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Appropriate prescribing

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1. RECOMMENDATIONS

A. Each clinical examination of geriatric DM patients should include a review of their existing therapies to minimize polypharmacy and reduce the risk of adverse reactions and drug interactions.
B. It is important to use decision support tools to assess possible pharmacological interactions (e.g., INTERCheck or other electronic support tools) at least once a year in geriatric DM patients who are taking 5 or more drugs.
C. Chlorpropamide, glimepiride, and glibenclamide should never be used in geriatric patients due to an excessive risk of prolonged hypoglycemia.
D. Metformin should not be used in patients with GFR < 30 ml/min/1.73m^2 due to the risk of lactic acidosis.
E. Rosiglitazione and pioglitazione should not be used in patients with co-existing heart failure, due to risks of exacerbating the condition.
F. In DM patients with limited life expectancy, stringent blood sugar target (HbA1c < 8%/64 mmol/mol) must be avoided.

2. STRENGTH OF THE RECOMMENDATIONS

The quality of the evidence is moderate. Recommendations are supported by published evidence and best practice (supported by expert opinion).

3. SUPPORTING EVIDENCE

See appendix.

4. AREAS OF UNCERTAINTY AND FUTURE PERSPECTIVES

Most clinical trials aimed at improving quality of prescribing and reducing inappropriateness have failed to show an impact on outcomes that are relevant to geriatric patients (e.g., adverse drug reactions, falls, hospitalization, delirium, death). Few of these studies have specifically focused on patients with diabetes. Therefore more evidence from well designed studies is needed to strengthen the recommendations issued in this area.

APPENDIX

Assessment of drug appropriateness: which criteria are best?

About 50% of people over the age of 65 suffer from two or more diseases, often chronically, and this increases to around 80% in people aged over 80

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years [1]. Older people, especially those with DM, often experience polypharmacy, sometimes due to evidence and guidelines being strictly applied rather than adapting them to the individual. Further, strategies to deal with polypharmacy are frequently based on data from studies on young adults with single diseases rather than trials on older populations [2]. Polypharmacy, in conjunction with reduced functional reserve and changes in metabolism and clearance capacity in geriatric patients, frequently leads to pharmacological interactions and adverse reactions, particularly in individuals with DM. Numerous international associations are working on producing criteria and guidelines for prescribing drugs in geriatric patients that aim to reduce the adverse effects of polypharmacy: the most widely used tools are the Beers, START/STOPP (Screening Tool to Alert doctors to Right Treatment/Screening Tool of Older Person's Prescriptions), and FORTA criteria.

The Beers Criteria [3], devised by the American Society of Geriatrics, mostly recently updated in 2019, contain an explicit list of 'Potentially Inappropriate Medications" (PIM) for specific conditions in geriatric patients, which are classified as 'Avoid' and 'Use with caution'. These fall under the Drug Oriented Listing Approach (DOLA) category.

START/STOPP [4] is a patient-centered assessment system for appropriate therapy; the "Patient In Focus Listing Approach" (PILA). The latest version from 2015 is based on 34 START criteria (or drugs with potential benefit for disease prevention or treatment), and 80 STOPP criteria (or drugs not specified or contraindicated in older people).

FORTA is a PILA instrument, updated in 2018, which indicates a list of drugs in relation to certain clinical conditions [5], using a patient-oriented approach, classified into 4 categories: A (Indispensable), B (Beneficial), C (Questionable), D (Avoid).

Most clinical trials conducted on DOLA instruments (such as the Beers criteria) have failed to evaluate outcomes that are relevant to geriatric patients (e.g., adverse drug reactions, falls, hospitalization, delirium, death). The patient-centered START/STOPP tools not only list PIMs but also propose drugs to be included for specific clinical conditions, based on available evidence. These instruments have been validated in several randomized controlled trials, with most showing a positive impact [6-8] on the quality of treatment in terms of under- and over-treatment, although none have demonstrated an impact on the clinical outcomes of patients.

For the use of drugs in DM patients, the Beers, START/STOPP, and FORTA criteria refer to the following drugs: The Beers criteria indicate avoiding long-acting sulfonylurea class drugs, in particular chlorpropamide, glimepiride, and glibenclamide. Because of their long life, these drugs can cause severe and prolonged hypoglycemia in geriatric patients. In addition, glimepiride and glibenclamide can cause the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

STOPP policy recommends to not use:

- metformin when GFR < 30 ml/min/1.73m^2 due to risk of lactic acidosis;
- long-acting sulfonylureas, particularly chlorpropamide, glimepiride, and glibenclamide, due to the risk of hypoglycemia;
- rosiglitazione and pioglitazione in patients with coexisting heart failure due to the risk of exacerbating the condition;
- beta-blockers in patients with frequent episodes of hypoglycemia due to the risk of masking symptoms of adrenergic hypoglycemia related to hyperactivity of the sympathetic nervous system.

The START criteria, however, advise the use of:

- angiotensin-converting enzyme (ACE) Inhibitors or angiotensin II receptor blockers (ARBs) in DM patients with proteinuria or microalbuminuria with or without kidney failure.

The FORTA criteria classify glimepiride as C (Questionable), and glibenclamide, rosiglitazione and pioglitazione as D (Don't, to be avoided). They also rate SGLT2 inhibitors as C (Questionable), due to an increased risk of dehydration, falls, genital mycosis, and urinary tract infections.

It should be noted that STOPP criteria have been specifically developed for patients with limited life expectancy [9]. These criteria indicate to:

- simplify pharmacological therapy and avoid strict therapeutic targets (HbA1c < 8%/64 mmol/mol);
- suspend therapy with ACE-Inhibitors or ARBs if they have only been prescribed to prevent diabetic nephropathy.

The criteria for drug appropriateness have been limited by the introduction of new diabetes treatments, such SGLT2 inhibitors.

It should also be noted that none of the above criteria have any clear indications for assessing the risk of drug-drug interactions. However, there may be many interactions that are extremely relevant from a clinical point of view [10]. Consequently, several web tools have been developed for evaluating pharmacological interactions, some of which have been validated in Italian [11,12].

Ethical consideration

Not applicable.

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Conflict of interest

The Author declares no conflict of interest.

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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