The Efficacy of Statin Therapy in Patients with Acute Coronary Syndromes and Concomitant Carotid Disease

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ABSTRACT

Background: Statins prevent recurrent ischemic coronary events after acute coronary syndrome (ACS) and improve cardiovascular outcome of patients with peripheral artery disease.

Aim: We sought to evaluate the interrelationship between statin use, phenotype of carotid plaques as assessed by ultrasound, and outcome of patients with ACS and concomitant carotid disease.

Methods: A total of 337 consecutive patients with ACS were assessed by coronary angiography and Doppler ultrasound of the carotid arteries and followed up for a median period of 19 months.

Results: Carotid plaques were detected in 144 (42%) patients. Of these patients, 99 (69%) had echogenic carotid plaques and 45 (31%) had echolucent plaques. The groups did not differ significantly with regard to the lipid profiles, the prevalence of risk factors, and 1-vessel, 2-vessel, or 3-vessel coronary artery disease. During follow-up, 227 (67%) patients were receiving statins. We observed 14 cardiac deaths and 17 myocardial infarctions. After adjustment for treatment strategy (medical therapy or myocardial revascularization), patients with echolucent carotid plaques receiving statin therapy (n = 32, 71%) showed a better event-free survival than did patients with echolucent plaques not treated with statins (log-rank $P = .038$). In patients with echogenic carotid plaques, the benefit of statin therapy on event-free survival was less evident (log-rank $P = .56$).

Conclusion: In patients with ACS and echolucent carotid plaques, statin therapy is associated with better event-free survival, while in patients with ACS and echogenic carotid plaques no clear benefit of statins is observed.

Introduction

We have previously shown that carotid disease is associated with adverse outcome of patients with acute coronary syndrome (ACS)[1] and that sonographic characteristics of carotid plaques have prognostic implications.[2] Statins have been shown to prevent recurrent ischemic coronary events after ACS[3] as well as to improve cardiovascular outcome of patients with peripheral artery disease.[4] The response to statin therapy varies from person to person as a result of various individual characteristics.[5] The interrelationship between carotid phenotype, statin therapy, and outcome has not been previously analyzed. The aim of the present study was to evaluate the interrelationship between statin use, phenotype of carotid plaques as assessed by ultrasound, and outcome of patients with ACS and concomitant carotid disease.

Methods

The study sample consisted of 337 consecutive patients who underwent coronary angiography because of an ACS, diagnosed according to present American College of Cardiology/American Heart Association (ACC/AHA) guidelines.[6] The patients were recruited in a single center (S. Giacomo Hospital, Castelfranco Veneto, Italy) in 2000 to 2001. Along with the coronary angiography, all patients underwent Doppler ultrasonographic assessment of carotid arteries. Both procedures were performed within 15 days after the acute coronary event. According to the decision of attending physicians, the patients were managed either conservatively or underwent coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention).

Coronary angiography was performed with the standard femoral or brachial technique. Several views of each coronary artery were analyzed. The severity of arterial stenoses, defined as the maximal percent reduction in the luminal diameter in any view compared with the nearest normal segment, was determined according to the caliper technique.[7] Significant coronary stenosis was defined as ≥70% lumen narrowing in any of the 3 major coronary branches (left anterior descending, left circumflex, and right coronary artery) or ≥50% lumen narrowing of the left main coronary artery. The extent of coronary artery disease (CAD) was classified as 1-vessel, 2-vessel, or 3-vessel disease according to the number of major coronary arteries with significant

Received: January 6, 2009
Accepted: February 21, 2009

Table 1. Baseline Characteristics

Variable	All Patients	Carotid Plaques			*P* Value
		0	Echolucent	Echogenic	
Number	337	193	45	99	
Age (years)	64±10	62±10	67±8	67±8	NS
Men	259 (77)	148 (77)	32 (71)	79 (80)	NS
Ejection fraction (%)	53±11	54±11	53±12	51±12	NS
Controlled hypertension	212 (63)	121 (63)	28 (62)	63 (64)	NS
Uncontrolled hypertension	50 (15)	27 (14)	7 (16)	16 (16)	NS
History of MI	49 (15)	26 (13)	3 (7)	20 (20)	.05
Smokers	236 (70)	131 (68)	30 (67)	75 (76)	NS
Diabetes mellitus	62 (18)	28 (15)	13 (29)	21 (21)	NS
Biochemical findings					
Total cholesterol (mg/dL)	204±39	205±41	203±37	201±38	NS
HDL cholesterol (mg/dL)	50±13	49±10	53±16	50±16	NS
LDL cholesterol (mg/dL)	127±35	127±36	127±38	128±33	NS
Triglycerides (mg/dL)	131±68	133±71	135±59	125±68	NS
Fibrinogen (g/L)	3.1±1.1	3.1±1.2	3.1±1.0	3.0±1.1	NS
C-reactive protein	0.70 [0.50–1.20]	0.70 [0.50–1.00]	1.05 [0.59–2.80]	0.60 [0.50–1.00]	.02
Diagnosis at admission					
ST-elevation acute MI	102 (30)	55 (28)	13 (29)	34 (34)	NS
Non-ST-elevation acute MI	147 (44)	113 (59)	13 (29)	21 (21)	NS
Unstable angina pectoris	88 (26)	25 (13)	19 (42)	44 (44)	NS
Number of coronary arteries narrowed:					
1	110 (33)	71 (37)	10 (22)	29 (29)	NS
2	74 (22)	41 (21)	10 (22)	23 (23)	NS
3	110 (33)	54 (28)	18 (40)	38 (38)	NS
Carotid Doppler ultrasound findings:					
Intima-media thickness (mm)	0.83±0.27	0.79±0.26	0.82±0.26	0.85±0.27	NS
Bilateral plaques		0	33 (73)	83 (84)	NS
Carotid stenosis >50%		0	8 (18)	11 (11)	NS
Carotid stenosis >70%		0	5 (11)	4 (4)	NS

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; NS, not significant.
Data presented are number (%) of patients or mean value ± SD. C-reactive protein values are presented as median (interquartile range). The Mann-Whitney test has been used to compare the C-reactive protein values. *P* value is calculated to compare the patients with echogenic and echolucent carotid plaques.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20610

stenosis. Significant left main artery stenosis was scored as 2-vessel disease.[8]

Ultrasonographic examinations were performed with Sonos 5500 Hewlett Packard equipment Sonos 5500 (Hewlett-Packard, Palo Alto, California). B-mode examination of the carotid was performed with a 7.0 MHz linear array transducer Hewlett-Packard, Palo Alto, California. All patients lay in the supine position with necks extended and heads turned contralateral to the test side. Plaques were identified as focal widenings of the vessel wall >50% relative to adjacent segments, with protrusion into the lumen, composed of calcified or noncalcified components.[9] Plaque echogenicity was graded from 1 to 5 according to Gray-Weale classification[10] in modification of Geroulakos et al.[11] In the analysis, plaques of type 1 and 2 were defined as echolucent plaques, and plaques of type 3 and 4 were defined as echogenic plaques. Plaques with acoustic shadowing artifact due to excessive calcification (type 5 plaques) were considered echogenic plaques. The degree of stenosis was established according to standard imaging and Doppler ultrasonography criteria.[12]

Follow-up data were collected following a review of the patient's hospital chart, contact with the patient's physician, telephone interview with the patient, and patients' visits to outpatient clinic. Median time from enrollment to last contact with patient or target event was 19 months (first quartile, 12 mo; third quartile, 28 mo). Target events (in order of significance) were cardiac death and nonfatal myocardial infarction (MI). Death was defined as cardiac if strictly related to proven cardiac causes (fatal MI, acute heart failure, malignant arrhythmias). Sudden death, defined as unexpected death, occurring outside the hospital and preceded by no apparent symptoms or by symptoms <1 hour in duration, was classified as cardiac in origin. Myocardial infarction was diagnosed on the basis of documented electrocardiographic changes and typical cardiac enzyme release (troponin I and creatine kinase-MB mass).[13] In patients with more than 1 event, only the most significant event (cardiac death) was used for statistical analysis.

Continuous variables are expressed as mean value ± SD. Differences in continuous variables were assessed with 1-way analysis of variance or the unpaired t test; the χ^2 test was used for categorical variables. Survival rates were estimated with Kaplan-Meier curves and compared by the log-rank test. A value of $P < .05$ was considered statistically significant. All analyses were performed with SPSS software (Chicago, IL SPSS 13.0 for Windows, SPSS Inc., Chicago, Illinois).

Table 2. Treatment

Variable	All Patients n = 337	Carotid Plaques			*P* Value
		0 n = 193	Echolucent n = 45	Echogenic n = 99	
Initial treatment strategy:					
Medical therapy	123 (36)	77 (40)	13 (29)	33 (33)	NS
CABG	92 (27)	44 (23)	16 (36)	32 (32)	NS
PCI	122 (36)	72 (37)	16 (36)	34 (34)	NS
Medical therapy during follow-up:					
β-Blockers	198 (59)	109 (56)	30 (67)	59 (60)	NS
ACE inhibitors	178 (53)	103 (53)	25 (56)	50 (51)	NS
Calcium channel blockers	75 (22)	22 (11)	15 (33)	21 (21)	NS
Nitrates	77 (23)	47 (24)	10 (22)	20 (20)	NS
Statins	227 (67)	123 (64)	32 (71)	72 (73)	NS
Aspirin	253 (75)	150 (78)	32 (71)	71 (72)	NS
Clopidogrel or ticlopidine	122 (36)	72 (37)	16 (36)	34 (34)	NS
Diuretics	87 (26)	37 (19)	14 (31)	36 (36)	NS

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.
Data presented are number (%) of patients. *P* value is calculated to compare the groups with echolucent and echogenic plaques.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20610

Results

The baseline characteristics of the entire study population have been previously reported in part[1] and are presented in Table 1. In brief, significant CAD was revealed in 286 (82%) patients, while 41 (12%) patients did not have significant coronary stenoses. Carotid artery disease was revealed in 144 (43%) patients. Of them, 99 (69%) patients had echogenic plaques and 45 (31%) patients had echolucent plaques. Patients with echolucent plaques, as compared with those with echogenic plaques, were borderline less likely to have a history of MI ($P = .05$) and had higher C-reactive protein ($p = .02$) levels. Compared with patients with simple coronary lesions, patients with complex coronary plaque morphology had a more frequent history of MI, at admission they were more often diagnosed as non-ST-elevation acute MI ($P = .04$), and had a higher prevalence of multivessel CAD at coronary angiography ($P = .01$). No patient had a previous history of symptomatic carotid disease.

Statins at discharge were taken by 227 (67%) of patients in standard doses. Of them, 121 (53%) were taking simvastatin (20–40 mg/d), 67 (30%) were taking atorvastatin (10–20 mg/d), and 39 (17%) were taking pravastatin (40 mg/d). Treatment strategies in subgroups of patients are summarized in Table 2.

Follow-up was complete on all of the 337 patients enrolled. During follow-up, 14 (4%) patients experienced cardiac death and 17 (5%) had a nonfatal MI. Also, 3 noncardiac deaths (1 stroke, 2 cancers) and 3 nonfatal strokes were registered. There was an unfavorable association between the presence of echogenic carotid plaques and cardiac events: cardiac death or nonfatal MI were registered in 18 of 99 (18%) patients with echogenic carotid plaques compared with 2 of 45 (4%) patients with echolucent carotid plaques ($P = .02$). After adjustment for the treatment strategy (medical therapy or coronary revascularization), the use of statins was associated with better survival of patients without carotid artery disease and patients with echolucent carotid plaques (Figure A,B). Survival of patients with echogenic carotid plaques was not influenced by the use of statins.

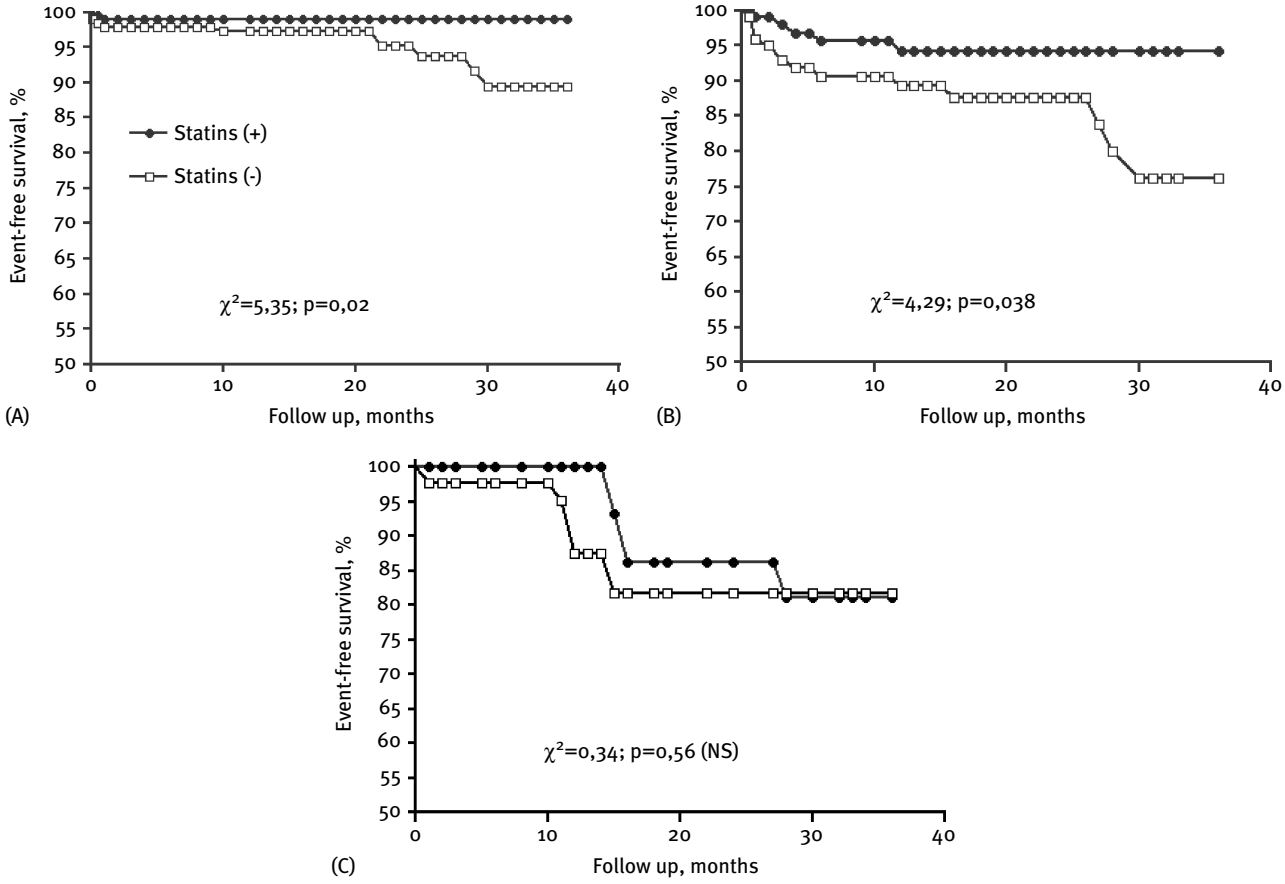

Figure 1. Kaplan-Meier survival curves of patients with acute coronary syndromes and (A) without concomitant carotid disease, (B) with echolucent carotid plaques, and (C) with echogenic carotid plaques depending on use of statins.

Discussion

In the previous studies, we have shown that echogenic carotid plaques are independently associated with an increased risk of death or MI in patients with ACS.[1,2] The present study is the first study evaluating the interrelationship between the efficacy of statins and ultrasound characteristics of carotid plaques. The main finding of our study is that in patients with ACS without concomitant carotid disease or with echolucent plaques the use of statins is associated with significantly better event-free survival, whilst this effect seems to be less evident in ACS patients with echogenic carotid plaques.

The favorable effect of statins on outcome of patients with ACS is associated not only with their lipid-dependent benefits, but also with their beneficial effects on plaque stabilization, endothelial function, blood coagulation, oxidative stress, modulation of inflammation, that is, the effects which have been collectively referred to as pleiotropic effects.[14] It might be assumed that that the effects of statins might be different depending on the plaque morphology and its anatomopathological characteristics.[15] The pleiotropic effects of statins seem to be especially important in patients with echolucent carotid plaques. Cardiac events in these patients are associated, first and foremost, with plaque instability and, possibly, with a more marked diffuse inflammation of the vascular bed. This is supported by higher C-reactive protein levels in patients with echolucent plaques as compared with patients with echogenic plaques (Table 1). Hence, in patients with echolucent plaques, plaque stabilization and modulation of inflammation represent important targets of therapy.

In patients with echogenic carotid plaques, systemic inflammation and plaque instability may be not the leading pathogenetic mechanisms of cardiac events and adverse outcomes may be associated with other factors. The presence of echogenic carotid plaques is associated with increased arterial stiffness[16] and more extensive coronary calcifications.[17] These factors, in their turn, have been associated with an increased likelihood of cardiac events.

Our study has potential limitations which are inherent to its observational retrospective design. Another limitation of our study is that only 67% of patients were receiving statins. Finally, a relatively small sample size could have hindered a minor statin effect in patients with echogenic carotid plaques.

In conclusion, we believe that patients with echogenic carotid plaques represent a group of high cardiovascular risk. Considering the recent meta-analysis results, according to which intensive lipid lowering with high dose statin therapy provides a significant benefit over standard dose therapy for preventing cardiovascular events,[18] further studies are needed which would show if high dose statin therapy can improve long-term outcomes of these high risk patients.

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20610