Care of the Aging Patient: From Evidence to Action

Polypharmacy in the Aging Patient
A Review of Glycemic Control in Older Adults With Type 2 Diabetes

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IMPORTANCE There is substantial uncertainty about optimal glycemic control in older adults with type 2 diabetes mellitus.

OBSERVATIONS Four large randomized clinical trials (RCTs), ranging in size from 1791 to 11 440 patients, provide the majority of the evidence used to guide diabetes therapy. Most RCTs of intensive vs standard glycemic control excluded adults older than 80 years, used surrogate end points to evaluate microvascular outcomes and provided limited data on which subgroups are most likely to benefit or be harmed by specific therapies. Available data from randomized clinical trials suggest that intensive glycemic control does not reduce major macrovascular events in older adults for at least 10 years. Furthermore, intensive glycemic control does not lead to improved patient-centered microvascular outcomes for at least 8 years. Data from randomized clinical trials consistently suggest that intensive glycemic control immediately increases the risk of severe hypoglycemia 1.5- to 3-fold. Based on these data and observational studies, for the majority of adults older than 65 years, the harms associated with a hemoglobin A_{1c} (HbA_{1c}) target lower than 7.5% or higher than 9% are likely to outweigh the benefits. However, the optimal target depends on patient factors, medications used to reach the target, life expectancy, and patient preferences about treatment. If only medications with low treatment burden and hypoglycemia risk (such as metformin) are required, a lower HbA_{1c} target may be appropriate. If patients strongly prefer to avoid injections or frequent fingerstick monitoring, a higher HbA_{1c} target that obviates the need for insulin may be appropriate.

CONCLUSIONS AND RELEVANCE High-quality evidence about glycemic treatment in older adults is lacking. Optimal decisions need to be made collaboratively with patients, incorporating the likelihood of benefits and harms and patient preferences about treatment and treatment burden. For the majority of older adults, an HbA_{1c} target between 7.5% and 9% will maximize benefits and minimize harms.

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Older patients with diabetes are increasingly common in clinical practice due to the aging US population, the decreased mortality rates among persons with diabetes, and the obesity epidemic.[1,2] Among US residents aged 65 years and older, 10.9 million (26.9%) had diabetes in 2010[3] and this number is projected to increase to 26.7 million by 2050.[4] The majority (> 95%) of older adults with diabetes have type 2 diabetes mellitus.

Insulin resistance and impaired beta-cell function both contribute to the pathogenesis of type 2 diabetes in older adults.[5,6] Aging is associated with accumulation of fat in muscle and liver tissues and reduced rates of mitochondrial activity in muscle and brain, contributing to insulin resistance.[7,8] Along with these changes, aging is associated with defects in insulin secretion, which further contribute to hyperglycemia and type 2 diabetes.[9-12]

In older adults, classic symptoms of diabetes, such as polyuria, and polydipsia, may be absent. Instead, diabetes may present with dehydration, confusion, incontinence, and diabetes complications, such as neuropathy or nephropathy. Typically, the disease is asymptomatic and usually diagnosed based on routinely performed laboratory studies (**Box 1**).[13,15]

The criteria for diagnosis are the same for younger and older adults.[13] They are based on plasma glucose and hemoglobin A_{1c} (HbA_{1c}) thresholds that increase the risk of developing retinopathy.[15] Incident diabetes among older compared with younger adults more often manifests as postprandial rather than fasting hyperglycemia.[16] Measurement of HbA_{1c} is often more convenient than obtaining a fasting plasma glucose, but there are some clinical conditions common in older persons, such as chronic kidney disease or anemia, that may restrict the ability of HbA_{1c} to accurately reflect average glycemia.[14]

In adults older than 70 years, the nonfatal diabetes complications with the highest incidence rates include congestive heart failure, coronary artery disease, and cerebrovascular disease.[17] How-

ever, among older patients with duration of diabetes of 10 years or more, rates of acute hypoglycemic events and eye disease slightly exceed rates of cerebrovascular disease and approximate those of coronary artery disease.[17] Therefore, both the risk of diabetes complications and the risk of therapy resulting in hypoglycemia become critically important to consider when setting therapeutic goals.

The goals of treatment of type 2 diabetes are to improve symptoms (if present), reduce the risk of acute and chronic diabetes complications, and minimize harms and burdens of therapy. Glycemic control has been the central focus of diabetes care for decades[18-23] and is the primary subject of this review. Randomized trials have shown that intensive glycemic control may lower the risk of some long-term complications (ie, microvascular disease[18,19]) but increase the risk of harm (ie, hypoglycemia[18-23]).

Decisions about glycemic treatment involve trade-offs between these possible benefits versus the potential harms and burdens of treatment. For some persons, the benefits of tight glycemic control may outweigh the harms. For others, the harms may be more important than the benefits. Recent guidelines on glucose-lowering treatment of older adults acknowledge that the likelihood of benefits and harms varies across patient subgroups and endorse individualized glycemic targets.[13,24-28] However, there is substantial uncertainty about how to individualize glycemic targets and treatment plans for older adults with multiple comorbidities and risk factors. The goal of this article is to synthesize the available evidence and provide clinicians practical information to guide discussions about glycemic treatment with these vulnerable patients.

Box 1. Special Considerations in the Diagnosis of Type 2 Diabetes Mellitus in Older Adults

Clinical Features

Most often asymptomatic and diagnosed based on routine laboratory evaluation

Classic symptoms (polyuria, polydipsia) may be absent

May present with dehydration, confusion, incontinence, and diabetes complications, such as neuropathy or nephropathy

Diagnosis

Standard diagnostic criteria apply (fasting plasma glucose ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL during an OGTT, HbA_{1c} ≥ 6.5%, or random blood glucose ≥200 mg/dL in the presence of classic symptoms of hyperglycemia[a])[13]

More likely to have abnormal 2-hour plasma glucose during an OGTT

Cautions

The HbA_{1c} level may not accurately reflect hyperglycemia in conditions common among older adults, including anemia, recent blood transfusions, treatment with erythropoietin, or chronic kidney disease[14]

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; OGTT, oral glucose tolerance test.

SI conversion: To convert glucose from mg/dL to mmol/L, multiply by 0.0555; HbA_{1c} in percentage to mmol/mol, subtract 2.152 and then multiply by 10.93.

[a] In the absence of hyperglycemic symptoms, these criteria must be repeated and confirmed.

Methods

We used the Cochrane review of randomized clinical trials (RCTs) for intensive glycemic control to identify studies from inception of the included databases through 2012. Using the same search strategy as the Cochrane review, we searched MEDLINE to identify additional studies published between January 2013 and June 2015. We included randomized, double-blind trials with more than 100 participants in each group with type 2 diabetes, with at least 2 years of follow-up after randomization, with prespecified cardiovascular and microvascular outcomes, and with follow-up of 90% or more of randomized participants for vital status (eTable 1 in the Supplement). We also determined how many of these trials included patients aged 80 years or older.

We used the American College of Cardiology/American Heart Association (ACC/AHA) methods[29] to assess the strength of the evidence on the benefits and harms of glucose-lowering treatment based on the obtained data. The goal was to provide information that would help an older patient better understand what to expect from glucose-lowering treatment, what the benefits and harms are, and in what time frame benefits and harms are most likely. Moreover, in order to make an informed decision, the patient needs to understand the strength of the evidence.

Results

Glucose-Lowering Treatment in Older Adults—Deficiencies of the Evidence Base

The evidence about the benefits and harms of intensive vs standard glycemic control comes primarily from 4 large RCTs: UK Prospective Diabetes Study (UKPDS),[18,19] Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[22] Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial,[21] and Veterans Affairs Diabetes Trial (VADT)[20] as well as several meta-analyses[30-34] (**Table 1**). These landmark trials allocated glucose-lowering treatments in a randomized and concealed fashion and maintained balance across the 2 groups throughout follow-up, resulting in a relatively low risk of bias.[36] The definitions of the outcomes in these trials are summarized in **Box 2**.

However, applying these data to questions of benefits and harms for older patients presents several challenges.

Trials Have Focused on Younger Patients

The mean age of participants in the major RCTs ranged between 53 and 66 years, and very few (if any) adults older than 80 years were included (Table 1).[37,38] One important reason for this underrepresentation is that intensive glycemic control in older patients raised safety concerns. Early on in the ACCORD trial, the data and safety monitoring board specifically recommended against further recruitment of participants older than 80 years because of frequent hypoglycemia observed in this group.[39] Therefore, applying the results of the major RCTs to older adults is problematic.

Trials Have Focused on Surrogate End Points Rather Than Clinical Outcomes

Clinical trials of glucose-lowering therapies often rely on intermediate or surrogate end points, such as albuminuria or worsening creatinine (Table 1). Although these end points are strongly associated with clinical outcomes such as dialysis or death due to renal failure, it often takes many years of albuminuria or worsening creatinine to

Table 1. Characteristics of Major Randomized Clinical Trials of Intensive Glycemic Control and Their Outcomes

	UKPDS[18]	ACCORD[22]	ADVANCE[21]	VADT[20]	
Trial Dates	1977-1998	1999-2008	2001-2008	2000-2008	Cochrane Review[a]
Trial participants					
No.	4209	10 251	11 440	1791	34 325
Age, mean (SD), y	53 (9)	62 (7)	66 (6)	60 (9)	62[b]
Age ≥80 y, No. (%)	0 (0)[c]	47 (0.5)	178 (1.6)	NR	NR
Duration of diabetes at baseline, mean (SD), y	Recent diagnosis	10 (NR)	8 (6)	11.5 (NR)	NR
Trial Intervention					
Target HbA_{1c}, %					
Intensive control	FPG < 108 mg/dL	< 6	≤ 6.5	< 6	Varied across trials
Standard control	Not defined	7-7.9	Per local guidelines	8-9	
Achieved HbA_{1c}, %					
Intensive control	7.0	6.4	6.5	6.9	Varied across trials
Standard control	7.9	7.5	7.3	8.4	
Trial Outcomes[d]					
Macrovascular complications composite[e]					
Intensive control, No./total (%)	169/2729 (6.2)	352/5128 (6.9)	557/5571 (10.0)	235/892 (26.3)	1745/17 444 (10.0)
Standard control, No./total (%)	87/1138 (7.6)	371/5123 (7.2)	590/5569 (10.6)	264/899 (29.4)	1681/15 402 (10.9)
Relative risks (95% CI)	0.80 (0.62-1.04)	0.90 (0.78-1.04)	0.94 (0.84-1.06)	0.90 (0.70-1.16)	0.91 (0.82-1.02)
Microvascular complications composite[e]					
Intensive control, No./total (%)	249/3071 (8.1)	556/5128 (10.8)	526/5571 (9.4)	NR	1402/13 933 (10.1)
Standard control, No./total (%)	121/1138 (10.6)	586/5123 (11.4)	605/5569 (10.9)	NR	1396/11 994 (11.6)
Relative Risks (95% CI)	0.76 (0.62-0.94)	0.95 (0.85-1.06)	0.87 (0.78-0.97)	NR	0.88 (0.82-0.95)
Retinopathy composite[e]					
Intensive control, No./total (%)	363/2729 (13.3)	81/1429 (5.7)	88/791 (11.1)	123/534 (23)	774/5932 (13.0)
Standard control, No./total (%)	172/1138 (15.1)	126/1427 (8.8)	99/811 (12.2)	154/534 (28.8)	706/4368 (16.2)
Relative risks (95% CI)	0.88 (0.74-1.04)	0.64 (0.49-0.84)	0.91 (0.70-1.19)	0.80 (0.65-0.98)	0.79 (0.68-0.92)
Nephropathy composite[e]					
Intensive control, No./total (%)	11/2729 (0.4)	3056/5128 (59.6)	230/5571 (4.1)	78/892 (8.7)	3429/14 838 (23.1)
Standard control, No./total (%)	11/1138 (1.0)	3077/5123 (60.1)	292/5569 (5.2)	78/899 (8.7)	3550/13 258 (26.8)
Relative risks (95% CI)	0.42 (0.18-0.96)	0.99 (0.96-1.02)	0.79 (0.67-0.93)	1.01 (0.75-1.36)	0.75 (0.59-0.95)
End-stage renal disease (dialysis, death due to renal disease)[30]					
Intensive control, No./total (%)	28/3071 (0.9)	140/5128 (2.7)	22/5571 (0.4)	2/892 (0.2)	193/15 036 (1.3)
Standard control, No./total (%)	11/1138 (1.0)	152/5123 (3.0)	33/5569 (0.6)	3/899 (0.3)	205/13 109 (1.6)
Relative risks (95% CI)	0.94 (0.47-1.89)	0.92 (0.73-1.15)	0.67 (0.39-1.14)	0.67 (0.11-4.01)	0.87 (0.71-1.06)
Severe hypoglycemia[e]					
Intensive control, No./total (%)	33/3071 (1.1)	830/5128 (16.2)	150/5571 (2.7)	76/892 (8.5)	1119/15 359 (7.3)
Standard control, No./total (%)	8/1138 (0.7)	261/5123 (5.1)	81/5569 (1.5)	28/899 (3.1)	395/13 435 (2.7)
Relative risks (95% CI)	1.53 (0.71-3.30)	3.18 (2.78-3.63)	1.85 (1.42-2.42)	2.74 (1.79-4.18)	2.18 (1.53-3.11)

Abbreviations: FPG, fasting plasma glucose; NR, not reported.

SI conversion: To convert HbA_{1c} in percentage to mmol/mol, subtract 2.152 and then multiply by 10.93.[35]

[a] Cochrane review included 24 trials. The 4 trials listed here contributed 80% of the sample for the Cochrane review.[30]

[b] SD not reported in the Cochrane review.

[c] Ages 25 to 65 years only.

[d] Relative risks less than 1 denote fewer events with intensive control.

[e] The trial outcome definitions are specified in Box 2.

lead to clinical outcomes. Because many older patients have limited life expectancy, the use of these intermediate end points may not be relevant.

Trials Provide Limited Data on Which Subgroups Are Most Likely to Benefit or Be Harmed

To make informed decisions, patients need individualized information on the relative benefits and risks of glycemic control. However, data about the likelihood of benefits and harms across large subgroups are currently limited. In both the ACCORD and ADVANCE studies, the effect of glycemic control on outcomes did not differ between younger and older (< 65 vs ≥ 65 years) patients.[21,39] In contrast, other subgroup analyses that explored whether intensive glycemic control is more beneficial in specific patient groups (ie, those with a history of microvascular disease, macrovascular disease, or < 15 years of diabetes) yielded conflicting results.[21,22,40]

Box 2. Definition of Trial Outcomes

Definition for Macrovascular Complications Composite[30]

UKPDS: Not defined. Composite measure of death from cardiovascular causes (including sudden death), nonfatal myocardial infarction, and nonfatal stroke as reported in the meta-analysis by Turnbull et al[31] (note: data were censored at 5 years after randomization)

ACCORD: Nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death

ADVANCE: Nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death

VADT: Myocardial infarction, stroke, cardiovascular death, new or worsening heart failure, surgical intervention for cardiac, cerebrovascular or peripheral vascular disease, amputation, or inoperable coronary artery disease

Cochrane: Nonfatal myocardial infarction, nonfatal ischemic stroke, nonfatal hemorrhagic stroke, amputation of lower extremity, or cardiac or peripheral revascularization

Definition for Microvascular Complications Composite[30]

UKPDS: Retinopathy requiring photocoagulation, vitreous hemorrhage, or renal failure

ACCORD: Fatal or nonfatal renal failure, serum creatinine more than 3.3 mg/dL, retinal photocoagulation or vitrectomy for diabetic retinopathy

ADVANCE: New or worsening nephropathy or retinopathy (development of proliferative retinopathy, macular edema, diabetes-related blindness, or retinal photocoagulation)

VADT: Retinopathy, nephropathy, or neuropathy

Cochrane: manifestation and progression of nephropathy, end-stage renal disease, manifestation and progression of retinopathy, or retinal photocoagulation

Definition for Retinopathy Composite[30]

UKPDS: 1 or more microaneurysms and 2 or more changes in the Early Treatment of Diabetic Retinopathy Study scale

ACCORD: Progression of 3 or more stages of the Early Treatment of Diabetic Retinopathy Study scale

ADVANCE: Progression of 2 or more steps in the Early Treatment of Diabetic Retinopathy Study classification

VADT: 2-point increase in the Early Treatment of Diabetic Retinopathy Study

Cochrane: Manifestation and progression of retinopathy (varied by individual study)

Definition for Nephropathy[30]

UKPDS: 2-fold plasma creatinine increase

ACCORD: Doubling of serum creatinine or a 20mL/min/1.73 m^2 decrease in estimated glomerular filtration rate, development of macroalbuminuria, or development of renal failure

ADVANCE: Development of macroalbuminuria or doubling of the serum creatinine level to at least 2.3 mg/dL, the need for renal replacement therapy, or death due to renal disease

VADT: Doubling of the serum creatinine level, a creatinine level of more than 3 mg/dL, or a glomerular filtration rate less than 15 mL per minute

Cochrane: Manifestation and progression of nephropathy (varied by individual study)

End-stage renal disease composite was defined in all trials as severe renal failure (dialysis, renal transplantat, or death due to renal failure)

Definition for Severe Hypoglycemia[30]

UKPDS: Hypoglycemia requiring third-party help or medical intervention

ACCORD: Hypoglycemia with documented blood glucose less than 50 mg/dL or symptoms that promptly resolve with oral carbohydrate, intravenous glucose, or glucagon that require any assistance (medical or nonmedical)

ADVANCE: Patients with transient dysfunction of the central nervous system who were unable to treat themselves

VADT: Medical intervention to avert a life-threatening event or hospitalization

Cochrane: Hypoglycemia requiring assistance

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

SI conversion: To convert creatinine from mg/dL to μmol/L, multiply by 88.4; glucose from mg/dL to mmol/L, multiply by 0.0555.

Few Studies on Which Medications Work Best for Which Patients

Clinicians and patients can now choose from 12 different classes of glucose-lowering agents, with many patients needing a combination of drugs. However, there are few comparative effectiveness outcomes studies to guide clinical practice, let alone guide practice for the oldest patients. Long-term clinical outcomes associated with the use of different medications are unknown. These deficiencies are particularly pronounced among higher-risk subpopulations, such as older adults and patients with underlying comorbid conditions.[41] A summary of advantages and disadvantages of commonly used agents is presented in **Table 2**, and patient decision aids incorporating this information are available for use in clinical practice.[50]

Making Glycemic Treatment Decisions With Limited Evidence

Despite limited evidence, patients and clinicians must make decisions on how to manage hyperglycemia. We synthesized the available evidence and developed a 4-step approach to help patients and clinicians individualize glycemic treatment. For each step, we included a discussion of the quality of the available evidence based on the ACC/AHA criteria (eTable 2 in the Supplement). In the following sections, intensive glycemic control is defined as an HbA_{1c} value lower than 7%.

Estimate Benefits of Intensive Glycemic Control

Cardiovascular Benefits | The UKPDS, ACCORD, ADVANCE, and VADT trials showed that intensive glycemic control (HbA_{1c} <7%; to convert HbA_{1c} in percentage to mmol/mol, subtract 2.152 and then multiply by 10.93)[35]did not significantly reduce major cardiovascular events (defined as myocardial infarction, stroke, or cardiovascular mortality) during each of these trials.[18,20-22] Long-term, observational follow-up of trial participants showed reductions in major cardiovascular events associated with intensive glycemic

Table 2. Comparison of Different Classes of Glucose Lowering Medication for Older Adults[a]

	Glycemic Control: Reduction of HbA_{1c}, %	Adverse Effects	Cardiovascular Safety	Cost per Month ($ US)[b]
Biguanides	1-2[42]	Risk of lactic acidosis Do not use below eGFR of 30 mL/min/1.73 m^2 Do not use in patients with decompensated heart failure Gastrointestinal adverse effects (nausea, diarrhea)	Reduced cardiovascular events and mortality[18]	Low (<10)
Metformin				
Sulfonylureas	1-2	Risk of hypoglycemia Avoid long-acting sulfonylureas (glyburide, glimepiride) Weight gain	Uncertain risk of increased cardiovascular events	Low (<10)
Glyburide				
Glipizide				
Glimepiride				
Thiazolidinediones	1-2[43]	Fluid retention Weight gain Heart failure risk Avoid use in class III or IV heart failure Fracture risk Uncertain bladder cancer risk	Increased risk of myocardial infarction (rosiglitazone)	Moderate (10-100)
Pioglitazone				
Rosiglitazone				
α-Glucosidase inhibitors	0.4-0.9	Gastrointestinal adverse effects (flatulence)	Reduced cardiovascular events in patients with impaired glucose tolerance[44]	Moderate cost (10-100)
Acarbose				
Glinides	0.4-0.9	Weight gain Risk of hypoglycemia Avoid nateglinide in renal dysfunction	Unknown	Moderate (10-100)
Repaglinide				
Nateglinide				
Amylin mimetics	0.6	Gastrointestinal adverse effects (nausea) Risk of hypoglycemia when used with insulin	Unknown	Very high (>300)
Pramlintide				
GLP-1 mimetics	1	Weight loss Gastrointestinal adverse effects (nausea, vomiting, diarrhea) Uncertain risk of acute pancreatitis	Unknown	High (100-300)
Exenatide				
Liraglutide				
DPP-4 inhibitors	0.5-0.8	Uncertain risk of acute pancreatitis Uncertain risk of severe joint pain Skin lesions	2 Cardiovascular outcomes trials showed neutral effects on major cardiovascular events[45,46]	Very high (>300)
Sitagliptin				
Saxagliptin				
Linagliptin				
Alogliptin				
SGLT2 inhibitors	0.5-0.7	Weight loss Blood pressure lowering Vulvovaginal candidiasis and urinary tract infections May lead to abnormalities in renal function; elderly patients with preexisting renal impairment may be at greater risk Avoid when eGFR < 60 mL/min/1.73 m^2 Risk of euglycemic diabetic ketoacidosis	Reduction in rates of cardiovascular events and mortality in one study[47]	Very high (>300)
Dapagliflozin				
Canagliflozin				
Empagliflozin				
Insulin	No limit	May challenge self-management capacity Risk of hypoglycemia Weight gain	1 Trial showed neutral effects[48]	Variable

Abbreviations: DPP, dipeptidyl peptidase; eGFR, estimated glomerular filtration rate; GLP, glucagon-like peptide; HbA_{1c}, hemoglobin A_{1c}; SGLT2, sodium-glucose cotransporter 2.

SI conversion: To convert HbA_{1c} in percentage to mmol/mol, subtract 2.152 and then multiply by 10.93.[35]

[a] Information about these medications that can be used in the shared decision-making process with patients is available at http://shareddecisions.mayoclinic.org/decision-aid-information/decision-aids-for-chronic-disease/diabetes-medication-management.

[b] Costs are the wholesale acquisition cost of a 30-day supply of the initial dose of each medication.[49]

control in the UKPDS,[51] ACCORD,[52] and VADT[53] trials, but not in the ADVANCE trial.[54] These reductions emerged after at least 10 years of follow-up and were not associated with improved mortality among ADVANCE[54] and VADT[53] trial participants. In the ACCORD trial, increased mortality was seen among intensively treated participants.[55] Therefore, RCTs do not support intensive glycemic control to reduce major cardiovascular events in older adults, at least in the first 10 years of intervention. Because patients

older than 80 years and those with other comorbidities were excluded from the trials, this conclusion may not apply to these patients (level B evidence).

Microvascular Benefits | The ACCORD, ADVANCE, and VADT trials did not show a significant effect of intensive treatment on clinical microvascular outcomes important to patients; however, multiple surrogate end points improved with intensive glycemic control.[20-22] For example, the ADVANCE trial showed a 14% (95% CI, 3%-23%) relative risk reduction in the primary microvascular end point, which combined nephropathy and retinopathy composites. This risk reduction was driven by a reduction in nephropathy. In turn, the only component of the nephropathy composite that was significantly reduced was the development of macroalbuminuria (2.9% vs 4.1% in intensive vs standard groups, respectively; P <.001). In the ACCORD and VADT trials, intensive glycemic control did not significantly reduce the secondary microvascular end points that were not based on albuminuria.[20,22,56]

In contrast, the UKPDS trial and its follow-up, which reflects medical practice common more than 20 years ago, showed a significant reduction in microvascular complications defined as a composite of photocoagulation, vitreous hemorrhage, and renal failure, ie, based on clinical outcomes important to patients.[51] In the first 8 years of the trial, the control and intensive treatment groups had the same rates of microvascular complications, suggesting no benefits from intensive treatment. In years 8 to 15, the control and intervention group curves diverged, suggesting that the intervention group was starting to benefit based on decreased microvascular complications. Beyond 15 years, the 2 curves did not diverge further, suggesting there was little additional benefit. The absolute benefits were small—microvascular events were reduced from 14.2 to 11.0 per 1000 patient-years.

Taken together, the results of these trials suggest that intensive glycemic control does not reduce microvascular outcomes important to patients, at least in the first 8 years of intervention. In contrast, there may be a small microvascular benefit that emerges after 8 to 15 years of treatment, based on the UKPDS trial follow-up. However, it must be noted that the UKPDS trial results are not readily applicable to older patients with long-standing diabetes because UKPDS trial included younger patients with newly diagnosed disease. In addition, the RCTs used surrogate end points that do not directly apply to clinical outcomes (level B evidence).

Estimate Harms of Intensive Glycemic Control

All 4 major RCTs showed that intensive glycemic control increases the risk of severe hypoglycemia.[18,20-22] Although both younger and older participants are at higher risk of severe hypoglycemia when randomized to intensive glycemic control,[57] the baseline risk of severe hypoglycemia (irrespective of trial group assignment) increases with age (hazard ratio, 1.03 per each 1 year increase, P < .001). For example, in the ACCORD trial, the annual risk of severe hypoglycemia requiring medical assistance for participants younger than 65 years was 0.8% in the standard glycemic control group vs 2.4% in the intensive glycemic control group.[22] For participants 75 years or older, the annual risk of severe hypoglycemia was much higher: 1.4% in the standard glycemic control group vs 5.3% in the intensive glycemic control group.[58]

Other data on harms associated with intensive glycemic control come primarily from epidemiologic analyses. Poor cognitive function has been associated with increased risk of severe hypoglycemia.[59] In addition, age, duration of diabetes, use of multiple medications, frequent hospitalizations, and cognitive impairment (markers of underlying frailty) increase the risk of hypoglycemia.[17,58,60-64] Furthermore, treatment with insulin is associated with the highest risk of hypoglycemia compared with other agents.[63]

Taken together, RCTs show that intensive glycemic treatment consistently increases the risk of hypoglycemia by 1.5- to 3-fold. Although the evidence is consistent and based on well-designed RCTs, few older patients were included in these trials. However, results from observational studies support extending these results to older patients (level B evidence).

Establish an Individualized Glycemic Target That Maximizes Benefits but Minimizes Harms According to the Patient's Values

Current evidence suggests that attempts to achieve intensive glycemic control will lead to net harm in the majority of older adults with type 2 diabetes. The ACCORD study showed an increased risk of mortality for patients randomized to intensive glycemic control compared with the standard group.[22] As discussed above, all 4 major trials of intensive glycemic control showed that intensive glycemic treatment increases the rates of severe hypoglycemia compared with standard glycemic control,[20-22] whereas the cardiovascular and microvascular benefits are uncertain for the majority of older adults. Furthermore, modeling studies, based on estimates of microvascular complications drawn from the UKPDS trial (ie, with the most optimistic estimates of benefit), suggest that the marginal benefits of decreasing HbA_{1c} lower than 7.5% are likely small.[65,66] Thus, for the vast majority of older patients with diabetes, the harms associated with an HbA_{1c} target lower than7.5% likely outweigh the benefits.

There is wide consensus that HbA_{1c} values higher than 9% should be avoided because they can lead to immediate symptoms.[25] These symptoms include polyuria, which can occur at blood glucose levels above the renal threshold (>180-200 mg/dL), and may lead to dehydration. In addition, hyperglycemia may lead to fatigue, increased risk for infection, and cognitive impairment. For these reasons, HbA_{1c} values higher than 9% may lead to harms. Most experts and guidelines suggest that HbA_{1c} values higher than 9% should be avoided because of these risks, especially because an HbA_{1c} below 9% can usually be safely achieved.[13,24,25,27,28,67] Despite the consensus, there is remarkably little data to support it.

Modeling studies suggest that patient preferences are critically important in modulating the target HbA_{1c} (within the 7.5%-9% range) because they influence the net benefit (or net harm) achieved from more vs less intensive glycemic control.[66] Different patients place different value on avoiding specific burdens (eg, insulin treatment and fingerstick monitoring).[66] An older patient with a life expectancy more than 15 years who perceives little burden from insulin injections may increase his or her chances of an improved quality of life with intensive glycemic control. In contrast, an older patient who expresses a strong desire to avoid burdensome treatments may experience reduced quality of life with more intensive treatment. Thus, patient preferences and values regarding treatments should play a major role in determining glycemic targets.

Table 3. Minimizing Polypharmacy in Older Adults With Type 2 Diabetes Mellitus

When to Consider Reducing or Stopping Medications	How to Modify Therapy
Lack of benefit	Reduce the dose or stop the medication with highest rates of adverse events, treatment burden, or patient costs Often, this will be the last medication started
HbA_{1c}<6.5% or 7.5% in persons with limited life expectancy	As above
Adverse events	Reduce or stop medications most likely to have caused adverse event
Hypoglycemia	Insulin, sulfonylureas
Weight gain	Insulin, sulfonylureas, thiazolidinediones
Heart failure, edema	Thiazolidinediones
Gastrointestinal adverse effects	Metformin, GLP-1 agonists
Patient preference for decreased intensity of treatment	Elicit and explore the rationale behind patient preferences
Less frequent monitoring of blood glucose	Decrease or stop insulin
High cost of medications	Stop newer, high-cost agents
Limited capacity	Support patient to enhance capacity or choose to accept some hyperglycemia
Cognitive impairment	Explore whether caregivers can administer diabetes medications Decreasing or stopping medications may be best approach if caregivers cannot help
Poor dexterity or vision	

Abbreviations: GLP, glucagon-like peptide; HbA_{1c}, hemoglobin A_{1c}.

SI conversion: To convert HbA_{1c} in percentage to mmol/mol, subtract 2.152 and then multiply by 10.93.[35]

Finally, the type of treatment that is required to achieve a specific target significantly impacts the likelihood of benefits and harms. Lifestyle modification is unlikely to result in harm. Metformin is also considered safe but may cause adverse gastrointestinal effects. An HbA_{1c} target lower than 7% may be reasonable for some patients with the use of this relatively safe medication. In contrast, insulin is associated with the highest risk of hypoglycemia[68] compared with other agents and confers about a 2-fold increased risk compared with sulfonylurea treatment.[63] Furthermore, insulin requires significant self-management capacity, and insulin therapy can frequently result in treatment errors. Thus, for some older patients who are unable to achieve their glycemic target with oral medications, the appropriate response may be to discuss the trade-offs involved in the decision to start insulin rather than reflexively intensify treatment. Other harms or adverse effects of therapy (Table 2) may also influence the decision to modulate the glycemic target.

Therefore, based on RCTs and observational data, the harms associated with an HbA_{1c} target lower than 7.5% or higher than 9% are likely to outweigh the benefits for the majority of older adults. A large part of the evidence is based on observational studies with a risk of bias. Some of the evidence is based primarily on expert opinion (level C evidence).

Minimize Polypharmacy

Most patients' HbA_{1c} levels increase over time, and patients and their clinicians must decide whether to intensify therapy. Decisions to de-intensify therapy must also be made when HbA_{1c} levels decline, the risk of harms increases, or the treatment burden becomes unacceptable to the patient (**Table 3**).

Evidence for Diminishing Benefits With Polypharmacy

The first glucose-lowering medication, which is often started at higher HbA_{1c} levels compared with the levels when the second agent is started, decreases HbA_{1c} more than subsequent medications. Starting a second or third medication for glycemic control leads to smaller reductions in HbA_{1c} than starting that same medication as monotherapy.[69,70] For example, a meta-analysis of trials examining the efficacy of oral glucose-lowering agents showed that for patients with baseline HbA_{1c} levels between 9.0% to 9.9%, oral agents decreased HbA_{1c} levels by 1.0%. For patients with baseline HbA_{1c} levels between 8.0% to 8.9%, oral agents decreased HbA_{1c} levels by only 0.6%; for patients with baseline HbA_{1c} levels between 6.0% to 6.9%, the average reduction was only 0.2%.[71]

Evidence for Increasing Harms With Polypharmacy

Multiple studies have shown that polypharmacy increases the number of adverse drug events,[72,73] including severe hypoglycemia,[63,74] drug-drug interactions,[75,76] interactions with coexisting comorbidities,[77] and patient costs.[78] In addition, the higher the number of medications, the less likely the patient will remain adherent with the treatment regimen.[79,80] Furthermore, diabetes treatments such as insulin and dietary restrictions impose burdens on patients with the consequence of decreased quality of life.[81]

Based on these data, in older patients with type 2 diabetes, increasingly intensive efforts to lower glucose levels with the use of multiple medications tend to be associated with diminishing benefits and greater risks of harm. Although there is consistent evidence with regards to harms of polypharmacy, the balance of benefits and harms has not been evaluated in RCTs (level C evidence).

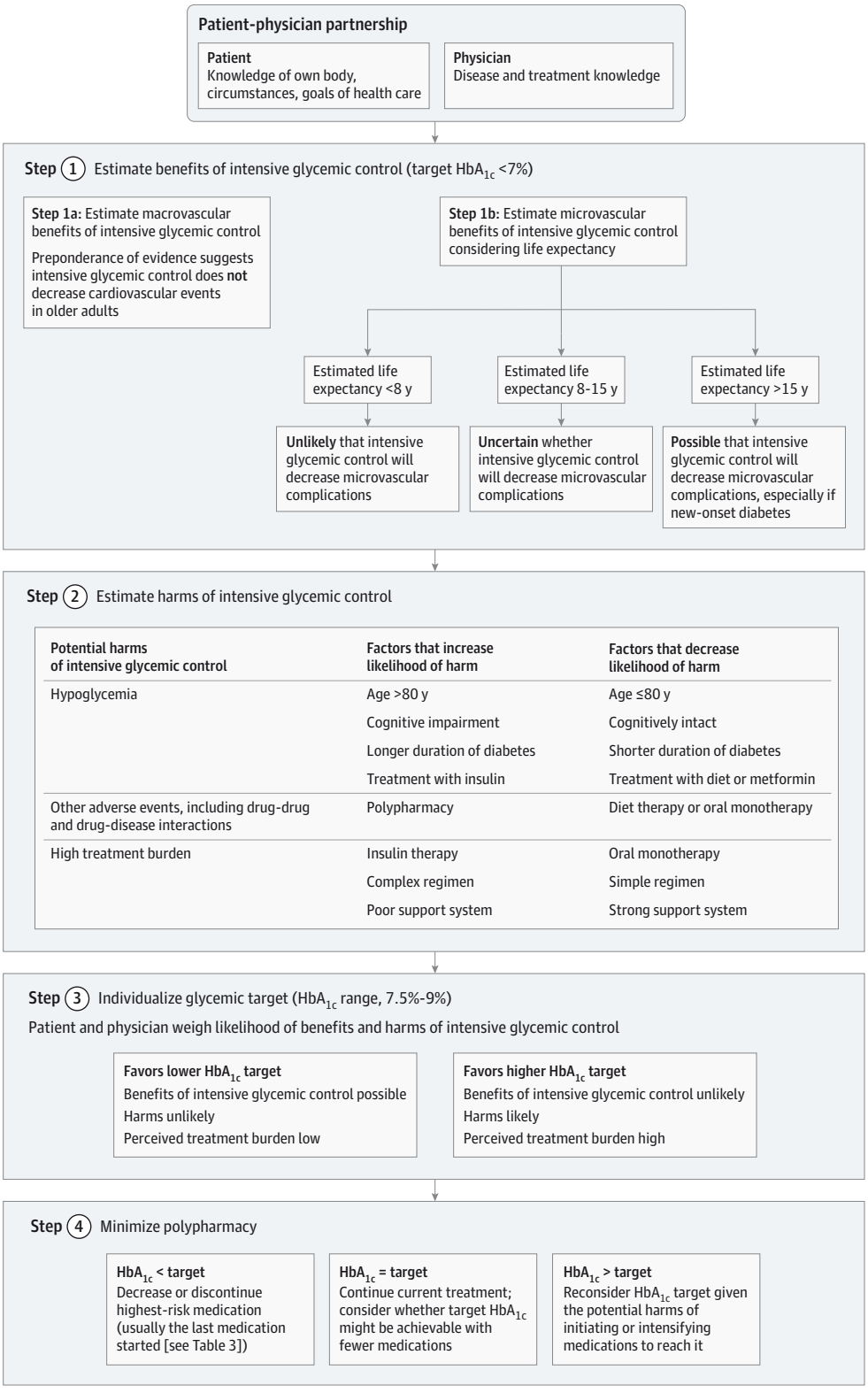
Table 3 outlines circumstances when clinicians and patients should consider decreasing or stopping medications and how this can be done.

Discussion

Currently, older patients with diabetes and their clinicians must make decisions on how best to manage hyperglycemia with limited evidence. These decisions need to balance what is known about the benefits and harms of treatment but require extrapolating evidence from younger, healthier patients, resulting in substantial uncertainty. Furthermore, different patients place different values on possible outcomes of treatment. Because these trade-offs are complex and because the strategies to lower glucose levels require active engagement of patients with respect to adherence and lifestyle behaviors, there is an imperative to involve the patients in the process. A shared-decision-making process, in the course of which a patient and his/her clinician discuss and weigh the likely outcomes from different treatment options, can take into account the best available evidence, as well as the patient's values and preferences about treatment.[82,83]

The **Figure** presents an approach to help older patients and their clinicians individualize glycemic treatment decisions. The process

Figure. Framework to Individualize Glycemic Treatment Decisions in Older Adults



of shared decision making starts with establishment of a strong partnership that serves as the basis for exchange of information.[84] Estimation of life expectancy can help determine whether it is possible for a patient to realize the potential long-term benefits of intensive glycemic control. Several important patient-level factors such as the need for insulin, duration of diabetes, and cognitive im-

pairment determine the likelihood of harms associated with treatment. Patient preferences should play a major role in determining the appropriate glycemic target.

In the following 4 clinical cases, we illustrate how our proposed decision-making framework can be applied to different older adults with diabetes.

Clinical Cases: Managing Glycemia in Older Patients

Case 1

Mrs K is 82 years old and functionally independent and has had a history of type 2 diabetes for the past 7 years. She has been treated with 1000 mg of metformin twice daily without any adverse effects. She also has dyslipidemia, hypertension, and chronic kidney disease. Her HbA_{1c} value is 7.6%, her creatinine level is 1.5 mg/dL (to convert creatinine from mg/dL to µmol/L, multiply by 88.4) with an estimated glomerular filtration rate (eGFR) of 40 mL/min/1.73 m^2.

Estimate Benefits

The lag time to benefit from intensive glycemic control is likely in the order of 10 years. Short-term benefits of reducing HbA_{1c} to lower than 7.5% for her are unclear.

Estimate Harms

Addition of oral medications or insulin may increase treatment burden, risk of adverse effects (including hypoglycemia), treatment errors, and increase costs of care.

Individualize HbA_{1c} Target

Current HbA_{1c} is reasonable, pending a discussion with the patient regarding preferences for treatment. Focus should be on reducing risk of cardiovascular events with blood pressure and lipid control.

Minimize Polypharmacy

Although metformin is contraindicated in women with a creatinine level of 1.5 mg/dL or higher, the risk of lactic acidosis appears to be very low.[85] Metformin monotherapy can be safely continued with more frequent monitoring of renal function (every 3-6 months depending on rate of decline) and at a reduced dose (500 mg twice daily).[85] Because metformin has an excellent safety record and is not associated with either weight gain or hypoglycemia, it remains the first choice agent for treatment of type 2 diabetes.

Case 2

Mrs B is 85 years old and has type 2 diabetes of 10 years' duration. She is functionally dependent, living in a nursing home, with moderate dementia (Mini-Mental State Examination score, 18), depression, hypertension, dyslipidemia, osteoporosis, history of falls, and urinary incontinence. She is taking metformin 500 mg twice daily, glipizide 10 mg twice daily, sitagliptin 100 mg once daily, and pioglitazone 15 mg once daily. Her HbA_{1c} value is 7.1%. She has not had any known hypoglycemia.

Estimate Benefits

Benefits of intensive glycemic control are unclear in functionally dependent patients with limited life expectancy like Mrs B.

Estimate Harms

Mrs B takes multiple medications and is at increased risk of falls and adverse effects from medications.

Individualize HbA_{1c} Target

Her HbA_{1c} target can be relaxed given her multiple comorbidities to reduce polypharmacy. It is reasonable for her HbA_{1c} value to be in the 8% range. The discussion with patient and caregivers should focus on lack of benefits for intensive glycemic control and potential risk of harm with 4 agents.

Minimize Polypharmacy

To minimize Mrs B's medication burden, she could stop taking pioglitazone because it is associated with weight gain, lower extremity edema, risk of heart failure, and osteoporosis in women.

Sitagliptin could also be stopped given its relatively low efficacy and high cost.

Metformin and glipizide could be continued. Routine monitoring of blood glucose is not recommended for patients taking oral medications; however, she is at risk of hypoglycemia, and intermittent monitoring may be helpful to assess for hypoglycemic events. Her glipizide dose can be reduced or stopped if there is any hypoglycemia.

Case 3

Mr C is 78 years old and has had type 2 diabetes for the past 10 years. He has nephropathy (eGFR ≈ 30 mL/min/1.73 m^2), mild retinopathy, and peripheral neuropathy. He has established coronary artery disease and had coronary artery bypass graft 6 years ago. He has osteoarthritis and limited mobility. For his diabetes, he takes glimepiride 4 mg twice a day and linagliptin 5 mg once daily. His HbA_{1c} value is 8.1%.

Estimate Benefits

The discussion with the patient should focus on trade-offs between escalating therapy (eg, with insulin) vs continuing current regimen (with glimepiride and linagliptin). Given that his HbA_{1c} value is higher than 8%, intensifying treatment may result in modest reductions in cardiovascular events and microvascular events. These benefits are likely to emerge after 10 years of treatment.

Estimate Harms

On the other hand, intensifying therapy may require insulin and can be associated with a high treatment burden.

The discussion with the patient should also focus on his risk of hypoglycemia. The patient has several risk factors for hypoglycemia, including chronic kidney disease and presence of established microvascular complications. He should be aware of hypoglycemia symptoms, be able to monitor blood glucose, and be asked to report any symptoms or low blood glucose results to the office.

Individualize HbA_{1c} Target

Current HbA_{1c} level is reasonable, pending a discussion with the patient regarding preferences for treatment. Rather than initiating insulin and increasing his risk of hypoglycemia, it is reasonable to continue current oral medications and accept a higher HbA_{1c} target.

Minimize Polypharmacy

Stopping medications is likely to result in an HbA_{1c} increase that is well above his glycemic target.

Case 4

Mrs D is a 79-year-old widow, functionally independent, living alone. She has hypertension, dyslipidemia, chronic obstructive pulmonary disease, chronic kidney disease, osteoarthritis, and osteoporosis. She has had type 2 diabetes for the past 40 years. She currently takes insulin glargine, 42 U at bedtime, and insulin aspart, 5 U with breakfast, 7 U with lunch, and 9 U with dinner. She takes additional insulin aspart based on a blood glucose scale with each meal. She has had symptomatic hypoglycemia over the past week, with blood glucose levels down to 50 mg/dL, without a clear pattern. Her blood glucose values range from 51 to 345 mg/dL, but she does not keep an organized log and admits that she sometimes forgets to take her insulin. Her HbA_{1c} level is 7.8%.

Estimate Benefits

Mrs D has long-standing diabetes that is unlikely to be safely managed without the use of insulin. However, benefits of intensive glycemic control in her case are unclear and unlikely to be realized during her lifetime.

Estimate Harms

Harms of insulin therapy include severe hypoglycemia, especially among older patients with complex health problems like Mrs D. Complex insulin regimen also increases treatment burden. Treatment errors are frequent and her cognitive status needs to be assessed to determine her capacity for self-management.

Individualize HbA_{1c} Target

Type 2 diabetes control may be too tight, and her insulin regimen overly complex, given the harms and burdens of treatment. Focus should shift to prevention of symptomatic hyperglycemia and keeping her HbA_{1c} values in the 8% range may be reasonable, while avoiding hypoglycemia.

Minimize Polypharmacy

Her insulin regimen needs to be simplified to reduce the risk for errors. A first step may be to reduce her glargine dose and prescribe a fixed dose of aspart with each meal. Depending on her schedule of meals, premixed insulin injections twice daily may be another option.

Conclusions

Although there are major gaps in the evidence base on how best to care for older adults with diabetes, 4 evidence-informed steps can help clinicians and patients make individualized treatment decisions. Patient-centered decisions start with a strong partnership between the clinician and the patient. The first and second steps include assessments of potential benefits and harms of intensive glycemic control. Estimation of life expectancy can be useful to determine whether long-term benefits of intensive glycemic control are possible. The need for insulin (or other type of therapy), duration of diabetes, and cognitive impairment can be used to determine the likelihood of harms associated with treatment. In the third step, patient preferences should play a major role in determining the appropriate glycemic target. Fourth, polypharmacy should be minimized. If a glycemic target cannot be easily achieved, the most appropriate course may be to modify the glycemic target rather than intensify treatment.

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