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Benefits of Statins in Elderly Subjects Without Established Cardiovascular Disease

A Meta-Analysis

Gianluigi Savarese, MD,* Antonio M. Gotto, Jr, MD, PhD,† Stefania Paolillo, MD,* Carmen D'Amore, MD,* Teresa Losco, MD,* Francesca Musella, MD,* Oriana Scala, MD,* Caterina Marciano, MD,* Donatella Ruggiero, MD,* Fabio Marsico, MD,* Giuseppe De Luca, MD, PhD,‡ Bruno Trimarco, MD, PhD,* Pasquale Perrone-Filardi, MD, PhD*

Naples and Novara, Italy; and New York, New York

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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From the *Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy; †Weill Cornell Medical College, New York, New York; and the ‡Division of Cardiology, Piemonte Orientale University, Novara, Italy. Dr. Gotto has served on the Board of Directors of Aegerion Pharmaceuticals and Arisaph Pharmaceuticals; has served on the Advisory Board of DuPont and Vetera Capital; and has served as a consultant for AstraZeneca Pharmaceuticals; Janssen, KOWA, Merck, and Roche. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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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

Table 1 Baseline Characteristics of Trials Included in Analyses

Trial (Ref. #)	Year	Patients (n)	Treatment	Follow-Up (yrs)	Age (yrs)	Baseline TC (mmol/l)	ΔTC (%)	Baseline LDL-C (mmol/l)	ΔLDL-C (%)	Baseline HDL-C (mmol/l)	ΔHDL-C (%)
AFCAPS/TexCAPS (25)	1998	1,416	Lovastatin 20/40 mg	5.2	NA	5.70	−6.80	4.06	−13.90	0.99	2.56
ALLHAT-LLT (26)	2002	5,707	Pravastatin 40 mg	4.8	NA	5.79*	−16.32*	3.77*	−22.69*	1.23*	−1.62*
ASCOT-LLA (30)	2011	4,445	Atorvastatin 10 mg	3.3	71	5.48*	−13.91*	3.44*	−18.54*	1.31*	−0.77*
Bruckert et al. (27)	2002	1,229	Fluvastatin 80 mg	1	75	7.28	−13.69	5.18	−17.89	1.36	0
CARDS (28)	2006	1,129	Atorvastatin 10 mg	3.9	69	5.36*	−12.38*	3.03*	−13.92*	1.40*	−11.36*
JUPITER (29)	2010	5,695	Rosuvastatin 20 mg	1.9	74	4.82*	NA	2.80	−25.27	1.27*	1.57*
MEGA (31)	2011	1,814	Pravastatin 10/20 mg	5	NA	6.27*	−7.32*	4.05*	−11.95*	1.49*	6.02*
PROSPER (7)	2002	3,239	Pravastatin 40 mg	3.2	75*	5.70†	NA	3.80+	−22.79†	1.30†	NA

	Baseline TG (mmol/l)	ΔTG (%)	Age (yrs)	Females (%)	HTN (%)	DM (%)	Smoking (%)	Inclusion Criteria
AFCAPS/TexCAPS (25)	1.96	−7.18	NA	25	NA	6*	12*	Patients with average cholesterol levels and without prior CV disease
ALLHAT-LLT (26)	1.71*	−6.41*	NA	49*	100	NA	NA	Moderate hypercholesterolemia, HTN
ASCOT-LLA (30)	1.65*	−15.92*	71	20	100	27	24	HTN and at least 3 CV risk factors
Bruckert (27)	1.53	−6.12	76	75	56	7	5	Primary hypercholesterolemia
CARDS (28)	1.94*	−9.64*	69	31	NA	100	16	Type 2 DM and at least 1 other CV risk factor
JUPITER (29)	1.33*	−7.98*	74	51	66	NA	8	CRP >2.0 mg/l
MEGA (31)	1.44*	−11.42*	NA	68*	52	21	14	Hypercholesterolemic Japanese patients
PROSPER (7)	1.50†	NA	75†	52†	62†	11†	27†	Raised risk of CV disease because of smoking, HTN, or DM

To convert total cholesterol, LDL-C, and HDL-C from mmol/l to mg/dl, divide by 0.0259. To convert triglycerides from mmol/l to mg/dl, divide by 0.0113. *Data from the published cohort of young and elderly patients. †Data from the published cohort of primary and secondary prevention patients.

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm; BB = beta-blocker; CARDS = Collaborative Atorvastatin Diabetes Study; CRP = C-reactive protein; CV = cardiovascular; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; HTN = hypertension; JUPITER = Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C = low-density lipoprotein cholesterol; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; MI = myocardial infarction; NA = not available; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; TC = total cholesterol; TG = triglycerides.

clinical studies having missing information that we could not obtain from the authors. Therefore, 8 trials (7,25–31) were finally included in the analyses, which enrolled 24,674 patients (42.7% females; mean age 73.0 ± 2.9 years; mean follow-up 3.5 ± 1.5 years), 12,292 of which were assigned to statin treatment and 12,382 to the placebo (Fig. 1).

Methodological quality. All studies included in analyses were randomized, high-quality trials without major methodological limitations (Table 2). In particular, no inconsistency of results, publication bias, or imprecision among studies were identified according to the SCORE grading method. Nonsignificant limitations were identified for 8 trials, 7 of which had double-blinded study design (7,25–30) and 1 was an open-label study (31).

Effects of statins on lipid profile. In statin-treated patients, baseline mean total cholesterol was 6.01 ± 0.70 mmol/l and decreased by 1.22 ± 0.31 mmol/l (20%) at the end of follow-up, whereas in placebo-treated patients, total cholesterol was 6.02 ± 0.70 mmol/l at baseline and decreased by 0.26 ± 0.24 mmol/l (4%) at the end of follow-up. In statin-treated patients, LDL cholesterol was 3.76 ± 0.73 mmol/l at baseline and decreased by 1.16 ± 0.26 mmol/l (31%) at the end of follow-up, whereas in placebo-treated patients, LDL cholesterol was 3.77 ± 0.74 mmol/l at baseline and decreased by 0.21 ± 0.24 mmol/l (6%) at the end of follow-up. In statin-treated patients, high-density lipoprotein cholesterol level was 1.29 ± 0.16 mmol/l at baseline and increased by 0.01 ± 0.07 mmol/l (1%) at the end of follow-up, whereas in placebo-treated patients, high-density lipoprotein cholesterol level was 1.29 ± 0.16 mmol/l at baseline and decreased by 0.02 ± 0.08 mmol/l (2%) at the end of follow-up. In statin-treated patients, triglycerides level was 1.66 ± 0.23 mmol/l at baseline and decreased by 0.24 ± 0.09 mmol/l (14%) at the end of follow-up, whereas in placebo-treated patients, triglycerides level was 1.64 ± 0.26 mmol/l at baseline and decreased by 0.06 ± 0.07 mmol/l (4%) at the end of follow-up.

Outcome analysis. MI occurred in 2.7% of subjects allocated to statins compared with 3.9% of those in placebo during a mean follow-up of 3.5 years. Thus, statins significantly reduced the risk of MI by 39.4% compared with placebo (RR: 0.606 [95% CI: 0.434 to 0.847]; comparison p = 0.003; heterogeneity p = 0.028; random effects model) (Fig. 2). Annual MI rate was 1.1% in patients allocated to placebo, and 24 patients needed to be treated for 1 year to

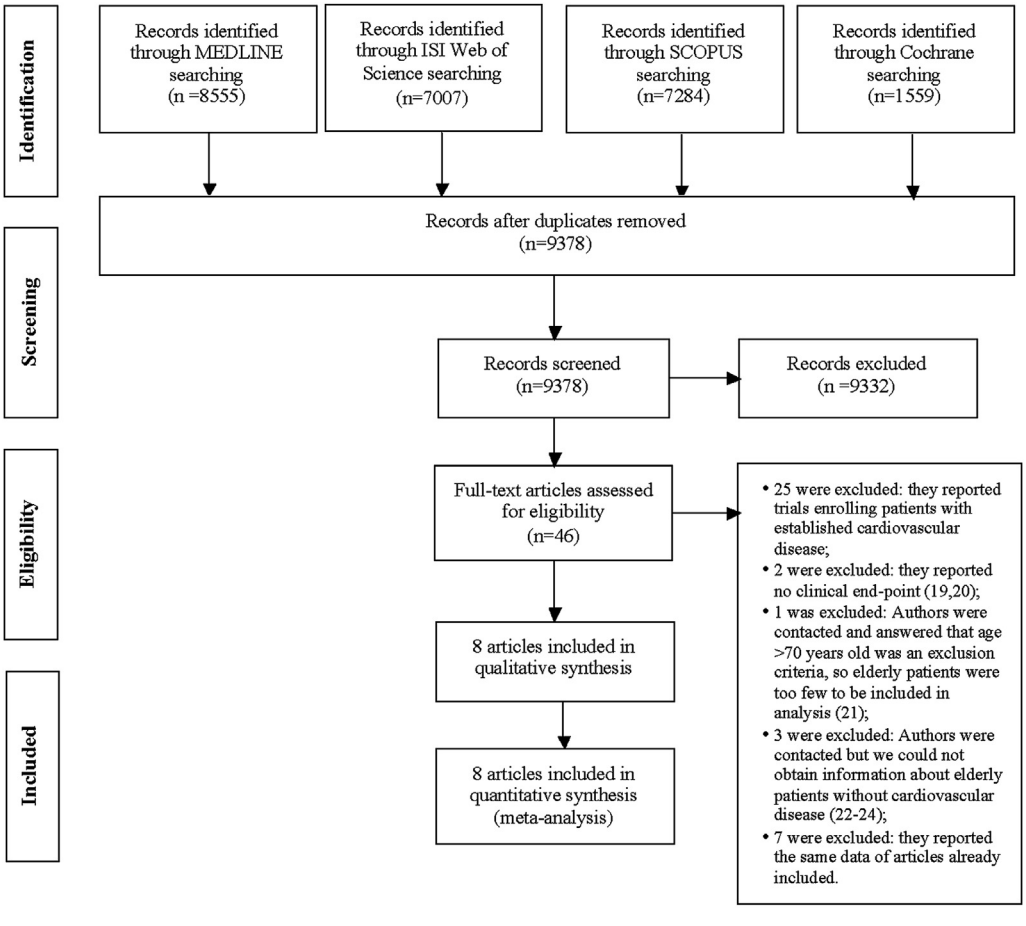

Figure 1 Meta-Analysis Flow Chart

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Table 2 GRADE Method Evidence Summarizing the Outcomes Measured

	Quality Assessment						Summary of Findings			
	No. of Studies (Participants)	Methodological Limitations	Consistency	Directness	Precision	Publication Bias	Relative Effect (95% CI)	Illustrative Comparative Risks (95% CI)		Quality of the Evidence (GRADE)
								Assumed Risk Placebo	Corresponding Risk Statin	
All-cause death	7 (21,435)	No serious limitations	No inconsistency	Direct	No uncertainty	Unlikely	RR: 0.941 (0.856–1.035)	5.1 per 100	4.8 per 100 (4.4–5.3)	++++ High
Cardiovascular death	5 (13,914)	No serious limitations	No inconsistency	Direct	No uncertainty	Unlikely	RR: 0.907 (0.686–1.199)	1.1 per 100	1.0 per 100 (0.7–1.3)	++++ High
Myocardial infarction	5 (15,929)	No serious limitations	No inconsistency	Direct	No uncertainty	Unlikely	RR: 0.606 (0.434–0.847)	3.7 per 100	2.2 per 100 (1.6–3.1)	++++ High
Stroke	5 (16,322)	No serious limitations	No inconsistency	Direct	No uncertainty	Unlikely	RR: 0.762 (0.626–0.926)	3.6 per 100	2.7 per 100 (2.2–3.3)	++++ High
New cancer onset	3 (11,556)	No serious limitations	No inconsistency	Direct	No uncertainty	Unlikely	RR: 0.989 (0.851–1.151)	5.5 per 100	5.4 per 100 (4.7–6.3)	++++ High

CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RR = relative risk.

prevent 1 event. Stroke was reported in 2.1% of subjects randomized to statins compared with 2.8% in placebo during a mean follow-up of 3.5 years. Thus, statins significantly reduced the risk of stroke by 23.8% compared with placebo (RR: 0.762 [95% CI: 0.626 to 0.926]; comparison p = 0.006; heterogeneity p = 0.130; fixed effects model) (Fig. 2). Annual rate of stroke was 0.8% in patients randomized to placebo, and 42 patients needed to be treated for 1 year to prevent 1 event.

Statins did not significantly reduce the risk of all-cause death compared with placebo (RR: 0.941 [95% CI: 0.856 to 1.035]; comparison p = 0.210; heterogeneity p = 0.570; fixed effects model) (Fig. 3) and the risk of CV death (RR: 0.907 [95% CI: 0.686 to 1.199]; comparison p = 0.493; heterogeneity p = 0.831; fixed effects model) (Fig. 3).

New cancer onset was reported in 5.4% of subjects in both treatment and placebo groups, with no significant difference of risk (RR: 0.989 [95% CI: 0.851 to 1.151]; comparison p = 0.890; heterogeneity p = 0.492; fixed effects model) (Fig. 4).

Sensitivity analysis. Results were confirmed when the meta-analysis was repeated removing 1 study at the time. Significant heterogeneity affecting analysis for MI was resolved by excluding the PROSPER trial, and the results were confirmed (RR: 0.542 [95% CI: 0.421 to 0.698]; comparison p = 0.001; heterogeneity p = 0.505).

By meta-regression analysis, no potential effect modifiers (including sex, diabetic status, and hypertension) influenced the findings of the meta-analysis.

Publication bias. No publication bias was found for each outcome considered in the analyses.

Discussion

The findings of this meta-analysis indicate that statins reduce the risk of MI and stroke in elderly subjects without established CV disease in a short-term follow-up, with a nonsignificant favorable trend toward reduction of mortality.

Primary CV prevention in the elderly. Due to aging of the population, a large and increasing number of CV events (more than two-thirds) occur in elderly (age ≥65 years) subjects (4). In addition, due to the higher number of elderly individuals without established CV disease, the majority of CV events occur in these patients, despite the relative lower risk for individuals without previous CV disease when compared with individuals with previous CV events (32).

Recent guidelines have broadened the indication for statin treatment and intensive cholesterol lowering to include subjects without coronary artery disease affected by comorbidities, including diabetes mellitus, peripheral arterial diseases, or renal dysfunction, which portend a very high CV risk (3). As these conditions are more common in elderly compared with younger individuals, there is a need to ascertain whether statin treatment should be advocated in elderly people without established CV disease but at high or very high CV risk.

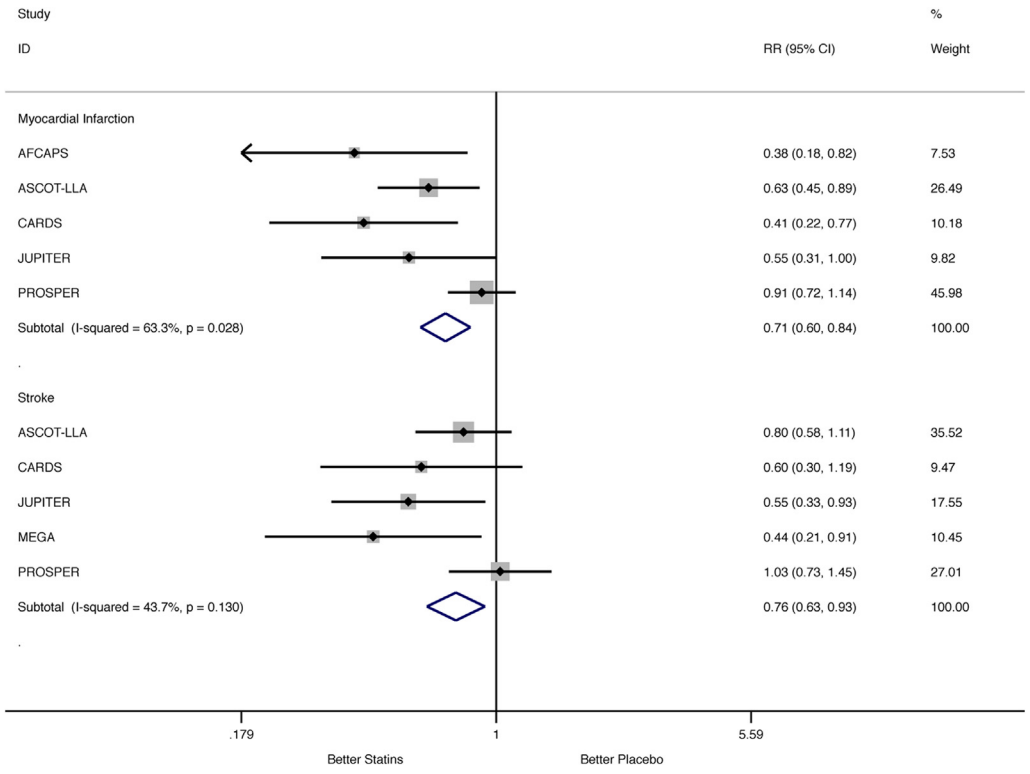

Figure 2 **RRs of Myocardial Infarction and Stroke**

Gray squares represent relative risks (RRs) in trials. The 95% confidence intervals (CIs) for individual trials are denoted by **lines** and those for the pooled RRs by **open diamonds**. Meta-analysis is performed by fixed effects model. AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study; JUPITER = Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk.

Yet, there is currently no definitive indication for statin treatment in elderly subjects with risk factors but without established CV disease. Recent European Society of Cardiology guidelines (3) assign statin treatment in this population Class IIb and Level of Evidence: B due to lack of clinical studies or meta-analysis. The Adult Treatment Panel III (4), instead, advises that treatment in elderly people should be driven by Framingham risk score calculation, although absolute CV risk calculation from the risk chart is not recommended in people older than age 80 years (4).

Previous studies. Despite a lack of clinical trials of primary prevention in the elderly, no meta-analysis has been conducted thus far. In fact, the only available information on the effects of statins in elderly individuals without CV disease comes from the meta-analysis of Brugts et al. (5), which reported the effects of statins in subjects without CV disease. At variance with the current analysis, this previous study was not focused on the elderly population, although in a subgroup analysis, authors reported no heterogeneity of the effects of statins on outcomes between patients older or younger than age 65 years. However, all CIs for outcomes in the subgroup of patients ≥65 years of age crossed the identity line, indicating no definitive evidence of benefit. Notably, the study did not report a separate analysis of stroke and MI risk in elderly people. Thus, these previous data did not allow a meaningful assessment of the benefit of statins in primary prevention in elderly individuals.

Current study. The current meta-analysis provides first-time evidence that the benefits of statins on major CV events extend to people ≥65 years without CV disease. These findings are consistent with the favorable effect of statins reported in subjects without CV disease in 2 previous meta-analyses (8,33). In fact, Mills et al. (34), in a meta-analysis on the effects of statins in primary prevention, reported a 23% reduction of MI and a 12% reduction of stroke by statin treatment, whereas more recently, Taylor et al. (33) reported a 27% reduction of fatal and nonfatal coronary events and a 22% reduction of stroke in subjects without CV events treated with statins. In their meta-analysis, Mills et al. (34) also reported a significant effect of statins on total mortality (7% risk reduction) and CV mortality (11%), whereas Taylor et al. (33) reported a significant 14% reduction of all-cause mortality in statin-treated subjects. These previous observations are consistent

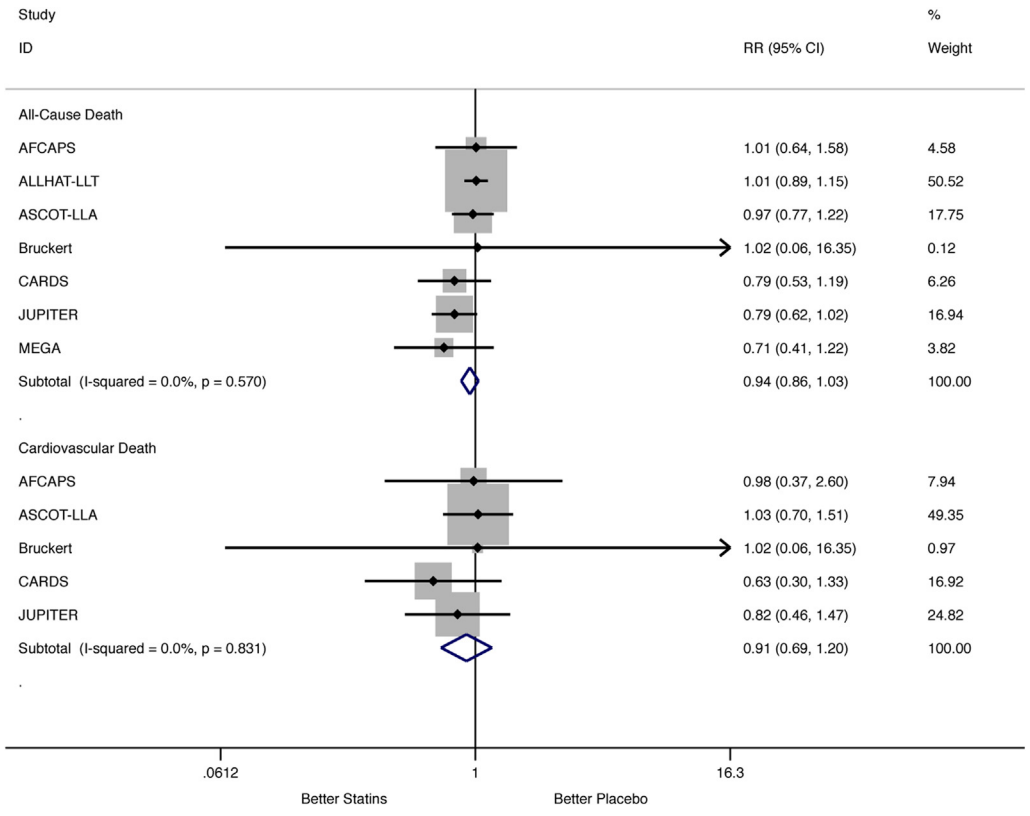

Figure 3 RRs of All-Cause Death and Cardiovascular Death

Gray squares represent RRs in trials. The 95% CIs for individual trials are denoted by **lines** and those for the pooled RRs by **open diamonds**. Meta-analysis is performed by fixed effects model. Abbreviations as in Figure 2.

with the 6% nonsignificant total mortality reduction and the 9% nonsignificant CV mortality reduction observed in our analysis.

In our study, a 39.4% MI risk reduction and a 23.8% stroke risk reduction over 3.5 years of follow-up were observed for a mean LDL cholesterol reduction of 0.69 mmol/l (difference of changes from baseline to the end of study LDL cholesterol values between treated and placebo patients for each trial). Thus, a 57.1% MI risk reduction and a 34.5% stroke reduction can be extrapolated for 1 mmol/l of LDL cholesterol reduction in elderly people without known CV disease, and this can be compared to the 29% MI risk and 15% stroke risk reduction per 1 mmol/l of LDL cholesterol reduction reported by the Cholesterol Treatment Trialists' Collaborators in their last meta-analysis in the general population of patients enrolled in randomized clinical trials (35). Our findings are also consistent with the 24% risk reduction of major CV events in people without vascular disease treated with statins, observed at all levels of CV risk and confirmed after stratification for age and sex, that was recently reported by the Cholesterol Treatment Trialists' Collaborators (35). In particular, a 63% reduction of major CV events was observed in elderly subjects (age >70 years) (35), showing a yearly event rate comparable to that observed in the current study. In the population of patients collected in our analysis, the annual event rate in placebo-treated subjects was 0.5% for CV death, 1.1% for MI, and 0.8% for stroke. According to recent guidelines (3), these event rates correspond to a high-risk category of patients in whom an LDL cholesterol target <100 mg/dl is recommended and in whom drug (statin) treatment should be started if cholesterol values are above target. Noteworthy, the on-treatment mean LDL cholesterol of trials included in this meta-analysis remained above the recommended target of 100 mg/dl, suggesting that a higher benefit could be achieved in this population if the current recommend targets are reached. Thus, the findings of the present meta-analysis provide evidence for treatment of subjects at high CV risk and older than age 65 years, and this may be relevant for upgrading the level of recommendation for treatment in this age group in future guidelines.

However, identification of high-risk elderly patients without established CV disease remains challenging, as risk charts' calculation of absolute CV risk over a 10-year period does not apply to subjects older than age 80 years (4). In the present analysis, elderly subjects in primary

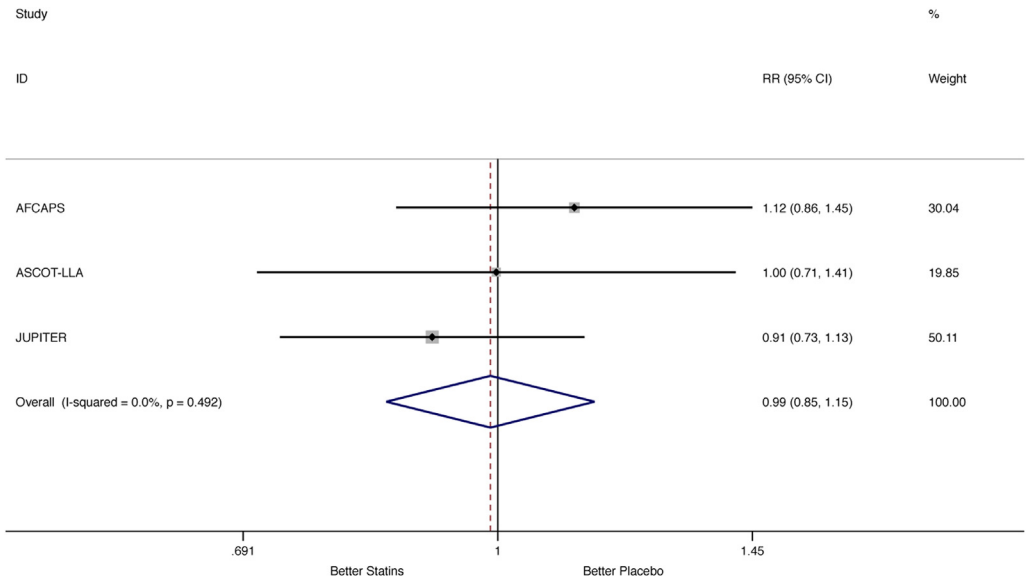

Figure 4 **RRs of New Cancer Onset**

Gray squares represent RRs in trials. The 95% CIs for individual trials are denoted by **lines** and those for the pooled RRs by **open diamonds**. Meta-analysis is performed by fixed effects model. Abbreviations as in Figure 2.

prevention were characterized as having more than 1 major risk factor (7,26,28,30), a single major risk factor as hypercholesterolemia (27,31), or elevated C-reactive protein levels (29). Thus, our results apply to these categories of elderly subjects and should not be generalized. Additional risk factors (36–38), and in particular subclinical atherosclerosis measuring carotid intima-media thickness (39) or coronary artery calcium scoring (40), may help selecting elderly high-risk subjects in whom statin treatment may reduce short-term CV risk, but this approach remains unproven and deserves investigation (4).

The cost-benefit evaluation of treatment in elderly people must also be considered. From our analysis, 24 or 42 elderly subjects without established CV disease would need to be treated with statins for 1 year to prevent 1 MI or 1 stroke, respectively. The cost of treatment should be weighed against the costs of disability and caregiving for subjects experiencing an MI or stroke, but these costs are highly variable among different health systems. However, the cost-benefit assessment of statin treatment in elderly subjects without CV disease must also take into account the reduced benefit of treatment associated with aging due to the increased incidence of competing non-CV clinical events that partially offsets the life expectancy gain provided by treatment (41). Finally, as emphasized by guidelines (3,4), medical (cognitive function, comorbidities) and social factors specific to elderly individuals and impacting on adherence to treatment must also be taken into account when considering drug prescription in this age group.

Study limitations. The current analysis was based on aggregate and not on patient-level data. In addition, only 2 studies (7,27) included in the meta-analysis were designed to enroll elderly patients, whereas the majority of patients included represent elderly subgroups of clinical trials. Three clinical trials (22–24) enrolling potentially eligible patients could not be included in our study as we could not obtain information from the authors. However, most of these patients were enrolled in the Heart Protection Study (23) that reported no difference in outcomes between younger and elderly subjects as well as between subjects with and without previous CV disease. Thus, although we could not obtain data for the subgroup of elderly patients without CV disease, it is unlikely that this would alter the results of our analysis. Moreover, whether more intensive compared with less intensive lipid lowering influences clinical outcomes in elderly patients without CV disease could not be assessed in the current analysis. We also could not separately assess whether the benefits of statins in elderly subjects without CV disease differ between male and female subjects or in diabetic versus nondiabetic patients, although previous meta-analyses in subjects without CV disease reported a significant benefit of statin treatment in both sexes (35,42). Finally, the short-term follow-up of trials included should also be acknowledged for 2 main aspects: 1) the potential impact on the nonsignificant effect on mortality that might need longer observation to reach statistical significance; and 2) the evaluation of side effects, and in particular of new cancer incidence, that needs longer observation to be adequately assessed.

Conclusions

In elderly subjects at high CV risk and without established CV disease, statins substantially reduce the incidence of MI and stroke in a short-term follow-up, with a favorable, albeit nonsignificant, trend for reduction in mortality.

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Reprint requests and correspondence: Dr. Pasquale Perrone-Filardi, Department of Advanced Biomedical Sciences, Federico II University, Via Pansini, 5-I80131 Naples, Italy. E-mail: fpperron@unina.it.

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