Primum Non Nocere: Refocusing Our Attention on Severe Hypoglycemia Prevention

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Severe hypoglycemia, defined as low blood glucose requiring assistance for recovery, is arguably the most dangerous complication of type 1 diabetes as it can result in permanent cognitive impairment, seizure, coma, accidents, and death (1,2). Since the Diabetes Control and Complications Trial (DCCT) demonstrated that intensive intervention to normalize glucose prevents long-term complications but at the price of a threefold increase in the rate of severe hypoglycemia (3), hypoglycemia has been recognized as the major limitation to achieving tight glycemic control. Severe hypoglycemia remains prevalent among adults with type 1 diabetes, ranging from ~1.4% per year in the DCCT/EDIC (Epidemiology of Diabetes Interventions and Complications) follow-up cohort (4) to ~8% in the T1D Exchange clinic registry (5).

One the greatest risk factors for severe hypoglycemia is impaired awareness of hypoglycemia (6), which increases risk up to sixfold (7,8). Hypoglycemia unawareness results from deficient counterregulation (9), where falling glucose fails to activate the autonomic nervous system to produce neuroglycopenic symptoms that normally help patients identify and respond to episodes (i.e., sweating, palpitations, hunger) (2). An estimated 20–25% of adults with type 1 diabetes have impaired hypoglycemia awareness (8), which increases to more than 50% after 25 years of disease duration (10).

Screening for hypoglycemia unawareness to identify patients at increased risk of severe hypoglycemic events should be part of routine diabetes care. Self-identified impairment in awareness tends to agree with clinical evaluation (11). Therefore, hypoglycemia unawareness can be easily and effectively screened using multiple, self-administered methods (11). These range from single questions (i.e., "Do you know when your hypos are coming?" [7] and "Can you feel when you are low?" [12]) to longer assessments characterizing hypoglycemia exposure and the glycemic threshold for symptomatic response, as in the 8-item Clarke questionnaire (11), and problematic hypoglycemia with unawareness during wake and asleep, as in the recently developed 33-item Hypoglycaemia Awareness Questionnaire (HypoA-Q) (13).

Interventions for hypoglycemia unawareness include a range of behavioral and medical options. Avoiding hypoglycemia for at least several weeks may partially reverse hypoglycemia unawareness and reduce risk of future episodes (1). Therefore, patients with hypoglycemia and unawareness may be advised to raise their glycemic and HbA_{1c} targets (1,2). Diabetes technology can play a role, including continuous subcutaneous insulin infusion (CSII) to optimize insulin delivery, continuous glucose monitoring (CGM) to give technological awareness in the absence of symptoms (14), or the combination of the two in newer sensor-augmented insulin pumps with automated low-glucose suspend to prevent hypoglycemia (14). For patients who are refractory to medical treatment, human islet cell transplantation has been shown to mitigate severe hypoglycemia over 2 years (15), although this approach carries additional risks, expenses, and uncertain long-term benefit (16).

Aside from medical management, structured or hypoglycemia-specific education programs that aim to prevent hypoglycemia are recommended for all patients with severe hypoglycemia or hypoglycemia unawareness (14). In randomized trials, psychoeducational programs that incorporate increased education, identification of personal risk factors, and behavior change support have improved hypoglycemia unawareness and reduced the incidence of both nonsevere and severe hypoglycemia over short periods of follow-up (17,18) and extending up to 1 year (19).

The study by Little et al. (20) in this issue of *Diabetes Care* is an elegant addition to existing data on the potential of

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psychoeducational intervention for this high-risk population. Previously, the authors reported findings at the close of the HypoCOMPaSS trial, a 6-month 2 × 2 factorial randomized trial to assess the effects of an intensive structured education approach to hypoglycemia avoidance, improved hypoglycemia awareness, and prevention of recurrent severe hypoglycemia without worsening overall glycemic control in adults with type 1 diabetes and impaired hypoglycemia awareness (21). The intervention emphasized four points of hypoglycemia—*1*) never delay hypoglycemia treatment, *2*) recognize personalized times of increased risk, *3*) detect subtle symptoms, and *4*) confirm low glucose levels through regular self-monitoring—as well as advice on adjusting insulin dose around blood glucose, carbohydrate intake, and activity levels (21). In addition, each randomization subgroup received education tailored for technical aspects of their respective insulin administration and glucose monitoring modality (21). Intervention benefits were seen among those randomized to CSII and multiple daily injections (MDI) and among those randomized to adjuvant real-time CGM and conventional self-monitoring of blood glucose (SMBG) (21). At the end of the 6-month intervention, the participants returned to routine clinical care with data collection every 6 months over 24 months (20). While participants were able to change insulin delivery regimen after the intervention ended, the CGM versus SMBG randomization assignment continued throughout follow-up (20). The benefits in terms of hypoglycemia awareness, reduced severe hypoglycemia, and improvements in patient reported outcomes were sustained. Finally, HbA_{1c} improved over follow-up (20). Although statistical power was limited for subgroup comparisons, there were no significant differences in outcomes between randomized assignments (CSII vs. MDI or SMBG vs. CGM) (20).

The trial included individuals with an increased risk for severe hypoglycemia (Gold score ≥4) (21), which reflects the relevant population for the specific intervention but limits generalizability to all individuals with type 1 diabetes. Universal screening guidelines may, in the future, help to establish an evidence-based threshold above which intervention is warranted and maximally beneficial. Moreover, all participants attended a single 1- to 3-h education session focused on avoiding hypoglycemia while maintaining overall glycemic control that was prior to randomization. The facilitated discussion was led by a trained research fellow or clinical provider (21). Although the intervention was only implemented in five U.K. tertiary referral diabetes centers, the magnitude and durability of effect reported by Little et al. (21) suggests that dissemination and implementation efforts toward avoiding severe hypoglycemia should have defined curricula and engage multiple members of the care team to promote ongoing education, especially clinic- or community-based certified diabetes educators.

A major strength is the study design itself, including a long follow-up period during which patients were seen in routine care, longitudinal extension of the original 2 × 2 factorial design, and the integration of patient-oriented outcomes alongside biochemical ones to characterize intervention effect. The protocol-specified flexibility in insulin regimen provides new data to challenge the assumption that reducing risk of severe hypoglycemia optimally requires insulin pump therapy as suggested in observational cohorts (4). Although current standards for care emphasize that CGM may be a useful tool in those with hypoglycemia unawareness (1,14), retention of the CGM versus SMBG randomization in the current study adds to a mixed literature on unique advantages of CGM for the incidence of severe hypoglycemia (22,23). This article offers insight into the durability of risk reduction methods among patients who are less inclined to adopt new technology and may lend flexibility to clinical care paradigm for these patients in the future.

Given that the presence of hypoglycemia unawareness increases the risk of severe hypoglycemia, which is the strongest predictor of a future episode (2,4), the implication that intervention can break the life-threatening and traumatizing cycle of hypoglycemia unawareness and severe hypoglycemia cannot be overstated. This new evidence of durability of effect across treatment regimen without increasing the risk for long-term complications creates an imperative for action. In combination with existing screening tools and a body of literature investigating novel interventions for hypoglycemia unawareness, these results make the approach of screening, recognition, and intervention very compelling as not only a best practice but something that should be incorporated in universal guidelines on diabetes care, particularly for individuals with type 1 diabetes (Fig. 1).

Little et al. (20) bring hypoglycemia to the forefront of a larger conversation.

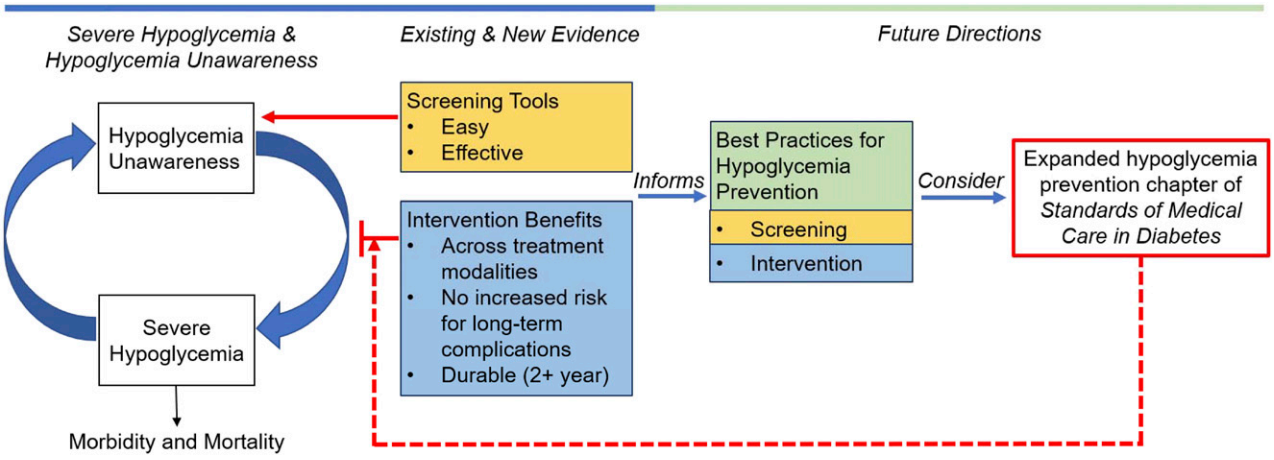

Figure 1—An overview of tools, evidence, and future considerations aimed to prevent severe hypoglycemia.

Hyperglycemia is, after all, only part of the puzzle in diabetes management. Long-term complications are decreasing across the population with improved interventions and their implementation (24). To this end, it is essential to shift our historical obsession with hyperglycemia and its long-term complications to equally emphasize the disabling, distressing, and potentially fatal near-term complication of our treatments, namely severe hypoglycemia. The American Diabetes Association (ADA) should assemble and expand current recommendations in the *Standards of Medical Care in Diabetes* with a dedicated chapter on both low-cost and technologically driven assessments for hypoglycemia unawareness and the prevention of severe hypoglycemia. The focus of such a chapter should be on implementation with an emphasis on individualization, patient autonomy, and overall well-being. The health care providers' first dictum is primum non nocere—above all, do no harm. ADA must refocus our attention on severe hypoglycemia as an iatrogenic and preventable complication of our interventions.

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