Drugs & Aging (2022) 39:251–256
https://doi.org/10.1007/s40266-022-00928-z

LEADING ARTICLE

Drug Treatment of Hypercholesterolemia in Older Adults: Focus on Newer Agents

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Accepted: 13 February 2022 / Published online: 12 March 2022

Abstract

There is increasing research interest in cholesterol-lowering therapy in older patients. The newer lipid-lowering agents (the proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors evolocumab and alirocumab; the PCSK9 synthesis inhibitor inclisiran, and the adenosine triphosphate–citrate lyase inhibitor bempedoic acid) might also provide more options for the future treatment of older patients. Data analyses of the phase III outcome trials of the PCSK9 inhibitors suggest that their clinical benefits are maintained at older ages and that there is no increased relative risk of adverse events in older patients; however, data from patients aged ≥ 75 years and particularly aged ≥ 85 years are limited, and the trials did not collect information on the frailty status of patients. Frailty is a predictor of adverse outcomes, including mortality, and might help guide therapy decisions. To date, no outcome data are available for cardiovascular endpoints for the low-density lipoprotein cholesterol-lowering drugs inclisiran and bempedoic acid. Except for the risk of gout and tendon rupture with bempedoic acid, which remains to be further characterized in larger populations, the safety profile of the novel lipid-lowering agents in older patients seems favorable. The newer lipid-lowering agents could be added to other lipid-lowering medication or used as an alternative treatment in older patients with documented statin intolerance (as is already recommended in guidelines for the PCSK9 inhibitors), such as myopathy. Especially in older patients needing high-intensity therapy despite polypharmacy or certain comedications, the absence of clinically relevant drug–drug interactions with the PCSK9 inhibitors and inclisiran might be an advantage.

Key Points

Newer lipid-lowering agents might widen the number of options for lowering low-density lipoprotein cholesterol in older patients, especially for those at high risk of drug interactions or with statin intolerance.

While evidence already exists for the clinical benefit of the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, including additional age-specific analyses, corresponding outcome data for inclisiran and bempedoic acid in both young and old patients remain lacking.

In general, more specific data on patients of advanced age would be desirable as a basis for treatment decisions, especially for very old patients and taking into account their frailty status.

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1 Introduction

In recent years, research interest in the value of preventive cholesterol-lowering therapy in the age group ≥ 70 years has increased. Increased life expectancy and improved functionality in older age have challenged the reluctance to initiate lipid-lowering therapy in this patient population. The reluctance in the past was mostly based on concerns about an unfavorable benefit–risk ratio associated with delays in the benefit of lipid-lowering medication (time to benefit), the limited remaining lifespan (life expectancy), and the general challenge of achieving good adherence levels in statin users [1]. Another concern has been the potentially lower efficacy of these agents in advanced age. A change of paradigm was observed following a meta-analysis recently published in *The Lancet* that demonstrated a clinical benefit of lipid-lowering drug therapy in advanced age [2]. In this meta-analysis, a risk reduction with lowering of low-density lipoprotein cholesterol (LDL-C) was demonstrated for cardiovascular death, myocardial infarction, stroke, and coronary revascularization in patients aged ≥ 75 years. The study included both data from trials with statin monotherapy and data for combination therapy with ezetimibe and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

The state of the art in lipid-lowering therapy is statins. Their use in patients of advanced age with established atherosclerotic disease is undisputed, and lipid-lowering therapy is recommended for this patient group "in the same way as for younger patients" [3]. In contrast, the picture is less clear for primary prevention in older patients because information from randomized controlled trials (RCTs) is limited to (post hoc) subgroup analyses and is sparse for patients aged ≥ 80 years [4]. Besides methodological critique of the meta-analysis published in *The Lancet*, mostly related to heterogeneity in populations, interventions, comparators, and endpoints of the included studies [5], it was pointed out that no significant reduction of relative risk from lipid-lowering therapy has been shown for older patients without preexisting cardiovascular disease [6]. This might be attributed to limitations in the data available. RCTs specifically addressing the question of clinical outcomes of statin therapy for primary prevention in older patients are underway, and results are eagerly awaited (STAREE: ClinicalTrials.gov identifier NCT02099123; PREVENTABLE: NCT04262206). In a large Danish cohort study, the risk of myocardial infarction and of atherosclerotic cardiovascular disease was associated with baseline LDL-C, with the increased number of events per 1.0 mmol/L highest in the age group 70–100 years. This not only shows an association between LDL-C and clinical endpoints, even in older patients, but also indicates that the number needed to treat is lowest in older patients [7].

Reservations about lipid-lowering drug therapy in older patients have also related to safety discussions, e.g., about myopathies limiting quality of life and triggering falls [8], diabetes, and hemorrhagic stroke [9]. Concerns remain about poorer tolerability of statin therapy in older adults with impaired renal function and polypharmacy [3]. To decrease the risk of adverse effects from statin therapy when impaired elimination is expected or when drug interactions are likely, a (common) consensus strategy is avoiding overdosing by starting at a low dose [3]; however, we are not aware of any data that actually prove the clinical utility of this concept. Newer drug classes—which we consider to possess a comparably low potential for drug interactions, as we discuss in this article—might open up more treatment options, especially in patients with a need for high-intensity therapy.

Another problem in lipid-lowering therapy is patient nonadherence. Nonadherence to statin therapy is associated with decreased survival, including in patients aged ≥ 80 years [10]. Although evidence indicates that age is positively associated with statin adherence in primary prevention [1, 11], a nationwide Australian cohort study reported that nonadherence in patients aged ≥ 65 years started on a statin was 55% after 1 year and even higher in very old patients [12]. Reasons for nonadherence or discontinuation might include adverse events, comorbidities, and complex treatment regimens, although polypharmacy was found to be associated with adherence in the aforementioned study [12].

We discuss the potential of PCSK9 inhibitors, inclisiran, and bempedoic acid as lipid-lowering agents for older patients.

2 Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors: Evolocumab and Alirocumab

Alirocumab and evolocumab are human immunoglobulin monoclonal antibodies that bind to and inhibit PCSK9 and, by this mechanism, prevent degradation of LDL receptors. They are administered as a subcutaneous injection every 2 or 4 weeks, depending on the individual dosing scheme. The two currently approved PCSK9 inhibitors have proven beneficial effects on LDL-C and other lipid parameters [13, 14], coronary plaque volume [15], and cardiovascular events [13, 14].

An additional analysis of the cardiovascular outcome trial FOURIER evaluated the use of evolocumab per age group [16]. Patients were eligible for participation in the FOURIER trial up to the age of 85 years [13]. Evolocumab significantly reduced the composite primary endpoint of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization across all age quartiles (< 56, 56 < age ≤ 63, 63 < age ≤ 69, age > 69

years). Absolute risk reduction with evolocumab was also found to be the same across all the age ranges analysed.

The clinical benefit of alirocumab in LDL-C reduction in older patients was also examined in a prespecified analysis of ODYSSEY OUTCOMES, evaluating cardiovascular outcomes after an acute coronary syndrome [14, 17]. In this trial, 5.3% of the patients included were aged ≥ 75 years, and 0.2% ($n = 42$) were aged ≥ 85 years. Alirocumab reduced the risk of the primary composite endpoint (major adverse cardiovascular events) across the age categories; similarly, preserved clinical benefit in LDL-C reduction was observed in both the dichotomized age ranges (< 65 and ≥ 65 years) analysed. Alirocumab was associated with a greater absolute risk reduction for the primary endpoint and a decreasing number needed to treat for patients aged > 65 years compared with patients aged < 65 years.

In both studies, adverse events increased with age, and older patients—both in the verum and in the placebo group—discontinued the trial regimen more frequently than did younger patients, defined as per the respective age cut-offs in the trials [16, 17].

Common adverse reactions reported in the European Medicines Agency (EMA) summaries of product characteristics include infections, hypersensitivity, rash, headache, nausea, back pain, arthralgia, myalgia, and injection site reactions for evolocumab, and upper respiratory tract signs and symptoms, pruritus, and injection site reactions for alirocumab [18, 19]. Notably, PCSK9 inhibitors do not appear to have a negative impact on cognition [20, 21] (nor do statins [9]). In contrast to bococizumab, a humanized monoclonal antibody for which the trials were discontinued because of high-titer antidrug antibodies [22], alirocumab and evolocumab are fully human immunoglobulin monoclonal antibodies.

3 Inclisiran

Inclisiran is a small interfering ribonucleic acid. It is administered as a subcutaneous injection every 6 months (after an additional loading dose 3 months after start of therapy). It is licensed as an additional treatment for patients with primary hypercholesterolaemia or mixed dyslipidemia on maximum tolerated statin therapy who do not reach recommended LDL-C levels or in patients with intolerability or contraindications for statins, either as a single treatment or in combination with other lipid-lowering medications [23].

In patients aged ≥ 65 years, no dose adjustment is recommended. More than half of the patients included in the phase III secondary prevention trials ORION 10 (patients with atherosclerotic cardiovascular disease) and ORION 11 (patients with atherosclerotic cardiovascular disease or risk equivalent) belonged to this age group [23]. A pooled analysis of 3660 patients from the ORION trials focused on different age groups and included 39.1% patients aged ≥ 65 to < 75 years and 13.4% patients aged ≥ 75 years. The LDL-C-lowering effect (approximately − 50%) did not differ across age groups [24]. The effect of inclisiran on relevant clinical endpoints (major adverse cardiovascular events) is unknown and is currently being examined in patients aged ≥ 55 years (ORION-4, NCT03705234, estimated primary study completion date July 2026).

The estimated glomerular filtration rate had to be > 30 mL/min in ORION 9 (patients with familial hypercholesterolemia), ORION 10, and ORION 11 [25, 26]. Because there is no daily dosing, and the mechanism of action is not directly linked to plasma exposure, no dose adjustment is recommended in renal disease. Although there is only limited evidence for patients with end-stage renal disease, and caution should be exercised in these patients, pharmacokinetic modelling suggests that no dose adjustment is required [23].

Generally, the profile and frequencies of adverse events reported in the ORION trials were similar in the actively treated and placebo groups and increased with age, indicating that they were not caused by the active compound [24]. The summary of product characteristics lists injection site reactions (including erythema, pain, rash) as the only but common adverse reaction related to inclisiran [23]. In contrast to the unrelated adverse events, injection site reactions were more frequent in patients aged < 65 years than in older patients [24]. Mild elevations of serum hepatic transaminases (below the threefold of the upper limit of normal usually judged as clinically relevant) were observed under inclisiran treatment [23]. Inclisiran did not induce an adverse immunological reaction as measured by platelet counts, lymphocyte, monocyte, neutrophil counts, tumor necrosis factor-α, interleukin-6, and antidrug antibodies [27].

Because inclisiran is metabolized by nucleases to inactive nucleotides, it is not likely to be a substrate of common transporters or cytochrome P450 (CYP) isozymes [23]. Moreover, it is not targeting relevant structures of drug elimination pathways or their expression. Therefore, inclisiran-induced drug interactions are not expected.

4 Bempedoic Acid

Like the statins, and unlike the newer lipid-lowering therapies discussed earlier, bempedoic acid is an oral medication administered daily at a dose of 180 mg, either as monotherapy or as a combination pill with ezetimibe [28, 29]. As a prodrug, bempedoic acid needs to be activated by very long-chain acyl-CoA synthetase 1, which is not expressed in skeletal muscle, thus limiting the exposure of other tissues to

the active compound. Therefore, muscle-related side effects are thought to be less likely than with statins [28, 30].

A large part (62.1%) of bempedoic acid and its conjugated inactive metabolites are eliminated into urine. Population pharmacokinetic models estimated a clinically irrelevant increase in exposure in patients with renal impairment (1.4-fold in mild impairment, 1.9-fold in moderate impairment) and in those with lower body weight (< 73 kg, 1.3-fold) [28]. Single-dose administrations to small numbers of patients with various degrees of renal impairment revealed exposure increases of 1.5-fold in mild, 2.3-fold in moderate, and 2.4-fold in severe renal impairment [31].

In vitro data indicate no interaction potential via CYP enzymes, but bempedoic acid (and its metabolites) weakly inhibit OATP1B1/B3 in vivo, OAT2 in vitro, and also OAT3; in addition, bempedoic acid glucuronide is an OAT3 substrate [28]. Although data on the interaction with statins show a twofold increase of exposure for simvastatin, and a 1.4- to 1.5-fold increase for atorvastatin, pravastatin, and rosuvastatin [28], no data on interactions with other OATP1B1/B3 substrates are available. OATP1B substrates include cardiovascular drugs such as angiotensin receptor inhibitors (e.g., telmisartan), endothelin receptor antagonists (e.g., bosentan), or repaglinide. Inhibition of OAT2/3 might explain the increase in serum creatinine [28], and it should not be forgotten that furosemide, frequently administered in patients with heart failure, is a substrate of OAT2/3 and needs to be secreted into urine to become active.

Bempedoic acid acts in the liver by inhibiting adenosine triphosphate–citrate lyase, which mediates an earlier step in cholesterol synthesis compared with HMG-CoA reductase, which is targeted by statins. As the pharmacokinetics are not affected by age, no dose adaptation is required in older adults. In the placebo-controlled trials, 58% of patients were aged ≥ 65 years [28]. RCTs with bempedoic acid were conducted with or without ezetimibe in both patients receiving maximum tolerated statin therapy and in patients who did not tolerate statins. Recent cardiovascular events were usually an exclusion criterion. A meta-analysis of RCTs (with significant heterogeneity between studies) showed substantial lowering of LDL-C (− 17.5%; 95% confidence interval − 22.9 to − 12.0, primary endpoint), non-high-density lipoprotein cholesterol, total cholesterol, and apolipoprotein B after the 12-week treatment with bempedoic acid. In meta-regression analyses, the lipid-lowering effect was more pronounced with older age [32].

In patients with diabetes mellitus, glycated hemoglobin was, on average, 0.2% lower in the bempedoic acid group than in the placebo group [28].

The CLEAR Outcomes trial in statin-intolerant patients aged 18–85 years with a history of cardiovascular disease or at high cardiovascular risk is ongoing and will provide data on the time to cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization under therapy with bempedoic acid 180 mg compared with placebo (NCT02993406).

The US FDA label for bempedoic acid contains a warning regarding the risk of tendon rupture (involving the rotator cuff, biceps tendon, or Achilles tendon) especially in patients aged > 60 years [33]. Even though the risk of 0.5% appears low, it should be kept in mind that a tendon rupture might be detrimental in older patients with already reduced mobility. For instance, Achilles tendon rupture in patients aged > 65 years is associated with complicated treatment and impairment of lower-limb function [34]. Common adverse reactions include gout and hyperuricemia (for which both the EMA and the FDA have issued a warning), which can be explained by the OAT2-inhibiting properties of bempedoic acid, and treatment should be stopped if gout symptoms occur [28]. Bempedoic acid can exacerbate preexisting gout [28] and therefore does not appear suitable for patients with this condition. Other common adverse reactions are anemia, elevated aspartate aminotransferase, and pain in the extremities [28]. Increases in uric acid were significantly associated with age, and muscle-related symptoms also showed a trend towards an increase with age [32].

5 Conclusion and Remaining Questions

A large body of evidence suggests that LDL-C is a relevant cardiovascular risk factor in older patients and that a significant risk reduction can be achieved by lowering LDL-C. Newer lipid-lowering agents widen the number of options for lowering LDL-C in older patients. The novel agents might be a particularly beneficial option for older patients with muscle-related statin intolerance or a need for combination therapy. To date, RCT data on inclisiran and bempedoic acid are limited to biomarkers (LDL-C-lowering effect), whereas direct evidence of a beneficial effect on relevant clinical outcomes from PCSK9 inhibitors already exists, both for young and for older patients, as reflected in the guideline recommendations [3].

The number of patients aged ≥ 65 years enrolled in the phase III trials of the newer lipid-lowering agents is substantial. However, the evidence for patients aged ≥ 75 years and even more so for patients aged ≥ 85 years remains limited. Moreover, it may be disputed whether chronological age, which is often quite different from biological age, is an appropriate marker for risk–benefit predictions in this patient population. Although information on renal and hepatic function is routinely collected in clinical drug trials, the functional status of participants remains insufficiently documented (e.g., cognitive function, limitations in activities of daily living). Evidence gaps regarding the risks and benefits of lipid-lowering therapy in frail older patients remain,

as we have previously discussed for statins [4]. Neither the ODYSSEY OUTCOMES trial nor the FOURIER trial included information detailing the frailty status of their aged participants [13, 14]. Frailty is associated with a number of adverse outcomes, such as increased mortality and a higher risk for adverse drug reactions [35, 36]. Accordingly, the risk–benefit profile of drugs may differ between robust and frail older adults. In a reflection paper on physical frailty in clinical trials, the EMA proposed to include the Short Physical Performance Battery, or at least gait speed as a biomarker for physical frailty in the baseline demographic data [37]. Measuring frailty as one likely determinant of the benefit and risk of lipid-lowering therapies might help identify older patients for whom the novel agents might be of (additional) interest compared with standard statin treatment. This will also require that such patients are not categorically excluded from such trials and that comprehensive phenotyping of the frailty status is performed and corresponding information collected.

The safety profile of the newer lipid-lowering agents generally appears favorable for older patients, except for the risk of tendon rupture and gout with bempedoic acid. From a practical perspective, evolocumab, alirocumab, and inclisiran have two properties that may be advantageous for use in older patients. First, they do not require daily dosing. Less frequent dosing might improve drug adherence, as known from other therapeutic areas [38, 39]. Second, the lack of drug–drug interactions with the CYP system or drug transporters could be beneficial in patients with polypharmacy or certain comedications.

Still, important questions remain about lipid-lowering therapy in older patients in general and, in particular, about the future role of the newer lipid-lowering agents, not least in the context of primary prevention. In this indication specifically, RCT data on the guideline-recommended, established statin therapy are also awaited for older patients in the near future. It is obvious that statins possess many advantages in daily practice, including comparably lower treatment costs. It should also be pointed out that interactions with statins could be avoided or minimized by choosing the appropriate substance according to its pharmacokinetic and pharmacodynamic properties [40]. In addition, further innovations in lipid-lowering therapy, such as gene-editing technologies with a knockdown of PCSK9 as a “once and done” approach, can be expected in the coming years [41].

Declarations

Funding No external funding was used in the preparation of this manuscript. Open Access funding was enabled and organized by Projekt DEAL.

Conflict of interest Felicitas Stoll, Annette Eidam and Lola Michael have no potential conflicts of interest that might be relevant to the contents of this manuscript. Jürgen M. Bauer has received speaker honoraria from Novartis, Pfizer, Bayer and UCB Pharma; all income from these activities go to his institution. Walter E. Haefeli has received honoraria from Daiichi-Sankyo, the manufacturer of bempedoic acid, for lectures and grants to conduct drug interaction trials unrelated to this topic.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Authors' Contributions Felicitas Stoll: data collection, writing. Annette Eidam, Lola Michael, Jürgen M. Bauer, and Walter E. Haefeli: reviewing.

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