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Appropriateness of statin prescription in the elderly

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ABSTRACT

Statins, the most widely used drugs in the Western world, have become a pivotal component in the primary and secondary prevention of vascular diseases. Although benefits have been well documented in younger-than-75-year-old individuals, the value of statins in people aged > 75 years and over is controversial. The CTT meta-analysis calculated an absolute risk reduction of 0.6%/year per 38.7 mg/dl reduction in LDL-C levels in patients aged > 75 years, that would translate into a number needed to treat of 167. However, the absolute effect of a 38.7 mg/dl cholesterol lowering on the rate of annual ischemic heart disease mortality is 10-fold larger in older *vs* younger patients. In order to advise physician prescription, three major Guidelines have been published over the last few years, *i.e.* the AHA/ACC and the NLA in the US, and the ESC/EAS in Europe. Moreover, statin prescription in the elderly should also consider the cardiovascular outcomes of elderly patients reported in classical statin preventive trials which give important clues on adherence and persistence of use, as well as on drug safety. The present review discusses benefits of intensive *vs* moderate statin therapy, justifications for the use of aggressive lipid management in the very old and the use of statins in frail elderlies. The final decision on the therapeutic strategy with statins in elderlies at higher risk to develop cardiovascular events should be always based on a careful analysis of the patient's general health and on the presence of metabolic abnormalities or drug interactions potentially leading to risk.

1. Introduction

Inhibitors of the hydroxymethylglutaryl-CoA (HMG-CoA) reductase enzyme, namely statins, are powerful cholesterol-lowering medications and have provided outstanding contributions to the primary and secondary prevention of coronary heart disease (CHD) [for a comprehensive review see [1]]. Indeed, low-density lipoprotein cholesterol (LDL-C) is one of the major modifiable cardiovascular risk factor, and a reduction in LDL-C can safely lower the incidence of heart attacks, revascularizations and ischaemic strokes [2].

Statins are among the most widely used drugs in the Western world: > 200 million individuals, mainly adults, are on chronic treatment [3]. These drugs markedly reduce morbidity and mortality in individuals with dyslipidemia and with a moderate to high risk of CHD younger than 75, whereas data from randomized clinical trials (RCTs) in individuals aged > 75 years and older are lacking. Indeed, the majority of RCTs with statins have excluded individuals above this age being participants in most of the trials between 55 and 66 [4]. Thus, given the increasing geriatric population (by 2050, the number of people aged > 65 years will be 16% of the global total) [5], there is a significant need of evidence-based strategies to address the choice of the most appropriate drug treatment for the prevention of atherosclerotic cardiovascular disease (ASCVD) in the elderly (*i.e.*, older than 75 years of age) as well as in the oldest old (> 80 years of age) [6]. Interestingly, while gerontologists variably identify younger old (60–69 or 65–74 years), middle-old (70–79 or 75–84 years), and very old (over 80 or 85 years of age), cardiologists and other clinicians simplify the older age classifications into two groups, *i.e.*, younger old (up to age 75–80 years) and very old (over age 80) [7].

The appropriateness of statin prescription in these age groups thus needs to be carefully evaluated. Indeed, while statin treatment in patients above 75 years is still widely applied, in the CTT meta-analyses, an absolute risk reduction of 0.6% per year per 38.7 mg/dl reduction in LDL-C levels in patients over 75 years of age was demonstrated [8]. This would translate into a number needed to treat (NNT) of 167 (*vs* 143 < 65 years), to prevent one vascular event per year of therapy

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(including nonfatal myocardial infarction (MI), coronary revascularization, stroke and coronary deaths). Therefore, a very small potential benefit would be distributed across several types of events. The applicability of these findings to patients ≥ 85 years of age merits further investigations.

Moreover, given the presence of clinically manifest CHD in a large number of subjects 75 years of age or older [9], targeting this population remains a challenge and becomes complicated when considering that cardiovascular (CV) outcomes may be far more serious (*i.e.*, causing long-term disability) in the elderly *vs* younger patients [10]. Of note, in the presence of diabetes mellitus, in older people (> 85 years of age), the prescription of lipid-lowering therapies requires careful attention because exposure to higher doses (or higher potency) may not increase life expectancy, but rather the risk of adverse effects [11].

From a strict clinical point of view the present review was aimed to discuss (i) the outcomes of elderly patients in the classical statin preventive trials, (ii) important information for physicians before assigning statin therapy to elderly adults and (iii) whether aggressive lipid management in the very old is justified. By using Pubmed.gov, for this purpose we have revised available English-language studies relevant to the key clinical questions, published up to December 2017.

2. Effects of age on statin pharmacology

Aging in humans is one of the factors affecting the response to drugs and this feature is to be taken into account when appropriate dosing regimens are prescribed. Aging affects drug pharmacokinetics (drug disposition) and pharmacodynamics, possibly increasing drug concentrations with a consequent risk of adverse effects by a number of potential mechanisms. A decline in glomerular filtration rate, liver flow and metabolic capacity can result in reduced drug clearance; reduction of albumin levels may lead to increased free drug concentrations; reduction in lean body mass may result in decreased tissue distribution of hydrophilic drugs, whereas a rise in body fat may result in increased distribution of lipophilic drugs [12–14].

However, it appears that statin kinetics may vary in general to a small extent when comparing young and elderly individuals. For some statins, *e.g.*, pitavastatin, relatively few data are available on the efficacy/safety in the elderlies. In a comparative evaluation of pitavastatin in patients of different age groups, the drug showed a similar kinetics in young *vs* elderlies [15] and was associated with a higher efficacy *vs*, *e.g.*, pravastatin in all age groups. Mean LDL-C changes in the < 65 years and > 65 years age groups were lower for pravastatin (− 25.5 *vs* − 27.6%) and higher for pitavastatin (− 36.3 *vs* − 41.9%), but again activity was similar in the two age groups [16]. For these two drugs, kinetics differs to a minimal extent between younger (aged 19–31 years) and elderly individuals (aged 65–78 years). Instead, in the case of rosuvastatin, a 6% higher $AUC_{0\text{-}t}$ and a 12% higher C_{max} were found in the young group compared with the elderly one thus indicating no need for dose adjustment [17].

Differently from other statins, atorvastatin shows a 42.5% higher C_{max} in the elderly (aged 66–92) *vs* young participants (aged 19–35) being 17.6% higher in women *vs* men. Similarly, mean $AUC_{0\text{-}\infty}$ and half-life ($t_{1/2}$) were 27.3% higher and 36.2% longer, respectively, in elderly *vs* young individuals. These differences, however, did not appear to be clinically relevant in later efficacy trials [18].

3. Guidelines

Clinical Guidelines are systematically developed statements helping practitioners and patients in the selection of the best management strategies [19]. As such, Guidelines should take into account the balance between benefit and risk. With respect to the management of dyslipidemia in elderly patients (> 75 years of age) and for readers' perusal, we summarized in Table 1 recommendations for statin prescription in primary and secondary prevention given by the AHA/ACC [20,21], the USPSTF [22], the NLA [23] and the ESC/EAS [24,25]. Table 2 reports statin dose intensity [26].

4. Outcomes of elderly patients in primary and secondary prevention

Numerous studies have addressed the efficacy of statins in CHD prevention, generally selecting a lower age limit > 18 years without, in most cases, clearly indicating an upper limit. Thus, all statin trials, from the historical 4S (Scandinavian Simvastatin Survival Study) [27] down to the most recent ones, *e.g.* HOPE-3 (Heart Outcomes Prevention Evaluation) [28] have been carried out in patients with a mean age above 55 years. The ongoing STAREE (STAtin Therapy for Reducing Events in the Elderly; NCT: 02099123) trial is likely to provide more direct evidence on the effects of statins in the elderly; indeed, primary endpoints are aimed at examining whether, in healthy elderlies (≥ 70 years), treatment with atorvastatin 40 mg *vs* placebo reduces (i) death, (ii) development of dementia or disability as well as (iii) major fatal or nonfatal CV events. Table 3 and Fig. 1 report studies and their NNT directly addressing older individuals.

4.1. Primary prevention

4.1.1. Randomized controlled studies

Focusing on patients aged > 70 years, the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) study was the most prominent among those involving the elderlies [29]. Among participants allocated to 40 mg pravastatin, the risk of the primary endpoint (*i.e.*, CHD death or nonfatal MI or fatal or nonfatal stroke) was reduced by 15%: Hazard Ratio (HR) = 0.85; 95%CI 0.74–0.97; NNT = 48 (Fig. 1). Specifically, in patients without vascular disease at baseline (*i.e.* in primary prevention, $n = 3239$), pravastatin did not reduce CHD or stroke during a mean 3.2 years of follow-up. Major CV outcomes were influenced to a larger extent in secondary prevention patients.

In the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm) trial, in which 63% of the patients were > 60 years of age, atorvastatin (10 mg) significantly reduced nonfatal MI and fatal CHD by 36% (HR = 0.64; 95%CI 0.50–0.83) [30]. Interestingly, an ~8-year follow-up analysis, after the end of the Lipid Lowering Arm (LLA), showed long-term benefits on all-cause mortality (− 14%) and non-CV deaths (− 15%); this latter apparently due to reduced deaths by infection and respiratory illnesses [31].

A major study including a large proportion of older individuals was JUPITER [32], with 5695 individuals 70 years of age or older without CHD at baseline but with a high-sensitivity C-reactive protein (hsCRP) 2 mg/l or higher. An analysis of these older participants found an all-cause mortality of 1.63 per 100 person-years in those receiving rosuvastatin *vs* 2.04 per 100 person-years in those on placebo, a non-statistically significant difference ($p = 0.09$) [33].

The most recent HOPE-3 (Heart Outcomes Prevention Evaluation) study enrolled men and women aged ≥ 55 and 65 years, respectively, with at least one CV risk factor, or women ≥ 60 years of age with at least two risk factors. No patient had a prior diagnosis of CV disease and all were randomized to rosuvastatin or placebo [mean ages (years): 65.8 (for men) and 65.7 (for women)] [28]. At a median follow-up of 5.6 years, the first co-primary outcome (composite of death from CV causes, nonfatal stroke or nonfatal MI) was less frequent with rosuvastatin than with placebo (3.7% *vs* 4.8% $p < 0.001$) but there was no difference in deaths from any cause between the two groups (5.3% *vs* 5.6%). Thus, in the case of primary prevention of CV outcomes, among a younger population of older adults, there was no benefit for all-cause mortality but some benefit for CV outcomes. There was no analysis of the subgroup of very old adults (particularly those > 80 years) in the HOPE-3 trial.

A most recent reevaluation of the ALLHAT-LLT (Antihypertensive and Lipid-Lowering treatment to Prevent Heart Attack Trial) was