Statins for primary and secondary prevention in the oldest old: an overview of the existing evidence

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Abstract

Hypercholesterolemia, although a modifiable risk factor for cardiovascular disease, is still one of the leading causes of death among older people in western countries. The use of statins among cholesterol reducing agents in both primary and secondary prevention has not been extensively studied in older patients in contrast to middle-aged patients. Despite a growing body of evidence in secondary prevention, statins are still under utilized in older patients with established vascular disease. On the other hand, the benefits of statins in primary prevention are not so clear. Therefore, the systematic use of statins in older patients with hypercholesterolemia needs to be further investigated.

Key words

Background

Cardiovascular disease (CVD) is one of the main causes of death among older patients in western countries. Smoking, hypertension, hypercholesterolemia, diabetes mellitus and obesity, although modifiable, remain important risk factors for CVD even at high ages. Hypercholesterolemia is present in over 50% of patients aged 65 or older (1).

Statins are the agents of first choice for treating hypercholesterolemia. The use of statins in both primary and secondary prevention has been extensively studied in middle-aged, but not in older patients. Moreover, studies have shown a steady decrease of statin prescription with increasing age. Currently, statins are under used in older patients due to various reasons such as lack of evidence, doubt of effectiveness and safety concerns. Guidelines divide older adults in three age categories: younger old (65 to 74 years), middle old (75-84 years) and oldest old (85 years and older). The scope of this narrative review article is to summarize current evidence for treating hypercholesterolemia in the vulnerable and frail oldest old.

Introduction

Statins, inhibitors of 3-hydroxy-3-methyl-glutaryl co-enzyme A (HMGCoA)-reductase, reduce the endogenous cholesterol production in the liver and peripheral tissues by blocking mevalonate synthesis, a cholesterol intermediary product. This reduced production of cholesterol leads to an increased expression of the hepatic LDL-receptor, which results in an increased LDL-clearance. Besides LDL and triglyceride reduction, there is evidence for both an anti-inflammatory and plaque stabilising effect of statins (2). Currently, statins are one of the most prescribed drugs in the western world. There are five different types of statins commercially available in Belgium, each characterized by their own pharmacokinetic profile.

Primary and secondary prevention of cardiovascular disease in older people is still under debate. First of all, there is a lack of age-specific studies. While most studies include middle-aged patients, patients

older than 80 years are under represented in clinical trials. Due to multiple co-morbidities and possible interaction of confounding factors, these patients are often excluded from clinical trials. Most of the current data for older patients is therefore extrapolated from subanalysis of various randomized studies. Since western population grows older, studies including patients older than 80 years are definitely needed.

As life expectancy decreases with advancing age, the benefits of initiating statins on survival become less clear. With advancing age, there is a less clear correlation between high cholesterol levels and mortality. Total serum cholesterol levels decline with increasing age, due to the normal physiology of ageing. In addition, a weaker association between cholesterol reduction and mortality is also observed. In a meta-analysis published by Lewington *et al.*, 61 prospective observational studies were analyzed on a total of 900 000 adults, aged 40 to 89 years, without previous cardiovascular disease. The findings of this meta-analysis showed that a prolonged reduction of 1 mmol/L in total cholesterol was associated with about a half lower ischemic heart disease mortality in early middle age (40-49 years), compared to only one sixth lower in old age (70-89 years). However, although the relative risk reduction might be lower in old age, the absolute difference in mortality is higher, due to the higher prevalence of ischemic heart disease in old age (3).

Classic cardiovascular risk-prediction tools such as the SCORE table or the Framingham coronary heart disease risk score become less accurate with advancing age (4,5,6). Since age is a non-modifiable risk factor for cardiovascular disease, and therefore an important parameter, using these prediction tools could imply initiating statins on the majority of older patients. Therefore, the use of these risk tools is respectively limited to 65 and 75 years old. Current guidelines for primary prevention in middle-aged patients, which rely on these tools, cannot be extrapolated to a geriatric and vulnerable population.

In older patients, factors such as polypharmacy, drug interactions, side-effects and cost should be additionally taken into account. Low cholesterol levels in older patients, could lead to higher mortality. Various studies found a reverse J-shaped association where both high as low total

cholesterol were associated with increased all-cause mortality and cardiovascular mortality (7,8,9). A cohort study by Schupf *et al.* confirmed that in non-demented older adults with levels of total cholesterol, non-HDL-cholesterol and LDL-cholesterol in the lowest quartile a twice as high mortality was observed than those in the highest quartile (RR 1,8, 95% CI 1,3-2,4) (10). Low total cholesterol is considered to be a marker of malnutrition and sarcopenia, illustrating a poor overall condition (11). An optimal level of total cholesterol in older patients could not be defined. Up till now, long term trials, such as the Heart Protection Study could not discern a cause and effect relation between statins and cancer incidence (12). Whether the pleiotropic anti-inflammatory effect of statins, could be beneficial in geriatric patients needs further investigation.

Primary prevention in older patients

The definition of primary prevention in older patients is less clear-cut than in middle-aged patients. With increasing age, the prevalence of progressive atherosclerosis and silent ischemia increases. Moreover, the difference between primary and secondary prevention becomes less distinct. The population for primary prevention includes patients both at low and high cardiovascular risk. Therefore, the existing guidelines for treating hypercholesterolemia in primary prevention cannot be easily used in older patients.

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial is one of the few trials which studied the effects of statins in both primary and secondary prevention in older patients. In this trial, 5804 patients, aged 70-82 years with a cardiovascular risk profile or history of vascular disease were included and assigned to pravastatin 40mg daily or placebo. Mean follow-up duration was 3,2 years. When analyzed separately, the risk reduction in primary prevention was less pronounced (RR 0,94, 95% CI 0,77-1,15) than in secondary prevention (RR 0,78, 95% CI 0,66-0,93) (13). The marginal effect in primary prevention is explained by the short follow-up period and the relative small population resulting in a lack of power (1).

The JUPITER (Justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin) trial studied the effect of rosuvastatin compared to placebo on patients with neither cardiovascular history nor diabetes, with normal LDL cholesterol levels but with increased high-sensitivity C-reactive protein (hs-CRP) levels of 2,0 mg/L or more (14). Elevated hs-CRP is considered as a non-classical risk factor associated with increased cardiovascular disease. The primary end-point was the occurrence of a first major fatal or non-fatal cardiovascular event or stroke. The trial was stopped prematurely after 2,2 years because of reaching the predefined goals earlier than expected. Rosuvastatin reduced the primary endpoint by 44% (RR 0,56, 95% CI 0,46-0,69). Glynn *et al.* published a retrospective sub-analysis on JUPITER, of patients aged 70 to 97, reporting a 39% reduction in primary endpoint (RR 0,61, 95% CI 0,46-0,82). The absolute reduction in the incidence of the primary end point was 48% larger in the over 70 years subgroup than in the younger group (0,77 versus 0,52 events per 100 person-years). This also leads to a lower number needed to treat (NNT) of 24 compared to 36 in the younger group. JUPITER suggests a benefit in initiating statins in older patients with elevated hs-CRP regardless of their lipid level (6). Hs-CRP however, increases with age, due to co-morbid conditions, and up-regulation of inflammatory pathways and oxidative stress (15).

A meta-analysis conducted by Tonelli *et al.* investigated 29 trials on primary prevention including a total of 80711 low cardiovascular risk patients (age range 51-76) (16). There was a reduction in all-cause mortality (RR 0,90, 95% CI 0,84-0,97) for trials with a 10-year risk of CVD < 20%. Statin use was also associated with a risk reduction of non-fatal myocardial infarction and non-fatal stroke. Neither difference in efficacy between high and low-potency statins, nor a difference in cholesterol reduction was found. These findings differ from the results of the meta-analysis by Ray *et al.* investigating the influence of statins on all-cause mortality in a high risk population without a history of CVD (17). Eleven studies on 65229 participants (mean age range 51-75 years) showed a risk reduction of 9% (RR 0,90, 95% CI 0,83-1,01), though statistically not significant.

A review by the Cochrane Collaboration, including 14 randomized controlled trials with a total of 34272 patients (age range 28 to 80 years) on primary prevention, showed a reduction in all cause mortality (RR 0,83, 95% CI 0,73-0,95) as in combined fatal and non-fatal CVD endpoints (RR 0,70,

95% CI 0,53-0,83) (18). Neither significant harm, nor an influence on the patient's quality of life was noted. The authors stress some important methodological shortcomings in the included trials such as selectively reporting, under reporting of adverse events and systematically use of composite endpoints. The use of composite endpoints and early stopping of trials can often lead to positive results. Two of the included trials, were stopped prematurely, due to early achievement of endpoints; this could lead to an overestimation of treatment effects when the number events is small. Some trials included patients with CVD, forcing the authors to set an arbitrary threshold of maximum 10% CVD patients to avoid a major interference on the results of primary prevention. Also, only one study was publically funded, while most were partially or fully sponsored by pharmaceutical companies. This Cochrane review does not support the use of statins in primary prevention in middle-aged patients with a low cardiovascular risk. No conclusion about statin use in older patients was formulated.

Secondary prevention in older patients

In the above discussed PROSPER trial, the results with regard to secondary prevention showed a relative risk reduction of the composite endpoint (coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke) by 15% (hazard ratio 0,85, 95% CI 0,74-0,97). Coronary heart disease death and non-fatal myocardial infarction was also reduced (hazard ratio 0,81, 95 % CI 0,69-0,94), but the hazard ratio for stroke was not affected. This can be explained by a lack of statistical power, or by the short follow-up. The stroke benefit of statins is considered to appear after 3 years, while the coronary benefits are observed earlier. This also seems to be the reason for the less than predicted risk reduction in the composite endpoint. Risk reduction was more pronounced in secondary than in primary prevention (13).

Afilalo *et al.* carried out a meta-analysis including published data in secondary prevention of older patients from four randomized trials: 4S study (Scandinavian Survival Simvastatin Study), CARE (Cholesterol and Recurrent Events Trial), LIPID (Long Term Intervention with Pravastatin in Ischemic Disease), HPS (Heart Protection Study Collaborative Group) (19). The meta-analysis

included also unpublished data of older patients from five randomized trials: PLAC-I (Pravastatin Limitation of Atherosclerosis in the Coronary Arteries I), REGRESS (Regression Growth Evaluation Statin Study), FLARE (Fluvastatin Angiographic Restenosis), LIPS (Lescol Intervention Prevention Study) and PROSPER. The meta-analysis included a total of 19569 patients with an age range of 65 to 82 years. Follow-up duration was 4,9 years. There was a relative risk reduction in all-cause mortality of 22% (relative risk 0,78, 95% CI 0,65-0,89). Coronary heart disease mortality was reduced by 30% (RR 0,70, 95% CI 0,53-0,83) and non-fatal myocardial infarction by 26% (RR 0,74, 95% CI 0,60-0,89). Stroke relative risk was reduced by 25% (RR 0,75, 95% CI 0,56-0,94). The NNT was 28 (95% CI 15-56).

This meta-analysis clearly supports the use of statins in secondary prevention in patients of 65 to 82 years old. Based on previous observational studies, the authors stress that these data could be extrapolated to even older patients (19). Allen Maycock *et al.* showed that statins can reduce all-cause mortality in patients with coronary heart disease even up to 97 years old. A greater relative risk reduction for all cause mortality was observed in older patients than in younger patients: 50% reduction in patients aged 80 to 97 years, compared to 44% in patients aged 65 to 79 years and 30% in patients younger than 65 years. Because of a higher baseline mortality risk, this finding reflects into a greater absolute risk reduction in old age patients (20). The CARE trial, also demonstrated a greater benefit in relative risk reduction of 39% in the 65-75 years population for its primary endpoint of CHD death and nonfatal myocardial infarction than in those under 65 years of only 13% (21). In the SAGE (Study Assessing Goals in the Elderly) trial intensive lipid-lowering therapy in patients aged 65 to 85 years compared to moderate therapy, showed no difference in the primary endpoint of ischemia reduction. On secondary endpoints, the SAGE trial resulted in a greater LDL-C reduction, fewer all-cause deaths and fewer major cardiovascular events (22).

Implementation of current evidence in older patients

Despite a growing evidence for treating hypercholesterolemia in secondary prevention in older patients, statins are still being under used in this indication, and mainly in this age subgroup. A retrospective analysis by Ko *et al.* revealed on a population of 396077 patients with coronary disease or diabetes, that only 19,1% was treated with statins (23). The authors found a significant correlation between age and cardiovascular risk profile. In patients aged 66 to 74 years, the probability of statin prescription was 37,7%, 26,7% and 23,4% in respectively the low, intermediate and high risk categories. The likelihood of statin prescription was 6,4% lower for each year of increasing age and each 1% increase in predicted 3-year mortality risk.

Cournot *et al.* analyzed two epidemiologic studies (ELIAGE and ELICOEUR) including 2637 coronary patients of which 1489 aged over 70 years (24). The authors observed an under prescription rate of 37% in coronary patients aged 70 years and older, while only 14% in the younger group did not receive proper statin treatment. The main reason given for non-prescription was the lack of a proper medical indication. This lack of indication was larger in the oldest old patient group. Other reasons for non-prescription were absence of lipidograms or when there was no prior history of myocardial infarction. Though low accountability of these factors, reasons of drug intolerance and poor patient compliance were also more specific for the older age group. The prescription of statins was related to the prescription of other cardiovascular drugs, used in secondary prevention such as beta-blockers, angiotensin-converting enzyme inhibitors and anti-platelet drugs, suggesting guideline based decisions.

Conclusion

There is still a remarkable statin under prescription rate in older patients in secondary prevention. In secondary prevention, studies have shown a clear benefit of statins in patients up to high ages. The initiation or continuation of statins in patients with established cardiovascular disease can therefore be recommended. However, treatment should be outweighed to the overall patient's condition and life

expectancy. Factors indicating a limited life expectancy such as advanced heart failure, metastatic cancers, patients on haemodialysis or quality of life issues, should be taken into account (1). The Hypertension in the Very Elderly Trial (HYVET) already proved the benefits of antihypertensive treatment in older patients (25). Since the findings in the SAGE trial with regard to primary and secondary endpoints differ, a general recommendation towards moderate or intensive treatment of hypercholesterolemia cannot be drawn so far. Whether intensive statin treatment could lead to an increased mortality due to low total cholesterol levels remains unclear.

The effects of statins on primary prevention in middle-aged patients are rather debatable. Also there is not a clear definition of low and high cardiovascular risk in older patients. Due to a growing older population, including frail care-dependent older patients in the western world, further studies and cost-benefit analyses are needed to draw a conclusion towards treating hypercholesterolemia in these groups. Unless randomized clinical trials specific to this age group are published, the systematic use of statins in primary prevention in older patients cannot be recommended.

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