# Glycemic Control in Older Adults: Applying Recent Evidence to Clinical Practice

*Ajay Sood, MD, Division of Clinical and Molecular Endocrinology, Case Western Reserve University School of Medicine; Louis Stokes Cleveland Veterans Affairs (VA) Medical Center, Cleveland, OH, USA.*

*David C. Aron, MD, MS, Division of Clinical and Molecular Endocrinology, Case Western Reserve University School of Medicine; VA Network 10 Geriatric Research, Education, and Clinical Centers, VA Health Services Research and Development Quality Enhancement Research Initiative Diabetes Clinical Coordinating Center; Louis Stokes Cleveland VA Medical Center, Cleveland, OH, USA.*

*Glycemic goals and the decision to intensify glycemic control among older adults with diabetes must be individualized based on comorbid conditions and the risks associated with treatment. The duration of diabetes mellitus, baseline glycosylated hemoglobin value, prior history of cardiovascular disease, and history of severe hypoglycemia are important factors to consider. This article reviews how the management of diabetes mellitus in this subgroup is changing in view of three recently reported randomized trials of intensive glycemic control.*

**Key words:** *diabetes, older adults, glycemic control, cardiovascular disease, glycemic goal*

## Introduction

Diabetes mellitus (DM) is a serious concern among older adults,[1] and its occurrence has increased both with the aging of the population as well as a rise in the prevalence of DM.[2] It has been pointed out in several articles that the approach to treatment of hyperglycemia in older adults is different from that in younger people with DM.[3–5] In 2003, the California Health Foundation and the American Geriatrics Association published guidelines for the care of older adults with DM[6] that focused on individualizing care for each patient, especially in terms of glycemic control targets. The issue of glycemic control in general has been brought to the forefront by three recently reported randomized controlled trials: Action to Control Cardiovascular Risk in Diabetes (ACCORD),[7] Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE),[8] and the Veteran Affairs Diabetes Trial (VADT).[9] The results from these trials are reshaping our thinking of how we should treat older adults with diabetes, especially the oldest adults. However, the fundamentals of clinical decision making remain the same: balance the risks and benefits for the individual patient.

This article reviews how management strategies in older adults with DM should differ from those in younger patients, and how the results of the above studies can impact our practice.

## Differences in Clinical Decision Making for the Management of Diabetes among Older Adults

Older adults, defined as those >65 years of age, constitute a heterogeneous group. The health issues of someone 65–70 years old may be different from the health issues of a person >80 years of age because of the physiological changes of aging. Other major considerations common to older adults are life expectancy and comorbidities. Although these apply to everyone, regardless of age, they tend to become more immediately relevant as one advances in years. Within the same age group, functional status varies from individual to individual. There may be a healthy 85-year-old individual with a life expectancy of 10+ years and a sicker 70-year-old with multiple comorbidities who has a life expectancy <5 years.

Several physiological changes in carbohydrate metabolism occur with aging that affect diabetes management. Older adults with diabetes:

- tend to be leaner and have a lesser insulin secretory response to a glucose load[10]
- tend to have a poorer glucagon response to hypoglycemia
- are more likely to have neuroglycopenic symptoms of hypoglycemia compared with the adrenergic symptoms[11]
- have a frequency of severe hypoglycemic episodes.

Hypoglycemia is the primary limiting factor in the achievement of tight glycemic control whether in older or younger individuals. However, complicating the picture is that neuroglycopenic symptoms are less likely to be recognized. These symptoms are subtle, especially in older adults. For example, hypoglycemia might become manifest as falls.

Diabetes can have its onset at older ages, and microvascular complications

**Table 1:** Recommendations for Older Adults with Diabetes

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| The choice of a target level for glycemic control in an older adult must be individualized. |
| The greatest benefit in improvement in microvascular complications is achieved when HbA1c is decreased from a high level to about 7.0%. |
| An individual's life expectancy is a key consideration in determining a target A1c level. |
| A tighter glycemic target of HbA1c <7.0% may not be appropriate for older adults who are at risk for or have a history of severe hypoglycemia or for older adults with previous macrovascular disease, advanced microvascular disease, a longer duration of diabetes, or multiple comorbid conditions. |
| A select subgroup of older diabetics with no previous cardiovascular disease, a shorter duration of diabetes, and a relatively lower HbA1c (around 8.0%) may benefit from tighter glycemic control of HbA1c (<7.0%). |
| Management of blood pressure and cholesterol and smoking cessation are critical aspects of diabetes care. |
| The treatment of diabetes has to be planned as part of holistic care for older individuals, in whom the treatment of multiple medical conditions must be prioritized and individualized. |

take many years to develop. Therefore, if a person's life expectancy is <5 years, it is not beneficial to use a treatment modality that will produce its benefit after 10 years. As life expectancy is shorter in the older population, the benefit from any treatment should be realized sooner than in a younger population. In fact, the practice guidelines of the American Geriatrics Society and the Veterans Health Administration–Department of Defense explicitly include life expectancy–based glycosylated hemoglobin (HbA1c) goals.[6,12] Vijan *et al.* evaluated the efficacy of glycemic control in type 2 diabetes using a Markov decision model and risk estimates extrapolated from studies of patients with type 1 diabetes.[13] They found that if diabetes developed before 50 years of age, reducing HbA1c levels from 9% (moderate control) to 7% (good control) resulted in an estimated decrease of 2.3 percentage points (from 2.6 to 0.3%) in lifetime risk for blindness due to retinopathy. The same HbA1c reduction in an individual with diabetes onset at 65 years of age would be expected to decrease the risk for blindness by 0.5 percentage points (from 0.5 to <0.1%). The benefit for a 75-year-old patient would be even less.

Similar findings were observed for the risk of end-stage renal disease, with a reduction of risk from 3.5 to 2.0% in a 45-year-old compared with 0.6 to 0.3% in a 65-year-old; there was virtually no risk reduction in a 75-year-old because the risk was already so low. However, for all ages, the model predicted substantially greater benefit when moving from poor (11%) to moderate glycemic control as compared with moving from moderate to good glycemic control. This is not an argument to ignore diabetes in older patients but, rather, to use this information in decisions about glycemic control targets. Of note, increased rates of complications, including excess mortality of 9.2%, have been documented with newly diagnosed diabetes in patients >65 years of age.[14]

Another major issue is that of comorbidities that may affect the disease progression, alter the outcomes of acute and chronic complications, and complicate diabetes management. Older adults with diabetes are more likely to have a greater burden of comorbid conditions. Thus, they are also likely to have geriatric syndromes such as falls, cognitive impairment, chronic pain, and depression.[15–20] Older adults with longstanding diabetes have a higher prevalence of microvascular complications.[14] The functional status of individuals with diabetes can change with time and is especially related to hospitalizations, which are more frequent among older adults.[19–21] Recovery from the debilitation of acute illness can be prolonged. Older adults are more prone to malnutrition, and diet restrictions may therefore not be appropriate. Renal function may change in association with concurrent illnesses and their treatment. Goals and therapeutic strategies must respond accordingly. These factors may necessitate changes in diabetes medication and adjustments in dosages. In addition, the presence of multiple comorbidities contributes to polypharmacy, with its potential for greater frequency of adverse effects, decreased medication adherence, and increased cost.[22]

The presence of comorbidities affects the impact of glycemic control. Huang *et al.* used a computer model with data extrapolated from the UK Prospective Diabetes Study (UKPDS) to assess the impact of intensive glucose control (HbA1c <7%) versus moderate glucose control (HbA1c 7.9) on lifetime differences in the incidence of complications and average quality-adjusted days.[17] Healthy older adults of different age groups had expected benefits of intensive glucose control ranging from 51 to 116 quality-adjusted days. Within each age group, the expected benefits of intensive control steadily declined as the levels of comorbid illness and functional impairment increased. For individuals 60–64 years of age with new-onset diabetes, the benefits declined from 106 days at baseline good health (life expectancy 14.6 years) to 44 days for those with a life expectancy of 9.7 years and 8 days for those with a life expectancy of 4.8 years.

A similar decline in benefits occurred among those with a prolonged duration of diabetes.

One must consider the competing demands at the time of the office visit. Time spent addressing diabetes competes with time required to address other concerns. More comorbidities means a greater demand and, hence, greater competition for that time. This does not mean ignoring issues such as the prevention of dehydration or other symptoms that may occur due to uncontrolled hyperglycemia. Rather, any potential benefit of tighter glycemic control in terms of prevention of late complications (micro- and macrovascular disease) must be measured against the benefit of addressing those other concerns. Similarly, the potential benefits of treating multiple conditions must be balanced with the potential risks of polypharmacy and its attendant increase in adverse drug events.

The management of cardiovascular risk in the diabetic patient illustrates how the benefits (and costs) of treating hyperglycemia, hyperlipidemia, and hypertension vary in magnitude. The Diabetes Cost-Effectiveness Group of the U.S. Centers for Disease Control and Prevention performed a computer simulation of diagnosed type 2 diabetes.[23] The incremental cost-effectiveness ratio for intensive glycemic control was $41,384 per quality-adjusted life year (QALY); this ratio increased with age at diagnosis from $9,614 per QALY for those age 25–34 years to $37,086, $71,816, $154,376, $401,883, and $2.1 million for individuals aged 45–54, 55–64, 65–74, 75–84, and 85–94 years, respectively. The cost-effectiveness ratio for reduction in serum cholesterol level is $51,889 per QALY; this ratio varied by age at diagnosis and is lowest for patients diagnosed between the ages of 45–84 years. However, for intensified hypertension control, the cost-effectiveness ratio was $1959 per QALY and provided cost savings at all age groups. From the point of view of effectiveness alone, intensive control of blood pressure was associated with a significant reduction in cardiovascular mortality in the UKPDS as compared with glycemic control. The limitations of these computer models notwithstanding, they do illustrate factors that need to be considered in clinical decision making, especially when time and money are finite and the risks of treatment are not negligible. Finally, we need to consider patient preferences that may not concord with those of the clinician.[24,25] For example, a patient with an HbA1c of 7.5% on oral medications may not wish to have the inconvenience of taking insulin to lower the HbA1c for the marginal benefit.

## Goals of Management of Diabetes Mellitus

Broadly speaking, the goals of treatment are to prevent symptoms of hyperglycemia, improve quality of life by preventing complications, and prolong life. The first goal can readily be accomplished by keeping the blood glucose within a reasonable range, albeit above normal. Usually an HbA1c level <9% is sufficient to achieve that goal. The debate on the treatment of hyperglycemia has focused on whether tighter control of glucose (nearer to normal blood glucose values) will prolong life and improve quality of life at an acceptable risk and with an acceptable regimen.

## Does Tight Glycemic Control Help in Achieving These Goals?

There is strong evidence that tight glycemic control with an HbA1c of 7.0% decreases the incidence and also prevents the progression of microvascular complications. This has been proven in individuals with type 1 and type 2 diabetes. Although the HbA1c achieved in the intensive group in the Diabetes Control and Complication Trial (DCCT) was about 7% (mean) and in the UKPDS[26–28] was 7.0% (median), in both studies no glycemic threshold for occurrence of microvascular complications was observed. However, these studies were carried out in a younger population with type 1 diabetes or recently diagnosed younger people with type 2 diabetes.

Cardiovascular disease is the leading cause of morbidity and mortality in older adults with diabetes mellitus.[29] It has been the hope that decreasing cardiovascular disease burden among these individuals would help in improving the quality as well the duration of life. At the time of initial report of the DCCT and UKPDS, there was a trend toward an improvement in cardiovascular complications with intensive glycemic control, although this was not statistically significant. Follow-up of patients in both the studies, several years after the intervention for tight glycemic control had been stopped, demonstrated that there was a reduction in cardiovascular events in both those with type 1 and type 2 diabetes. As reported in DCCT/Epidemiology of Diabetes Interventions and Complications study (DCCT-EDIC), patients of DCCT when followed up for 9 years after the trial showed a 42% reduction in the cardiovascular outcomes and a 57% reduction in risk of myocardial infarction, stroke, or death due to cardiovascular disease.[30] A 10-year follow up of patients in the UKPDS showed 15% and 33% reductions in myocardial infarction with sulphonylurea or insulin and metformin respectively.[31] It also showed 13% and 27% decreases in all-cause mortality in the two subgroups. The above reports suggested that tight glycemic control to an HbA1c value of around 7% in younger people with diabetes mellitus and those with recent-onset diabetes mellitus leads to improved cardiovascular outcomes over many years.

### Information from the New Studies

Three studies, ACCORD, ADVANCE, and VADT, were recently carried out to address whether tight glycemic control would improve macrovascular and microvascular complications in this group.[7–9,32] In the aggregate, the average age of people at the time of enrolment in these studies was 60–66 years, and the average duration of diabetes was 8–11.5 years. Thus, a majority of the patients could not be considered "elderly" and extrapolation of the findings to an older population must be done with caution. A prior history of cardiovascular disease was present in 32–40% of these patients.

The intensively treated group in these studies was targeted to achieve an HbA1c <6.0–6.5%. The achieved median HbA1c was 6.3–6.9% in the intensive treatment group compared with 7.0–8.4% in the standard treatment group. The median duration of follow-up was 3.5–5.6 years. All these patients received treatment for hypertension and hyperlipidemia and were given acetylsalicylic acid according to current guidelines.

In February 2008, the glycemic arm of the ACCORD study was terminated prematurely because of the increased mortality observed in the group of diabetic individuals who were treated intensively with the aim of achieving an HbA1c <6%. There was increased all-cause mortality in the intensively treated group (hazard ratio [HR] 1.22, confidence interval [CI] 1.01–1.46) resulting from increased cardiovascular mortality (HR 1.35, CI 1.04–1.76); interestingly, there was a decrease in the number of nonfatal myocardial infarctions.[7–9,32] In contrast, ADVANCE and VADT showed no change in the rates of all-cause mortality or cardiovascular mortality in the intensively treated groups.[7–9] Thus, there was no evidence of benefit in terms of improvement in the cardiovascular or macrovascular event rates in patients in any of these three studies.

The results of the ACCORD trial came as a shock to researchers, and a variety of hypotheses, based on post hoc analyses, have been put forward to account for the results.[32] These include hypoglycemia, unknown drug interactions among the larger number of medications used for glycemic control, weight gain, the intensity of treatment, and even just chance alone. Of note, neither ADVANCE nor VADT showed increased mortality in the intensive glycemic control arm.[7–9] However, no definitive explanation for the ACCORD results has been identified. Of the leading candidates, hypoglycemia would seem to be the most obvious. The intensively treated patients in all the three studies had a three times higher rate of severe hypoglycemic events, occurring in 16.2% of the patients in the ACCORD trial.[7–9] However, hypoglycemia did not seem to be the cause of the increased mortality. In a joint statement from the American Diabetes Association, American College of Cardiology Foundation, and American Heart Association, it was pointed out that while severe hypoglycemia was associated with higher mortality, the interaction was complex.[32]

Another possibility is baseline cardiovascular disease. A subgroup analysis of participants in ACCORD suggested that those in the intensively treated group, who had no prior cardiovascular event, or those who had a lower HbA1c (<8.0%) at the time of enrolment into the study may have had fewer fatal or nonfatal cardiovascular events compared with those in the standard treatment group. A subgroup analysis of VADT patients indicated that the patients with a shorter duration of diabetes (<12 years) may have some cardiovascular benefit with intensified glycemic control.[9] However, in general, the intensification of glycemic control in older adults with diabetes needs to be viewed with caution and individualized.

Whether subgroup analyses should be the basis for targeting specific groups of patients can be debated. It should be pointed out that in these recently reported studies, the overall mortality was lower than expected, even in the standard group. This is likely due to improved comprehensive care of other comorbid conditions such as hypertension and hyperlipidemia and to the use of acetylsalicylic acid. That this approach works has been substantiated in the Steno-2 multiple risk factor intervention trial.[33]

## Recommendations for Older Adults with Diabetes

In summary, the choice of a target level for glycemic control in an older adult must be individualized, but there are a number of general principles (see Table 1).[11,19,20,25,34,35] The greatest benefit in improvement in microvascular complications is achieved when HbA1c is decreased from a high level to about 7.0%.[36] In considering how close to 7% needs to be achieved, strong consideration should be given to the life expectancy of an individual. In an individual who has a short life expectancy, such as <5 years, further intensification of glycemic control is not going to be of any benefit since the benefits would not be realized for several years. A tighter glycemic target of HbA1c <7.0% may

### Key Points

- Glycemic goals in older adults with diabetes may not be similar to younger population.
- Glycemic goals have to be individualized to each patient's unique medical condition.
- Tighter glycemic control with HbA1c value of less than 7.0% is not desirable for certain older adults with diabetes.
- Individuals with longer duration of diabetes, prior cardiovascular disease, difficult to control diabetes, history of severe hypoglycemia, advanced microvascular disease, and poor cognitive function are not good candidates for tight glycemic control of HbA1c below 7.0%.
- Intensive glycemic control may help older individuals with shorter duration of diabetes, easy to control blood glucose levels, and with no prior history of cardiovascular disease.

### Clinical Pearls

- The presentation of hypoglycemia in older adults can be both subtle and insidious. Evidence of its occurrence should be carefully sought.
- Consider glycemic control as only one aspect of diabetes care in a broader and holistic context.

not be appropriate for older adults who are at risk for or have a history of severe hypoglycemia. It may also not be appropriate for older adults with previous macrovascular disease, advanced microvascular disease, a longer duration of diabetes, or multiple comorbid conditions.

A select subgroup of older diabetics with no previous cardiovascular disease, a shorter duration of diabetes, and a relatively lower HbA1c (around 8.0%) may benefit from tighter glycemic control of HbA1c (<7.0%). However, it is important to follow guidelines such as those related to blood pressure, cholesterol control, and smoking cessation as these have a greater impact than does moving from moderate to tight glycemic control. Finally, the treatment of DM has to be planned as part of holistic care for older individuals, in whom the treatment of multiple medical conditions must be prioritized and individualized.

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## References


1. Harris MI. Diabetes in America: epidemiology and scope of the problem. Diabetes Care 1998;21:C11–C14.
2. Centers for Disease Control and Prevention. National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2005.
3. Baines A. Treatment of hyperglycemia in the elderly. Geriatr Aging 2003;6:42–6.
4. Hornick T, Aron D. Managing diabetes in the elderly: go easy, individualize. Cleve Clin J Med 2008;75:70–8.
5. Segal A, Munshi M. Insulin therapy for older adults with diabetes. Geriatr Aging 2008;11:357–62.
6. Brown A, Mangione C, Saliba D, et al. Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc 2003;51:S265–80.
7. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–59.
8. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–72.
9. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–39.
10. Meneilly G, Tessier D. Diabetes in elderly adults. Sciences 2001;56A:M5–13.
11. Zammitt N, Frier B. Hypoglycemia in type 2 diabetes: pathophysiology, frequency, and effects of different treatment modalities. Diabetes Care 2005;28:2948–61.
12. Pogach L, Brietzke S, Weinstock R, et al. Development of evidence-based guidelines for diabetes mellitus: the Veterans Health Administration–Department of Defense guidelines initiative. Diabetes Care 2004;27:B82–9.
13. Vijan S, Hofer T, Hayward R. Estimate benefits of glycemic control in microvascular complications in type 2 diabetes. Ann Intern Med 1997;127:788–95.
14. Bethel M, Sloan F, Belsky D, et al. Longitudinal incidence and prevalence of adverse outcomes of diabetes mellitus in elderly patients. Arch Intern Med 2007;167:921–7.
15. Suh D, Kim C, Choi I, et al. Comorbid conditions and glycemic control in elderly patients with type 2 diabetes mellitus 1988 to 1994 to 2004. J Am Geriatr Soc 2008;56:484–92.
16. Munshi M, Grande L, Hayes M, et al. Cognitive dysfunction is associated with poor diabetes control in older adults. Diabetes Care 2006;29:1794–9.
17. Huang E, Zhang Q, Gandra N, et al. The effect of comorbid illness and functional status on the expected benefits of intensive glucose in older patients with type 2 diabetes: a decision analysis. Ann Intern Med 2008;149:11–9.
18. Huang E. Appropriate applications of evidence to the care of elderly patients with diabetes. Curr Diabetes Rev 2007;3:260–3.
19. Trief P, Morin P, Izquierdo R, et al. Depression and glycemic control in elderly ethnically diverse patients with diabetes: the IDEATel project. Diabetes Care 2006;29:830–5.
20. Sinclair A, Conroy S, Bayer A. Impact of diabetes on physical function in older adults. Diabetes Care 2008;31:233–5.
21. Hardy S, Gill T. Recovery from disability among community dwelling older persons. JAMA 2004;291:1596–602.
22. Boyd C, Darer J, Boult C, et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA 2005;294:716–24.
23. CDC Diabetes Cost-Effectiveness Study Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. JAMA 2002;287:2542–51.
24. Chin M, Drum M, Jun L, et al. Variation in treatment preferences and care goals among older patients with diabetes and their physicians. Med Care 2008;46:275–86.
25. Aron DC, Pogach L. One size does not fit all: a continuous measure for glycemic control in diabetes: the need for a new approach to assessing glycemic control. Jt Comm J Qual Patient Saf 2007;33:636–43.
26. Diabetes Control and Complications Trial Research Group. The effects of intensive diabetes treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–86.
27. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–65.
28. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53.
29. Katz P, Gilbert J. Diabetes and cardiovascular disease among older adults: an update on the evidence. Geriatr Aging 2008;11:509–14.
30. Nathan D, Cleary P, Backlund J, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;22:2643–53.
31. Holman R, Paul S, Bethel M, et al. Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med 2008;359:1576.
32. Skyler J, Bergenstal R, Bonow R, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and the VA diabetes trials. Diabetes Care 2009;32:187–92.
33. Gaede P, Lund-Andersen H, Parving H. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580–91.
34. Romney J. Diabetes and the Elderly Geriatrics Grand Rounds. Edmonton (AB): University of Alberta; 2008.
35. Hayward R, Hofer T, Vijan S. Intensive glucose control in elderly adults. JAMA 2007;297:2195–6.
36. Pogach L, Engelgau M, Aron D. Measuring progress towards achieving hemoglobin A1c goals: pass/fail or partial credit. JAMA 2007;297:520–3.