Statin treatment in the elderly: how much do we know?

Manfredi Rizzo¹, Dragana Nikolic¹, Maciej Banach³, Giuseppe Montalto¹

Introduction

Cardiovascular disease (CVD) risk increases progressively with advancing age [1]. Yet life expectancy has increased [2]. In Europe the average life expectancy at birth has risen from around 45 years in the 1900s to 75.1 years in 2005–2010, and it is expected to rise to 85.3 years for women and 80.0 years for men [3, 4]. Approximately 34 million Americans are currently ≥ 65 years of age and this number is expected to reach 75 million by 2040, representing more than 20% of the US population [5, 6]. This increase in life span could be due to a decline in mortality rates (cardiovascular and all-cause), although a risk for coronary heart disease (CHD), stroke and mortality associated with diabetes has been reported as a two-fold excess in recent decades [7, 8]. This extended duration of life has fuelled the increase in population size, including the explosion in numbers of the elderly.

Cardiovascular disease remains a leading cause of death among the elderly [9]. Increased low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels as well as decreased levels of high-density lipoprotein cholesterol (HDL-C) may predict risk in the elderly [10]. It has been suggested that HDL-C is the most important factor in determining mortality risk in persons aged > 85 years with an inverse relationship with CHD [9]. However, currently the evidence on the role HDL-C in CVD and mortality risk reduction is ambiguous and contradictory [11]. Also, there is a very limited number of such studies in this group of patients. Furthermore, both the quality and quantity of small, dense LDL (sdLDL) may increase CVD risk and the proportion of sdLDL correlates negatively with plasma HDL-C concentrations and positively with plasma TG levels [12]. LDL particle size is influenced by age, gender and other factors [13]. Thus, the prevalence of phenotype B (the atherogenic lipoprotein phenotype with a predominance of sdLDL) was 30–35% in adult men and significantly lower in young men (< 20 years old) [13]. In the Apolipoprotein-Related Mortality Risk Study (AMORIS) apolipoprotein B (Apo B) was superior to LDL-C as a predictor of CHD in participants older and younger than 70 years [14]. In addition, a predominance of sdLDL particles is a predictor of type 2 diabetes (T2DM) and sdLDL contributes to the risk of CHD in the pre-diabetic elderly [15]. A comprehensive consensus statement on the pathophysiology, atherogenicity and clinical significance of LDL subclasses has been published [16].


Aspects of statin treatment in the elderly

The evidence indicates that an increase in atherogenic particles occurs with age and points to the need for cholesterol lowering therapy in the elderly [17]. Statins are the first-line drug choice and they also reduce the risk of CVD events and CHD in the elderly similarly as in younger individuals [17, 18]. The benefits of statin treatment on CHD or surrogate end points in higher-risk elderly patients have been reported in clinical trials [19–21]. Some studies suggest that statin treatment reduces the risk of CVD-related events in patients > 65 years old to a similar level as for younger participants [17] while some data show an even greater absolute risk reduction in the elderly [22]. However, many older individuals at risk of CVD do not receive adequate lipid-lowering therapy. Several factors may account for this omission: confusion surrounding the relevance of risk factors, the cost-effectiveness of preventing CHD in older patients and doubts about the impact of treatment on safety and quality of life [17]. Another important factor is the exclusion of older subjects from many clinical trials. There are often concerns that older participants have more comorbidity, may be more difficult to follow up or have higher dropout rates. Furthermore, a protocol restriction on comorbidities (such as renal insufficiency) may eliminate many older adults as potential trial candidates. Additionally, polypharmacy and complications from drug interactions may be increased in these subjects. Therefore, the maximum benefits of statin in this patient group may not be fully realized [17, 23]. Finally, currently it has been suggested that lowering cholesterol in the elderly is not necessary and possibly even harmful as the level of total cholesterol in the elderly (especially in the very elderly) is low without therapy (the lipid paradox) [24, 25].

In daily clinical practice elderly individuals are less likely to receive lipid-lowering medications or adhere to statin therapy [26, 27]. Physicians are usually aware of the dangers of interactions of statins with other drugs. This has been described as the treatment-risk paradox [28]. Namely, patients at the highest risk are often those who are not treated because of fear of risk of treatment, although the highest risk population may actually have the greatest benefit (given the very high baseline risk and guideline recommendations to use statins according to individual baseline risk) [28]. In addition, the literature suggests that physicians tend to assume that older adults do not want certain treatments whereas in many cases older adults will indicate a willingness for the treatment or care if asked [23]. The American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute (ACC/AHA/NHLBI) Clinical Advisory recommended that statin therapy should be administered cautiously in older persons, particularly older thin or frail women, but it is not contraindicated in these or other high-risk patients [26]. Furthermore, the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) guidelines advised that statins should be started at a low dose to avoid adverse events, and then titrated to an appropriate dose to achieve optimal LDL-C levels [27]. Such a treatment approach applies in cases of CVD as well as in the presence of at least one risk factor besides age [27]. However, there is no evidence on the effect of statin therapy on the length of life in elderly patients without CVD [26, 27]. Older men and women with CVD and a serum LDL-C > 125 mg/dl, despite dietary therapy, should be treated with lipid-lowering drug therapy to reduce serum LDL-C to < 100 mg/dl [29]. In primary prevention, the physician should consider lipid-lowering therapy based on a careful and individual risk stratification, when non-pharmacological methods fail [29, 30]. Among different statins, in order to lower the risk of myopathy, an effective statin (e.g. rosuvastatin or atorvastatin) may be a good choice [31–33].

Finally, despite all the prejudice and fears of “aggressive” treatment in the elderly, most experts feel that based on the available evidence these patients are likely to benefit from lipid-lowering therapy, especially if they have co-existing CVD [17].

Results from selected clinical trials

Subjects aged 70–82 years, who had risk factors for vascular disease, were randomized to pravastatin 40 mg/daily or placebo, in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) [21]. After 3 years of follow-up, pravastatin reduced LDL-C levels by 34% and TG by 13% as well as the risk from coronary death, non-fatal myocardial infarction (MI) and stroke by 15%. However, total mortality was not reduced and cognitive dysfunction was not improved [21]. The benefit from statin therapy was supported by another randomized, controlled trial that exclusively included older subjects – the Study Assessing Goals in the Elderly (SAGE) trial [19]. There were 893 CHD subjects, 65–85 years old, with ≥ 1 episode of myocardial ischaemia, randomized to atorvastatin 80 mg/daily or pravastatin 40 mg/daily. The duration of ischaemia was significantly reduced from baseline in both groups without difference (for both \( p < 0.001 \)), while greater LDL-C reduction with fewer major CVD events, as well as a greater reduction in all-cause death, was achieved by atorvastatin treatment (\( p = 0.114 \) and \( p = 0.014 \), respectively). However, this study was limited by the number of patients, short follow-up (12 months) and small number of endpoints [19].
The Heart Protection Study (HPS) randomized 20,536 subjects (4,891 were aged 65–69 years and 5,806 were 70 years or older) with CHD, other occlusive arterial disease or diabetes to simvastatin 40 mg/daily or placebo [20]. All-cause mortality decreased by 14.7% and CVD events decreased by about 25% among elderly individuals (75–80 years old) ($p = 0.0003$).

The results discussed above are in line with the outcomes of a post hoc analysis of the GREek AtoRvastatin and Coronary-Heart-disease Evaluation (GREACE) study [32] published in a recent issue of *Archives of Medical Science*. The authors investigated the effect of statin treatment (targeted to achieve guideline goal: LDL-C $< 100$ mg/dl) on CVD outcomes in age groups. Patients were randomized either to "structured care" (starting dose of atorvastatin was 10 mg daily) followed up by the university clinic, or to the "usual care" group (including style changes), followed up by specialists or general practitioners outside the hospital. Then, patients in each "care" category were divided into quartiles and participants in each quartile of "structured care" were compared with the respective quartile of the "usual care" group. The authors reported that the clinical benefit of statin increases with increasing age [32]. This benefit could be related to the greater improvement of factors such as chronic kidney disease, hyperuricaemia and non-alcoholic fatty liver disease in the older age groups. There was no significant increase in new onset diabetes but the mean follow-up was only 3 years. As expected, the CVD risk increased in the older patients on "usual care" [32].

**Expert opinion and conclusion**

Older age should not be a reason for excluding patients from receiving lipid-lowering therapy. In addition, it seems that the elderly (especially with CVD) may benefit even more from such treatment than younger subjects. However, further well-designed, interventional randomized controlled trials to define optimal lipid-lowering therapy with statins (statin dose and type, treatment goals, etc.), especially for primary prevention, are needed in this group of patients [22, 32–35]. All future trials should also take into account an individual's frailty status. Whether such studies will ever be carried out is doubtful.

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