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REVIEW

Hypolipidemic drugs in elderly subjects: Indications and limits

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Abstract *Aims:* Cardiovascular disease is a major cause of death worldwide. Safety and efficacy of lipid lowering therapy have been clearly established for either primary and secondary prevention of cardiovascular events in adults. Nevertheless, the use of hypolipidemic drugs in elderly individuals, especially in the oldest ones, still raises some concerns. Aim of this paper is to review indications and limits of lipid lowering in advanced age, furnishing a practical medical attitude tempered by clinical and geriatric competences.
Data synthesis: While figures from randomized controlled trials and from observational studies seem to support the use of lipid lowering drugs for secondary prevention in the elderly, drawing inferences from primary prevention in old populations is far more challenging. Although these pharmacological agents seem to reduce the incidence of cardiovascular events, they do not prolong survival. In addition, there is some doubt about the cost-effectiveness of treatment because of a more delicate balance between benefit and potential adverse reactions. However, lipid-lowering drugs seem largely underutilized in older age, mainly due to safety concerns that must be reconsidered, at least in part, given the somewhat reassuring results deriving from specific cohort surveys.
Conclusions: Data on the use and on the effects of lipid lowering drugs in elderly populations are incomplete, especially those concerning very old subjects without established cardiovascular disease. Comprehensive guidelines for the management of dyslipidemias in this rapidly-growing population is a urgent need, and treatment should be based, besides the aforementioned considerations, on patient preferences, cognitive function and life expectancy.

Introduction

Cardiovascular disease (CVD) is a major cause of death worldwide and the burden remains high, even if death rates have substantially declined in some western countries during the last decades [1]. Age is one main determinant of cardiovascular (CV) risk, while old age represents a heterogeneous term and classes such as old (65–75), very old (75–85) and oldest old (85+) individuals [2] are necessary to permit better functional grouping. Eight hundred thousand people died from CVD in 2013 in the USA (1 in 3) and about 80% of these were over 65, 65% over 75 while 40% were more than 85 years of age [3]. Furthermore the proportion of elderly subjects is expecting to nearly double in the upcoming years [4], and it may become an issue that global public health programs will have to face.

While the causal relationship between high plasma LDL-cholesterol (LDL-C) and coronary heart disease (CHD)

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morbidity has been clearly proven in middle-aged populations [5], this bond weakens with increasing age [6] and it has been claimed that low plasma cholesterol in persons next to their eighties shows better predictive power for all-cause mortality [7,8]. The Established Populations for Epidemiologic Studies of the Elderly (EPESE) study [9] related the apparent adverse effects associated with low TC levels in very old patients (average baseline age of 79) to comorbidity and frailty (i.e. the multisystem deterioration and loss of physiological reserve frequently occurring in lately in life). The adjustment for potential confounders (CV risk factors, markers of poor health and excluding early-onset events) restored the direct relationship between total cholesterol (TC) and CHD in this heterogeneous population, indicating that the burden of disease may alter the direct association linking plasma cholesterol and CHD with advancing age.

The decision to start or continue lipid lowering medication in elderly persons is complex and may be influenced by several coexisting condition such as renal or liver impairment, sarcopenia, cognitive function, cancer and polypharmacy. Our investigations in this field showed also the relevant role that other lipid parameters differing from LDL-C may also play, e.g. HDL-cholesterol, Lipoprotein(a) and oxidized lipoproteins [10–12]. Furthermore, life expectancy must be taken into account when considering drug-treatment, and it should not be exceedingly short to predict benefit from assumption. A recent trial showed that when patients are anticipated to live less than 12 months, suspending statin treatment is not only safe but could also improve their quality of life [13]. Evidence-based conclusions and Guidelines suggestions for lipid-treatment in advanced decades of life must face scarce and partially contradictory data: dedicated randomized controlled trials (RCTs) are almost absent and figures must be meta-analyzed from more nonspecific investigations after stratifying by age to furnish some valuable indication. It should be recognized that most elderly individuals have manifest CVD or disclose a high prevalence of hidden atherosclerotic lesions: therefore it seems particularly hard discriminating between primary and secondary vascular prevention, mainly in the very-old or oldest-old subjects. Besides safety concerns must be adequately considered when prescribing lipid-lowering drugs particularly in elderly subjects, given some potential muscular, hepatic and cognitive adverse effects that may curtail drug adherence or its use. In the following sections we will try to summarize available information.

Prevention in elderly subjects with established CVD

In 7220 patients with angiographically proven coronary artery disease, statin therapy was associated with a decreased in overall mortality in the following 40 months up to 97 years of age [14]. Aronow et al. documented that the use of statins reduced myocardial infarction (MI) or CHD-related death by 50%, stroke by 60% and heart failure by 48% in a group of 1410 patients (mean age 81 years) with history of MI and LDL-C above 125 mg/dl [15]; in addition, coronary event reduction could be seen also in subjects aged above 90 years. A recent investigation based on 35.903 CHD older patients showed that statin treatment at hospital discharged improved long-term outcomes irrespective of age (65–75 or >75 years), while high-intensity statin-therapy was not associated with incremental benefit [16]. Other observational studies corroborate these findings [17] but all must be interpreted with caution since an insidious bias may have been introduced. In particular treated patients disclose lower CV risk than untreated ones, in an apparent odd occurrence that has been defined the “treatment-risk paradox”, as will be described in a later paragraph. If this is the case, benefits do not come from statin-therapy but by the somewhat lower-risk population that has been given therapy.

Only RCTs individually or cumulatively analyzed may furnish more reliable evidences. The Heart Protection Study [18] was not devoted exclusively to elderly subjects, but randomised 20.536 men and women aged 40–80 years. Their non-fasting blood total cholesterol concentrations was at least 3.5 mmol/L (135 mg/dL), and they were all at high CV risk since affected by CHD, stroke, lower-limb vascular disease or diabetes. Treatment with simvastatin 40 mg qd decreased all-cause mortality by 14.7% and cardiovascular events by about one-quarter. These effects were irrespective of age, and among a group of 1263 individuals 75–80 years old at entry, and so more than eighty by the end of the study, the reduction in the event rate was even more substantial (−30%, $p < 0.001$). The PROSPER study [19] represents perhaps the most informative trial in this context and specifically focused on elderly subjects. It evaluated the effects of 40 mg pravastatin in a cohort of men and women (5804 subjects, 70–82 years) with a history of CVD or risk factors for atherosclerosis. After a follow-up of 3.2 years, the primary endpoint (coronary death, MI, and stroke) was significantly reduced by 15%, and treatment disclosed better effects in men than in women and in those individuals with previous CVD manifestation. A later evaluation of a subgroup of 1833 patients with a history of CHD (and mean age 75.6 ± 3.4 years) showed a significant reduction in all-cause mortality (−18%), CHD mortality (−30%), non-fatal MI (−22%) and need for coronary revascularization (−29%) [20]. Results of a long-term follow-up (8.6 years) have recently been published on the whole-study population. They indicated that even after the end of the trial, a 20% reduction of fatal coronary events was still a persistent finding; no effect was disclosed on cancer or stroke deaths and on life expectancy, possibly due to competing mortality from not-evaluated causes [21]. The IMPROVE-IT trial, published in 2015, evaluated the addition of a nonstatin lipid-lowering agent, ezetimibe, to simvastatin 40 mg vs. simvastatin alone in 18.144 patients of both genders, and more than fifty years of age, who had recently suffered from an acute coronary syndrome. After a median follow-up of 6 years the combined-treatment group experienced 6.4% fewer events (primary composite end-point: death for CVD, major coronary event or stroke) than the simvastatin-alone group.