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Clinical research

Statin therapy improves cardiovascular outcome of patients with peripheral artery disease

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KEYWORDS
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Aims We sought to examine the interrelationship between statin use, inflammation, and outcome of high-risk patients with advanced atherosclerosis.
Methods and results We prospectively studied 515 patients with severe peripheral artery disease (median age 70 years, 296 males). The cardiovascular risk profile and laboratory parameters of inflammation (high-sensitivity C-reactive protein [hs-CRP], serum amyloid A [SAA], fibrinogen, serum albumin, neutrophil counts) were obtained, and patients were followed for a median of 21 months (interquartile range 12–25) for the occurrence of myocardial infarction (MI) and death. We observed 19 MIs (5 fatal and 14 nonfatal) and 65 deaths. Cumulative survival and event-free survival rates (freedom from death and MI) at 6, 12, and 24 months were 97%, 95%, and 89%, and 96%, 93% and 87%, respectively. Patients receiving statin therapy ($n = 269$, 52%) had a lower level of inflammation (hs-CRP $p < 0.001$, SAA $p = 0.001$, fibrinogen $p = 0.007$, albumin $p < 0.001$, neutrophils $p = 0.049$) and better survival (adjusted hazard ratio [HR] 0.52, $p = 0.022$) and event-free survival rates (adjusted HR 0.48, $p = 0.004$) than patients not treated with statins. However, patients with low inflammatory activity (hs-CRP $\leqslant$0.42 mg/dl) had no significant benefit from statin therapy ($p = 0.74$ for survival; $p = 0.83$ for event-free survival), whereas in patients with high hs-CRP (>0.42 mg/dl) statin therapy was associated with a significantly reduced risk for mortality (adjusted HR 0.58, $p = 0.046$) and the composite of myocardial infarction and death (adjusted HR 0.46, $p = 0.016$).
Conclusion Statin therapy is associated with a substantially improved intermediate-term survival of patients with severe peripheral artery disease and a high inflammatory activity, whereas in patients with low hs-CRP no survival benefit was observed.

Introduction

HMG-Co-A reductase inhibitor drugs (statins) exert several beneficial properties in atherosclerotic disease and

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have been demonstrated unequivocally to reduce cardiovascular events and mortality in cardiovascular high-risk patients.[1–8] Cholesterol lowering, stabilisation of the atherosclerotic plaque, reduction of oxidative stress, and potent inhibition of vascular inflammation have also been attributed to the use of statins.[9] In patients with peripheral artery disease (PAD) statins seem to favourably influence leg function,[10] in addition to reducing cardiovascular events and improving survival rates.[1,3] Nevertheless, reports on the effects of statins in patients with widely advanced peripheral atherosclerosis, who are at particularly high risk for poor cardiovascular outcome, are scarce.

Recent data from the coronary vessel area suggest that the benefits of statin therapy occur predominantly amongst patients with intense inflammatory activity.[11,12] In patients with peripheral atherosclerosis, the beneficial effects of statins on leg function were attenuated by adjustment for inflammation.[10] However, it remains unclear whether mainly lipid-lowering or anti-inflammatory effects contribute to the beneficial role of statins in patients with advanced atherosclerosis. Therefore, in the present study we sought to examine the effects and interrelationship of statin treatment, inflammation parameters, and cardiovascular outcome of patients with clinically advanced peripheral atherosclerosis. All-cause mortality and a composite of myocardial infarction and death were the study endpoints defined.

Methods

Study design

We prospectively enrolled all consecutive patients with angiographically proven, advanced peripheral artery disease in a cohort study who were admitted to the angiology department of a tertiary care university hospital from 1 March 2000 to 1 March 2001 for a percutaneous catheter intervention. The study was approved by the local review board and ethics committee, and all patients gave their written informed consent.

Patient data

Patients were seen one to two months before admission to the outpatient ward of the angiology department and were scheduled for a peripheral percutaneous intervention due to symptomatic atherosclerotic disease. Atherothrombotic risk factors were evaluated and cardiovascular therapy, including statin therapy, was adjusted at this time at the discretion of the treating physician.

At admission, the patients' medical history and data from physical examination were recorded by two independent observers using a standard questionnaire, with special attention to cardiovascular risk factors and comorbidities (age, gender, smoking habits, hyperlipidaemia, arterial hypertension, diabetes mellitus, coronary artery disease, history of myocardial infarction and stroke, ankle-brachial index [ABI], and current medication). In particular, antithrombotic drugs, and statin use versus nonuse was recorded; doses of medications were not documented. Data were evaluated for interobserver agreement at the day of patients' discharge. In case of discrepancies, the patient was re-evaluated by both investigators in consensus.

Efforts to detect undiagnosed diabetes at admission were routine measurement of overnight fasting blood glucose and HbA1c levels. During the hospital stay, repetitive blood pressure measurements were made two to four times daily to detect previously undiagnosed arterial hypertension.

Laboratory parameters

Laboratory investigations included a complete blood cell count, global coagulation tests, glycated haemoglobin A1 (Hb1Ac), low-density-lipoprotein (LDL) and high-density-lipoprotein (HDL) cholesterol, serum triglycerides, liver enzymes, and serum creatinine. Blood samples for the determination of laboratory inflammatory parameters were obtained from all patients at the day of admission and were analysed within 1 h. We used a high-sensitivity assay for measurement of serum hs-CRP (*N Latex CRP Mono*®, DADE Behring, Vienna, Austria), with a lower detection level of 0.03 mg/dl, and a coefficient of variation of 4.6%. Serum amyloid A (SAA) was measured by *N Latex SAA*® (DADE Behring), with a sensitivity of 3.8 mg/l and a coefficient of variation of 6.4%. For the measurement of fibrinogen, *Fibrinogen Clauss*® (Stago, Roche), with a sensitivity of 20 mg/dl and a coefficient of variation of 5.2%, was used. Automated blood cell counts were performed on a Sysmex NE-8000 haematology analyser (TOA Medical Electronics, Kobe, Japan). Neutrophil counts are given in g/l with a reference value of 2.0—7.5 g/l. Serum albumin was measured with the bromocresol-green method on a Roche/Hitachi MODULAR (Roche Diagnostics, Indianapolis, USA) according to the manufacturer's instructions, with a coefficient of variation of 1.8% and reference values of 34—48 g/l.

Study endpoints

All-cause mortality was considered as the primary study endpoint, a composite of myocardial infarction and death was analysed as a secondary objective.

Follow-up procedure

Patients were scheduled for clinical re-evaluation at 3, 6, and 12 months after hospital discharge and then annually at the outpatient ward of our department to record any myocardial infarction or death until December 2002. Furthermore, a follow-up questionnaire was sent to each patient during December 2002 to re-evaluate the occurrence of a study endpoint during the whole follow-up period. If the follow-up questionnaire was not returned, the patient, relatives, or the treating physicians was contacted personally by telephone. Further information was obtained by reviewing the hospital discharge reports of any re-admission during the follow-up period. Survival was assessed by two independent observers who did not know the patients' baseline clinical and laboratory data.

Definitions

Diabetes mellitus was defined as fasting blood glucose levels above 126 mg/dl measured 3 times, and was considered to be present in all patients taking antidiabetic medication. Arterial hypertension was diagnosed in patients with blood pressure values above 140/90 mmHg in repetitive measurements, and was assumed to be present in patients with a history of hypertension taking antihypertensive drugs. The diagnosis of peripheral artery disease (PAD) was assessed by clinical evaluation, oscillography, ankle-brachial index measurements, and duplex sonography, and was confirmed by lower limb angiography. The

Fontaine classification was used for categorisation of PAD.[13] The severity of coronary artery disease was categorised according to the Canadian Cardiovascular Society (CCS) classification and routine evaluation included treadmill exercise testing, dobutamine echocardiography, myocardial scintigraphy, and coronary angiography in selected cases. MI was defined according to the consensus document, *The Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction*, as a transient increase of laboratory markers specific to myocardial necrosis (CK-MB or troponin T) in combination with ischaemic symptoms and/or typical electrocardiogram (ECG) signs (development of pathologic Q-waves or ST-segment elevation or depression).[14]

Statistical analysis

Continuous data are presented as the median and interquartile range (IQR, range from the 25th to the 75th percentile). Discrete data are given as counts and percentages. We used χ-square tests to compare proportions and Mann–Whitney *U* tests for univariate comparison of continuous data. Survival rates according to use or nonuse of statins are presented as Kaplan–Meier curves and compared by means of the log-rank test. Multivariate Cox proportional hazards analysis was applied to assess the effect of statin therapy on survival and adjusted for potential confounders. Baseline variables were considered for inclusion in the multivariate model (a) if they were imbalanced between patients with and without statin therapy, as indicated by a univariate *p*-value <0.2 (Table 1), or (b) if they were clinically established risk factors for poor cardiovascular outcome. We tested for interactions between baseline variables by multiplicative interaction terms and log likelihood χ-square tests. The results of the Cox proportional hazards model are presented as the hazard ratio (HR) and the 95% confidence interval (95% CI). We assessed the overall model fit using Cox–Snell residuals. Furthermore, we tested the proportional hazard assumption for all covariates using Schoenfeld residuals (overall test) and the scaled Schoenfeld residuals (variable-by-variable testing). According to the tests, the proportional hazards assumption was not violated. A two-sided *p*-value <0.05 was considered as statistically significant. Calculations were performed with Stata (release 8.0) and SPSS for Windows (Version 10.0, SPSS Inc, Chicago, IL, USA).

Results

Patients

We studied 515 of 535 patients (96%), who were admitted with peripheral artery disease during the study period. Twenty patients (4%) had to be excluded due to incomplete follow-up data. These 20 patients with incomplete data closely resembled patients with complete data with respect to baseline demographic data and clinical characteristics (no significant differences, data not shown). The median age of the 515 patients eligible for the final analysis was 70 years (IQR 59–76) and 296 patients (58%) were male. The median ABI was 0.51 (IQR 0.31–0.69).

Statin therapy

Statin therapy was prescribed in 269 patients (52%) for at least 4 weeks before hospital admission. Demo-

Table 1 Demographic data and clinical characteristics of 515 patients with advanced atherosclerosis comparing patients with and without statin pretreatment for at least 4 weeks

	No statin therapy ($n = 246$, 48%)	Statin therapy ($n = 269$, 52%)	*p*-value
Age, years	70 (60–76)	69 (59–76)	0.34
Male sex	134 (55%)	162 (60%)	0.19
BMI, kg/m^2	25.5 (23.1–27.8)	26.3 (23.9–28.7)	0.022
Arterial hypertension	163 (66%)	217 (81%)	<0.001
Diabetes mellitus	84 (34%)	116 (43%)	0.037
HbA1c,%	6.1 (5.7–6.9)	6.3 (5.8–7.1)	0.029
Smoking	115 (47%)	99 (37%)	0.022
Total cholesterol, mg/dl	218 (188–243)	205 (177–243)	0.020
LDL cholesterol, mg/dl	132 (112–159)	115 (92–148)	<0.001
HDL cholesterol, mg/dl	47 (41–58)	47 (41–56)	0.76
Critical limb ischaemia	67 (27%)	38 (14%)	<0.001
Ankle-brachial index	0.51 (0.31–0.67)	0.52 (0.35–0.71)	0.60
Coronary artery disease (CCS)			0.017
I	60 (24%)	62 (23%)	
II	33 (13%)	64 (24%)	
III	5 (2%)	8 (3%)	
IV	–	–	
History of myocardial infarction	42 (17%)	75 (28%)	0.003
History of stroke	24 (10%)	41 (15%)	0.061
Aspirin therapy	176 (72%)	180 (67%)	0.26
Clopidogrel therapy	53 (22%)	94 (35%)	0.001
Phenprocoumon therapy	25 (10%)	20 (7%)	0.27
hs-C-reactive protein, mg/dl	0.50 (0.24–1.05)	0.29 (0.17–0.80)	<0.001

Data are given as counts and percentages or median and interquartile range (range from the 25th to the 75th percentile).

BMI: body mass index; *HbA1c*: glycated haemoglobin; *LDL*: low-density lipoprotein; *CCS*: Canadian Cardiovascular Society classification of coronary artery disease.

graphic data and clinical characteristics of patients with and without statin therapy are presented in Table 1. Patients receiving statins had a higher body mass index, more frequent hypertension and diabetes mellitus (and a higher median HbA1c level), and more often had a history of coronary artery disease, myocardial infarction, or stroke. Clopidogrel was given more frequently in statin users. Statin users were less frequently smokers and had a lower cholesterol level at the time of hospital admission (after at least one month of treatment).

Laboratory parameters of inflammation

Hs-CRP, SAA, fibrinogen, albumin, and neutrophil counts were a median of 0.42 mg/dl (IQR 0.18—0.90), 7.1 mg/l (IQR <3.8—13.8 mg/dl), 400 mg/dl (IQR 344—463 mg/dl), 40.4 g/l (IQR 38.8—42.7 g/dl), and 5.0 g/l (IQR 3.9—6.2 g/l), respectively, at admission. Patients with statin use had significantly less inflammatory activity, as indicated by a lower median level of hs-CRP ($p < 0.001$) and SAA ($p = 0.001$), lower fibrinogen ($p = 0.007$) and higher albumin values ($p < 0.001$), and lower neurophil counts ($p = 0.049$) as compared to patients without statin therapy (Fig. 1).

Mortality and myocardial infarction

During the median follow-up period of 21 months (IQR 12—25 months), 65 patients died. Of these, 61 patients died of cardiovascular causes and 4 patients died of other causes. Of 65 nonsurvivors, 25 patients were statin users and 40 patients were not. Cumulative survival rates at 6, 12, and 24 months were 97%, 95%, and 89%, respectively. Overall, 19 patients suffered myocardial infarction (5 fatal, 14 nonfatal) during the follow-up period. Of 79 patients with MI or death, 31 were statin users and 48 were not. Cumulative event-free survival rates (freedom from myocardial infarction and death) were 96%, 93%, and 87% at 6, 12, and 24 months, respectively. Patients with statin therapy had a significantly improved survival rate in univariate analysis (log-rank $p = 0.0036$; Fig. 2). Consistently, patients with statin therapy had a significantly reduced risk for the composite of myocardial infarction and death (log-rank $p = 0.0014$).

We then applied multivariate Cox proportional hazards models to assess the association between statin therapy and the study endpoints, adjusting for possible confounding factors (Table 2). Patients with statin therapy had significantly improved adjusted survival and event-free survival rates than patients without statin therapy (adjusted HR 0.52, $p = 0.022$ for survival; adjusted HR 0.48, $p = 0.004$ for event-free survival, respectively) (Table 2). Testing for interaction between statin therapy, inflammation, and survival, we observed a significant change of the model fit (log likelihood ratio χ-square test $C = 10.91$, df $= 2$, $p < 0.01$). Therefore, we stratified for the level of inflammatory activity, as indicated by baseline hs-CRP levels (using the median hs-CRP level of 0.42 mg/dl as a cut-off), and reanalysed the association between statin therapy and cardiovascular outcome (Fig. 3). Patients with low inflammatory activity (hs-CRP $\leqslant$0.42 mg/dl) seemed to have no significant benefit from statin therapy with respect to survival or event-free survival rates, whereas statin therapy in patients with high hs-CRP (>0.42 mg/dl) was associated with a significantly reduced risk for mortality (adjusted HR 0.58, $p = 0.046$) or the composite of myocardial infarction and death (adjusted HR 0.46, $p = 0.016$) (Table 2, Fig. 3).

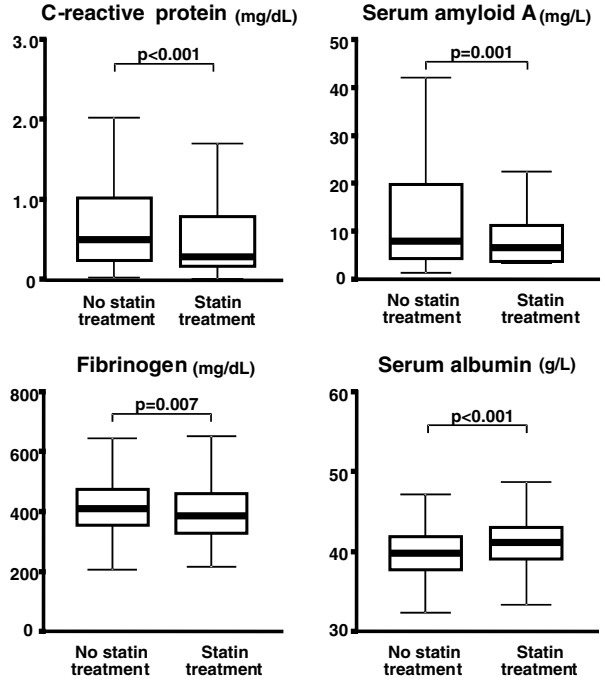

Fig. 1 Laboratory parameters of inflammation in 269 patients with and 246 patients without statin pretreatment (for at least 4 weeks). Box plots indicate median, interquartile range (range from the 25th to the 75th percentile), and total range.

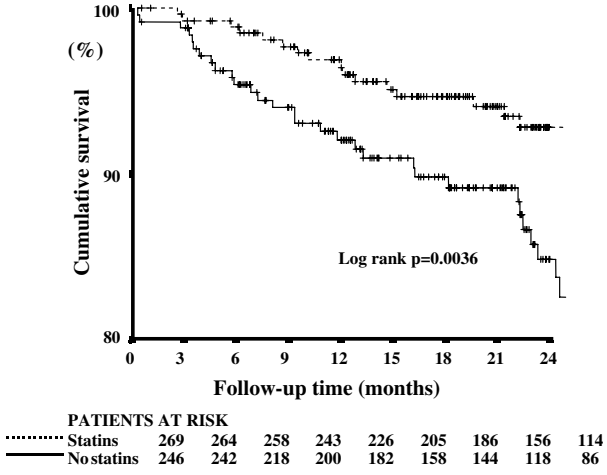

Fig. 2 Cumulative survival of 515 patients with and without statin pretreatment.

Table 2 Multivariate Cox proportional hazards models assessing the association between statin therapy, LDL cholesterol, high sensitivity C-reactive protein (hs-CRP), and cardiovascular outcome in 515 patients with advanced atherosclerosis

	Adjusted[a] hazard ratio	95% confidence interval	*p*-value
Risk of mortality			
All patients ($n = 515$)			
Statin therapy	0.52	0.30—0.91	0.022
Patients with low hs-CRP ($\leqslant$0.42 *mg/dl*) ($n = 257$)			
Statin therapy	1.28	0.30—5.42	0.74
Patients with high hs-CRP ($>$0.42 *mg/dl*) ($n = 258$)			
Statin therapy	0.58	0.33—0.99	0.046
Risk of myocardial infarction and death			
All patients ($n = 515$)			
Statin therapy	0.48	0.29—0.79	0.004
Patients with low hs-CRP ($\leqslant$0.42 *mg/dl)* ($n = 257$)			
Statin therapy	1.14	0.35—3.72	0.83
Patients with high hs-CRP ($>$0.42 *mg/dl)* ($n = 258$)			
Statin therapy	0.46	0.25—0.87	0.016

[a] Adjusted for age (in quartiles), gender, body mass index (logarithmically transformed), LDL cholesterol (in quartiles), hypertension, diabetes mellitus (yes vs. no), current smoking (yes vs. no), history of myocardial infarction, history of stroke, critical limb ischaemia, and clopidogrel therapy.

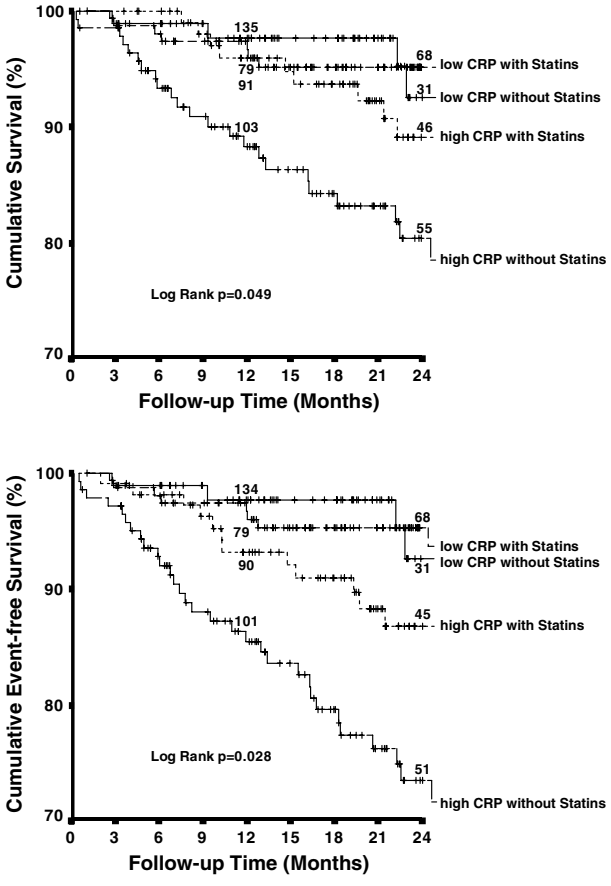

Fig. 3 Cumulative survival and event-free survival (freedom of myocardial infarction and death) of 515 patients with and without statin pretreatment according to the baseline level of inflammatory activity. Low CRP indicates hs-CRP level at baseline $\leqslant$0.42 mg/dl (lower quartiles). High CRP indicates hs-CRP level at baseline $>$0.42 mg/dl (upper quartiles).

Discussion

We found that statin therapy was associated with improved survival and event-free survival rates in patients with severe peripheral artery disease in states of high inflammatory activity. Statins therefore should be rigorously prescribed in these patients. The observed interaction with inflammation supports the view that statins exert their beneficial effects in patients with advanced atherosclerosis partly via an anti-inflammatory pathway or, alternatively, attenuate the deleterious effects of inflammation.

This study corroborates and adds to the findings of several previous observations. A large body of literature has established that statins exert pleiotropic actions on vascular properties and favourably influence atherosclerosis.[9] In particular, statins are known to lower the levels of acute-phase proteins independently of their effects on cholesterol[11,15,16] and thereby seem to substantially retard the deleterious effects of advanced atherosclerotic disease. There is growing evidence that inflammation and the underlying cellular and molecular mechanisms contribute to the progression of atherosclerosis.[17–20] The vascular inflammatory process seems to promote plaque rupture and atherothrombosis, resulting in the clinical complications of atherosclerotic disease. The association between statin use and survival in the present study was markedly influenced by the inflammatory status of the patient, suggesting that a reduction of vascular inflammation or attenuation of the effects of inflammatory activity may be important mechanisms by which statins are associated with improved event-free survival. The reduction of baseline inflammatory activity in statin users, indicated by the current data and described by others previously, supports this view.[9] Furthermore, our data

are in line with findings of the CARE study,[5] where the clinical benefit of statin use was markedly greater in coronary artery disease patients with high concentrations of inflammatory markers; the respective sizes of the cardiovascular benefits obtained were widely comparable to the present findings. It seems reasonable to speculate that in patients with advanced atherosclerotic disease the anti-inflammatory properties of statins are more relevant in preventing cardiovascular events in the short-term than their lipid-lowering effects, which seem crucial for curtailing the initiation of atherosclerosis and its progression in the initial stages.

Although a positive relation between the statin dose or duration of statin therapy with cardiovascular outcome would strengthen our findings, we did not fully document these data. However, patients were on statin therapy for at least 4 weeks and recent data confirm that the anti-inflammatory actions of statins are effective within this time,[21] suggesting a plausible association between statin use and lower inflammatory activity at admission.

The protective effects of statins have been demonstrated mainly in patients with coronary and cerebrovascular atherosclerosis,[4–6,11,22] and the role of statins in patients with widely advanced peripheral atherosclerosis is uncertain. The 4S Study[3] and the Heart Protection Study[1] suggested that PAD patients benefit from statin therapy with respect to cardiovascular outcome. In the present study, we included only highest-risk patients with widely advanced peripheral atherosclerosis, as indicated by a low ankle-brachial index and a high proportion of patients with critical limb ischaemia. Even in these patients, statins proved to be substantially effective after a relatively short follow-up period, underlining the idea that these drugs should be prescribed more often in this patient population.

We can only speculate about the causes of baseline imbalances between statin users and nonusers referring to the different proportions of smokers in the two treatment groups. Data on smoking habits were limited to current smoking status; however, it is likely that patients receiving statins more frequently discontinued smoking.

Limitations

Inherent to any observational study, the assignment to statin therapy was not randomised. Despite the use of statistical methods to adjust for statin pretreatment, unmeasured confounders may have affected the decision for statin therapy and the mortality during follow-up. Furthermore, patients not treated with statins may be started on a statin during the follow-up period and vice versa, influencing the observed effect. However, given the fact that statins were increasingly prescribed in recent years, the use of statins in the group of patients not treated with statins may have only attenuated the observed effect and thus does not invalidate our conclusions. Furthermore, although we analysed a relatively large cohort of high-risk patients, only 84 events were recorded, resulting in rather wide confidence intervals in the multivariate analysis. Larger randomised controlled trials on patients with peripheral artery disease will therefore be necessary to confirm our findings.

It must be acknowledged that data on left ventricular function and the use of ACE inhibitors or beta-blockers were not available in these patients.

Conclusion

Statin therapy is associated with substantially improved intermediate-term survival of patients with severe peripheral artery disease and intense inflammatory activity, whereas in patients with low hs-CRP no survival benefit was observed.

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