

4. Naylor MD, Brooten DA, Campbell RL et al. Transitional care of older adults hospitalized with heart failure: A randomized, controlled trial. *J Am Geriatr Soc* 2004;52:675–684.
5. Ota KS. The transitionalist: Optimizing inpatient-to-outpatient transitions of care. *Arch Intern Med* 2012;172:81.

## EFFECT OF DIFFERENT DIABETES MELLITUS TREATMENTS ON FUNCTIONAL DECLINE AND DEATH IN ELDERLY ADULTS WITH DIABETES MELLITUS

*To the Editor:* There is no agreement on the optimal target of glycosylated hemoglobin (HbA1c) in elderly adults with diabetes mellitus, so the recent study by Yau and colleagues is important, because it evaluated the effect of glycemic control on functional decline and death in an elderly population with diabetes mellitus.<sup>1</sup> The results of the study have shown that the current American Geriatrics Society (AGS)<sup>2</sup> HbA1c target of 8.0% or less might be lower than necessary to obtain better functional outcomes and to delay death. So the authors have suggested updating the current AGS recommendations, considering that a HbA1c between 8.0% and 8.9% was associated with better function.<sup>1</sup> Nevertheless, the recent consensus of the International Association of Gerontology and Geriatrics, the European Diabetes Working Party for Older People, and the International Task Force of Experts in Diabetes has recommended an HbA1c target between 7.0% and 7.5%.<sup>3</sup>

It is surprising that better functional outcomes were observed in elderly persons with worse glycemic control<sup>1</sup> if one considers that other studies have shown that hyperglycemia per se is associated with disability in older people.<sup>4,5</sup> To explain the results of the study by Yau and colleagues,<sup>1</sup> it is important to remember that not only hyperglycemia per se,<sup>4,5</sup> but also insulin resistance,<sup>6,7</sup> hypoglycemia,<sup>8</sup> and glycemic variability<sup>9</sup> are strongly involved in disability of older individuals with diabetes mellitus and that those parameters were not taken into account in the study. If insulin resistance, hypoglycemia, and glycemic variability are not adequately contrasted, the positive effects of better glycemic control on functional outcomes can be attenuated or canceled. With this in mind, it is possible that the results of the study by Yau and colleagues may be due at least partially to the type of medications used in that population, although the study refers to the period between 2002 and 2008, and innovative treatments for diabetes mellitus were less available. Half (51%) of the participants in the study took sulfonylureas, and it was not reported what type of insulin was used; in particular, it is unclear whether regular and neutral protamine Hagedorn insulin were used. Sulfonylureas and “old” insulins can be associated with greater incidence of hypoglycemia, especially in individuals with good glycemic control and can increase insulin resistance and glycemic variability. To obtain tighter control, it is important to avoid or greatly reduce the risk of hypoglycemia; therefore sulfonylureas and some insulins should be avoided, whereas other drugs at very low risk of hypoglycemia, such as metformin, pioglitazone, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagonlike

peptide 1 agonists, and insulin analogs are preferred. Metformin should be first-line therapy in individuals without contraindications, because it can improve insulin resistance and does not cause hypoglycemia. Metformin might also improve functional impairment.<sup>7</sup> In the study by Yau and colleagues,<sup>2</sup> the positive effects of metformin on the outcomes may not be evident, because all of the individuals treated with oral agents (sulfonylurea and metformin) were grouped together in the same group. Pioglitazone has some of the same features as metformin and could be used as a safe second-line therapy in selected elderly adults with diabetes mellitus not at high risk of heart failure, bone loss, or bladder cancer or with osteoporosis.<sup>3</sup> DPP-4 inhibitors and glucagon-like peptide 1 agonists can be considered as second-line therapy in frail and debilitated elderly adults;<sup>10</sup> they have an excellent tolerability profile, are safe (low risk of hypoglycemic events based on their synergic action on glucose-dependent insulin secretion and glucose-dependent glucagon suppression), and have composite metabolic efficacy, leading to better peripheral glucose homeostasis and beta cell function preservation and lowering body weight.<sup>10</sup>

Therefore, tight control can be reached in most elderly adults with diabetes mellitus if newer antidiabetic drugs are used, and this can improve functional outcomes and delay death. This seems to indicate that it is necessary to obtain data from populations treated with newer treatments for diabetes mellitus before modifying guidelines or recommendations on HbA1c targets in elderly adults with diabetes mellitus.

Carmine Gazzaruso, MD, PhD

*Internal Medicine, Diabetes, Vascular and Endocrine-Metabolic Diseases Unit, Centre for Applied Clinical Research, Clinical Institute Beato Matteo Vigevano, Italy  
Department of Internal Medicine, Istituto di Ricovero e Cura a Carattere Scientifico, Policlinico San Donato, San Donato Milanese, Italy*

Adriana Coppola, RN, MSN

*Chiara Luppi, MD  
Internal Medicine, Diabetes, Vascular and Endocrine-Metabolic Diseases Unit, Centre for Applied Clinical Research, Clinical Institute Beato Matteo Vigevano, Italy*

Andrea Giustina, MD

*Department of Medical and Surgical Sciences, University of Brescia, Brescia, Italy*

Sebastiano B. Solerte, MD

*Department of Internal Medicine, School of Geriatrics University of Pavia, Pavia, Italy*

## ACKNOWLEDGMENTS

**Conflict of Interest:** The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

**Author Contributions:** Gazzaruso, Solerte: Concept, preparation, and final revision of manuscript. Coppola, Luppi, Giustina: Preparation of manuscript.

**Sponsor's Role:** No sponsor for any part of the manuscript.

## REFERENCES

1. Yau CK, Eng C, Cenzer IS et al. Glycosylated hemoglobin and functional decline in community-dwelling nursing home-eligible elderly adults with diabetes mellitus. *J Am Geriatr Soc* 2012;60:1215–1221.
2. Brown AF, Mangione CM, Saliba D et al. Guidelines for improving the care of the older person with diabetes mellitus. *J Am Geriatr Soc* 2003;51(Suppl):S265–S280.
3. Sinclair A, Morley JE, Rodriguez-Mañás L et al. Diabetes mellitus in older people: Position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes. *J Am Med Dir Assoc* 2012;13:497–502.
4. Wu H, Flaherty J, Dong B et al. Impact of geriatric conditions versus medical diagnoses on ADL disability among nonagenarians and centenarians. *J Aging Health* 2012;24:1298–1319.
5. Bossoni S, Mazziotti G, Gazzaruso C et al. Relationship between instrumental activities of daily living and blood glucose control in elderly subjects with type 2 diabetes. *Age Ageing* 2008;37:222–225.
6. Abbatecola AM, Paolisso G. Is there a relationship between insulin resistance and frailty syndrome? *Curr Pharm Des* 2008;14:405–410.
7. Mazziotti G, Bossoni S, Orini S et al. Treatment with metformin is protective against limitations in instrumental activities of daily living in older subjects with type 2 diabetes mellitus. *J Am Geriatr Soc* 2009;57:562–564.
8. Abdelhafiz AH, Sinclair AJ. Hypoglycemia in residential care home. *Br J Gen Pract* 2009;59:49–50.
9. Wang CP, Hazuda HP. Better glycemic control is associated with maintenance of lower-extremity function over time in Mexican American and European American older adults with diabetes. *Diabetes Care* 2011;34:268–273.
10. Abbatecola AM, Maggi S, Paolisso G. New approaches to treating type 2 diabetes mellitus in the elderly: Role of incretin therapies. *Drugs Aging* 2008;25:913–925.

## RESPONSE LETTER TO GAZZARUSO AND COLLEAGUES

*To the Editor:* We would like to thank Gazzaruso and colleagues for their thought-provoking letter, which suggests that our conclusion (HbA1c target of 8.0% may be lower than necessary for maintaining function in nursing home – eligible elderly adults) may be premature for two reasons.<sup>1</sup> First, they note that our study results run counter to previous studies in which hyperglycemia was associated with disability. However, both of the cited studies were cross-sectional, raising the possibility that the observed association was due to reverse causation. Specifically, providers may have appropriately decreased the intensity of glycemic treatments for disabled individuals, because these individuals are often older and have a greater burden of comorbidities, putting them at higher risk for hypoglycemia.<sup>2,3</sup> Thus, we believe that our longitudinal study is an important advance from previous studies.

Second, Gazzaruso and colleagues note that our studies occurred before the widespread use of dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) agonists. Newer agents hold the promise of tighter glycemic control in older adults with less hypoglycemia, but there are currently few data to suggest that these newer medications lead to better outcomes such as less functional decline. Because these newer medications

cost many times more than older medications and long-term safety is unknown, we believe that older medications should be tried first in the vast majority of older adults with diabetes mellitus.

For healthier elderly adults with a long life expectancy, we agree with Gazzaruso that a reasonable HbA1c target would be 7.0–7.5%, as the International Association of Gerontology and Geriatrics (IAGG) recommends,<sup>4</sup> but our study and conclusions focused on elderly adults eligible for nursing home admission for whom consensus statements recommend less-stringent glycemic targets. The IAGG panel states that “in cases of functional dependence, care home residence...and other high dependency states, [HbA1c target] may need to be adjusted to reduce the risk of hypoglycemia and enhance patient safety.”<sup>4</sup> Furthermore, a recent American Diabetes Association and European Association for the Study of Diabetes consensus statement recommended that “less stringent goals—e.g. 7.5–8.0% or even slightly higher—are appropriate for patients with...a limited life expectancy [or] extensive comorbid conditions.”<sup>5</sup> Thus, for elderly adults with functional limitations and limited life expectancy, expert consensus statements appear to support our conclusion that an HbA1c target of 8.0% may be lower than necessary to maintain function.

Sei J. Lee, MD, MAS

*Division of Geriatrics, University of California at San Francisco, San Francisco, California  
San Francisco Veterans Affairs Research Enhancement Award Program, San Francisco, California*

Celia K. Yau, MD

*Kaiser Permanente, Santa Clara, California*

Catherine Eng, MD

*Division of Geriatrics, University of California at San Francisco, San Francisco, California  
On Lok Lifeways, San Francisco, California*

## ACKNOWLEDGMENTS

**Conflict of Interest:** Dr. Lee's effort was supported by National Institutes of Health, National Center for Research Resources, University of California at San Francisco, Clinical and Translational Science Institute Grant KL2 RR024130 and the Hellman Family Award for Early Career Faculty at University of California at San Francisco.

**Author Contributions:** S. Lee: Concept, preparation, final revision of manuscript. C. Yau and C. Eng: Preparation of manuscript.

**Sponsor's Role:** The funding sources had no role in the design or conduct of the study, data management or analysis, or manuscript preparation.

## REFERENCES

1. Yau CK, Eng C, Cenzer IS, et al. Glycosylated hemoglobin and functional decline in community-dwelling nursing home-eligible elderly adults with diabetes mellitus. *J Am Geriatr Soc* 2012;60:1215–1221.
2. Bossoni S, Mazziotti G, Gazzaruso C, et al. Relationship between instrumental activities of daily living and blood glucose control in elderly subjects with type 2 diabetes. *Age Ageing* 2008;37:222–225.