

Statins and cardiovascular outcomes in elderly and younger patients with coronary artery disease: a post hoc analysis of the GREACE study

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Abstract

Introduction: The effect of cardiovascular disease (CVD) prevention measures aimed at elderly patients requires further evidence. We investigated the effect of statin treatment (targeted to achieve guideline goals) on CVD outcomes in different age groups to determine whether statins are more beneficial in the elderly.

Material and methods: The primary endpoint of this post hoc analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study ($n = 1,600$ patients with established coronary heart disease (CHD), mean follow-up 3 years) was the absolute and relative CVD event (a composite of death, myocardial infarction, revascularization, unstable angina, heart failure and stroke) risk reduction in age quartiles (each $n = 200$). Patients on "structured care" with atorvastatin ($n = 800$) followed up by the university clinic and treated to lipid goal were compared with the corresponding quartiles on "usual care" ($n = 800$) followed up by specialists or general practitioners of the patient's choice outside the hospital.

Results: In the elderly (mean age 69 ± 4 and 70 ± 3 years in the "structured" and "usual care", respectively) the absolute CVD event reduction between "structured" and "usual care" was 16.5% ($p < 0.0001$), while in the younger patients (mean age 51 ± 3 years and 52 ± 3 years in the "structured" and "usual care", respectively) this was 8.5% ($p = 0.016$); relative risk reduction (RRR) 60% ($p < 0.0001$) vs. 42% respectively ($p = 0.001$). The elderly had higher rates of chronic kidney disease and higher uric acid levels, plus an increased prevalence of diabetes, metabolic syndrome and non-alcoholic fatty liver disease. These factors might contribute to the increased CVD risk in older patients.

Conclusions: All age groups benefited from statin treatment, but the elderly on "structured care" had a greater absolute and relative CVD risk reduction than the younger patients when compared with the corresponding patients assigned to "usual care". These findings suggest that we should not deprive older patients of CVD prevention treatment and lipid target achievement.

Key words: cardiovascular disease, age, statin, chronic kidney disease, GREek Atorvastatin and Coronary-heart-disease Evaluation.

Introduction

Coronary heart disease (CHD) is the leading cause of death among the elderly and > 80% of all CHD deaths occur in patients > 65 years old [1]. Life expectancy is steadily increasing but cardiovascular disease (CVD) risk substantially increases with age, creating a heavy burden of morbidity and mortality [1].

Studies such as the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) showed that the benefits of statin therapy extend to patients > 70 years of age [2]. Nevertheless, there was no beneficial effect of pravastatin on stroke [2]. Other studies suggest that statin treatment benefits all age groups. Subgroup analyses from clinical trials (Scandinavian Simvastatin Survival Study (4S), Cholesterol and Recurrent Events (CARE), Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID)) [3-5] demonstrated that simvastatin or pravastatin therapy significantly reduced the risk of CVD-related events in older patients (> 65 years old) to a similar level as for younger participants. Moreover, in the Treating to New Targets (TNT) [6] trial, older patients on atorvastatin 80 mg had a relative risk reduction (RRR) in major CVD events that was similar to that for patients < 65 years on atorvastatin 10 mg [6].

Some survival studies showed that older people benefit more from statin treatment compared with younger people. In the Heart Protection Study (HPS) [7], the absolute RR in major CVD events among patients \geq 65 years of age on simvastatin (40 mg/day), compared with placebo, was higher than that in patients < 65 years [6]. Moreover, the very old patients reported a better quality of life and more often achieved treatment targets than young stable angina patients [8]. Data also showed that in the elderly, the risk reduction (RR) is greater or equal to that in younger patients, but absolute RR was greater in the elderly because the event rate was higher [1].

In a large study on 20,132 male veterans, in all age groups, the magnitude of low-density lipoprotein cholesterol (LDL-C) reduction was proportional to the magnitude of CVD risk reduction [9], largely irrespective of the initial lipid profile or other presenting characteristics (including age). In a population study on 5,152 older people with diabetes mellitus (DM), statins reduced excess cardiovascular and all-cause mortality risk, irrespective of the presence or absence of CHD or glucose-lowering medication [10].

The magnitude and the mechanisms of CVD risk reduction in the elderly are not yet defined. This *post hoc* analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study [11] was undertaken to investigate the effect of statin treatment (targeted to achieve guideline

goals) on CVD outcomes in age groups divided by quartiles and not in a dichotomous way as for most studies [2-7].

Material and methods

Study protocol

The design and results (mortality, morbidity, cost-effectiveness and long-term safety) of the GREACE study, a "real-world study", have been described [11]. Briefly, this was a prospective, randomized, open label, intention-to-treat, and survival study. GREACE was conducted between 1998 and 2002 and was an unsponsored (investigator driven) study. Patients enrolled ($n = 1,600$) were men (78%) and women (22%) with CHD, aged < 75 years old (mean age 58.3 ± 13 years). Baseline serum LDL-C levels were > 100 mg/dl (2.6 mmol/l) and serum triglyceride (TG) levels < 400 mg/dl (4.5 mmol/l).

All patients attended the outpatient atherosclerosis clinic of the Hippocraton University Hospital, Thessaloniki, Greece, and if eligible were randomized either to "structured care" ($n = 800$), followed up by the university clinic, or to the "usual care" group ($n = 800$), followed up by specialists or general practitioners of the patient's trust and choice outside the hospital. In the "structured care" group, the starting dose of atorvastatin was 10 mg/day. If the National Cholesterol Educational Program (NCEP) LDL-C goal (<100 mg/dl (2.6 mmol/l)) [12] was not reached, the dose was titrated up to 80 mg/day at 6-week intervals. Patients in the "usual care" group were treated according to their physicians' standard of care.

"Usual care" included life style changes, such as low-fat and hypocaloric (if needed) diet, weight loss, exercise plus all necessary drug treatment, including lipid-lowering agents. All patients were followed up for a mean 3-period with visits every 6 months.

In the present post hoc analysis participants in each "care" category were divided into quartiles ($n = 200$) and patients in each quartile of "structured care" were compared with the respective quartile of the "usual care" group. We did not use any cut-off age points. We included 200 patients in each quartile as their age was descending from the highest age to the lowest age.

Laboratory investigations

Serum lipids (total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), and TGs), glucose, transaminase activities (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) and γ -glutamyl transpeptidase (GGT) were assessed at baseline, at the 6th treatment week (dose titration visit) and every 6 months thereafter. Biochemical measurements were made on each serum sample using an Olympus AU 560 auto-

analyser and appropriate reagents (Olympus GmbH, Clare, Ireland). The reference range for ALT was 10-45 IU/l, for AST 10-37 IU/l and for GGT 0-55 IU/l. All biochemical measurements were performed at the 6th week (for statin dose titration purposes) and then every 6 months in all patients regardless of treatment or baseline levels of LTs. Serum creatinine (SCr) was measured using the Jaffé method (reference range 0.6-1.3 mg/dl (55-115 µmol/l)). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula ($eGFR = 175 \times Scr^{-1.154} \times age^{-0.203}$ ($\times 0.742$ if female)) [11]. Serum uric acid (SUA) concentrations were assessed using an enzymatic (uricase) colorimetric assay (reference range 150-415 µmol/l (2.5-7.0 mg/dl)). All the patients participating in the original study were included in the present *post hoc* analysis.

Comorbidities

All patients had an eGFR evaluation. Those with an eGFR value of 30-59 ml/min/1.73 m² (stage 3 chronic kidney disease (CKD)) were compared with those with an eGFR > 60 ml/min/1.73 m² (normal renal function or stage 1-2 CKD). Patients with an eGFR < 30 ml/min/1.73 m² were excluded from the study by the original study protocol.

In patients with abnormal liver tests (LTs), this was attributed to non-alcoholic fatty liver disease (NAFLD), after ultrasonographic diagnosis of this disease and after excluding other causes of elevated LTs (alcohol abuse (average use of pure alcohol > 20 g/day for men and > 10 g/day for women), chronic hepatitis B and C, Wilson's disease and autoimmune hepatitis). Thus, given that all patients had dyslipidaemia and that the vast majority of patients with abnormal LTs were obese, or had the metabolic syndrome (MetS) and/or diabetes mellitus (DM), abnormal LTs were mainly attributed to NAFLD. Liver-related adverse effects of statin treatment were defined as an elevation in ALT and/or AST activity > 3-fold the upper limit of normal (ULN).

Endpoints

In this *post hoc* analysis of the GREACE study the primary endpoint was the decrease in CVD adverse events (all-cause and CVD mortality as well as CVD morbidity (non-fatal myocardial infarction, revascularization, unstable angina, congestive heart failure, and stroke)) in all age quartiles of patients ($n = 200$) on "structured care" compared with the corresponding age quartile of patients ($n = 200$) on "usual care". In respect to CVD events saved, the absolute and CVD relative risk reductions (RRR) were also calculated in all age quartiles and were compared with those of the other age quartiles. Secondary endpoints were the changes in eGFR,

SUA, and LTs in all age quartiles irrespective of the level of care. Other secondary endpoints were the differences between age groups in incidence of CKD, DM, MetS and smoking status.

Statistical analysis

All studied variables had a normal distribution as assessed by the Kolmogorov-Smirnov test. Variables are reported as mean and standard deviation (SD). The χ^2 test was used for categorical variables, and Student *t* test for continuous variables. Analysis of covariance (ANCOVA) was used to estimate significance among CVD event decrease in each age quartile, although the statistical power was substantially reduced by the separation of the study population in quartiles. The numbers need to treat (NNT) in each age quartile of structured care and their trend (*p* for trend) were calculated. At the end of the study ALT, AST, GGT, eGFR, and SUA values were calculated and were compared with baseline values. A 2-tailed $p < 0.05$ was considered significant. All analyses were carried out using the SPSS 21.0 software (SPSS Inc., Chicago, IL).

Results

There were no significant differences in secondary CVD prevention treatments (aspirin, β -blockers, angiotensin-converting enzyme inhibitors) or patient parameters (arterial blood pressure or glycaemic control at baseline and on study) between the "structured" and "usual care" groups, except for statin treatment (at the start of the study in 1998 not all physicians in Greece prescribed statins for CHD patients). In the structured care group all patients were on atorvastatin; thus, in this group the NCEP LDL-C treatment goal was reached by 95% ($n = 759$) of patients after dose titration of atorvastatin [11]. Only 14% of the "usual care" patients received any hypolipidaemic drugs throughout the study; 12% were on statins and only 3% of them reached the NCEP LDL-C treatment goal [11]. Thus, any difference recorded among the groups should be attributed to statin treatment.

Biological parameters in all age and different degrees of care categories are listed in Table I.

The mean age of patients in each age quartile was 51 ± 3 , 57 ± 4 , 63 ± 3 , 69 ± 4 (ANCOVA $p = 0.01$) for the "structured care" quartiles, and 52 ± 3 , 58 ± 3 , 64 ± 4 , 70 ± 3 (ANCOVA $p = 0.008$) for the "usual care" quartiles. The mean age difference in both levels of care between the lower and the upper age quartiles was 18 s.

Endpoints

The primary endpoint was the difference in the CVD events reduction in the upper age quartile ($n = 200$) on "structured care" as compared with

Table I. Parameters of study participants at baseline and at the end of the study in the upper age and lower age quartile, according to degree of care

Parameter	Lower age quartile of structured care patients (n = 200)			Upper age quartile of structured care patients (n = 200)		
	Baseline	End of study	Percent change	Baseline	End of study	Percent change
Total cholesterol [mg/dl]	286 ±36	167 ±12	-41 ^{†‡}	245 ±38	160 ±14 ^{†‡}	-35 ^{†‡}
LDL cholesterol [mg/dl]	188 ±31	102 ±4	-46 ^{†‡}	171 ±12	96 ±8 ^{†‡}	-44 ^{†‡}
HDL cholesterol [mg/dl]	36 ±5	38 ±4	5	38 ±6	41 ±5 [†]	5 [†]
Triglycerides [mg/dl]	176 ±37	125 ±42	-29 ^{†‡}	182 ±29	124 ±15 ^{†‡}	-32 ^{†‡}
ALT [IU/l]	32 ±9	30 ±11 [‡]	-6 [‡]	42 ±14	29 ±6 ^{†‡}	-31 ^{†‡*}
AST [IU/l]	30 ±8	27 ±9 [‡]	-10 ^{†‡}	37 ±11	26 ±6 ^{†‡}	-30 ^{†‡*}
GGT [IU/l]	35 ±7	30 ±8	-14 ^{†‡}	53 ±13	30 ±5 ^{†‡}	-44 ^{†‡*}
eGFR [ml/min/1.73 m ²]	72 ±12	70 ±11	2	63 ±10 [†]	73 ±8 ^{†‡}	10 ^{†‡*}
Serum uric acid [mg/dl]	6.5 ±1	6.4 ±2	-1	7.4 ±1	6.6 ±1 ^{†‡}	-11 ^{†‡*}

Parameter	Lower age quartile of usual care patients (n = 200)			Upper age quartile of usual care patients (n = 200)		
	Baseline	End of study	Percent change	Baseline	End of study	Percent change
Total cholesterol [mg/dl]	268 ±35	257 ±33	-4	242 ±38	234 ±14	-3
LDL cholesterol [mg/dl]	176 ±34	170 ±29	-3	165 ±12	161 ±11	-3
HDL cholesterol [mg/dl]	38 ±5	39 ±4	3	38 ±6	39 ±4 [†]	3
Triglycerides [mg/dl]	173 ±37	168 ±42	-4	179 ±28	171 ±15	-4
ALT [IU/l]	34 ±9	38 ±11	9	41 ±12	45 ±13	10
AST [IU/l]	31 ±8	32 ±9	3	38 ±10	42 ±12	10
GGT [IU/l]	28 ±7	30 ±8	7	51 ±15	55 ±17	8
eGFR [ml/min/1.73 m ²]	71 ±14	70 ±10	1	62 ±11	58 ±13	-6
Serum uric acid [mg/dl]	6.4 ±1	6.8 ±1	6	7.5 ±2	7.9 ±2	5

[†] $p < 0.05$ vs. baseline, [‡] $p < 0.05$ vs. respective quartile of "usual care", ^{*} $p < 0.05$ vs. lower age quartile of "structured care". LDL – low-density lipoprotein cholesterol, HDL – high-density lipoprotein cholesterol, ALT – alanine aminotransferase, AST – aspartate aminotransferase, GGT – γ -glutamyl transpeptidase, e-GFR – estimated glomerular filtration rate

the respective quartile on "usual care" ($n = 200$) vs. respective reductions in the lower age quartile ($n = 200$) on "structured care" as compared with the respective quartile on "usual care" ($n = 200$). The observed differences vs. "usual care" were 17 events (8.5% reduction, $p = 0.016$) in the lowest age quartile, 22 events (11% reduction, $p = 0.004$) in the second lowest age quartile, 28 events (14% reduction, $p = 0.0003$) in the third age quartile, and 33 CVD events (16.5% reduction, $p < 0.0001$) in the highest age (elderly) quartile (Figure 1). However, significance using ANCOVA and χ^2 test in pairs of quartiles did not reach statistical significance, probably as a result of the lack of statistical power due to the relatively small number of patients in each age quartile. The RRR were 42%, 48%, 53%, and 60%, as age increased in respective quartiles. The NNT with atorvastatin for 3 years were 11.7, 9.1, 7.2, 6.1 (p for trend = 0.001), as age increased in respective quartiles, to avoid one CVD event. The NNT of the initial GREACE study (all patients on structured care) was 8. The results on secondary endpoints, i.e. differences between age groups in the incidence

of CKD, hyperuricaemia, DM, MetS, and smoking status (all CVD risk factors), are shown in Table II. The incidence of all the above were, as expected, higher in the elderly than in the younger patients. The values of biochemical parameters and the rate

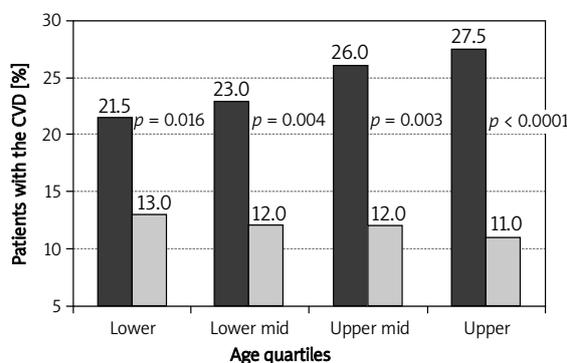


Figure 1 Percent of patients with any major cardiovascular (CVD) event (all-cause and CVD mortality as well as CVD morbidity (non-fatal myocardial infarction, revascularization, unstable angina, congestive heart failure, and stroke)) in all age quartiles in the "structured care" and the "usual care" groups

Table II. Comorbidities in study participants at baseline and at the end of the study in the upper age and lower age quartile, according to degree of care

Parameter	Lower age quartile of structured carepatients (n = 200)			Upper age quartile of structured care patients (n = 200)		
	Baseline	End of study	Percent change	Baseline	End of study	Percent change
Men [%]	87	–	–	75	–	–
Age [years]	51 ±3	–	–	69 ±4*	–	–
Patients with AH or on antihypertensive drugs [%]	36*	35*	–3*	50*	52*	4*
Patients with DM or on hypoglycemic drugs [%]	12*	13*	8*	25*	27*	8*
Patients with MetS [%]	28*	27*	–1*	41*	22†*	–19†**
Patients with stage 3 CKD [%]	19*	18*	–1*	32*	21†*	–11†**
Patients with NAFLD [%]	20*	9*	–11*	32*	9†*	–23†**
Patients with hyperuricaemia [%]	17*	15*	–2*	29*	17†*	–12†**
Current smokers [%]	18*	16*	–11*	8*	6*	–25†**
Parameter	Lower age quartile of usual care patients (n = 200)			Upper age quartile of usual care patients (n = 200)		
	Baseline	End of study	Percent change	Baseline	End of study	Percent change
Men [%]	89	–	–	74	–	–
Age [years]	52 ±3	–	–	70 ±3*	–	–
Patients with AH or on antihypertensive drugs [%]	35*	37*	2*	52*	55*	6*
Patients with DM or on hypoglycemic drugs [%]	11*	11*	–	22*	24*	9*
Patients with MetS [%]	29	32	10*	40*	44**	10*
Patients with stage 3 CKD [%]	21*	23*	9*	30*	35**	16*
Patients with NAFLD [%]	20	21	5*	31*	35*	13*
Patients with hyperuricaemia [%]	18*	20*	10**	27*	30**	11***
Current smokers [%]	20*	18*	–2*	10*	9*	–1*

†p < 0.05 vs. baseline, ‡p < 0.05 vs. respective quartile of "usual care", *p < 0.05 vs. lower age quartile of "structured care". DM – diabetes mellitus, AH – arterial hypertension, NAFLD – non-alcoholic fatty liver disease, MetS – metabolic syndrome, CKD – chronic kidney disease

of comorbidities in the middle lower and the middle upper age quartile were in between those of the lowest and the upper age quartiles without significant differences with the upper and lowest quartiles of the respective level of care (data not shown).

Discussion

This *post hoc* analysis of the GREACE trial suggests that the clinical benefit increases with increasing patient age (Figure 1). It is of interest that the benefit of statin treatment in CHD patients during the 3-years follow-up was practically similar (the incidence of CVD events in structured care patients ranged from 11% to 13% for all age quartiles). However, the percentage and the absolute number of CVD events saved were increasingly higher with

older age, because the "usual care" patients showed an increasing incidence of CVD events as age increased (from 21.5% in the lowest age quartile to 27.5% in the highest age quartile, *p* = NS) (Figure 1). Thus, the increased CVD risk of the older patients on "usual care" shaped the difference. This was also the case for the Intermountain Heart Collaborative Study, which included 7,220 individuals with angiographically defined significant CHD (≥ 70% stenosis) [13]. The mean follow-up was 3.3 years (similar to ours), and patients were divided into 3 age groups (< 65, 65-79 and ≥ 80 years) [13]. All age groups benefited, but although older patients were less likely to receive statin therapy, they had a greater absolute risk reduction. Relative risk reductions in mortality reached 50% for those

≥ 80 years compared with 44% and 30% for individuals 65-79 years old and those < 65 years old, respectively, after adjusting for potential confounders [13].

Any clinical benefit in the upper age quartile in the present study could be related to the greater improvement of factors such as CKD, hyperuricaemia, and NAFLD in this age group than in the lower age quartile group. The risk of CVD in patients with CKD appears to be greater than in the general population, and a low GFR is an independent risk factor for CVD, *de novo* CVD, and all-cause mortality in the elderly based on population data [14, 15], registry data [16] and clinical studies [17, 18]. An independent and graded association was detected between reduced eGFR and the risk of death, CVD events and all-cause hospitalizations [16]. Age-related decline in renal function in elderly subjects is associated with co-existing CVD and its risk factors [17]. Even mild CKD correlates with a higher CVD prevalence; the association of CKD with risk for adverse outcomes is strongly related to co-existing CVD and CVD risk factors [18]. It has been shown in survival studies that patients with CKD (up to stage 3) are indeed at a higher CVD risk but exhibit greater CVD risk reduction with effective treatment than those with normal kidney function [19, 20]. A GREACE *post hoc* analysis showed that renal function declines over time and statin (mainly atorvastatin) treatment significantly improves renal function, thus offsetting an additional CVD risk factor [19]. The GFR increase was shown to be associated with CVD risk reduction, independent of the hypolipidaemic effect of the drug (backward stepwise regression analysis, adjusting for other CVD risk factors) [19]. The renal TNT *post hoc* analysis ($n = 9,656$) [20] confirmed that patients with stage 3 CKD ($n = 3,107$) have a higher risk for CVD events (11.3%) vs. those with normal renal function (8.6%) (hazard ratio (HR) = 1.35; 95% confidence interval (CI) 1.18-1.54; $p < 0.0001$). However, CKD patients on 80 mg/day of atorvastatin had a 32% CVD event risk reduction (HR = 0.68; 95% CI 0.55 to 0.84; $p = 0.0003$) compared with CKD patients on 10 mg/day of atorvastatin vs. a 15% CVD event risk reduction in patients with normal eGFR on 80 mg/day of atorvastatin (HR = 0.85; 95% CI 0.72 to 1.00; $p = 0.049$), compared with those on 10 mg/day of atorvastatin [20]. eGFR was increased by up to 9.9% in those with CKD and 5.5-7.6% in those with normal renal function [21]. These findings suggest that in TNT, CVD risk reduction was greater in those patients with greater improvement of renal function, irrespective of LDL-C levels, supporting the earlier results of GREACE [19]. We also reported benefits in high-risk patients with MetS, DM, arterial hypertension and dyslipidaemia [22, 23]. Therefore, statins (mainly atorvastatin [24]) seem

to offer protection in terms of vascular events across several stages of CKD and in CHD events ranging from acute myocardial infarction to stable CHD as well as in primary prevention [25]. These data might partly explain the greater reduction in CVD events in elderly patients, who had worse renal function than the younger ones, but also the greater improvement in eGFR, closely related to CVD event reduction [19-25]. Of note, clinicians should evaluate kidney function using certain formulae including MDRD, Cockcroft-Gault or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), as CKD patients may have normal serum creatinine levels, especially in the elderly population [26].

Whether SUA is a CHD risk factor [27] has remained controversial; for example, a correlation between SUA level and CVD events was not observed in the Framingham study [28]. Data from the National Health and Nutrition Examination Survey (NHANES) I epidemiological study ($n = 5,926$, mean follow-up 16.4 years, 1,593 deaths) suggest that increased SUA levels are independently and significantly associated with risk of CVD mortality, after adjustment for several factors [29]. Similar were the conclusions of another study with a 14,262 person-years follow-up [30]. From the other side of the Pacific Ocean a prospective cohort study of 41,879 men and 48,514 women with a mean follow-up of 8.2 years recorded 1,151/5,427 (21.2%) deaths that were attributed to CVD [31]. The results of this study reported that hyperuricaemia is an independent risk factor of mortality from all causes, CVD, and ischaemic stroke in the Taiwanese general population, in high-risk groups, and potentially in low-risk groups [31]. There is evidence linking SUA levels with CVD morbidity and mortality in high CVD risk patients [23, 32-38].

Atorvastatin treatment significantly reduces SUA levels in patients with CHD, thus offsetting another CHD risk factor [39]. After adjustment for 19 CHD predictors, multivariate analysis involving backward stepwise logistic regression showed a HR of 0.89 (95% CI, 0.78 to 0.96; $p = 0.03$) with every 0.5 mg (30 $\mu\text{mol/l}$) reduction in SUA levels, and an HR of 0.76 (95% CI, 0.62 to 0.89; $p = 0.001$) with every 1 mg (60 $\mu\text{mol/l}$) reduction in SUA levels. On the other hand, in patients untreated with a statin, SUA levels increased during the 3-duration of the GREACE study, recording an HR of 1.14 (95% CI, 1.03 to 1.27; $p = 0.02$) with every 0.5 mg increase, and an HR of 1.29 (95% CI, 1.17 to 1.43; $p = 0.001$) with every 1 mg increase in SUA levels [39]. This association of SUA levels and estimated or actual CVD risk was also found in high-risk patients (with MetS, dyslipidaemia or hypertension) with or without CHD or DM [22, 23]. These data might explain in part the greater reduction in CVD events in elderly patients,

who had higher SUA levels at baseline compared with the younger participants, but also had the greater reduction during atorvastatin treatment.

The NAFLD is very common; one fifth to one third of adults worldwide have NAFLD [40-42]. Furthermore, NAFLD is even more frequent in the elderly (35.1% in the Rotterdam Study) [43]. Patients with NAFLD have 69% higher all-cause mortality rates compared with the general population [44]. This higher risk was mainly due to CVD and to a lesser extent due to liver disease [44, 45]. Patients with non-alcoholic steatohepatitis (NASH; NAFLD + inflammation and fibrosis) had an even higher level of all-cause mortality [44]. Statin treatment may be safe in patients with NAFLD and can improve transaminase activity and the ultrasound features related to NAFLD [46]. Moreover, statin treatment reduces CVD morbidity in patients with mild to moderately abnormal transaminase activity due to NAFLD to a greater extent than in those without NAFLD (68% vs. 39% relative risk reduction, $p = 0.0074$) [46]. Similar benefit was recorded in other high-risk patients (with MetS, dyslipidaemia or hypertension) with or without CHD or DM [47-53]. These data might explain at least in part the greater reduction in CVD events in elderly patients, who had a higher incidence of NAFLD at baseline compared with the younger participants and a greater reduction in markers of NAFLD.

As expected, the elderly patients in the GREACE trial had a higher prevalence of DM than the younger ones. Of interest, there was not a significant number of new cases of DM with statin treatment [54-57] when statin therapy was part of a multifactorial approach. Furthermore, it is safe to prescribe statins in CHD patients with DM, even with CKD or NAFLD [46, 56, 57]. Finally, CHD patients with DM benefit more from statin treatment than those without DM [58, 59]. Thus, better performance of the elderly might in part be attributed to the fact that there were more patients with DM in this age group.

Statin treatment decreases CVD events in both smokers and non-smokers [60] although this effect may be reduced in smokers [61]. There were fewer smokers in the elderly group than in the younger group and this may have played a role in the findings of the present study.

This study has several limitations. First, this is a *post hoc* analysis. Second, the number of patients included in each quartile was relatively small and did not allow multivariate analysis involving backward stepwise logistic regression in each group to show the exact level of significance. Also, only 22% of the study population were women and fewer were included in the lower age quartiles.

In conclusion, further studies are needed to clarify the precise level of benefit from anti-athero-

sclerotic treatment in the elderly. Meanwhile, we should not deprive the elderly of lifestyle advice and optimal medical treatment and we should aim to achieve lipid guideline goals. Therefore, based on the results of the present analysis as well as other available clinical data [62, 63], statins should be used in the elderly, who are likely to benefit more than younger individuals.

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