COMMENTARY

How Significant Is Severe Hypoglycemia in Older Adults With Diabetes?

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Diabetes Care 2020;43:512–514 | https://doi.org/10.2337/dci19-0069

Severe hypoglycemia is a devastating event in the lives of people with diabetes treated with insulin and/or insulin secretogogues. Severe hypoglycemia is defined as an episode in which the person with diabetes requires the assistance of another to increase blood glucose, usually by administration of glucagon or contacting a medical professional. These occurrences are not rare. More than 10% of adult patients in the T1D Exchange registry reported at least one episode of severe hypoglycemia over the past 12 months (1). These events elicit profound fear in patients with diabetes. By depriving the brain of glucose, severe hypoglycemia acutely alters brain function, resulting in neuroglycopenic symptoms, seizures, or even death. The impact extends beyond the acute event. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial reported that patients with type 2 diabetes who experience severe hypoglycemia were at higher risk for a major macrovascular event or death over the subsequent 12 months (2). As the population ages, there remains a critical need to understand the significance and impact of severe hypoglycemia in older patients with diabetes.

In this issue of *Diabetes Care*, complementary articles provide new insights into the consequences of severe hypoglycemia in older adults. Lacy et al. (3) report that severe hypoglycemia is associated with reduced cognitive function in older adults with type 1 diabetes, and Standl et al. (4) confirm the bidirectional nature of the association between severe hypoglycemia and cardiovascular (CV) events in adults with type 2 diabetes. Both investigations support reducing severe hypoglycemia as a clinical imperative in reducing diabetes-associated morbidity.

Lacy et al. (3) used data collected from the 718 patients with type 1 diabetes (mean age 67.2 years) in the Study of Longevity in Diabetes (SOLID) to perform a cross-sectional analysis between cognitive function, recent severe hypoglycemia (self-reported within the last 12 months), and lifetime severe hypoglycemia (self-reported event requiring emergency room visit or hospitalization). Their key finding was that both recent and lifetime severe hypoglycemia were associated with impaired cognition, with the greatest impairment found in those with recent severe hypoglycemia. While it is possible that the severe hypoglycemia caused cognitive impairment in this population, it is also possible that cognitive impairment contributed to the occurrence of severe hypoglycemia, as suggested by the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) study, where severe hypoglycemia was seen most frequently in subjects with the greatest cognitive decline over 20 months (5). The Lacy et al. study was limited by lack of HbA_{1c} measurement, and therefore the contribution of glycemic control could not be assessed. This is an important limitation, as poor glycemic control is associated with worse cognitive function in patients with type 1 diabetes (6).

Standl et al. (4) leveraged the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) study (7), a CV outcome trial of exenatide that enrolled 14,752 patients with type 2 diabetes (mean age 62 years), to examine the bidirectional relationship between CV events and severe hypoglycemia (median follow-up 3.2 years). Their key findings include the following: *1*) severe hypoglycemia was significantly associated with high risk for subsequent CV events, *2*) CV events were significantly associated with high risk for subsequent severe hypoglycemia, and *3*) high levels of comorbidity were associated with having both severe hypoglycemia and CV events. A major study limitation is lack of data collection describing less severe episodes of hypoglycemia, which prevents determination of a bidirectional relationship between level 2 hypoglycemia (glucose $<$3.0 mmol/L [54 mg/dL] [8]) and CV events. Their study remains remarkable for its large sample size and the durability of the findings after adjustment for multiple baseline factors. It also convincingly demonstrated that

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See accompanying articles, pp. 541 and 643.

subjects with severe hypoglycemia and CV disease presented with a frailer phenotype than subjects who did not experience these outcomes. This has been suggested by other studies (2,9–12), but the study by Standl et al. is the first one to characterize its participants using the Charlson comorbidity index (13).

Older adults are at higher risk for frailty. The Charlson comorbidity score is a surrogate of frailty and takes into account the number and the seriousness of a patient's comorbid conditions (13). It was derived from patients ($n = 607$) who were admitted to New York Hospital–Cornell Medical Center in 1984 with follow-up over 1 year, 5 years, and 10 years. The Charlson comorbidity score encompassed a wide range of comorbid conditions, including dementia as is relevant to the article by Lacy et al., and generally found that higher scores and greater age are associated with higher mortality risk (13). The complementary articles presented in this issue of *Diabetes Care* augment this literature by describing the significance of severe hypoglycemia in older adults with frailty (Fig. 1).

Since intensification of glycemic treatment has been repeatedly linked to increased rates of hypoglycemia (14–17), clinicians commonly believe that relaxing glycemic control will reduce the risk for hypoglycemia. Yet, numerous studies have reported that hypoglycemia is not exclusive to patients who achieve a low HbA_{1c} (18–20). This point is reinforced by Standl et al. (4), who reported similar HbA_{1c} levels between participants who did and did not experience severe hypoglycemia.

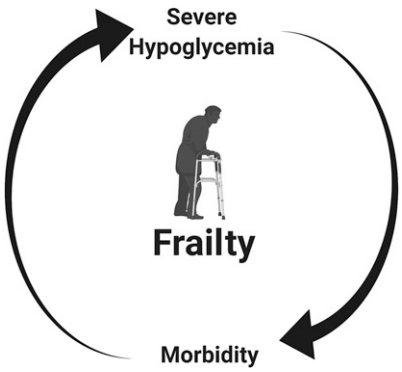

Figure 1—The bidirectionality between severe hypoglycemia and morbidity is likely exacerbated by frailty. Reducing severe hypoglycemia in patients with frailty may significantly reduce morbidity, but this will need to be tested in future studies.

As liberalizing glycemic goals does not necessarily reduce hypoglycemia, alternative measures need to be considered. The American Diabetes Association/European Association for the Study of Diabetes Working Group developed a pathway of treatment optimization recommending drugs with low risk of hypoglycemia (sodium–glucose cotransporter 2 inhibitors, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 receptor agonists) to be used in addition to metformin (20). However, avoidance of hypoglycemia by medication selection is limited by medication cost, side effects, and usage limitations, particularly in the setting of renal disease (21). Another option is the use of continuous glucose monitoring (CGM) systems, which reduce hypoglycemia in patients type 2 diabetes treated by multiple daily injections (22) or patients with type 1 diabetes treated by insulin pump (23) or multiple daily insulin injections (24)

In summary, these studies emphasize the need for glycemic treatment to move beyond glycemic control and include reduction of severe hypoglycemia, particularly in an older population with comorbidities. While Standl et al. (4) clearly demonstrate a bidirectional relationship between severe hypoglycemia and CV events, Lacy et al. (3) could not address the bidirectionality between severe hypoglycemia and impaired cognition because of the study's cross-sectional design. Regardless, practitioners need to consider comorbidities such as frailty and cognitive dysfunction when making glycemic treatment recommendations for their patients with diabetes. Reducing the frequency of severe hypoglycemia, either by altering the medication program or use of CGM systems, needs to be a priority in reducing diabetes-associated morbidity and mortality.

Funding. E.R.S. has funding from the National Institutes of Health National Institute of Neurological Disorders and Stroke (R01 NS035192) and JDRF (3-SRA-2017-483-S-B).

Duality of Interest. E.R.S. has served as an advisor/consultant for Sanofi, Zucara, MannKind, and Eli Lilly. Her university has received grant funding from Eli Lilly for an investigator-initiated project developed and implemented by E.R.S. No other potential conflicts of interest relevant to this article were reported.

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