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Primary Prevention of Cardiovascular Disease with Statins in the Elderly

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Abstract Owing to the progressive aging of the population, and the fact that cardiovascular disease (CVD) is the leading cause of death among the elderly, the prevention of CVD in the elderly is becoming increasingly important. Although there is no doubt that statin treatment should be used for reducing CVD risk in the elderly in secondary prevention in the same way as in younger individuals, the evidence that such treatment really prolongs life in elderly subjects in primary prevention is still not so clear. However, it seems that it does reduce CVD morbidity in elderly individuals. Because of limited evidence regarding the benefit of such therapy, particularly in very old subjects (older than 80–85 years), the decision whether to treat or not treat an elderly individual with statins in primary prevention should be based on good clinical judgment and considering the individual subject's situation regarding comorbidities, polypharmacy, and possible adverse effects.

Keywords Cardiovascular disease · Statins · Elderly · LDL-cholesterol · Adverse effects · Guidelines

Introduction

Cardiovascular disease (CVD) is the leading cause of death and disability as well as the burden of disease in the whole world [1]. The proportion of older people in all societies is rapidly increasing. More than 80 % of individuals who die of coronary heart disease are older than 65 years, and most CVD events and deaths occur in the elderly. Mainly owing to the progressive aging of the population, the projections of the growing incidence of coronary heart disease events and deaths for the next few decades are alarming, not only for the most developed countries, but also for developing countries [2, 3]. Therefore, the prevention of CVD in the elderly (older than 65–75 years) and very old people (older than 80–85 years) is becoming increasingly important. Age is one of the well-acknowledged CVD risk factors, and is to a certain extent reflected in Systematic Coronary Risk Evaluation (SCORE) risk charts, which have been used in clinical practice in most European counties and also in many non-European countries for a number of years [4]. However, it has to be stressed that SCORE risk charts do not include people older than 65 years.

Dyslipidemia, most specifically hypercholesterolemia, is together with hypertension, smoking, diabetes mellitus, and obesity one of the leading risk factors for CVD in people of all ages, and the risk is believed to be multiplied in the elderly [5]. On the other hand, almost 25 % of men and 42 % of women older than 65 years have a serum total cholesterol concentration higher than 6.2 mmol/L (approximately 240 mg/dL). The question whether to treat or not treat elderly subjects who do not have any clinical signs of CVD with statins, i.e., in primary prevention, particularly those with hypercholesterolemia, is also becoming more and more important since life expectancy for the general population is rapidly increasing and more people are living to an older age. Evidence supports the reduction of not only plasma total cholesterol concentration but even more so low-density lipoprotein cholesterol (LDL-C) concentration as the primary objective of dyslipidemia management, and statins are the treatment of choice for lowering LDL-C levels in the vast majority of such patients. The importance of preventing CVD with statins in the elderly is even more important in the light of evidence that substantial underuse of statin treatment in the elderly is characteristic for

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such populations all over the world, although they have, on average, the highest CVD risk [6–11].

The issue of primary prevention of CVD with statins in the elderly is a very complex one. Namely, although on the basis of many large-scale randomized clinical trials and meta-analyses it has been established beyond any doubt that statins reduce CVD morbidity and mortality in secondary prevention, the use of statins in primary prevention in general, and not only in older individuals, still seems to raise some questions. It seems that their use for primary prevention in high-risk individuals is undoubtedly justified, but their use in subjects at low or moderate risk is not so certain, and an individualized approach is recommended, even for middle-aged people [12••].

What Do the Guidelines Recommend?

The European Society of Cardiology/European Atherosclerosis Society guidelines for the management of dyslipidemias recommend that primary prevention of dyslipidemia in the elderly should not differ from that in younger subjects [13••]. It is interesting, however, that the joint European guidelines on CVD prevention in clinical practice (2012 version) do not mention anything about dyslipidemia treatment in the elderly [14]. On the other hand, the most recently published American College of Cardiology/American Heart Association guidelines on the treatment of blood cholesterol refer in several places to the treatment of hypercholesterolemia in the elderly [15••]. Since these guidelines have adopted an approach different from that of the European guidelines, they mention quite properly a concern that a person aged 70 years or more without risk factors other than age according to these guidelines will receive statin treatment on the basis of age alone. Such a concern has been expressed also by many who have clearly spelled out their criticism regarding these guidelines [16]. However, the American College of Cardiology/American Heart Association guidelines justify such an approach by claiming that the estimated 10-year risk of such an individual is still 7.5 % or more, a risk threshold for which a reduction in the incidence of CVD risk events has been demonstrated in randomized controlled trials, and that most such events occur after the age of 70 years, giving these individuals the greatest potential for absolute risk reduction. Regarding primary prevention, these guidelines mention in several places individuals aged between 40 and 75 years as a group. When discussing primary prevention in patients with diabetes and LDL-C concentration of 1.8–5.0 mmol/L (approximately 70–189 mg/dL) but also other individuals older than 75 years, they recommend considering additional factors, including comorbidities, safety considerations, and priorities of care, when deciding to initiate, continue, or intensify statin treatment. They also recommend evaluating the potential beneficial effects of such treatment in light of possible adverse effects, drug–drug interactions, and patient preferences before starting the therapy.

An additional problem when discussing different guidelines and the primary prevention of CVD in the elderly with statins is the fact that according to most of them, CVD risk estimation is crucial for the treatment decision [13••, 17, 18]. However, the standard risk assessment methods, such as SCORE risk charts or the Framingham 10-year risk score, are not appropriate for risk estimation in the population older than 65 years (SCORE) or 79 years (Framingham) [13••, 19]. Even the recent position articles on CVD risk estimation do not give advice on how to estimate CVD risk in the elderly [20, 21].

Evidence for Primary Prevention With Statins in the Elderly

Since the guidelines recommend treatment of the elderly with statins, what is the evidence on which all these recommendations are based? It seems that there is not much doubt today that statin treatment should be used for reducing CVD risk in the elderly in secondary prevention in the same way as in younger subjects. However, there is no clear evidence so far that such treatment really prolongs life in elderly subjects [22]. On the other hand, there are many data indicating that statin therapy does reduce CVD morbidity in elderly subjects even in primary prevention [23].

Earlier primary prevention trials with statins did not include many elderly individuals. In the AFCAPS/TexCAPS trial, 21 % of subjects were older than 64 years (65–73 years), and a subgroup analysis based on gender-stratified median age (more than 57 years in men and 62 years in women) did not show any difference in CVD risk reduction owing to lovastatin therapy [24]. In the ASCOT trial, the CVD-risk-reducing effects of atorvastatin did not differ in those younger than 60 years from those older than 60 years [25]. In the MEGA trial, in which postmenopausal women aged up to 80 years and men aged 40–70 years were included, a subgroup analysis also did not show any significant difference in a beneficial CVD risk reduction with pravastatin between those younger than 60 years and those older than 60 years, despite differences in the prevalence of CVD risk factors. However, statin therapy reduced CVD risk more strongly in older women than in younger women [26]. In the only early clinical trial on primary prevention performed on individuals older than 65 years—the Cardiovascular Health Study—which unfortunately was not randomized, all-cause mortality decreased because of statin treatment, and the results were similar in the subgroup of subjects who were older than 75 years [27]. All these observations are important, but today the age of 60

or 65 years, which was used in most of the trials, is clearly not considered as "elderly."

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) was the first trial designed specifically to investigate the effects of a statin (pravastatin, 40 mg/day) in the elderly aged 70–82 years, but it was performed in patients with preexisting vascular disease or at high risk of CVD, including stroke [28]. Although this was not a primary prevention trial, it has to be mentioned that no benefit in terms of reducing total mortality was seen in subjects without previously diagnosed CVD.

A substudy of the JUPITER trial analyzed the effects of rosuvastatin treatment or placebo in an asymptomatic population of 5,695 subjects older than 70 years [29]. The absolute risk reduction of the incidence of nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, arterial revascularization, or CVD death was 48 % greater in the elderly treated with a statin, and the number needed to treat for 4 years to prevent one cardiovascular event was 24 as compared with 36 in subjects aged 50–69 years. The population studied tended to represent the "younger old," with a median age of 74 years and 75 % younger than 77 years. The results of this trial also demonstrated a relatively short time to achieve this benefit. Although subjects receiving rosuvastatin had higher rates of some adverse effects, including incident diabetes, than those receiving placebo, none of these associations were statistically significant, so it could be concluded that the safety profile of the drug in the elderly is acceptable. Nevertheless, it has to be stressed that the benefit of statin treatment was absent in elderly subjects without hypertension [30].

A meta-analysis of primary prevention trials with statins including more than 70,000 subjects found some benefits particularly for all-cause mortality and major coronary and cerebrovascular events in subjects older than 65 years, but they did not reach significance [23]. The most recent meta-analysis, of eight trials enrolling 24,674 subjects, showed that primary prevention with statins in elderly individuals at high cardiovascular risk significantly reduces the incidence of myocardial infarction and stroke, but does not significantly prolong survival in the short term [31••].

Adverse Effects of Statins in the Elderly

As there is always concern that in the elderly some adverse effects might occur more often, particularly after long-term treatment, it has to be clearly stated that there are no convincing data indicating that older people experience adverse effects of statins more often than those who are middle-aged. Still, to be on the safe side, the advice is that statin treatment in the elderly should be started at a low dose, and then carefully uptitrated.

The adverse effects of statins when they are administered to patients of all ages include myopathy ranging in severity from asymptomatic increases in creatine kinase concentration to muscle aches or weakness (even in the absence of blood creatine kinase concentration elevation), which is rare, and potentially life threatening rhabdomyolysis, which is extremely rare [32, 33]. Statin-induced myotoxicity is dose-dependent, but the risk of myopathy increases particularly if statins are co-administered with other drugs which interact to increase plasma statin levels [34]. Since older people often have different comorbidities and therefore are treated with several drugs at the same time, possible drug–drug interactions, particularly concomitant use of drugs that could increase the plasma concentration of statins, have to be taken into consideration much more carefully in this group of individuals in order to minimize the risk of myopathy. It has to be stressed that in the PROSPER trial, which was performed exclusively in the elderly, there was similar incidence of myalgia in those receiving pravastatin and those receiving placebo, and no cases of elevated creatine kinase concentration more than ten times the upper limit of normal or rhabdomyolysis were recorded [28]. However, it cannot be ignored that older age has been associated in a number of studies with increased risk of statin-induced myopathy, as well as with a greater incidence of severer forms of this disorder reported among the oldest groups of statin-treated individuals [35, 36]. It also seems that elderly women may be especially vulnerable to statin-related muscle disorder [37].

Higher activity of liver enzymes, another adverse effect of statins, might occasionally occur in subjects of all ages, but is reversible and virtually never reflects a serious liver injury [38]. It has been shown recently that there is no association between statin use and the presence of and the severity of nonalcoholic fatty liver disease or liver-related mortality [39, 40]. There are no data showing that the elderly are more prone to an increase in the activity of liver enzymes or in the risk of liver injury caused by statins than middle-aged individuals.

Observational data suggest that the cancer incidence in the elderly is not affected by statin treatment [41]. This is so despite the data from two earlier trials with pravastatin which introduced speculations that elderly individuals might be particularly sensitive to such an adverse effect of statins, at least this particular statin. The first such trial was the PROSPER study, which demonstrated an increased total cancer incidence in patients who were receiving pravastatin, whereas the resulting increase in cancer mortality equaled in magnitude the decrease in CVD mortality, leaving the overall mortality unchanged [28]. The second trial was the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, which although it was not a primary prevention trial, also revealed an increase in cancer incidence in the elderly subgroup [42]. In contrast to these results, the follow-up of the WOSCOPS primary prevention trial, which was also

performed with pravastatin, did not show any evidence of an increased risk associated with assignment to pravastatin at any time in the trial with the exception of the risk of prostate cancer, for which there was a trend toward an increase in the pravastatin group both during and 10 years after completion of the trial. However, this finding was not significant after adjustment for multiple testing [43]. On the basis of all the trials and meta-analyses performed on patients of all ages, it can be concluded that statin therapy does not increase the overall cancer incidence, and some of them indicated even a potentially beneficial effect of statins on several types of cancer [12••]. The most recent meta-analysis, involving 175,000 patients, also confirmed that a median of 5 years of statin treatment had no effect on the incidence of, or mortality from, any type of cancer or in any particular subgroup of patients, including the elderly—even those aged 75 years or older at the baseline—irrespective of the type of statin [44].

Despite significant difficulties in diabetes risk assessment because patients with higher CVD risk also have an increased baseline risk of developing diabetes because of similar risk factors, convincing evidence has been presented that statins are associated with a small but statistically significant risk of developing new-onset diabetes [45, 46]. Accordingly, their use is associated with an 2.4–8.5 % increase in the risk of incident type 2 diabetes, translating to one new diabetes event per 1,000 person-years of treatment, which is very small [47, 48]. An observational study involving 153,840 postmenopausal women—the Women's Health Initiative—found an even greater risk of developing diabetes because of statin treatment [49]. Some quite opposite results were published too. For example, pravastatin was shown to reduce the risk of new-onset diabetes in men aged 65 years by 30 % in the WOSCOP study [50]. In general, all the studies agree that the morbidity and mortality benefits of statin therapy in primary prevention far outweigh the diabetes hazard, including among those at higher risk of developing diabetes [51]. It seems that age is associated with the risk of incident diabetes in subjects treated with statins since greater statin-attributable risk was found in trials with elderly patients. Besides, intensive-dose statin treatment seems to be associated with higher risk of diabetes type 2 than does moderate-dose therapy [46]. It also seems that the type of statin is important as well, since in subjects older than 66 years, treatment with atorvastatin and simvastatin, compared with pravastatin, might be associated with an increased risk of new-onset diabetes [52]. As age has been clearly pointed out as a risk factor for developing incident diabetes during extended statin use, caution is advised when prescribing statins as primary prevention to elderly individuals, particularly in higher doses [45].

Earlier doubts that lipid-lowering treatment may contribute to an increase in depression, suicides, memory loss, or mental disorders, which would be particularly important in older patients, have not been confirmed [53, 54]. However, it has been shown recently that the risk of cataract is increased among statin-treated subjects as compared with nontreated subjects. Therefore, the risk–benefit ratio of statin therapy concerning this issue, specifically for primary prevention in the elderly, should be carefully weighed [55].

Conclusions

Despite all these very convincing data about the beneficial effects of statins in the elderly, it has been shown that elderly people often do not receive proper CVD primary prevention treatment in general, and that low use of statins in primary prevention when older people are concerned, particularly individuals older than 75 years, is more the rule than the exception [56]. A substantial increase in the prevalence and incidence of prescribing statins in the elderly, with the greatest relative increase being in those older than 80 years, can be seen in the last decade across all CVD risk categories, at least in most developed countries [57]. However, the proportion of statin users at low CVD risk remains unchanged, thus indicating the directing of statin prescription in the elderly almost exclusively towards high-risk subjects. Opposite opinions exist as well suggesting that too many patients aged 80 years or older receive statin therapy for primary prevention and are treated to aggressively low LDL-C levels although the efficacy of such treatment is uncertain [58].

Anyhow, the decision whether to treat or not treat elderly subjects with statins in primary prevention is not an easy one. It should be made taking into consideration the individual patient's situation, and good clinical judgment is essential. Many aspects have to be considered, starting from balancing the benefits of such treatment with the risks of adverse effects and polypharmacy problems to health-economic considerations (at least in some health systems) and the patient's wishes. Adherence to statin treatment might be a problem as well because elderly individuals are less likely not only to receive lipid-lowering medications but also to adhere to statin therapy [59]. There are convincing data indicating that subjects aged 70 years or older have lower adherence than younger subjects (younger than 50 years) or middle-aged subjects (50–69 years) [60]. Since adherence to statin treatment is a big problem not only in the elderly, it has to be stressed that the barriers to better adherence include the patient's fear of possible adverse effects, forgetfulness, and the lack of belief in benefits [61, 62]. To be frank, quite a number of barriers on the physicians' side exist as well which prevent better supporting patients' adherence to treatment. They include insufficient physicians' knowledge, their failure to titrate the statin dose appropriately, and also often prescribing less potent statins instead of more potent ones when needed [63–66].

Although studies have not consistently demonstrated an overall beneficial effect on total mortality, it seems that the

risks of CVD morbidity and mortality are favorably affected by statin treatment when it is used for primary prevention in the elderly. However, the evidence for an overall benefit of starting statin treatment in primary prevention in individuals aged 80 years or older still remains very limited. The optimal LDL-C level for those individuals is not known, neither is it known what LDL-C level should be the treatment target. Therefore, a primary prevention statin trial, particularly in the very old, i.e., subjects older than 80–85 years, is urgently needed to be able to answer all these questions, which are still open.

Compliance with Ethics Guidelines

Conflict of Interest Željko Reiner has received personal fees from Abbott, AstraZeneca, and Merck, and grants and personal fees from Sanofi.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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