ORIGINAL ARTICLE

Efficacy of chronic statin therapy on major cardiac events after coronary artery bypass grafting: low-dose versus high-dose

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ABSTRACT

Aim To investigate whether chronic statin treatment after coronary artery bypass grafting (CABG) protects patients from major cardiac events and provides percutaneous coronary intervention (PCI) free survival.

Methods A total of 232 patients with previous CABG and chronic statin therapy were selected retrospectively and were divided into two groups according to a dosage of atorvastatin per day, e. g., 20 mg or 40 mg. Groups were compared for the major cardiac events and freedom from PCI by Kaplan Meier analysis as the primary end point. Patency of grafts including left internal thoracic artery (LITA) and saphenous vein (SVG) and progression of non-grafted native vessel disease were also evaluated as secondary end points.

Results Cardiac mortality, periprocedural myocardial infarction (MI), target vessel revascularization and percutaneous coronary intervention free survival were as follows: 2.9% versus 2.1% (p=1.000); 16.1% versus 21.1% (p=0.331); 56.93% versus 52.63% (p>0.005); 58.4% versus 63.2% (log-rank test; p= 0.347) in atorvastatin 20 mg and atorvastatin 40 mg groups, respectively. However, these results were not statistically significant between two groups (p>0.005). Patency of openness of grafts including LITA and SVG and progression of non-grafted native vessel disease were similar between groups (p=0.112, p=0.779, p=0.379 and p=0.663**,** respectively).

Conclusion Low-dose long-term statin treatment had similar outcomes on major cardiac events and identical rate of freedom from percutaneous coronary intervention after coronary artery bypass grafting compared with high-dose long-term statin treatment. It is better to start from low dose statin treatment after surgical interventions.

Key words: chronic statin treatment, major cardiac events, coronary bypass grafting

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INTRODUCTION

Coronary artery bypass grafting (CABG) is a therapeutic choice for advanced coronary artery disease. However, patients are still at significant risk for postoperative major cardiac events (1). Although statins protect patients from subsequent coronary ischemic events, optimal selection of drug and ideal dosage are still open to debate (2-3). Moreover, it is not clear whether long-term statin therapy would have improved clinical outcomes in patients after CABG (3).

The aim of this study is to show low-dose versus high dose of non-stop atorvastatin therapy after CABG would keep the patients away from major cardiac events and provide PCI-free survival. Cardiac death, periprocedural myocardial infarctus (MI), target vessel revascularization and percutaneous coronary intervention (PCI), free survival were considered as primary end points. Patency of grafts including left internal thoracic artery (LITA) and saphenous vein graft (SVG) and progression of coronary ischemic disease in native coronary arteries after CABG were also evaluated.

PATIENTS AND METHODS

Patient selection

This study was performed retrospectively. A total number of 13,558 patients who underwent conventional coronary angiography at Ankara Ataturk Education and Research Hospital between 2009 and 2012 (inclusion criteria were stable angina and indication to coronary angiography, ST and non–ST-segment elevation acute MI; exclusion criteria were bypass of left anterior descending artery other than LITA, free LITA) were initially reviewed for patients with previous CABG. Patients were then reviewed for postoperative PCI. A total number of 289 patients fulfilling the inclusion criteria were re-evaluated; 57 patients (19.7%) met the exclusion criteria: not on statin therapy (n=35, 12.1%), for free LITA (n=13), bypass of left anterior descending artery other than LITA (n=9). Finally, 232 patients with previous CABG and postoperative PCI and chronic statin therapy represented the study population. These eligible patients were divided into two groups according to the statin dose: as 20 mg or 40 mg atorvastatin per day

Percutaneous coronary intervention

Percutaneous coronary interventions were performed with the standard technique; patients were pre-treated with aspirin (100 mg/day) and clopidogrel (600-mg loading dose at least 3 h before the procedure) (1-3). Following PCI, aspirin (100 mg/day) was continued indefinitely, whereas clopidogrel (75 mg/day) was administered for at least 1 month (12 months in patients treated for acute coronary syndrome or receiving stents).

Primary end points

Cardiac death was defined as in-hospital 30-day mortality. Periprocedural MI was evaluated as elevated cardiac biomarkers (troponin or CK-MB) and electrocardiographic findings. Target vessel revascularization was defined as PCI, which was divided into 3 separate periods and target vessels. Target vessel non-revascularization was described as PCI-free survival.

Secondary end points

Stenosis of over 80% of LITA and over 60% of SVG were evaluated as occluded. Progression of the coronary ischemic disease in native coronary arteries was classified according to the degree of the stenosis. Stenosis was classified as over and above 50%. These native coronary arteries had not been bypassed earlier.

Statistical analysis

Univariate analysis was performed to examine differences in variables between patients receiving atorvastatin 20 and 40 mg groups. Categorical variables between groups were evaluated by using the chi-square test or Fisher's exact test. Continuous variables were conducted by using Mann-Whitney U test. Value of $p < 0.05$ was considered statistically significant. Moreover, PCI-free survival analysis was performed by Kaplan-Meier analysis and compared by the log rank test in both groups. Stent insertion was considered as the failure event (hazard) and no-stent insertion (PCI-free) was considered as the survival.

RESULTS

Patients' characteristics

Both groups were similar at the time of PCI, except for recent ex-smoker and using clopido-

grel. The group of atorvastatin-40 mg had higher recent ex-smoker (patients who used to smoke but quitted recently) and taking clopidogrel (p<0.001 and p=0.004 respectively) (Table 1).

Table 1. Demographic characteristics and other medical therapy of atorvastatin-20 mg and atorvastatin-40 mg groups

Variables	No (%) of patients		p
	Atorvastatin-20 mg group (n=137)	Atorvastatin-40 mg group (n=95)	
Age	62.69 ± 9.75	62.99 ± 9.09	0.822
Females	33 (24.1%)	20 (21.1 %)	0.588
Diabetes mellitus	54 (39.4%)	30 (31.6 %)	0.222
Hypertension	72 (52.6%)	44 (46.3 %)	0.350
Chronic obstructive pulmonary disease	10 (7.3%)	4 (4.2 %)	0.409
Peripheral arterial disease	6 (4.4%)	6 (6.3 %)	0.513
Dialysis	3 (2.2%)	1 (1.1%)	0.646
Total cholesterol	145.91 ± 80.46	145.79 ± 79.31	0.963
Triglyceride	154.93 ± 149.82	138.39 ± 97.13	0.681
High density lipoprotein	31.35 ± 16.7	32.44 ± 16.94	0.664
Low density lipoprotein	85.69 ± 53.93	93.54 ± 57.79	0.219
Cigarette smoker	19 (13.9%)	12 (12.6%)	0.785
Recent ex-smoker	10 (7.3%)	23 (24.2%)	<0.001
Ex-smoker	108 (78.8%)	60 (63.2%)	0.009
ß-blocker	119 (86.9%)	83 (87.4%)	0.910
Angiotension converting enzyme	97 (70.8%)	77 (81.1%)	0.076
Ca+2 channel blocker	43 (31.4%)	30 (31.6%)	0.975
Nitrate	132 (96.4 %)	91 (95.8%)	0.828
Clopidogrel	68 (49.6%)	65 (68.4%)	0.004

Cardiovascular profiles of both groups were also similar, related with the Canadian Cardiovascular Society classification and unstable angina pectoris (USAP). The group of Atorvastatin-40 mg had higher Canadian Cardiovascular Society classification and USAP (p=0.005 and p<0.001 respectively) (Table 2).

Table 2. Cardiovascular profile of atorvastatin-20 mg and atorvastatin-40 mg groups

Variables*	No (%) of patients		p
	Atorvastatin-20 Group (n=137)	Atorvastatin-40 Group (n=95)	
CCS III/IV	86 (62.8 %)	76 (80%)	0.005
NYHA III/IV	26 (19%)	13 (13.7%)	0.289
Chronic heart failure	13 (9.5%)	4 (4.2%)	0.199
Cardiogenic shock	5 (3.6%)	0	0.080
Cardiopulmonary resuscitation	5 (3.6%)	0	0.080
Unstable angina pectoris	44 (32.1 %)	53 (55.8 %)	<0.001
Stable angina pectoris	64 (46.7 %)	27 (28.4%)	0.005
Previous myocardial infarction	18 (13.1%)	22 (23.2%)	0.047
Previous PCI	7 (5.1%)	4 (4.2%)	1.000
Ejection fraction < 50	62 (45.3%)	43 (45.3%)	0.999
Left main coronary artery	18 (13.1%)	13 (13.7%)	0.897

*Categorical data are numbers (percentage); continuous data are means ± standard deviation. CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; PCI, percutanous coronary intervention.

Operative characteristics, follow-up, patency of grafts and stenosis of non-grafted native coronary arteries and PCI of target vessel(s) were similar for both groups (Tables 3-5)

During the follow-up, conventional coronary angiography was performed in all patients at the first hospitalization, in 43 patients at the second hospitalization and in five patients at the third hospitalization (Table 3).

Table 3. Operative characteristics of atorvastatin-20 mg and atorvastatin-40 mg groups

Variables*	Atorvastatin-20 Group (n=137)	Atorvastatin-40 Group (n=95)	p
Number of distal anastomosis	2.32 ± 0.94	2.4 ± 1.1	0.693
Sequential bypass	18 (13.1%)	15 (15.8%)	0.570
Number of venous graft	1.24 ± 0.94	1.38 ± 1.07	0.388
Number of arterial graft	1.08 ± 0.34	1.04 ± 0.25	0.492
Distal insertion site other than left anterior descending artery (No (%) of patients)			
Diagonal artery	30 (21.9%)	20 (21.1%)	0.878
Optional diagonal artery	1 (0.7%)	3 (3.2%)	0.308
Circumflex artery	82 (59.9%)	61 (64.2%)	0.502
Right coronary artery	69 (50.4%)	45 (47.4%)	0.653
RCAPDA	13 (9.5%)	7 (7.4%)	0.571
RCAPL	1 (0.7%)	1 (1.1%)	1.000

*Categorical data are numbers (percentage), continuous data are means ± standard deviation. RCAPD, right coronary artery posterior descending artery; RCAPL, right coronary artery posterolateral artery

Cardiac death occurred in four (2.9%) patients in the group of atorvastatin-20 mg and in two (2.1%) patients in the group of atorvastatin-40 mg (p=1.000) (Table 4).

Periprocedural MI happened in 22 (16.1%) patients in the group of atorvastatin-20 mg and in 20 (21.1%) patients in the group of atorvastatin-40 mg (p=0.331) (Table 4).

Table 4. Follow-up of atorvastatin-20 mg and atorvastatin-40 mg groups

Variables*	Atorvastatin-20 Group (n=137)	Atorvastatin-40 Group (n=95)	p
Number of outpatient control after CABG	11.03 ± 10.68	10.48 ± 11.63	0.312
Number of hospitalization	1.88 ± 1.44	1.79 ± 1.35	0.720
Time interval	6.49 ± 4.47	6.33 ± 4.58	0.722
Periprocedural myocardial infarction	22 (16.1%)	20 (21.1%)	0.331
Mortality	4 (2.9%)	2 (2.1%)	1.000

*Categorical data are numbers (percentage), continuous data are means ± standard deviation. CABG, coronary artery bypass grafting

Time interval between CABG and last coronary angiography was 6.49 ± 4.47 years and 6.33 ± 4.58 years in the group of atorvastatin-20 mg and 40 mg, respectively. The total number of PCI was 56.93% in 78 patients in the group of atorvasta-

tin-20 mg and 52.63% in 50 patients in the group of atorvastatin-40 mg (p>0.005)

Primary end points

The total number of intervention was 61 (44.52%) versus 36 (37.89%) during the first procedure, 12 (8.75%) versus 10 (10.52%) during the second procedure and 5 (3.64%) versus 4 (4.21%) during the third procedure in the group of atorvastatin 20 and in the group of atorvastatin 40 mg respectively.

PCI-free survival was 58.4% in the group of atorvastatin-20 mg and 63.2% in the group of atorvastatin-40 mg in this period (p=0.347)

Secondary end points

Patent and occluded LITA were observed in 200 (86.2%) and in 32 (13.79%) out of 232 patients in both groups (atorvastatin-20 mg and atorvastatin-40 mg), respectively (p=0.112). Patent SVG was visualized in 186 (80.17%) patients of both groups (p=0.779). Stenosis of circumflex artery over 50% obstruction was seen in 38 (33.5%) patients (p=0.379) in both groups. Stenosis of right coronary artery over 50% was seen in 60 (52.2%) patients (Table 5).

Table 5. Patency of grafts and stenosis of native coronary arteries of atorvastatin-20 mg and atorvastatin-40 mg groups

Variables*	Atorvastatin-20 Group (n=137)	Atorvastatin-40 Group (n=95)	p
LITA-patent	114 (83.2%)	86 (90.5%)	0.112
LITA-occluded	23 (16.8%)	9 (9.5%)	0.112
SVG-patent	109 (79.6%)	77 (81.1%)	0.779
Cx >50% stenosis	20 (14.6%)	18 (18.9 %)	0.379
RCA >50% stenosis	34 (24.8%)	26 (27.4 %)	0.663

*Categorical data are numbers (percentage), continuous data are means ± standard deviation. Cx, circumflex artery; LITA, left internal thoracic artery; RCA, right coronary artery; SVG, saphenous vein graft

DISCUSSION

Coronary artery bypass grafting is an effective treatment for patients with coronary artery disease (4,5). However, hyperlipidemia can cause recurrent ischemic cardiac events in this patient population in the postoperative period (6). Guidelines by the American College of Cardiology and American Heart Association recommended statins for CABG patients with LDL concentrations greater than 100 mg/dL (7). Although statins reduce major cardiac events after CABG, there is no available data for PCI-free survival in patients with long-term statin intake in the postoperative period. We also sought primarily the influence of different doses of atorvastatin on major cardiac events and secondary patency of LITA and SVG and progression of native vessel disease in long-term period after CABG.

The Post Coronary Artery Bypass Graft Trial was designed to compare the effects of 2 lipid-lowering regimens in patients who had CABG (8-10). The primary endpoint had been planned as cardiac death or nonfatal acute MI and found 15.1% in the aggressive strategy group and 20.3% in the moderate strategy group. The investigators could not have shown significant difference between two strategies in the occurrence of death. We could not show any difference between groups in the occurrence of cardiac mortality in patients after CABG either.

The CARE (In the Cholesterol and Recurrent Events) trial included 1,091 patients (pravastatin (n=527) and placebo (n=564)) who had previously undergone CABG for a mean period of 5 years (11). In our study, follow-up period was: 6.49 ± 4.47 and 6.33 ± 4.58 in the Group of Atorvastatin 20 and 40 mg respectively. The authors demonstrated that pravastatin produced a statistically significant reduction (24%) in the relative risk of a composite endpoint of fatal coronary event or nonfatal acute MI relative risk of a composite endpoint of fatal coronary heart disease death (33%) or nonfatal acute MI (absolute risk 9.1% versus 12.9% in the placebo group), by 41% of the incidence of coronary death (4.6% versus 7.8%), and by 35% total mortality (8% versus 12.4%). In the trial, the authors divided MI as fatal and nonfatal; we reported periprocedural MI together in our study. The rates of total and cardiac mortality had been given separately in the trial. We excluded the death from non-cardiac reasons in order not to affect the cardiac results.

Some clinical data indicated that pretreatment with statins may significantly reduce periprocedural complications and major adverse cardiac events in patients undergoing PCI (13-15). Patti et al. performed a collaborative meta-analysis using data from 13 randomized studies in which 3.341 patients received either high-dose statin (n=1.692) or no statin/low-dose statin (n=1.649) before PCI, with all patients receiving statin therapy after intervention (16). Our patient population had prior CABG, which means that patients received statin before PCI. The authors found that periprocedural MI was

lower in the high-dose statin versus control group, which corresponds to a 44% risk reduction in the active-treatment arm. They also demonstrated that major adverse cardiac events within 30 days was significantly lower in the high-dose statin group , and 1-month major adverse cardiac events, excluding periprocedural events, were also reduced: the results were much more reliable as expected. In our study, we evaluated not only PCI but also PCI-free survival after surgery; both groups were similar for PCI and PCI-free survival under the statin treatment after CABG . We thought that PCI-free survival was higher in Atorvastatin-40 mg, because this group of patient had a higher incidence of unstable angina pectoris (USAP)

Carrier et al analyzed the benefit of statin treatment on single and bilateral ITA grafts on long-term survival after CABG (17). The paper included 6.655 patients. The authors reporteded that the patients with bilateral ITA grafts had an average 10-year-survival rate of 83% compared with 67% in patients with single ITA grafts. The authors also demonstrated that statin treatment caused a significant decrease in the long-term risk of death among patients who underwent single ITA grafting, but not in those with bilateral ITA grafting. However, they demonstrated that survival of statin-treated patients with single ITA grafts was similar to bilateral ITA patients. In our study, we only evaluated patency of LITA grafting in two groups separately, showing that patency of ITA grafting is appropriate with the literature in each group because over 90% of LITAs remain patent within 10 years after surgery.

The CASCADE (Clopidogrel After Surgery for Coronary Artery Disease) trial was designed to evaluate the addition of clopidogrel (75 mg) to aspirin (162 mg) on the development of saphenous vein graft disease after CABG. The patients received statin therapy after operation achieved an LDL level less than 100 mg/dL (18-20) and underwent angiography of the bypass grafts and the native coronary arteries; statin therapy was independently associated with improved graft patency. In our study, patients reached LDL level less than 100 mg/dL in both atorvastatin groups, but without improved graft patency of SVG between the groups. Our result of patency of SVG is in accordance with the literature in each group because within 10 years after surgery, only 60% of the SVGs remain patent and half of those that are patent have clinically important stenosis (5,21,22).

CLAS (The Cholesterol Lowering Arteriosclerosis Study) showed that aggressive cholesterol reduction for a period of 2 to 4 years significantly reduces new lesion formation in native vessels (23). In our study, comparing old clinical reports of coronary angiograms with the last ones, and evaluating only the previously non-grafted vessels we could not find any difference between the atorvastatin groups for the stenosis over 50%.

The major limitation of the present study is its retrospective and nonrandomized design. Furthermore, we are unable to obtain the third group of patients who had not received statins. Of course, there could be changes in the dosage of statin throughout the study.

Essentially all patients should be prescribed long-term statin therapy independent from the dose to reduce cardiac events after CABG. This confirms earlier studies within a contemporary surgical population and supports the current clinical guidelines.

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TRANSPARENCY DECLARATION

Competing interests: None to declare.

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