Challenges and Strategies for Inpatient Diabetes Management in Older Adults

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Adults older than 65 years of age are the fastest growing segment of the U.S. population. Aging is also one of the most important risk factors for diabetes, and about one-third of all individuals with diabetes are in this age-group. Older people with diabetes are more likely to have comorbidities such as hypertension, ischemic heart disease, chronic kidney disease, and cognitive impairment, which lead to higher rates of hospital admissions compared with individuals without diabetes. Professional organizations have recommended patient-centric individualized glycemic reduction approaches, with an emphasis on potential harms of intensive glycemic control and overtreatment in older adults. Insulin therapy remains a mainstay of diabetes management in the inpatient setting regardless of patients’ age; however, there is uncertainty about optimal glycemic targets during the hospital stay. Increasing evidence supports selective use of dipeptidyl peptidase-4 inhibitors, alone or in combination with low-dose basal insulin, in older noncritically ill patients with mild to moderate hyperglycemia. This article reviews the prevalence, diagnosis, and monitoring of, and the available treatment strategies for, diabetes among elderly patients in the inpatient setting.

The Centers for Disease Control and Prevention estimates that 12.2% of U.S. adults had diabetes in 2015 (1). The prevalence is highest in elderly individuals; 25% of the U.S. population >65 years of age has diabetes (2). According to a 2015 analysis of claims from the Centers for Medicare & Medicaid Services chronic conditions database, a diabetes diagnosis was listed for nearly one in three Medicare beneficiaries (3).

People with diabetes are more likely than individuals without diabetes to require hospital admissions. The National Hospital Discharge Survey revealed that an estimated 250,000 hospitalized patients had diabetes as a first-listed diagnosis in 2010, with the rates of hospitalization being more than three times higher for individuals ≥65 years of age than for those <45 years of age (4).

Several clinical investigations have reported strong associations between inpatient hyperglycemia and poor clinical outcomes with regard to mortality, morbidity, length of stay, infections, and overall complications (5,6), as well as evidence that correction of hyperglycemia reduces infections, hospital complications, and mortality (6–8). These findings, however, may not be representative of older patients, who tend to have multiple comorbid conditions and are often excluded from diabetes treatment trials (9).

Epidemiology of Inpatient Diabetes in the Elderly

Several cross-sectional studies have estimated a prevalence of diabetes in older adults 65–75 and >80 years of age at 20 and 40%, respectively (10). The Atherosclerosis Risk in Communities study (11) reported higher rates of hospitalization with increasing age in subjects with and without diabetes, with rates of hospitalization 3.1 times higher in those with diagnosed diabetes compared with those without a history of diabetes. In general, ~25–30% of hospitalized patients have a known diagnosis of diabetes, and an additional 5–10% of patients will have the diagnosis made during admission (12). The prevalence of diabetes in the intensive care unit (ICU) setting mirrors the non-ICU statistics (13).

Patients >65 years of age with diabetes are less likely to be discharged to home, frequently requiring transfer to a transitional care unit or nursing home facility, which increases medical costs (5). Similarly, elderly residents with diabetes in long-term care (LTC) facilities have a
significantly higher number of comorbidities, including cardiovascular disease, kidney disease, visual impairment, and foot problems (including amputations), and have higher odds of having emergency room visits compared with residents without diabetes (14,15).

Several epidemiological studies have reported that admissions for hypoglycemia have significantly increased during the past decade among older adults with diabetes. In a study that looked at hospital admission rates due to adverse drug reactions in a cohort of U.S. adults, investigators found that about half of the hospital admissions for adverse drug reactions were for adults >65 years of age and that half of these hospitalizations were for people >80 years of age (16). In individuals ≥65 years, glucose-lowering agents with an increased risk of hypoglycemia (i.e., insulin and sulfonylureas) were the second most common medications class associated with emergency department visits or hospitalizations. Furthermore, among older Medicare beneficiaries with diabetes, hospital admissions for hypoglycemia now outpace those for hyperglycemia (17), which is likely the result of increased efforts to intensify glycemic control, overuse of insulin and sulfonylureas, and/or insufficient patient education.

Goals of Inpatient Diabetes Care

Although no prospective studies are available to determine optimal targets of glycemic control in the elderly inpatient population, general recommendations have been produced by different organizations (Table 1). In noncritical-care settings, the Endocrine Society in 2012 (4) and the American Diabetes Association (ADA)/American Association of Clinical Endocrinologists (AACE) in 2009 (18) recommended premeal glucose levels <140 mg/dL and random blood glucose levels of <180 mg/dL (18). More recently, the ADA recommended a target blood glucose of 140–180 mg/dL, with a caveat that higher blood glucose targets may be acceptable in situations that are often seen in the elderly, such as terminal illness, presence of severe comorbidities, and/or when close nursing supervision is not feasible (19). The Society of Critical Care Medicine recommended starting therapy for blood glucose ≥150 mg/dL, with a glycemic target of <180 mg/dL to minimize the risk of hypoglycemia (20). Importantly, all clinical practice guidelines are unanimous in concluding that avoiding hypoglycemia is as important as improving glycemic control (21–24).

### Treatment Strategies

**Insulin Therapy**

Insulin therapy remains the preferred therapy for the management of hyperglycemia in most hospitalized patients regardless of patients’ age (19). For the critically ill, the use of paper or computerized intravenous infusion protocols that consider current, previous, and goal glucose levels has proven safe and effective and is generally recommended (18). Subcutaneous insulin administration continues to be recommended as the favored strategy for the management of hyperglycemia in noncritically ill hospitalized patients (19,23).

Notwithstanding this recommendation, insulin has been identified as a frequent source of medication errors with increased risk for hyperglycemia (omission) and, more importantly, iatrogenic hypoglycemia (25). An analysis of medication errors between 2006 and 2008 revealed that insulin was the drug with the greatest number of medication errors in hospitals (26). Subsequently, in recent years, distinct insulin regimens or alternatives to insulin have been studied in the inpatient setting with the goal of

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<tr>
<th>Society, Year (reference)</th>
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<th>Noncritically Ill, mg/dL</th>
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<tr>
<td>ADA/AACE, 2009 (18)</td>
<td>110–180</td>
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<td>Diabetes Canada, 2018 (21)</td>
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<td>Endocrine Society, 2019 (23)</td>
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<td>These targets are for older patients.</td>
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<td>Joint British Diabetes Societies for Inpatient Care, 2019 (24)</td>
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<td>100–216 mg/dL (6–12 mmol/L) is acceptable for older patients.</td>
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<td>American Diabetes Association, 2020 (19)</td>
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<td>No specific recommendations for older patients; &gt;180 mg/dL (10.0 mmol/L) in patients with severe comorbidities</td>
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achieving glycemic control while reducing the risk of hypoglycemia.

**Basal-Bolus Insulin Regimen**

Multiple regimens with human insulin and insulin analogs administered subcutaneously are available for the management of noncritically ill patients. Several observational and randomized controlled trials (RCTs) have reported that basal-bolus insulin approaches result in improved glycemic control and are considered preferred regimens in non-ICU settings (6). Basal insulin requirements include once-daily administration of a long-acting insulin analog (i.e., glargine, detemir, or degludec) or twice-daily administration of intermediate-acting NPH insulin. Regular insulin and rapid-acting insulin analogs (i.e., lispro, aspart, or glulisine) are used before meals to meet nutritional needs. Although the use of correctional or supplemental dosing based on a sliding-scale insulin (SSI) algorithm alone is common in hospitalized patients, its sole use is discouraged because of its lower effectiveness in achieving glucose control and higher risk for hypoglycemia (27,28).

Calculation of a patient’s total insulin requirements is based on body weight, kidney function, prior outpatient insulin use, and nutrition status. Pending the results of prospective trials, it is the authors’ opinion that, for most elderly patients with diabetes, an appropriate starting total daily insulin dose is 0.15–0.3 units/kg body weight (Figure 1), with lower doses of 0.1–0.15 units/kg recommended for older patients with renal failure (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m²), history of hypoglycemia, or poor nutrition intake. Patients with inadequate oral intake or who will be NPO should be considered to receive basal insulin at lower doses (0.1 units/kg/day) without scheduled prandial insulin. Correction doses with rapid-acting insulin analogs or short-acting insulin are usually given in older adults to correct hyperglycemia for glucose levels >180 mg/dL before meals. However, the benefit of this approach when added to a basal-bolus insulin regimen has not been fully established (29).

The superiority of a basal-bolus insulin regimen over SSI is well established in noncritically ill patients. In medical wards, the prospective, randomized, multicenter RABBIT 2 (Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes) trial (30) showed that the use of a basal-bolus insulin regimen led to greater improvement in blood glucose control than correction insulin per SSI alone, with an incidence of hypoglycemia that was not different between groups. In general surgery patients in the RABBIT 2 Surgery (Randomized Study of Basal Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes Undergoing General Surgery) trial (7), a basal-bolus regimen resulted in significant improvement in glucose control and a significant reduction in the frequency of the composite of hospital complications including wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia when compared with SSI. However, blood glucose levels <70 mg/dL were reported in 23.1% of patients in the basal-bolus group and 4.7% in the SSI group (P <0.001) with no significant difference in the frequency of blood glucose <40 mg/dL between groups (P = 0.057).

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**FIGURE 1** Management approach for inpatient hyperglycemia in elderly patients with type 2 diabetes in the non-ICU setting. *Basal insulin glargine, detemir, or degludec once daily starting at 0.1 unit/kg/day and adjusting as needed to achieve target blood glucose. **Reduce home insulin dose by 25% on admission if patient is eating or by 50% if patient has poor oral intake. Basil, basil insulin; BG, blood glucose; d, day; DPP4i, DPP-4 inhibitor; prandial, prandial insulin; U, units.
Basal-Plus Insulin Regimen

Variability in the nutritional status of noncritically ill, hospitalized patients is common (31), and when prandial or bolus insulin is given in discord with the timing or quantity of meals consumed, the risk for hypoglycemia increases (32). Thus, the determination of the need for bolus insulin at the beginning of therapy has been a topic of interest.

In the Basal Plus trial (33), patients with type 2 diabetes admitted to the hospital on oral antidiabetic drugs (OADs) or an outpatient insulin regimen ≤0.4 units/kg were randomly assigned to receive a basal-bolus regimen (glargine once daily and glulisine before meals), a basal-plus regimen with glargine once daily plus correction glulisine for hyperglycemia (>140 mg/dL) per an SSI algorithm, or SSI only. Basal insulin doses were calculated as 0.25 or 0.15 units/kg/day in patients <70 or ≥70 years of age, respectively. Results of the study showed that the basal-plus regimen achieved glycemic control similar to that of the basal-bolus regimen and had fewer treatment failures than with SSI as a sole regimen. Hypoglycemia (blood glucose <70 mg/dL) still occurred in 16% of patients in the basal-bolus group, 13% in the basal-plus group, and 3% in the SSI group, but there was no difference among the groups in the frequency of severe hypoglycemia (blood glucose <40 mg/dL, P = 0.76).

Thus, a basal-plus regimen can be considered as an effective alternative to basal-bolus insulin and could be applied initially for most elderly patients with diabetes who are admitted to the hospital, especially if they are insulin-naive or their nutritional intake is unknown or reduced. Subsequently, if hyperglycemia (blood glucose >180 mg/dL) persists, transition to a basal-bolus regimen would be indicated (Figure 1).

Noninsulin Therapies

Given the risk of hypoglycemia associated with insulin therapy, the use of noninsulin agents that provide glucose-lowering benefit with a low adverse side effect profile is highly appealing. The use of many OADs in the hospital setting can be associated with adverse outcomes. Metformin is contraindicated in patients with acute congestive heart failure, liver or kidney failure, hypoxia, or hypoperfusion because of the risk of lactic acidosis (34). Sulfonylureas and insulin secretagogues may increase the risk of hypoglycemia in hospitalized patients with poor appetite or ordered dietary restrictions. These concerns are particularly relevant to elderly patients, who are prone to have multiple comorbidities.

Several recent clinical studies have reported that incretin therapy is an attractive option for the inpatient management of patients with type 2 diabetes and mild to moderate hyperglycemia (>200 mg/dL). To date, several RCTs have reported similar improvement in glycemic control with the use of dipeptidyl peptidase-4 (DPP-4) inhibitors alone or in combination with basal insulin compared with a basal-bolus insulin regimen in non-ICU patients with type 2 diabetes (35–38).

The safety and efficacy of the DPP-4 inhibitor sitagliptin plus basal insulin compared with a basal-bolus insulin regimen was previously evaluated for the management of patients with type 2 diabetes in general medicine and surgery wards (37). Patients treated in the outpatient setting with diet or OADs or who had an insulin total daily dose (TDD) ≤0.6 units/kg/day were randomized to receive either sitagliptin plus basal glargine once daily (the sitagliptin-basal group) or a basal-bolus regimen with glargine once daily and rapid-acting insulin lispro or aspart before meals (the basal-bolus group) during the hospital stay. Glycemic control in the sitagliptin-basal group was found to be noninferior to that in the basal-bolus group, and hypoglycemia occurred in 13 patients (9%) in the sitagliptin-basal group and 17 (12%) in the basal-bolus group (P = 0.45).

In the Linagliptin Surgery Trial (35), patients with admission blood glucose levels between 140 and 400 mg/dL with diet or OADs or who had an insulin TDD <0.5 units/kg/day were randomized to treatment with another DPP-4 inhibitor, linagliptin, or basal-bolus insulin with glargine once daily and a rapid-acting insulin before meals. In patients with randomization blood glucose <200 mg/dL, linagliptin use resulted in similar improvement in glycemic control, fewer hypoglycemic events (86% relative risk reduction), and lower number of daily insulin injections compared with a basal-bolus regimen. However, insulin therapy was more effective than linagliptin in patients admitted with severe hyperglycemia and glucose values >200 mg/dL.

In agreement with these results, Garg et al. (36) recently reported that the use of saxagliptin with supplemental rapid-acting insulin showed similar efficacy in glycemic control compared with basal-bolus insulin in noncritically ill, hospitalized patients with type 2 diabetes and mild hyperglycemia who were treated before admission with up to two OADs (36).

These reports indicate that treatment with DPP-4 inhibitors alone or in combination with basal insulin can be considered for the management of patients with mild hyperglycemia.
to moderate hyperglycemia of <200 mg/dL. In elderly patients with known or suspected heart failure, we recommend caution in initiating a DPP-4 inhibitor in the hospital. The SAVOR-TIMI (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction) trial (39) reported that saxagliptin can increase the risk of hospitalization for heart failure compared with placebo. A similar trend was observed in the EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) trial (40).

In LTC settings and skilled nursing facilities, the use of linagliptin was compared with glargine insulin in 140 patients (38). For this study, subjects with previous insulin treatment with a dose >0.1 units/kg/day were excluded. Researchers found that treatment with linagliptin was noninferior to glargine in achieving glycemic control. Of note, linagliptin treatment resulted in fewer mild hypoglycemic events with blood glucose <70 mg/dL (3 vs. 37%, P < 0.001), but there were no differences in severe hypoglycemia compared with glargine.

In a different prospective, controlled study, 150 geriatric patients admitted to LTC facilities were randomized to receive low-dose basal insulin (glargine at a starting dose of 0.1 unit/kg/day) or OAD therapy at primary care provider discretion, including metformin, sulfonylureas, and other OADs, for 26 weeks (41). Of interest, there was no difference in mean fasting glucose level between the insulin and OAD groups, but patients treated with insulin had a greater mean daily blood glucose than those treated with OADs. No differences in the rate of hypoglycemia (<70 mg/dL) were reported between the insulin and OAD groups (27 and 31%, respectively), with most patients in the OAD group taking insulin secretagogue agents.

Inpatient Hypoglycemia

Hypoglycemia is common in hospitalized elderly patients and is associated with poor outcomes. In the noncritically ill setting, hypoglycemia occurs in 12–38% of patients with type 2 diabetes receiving insulin therapy (26). In critically ill patients enrolled in clinical trials, the prevalence of severe hypoglycemia (glucose ≤40 mg/dL) ranged between 5.0 and 18.7% (42–44). Elderly patients are especially vulnerable to the adverse effects of inpatient hypoglycemia (45). Importantly, hypoglycemia in elderly patients is associated with longer lengths of stay and increased hospital or post-discharge mortality rates (46–48). A recent retrospective analysis of discharged patients and their short-term outpatient outcomes from the database of the Veterans Health Administration hospitals showed that blood glucose levels in the near-normoglycemic or hypoglycemic range during the last day of the hospital stay were associated with higher rates of 30-day readmission and post-discharge mortality (49).

Many risk factors contribute to the development of inpatient hypoglycemia. Treatment with insulin is the most common risk factor for hypoglycemia (45,50). In the inpatient trials, the use of SSI and/or attempts to achieve intensive glycemic targets may have contributed to hypoglycemic events (7,30,33). Hence, caution should be exercised when treating older patients with diabetes with insulin (Figure 1). In addition, insulin regimens that include the use of NPH insulin may have a higher risk of hypoglycemia than approaches using basal insulin analogs (51). Other risk factors include continuous use of sulfonylurea therapy, failure to adjust insulin to nutritional intake, and changes to hospital routine (50,52,53). Interruptions in usual nutritional intake and changes in medications frequently occur during hospitalization and can precipitate hypoglycemia when hypoglycemic agents are used. Elderly people are more prone to hypoglycemia during hospitalization because of their higher rates of comorbidities such as renal failure, malnutrition, malignancies, dementia, and frailty (47). In addition, older hospitalized patients often experience failure of regulatory mechanisms, such as reduced release of glucagon and epinephrine in response to hypoglycemia (54) or failure to exhibit hypoglycemic symptoms (55), which can delay action to treat a hypoglycemia episode by the hospital staff. Factors that can increase the risk of asymptomatic hypoglycemia in hospitalized patients are the use of insulin, age >65 years, and male sex (56). Finally, the presence of renal failure or low albumin levels can also predict hypoglycemia in elderly, hospitalized patients (48).

Recent studies have reported that inpatient hypoglycemia was associated with higher mortality rates. However, it is not known if the higher mortality rates are caused directly by hypoglycemia per se or may result from the presence of more severe illnesses and comorbidities (45,57,58). Nevertheless, these studies have shown that, in patients with or without diabetes, mortality was higher only among those with spontaneous hypoglycemia and not in those with iatrogenic-induced hypoglycemia (i.e., insulin therapy). Thus, it is possible that antihyperglycemic therapy may unmask a propensity to develop hypoglycemia in the severely ill rather than directly cause death. It has not been and will not be possible to determine whether hypoglycemia is a marker of severity of illness or a direct cause of mortality in elderly patients.
Hospital Discharge Planning

The discharge period is often a further opportunity to improve the global care of older patients with diabetes. At the time of discharge, decisions should be made on the selection of a glycemic target and the choice of diabetes medications to achieve the desired target (23,59,60). In older adults, including those who will be discharged into LTC or skilled nursing facilities, achieving an A1C of 7.5–8.5% without hypoglycemia is feasible depending on the person’s degree of frailty and the presence of vascular complications (59,61,62). Supporting this notion is the recent analysis of the 2011–2016 National Health and Nutrition Examination Survey data that demonstrated a lack of cost-effectiveness of achieving a stringent A1C target of <7.5% in individuals who had one or more macrovascular complications or <7 years of expected life remaining (63).

It is also important to recognize that perceptions about diabetes treatment effectiveness can be different in patients compared with prescribers. One recent study demonstrated that, in selecting an appropriate antihyperglycemic treatment, older patients with type 2 diabetes perceived the risk of adverse effects as the most important factor in choosing the most optimal diabetes treatment (64). The top priority in selecting antihyperglycemic treatment for all patients with type 2 diabetes, including the elderly population, is prevention of hypoglycemia (65). In addition, providers should be mindful of the presence of geriatric syndromes such as urinary incontinence, impaired mobility, pain, cognitive impairment, and depression in selecting appropriate diabetes treatments (61).

Although insulin is used in the hospital for many patients with diabetes, most older patients may not require insulin after discharge. Most elderly patients with type 2 diabetes who are clinically stable and have no contraindications can restart OADs.

Admission A1C has been shown to help in tailoring diabetes treatment after hospital discharge (66). Elderly patients with acceptable diabetes control (A1C <7.5–8.0%) could be discharged on their pre-hospitalization treatment regimen (OAD and/or insulin). Those with above-goal A1C ≤9.0% could be discharged on OAD plus basal insulin at 50% of the hospital basal dose, whereas those with an A1C >9.0% could be discharged on basal-bolus insulin at 80% of the hospital dose or OADs plus basal insulin with quick follow-up in the outpatient setting (66).

Pre-discharge reassessment of renal function in older patients is important in light of the 2016 U.S. Food and Drug Administration guidance recommending initiation of metformin in patients with an eGFR >45 mL/min/1.73 m² and continuation of previously prescribed medication, although at a lower dose, in the patients with an eGFR >30 mL/min/1.73 m² (67). Simple treatment regimens should be preferred in elderly patients because complex treatments that include insulin may be associated with an increased risk of hypoglycemia (68,69).

Patients who are either newly started on diabetes medications or those with diabetes who have treatment modifications during their hospital stay are at risk for medication errors and adverse effects after hospital discharge if clear information about glycemic management is not provided at
the likelihood of readmission, it is important to effectively communicate the discharge diabetes regimen to both the patient (and/or the caregiver) and the patient’s primary care physician. If possible, polypharmacy should be avoided because it can be associated with all-cause mortality and an increased risk of hospitalization in the elderly (71).

Although glucose control may be beneficial in decreasing diabetes complications, the risk of hypoglycemic events can be detrimental in the elderly and may lead to increased morbidity and mortality. A recent analysis of fracture incidence in older patients with diabetes receiving care in the Veterans Health Administration system demonstrated that A1C <6.5% was independently associated with higher clinical and hip fracture risks compared with the reference A1C of 7.5–8.5% (72). Providers should keep in mind that no RCTs have shown benefits of tight glycomic control on clinical outcomes and quality of life in ambulatory elderly patients or in residents of LTC facilities. Until such studies become available, we believe that safe, less intense glycomic control that minimizes the risk of hypoglycemia, is indicated for elderly patients with diabetes. An algorithm for pre-discharge patient evaluation is shown in Table 2.

### Conclusion

Diabetes is common and is associated with increased risks of complications among elderly, hospitalized patients. Individualized glycemic management approaches can help avoid complications of uncontrolled hyperglycemia and reduce the risk of hypoglycemia in these patients. Scheduled insulin therapy can be recommended for the majority of hospitalized patients with type 2 diabetes. Patients treated with insulin before admission can continue to receive their usual home regimen modified according to their severity of illness, risk of hypoglycemia, and level of glycemic control. For patients not previously treated with insulin, weight-based dosing algorithms can be used for calculation of basal and/or basal-bolus regimens as the preferred treatment alternative in the hospital. Increasing evidence indicates that the use of a DPP-4 inhibitor alone or in combination with low-dose basal insulin may represent an effective and safe alternative to a basal-bolus insulin regimen for patients with less severe hyperglycemia on admission. Providing patients and their caregivers with the skills and information necessary to manage their regimen as outpatients can contribute to improved glycemic control and lower risks of hypoglycemia and readmission. Finally, well-designed research programs are needed to determine appropriate glycemic targets and assessed the potential benefits and harms of different antidiabetic agents in the older adult population.

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### AUTHOR CONTRIBUTIONS

A.R.G. and C.E.M. researched data and wrote the manuscript. G.E.U. contributed to discussion and reviewed/edited the manuscript. A.R.G. is the guarantor of this work and, as such, had full access to all the data included and takes responsibility for the integrity of the data included and the accuracy of the review.

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