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REVIEW ARTICLE

Lipid-Lowering Therapy and Cardiovascular Prevention in Elderly

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Abstract

The global population aged 80 years and older will reach approximately half a billion in the coming years, and cardiovascular prevention in this group of patients will become a global health challenge. In the era of evidence-based medicine, the use of lipid-lowering therapies (LLTs) in the elderly, particularly in primary and secondary cardiovascular prevention, remains an area of active research. Although there is broad consensus on the use of LLTs in the elderly to prevent recurrent cardiovascular events in secondary prevention, there is considerable debate about their use in primary prevention. Many efforts have been made to improve cardiovascular risk stratification in patients over 75 years of age in primary prevention. In recent years, some specific risk scores have been developed, including the Systematic Coronary Risk Evaluation 2 for Older Persons (SCORE2-OP). While there are very few specific warnings to consider for LLTs in the elderly, an important challenge in this patient population is to identify the turning point at which the disutility risk outweighs the potential benefits. However, despite the widespread recognition of the importance of this issue, there is a lack of guidance on how to identify patients who should be withdrawn from therapy. The aim of this narrative review is to examine the current state of knowledge regarding the indications for LLT in elderly patients, identify outstanding issues, and discuss future developments.

1 Introduction

In 2021, the global population aged over 65 years reached 761 million, and this number is expected to grow to 1.6 billion by 2050. The population aged over 80 years is projected to increase from 155 million in 2021 to 459 million,

Key Points

Cardiovascular prevention in the elderly represents one of the most significant health challenges of the present era. Despite the majority of cardiovascular events occur in the geriatric population, uncertainties and debates persist on the use of lipid-lowering therapies in the elderly.

The opportunity to initiate therapy in primary prevention in patients over 75 years remains ambiguous, and the discussion becomes even more intricate when considering the very elderly.

Concepts such as tertiary prevention, the risk of disutility, and a simple definition of frailty are not yet an integral part of the evaluation in clinical trials on cardiovascular prevention in geriatric age. The present review aims to highlight the state of the art on this topic and outline the challenges that await us in this regard.

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with the fastest growth occurring in Eastern and South-Eastern Asia [1]. The aging of the population presents several economic, social, and healthcare challenges, one of which is the approach to cardiovascular prevention in the elderly.

A 2015 Mendelian randomization study investigated the impact of genetic predisposition to high low density lipoprotein cholesterol (LDL-C) levels in the elderly. The results confirmed that genetically determined high LDL-C levels are a lifelong risk factor for all-cause mortality, including in individuals over 90 years [2]. However, until 2018, data supporting the use of lipid-lowering therapies in cardiovascular prevention were robust primarily for individuals under the age of 66 years [3]. In the last years, little has changed, with a specific focus on secondary prevention [4, 5].

While high LDL-C levels are a significant risk factor throughout life, the benefit of statins in those aged 75 years and older remains controversial [6]. In addition, data on statin cost-effectiveness in elderly are not univocal [7]. Data from the Jupiter study showed a lower number needed to treat (NNT) in patients aged ≥ 70 years (NNT = 62) compared with those < 70 years (NNT = 94) during a 2-year follow-up conducted in primary prevention patients [8]. Similarly, the PROVE IT-TIMI study showed lower NNT in patients aged ≥ 70 years (NNT = 44) compared with those < 70 years (NNT = 13) by reaching the target of 70 mg/dl during a 2-year follow-up of patients in secondary prevention [9]. Conversely, a meta-analysis of data from patients in primary prevention set the NNT to 83 and 142 for myocardial infarction and stroke, respectively, with a mean time of 3.5 years [10]. Further, data from Cholesterol Treatment Trialists' (CTT) collaboration, the most comprehensive meta-analysis on individual patient data, showed that the NNT for avoiding a cardiovascular event by reducing LDL cholesterol by 1 mmol/L with a statin is 167 in patients aged > 70 years versus 143 in those aged < 65 years [11].

Although the NNT is a key measure of clinical effectiveness, it also plays an essential role in cost-effectiveness evaluations. Nevertheless, several pharmacoeconomic data, mainly derived from UK studies, indicated that statins remain cost-effective in elderly patients [12, 13], irrespectively of their cardiovascular disease (CVD) history or LDLC level [13], even though the cost-effectiveness decreases with later intervention [12]. All cardiovascular risk scores, even those specifically designed for the elderly, do not account for competing risks, and intercepting statin disutility requires an individualized approach. Nonetheless, the absence of competing risk analysis in cardiovascular risk scores does not inherently reduce the cost-effectiveness of these tools when selecting patients for statin therapy. This emphasizes the importance of an individualized approach that balances clinical efficacy, economic considerations, and patient-specific factors [14]. Therefore, identifying the point at which statin disutility outweighs its benefits is challenging.

Despite these limitations, current evidence supports the treatment of elderly patients in a manner analogous to younger individuals for the purpose of secondary prevention [13]. In contrast, the use of lipid-lowering therapies for primary cardiovascular prevention in this population remains a subject of ongoing debate [14], reflecting uncertainties regarding the balance of risks and benefits in the context of competing health priorities. The aim of this review is to summarize the evidence regarding the use of lipid-lowering therapies to reduce cardiovascular events in elderly patients.

2 Literature Search Methods

The structure and heading titles of the review were prespecified. Literature search was performed in December 2024 on PubMed, using the combination of the following terms: "old-person," "old-subjects," "old-patients," "older patients," "elderly," and "lipid-lowering therapies," "statin," "ezetimibe," "Proprotein Convertase Subtilisin/Kexin type 9," "PCSK9," "fibrates," "bempedoic acid," "icosapent ethyl acid," "EPA," "cardiovascular prevention." Articles without an abstract and in a language different than English were excluded. Two authors (F.B. and F.M.) reviewed PubMed results and evaluated the presence of data useful for the discussion of the topics, which were identified by paragraph titles. In case of discordance between the two authors, a third author (I.L.) guided a collegial discussion to decide to include or exclude the article. The most recent guidelines were a priori included in the review. When overlapping meta-analyses were found, the most recent and comprehensive was included.

3 The Importance of Cardiovascular Risk Estimation in the Elderly

The use of lipid-lowering therapy in elderly patients, particularly regarding primary and secondary cardiovascular prevention, remains an area of active research. Life expectancy and polypharmacy play a crucial role in therapeutic strategies. Cardiovascular risk stratification has been universally recognized as a cornerstone in managing elderly patients, as emphasized by all major international guidelines. Several risk assessment tools are available to guide clinical decision-making, and some of these have been specifically adapted for use in older populations to account for age-related factors.

However, for secondary prevention, the benefits of statin therapy are well-established and generally outweigh the risks. International guidelines, including those from the American College of Cardiology (ACC)/American Heart Association (AHA) and the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS), recommend lipid-lowering therapy for patients aged 75 years and older in secondary prevention with minimal differences compared with younger patients. [4, 5]. Meta-analyses have confirmed that statins reduce cardiovascular events and mortality in elderly patients with history of cardiovascular disease, though the absolute risk reduction may be smaller than in younger populations [15]. The evidence on secondary prevention undeniably proved the efficacy of lipid-lowering therapies in elderly high-risk patients.

The JUPITER trial [16] and the ASCOT-LLA study [17] have shown that statins are effective in reducing cardiovascular events in older adults, particularly in those with elevated LDL-C or other risk factors. However, the evidence in individuals aged 75 years and older is less robust compared with younger populations. [18, 19]. The same results were found also for non-statin lipid-lowering therapies (LLTs) [20].

Considering the weaker evidence, both American and European guidelines recommend an individualized approach to primary prevention in the elderly, weighing the benefits against potential risks. To evaluate the potential benefits, a correctly risk-stratified evaluation is mandatory in elderly patients without a history of atherosclerotic cardiovascular disease (ASCVD). Indeed, the ESC/EAS guidelines suggest initiating statin therapy in individuals aged > 75 years only if they are at high risk or above [4].

For these reasons, a well-performing cardiovascular (CV) risk estimator could be pivotal in determining whether to start statin therapy in the elderly for primary prevention. The Framingham Risk Score [21] was initially developed for middle-aged populations, and has since been employed in elderly populations with age-specific adjustment. The variables included are cholesterol levels, blood pressure, smoking status, and diabetes. More recently, the American College of Cardiology and American Heart Association (ACC/AHA) developed the ASCVD Risk Calculator [5] to evaluate the 10-year risk for atherosclerotic cardiovascular disease. The tool can be used in older adults, but its accuracy decreases with advanced age owing to changes in risk factors and mortality risk. Furthermore, the official ACC tool has a maximum age limit of 79 years owing to the lack of an adequate number of patients aged ≥ 80 years in the validation cohort [22]. A recent study demonstrated the failure of the atherosclerotic cardiovascular disease (ASCVD) risk estimator in the elderly, with progressively decreasing accuracy with age and a complete lack of predictive power in patients aged 85 years and above [23].

Conversely, the Systematic Coronary Risk Evaluation 2 for Older Persons (SCORE2-OP) [24] is a risk prediction tool that has been specifically developed for elderly individuals with the aim of estimating the 10-year risk of cardiovascular events. It incorporates age-specific data and considers factors that are pertinent to the elderly, such as comorbidities and functional status. This tool assists clinicians in more accurately assessing cardiovascular risk in older patients, who have been underrepresented in traditional score models.

4 Secondary Prevention in Elderly

Despite the elderly representing a minority of the global population (approximately 5–6% of the global population) [25], among individuals over the age of 80 years, three out of ten men and one out of four women have been diagnosed with coronary artery disease [26], and they account for 20% of all hospitalizations for myocardial infarction and 30% of all myocardial infarction-related hospital deaths [27], with a total of 80% of coronary deaths occurring in patients over the age of 65 years [29]. For many years, there has been a consistent body of evidence confirming the effectiveness of long-term lifestyle modifications, particularly statin therapy, in the secondary prevention of cardiovascular disease in the elderly.

In 2008, Jonathan Afilalo and colleagues [28] published pivotal meta-analytic data from placebo-controlled randomized controlled trials (RCT) investigating the efficacy of statins in secondary prevention, with a particular focus on elderly individuals. Notwithstanding the fact that the sole trial conducted on the elderly was the PROSPER trial, the authors managed to obtain data on elderly patients from eight other studies, both published and unpublished. The authors demonstrated the efficacy of statins in all the predetermined outcomes, including both hard and soft endpoints. Statins demonstrated a 28% reduction in all-cause mortality, a 30% reduction in coronary artery disease (CAD) mortality, a 26% reduction in nonfatal myocardial infarction (MI), and a 25% reduction in stroke. This corresponds to the treatment of 28 patients over a 5-year period to prevent one death. At the time of the Afilalo meta-analysis, the proportion of elderly patients with a history of CAD who were receiving statin therapy was estimated to be between 40% and 60% [29–32]. The Afilalo publication, along with subsequent similar studies, contributed to a reduction in the proportion of elderly patients with previous CAD who remained untreated [33].

Finally, in 2019, the Cholesterol Treatment Trialists' (CTT) Collaboration group published a comprehensive meta-analysis of individual participant data from 28 randomized controlled trials [19]. The findings of the study corroborate the notion that aggressive lipid-lowering therapies,

predominantly statins, confer a favorable outcome, even in patients aged 75 years or above, with a 15% relative risk reduction for major cardiovascular events for each mmol/L of LDL-C reduction. In contrast, no statistically significant reduction in relative risk was observed in patients aged 70 years or above.

All this evidence together leads the ESC/EAS to recommend, with level 1A evidence, to treat elderly patients with ASCVD in the same way as younger ones [4]. It is noteworthy that the ACC/AHA, in their revised 2008 guidelines, reaffirmed a more conservative approach in the management of patients aged 75 years [34]. In particular, the task force proposed that age differences in patients' treatment should be made only in those at very high risk of ASCVD recurrence (i.e., in those with a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions). Conversely, other authors have suggested treating patients with moderate- or high-intensity statins, without mentioning the possibility of adding second- or third-line drugs. The Canadian Cardiovascular Society proposes a similar approach to that put forth by ESC/EAS [35].

5 Prescription of Statin in Elderly without a History of ASCVD

The current guidelines lack clarity and consistency regarding the risk and benefit of initiating statin therapy in elderly patients (aged 75 years and above) in primary prevention. Significant discrepancies exist between the recommendations set forth by different scientific societies. To facilitate a more straightforward discussion, we will consider and compare the two most impactful guidelines: the AHA/ACC and ESC/EAS guidelines.

Prior to undertaking a comparative analysis of the specific issue, it is imperative to acknowledge that most of the discrepancies between the AHA/ACC and ESC/EAS guidelines can be attributed to a divergence in their respective drafting approaches. The 2019 European guidelines were based on an LDL cholesterol targeted approach, which required the extrapolation of an LDL-C goal to be achieved in specific CVD risk groups. In contrast, the 2018 American guidelines have continued the approach pioneered in 2013 of maximizing statin therapy depending on the extent of cardiovascular risk. This approach is strictly evidence-based, limiting experts' extrapolation and interpretation [36]. However, the 2018 guidelines marked a return to LDL targets for identifying patients who require the addition of non-statin therapies in high- and very high-risk patients already on maximal statin therapy. This concept was further expanded by the 2022 Multisociety Consensus on the role of non-statin therapy in the treatment of ASCVD [37]. In any case, the reinforcement of maximal statin therapy is an approach that is not particularly indicated in primary prevention, particularly in the elderly.

This topic has been specifically addressed in the European guidelines, which include a dedicated discussion on the treatment of dyslipidemia in the elderly, with a particular focus on the use of statins in this population group [4]. In referencing the CTT meta-analysis [19], the authors emphasize the efficacy of statins in elderly patients, irrespective of age. However, they also highlight a lower strength of evidence in primary prevention in patients over 75 years and the necessity to acquire data from the STAREE project to set more robust indications.

5.1 Guideline Indications for Patients Over 75 Years

To date, the specific ESC/EAS indications for the treatment of dyslipidemias in older people in primary prevention are as follows: (1) statin treatment is recommended for older people aged ≤ 75 years, according to the level of risk, as class I evidence indicates that this is an effective approach (class of evidence, I); (2) for older people aged > 75 years who are at high risk or above, initiation of statin treatment may be considered as a potential strategy (class of evidence, IIb); (3) in contrast to younger patients, statin treatment in the elderly should be initiated at a low dose if there is significant renal impairment and/or the potential for drug interactions and then titrated upward to achieve LDL-C treatment goals (class of evidence, I) [4].

In addition, the ACC/AHA guidelines provided detailed indications for primary prevention in the elderly, particularly regarding the evaluation of the suitability for the initiation of statin therapy. They are the following: (1) in adults aged 75 years or older with an LDL-C level of 70–189 mg/dL (1.7–4.8 mmol/L), initiating a moderate-intensity statin may be reasonable (class of evidence, IIb); (2) in adults aged 76–80 years with an LDL-C level of 70–189 mg/dL (1.7–4.8 mmol/L), it may be reasonable to measure coronary artery calcium (CAC) to reclassify those with a CAC score of zero to avoid statin therapy (class of evidence, IIb). As with European societies, the Americans support their indication mostly on the basis of CTT metanalysis. However, the specific indication on CAC score analysis measurement in elderly expresses a cautious approach by American experts on the use of statins in elderly. The indication is supported by a large-scale study that used the CAC score to reclassify the CV risk score in elderly patients in primary prevention, thereby reducing the risk when the CAC score is ≤ 100 Agatston [38].

An ACC expert consensus has identified the specific group of patients to whom non-statin therapies for lowering LDL cholesterol should be prescribed in addition to statins, delineating the decision-making pathway for their prescription [37]. The committee discussed the potential benefit of

adding ezetimibe to the treatment regimen of patients aged 75 years and older in the context of secondary prevention. However, no indications were provided for its use in primary prevention. Together, the consensus also emphasized the importance of an individualized assessment for each elderly patient and the necessity of a clinician–patient discussion in which the potential benefits and risks of initiating statin therapy are outlined, along with the paucity of evidence on the use of these drugs in this subset of patients [37].

5.2 Special Consideration before Starting Therapy

As reported by the ACC/AHA guidelines, the decision-making process regarding the initiation of statin therapy should be tailored to the individual patient, taking into account factors such as expected longevity, frailty, polypharmacy, susceptibility to adverse effects of treatment, and the patient's goals of care. In parallel with the continuous ageing of the global population, the concept of frailty has gained increasing attention from healthcare providers and the scientific community [39]. Frailty is defined as an age-related decline in multiple physiological systems, which increases vulnerability to even minor stressors [40]. As is often the case, the guidelines indicate frailty as a significant factor in the decision-making process, yet they do not provide a clear definition of how to evaluate it for this purpose. To date, the diagnosis of frailty has remained challenging owing to the absence of a widely accepted tool for its straightforward diagnosis [39]. The two most commonly employed instruments for diagnosing and characterizing frailty are the frailty phenotype (FP) and the frailty index (FI) [41]. The FP is a straightforward assessment tool that examines a range of physiological domains, including weakness, slowness, low levels of physical activity, exhaustion, and weight loss. However, the level of severity of frailty is not defined by FB. The FI considers 15 variables, investigating the presence of comorbidities (cancer history, coronary heart disease, and dementia), daily activities, health attitude, function, and nutrition. In contrast to FP, FI can discriminate between severity levels of frailty, although it is less straightforward to investigate.

The potential disutility risk in starting statin treatment, particularly in frail elderly patients undergoing primary prevention, is a subject of considerable debate. The few studies that explored this issue indicate that statin treatment remains beneficial for frail elderly individuals, even in the presence of fragility and significant comorbidities [14, 42].

5.3 Ongoing Randomized Clinical Trials on Primary Prevention in Elderly

In our opinion, two ongoing studies have the potential to address the abovementioned debate by shifting the focus from the balance between competing risks and benefits to a comprehensive approach to tertiary prevention in the elderly. The STAREE trial ("Statins for extension of disability-free survival and primary prevention of cardiovascular events among older people: protocol for a randomized controlled trial in primary care," ClinicalTrials.gov ID: NCT02099123) is a randomized controlled trial designed to test the hypothesis that statins can enhance disability-free survival and reduce major cardiovascular events in individuals aged 70 years and older without a history of cardiovascular disease. This trial combines cardiovascular events and frailty-related outcomes as its primary endpoint [43].

Similarly, the PREVENTABLE trial ("Pragmatic evaluation of events and benefits of lipid lowering in older adults," ClinicalTrials.gov ID: NCT04262206) has comparable objectives [44]. Both studies aim to recruit 20,000 participants with a 1:1 allocation of placebo to atorvastatin. In the PREVENTABLE trial, atorvastatin is administered at a fixed dose of 40 mg, whereas the STAREE trial employs a dose titration strategy, beginning with 20 mg of atorvastatin. Both studies identify as their primary outcome the prevention of new dementia or persistent disability, with a secondary outcome comprising a composite of cardiovascular events. Notably, the PREVENTABLE trial also includes a co-secondary outcome that encompasses a composite of mild cognitive impairment (MCI) and dementia, aimed at detecting differences in the onset of early cognitive alterations. In addition, both protocols have prespecified sex-specific subgroup analyses. This aspect is crucial, given the established gender differences in response to lipid-lowering therapies While the efficacy of these therapies in cardiovascular prevention does not appear to differ by sex—especially in secondary prevention—the effectiveness in women for primary prevention remains a topic of ongoing debate [47]. By focusing on the elderly population, the STAREE and PREVENTABLE trials are expected to yield valuable data on a largely underrepresented demographic in previous clinical trials, particularly on older women in primary prevention [48].

6 Lipid-Lowering Therapies Discontinuation

Another approach that has been the subject of debate is the discontinuation of LLTs, particularly statins, in the elderly.

All the guidelines agree that in older patients who are tolerating statin therapy well, statins should not be discontinued [49]. A large-scale study was conducted to investigate

the effect of statin discontinuation over a 2.4-year follow-up period in a cohort of 120,174 patients aged 75 years and above in primary prevention. During the abovementioned period, those who discontinued statin therapy (14.3%, n = 17,204) exhibited a 33% elevated risk of being admitted to the hospital for a cardiovascular event. [50]. The same data were found in a cohort of elderly Danish patients in whom statin discontinuation was associated with an increase in the incidence of coronary, cerebrovascular, peripheral, and cardiovascular events, as well as mortality, in both primary and secondary prevention [51]. The question of whether statin discontinuation could be beneficial in certain patients is a complex one, and the identification of these patients is a topic of considerable debate.

The ACC/AHA has defined circumstances in which it is reasonable to stop statin therapy, in patients aged ≥ 75 years. These circumstances include functional decline, multimorbidity, frailty, and a reduction in life expectancy, which limit the potential benefit of the patient (class of evidence, IIb) [5]. In addition, the AHA Scientific Statement on Palliative Pharmacotherapy for Cardiovascular Disease [52] provides additional insight by indicating that in patients with a life expectancy of < 1 year, whether in primary or secondary prevention, statin discontinuation was associated with improved quality of life and cost savings, with no significant difference in 60-day mortality [53]. The statement encourages physicians to consider the benefits and risks, as well as the patients' preferences and goals of care when deciding whether to discontinue statins in patients in end-stage of life [52]. As previously discussed, accurately estimating the life expectancy and frailty status of the elderly remains a significant challenge that has yet to be fully resolved.

It is noteworthy that neither the 2019 ESC/EAS [4] guidelines on dyslipidemia nor the 2021 ESC guidelines on cardiovascular disease prevention in clinical practice [54] address the issue of LLTs discontinuation.

7 Statins in Elderly: Side Effects, Concerns, and Possible Drug–Drug Interactions

As previously outlined, most data on the efficacy of LDL reduction in elderly patients come from statin studies not specifically designed for elderly. A meta-analysis of CTT data [19] showed an efficacy in preventing cardiovascular events with a reduction of cardiovascular risk by statins estimated at 18% per each mmol/L LDL cholesterol reduction. Although cumulative data from statin and non-statin trials show no age-related differences in the efficacy of drug-induced lipid reduction, a more detailed analysis of the efficacy data for statins alone in older people showed a significant reduction in CV events with statins in secondary prevention (relative risk (RR) 0.74 (95% confidence interval (CI) 0.63–0.87)) but not in primary prevention (RR 0.92 (95% CI 0.77–1.10)). However, recent data have shown that although there are no differences in the prevention of myocardial infarction (MI) and stroke when all elderly patients are considered together, when patients are stratified by risk (as in diabetics), there are no differences in the prevention of acute myocardial infarction (AMI), but statins become effective in the prevention of ischemic stroke and more effective in the prevention of CV death [55].

Beyond their efficacy, the use of statins in the elderly is a cause for concern owing to potential side effects and the increased risk of drug–drug interactions due to the polypharmacotherapy usually prescribed to the elderly with comorbidities [4]. The main concerns about the use of statins are the risk of developing diabetes, the development of musculoskeletal symptoms, and the effects on cognitive decline [56]. Several studies have indicated that statin therapy is associated with the onset of diabetes in patients at high risk of developing the disease, although this is rarely observed in patients without such risks [16, 57]. Furthermore, the HbA1c variation following the initiation of statin therapy in patients with diabetes is minimal. Finally, the potential benefits of initiating statin therapy are believed to outweigh the increased risk of developing new-onset diabetes mellitus [56, 58].

Regarding muscular effects, the precise definition of statin-associated muscle symptoms (SAMS) and the process of diagnosing them are inherently complex issues that do not vary with age [59]. Furthermore, it is more challenging to ascertain whether musculoskeletal symptoms, which are prevalent in the elderly, are attributable to statins [56]. The results of another recent meta-analysis from the CTT group indicate a significant increase in musculoskeletal side effects associated with statin use, only when all potential manifestations are considered together, including also those that may not have a clear pharmacodynamic or pharmacokinetic correlation with statin use [60]. Nevertheless, a dedicated subanalysis stratified by age revealed no significant differences in musculoskeletal symptoms between younger and older individuals undergoing statin therapy [60]. In addition, data from the PALMA registry demonstrated a reduced prevalence of myalgia in the elderly cohort relative to the younger cohort [61]. Furthermore, the PALMA registry demonstrated a comparable level of adherence across all age groups, thereby disproving concerns about the willingness of the elderly to adhere to statin therapy. Other concerns include the potential for adverse effects on the central nervous system, including the risk of hemorrhagic stroke and accelerated cognitive decline. The data on the increased risk of hemorrhagic stroke are inconclusive and conflicting [4]. When the data are divided into primary and secondary stroke prevention, there are no data on an increased risk of hemorrhagic stroke in primary prevention, while the data become

more conflicting in secondary prevention [62]. However, although some meta-analysis data reported an increase in the relative risk of hemorrhagic stroke of approximately 20%, the absolute risk is minimal and is clearly outweighed by the benefits of statin use [11, 62, 63]. However, following a number of safety reports, the Food and Drug Administration (FDA) raised the alert in 2012 about the possible effects of statins on cognitive decline [64]. Anyhow, subsequent data published in the following years have refuted this theory, indicating that statins, whether lipophilic or hydrophilic, do not have a significant impact on cognitive decline. [65–67].

As previously mentioned, the STAREE trial will provide insights into the overall balance of the benefits and risks of statins in elderly patients in primary prevention. The trial will primarily focus on outcomes that are relevant to the health of elderly patients, including those that may limit their quality of life [43].

It is of the utmost importance that physicians prescribing statins consider the potential for drug–drug interactions that could exacerbate the adverse effects of both statins and other pharmaceutical agents. These interactions are attributable to the shared hepatic metabolism via the cytochrome 3A4 (CYP3A4) system and the potential competition as a substrate, with the exception of fluvastatin, pitavastatin, pravastatin, and rosuvastatin, which are metabolized by non-3A4 CYP pathway [68]. Major interactions were reported with some antimicrobials, such as antifungals (itraconazole, ketoconazole, and posaconazole), macrolides (erythromycin, clarithromycin, and telithromycin) and the human immunodeficiency virus (HIV) protease inhibitors. In addition, interactions were observed with calcium channel blockers (verapamil, diltiazem, and amlodipine), ciclosporin, danazol amiodarone, ranolazine, nefazodone, and also grapefruit juice. Finally, gemfibrozil is the only fibrate that highly increases the risk of myopathy/rhabdomyolysis in combination with statins [4].

In light of the abovementioned considerations, the ESC/EAS guidelines advise the initiation of statin therapy at a low dosage in cases of substantial renal impairment and/or a heightened risk of pharmacodynamic interactions, with upward titration to achieve LDL-C treatment goals [4].

8 Non-Statin Lipid-Lowering Drugs in Elderly

8.1 Ezetimibe

A prespecified post hoc analysis of the IMPROVE-IT trial demonstrated that adding ezetimibe to simvastatin resulted in a greater reduction in the risk of recurrent cardiovascular events among patients aged 75 years or above compared with those below this age threshold. The risk reduction was 30.8% for patients below 65 years of age, 35.8% for patients aged 65–74 years, and 47.6% for patients aged 75 years or above [69].

Furthermore, a post hoc analysis of the RACING trial investigated the comparative efficacy of high-dose statins with low-dose statins combined with ezetimibe in patients aged below and above 75 years. In patients aged 75 years and above, the combination therapy demonstrated superior efficacy in LDL-c reduction (LDL-c goal: 58 mg/dL versus 62 mg/dL) with noninferiority in cardiovascular outcomes in comparison with the high statin dose group. However, combined therapy was associated with a reduced incidence of intolerance-related discontinuation or dose reduction (2.3% versus 7.2%, $p = 0.010$) and a lower incidence of new-onset diabetes mellitus (10.0% versus 18.7%, $p = 0.025$) [70].

In a cohort of octogenarian patients with acute coronary syndrome who underwent coronary angiography, a 2017 study demonstrated that the addition of ezetimibe to atorvastatin 10 mg yielded equivalent long-term (12 months) efficacy in the reduction of cardiovascular recurrence to that achieved by doubling the atorvastatin dose [71]. The MESIA study showed similar results in patients who underwent secondary cardiovascular prevention after ischemic stroke [72]

The EWTOPIA 75 was a randomized open-label trial that tested the efficacy of ezetimibe in primary prevention in patients aged 75 years or older, with dyslipidemia and high cardiovascular risk, in comparison with standard nonpharmacological usual care. Furthermore, ezetimibe was associated with a 34% reduction in the incidence of the composite cardiovascular outcome, a 40% reduction in composite cardiac events, and a 62% reduction in coronary revascularization [66].

The evidence collectively indicates that the addition of ezetimibe to a moderate-dose statin may represent a potential strategy for achieving therapeutic goals in elderly patients, while simultaneously reducing adverse effects, increasing tolerability, and reducing instances of nonadherence and discontinuation.

8.2 Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Modulators

PCSK9 Inhibitors Monoclonal Antibodies No ad hoc studies were conducted to evaluate the efficacy and safety of PCSK9 inhibitors in elderly patients [73]. Few available data derive from validation studies subanalyses. Alirocumab and evolocumab are human monoclonal antibodies binding PCSK9. Subanalyses of both alirocumab (Odissey outcome) [74] and evolocumab (Fourier) [75] phase 3 studies were conducted by dividing patients using 65 years as the cutoff age. Instead, a prespecified post hoc analysis of the Odissey outcomes data demonstrated that the efficacy in achieving the primary outcome (the reduction of cardiovascular

events) was maintained across age groups [76]. In addition, a post hoc analysis of the Fourier trial showed a persistent evolocumab effect on the primary study outcome across age groups [77]. Finally, a pooled analysis confirmed the safety of alirocumab, demonstrating no differences on the basis of patient age. [78].

PCSK9 Synthesis Inhibitors Similarly, as with PCSK9 inhibitors, there is a paucity of ad hoc data on the use of siRNAs in the elderly. A post hoc pooled analysis of Orion 9, 10, and 11 demonstrated a consistent lipid-lowering effect of inclisiran in any age group, with no differences in the safety profile. To date, no data have been published on the efficacy of inclisiran with regard to clinical outcomes. [79].

8.3 Bempedoic Acid

No ad hoc or post hoc studies, nor pooled data analyses, have been conducted to investigate the effect of bempedoic acid in elderly patients. Nevertheless, the CLEAR studies series included a considerable number of elderly patients (up to 85 years of age), with over 2100 individuals enrolled in the CLEAR outcome trial [80]. This allows the results to be considered valid in the elderly population.

8.4 Fibrates

There is currently a lack of ad hoc data on the use of fibrates in elderly people to reduce cardiovascular risk. Two comprehensive Cochrane reviews have been conducted on the role of fibrates in cardiovascular prevention, focusing on primary prevention (2016) [81] and secondary prevention (2015) [82]. The primary prevention studies involved mainly young patients, with median ages ranging from 47.3 to 62.3 years and did not account for age-related differences [81]. In contrast, the pooled data from secondary prevention studies allowed for a subanalysis by age group, and D. Weng et al. indicated that fibrates offer cardiovascular protection for both patients under and over 65 years of age [82]. However, a more recent meta-analysis [83] concluded that fibrates do not significantly reduce the risk of stroke, cardiovascular mortality, or coronary artery disease.

8.5 Icosapent Ethyl Acid

There are no ad hoc data on the use of eicosapentaenoic acid (EPA) in elderly. The REDUCE-IT trial revealed no significant differences in outcomes among patients stratified by an age cutoff of 65 years [84]. However, within the subgroup of patients aged over 65 years, the reduction in cardiovascular events did not achieve statistical significance. In addition, a targeted randomized controlled trial (RCT) involving patients older than 70 years with recent myocardial infarction found no differences in outcomes with the administration of a compound containing 930 mg of EPA and 660 mg of docosahexaenoic acid (DHA) [85].

9 Conclusions

Despite the uncertainties and ongoing debate regarding the use of lipid-lowering therapies in the elderly, particularly in those without a history of cardiovascular disease, it is crucial to advance research in this area. Figure 1 summarizes evidence on clear current indications and special warnings for statin use in the elderly. Future studies should focus on assessing the clinical benefits, efficacy, and safety of these therapies in this specific population. The balance of risks and benefits should take into account competing health

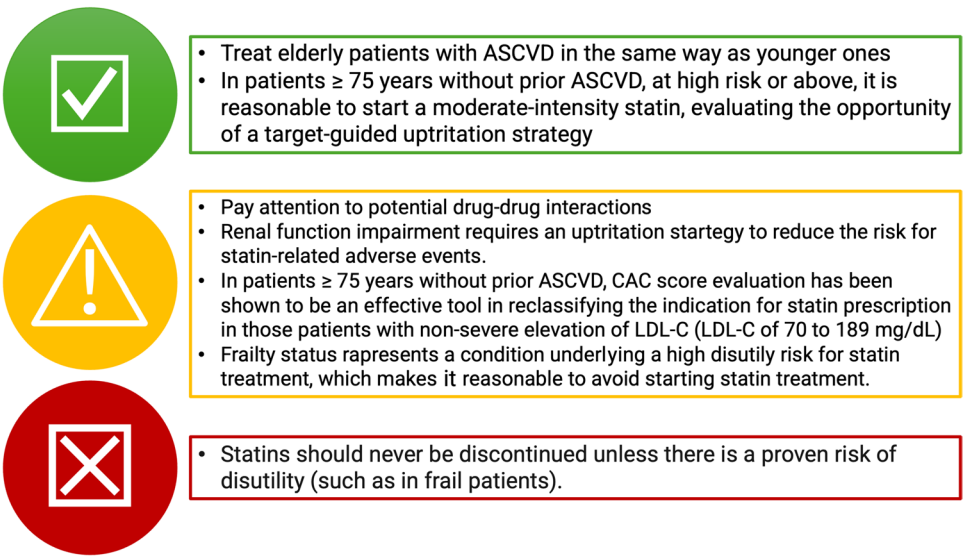

Fig. 1 Indications (in green), cautions (in yellow) and choices to avoid (in red) for prescribing statins in elderly patients. *ASCVD* atherosclerotic cardiovascular disease; *CAC* coronary artery calcium; *LDL-C* low density lipoprotein cholesterol

Table 1 Evidence gaps making cardiovascular prevention in the elderly challenging

Under-representation in clinical trials
Elderly patients (≥ 75 years) often excluded owing to comorbidities and polypharmacy
The evidence gaps are particularly wide for frail or multimorbid individuals
Risk–benefit balance
Myopathy and liver dysfunction are often misjudged much more frequently in elderly
Potential benefits of initiating statin therapy are believed to outweigh the increased risk of developing new-onset diabetes mellitus
Cognitive effects of statins remain a debated topic, although recent meta-analyses suggest minimal risk
Drug–drug interactions are more common in the elderly
Life expectancy and treatment goals
For patients with adequate life expectancy, aggressive LDL-C lowering can prevent events, even in primary prevention
When the disutility risk significantly increases, such as in frail patients and in those with limited life expectancy, symptom management and quality of life should take precedence, choosing not to start the lipid-lowering therapy or discontinue the current one
Easy to apply tools are needed to evaluate the disutility risk to guide physician decision on lipid-lowering therapy in elderly
Adherence challenges
Cognitive decline and polypharmacy could hinder adherence in elderly populations

priorities and enhance the evidence-based decision-making process. This process should not only be focused on cardiovascular prevention but should also be conducted from a tertiary prevention perspective (Table 1).

The only indication with an indisputable level of evidence pertains to lipid-lowering treatment in secondary prevention, which should be conducted in a manner consistent with that employed for younger patients. In the context of primary prevention, the evidence base regarding the use of hypolipidemic drugs becomes increasingly inconsistent for patients over the age of 75 years. Nevertheless, recent data, albeit of a relatively low-level of evidence, have demonstrated the efficacy of statins in healthy patients over the age of 75 years. Furthermore, a recent pharmacoeconomic study has demonstrated that the application of conventional scoring systems in the decision-making process for statin prescription is cost-effective, despite the absence of consideration for disutility risk in this specific subgroup of patients. The STAREE study will provide a more comprehensive assessment of the impact of statins on outcomes affecting the quality of life of elderly patients, beyond the cardiovascular domain. It seems reasonable to posit that, should the results of the study prove positive, we will have incontrovertible evidence on the usefulness of statins in primary cardiovascular prevention in patients over the age of 75 years.

A further challenge that remains to be addressed is the identification of the precise point at which the potential disadvantages of lipid-lowering therapy outweigh its benefits. This would enable clinicians to make informed decisions about whether to withhold therapy despite indications or to discontinue it in patients who are already taking it. The current guidelines merely mention the necessity of an individualized assessment of the risk–benefit balance and life expectancy to apply in the prescription process of lipid-lowering therapies in the elderly. It is therefore evident that further studies are required to identify suitable scores or tools that are capable of detecting patients with an excessively high disutility risk for lipid-lowering drugs, in whom the initiation or continuation of therapy should be avoided.

Declarations

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Consent to Participate Not applicable.

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