# The appropriateness of cholesterol-lowering medication in old age

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# Chapter 1

General introduction

Economic, social and medical developments have drastically improved human survival, resulting in more and more people living longer and thus spending an increasing number of years in old age (75 years and older). In 2019, there were approximately 23 million people in America and 42 million people in the European union aged 75 years and older(1, 2). Worldwide, both the number and proportion of older persons has increased rapidly, growth that's projected to continue for at least the next decades(3).

Health problems tend to increase in number and complexity as people age, often spanning multiple domains and tending to interact(4). Nevertheless, the health status of older adults' shows considerable heterogeneity(5-7) in the timing and extent to which health problems occur(7). While one person may reach 100 or more without serious disability, another person in their 70's may develop complex health problems and require nursing home care due to functional and/or cognitive impairment(7).

Variation in complexity is often accompanied by heterogeneity in susceptibility to adverse health outcomes such as functional loss and death. A subgroup of older adults has been recognized as especially likely to have a poor prognosis, the group often referred to as "frail"(8, 9). However, consensus is lacking on how this group can best be defined, and many definitions and instruments relate to frailty(10). Nonetheless, acknowledging that older adults vary greatly in the complexity of their health problems is important in clinical practice because health status may impact the appropriateness of treatment(11), a process which involves balancing the harms and benefits of treatment. A treatment can be considered appropriate and worthwhile when benefit outweighs harm by a sufficient margin(12). Naturally, the appropriateness of a treatment varies from person to person, and may even vary for one individual in the event of a change in health status.

Pharmacological treatment is extremely common in old age, and most older adults use medication on a daily basis. Approximately 38% of all Europeans between the ages of 75 and 85 years use at least five medications a day(13). The importance of appropriate prescribing of medication for older adults is well recognized, as older adults are at risk for over- and undertreatment, which is itself associated with adverse outcomes and avoidable health care costs(14-19).

Nevertheless, determining the appropriateness of pharmacological treatment for older adults can be challenging. Complex health problems and heterogeneity mean that available evidence for pharmacological treatment of older adults has limitations. Older adults are generally underrepresented in randomized controlled trials that provide crucial high-level evidence regarding the risks and benefits of pharmacological treatment. And when included, they are generally younger and healthier than their unselected peers(20, 21). Age-related

factors, such as the co-existence of multiple morbidities, as well as pharmacokinetic and pharmacodynamic changes, make older adults more susceptible to medication related side effects and adverse events(22-24). Consequently, the results of RTCs cannot be easily generalized to the older population(20, 21). Similarly, the majority of clinical trials neglect to include geriatric-centred outcomes such as quality of life, health status or function, further complicating the evaluation of treatment benefits(20, 21).

A class of medications that has received particular attention in this context are the cholesterol-lowering drugs(25-27). As discussed below, although these medications are amongst the most commonly used by older adults, for some groups of older adults these drugs are of questionable benefit and may produce significant side effects.

# BACKGROUND INFORMATION

## Rationale and prevalence of cholesterol-lowering medication

Together with antihypertensive medication and anticoagulants, cholesterol-lowering medications form the cornerstone of medication-related cardiovascular prevention. Cardiovascular disease is the leading cause of death and a major cause of disability, loss of independence and decreased quality of life in survivors(28, 29). The prevalence of cardiovascular disease increases steeply with age; in 2019 there were 523 million prevalent cases of total cardiovascular disease and 18.6 million deaths worldwide(30). Cardiovascular preventive medications are well represented in top 10 listings of medications used most frequently by older adults(31, 3), and approximately one-third of the older population are thought to use cholesterol-lowering medication in western countries(33).

## Statins

Statins are the drug of first choice, and by far the most commonly used cholesterol-lowering medication. For example, in 2020 at least 96% of people using a cholesterol-lowering medication in the Netherlands, Belgium, Denmark, Norway and Sweden received a statin(34).

Statins reduce low-density lipoprotein cholesterol (LDL-C) levels through the inhibition of 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase, the rate limiting enzyme in the synthesis of cholesterol. Cholesterol, an essential component of cell membranes and a precursor of bile acids and steroid hormones, is formed in the liver and transported through the vascular system by various lipoproteins. Of the lipoproteins, LDL-C is considered especially important in the pathogenesis of arteriosclerotic cardiovascular disease(35-37). Atherosclerosis is a condition in which arteries become obstructed due to atheromatous plaques. When severe, plaques may restrict blood flow and oxygen supply to tissues, leading

to symptoms and organ damage. LDL-C is the most abundant atherogenic lipoprotein in plasma and the main transporter of cholesterol to the artery wall(35). Lowering LDL-C levels via medication has proven to be an effective strategy that reduces the risk of cardiovascular events(36-38). Besides reducing LDL-C levels, statins are also thought to have other beneficial "pleiotropic" effects, effects other than those for which a drug was specifically developed. Although not fully understood, these include plaque stabilization, antioxidative and anti-inflammatory effects, immune modulation, changes in the endothelium and decreased thrombogenicity(35, 39).

## Cardiovascular risk

In general[1], an indication for cholesterol-lowering medication depends on a person's cardiovascular disease risk. Older adults with established cardiovascular disease are at such high risk that cholesterol-lowering medication is generally indicated. However, for older persons in general there is currently no threshold in international guidelines regarding the level of cardiovascular disease risk appropriate for initiating cholesterol-lowering medication(40).

To determine an individual's cardiovascular risk, a number of risk prediction models have been developed based on various cardiovascular risk factors such as age, smoking status, blood pressure and cholesterol. Examples of widely used risk prediction models include pooled cohort equations or the SCORE(41, 42). However, few of these tools are validated in older populations.

Recently, a risk model specifically aimed at older persons (OP), "SCORE2-OP", was published by the European Society of Cardiology. This model estimates 5- and 10-year absolute risk of cardiovascular events in people aged over 70 years. One of the strengths of this model is adjustment for competing risks of non-vascular mortality, which means that it is less likely to overestimate cardiovascular risk and the associated treatment benefit amongst older adults. As older adults are invariably at higher risk for cardiovascular disease than younger individuals with the same risk factors, this translates to higher absolute risk reduction due to treatment, which may give the impression that a risk factor such as LDL-C cholesterol should always be treated in advanced age. However, as the authors of the SCORE-2-OP point out, risk factor treatment does not necessarily yield a treatment benefit for older adults, and risk assessment should therefore always be combined with assessment of actual treatment benefit.

1 This section, and the content of this thesis, does not apply to people with specific lipid disorders such as familial hypercholesterolemia

## Benefits of statins for people 75 years and older

The first clinical trial designed to establish the therapeutic benefit of statin treatment for older adults was PROSPER(43). This trial, published in 2002, included 5,804 adults aged 70-82 years (mean age 75.4 years), with or without cardiovascular disease. Participants were randomized to a daily dose of 40mg pravastatin or a placebo. Pravastatin lowered LDL-C by 34%, and in the three years of follow-up there was a 15% reduction in the primary end point, which consisted of a composite of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke. However, in older participants without prior cardiovascular disease no reduction in overall mortality was noted and there was no net benefit in terms of cardiovascular events.

Since the PROSPER study, several other trials have investigated the benefits of statin treatment in the older population. Recently, a large meta-analyses on this topic was published(44). The primary outcome was a composite of major coronary events, strokes, and coronary revascularisations, collectively referred to as 'major cardiovascular events'. Combining data from 28 clinical trials that included participants with and/or without cardiovascular disease, participants were divided into six age groups, with the oldest group including participants ages above 75 years (n=14,483, mean age 78.8 years). In people with a history of cardiovascular disease, there was a clear benefit of treatment in the age group older than 75 years. In this subgroup statins reduced the proportional risk of major cardiovascular events by 15% per 1 mmol/L LDL-C reduction. However, there was no direct evidence of a statistically significant reduction in major cardiovascular events for participants older than 75 years without a history of cardiovascular disease. Results for mortality were not separately reported for the subgroups of vascular history. In the total group older than 75 years, there was no statistically significant reduction in vascular or all-cause mortality.

In conclusion, while there is evidence for the benefits of statins in relatively healthy older adults with a history of cardiovascular disease, for a large proportion of older adults the evidence is less convincing. These include 1) people aged 75 years and older without a history of cardiovascular disease(44, 45), 2) people aged 85 years and over for whom data is particularly scarce, and 3) a group especially underrepresented in clinical trials: older adults with complex health problems(20, 21, 46).

## Statin-associated side effects

Serious adverse events caused by statins are rare, and in trials statin are well tolerated(47). However, older adults participating in cholesterol-lowering trials are not representative of all patients managed in clinical practice. Patients with common diseases, such as moderate-to-severe kidney disease, heart failure or dementia, as well as people with or complex health problems or multimorbidity, have often been excluded from cholesterol-lowering trials(46).

In observational studies, muscle-related symptoms are typically reported by approximately 10% of statin-users(48). Other, less frequently reported, side effects include elevated liver enzymes (0.5-2%) and new-onset diabetes (9-27% increased risk)(49). Muscle-related symptoms are also the most important reason to discontinue statin treatment(50). While there is debate about the extent to which statins are truly responsible for associated symptoms, there is evidence that statins can directly cause muscle complaints and that the oldest and most frail are especially susceptible(50-52).

The impact of muscle symptoms (such as pain or weakness) on daily functioning may be significant, especially if there is already reduced mobility and self-reliance(50, 53). People on statins may also present with other symptoms that negatively influence quality of life such as headache, various psychological symptoms, or skin problems(49, 54, 55). In addition, statins with extensive CYP450 metabolism, like the frequently used simvastatin and atorvastatin, may lead to a higher risk of drug interactions(56), a problem particularly relevant for older adults using multiple medications.

## AIM AND OUTLINE OF THIS THESIS

The **general aim** of this thesis is to study the appropriateness of cholesterol-lowering medication for older adults, and thus contribute to better evidence-based treatment choices in this population.

In Chapter 2, we address the question "What recommendations for discontinuing statin treatment in older adults are provided by clinical treatment guidelines?" This chapter describes the results of a systematic review of clinical practice guidelines for cardiovascular disease prevention in the general adult population.

Chapter 3 focuses on the influence of patient characteristics on general practitioners' (GP's) treatment advice regarding discontinuing statin treatment in older adults. This chapter presents a collaborative research project that enrolled practising GPs from 27 European countries, plus Brazil, Israel, and New Zealand. GPs were presented with case vignettes describing older patients with varying characteristics who were using a statin. For each case vignette, GPs were asked whether they would advise discontinuation of statin treatment.

In Chapter 4, we systematically studied the appropriateness of cholesterol-lowering medication (and other cardiovascular preventive medication) for adults aged 75 years and older. For this study we used the RAND/UCLA (University of California at Los Angeles) Appropriateness Method, which combines scientific literature with expert opinion. A multi-

disciplinary panel then discussed and judged the appropriateness of starting and discontinuing cholesterol-lowering medication, platelet inhibitors and antihypertensives in various clinical scenarios.

In the final two chapters, we present two in-depth studies. Chapter 5 concerns the prevalence of self-reported muscle complaints in relation to statin use in community-dwelling older adults participating in the Integrated Systematic Care for Older Persons (ISCOPE) study.

Chapter 6 addresses the question of whether the association between low-density cholesterol level and mortality is modified by a composite fitness score. This study used data from four studies conducted by the Towards Understanding Longitudinal International older People Studies (TULIPS) Consortium, which included data from the Netherlands, Japan, the United Kingdom and New Zealand.

In Chapter 7, the general discussion, the main findings of this thesis are discussed, and recommendations for clinical practice are provided.

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