Treatment of Diabetes in Hospitals With Noninsulin Medications Is a Research Priority

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In the U.S., nearly one in four hospitalized patients has diabetes, resulting in approximately 8 million annual admissions where diabetes is either the primary or secondary cause of hospitalization (1,2). Current practice guidelines (3,4) recommend that most hospitalized patients with diabetes receive insulin monotherapy regardless of their home diabetes treatment. The recommendation to transition to insulin is informed by several considerations: *1*) elevated risk of adverse effects from noninsulin medications during acute illness or surgery, *2*) rapidly changing factors, such as diet or medications, that can impact glucose levels, and *3*) strong support from clinical trials demonstrating the effectiveness of insulin for inpatient glycemic control.

Although current guidelines recommend transitioning from noninsulin to insulin therapies, it is important to explore the potential drawbacks of this universal approach. Discontinuation of home diabetes medications could lead to higher insulin doses and wider fluctuations in blood glucose levels, thereby increasing the risk of hypoglycemia and potentially prolonging hospitalization. Replacing home diabetes medications with multiple daily insulin injections may be a source of patient dissatisfaction. Home medications that are discontinued on admission are often not resumed on discharge, which may adversely impact long-term outcomes (5,6). Given these concerns, continuation of home diabetes medications could be considered for select hospitalized patients. For instance, dipeptidyl peptidase 4 (DPP-4) inhibitors have an excellent safety profile and have been shown in a randomized trial to be a reasonable alternative or adjunct to basal-bolus insulin (3,7–11). In addition, multiple trials have demonstrated that home diabetes medications, including DPP-4 inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and metformin, can be safely continued perioperatively in select patients (12–14). Besides glycemic control, continuation of cardioprotective antihyperglycemic medications such as GLP-1 receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors during hospitalization may provide substantial cardiovascular benefit that could outweigh the benefits of insulin. As discussed in the article by Singh et al. in this issue of *Diabetes Care* (15), three randomized trials have demonstrated favorable cardiovascular outcomes of initiating SGLT2 inhibitors during or shortly after discharge among patients hospitalized for heart failure (16–18).

Nevertheless, there are notable concerns associated with continuing cardioprotective diabetes medications in a hospital setting. For GLP-1 receptor agonists, gastrointestinal side effects may complicate admissions for acutely ill patients or those admitted for gastrointestinal illness. Furthermore, the American Society of Anesthesiologists recently recommended discontinuing weekly GLP-1 receptor agonists at least 1 week before surgery to mitigate the risk of aspiration (19). However, this recommendation, primarily based on anecdotal and observational evidence, has sparked debate (20). Similarly, SGLT2 inhibitors, known to increase the risk of euglycemic diabetic ketoacidosis, are typically stopped 3–4 days before surgical procedures. These drugs can also cause polyuria, hypovolemia, and associated kidney injury. However, these side effects could be diligently monitored in an inpatient setting, and patient selection criteria could be established to exclude individuals at risk. To date, there have been limited randomized trials to assess the clinical benefits or risks of continuing these cardioprotective diabetes medications during hospitalization.

Therefore, Singh et al. (15) conducted an important observational analysis using national data from the Veterans Affairs health care system to evaluate, among people with diabetes on home treatment with SGLT2 inhibitors, the clinical effects of continuation of the SGLT2 inhibitor during hospitalization. They found that SGLT2 inhibitor continuation, compared with discontinuation, was associated with a significant 45% lower in-hospital mortality as well as a small decrease in length of hospital stay; there was no

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effect on the incidence of acute kidney injury. In absolute terms, they found an adjusted death rate of 10 deaths per 1,000 admissions with SGLT2 inhibitors continued compared with 18 deaths per 1,000 admissions where they were discontinued. Notably, these findings were consistent regardless of whether the admission was to an intensive care unit.

The authors used advanced statistical methods to account for the confounders available to them in their national data set (15). However, observational analyses of the clinical effects of treatment decisions should always be interpreted cautiously. A major threat to validity is confounding by indication, which occurs when a factor affecting the treatment decision is correlated with the study outcome (21). For example, confounding would occur if treating clinicians reserved continuation of SGLT2 inhibitors for only the healthiest patients, who would naturally be less likely to die during admission. Singh et al. (15) appropriately accounted for illness severity with propensity score matching by a comorbidity index, but this may not fully capture an individual's risk of inpatient mortality, highlighting the limitations of analyses using solely electronic health records data. Some factors that affect clinical decisions are impossible to precisely quantify, such as the "sick versus not-sick" gestalt that all medical trainees learn to judge. Notably, SGLT2 inhibitors were continued in only a small proportion of admissions (16%), consistent with this being an uncommon clinical decision potentially prompted by unusual circumstances that could not be accounted for statistically (15).

Despite these limitations, the finding by Singh et al. (15) of a 45% reduction in mortality with SGLT2 inhibitor continuation should not be ignored. If confirmed, this would yield incredible improvements in hospital outcomes for patients with diabetes, making a definitive randomized trial a research imperative. To date, a limited number of trials have evaluated the use of DPP-4 inhibitors (7–11) and GLP-1 receptor agonists (22,23) in patients with type 2 diabetes admitted to hospitals (beyond just perioperative management). However, these trials do not address several knowledge gaps. First, they did not evaluate the effects of medication continuation; rather, they discontinued all home diabetes therapy and randomized to basal-bolus insulin versus the noninsulin medication with or without insulin. Second, the primary outcome was inpatient glycemic control, and these studies were underpowered to detect differences in clinical outcomes such as mortality and hypoglycemia. Third, the studies were conducted in carefully selected populations not generalizable to all inpatients with diabetes. Nevertheless, these studies largely found that inpatient use of DPP-4 inhibitors or GLP-1 receptor agonists resulted in equivalent or better glycemic control with lower insulin doses required.

Future randomized trials should address limitations of prior studies by incorporating patients' home medications in a way that is clinically actionable and by evaluating clinical and patient-oriented

Table 1—Challenges and potential solutions to conducting randomized trials of continuation of outpatient noninsulin diabetes medications on hospital admission

Challenges	Potential solutions
Noninsulin diabetes medications may be unsafe for certain admission indications (e.g., critical illness, prolonged fasting, major surgery)	• Multidisciplinary input in trial design including experts in diabetes pharmacotherapy • Expanded expert guidelines on the circumstances under which inpatient use of noninsulin diabetes medication is permissible
Noninsulin diabetes medications have class-specific risks for inpatient use (e.g., delayed gastric emptying in GLP-1 receptor agonists, ketoacidosis in SGLT2 inhibitors)	• Multidisciplinary input in trial design including experts in diabetes pharmacotherapy • Individualized selection of patients for noninsulin diabetes medication continuation
Frequent changes in illness severity and clinical circumstances for hospitalized patients	• Development of class-specific discontinuation protocols for noninsulin diabetes medications
Lack of inpatient insulin protocols designed to accommodate concurrent noninsulin therapy	• Development of inpatient insulin protocols that incorporate concurrent use of noninsulin diabetes medications and combinations
Diabetes therapy affects the care provided by multiple hospital teams (e.g., nursing, medicine, surgery, anesthesia)	• Incorporate input from multiple hospital stakeholders in trial design • Include protocols to facilitate collaborative inpatient diabetes care
Need to evaluate patient outcomes beyond glycemia	• Select clinically relevant primary outcomes such as in-hospital mortality • Evaluate effects on other important outcomes including hypoglycemia, drug safety measures, postdischarge outcomes and cost of care
Need to incorporate patients' views and preferences	• Use qualitative and participatory research approaches to understand and incorporate patients' perspectives • Evaluate patient-reported outcome measures in clinical trials of noninsulin diabetes medication continuation
Need for sufficient statistical power to evaluate clinical outcomes	• Larger trials with sufficient sample size and duration to evaluate clinical effects • New funding mechanisms directed at achieving this

outcomes. There are undoubtedly major scientific and pragmatic challenges to the design and execution of these types of studies (Table 1). Protocols will need to be developed for an individualized approach to home medication continuation in terms of single or combination agents and for incorporating these medications into inpatient insulin algorithms. Expert guidelines can take the lead by expanding recommendations about the circumstances where noninsulin diabetes medications are permissible for inpatient use. Notably, the 2024 update to the American Diabetes Association *Standards of Care in Diabetes* (4) now recommends that SGLT2 inhibitors be initiated or continued during hospitalization and upon discharge in most patients with type 2 diabetes hospitalized for heart failure. Further, while the analysis by Singh et al. (15) focuses on SGLT2 inhibitors, future trials should also evaluate continuation of other classes of diabetes medications with proven cardiovascular or renal benefits (GLP-1 receptor agonists and metformin) or an excellent safety profile (DPP-4 inhibitors). One such trial is currently recruiting (24). Overall, the rapid advances in outpatient diabetes therapy necessitate interventional research in the inpatient setting to potentially expand the benefits of noninsulin diabetes medications to hospitalized patients.

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