



Type 2 Diabetes: Approach to Management in Older Adults



Volume 3 Issue 5

In this Issue...

Older adults make up a significant proportion of those with type 2 diabetes but require unique considerations for management. They represent a high-risk group with a significantly increased risk of hypoglycemia and cognitive dysfunction, and medication management must take into account these and other comorbidities. Recent development of new classes of medications with either reduced hypoglycemic risk or additional benefits such as protection from cardiovascular (CV) events or weight loss are now available for potential use, as long as they are used in the right older adult population.

In this issue, Drs. Amisha Wallia and Susan Karam from Chicago's Northwestern University Feinberg School of Medicine analyze recent publications providing guidance for all clinicians managing elderly patients with type 2 diabetes mellitus.

Program Information

- [CME Information](#)
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Length of Activity

- 1.0 hour Physicians
- 1.0 hour Nurses

Launch Date

March 09, 2018

Expiration Date

March 08, 2020

LEARNING OBJECTIVES

- Discuss the need for individualized care as well as recommended glycemic targets in older adults.
- Summarize the efficacy and safety of different classes of antihyperglycemic medications in older adults.
- Explain the association between hypoglycemia and cognitive decline in older adults with type 2 diabetes.

GUEST AUTHORS OF THE MONTH

Commentary & Reviews



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Guest Faculty Disclosure

Dr. Wallia has indicated that she has received honoraria from Lexicon, has consulted for Glytech, and has served as a co-investigator on a research study for Eli Lilly and Company.

Dr. Karam has indicated that she has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of this presentation.

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Dr. Wallia and Dr. Karam have indicated that there will be no

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KEY TAKEAWAYS

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The incidence and prevalence of diabetes in older adults are rising¹; in addition, other comorbidities such as renal insufficiency/failure, cardiovascular (CV) disease, and cognitive dysfunction are affecting more of this population. Studies evaluating clinical treatment paradigms in diabetes in older adults are limited; older patients or those with comorbidities are often excluded from large randomized controlled trials. However, other research design methods such as (prospective) case-cohort studies, meta-analyses, and post hoc analyses of randomized controlled trials give us valuable data and allow us to draw inferences about the management of diabetes in older adults.

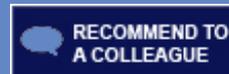
Inzucchi et al have appropriately emphasized the need for a patient-centered approach with individualized treatment and glycemic targets in this population.² While the various guidelines differ slightly,^{3,4} generally the HbA1c goal can be relaxed to around 8%. It is important to: 1) not drive down to a precise treatment goal, and 2) understand that a high incidence and prevalence of hypoglycemia may be present at any HbA1c level, which unfortunately is not a good predictor of hypoglycemia risk. Older adults are at increased risk of hypoglycemia for various reasons, including declining functional status limiting self-care, visual impairment, renal impairment, and poor appetite or inconsistent access to food.⁵ As demonstrated by Feinkohl et al and discussed in detail elsewhere in this review, hypoglycemia can have severe consequences in older adults, including increased rates of cognitive decline. Screening in the older population must include not only acute (hypoglycemia) and chronic (vision, neuropathy) diabetes related complications, but also general health screening such as cognitive dysfunction, nutritional status, and fall/fracture risk. A full understanding of these complications as well as concomitant comorbidities such as renal insufficiency, obesity, and CV disease (including hypertension and heart failure) is needed to help guide drug choice.

Drug selection in any patient with diabetes can be complex; second-line therapy after metformin can include any number of old or new medications as discussed by Inzucchi et al and in guidelines from other societies such as the American Academy of Clinical Endocrinology (AACE).⁶ In nonelderly patients, cost, weight, and HbA1c all must be taken into account, while in elderly patients a more nuanced review of each medication choice needs to occur, keeping in mind individual complications and comorbidities. Although the level of evidence is not robust, there is enough evidence (as seen in the articles reviewed here) to help guide the use of both older and newer agents. Sulfonylureas, in general, should likely be avoided in older adults given both hypoglycemia and CV risks.

Nonfrail older adults with minimal comorbidities who are obese or have CV disease (including HTN and heart failure) could consider GLP-1 agonists and/or SGLT2 inhibitors and should keep metformin in their regimen when able. However, it is important to note that all medications in each class are not comparable; and results of CV trials demonstrate different side effect profiles and different effects on glycemic outcomes and CV disease. It will be interesting to note how pharmacy benefit managers, providers, and future guidelines will take this into account.

Unfortunately, when moderate or severe renal insufficiency is present, drug choice can be difficult. In those older patients with severe diabetes and/or insulin resistance, an oral regimen alone may not be sufficient. It is important here to note that on our review of several trials and post hoc analyses, the mean drop in HbA1c in older adults (minus sulfonylureas and insulin) is only 0.6%-0.5%. When insulin is needed (eg, HbA1c > 10% with symptoms), simplification of the insulin regimen can be very helpful as described in the article by Munshi et al. Several studies in type 2 diabetes have noted that once a day basal insulin and a bolus dose with the largest meal can be just as efficacious as 4x daily basal bolus therapy, with less hypoglycemia.⁷ Anecdotally, we find that simplification of an insulin regimen to a daily dose of basal insulin with a DPP-4 inhibitor can be very effective in an older population.

In conclusion, the management of diabetes in older adults is complex and requires a thoughtful and individualized approach which takes into account adequate glycemic control as well as patient-specific factors such as comorbidities, functional status, and the presence of cognitive impairment. Newer diabetes medications may provide good alternatives to older drugs that can have higher rates of hypoglycemia; however, data to guide their use is limited. Ongoing research and attention to the unique challenges of managing older adults



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with type 2 diabetes is essential to providing care to this growing population.

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Individualizing Glycemic Targets in Older Adults

Inzucchi SE, Bergenstal RM, Buse JB, et al; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012 Jun;35(6):1364-1379.



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In 2012, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) released a joint position statement on the management of hyperglycemia in those with type 2 diabetes, emphasizing the need for a patient-centered approach with individualized treatment goals and glycemic targets. An update was released in 2015 to reflect new data from recent clinical trials, including the FDA-mandated cardiovascular safety trials of saxagliptin¹ and alogliptin² as well as data on the then new class of sodium-glucose cotransporter 2 (SGLT2) inhibitors.³ According to the authors, a patient-centered approach to management and determination of glycemic targets should take into consideration nonmodifiable factors such as life expectancy, risk of hypoglycemia, disease duration, comorbidities, and known vascular complications. Consideration should also include modifiable factors like patient attitude, resources, and support system. Older patients are at higher risk for polypharmacy, renal dysfunction, cardiac events, and lack of reliable access to nutrition. Hypoglycemia in this population can be particularly problematic and associated with cognitive dysfunction, cardiovascular events, and falls leading to fracture.⁴ For these reasons, the authors suggest that an HbA1c target of < 7.5% - 8.0% may be appropriate for older patients with higher targets as health declines. Alternatively, glycemic control is directly linked to risk of microvascular and macrovascular complications, so healthier patients with longer life expectancies may benefit from a lower target, such as < 6.5% - 7.0%, and stricter control of known comorbidities.

More recently in the ADA Standards of Care,⁵ the following glycemic targets were proposed to be used as a framework when making treatment decisions for older adults (≥ 65 years old): goal HbA1c of < 7.5% for healthy individuals with longer life expectancy, < 8.0% for those with multiple chronic illnesses, 2+ activities of daily living (ADL) impairments and mild to moderate cognitive impairment; and < 8.5% for those with poor health and limited life

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expectancy. The American Geriatric Society (AGS) similarly recommends a goal HbA1c between 7.5%-8.0% for most older adults (≥ 65 years old) with higher targets (8%-9.0%) for those with multiple comorbidities, poor health, and limited life expectancies. They also note that a goal of 7%-7.5% may be appropriate for healthier patients who have few comorbidities in whom this can be safely achieved but note that there is possible harm with HbA1c $< 6.5\%$ in older adults.⁶

As with target HbA1c, the choice of treatment with antihyperglycemic agents should be patient-specific. All patients are candidates for lifestyle modification; however the choice of pharmacologic agent is more complex. Inzucchi et al emphasize safety as a primary consideration, with special care paid to preventing hypoglycemia, drug-drug interactions, renal injury, heart failure, and fracture. These decisions should again be made after discussion with patients and in the context of age, comorbidities, and functional and cognitive status, and readdressed with changes in these factors.

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Safety and Efficacy of DPP-4i vs Sulfonylureas in the Elderly

Shankar RR, Xu L, Golm GT, et al. A comparison of glycaemic effects of sitagliptin and sulfonylureas in elderly patients with type 2 diabetes mellitus. *Int J Clin Pract.* 2015 Jun;69(6):626-31.

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Sulfonylureas (SFUs), the oldest class of oral antihyperglycemic medications, are used more frequently in the elderly, even with their higher risk for hypoglycemia.¹ While SFUs are known to be effective, more research is needed to understand the benefits and risks of SFU in comparison to newer agents, especially in older adults. Dipeptidyl peptidase 4 (DPP-4) inhibitors have been shown to be efficacious in improving glycemic control with low risk of hypoglycemia both in combination with other antihyperglycemic agents and when used alone.² In addition, the ability to use linagliptin and sitagliptin in renal disease and their side effect profiles and general tolerability make them attractive agents for older adults.

Shankar et al completed a post hoc analysis on pooled data from three double-blind studies which compared the DPP-4 inhibitor sitagliptin at full dose (100 mg/dL) to a titrated SFU (2-glipizide, 1-glimiperide). Patients ≥ 65 years old with uncontrolled diabetes, who had HbA1c data at 25-30 weeks and no major protocol violations were included (N= 372; 178 sitagliptin, 194 sulfonylurea). The endpoint of the post hoc analysis included change in HbA1c, fasting plasma glucose, and body weight compared to baseline, as well as episodes of symptomatic hypoglycemia. Duration of diabetes (~ 6 years) and baseline HbA1c ($\sim 7.5\%$) were similar in both groups.

Sitagliptin showed similar efficacy to sulfonylurea as HbA1c (-0.72% vs. -0.77% , $P = .399$) and fasting plasma glucose decreased from baseline to a similar degree (-21.0 vs. -22.9 respectively, $P = .457$). When taking into account lack of hypoglycemia and no increase in body weight along with HbA1c reduction $> 0.5\%$ into the composite end point, a higher percentage of those on sitagliptin achieved this combined end point (44.1% sitagliptin vs. 16.0% SFU [$P < .001$]). Sitagliptin also was shown to have a more favorable effect on weight with a decrease of 1.7 kg ($P < .001$) compared to an increase of 0.5 kg ($P = .066$) in the SFU group. In the sitagliptin group, 6.2% of patients reported at least one hypoglycemic event compared to 27.8% of those treated with SFU ($P < .001$), likely due to differences in mechanisms of action.

In 2008, the FDA mandated trials demonstrating cardiovascular safety of any new antihyperglycemic medications. Since that time, trials of the DPP-4 inhibitors including sitagliptin (TECOS)³ and alogliptin (EXAMINE)⁴ have been neutral. The SAVOR-TIMI-53 trial of saxagliptin⁵ demonstrated no difference in ischemic cardiac event rates but an increased rate of hospitalization for heart failure. Subsequent analysis of the TECOS cohort aged ≥ 75 years showed neutral cardiovascular effects without increased rates of severe hypoglycemia, death or hospitalization for heart failure compared to the larger cohort.⁶ A similar analysis of patients ≥ 65 years old in the SAVOR-TIMI 53 trial demonstrated no increased rates of ischemic heart disease or hypoglycemia in this older population. Hospitalization for heart failure was increased in all age groups compared to placebo with hazard ratio (HR) 1.32 (95% CI $0.99, 1.77$; $P = .062$) in those < 65 years; HR 1.25 (95% CI $1.01, 1.56$; $P = .042$) in those ≥ 65 years; and HR 1.47 (95% CI $1.05, 2.08$; $P = .026$) in participants ≥ 75 years. However, while the overall risk of hospitalization for heart failure was increased in the saxagliptin group compared to placebo, the risk was not found to increase further with advancing age.⁷

Based on current available data, DPP-4 inhibitors appear to be a safe and efficacious treatment in older adults. The results from Shankar et al reassure us that a DPP-4 inhibitor such as sitagliptin can have similar glycemic improvements with a potentially more favorable adverse event profile compared with a SFU. However, as with all pharmacologic choices, the use of these medications should be considered in the context of individual patients.

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Simplifying Insulin Regimens in Older Adults

Munshi MN, Slyne C, Segal AR, Saul N, Lyons C, Weinger K. Simplification of insulin regimen in older adults and risk of hypoglycemia. *JAMA Intern Med.* 2016 Jul 1;176(7):1023-5.



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Insulin therapy in older patients can be somewhat difficult to manage. While highly effective, insulin carries a greater burden and higher risks (eg, hypoglycemia)¹ than other agents. Providers, patients, and caregivers therefore must weigh the benefits and risks of insulin use and share in decision-making. Although using studies based on lower levels of evidence, some investigators believe insulin should be stopped altogether in older patients;² however, it is unclear how feasible this may be for those with elevated HbA1c or financial constraints. While methods for simplification of insulin regimens are needed, few have been tested or validated.

Munshi et al recently reported glycemic outcomes related to their algorithm for simplification of insulin regimens in high risk older adults. This single arm intervention study recruited patients with type 2 diabetes, > 65 years of age, taking > 2 insulin injections, with + c-peptide and a history of hypoglycemia (glucose < 70 mg/dl) in the past five days (based on continuous glucose monitoring). This study, although without a control arm, did recruit a highly vulnerable population, with a mean age of 76, 25% with cognitive dysfunction and/or falls, and a high rate of depression (> 40%). The algorithm for simplification for those on long acting insulin included a change from bedtime dosing to morning dosing, change from mixed insulin to basal insulin, and insulin titration to a goal glucose of 90 mg/dL-140 mg/dL in increments of 2 units. For those on bolus insulin, possible discontinuation or 50% reduction along with the addition of metformin (should renal function be optimal) and other oral agents were implemented. Interestingly, hypoglycemia duration decreased at 5 and 8 months ($P < .001$) without change in HbA1c, and diabetes-related distress score improved at both time intervals ($P < .001$). Two other helpful findings were also noted: 1) participants were able to titrate glargine on their own during high risk times, and 2) when HbA1c was stratified by level at any of the time periods during the study (baseline, five months, or eight months), the duration of hypoglycemia was not different. This suggests that patients may be able to self-manage long acting insulin to decrease hypoglycemia and that liberalizing HbA1c goals alone may not be adequate to prevent hypoglycemia in older adults.

This study shows great promise, and future studies with the use of similar algorithms are ongoing. The Munshi algorithm overall was simple for both patients and practitioners and

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effective in both reducing hypoglycemia and maintaining glycemic control. Taking patients who have long-standing diabetes off insulin altogether may not always be feasible; simplification can allow for preservation of glycemic control and decrease patient burden. Self-efficacy in any population of patients with diabetes improves outcomes and safety parameters, and this study confirms this concept in an older, high-risk cohort. However, HbA1c levels alone should not reassure anyone, and assumptions should not be made about hypoglycemia based on these values.

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GLP1 Efficacy and Safety in Older Adults

Meneilly GS, Roy-Duval C, Alawi H, et al; GetGoal-O Trial Investigators. Lixisenatide therapy in older patients with type 2 diabetes inadequately controlled on their current antidiabetic treatment: The GetGoal-O randomized trial. *Diabetes Care.* 2017 Apr;40(4):485-493.



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Postprandial glycemic excursions appear to be more prominent in older adults with diabetes. Glucagon-like peptide receptor agonists (GLP1s), which have a significant postprandial effect, could potentially be used in this elderly population. More recent guidelines have added these agents as second or third line therapy, especially for those who are overweight (given observed weight reduction, which is partially mediated through delay in gastric emptying and increase in satiety).¹ However, this class of drugs should be avoided in those with medullary thyroid cancer, severe gastrointestinal disease such as gastroparesis or significant gallbladder disease, and those with a history of pancreatitis and/or pancreatic cancer.

Several large randomized controlled trials reported on use of GLP1s, but few have studied older patients. Meneilly et al recently evaluated the use of lixisenatide (a once daily injection) therapy in older patients with type 2 diabetes inadequately controlled on their current antidiabetic treatment. The GetGoal-O trial randomized nonfrail participants > 70 years of age with type 2 diabetes, and included those with HbA1c 7%-10%, with many participants on insulin (30.7% lixi, 31.6% placebo), and/or sulfonylurea (39.8% lixi, 33.9% placebo). Those with mild renal insufficiency or impairment (28%), mild cognitive impairment (percentage not reported), or history of cerebrovascular/cardiovascular disease (93%) were also included in this study. All participants had a long screening and run-in phase (seven weeks) prior to randomization, and insulin doses were preadjusted to a reduction of 20%. Three hundred fifty patients were randomized, but 12% in both arms discontinued due to adverse events. Lixisenatide was found superior to placebo with a change in HbA1c (least squares mean difference [LSM] - 0.64% ($P < .001$) at 24 weeks and significant weight reduction (LSM difference -1.32 kg, $P < .0001$). Interestingly, quality of life also showed a small but clinically meaningful difference (LSM difference of 1.73 [95% CI 0.011, 3.456]). The rate of hypoglycemia (symptomatic or asymptomatic) was higher in those on lixisenatide (17.6%) than in those on placebo (10.3%), largely driven by those on SFU and/or insulin in the background. An increase in mild to moderate GI events was found in the treatment group and did lead to discontinuation. Similarly, a study by Thong et al evaluating the rates of GI side effects in those treated with the GLP1 liraglutide found increased rates as age increased and in those who were not also treated with metformin.²

This study suggests that the addition of a GLP1 to older patients with suboptimally controlled diabetes may be beneficial in a specific population (obese, low risk for hypoglycemia). It is important to note that cardiovascular outcome trials have demonstrated improvement in CV outcomes with liraglutide³ and CV neutrality with lixisenatide,⁴ weekly exenatide,⁵ and

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semaglutide⁶ — although not specifically studied in an elderly population. GLP1 use should be avoided in those with history of pancreatic disease as well as in those with GI distress or history of gallbladder disease. While GLP1s may be helpful in obese older adults who are relatively healthy and have longer life expectancies, one should reconsider in those with severe renal insufficiency, who are frail, or who have moderate or poor nutritional status at baseline.

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SGLT2 Inhibitors in Older Adults

Mikhail N. Use of sodium-glucose cotransporter type 2 inhibitors in older adults with type 2 diabetes mellitus. *South Med J*. 2015 Feb;108(2):91-6.



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There is little debate that metformin should be considered the first line agent for diabetes, even in those who are older, as long as they have no contraindications (eg, severe renal dysfunction, GI distress). Current guidelines allow other agents as second line therapy, depending on the patient and factors such as cost, weight, and risk of hypoglycemia.^{1, 2} When choosing second or third line agents, practitioners must understand the benefits and risks of different agents in the context of comorbidities often present in older adults.

The recent review by Mikhail evaluated all studies involving sodium-glucose cotransporter type 2 inhibitors in humans, published from 1996-2014. Four randomized trials evaluated the use of canagliflozin and dapagliflozin in older adults with type 2 diabetes (mean age 64-68 years, but < 10% were > 75 years of age). Advantages included improvement in glycemic control (change in HbA1c -0.45% with 100 mg canagliflozin and -0.5% with 300 mg; -0.4% with dapagliflozin), weight loss (2/3 weight loss from fat mass with mild fluid loss), and reduction of blood pressure (SBP -4.5 mmHg with 100 mg canagliflozin and -7 mmHg with 300 mg; -3.0% with dapagliflozin). However, genital mycotic infections, urinary tract infections, and hypotension related to volume depletion were determined to be limitations. In addition, dehydration, renal impairment, and fractures are potential side effects that may be especially problematic for older adults. Although not included in this review, euglycemic diabetic ketoacidosis and increase in amputations have also been reported.^{3,4}

Older, obese adults with or without hypertension and heart failure and with optimal renal function may benefit from SGLT2 inhibitors. Both EMPAREG,⁴ a cardiovascular safety trial evaluating empagliflozin, and CANVAS,⁵ a cardiovascular safety trial evaluating canagliflozin in high CV risk populations, demonstrated decreased CV events; and in the case of empagliflozin, significant decrease in CV death (38% risk reduction). Pooled data

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from six randomized controlled trials (N = 183) using canagliflozin (100 mg and 300 mg) in adults > 75 years of age did show improvement in glycemic control (-0.65%, and -0.55%) along with weight and BP; however, higher adverse events related to volume depletion in those age 75 and older were noted. Potential cardiovascular benefits of SGLT2 inhibitors, especially in relation to heart failure and hypertension, make it an attractive second line agent for those with diabetes. Because of the differences in the molecular profile of the individual drugs and lack of large-scale phase IV data, more studies are needed to understand which patient populations would benefit most from these agents. Based on current data, frail older adults with risk of fracture, volume depletion, renal insufficiency, or history of infection such as UTI, should likely avoid use.

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Severe Hypoglycemia and Cognitive Decline

Feinkohl I, Aung PP, Keller M, et al; Edinburgh Type 2 Diabetes Study (ET2DS) Investigators. Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the Edinburgh type 2 diabetes study. *Diabetes Care*. 2014 Feb;37(2):507-15.

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It has been demonstrated that elderly patients with diabetes have a greater decline in cognitive function as well as a greater risk of dementia than those without type 2 diabetes.¹ Cognitive decline is likely multifactorial, but the presence of hypoglycemia may worsen functional status.

Feinkohl et al set out to determine the association between severe hypoglycemia (defined as self-reported hypoglycemia requiring assistance) and cognitive function (defined by factor g, a combination of seven neuropsychological tests) in a prospective cohort of 60-75 year old men and women with type 2 diabetes. Cognitive function was measured at baseline and then again in four years, along with episodes of severe hypoglycemia measured with a short prospective hypoglycemia survey embedded into the main study. The population was heterogeneous and had not yet progressed to dementia. Participants were on a spectrum of medication regimens: 16.7% on insulin, 25.3% on sulfonylurea, 34.1% on other tablets, and 13.8% diet-controlled at baseline. The initial group surveyed included 1,066 patients and had a high rate of follow-up, with 831 (78%) presenting for follow-up at four years. Hypoglycemia was reported in 9.3% of participants at baseline and 10.2% at follow-up. As suspected, incident hypoglycemia was associated with decreased cognitive ability at baseline (OR lowest tertile g 2.04 [1.25-3.31, $P = .004$]). Those with lower cognitive ability at baseline had a twofold increase in rates of severe hypoglycemia over the four-year follow-up period. More interesting, however, hypoglycemia (both historical and incidental) was associated with a steeper cognitive decline.

The relationship between cognitive impairment and severe hypoglycemia is obviously complex, but given the large heterogeneous population that completed the battery of

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cognitive studies, the concern over worsening cognitive decline that this study invokes is likely warranted. In addition, the high prevalence of agents known to cause hypoglycemia and the high baseline presence of severe hypoglycemia in this cohort should raise alarms for providers.

The management of diabetes as it relates to cognitive function can be challenging, as both severe hypoglycemia and uncontrolled hyperglycemia have been linked to cognitive decline in the elderly and vice versa (e.g., the chicken or the egg phenomenon). A loss of cognitive ability can in turn make diabetes more difficult to manage as patients become more prone to hypoglycemia. The underlying cause is likely multifactorial and includes impaired hypoglycemia awareness,² decline in cognition and functional status limiting self-care, visual impairment, renal impairment, and poor appetite or inconsistent access to food.³ As a result, screening for cognitive impairment is included in several recommendations regarding screening of older adults with diabetes. The American Diabetes Association (ADA) recommends annual screening for adults 65 years or older with a tool such as the Mini-Mental State Examination or the Montreal Cognitive Assessment.⁴ The American Geriatric Society also recommends screening with a standardized tool such as the Montreal Cognitive Assessment at the initial assessment and with any significant decline in clinical status, including increased difficulty with self-care.⁵ A comprehensive care program with geriatricians and diabetologists may be beneficial, and if cognitive impairment is identified, aggressive changes in regimens and in-depth follow up with the patient and caregivers and/or family members is warranted.

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KEY TAKEAWAYS

- Older adults with diabetes are at an increased risk for hypoglycemia and cognitive decline compared to the general population, and both diabetes and hypoglycemia can lead to significant adverse events.
- Diabetes care should be individualized and glycemic targets chosen in the context of a patient's overall health, comorbidities, and treatment goals.
- The choice of medications used for older adults should be made carefully, with consideration of the risks and benefits to the individual.

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