring guidelines, AACE/ACE and ADA, scored lowest on stakeholder involvement, applicability, editorial independence, and scientific rigor. A systematic review is the backbone for any trustworthy guideline, but some guidelines might not be based on a systematic review or may not have made the review publicly available (14, 15).

Several factors were important in considering guideline quality. For example, although many guidelines described benefits, adverse effects, and the strength and limitations of evidence or linked the evidence to the recommendation, they often inadequately described how they had considered or weighted these factors in developing the final recommendations. The guidelines frequently relied on selective reporting of studies or outcomes and focused on relative versus absolute effects and asymptomatic surrogate measures rather than patient-centered health outcomes.

All of the reviewed guidelines recommend individualizing HbA_{1c} targets on the basis of patient characteristics, such as comorbid conditions and risk for hypoglycemia (Appendix, available at Annals.org). The ADA and SIGN guidelines recommend a target of 7% for the general population, whereas AACE/ACE recommends 6.5% (if it can be achieved safely). The NICE guideline specifies 6.5% or 7%, depending on the patient's treatment regimen. Both ICSI and VA/DoD recommend target ranges. The ICSI guideline recommends less than 7% to less than 8% based on patient factors, whereas the VA/DoD recommends the following target ranges based on life expectancy and comorbid conditions: 6% to 7% for patients with a life expectancy greater than 10 to 15 years and no or mild microvascular complications; 7% to 8.5% for those with established microvascular or macrovascular disease, comorbid conditions, or a life expectancy of 5 to 10 years; and 8% to 9% for those with a life expectancy less than 5 years, significant comorbid conditions, advanced complications of diabetes, or difficulties in self-management attributable to mental status, disability, or other factors (12). All guidelines recognize that HbA_{1c} targets can be higher in patients with comorbid conditions and limited life expectancy.

We looked into the evidence presented in these guidelines, specifically 5 large, long-term randomized trials with a "treat-to-target" strategy and corresponding reports on extended follow-up (16–23). We summarize below the individual studies and resulting benefits and harms. Note that recent studies evaluating the effectiveness and safety of several newer diabetes drugs (for example, recently approved sodium–glucose cotransporter-2 inhibitors, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 receptor agonists) were not considered in guideline sections pertaining to HbA_{1c} targets because these studies were not designed to evaluate treat-to-target strategies. Therefore, their findings are not described here.

Benefits and Harms of Lower HbA_{1c} Targets: Evidence From Clinical Trials

Five large, long-term randomized controlled trials investigated intensive (achieved HbA_{1c} levels, 6.3% to 7.4%) versus less intensive (achieved HbA_{1c} levels, 7.3% to 8.4%) treatment target strategies in adults (average baseline age, 53 to 66 years). They found that the main effect of more intensive glycemic control is small absolute reductions in risk for microvascular surrogate events, such as retinopathy detected on ophthalmologic screening or nephropathy defined by development or progression of albuminuria (Appendix Table 2, available at Annals.org) (16–23). Studies have not consistently shown that intensive glycemic control to HbA_{1c} levels below 7% reduces clinical microvascular events, such as loss or impairment of vision, end-stage renal disease, or painful neuropathy, or reduces macrovascular events and death. One trial of metformin in overweight adults showed a reduction in all-cause and diabetes-related death through at least 10 years (22).

In all studies, patients randomly assigned to more intensive therapy required more antiglycemic medications at higher doses, which led to more adverse events than in the less intensive groups. In 1 study, very intensive control resulted in an increased risk for death (18).

Appendix Table 2 summarizes data from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) (18), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) (20), UKPDS (United Kingdom Prospective Diabetes Study) (22, 23), and VADT (Veterans Affairs Diabetes Trial) (17) trials.

ACCORD Trial

The ACCORD trial compared the effects of intensive therapy (target HbA_{1c} levels <6.0%) with those of standard therapy (target HbA_{1c} levels, 7.0% to 7.9%; achieved levels, 6.4% vs. 7.5%). Participants had a mean age of 62.2 years and median baseline HbA_{1c} level of 8.1%. The trial was terminated early (mean follow-up, 3.5 years) because of increases in all-cause mortality (hazard ratio [HR], 1.22 [95% CI, 1.01 to 1.46]), cardiovascular-related death (HR, 1.35 [CI, 1.04 to 1.76]), and hypoglycemic events requiring assistance in the group assigned to the lower HbA_{1c} target. Intensive treatment did not reduce risk for major adverse cardiovascular events (HR, 0.90 [CI, 0.78 to 1.04]), fatal or nonfatal stroke, or fatal or nonfatal congestive heart failure. Participants receiving intensive treatment had fewer nonfatal myocardial infarctions (HR, 0.76 [CI, 0.62 to 0.92]). Intensive therapy did not reduce risk for microvascular outcomes (including renal failure, doubling of serum creatinine, visual impairment, retinal photocoagulation, and neuropathy) but led to small absolute reductions in the onset of albuminuria. Additional follow-up through a median of 5 years confirmed the original report's findings (achieved HbA_{1c} levels: intensive group, 7.2%; standard group, 7.6%) (19).

The trial was stopped early because more intensive glycemic control was associated with a 22% increase in all-cause mortality, a 35% increase in cardiovascular-related death, and a 3-fold increase in risk for severe hypoglycemia (18). More intensive treatment also resulted in increased weight gain of more than 10 kg (27.8% vs. 14.1%) and increased fluid retention.

ADVANCE Trial

The ADVANCE trial enrolled participants with a mean baseline age of 66 years and mean baseline HbA_{1c} level of 7.5%. Intensive treatment (HbA_{1c} levels: target ≤6.5%; achieved, 6.5%) compared with standard treatment (achieved HbA_{1c} level, 7.3%) did not reduce major macrovascular events (HR, 0.94 [CI, 0.84 to 1.06]), all-cause mortality (HR, 0.93 [CI, 0.83 to 1.06]), or cardiovascular-related death (HR, 0.88 [CI, 0.74 to 1.04)]) over a median of 5 years (20). Intensive treatment resulted in reduced incidence of combined macrovascular and microvascular events (18.1% vs. 20.0%; HR, 0.90 [CI, 0.82 to 0.98]) and microvascular events (9.4% vs. 10.9%; HR, 0.86 [CI, 0.77 to 0.97]) over a median of 5 years. This was primarily because of a small absolute reduction in the incidence of nephropathy (4.1% vs. 5.2%; HR, 0.79 [CI, 0.66 to 0.93]) mostly due to the development of macroalbuminuria. The lower target did not affect doubling of serum creatinine, neuropathy, retinopathy, or visual deterioration. Effects were consistent across subgroups, including those with a history of microvascular or macrovascular disease.

More severe hypoglycemic events were seen with intensive glycemic control (2.7% vs. 1.5%; HR, 1.86 [CI, 1.42 to 2.40]) (20). Minor hypoglycemia also occurred more frequently, and hospitalization was more common (44.9% vs. 42.8%; HR, 1.07 [CI, 1.01 to 1.13]).

UKPDS Trials

The UKPDS trials involved 2 separate studies evaluating intensive glycemic control versus conventional therapy (diet and subsequent treatments if marked hyperglycemia persisted) in adults (mean age, 54 years) with newly diagnosed type 2 diabetes. One third of participants had retinopathy at baseline. The larger UKPDS 33 trial (23) (n = 3867; mean baseline age, 54 years) compared intensive glycemic control (target fasting plasma glucose level <6 mmol/L [108 mg/dL]; median attained HbA_{1c} level, 7%) using either sulfonylureas or insulin versus less stringent control (target fasting plasma glucose best achievable with diet; median attained HbA_{1c} level, 7.9%) using diet and added hypoglycemic agents if patients developed marked hyperglycemia. At a median follow-up of 10 years, intensive control reduced any diabetes-related end point by a relative 12% (CI, 1% to 21%) (P = 0.029). The absolute difference was 5.1 events per 1000 patient-years. This was largely due to a reduction in the composite outcome of microvascular end points, which comprised retinal photocoagulation for asymptomatic retinal findings detected on screening (relative risk reduction, 25% [CI, 7% to 40%]; P = 0.0099). The study found no differences in diabetes-related death (relative reduction, 10% [CI, −11% to 27%]; P = 0.34), all-cause mortality (relative reduction, 6% [CI, −10% to 20%]; P = 0.44), myocardial infarction, stroke, or amputation (23).

The UKPDS 34 trial (22) assessed intensive therapy with metformin (median attained HbA_{1c} level, 7.4%) versus conventional therapy (median attained HbA_{1c} level, 8.0%), primarily in overweight adults (n = 753). Supplementary and secondary analyses included participants from UKDPS 33 who subsequently received metformin for fasting plasma glucose levels that were persistently high. Compared with the conventional treatment group (receiving dietary advice or additional nonintensive pharmacologic therapy if they had marked hyperglycemia), patients initially allocated to metformin (n = 342) had relative risk reductions of 32% (CI, 13% to 47%) (P = 0.0023) for any diabetes-related end point, 42% (CI, 9% to 63%) (P = 0.017) for diabetes-related death, and 36% (CI, 9% to 55%) (P = 0.011) for all-cause mortality. This equates to absolute reductions in diabetes-related and all-cause mortality of approximately 5 and 7 deaths per 1000 patient-years, respectively. These reductions were greater than those attained with intensive therapy with sulfonylureas or insulin. However, early addition of metformin to sulfonylureas resulted in an increased risk for diabetes-related death (P = 0.039) compared with continued treatment with sulfonylureas alone.

On extended follow-up (median time from randomization, 17 years), 3277 patients originally enrolled in UKPDS 33 or 34 who received intensive glucose control with sulfonylureas or insulin had a 9% relative reduction of borderline statistical significance in any diabetes-related end point (risk ratio, 0.91 [CI, 0.83 to 0.99]; P = 0.04) and an absolute reduction in all-cause mortality (3.5 deaths per 1000 patient-years; P = 0.007) (16). In the metformin-intensive therapy group, risk reductions persisted for any diabetes-related end point (risk reduction, 21%; 8.2 events per 1000 patient-years; P = 0.01), myocardial infarction (risk reduction, 33%; 6.3 events per 1000 patient-years; P = 0.005), and all-cause mortality (risk reduction, 27%; 7.2 deaths per 1000 patient-years; P = 0.002).

Hypoglycemic events were much more common in the intensive than standard treatment groups of the UKPDS trials (approximately 30% vs. 1% annually) (23). Early addition of metformin to sulfonylureas resulted in an increased risk for diabetes-related death (P = 0.039) compared with continued treatment with sulfonylureas alone.

VADT

The VADT compared patients (mean age, 60 years; median baseline HbA_{1c} level, 9.4%) in an intensive therapy group (median achieved HbA_{1c} level, 6.9%) with those in a standard therapy group (median achieved HbA_{1c} level, 8.4%). The trial targeted an absolute between-group difference in HbA_{1c} level of 1.5 percentage points and found no reduction in major cardiovascular events, death, or microvascular events, except for "any increase in albuminuria," over a median follow-up of 5.6 years (21). The intensive therapy group had fewer cardiovascular events over an extended follow-up of about 12 years (HR, 0.83 [CI, 0.70 to 0.99]; P = 0.04). However, the absolute effect was small (8.6 events per 1000 patient-years), and the outcome included hospitalization for new or worsening heart failure and asymptomatic ejection fractions of less than 40%. The investigators found no reduction in all-cause mortality (HR, 1.05 [CI, 0.89 to 1.25]) or cardiovascular-related death (HR, 0.88 (CI, 0.64 to 1.20) (17).

Severe and any hypoglycemia were more common in the intensive therapy group than the standard therapy group. This included a 3-fold higher rate of episodes with impaired consciousness (9 vs. 3 episodes per 100 patient-years). Serious adverse events were also more common in the intensive therapy group (24.1% vs. 17.6%; P = 0.05); dyspnea was the most common (P = 0.006) (21).

Guidance Statements

Guidance Statement 1: Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.

All of the assessed guidelines recommend personalizing HbA_{1c} goals for individual patients (**Appendix**) (7–12). The benefits and harms of more versus less intensive glycemic control may be finely balanced for many persons and vary according to expected duration of treatment, comorbid conditions, risk factors for hypoglycemia, and choice of medication. The choice of glycemic target also depends on consideration of other variables, such as risk for hypoglycemia, weight gain, and other drug-related adverse effects, as well as the patient's age, life expectancy, other chronic conditions, functional and cognitive impairments, fall risk, ability to adhere to treatment, and medication burden and cost.

Guidance Statement 2: Clinicians should aim to achieve an HbA_{1c} level between 7% and 8% in most patients with type 2 diabetes.

Most of the guidelines referred to 5 trials as the rationale for their HbA_{1c} targets of 7% or 8% (**Appendix Table 2**) (19–23). Collectively, these trials showed that treating to targets of 7% or less compared with targets around 8% did not reduce death or macrovascular events over about 5 to 10 years of treatment but did result in substantial harms, including but not limited to hypoglycemia. Our guidance statement is adapted from and is most consistent with the ICSI guideline, which recommends an HbA_{1c} target range between less than 7% and less than 8% (8). The VA/DoD guideline also specifies ranges rather than specific targets and selects them according to life expectancy, comorbid conditions, and other factors (12). Including ranges for recommended goals also allows for variability in individual HbA_{1c} measurements.

The ICSI guideline highlights that efforts to achieve HbA_{1c} levels below 7% may increase risk for death, weight gain, hypoglycemia, and other adverse effects in many patients (8), and we share these concerns. Of the 3 trials achieving an HbA_{1c} level less than 7%, none showed a reduction in all-cause or cardiovascular-related death (18, 20, 21).

The guidelines recommending lower targets (below 7% or below 6.5%) give the rationale that more intensive glycemic control reduces microvascular events over many years of treatment. Of note, however, the evidence for reduction is inconsistent, and reductions were seen only in surrogate microvascular end points, such as progression of proteinuria or receipt of retinal photocoagulation. Trials did not show substantial reductions in clinical microvascular events. In addition, the ACCORD trial found an increased risk for death with an HbA_{1c} target of less than 6.5% (18).

Most of the guidelines noted that a target in the lower end of the range (7%) applied best to patients with newly diagnosed diabetes and those without substantial diabetes-related complications. The rationale for this is based on results from the UKPDS. This trial showed that treatment to a target of about 7% with a sulfonylurea and insulin (if needed) in adults with newly diagnosed diabetes did not reduce risk for any diabetes-related end point or all-cause mortality after 10 years but was associated with a small absolute reduction in these outcomes after 17 years (16, 23). A substudy (UKPDS 34) also showed a modest reduction in diabetes-related end points and all-cause mortality with metformin in overweight or obese adults (2, 12).

All laboratory measurements, including HbA_{1c} levels, are associated with variability. Therefore, a clinician should consider the variability of HbA_{1c} test results when selecting goals or making therapeutic decisions.

Any benefit of more intensive glycemic control likely requires a long time to manifest. Thus, more stringent targets may be appropriate for patients who have a long life expectancy (>15 years) and are interested in more intensive glycemic control with pharmacologic therapy despite the risk for harms, including but not limited to hypoglycemia, patient burden, and pharmacologic costs.

Although this guidance statement focuses on pharmacologic glycemic control, a lower treatment target is appropriate if achievable with diet and lifestyle modifications. Clinicians should counsel patients and emphasize the importance of lifestyle interventions, including exercise, dietary changes, and weight loss, to achieve good glycemic control. Smoking cessation, adequate blood pressure control, and lipid management are also indicated in patients with type 2 diabetes and, for many patients, may take priority over achieving glycemic control, especially for preventing macrovascular complications.

Guidance Statement 3: Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA_{1c} levels less than 6.5%.

No trials show that targeting HbA_{1c} levels below 6.5% in diabetic patients improves clinical outcomes, and pharmacologic treatment to below this target has substantial harms. The ACCORD trial, which targeted an HbA_{1c} level less than 6.5% and achieved the lowest level of the included studies (6.4%), was discontinued early because of increased overall and cardiovascular-related death and severe hypoglycemic events (18). The ADVANCE study also failed to find a statistically significant clinical benefit and had more adverse effects with an achieved median HbA_{1c} level of 6.4% than with 7.0%. In addition, more intensive treatment to achieve a lower target is more costly and is associated with increased patient burden. Therefore, if a patient achieves an HbA_{1c} level less than 6.5%, the clinician should deintensify treatment by reducing the dosage, removing a medication if the patient is receiving more than 1, or discontinuing pharmacologic treatment.

Although other drugs have been associated with harms, the balance between benefits and harms is uncertain with metformin for lower HbA_{1c} levels. Metformin is not associated with hypoglycemia and is gen-

Figure. Summary of the American College of Physicians guidance statement on HbA_{1c} targets for glycemic control with pharmacologic therapy in nonpregnant adults with type 2 diabetes mellitus.

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Summary of the American College of Physicians Guidance Statement on HbA_{1c} Targets for Glycemic Control With Pharmacologic Therapy in Nonpregnant Adults With Type 2 Diabetes Mellitus

Disease/Condition	Type 2 diabetes
Target Audience	All clinicians
Target Patient Population	Outpatient nonpregnant adults with type 2 diabetes
Outcomes Evaluated	Microvascular and macrovascular outcomes, mortality
Benefits	Reduced microvascular and macrovascular outcomes, reduced mortality
Harms	Harms of achieving lower HbA_{1c} targets with pharmacologic interventions include increased hypoglycemia (including severe), hospitalizations, weight gain, water retention, and death. Adverse effects associated with pharmacologic treatments for diabetes include but are not limited to gastrointestinal side effects, hypoglycemia, weight gain, congestive heart failure, joint pain, fractures, and genital mycotic infections. These adverse effects increase with higher doses and greater numbers of medications likely required to achieve lower HbA_{1c} levels.
Guidance Statements	*Guidance Statement 1: Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.* *Guidance Statement 2: Clinicians should aim to achieve an HbA_{1c} level between 7% and 8% in most patients with type 2 diabetes.* *Guidance Statement 3: Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA_{1c} levels less than 6.5%.* *Guidance Statement 4: Clinicians should treat patients with type 2 diabetes to minimize symptoms related to hyperglycemia and avoid targeting an HbA_{1c} level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic conditions (such as dementia, cancer, end-stage kidney disease, or severe chronic obstructive pulmonary disease or congestive heart failure) because the harms outweigh the benefits in this population.*
High-Value Care	Deescalation of therapy, by reducing dosage or number of drugs, is warranted in many persons with HbA_{1c} levels persistently <6.5% after treatment with drugs. Persons with advanced age and lower life expectancy should be treated to reduce symptoms rather than strictly focusing on specific HbA_{1c} target levels.
Clinical Considerations	Encourage a healthy lifestyle (e.g., tobacco cessation, diet and exercise, and attaining ideal body weight), including for risk reduction in patients with known or high risk for cardiovascular disease. Consider individual patient-level variables, such as polypharmacy issues, limited life expectancy, extensive multiple comorbid conditions, and cognitive impairment. Consider patient preference when deciding on treatment strategies and goals. Test results for HbA_{1c} levels can vary because of such conditions as anemia and chronic kidney disease; therefore, clinicians should aim for a target range rather than a specific target.

To arrive at these guidance statements, the authors reviewed guidelines from the National Institute for Health and Care Excellence, the Institute for Clinical Systems Improvement, the American Association of Clinical Endocrinologists and American College of Endocrinology, the American Diabetes Association, the Scottish Intercollegiate Guidelines Network, and the U.S. Department of Veterans Affairs and Department of Defense. HbA_{1c} = hemoglobin A_{1c}.

erally well-tolerated and low cost, but it is associated with other known adverse effects and results in use of additional medication with little to no benefit at HbA_{1c} levels below 7%. The ACP guideline on oral pharmacologic treatment of diabetes (24) provides information on metformin and other medications.

Guidance Statement 4: Clinicians should treat patients with type 2 diabetes to minimize symptoms related to hyperglycemia and avoid targeting an HbA_{1c} level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic conditions (such as dementia, *cancer, end-stage kidney disease, or severe chronic obstructive pulmonary disease or congestive heart failure) because the harms outweigh the benefits in this population.*

All of the evaluated guidelines suggest relaxing HbA_{1c} targets for patients with multiple comorbid conditions, limited life expectancy, or increased risk for hypoglycemia (7–11). Setting stringent targets in these populations is not an optimal approach, and clinicians should instead focus on treating to reduce symptoms from both disease and treatment. The ACP guidance statement in persons with a life expectancy less than 10 years is based on the small death or cardiovascular benefit of lower HbA_{1c} targets through at least 10 years, which should be balanced with treatment harms, including but not limited to hypoglycemia and patient views of treatment burden. For example, a modeling study has examined how treatment burden affects the benefits of intensive versus moderate glycemic control in patients with type 2 diabetes (25). Authors used microvascular benefits shown in UKDPS 33, as well as reductions in congenital heart disease events from observational studies and the long-term follow-up of UKPDS, to assess lifetime benefits of glycemic targets. Even with low estimates of treatment-related adverse effects and patient-perceived treatment burden, achieving more intensive target HbA_{1c} levels of 7.5% or below rather than 8.5% (especially if using insulin) resulted in net harm in most patients aged 55 years or older.

The **Figure** summarizes the guidance statements and clinical considerations.

Multiple Chronic Conditions: Application to Older Populations

Consideration of how this evidence base applies in older populations is important because of the high proportion of older patients with multiple chronic comorbid conditions, the frequency of polypharmacy and potential for drug interactions, and the consequent likelihood that the balance of benefits and harms is different in older patients. For patients with multiple comorbid conditions, including renal failure, liver failure, end-stage disease complications, cognitive impairment, advanced microvascular or macrovascular complications, or any other conditions that limit life expectancy, the harms of more intensive HbA_{1c} targets outweigh the benefits. Many guidelines also discuss the role of less intensive targets for older adults. In these patients, the goal should be to minimize symptoms rather than achieve a specific HbA_{1c} target.

Insufficient Areas of Evidence

Evidence from trials included here is insufficient to evaluate the effect of HbA_{1c} targets between 6.5% and 7% on clinical outcomes, and further research would be needed to close this gap.

High-Value Care

ACP believes that clinicians should reevaluate HbA_{1c} levels and revise treatment strategies on the basis of changes in the balance of benefits and harms due to changed costs of care and patient preferences, general health, and life expectancy. In persons who reach HbA_{1c} levels less than 6.5% with drug treatment, deescalation of therapy (by reducing dosage or number of drugs) is warranted to reduce harms, patient burden, and costs of treatment. Generic medications are preferred when available. ACP recently provided recommendations on pharmacologic treatment of type 2 diabetes (24).

Policy Implication for Performance Measures

ACP suggests that any physician performance measures developed to evaluate quality of care should not have a target HbA_{1c} level below 8% for any patient population and should not have any HbA_{1c} targets for older adults (for example, aged ≥80 years) or younger persons with limited life expectancy due to serious comorbid conditions.

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Note: Guidance statements are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP guidance statements are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

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Appendix: Summary and Evaluation of Reviewed Guidelines

AACE/ACE

Recommendations

> Glucose targets should be individualized and take into account life expectancy, disease duration, presence or absence of micro- and macrovascular complications, CVD [cardiovascular disease] risk factors, comorbid conditions, and risk for hypoglycemia, as well as the patient's psychological status (Grade A; BEL [best evidence level] 1). In general, the goal of therapy should be an A1C level ≤6.5% for most nonpregnant adults, if it can be achieved safely . . . (Grade D; BEL 4). . . .
> In adults with recent onset of T2D [type 2 diabetes] and no clinically significant CVD, glycemic control aimed at normal (or near-normal) glycemia should be considered, with the aim of preventing the development of micro- and macrovascular complications over a lifetime, if it can be achieved without substantial hypoglycemia or other unacceptable adverse consequences (Grade A; BEL 1). . . . A less stringent glucose goal should be considered (A1C 7 to 8%) in patients with history of severe hypoglycemia, limited life expectancy, advanced renal disease or macrovascular complications, extensive comorbid conditions, or long-standing DM [diabetes mellitus] in which the A1C goal has been difficult to attain despite intensive efforts, so long as the patient remains free of polydipsia, polyuria, polyphagia, and other hyperglycemia-associated symptoms (Grade A; BEL 1). (9)

Comments

According to the AACE/ACE grading scheme, "Grade A; BEL 1" indicates highest-quality evidence with little or no effect from subjective factors on recommendation (evidence mapped to recommendation) and "Grade D; BEL 4" indicates lowest-quality evidence with little or no effect from subjective factors on recommendation (9).

This guideline is a consensus, expert-based guideline, with no systematic review of evidence. In general, the methods behind the clinical recommendations were not clearly presented. This guideline recommends a very low target HbA_{1c} level in most adults (≤6.5%) if it can be achieved safely, although a higher target (7% to 8%) is recommended in patients with multiple chronic conditions or shorter lifespan.

ADA

Recommendations

> A reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol). ([Grade] A)
> Providers might reasonably suggest more stringent A1C goals (such as <6.5% [48 mmol/mol]) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment (i.e., polypharmacy). Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease. ([Grade] C)
> Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. ([Grade] B). (10)

Comments

According to the ADA grading scheme, Grade A is "[c]lear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered." Grade B is "[s]upportive evidence from well-conducted cohort studies" (10).

This guideline does not clearly present methods or details about the systematic reviews that were used to develop the recommendations. It states that HbA_{1c} targets should be less than 7% in most adults, even more stringent (<6.5%) in select cases treated with lifestyle or metformin alone, and less stringent (<8%) in patients with multiple chronic conditions.

ICSI

Recommendation

> A clinician should personalize goals with patients diagnosed with T2DM [type 2 diabetes mellitus] to achieve glycemic control with a hemoglobin A1c < 7% to < 8% depending on individual patient factors [strong recommendation, high-quality evidence]. (8)

Comments

The ICSI clearly presents the evidence and methodology behind their clinical recommendations. It specifies that an HbA_{1c} target of less than 8% may be more appropriate than 7% in persons with cardiovascular disease or high cardiovascular risk, history of severe hypoglycemia requiring assistance, polypharmacy issues, limited life expectancy (<10 years), cognitive impairment, or extensive comorbid conditions (renal or liver failure or end-stage disease complications). It highlights that efforts to achieve HbA_{1c} levels below 7% may increase risk for death, weight gain, hypoglycemia, and other adverse effects in many patients.

NICE

Recommendations

> Involve adults with type 2 diabetes in decisions about their individual HbA1c target. Encourage them to achieve the target and maintain it unless any resulting adverse effects (including hypoglycaemia), or their efforts to achieve their target, impair their quality of life. . . .
>
> For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycaemia, support the person to aim for an HbA1c level of 48 mmol/mol (6.5%). For adults on a drug associated with hypoglycaemia, support the person to aim for an HbA1c level of 53 mmol/mol (7.0%). . . .
>
> In adults with type 2 diabetes, if HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher:
>
> • reinforce advice about diet, lifestyle and adherence to drug treatment and
>
> • support the person to aim for an HbA1c level of 53 mmol/mol (7.0%) and
>
> • intensify drug treatment. . . .
>
> Consider relaxing the target HbA1c level . . . on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes:
>
> • who are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy
>
> • for whom tight blood glucose control poses a high risk of the consequences of hypoglycaemia, for example, people who are at risk of falling, people who have impaired awareness of hypoglycaemia, and people who drive or operate machinery as part of their job
>
> • for whom intensive management would not be appropriate, for example, people with significant comorbidities. (7)

Comments

The NICE guideline is based on a clear description of the benefits and harms of tight glycemic control. It encourages patients to be involved in decisions about their HbA_{1c} target. Target levels range from 6.5% when only diet and exercise are used to manage diabetes, 7% when patients are treated with monotherapy associated with hypoglycemia, and 7.5% when they are treated with combination therapy. The guideline stresses an individualized approach in patients with multiple chronic conditions or limited life expectancy, although it does not define limited life expectancy.

SIGN

Recommendations

> An HbA1c target of 7.0% (53 mmol/mol) among people with type 2 diabetes is reasonable to reduce risk of microvascular disease and macrovascular disease. A target of 6.5% (48 mmol/mol) may be appropriate at diagnosis. Targets should be set for individuals in order to balance benefits with harms, in particular hypoglycemia and weight gain (Grade A). (11)

Comments

According to the SIGN grading scheme, grade A corresponds to at least 1 meta-analysis, systematic review, or randomized controlled trial rated as high quality and directly applicable to the target population or a body of evidence consisting principally of studies rated well with low risk of bias, directly applicable to the target population, and showing overall consistency of results (11).

The SIGN guideline is based on a clear description of the benefits and harms of tight glycemic control. It recommends an HbA_{1c} target less than 7%. It also recommends individualized targets with no clarity on specific target levels when individualized.

VA/DoD

Recommendations

> We recommend setting an HbA1c target range based on absolute risk reduction of significant microvascular complications, life expectancy, patient preferences and social determinants of health. [Strong recommendation]

We recommend developing an individualized glycemic management plan, based on the provider's appraisal of the risk-benefit ratio and patient preferences. [Strong recommendation]
We recommend assessing patient characteristics such as race, ethnicity, chronic kidney disease, and non-glycemic factors (e.g., laboratory methodology and assay variability) when interpreting HbA1c, fructosamine and other glycemic biomarker results. [Strong recommendation]
We recommend an individualized target range for HbA1c taking into account individual preferences, presence or absence of microvascular complications, and presence or severity of comorbid conditions. [Strong recommendation]
We suggest a target HbA1c range of 6.0-7.0% for patients with a life expectancy greater than 10-15 years and absent or mild microvascular complications, if it can be safely achieved. [Weak recommendation]
We recommend that in patients with type 2 diabetes, a range of HbA1c 7.0-8.5% is appropriate for most individuals with established microvascular or macrovascular disease, comorbid conditions, or 5-10 years life expectancy, if it can be safely achieved. [Strong recommendation]
We suggest a target HbA1c range of 8.0-9.0% for patients with type 2 diabetes with life expectancy <5 years, significant comorbid conditions, advanced complications of diabetes, or difficulties in self-management attributable to e.g., mental status, disability or other factors such as food insecurity and insufficient social support. [Weak recommendation]
We suggest that providers be aware that HbA1c variability is a risk factor for microvascular and macrovascular outcomes. [Weak recommendation] (12)

Comments

The VA/DoD guideline is based on a description of the benefits and harms of glycemic control. It emphasizes the importance of shared decision making in setting HbA_{1c} goals and recommends target ranges based on comorbid conditions, life expectancy, and other factors rather than setting a fixed target HbA_{1c} level. It emphasizes that the lower targets of 6.0% to 7.0% and 7.0% to 8.5% should be attained if they can be reached safely.

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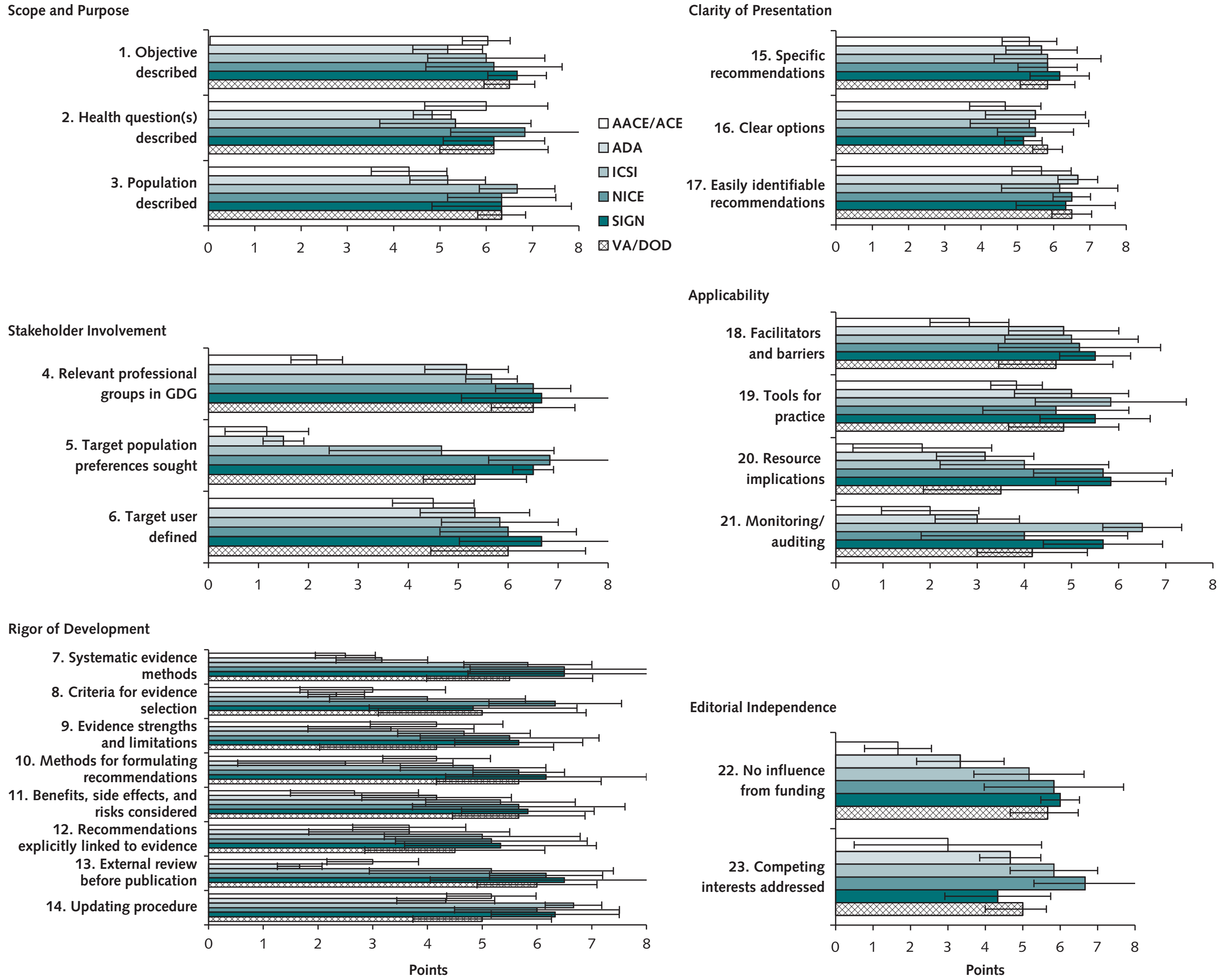
Appendix Figure. Mean AGREE II scores for items in each domain across the 6 reviewers.



Each question was rated on a Likert scale with a minimum of 1 point and a maximum of 7 points. The scores were averaged for each of the 6 reviewers. Error bars represent calculated standard deviation. AACE/ACE = American Association of Clinical Endocrinologists and American College of Endocrinology; ADA = American Diabetes Association; AGREE II = Appraisal of Guidelines for Research and Evaluation II; GDG = guideline development group; ICSI = Institute for Clinical Systems Improvement; NICE = National Institute for Health and Care Excellence; SIGN = Scottish Intercollegiate Guidelines Network; VA/DoD = U.S. Department of Veterans Affairs and Department of Defense.

Appendix Table 1. Scaled AGREE II Domain Scores for Each Guideline and Overall Assessment

Variable	AACE/ ACE	ADA	ICSI	NICE	SIGN	VA/DoD
Scaled domain score, %*						
Scope and purpose	74	68	83	91	90	89
Stakeholder involvement	27	50	73	91	94	82
Rigor of development	42	36	70	81	82	70
Clarity of presentation	70	82	80	82	81	84
Applicability	27	50	72	65	77	55
Editorial independence	21	49	74	86	68	72
Overall guideline assessment†						
Average overall quality rating‡	2.8	3.7	5.3	5.7	5.8	5.7
I would recommend this guideline for use	6 no	1 yes 4 yes with modifications 1 no	3 yes 3 yes with modifications§	3 yes 3 yes with modifications§	3 yes 3 yes with modifications§	3 yes 3 yes with modifications§

AACE/ACE = American Association of Clinical Endocrinologists and American College of Endocrinology; ADA = American Diabetes Association; AGREE II = Appraisal of Guidelines for Research and Evaluation II; ICSI = Institute for Clinical Systems Improvement; NICE = National Institute for Health and Care Excellence; SIGN = Scottish Intercollegiate Guidelines Network; VA/DoD = U.S. Department of Veterans Affairs and Department of Defense.

* Calculated as follows: (obtained score − minimum possible score) ÷ (maximum possible score − minimum possible score).

† Final overall assessment questions on AGREE II.

‡ Out of 7 possible points; average score from all raters.

§ Although this guideline scored high on the AGREE II domains and was methodologically sound, the reviewers did not fully agree with its final recommendations and therefore recommend with modifications.

Appendix Table 2. Study, Patient, and Outcome Characteristics of Major Type 2 Diabetes Trials Included in the Assessed Guidelines

Study, Year (Reference) Mean or Median Follow-up Patients Enrolled	Age at Baseline, *y*	Diabetes Duration	Intensive vs. Control					
			HbA_{1c} Level, %		Microvascular and Combined Microvascular/ Macrovascular Events	Mortality	Macrovascular Events	AEs
			Baseline	Achieved				
ACCORD, 2008 (18) Mean: 3.5 y *n* = 10 251	62.2	10 y (35% with prior CV event)	Median: 8.1 vs. 8.1	Median: 6.4 vs. 7.5	MACE* (first occurrence of nonfatal MI, nonfatal stroke, or death from CVD): HR, 0.90 (95% CI, 0.78 to 1.04); 6.9% vs. 7.2% No difference in microvascular outcomes (including renal failure, creatinine doubling, visual impairment, retinal photocoagulation, and neuropathy)	All-cause mortality: HR, 1.22 (95% CI, 1.01 to 1.46) Trial stopped early due to increased all-cause mortality, which did not vary by baseline sex, age, HbA_{1c} level, race, or previous CV event CV mortality: HR, 1.35 (95% CI, 1.04 to 1.76); 2.6% vs. 1.8%	Nonfatal MI: HR, 0.76 (95% CI, 0.62 to 0.92); 3.6% vs. 4.6% Nonfatal stroke: HR, 1.06 (95% CI, 0.75 to 1.50) Fatal/nonfatal CHF: HR, 1.18 (95% CI, 0.93 to 1.49)	Hypoglycemia (requiring assistance): 10.5% vs. 3.5%; *P* < 0.001 Any nonhypoglycemic serious AEs: 2.2% vs. 1.6%; *P* = 0.03 Mean weight gain: 3.5 kg vs. 0.4 kg Weight gain >10 kg: 27.8% vs. 14.1%; *P* < 0.001 Fluid retention: 70.1% vs. 66.8%; *P* < 0.001 Greater use of oral hypoglycemic drugs and insulin
ACCORD, 2010 (26) ACCORD, 2011 (19) Mean extended follow-up: 4.9 y				Median: 7.2 vs. 7.6	MACE*: HR, 0.91 (95% CI, 0.81 to 1.03) "First composite microvascular complications" (development of renal failure, retinal photocoagulation, or vitrectomy to treat retinopathy): HR, 0.95 (95% CI, 0.85 to 1.07) "2nd composite microvascular complications" (first composite + Michigan neuropathy screening instrument score >2.0): HR, 0.95 (95% CI, 0.89 to 1.01)	All-cause mortality: HR, 1.19 (95% CI, 1.03 to 1.38); 1.53 vs.1.27 CV mortality: HR, 1.29 (95% CI, 1.04 to 1.60); 0.74% vs. 0.57%	Nonfatal MI: HR, 0.82 (95% CI, 0.70 to 0.96); 1.18 vs. 1.42 Fatal/nonfatal stroke: HR, 0.86 (95% CI, 0.65 to 1.13) Fatal/nonfatal CHF: HR, 1.09 (95% CI, 0.91 to 1.32)	

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Appendix Table 2–Continued

Study, Year (Reference) Mean or Median Follow-up Patients Enrolled	Age at Baseline, *y*	Diabetes Duration	Intensive vs. Control					
			HbA_{1c} Level, %		Microvascular and Combined Microvascular/ Macrovascular Events	Mortality	Macrovascular Events	AEs
			Baseline	Achieved				
ADVANCE, 2008 (20) Median: 5 y *n* = 11 140	Mean: 66.0	7.9 y (32% with prior CVD)	Mean: 7.5 vs. 7.5 Median: 7.2 vs. 7.2	Mean: 6.5 vs. 7.3 Median: 6.4 vs. 7.0	Combined major macrovascular and microvascular events*: HR, 0.90 (95% CI, 0.82 to 0.98); ARR, 1.9%; 18.1% vs. 20.0% Results were similar regardless of baseline micro/macrovascular disease status Major microvascular events: HR, 0.86 (95% CI, 0.77 to 0.97); 9.4% vs. 10.9% (primarily due to reduction in nephropathy incidence [HR, 0.79 {95% CI, 0.66 to 0.93}] mostly development of macroalbuminuria 2.9% vs. 4.1% without effect on doubling of serum creatinine level or renal replacement therapy) New or worsening neuropathy or retinopathy and visual deterioration were not significantly reduced	All-cause mortality: HR, 0.93 (95% CI, 0.83 to 1.06) CV mortality: HR, 0.88 (95% CI, 0.74 to 1.04)	Macrovascular events: HR, 0.94 (95% CI, 0.84 to 1.06) Nonfatal MI: RRR, 2% (95% CI, −23% to 22%) All CV events: RRR, 2% (95% CI, −10% to 13%) Heart failure: RRR, 5% (95% CI, −14% to 21%) Nonfatal stroke: RRR, −2% (95% CI, −24% to 15%)	Severe hypoglycemia: HR, 1.86 (95% CI, 1.42 to 2.40); 2.7% vs. 1.5%; 0.7 vs. 0.4 per 100 patient-years Minor hypoglycemia: 120 vs. 90 per 100 patient-years Hospitalization: 44.9% vs. 42.8%; HR, 1.07 (95% CI, 1.01 to 1.13) Greater use of oral hypoglycemic drugs and insulin

Continued on following page

***Appendix Table 2*–Continued**

Study, Year (Reference) Mean or Median Follow-up Patients Enrolled	Age at Baseline, *y*	Diabetes Duration	Intensive vs. Control					
			HbA_{1c} Level, %		Microvascular and Combined Microvascular/ Macrovascular Events	Mortality	Macrovascular Events	AEs
			Baseline	Achieved				
UKPDS 33, 1998 (23) Sulfonylurea ± insulin ± metformin Median: 11.1 y *n* = 3867	54	Newly diagnosed (36% with retinopathy)		Median: 7.0 vs. 7.9	Any diabetes-related end point* (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation, vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in 1 eye or cataract): RR, 0.88 (95% CI, 0.79 to 0.99); 40.9 vs. 46.0 per 1000 patient-years Results did not vary by use of sulfonylurea or insulin for intensive control Microvascular end point: RR, 0.75 (95% CI, 0.60 to 0.93); 8.6 vs. 11.4 per 1000 patient-years Retinal photocoagulation: RR, 0.71 (99% CI, 0.53 to 0.96); 7.9 vs. 11.0 per 1000 patient-years	All-cause mortality: HR, 0.94 (95% CI, 0.80 to 1.10) Diabetes-related mortality: HR, 0.90 (95% CI, 0.78 to 1.11) Fatal MI: RR, 0.94 (95% CI, 0.68 to 1.30) Fatal stroke: RR, 1.17 (95% CI, 0.54 to 2.54)	No single macrovascular end point was statistically significant, including nonfatal MI, heart failure, angina, nonfatal stroke, amputation, renal failure; risk differences were ≤2 per 1000 patient-years	Increased hypoglycemia, including major hypoglycemia Major hypoglycemic episodes per year: chlorpropamide, 1.0%; glibenclamide, 1.4%; insulin, 1.8%; and diet, 0.7%; all *P* < 0.0001 Any hypoglycemic episodes: chlorpropamide, 16%; glibenclamide, 21%; insulin, 28%; diet, 10% Hypoglycemic episodes in patients on diet therapy were reactive and occurred either after meals or after termination of glucose infusions given while in hospital Weight gain: 3.1 kg (99% CI, −0.9 to 7.0 kg); *P* < 0.0001

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Appendix Table 2–Continued

Study, Year (Reference) Mean or Median Follow-up Patients Enrolled	Age at Baseline, *y*	Diabetes Duration	Intensive vs. Control					
			HbA_{1c} Level, %		Microvascular and Combined Microvascular/ Macrovascular Events	Mortality	Macrovascular Events	AEs
			Baseline	Achieved				
UKPDS 34, 1998 (22) Metformin Median: 10.7 y *n* = 753 Sulfonylurea or insulin added if hyperglycemic symptoms developed	53	New diagnosis (35% with retinopathy)	Median: 7.2	Median: 7.4 vs. 8.0	Any diabetes-related end point*: RR, 0.68 (95% CI, 0.53 to 0.87) (mostly clinical and macrovascular but includes photocoagulation); 43.3 vs. 29.8 per 1000 patient-years Microvascular: RR, 0.71 (95% CI, 0.42 to 1.19) Sulfonylurea + metformin, any DM end point: RR, 1.04 (95% CI, 0.77 to 1.42)	Any diabetes-related death: RR, 0.58 (95% CI, 0.37 to 0.91); 7.5 vs. 12.7 per 1000 patient-years All-cause mortality: RR, 0.64 (95% CI, 0.45 to 0.91); 13.5 vs. 20.6 per 1000 patient-years Fatal stroke: RR, 0.75 (95% CI, 0.19 to 2.93) Fatal MI: RR, 0.50 (95% CI, 0.23 to 1.09) Early addition of metformin to sulfonylureas resulted in increased all-cause mortality: RR, 1.60 (95% CI, 1.02 to 2.52) and diabetes-related death: RR, 1.96 (95% CI, 1.02 to 3.75), compared with continued sulfonylurea alone	MI: RR, 1.09 (95% CI, 0.67 to 1.18) Stroke: RR, 1.21 (95% CI, 0.58 to 2.65) No significant difference in heart failure, angina, nonfatal stroke, amputation, or renal failure	The addition of metformin to sulfonylurea was associated with a 96% increased risk for diabetes-related death (*P* = 0.039); addition of metformin to sulfonylurea therapy also increased the risk for death from any cause (60% increase; *P* = 0.041)

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Appendix Table 2–Continued

Study, Year (Reference) Mean or Median Follow-up Patients Enrolled	Age at Baseline, y	Diabetes Duration	Intensive vs. Control					
			HbA$_{1c}$ Level, %		Microvascular and Combined Microvascular/ Macrovascular Events	Mortality	Macrovascular Events	AEs
			Baseline	Achieved				
UKPDS 33, 2008 (16) Follow-up for sulfonylurea Median: 16.8 y *n* = 3867				Median: 7.9 vs. 8.5	Any diabetes-related end point*: RR, 0.91 (95% CI, 0.83 to 0.99); 48.1 vs. 52.2 per 1000 patient-years Microvascular disease: RR, 0.76 (95% CI, 0.64 to 0.89); 11.0 vs. 14.2 per 1000 patient-years	All-cause mortality: RR, 0.87 (95% CI, 0.79 to 0.96); 26.8 vs. 30.3 per 1000 patient-years Diabetes-related mortality: HR, 0.83 (95% CI, 0.73 to 0.96); 14.5 vs. 17.0 per 1000 patient-years	MI: RR, 0.85 (95% CI, 0.74 to 0.97); 16.8 vs. 19.6 per 1000 patient-years Stroke: RR, 0.91 (95% CI, 0.73 to 1.13) Peripheral vascular disease: RR, 0.82 (95% CI, 0.56 to 1.19)	
UKPDS 34, 2008 (16) Follow-up for metformin Median: 17.7 y n = 753				Median: 8.4 vs. 8.9	Any diabetes-related end point*: RR, 0.79 (95% CI, 0.66 to 0.95); 45.7 vs. 53.9 per 1000 patient-years Microvascular disease: RR, 0.84 (95% CI, 0.60 to 1.17); 12.4 vs. 13.4 per 1000 patient-years	All-cause mortality: RR, 0.73 (95% CI, 0.59 to 0.89); 25.9 vs. 33.1 per 1000 patient-years Diabetes-related mortality: HR, 0.70 (95% CI, 0.53 to 0.92); 14.0 vs. 18.7 per 1000 patient-years	MI: RR, 0.67 (95% CI, 0.51 to 0.89); 14.8 vs. 21.1 per 1000 patient-years Stroke: RR, 0.80 (95% CI, 0.50 to 1.27) Peripheral vascular disease: RR, 0.63 (95% CI, 0.32 to 1.27)	

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Appendix Table 2–Continued

Study, Year (Reference) Mean or Median Follow-up Patients Enrolled	Age at Baseline, *y*	Diabetes Duration	Intensive vs. Control					
			HbA_{1c} Level, %		Microvascular and Combined Microvascular/ Macrovascular Events	Mortality	Macrovascular Events	AEs
			Baseline	Achieved				
VADT, 2009 (21) Median: 5.6 y *n* = 1791	Mean: 60.4	11.5 y (prior CVD: 40.7%)	Median: 9.4	Median: 6.9 vs. 8.4	Microvascular complications: No difference between intensive and standard control, including ophthalmologic disorder (cataract surgery, photocoagulation, vitrectomy, retinopathy [progression to proliferative disease, progression to clinically significant macular edema, increase of 2 steps in severity of disease, new onset]); neuropathy (including any, mononeuropathy, peripheral, autonomic); nephropathy (doubling of serum creatinine; creatinine level >3 mg/dL; GFR <15 mL/min) Any increase in albuminuria, 9.1% vs. 13.8%; *P* < 0.01	All-cause mortality: HR, 1.07 (95% CI, 0.81 to 1.42) CV mortality: HR, 1.32 (95% CI, 0.81 to 2.14)	MACE* (MI; stroke; death from CV causes; new or worsening CHF; surgical intervention for cardiac, cerebrovascular, or peripheral vascular disease; inoperable coronary artery disease; amputation for ischemic gangrene): HR, 0.88 (95% CI, 0.74 to 1.05) (or any component of MACE)	Hypoglycemic episode with impaired consciousness: 9 vs. 3 per 100 patient-years; *P* < 0.001 Hypoglycemia with complete loss of consciousness: 3 vs. 1 per 100 patient-years; *P* < 0.001 Hypoglycemia as serious AE: 8.5% vs. 3.1%; *P* < 0.0001 With documented glucose <50 mg/dL: 203 vs. 52 per 100 patient-years; *P* < 0.001 Any serious AE: 24.1% vs. 17.6%; *P* = 0.05 Dyspnea: 11.0% vs. 7.2%; *P* = 0.006 End of study weight: 232 lb vs. 223 lb; *P* = 0.01 BMI: 33.8 vs. 32.3 kg/m^2; *P* = 0.01

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Appendix Table 2–Continued

Study, Year (Reference) Mean or Median Follow-up Patients Enrolled	Age at Baseline, *y*	Diabetes Duration	Intensive vs. Control					
			HbA_{1c} Level, %		Microvascular and Combined Microvascular/ Macrovascular Events	Mortality	Macrovascular Events	AEs
			Baseline	Achieved				
VADT, 2015 (17) follow-up Median: 11.8 y				~8.2	MACE* (time to first major CV event: heart attack, stroke, new or worsening CHF [including hospitalization with EF <40%], amputation for ischemic gangrene, or CV-related death): HR, 0.83 (95% CI, 0.70 to 0.99); 44.1 vs. 52.7 per 1000 person-years Results did not differ between patients with lower overall vs. higher overall CV risk at baseline or with respect to a prior CV event or baseline HbA_{1c}	All-cause mortality: HR, 1.05 (95% CI, 0.89 to 1.25) CV mortality: HR, 0.88 (95% CI, 0.64 to 1.20)		

ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; AE = adverse event; ARR = absolute risk reduction; BMI = body mass index; CHF = congestive heart failure; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; EF = ejection fraction; GFR = glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c}; HR = hazard ratio; MACE = major adverse cardiac event; MI = myocardial infarction; RR = relative risk; RRR = relative risk reduction; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.
* Primary study outcome.