Invited Commentary

Glucose Control in Older Adults With Diabetes Mellitus—More Harm Than Good?

Kasia J. Lipska, MD, MHS; Victor M. Montori, MD

Ms Andrews, your 83-year-old patient, is proud. She walks daily, watches her diet, and never misses her appointments. Her glycated hemoglobin (HbA_{1c}) level is 6.9%. As she readies to leave, you notice her bruised arm. It is from one of her fainting spells, she says. After asking a few more questions, you realize she has been having hypoglycemic episodes, including at least 1 last week in which she lost consciousness and needed her son's assistance. Perhaps not all is as it seems. Based on multiple performance metrics, her care has been exemplary. But has your treatment caused more harm than good?

Hypoglycemia is a major adverse consequence of glucose-lowering therapy in patients with type 2 diabetes mellitus (DM). For the last decade, DM care guidelines and quality metrics have been almost exclusively focused on prevention of hyperglycemia and its complications. However, target-based glucose lowering can potentially lead to one-size-fits-all clinical practice and result in adverse events. Although hypoglycemia may not always be overlooked, as it was in Ms Andrews' case, it commonly occurs among patients with type 2 DM. Among 100 patient-years of treatment with insulin or insulin secretagogues, an estimated 35 to 70 recognized severe hypoglycemic episodes occur.[1]

Older patients are at higher risk of hypoglycemia.[2] Aging-related changes in renal function and drug clearance may contribute to this vulnerability. In addition, polypharmacy, common in older individuals and in younger patients with multiple chronic conditions, increases the risk of interactions that result in lower glucose levels or in an impaired sensing of hypoglycemic symptoms. Intercurrent illnesses and variable caloric intake may also contribute to an increased risk of hypoglycemia in older adults.

Related article page 1300

Hypoglycemia is associated with poor outcomes. Patients with severe hypoglycemia have a 3.4-fold higher risk of death within 5 years,[3] and they experience more acute cardiovascular events, fall-related fractures, and driving-related accidents and falls compared with DM patients without severe hypoglycemia. Hypoglycemia also reduces quality of life, a reduction that may be similar to that caused by DM complications.[4]

Among the more serious consequences of hypoglycemia is cognitive dysfunction. Our understanding of the interplay between cognitive dysfunction and hypoglycemia continues to evolve: impaired cognition is a risk factor for hypoglycemia[5] and may result in diminished ability to self-manage DM, but serious hypoglycemia may also, in turn, be associated with a risk of dementia.[6] In this issue of *JAMA Internal Medicine*, Yaffe et al[7] report a reciprocal relationship between hypoglycemia and dementia in a cohort of older Americans, with a higher risk of hypoglycemia among patients with dementia and a higher risk of dementia among patients with hypoglycemia, potentially setting up a vicious cycle of adverse events.

Efforts to mitigate the risk of hypoglycemia are clearly warranted to improve quality of life and potentially prevent the associated adverse events. After problem solving through fixable causes of hypoglycemia,[1] patients and clinicians should consider setting higher HbA_{1c} targets that may yield a safer management program.

Less intensive glycemic control may permit lower dosages of hypoglycemic medications and a simpler DM regimen, reducing treatment errors and decreasing risk of hypoglycemia. Furthermore, we understand that more benefits might accrue for prevention of complications and symptomatic hyperglycemia when HbA_{1c} is lowered from 9% to 8% than from 8% to 7%. In contrast, the burden of treatment associated with therapeutic complexity and risk of harms increases with lower targets. Insisting on lower targets in older patients requires high-quality evidence that the benefits exceed the harms, costs, and burden. However, the likelihood that tight glycemic control will favorably influence the outcomes that matter to Ms Andrews (living independently with good mental and physical function) is unclear. Extant trials of tight glycemic control show inconsistent effects on microvascular and macrovascular complications and consistent increases in the risk of polypharmacy, hypoglycemia, and weight gain with lower HbA_{1c} targets.[8] Although most trials did not enroll older patients, we judge that the available evidence applies to Ms Andrews and that she is unlikely to experience more benefit than harm from targeting an HbA_{1c} level below 7%.

Avoiding hypoglycemia is also possible for patients who respond to antihyperglycemic medicines that do not cause hypoglycemia. Unfortunately, these therapies are associated with other adverse events in older patients. Metformin is first-line therapy in most patients, but the Food and Drug Administration label warns that treatment should not be initiated in patients 80 years or older unless measurement of creatinine clearance demonstrates that renal function is not reduced, because these patients may be more susceptible to developing lactic acidosis. These precautions are not based on high-quality evidence and may inappropriately limit access to this medication for many patients who could safely use it and avoid hypoglycemia. Pioglitazone use increases the risk of edema, heart failure, bladder cancer, and fragility fractures. Incretin-based therapies are very expensive, and their long-term safety remains uncertain.

Many patients cannot achieve target glycemic control with these agents, and insulin or its secretagogues may be necessary. Sulfonylureas may cause frequent and prolonged hypoglycemia, and there are long-standing concerns about their po-

tential to increase cardiovascular risk. Insulin use is associated with the highest risk of hypoglycemia and may burden patients with expense, weight gain and fluid retention, and complex self-management tasks. Insulin administration also stresses the older patient's dexterity and visual acuity. In general, these drugs can be used safely, particularly when HbA_{1c} targets are moderated.

To minimize the risk of hypoglycemia, patients and clinicians need to consider changes in the HbA_{1c} target and antihyperglycemic approach. We do not believe that these choices are technical (ie, that there is a "right" answer that clinicians can expertly offer to each patient). Rather, the right choice for a patient at a given point in time requires a careful balance of the circumstances of the patient, his or her goals and preferences, and the research evidence about the alternatives. Shared decision making promotes patient involvement in treatment decisions to achieve DM care that is both evidence based and consistent with the patient's context, values, and preferences. The HbA_{1c} target and antihyperglycemic approach should reflect what matters most to patients! Tools and tactics that encourage involvement of patients and their caregivers in choosing their DM treatment are both feasible and effective.[9]

*Ms Andrews wants her life back; her fainting spells have limited her daily walks and social visits, and she lives in fear of getting hurt and of losing her independence. She now recognizes that hypoglycemia did not need to be an obligatory consequence of her treatment. Her cognition is briefly tested, and results suggest normal function. After discussing her options using a decision aid (*http://diabetesdecisionaid.mayoclinic.org*), she prefers a simpler insulin regimen to achieve an HbA_{1c} level of about 8%.*

Hypoglycemia in the course of type 2 DM treatment is both common and associated with poor outcomes. Therefore, decisions about the intensity and type of antihyperglycemic therapy must take into account the harms of hypoglycemia. Involving patients in these treatment decisions may favorably shift the current glucose-centric paradigm to a more holistic patient-centered one. In turn, Ms Anderson's exemplary DM care, as measured by the disease-centered performance metrics, can be revealed for what it was—a poor treatment experience, resulting in more harm than good.

ARTICLE INFORMATION

Author Affiliations: Section of Endocrinology, Department of Medicine, Yale University School of Medicine, New Haven, Connecticut (Lipska); Knowledge and Evaluation Research Unit, Mayo Clinic, Rochester, Minnesota (Montori).

Corresponding Author: Kasia J. Lipska, MD, MHS, Section of Endocrinology, Department of Medicine, Yale University School of Medicine, PO Box 208020, New Haven, CT 06520-8020 (kasia.lipska@yale.edu).

Published Online: June 10, 2013. doi:10.1001/jamainternmed.2013.6189.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported in part by a T32-AG019134 fellowship from the National Institutes on Aging (Dr Lipska).

REFERENCES

1. Cryer PE, Axelrod L, Grossman AB, et al; Endocrine Society. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009;94(3):709-728.

2. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. *Diabetes Care*. 2012;35(12):2650-2664.

3. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. *Diabetes Care*. 2012;35(9):1897-1901.

4. Laiteerapong N, Karter AJ, Liu JY, et al. Correlates of quality of life in older adults with diabetes: the Diabetes & Aging Study. *Diabetes Care*. 2011;34(8):1749-1753.

5. Punthakee Z, Miller ME, Launer LJ, et al; ACCORD Group of Investigators; ACCORD-MIND Investigators. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. *Diabetes Care*. 2012;35(4):787-793.

6. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA*. 2009;301(15):1565-1572.

7. Yaffe K, Falvey CM, Hamilton N, et al; Health ABC Study. The association between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus [published online June 10, 2013]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2013.6189.

8. Montori VM, Fernández-Balsells M. Glycemic control in type 2 diabetes: time for an evidence-based about-face? *Ann Intern Med*. 2009;150(11):803-808.

9. Mullan RJ, Montori VM, Shah ND, et al. The diabetes mellitus medication choice decision aid: a randomized trial. *Arch Intern Med*. 2009;169(17):1560-1568.