Statins in the very elderly, should they be stopped, should they be initiated in primary prevention?

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Abstract

Background

Recently, the Swiss Working Group on Atherosclerosis recommended against the use of preventive statins in primary care in very elderly patients.

Method

We reviewed the literature regarding statins in patients aged 75 years or more and excluded studies with insufficient design. Data was extracted in order to perform a meta-analysis with fixed and random effects regarding ASCVD and death.

Results

The prevention of atherosclerotic diseases (ASCVD) and all-cause mortality was significantly reduced by 40% and by 31% respectively, in a fixed-effect meta-analysis which included 39’131 patients with 5’542 cardiovascular events during follow-up.

Conclusion

The recommendation to exclude very elderly patients from preventive statin therapies in primary prevention is not based on current evidence from randomized clinical trials or from observational studies.

Summary

Recently, the Swiss Working Group on Atherosclerosis recommended against the use of preventive statins in primary care in very elderly patients. We reviewed the literature regarding statins in patients aged 75 years or more and excluded studies with insufficient design. Data was extracted in order to perform a meta-analysis with fixed and random effects regarding ASCVD and death. The prevention of atherosclerotic diseases (ASCVD) and all-cause mortality was significantly reduced by 40% and by 31% respectively, in a fixed-effect meta-analysis which included 39'131 patients with 5'542 cardiovascular events during follow-up. The recommendation to exclude very elderly patients from preventive statin therapies in primary prevention is not based on current evidence from randomized clinical trials or from observational studies.

Introduction

Atherosclerosis is a main cause of myocardial infarction and stroke, as reviewed recently for the presence and extent of carotid atherosclerosis and coronary calcifications [1]. As the absolute risk increases with age, even small benefits from statins should translate in to major reduction in the occurrence of myocardial infarction and stroke in patients aged 75 years or more [2]. In a publication of the National Working Group of Atherosclerosis (AGLA), it was recommended, not to use statins in primary care patients aged 75 years or more [3]. This AGLA recommendation was referenced with a study published by Ramos et al [4] and this recommendation is in contradiction with the lipid guidelines of the European Society of Cardiology 2019 [5] and possibly in contradiction with several randomised and observational studies in the very elderly. In order to elucidate this controversy, we reviewed meta-analyses and extracted observational and randomised studies that had sufficient quality to address the questions in an updated metaanalysis regarding the efficacy of statins for the prevention of atherosclerotic disease (ASCVD) and death from any cause in primary care of very elderly patients.

Method

First, we reviewed the literature regarding statins in patients aged 75 years or more and extracted all available studies containing the data of interest. Second, we excluded studies with insufficient design, for cross-over issues or for other reasons as discussed later. Third, we extracted the available data to perform a meta-analysis with fixed and random effects regarding ASCVD and death. Meta-analysis was performed with MedCalc Software, version 19.1.5.

Results

Randomised statin trials rarely included patients aged 75 years or more. In the ALLHAT-LLT trial, a separate analysis of outcome was performed by Han [6], however, in that study there was a substantial cross-over in patients randomised to statins or placebo and the adherence-rates to statins were low. E.g., 29% of patients were taking statins at year 6 in the placebo group and 22% percent for not taking pravastatin in the intervention group at year 6. Because of these uncertainties in the intention-to-treat analysis we omitted ALLHAT-LLT in elderly patients from further analysis. Available observational studies were published by Ramos [4] and Eilat [7]. The Ramos study was excluded from further analysis for several reasons: information about invoices for statins were collected only for patients before study entry and were not controlled for during the study. Therefore, authors did not present a surrogate or a direct evidence that patients actually ingested statins. More than 40% of non-diabetic patients presented no data about lipids and patients did not report statin side effects. Patient thus did not take statins in a sufficient amount or duration and therefore absolutely no preventive effect was observed. Indeed, the complete lack of preventive effects is counterintuitive and raises many questions about the study design and the lack of proof of statin ingestion during the study period or during a pilot-study, that was unfortunately also not performed. Also, in the limitation section, the problem of statin adherence was not even mentioned in the paper. Therefore, we excluded the Ramos study from our meta-analysis because it does not fulfill the criteria of good epidemiological practice [8] and it may even be stated, that such a study should be withdrawn. Eilat et al analyzed the effect of statins in an observational study, where the number of statin pills was controlled and therefore patients could be stratified into adherence and non-adherence groups. Additionally, they were able to stratify the data for patients aged 75 or more against those aged below 75 years.

Ridker and Yusuf presented a metaanalysis of patients aged 70 years or more included in the Jupiter und HOPE-3 trials [9] and found a relative risk reduction of 26% for ASCVD (composite endpoint of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) using a fixed-model meta-

analysis as the golden-standard. This study was therefore included in our meta-analysis. In a CTT analysis published 2019, authors found a non-significant ASCVD relative risk reduction in participants aged 75 years or more of 8% [10] per 1 mmol/l LDL reduction. With the use of more potent statins, such effects could be substantially improved. The results of this meta-analysis were included in our meta-analysis. Finally, the EWTOPIA trial randomised healthy elderly patients to Ezetimibe or placebo as an add-on therapy to statins and found a 36% relative risk reduction for the primary ASCVD outcome (sudden cardiac death, fatal or nonfatal myocardial infarction, coronary revascularization, or fatal or nonfatal stroke)[11]. Although this study did not formally address statin effects, Ezetimibe added to Simvastatin did significantly reduce LDL cholesterol and therefore we used Ezetimibe as a surrogate for statins in the meta-analysis. . In total, we could identify 5 trials with acceptable study design and results regarding ASCVD outcome are summarized in Table 1 with 39131 patients and 5542 events during various duration of follow-up.

Regarding mortality, only two studies showed sufficient data to be included in the meta-analysis and are summarized in Table 2.

For the meta-analysis of ASCVD events we used a relative-risk based analysis with fixed effect model as the main measure of statin performance and added a random effect-model in order to account for the different study designs (randomized vs. observational). Results are outlined in Table 3 and Figure 1. Test for heterogeneity showed some inconsistency (I^2=93%, 95% CI 86-96%), which was significant ($p<0.0001$). However, both for random and fixed effects, results were statistically significant ($p=0.029$ and $p<0.001$ respectively). For all-cause mortality, the fixed effects model remained significant ($p<0.001$), however regarding the random effect model, only a non-significant trend in mortality reduction could be observed, as shown in Table 4 and Figure 2, and the test for heterogeneity was again statistically significant (I^2=97%, $p<0.0001$). Sensitivity analysis included the Ramos study, which lead to a loss of significance regarding ASCVD in the random effects model, but still with a trend towards positive treatment effects of statins (RRR 0.76, 95%CI: 0.49 to 1.19), whereas the fixed effect model remained highly significant (RRR 0.761, 95%CI: 0.72 to 0.80). Similar

results occurred, when HOPE-3 and Jupiter numbers were excluded from the final model (random model RRR: 0.68, 95%CI: 0.43 to 1.07, p=0.094; fixed effect model RRR: 0.58, 95%CI: 0.54 to 0.63).

Discussion

Atherosclerosis is a continuous process which progresses over decades and therefore affects mainly the elderly [2]. There are no data that report a lower risk attributable to atherosclerosis in patients living beyond their 75th birthday. There is also abundant proof that statins are effective in reducing the effects of atherosclerosis in primary care [12] and there are no reports that statins act differently on atherosclerosis in patients aged 75 years and beyond. By inference, very elderly patients with atherosclerosis in primary prevention should be treated with statins, unless contraindications are present.

Unfortunately, only two low-quality studies [4,6] were needed to cause confusion and uncertainty about a statin-treatment of atherosclerosis in the very elderly and have even led the AGLA to issue the recommendation, not to treat primary care patients aged 75 years or more with statins. Unfortunately AGLA did not specify, whether patients on statin treatment should stop their statin medication on their 75th birthday. The AGLA recommendation was made irrespective of risk assessments in such patients, which may even lead to the situation, where the very elderly with advanced atherosclerosis on imaging are denied preventive medications with statins.

Our brief review of the literature and the calculated meta-analysis show that the current standard for such an analysis, the fixed-effect meta-analysis [9], is associated with a highly significant reduction in ASCVD and all-cause mortality. The sensitivity analysis with exclusion of patients between 70-74 years from the randomized trials HOPE-3 and Jupiter or the inclusion of the Ramos study [4] did not change the significance of LDL-lowering with statins / ezetimibe in very elderly patients on reduction of ASCVD.

This observation adds strong evidence in the discussion regarding unnecessary statin use in high risk primary care patients having lived beyond the age of 75, because the weight of evidence strongly favors such a preventive strategy in primary care and is in line with the ESC lipid guidelines 2019. Looking forward, the randomized STAREE trial using 40 mg of Atorvastatin versus Placebo in patients

aged at least 70 years (https://clinicaltrials.gov/ct2/show/NCT02099123) will produce more direct evidence from Australia.

In view of our results, statins should be prescribed in patients with a high ASCVD risk aged 75 years or more and will avoid high treatment and social costs resulting from ASCVD events.

Conclusions

In very elderly patients, preventive therapies with statins and ezetimibe produce a highly significant relative risk reduction for ASCVD of 40% and for all-cause death of 31%. The recommendation to exclude very elderly patients from preventive statin therapies in primary prevention is not based on current scientific knowledge.

Conflict of interest

None to declare.

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Tables

Table 1: Evidence from 5 trials in patients aged 70 years (HOPE-3, Jupiter) or 75 years or more on ASCVD outcome

	ASCVD			
	Verum		Placebo	
	N	Event	N	Event
CTT [10]	10926	295	7429	208
EILAT [7]	1255	347	7328	4105
EWTOPIA [11]	1716	89	1695	133
Jupiter [9]	2848	51	2848	82
HOPE-3 [9]	1543	107	1543	125
SUM	18288	889	20843	4653

Table 2: Evidence from 2 trials in patients aged 75 years or more on death as the outcome variable

	All Cause Mortality			
	Verum		Placebo	
	N	Event	N	Event
EILAT [7]	436	67	2146	764
EWTOPIA [11]	1716	188	1695	173
SUM	2152	255	3841	937

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Table 3: Relative risk for ASCVED meta-analysis using fixed and random effects

Study	Intervention	Controls	Relative risk	95% CI	z	P	Weight (%)	
							Fixed	Random
CTT [10]	295/10926	208/7429	0.964	0.810 to 1.149			17.12	20.98
EILAT [7]	347/1255	4105/7328	0.494	0.450 to 0.541			62.24	21.97
EWTOPIA [11]	89/1716	133/1695	0.661	0.510 to 0.857			7.76	19.52
Jupiter [9]	51/2848	82/2848	0.622	0.440 to 0.879			4.39	17.78
HOPE-3 [9]	107/1543	125/1543	0.856	0.668 to 1.097			8.5	19.74
Total (fixed effects)	889/18288	4653/20843	0.602	0.561 to 0.647	-13.842	<0.001	100	100
Total (random effects)	889/18288	4653/20843	0.699	0.506 to 0.964	-2.187	0.029	100	100

Table 4: Relative risk for all-cause death meta-analysis using fixed and random effects

Study	Intervention	Controls	Relative risk	95% CI	z	P	Weight (%)	
							Fixed	Random
EILAT [7]	67/436	764/2146	0.432	0.344 to 0.542			42.42	49.79
EWTOPIA [11]	188/1716	173/1695	1.073	0.883 to 1.305			57.58	50.21
Total (fixed effects)	255/2152	937/3841	0.69	0.597 to 0.798	-4.995	<0.001	100	100
Total (random effects)	255/2152	937/3841	0.682	0.277 to 1.677	-0.834	0.404	100	100

Figures

Figure 1: Meta-analysis of medical trials in the elderly for ASCVD outcomes.

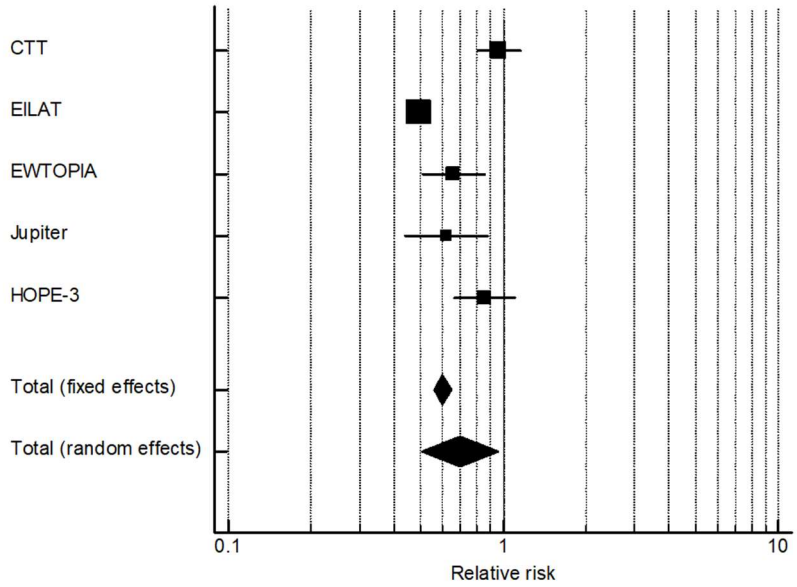

Figure 2: Meta-analysis of medical trials in the elderly for all-cause mortality.