Update on the management of diabetes in long-term care facilities

Thaer Idrees, Iris A Castro-Revoredo, Alexandra L Migdal, Emmelin Marie Moreno, Guillermo E Umpierrez

ABSTRACT

The number of patients with diabetes is increasing among older adults in the USA, and it is expected to reach 26.7 million by 2050. In parallel, the percentage of older patients with diabetes in long-term care facilities (LTCFs) will also rise. Currently, the majority of LTCF residents are older adults and one-third of them have diabetes. Management of diabetes in LTCF is challenging due to multiple comorbidities and altered nutrition. Few randomized clinical trials have been conducted to determine optimal treatment for diabetes management in older adults in LTCF. The geriatric populations are at risk of hypoglycemia since the majority are treated with insulin and have different levels of functionality and nutritional needs. Effective approaches to avoid hypoglycemia should be implemented in these settings to improve outcome and reduce the economic burden. Newer medication classes might carry less risk of developing hypoglycemia along with the appropriate use of technology, such as the use of continuous glucose monitoring. Practical clinical guidelines for diabetes management including recommendations for prevention and treatment of hypoglycemia are needed to appropriately implement resources in the transition of care plans in this vulnerable population.

INTRODUCTION

Diabetes mellitus (DM) prevalence is high among older adults, with more than 25% of individuals between 65–75 years and 40% older than 80 years of age are diagnosed with diabetes.1 According to a 2015 analysis of claims from the Centers for Medicare & Medicaid Services (CMS) chronic conditions database, a diabetes diagnosis was listed in nearly one in three Medicare beneficiaries.2 In the US, the majority of older adults with diabetes having type 2, and less than 10% of diabetes having type 2, and less than 10% of adults include lower extremity amputations, diabetic nephropathy, cardiovascular disease and stroke compared with patients without diabetes.19 In the outpatient settings, more than half of adults with diabetes are co-diagnosed with other diseases, and two out of five individuals have more than four comorbidities.20–23 In addition, diabetic nephropathy is highly prevalent among older adults with diabetes as nearly half of this population has impaired glomerular filtration rate (GFR), albuminuria or end-stage kidney disease.24 Many other comorbidities occur at high rate among older adults including lower extremity amputations related to diabetic neuropathy, β-amyloid variant Alzheimer disease, dyslipidemia, falls that lead to fractures, and hypoglycemia unawareness.27 28 29 Therefore, older adults are at higher risk of disability and premature death compared with patients without diabetes31 (figure 1). In addition, older adults with diabetes are at greater risk than persons without diabetes for several common geriatric syndromes,32 which make

CHALLENGES OF DIABETES MANAGEMENT IN OLDER ADULTS

Older adults with diabetes are at higher risk of complications including cardiovascular disease and stroke compared with patients without diabetes. In the outpatient settings, more than half of adults with diabetes are co-diagnosed with other chronic diseases, and two out of five individuals have more than four comorbid conditions. In addition, diabetic nephropathy is highly prevalent among older adults with diabetes as nearly half of this population has impaired glomerular filtration rate (GFR), albuminuria or end-stage kidney disease. Many other comorbidities occur at high rate among older adults including lower extremity amputations related to diabetic neuropathy, β-amyloid variant Alzheimer disease, dyslipidemia, falls that lead to fractures, and hypoglycemia unawareness. Therefore, older adults are at higher risk of disability and premature death compared with patients without diabetes (figure 1). In addition, older adults with diabetes are at greater risk than persons without diabetes for several common geriatric syndromes, which make
Emerging technologies, pharmacology and therapeutics

the older adults in LTC settings more vulnerable to hypo-
glycemia and other complications (figure 2). Screening and appropriate management of diabetes and comor-
bidities can improve outcomes in LTCF residents with diabetes.32

ECONOMIC BURDEN OF DIABETES WHEN TREATING OLDER ADULTS

Older adults with diabetes have a threefold increased risk of being admitted to a hospital or to an acute care setting compared with younger patients.33 34 In fact, national data report more than half of all diabetes-related hospital admissions were in older adults in the period of 2007–2014, with an estimated number of 32 million patients with diabetes over the age of 65 being hospitalized during the same period.3 35

The American Diabetes Association (ADA) estimates the total cost of caring for diabetes has sharply increased by 26% from 2012 to 2017, from $245 billion to $327 billion. The majority of these costs were spent on hospital inpatient care (30%) and treating diabetes complications (30%), with the remaining cost being directed to medi-
cations and office visits. Adults over 65 years of age use more health resources compared with younger adults regarding hospital admissions (63% vs 37%), long-term facility use (65% vs %35), and medication prescription (70% vs %30) according to the 2017 ADA report.36 Furthermore, the diabetes-attributable nursing home (NH) costs were estimated to equal $10–11 billion for LTCF residents aged 65–84 in 2013.37

One of the major complications of managing diabetes is hypoglycemia, which contributes to the economic burden of diabetes in older adults. Data from several trials revealed that hypoglycemia in older adults is associ-
ated with longer length of stay, complications and further increase in hospitalization cost.38–40 In fact, the yearly cost of medication-induced hypoglycemia among older adults was estimated to equal $509 214 473.41

TRANSITIONS OF CARE TO LTCFS

LTC refers to a wide variety of services for individuals who require assistance with the activities of daily living (ADLs) or medical care services related to age and/or permanent or temporary conditions that affect the patients’ inde-
pendent abilities.42 LTCFs provide medical and personal care to their residents. They include NHs, skilled nursing facilities, assisted living facilities, or shorter stay rehabilita-
tive services.43

Most patients admitted to LTCFs are channeled from hospitals following Medicare rule of having three consecutive inpatient calendar days prior to acceptance. However, a smaller number of patients can acquire authorization to be admitted directly from the outpa-
tient settings if they meet certain criteria.44 Providers at LTCFs count on the hospital discharge summaries or the primary care professionals’ instruction to deliver the continuum of care. This transition is generally governed by several guidelines to help providers organize and coordi-
rate health information transmitted so the quality of patient care is assured. One of the major clinical practice guidelines on transition of care comes from the Amer-
ican Medical Directors Association, which fails to incor-
porate detailed diabetes management strategies in their handbook or in the universal transfer form.45

There is a lack of standardized diabetes management in the older population due to the diverse constellation of comorbidities and the lack of clinical trials in this popu-
lation. Considering the numerous challenges to manage diabetes in older adults (table 1), several societies have published guidelines for the management of diabetes. These recommendations revolve around improving glycemic control and avoidance of hypoglycemia. It is recommended to follow a conservative glycemic target at LTCF aiming for fasting blood glucose of 100–140 mg/dL and 140–180 postprandially while preventing

Figure 1 Common diabetes-related comorbidities and frequency of occurrence per age. The incidence of diabetes complications divided by age groups among patients with diabetes (per 1000).39 This figure was reproduced from the CDC data (http://www.cdc.gov/diabetes, accessed 2021). No permission was needed since these data were in the public domain and may be reproduced or copied without permission from CDC. CDC, Centers for Disease Control and Prevention; CHF, congestive heart failure; ESRD, end-stage renal disease; IHD, ischemic heart disease.

Figure 2 Common geriatric syndromes in patients with diabetes in long-term care facilities. DM, diabetes mellitus.
Hypoglycemia. The ADA recommends, in healthy functional patients with few coexistent chronic conditions, to target a glycated hemoglobin (HbA1c) of less than 7.5% (55–58 mmol/L). This target is raised to 8.0%–8.5% (64–69 mmol/L) in older adults with multiple coexisting chronic illnesses and cognitive impairment or those who are functionally dependent. In older adults who are not treated with insulin or insulin secretagogues, the Endocrine Society clinical practice guideline recommends targeting an HbA1c of less than 7.5%, 8.0%, or 8.5% for patients who are in good, intermediate, and poor health, respectively. For patients using drugs that may cause hypoglycemia (insulin and insulin secretagogues), the Endocrine Society recommends increasing the HbA1c target by 0.5%. Further recommendations from Japan Diabetes Society/Japan Geriatrics Society joint committee’s clinical practice guidelines, European Diabetes Working Party for Older People 2011 Clinical Guidelines for Type 2 Diabetes Mellitus, Diabetes Canada, and International Diabetes Federation are summarized in Table 1.

Currently, guidelines for older adults with diabetes in LTCF prioritize the avoidance of hypoglycemia and the individualization of therapy. The ADA recommends simplifying treatment regimens and avoiding the use of sliding scale insulin alone. Addressing diabetes goals in older adults residing in LTCF should be conducted in an interdisciplinary manner based on individual comorbidities.

Several studies have confirmed that glucose control is often tight rather than poor at LTCFs with HbA1c that is lower than the goal for this population. This may indicate overtreatment since more than 50% of older adults being treated with hypoglycemia-associated drugs (insulin and insulin secretagogues) have an HbA1c that is less than 7% as reported from the National Health and Nutrition Examination Survey.

Recent developments in antidiabetic drugs portfolio provide an opportunity to optimize diabetes care in LTCFs. Currently, there are 12 glucose-lowering agents with different mechanisms of action. Some of the newer agents (dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists and sodium–glucose cotransport 2 inhibitors (SGLT-2i)) are associated with a lower risk of hypoglycemia compared with insulin and sulfonylureas (SUs). In addition, newer long-acting insulin analogs, such as glargine U300 and degludec insulin, are associated with lower rates of hypoglycemia compared with first-generation basal insulins (Neutral Protamine Hagedorn insulin (NPH), glargine U100 and detemir).

### HYPOGLYCEMIA AMONG OLDER ADULTS IN LTCFS

Hypoglycemia is a major problem in LTC residents with type 2 diabetes (T2D). A retrospective study of over 1400 residents found that 42% of patients in LTCFs had at least one episode of blood glucose (BG) of <70 mg/dL, and 7% experienced BG of <54 mg/dL. Hypoglycemia is most common in patients treated with SUs and/or insulin, with SUs accounting for 18.8% of hypoglycemic episodes and insulin responsible for 64%. Other studies have documented hypoglycemia rates up to 34% in patients treated with SUs.

Hypoglycemia is the main limiting factor for optimizing glycemic control in patients with diabetes. Target HbA1c range should be modified on an individual basis and determined by the patient’s history of hypoglycemia, life expectancy, presence of comorbidities and diabetes complications. Dementia and cognitive impairment put residents at higher risk of hypoglycemia due to failure to recognize symptoms or to communicate those symptoms to caregivers. Furthermore, caregivers may be less able to recognize symptoms of hypoglycemia in patients with underlying cognitive impairment. Decrease in

---

**Table 1** Challenges facing diabetes management at long-term care facility from American Diabetes Association guidelines.

| Patient related                  | Facility related                              | Diabetes management related                      |
|---------------------------------|-----------------------------------------------|--------------------------------------------------|
| Irregular eating habits         | Staff turnover                                | Sole use of sliding scale insulin                |
| Altered cognition, anxiety and depression | Lack of nutritional individualization         | Mismatch insulin administration timing in relation to feeding time |
| Impaired mobility               | Lack of or insufficient glucose monitoring    | Inappropriate hypoglycemia management            |
| Polypharmacy and medication reconciliation errors | Limited staff diabetes-specific knowledge and training | Limited knowledge of advanced technologies (continuous glucose monitoring) |
| Variable levels of social support | Lack of pharmacist and dietitian support     | Lack of comprehensive transitional diabetes management protocol |
| Variable nutritional needs      | Lack of comprehensive notification system    | Lack of diabetes management protocols           |
| Persistent pain                 |                                               |                                                  |
| Oral health, skin and vision problems |                                               |                                                  |
β-adrenergic function and lack of adrenergic symptoms, such as palpitations, sweating and tremors, have been reported in older adults with hypoglycemia.\(^6^4\) Neuroglycopenic symptoms, such as confusion, delirium, and dizziness, may be the presenting indicator of hypoglycemia, which can be difficult to differentiate from underlying dementia.\(^6^5\) Other physiological changes in the elderly also exacerbate risk of hypoglycemia. Renal and hepatic impairment can interfere with metabolism of medications, specifically SUs and insulin.\(^6^6\) Age-related changes in counter-regulatory responses also increase the risk of hypoglycemia unawareness.\(^6^7\)

Significant morbidity and mortality are associated with hypoglycemia in LTCF residents. The prevalence of hypoglycemia is estimated between 28% and 40%.\(^6^8\) Hypoglycemia has been associated with increased risk of falls and fractures and cardiac arrhythmias.\(^6^9\) In addition, patients suffering from hypoglycemia have longer length of stay (52 vs 29 days, p<0.001), higher rates of emergency room visits or hospitalization (44% vs 31%, p=0.005), and greater mortality 20% vs 10% (p=0.002) than those without hypoglycemia.\(^8\) Moreover, a randomized controlled trial confirmed increased complications and more episodes of acute kidney injury in patients with hypoglycemia compared with those without.\(^8\)

Polypharmacy was considered one of the major predictors of severe hypoglycemia in LTCF.\(^8^0\)\(^8^1\) One study reported that LTCF residents receive an average of 7.2 medications, and 69.5% of them had at least one error in their medication reconciliation.\(^7^2\) In Europe, The Services and Health for Elderly in Long Term Care study observed polypharmacy (>5 medications) in 50.7% and excessive polypharmacy (≥10 drugs) in 16.9% of older adults with cognitive impairment.\(^7^3\) Other factors that could lead to hypoglycemia in LTCFs include the partial or full dependence for ADLs, heterogeneity of nutritional needs, and errors on medications administration.\(^7^4\) Clinical guidelines from professional organizations recommend the use of subcutaneous insulin, as the preferred therapy for glycemic control for most patients with T2D in LTCFs. Although effective in improving glycemic control, observational and prospective randomized studies have reported rates of hypoglycemia between 30% and 37% with insulin administration in LTCF residents with T2D.\(^6^8\)\(^7^5\) Errors in insulin administration can cause severe hypoglycemia that can impact the individual’s cognition and, if not corrected in a timely manner, can be lethal.\(^3^2\)

Several strategies have been proposed to minimize risk of hypoglycemia. Recommendations include simplification of medication regimens, avoidance of insulin secretagogues (SUs), and minimization of sole use of sliding scale insulin. Liberalization of diet may improve food and drink intake and minimize risk of unintentional weight loss. Physical activity should be targeted to the individual resident’s functional capability.\(^5^9\)

| Table 2 | Guideline recommendations for key clinical outcomes for older people with diabetes |
|---------|--------------------------------------------------------------------------------|
| ADA\(^5^1\) | ES\(^3^0\) | DC\(^4^8\) | IDF\(^3^9\) | European\(^4^7\) | Japan\(^4^6\) |
| Healthy (few coexisting chronic illnesses, intact cognitive and functional status) | Good health (no comorbidity or 1–2 comorbidities and no ADL impairments) | Functionally independent | Functionally independent (no impairments of ADLs, and receiving none or minimal caregiver support) | Free of other major comorbidities | Intact/mild cognition and functionality |
| Complex (multiple coexisting chronic illnesses, cognitive or functional impairment) | Intermediate health (>3 comorbidities and mild cognitive or ADL impairment) | Functionally dependent | Functionally dependent (impairments of ADL, and requiring additional medical and social care) | Dependent; multisystem disease, care home residency, and including dementia | Significant cognitive, presence of multiple comorbidities & functional impairment |
| Poor health (end-stage medical condition, moderate to severe dementia, or long-term care facility resident) | Frail and/or dementia | Sublevel frail or dementia | 7.0%–7.5% | 7%–7.5% | 7%–8%* |
| <8.5%* | 7.1%–8.0% | 7.0%–8.0% | 7.6%–8.5% | 8.0%–8.5%* |
| <8.5%* | 7.1%–8.5% | 8.5% |

*The A1C targets varies among older adults who are using medications known to cause hypoglycemia (eg, insulin and sulfonylureas). ADA, American Diabetes Association; ADLs, activities of daily living; DC, Diabetes Canada; ES, Endocrine Society; IDF, International Diabetes Federation.
HYPOGLYCEMIA TREATMENT IN LTCFS

The best approach to minimize hypoglycemia is by preventing its occurrence in the first place. Most hypoglycemia episodes are preventable, and minimizing their duration and frequency has been proven to decrease mortality.86 Hospitals have implemented several strategies to decrease the occurrence of hypoglycemia such as reviewing patients’ treatment regimen when BG is less than <70 mg/dL.79 This includes monitoring glucocorticoids doses, activity level, oral intake, and enteral or parenteral feedings as well. Hospital protocols aim to evaluate root causes to address systemic issues when hypoglycemia occurs rather than treating it as a separate event.80 To improve synchronization of prandial insulin with mealtime, several strategies are executed in the hospital settings. Some methods include alerting the nurse of meals tray delivery by food staff or standardizing the food delivery schedules.81 A remote surveillance system that allows a diabetes specialist to make recommendations in the patient chart has also been tested. It demonstrated decrease in the hypoglycemia frequency and the approach was widely accepted.82 85 Furthermore, novel approaches are also being studied in hospitalized patients to predict hypoglycemia using machine learning or artificial intelligence embedded in the electronic medical record.84 85 Providers at LTCF could implement some of the strategies that are followed in the hospital, but quality improvement projects and research trials are needed to explore the full effects in such environments.

All hospitals and long-term facilities have instituted a hypoglycemia treatment protocol. These are usually executed by nurses when blood glucose falls below 70 mg/dL and providers are ought to alter the diabetes management regimen to decrease the risk of further severe and very severe hypoglycemia.86 If the patient is able to swallow or has an oral access using gastric or nasogastric tubes, 15 g of carbohydrate should be administered. This equals 4 oz of juices or regular soda, 8 oz of skim milk, or one instant glucose of 31 g tube. If the patient is not able or allowed (nil per os (NPO)) to swallow, a half of dextrose 50 ampule should be given intravenously for a BG between 41 mg/dL and 70 mg/dL, or a full ampule when blood glucose is less than 40 mg/dL. In both cases, blood glucose should be rechecked in 15 min and the approach can be repeated if glucose remains less than 70 mg/dL. Once hypoglycemia is resolved (>70 mg/dL), the treatment plan should be examined carefully for any possible contributors such as the presence of glucose-lowering medications (eg, SUs) or higher than needed insulin dosage.

USE OF GLUCAGON

Glucagon is a hormone that is secreted directly from the α cells of the pancreas.87 It raises blood glucose levels through glycogenolysis and gluconeogenesis in the liver.87 88 The administration of glucagon is considered one of the most important approaches in the treatment of hypoglycemia since it is the primary counter-regulatory hormone to insulin.89 90 The available emergency kits contain a dose of 1 mg of glucagon. After intramuscular, subcutaneous, or inhaled administration, plasma blood glucose levels peak at 26–30 min.91–93

The ADA recommends prescribing glucagon for all patients who are at high risk of severe hypoglycemia. Additionally, instruction should be provided to caregivers or family members of these patients about its administration.94 Despite this recommendation, glucagon safety and availability, it is still underused among patients with diabetes.95–97 Several studies of family members and trained caregivers suggest difficulties using available emergency kits which might indicate the lack of user-friendly products.98 In addition, many physicians and patients with diabetes fail to recognize the importance of glucagon injection. Studies from Japan and Croatia report the underuse of glucagon for both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).96 99 In Canada, the percentage of glucagon administration to patients being transferred to the hospital for hypoglycemia was only 40% prehospitalization and less than 1% in the emergency department. Furthermore, the lack of discharge protocol was evident from several emergency departments, with instructions being documented in less than half of the patients, and only 20% were referred to diabetes services.100 In fact, patients discharged from the emergency department following hypoglycemic episodes are at a higher risk of being readmitted within 2 days of a recurrent hypoglycemia.101

If a person is unable to swallow or is unresponsive, subcutaneous, intramuscular, or intranasal glucagon or intravenous glucose should be given by a trained family member or medical personnel. Glucagon for injection is available in prefilled forms ready for intramuscular, subcutaneous, or intravenous administration. Two standard Food and Drug Administration (FDA)-approved formulations of standard glucagon are the GlucaGen HypoKit (Novo Nordisk, Copenhagen, Denmark) and the Glucagon Emergency Kit (Eli Lilly, Indianapolis, Indiana, USA). Both formulations are supplied as lyophilized white powder requiring reconstitution prior to injection as 1 mg per vial. New, more stable formulations of glucagon have recently become available for clinical use: intranasal glucagon, daslgucagon, and non-aqueous soluble glucagon. These new FDA-approved formulations have demonstrated glycemic responses similar to standard glucagon formulations for the treatment of hypoglycemia but without the need for reconstitution.102 Intranasal glucagon is FDA-approved under the trade name Baqsimi (Eli Lilly) comprising 1 mg glucagon per 10 mg dry powder. Absorption of the powder occurs across the nasal mucosa with a 3 mg glucagon having the maximal effect.103–105 Non-aqueous glucagon solutions (trade name GVOKE) was the first glucagon product approved that can be administered via a prefilled syringe (GVOKE PFS) or autoinjector (GVOKE HypoPen), reducing the steps to prepare and administer glucagon in
the event of hypoglycemia. Dasiglucagon is a novel stable peptide analog of human glucagon consisting of 29 amino acids with 7 amino acid substitutions relative to native glucagon (trade name Zegalogue). In clinical trials, the time taken to increase glucose concentration to above 70 mg/dL was 6 min with doses of 0.3 and 0.6 mg of dasiglucagon, which is comparable to standard glucagon at doses of 0.5 and 1.0 mg.  

There is a lack of clinical trials regarding the use and implementation of glucagon in LTCF protocols. One quality improvement project reported no hospital transfer for hypoglycemia episodes after glucagon was implemented in their protocol. Such application could decrease the frequency of severe hypoglycemia in LTC populations and would minimize unnecessary health-care costs related to hypoglycemic episodes and its poor outcome.

USE OF TECHNOLOGY IN LTCFS

Currently, capillary point-of-care (POC) monitoring is the standard of care to measure glucose levels in the LTCF, which is usually done before meals and at bedtime. In recent years, the use of continuous glucose monitoring (CGM) that measures interstitial glucose levels every 5–15 min has been shown to provide a better assessment of glycemic control and hypoglycemia detection compared with POC capillary testing.

Several randomized trials have shown that CGM technology facilitates and improves diabetes care in insulin-treated ambulatory patients as well as in hospitalized patients. Subjects with T2D treated with basal-bolus insulin therapy in the hospital were studied in combination with CGM use. The detection of both hypoglycemic and hyperglycemic events with the use of CGM was increased compared with the standard-of-care POC testing. Furthermore, novel technology has been developed to allow CGM glucose values to be transmitted wirelessly from the patient’s bedside to a central monitoring device in the hospital nursing station. This approach, known as glucose telemetry system with Bluetooth technology, allows for early recognition and treatment of hypoglycemia, thereby reducing the frequency of events in insulin-treated patients with T2D. About half of the hypoglycemic events in older adults are asymptomatic and occurred between dinner and breakfast, indicating that these episodes would be missed by standard POC testing as glucose testing is rarely done during night-time. A recent panel of experts in patient diabetes care reported that CGM could effectively identify trends toward hypoglycemia and hyperglycemia, allowing for better and safer management of patients with T2D in facilities.

A recent large study evaluated CGM and POC glucose data from hospitalized patients in the general wards. The results demonstrated a very good overall accuracy of CGM despite comorbidities such as CVD, renal dysfunction, mild–moderate anemia, and respiratory diseases. However, CGM accuracy might be lower in hypoglycemia (<70 mg/dL) or in severe anemia. CGM might also have interferences with some molecules in the bloodstream (acetaminophen >4 g/day, vitamin C, and hydroxyurea); and it is not recommended for patients who are planning to have MRI. Further research is needed to determine the potential benefits of real-time CGM to improve glycemic control and to prevent hypoglycemia in vulnerable population of adult patients admitted to LTCFs particularly in the era of COVID-19 pandemic.

MEDICAL APPROACHES FOR OLDER ADULTS WITH DIABETES IN LTCFS

Several oral and injectable antidiabetic agents are available for the treatment of diabetes in older adults, which can be used as monotherapy or in combination with insulin (table 3). Claims data from the ambulatory settings suggest that older adults were found to use more long-acting insulin and less of the newer DM medication such as GLP-1a. The evidence shows that newer oral antidiabetic drugs can be effective for disease control and less likely to cause hypoglycemia.

Insulin

Insulin is frequently used in older adults in LTCFs. It is mostly used when diabetes is not controlled with oral medications, as well as during acute illness, preoperative period, or when the person has severe renal or liver disease. Basal insulin analogs (glargine, detemir or degludec) administered starting at 0.1 units/kg/day (or 10 units/day) with slower titration increasing once or two times per week until fasting glucose is less than 150–180 mg/dL or HbA1c<7.5%–8.0%. Basal insulin glargine is also available in a concentrated formulation as insulin glargine 300 units/mL (Gla-300; Sanofi, Paris, France) and degludec U-200 (Novo Nordisk). These formulations of insulin have been studied in older adults with comparable glycemic control to insulin glargine 100 units/mL.

Clinical studies have reported that replacing a sliding scale with a lower dose of basal insulin analogs at a total daily dose of 0.1–0.15 units/kg/day might decrease the risk of hypoglycemia in this frail population. If basal insulin is not sufficient to control hyperglycemia, the basal bolus approach is recommended starting at 0.2–0.3 U/kg/day divided as 50% basal and 50% prandial coverage. However, the use of rapid-acting insulin should be individualized since older adults might have different types of day-to-day living behaviors, which correlate with their dining time and location. Practitioners should also consider LTCF policies in reference to mealtime insulin administration since numerous logistical planning need to be in place. For example, the location of administration (resident private room vs dining room) and the timing of insulin injection in reference to food arrival could significantly affect blood glucose levels.
Emerging technologies, pharmacology and therapeutics

More data are needed to generate guidelines which are specific to diabetes management in LTCF.

**Metformin**
Metformin is the most commonly used antidiabetic drug for the management of T2D and acts by decreasing hepatic glucose production through multiple molecular mechanisms. Metformin has a low risk of hypoglycemia and is weight neutral, making it an attractive option. Metformin contraindications are limited to impaired renal function with estimated glomerular filtration rate (GFR) less than 30 mL/min/1.73 m² and severe liver disease. Metformin is also contraindicated in patients with lactic acidosis or severe hypoxia. In summary, metformin is a safe and effective choice for the management of T2D in older adults with diabetes. **Table 3**

| Antidiabetic drug | Mechanism of action | Effect on decreasing HbA1c | Pros (benefits) in older adults | Cons (side effects in older adults) | Practical tips |
|-------------------|----------------------|-----------------------------|-------------------------------|-------------------------------------|---------------|
| Metformin         | Decreases gluconeogenesis and increases glycogenolysis | 1%–2% | No hypoglycemia, No weight gain, Low cost, Positive effect on lipids, Decreases macrovascular complications | Lactic acidosis in severe CKD, GI symptoms | Take on full stomach, Start low dose to minimize GI side effects and titrate up slowly, Cautiously in older adults with increased risk of lactic acidosis |
| Insulin secretagogues (SUs and glinides) | Stimulates insulin secretion by inducing a B-cell interaction with a SU receptor | 0.5%–1.0% | Once a day, Works fast | Hypoglycemia | Non preferred in older adults because of the risk of hypoglycemia |
| Alpha glucosidase inhibitors | Slow carbohydrate absorption by blocking alpha glucosidase and increase GLP-1 level | 0.5%–1.0% | Improves postprandial BG | GI symptoms | To be taken with first bite of food |
| Thiazolidinedione | PPARγ agonist and regulate carbohydrate and lipid metabolism, enhance tissue response to insulin | 0.9%–1.5% | No hypoglycemia when used as monotherapy | Slow onset of action, HF | Don't use if patient has osteoporosis or macular degeneration, which are common in older adults. |
| DPP-4 inhibitors | Stimulates insulin secretion and inhibits glucagon secretion by increasing endogenous GLP-1 | 1% | No hypoglycemia when used as monotherapy | Risk of hypoglycemia if used with SU | Well-tolerated and low risk of hypoglycemia, Can be used even in the presence of CKD, Avoid if there is history of pancreatitis |
| GLP-1 receptor agonists | Stimulate insulin secretion, inhibit hepatic glucose and delay gastric emptying | 1% | Cardiac (IHD) and renal protective | GI symptoms | Once a week or daily formulations, Start with lowest dose possible and titrate up, May cause weight loss, Avoid if there is history of pancreatitis or medullary thyroid carcinoma or MEN |
| SGLT-2i | Prevent glucose reabsorption in the nephron and increase glucose excretion in the urine by inhibiting the SGLT-2 protein | 1% | HF and renal protection, Low risk of hypoglycemia, Can be used in diabetes of any duration | Dehydration, GU infections, DKA | Recommended for patients with diabetes and HF and/or renal disease, Monitor for cystitis and yeast infections, Keep up with oral hydration to volume depletion, Avoid in patients with T1DM |

BG, blood glucose; CKD, chronic kidney disease; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; HF, heart failure; IHD, ischemic heart disease; MEN, multiple endocrine neoplasia; PPARγ, peroxisome proliferator-activated receptor; SGLT-2i, sodium–glucose cotransport 2 inhibitor; SU, sulfonylurea; T1DM, type 1 diabetes mellitus.
filtration rate (eGFR) of <30 mL/min/1.73 m², acute HF or active decompensated liver disease. In addition to the clinical benefits, metformin is inexpensive, which allows for its use as first oral choice in the treatment of T2D, including institutionalized older adults. Metformin is known to cause gastrointestinal (GI) adverse events such as nausea and diarrhea, complicating the management in older adults who might suffer from decreased oral intake and are at a higher risk of dehydration. Metformin has been associated with increased risk of lactic acidosis if used in patients with impaired kidney function. Guidelines for diabetes management recommend holding metformin in the hospital. The acute changes during hospitalization such as dehydration and renal or hepatic dysfunction might further exacerbate the possibility of developing lactic acidosis, particularly if they receive contrast media. However, the environment at LTCF is considered less acute, yet no studies have evaluated the use of metformin in these settings. In summary, more trials are needed to evaluate the benefits and risks of using metformin among LTCF residents. Metformin remains a preferred option for geriatric individuals compared with other agents that could cause hypoglycemia and increase mortality risk. Nonetheless, practitioners could prescribe this agent in the older adult population, taking into consideration the risk of lactic acidosis and dehydration from the decrease oral intake. Metformin dosage can be started at 500 mg/day and titrated up as tolerated to a maximum of 2000 mg/day in a normal GFR. Providers could opt for extended-release versions to minimize the risk of intolerance.

**Insulin secretagogues**

SU stimulates insulin secretion by activating SU receptors on B cells. The major side effect is hypoglycemia, especially in the case of irregular caloric intake, decreased renal function, and polypharmacy, which are common in older adults in LTCF. Studies have associated SU use with poor outcome and a 7% to 10% mortality rate among patients with SU-induced hypoglycemia. The use of SU has been associated with higher all-cause mortality compared with metformin and an increased risk of fractures in older population with T2DM.

Metiglinides have a shorter half-life and include nateglinide and repaglinide. They are used preprandially and have a similar mechanism of action as SUs which could lead to hypoglycemia risk. It is worth noting, however, the lower rates of severe hypoglycemia with metiglinides when compared with SU in RCTs involving older adults.

Clinical studies on the use of insulin secretagogues in LTCF are lacking. On the other hand, their use in hospital settings is not recommended by professional societies due to the possible risk of hypoglycemia among older adults who might suffer from renal dysfunction. Providers should probably follow these recommendations in LTCF pending more concrete evidence about their safety and benefits. Nonetheless, if these agents are to be considered in LTCFs, health professionals should elect short-acting insulin secretagogues that have lower risk of hypoglycemia in the settings for renal impairment such as glipizide or metiglinides. Additionally, metiglinides are usually more expensive than SU, should be adjusted for GFR, and ought not be used in older patients with erratic eating behaviors.

**Thiazolidinediones (TZDs)**

These drugs work as peroxisome proliferator-activated receptor (PPAR) agonists and regulate carbohydrate and lipid metabolism, enhance tissue response to insulin, and have favorable effects on endothelial function and inflammation. TZDs are metabolized by the liver, so they can be used in the setting of impaired renal function. The use of TZDs can cause fluid retention, peripheral edema, weight gain, macular edema and heart failure (HF).

Prescribing this class of medicine to LTCF residents should be considered after exhausting other options. The prevalence of HF among older adults in LTCF is estimated to equal 20%–37.4% and using TZD might increase the risk of readmission to the hospital for HF exacerbation or even death. Furthermore, older adults have more prevalence of osteoporosis or osteopenia and TZD has been associated with a higher rate of fractures, particularly in postmenopausal women.

**Alpha-1 glucosidase inhibitors**

This family of medications include miglitol and acarbose. They are a group of drugs that slow carbohydrates absorption by blocking the action of brush border enzymes (alpha glucosidases) and increasing GLP-1 levels. They primarily work on postprandial hyperglycemia. These agents have the advantage of not causing hypoglycemia; however, use is limited due to GI side effects such as flatulence, abdominal pain and abdominal cramp.

Despite their safety, the use of this agent in older adults residing at LTCF is not routinely followed due to the lack of clinical trials in this population and the higher rate of GI side effects. The half-life of this medicine is short and requires frequent administration, which might be challenging in LTCF.

**Dipeptidyl peptidase-4 (DPP-4) Inhibitors**

This class of medication acts on dipeptidyl peptidase-4 enzyme that degrades endogenous secretion of GLP-1. Inhibiting this enzyme increases the availability of GLP-1, resulting in increased insulin secretion and reducing glucagon release. This family of drugs improves fasting and postprandial glucose levels; they are well tolerated and can be taken as monotherapy or in combination with other oral antidiabetic medications. These drugs are convenient to use in older adults because they can be used in the setting of renal dysfunction, have limited side effects, and have a low rate of hypoglycemia. A randomized controlled study showed that the DPP-4 inhibitor is as effective as insulin glargine for glucose control with significant lower risk of hypoglycemia in LTCF residents.
with T2D. With more effective and safer antidiabetic agents, T2D management has been revolutionized. A prospective randomized 6-month open-label randomized controlled trial compared the efficacy and safety of linagliptin versus basal insulin glargine of a total of 140 residents with T2DM in three LTCFs affiliated with community safety-net hospitals. Both groups had similar mean daily glycemic control, but compared with glargine, the group treated with linagliptin had fewer mild hypoglycemic events of <70 mg/dL (3% vs 37%).

**Glucagon-like peptide 1 receptor agonists (GLP1-RAs)**

GLP1 is an incretin hormone that stimulate insulin secretion in a glucose-dependent manner. In addition, they promote delayed gastric emptying and inhibit the production of glucagon, which further decrease glucose levels. HbA1c can decrease by approximately 1.0%–1.5% when using this drug, along with weight loss of about 2–5 kg. Clinical trials have demonstrated that GLP1-RA have cardiovascular benefits among patients with established atherosclerotic cardiovascular disease. Several studies have demonstrated the renal protection of GLP1-RA and possible positive effects on cognitive and memory functions. They may work through blood glucose and blood pressure lowering, reduction of insulin levels and weight loss, and lower inflammatory state, which can reduce albuminuria and prevent the decline of renal function in patients with diabetes.

Healthcare professionals should be aware that most of GLP1-RAs are injectable once per day or per week and require visual, motor, and cognitive skills for administration. Furthermore, the GI side effects such as nausea and diarrhea are reportedly common (10%–28%), whereas vomiting and other adverse effects were not less frequently (2%–12%), and these add to the limitation of their use in older adults. To minimize GI side effects, providers at LTCFs should start with the lower dosage and increase gradually every 1–2 weeks to reach the maximal tolerated dose. The nutrition status of the resident should be also considered since the prevalence of malnutrition is estimated to equal 18%–21% across studies.

**Sodium–glucose cotransport 2 inhibitors (SGLT-2is)**

SGLT-2is are a group of drugs that lowers the reabsorption of glucose in the proximal convoluted tubule of the nephron by inhibiting the sodium-glucose transport protein 2, therefore promoting the excretion of the glucose in the urine and lowering blood glucose. These drugs lower the HbA1c by approximately 1% and contribute to modest weight loss of 1–3 kg. It can be used as monotherapy or combined with other oral antidiabetic drugs and/or insulin. Apart from the antidiabetic effect, SGLT-2is have been found to have cardioprotective effects in patients with diabetes. SGLT-2is reduced hospitalization for HF by 23% in patients with diabetes and reduced the progression of renal disease by 45%. The use of SGLT-2is is now recommended by clinical guidelines for the management of T2D in patients with coexisting HF and diabetic kidney disease. Nearly 20.0%–37.4% of LTCF residents are diagnosed with HF, however, no studies have evaluated SGLT-2i safety and efficacy on decreasing HF admission in these settings.

A meta-analysis on the cardiovascular outcome trial on the use of this drug class showed that the efficacy for older adults reported an OR for major adverse cardiovascular events (MACEs) of 0.95 (95% CI 0.86 to 1.05) in people <65 years old and 0.83 (95% CI 0.71 to 0.96) for people >65 years old.

Adverse effects reported with the use of SGLT-2is include urinary tract infections (UTIs) and yeasts infections. In patients with T1DM, SGLT-2is have been associated with increased risk of euglycemic diabetic ketoacidosis, but this complication is rare in patients with T2D. The use of SGLT-2is in LTCF has not been evaluated by RCT, but previous clinical trials have included older adults. This class of medicine was found to be effective, safe, and provided cardio renal benefits in the geriatric population, but caution should be exercised when initiating in LTCF.

First, UTI is the second most common infection in LTCF and the prevalence of asymptomatic bacteriuria is estimated at 18%–57%. Administering SGLT-2is might theoretically increase the risk of developing or worsening UTI if perineal hygiene was not followed in these settings. Second, the osmotic diuresis effects of using this class of medicine might be problematic in older adults who are at risk of dehydration, particularly if they are on loop diuretics. Blood pressure and GFR should be monitored if SGLT-2is were to start or continued in LTCF. A slight decrease in GFR is expected after initiating this medicine, but there is evidence that their use is safe in mild or moderate renal dysfunction.

Furthermore, almost 70.3% of LTCF residents suffer from urinary incontinence and the use of these medications might impact this issue negatively due to the diuretic effects. Third, the scarcity of data in older adults with frailty and these agents might not support using them in this population yet. Therefore, more studies are needed to evaluate the safety and efficacy of using SGLT-2is in LTCF.

**Combination therapy**

Many diabetes agents are available in combination therapies which might be beneficial in older adults to decrease the burden of polypharmacy. It is possible now to offer different oral agents in one tablet. This will improve compliance and lead to lower HgA1c. The most common agents include combination of metformin with either SGLT-2i, or incretin agents and a newly approved triple combination therapy of metformin, SGLT-2i, and incretin agents. Furthermore, new advances have allowed the combination of long-acting insulin and GLP1a therapy in one injection. This approach might be favorable to older adults since it will decrease the number of injections significantly. In addition, long-acting insulin/GLP1a combination might replace insulin-bolus therapy, which will probably lead to a decrease in the risk
of hypoglycemia in older adults and possibly improve the quality of life.\textsuperscript{205–208}

**CONCLUSION**

Older adults have diverse clinical profiles and their health status undergo rapid and acute changes which can affect glucose control. Thus, the management of diabetes can be affected based on the living environment and the amount of social, physical, and psychological support provided. With the prevalence of older adults with diabetes increases in the future, the percentage of older patients with diabetes in LTCFs will also rise. This will generate numerous challenges to control blood glucose in these settings since older adults admitted will have various levels of functionality, different sets of comorbidities, and distinct life expectancy. Most of the LTCF residents are on insulin alone and/or oral regimens, resulting in increased risk of hypoglycemia.

Optimizing cost-effective approaches to treat older adults with diabetes safely will provide an improved outcome in morbidity and mortality along with decreasing the economic burden. Currently, major diabetes guidelines lack the direction needed to screen and recognize hypoglycemia risks, or the interventions needed to treat acute severe hypoglycemia for older adults in long-term settings. These facilities are expected to develop their own practice procedure to treat hypoglycemia which currently lacks the use of glucagon. This agent might effectively reduce prehospital hypoglycemic complications if encompassed in the transition of care plans of older adults.

**Contributors** TI, IAC-R, ALM, and GEU have participated in writing and reviewing the manuscript. EMM has participated in reviewing the manuscript. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** GEU is a member of the BMJ editorial board.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

**ORCID iDs**
Thaer Idrees http://orcid.org/0000-0001-9036-995X
Guillermo E Umpierrez http://orcid.org/0000-0002-3252-5026

**REFERENCES**
1 Kirman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. *Diabetes Care* 2012;35:2650–64.
2 Andes LJ, Li Y, Srinivasan M, et al. Diabetes Prevalence and Incidence Among Medicare Beneficiaries - United States, 2001-2015. *MMWR Morb Mortal Wkly Rep* 2019;68:961–6.
3 Laieteerapong N, Karter AJ, Liu JY, et al. Correlates of quality of life in older adults with diabetes: the diabetes & aging study. *Diabetes Care* 2011;34:1749–53.
4 Menke A, Casagrande S, Geiss L, et al. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. *JAMA* 2015;314:1021–9.
5 Centers for Disease Control and Prevention. *National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011. http://www.cdc.gov/diabetes/pubs/factsheet11.htm.
6 Narayan KMV, Boyle JP, Geiss LS, et al. Impact of recent increase in incidence on future diabetes burden: U.S., 2005-2050. *Diabetes Care* 2006;29:2114–6.
7 Resnick HE, Heineman J, Stone R, et al. Diabetes in U.S. nursing homes. *Diabetes Care* 2008;31:287–8.
8 Newton CA, Adeel S, Sadeghi-Yarandi S, et al. Prevalence, quality of care, and complications in long term care residents with diabetes: a multicenter observational study. *J Am Med Dir Assoc* 2013;14:842–6.
9 Dybicz SB, Thompson S, Molotsky S, et al. Prevalence of diabetes and the burden of comorbid conditions among elderly nursing home residents. *Am J Geriatr Pharmacother* 2011;9:212–23.
10 Mooradian AD, Osterweil D, Petrasek D, et al. Diabetes mellitus in elderly nursing home patients. A survey of clinical characteristics and management. *J Am Geriatr Soc* 1988;36:391–6.
11 Funnell MM, Herman WH. Diabetes care policies and practices in Michigan nursing homes, 1991. *Diabetes Care* 1995;18:862–6.
12 Hauner H, Kurnaz AA, Haastert B, et al. Undiagnosed diabetes mellitus and metabolic control assessed by HbA1c among residents of nursing homes. *Exp Clin Endocrinol Diabetes* 2001;109:326–9.
13 Travis SS, Buchanan RJ, Wang S, et al. Analyses of nursing home residents with diabetes at admission. *J Am Med Dir Assoc* 2004;5:320–7.
14 Szczersiakas K, Topinková E, Brzyski P, et al. The characteristics of diabetic residents in European nursing homes: results from the shelter study. *J Am Med Dir Assoc* 2015;16:334–40.
15 Da Porto A, Coracina A, Fiore V, et al. Quality of care to institutionalized patients with diabetes in Italy: a national survey. *Eur Geriatr Med* 2020;11:753–9.
16 Harris-Kojetin L, Sengupta M, Park-Lee E, et al. Long-term care providers and services users in the United States: data from the national study of long-term care providers, 2013-2014. *Vital Health Stat 3* 2016;3:x–xii.
17 Centers for Medicare & Medicaid Services (CMS). Annual nursing home data compendium. Available: https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/CertificationandCompliancy/Downloads/nursinghomedatacompendium_508-2015.pdf2021
18 McNabney MK, Pandya N, Iwagwugnu C, et al. Differences in diabetes management of nursing home patients based on functional and cognitive status. *J Am Med Dir Assoc* 2005;6:375–82.
19 Morley JE. An overview of diabetes mellitus in older persons. *Clin Geriatr Med* 1999;15:211–24.
20 Druss BG, Marcus SC, Olsson M, et al. Comparing the National economic burden of five chronic conditions. *Health Aff* 2001;20:233–41.
21 Lee PG, Cigolle C, Blaum C. The co-occurrence of chronic diseases and geriatric syndromes: the health and retirement study. *J Am Geriatr Soc* 2009;57:511–6.
22 Schneider KM, O’Donnell BE, Dean D. Prevalence of multiple chronic conditions in the United States’ Medicare population. *Health Qual Life Outcomes* 2009;7:82.
23 Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med* 2002;162:2269–76.
24 Halter JB, Musi N, McFarland Horne F, et al. Diabetes and cardiovascular disease in older adults: current status and future directions. *Diabetes* 2014;63:2578–89.
25 De Felice FG, Vieira MNN, Bomfim TR, et al. Protection of synapses against Alzheimer’s-linked toxins: insulin signaling prevents the pathogenic binding of Abeta oligomers. *Proc Natl Acad Sci U S A* 2009;106:1971–6.
Emerging technologies, pharmacology and therapeutics

Defronzo RA, Lecture B. Banting lecture. from the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 2009;58:773-95.

Epstein S, LeRoith D. Diabetes and fragility fractures - a burgeoning epidemic? *Diabetes* 2019;68:43-6.

Mauer MS, Burnham J, Cheng H. Diabetes mellitus is associated with an increased risk of falls in elderly residents of a long-term care facility. *J Gerontol A Biol Sci Med Sci* 2005;60:1157–62.

Cryer PE. Mechanisms of sympathoadrenal failure and hyperglycemia in diabetes. *J Clin Invest* 2006;116:1470–3.

LeRoith D, Biessels GJ, Brathwaite SS, et al. Treatment of diabetes in older adults: an endocrinology Society clinical practice guideline. *J Clin Endocrinol Metab* 2019;104:1520–74.

Brown AF, Mangione CM, Saliba D, et al. Guidelines for improving the care of the older patient with diabetes. *J Am Geriatr Soc* 2003;51:5265–80.

American Diabetes Association. 12. Older Adults: Standards of Medical Care in Diabetes-2021. *Diabetes Care* 2021;44:S168–79.

Schneider ALC, Kalyani RR, Golden S, et al. Diabetes and prediabetes and risk of hospitalization: the Atherosclerosis risk in communities (ARIC) study. *Diabetes Care* 2016;39:772–9.

Centers for Disease Control and Prevention. National hospital discharge survey ’rate of discharges from short-stay hospitals, by age and first-listed diagnosis:United States, 2010. Available: http://www.cdc.gov/nchs/data/nhds/3firstlisted/2010first3_rateage.pdf. [Accessed July 2021].

Desai R, Singh S, Syed MH, et al. Temporal trends in the prevalence of diabetes decapensation (diabetic ketoacidosis and hyperosmolar hyperglycemic state) among adult patients hospitalized with diabetes mellitus: a nationwide analysis stratified by age, gender, and race. *Cureus* 2019;11:e4353.

American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care* 2018;41:917–28.

Neuwahl SJ, Honeycutt AA, Poehler DC, et al. Diabetes-attributable nursing home costs for each U.S. state. *Diabetes Care* 2018;41:1455–61.

Kagansky N, Levy S, Rimon E, et al. Hypoglycemia as a predictor of mortality in hospitalized elderly patients. *Arch Intern Med* 2003;163:1825–9.

Shilo S, Berezovski S, Friedlander Y, et al. Hypoglycemia in hospitalized nondiabetic older patients. *J Am Geriatr Soc* 1998;46:976–82.

Shorr RI, Ray WA, Daugherty JR, et al. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Intern Med* 1997;157:1681-6.

Boulin M, Diaby V, Tannenbaum C. Preventing unnecessary costs of drug-induced hypoglycemia in older adults with type 2 diabetes in the United States and Canada. *PLoS One* 2011;6:e1062951.

Sultz H, Young K. Health Care USA. Understanding its organization and delivery. *J of Geralt & Bartlett learning*, 2014.

Centers for Disease Control and Prevention. Long-term care settings. Available: https://www.cdc.gov/longtermcare/ accessed [Accessed 09 Jan 2021].

CDC. Medicare benefit policy Manual - coverage of extended care (nft) services. Available: https://www.cms.gov/regulations-and-guidance/guidance/manuals/downloads/bp102c08pdf.pdf [Accessed 29 Apr 2022].

American Medical Directors Association. Transitions of care in the long-term care continuum clinical practice guidelines. *Columbia*, MD: AMDA, 2010.

Araki E, Goto A, Kondo T, et al. Japanese clinical practice guideline for diabetes 2019. *J Diabetes Investig* 2020;11:1020–76.

Sinclair AJ, Paolissio G, Castro M, et al. European diabetes Working Party for older people 2011 clinical guidelines for type 2 diabetes mellitus, executive summary. *Diabetes Metab* 2011;37 Suppl 3:S27–38.

Ivers NM, Jiang M, Alloo J, et al. Diabetes Canada 2018 clinical practice guidelines: key messages for family physicians caring for patients living with type 2 diabetes. *Can Fam Physician* 2019;65:14–24.

International Diabetes Federation. Recommendations for managing type 2 diabetes in primary care, 2017. Available: www.idf.org/managing-type2-diabetes2021

Munshi MN, Florez H, Huang ES, et al. Management of diabetes in long-term care and skilled nursing facilities: a position statement of the american diabetes association. *Diabetes Care* 2016;39:308–18.

American Diabetes Association. 11. Older Adults: Standards of Medical Care in Diabetes-2018. *Diabetes Care* 2018;41:S119–25.

American Medical Directors Association. Diabetes management in the long-term care setting clinical practice guideline. *Columbia* MA.

Sjöblom P, AndersTengblad LUB, Löfgren U-B, et al. Can diabetes medication be reduced in elderly patients? an observational study of diabetes drug withdrawal in nursing home patients with tight glycaemic control. *Diabetes Res Clin Pract* 2008;82:197–202.

Löfgren U-B, Rosenqvist U, Lindström J, et al. Diabetes control in Swedish community dwelling elderly: more often tight than poor. *J Intern Med* 2004;255:96–101.

Gill EA, Corwin PA, Mangin DA, et al. Diabetes care in rest homes in Christchurch, New Zealand. *Diabet Med* 2006;23:1525-6.

Boulet L, Valiant G, Petit J-M, et al. Are elderly patients with diabetes being overtreated in French long-term-care homes? *Diabetes Metab* 2010;36:272–7.

Holt RM, Schwartz FL, Shubrook JH. Diabetes care in extended-care facilities: appropriate intensity of care? *Diabetes Care* 2007;30:1454–8.

Pasquel FJ, Powell W, Peng L, et al. A randomized controlled trial comparing treatment with oral agents and basal insulin in elderly patients with type 2 diabetes in long-term care facilities. *BMJ Open Diabetes Res Care* 2015;3:e000104.

Lipska KJ, Ross JS, Miao Y, et al. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. *JAMA Intern Med* 2015;175:356–62.

American Diabetes Association. Standards of Medical Care in Diabetes-2017 Abridged for Primary Care Providers. *Clin Diabetes* 2017;35:5–26.

American Diabetes Association. 11. older adults. *Diabetes Care* 2017:40:S99–104.

Garber AJ, Abrahamson MJ, Barzilay JI, et al. CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM – 2018 EXECUTIVE SUMMARY. *Endocr Pract* 2018;24:91–120.

Bradley MC, Chillarige Y, Lee H, et al. Severe hypoglycemia risk with long-acting insulin analogs vs neutral protamine Hagedorn insulin. *JAMA Intern Med* 2011;211:589–607.

Matyka K, Evans M, Lomas J, et al. Altered hierarchy of protective responses against severe hypoglycemia in normal aging in healthy men. *Diabetes Care* 1997;20:135–41.

Thompson FJ, Mason AS, Leeming JT, et al. Lack of knowledge of symptoms of hypoglycemia by elderly diabetic patients. *Age Ageing* 1991;20:404–6.

Sinclair A, Dunning T, Rodriguez-Mañas L. Diabetes in older people: new insights and remaining challenges. *Lancet Diabetes Endocrinol* 2017;3:275–85.

Kalyani RR, Egan JM. Diabetes and altered glucose metabolism with aging. *Endocr Metab Clin North Am* 2013;42:333–47.

Migdal A, Yarandi SS, Smiley D, et al. Update on diabetes in the elderly and in nursing home residents. *J Am Med Dir Assoc* 2011;12:627–32.

Geller A, Shehab N, Lovegrove MC, et al. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. *JAMA Intern Med* 2014;174:878–86.

Stahn A, Pistrosch F, Ganz X, et al. Relationship between hypoglycemic episodes and vascular arrhythmias in patients with type 2 diabetes and cardiovascular diseases: silent hypoglycemas and silent arrhythmias. *Diabetes Care* 2014;37:516–20.

Lipska KJ, Ross JS, Wang Y, et al. National trends in US hospital admissions for hypertensive urgency and moderate hypertension among Medicare beneficiaries, 1999 to 2011. *JAMA Intern Med* 2014;174:1116–24.

Barber ND, Alldred DP, Raynor DK, et al. Care homes’ use of medicines study: prevalence, causes and potential harm of medication errors in care homes for older people. *Qual Saf Health Care* 2009;18:341–6.

Vetrano DL, Tosato M, Colloca G, et al. Polypharmacy in nursing home residents with severe cognitive impairment: results from the shelter study. *Alzheimers Dement* 2013;9:587–93.

Moghissi ES, Koryolis and AMERICAN COLLEGE OF ENDOCRINOLOGY association of clinical endocrinologists and American diabetes association consensus statement on inpatient glycemic control. *Diabetes Care* 2009;32:1119–31.

Schnipper JL, Magee M, Larsen K, et al. Society of hospital medicine glycemic control Task force summary: practical recommendations for assessing the impact of glycemic control efforts. *J Hosp Med* 2008;3:66–75.

Selye JJ, D’Hondt N, Longo R. Position statement: inpatient glycemic control. *Diabetes Educator* 2009;35:65–9.

Lavandier C, Massin G, Schechter D, et al. A randomized controlled study comparing a DPP4 inhibitor (linagliptin) and basal insulin (Glargine) in patients with type 2 diabetes in long-term care.
Emerging technologies, pharmacology and therapeutics

80 Akio IV, Grossman A, Shachat T, et al. Mortality among hospitalized patients with hypoglycemia: insulin related and non-insulin related. Curr Clin Pract 2017;10:416–24.

81 American Diabetes Association Professional Practice Committee, American Diabetes Association Professional Practice Committee. Standards of medical care in diabetes-2022. Diabetes Care 2022;45:S244–53.

82 Braithwaite SS, Bui MM, Thompson CL, et al. Hospital hypoglycemia: not only treatment but also prevention. Endocr Pract 2004;10 Suppl 2:89–99.

83 Houck PM, Tirumalasetty MN, Meadows RY. Insulin administration and meal delivery coordination for hospitalized patients. Ochsner J 2013;13:127–33.

84 Rushakoff RJ, Sullivan MM, MacMaster HW, et al. Association between a virtual glucose management service and glycemic control in hospitalized adult patients: an observational study. Ann Intern Med 2017;166:621–7.

85 Sheen Y-J, Huang C-C, Huang S-C, et al. Implementation of an electronic DASHBOARD with a remote management system to improve glycemic management among hospitalized adults. Endocr Pract 2020;26:179–91.

86 Mathioudakis NN, Abusaman MA, Shakarchi AF, et al. Development and validation of a machine learning model to predict near-term risk of iatrogenic hypoglycemia in hospitalized patients. JAMA Netw Open 2021;4:e2030913.

87 Mujahid O, Contreras I, Vehi J. Machine learning techniques for hypoglycemia prediction: trends and challenges. Sensors 2021;21:547–53.

88 Tracy MF, Manchester C, Mathisson MA, et al. Adherence to a hypoglycemia protocol in hospitalized patients: a retrospective analysis. Nurs Res 2021;70:15–23.

89 Unger RH, Orlic L. The essential role of glucagon in the pathogenesis of diabetes mellitus. Lancet 1975;1:14–16.

90 Glucagon rDNA origin (GlucGen) and recombinant LH. (NO. 12 in a series of articles to promote a better understanding of the use of genetic engineering). J Biotechnol 2000;76:185–9.

91 Chelliah A, Burge MR. Hypoglycemia in elderly patients with diabetes mellitus: causes and strategies for prevention. Drugs Aging 2004;21:511–53.

92 Pearson T. Glucagon as a treatment of severe hypoglycemia: safe and efficacious but underutilized. Diabetes Educ 2008;34:128–34.

93 Eli Lilly Inc. Glucagon (for injection, recombinant origin) [package insert]. Indianapolis, IN, 2005.

94 Novo Nordisk Inc. Glucagon hypokit [package insert]. Princeton, NJ, 2005.

95 Graf CJ, Woodworth JR, Seger ME, et al. Pharmacokinetic and glucomynamic comparisons of recombinant and animal-source glucagon after IV, IM, and SC injections in healthy volunteers. J Pharm Sci 1999;88:991–5.

96 American Diabetes Association. Standards of medical care in diabetes—2014. Diabetes Care 2014;37 Suppl 1:S14–80.

97 Harrism G, Diment A, Sulway M, et al. Glucagon administration - underevaluation and undertaught. Pract Diab Int 2018;25:18–22.

98 Murata T, Okazaki K, Yanagisawa K, et al. Glucagon underutilized among type 1 diabetes mellitus patients in Japan. Diabetes Technol Ther 2013;15:748–50.

99 Mitchell BD, Harb H, Sturdy IM, et al. Glucagon prescription patterns in patients with diabetes mellitus and type 2 diabetes with newly prescribed insulin. Endocr Pract 2016;22:123–35.

100 Yale J-F, Dulude H, Egert M, et al. Faster use and fewer failures with Needle-Free nasal glucagon versus injectable glucagon in severe hypoglycemia rescue: a simulation study. Diabetes Technol Ther 2017;19:243–32.

101 Vilovic M, Kurir TT, Novak A, et al. Hypoglycemia and glucagon utilization in insulin-treated diabetic patients. Exp Clin Endocrinol Diabetes 2020;128:493–8.

102 Hove BH, Singh M, Vild-Remo C, et al. Acute management and outcomes of patients with diabetes mellitus presenting to Canadian emergency departments with hypoglycemia. Can J Diabetes 2015;39 Suppl 4:9–18.

103 Betten DP, Castle DJ, Hughes MJ, et al. Frequency of return visits to the emergency department in patients discharged following hypoglycemia episodes. Int J Emerg Med 2018;11:28.

104 Hawkes CP, De Leon DD, Rickels MR. Novel preparations of glucagon for the prevention and treatment of hypoglycemia. Curr Diab Rep 2019;19:97.

105 Pontiroli AE. Intranasal glucagon: a promising approach for treatment of severe hypoglycemia. J Diabetes Sci Technol 2015;9:38–43.

106 Sherr JL, Ruedy KJ, Foster NC, et al. Glucagon nasal powder: a promising alternative to intramuscular glucagon in youth with type 1 diabetes. Diabetes Care 2016;39:555–62.

107 Cersosimo ECM, Kinzel JH, et al. A phase 2 comparative safety PK/PD study of stable nonaqueous glucagon (G-Pre) vs. lilly glucagon for treatment of severe hypoglycemia. Diabetes Care 2014;63:LB1.

108 Hövelmann U, Bysted BV, Mourtzou U, et al. Pharmacokinetic and pharmacodynamic characteristics of Dasiglucagon, a novel soluble and stable glucagon analog. Diabetes Care 2014;37:931–7.

109 Newsngaret B, Ammons S, Phadnis N, et al. Development of a highly stable, nonaqueous glucagon formulation for delivery via infusion pump systems. J Diabetes Sci Technol 2015;9:24–33.

110 DLJ-R GL. Creating glucagon standing order to treat severe hypoglycemia in long-term care. Annals of long-term care. 2021;45:S244–53.

111 Chico A, Vidal-Rios P, Subirà M, et al. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemia in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. Diabetes Care 2003;26:1153–7.

112 Grunberger G, Handelsman Y, Bloomgarden ZT, et al. American association of clinical endocrinologists and American College of endocrinology 2018 position statement on integration of insulin pumps and continuous glucose monitoring in patients with diabetes mellitus. Endocr Pract 2019;25:302–8.

113 Vigersky R, Shrivastav M. Role of continuous glucose monitoring for type 2 diabetes in management and research. J Diabetes Complications 2017;31:280–7.

114 Rodríguez LM, Knight RJ, Hepulilla RA. Continuous glucose monitoring in subjects with type 2 diabetes after simultaneous pancr-eatic-kidney and kidney-alone transplantation. Diabetes Technol Ther 2010;12:347–51.

115 Schuapp L, Donsa K, Neubauer KM, et al. Taking a Closer Look-Continuous Glucose Monitoring in Non-Critically Ill Hospitalized Patients with Type 2 Diabetes Mellitus Using Basal-Bolus Insulin Therapy. Diabetes Technol Ther 2015;17:611–8.

116 Gomez AM, Umpierrez GE. Continuous glucose monitoring in insulin-treated patients in non-ICU settings. J Diabetes Sci Technol 2014;8:930–6.

117 Gomez AM, Umpierrez GE, Muñoz OM, et al. Continuous glucose monitoring versus capillary point-of-care testing for inpatient glycemic control in type 2 diabetes patients hospitalized in the general ward and treated with a basal bolus insulin regimen. J Diabetes Sci Technol 2015;10:325–31.

118 Gu W, Liu Y, Chen Y, et al. Multicentre randomized controlled trial with sensor-augmented pump vs multiple daily injections in hospitalized patients with type 2 diabetes in China: time to reach target glucose. Diabetes Metab 2017;43:359–63.

119 Burt MG, Roberts GW, Aguilar-Loza NR, et al. Brief report: comparison of continuous glucose monitoring and finger-prick blood glucose levels in hospitalized patients administered basal-bolus insulin. Diabetes Technol Ther 2013;15:241–5.

120 Spanakos EK, Kevitt DL, Siddiqui T, et al. The effect of continuous glucose monitoring in preventing inpatient hypoglycemia in general wards: the glucose telemetry system. J Diabetes Sci Technol 2018;12:20–5.

121 Singh LG, Satyarenggga M, Marcano I, et al. Reducing inpatient hypoglycemia in the general wards using real-time continuous glucose monitoring: the glucose telemetry system, a randomized clinical trial. Diabetes Technol Ther 2020;43:736–43.

122 Singh LG, Kevitt DL, Satyarenggga M, et al. Continuous glucose monitoring in general wards for prevention of hypoglycemia: results from the glucose telemetry system pilot study. J Diabetes Sci Technol 2020;14:783–90.

123 Cardona S, Gomez PC, Vellanti P, et al. Clinical characteristics and outcomes of symptomatic and asymptomatic hypoglycemia in hospitalized patients with diabetes. BMJ Open Diabetes Res Care 2018;6:e000607.

124 Walla A, Umpierrez GE, Rushakoff RJ, et al. Consensus statement on inpatient use of continuous glucose monitoring. J Diabetes Sci Technol 2017;11:1036–44.

125 Krinsley JS, Chase JG, Gunst J, et al. Continuous glucose monitoring in the ICU: clinical considerations and consensus. Crit Care 2017;21:197.

126 Galindo RJ, Allego G, Klonoff DC, et al. Implementation of continuous glucose monitoring in the hospital: emergent considerations for remote glucose monitoring during the COVID-19 pandemic. J Diabetes Sci Technol 2020;14:822–32.

127 Thigpen GM, Spanel KM, Migdal AL, et al. Accuracy of Dexcom G6 continuous glucose monitoring in Non-Critically Ill hospitalized patients with diabetes. Diabetes Care 2021;44:1641–6.

BMJ Open Diab Res Care 2022;10:e002705. doi:10.1136/bmjdrctc-2021-002705

下行部分没有显示，可能被裁剪或超出页面范围。
Pilla SJ, Segal JB, Alexander GC, et al. Differences in national diabetes treatment patterns and trends between older and younger adults. J Am Geriatr Soc 2019;67:1066–73.

Halimi S, Raccah D, Schweizer A, et al. Role of vildagliptin in managing type 2 diabetes mellitus in the elderly. Curr Med Res Opin 2010;26:1647–56.

Haas LB, Burke SD. Diabetes Management in Long-Term Settings: A Clinician’s Guide to Optimal Care for the Elderly. American Diabetes Association, 2014.

Yale J-F, Arorda VR, Charbonnel B, et al. Glycaemic control and hypoglycaemia risk with insulin glargine 300 U/mL versus glargine 100 U/mL: A patient-level meta-analysis examining older and younger adults with type 2 diabetes. Diabetes Metab 2020;46:110–8.

Klitzel R, Harris SB, Baron H, et al. A randomized controlled trial comparing efficacy and safety of insulin Glargine 300 Units/ml versus 100 Units/mL in older people with type 2 diabetes: results from the senior study. Diabetes Care 2018;41:1672–80.

Umpierrez GE, Smiley D, Herrmayr K, et al. Randomized study comparing a Basal-bolus with a basal plus correction insulin regimen for the hospital management of medical and surgical patients with type 2 diabetes: basal plus trial. Diabetes Care 2013;36:2169–74.

Franchin A, Maran A, Bruttomesso D, et al. The GesTIO protocol experience: safety of a standardized order set for subcutaneous insulin regimens in elderly hospitalized patients. Aging Clin Exp Res 2017;29:1087–93.

Umpierrez GE, Pasquel FJ. Management of inpatient hyperglycemia and diabetes in older patients. Diabetes Care 2017;40:509–17.

Rena G, Harvey A, Pearson ER. The mechanisms of action of metformin. Diabetologia 2017;60:1577–85.

Crowley MJ, Diamantidis CJ, McDuffie JR, et al. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. Ann Transl Med 2017;5:161–99.

Chamberlain JJ, Johnson EL, Leal S, et al. Efficacy and safety of metformin in the management of type 2 diabetes mellitus in older adults: a systematic review for the development of recommendations to reduce potentially inappropriate prescribing. BMC Geriatr 2017;17:227.

Brodsky HW, Bloch J, Braithwaite SS, et al. American association of clinical endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract 2007;13 Suppl 1:1–68.

Goergen SK, Rumbold G, Compton G, et al. Systematic review of current guidelines, and their evidence base, on risk of lactic acidosis after administration of contrast medium for patients receiving metformin. Radiology 2010;254:261–9.

Kodner C, Anderson L, Pohlgeers K. Glucose management in hospitalized patients. Am Fam Physician 2017;96:648–54.

Lv W, Wang Y, Zhang B, et al. Characteristics of sulfonylurea and Glinides. Curr Top Med Chem 2020;20:37–56.

Ashcroft F. Mechanisms of the glycaemic effects of sulfonylureas. Horm Metab Res 1996;28:456–63.

Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycaemia and risks of vascular events and death. N Engl J Med 2010;363:1410–8.

Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011;154:602–13.

Scheen AJ. Options for combination therapy in type 2 diabetes: 1) likes Alzheimer’s disease. BMJ Open Diab Res Care 2022;10:e002705. doi:10.1136/bmjdrc-2021-002705

Papa G, Fedele V, Rizzo MR, et al. Safety of type 2 diabetes treatment with repaglinide compared with glibenclamide in elderly people: a randomized, open-label, two-period, cross-over trial. Diabetes Care 2006;29:1918–20.

Stuart K, Adderley NJ, Marshall T, et al. Predicting inpatient hypoglycaemia in hospitalized patients with diabetes: a retrospective analysis of 9584 admissions with diabetes. Diabet Med 2017;34:1385–91.

Heaton PC, Desai VCA, Kelton CML, et al. Sulfonylurea use and the risk of hospital readmission in patients with type 2 diabetes. BMC Endocr Disord 2016;16:4.

National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis 2012;60:850–86.

By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel, American geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015;63:2227–46.

Albertini J-P, McMorn SO, Chen H, et al. Effect of rosiglitazone on factors related to endothelial dysfunction in patients with type 2 diabetes mellitus. Atherosclerosis 2007;195:159–66.

Day C. Thiazolidinediones: a new class of antidiabetic drugs. Diabet Med 1999;16:179–92.

Jurgens CY, Goodlin S, Dolansky M, et al. Heart failure management in skilled nursing facilities: a scientific statement from the American heart association and the heart failure Society of America. Circ Heart Fail 2015;8:655–87.

Wang HE, Shah MN, Allman RM, et al. Emergency department visits by nursing home residents in the United States. J Am Geriatr Soc 2011;59:1864–72.

Wolverton D, Blair I. Fracture risk associated with common medications used in treating type 2 diabetes mellitus. Am J Health Syst Pharm 2017;74:1143–51.

Guja C, Guja L, Miulescud RD. Effect of type 2 diabetes medications on fracture risk. Ann Transl Med 2019;7:580.

Dornmuth CR, Carney G, Carleton B, et al. Thiazolidinediones and fractures in men and women. Arch Intern Med 2009;169:1395–402.

Bischoff H. The mechanism of alpha-glucosidase inhibition in the management of diabetes. Clin Invest Med 1995;18:303–11.

Chiasson JL, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. Ann Intern Med 1994;121:928–35.

Charbonnel B, Karakas A, Liu J, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care 2006;29:2638–43.

Bosi E, Carmisasca RP, Colober C, et al. Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Care 2007;30:890–5.

Silverberg AB, Libary KPL. Oral diabetic medications and the geriatric patient. Clin Geriatr Med 2008;24:541–9. viii.

Norns SL, Lee N, Thakurta S, et al. Exenatide efficacy and safety: a systematic review. Diabet Med 2009;26:837–46.

Jia X, Alam M, Ye Y, et al. Glp-1 receptor agonists and cardiovascular disease: a meta-analysis of recent cardiac outcome trials. Cardiovasc Drugs Ther 2018;32:65–72.

Del Olmo-Garcia MJ, Merino-Torres JP. Glp-1 receptor agonists and cardiovascular disease in patients with type 2 diabetes. J Diabetes Res 2018;2018:1–12.

Zavattaro M, Caputo M, Samà MT, et al. One-Year treatment with liraglutide improved renal function in patients with type 2 diabetes: a pilot prospective study. Endocrinology 2015;50:620–6.

von Scholten BJ, Hansen TW, et al. Liraglutide analogue liraglutide in Alzheimer’s disease: a randomized double-blind placebo controlled trial. Exp Clin Invest Med 2017;34:1385–91.

Fonseca V, Kelley DE, Cefalu W, et al. Hypoglycemic potential of nateglinide versus glyburide in patients with type 2 diabetes mellitus. Metabolism 2004;53:1331–5.

Bailey T. Options for combination therapy in type 2 diabetes: comparison of the ADA/AESD position statement and AACE/ACE algorithm. Am J Med 2013;126:S10–20.

Schwarz LS, Gerich JE, Marcellari A, et al. Nateglinide, alone or in combination with metformin, is effective and well tolerated in treatment-naïve elderly patients with type 2 diabetes. Diabetes Obes Metab 2008;10:652–60.

Omori K, Nomoto H, Nakamura A, et al. Reduction in glucose fluctuations in elderly patients with type 2 diabetes using repaglinide: a randomized controlled trial of repaglinide vs sulfonylurea. J Diabetes Investig 2019;10:367–74.
Emerging technologies, pharmacology and therapeutics

study protocol for a randomised controlled trial (ELAD study). *Trials* 2019;20:191.

176 Rowlands J, Heng J, Newsholme P, et al. Pleiotropic effects of GLP-1 and analogs on cell signalling, metabolism, and function. *Front Endocrinol* 2018;9:672.

177 Thomas MC. The potential and pitfalls of GLP-1 receptor agonists for renal protection in type 2 diabetes. *Diabetes Metab* 2017;43 Suppl 1:2S20–2.

178 Reusch J, Stewart MW, Perkins CM, et al. Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonist albiglutide (harmony 1 trial): 52-week primary endpoint results from a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes mellitus not controlled on pioglitazone, with or without metformin. *Diabetes Obes Metab* 2014;16:1257–64.

179 Filippatos TD, Yasis, Ann Intern Med 2013;158:24–32. Effects of GLP-1 receptor agonists. *Rev Diabet Stud* 2014;11:202–30.

180 Russell-Jones D, Cuddihy RM, Hanefeld M, et al. Efficacy and safety of exenatide once Weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. *Diabetes Care* 2012;35:252–8.

181 ten Kulve JS, Veitman DJ, van Bloemendaal L, et al. Endogenous GLP1 and GLP1 analogue alter CNS responses to palatable food in the diabetic Kidney-From mechanisms to clinical outcome. *Clin J Am Soc Nephrol* 2017;12:700–10.

182 Bashier A, Khalifa AA, Rashid F, et al. Sodium-glucose cotransporter 2 inhibitors in reducing glycated hemoglobin and weight in Emirati patients with type 2 diabetes. *J Clin Med Res* 2014;16:1257–64.

183 Peters AL, Buschur EO, Buse JB, et al. Infections associated with sodium-glucose cotransporter-2 inhibitors: a potential complication of treatment with sodium-glucose cotransporter-2 inhibition. *Diabetes Care* 2015;38:1887–93.

184 Cahn A, Mosenzon O, Wiviott SD, et al. Efficacy and safety of dapagliflozin in the elderly: analysis from the DECLARE-TIMI 58 study. *Diabetes Care* 2020;43:468–75.

185 Monteiro P, Bergensdal RM, Towal E, et al. Efficacy and safety of empagliflozin in older patients in the EMPA-REG OUTCOME® trial. *Age Ageing* 2019;48:859–66.

186 Smith PW, Bennett G, Bradley S, et al. SHEA/APIC guideline: infection prevention and control in the long-term care facility. *Am J Infect Control* 2008;36:504–35.

187 Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the infectious diseases Society of America. *Clin Infect Dis* 2010;50:625–63.

188 Scheen AJ. An update on the safety of SGLT2 inhibitors. *Expert Opin Drug Saf* 2019;18:295–311.

189 Scheen AJ. Efficacy and safety profile of SGLT2 inhibitors in patients with type 2 diabetes and chronic kidney disease. *Expert Opin Drug Saf* 2020;19:243–56.

190 Gorina Y, Schappert S, Bercovitz A. Prevalence of incontinence among older Americans. *Vital Health Stat 1* 2014;3:1–33.

191 Hadjadi S, Rosenstock J, Meinicke T, et al. Initial combination of Empagliflozin and metformin in patients with type 2 diabetes. *Diabetes Care* 2016;39:1718–28.

192 Goldstein BJ, Feinglos MN, Lunceford J, et al. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. *Diabetes Care* 2007;30:1979–87.

193 DeFronzo RA, Lewin A, Patel S, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. *Diabetes Care* 2015;38:384–93.

194 Kim NH, Lim S, Kwak SH, et al. Efficacy and tolerability of novel triple combination therapy in drug-naive patients with type 2 diabetes from the TRIPLE-AXEL trial: protocol for an open-label randomised controlled trial. *BMJ Open* 2018;8:e022448.

195 David J, Fonseca V, et al. Use and effectiveness of a fixed-ratio basal insulin/glucagon-like peptide-1 receptor agonists combination products be considered? *J Diabetes Complications* 2019;33:107473.

196 Price H, Blüher M, Prager R, et al. Use and effectiveness of a fixed-ratio combination of insulin degludec/liraglutide (IDegLira) in a real-world population with type 2 diabetes: results from a European, multicentre, retrospective chart review study. *Diabetes Obes Metab* 2018;20:954–62.

197 Home P, Blon J, Kalra S, et al. Insulin glargine/lixisenatide fixed-ratio combination (iGlarLixi) compared with premix or addition of meal-time insulin to basal insulin in people with type 2 diabetes: a systematic review and Bayesian network meta-analysis. *Diabetes Obes Metab* 2020;22:2179–88.

198 Rizza R, Piccucci G, Mavilino M, et al. Effect of deprecising in elderly patients with type 2 diabetes: iDegLira might improve quality of life. *Biomed Pharmacother* 2021;144:112341.