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VIEWPOINT

Management of diabetes in older adults

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Abstract Type 2 diabetes prevalence is high in older adults and is expected to rise in the next decades. Diabetes in the population of frail older adults is accompanied by functional disability, several comorbidities, and premature mortality. A comprehensive geriatric assessment, including functional, cognitive, mental and social status, is advisable for identifying the glycemic targets and glucose-lowering therapies, focused on patient preferences, needs, and risks. The therapeutic options for older adults with diabetes are like those for the adult population. However, the pharmacological treatments must be carefully prescribed and monitored, taking into consideration the patient cognitive capacities, the potentially life-threatening drug–drug interactions, the cardiovascular risk, and with the main goal of avoiding hypoglycemia. Also, a careful nutritional evaluation with appropriate tools, as well as a balanced and periodically monitored physical activity, contribute to an effective tailored care plan, as needed by older adults with diabetes. This review evaluates the currently available hypoglycemic drugs and the current indications to the Italian diabetology community, specifically with regard to the treatment of adults aged 75 years or older with diabetes, including the unmet needs by the guidelines.

Introduction

The high prevalence of type 2 diabetes among older adults reflects the increase in life expectancy of the general population. Several factors are involved: 1) the multi-organ functional alterations typical of older age are linked to impaired function of insulin-secreting beta-cells and to impaired insulin sensitivity [1]; 2) the age-related variations in body composition related to aging include the reduction of the fat-free mass (muscle, bone, water) and

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the relative increase of the fat mass, with visceral obesity leading to alterations of insulin sensitivity [2,3]; 3) the currently improved survival of patients with diabetes contributes to the increased rate of this disease among older adults [1]; 4) the greater attention paid to diabetes.

In addition to geriatric conditions, diabetes in older adults is associated with a higher absolute risk of cardiovascular (CV) or microvascular diseases – even if the relative CV risk is higher in young adults with early onset of type 2 diabetes [4] – and with hypoglycemia, leading to high mortality rate, increased hospital admission and institutionalization, as well as to social and economic burden [5].

Diagnosis and care of older adults with diabetes are challenged at clinical level by the heterogeneity of comorbidities and functional impairments of these patients. The diversity of the living conditions of patients, who may live either independent or in supporting facilities, impacts on the management of older adults with diabetes. Moreover, the frequent exclusion of frail older persons from randomized controlled studies results in few available data supporting specific treatment strategies for the population of patients aged >75 years [6].

These issues altogether make it particularly difficult to establish a standard of care that may fit all older adults with diabetes. Therefore, the therapeutic approach, as well as the glycemic targets, must be carefully evaluated for each individual patient. Health and functional status, types of comorbidities, life expectancy must be considered for each single patient and treatment tailored according to them as well as to patients medical, cultural, and social conditions [7].

It is possible that diabetic individuals who become old have different characteristics compared to older individuals who become diabetic highlighting the need for personalizing the treatment for the older patients, who are heterogenous in terms of functional status, comorbidities, and degree of frailty. This review provides a discussion of the clinical classification, the management, and the treatment options available relative to diabetes care in older adults over the age of 75 years. It also provides an expert opinion on this topic gathered by a panel of Italian specialists in the areas of diabetes and geriatric medicine.

Epidemiology of type 2 diabetes in elderly population

The prevalence of diabetes in elderly people is high in general, with some differences among different countries. In the United States, more than 25% of older adults (aged >65 years) are diagnosed with diabetes and 51% have prediabetes. The rate of newly diagnosed diabetes among people aged 65 years or older is 11.5 cases per 1000 persons per year [8]. In Europe, prevalence data are slightly lower, with an average 20% prevalence [5,9], but with some differences among nations, ranging 14%–16% in Denmark [10], 15%–18%. In UK [11], 19%–31% in Greece [12] and 15%–26% in Italy, where the highest percentage of diabetes cases (66.3%) occurs among patients aged over 65 years [13], making the development of therapeutic strategies targeted to this broad population of patients particularly challenging. The trend of global prevalence is increasing with an estimated double number of cases of diabetes among older adults in the next two decades [9].

Distinctive features of the older adult with diabetes

Aging is accompanied by changes in body composition, mainly a decrease in lean mass and skeletal mineral density opposed to an increase in body fat [14]. The reduction of non-fat tissue includes loss of muscle mass, leading to sarcopenia with decreased muscle functions, while the change in total body fat mass is associated with a higher risk of developing diabetes [2,3]. When occurring in older patients, diabetes is frequently accompanied by complications and/or comorbidities, at least one in 60% and four or more in 40% of older people with diabetes [15]. A geriatric syndrome frequently occurring in patients with diabetes is the cognitive impairment, which has been linked to the frailty state. Cognitive impairment and frailty share common mechanisms at the molecular level (oxidative stress, impaired repair processes, autophagy), are closely related to each other and both linked to aging [16]. The condition of frailty entails increased vulnerability to stressors and external insults, which puts the patient at increased risk of adverse outcomes, such as disability, hospitalization, and mortality [1]. In particular, midlife early onset of diabetes and hypertension are associated with late-life brain atrophy and cognitive impairment [17]. Therefore, older adults with diabetes should be carefully screened and monitored for cognitive impairment [7,18], since diabetes and its complications increase the incidence of all-cause dementia, Alzheimer's disease, and vascular dementia when compared with the rates of the same disturbances in people with normal glucose tolerance [19,20].

Diabetes in older adults is associated with polypharmacy, increasing the risk of drug adverse events and potentially life-threatening drug–drug interactions, because of changes in pharmacokinetics and pharmacodynamics related to aging [7,21]. Therefore, pharmacological treatments should be cautiously prescribed and carefully monitored in elderly with diabetes. Notably, it has been shown that the perception of the impact of the treatments on the quality of life of patients must be considered in the cost-effectiveness analysis of glucose control in older patients with diabetes [22].

Older adults with diabetes are at higher risk of institutionalization. Older diabetic patients institutionalized in nursing home represent an even frailer population in whom treatment needs to be monitored very carefully with the main goal of avoiding hypoglycemia (see below) [23]. Indeed, a large study in a cohort of patients with diabetes from 150 nursing homes across Italy demonstrated that severe hypoglycemia was significantly higher in patients with dementia, compared with those without dementia [24]. Similar results were obtained in a retrospective study on older patients with diabetes from the UK clinical practice database [25].

In diabetic patients over 65 years of age, the screening for depression and its possible treatment are at high-priority [18,26,27]. Furthermore, the underlying multiple comorbidities (often ignored or underestimated) must be taken into consideration, especially when setting the best treatment goals in older patients with diabetes. The awareness of the need to screen for the main comorbidities (e.g., sarcopenia-related renal failure with normal creatinine levels, chronic heart failure with prolonged asthenia) in diabetic patients in general, and in the older patients in particular, should be actively promoted.

Moreover, older adults with diabetes are at increased risk of severe of fatal hypoglycemia for several different reasons, including progressive renal failure, and age-related reduction of the secretion of glucagon [28], which is the most important counterregulatory hormone to prevent hypoglycemia [29].

Finally, even if microvascular complications and CV diseases are strongly associated with diabetes in any age group, the risk is higher in elderly patients compared to younger patients. Therefore, prevention and treatment of CV complications must be included in the management of these patients [30].

Older adults with diabetes need tailored care plans

The best approach to the management of hyperglycemia implicates implementation – in parallel to glucose control – of prevention plans aimed at reducing CV risk, including lifestyle, blood pressure, and lipid control. Moreover, antihyperglycemic therapy in older adults with intact cognitive and physical functions and with long life expectancy should pursue the same targets adopted for younger adults [18,31]. This is because it is well established a strong relation between reduced hyperglycemia, also obtained by intensive blood-glucose control, and reduced risk of micro- and macrovascular [32,33].

On the other hand, when frail aging diabetic patients are considered, the propensity to hypoglycemia emerges as one of the most unfavorable comorbidity. Hypoglycemia may frequently occur upon intensive antihyperglycemic treatments conducted with insulin or sulphonylureas/glinides, causing an increase in incident falls and exacerbation of existing comorbidities [30,34,35]. The high risk of hypoglycemia in diabetes care has been highlighted by the large HYPOTHESIS study conducted in 46 Italian centers, revealing that considerably high hospitalization and death rates occur when severe hypoglycemic events require referral to the emergency department, especially in elderly and frail patients [36]. More recently, the multicenter, retrospective HYPOS-1 study further investigated incidence and risk factors of hypoglycemia in more than 2000 Italian patients with diabetes. The results highlighted differences between severe and symptomatic episodes [37] and demonstrated that patients with type 2 diabetes less frequently need access to the emergency room, compared with those with type 1 diabetes, but have a higher hospitalization rate [38].

Therefore, in older adults with diabetes, any hypoglycemic event should be carefully monitored and pharmacological interventions must be modulated to avoid hypoglycemia, on condition that glycemic targets are personalized for each individual patient [7,18,39]. Prevention of hypoglycemia is also beneficial in reducing morbidity and mortality of elderly patients with diabetes, especially when it is accompanied by treatment targeting the cardiovascular risk factors. Treatment of hypertension is indicated in all elderly patients [40] and can be beneficial also in patients aged over 80 years [41]. Primary and secondary prevention with lipid-lowering agents and aspirin therapy may also be beneficial, at least in patients who have a good life expectancy.

The importance of preventing hypoglycemia is highlighted by the results of a retrospective observational analysis of a large US cohort of patients with diabetes, evaluating the impact of hypoglycemic events on acute CV events over a 2-year period. This study revealed that patients experiencing hypoglycemic events had a significantly higher risk – odds ratio (OR) = 1.79; confidence interval (CI) = 1.69–1.89 – of acute CV events [42]. The first results of the ACCORD study suggested an increase of mortality rates among diabetic patients undergoing intensive anti-glycemic treatment [43]. However, further studies did not confirm this data, even if provided evidence of the relationship between excess hypoglycemia and adverse clinical outcomes [44–46]. In conclusion, a particular attention must be paid in monitoring hypoglycemic events in older adults with diabetes and a personalized anti-hyperglycemic therapy must be implemented.

In elderly diabetic patients, the glycemic target to pursue and the means to achieve it, represent critical clinical decisions that must be adopted evaluating patient functional and disease status based on a comprehensive geriatric assessment. According to the position statements of the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and to the recent position statement jointly issued by the Italian Diabetes Society and of the Italian Society of Gerontology and Geriatrics (SIGG) [31] in most patients the level of glycated hemoglobin (HbA1c) recommended as the optimal target is <7%. The optimal HbA1c target for each patient should be determined by considering the potential risks associated with hypoglycemia in the case of treatments based on sulfonylureas, repaglinide or insulins. Notably, a concern was raised in Italy about the increase of cases treated with sulfonylureas or repaglinide among older adults with diabetes, and particularly worrying, among frail older patients. The ratio of older patients treated with gliclazide, glimepiride, repaglinide and sulfonamides (alone or in combination with metformin) accounts for 43.5% of patients aged >65 years and 54.3% of patients aged ≥80 years), who frequently have multiple comorbidities and should receive a different therapy [13]. In general, patient-tailored decisions must be balanced between the appropriateness of reducing the glucose control stringency (targets above 7% HbA1c) and the need to avoid hyperglycemic complications leading to

functional impairment [39]. Furthermore, it should be emphasized that the results of blood glucose tests should also be evaluated, because discrepancies between HbA1c and home blood glucose measurements are often observed, especially in older patients. In these particular cases, blood glucose level may be a useful indicator of treatment efficacy.

An algorithm-style set of recommendations has been developed by ADA, portraying potential sequences of anti-hyperglycemic therapy. The transition from monotherapy stage with metformin (at diagnosis or afterward), to dual and triple therapy stages, including different anti-hyperglycemic agents, and to combination injectable therapy, is decided according to the non-achievement of the HbA1c target determined for any therapy stage. The decision steps are determined on the basis of efficacy, the relative risk of hypoglycemia, the effect on body weight, adverse effects and cost of each drug class [47].

In conclusion, tailoring drug regimens and involving caregivers in all aspects of patient care are highly advisable strategies for an effective management of diabetes in older adults.

Available therapeutic options for older adults with diabetes

The treatment of diabetes first relies on an active education promoting proper diet and adequate exercise, especially in elderly patients. Then, the identification of glycemic targets and glucose-lowering therapies must follow, as much as possible focusing on patient preferences and needs, and anyway in view of reducing the CV risk.

The main oral anti-hyperglycemic agents used in elderly patients with diabetes are summarized here.

Sulfonylureas. This is the oldest class of oral anti-hyperglycemic drugs. The agents of this class are inducers of insulin secretion, acting on ATP-sensitive Potassium (K_{ATP}) channels of plasma membranes in pancreatic β-cells. The K_{ATP} channel is a complex of two subunits: the common Kir6.2 structural subunit, combined with one of the three different tissue-specific SUR regulatory isoforms, bearing the binding sites for sulfonylureas. The different sulfonylureas differ in affinity towards their different receptors: pancreatic SUR1, myocardial SUR2A, and vascular smooth muscle SUR2B [48]. Among the most common molecules of this class, when used at therapeutic doses gliclazide binds selectively to SUR1 while glibenclamide binds also to SUR2 isoforms [49]. Accordingly, gliclazide is associated with lower all-cause and CV mortality, compared with glibenclamide [50–56].

Moreover, sulfonylureas were demonstrated particularly active in reducing the risk of microvascular complications in intensive treatment protocols [57]. However high rates of hypoglycemia occurred in patients intensively treated with chlorpropamide or glibenclamide sulfonylureas. Major weight gain was also recorded in these patients [33]. Similar results were obtained during the ADVANCE study in patients under intensive treatment with the sulfonylurea gliclazide who experienced a significantly higher number of hypoglycemic events compared to the group of patients under standard glucose control with a higher glycemic target, even if the overall risk of this adverse event was lower than in the UKPDS study on other agents of the class [58]. Glibenclamide (also known as glyburide) has been classified as a potentially inappropriate medication in older adults by the American Society of Geriatrics [59] and has been replaced with gliclazide by the World Health Organization in the diabetes section of the list of essential medicines [60].

Metformin. The biguanide metformin is a widely used antihyperglycemic agent, which reduces liver glucose production and increases peripheral insulin sensitivity by activating cyclic AMP-dependent kinase. No significant hypoglycemic effects or weight loss have been associated with its use [61], but its contraindications, including renal failure, are of particular relevance in older patients [18]. However, the previously reported association of metformin with an increased risk of heart failure has been reassessed and ruled out [62,63], and its use in patients with chronic respiratory or liver disease has been re-evaluated. Overall, old age per se should not be considered a contraindication, in the absence of other absolute contraindications [62,64].

Thiazolidinediones (TZDs). TZDs are agonists of the peroxisome proliferator-activated receptor γ (PPARγ), a nuclear receptor forming heterodimers with retinoid X receptors (RXRs) with transcriptional activity [65] that activates specific gene subsets, resulting in the increase of peripheral insulin sensitivity and the reduction of glucose production at hepatic level [57]. Pioglitazone is among the few anti-hyperglycemic agents that can be used even in the presence of a severe reduction of the estimated glomerular filtration rate (GFR) values [66]. Pioglitazone is associated with an increased risk of non-osteoporotic bone fractures [67], however it reduces the risk of major adverse cardiovascular events, and of further myocardial infarction and stroke in patients who previously experienced these CV events [68,69]. The use of TZDs is not recommended in patients at risk of congestive heart failure [18].

GLP-1 receptor agonists. The agonists of the Glucagon-like peptide-1 (GLP-1) receptor are incretin mimetics that acts on pancreatic islets promoting glucose-dependent insulin release from the β cells and inhibiting glucagon secretion from the α cells. Drugs of this class have been never associated with hypoglycemia when used in monotherapy, and have been approved by regulatory agencies also for use in combination therapy with insulin [47]. Following a warning on the potential association of incretin mimetics with pancreatic neoplasia [70], no significant differences in the incidence of pancreatic cancer were found between the treatment and placebo groups for lixisenatide in the ELIXA study [71] and for liraglutide in the LEADER study [72]. Nevertheless, the US and European regulatory agencies reviewed the literature on the pancreatic safety of incretin-based medications available so far and found inconsistent data on the possible association of these drugs with pancreatitis or pancreatic cancer. However, Food and Drug Administration (FDA) and

European Medicines Agency (EMA) are still assessing the pancreatic safety of incretins and agreed to consider the risk of pancreatitis as associated with these drugs, until the results of new studies will be available [73].

Other established adverse events of GLP-1 receptor agonists are nausea and diarrhea. Moreover, weight loss may also be present and therefore these drugs may be not advisable in some frail older patients, particularly those suffering from malnutrition and cachexia [18]. On the other hand, GLP-1 receptor agonists may represent a sound therapeutic option in obese older patients with diabetes [74] and in diabetic patients with mild cognitive impairment or early Alzheimer's disease, due to the evidence of neuroprotective effects exerted by exenatide [75], liraglutide and lixisenatide [76].

DPP-4 inhibitors. The activity of GLP-1 on glucose homeostasis can be fueled also by antagonizing the enzymatic proteolysis of GLP-1 by dipeptidyl-peptidase-4 (DPP-4). Several DPP-4 inhibitors (e.g. alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin) have been developed as effective drugs reducing blood glucose in patients with diabetes [77]. Drugs of this class are generally well tolerated, with few adverse events and negligible hypoglycemia. Moreover, several studies demonstrated that treatment with DPP-4 inhibitors is not associated with the increased risk of CV risk in patients with diabetes [78–80]. Studies performed in older adults with diabetes established the efficacy and safety of DPP-4 inhibitors with minimal hypoglycemic events [81–86], no risk of fractures [87,88] and neutral or even reduced risk of CV complication and mortality [89–91]. The SAVOR, TECOS and EXAMINE studies revealed that the incidence of pancreatic cancer did not differ between drug and placebo groups [92,93]. An evaluation of SAVOR TIMI 53 study for heart failure as an endpoint, revealed an increased risk or hospitalization for heart failure (HF), particularly in presence of high levels of natriuretic peptides, previous HF or chronic renal disease [94]. A subgroup analysis of EXAMINE trial showed a non-significant increase of hospital admission for HF in patients treated with alogliptin who previously experienced HF, while the hospitalization for HF significantly increased in patients with no history of HF [95]. Based on this evidence, FDA issued a warning about the potential increased risk for HF associated with the use of drugs containing saxagliptin and alogliptin [96]. On the contrary, in diabetic patients treated with sitagliptin, the TECOS study showed no increase in HF-related hospitalization [91,97] and no label warning has been mandated by FDA. Interestingly, two recent large observational studies and a clinical study revealed that the treatment of diabetic patients with incretin-based drugs (including alogliptin, saxagliptin, and sitagliptin) was not associated with an increased risk of hospitalization for HF, irrespective of the presence of a previous history of HF [98–100].

These data point at DPP-4 inhibitors as effective and safer therapeutic alternative for older adults with diabetes, compared with other antihyperglycemic agents.

SGLT2 inhibitors. The inhibitors of sodium-glucose cotransporter 2 (SGLT2) exert an effective antihyperglycemic effect by increasing urinary glucose excretion. Antihyperglycemic agents of this class (canagliflozin, dapagliflozin, empagliflozin) represent a novel therapeutic option recently developed for the management of diabetes. They have demonstrated efficacy, tolerability, and favorable CV outcome [101–104]. Even if few data are available to date in the elderly population, the SGLT2 inhibitors canagliflozin [105], empagliflozin [106], and dapagliflozin [107,108] were associated with favorable effects on CV risk in older patients with diabetes. Interestingly, a subgroup analysis of the EMPA-REG OUTCOME study revealed that the reduction in the risk of MACE associated with empagliflozin treatment was significantly greater in patients aged $\geq$65 years [103]. Indeed, SGLT2 inhibitors exert favorable effects on some CV risk factors, like body weight, blood pressure, and uric acid levels, which may contribute to the CV protection observed in this study. Moreover, in the EMPA-REG OUTCOME study, empagliflozin was also associated with a lower risk of developing nephropathy [109]. Furthermore, the results of the CVD-REAL study revealed that SGLT2 inhibitor therapy (canagliflozin, dapagliflozin, and empagliflozin) in more than 150,000 patients with diabetes was associated with a significant higher CV protection, compared to other antidiabetic drugs, suggesting a possible class effect [110]. The CANVAS Program, including two sister trials in more than overall 10,000 patients from 30 different countries, assessed cardiovascular safety and efficacy of canagliflozin, and its potential associated risks [111]. The results indicated that the treatment with canagliflozin of patients with diabetes and established CV disease, or at high CV risk resulted in lower rates of death from CV causes, nonfatal myocardial infarction, and nonfatal stroke, compared to the placebo group. Increased renal protection was also observed in the CANVAS studies, as previously reported with other drugs of this class [103,104]. However, a significant increase ($P < 0.001$) of the risk of amputation (at the toe or metatarsal levels) was associated with canagliflozin treatment, warranting the use of this drug in patients at risk for amputation [111].

The main adverse effects of SGLT2 inhibitors are generally mild genital infection, more frequently occurring in female patients and in subjects with previous genital infections [112]. An increased fracture risk in older patients with diabetes was associated with canagliflozin treatment [113], possibly due to increased urine calcium excretion and leading to a warning issued by the FDA about the risk of fractures in canagliflozin treated patients [114]. FDA has also strengthened an existing warning about the risk of acute renal failure for canagliflozin and dapagliflozin [115]. Moreover, after an FDA warning in 2015, a twofold risk of diabetic ketoacidosis was recently associated with SGLT2 inhibitor treatment, compared to the one with DPP4 inhibitors, shortly after therapy initiation and after a 180-day follow-up [116]. Further limiting factor in the use of SGLT2 inhibitors is inherent in their mechanism of action that

make these drugs less effective in the presence of GFR <60 mL/min [117].

Therefore, although SGLT2 inhibitors may be a convenient option for elderly diabetes patients because of the oral route of administration, negligible hypoglycemia, and good tolerability, these agents should be used with caution in older adults. As an example, due to the CV and renal favorable effects, before initiating a treatment with SGLT2 inhibitors in older patients under hypotensive therapy, adjusting drug doses – especially diuretics – is highly advisable to reduce the risk of hypotension and dehydration.

Current indications to the Italian diabetology community

Since 2007 a joint project of the Italian Association of Diabetologists – *Associazione Italiana dei Medici Diabetologici* (AMD) and the Italian Diabetes Society *Società Italiana di Diabetologia* (SID) – provides up-to-date standards for all different facets of diabetes mellitus care, including the management of diabetes mellitus in older adults. The last update of the online, interactive document issued for 2016 [118] is discussed relative to older adults with diabetes. An introductory statement of this AMD/SID document points out that elderly with diabetes are at higher risk of comorbidity and therefore prone to be suffering from common geriatric syndromes, such as adverse drug reactions due to polypharmacy, depression, cognitive impairment and dementia, urinary and fecal incontinence, traumatic falls, functional impairments, disabilities, syncope, and mixed chronic pain [118]. More recently, a Position Statement on the personalization of hyperglycemia treatment in older adults with diabetes has been jointly prepared by SID and SIGG [31]. This consensus paper underscores that the management of diabetes in older adults must be personalized by individualization of the glycemic goals according to the medication used and to its risk of hypoglycemia. In older patients, the risk of severe hypoglycemia is enhanced and associated with the extent of the disease, the age, and a longer duration of insulin treatment. Moreover, an information strategy targeted to both patients and their families, and to caregivers as well, should be implemented to minimize the risks of further episodes of hypoglycemia [31].

Moreover, in elderly patients, the glycemic threshold that induces symptoms related to hypoglycemia is impaired and a substantial cognitive dysfunction may contribute to the altered perception of symptoms, known as hypoglycemia unawareness. Therefore, care, metabolic targets, and choice of drugs must be effectively personalized. Consistently, a therapeutic program dedicated to frail elderly patients and/or to patients with significant comorbidities has been proposed, with the following recommendation [118].

Functional assessment. Patients with diabetes aged >75 years should receive a multidimensional geriatric assessment, including the measurement of global physical, cognitive and affective functions, as well as of nutritional status. The ability to perform physical activity should be routinely assessed, informing the patients about the benefits that may result from and the resources available to increase the level of activity practiced. These patients should be invited to keep an updated record of the medications taken, to be shown to the primary care physician. Adults over 75 years with diabetes have an increased risk of major depression, therefore particular attention should be paid to symptoms that are suggestive of this condition, both during the initial evaluation and at worsening of clinical status not otherwise justifiable. The detection of symptoms of incontinence must be included in the annual screening of an older patient with diabetes and patients should be asked about any episodes of falls, investigating the cause (medication, environmental factors, etc.). During the initial evaluation, the elderly diabetic should be questioned on the possible presence of chronic pain.

Glucose-lowering treatment. In elderly diabetes patients, glycemic goals should be personalized. According to the Position Statement of SID-SIGG, when anti-hyperglycemic agents associated with a low risk of hypoglycemia are used (metformin, DPP-4 inhibitors, pioglitazone, SGLT2 inhibitors, GLP-1 receptor agonists, and acarbose, or a combination of these drugs), the HbA1c goal is <7.0% (<53 mmol/mL). In older patients who need treatment with agents with potential hypoglycemia risk (sulfonylureas, repaglinide, insulin or its analogs) a less stringent goal (HbA1c 7.0%–7.5%; 53–58 mmol/mL) is more appropriate. This may be further increased (HbA1c 7.5%–8.0%; 58–64 mmol/mL) in the presence of a frailty condition (severe complications, cognitive impairment, dementia, comorbidities) [31].

Metabolic goals should be pursued safely, by avoiding, or trying to minimize, the risk of hypoglycemia. A fasting blood glucose level <110 mg/dL is not recommended, as it is not advisable to start a hypoglycemic treatment if the fasting blood sugar is not persistently >126 mg/dL. If an elderly subject needs therapy with oral antihyperglycemic agents, the use of glibenclamide should be avoided, and in general sulfonylureas and glinides should be considered exclusively when the only possible alternative to achieve the proper HbA1c goal is insulin. Gliclazide must be favored among other sulfonylureas because it is associated with a lower risk of hypoglycemia. Also in older adults with diabetes the first-line medication is metformin, which is harmless as regards the risk of HF [62,63], albeit it may be contraindicated in the presence of a certain degree of hypoxia [18], and in patients at risk of renal failure GFR must be controlled, carefully evaluating all risk factors of worsening renal function [118]. Metformin must be used at reduced doses with GFR values in the range 30–45 mL/min – cumulative dose ≤1000 mg and in the range 45–60 mL/min – cumulative dose ≤2000 mg, provided that risk factors for renal function worsening are carefully considered; below the GFR value of 30 mL/min/1.73 m^2 the use of metformin is contraindicated [118]. Notably, the risk associated with the use of metformin in presence of patients with renal failure has been recently re-evaluated by FDA, which concluded that this drug can be used safely in patients with mild/moderate impairment in kidney func-

tion [119,120]. The control of estimated GFR should be carried out at least once a year and at each increase in metformin dosage. Self-monitoring scheme should correspond to the degree of patient's self-sufficiency and to his/her individual functional, affective, and cognitive capacities. The scheme must be based on the planned glycemic targets and HbA1c levels, on the actual feasibility of therapy modification, and on the risk of hypoglycemia [118].

CV risk. The CV risk profile must be evaluated first at the presentation of older adults with diabetes. All classes of anti-hypertensive agents are eligible for use in elderly with diabetes, however, angiotensin converting enzyme (ACE)-inhibitors and angiotensin receptor blockers (ARB) can be favored in presence of proteinuria and microalbuminuria, while diuretics and calcium antagonists can be favored for isolated systolic hypertension. In elderly diabetics treated with ACE inhibitors or ARBs, creatinine levels should be controlled calculating estimated GFR and serum potassium levels and in those treated with thiazides or loop diuretics, serum sodium and potassium levels should be checked, in both cases within 1–2 weeks from starting therapy, at each dosage increase and at least annually in any case. In older adults with diabetes and dyslipidemia, the alterations of the lipid profile must be managed according to the evaluation of the overall patient's health status and treatment shall be carefully evaluated in primary prevention in the case of a short life expectancy (less than 2–3 years). In the population of elderly diabetes patients, LDL cholesterol levels <100 mg/dL are recommended, while a further lowering of the values (<70 mg/dL LDL cholesterol) must be considered for elderly patients with severe CV disease, such as previous myocardial infarction, previous stroke, or major vascular diseases. Although statins use is associated with a higher risk of developing diabetes in older adults, in hyperglycemic patients with non-target cholesterol levels, therapy with statins is recommended at moderate intensity and in combination with ezetimibe, according to the European guidelines for the management of dyslipidemias [121]. Blood pressure goals must include values <150/90 mmHg. In older adults, less than 80 years old in good conditions, a further lowering of blood pressure (<140 mmHg systolic and <80 mmHg diastolic) can be envisaged if the treatment is tolerated. A reduction of blood pressure to less than 70 mmHg diastolic pressure is not recommended, especially in patients with GFR <60 mL/min. Elderly subjects may experience a poor tolerance to blood pressure reduction, especially in the case of previous episodes of syncope, falls, and orthostatic hypotension and the antihypertensive treatment should be initiated and titrated gradually [118].

Nutritional evaluation and physical activity. In elderly diabetics, dietary intake, nutritional status, and hydration should be regularly verified, providing indications for potential adequate interventions Advice on diet content and potential benefits of weight reduction should be provided, always by assessing the risk of calorie-protein malnutrition, a very common condition in elderly patients. As for the general population, vitamin D supplementation is recommended as a strategy for promoting bone health [122]. A more careful nutritional evaluation with the mini-Nutritional Assessment (MNA) is preferred in the older adult with diabetes. This screening tool allows the identification of malnourished subjects and those at risk of malnutrition, providing the indication for the nutritional intervention. The body mass index (BMI) per se is not the most appropriate predictor of nutritional status in the older individuals, because of its inability to discern or detect age-related body fat redistribution. In older adults, the obesity is a risk factor, but morbidity, disability, and mortality are related to waist circumference and not to BMI. Waist circumference correlates with visceral obesity and the related CV risk. Excessive hypocaloric diets possibly compromising the nutritional status of elderly must be avoided and the calories should not be below 1300–1400 kcal for women and 1500–1600 kcal for men. Finally, for older adults in general, a physical activity plan integrating preventive and therapeutic recommendations is indicated to reduce the risk of developing comorbidity. In individuals with no activity limitations, aerobic, muscle-strengthening, flexibility activities, and balance exercises should be included in the plan, with emphasis on the need of reducing the sedentary behavior, increasing moderate activity rather than attaining high levels of activity, and taking a gradual or stepwise approach [123]. Similarly, the older adult with diabetes should be periodically evaluated for the ability to perform physical activity. The patient should be informed about the benefits of practicing physical activity on a regular basis and encouraged to increase the level of the activity currently practiced, according to the available resources [118].

A specific indication refers to patients hosted in nursing or retirement homes that should have a plan or an agreed protocol of diabetes care, which should be regularly evaluated.

Unmet needs by guidelines

A comprehensive geriatric assessment (CGA), tailoring therapy to the patient's individual needs and possibilities, should be placed in the frame of everyday practice. CGA allows to take into consideration the high heterogeneity of older patients in terms of physical and cognitive functioning, comorbidity and family/social support.

At present, based on the available evidence for the overall frail and multimorbid elderly, a small set of simple and user-friendly instruments may be suggested. For instance, 15-item Geriatric Depression Scale, Mini Mental Status Examination, and Activities of Daily Living and Instrumental Activities of Daily Living (ADL/IADL) qualify as universally known and exploited tools to assess mood, cognition, and personal capabilities, respectively.

It is of relevance defining how therapy should be modified in acute conditions, such as surgery or severe infections because the rules currently recommended for the overall acute care patient might not fit the needs of the elderly and frail diabetic patient. Concealed factors such as subclinical infections, obstructive sleep apnea syndrome, worsening renal function or declining physical activity

may frequently change the hypoglycemic therapy required in the elderly. A short practical guideline aimed at screening the patients for these conditions might help the practicing physician.

Regulatory standards or at least consensus guidelines on the development of novel drugs to be made available to elderly patients would be desirable. Indeed, the results from randomized clinical trials (RCTs) do not apply to real

DIAGNOSIS OF TYPE 2 DIABETES IN OLDER ADULTS

↓

Nutritional evaluation → promote **appropriate diet**
Plan adequate and balanced **physical activity**

↓

Personalization of glycemic targets → avoid hypoglycemia
Also consider: degree of hyperglycemia, overweight or obesity, CV disease, other risk factors, comorbidities (renal, heart, hepatic, pulmonary failure; cancer, dementia), patient preferences and needs

HbA1c < 7.0%	7.0% < HbA1c < 7.5%	7.5% < HbA1c < 8.0%
When treated with drugs with no hypoglycemia risk	*When treated with drugs with hypoglycemia risk*	*In presence of frailty condition* – *severe complications* – *cognitive impairment* – *dementia* – *comorbidities*

↓

Personalized antihyperglycemic therapy
according to patient characteristics

↓

Class/drug	Risk of Hypoglycemia	Notes	Contraindications, major side effects and warnings
Metformin	No	May cause weight loss	Contraindicated in case of renal insufficiency (GFR<30 mL/min)
Acarbose	No	Good safety profile	Gastrointestinal adverse effects
DPP-4 inhibitors	No	- No interactions - No HF risk with sitagliptin	- Increased level of hepatic enzymes (linagliptin) - Potential risk of pancreatitis (saxagliptin) - Potential slight increased risk for heart failure with saxagliptin and alogliptin; no data for vildagliptin and linagliptin
GLP-1R agonists	No	- Advisable if weight loss is a goal - Possible neuroprotective effects - Reduced CVD risk (some molecules)	- Potential risk of pancreatitis - Nausea, diarrhea, weight loss - Not suitable in patients with malnutrition and cachexia
SGLT2 inhibitors	No	Highest CV protection among anti-hyperglycemic drugs	- Genital infections (<10% cases) - Increased risk of diabetic ketoacidosis in some conditions - Less effective with GFR<60 mL/min
Sulphonylureas and glinides	Yes	Gliclazide has a more favorable risk/benefit ratio	Many interactions (increased risk of hypoglycemia)
Pioglitazone	No	Reduced risk of major adverse CV events	Increased risk of non-osteoporotic fractures increased risk of heart failure

↓

Strict monitoring for hypoglycemia, drug interactions, temporary and definitive contraindication for organ failure, side effects, inability to manage correct treatment

Figure 1 Scheme summarizing the most relevant steps of diabetes treatment in older adults.

life elderly patients, and adverse drug reactions are frequently detected by the post marketing surveillance, as shown by the recent FDA warning referred to canagliflozin and the increased risk of leg and foot amputation [114]. A scheme summarizing the most relevant steps of diabetes treatment in older adults and the characteristics of the available hyperglycemic agents for the treatment of older adults is reported in Figure 1.

Conclusions

The management care of older adults with diabetes must take into consideration the heterogeneity of the multiple morbidities, the functional and cognitive status, and the living conditions of these patients. The following points may help to focus on the specific therapeutic strategies for this population of patients.

1) Diabetes is highly prevalent and incident in the elderly population, in a context of variable combinations of multiple morbidities, polypharmacy, frailty, and disability in patients aged 75 years and older. Accordingly, the therapeutic strategy should be individually tailored to consider individual needs, possibilities, and risks.
2) To comply with the recommendation of point 1, a comprehensive geriatric assessment aimed at exploring at least social status and available support, mood, cognition, and personal capabilities, is highly recommended in patients with diabetes over 75 years. At present, assessment instruments may be suggested based on the experience with the elderly multimorbid patient population on the whole.
3) The hypoglycemic therapy in the older adult with diabetes relies upon the same set of drugs used in the adult, but dosage and objectives should be downsized in an important proportion of elderly patients, due to futility (e.g. because of short life expectancy), the multifactorial nature of hypoglycemic risk, or to existing pharmacologic interactions.
4) Based on point 3, the HbA1c goal needs to be strictly personalized according to selected common-sense rules.
5) The practicing physician should be aware that antidiabetic drugs are commonly released after RCTs in which the real-life, multimorbid patient with diabetes over 75 years is absent or underrepresented. Therefore, the indications based on RCT data obtained in patients younger than 75 years of age are directed also to the older ones. Accordingly, port marketing surveillance requires a high degree of cautiousness and alertness.
6) Due to the age-related decline of homeostatic mechanisms, the elderly diabetic patient frequently suffers from major metabolic derangement on acute medical or surgical conditions. Close monitoring and tailoring of the hypoglycemic therapy are needed.
7) Treatment of diabetic complications and comorbid conditions is as important in the elderly as in the adult diabetic patient and should conform to the general rules.

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Conflicts of interest

Outside the submitted work, the authors report the following conflict of interests: E.B. reports consultancy from Abbott, Astra Zeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Bruno Farmaceutici, Janssen, Johnson & Johnson, Eli Lilly, MSD, Novartis, Novo Nordisk, Roche, Sanofi, Servier, Takeda; participation in sponsored clinical trial: Amgen, Janssen, Eli Lilly, MSD, Novartis, Novo Nordisk, Pfizer, Sanofi; research support: Astra Zeneca, Genzyme, Menarini Diagnostics, Novo Nordisk, Roche, Takeda; A.C. reports personal fees from Merck Sharp & Dohme, Eli Lilly, Boehringer Ingelheim; grants and personal fees from AstraZeneca, Novo Nordisk, Sanofi Aventis, Sigma Tau, Abbot, personal fees from Menarini Diagnostici, personal fees from Janssen, personal fees from Takeda, A.G. reports speaker's fees from AstraZeneca, Eli Lilly, MSD, Sanofi and Takeda, S. M. reports grants from Takeda and Sigma Tau.

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