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Benefits of Statins in Elderly Subjects Without Established Cardiovascular Disease

A Meta-Analysis

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Objectives The purpose of this paper was to assess whether statins reduce all-cause mortality and cardiovascular (CV) events in elderly people without established CV disease.

Background Because of population aging, prevention of CV disease in the elderly is relevant. In elderly patients with previous CV events, the use of statins is recommended by guidelines, whereas the benefits of these drugs in elderly subjects without previous CV events are still debated.

Methods Randomized trials comparing statins versus placebo and reporting all-cause and CV mortality, myocardial infarction (MI), stroke, and new cancer onset in elderly subjects (age ≥65 years) without established CV disease were included.

Results Eight trials enrolling 24,674 subjects (42.7% females; mean age 73.0 ± 2.9 years; mean follow up 3.5 ± 1.5 years) were included in analyses. Statins, compared with placebo, significantly reduced the risk of MI by 39.4% (relative risk [RR]: 0.606 [95% confidence interval (CI): 0.434 to 0.847]; p = 0.003) and the risk of stroke by 23.8% (RR: 0.762 [95% CI: 0.626 to 0.926]; p = 0.006). In contrast, the risk of all-cause death (RR: 0.941 [95% CI: 0.856 to 1.035]; p = 0.210) and of CV death (RR: 0.907 [95% CI: 0.686 to 1.199]; p = 0.493) were not significantly reduced. New cancer onset did not differ between statin- and placebo-treated subjects (RR: 0.989 [95% CI: 0.851 to 1.151]; p = 0.890).

Conclusions In elderly subjects at high CV risk without established CV disease, statins significantly reduce the incidence of MI and stroke, but do not significantly prolong survival in the short-term. (J Am Coll Cardiol 2013;62:2090–9) © 2013 by the American College of Cardiology Foundation

Cardiovascular (CV) diseases account for more than 81% of deaths in individuals older than age 65 years who are more frequently affected by comorbidities, including diabetes mellitus, hypertension, hyperlipidemia, and renal dysfunction, compared with younger people (1). Because of population aging, prevention of CV disease in the elderly will assume increasing relevance in the future, influencing health policies worldwide.

The benefit of hydroxyl methyl glutaryl coenzyme A reductase inhibitors (statins) is established in patients with previous CV events (2), and intensive low-density lipoprotein (LDL) cholesterol lowering is recommended by guidelines (3,4). In addition, evidence indicates that statins substantially reduce CV events and all-cause mortality in patients without previous CV events (5) or at low CV risk (6). In elderly patients (age ≥65 years) with previous CV events, the use of statins is recommended by guidelines (3,4) based on evidence from 1 clinical trial enrolling elderly patients with and without CV disease (7) and 1 meta-analysis (8). In contrast, in elderly patients without CV events, the use of statins is not advocated by guidelines (Level of Recommendation: IIb in European Society of Cardiology guidelines [3]) because no clinical trials have assessed the

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risk-benefit of statin use in this age group and only subgroup analyses from randomized studies are available (5).

Thus, we designed a meta-analysis to assess whether statins reduce all-cause mortality and CV events in elderly people without established CV disease.

Methods

Search strategy. The study was designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (9). MEDLINE, Cochrane, ISI Web of Science, and SCOPUS databases were searched for articles published until January 2013 combining the following medical subject heading terms: "hydroxymethylglutaryl-CoA reductase inhibitors" and ("aged" or "aged, 80 and over") and "randomized controlled trial" and the following search terms ("pravastatin" or "lovastatin" or "simvastatin" or "rosuvastatin" or "atorvastatin" or "pitavastatin" or "mevastatin" or "fluvastatin" or "statin") and "randomized controlled trial." No language restrictions were applied.

Study selection. Study inclusion criteria were: randomized allocation to statin or placebo; report of outcomes in the subgroup of patients with age at randomization ≥65 years and without established CV disease; and report of at least 1 clinical event among all-cause death, CV death, myocardial infarction (MI), stroke, and new cancer onset.

Data extraction and quality assessment. Papers identified in the literature search were screened by 2 independent reviewers (G.S., S.P.) to assess their eligibility for the analysis. Discrepancies were resolved by the senior author (P.P.F.). Corresponding authors were asked to provide full-text papers, if they were not available. From each study, information about methods, year of publication, number of patients in treatment and control arms, duration of follow-up, age, sex, CV risk factors, medications, baseline and change in lipid levels, and treatment drug and dose were collected and entered into STATA (version 12.0, StataCorp., College Station, Texas) by 1 author (G.S.) and checked by the senior author (P.P.F.). The pre-specified outcomes abstracted from selected trials were all-cause death, CV death, MI, stroke, and new cancer onset. When a potentially eligible trial that lacked essential information (outcomes) was identified, the corresponding author was asked to complete a form that included the required information. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) method was used to summarize the findings and score the overall quality of evidence (10).

Data synthesis and analysis. Relative risks (RRs) of the effect of randomized treatments were calculated using the "metan" routine (STATA version 12.0, Statacorp, College Station, Texas) to account for the probability of events occurring in the treatment group versus the placebo group (11). The RR and 95% confidence interval (CI) for each outcome were separately calculated for each trial with grouped data, using the intention-to-treat principle (12). Pooled RRs were logarithmically transformed and weighted for the inverse of variance. Overall estimates of effect were calculated with a fixed-effects model or with a random-effects model when heterogeneity could not be explained (13). The assumption of homogeneity between the treatment effects in different trials was tested by Q statistic and further quantified by I^2 statistic. The significance level for the overall estimates of effect was set at $p \leq 0.05$, whereas it was set at $p \leq 0.10$ for the presence of heterogeneity and publication bias. The objective of the study was to investigate the effects of statin therapy on all-cause death, CV death, MI, stroke, and new cancer onset in elderly patients without established CV disease.

Abbreviations and Acronyms

CI = confidence interval
CV = cardiovascular
LDL = low-density lipoprotein
MI = myocardial infarction
RR = relative risk

Sensitivity analysis. To verify the consistency of outcome meta-analysis results, the influence of each individual study on the summary effect estimate was assessed by the 1-study removed sensitivity analysis using the "metaninf" command (STATA) (14). To explore the influence of potential effect modifiers on outcomes, weighted random-effects meta-regression analysis was performed with the "metareg" command (STATA) to test demographic characteristics of the study population, duration of follow-up, CV risk factors (including diabetes mellitus and hypertension), type of statin, concomitant medications, and changes in lipid profile from baseline to the end of follow-up (15,16). For all meta-regression analyses, the weight used for each trial was the inverse of the sum of the within-trial variance and the residual between trial variance. Additionally, the residual maximum likelihood methods were employed to explain residual heterogeneity not explained by potential effect modifiers, including an additive between-study variance component Tau^2 (16,17).

Publication bias. To evaluate potential publication bias, a weighted linear regression was used with the natural log of the odds ratio as the dependent variable and the inverse of the total sample size as the independent variable. This is a modified Macaskill's test, which gives more balanced type I error rates in the tail probability areas in comparison with other publication bias tests (16,18).

Results

Characteristics of included trials. The characteristics of included trials are outlined in Table 1. Of 24,405 papers identified in the initial search, 46 were retrieved for more detailed evaluation. Thirty-eight studies were subsequently excluded: 25 trials enrolled patients with established CV disease; 7 trials reported duplicate data; 2 trials reported no clinical endpoint (19,20); 1 trial excluded patients age >70 years, leaving too few elderly patients to be included in analyses (21); 1 large (22) and 2 small (23,24) randomized