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Statin therapy for the octogenarian?

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Abstract

Cardiovascular risk increases progressively with age. Statins in octogenarians may therefore potentially bring about large reductions in absolute risk. Epidemiological studies, however, show that statin prescription declines with age and is lowest in the oldest patients with the highest cardiovascular risk. Reasons for low statin utilisation in the elderly include safety concerns, doubts about the utility of statin therapy in those of advanced age and a paucity of definite trial evidence supporting statin prescription in octogenarians. Some of the more recently completed statin outcome trials have randomised patients as old as 82 years. A meta-analysis of secondary prevention, with patients aged 65-82 years at randomisation, supported statin prescription in this age group, as statin therapy was associated with relative risk reduction similar to that observed in younger patients. A Swedish registry study showed improved survival in octogenarians prescribed a statin following hospitalisation with an acute myocardial infarction. Currently there is no definite evidence that statin therapy prevents or ameliorates cognitive impairment or dementia. Statin therapy should be considered in octogenarians at high cardiovascular risk, taking into account factors such as biological vs. chronological age, life expectancy, quality of life, risk of interaction with medications taken for co-morbidities and the ability of the patient to take the statin safely.

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Introduction

Western populations are currently undergoing a major demographic shift as birth rates decline and survival into old age increases. The elderly therefore constitute an increasing proportion of the general population, and doctors are more and more likely to encounter octogenarians or even nonagenarians in their daily practice. Medical management of the very elderly (over 80 years) is often challenging, and one of the clinical conundrums that the clinician is very likely to face is management of dyslipidaemia and cardiovascular risk in octogenarians.

Even a cursory glance at the Framingham risk algorithm or the European System for Cardiac Operative Risk Evaluation (euroSCORE) charts makes it obvious that age is one of the strongest determinants of cardiovascular risk. Absolute cardiovascular risk increases progressively with age and is highest in the very elderly population segment. More than 80% of all cardiovascular disease (CVD) -related deaths in the USA occur in those over 65, and the prevalence of CVD in those above 80 years of age is estimated to be 79% in men and 85% in women.[1] Octogenarians only account for 5% of the USA population, but 20% of myocardial infarction (MI) and 30% of MI-related hospital deaths occur in this group.[2] Because absolute cardiovascular risk is highest in octogenarians, statin therapy could potentially achieve large reductions in absolute risk. This prediction is based on the premise that the relative risk reduction seen in statin-treated patients is independent of age. This is not an unreasonable assumption, but there is little randomised clinical trial evidence of statin therapy in those above 80 years of age that conclusively proves the case.

Although octogenarians may therefore potentially benefit significantly from statin therapy, epidemiological surveys show that statin use declines with age and is lowest in those at highest risk.[3] This finding has been described as the treatment-risk paradox.

Age-related changes in lipoprotein metabolism

Mean plasma low-density lipoprotein cholesterol (LDL-C) rises with age. In men LDL-C plateaus around the age of 50 years. In women LDL-C plateaus on average 10 years later than in men.[4] After the age of 60 years, mean LDL-C is higher in women than in men, with menopausal hormonal changes contributing to the higher LDL-C observed in women. Mechanistically LDL-C rises in older individuals because of a decreased LDL-C fractional catabolic rate, which is likely secondary to decreased hepatic LDL receptor expression.[5] High-

density lipoprotein cholesterol (HDL-C) remains higher in women than in men, irrespective of age. Ageing is also associated with an increase in body fat, with the visceral adipose tissue compartment expanding most.[6] Excess release of free fatty acids from visceral adipocytes, together with a decrease in the oxidative capacity of tissues, may lead to insulin resistance, increased generation of very low-density lipoproteins (VLDL) and ultimately an atherogenic lipid profile characterised by mild hypertriglyceridaemia, low HDL-C and small dense LDL particles.

Occasionally the diagnosis of a monogenic dyslipidaemia, such as familial hypercholesterolaemia (FH), may be made for the first time in old age. Premature CVD is very common but not universal in FH. Although asymptomatic patients diagnosed late in life with FH have demonstrated relative "resistance" against atherosclerotic complications, one cannot assume that they are fully protected and treatment should still be considered. The children of such patients are likely to be adults, with correspondingly high risk if they have inherited the mutation, and family screening should form part of the therapeutic plan.

Secondary causes of dyslipidaemia should also be considered in the elderly presenting with dyslipidaemia. The prevalence of hypothyroidism increases with age, and the manifestations may initially be subtle and easily overlooked; thyroid-stimulating hormone (TSH) should be measured before lipid-lowering therapy is considered. Other potential causes of secondary dyslipidaemia include medications, as well as renal and hepatic disease.

Dyslipidaemia and cardiovascular risk in the elderly

The relative importance of hypercholesterolaemia in predicting cardiovascular risk decreases in the elderly, as age progressively becomes the dominant cardiovascular risk factor. However, hypercholesterolaemia does remain predictive of cardiovascular risk, at least in the 60-70-year age group, as data from the Framingham study show.[7] Initial studies in the very elderly suggested that there may be a U-shaped relationship between total cholesterol and cardiovascular risk and that low cholesterol values are associated with increased cardiovascular risk. Adjusting the data for markers of frailty and malnutrition, such as serum iron and albumin, abolishes this relationship.[8] Low cholesterol values in the elderly therefore most likely reflect frailty, poor nutrition, chronic disease and possibly congestive cardiac failure, all conditions associated with a poor outcome. Hypercholesterolaemia in patients well advanced in age therefore remains predictive of cardiovascular risk, while low cholesterol coupled with frailty or chronic disease may be a poor prognostic sign.

The treatment-risk paradox

Although cardiovascular risk is highest in the elderly, epidemiological surveys consistently show that statin prescription decreases with age. High risk therefore does not translate to a high probability of being treated. A Canadian registry data survey found that the adjusted likelihood of being prescribed a statin decreased by 6.4% for each year of age and was lower in high-risk patients than in low-risk patients.[3] In an Italian study of patients discharged from hospital following an admission for ischaemic heart disease (IHD), it was found that patients older than 75 years were 40% less likely to be prescribed a statin than younger patients.[9] The treatment-risk paradox is not specific to statins, and the elderly are also less likely to be offered interventional therapies, thrombolysis or β blockers, to name only a few examples.

Possible explanations for the treatment-risk paradox

Safety concerns

The elderly, and especially the very elderly, are at high risk of developing drug-related adverse effects. Factors such as decreased drug metabolism, altered volumes of distribution, decreased physiological reserve and altered pharmacodynamics all play a role.[10] Polypharmacy is very common in the elderly and may contribute further to the risk of drug-related adverse effects. The risk of drug-drug interactions rises exponentially with the number of prescribed drugs.

The most common adverse effect of statins is myotoxicity, which may range in severity from mild myalgia to potentially fatal rhabdomyolysis. The risk of developing statin-related muscle problems rises with age. Cerivastatin-related muscle toxicity, for instance, was particularly common in elderly women with low body mass.[11,12] However, this drug is now no longer on the market. The risk of myotoxicity may be increased by commonly prescribed drugs such as amiodarone, verapamil or macrolides that inhibit hepatic cytochrome p450 3A4 (CYP3A4) statin metabolism. Not all statins utilise CYP3A4, and the risk of drug-drug interactions can vary widely amongst statins. An example of a clinically relevant risk is the recent warning by the Federal Drug Administration regarding the risk of myopathy in patients on simvastatin and calcium-channel blockers or amiodarone. In octogenarians, where polypharmacy is the rule rather than the exception, statins are not all "created equal"

and the risk of drug-drug interactions should be a major consideration when choosing a statin. Co-prescription of fibrates with statins and high-dose statin therapy are also associated with an increased risk of myopathy.

Statin therapy is associated with a small but statistically significant increase in the incidence of diabetes. This effect is most marked in trials enrolling predominantly older patients. Overall the estimated benefit of statin therapy outweighs potential deleterious effects related to new-onset diabetes, but the risk of diabetes should be considered when low-risk elderly patients are started on statins for primary prevention.[13]

There has been concern that statins may increase the risk of cancer in the elderly. This concern stems from the 25% increased cancer incidence observed in the active treatment arm of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), in which patients aged 70-82 years were randomised either to pravastatin (40 mg per day) or to a placebo.[14] The study authors attributed the increased cancer incidence to chance, and a subsequent meta-analysis of all major statin studies also found no link between statins and cancer.[15] In a large Swedish registry study of octogenarian MI survivors, the incidence of cancer was also not higher in those prescribed a statin at hospital discharge.[16]

Statins are thus often withheld in the elderly, the very elderly, because of safety concerns. The physician may also attempt to avoid polypharmacy and use as few drugs as possible. Statins offer little immediate benefit or symptom relief and are often regarded as expendable.

Limited evidence base

The elderly, and especially the very elderly (over 80 years), are not well represented in statin trials. All statin studies thus far have used age as an exclusion criterion. The upper age limit varies among trials but has usually been around 65-75 years with only a few trials enrolling older patients. Trials often exclude patients with comorbidities such as renal, cardiac or hepatic dysfunction and may not be applicable to an elderly population with a high prevalence of multiple comorbidities. Uncertainty regarding the risk-benefit ratio of statin therapy in the elderly may result in the withholding of statins.

Evidence base for statin prescription in the elderly

This section presents selected evidence for the prescription of statins in the elderly and does not review the available literature comprehensively. More detailed reviews may be found under References.[17-21]

Patients aged 65-82 years

A recent meta-analysis identified nine studies that had randomised patients older than 65 years with documented IHD at baseline (secondary prevention) to either placebo or statins for at least six months with assessment of clinical outcome variables.[22] Of the nine studies analysed, PROSPER was the only study that specifically only recruited older subjects.[14] For the other studies, investigators were contacted to provide data for elderly subgroups, which were unpublished in many cases. Data were analysed utilising hierarchical Bayesian modelling.

The meta-analysis included 19 569 patients. About a quarter of the patients were female. Patients were 65-82 years old at enrolment. Statin therapy was associated with a 22% relative risk reduction in all-cause mortality [relative risk (RR) 0.78, 95% confidence interval (CI) 0.65-0.89]. IHD mortality was reduced by 30% (RR 0.70, 95% CI 0.53–0.83) and stroke was reduced by 25% (RR 0.75, 95% CI 0.56–0.94).[22] This meta-analysis therefore confirms that statins are effective in secondary-prevention patients aged 65–82 at the time of statin initiation.

Statins as primary preventive therapy in the elderly have not been studied as extensively as statins in secondary prevention. The PROSPER study included primary-prevention patients with additional risk factors such as smoking, hypertension or diabetes. In a post-hoc subanalysis, the risk reductions seen in the primary-prevention group were not statistically significant in their own right, but the statistical test for interaction between the primary- and secondary-prevention subgroups was negative, suggesting that the failure to achieve statistically significant results may have been due to a lack of statistical power. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) of lovastatin as primary prevention in subjects with low HDL-C, 22% of the 6 605 participants were aged 65-73 years at enrolment. In this subgroup, lovastatin was associated with a 37% reduction in major coronary events.[23]

Octogenarians

Very few randomised statin studies have included significant numbers of octogenarians. The PROSPER trial had an age cut-off of 82 years, but the mean age of participants at enrolment was 75 years.[14] The Study Assessing Goals in the Elderly (SAGE) enrolled participants aged 60-85 years with documented IHD and at least one episode of ischaemia lasting a minimum of three minutes on a 48-hour ambulatory electrocardiogram. Patients were randomised to either atorvastatin 80 mg daily or pravastatin 40 mg daily. The

primary efficacy parameter of total ischaemia duration was significantly reduced in both groups with no significant differences between the treatment groups. The all-cause mortality was lower in the intensive treatment group (atorvastatin 80 mg/day) with a trend towards fewer major acute coronary events. However, the mean age at enrolment in this study was 72 years and the authors do not report results for those over 80 separately.[24]

In a recently published study, Gränsbo et al analysed data from the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA).[16] The registry had complete data for 14 907 patients that were 80 years or older when admitted to hospital with an acute MI. Patients were followed for a median of 296 days and all-cause mortality, cardiovascular mortality and cancer mortality were analysed. Analysis was by statin prescription at discharge. Statin therapy was associated with a marked reduction in all-cause mortality (RR 0.55, 95% CI 0.51-0.59) and cardiovascular mortality (RR 0.55, 95% CI 0.51-0.60). This mortality reduction was attenuated when patients that survived less than a year were excluded from the analysis. In patients that survived for at least a year postdischarge, the reduction in all-cause mortality was 36% (RR 0.64, 95% CI 0.57-0.73) and the reduction in cardiovascular mortality was 39% (RR 0.61, 95% CI 0.52-0.72).

These non-randomised nature of registry studies requires that these results be interpreted with caution. One of the greatest problems of registry studies is allocation bias: baseline factors associated with prognosis may also influence the likelihood of statin prescription. Results can be statistically adjusted for this using a propensity score, as was done in the study by Gränsbo et al, but unknown confounders may remain. Physicians likely withheld statins if they thought patients had poor life expectancy or poor quality of life, with little to be gained from statin therapy. Such treatment decisions would skew outcome in favour of statin-treated patients and lead to the unusually large risk reduction observed in the complete cohort. The relative risk reduction observed in patients that survived for at least one year thus probably comes closest to the risk reduction one may have found in a randomised study. Although the data supporting statin use in octogenarians are limited and come almost exclusively from secondary-prevention patients, the totality of evidence does suggest that the relative risk reduction achieved in octogenarians does not differ substantially from that observed in younger patients.

Heart failure

Heart failure is a common problem in the elderly, and the role of statins in heart failure has been controversial. Some authors have voiced concerns that statins may cause or aggravate heart failure as they lower serum ubiquinone levels (co-enzyme Q10) with subsequent impairment of myocardial contractility.[25] In advanced heart failure, low cholesterol is associated with worse outcomes but low cholesterol is likely a marker of frailty and advanced disease in this setting.[26,27] The Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) randomised patients over the age of 60 (mean age 73 years) with systolic heart failure to rosuvastatin 10 mg or a placebo. Rosuvastatin did not reduce mortality or coronary events but did reduce cardiovascular hospitalisations.[28] Importantly, treatment with rosuvastatin did not increase mortality or worsen heart failure in this group.

The most important role of statins with regard to heart failure is probably the prevention of heart failure secondary to ischaemic cardiomyopathy.[29] Statins should not be started in patients with advanced heart failure (lack of efficacy), but many authors argue that they should not be discontinued in patients with known coronary artery disease that develop heart failure, especially if the heart failure is not severe.[30] It is important to remember that most of these conclusions are drawn from studies that included no or very few octogenarians.

Hypertriglyceridaemia

As shown above, there are limited data that support statin prescription in octogenarians with the primary therapeutic aim of cardiovascular risk reduction and LDL-C as the primary lipid target. The management of other lipid phenotypes in octogenarians is largely empirical and extrapolated from experience in younger patients as none of the relevant trials enrolled octogenarians. Severe hypertriglyceridaemia (triglycerides in excess of 10-15 mmol/l) may cause acute pancreatitis and after correction of secondary factors, fibrates may be necessary. Fibrates are mainly excreted renally and dosing should take into account that glomerular filtration rate is often reduced in the elderly.

Cognitive function

Because hypercholesterolaemia in middle age is a risk factor for dementia and cognitive impairment in old age, it has been hypothesised that statin therapy may have the potential to improve cognitive outcomes in octogenarians.[31] Statins could protect the brain by reducing the risk of vascular disease and strokes, but could also exert a direct effect, as high serum cholesterol has been shown to associate with lower

levels of β-amyloid in the cerebrospinal fluid and more β-amyloid deposition in the brain.[32,33]

Many cross-sectional and case-control studies have found improved cognitive outcomes in statin-treated patients.[34-37] However, other studies, especially those of longer duration, have failed to confirm these results.[31,38] Some studies have suggested that statins only slow the rate of decline of cognitive function in cognitively healthy individuals, while patients with mild cognitive impairment at baseline do not benefit.[39] All these non-randomised studies may be affected by prescription bias, as statin prescription rates are likely to be lower in those with even mild cognitive impairment at baseline. There may also be unrecognised confounders such as social class or baseline intelligence, both of which correlate with the risk of developing dementia and the likelihood of being prescribed a statin. Cognitive outcome has not been an endpoint in most of the major randomised statin studies, but was assessed in the Heart Protection Study (HPS) and PROSPER. In the HPS, cognitive function was assessed at the end of the study by means of a single telephonic questionnaire, and randomisation to simvastatin was not associated with a lower incidence of dementia.[40] In the PROSPER study, cognitive function was assessed repeatedly during the study (at six time points) using four different neuropsychological tests. Cognitive function declined in both treatment groups, but there was no difference in the rate of decline between the pravastatin and placebo groups.[41] A recent Cochrane meta-analysis identified three randomised trials of statin therapy in patients with established Alzheimer-type dementia. Statin therapy was not associated with improved cognition or functioning, although the results of one large randomised trial were still outstanding.[42]

Conclusion

Cardiovascular risk is very high in octogenarians, and statin therapy has the potential to reduce absolute cardiovascular risk substantially. However, physicians are less likely to prescribe statins to octogenarians than to younger patients despite the higher risk in the former group. Much of the reluctance to prescribe statins stems from a lack of evidence and therapeutic uncertainty. Although the evidence base for using statins in octogenarians is limited, there is conclusive evidence that the therapeutic benefit of statin therapy for secondary prevention is similar in those under 65 and the 65–82-year age group. More limited evidence suggests that relative risk reductions of comparable magnitude may be achievable in even older patients, especially in the setting of secondary prevention.

It is unlikely that the large, randomised, placebo-controlled clinical outcome trial that would finally prove the benefit of statins in octogenarians will be conducted in the near future, or ever. Statin prescription in octogenarians requires clinical judgement in assessing factors such as biological vs. chronological age, estimated life expectancy, quality of life, co-morbidities and the ability of the patient to take medication safely. Laboratory screening for renal, liver and thyroid dysfunction should be performed prior to statin initiation. If the patient is taking other medications, these should be carefully assessed for possible drug-drug interactions and the statin least likely to lead to interactions should be chosen. Statin therapy should be initiated at low doses with careful titration. Patients and their families should be given realistic expectations of what to expect from statin therapy. Preservation of or even improvements in cognitive function are currently not evidence-based indications for statin therapy, and one should not create false expectations in this regard.

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