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Note of disclosure: Dr. Weinstock has participated in multicenter trials funded by AstraZeneca, Bidel, Eli Lilly, GlaxoSmithKline, Medtronic, and Sanofi, all of which develop or sell products for the treatment of diabetes.

In Brief

Physiological changes associated with aging have the potential to affect the treatment of diabetes. However, evidence regarding treatment of diabetes in geriatric patients has been limited, especially for “oldest-old” patients. Recent research has provided greater insight into the risks and benefits of treatment, and new guidelines provide more specific information regarding treatment goals in older people with diabetes and encourage greater individualization of treatment.

Physiological Changes in Older Adults and Their Effect on Diabetes Treatment

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Geriatric patients make up an important part of the overall diabetes population. The Centers for Disease Control and Prevention estimates that, including undiagnosed patients, 10.9 million, or 26.9% of the population \geq 65 years of age have diabetes.¹

One challenge in treating geriatric patients is that this group can have a wide range of ages and medical conditions. For example, one geriatric patient could be a 65-year-old man who has been recently diagnosed with type 2 diabetes and has mild hypertension and hyperlipidemia but who is otherwise healthy, whereas another patient could be an 86-year-old woman with a history of type 2 diabe-

tes for several years, an A1C of 8.6%, and concurrent conditions, including hypertension, hyperlipidemia, coronary artery disease, arthritis, and vision and hearing impairments. Given this level of heterogeneity, it is important to identify in all patients any changes associated with aging and to consider how these circumstances will affect treatment as aging continues.

More specifically defining the term “geriatric” can aid in this process. Although the age of 60 or 65 years is often used as the defining criterion, there can be significant differences between a patient who is 65 and someone who is 90 years of age.

Other definitions divide geriatrics into broader age ranges, and, although this can vary, a common classification system is youngest-old (65–74 years of age), middle-old (75–85 years), and oldest-old (> 85 years).

Despite the changes that occur with aging, individuals with advanced age and comorbidities often are excluded from randomized, controlled trials.² Therefore, providing true evidence-based care to geriatric patients may be difficult, making it all the more important for clinicians to be aware of key changes that occur with aging and how these can affect the use of various medications for the treatment of diabetes. This article reviews some of the significant aging-related physiological and social changes that could affect diabetes care, recent changes in treatment recommendations for older patients with diabetes, and medication considerations that are especially important in the elderly population.

Age-Related Changes that May Affect Diabetes Treatment

Some important changes associated with aging that can affect medication use are classified as either pharmacokinetic (what the body does to a medication) or pharmacodynamic (what the medication does to the body). However, as discussed below, there are additional factors that also may affect how particular medications will act in elderly patients.

Pharmacokinetic changes

Perhaps the most commonly considered aging-related physiological change with regard to medications is the potential decrease in renal function that can occur with advancing age and affect some medications. However, the rate of renal decline is not uniformly predictable as patients age;³ hence, the doses of a renally adjusted medication may not need to be decreased for all older patients. Although some diabetes medications are affected by changes in renal function, the variability of age-related renal decline means that dosing decisions should not be based on patients' age alone.

Hepatic drug metabolism also can be affected by aging. However, aging does not affect all metabolic pathways in the liver to the same degree, and changes in drug metabolism can vary substantially from one patient to another.^{4–7} The first-generation sulfonyleurea chlorpropamide is a classic

example of a diabetes therapy that is affected by aging-related physiological changes. This agent should be avoided in older patients because decreased hepatic metabolism brought on by aging can lengthen its half-life in the body.⁸

Pharmacodynamic changes

Older patients may be more sensitive to the effects of medications, such as the glucose-lowering action of antihyperglycemic agents or the orthostatic effects of antihypertensive therapies.⁹ On the other hand, in some cases, older patients may demonstrate a decreased response to some medications. For example, older patients tend to have reduced sympathetic nervous system responses⁹ and thus may also have a decreased response to medications such as β -blockers or β -agonists, which affect the adrenergic system.¹⁰

Hypoglycemia unawareness

The decreased central nervous system responses that are common with aging also may play a role in the development of hypoglycemia unawareness. In one study comparing 13 people with diabetes \geq 65 years of age to 13 people with diabetes aged 39–64 years,¹¹ those in the older age-group maintained hormonal responses to hypoglycemia but exhibited more hypoglycemia unawareness, indicating a possible decreased sensitivity to hormonal responses. The authors noted that a lack of hypoglycemia symptoms also has been linked to a longer duration of diabetes, which could have been an additional contributing factor.¹¹ Because some older patients may have had diabetes for an extended period of time, the possibility of increased hypoglycemia unawareness must be considered.

Changes in functional status

Diabetes may have an effect on patients' functional status, which could, in turn, affect their medical care. In the Study of Osteoporotic Fractures,¹² women with diabetes had a 42% increased risk of any functional disability, as well as an increased risk of disability for specific tasks. Women with diabetes also had an increase in the number of falls.¹³ Interestingly, women with diabetes who were not taking insulin had a higher risk of falling than those who took insulin. This was attributed to a greater number of risk factors for falls in the group not

treated with insulin¹³ and highlights the high number of comorbidities that could be present in some people with diabetes. Because hyperglycemia can cause functional impairment, it is important to adequately control glycemia to avoid complications that could complicate treatment later in life.

Diabetes was been found to be an independent risk factor for hearing loss based on audiometric testing as part of the National Health and Nutrition Examination Survey.¹⁴ Multiple diabetes-related factors, including peripheral neuropathy, coronary heart disease, low HDL cholesterol, and general poor health, were all associated with an increased likelihood of hearing impairment.¹⁵

Multiple studies have also investigated cognitive function and diabetes. Cognitive dysfunction has been linked to both hyper¹⁶ and hypoglycemia.¹⁷ Further, it has been linked to a greater likelihood of experiencing severe hypoglycemia.¹⁸ Although dementia tends to increase with age in the general population, a systematic review and meta-analysis¹⁹ found that diabetes is associated with a faster rate of decline in cognitive function among older adults, with the relative risk for dementia in people with diabetes being 1.47 (95% CI 1.25–1.73) compared to people without diabetes.

In addition to these limitations, concomitant conditions, whether related to diabetes (e.g., visual impairment), or not (e.g., arthritis), could affect older patients' ability to perform tasks such as reading prescription labels and administering insulin. Consideration of such limitations is important when designing a therapy regimen for older adults. For those with cognitive or other functional impairments, keeping the regimen as simple as possible is essential.^{2,20}

Multiple chronic conditions

In treating older patients, the existence of comorbidities must be considered along with natural changes of the aging process. Huang et al.²¹ analyzed data in older people with diabetes and determined that multiple comorbidities (and the functional impairments that may accompany them) were greater predictors than age alone of both shorter life expectancy and lack of benefit of intensive blood glucose control. The presence of comorbidities also can increase the risk of medication-related complications. For

example, the possibility of drug-drug interactions and the use of medications that could negatively affect diabetes (e.g., corticosteroids) can increase as more medications are needed to treat comorbidities. In addition, hyperglycemia can be an even greater problem for patients with comorbidities. For example, nephropathy can compound age-related changes in renal function, neuropathy can complicate other functional impairments, and bed-bound patients are potentially at greater risk of problematic wounds if their glyce-mic control is poor.

The presence of multiple medical conditions also may affect patients' attitudes toward treatment. A study using a semi-structured interview²² found that older people with diabetes were more concerned about their functional status and ability to maintain activities of daily living than they were about their specific diabetes treatment goals. The authors recommended that practitioners explore patients' goals and individual circumstances as part of developing an appropriate treatment plan.²² This type of discussion allows patients to help with prioritization and encourages shared decision-making.²³

Cost Issues Affecting the Care of Older Adults With Diabetes

Cost can be an important issue for older adults, many of whom are living on a fixed income. Even for patients with Medicare Part D (prescription coverage), clinicians must remember that more expensive medications may have a high-tier status and therefore a high and potentially unaffordable required copayment. The so-called "doughnut hole" in Medicare Part D (i.e., the gap in prescription coverage between the upper limit of initial coverage and the threshold for catastrophic care coverage) may also become an issue even for patients who can afford their initial prescription copayments. Although the doughnut hole is scheduled to be gradually eliminated by 2020,²⁴ additional out-of-pocket costs for patients whose expenses fall within that gap may remain a significant hurdle for some patients until then.

Safety of Intensive Glycemic Control in Older Patients

There is no doubt that glycemic control remains important even as patients continue to age. Geriatric patients are prone to develop all of the same diabe-

tes complications as younger patients. However, the question of how aggressively glycemia should be targeted in geriatrics has been the subject of much debate.

Recent research studies have suggested the need for greater caution with regard to intensive glycemic control as patients age or develop serious comorbidities. The Veterans Affairs Diabetes Trial (VADT)²⁵ and the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation) trial²⁶ did not find a decrease in mortality with intensive glycemic control but did find benefits for albuminuria and nephropathy, respectively. Although the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial²⁷ was halted early because of concerns about increased mortality with intensive control in younger patients, no increase in mortality was found in patients ≥ 65 years of age. Because those studies identified some overall benefits to intensive control of diabetes, they did not result in changes to general diabetes treatment guidelines. However, all three of these studies, for which the mean age of subjects was in the range of 60–70 years, emphasized the need for individualized treatment, taking factors such as age and comorbidities into account.²⁸ Still, the extent to which their findings can be extrapolated to the oldest geriatric patients and those with increased comorbidities is limited because of the studies' exclusion criteria.

Retrospective analyses of large patient databases have provided some evidence to further quantify the results from these trials. These analyses have the advantage of including frail patients who generally are excluded from randomized trials, but their findings must be interpreted carefully with regard to the number of variables potentially affecting outcomes. Two such analyses,^{29,30} which focused specifically on older patients (one involved patients ≥ 50 years and the other involved patients ≥ 60 years), found a U-shaped relationship between A1C and mortality, indicating both the importance of glycemic control and the need for caution against overtreatment in older patients. Additionally, a 5-year observational study designed to assess the impact of comorbidity on cardiovascular outcomes³¹ found that tight glycemic control at baseline

(target A1C < 6.5 or $< 7.0\%$) was beneficial for cardiovascular outcomes for patients with mild comorbidity but not for those with a high level of comorbidity.

One likely explanation for these observations is increased hypoglycemia from intensive control. Like hyperglycemia, hypoglycemia has been linked to cardiovascular disease (CVD),³² and older patients may be at greater risk of hypoglycemia for a variety of reasons. The emergency room visitation rate for hypoglycemia increases substantially with age, with those ≥ 75 years of age having nearly double the rate of those 65–74 years of age and triple the rate of those 45–64 years of age.³³ An article examining the reasons for medication-related emergency department visits by older adults found that insulin and oral hypoglycemic agents were two of the most common causes, resulting in 13.9 and 10.7% of the hospitalizations, respectively.³⁴

Findings such as these, coupled with the fact that a time period of as long as 8 years may be required to see the benefits of intensive glucose treatment,³⁵ have shaped more recent guidelines for appropriate blood glucose targets in older individuals. A summary of recommendations for the management of hyperglycemia in older patients is offered in Table 1.^{2,20,35,36} When considering the effects of hypoglycemia and the individualization of treatment, daily blood glucose readings may be a better indicator than A1C alone. Some older or frail patients may be able to maintain a lower A1C safely if there are no issues with hypoglycemia, but others may need a higher A1C target to avoid the consequences of hypoglycemia.

Medication Recommendations for Geriatric Patients With Diabetes

After appropriate targets are determined, medication choices can be determined based on patients' risk of hypoglycemia and concurrent medical conditions. Brief highlights related to the use of the major groups of antihyperglycemic agents in older patients are offered below. Information is given on the relative risk of hypoglycemia with each drug class. However, antihyperglycemic agents used in combination will have a higher risk of causing hypoglycemia even if the individual components of the combination therapy have a low risk of hypoglyce-

mia when used as monotherapy.

Not all medications offer specific geriatric dosing guidance. Therefore, it may be prudent to start a medication at a lower dose—even one-half or one-fourth of the typical adult starting dose, if feasible. In many cases, it is not necessary in the outpatient setting to bring a chronic condition such as diabetes under control rapidly, and it may be beneficial to titrate more slowly to allow geriatric patients to become tolerant of the medication.³⁷ This does not mean that patients should remain on their low starting dose; some older patients will ultimately be able to tolerate the same maintenance dose as younger people with diabetes if the dose is titrated slowly. Ongoing monitoring of adverse events and effectiveness is important to determine whether the dose should be increased. A motto that sums up these principles for geriatric dosing is “Start low, go slow, but still get somewhere.”³⁷

Metformin

Metformin is considered the first-line treatment for type 2 diabetes in older patients because it is efficacious, inexpensive, and has a low risk of causing hypoglycemia.^{20,36,38} The most common side effects are gastrointestinal (GI) in nature and may be attenuated in older patients by using a more gradual dose titration schedule. Rather than the typical metformin starting dose of 500 mg twice daily, older patients and those who seem to have poor GI tolerability may benefit from a regimen that starts at 500 mg once daily, with dose titration every 2–4 weeks.³⁹

The use of metformin extended release (XR) may help to reduce GI side effects in some people. However, a retrospective review found that metformin XR was linked to better GI tolerability in some patient cohorts, but not in all patients.⁴⁰ Therefore, gradual dose titration may still be important for older adults even when using metformin XR.

Because of the expected aging-related decline in renal function, the possibility of metformin-induced lactic acidosis in older patients has been a concern. However, as the evidence base for this issue has expanded, more recent dosing guidance in the United States and internationally has focused on patients' estimated glomerular filtration rate (GFR) rather than their serum creatinine level.⁴¹

No dosing changes are recommended until the estimated GFR is ≥ 30 and < 45 ml/min/1.73 m², at which point one-half of the maximum dose is recommended.⁴¹ Stopping metformin is recommended when the estimated GFR is < 30 ml/min/1.73 m².⁴¹ Use of these criteria may prevent unnecessary discontinuation of metformin in older people with diabetes who could benefit from it.

Sulfonylureas

Sulfonylureas long have been considered a first-line treatment for diabetes in older patients,³⁶ but some guidelines have raised concerns about their association with an increased risk of hypoglycemia.^{20,38} Some drugs in the sulfonylurea class may pose less hypoglycemia risk than others, although evidence is contradictory. According to the Beers Criteria for potentially inappropriate medications in older adults, glyburide should be avoided in elderly patients because of its potential for prolonged hypoglycemia (related to its potentially extended half-life in older patients).⁸ Some sources consider glimepiride to pose less of a risk for hypoglycemia than glipizide.³⁷ However, the U.S. Department of Veterans Affairs/Department of Defense guidelines³⁶ state that glipizide causes less hypoglycemia.

All sulfonylureas are inexpensive and available generically, which may be an important benefit for older adults living on fixed incomes.

Meglitinides

The meglitinides (also called glinides) offer the advantage of flexible dosing for patients who have irregular eating patterns, including some older patients who may not eat three meals per day or follow a consistent meal schedule. Meglitinides may also cause less hypoglycemia than sulfonylureas when they are dosed correctly and only taken when patients eat a meal. However, these agents must be used with caution in patients who have renal impairment, and repaglinide must be used cautiously in those with hepatic impairment.²⁰

Thiazolidinediones

Thiazolidinediones (TZDs) have a potential advantage in older adults because they have a low risk of causing hypoglycemia.³⁶ However, they have been associated with several other issues that may be a problem for

some older adults with diabetes. These include possible links to chronic heart failure, the development of fractures, and bladder cancer.⁴²

Because of these concerns, TZDs are no longer recommended as a first-line treatment.^{20,38} When they are used, pioglitazone generally has been preferred over rosiglitazone because the U.S. Food and Drug Administration (FDA) had placed restrictions on the latter based on possible links to myocardial infarction (MI).⁴³ However, in late November 2013, the FDA proposed easing some of these restrictions on rosiglitazone.

TZDs are comparatively expensive options, although a generic form of pioglitazone is now available.

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors are considered to be one of the first agents to use either along with or as an alternative to metformin because of their efficacy and low risk of hypoglycemia.^{36,38} Sitagliptin, saxagliptin, and alogliptin require dose adjustment for renal impairment but can still be given to people with renal disease.^{44–46} No renal adjustment is needed for linagliptin.⁴⁷ These agents are not available generically and are expensive.

α -Glucosidase inhibitors

The α -glucosidase inhibitors (AGIs) are considered to have a low risk of hypoglycemia because they delay the absorption of carbohydrates. However, caution must be used if they are not discontinued with initiation of prandial insulin because AGIs could cause a delay in peak postprandial blood glucose levels in relation to the onset of action of prandial insulin doses.³⁷

The most limiting side effects of these agents have been GI complaints. Although these agents are typically initiated with dosing three times daily, tolerability may be improved in older people by starting with once-daily dosing with the largest meal and adding a dose with an additional meal every 2 weeks.⁴⁸ Because older patients may be more sensitive to GI upsets than the general population, monitoring is important. Renal impairment is also a concern, and AGIs are contraindicated when serum creatinine values are > 2.0 mg/dl.^{49,50}

Table 1. Brief Comparison of Treatment Goal Recommendations for Older Adults^{2,20,35,36}

Target	American Diabetes Association Position Statement on Diabetes in Older Adults ²	Department of Veterans Affairs/Department of Defense Clinical Practice Guidelines ³⁶	Joint International Position Statement on Diabetes Mellitus in Older People ²⁰	California Healthcare Foundation/American Geriatrics Society ³⁵
Glycemic control	<ul style="list-style-type: none"> • A1C < 7.5% if healthy • A1C < 8% with multiple chronic conditions or mild to moderate cognitive impairment • A1C < 8.5% with an end-stage condition or moderate to severe cognitive impairment or in long-term care 	<ul style="list-style-type: none"> • A1C < 7.0% if mild or no microvascular complications of diabetes, no major concurrent illnesses, and life expectancy of at least 10–15 years • A1C < 8.0% for patients who have had diabetes for > 10 years with comorbidities that are manageable and not end-stage • A1C 8.0–9.0% for patients with major comorbidities, life expectancy < 5 years, or severe microvascular complications 	<ul style="list-style-type: none"> • A1C 7.0–7.5% for most patients • Within this A1C range, blood glucose < 90 mg/dl and > 198 mg/dl should be avoided; anti-hyperglycemic treatment should not be initiated until fasting glucose is consistently ≥ 126 mg/dl 	<ul style="list-style-type: none"> • A1C ≤ 7.0% for healthy adults • A1C > 8.0% may be appropriate for more frail individuals
Blood pressure	<ul style="list-style-type: none"> • < 140/80 mmHg for most older people with diabetes • < 150/90 mmHg if very complex medical history or poor health 	<ul style="list-style-type: none"> • < 140/80 mmHg • < 125/75 mmHg may be appropriate if tolerated 	<ul style="list-style-type: none"> • Patients < 75 years of age: 140/80 mmHg is treatment threshold • Patients ≥ 75 years of age: 150/90 mmHg is treatment threshold • < 150/90 mmHg considered acceptable in presence of functional dependence • A lower systolic blood pressure may be appropriate if there is evidence of renal impairment 	<ul style="list-style-type: none"> • < 140/80 mmHg for older patients, if tolerated
Lipids	Statins may be indicated in all older adults with diabetes except those with limited life expectancy	Statin initiated based on lipid levels and cardiovascular history	Statin considered to be a priority medication	Dyslipidemia should be corrected if feasible after evaluation of overall health status is considered

AGIs are moderately priced, and acarbose is available in a generic formulation.

Sodium-glucose co-transporter 2 inhibitors

Canagliflozin is the first available agent in the sodium-glucose co-transporter 2 (SGLT2) inhibitor class. These medications work by increasing

renal glucose excretion and therefore are considered to have a low risk of causing hypoglycemia when used as monotherapy.

Canagliflozin has been studied specifically in older patients, including those ≥ 75 years of age.⁵¹ Compared to younger patients, those ≥ 65 years of age have been found to experience a higher rate of volume depletion,

causing problems such as dizziness and orthostasis. These effects were more noticeable in those ≥ 75 years of age and were dose-dependent. Therefore, dose titration is important, and, in older patients, it may be best to initiate therapy with 100 mg daily and increase if needed and tolerated. Canagliflozin also has been found to

have decreased benefit in older compared to younger patients.

Renal function must be considered because canagliflozin is ineffective in patients with a GFR < 30 ml/min/1.73 m². Canagliflozin can cause hyperkalemia and therefore will require monitoring if given to patients who take diuretics or medications such as ACE inhibitors, which increase potassium levels. This is a particularly important consideration for many geriatric patients.⁵¹ Canagliflozin is also comparatively expensive.

Colesevelam

Colesevelam is a bile acid sequestrant that has a low risk of hypoglycemia when used as monotherapy and does not require any adjustments for elderly patients. However, it has potential for drug interactions by preventing absorption of some medications. This may be of particular concern for older people or those with multiple comorbidities who are more likely to take numerous medications.⁵²

Colesevelam has been associated with esophageal obstruction, a potential issue for patients who have difficulty swallowing. It has a high pill burden (up to six tablets per day), which may be of concern for patients who take a large number of medications. It also can cause constipation and is not recommended for those with gastroparesis or other GI disturbances.⁵² This agent is not available generically and is expensive.

Bromocriptine

Bromocriptine is a dopamine agonist and one of the more recently approved agents for type 2 diabetes. Data on its use in geriatric patients are limited. However, bromocriptine is believed to reduce insulin resistance and therefore should have a low risk of causing hypoglycemia when used as monotherapy.

Dopamine agonists can cause orthostasis and sleep attacks, in which the patient suddenly falls asleep, and can interfere with the action of antipsychotic agents.⁵³ Bromocriptine is moderately expensive.

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists are considered to be an effective and generally safe option for the treatment of type 2 diabetes. In general, these do not need special

consideration in geriatric patients. Exenatide should not be used in people with a creatinine clearance < 30 ml/min, and caution is recommended when increasing the dose from 5 to 10 µg in those with moderate renal impairment (30–50 ml/min).⁵⁴ Liraglutide does not require dosing adjustment for renal impairment. Worsening renal function has been reported with GLP-1 receptor agonists, but it is unclear whether these were responsible for the dysfunction because other medications affecting renal function or hydration often were also present.^{54,55}

Because these agents slow GI transit time, they are not recommended for people with gastroparesis or other GI motility disorders. It is also important to monitor patients for GI symptoms and weight loss, which can be significant.^{54,55}

Because GLP-1 receptor agonists are injectable medications, due consideration must be given to ensure that patients can self-inject or receive injections from others appropriately. These agents are expensive.

Insulin

Insulin is the most effective treatment available for diabetes but also has substantial potential for causing hypoglycemia. Insulin will clearly be needed and can have substantial benefit in some older people with diabetes. However, the changes that occur with aging and the likely presence of additional comorbidities (e.g., problems with vision, cognition, and dexterity), may require further consideration to ensure that patients who use insulin can avoid potential harm. This does not mean insulin should be avoided in the elderly, but rather that clinicians should consider helpful options such as insulin pens, pre-drawn insulin, and direct assistance from a family member or caregiver for some of their older patients with diabetes.

Some insulins may have a lower risk of causing hypoglycemia. A pooled analysis of five randomized, controlled trials comparing the addition of NPH insulin or insulin glargine to oral agents found no difference between the treatments with regard to daytime symptomatic hypoglycemia or hypoglycemia severity.⁵⁶ However, the glargine group had a lower incidence of both nocturnal symptomatic and nocturnal severe hypoglycemia.⁵⁶ This study found no age-related dif-

ferences with regard to hypoglycemia, but patients in the study were all ≤ 80 years of age.

A joint position statement of the International Association of Gerontology and Geriatrics, the European Diabetes Working Party for Older People, and the International Task Force of Experts in Diabetes²⁰ states that a regimen of basal insulin only may cause less hypoglycemia than basal-bolus or premixed insulin regimens. Sliding-scale insulin, in which the dose of insulin varies based on the blood glucose level, is not recommended by the Beers Criteria because such a dosing algorithm is more likely to cause hypoglycemia without improving glycemic control.⁸ The American Diabetes Association (ADA) position statement on the treatment of diabetes in older adults recommends against sliding-scale insulin as the sole treatment for glycemic control in inpatient and long-term care settings,² and sliding-scale dosing may be even more problematic for patients who live in their own homes where insulin is not administered by a health care professional. Because sliding-scale doses are not consistent, this may be a particular issue for patients with vision, dexterity, or cognition problems.

Pramlintide

Pramlintide is indicated as an add-on therapy to insulin. No specific information is provided for its use in the elderly. However, pramlintide packaging information includes specific warnings that it could potentially increase the likelihood of insulin-induced hypoglycemia and that patients who use pramlintide should understand how to use insulin and check their blood glucose appropriately. Insulin doses should be reduced, usually by 50%, when pramlintide is initiated.⁵⁷ Pramlintide is a very expensive option.

Aspirin

Aspirin treatment is still recommended for most older people with diabetes because of its clear benefit for secondary prevention of cardiovascular events, and it is also generally recommended for primary prevention in patients with both diabetes and other cardiovascular risk factors.^{2,58} However, as with other aspects of CVD in older people with diabetes, aspirin has not been well studied. A Japanese study⁵⁹ of people with diabe-

tes who had no history of CVD did not find benefit of aspirin for the general study cohort but did find a reduction in combined cardiovascular endpoints in a subgroup analysis of participants who were ≥ 65 years of age. In a population-based cohort study,⁶⁰ taking ≤ 300 mg/day of aspirin was found to increase the risk of major bleeding (GI or cerebral hemorrhage) in the general population. However, aspirin did not cause a higher rate of bleeding in people with diabetes. Interestingly, these results may have been confounded by the fact that diabetes is an independent risk factor for increased bleeding. Thus, caution is still advised in using daily aspirin therapy for older people with diabetes.

The GI risk associated with aspirin treatment potentially can be prevented by the use of proton pump inhibitors or other gastroprotective agents.⁶¹ However, for older patients with diabetes who are at risk for other types of bleeding, clinicians must evaluate whether the risk of bleeding merits such treatment.

Joint professional guidance from the ADA, American Heart Association, and American College of Cardiology Foundation recommends aspirin at a dose of 75–162 mg daily.⁵⁸

Treatment of Hypertension in Older Adults With Diabetes

Treating hypertension is important for preventing CVD, nephropathy, and retinopathy in older adults with diabetes.^{2,20,36} However, research has raised questions about whether some older patients—especially the oldest-old and those who are more frail—should have less intensive blood pressure targets than younger patients.

The ACCORD blood pressure trial (ACCORD-BP)⁶² compared systolic blood pressure targets of < 120 and < 140 mmHg and enrolled patients with a mean age of 62 years who had either CVD or cardiovascular risk factors. There was no benefit for the primary composite cardiovascular endpoint (nonfatal MI, nonfatal stroke, and death from cardiovascular causes) with more intensive blood pressure control. There was benefit for stroke reduction (number needed to treat: 89 for 5 years to prevent 1 stroke) but not for other secondary endpoints. Patients in the intensive group experienced some medication-related side effects at a significantly higher rate.

In the VADT to assess glycemic control and cardiovascular risk, patients (mean age 60 years) were given stepwise treatment to maintain blood pressure at a target of $< 130/80$ mmHg. A retrospective analysis indicated increased cardiovascular mortality at systolic blood pressure level > 140 mmHg but also at diastolic blood pressure levels < 70 mmHg.⁶³ The diastolic result was in contrast to the ACCORD-BP results, in which the group with a systolic blood pressure target of < 120 mmHg had a mean diastolic pressure of 64.4 mmHg and those in the group with a systolic blood pressure target of < 140 mmHg had a mean diastolic blood pressure of 70.5 mmHg, but mortality was not increased.⁶²

Post-hoc analyses^{64,65} of two different trials treating patients with known coronary artery disease found that the relationship between blood pressure and mortality followed a J-shaped curve, in which mortality increased for both high and low blood pressure levels. Although evidence of a J-curve has been debated, the potential increased mortality at low blood pressure levels has been hypothesized to be related to poor perfusion of the heart and other organs. Poor perfusion may be a greater issue in older patients because of increasing arterial wall stiffness with aging.⁶³

These data indicate a clear benefit to treating hypertension in older people with diabetes but also support the need to consider less aggressive targets, including a minimum blood pressure level, to avoid causing harm in some elderly patients. The VADT considered 105/70 mmHg to be the minimum blood pressure, but a true minimum would need to be confirmed in a randomized, controlled trial. One challenge in interpreting these findings is that isolated systolic hypertension occurs more commonly in the geriatric population. Therefore, weighing the benefit of lowering systolic blood pressure against the risk of excessively lowering diastolic blood pressure must occur on an individual basis when planning each patient's therapy regimen.

Medications recommended for treating hypertension in older people with diabetes are the same as for younger patients. However, one consideration in older patients may be a possible link between hypoglycemia unawareness and β -blockers, given

that many older patients already have a blunted response to sympathetic activation in the presence of hypoglycemia. β -Blockers are important for treating comorbidities such as heart failure or MI and therefore should not be withheld; however, avoiding hypoglycemia by setting less aggressive glucose and A1C targets may be prudent for older patients who are also taking a β -blocker.

Treatment of Hyperlipidemia in Older Adults With Diabetes

Lipid control also plays an important role in reducing CVD in people with diabetes. Statins are considered the primary hyperlipidemia treatment and have been shown to have significant clinical benefit over the course of just a few years.⁶⁶ However, there has been controversy regarding the use of statins in the oldest segment of geriatric patients, because of both a dearth of data and recent evidence indicating potential harm in patients ≥ 80 years of age. A meta-analysis of 14 key statin trials⁶⁷ indicated that statins offer a similar degree of cardiovascular risk reduction in patients > 75 years of age as in younger patients. However, the majority of the studies in this analysis (11 of 14) only enrolled patients ≤ 80 years of age.

Some trials have focused more specifically on geriatric patients. An analysis as part of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) examined treatment with pravastatin in older patients (aged ≥ 55 years; mean age 66 years) with moderate hypercholesterolemia and controlled hypertension. This study did not find a treatment benefit in terms of all-cause mortality or coronary heart disease, although the placebo group had a greater than expected benefit.⁶⁸ The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial enrolled geriatric patients 70–82 years of age who were given pravastatin.⁶⁹ This trial found a benefit of therapy in terms of heart disease but not for overall mortality or stroke.

Potentially more concerning than the mixed findings from these studies is the possibility of harm suggested in other analyses. A systematic review of statin trials⁷⁰ found that the use of statins may increase overall mortality in patients ≥ 80 years of age.⁷⁰ Another analysis from the Rotterdam study⁷¹ found an increasing inverse

relationship between cholesterol levels and mortality with increasing age. This inverse relationship was found to begin at age 65. It has been hypothesized that the increased mortality observed in older patients may be related to statins lowering both smaller and larger LDL molecules. The larger and less dense LDL cholesterol molecules may have a protective benefit in aging.⁷² These studies do not mean that statins are contraindicated in older patients, although clinicians should evaluate whether a patient has known CVD or whether the issue is merely an elevated LDL level that is first detected in someone ≥ 80 years of age. It has been suggested⁷² that obtaining an analysis of the molecular structure of older patients' LDL may be helpful to ensure that patients with small, dense LDL particles receive statin therapy, whereas those with primarily larger and potentially more beneficial LDL particles do not.⁷²

General guidance on the use of statins in older people with diabetes is included in Table 1.

Conclusion

Diabetes is a significant concern requiring treatment in many older patients. However, patients with increasing age and comorbidities may have different needs than younger people with diabetes, and research indicates that less aggressive goal setting and more cautious use of medications may be prudent in this population. Clinicians should not interpret the need for such adjustments as an indication that diabetes treatment is not important in elderly patients. Rather, the treatment of diabetes in the elderly must be individualized to address specific age-related issues, keeping in mind the potential for greater harm and reduced benefits of standard diabetes therapies as patients age and develop more comorbidities.

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In Brief

The growing older adult population and its higher incidence of diabetes are creating demands on health care providers to address the special needs of these patients. Because nutrition is essential to the proper treatment and self-management of diabetes, clinicians must develop and adopt various strategies to address some of the common nutritional, lifestyle, and self-management barriers that older adults face. Nutrition assessments of older adults with diabetes should be comprehensive, with attention to each patient's unique nutritional needs. Constructing a realistic nutrition care plan is essential for success. This article addresses some of the key nutrition-related aspects of diabetes self-care in older adults with diabetes.

Nutrition Considerations for the Growing Population of Older Adults With Diabetes

Kathleen Stanley, CDE, RD, LD, MSEd, BC-ADM

Diabetes in Older Adults

Etiology of type 2 diabetes in older adults

The incidence of type 2 diabetes in older adults is attributable to two primary factors: 1) changes in metabolism (e.g., increased insulin resistance and decreased insulin production) and 2) changes in weight and physical activity. The development of glucose intolerance is a recognizable metabolic change that occurs during aging, and some degree of glucose intolerance is normal later in life, even in otherwise healthy people. Studies have reported increases of 5.3 mg/dl in postprandial glucose levels and 1–2 mg/dl in fasting glucose levels for every decade of life after the age of 30 years.¹

The etiology of glucose intolerance in older adults is multifaceted. Factors such as slower glucose

absorption, altered gluconeogenesis, decreased insulin production, reduced lean body mass, decreased physical activity, and altered digestion all contribute to reduced glucose utilization.² Alterations in physical activity in older adults are common and often related to physical limitations, conditions such as atherosclerosis, and an increased risk of injury.³ In addition, many people in this age category also have one or more chronic health condition requiring prescription and nonprescription medications that may affect glucose metabolism.^{1,4}

Identifying diabetes and diabetes risk in older adults

Although it is widely known that older adults are a high-risk group, diagnosis of diabetes in this population can be difficult. Despite American Diabetes Association (ADA) recommenda-