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Which antidiabetic drug indications are recommended for geriatric DM patients?

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1. RECOMMENDATIONS

A. Metformin is effective in geriatric patients but contraindications must be considered, with particular attention paid to the highest doses.
B. Pioglitazone can be used in male patients without clinical or objective signs of heart failure.
C. Sulphonylureas and repaglinide should not be used, if possible, due to an increased risk of hypoglycemia. Glibenclamide should not be used under any circumstances.
D. There is sound evidence of reasonable efficacy and optimal tolerability of DPP-4 inhibitors in geriatric patients.
E. Long-term GLP-1 receptor agonists and SGLT2 inhibitors should be included among therapeutic options in elderly obese patients and those with a history of cardiovascular events, while considering specific adverse events related to these drugs.
F. Insulin therapy is effective and sometimes necessary, but it is complex to administer and monitor and involves an increased risk of hypoglycemia. Therefore, the cost-benefit ratio must be carefully assessed in individual cases. Where insulin therapy is required, blood sugar control targets should be less stringent.

2. STRENGTH OF THE RECOMMENDATIONS

The quality of the evidence is low. Recommendations are mostly based on best practice (supported by expert opinion) and only partially supported by published evidence.

3. SUPPORTING EVIDENCE

See appendix.

4. AREAS OF UNCERTAINTY AND FUTURE PERSPECTIVES

Available evidence in older individuals is limited, since the large majority of patients enrolled in clinical trials on diabetes drugs are less than 65 years old. In addition, the most relevant outcomes in elderly patients may differ from those of younger and middle-aged adults. Specific trials on appropriate endpoints comparing different glucose-lowering drugs in patients over 75 years old should be actively pursued.

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APPENDIX

Choice of drug therapy

It is theoretically possible that some drugs have different efficacy in different age groups. However, this has currently not been confirmed in age-specific analyses in the available controlled studies because more than a third of them exclude patients over 65 years of age, and few recruit patients over 75 [1]. However, the efficacy of some drugs on HbA1c levels may be smaller in older people than in younger adults, whereas the risk of hypoglycemia is a key element in deciding treatment for geriatric patients; currently, hospital admissions due to hypoglycemia are more frequent than for hyperglycemia, particularly in geriatric patients [2]. Aging leads to a decline in adrenergic counter-regulatory systems and reduces gluconeogenic action in the liver and kidney, increasing the risk of severe hypoglycemia [3]. In DM patients with a long disease duration, severe and recurrent hypoglycemia and autonomic neuropathy contribute to difficulties in recognizing hypoglycemia, which further increases hypoglycemic risk [3]. In addition, hypoglycemia in geriatric patients is associated with an increased risk of cognitive decline and cardiovascular morbidity [4], as well as being a primary risk factor for falls and fractures [4]. Therefore, many guidelines suggest that low-risk antihyperglycemic drugs should be used in geriatric DM patients whenever possible [5,6].
In addition to the specific characteristics of the drug, the choice of medication should include consideration of possible interactions of drugs with comorbidities and co-treatments [7] and the quality of available family support [8].

Metformin

According to most guidelines, metformin is the first line medication for the treatment of all patients with T2DM, including geriatric patients, unless it is contraindicated or not tolerated [5,6,9]. Metformin contraindications include moderate to severe renal insufficiency, heart failure, liver failure, or respiratory failure, which increases the risk of metformin-associated lactic acidosis. In particular, according to the USA Food and Drug Administration a serum creatinine level greater than 1.5 mg/dl (≥ 114.4 mmol/l) in men or ≥ 1.4 mg/dl (106.8 mmol/l) in women contraindicates metformin use, while the European Society of Cardiology and the European Association for the Study of Diabetes contraindicate the use of metformin when the eGFR is less than 60 ml/min for the full dose, or 30 ml/min for doses of less than 1500 mg/day [10,11]. In geriatric patients, serum creatinine levels do not always accurately reflect kidney function because of sarcopenia. In addition, geriatric patients are at greater risk of dehydration, which may result in a further reduction in GFR. Therefore, patients and caregivers must be instructed to suspend metformin during periods of extended fever, vomiting, or diarrhea. Long-term use of metformin in geriatric patients is associated with vitamin B12 deficiency [12]. A retrospective observation study also reported that metformin is associated with an increased risk of cognitive decline, which may be partly due to vitamin B12 deficiency [12] but results from clinical trials are not yet available [13]. However, some guidelines suggest yearly monitoring of vitamin B12 serum levels in geriatric patients who are taking metformin [9].
In conclusion, metformin is a useful therapeutic tool for T2DM even in geriatric patients, but potential contraindications should be carefully excluded. In addition, greater caution should be applied when prescribing higher than recommended doses in geriatric age groups.

Pioglitazone

Pioglitazone is the only thiazolidinedione currently available in Europe. Its main adverse effect, water retention, which appears to be more frequent in geriatric patients [14,15], can cause severe heart failure in patients with left ventricular dysfunction. As heart failure is often asymptomatic in geriatric patients, assessment of left ventricular function is recommended before prescribing pioglitazone in this age group. In addition, thiazolidinediones lead to bone mass loss, which increases the development osteoporosis in women [16]. This effect is suppressed by androgens [17] and is, therefore, not evident in men, whereas the use of thiazolidinediones in post-menopausal women is associated with an increased risk of fractures [18,19]. A possible beneficial effect of pioglitazone on cognitive functioning and stroke prevention has been suggested, but results are still conflicting [20]. In conclusion, pioglitazone should be considered as a possible therapeutic option in male geriatric DM patients, as long as they have normal heart functioning.

Sulfonylureas and glinides

All sulfonylureas are associated with a risk of hypoglycemia, which is more evident in geriatric patients. Glibenclamide, which is associated with a higher risk of hypoglycemia than other sulfonylureas [21], should never be used in geriatric patients [5]. Despite having a lower hypoglycemic risk, glipizide, gliclazide, and glimepiride should, if possible, be avoided in geriatric patients (due to an unfavorable risk-benefit ratio [5,9]. In fact, the risk of severe hypoglycemia with sulfonylureas is not lower than that of insulin therapy [21,22]. Hypoglycemia associated with sulfonylurea use may cause falls and fractures, but data on this is limited [23]. In addition, clinical trials report an increase in all-cause mortality associated with sulfonylurea [24].

Although repaglinide has a different chemical structure other than sulfonylureas, it shares the same mechanisms of action and side effects and is characterized by a shorter kinetic. There have been no clinical trials investigating repaglinide in patients over the age of 70 years, as specified in the approved summary of product characteristics.

Dipeptidyl peptidase-4 (DPP-4) inhibitors

Pooled analyses [25,26] from placebo-controlled studies have shown that there are no age-related differences in effectiveness or adverse effects for DDP-4 inhibitors. This is also confirmed by specific trials in older people [25,27,28]. A post-ad-hoc analysis of retrospective studies confirmed the safety of DDP-4 inhibitors even in geriatric patients with renal insufficiency, who have a high risk of adverse effects [1].

Sub-group analyses from cardiovascular safety trials on DDP-4 inhibitors showed similar results among patients over 65 years of age [29-31]. Two studies [32,33] specifically on patients over 75 years of age also provided the same findings.

Experimental studies suggest that DPP-4 inhibitors may have a neuroprotective effect, delaying cognitive decline in Alzheimer's disease and Parkinson's disease [34], but no clinical data are currently available to support this. Another interesting feature of DPP-4 inhibitors is that they can be safely used in patients with kidney failure, which strengthens its suitability in geriatric patients.

DPP-4 inhibitors are possibly the most extensively studied anti-hyperglycemic drugs in geriatric patients. The available evidence suggest that they are safe in geriatric patients, with comparable efficacy to that found in younger patients. Therefore, they are one of the most interesting treatment options for geriatric patients, particularly when adequate glycemic control cannot be achieved with metformin monotherapy or when there is a contraindication.

Sodium-glucose co-transporter-2 (SGLT2) inhibitors

Both observational studies [35] and clinical trials [36-39] have shown that SGLT2 inhibitors are effective and generally well tolerated in geriatric DM patients, including those with chronic kidney disease [40]. Empagliflozin and canagliflozin are also associated with a reduced risk of major cardiovascular events; all molecules in this drug class seem to reduce hospitalization in patients with heart failure and progression of diabetic nephropathy [41-43]. In addition to reducing cardiovascular risk, SGLT2 inhibitors also have a long-term neuroprotective effect but no specific data is available in persons aged over 75 years [41].

The main adverse effects of SGLT2 inhibitors are genitourinary infections. In geriatric patients, the use of SGLT2 inhibitors can lead to dehydration, which can possibly reduce GFR [39]. To avoid this risk, it is recommended that the dose of canagliflozin should not exceed 100 mg per day for geriatric patients [44]. For older people who also take diuretics, a dose reduction is recommended when SGLT2 inhibitors are initiated, in order to prevent hypotension and dehydration [11]. In conclusion, SGLT2 inhibitors have a potential beneficial effect for cardiovascular and renal complications and have a simple regimin (usually once daily oral administration), but caution is needed for use in geriatric patients because of adverse effects.

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

In addition to significantly reducing hyperglycemia with low hypoglycemic risk, gGLP-1 receptors agonists also reduce the incidence of cardiovascular disease in high-risk patients [45], including those over 65 years [45], while no specific data are available for people over the age of 75. Results from pre-clinical and clinical trials have also shown favorable effects of GLP-1 receptor agonists on neural protection and cognitive performance [4]. Data from the REWIND study show that long-term therapy with dulaglutide can prevent cognitive decline in T2DM patients, even those over 70 years of age [46], but these benefits need further confirmation in specifically designed studies. The dosage regimen is another advantage; although they need to be administered by subcutaneous injection, most GLP-1 receptor agonists have a weekly, one-dose regimen. The most frequent side effect of GLP-1 receptor agonists is nausea [11]. They can also induce anorexia and weight loss, which can have adverse effects in some geriatric patients [6]. In fact, although obesity is a risk factor for frailty [47], weight loss is not necessarily beneficial in geriatric patients [48]. In conclusion, GLP-1 receptor agonists are an interesting option for treating T2DM, although their use in geriatric patients is limited due to associated weight loss.

Insulin therapy

Sub-group analyses on the only three insulin studies that enrolled geriatric patients [49] confirms the safety and efficacy of insulin analogues in elderly individuals. However, these conclusions are not fully generalizable to all geriatric DM patients; capillary glycaemia needs to be self-monitored to achieve effective and safe insulin use, and this may be difficult for geriatric patients, especially if they have visual impairments or reduced dexterity. Insulin is associated with an increased risk of fractures, particularly in patients with lower mean glucose and HbA1c levels, which is likely due to hypoglycemic episodes causing falls [4]. In addition, HbA1c lower than 48 mmol/mol (6.5%) has been reported to be associated with an increase in all-cause mortality in geriatric patients taking insulin [50]. These results suggest that glucose targets should be relaxed when insulin therapy is introduced.

Insulin regimens must be individualized according to the needs of the individual patient, by administering basal insulin, fast-acting mealtime insulin, or a combination of the two, according to patterns of patient's self-monitored glucose levels. The number of injections and available family support should also be taken into account when selecting the regimen, in line with glucose patterns. Although it can be easier for patients to correctly administer medication on a daily basal insulin monotherapy, there is a reduction in postprandal insulin secretion associated with older age [51], which in some cases leads to a need for fast-acting mealtime insulin, alone or in combination with basal insulin in a basal-bolus regimen [52].

Regarding basal insulin, the use of long-acting insulins (glargine, detemir, and degludec) is preferable to older Neutral Protamine Hagedorn (NPH insulins), both in younger and older people, as they are characterized by a reduction in glycemic variability and risk of hypoglycemia [53], thus allowing a more accurate insulin titration [54]. Glargine U300 is a basal insulin with a longer-acting duration and a lower risk of nocturnal hypoglycemia than glargine U100, even in people over the age of 65 [55,56]. Degludec insulin has a longer duration than glargine U100, and greater administration flexibility, which can be an advantage for those who need help with drug injection [57]. In addition, it has been associated with lower nocturnal hypoglycemia [58]. When fast-acting mealtime insulin is needed, short-term regimens (lispro, aspart, glulisine) ensure better control of post-prandial hyperglycemia with less risk of hypoglycemia than regular human insulin [59]. When insulin treatment needs to be initiated in a geriatric patient, education for both the patient and their caregiver should be provided, with frequent follow-ups [10]. The need to achieve glucose targets should, therefore, be weighed up by the clinician, taking into account the increased treatment complexity and risk of hypoglycemia.

Insulin is still a valuable therapy in many geriatric patients, without which, in many cases, it would be impossible to achieve and maintain good blood sugar control. Nevertheless, caution is needed due to the complexity of the treatment and risk of hypoglycemia, which can result in falls and fractures, and the use of other oral antidiabetic drugs is preferable where possible. When insulin is unavoidable, glucose targets should be less stringent, to reduce the risk of hypoglycemia.

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This statement is:	**Quality of the evidence** (in the case of recommendation):
☐ Recommendation (supported by published evidence) ☒ **Best practice** (supported by expert opinion)	☒ **Low** ☐ Moderate ☐ High