 doi:10.20944/preprints202108.0065.v1

Review

Optimal type 2 diabetes mellitus management and active ageing

Alessia Maria Calabrese 1, Valeria Calsolaro 1, Sara Rogani 1, Chukwuma Okoye1, Nadia Caraccio 1, Monzani Fabio1*

[1] Geriatrics Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
* Correspondence: fabio.monzani@unipi.it; Tel.: +393337733135 (Geriatrics Unit, Department of Clinical and Experimental Medicine University of Pisa, Via Savi 10, 56126 – Pisa, Italy)

Abstract

Type two diabetes mellitus (T2DM) represents a chronic condition with increasing prevalence worldwide among the older population. T2DM condition increases the risk of micro and macrovascular complications as well as the risk of geriatric syndromes as falls, fractures and cognitive impairment. The management of T2DM in the older population represents a challenge for the clinician, and a Comprehensive Geriatric Assessment should always be prioritized, in order to tailor the glycate haemoglobin target according to functional and cognitive status comorbidities, life expectancy and type of therapy. According to the most recent guidelines, older adults with T2DM should be cathegorized in three groups: healthy patients with good functional status, patients with complications and reduced functionality and patients at the end of life; for each group the target for the glycemic control is different, also according to the type of treatment drug. The therapeutic approach should always begin with lifestyle changes; after that, several lines of therapies are available, with different mechanism of action and potential effect other than glucose level reduction. Particular interest is growing around sodium-glucose cotransporter-2 inhibitors, due to their effect on the cardiovascular system. In this review we evaluate the therapeutic options available for the treatment of older diabetic patients, to ensure a correct treatment approach.

Keywords: type 2 diabetes mellitus (T2DM), older people; frailty; antidiabetic drugs; comprehensive geriatric assessment; therapeutic targets; hypoglicemia

1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) among the older people is growing in relation to global population ageing. According to the latest data of the International Diabetes Federation (IDF), in 2019 the prevalence of diabetes in people older than 65 years was around 19%; thus, over 130 milion older adults were affected by diabetes with an estimated further increase to 276.2 million by 2045 [1].

Beyond the higher risk of well known macrovascular and microvascular complications [2], older adults with diabetes are also at greater risk of geriatric syndromes compared to not diabetic. As a matter of fact, due to pain, impaired vision, motor and sensory neuropathy, T2DM is associated with 64% increased risk of falls (in particular for patients treated with hypoglicemic drugs like insulin)[3], and fragility fractures[4].

Older people with T2DM are more likely to develop cognitive impairment, ranging from mild cognitive impairment (MCI) to overt dementia[5], and both hypo- and hyperglycemia seem to be related to neurocognitive dysfuncion[6,7].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 August 2021 doi:10.20944/preprints202108.0065.v1

Moreover, the high prevalence of urinary incontinence, chronic pain[2,8], delirium[9,10] and depression[2,8,9] among diabetic older adults negatively affects the quality of life.
These conditions, along with compliance issues, polipharmacy and, often, inadequate hydratation and nutrition, have a negative impact on older adults' functional status, leading to higher risk of disability and institutionalisation[2,8,9,11].
Optimal T2DM management in older people represents a challenge, given the extreme heterogeneity of this population in terms of functional and cognitive status, comorbidities and life expectancy and, a comprehensive geriatric assessment (CGA) should be always performed in order to assess the best therapeutic approach.
In this Review, we discuss CGA-based treatment goals in older people and evaluate the current antidiabetic therapies.
The search was conducted in PubMed, with the keywords "Diabetes mellitus, older people, older patients, antidiabetics, metformin, gliflozins, insulin, DPP4-I, GLP-1R agonists"; meta-analysis, randomised clinical trials, reviews and abstracts in English published within the last 10 years were selected and reviewed. We also included current guideline recommendations.

Type 2 Diabetes Mellitus: treatment targets

Despite the heavy social and economic burdens, older diabetic population (especially the ones with higher degree of frailty) was historically underrepresented in clinical randomized trials[12–14]. Though, in the last 15 years, several organisations have endorsed the concept of tailoired diabetes care on the basis of functional status, life-expectancy and risk of drug-induced hypoglicemia.
The glycated hemoglobin (HbA1c) level generally recommended in older adults receiving antidiabetic drugs not associated with hypoglycemia is < 7 – 7.5%, similar to that advised for younger people according to the current standards of care of the American Diabetes Association (ADA)[15], to the guidelines of the International Diabetes Federation (IDF)[16] and to the position paper developed by Italian Diabetes Society (SID) and Italian Society of Gerontology and Geriatrics (SIGG)[17].
Nevertheless, this is a simplified vision of the clinical decision-making; as a matter of fact, older adults should be further classified through CGA, especially in older patients receiving insulin or other drugs potentially associated with hypoglicaemia.
According to ADA, older adults with diabetes can be categorized into three groups: healthy patients with good functional status, patients with complications and reduced functionality and vulnerable patients at the end of life. The first group includes patients with few comorbidities, good cognitive and functional status and long life expectancy and may be treated using therapeutic strategies and targets similar to those for young diabetic adults, aiming for values of HbA1c < 7 – 7.5%, fasting or preprandial glucose 80-130 mg/dL and bedtime glucose 80-180 mg/dL. Patients with at least three coexisting chronic illnesses, cognitive or functional impairment or advanced diabetes complications belong to the second group, andmay benefit from less stringent glycemic control (HbA1c < 8%, fasting or preprandial glucose 90-150 mg/dL, bedtime glucose 100-180 mg/dL).
The last group is composed by older adults receiving palliative care and end-of-life care, and/or with cognitive or functional disability. For such patients, physicians should apply strategies to preserve quality of life, avoid hypoglycemia and symptomatic hyperglycemia (avoid reliance on HbA1c, fasting or preprandial glucose 100-180 mg/dL, bedtime glucose 110-200 mg/dL).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 August 2021 doi:10.20944/preprints202108.0065.v1

Some patients will not fit into a particularly category and it will be necessary to draw up individualized care plans. Patient and caregiver preferences should always be considered and periodically reassessed, together with health status, in order to adapt to changes over time[15]. Similarly to ADA, IDF identified three main categories of older adults with diabetes. The first one is characterized by people functionally independent with a HbA1c target of 7 - 7.5%. The second group includes functionally dependent people with higher risk of hypoglycemia or hyperglycemia, poor self-management ability and increased risk of hospitalization. For such individuals, the recommended target of HbA1c is 7 – 8% up to 8.5%, avoiding drugs that might cause nausea or gastrointestinal disorders and drugs with increased risk of hypoglycemia. The third category consists of patients approaching the end of life, therefore the main goal is to avoid symptomatic hypo- and hyperglycemia, considering withdrawal of therapy (including insulin)[16]. Treatment goals according to patients' functional status and guidelines is summarised in Table 1.

Partially at odds with the above described guidelines, beside assessing frailty status, the position statement developed by SID and SIGG suggests to tailor glycemic target on the basis of the chosen antidiabetic aiming for HbA1c < 7% when using drugs with low potential of hypoglycemia (metformin, gliflozins, incretin-based drugs and acarbose), which should be be always considered the preferred first line drugs for older people. If the use of antidiabetic drugs with high risk of hypoglycemia is required (sulfonylureas, repaglinide, insulin) a less restrictive target should be pursued (HbA1c up to 8% for patients with impaired functional and cognitive status)[17].

It is extremely important, however, to consider the potential limitations of HbA1c. Even though the measurement of HbA1c is the standard biomarker for glycemic control, it may not be reliable in particular situations such as anemia or other conditions that influence red blood cell turnover (hemoglobinopathies, hemodialysis, recent transfusions, erythropoietin therapy, chronic liver diseases). In these settings, glucose fingerstick or continuous glucose monitoring (CGM) should be used[18].

In order to improve clinical outcomes, educational programs should be patient- and caregiver-centered. Information and instructions should be always given in clear and simple way. Patients and caregivers should be trained to recognize signs and symptoms of hypoglycemia and should be encouraged to always have glucose or carbohydrate containing food at their disposal. The number of daily glucose checks should be assessed in relation to the antidiabetic drug, keeping a record of blood sugar to show to the healthcare team even through telemedicine[16,17,19].

T2DM treatment options in older patients

Lifestyle changes

Similarly to younger patients, lifestyle modification represents the first-line treatment of T2DM in older adults[15,16,20,21].

One of the primary causes of T2DM, at least in the Western Countries, is believed to be the energy-dense diet and sedentary life, directly responsible for the obesity surge as well. However, the increased visceral obesity, rather than the higher BMI, seems to be related to T2DM development[22]. Diet is certainly one of the most involved factors in T2DM development; as a general view, plant food or low energy density food are less associated with diabetes compared to

 doi:10.20944/preprints202108.0065.v1

meat and high density energy food; refined grains and sugar sweetened drinks are associated with higher risk of diabetes, and nuts daily consumption seems to be somehow protective [22] . The studies aiming at investigating the diet impact on the risk of diabetes are widely available. It is important to notice that several dietary studies showed improvement in metabolic control, which could actually be due to the behavioral changes in at least the first phases of the study, when the volunteers change the eating habit and lose weights as a possible "study effect" [22]. Unfortunately, poor compliance has been seen in long-term studies, but few studies have been conducted with interesting results. In particular, the PREDIMED trial compared the Mediterranean diet supplemented with either olive oil or nuts compared to low fat diet [23]. After 4 years, the progression to T2DM in the Mediterranean diet was 50% of that of the low fat diet control group [23]. The study, which did not have any weight loss requirement or outcome, suggested that some components of the Mediterranean diet would help decreasing the risk of developing diabetes.

Nutritional status should always be assessed on admission and periodically with the purpose of drawing up an individualized nutrition plan. In overweight/obese patients with high functional status, a 5-7% weight loss should be promoted in order to improve glycemic control. Patients with a higher degree of frailty should follow a diet rich in protein and energy to prevent malnutrition and weight loss.

Strict dietary restrictions should be avoided in older adults with severe comorbidities and cognitive or functional disability[15,16,21]. Spreading carbohydrates throughout the day may be a reasonable strategy in order to reduce blood glucose spikes.

Functionally independent older adults should be encouraged to perform moderate aerobic activity of at least 30 minutes for 5 days each week[15,16,20,21]. Prior to physical activity, exercise capacity, blood pressure and heart rate should be evaluated and further test should be performed in patients at high risk of cardiovascular disease. Low intensity home-based exercise plan should be suggested to functional dependent patients in order to improve physical performance, flexibility and balance[16].

Pharmacologic therapy

Lifestyle changes may be unsufficient to achieve adequate glycemic control, therefore pharmacological therapy should be started.

Metformin

The biguanid metformin is indicated as first-line therapy for the treatment of type 2 diabetes at any age. It acts inhibiting gluconeogenesis in the liver and increasing peripheral insulin sensitivity. Compared with sulfonylureas, metformin is effective and more safe, presenting a reduced risk of adverse events such as hypoglycaemia. Nevertheless, its use has been discouraged in patients with chronic kidney disease, hepatic impairment and congestive heart failure due to increased risk for lactic acidosis, though it is a rare condition[11,15,24,25]. Metformin may be safely used in patients with preserved renal function (1000 mg/day the maximal suggested dose) but is contraindicated in case of estimated glomerular filtration rate (eGFR) less than 30 ml/min. In addition, it can be initiated when eGFR is 45-60 ml/min and can be continued when eGFR is 30-45 ml/min, although

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 August 2021 doi:10.20944/preprints202108.0065.v1

with a maximal suggested dose of 1000 mg/day[15,24]. Metformin may be temporarily discontinued before procedures, during hospitalizations, and when acute illness may compromise renal or liver function.

Adverse effects are common and mainly involve gastrointestinal tract with bloating, abdominal discomfort and diarrhea, which can be mitigated by gradual dose titration. Additionally, metformin can cause a reduction in appetite involuntary weight loss, which can be problematic for some older adults. Reduction or elimination of metformin may be necessary for patients experiencing persistent gastrointestinal side effects. The use of metformin has also been associated with vitamin B12 deficiency, so periodic testing of vitamin B12 levels should be performed especially in older people on long-term metformin therapy[26–28].

As a matter of fact, metformin, either in monotherapy or in combination with other glucose-lowering medications, is generally well tolerated and, the improved glycemic control seems to be associated with decreased total serum cholesterol and serum LDL cholesterol, cardiovascular benefits and lower risk for all-cause mortality in elderly diabetic populations[29,30].

Insulin secretagogues: sulfonylureas and glitinides

Sulfonylureas (SUs) and glitinides are the oldest class of oral antihyperglycemic drugs, still commonly used in clinical practice. They work by increasing insulin secretion in pancreatic β-cells, binding ATP-sensitive Potassium (KATP) channels of plasma membranes.

SUs and other insulin secretagogue are associated with high rates of hypoglycaemia and major weight gain, thus they should be possibly avoided and used with caution in the geriatric populations. Short-acting SUs such as gliclazide should be preferred as safer option, especially in patients with renal impairment, while long-acting sulfonylureas should definitely be avoided in older people, due to their higher risk of hypoglycaemia[15,31–33].

Thiazolidinediones

Thiazolidinediones (TZDs), such as rosiglitazone and pioglitazone, are oral insulin-sensitizing glucose-lowering medication, acting as agonists of the peroxisome proliferator-activated receptor γ (PPARγ).

The most important side effects are weight gain and fluid retention, therefore their use has been widely limited, given the high prevalence and incidence of heart failure and chronic kidney disease in patients with diabetes mellitus[11,15,24].

Even if the pathological mechanism remains unclear, thiazolidinediones have also been associated with loss of bone mineral density (BMD) and increased risk of non-osteoporotic bone fractures, thus further limiting their use in the older populations[34]. Thus, if used at all, thiazolidinediones should be used very cautiously in those patients with or at risk for congestive heart failure, osteoporosis and/or falls or fractures.

Incretin-based therapies

Incretins are a group of hormones released by gut after nutrient ingestion that promote glucose-dependent insulin secretion, glucagon inhibition, delay in gastric emptying and appetite reduction. Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are the most important incretins and they are rapidly inactivated by dipeptidyl peptidase-4 (DPP-4)[35,36].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 August 2021 doi:10.20944/preprints202108.0065.v1

Given their biological action, incretins have become an attractive target for the treatment of T2DM and this led to the development of DPP-4 inhibitors and degradation-resistant GLP-1-receptor (GLP-1R) agonists.

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors are generally well tolerated in older adults. They can be administered once daily, have few side effects and low risk of hypoglycemia[37–42].

DPP-4 inhibitors have proven to be safe in terms of cardiovascular (CV) events, CV death and all-cause mortality [41–44]. Several concerns have been raised about the increased risk of hospitalisation for heart failure (HF), in particular the SAVOR-TIMI 53[42] trial reported a significant increase in hospitalisations for HF in patients treated with saxagliptin (3.5 vs. 2.8%; HR 1.27; 95% CI 1.07–1.51; p = 0.007). An increased risk was also found with alogliptin in patients with no previous history of HF in a post-hoc analysis of the EXAMINE trial[45] while the TECOS[41], VIVIDD[46] and CARMELINA[47] trials showed no increased risk in patients receiveing, respectively, sitagliptin, vildagliptin and linagliptin.

DPP-4 inhibitors have also been associated with higher risk of pancreatitis[48,49] though a recent meta-analysis failed to detect any relation to pancreatits, even if it cannot be excluded in patients at higher risk (history of pancreatitis, alcohol abuse, hypertriglyceridemia, etc)[50]. Pharmacovigilance reports suggested an association also with pancreatic cancer[48,49] nevertheless available data, although insufficient because of limited duration of trials, seem to exclude such relationship[50–52].

DPP-4 inhibitors are able to lower HbA1c levels by 0.5-0.8%[53–55], therefore monotherapy may be used in patients with HbA1c value close to the target.

The most widely used dual combination is the one with metformin; however, DPP-4 inhibitors can also be added to metformin and Sodium-glucose Cotransporter-2(SGLT-2) inhibitors or to metformin and insulin. Concomitant use of DPP-4 inhibitors and GLP-1R agonists is not recommended due to scant synergistic effects[56].

Glucagon-like peptide 1 receptor (GLP-1R) agonists

GLP-1R agonists are highly effective, capable of lower HbA1c by 1% up to 1.8%[57] and well tolerated in older adults without causing hypoglycemia when used in monotherapy[58–63].

Several trials demonstrated cardiovascular benefits. In the Harmony Outcomes study, the addition of albiglutide to standard care versus placebo reduced the risk of major cardiovascular events (MACE) by 22%[64]. In the LEADER trial, liraglutide reduced the risk of MACE by 13%[65] and a subsequent post-hoc analysis showed a 34% risk reduction of MACE in patients 75 years or older[66].

Semaglutide and dulaglutide were also associated with decreased risk of cardiovascular events, as reported in the SUSTAIN-6[67] and REWIND[68] trials. Oral semaglutide resulted similar to placebo in terms of CV outcomes[69]; neutral effect on cardiovascular outcomes were also described in the ELIXA trial, investigating the effect of lixisenatide in patients with T2DM and recent acute coronary event (within 180 days)[70]. Similarly, the EXSCEL trial showed that the incidence of MACE did not differ significantly between patients treated with exenatide compared to placebo[71].

However, a recent meta-analysis reported that treatment with GLP-1R agonists reduces MACE by 12% (HR 0.88, 95% CI 0.82 – 0.94; p < 0.0001)[72]. In terms of renal outcomes, this class of drugs have

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 August 2021 doi:10.20944/preprints202108.0065.v1

proven to lower kidney events, mainly reducing macroalbuminuria, although there was a nonsignificant effect of GLP1-R agonists on the risk of doudbling serum creatinine[73].
While the evidence for this class for older patients continues to grow, there are a number of practical issues that should be considered for older patients. GLP-1R agonists are administered through injection (except for oral semaglutide), therefore older adults with impairment of vision, functional or cognitive status could experience some difficulties; on th other hand, the once-weekly formulation could be a valid option. Moreover, they are related to nausea and weight loss, in particular at the beginning of the treatment, hence they are not suitable for frail malnourished patients[15].

Sodium-glucose cotransporter 2 inhibitors

Sodium-glucose cotransporter 2 inhibitors (SGLT2-i) represent a novel class of oral anti-diabetic agents, emerged as an important therapeutic option for the management of type 2 diabetes. SGLT-I inhibitors act inducing glycosuria, and consequently osmotic diuresis, by inhibiting the cotransport of glucose coupled with sodium in the renal proximal tubules; the glucose excreted, acts like a non-readsorbible substance under SGLT2 inhibitors administration[74]. Due to this mechanism, SGLT2-i lower blood glucose levels independently of insulin, resulting in insulin secretion reduced. A recent review showed that the use of SGLT2-i in type 2 diabetes on insulin had major advantages in terms of insulin dose reduction[75].
Nevertheless, the diuretic action induced by SGLT2-i is actually mainly based on secondary inhibition in the loop of Henle. In order to keep the tubular fluid isotonic to blood, water is reabsorbed from the proximal tubules, which are highly permeable to water, while the reabsorption of sodium and chloride proceeds through the proximal tubules with different multiple mechanisms, even after the administration of SGLT2 inhibitors. The proximal tubular fluid is transferred to the loop of Henle with a progressively reduced concentration of sodium and chloride, resulting in a significant inhibition of reabsorption due to a decrease in chloride concentration, probably because chloride plays an essential role for the functioning of sodium-chloride-potassium cotransporters (NKCC)[76,77].
Basically, SGLT2 inhibitors act as the loop diuretics reducing body fluid volume that may partly explain their cardiovascular benefits. In addition to glycaemic control, indeed, SGLT2-i have been reported to decrease the risk of cardiovascular events and mortality, primarily through reduction of heart failure development or progression[78,79].
SGLT2 inhibitors induce plasma volume contraction without activation of the sympathetic nervous system; moreover, they reduce arterial stiffness and improve endothelial function. Natriuresis and vascular stiffness reduction are probably the most significant mediators responsible for the antihypertensive effects of SGLT2-i. Finally, SGLT-2 inhibitors induce oxidation of β-hydroxybutyrate, reduce oxygen consumption and increase oxygen delivery, improving the efficiency of myocardial energetics[75,80–82].
Clinically available SGLT2-i are canagliflozin, dapagliflozin and empagliflozin. New emerging data show they are associated with beneficial effects on cardiovascular events even in older adults[11,83]. The EMPA-REG OUTCOME trial reported positive cardiovascular outcomes in patients with diabetes at high risk for cardiovascular events receiving empagliflozin in addition to standard therapy,

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 August 2021 doi:10.20944/preprints202108.0065.v1

showing a significant reduction in cardiovascular mortality and hospitalization for heart failure[84–86].

Dapaglifozin appears to reduce the risk of hospitalization for heart failure, cardiovascular death and major adverse cardiovascular events in patients with previous myocardial infarction (MI), as shown in a subanalysis from the DECLARE-TIMI 58 trial[87,88]. Moreover, dapagliflozin appears to reduce weight, blood pressure and urinary albumin/creatinine ratio (UACR) in patients with type 2 diabetes, albuminuria and moderate renal impairment[89,90]. In two sister trials involving more than 10,000 patients with type 2 diabetes and established cardiovascular disease or at high cardiovascular risk, the CANVAS and CANVAS-R trials, canaglifozin treatment was associated with lower rates of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, compared to the placebo group, but an elevated risk of amputation[91–94]. Finally, increased renal protection with reduced kidney function decline was also observed in the CANVAS studies, as also reported with empagliflozin and dapagliflozin[94].

Since SGLT2 inhibitors are giving excellent results in the treatment of diabetes mellitus also reducing cardiovascular events and death they, overall, represent a promising novel therapeutic option for elderly patients[11,21,95]. Indeed, the stratified analyses of the trials of this drug class indicate that older patients have similar or greater benefits than younger patients.

The main adverse effects are generally mild urogenital infection, candidiasis risk and polyuria. In addition, an increased risk of fracture was observed with canagliflozin treatment, especially in those with high risk of cardiovascular disease and lower filtration rate, probably due to increased urine calcium excretion[96]. Overall, the safety profile of SGLT2i is good, especially because of oral route of administration, lower risk of hypoglycaemia and good tolerability.

As new evidences on cardiac and renal benefits related to SGLT-2 inhibitors and GLP-1R agonists started to emerge, guidelines markedly shifted recommendations, although side effects such as volume depletion may be more common among older patients. Overall, metformin remains the cornerstone of T2DM treatment and, both American Diabetes Association [24] and the European Association for the study of Diabetes (EASD)[97] suggest that the add-on therapy should be based on evaluation of cardiovascular disease, chronic kidney disease and heart failure. For patients with established CV disease, they now advise the use of either a SGLT-2 inhibitor or GLP-1R agonist with proven cardiovascular benefit. For those with HF the early use of a SGLT-2 inhibitor with proven benefit is recommended. Finally, for those with chronic kidney disease, a SGLT-2 inhibitor should be preferred or, if not tolerated or controindicated, a GLP-1R agonist should be started.

Table 2 summarizes oral T2DM treatments, contraindications and possible side effects.

Insulin therapy

Lifelong insulin treatment remains the cornerstone of management of type 1 diabetes, where slow destruction of pancreatic β-cell occurs with loss of function and insulin deficiency, providing the best combination of effectiveness and safety. Insulin therapy is usually initiated in older patients with type 2 diabetes often added on top of oral agents when the glycemic control is not sufficient. On the other hand, a strict glycemic control may increase the risk of adverse events, like hypoglycemia and falls[96].

 doi:10.20944/preprints202108.0065.v1

The optimal management of diabetes in the elderly is more complicated than in their younger counterparts because of the heterogeneity and the unique characteristics of these patients; thus, a careful consideration of concomitant geriatric syndromes and chronic conditions is needed. Functional status, cognitive decline, comorbid illnesses and patient's setting should be considered while chosing insulin as the most appropriate therapeutic regimen for older people with diabetes[24]. Insulin treatment in the elderly has been limited because of the risks associated to its use, including hypoglycemia and risk of falls. For patients with life-limiting comorbid illnesses and limited functional status, multiple daily injection of insulin may be too difficult to manage. Patients and caregivers should be educated to understand insulin injection and to recognize and manage hypoglycemia. Insulin pen devices are recommended for patients with limited manual ability or visual impairment, in order to facilitate insulin dosing, maintain their independence and facilitate patient adherence to therapy[15,24].

Long-acting insulin analogues (insulin detemir and glargine) are associated with minimal side effects and may represent the most reasonable choice for basal insulin therapy in elderly patients. After injecting, they form a slowly absorbed precipitate in the subcutaneous tissue, determining their long half-life. Once-daily approach would provide a modest peak in insulin availability, coinciding with the main meal of the day, minimizing the risk of nocturnal hypoglycemia[95,98,99]. Thus, once-daily basal insulin injection therapy may be a reasonable option in many older patients.

Conclusions

Diabetes is an increasingly prevalent disease among the older adults, representing a tough challenge for physician, due to the high heterogeneity of such population. The onset of diabetes in the older population may be unrecognised, due to non specific symptoms and the concomitant other chronic diseases, usually characterising geriatric syndromes. The advanced age, together with malnutrition and/or weight loss, reduced physical activity, isolation, depression may be responsible for increased rate of complications due to unrecognised hyper or hypoglicemia. Given that, managing diabetes in older age remains an important clinical challenge for all physicians, either primary care providers or specialists; considering frailty and/or multiple comorbidities, the therapeutic intervention has to be individualized and the patient-centered glycemic target is needed. The targeted approach is necessary to achieve glycemic control, avoiding dangerous hypo- and hyperglycemic events and, therefore, favouring a healthy aging. Lifestyle changes, with particular attention to diet and physical activity, must be encouraged as a first therapeutic approach. A comprehensive geriatric assessment should be performed at diagnosis of diabetes to better understand cognitive, visual and motor abilities, and coexisting comorbidities. In the choice of anti-hyperglycemic strategies, drugs with proven tolerability, safety, and minimal hypoglycemic risk should be preferred. Anti-diabetes treatment regimens in elderly must be simple, sustainable, and safe to best mirror patients' preferences, wishes, and needs. In conclusion, a comprehensive geriatric assessment has become crucial for the optimal management of T2DM; more attention should be focused on functional and cognitive status as well as social environment. Screening for traditional diabetes complications and geriatric issues (polypharmacy, falls, delirium, malnutrition, urinary incontinence, etc) should be regularly performed. Treatment targets need to be outlined on the basis of the kind of drug

 doi:10.20944/preprints202108.0065.v1

prescribed and the overall function in order to avoid both hypo- and hyperglycemia, to reduce the incidence of complications and to prevent or, at least, delay disability.

References

1. Rhys Williams (Chair), Stephen Colagiuri (Deputy Chair), Reem Almutairi, Pablo Aschner Montoya, A.; Basit, David Beran, Stéphane Besançon, Christian Bommer, Wenche Borgnakke, Edward Boyko, D.; Bright, Juliana Chan, Gisela Dahlquist, Hema Divakar, Alireza Esteghamati, Nita Forouhi, L.F.; Edward Gregg, Leonor Guariguata, Mohamed Hassanein, Calvin Ke, Dinky Levitt, Lee-Ling Lim, A.; Motala, Graham Ogle, Katherine Ogurstova, David Owens, Chris Patterson, Meda Pavkov, J.; Pearson-Stuttard, Ambady Ramachandran, Wolfgang Rathmann, Musarrat Riaz, Gojka Roglic, J.; Shaw, David Simmons, Alan Sinclair, Eugene Sobngwi, Gyula Soltesz, Rebecca Thomas, N.U.; Heather Ward, Sarah Wild, Xilin Yang, Lili Yuen, P.Z. IDF DIABETES ATLAS Ninth edition 2019. *Int. Diabetes Fed.* **2019**.
2. Corriere, M.; Rooparinesingh, N.; Kalyani, R.R. Epidemiology of Diabetes and Diabetes Complications in the Elderly: An Emerging Public Health Burden. 10.1007/s11892-013-0425-5.
3. Yang, Y.U.; Hu, X.; Zhang, Q.; Zou, R. Diabetes mellitus and risk of falls in older adults: a systematic review and meta-analysis. *Age Ageing* **2016**, *45*, 761–767. 10.1093/ageing/afw140.
4. Bai, J.; Gao, Q.; Wang, C.; Dai, J. Diabetes mellitus and risk of low-energy fracture: a meta-analysis. *Aging Clin. Exp. Res.* **2020**, *32*, 2173–2186. 10.1007/s40520-019-01417-x.
5. Xue, M.; Xu, W.; Ou, Y.N.; Cao, X.P.; Tan, M.S.; Tan, L.; Yu, J.T. Diabetes mellitus and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 144 prospective studies. *Ageing Res. Rev.* **2019**, *55*, 100944. 10.1016/j.arr.2019.100944.
6. van Sloten, T.T.; Sedaghat, S.; Carnethon, M.R.; Launer, L.J.; Stehouwer, C.D.A. Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression. *Lancet Diabetes Endocrinol.* **2020**, *8*, 325–336. 10.1016/S2213-8587(19)30405-X.
7. Kim, Y.G.; Park, D.G.; Moon, S.Y.; Jeon, J.Y.; Kim, H.J.; Kim, D.J.; Lee, K.W.; Han, S.J. Hypoglycemia and dementia risk in older patients with type 2 diabetes mellitus: A propensity-score matched analysis of a population-based cohort study. *Diabetes Metab. J.* **2020**, *44*, 125–133. 10.4093/dmj.2018.0260.
8. Laiteerapong, N.; Huang, E.S.; Laiteerapong, N. Chapter 16: Diabetes in older adults. *Diabetes Am.* **2016**, 1–26.
9. Sinclair, A.; Dunning, T.; Rodriguez-Mañas, L. Diabetes in older people: New insights and remaining challenges. *Lancet Diabetes Endocrinol.* **2015**, *3*, 275–285. 10.1016/S2213-8587(14)70176-7.
10. Fortini, A.; Morettini, A.; Tavernese, G.; Facchini, S.; Tofani, L.; Pazzi, M. IM-ORIGINAL Delirium in elderly patients hospitalized in internal medicine wards. 10.1007/s11739-013-0968-0.
11. Sesti, G.; Antonelli Incalzi, R.; Bonora, E.; Consoli, A.; Giaccari, A.; Maggi, S.; Paolisso, G.; Purrello, F.; Vendemiale, G.; Ferrara, N. Management of diabetes in older adults. *Nutr. Metab. Cardiovasc. Dis.* **2018**, *28*, 206–218. 10.1016/j.numecd.2017.11.007.
12. (No Title). 10.1136/bmj.b5444.
13. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes A bs t r ac t. **2008**. 10.1056/NEJMoa0802987.
14. Duckworth, W.; Abraira, C.; Moritz, T.; Reda, D.; Emanuele, N.; Reaven, P.D.; Zieve, F.J.; Marks, J.; Davis, S.N.; Hayward, R.; et al. H.) and Hines VA Hospital (N.E.)-both in Hines. *N*

Engl J Med **2008**, *17*, 129–168. 10.1056/NEJMoa0808431.

15. Care, D.; Suppl, S.S. Older adults: Standards of medical care in diabetes-2021. *Diabetes Care* **2021**, *44*, S168–S168. 10.2337/dc21-s012.
16. Dunning, T.; Sinclair, A. *The IDF global guideline for managing older people with type 2 diabetes: Implications for nurses*; 2014; Vol. 18; ISBN 2930229861.
17. Incalzi, R.A.; Ferrara, N.; Maggi, S.; Paolisso, G. Personalizzazione del trattamento dell ' iperglicemia nell ' anziano con diabete tipo 2. *Www.Sigg.It* **2017**.
18. Care, D.; Suppl, S.S. Glycemic targets: Standards of medical care in diabetes−2021. *Diabetes Care* **2021**, *44*, S73–S84. 10.2337/dc21-S006.
19. Care, D.; Suppl, S.S. 5. Facilitating behavior change and well-being to improve health outcomes: Standards of medical care in diabetes−2021. *Diabetes Care* **2021**, *44*, S53–S72. 10.2337/dc21-S005.
20. Press, Z.W. World Journal of Management. **1838**, *3726*.
21. Leroith, D.; Biessels, G.J.; Braithwaite, S.S.; Casanueva, F.F.; Draznin, B.; Halter, J.B.; Hirsch, I.B.; Mcdonnell, M.E.; Molitch, M.E.; Murad, M.H.; et al. *Treatment of Diabetes in Older Adults: An Endocrine Society*; 2019; Vol. 104; ISBN 0000000279208. 10.1210/jc.2019-00198.
22. H, K.; S, M. Environmental/lifestyle factors in the pathogenesis and prevention of type 2 diabetes. *BMC Med.* **2017**, *15*. 10.1186/S12916-017-0901-X.
23. J, S.-S.; M, B.; N, B.; MÁ, M.-G.; N, I.-J.; J, B.; R, E.; MI, C.; D, C.; F, A.; et al. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care* **2011**, *34*, 14–19. 10.2337/DC10-1288.
24. Care, D.; Suppl, S.S. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetesd2021. *Diabetes Care* **2021**, *44*, S111–S124. 10.2337/dc21-S009.
25. R, D.; GA, F.; K, C.; TA, B. Metformin-associated lactic acidosis: Current perspectives on causes and risk. *Metabolism.* **2016**, *65*, 20–29. 10.1016/J.METABOL.2015.10.014.
26. J, F.; K, L. Metformin in 2019. *JAMA* **2019**, *321*, 1926–1927. 10.1001/JAMA.2019.3805.
27. L, S.; YV, M.; C, A.; D, R.; B, F.; C, S.; T, A.Q.; A, W.; I, K.; A, 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*. 10.1186/S12877-017-0574-5.
28. M, S.; I, I.; L, P.; P, H.; A, G.; P, H.; E, P.; L, C.; A, H.; Z, G.; et al. Metformin induces significant reduction of body weight, total cholesterol and LDL levels in the elderly - A meta-analysis. *PLoS One* **2018**, *13*. 10.1371/JOURNAL.PONE.0207947.
29. G, S.; GH, S. The right place for metformin today. *Diabetes Res. Clin. Pract.* **2020**, *159*. 10.1016/J.DIABRES.2019.107946.
30. E, S.-R.; SE, I. Metformin: clinical use in type 2 diabetes. *Diabetologia* **2017**, *60*, 1586–1593. 10.1007/S00125-017-4336-X.
31. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J. Am. Geriatr. Soc.* **2019**, *67*, 674–694. 10.1111/JGS.15767.
32. DR, W.; MJ, D.; J, J.; S, S.; K, K. The right place for Sulphonylureas today. *Diabetes Res. Clin. Pract.* **2019**, *157*. 10.1016/J.DIABRES.2019.107836.
33. Huang, C.-H.; Umegaki, H.; Watanabe, Y.; Kamitani, H.; Asai, A.; Kanda, S.; Nomura, H.; Kuzuya, M. Potentially inappropriate medications according to STOPP-J criteria and risks of

hospitalization and mortality in elderly patients receiving home-based medical services. **2019**. 10.1371/journal.pone.0211947.

34. SV, A.; SE, I.; JB, E.-T.; F, T.; CSP, L.; LS, S.; M, K. Understanding Contemporary Use of Thiazolidinediones. *Circ. Heart Fail.* **2019**, *12*. 10.1161/CIRCHEARTFAILURE.118.005855.
35. MA, N.; JJ, M. Incretin hormones: Their role in health and disease. *Diabetes. Obes. Metab.* **2018**, *20 Suppl 1*, 5–21. 10.1111/DOM.13129.
36. JE, C.; DJ, D. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab.* **2013**, *17*, 819–837. 10.1016/J.CMET.2013.04.008.
37. G, S.; YV, M.; RE, E. de S.; A, R.-G.; A, V.; D, R.; I, K.; M, M.-V.; A, S. Effectiveness and safety of dipeptidyl peptidase 4 inhibitors in the management of type 2 diabetes in older adults: a systematic review and development of recommendations to reduce inappropriate prescribing. *BMC Geriatr.* **2017**, *17*. 10.1186/S12877-017-0571-8.
38. RE, P.; J, R.; FX, P.-S.; MA, B.; A, S.; A, C.; S, D. Management of type 2 diabetes in treatment-naive elderly patients: benefits and risks of vildagliptin monotherapy. *Diabetes Care* **2007**, *30*, 3017–3022. 10.2337/DC07-1188.
39. S, S.; D, E.; GS, M. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin in older adults with type 2 diabetes mellitus. *J. Am. Geriatr. Soc.* **2011**, *59*, 1148–1149. 10.1111/J.1532-5415.2011.03438.X.
40. Umezawa, S.; Kubota, A.; Maeda, H.; Kanamori, A.; Matoba, K.; Jin, Y.; Minagawa, F.; Obana, M.; Iemitsu, K.; Ito, S.; et al. Two-year assessment of the efficacy and safety of sitagliptin in elderly patients with type 2 diabetes: Post hoc analysis of the ASSET-K study. *BMC Endocr. Disord.* **2015**, *15*. 10.1186/S12902-015-0033-2.
41. MA, B.; SS, E.; JB, G.; Z, H.; RG, J.; KD, K.; E, S.; S, S.; F, V. de W.; DK, M.; et al. Assessing the Safety of Sitagliptin in Older Participants in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). *Diabetes Care* **2017**, *40*, 494–501. 10.2337/DC16-1135.
42. LA, L.; H, T.; E, B.; O, M.; A, C.; KM, K.; A, S.; B, H.; C, S.; R, F.; et al. Efficacy and safety of saxagliptin in older participants in the SAVOR-TIMI 53 trial. *Diabetes Care* **2015**, *38*, 1145–1153. 10.2337/DC14-2868.
43. White, W.B.; Cannon, C.P.; Heller, S.R.; Nissen, S.E.; Bergenstal, R.M.; Bakris, G.L.; Perez, A.T.; Fleck, P.R.; Mehta, C.R.; Kupfer, S.; et al. Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes. *http://dx.doi.org/10.1056/NEJMoa1305889* **2013**, *7*, 77. 10.1056/NEJMOA1305889.
44. Rosenstock, J.; Perkovic, V.; Johansen, O.E.; Cooper, M.E.; Kahn, S.E.; Marx, N.; Alexander, J.H.; Pencina, M.; Toto, R.D.; Wanner, C.; et al. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. *JAMA* **2019**, *321*, 69–79. 10.1001/JAMA.2018.18269.
45. F, Z.; CP, C.; WC, C.; GL, B.; V, M.; AT, P.; PR, F.; CR, M.; S, K.; C, W.; et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet (London, England)* **2015**, *385*, 2067–2076. 10.1016/S0140-6736(14)62225-X.
46. Effects of Vildagliptin on Ventricular Function in Patients With Type 2 Diabetes Mellitus and Heart Failure | Elsevier Enhanced Reader Available online:

https://reader.elsevier.com/reader/sd/pii/S2213177917305358?token=9486F6A8E2D2C005C40382DF6E3D65FDE2FDF5F6BB8D33B7E0ED066FEE10982B0FAD7BFBA591A3EBD724E9BB36FA34D5&originRegion=eu-west-1&originCreation=20210716093512 (accessed on Jul 16, 2021).

47. McGuire, D.K.; Alexander, J.H.; Johansen, O.E.; Perkovic, V.; Rosenstock, J.; Cooper, M.E.; Wanner, C.; Kahn, S.E.; Toto, R.D.; Zinman, B.; et al. Linagliptin Effects on Heart Failure and Related Outcomes in Individuals With Type 2 Diabetes Mellitus at High Cardiovascular and Renal Risk in CARMELINA. *Circulation* **2019**, *139*, 351–361. 10.1161/CIRCULATIONAHA.118.038352.
48. Faillie, J.-L.; Azoulay, L.; Patenaude, V.; Hillaire-Buys, D.; Suissa, S. Incretin based drugs and risk of acute pancreatitis in patients with type 2 diabetes: cohort study. *BMJ* **2014**, *348*. 10.1136/BMJ.G2780.
49. Elashoff, M.; Matveyenko, A. V.; Gier, B.; Elashoff, R.; Butler, P.C. Pancreatitis, Pancreatic, and Thyroid Cancer With Glucagon-Like Peptide-1–Based Therapies. *Gastroenterology* **2011**, *141*, 150–156. 10.1053/J.GASTRO.2011.02.018.
50. Dicembrini, I.; Montereggi, C.; Nreu, B.; Mannucci, E.; Monami, M. Pancreatitis and pancreatic cancer in patientes treated with Dipeptidyl Peptidase-4 inhibitors: An extensive and updated meta-analysis of randomized controlled trials. *Diabetes Res. Clin. Pract.* **2020**, *159*. 10.1016/J.DIABRES.2019.107981.
51. LC, P.; DV, R.; SS, B.; CB, L.; JL, G. Dipeptidyl peptidase-4 inhibitors, pancreatic cancer and acute pancreatitis: A meta-analysis with trial sequential analysis. *Sci. Rep.* **2018**, *8*. 10.1038/S41598-017-19055-6.
52. Monami, M.; Dicembrini, I.; Martelli, D.; Mannucci, E. Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. *http://dx.doi.org/10.1185/03007995.2011.602964* **2011**, *27*, 57–64. 10.1185/03007995.2011.602964.
53. Sesti, G.; Avogaro, A.; Belcastro, S.; Benedetta, ·; Bonora, M.; Croci, M.; Daniele, G.; Dauriz, M.; Dotta, F.; Formichi, C.; et al. Ten years of experience with DPP-4 inhibitors for the treatment of type 2 diabetes mellitus. *Acta Diabetol.* **2019**, *56*, 605–617. 10.1007/s00592-018-1271-3.
54. Deacon, C.F.; Holst, J.J. Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes: Comparison, efficacy and safety. *Expert Opin. Pharmacother.* **2013**, *14*, 2047–2058. 10.1517/14656566.2013.824966.
55. Fonseca, V.; Baron, M.; Shao, Q.; Dejager, S. Sustained efficacy and reduced hypoglycemia during one year of treatment with vildagiiptin added to insulin in patients with type 2 diabetes mellitus. *Horm. Metab. Res.* **2008**, *40*, 427–430. 10.1055/S-2008-1058090.
56. Gallwitz, B. Clinical Use of DPP-4 Inhibitors. *Front. Endocrinol. (Lausanne).* **2019**, *10*, 389. 10.3389/FENDO.2019.00389.
57. Sposito, A.C.; Berwanger, O.; Carvalho, L.S.F. de; Saraiva, J.F.K. GLP-1RAs in type 2 diabetes: mechanisms that underlie cardiovascular effects and overview of cardiovascular outcome data. *Cardiovasc. Diabetol. 2018 171* **2018**, *17*, 1–19. 10.1186/S12933-018-0800-2.
58. Meneilly, G.S.; Roy-Duval, C.; Alawi, H.; Dailey, G.; Bellido, D.; Trescoli, C.; Hurtado, H.M.; Guo, H.; Pilorget, V.; Perfetti, R.; et al. Lixisenatide Therapy in Older Patients With Type 2 Diabetes Inadequately Controlled on Their Current Antidiabetic Treatment: The GetGoal-O Randomized Trial. *Diabetes Care* **2017**, *40*, 485–493. 10.2337/DC16-2143.

 doi:10.20944/preprints202108.0065.v1

59. MA, B.; I, P.; M, Y.; VT, T.; OJ, V.; R, J. Similar efficacy and safety of once-weekly dulaglutide in patients with type 2 diabetes aged ≥65 and. *Diabetes. Obes. Metab.* **2016**, *18*, 820–828. 10.1111/DOM.12687.
60. Raccah, D.; Miossec, P.; Esposito, V.; Niemoeller, E.; Cho, M.; Gerich, J. Efficacy and safety of lixisenatide in elderly (≥65 years old) and very elderly (≥75 years old) patients with type 2 diabetes: an analysis from the GetGoal phase III programme. *Diabetes. Metab. Res. Rev.* **2015**, *31*, 204–211. 10.1002/DMRR.2588.
61. Hanefeld, M.; Berria, R.; Lin, J.; Aronson, R.; Darmon, P.; Evans, M.; Van Gaal, L. Lixisenatide treatment for older patients with type 2 diabetes mellitus uncontrolled on oral antidiabetics: meta-analysis of five randomized controlled trials. *Adv. Ther.* **2014**, *31*, 861–872.
62. Pencek, R.; Blickensderfer, A.; Li, Y.; Brunell, S.C.; Chen, S. Exenatide once weekly for the treatment of type 2 diabetes: effectiveness and tolerability in patient subpopulations. *Int. J. Clin. Pract.* **2012**, *66*, 1021. 10.1111/J.1742-1241.2012.03006.X.
63. BW, B.; J, B.; A, F.; RE, P. Comparison of the efficacy and tolerability profile of liraglutide, a once-daily human GLP-1 analog, in patients with type 2 diabetes ≥65 and. *Am. J. Geriatr. Pharmacother.* **2011**, *9*, 423–433. 10.1016/J.AMJOPHARM.2011.09.007.
64. Hernandez, A.F.; Green, J.B.; Janmohamed, S.; D'Agostino, R.B.; Granger, C.B.; Jones, N.P.; Leiter, L.A.; Rosenberg, A.E.; Sigmon, K.N.; Somerville, M.C.; et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* **2018**, *392*, 1519–1529. 10.1016/S0140-6736(18)32261-X.
65. SP, M.; GH, D.; K, B.-F.; P, K.; JF, M.; MA, N.; SE, N.; S, P.; NR, P.; LS, R.; et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N. Engl. J. Med.* **2016**, *375*, 101. 10.1056/NEJMOA1603827.
66. Gilbert, M.P.; Bain, S.C.; Edward Franek; Esteban Jodar-Gimeno; Nauck, M.A.; Richard Pratley; Rosangela Roginski Rea; Jose Francisco Kerr Saraiva; Soren Rasmussen; Buse, J.B. Effect of liraglutide on cardiovascular outcomes in elderly patients: A post hoc analysis of a randomized controlled trial. *Ann. Intern. Med.* **2019**, *170*, 423–426. 10.7326/M18-1569.
67. SP, M.; SC, B.; A, C.; FG, E.; E, J.; LA, L.; I, L.; J, R.; J, S.; ML, W.; et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N. Engl. J. Med.* **2016**, *375*, 1834–1844. 10.1056/NEJMOA1607141.
68. HC, G.; HM, C.; GR, D.; R, D.; M, L.; P, P.; J, P.; JS, R.; MC, R.; L, R.; et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet (London, England)* **2019**, *394*, 121–130. 10.1016/S0140-6736(19)31149-3.
69. Husain, M.; Birkenfeld, A.L.; Donsmark, M.; Dungan, K.; Eliaschewitz, F.G.; Franco, D.R.; Jeppesen, O.K.; Lingvay, I.; Mosenzon, O.; Pedersen, S.D.; et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *https://doi.org/10.1056/NEJMoa1901118* **2019**, *381*, 841–851. 10.1056/NEJMOA1901118.
70. MA, P.; B, C.; R, D.; K, D.; HC, G.; LV, K.; FC, L.; L, P.; X, W.; EF, L.; et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N. Engl. J. Med.* **2015**, *373*, 2247–2257. 10.1056/NEJMOA1509225.
71. RR, H.; MA, B.; RJ, M.; VP, T.; Y, L.; JB, B.; JC, C.; J, C.; SM, G.; N, I.; et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N. Engl. J. Med.* **2017**, *377*,

1228–1239. 10.1056/NEJMOA1612917.

72. SL, K.; R, R.; PS, J.; KF, D.; N, S.; D, P.; L, K.; MC, P.; JJV, M. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *lancet. Diabetes Endocrinol.* **2019**, *7*, 776–785. 10.1016/S2213-8587(19)30249-9.
73. Zelniker, T.A.; Wiviott, S.D.; Raz, I.; Im, K.; Goodrich, E.L.; Furtado, R.H.M.; Bonaca, M.P.; Mosenzon, O.; Kato, E.T.; Cahn, A.; et al. Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus. *Circulation* **2019**, *139*, 2022–2031. 10.1161/CIRCULATIONAHA.118.038868.
74. G, K. Diuretic Action of Sodium-Glucose Cotransporter 2 Inhibitors and Its Importance in the Management of Heart Failure. *Circ. J.* **2016**, *80*, 2277–2281. 10.1253/CIRCJ.CJ-16-0780.
75. John, M.; Gopinath, D.; Jagesh, R. Sodium-glucose cotransporter 2 inhibitors with insulin in type 2 diabetes: Clinical perspectives. *Indian J. Endocrinol. Metab.* **2016**, *20*, 22. 10.4103/2230-8210.172268.
76. G, K. Importance of inhibiting sodium-glucose cotransporter and its compelling indication in type 2 diabetes: pathophysiological hypothesis. *J. Am. Soc. Hypertens.* **2016**, *10*, 271–278. 10.1016/J.JASH.2016.01.009.
77. T, M.; S, M.; K, F.; M, W.; K, O.; H, K.; V, V.; D, N. Osmotic diuresis by SGLT2 inhibition stimulates vasopressin-induced water reabsorption to maintain body fluid volume. *Physiol. Rep.* **2020**, *8*. 10.14814/PHY2.14360.
78. A, P.; S, V.; P, V.; R, S. Review on sodium-glucose cotransporter 2 inhibitor (SGLT2i) in diabetes mellitus and heart failure. *J. Fam. Med. Prim. care* **2019**, *8*, 1855. 10.4103/JFMPC.JFMPC_232_19.
79. M, P.; SD, A.; J, B.; G, F.; F, Z. Effects of Sodium-Glucose Cotransporter 2 Inhibitors for the Treatment of Patients With Heart Failure: Proposal of a Novel Mechanism of Action. *JAMA Cardiol.* **2017**, *2*, 1025–1029. 10.1001/JAMACARDIO.2017.2275.
80. K, K.; T, B.; A, K.; S, A. SGLT-2 inhibitors: Ideal Remedy for Cardioprotection in Diabetes Mellitus. *Curr. Mol. Pharmacol.* **2020**, *13*. 10.2174/1874467213666201012161439.
81. HJ, H.; BA, P.; DH, F.; M, H.; DZ, C. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. *Circulation* **2016**, *134*, 10–30. 10.1161/CIRCULATIONAHA.116.021887.
82. P, M.; C, M.; FH, V. Promise of SGLT2 Inhibitors in Heart Failure: Diabetes and Beyond. *Curr. Treat. Options Cardiovasc. Med.* **2017**, *19*. 10.1007/S11936-017-0522-X.
83. P, V.; F, A.; C, C.; A, A.; D, T.; G, R. The revolution of the anti-diabetic drugs in cardiology. *Eur. Heart J. Suppl.* **2020**, *22*, E162–E166. 10.1093/EURHEARTJ/SUAA084.
84. Braha, A.; Timar, B.; Diaconu, L.; Lupusoru, R.; Vasiluta, L.; Sima, A.; Vlad, A.; Munteanu, M.; Albai, A.; Cipu, D.; et al. Dynamics of Epicardiac Fat and Heart Function in Type 2 Diabetic Patients Initiated with SGLT-2 Inhibitors. *Diabetes, Metab. Syndr. Obes. Targets Ther.* **2019**, *12*, 2559. 10.2147/DMSO.S223629.
85. B, Z.; C, W.; JM, L.; D, F.; E, B.; S, H.; M, M.; T, D.; OE, J.; HJ, W.; et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N. Engl. J. Med.* **2015**, *373*, 17–18.

10.1056/NEJMOA1504720.

86. D, F.; SE, I.; CP, C.; DK, M.; BM, S.; OE, J.; S, S.; S, K.; E, P.; JT, G.; et al. Empagliflozin Reduced Mortality and Hospitalization for Heart Failure Across the Spectrum of Cardiovascular Risk in the EMPA-REG OUTCOME Trial. *Circulation* **2019**, *139*, 1384–1395. 10.1161/CIRCULATIONAHA.118.037778.
87. RHM, F.; MP, B.; I, R.; TA, Z.; O, M.; A, C.; J, K.; SA, M.; DL, B.; LA, L.; et al. Dapagliflozin and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus and Previous Myocardial Infarction. *Circulation* **2019**, *139*, 2516–2527. 10.1161/CIRCULATIONAHA.119.039996.
88. SD, W.; I, R.; MP, B.; O, M.; ET, K.; A, C.; MG, S.; S, B.; DL, B.; LA, L.; et al. The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 Trial. *Am. Heart J.* **2018**, *200*, 83–89. 10.1016/J.AHJ.2018.01.012.
89. DE, K.; P, F.; W, T.; JF, L. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney Int.* **2014**, *85*, 962–971. 10.1038/KI.2013.356.
90. P, F.; BV, S.; E, J.; VA, C.; CD, S. Dapagliflozin reduces albuminuria over 2 years in patients with type 2 diabetes mellitus and renal impairment. *Diabetologia* **2016**, *59*, 2036–2039. 10.1007/S00125-016-4017-1.
91. B, N.; V, P.; KW, M.; D, de Z.; G, F.; N, E.; W, S.; G, L.; M, D.; DR, M. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N. Engl. J. Med.* **2017**, *377*, 644–657. 10.1056/NEJMOA1611925.
92. V, P.; D, de Z.; KW, M.; G, F.; N, E.; W, S.; TD, B.; M, W.-W.; H, D.; DR, M.; et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. *lancet. Diabetes Endocrinol.* **2018**, *6*, 691–704. 10.1016/S2213-8587(18)30141-4.
93. Mahaffey, K.W.; Neal, B.; Perkovic, V.; Zeeuw, D. de; Fulcher, G.; Erondu, N.; Shaw, W.; Fabbrini, E.; Sun, T.; Li, Q.; et al. Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). *Circulation* **2018**, *137*, 323. 10.1161/CIRCULATIONAHA.117.032038.
94. AY, K.; KM, T.; CM, B.; AY, L.; EV, L.; ZP, R.; J, R.; NE, L.; ME, C.; PA, M. Cardiorenal Outcomes in the CANVAS, DECLARE-TIMI 58, and EMPA-REG OUTCOME Trials: A Systematic Review. *Rev. Cardiovasc. Med.* **2018**, *19*. 10.31083/J.RCM.2018.02.907.
95. WD, S.; SV, H.; A, G.; P, K.; J, V.; AJ, S. Type 2 diabetes mellitus in older people: a brief statement of key principles of modern day management including the assessment of frailty. A national collaborative stakeholder initiative. *Diabet. Med.* **2018**, *35*, 838–845. 10.1111/DME.13644.
96. JL, C.; M, M.; K, G.; S, R.-T.; DA, C.; J, G. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* **1994**, *44*, 2308–2314. 10.1212/WNL.44.12.2308.
97. Buse, J.B.; Wexler, D.J.; Tsapas, A.; Rossing, P.; Mingrone, G.; Mathieu, C.; D'Alessio, D.A.; Davies, M.J. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetol. 2019 632* **2019**, *63*, 221–228. 10.1007/S00125-019-05039-W.
98. C, W.; A, B.; L, C.; R, de la R.; Y, H.; LN, T.; K, K.; P, N. Effect of Insulin Degludec vs Insulin

Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial. *JAMA* **2017**, *318*, 45–56. 10.1001/JAMA.2017.7117.

99. JG, E.; MK, L. Insulin therapy in the elderly with type 2 diabetes. *Minerva Endocrinol.* **2015**, *40*, 283–295.
100. Association, A.D. Older adults: Standards of medical care in diabetes-2021. *Diabetes Care* **2021**, *44*, S168–S168. 10.2337/dc21-s012.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 August 2021 doi:10.20944/preprints202108.0065.v1

Table 1. Treatment goals for glycemia in older adults with diabetes

	Healthy (few coexisting chronic illnesses, intact cognitive and functional status), long life expectancy	Complex/intermediate (multiple coexisting chronic illnesses, functional impairments, mild to moderate cognitive impairment)	Very complex/poor health (long-term care or end-stage chronic illnesses, moderate to severe cognitive impairment), approaching to end of life
ADA 2021[100]	HbA1c < 7-7.5% Fasting glucose 80-130 mg/dL Bedtime glucose 80-180 mg/dL	HbA1c < 8% Fasting glucose 90-150 mg/dL Bedtime glucose 100-180 mg/dL	Avoid symptomatic hypo- and hyperglycemia Avoid reliance on HbA1c Fasting glucose 100-180 mg/dL Bedtime glucose 110-200 mg/dL
IDF [16]	HbA1c 7-7.5%	HbA1c 7-8%	Avoid symptomatic hypo- and hyperglycemia, consider withdrawal of therapy
SID/SIGG [17]	In the older diabetic patients, the glycemic targets should be targeted basing on the drug chosen and the potential risk of hypoglycemia. HbA1c < 7% when using drugs with low potential of hypoglycemia (metformin, gliflozins, incretin-based drugs and acarbose) HbA1c 7-7.5% when the use of drugs with high potential of hypoglycemia (insulin, sulfonylureas) is necessary; HbA1c 7.5%-8% as above, in patients with higher degree of frailty (cognitive impairment, serious T2DM complications, polypathology)		

Abbreviations. T2DM: Type 2 Diabetes Mellitus. ADA: American Diabetes Association. SID: Italian Diabetes Society. SIGG: Italian Society of Gerontology and Geriatrics. HbA1c: glycated hemoglobin.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 August 2021 doi:10.20944/preprints202108.0065.v1

Table 2. Oral antidiabetic agents: contraindications and side effects

Class/drug	Risk of Hypoglycemia	Contraindications	Major side effects and warnings
Metformin	no	eGFR < 30 ml/min	Bloating, abdominal discomfort, diarrhea, vitamin B12 deficiency, weight loss
DPP-4 inhibitors	no		Potential risk of pancreatitis, potential slight increased risk for heart failure with saxagliptin and alogliptin
GLP-1R agonists	no	Not suitable in frail malnourished patients	Potential risk of pancreatitis, nausea, diarrhea, weight loss
SGLT2 inhibitors	no	Less effective with eGFR < 60 ml/min	Genital infections, increased risk of diabetic ketoacidosis
Sulphonylureas and glinides	yes		Increased risk of hypoglycaemia, major weight gain
Thiazolidinediones	no	Not suitable in patients with heart failure	Weight gain, fluid retention, loss of bone mineral density, increased risk of non-osteoporotic bone fractures

Abbreviations. eGFR: estimated glomerular filtration rate. DPP-4: Dipeptidyl peptidase-4. GLP-1: Glucagon-like peptide 1. SGLT2-i: Sodium-glucose Cotransporter-2 inhibitors