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The appropriateness of cholesterol-lowering medication in old age

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Chapter 8

Summary



SUMMARY

Economic, social and medical developments have substantially increased human life-expectancy. Consequently, more and more people are living longer, and thus spending an increasing number of years in old age (75 years and older). As people age, health problems tend to increase in number and complexity, often spanning multiple domains, and tending to interact. The health status of older adults shows considerable heterogeneity in the timing and extent to which health problems occur.

One of the consequences of this heterogeneity is that the appropriateness of medical treatments vary between patients. In order to determine the appropriateness of a medical treatment, it is crucial that all possible advantages and disadvantages of the treatment are carefully weighed. A treatment can be considered appropriate and worthwhile when benefit outweighs harm by a sufficient margin.

The importance of appropriate prescribing of medication for older adults is well recognized. Older adults are at risk for over- and undertreatment, which is associated with adverse outcomes and avoidable healthcare costs. In Europe, most older adults use medication, 40% even more than five a day. 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, and cannot be generalized to all older adults.

A class of medications that has received particular attention in this context is cholesterol-lowering medication. Cholesterol-lowering medications aim to prevent cardiovascular events, caused by arteriosclerosis. Cardiovascular disease is one of the leading causes of death and a major cause of disability, loss of independence and decreased quality of life in survivors. Older adults have a high cardiovascular risk based on age alone, and it is estimated that approximately 1 in 3 older adults use cholesterol-lowering medication. The vast majority (96% in the Netherlands) use a statin. Statins are the drug of first choice. However, the appropriateness of statins for older adults is under debate. 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. Also, statins are associated with hindering side effects, of which the impact may be more especially significant in older age.

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

Main findings

Chapter 2 describes a systematic review of clinical practice guidelines for cardiovascular disease prevention in the general adult population. The aim of the study was to provide insight into recommendations available in international cardiovascular disease prevention guidelines regarding discontinuation of statin treatment applicable to older adults. Thirty-three English guidelines from 11 different countries were found. Almost half of these guidelines did not provide any recommendations regarding discontinuation of statin treatment. The guidelines that did provide recommendations regarding discontinuation, almost always did so because of (serious) side effects and contraindications. None of the guidelines reported instructions for statin discontinuation that were exclusively aiming at older adults. Three guidelines included suggestions (“it might be reasonable to consider”) for statin discontinuation in patients with (development of) poor health status. Most guidelines included at least one recommendation concerning statin treatment in older adults. Details on how these recommendations should be implemented in practice were not provided. This chapter showed that the topic of discontinuing statins in older adults was underexposed in international guidelines.

However, in clinical practice doctors are confronted with questions about statin discontinuation, and treatment choices are made. This led us to investigate the influence of various patient characteristics on general practitioners’ (GPs) advice to discontinue statin treatment.

In **chapter 3**, the influence of different patient characteristics on GPs’ advice to discontinue a statin was investigated. A survey, using eight case vignettes, was sent by e-mail to GPs. All vignettes described a patient aged over 80 years using a statin. For each vignette, participating GPs were asked if they would advise stopping statin treatment. GPs were also asked if they would advise stopping statin treatment for each vignette if the patient additionally had a life expectancy of <1 year due to a diagnosis of metastatic, non-curable cancer. In total 2250 GPs from 30 countries participated. It was found that absence of cardiovascular disease, presence of statin related side effects, and frailty were all independently associated with GPs’ advice to stop statins in older patients. Overall, and within all countries, cancer related short life expectancy was the strongest independent predictor of GPs’ advice to stop statins. There was considerable (international) variation in GPs’ advice to stop statin treatment.

To build on these results, in **Chapter 4** the influence of these patient characteristics on the appropriateness of cholesterol-lowering medication in older adults was studied, using the RAND/UCLA Appropriateness Method (RAM). The RAM is a validated scientific method which integrates scientific evidence with the collective judgment of experts. The panellists emphasized the importance of the individual context of the patient for appropriateness of cholesterol-lowering medication. They judged that in general, a history of atherosclerotic cardiovascular disease strongly adds to the appropriateness of cholesterol-lowering medica-

tion, while increasing complexity of health problems, presence of hindering or severe side effects, and life expectancy <1 year all contribute to the inappropriateness of cholesterol-lowering medication. Age had only minor influence on the appropriateness judgments. The literature, time-to-benefit, remaining life expectancy, number needed to treat, and quality of life, were major themes in the panel discussions. The considerations to discontinue cholesterol-lowering medication were different from the considerations not to start.

In **Chapter 5** it was investigated whether statin users reported muscle complaints more often than non-statin users, as side effects play an important role in the debate about the appropriateness of statins. For this study data from the Integrated Systematic Care for Older Persons (ISCOPE) study in the Netherlands, was used. In the screening questionnaire at baseline participants were asked: *'At the moment, which health complaints limit you the most in your day-to-day life?'* Data on medication use and medical history were collected from the electronic patient records. There was no difference in the prevalence of self-reported hindering muscle complaints in statin users compared to non-statin users. Also, it was found that discontinuation of statin use during follow-up was independent of self-reported hindering muscle complaints. Thus, in this community-dwelling older population, prevalent statin use was not associated with self-reported hindering muscle complaints. However, the results might be different for incident users.

The study described in **Chapter 6** aimed to investigate whether the association between low-density cholesterol (LDL-C) and all-cause mortality in the very old was modified by a composite fitness score. A two-stage individual participants data meta-analysis, including data from four studies conducted by the Towards Understanding Longitudinal International older People Studies (TULIPS) Consortium, was performed. The TULIPS Consortium included cohorts of very old people (mean age of 85 years), from The Netherlands, New-Zealand, the United Kingdom, and Japan. Four individual markers of fitness (functional ability, cognitive function, grip strength, and morbidity) were combined into the composite fitness score. Results of this study confirmed an inverse association between LDL-C and all-cause mortality in very old participants. Interestingly, it was found that this association was most pronounced in people with a low composite fitness score.

In **Chapter 7**, the general discussion, it was concluded that throughout this thesis, five recurrent themes are of the utmost importance in the assessment of the appropriateness of cholesterol-lowering medication in older adults. First, it was set out that the individual context is decisive in the final decision to start or discontinue statin, and that this touches the core of evidence-based-medicine. Second, low life expectancy (less than one year) was the most consistently accepted basis for discontinuing statin treatment, and considered to be more important than age. Third, it was found that hindering side effects negatively influence

the appropriateness of cholesterol-lowering medication, a major element of which was the negative impact on quality of life. Fourth, an older person's cardiovascular history remains an important factor in determining the appropriateness of cholesterol-lowering medication. In general, cholesterol-lowering medication is appropriate for older adults with a history of cardiovascular disease, although it can sometimes be (come) inappropriate in combination with the other factors. The assessment of appropriateness of cholesterol-lowering medication for older adults without cardiovascular disease is less well defined, and is even more depended on the other factors. Fifth, with an increase in the complexity of health problems, cholesterol-lowering medication tends to become progressively less appropriate.

Based on the key findings and the five recurrent themes in this theses, five questions were distilled that can be used in a systematic evaluation of the appropriateness of cholesterol-lowering treatment for an individual patient:

1. What is the patient's individual context?
2. What is the patient's life expectancy?
3. Is this patient experiencing hindering symptoms which may be caused by cholesterol-lowering medication?
4. Does this patient have a history of cardiovascular disease?
5. Does this patient have health problems, and to what extent are these health problems complex?

It was recommended that these questions should be integrated in clinical guidelines on cardiovascular disease prevention.