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Changes in cholesterol homeostasis associated with aging and with age-related conditions: pathophysiological and clinical implications

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The increase in life expectancy is leading to a progressive rise in the percentage of older people in the general population, and consequently in the prevalence of chronic diseases, often leading to disability. Age-related modifications in cholesterol homeostasis, the increase in plasma cholesterol levels due to aging, represents a cardio- and cerebrovascular risk factor in adjunct to age itself.
Direct knowledge about the pathophysiological alterations of cholesterol metabolism is limited. Clinical-experimental evidence about cholesterol lowering treatment suggests that the benefits observed in the general population are also observed in older age groups. However, patients enrolled in clinical trials often do not represent real-life clinical scenarios, limiting the generalizability of research findings. Issues of complexity and frailty are mostly inadequately addressed in published studies and guidelines. Further, effects of cholesterol itself and cholesterol lowering on cognitive function are still controversial.
This narrative review focuses on current evidence about the pathophysiology and clinical implications of the relationship between cholesterol and aging. Some suggestions will be provided, underlining the need for careful, personalized evaluation of the patient's functional status, along with clinical competence and geriatric skills.

Key words: nutrition and metabolism, dementia, frailty

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INTRODUCTION

Aging of a population is the modification of the relative representation of older subjects compared to younger subjects, which translates into an increase in the population mean and median ages. The proportion of the world's population over 65 years of age was 9.3% in 2020 and is expected to exceed 16% in 2050 [1]. The Italian population already has a high proportion of elderly subjects which is also expected to rise considerably, from 23% in 2020 to 36% in 2050. The progressive increase in life expectancy is associated with a rise in the prevalence of chronic, non-communicable conditions [2]. This burden represents an enormous challenge in terms of public health and resource allocation. Adequate management of chronic conditions, especially cardiovascular diseases and associated risk factors, will be essential for sustainable healthcare delivery and quality of life.

Chronological age is one of the major determinants of absolute cardiovascular risk [3-5], especially coronary heart disease. Other risk factors which are potentially treatable, include hypertension, high plasma cholesterol and diabetes. These conditions, whose prevalence steadily increases with ongoing aging, require appropriate management. The treatment of high cholesterol levels is a treatment strategy of paramount importance, particularly considering the widespread availability of effective and safe pharmacological options.

Among the elderly, other aspects, such as age-associated changes in drug pharmacokinetics and pharmacodynamics [6], need to be considered. As these changes can predispose the patient to drug-associated adverse events, often mediated by pharmacological interaction, lipid lowering treatment in older patients is still a matter of debate [7-9]. The role of cholesterol in neurodegenerative conditions, such as Alzheimer's disease, is also controversial [10].

This narrative, non-systematic review will present the available evidence about alterations of cholesterol metabolism associated with aging, with a focus on the cost-benefit balance and evaluation of the patients' functional status. These issues may impact the most appropriate treatment choice.

AGING AND CHOLESTEROL HOMEOSTASIS

Theoretically, aging might associate with modifications in one, or more, of the different metabolic steps which control cholesterol homeostasis, ultimately changing circulating cholesterol levels. However, direct experimental evidence concerning age-associated alterations of cholesterol metabolism is relatively scarce, particularly in humans. This is likely due to the difficulty in identifying appropriate clinical-experimental models in older subjects [11].

Data about cholesterol absorption largely come from the analysis of circulating levels of hydroxylated sterols, campesterol and sitosterol, and provide conflicting evidence regarding the effects of aging [12-14]. Data on cholesterol synthesis also derive from the analysis of circulating precursors (particularly lathosterol, and the lathosterol/cholesterol ratio) as indirect markers of biosynthesis. Again, evidence is conflicting, with some studies reporting no change in cholesterol synthesis with aging, and others suggesting a reduction in the biosynthetic process, mostly among the oldest age range [12-14].

Bile acid synthesis is a key regulator of the hepatic degradation of cholesterol, and modifications of this pathway may have a profound impact on cholesterol homeostasis. Data from human subjects, collected *in vivo,* suggest that a reduction in bile acid production may take place with aging [15,16]. This hypothesis seems to support the analysis of the hepatic expression of cholesterol 7α-hydroxylase, the limiting enzyme of bile acid synthesis, and its transcriptional coactivators [17]. Indirect data on circulating precursors in the biosynthetic pathway are not always consistent with this perspective, with reports of negative [17] or no correlations with aging [14]. Different patient settings might account for these discrepancies.

These alterations might be expected to influence hepatic lipoprotein uptake and consequently circulating concentrations of cholesterol. Direct evidence with isotope analysis showed an association between aging and a reduction in the systemic clearance of low density lipoprotein (LDL) [18,19]. Such a reduction in LDL clearance is consistent with the increased concentration of total and LDL-cholesterol observed in epidemiological studies [12,20]. Interestingly, the correlation tends to disappear among the oldest age range [13,14].

Overall, a reduction in the requirement of metabolic substrates seems to be plausible in older age, which probably affects both bile acid and cholesterol production, and hepatic LDL uptake and consequently circulating LDL-cholesterol and total cholesterol levels, see Figure 1. Age-associated alterations in the intestinal microbiota might also profoundly affect lipid metabolism [21,22].

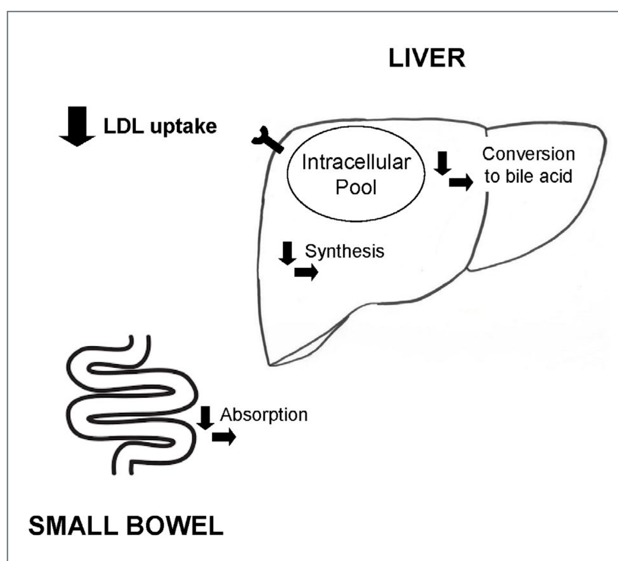

Figure 1. Schematic illustration of the alterations in the main pathways controlling cholesterol homeostasis reported in association with the aging process. This representation illustrates the biomarkers of different metabolic steps, and is derived from published evidence in humans: including *in vitro* analyses, *in vivo* studies or assays of circulating hydroxysterols (see text for details; adapted from Bertolotti et al., 2019) [49].

These aspects will be recalled later, along with the inherent implications in cognitive impairment.

THE ASSESSMENT OF FRAILTY

Frailty is characterized as a physiological decline across multiple body systems resulting in a lack of reserve for tolerating health stressors, and this decline is associated with an increased vulnerability to numerous adverse health outcomes [23].
Conflicting literature exists as to whether the presence of frailty predicts CVD. A recent meta-analysis found that frailty led to an increased risk of CVD [24]. Even more recently, a large study found that frail individuals were at higher risk of a CVD event and CVD mortality compared to robust peers [25].
Frailty and CVD are hypothesized to have a bidirectional relationship, as chronic inflammation and insulin resistance share proposed processes of decline [26,27]. Therefore, early identification of frail individuals may strengthen primary prevention efforts to reduce CVD risk. Given the relationship between frailty and CVD, similar interventions aimed at attenuating physiological decline may ameliorate the risk for both, and frail individuals may gain an additional benefit from CVD prevention compared to robust individual [25,28].
Assessment of frailty is instrumental in refining risk estimates and guiding patients toward personalized treatment plans, thereby maximizing the likelihood of a positive outcome. More than 20 tools have been developed to measure frailty [29]. Most of these tools focus on one or more of the five core domains that define the Frailty Phenotype, first described by Fried et al. [23] including slowness, weakness, low physical activity, exhaustion, and shrinking. These elements can be objectively measured. The most frequently cited frailty scale in research settings is the Frailty Phenotype by Fried [23]. Some of the other commonly used assessment scores include the Short Physical Performance Battery (SPPB) [30], the "Accumulation of Deficits" by Rockwood [31], the Multidimensional Prognostic Instrument (MPI) [32] and the Clinical Frailty Scale (CFS) [33-35]. The SPPB and the "accumulation of deficits" by Rockwood, have been demonstrated to predict mortality and disability in patients with CVD [24-28]. The MPI, a prognostic tool for hospitalized older patients, and the CFS, a scale of frailty based on clinical judgement and complemented by a visual chart, are the currently preferred frailty tools applied in clinical practice.
Frailty confers a 2-fold increase in mortality, an effect that persists even after adjustment for age and comorbidities. The relevance and impact of frailty has been demonstrated across a broad spectrum, including stable and subclinical CVD, heart failure, coronary syndromes, cardiac surgery, and transcatheter aortic valve replacement [27]. However, when we consider lipid lowering treatment, frailty may represent a risk factor for statin-induced side effects, in particular muscle damage [36]. This might relate to the frequent association of sarcopenia.

CHOLESTEROL-LOWERING AGENTS: REDUCTION OF CARDIOVASCULAR RISK IN OLDER PATIENTS AND SAFETY ISSUES

Age and circulating cholesterol levels are considered by all commonly employed tools for the prediction of cardiovascular risk [3-5]. Therefore, the compresence of old age and high cholesterol levels has an additive effect on cardiovascular risk estimate, even if the relative impact of plasma cholesterol however is lesser in older patients, where age tends to have a prominent effect over other variables [37].
Proper evaluation of cardiovascular risk in old age is hampered by guidelines upper age ranges, which in many cases is referenced up to the sixth decade of life [38,39]. Some more recent functions and algorithms at least partly overcome this problem. The updated version of the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines, which report the cardiovascular risk function of the European Systematic COronary Risk Estimation (SCORE) project, offers recommendations up to 70 years of age [40]. SCORE also has an Older Persons function (SCORE O.P.) derived from the older age group enables the calculation of cardiovascular risk up to 90 years of age [41,42]. A correct estimation of cardiovascular risk may be essential to define the strength for a correct management of high cholesterol levels, and to avoid unnecessary lipid-lowering drug treatment. Most persons over 70 years old present high risk levels, and distinction between primary and secondary prevention might be labile.
Lifestyle intervention has proven to be effective and safe [43], but adherence to a correct exercise regimen and/or to an appropriate diet is difficult in old age. A number of studies have investigated the effects of therapeutic interventions on cardiovascular risk prevention. Most evidence comes from observational or interventional studies with competitive inhibitors of HMG-CoA reductase, the limiting enzyme of cholesterol synthesis, or statins.
Observational studies generally show a protective effect of statins, both in primary and in secondary cardiovascular prevention [7,44,45]. Prospective randomized controlled trials, specifically addressing statin use in

older patients, are extremely scarce. Only two trials were specifically designed to investigate the protective effects of statins in older patients. The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial utilized a standard dose of pravastatin versus placebo in a cohort of older patients, both in primary and secondary prevention [46]. The Study Assessing Goals in the Elderly (SAGE) compared the effects of standard treatment (pravastatin) and intensive treatment (high dose atorvastatin) in patients with coronary heart disease [47]. Both studies showed a significant protective effect of the intervention arm when compared to the control arm.

Even if direct evidence from specifically designed trials is limited, wider evidence from studies performed in the general population are available by means of subset, post-hoc analysis. The largest was the Heart Protection Study (HPS), which included a cohort of 5806 patients over 70 years old. In this cohort, a standard dose of simvastatin significantly reduced relative and absolute cardiovascular risk [48].

Many other studies have confirmed the protective effects of statins versus placebo, or of more "aggressive" statin treatment compared with standard therapy, in the older cohorts. Such evidence has been summarized in several reviews and meta-analyses [49-52]. A protective effect of statin treatment was also shown on ischemic stroke recurrence [53].

A report from the Cholesterol Treatment Trialist Collaboration confirmed the reduction in major cardiovascular events, associated with statin treatment, in all age ranges, but with less direct evidence in primary prevention in subjects over 75 years old [54]. Subsequent clinical-experimental evidence, including treatment with non-statin drugs, has further integrated this view.

A post-hoc analysis of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) compared the effects simvastatin alone with simvastatin plus ezetimibe treatment, a selective inhibitor of intestinal cholesterol absorption, in older subjects. This analysis showed an even greater reduction of events with combined intervention in patients older than 75 years *versus* younger patients. In this subgroup, an extremely low number to treat (NTT) was observed, and combined treatment was not associated with an increase in adverse events [55].

A prespecified secondary analysis of the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY OUTCOMES) trial also showed that the protective effects of the PCSK9 inhibitor alirocumab were clearly extended to older patients included in the study [56].

A more recent meta-analysis combined all statin trials with the studies including "non-statin" drugs, still keeping in mind that in the latter studies the interventional treatment was almost always on top of a maximal (or the maximal tolerated) statin regimen [57]. This study included more than 21,000 subjects aged 75 or older. Once again, a clear reduction in the risk of major vascular events was found, and the protective effect appeared to be even greater (even if not significantly) in the older, compared with the younger cohort.

The evidence available in literature therefore suggests that lipid-lowering treatment with statins and/or other agents is protective against cardiovascular risk, also in older subjects. However, the observed benefits must be carefully weighed against possible drug-related adverse events, which are particularly frequent and clinically relevant in older subjects, due to changes in body composition, comorbidity and polypharmacy, which profoundly affect drug pharmacokinetics and pharmacodynamics [6,49].

Muscle damage represents the most frequent concern, for both physicians and patients. The causes of this phenomenon is likely to involve an impairment of cell respiration mediated by ubiquinone deficiency [29]. When data from controlled trials were systematically analyzed, there was no evidence for a higher risk of myopathy in older people [58]. Studies utilizing intensive drug dosages showed a dose-dependent increase in liver and muscle enzymes, although with limited clinical implications [47]. However, frail and complex patients are generally excluded from randomized studies [59] and limits the generalizability of study outcomes.

The 2002 American College of Cardiology (ACC) – American Heart Association (AHA) and National Heart, Lung, and Blood Institute (NHLBI) Statin Advisory document recommends cautiousness when considering statin treatment in older and frail patients [29]. Careful evaluation of the functional status of the patient, is justified.

A relatively recent meta-analysis ruled out correlation between statin use and the incidence of malignancy [60]. Recently, attention has focused on a higher incidence, or worsening, of type 2 diabetes mellitus [61,62]. However, the benefits of statins largely outweigh the possible risks associated with the onset of diabetes, particularly for older subjects with a relatively limited life span.

Two ongoing clinical trials, the Statins in Reducing Events in the Elderly (STAREE) and the Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in Older Adults (PREVENTABLE) studies, are specifically designed to address the risk-to-benefit ratio in older subjects [63,64]. The results of these trials will be available in 2023 and in 2027 respectively and will hopefully help to shed more light on this field.

CHOLESTEROL HOMEOSTASIS AND COGNITIVE IMPAIRMENT

The highest levels of cholesterol accumulation in the body are in the central nervous system, which is a major structural component of cell membranes and myelin. The relationships between alterations in cholesterol metabolism and neurodegenerative disorders, in particular the different forms of dementia, are poorly defined. In theory, alterations in membrane cholesterol composition and intracellular cholesterol content might affect the functional properties of the nervous system.

The blood-brain barrier allows an efficient protection from exchange with circulating lipoproteins. Consequently, most brain cholesterol is synthesized locally, mainly within glial cells, and transferred to neurons by means of apoE-containing lipoproteins. The isoform apoE4 of this lipoprotein in particular has a low efficiency in transporting amyloid beta, and represents a genetic risk factor for Alzheimer's disease (AD).

Excess cholesterol may be hydroxylated in the 24 position by neuronal 24-hydroxylase (CYP46A1). The hydroxysterol is then partially secreted into systemic circulation and is further metabolized by the liver [65,66].

Another degradation product of cholesterol detected in the brain is the 27(OH)cholesterol. The formation of this hydroxysterol is catalyzed by the ubiquitous enzyme 27-hydroxylase (CYP27A1) [67], Cholesterol 27-hydroxylation, which seems to be influenced by circulating levels of cholesterol [68], also represents the first step of the accessory pathway of bile acid synthesis. In its unbound form, 27(OH)cholesterol can be taken up by the central nervous system, where it can be converted into its acidic derivative, 7α(OH)-3-oxo-cholestenoic acid. This compound in turn can be resecreted into the systemic circulation and ultimately taken up by the liver. The metabolism of these two sterols and their relationship has been extensively investigated in neurodegenerative conditions, particularly in AD [69-72].

Evidence about hydroxysterol levels, both in plasma and in cerebrospinal fluid (CSF), is conflicting. Most of the findings, from experiments performed on animals and clinical studies in humans, suggest that the formation of 24(OH)cholesterol appears to represent a protective mechanism towards excess accumulation of cholesterol. Concentrations of 24(OH)cholesterol in the CSF increase in early stages of AD, but tend to decrease at more advanced stages of the disease, due to more severe atrophy. Plasma levels tend to mirror CSF concentrations [71,72].

In AD, CSF concentrations of 27(OH)cholesterol also tend to increase, possibly as a consequence of reduced degradation by oxysterol hydroxylases. Interestingly, modifications of 24(OH)cholesterol and 27(OH) cholesterol seem to follow distinct patterns in different neurological diseases. When the neurodegenerative process is prevalent, as is the case in AD, the increase in 24(OH)cholesterol prevails, whereas in conditions where damage of the blood-brain barrier predominates (such as in subarachnoidal hemorrhage) the increase in 27(OH)cholesterol is more evident than that of 24(OH) cholesterol [69].

The relationship between plasma cholesterol and the onset, or progression, of cognitive impairment has also been investigated. Most evidence in literature support a direct relationship between total (or LDL-) cholesterol and the risk of AD [69,73,74], particularly when observed along a wide temporal range, i.e. from midlife to older age. A reduction of high density lipoprotein (HDL)-cholesterol was also shown to be associated with dementia [75].

Pharmacological lowering of total and LDL-cholesterol might be expected to impact favorably on the incidence and progression of cognitive impairment, via a number of biological effects [76]. Some reports suggest a protective effect of early statin use on the impairment of cognition over age [77,78] whereas other studies have found contradictory evidence, sometimes even suggesting that statins have a a detrimental effect on cognition [79].

The possibility of reverse causation should be taken into account in association studies, when both a protective or a detrimental effect of statins is suggested. Comorbid patients (i.e., with a greater likelihood to suffer from cognitive impairment) are more likely to receive lipid-lowering drugs [80] and, on the other, more compromised patients are less likely to be prescribed a statin, or to be adherent to its use [81]. A recent large metanalysis addressing the association between statin use and cognitive function was inconclusive in any causation [82].

The timing of cholesterol-lowering treatment may play an important role. A Cochrane analysis showed that statin treatment in later life does not prevent cognitive decline. However, authors underlined the presence of significant bias in some studies [83].

The reduction of plasma total and LDL-cholesterol can certainly contribute to improve cardiovascular health and therefore, reduce the impact of age-related conditions [84], including cognitive impairment. Furthermore, the use of cholesterol-lowering drugs can be considered safe in most conditions [85]. However, lipid lowering treatment is not recommended in advanced dementia, given patients' limited life expectancy and an unfavorable cost-to-benefit ratio [86].

Recently, interest has also grown regarding proprotein convertase subtilisin/kexin type 9 (PCSK9), as it is capable of modulating circulating cholesterol levels. Data in literature have shown increased concentrations in CSF concentrations in AD compared to control subjects [87,88].

The topic is of particular importance, considering the clinical implications inherent in the use of specific PCSK9 inhibitors as cholesterol-lowering drugs.

Preliminary findings from our research group revealed lower serum PCSK9 concentrations in AD patients, compared to subjects with mild cognitive impairment (MCI). In the CSF of AD patients, PCSK9 concentrations were lower in carriers of the apoE4 isoform, confirming its potential role in modulating the relationships between cholesterol metabolism and neurodegeneration [89].

It is difficult to reconcile the observed alterations with their possible clinical implications, and the role of PCSK9 in cognitive impairment conditions. It is interesting to recall, however, that treatment with PCSK9 inhibitors is devoid of negative effects on cognition, as demonstrated in the EBBINGHAUS trial with evolocumab [90].

In summary, the use of cholesterol-lowering drugs (including statins and PCSK9-inhibitors) can be considered safe in most conditions, and might be expected to have a protective effect on cardio- and cerebrovascular health, including neurodegeneration. However, lipid lowering treatment seems unjustified in most advanced diseases with reduced life expectancy [91].

DECISIONS CONCERNING LIPID LOWERING TREATMENT

As discussed in previous sections, the advantages of cholesterol-lowering treatment have to be carefully weighed against the risk of drug-related adverse events in a frequent context of polypharmacy. Published guidelines are often unsatisfactory in offering indications.

The 2018 document on blood cholesterol risk management, issued by several Northern America scientific societies, including the AHA and the ACC [92], suggests treatment initiation with a moderate-intensity statin. It recommends the interruption of statin treatment in patients over age 75 with an important frailty or complexity profile.

The 2019 ESC/EAS guidelines for the management of dyslipidaemias [40] and the 2021 ESC guidelines on cardiovascular prevention [41] state that statin treatment is recommended in older people with cardiovascular disease in the same way as in younger subjects. Statin treatment in primary prevention can be considered in a high-risk condition, and dose titration is recommendable. However, there is no direct mention about frailty or complexity, but a note of caution about possible adverse events and interactions.

In our opinion, the decision about whether to undertake cholesterol lowering treatment depends on the combination of the expected benefits in terms of risk reduction and the evaluation of the conditions which do not recommend drug treatment. In this view, the evaluation of frailty is of paramount importance.

Several reports in literature have attempted to systematically address this issue, through the adoption of schemes or flow charts, considering different aspects that influence the propensity to suggest treatment [49,93-97].

The presence of a high cardiovascular risk (or an established diagnosis of cardiovascular disease), together with good functional status, and limited and well controlled burden of comorbidity, will encourage drug initiation. However, frailty, overt disability, polypharmacy, cognitive impairment, or poor life expectancy will orient towards a more prudent attitude against drug treatment. Individual patient preference will also play a relevant role in the decision. Table I summarizes elements that favor the implementation of a pharmacological approach.

Interestingly, chronological age might be expected to weigh on both sides of the scale, being one of the most relevant and acknowledged cardiovascular risk factors and, at the same time, a major determinant of frailty and comorbidity.

The adoption of a specific tool for frailty estimation is therefore important. Depending upon the experience of the physician and local capabilities, a simple but adequate measurement of frailty can and should be performed in all clinical settings.

Recent evidence has addressed the issue of complexity and frailty with advanced statistical tools, such as multiple correspondence analysis and hierarchical clustering analysis, enabling the definition of specific clusters of disease [98]. These reports confirm that patients more likely to receive cholesterol lowering treatment are at high cardiovascular risk and multimorbid, albeit cognitively preserved. The lowest prevalence in lipid-lowering drug use is associated with the oldest, frail patients with severe cognitive impairment.

We may expect that in some conditions the choice will be relatively simple: in patients with established cardiovascular disease but with a good functional status and prognosis, treatment will be strongly recommended and the overall attitude will approximate that adopted

Table I. Factors encouraging the adoption of a pharmacological based, cholesterol lowering approach in older subjects (adapted from Bertolotti et al., 2019; Strandberg et al., 2014) [49,93].

High cardiovascular risk/secondary prevention
Chronological age < 75
Good functional status
Preserved cognitive function
Absence of systemic comorbidity, or well controlled disease
No polypharmacy (< 5 drugs)
Individual preference by the patient

in middle-aged subjects. Similarly, treatment will appear largely unjustified in disabled and cognitively impaired patients, and generally in end-stage conditions [49]. Clearly, many grey areas exist, where the experience of the physician and full patient history, including patients' preferences, will orient the choice of lipid-lowering treatment. Finally, in the oldest age category, direct evidence is extremely limited [95].

Once the decision to undertake treatment has been taken, the choice of the appropriate drug and dosage is required, including the cholesterol lowering properties of available compounds and the potential for drug interactions and adverse events [99]. As far as we know, this point has never been addressed directly in controlled clinical trials.

Considering the pharmacological properties of lipid lowering agents, the use of hydrophilic drugs, such as pravastatin, or drugs with a limited potential for pharmacometabolic interactions, such as fluvastatin [100], might be preferable. Pravastatin was utilized in the PROSPER trial, the only primary prevention trial specifically performed in older subjects [46], whereas direct evidence about the use of fluvastatin in the elderly is relatively scarce.

The association of statins with ezetimibe represents a plausible and rational alternative to unnecessary high statin dosages. Ezetimibe in adjunct to statin treatment enables target LDL-cholesterol levels more effectively than increasing statin dosage alone [101] and improves the efficacy profile compared to statin alone, as shown by a subgroup analysis in the IMPROVE-IT study [55].

The post-hoc analysis of the data of the Odyssey trial with a monoclonal antibody targeting PCSK9, alirocumab, also provides encouraging evidence [56], but it seems unlikely that this approach will be able to be adopted in older people, on a wide scale.

Despite published evidence from clinical studies and knowledge of the pharmacological and pharmacokinetic properties of these agents, prescription patterns in older people do not differ from the general population, as proven in real-life studies performed in hospitalized patients [80]. However, there seems to be evidence of a recent trend towards a wider use of associations, including ezetimibe, in the elderly [98].

Less stringent LDL-cholesterol targets also seem to be reasonable in older patients, but this issue is still controversial. Recent ESC guidelines suggests the attainment of LDL-cholesterol levels below 100 mg/dl[41]. If we follow the widely accepted concept of "the lower, the better" LDL-cholesterol levels, we may reasonably pursue the lowest acceptable LDL-cholesterol levels which can be reached with minimal risks for the patients; this can also help to obtain a satisfactory patient adherence, which is instrumental in the achievement of good results in terms of cardiovascular prevention [102,103].

CONCLUSIONS

The impact of the aging process on cholesterol homeostasis is presently ill-defined. There is a scarcity of direct experimental evidence, particularly in humans. Further, the relationships between cholesterol metabolism, and its modifications induced by drug treatment, and cognitive function are also largely unclear. Currently, cognitive function and drug treatment is an active field of research, especially following the recent introduction of PCSK9 inhibitors in clinical practice.

Cholesterol lowering treatment has been demonstrated to be efficacious in cardiovascular prevention and safe, also in older subjects. Nonetheless, the benefits of drug treatment should be weighed against possible adverse events. Careful personalized evaluation of functional status is necessary, along with clinical competence and geriatric skills. Clinical trials are still ongoing and will hopefully help to design the most appropriate management strategies for high cholesterol levels in older subjects. Well designed and conducted observational studies will also prove useful in examining the impact of treatment in a real-life context. A personalized approach to cholesterol homeostasis is essential for the upcoming epidemiological transition, that will prove to be more challenging in the next few decades.

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Conflict of interest statement

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Author contributions

MB: designed the overall layout of the paper; MB, GL, CM: wrote the initial draft of the manuscript and subsequently approved its final version.

Ethical consideration

Not applicable.

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