

## **Risks of tight glucose control in older adults: time to focus beyond mortality**

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## MANUSCRIPT

The therapeutic management of older adults living with type 2 diabetes presents important clinical challenges. Age-related physiological and pathophysiological changes - such as altered pharmacokinetics, impaired glucose homeostasis, and declining renal function - make older patients more susceptible to adverse drug effects, particularly from glucose-lowering therapies (1, 2). In this context, intensive glycemic control strategies must be approached with caution, as they may confer greater risks than benefits (3). This is especially relevant for individuals with limited life expectancy, in whom the potential long-term benefits of tight glycemic control are unlikely to be realized and may be outweighed by immediate harms.

Over the past 15 years, clinical guidelines have increasingly acknowledged the heterogeneity of the older population with diabetes and have endorsed individualized treatment goals. Rather than applying uniform (“one-size-fits-all”) glycemic targets, current recommendations emphasize the need to tailor glucose control based on the patient’s overall health status, functional ability, comorbidities, and life expectancy. More relaxed HbA1c targets are generally advised for patients with frailty, cognitive impairment, or multiple chronic conditions (3, 4). This paradigm shift toward personalized care was largely influenced by the ACCORD trial, which reported a potential association between intensive glucose lowering and increased all-cause mortality in high-risk patients (5). Since then, much of the literature in this field has focused on the relationships between glycemic control and either mortality or hypoglycemia in older adults (6-9). However, critical knowledge gaps persist regarding the association between glucose control and other clinically relevant outcomes in this population (10). In this issue of *Diabetes Care*, Shabnam et al. address a timely and underexplored question by examining the relationship between sustained tight glycemic control and the risk of serious fall-related events in older adults with type 2 diabetes (11).

In this large observational cohort study using UK primary care data linked to hospital and mortality records, Shabnam et al. examined whether sustained tight glycemic control - defined as three consecutive HbA1c values below 7% while on insulin and/or sulfonylurea therapy - was associated with an increased risk of hospitalization for falls and fractures in older adults with type 2 diabetes (11). The study included 21,365 individuals aged 70 years or older (mean age 77.5 years; 45% women), with an average diabetes duration of 5 years. Most participants had multiple chronic conditions, including cardiovascular disease, chronic kidney disease, and dementia, and nearly all in the exposed group were treated with sulfonylureas (90%) and/or insulin (9%). The median HbA1c in the exposed group was 6.4% (46 mmol/mol), compared with 6.8% (51 mmol/mol) in the non-exposed. Compared with matched non-exposed individuals, there is no evidence of increased risk of falls, fractures, or combined outcomes in the exposed group (e.g., HR for falls: 1.04 [95% CI 0.96–1.11]). Over a 10-year period, absolute risks of hospitalization for falls increased with age in both groups, ranging from 15.6% to 36.8% among exposed individuals versus 15.1% to 36.0% among non-exposed, with no evidence of a difference between groups in absolute risk across age strata. While a separate association was observed between severe hypoglycemia and fall risk, the study did not identify a meaningful increase in serious fall or fracture events specifically linked to sustained HbA1c <7% during treatment with insulin or sulfonylureas.

Inherent of observational studies using real-world data from electronic health records (EHRs), the potential for unmeasured confounding remains an important limitation (12, 13). Although the study accounted for many clinical and demographic characteristics, residual confounding by factors such as frailty, cognitive status, or psychosocial conditions cannot be fully excluded. In addition to these concerns, the use of EHRs to define outcomes such as falls presents further challenges. Falls are often under coded or misclassified - sometimes recorded as their resulting injuries rather than the fall itself - particularly in primary care settings,

where awareness of glycemic control targets may influence the likelihood of documentation. Recent work by Wang et al. demonstrated substantial discrepancies in outcome ascertainment across EHR sources, reinforcing the need for caution when relying on routine data to identify complex clinical events (14). These limitations may contribute to outcome misclassification and attenuate observed associations, and should be considered when interpreting the study's findings. However, this constraint is largely offset by the high methodological rigor of the study - particularly the careful matching on key clinical characteristics and the extensive multivariable adjustment of other important confounding variables. The strengths of the approach taken enable the investigation of clinically relevant questions that would be challenging - or ethically problematic - to address through prospective experimental designs (15).

Several aspects of Shabnam et al.'s work are worth highlighting, particularly for their implications for future research in this field. First, the authors' careful decision to describe the exposure as "sustained HbA1c <7%" (or tight glycemic control) rather than labeling it as "diabetes overtreatment" reflects a nuanced and appropriate approach. For over 15 years, literature has often considered this situation as a potential marker of overtreatment (6, 7, 9, 16). However, sustained HbA1c <7% while on insulin or sulfonylureas can only be considered overtreatment if it leads to net harm which was not demonstrated in this study (17). This supports the authors' cautious and precise terminology. In recent years, particularly with the development of continuous glucose monitoring and new evidence published in *Diabetes Care* (8, 18), the previously assumed link between sustained glycemic control and elevated hypoglycemia risk in older adults has been increasingly challenged (Fig. 1A). This study by Shabnam et al. therefore illustrates a more reasoned and evidence-informed use of the concepts of low HbA1c and overtreatment.

Second, the study focuses on a clinically meaningful yet underexplored outcome: serious fall-related events leading to hospitalization. This is highly relevant to the day-to-day wellbeing of older patients and underscores the importance of investigating a broader range of outcomes when assessing the risks and benefits of glucose-lowering therapies in this population (Fig. 1B). Similarly, accounting for the clinical complexity of older patients - including age-related conditions and broader health context - is essential to understanding how the benefit-risk balance may be altered (3). Moving beyond a narrow explanation centered only on treatment, hypoglycemia, and mortality is not sufficient (Fig. 1A). Expanding our view of treatment-related risks and benefits by broadening the scope of outcomes considered in this field is essential to better inform clinical decision-making.

Finally, future studies would benefit from incorporating the perspectives of older adults themselves. Understanding patient preferences and what matters most to them is critical to identifying and prioritizing outcomes that have previously been overlooked but may be highly valued by this population.

The work by Shabnam et al. represents an important step toward improving our understanding of the benefit-risk balance of glucose-lowering treatments in older adults with type 2 diabetes (Fig. 1). It provides valuable insights that can help refine treatment strategies and support a more individualized and patient-centered approach to care.

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#### CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

#### AUTHOR CONTRIBUTIONS AND GUARANTOR STATEMENT

Both AC and JPS drafted, critically reviewed, edited and approved the manuscript. AC is the guarantor of this work.

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## **FIGURE 1**

**Figure 1 legend:** This figure illustrates the necessary shift from the traditional, assumption-driven model of research (**A**) to a more comprehensive and patient-centered framework (**B**). The new model emphasizes the importance of balancing the potential risks and benefits of glucose-lowering treatments when studying their use in older adults living with type 2 diabetes.