Atherosclerosis xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Early intensive statin treatment for six months improves long-term clinical outcomes in patients with acute coronary syndrome (Extended-ESTABLISH trial): A follow-up study

Tomotaka Dohi, Katsumi Miyauchi*, Shinya Okazaki, Takayuki Yokoyama, Naotake Yanagisawa, Hiroshi Tamura, Takahiko Kojima, Ken Yokoyama, Takeshi Kurata, Hiroyuki Daida

Department of Cardiovascular Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

ARTICLE INFO

Article history:
Received 23 August 2009
Received in revised form
24 November 2009
Accepted 1 December 2009
Available online xxx

Keywords:
Acute coronary syndrome
Statin
Long-term mortality rates
Percutaneous coronary intervention

ABSTRACT

Background: The ESTABLISH trial found using volumetric intravascular ultrasound that atorvastatin therapy started early and continued for 6 months significantly reduced plaque volume in patients with acute coronary syndrome (ACS). However, the benefits of early statin administration on long-term outcomes remain unclear. We therefore examined whether the early initiation of statin in patients with ACS improves long-term prognosis.

Methods and results: The Extended-ESTABLISH trial included 180 patients with ACS who underwent emergency percutaneous coronary intervention (PCI). These patients were randomized here to groups given either early intensive lipid-lowering therapy ($n = 90$; atorvastatin 20 mg/day) or standard care (control, $n = 90$) within 48 h of events. Baseline characteristics between the two groups did not significantly differ at the time of ACS onset. Six months after PCI, all patients were treated with statins to achieve an LDL-C value of <100 mg/dL. We compared the first occurrence of major adverse cardiac and cerebrovascular events (MACCE). Prognostic data were fully documented during the entire follow-up period (mean, 1538 ± 707 days). Cumulative event-free survival was significantly higher in the atorvastatin, than in the control group ($p = 0.041$; log-rank test). Furthermore, by adjusting for validated prognosticators, early statin administration was identified as a good predictor of MACCE (HR 0.46, 95%CI 0.23–0.86; $p = 0.015$).

Conclusions: In-hospital initiation of statin therapy immediately after ACS conferred long-term benefits and 6 months of intensive lipid-lowering therapy improved long-term clinical outcomes after PCI in patients with ACS.

1. Introduction

Acute coronary syndrome (ACS) is associated with high rates of morbidity and mortality [1,2]. The early period after ACS onset represents a critical stage with a high-risk for recurrent events and death due to vessel occlusions from vulnerable coronary plaques [3]. Therefore, strategies to stabilize vulnerable coronary plaques during this period are arguably paramount. Evidence from several large, randomized control trials have unequivocally shown that statins reduce coronary morbidity and mortality [4–6]. Although the benefits of statin therapy in patients with stable coronary disease are obvious, the possibility that starting such therapy immediately after ACS might also have a positive impact has only recently been recognized [7–10]. Furthermore, whether statin administration from the acute phase of ACS improves the short-term prognosis [11,12] or influences the long-term prognosis (about 4 years) remains unclear. The prolonged effects of early intensive statin administration among patients in the chronic phase of ACS are also unknown.

The ESTABLISH trial (demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event) found that early atorvastatin therapy resulted in statistically significant coronary plaque regression in patients with ACS over a period of 6 months [13]. The limitations of the ESTABLISH study were the small sample size ($n = 70$) and unknown long-term outcomes. Therefore, we decided to extend the study of the recruited patients and applied the same protocol as the ESTABLISH trial to verify the effect of atorvastatin or changes in coronary plaque on the long-term clinical outcomes of patients with ACS (the Extended-ESTABLISH trial). We determined whether the early initiation of statin therapy during

* Corresponding author. Tel.: +81 3 5802 1056; fax: +81 3 5689 0627.
E-mail address: ktmmy@med.juntendo.ac.jp (K. Miyauchi).

0021-9150/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2009.12.001

ACS improves long-term prognosis, and whether the clinical benefit of early intensive statin therapy is prolonged.

2. Methods

2.1. Study design

The ESTABLISH trial was a prospective open-label, randomized, single-center study of patients with ACS for whom percutaneous coronary intervention (PCI) under IVUS guidance had been successful ($n = 70$) [13]. The Extended-ESTABLISH trial extended the recruitment period of the ESTABLISH trial to evaluate associations among clinical prognosis, coronary plaque change and early intensive statin treatment. Accordingly, we added 110 patients with ACS until July 2005, bringing the total number of such patients to 180 in the present study. The present study follows up the effect of early statin initiation and is a prospective observational follow-up cohort study regardless of whether the patients underwent complete IVUS twice. Our institutional review board approved the study protocol and written informed consent was obtained from each patient to participate.

2.2. Patient population

Patients were eligible for inclusion if they had ACS with significant stenosis on initial coronary angiograms and underwent PCI. Acute coronary syndrome was defined as high-risk unstable angina, non-ST-elevated myocardial infarction (MI) or ST-elevated MI. An increase (≤2-fold) in serum creatine phosphokinase and troponin T positivity indicated a diagnosis of MI. Exclusion criteria comprised failed PCI, diseased bypass graft, recommended for CABG, cardiogenic shock, and already under the administration of lipid-lowering drugs (statins, clofibrate, probucol or analogs, nicotinic acid, or other prohibited drugs) at the time of enrollment.

2.3. Treatment strategies

Patients were randomized within 48 h of ACS onset to receive either intensive lipid-lowering therapy (atorvastatin 20 mg p.o. daily) immediately after the PCI procedure or standard care (lipid-lowering diet). A cholesterol absorption inhibitor was also prescribed if a high (>150 mg/dL) value of low-density lipoprotein cholesterol (LDL-C) persisted as an outpatient after PCI and intravascular ultrasound (IVUS). The patients were randomized using the minimization method controlling for culprit vessels, baseline total cholesterol level, and diabetes mellitus. We used the minimization method as a dynamic allocation way to minimize imbalances among important factors in both groups. In addition, patients underwent standard PCI with or without stent implantation followed by post-PCI management. Intravenous heparin and oral aspirin (162 mg) were administered during the procedures. After PCI, All patients received aspirin (100 mg/day) and ticlopidine (2×100 mg/day) for >3 weeks, and cilostazol (100 mg twice daily) for 4 days. After an IVUS examination at 6 months after ACS in the Extended-ESTABLISH trial, structured treatment was discontinued for all patients in both groups. Thereafter, their attending physicians administered all of them with statins to achieve an LDL-C value of <100 mg/dL as much as possible [14].

2.4. Clinical endpoints

The primary endpoint was the first occurrence of major adverse cardiac and cerebrovascular events (MACCE); that is, all-cause death, recurrent ACS and stroke. Recurrent ACS was defined as AMI and unstable angina requiring emergency hospitalization for either PCI or coronary artery bypass grafting. Stroke was diagnosed based on the presence of a neurologic deficit that was confirmed by computed tomography or magnetic resonance imaging.

Outcome data were collected by serial contact with the patients or their families until August 31, 2008. The medical records of patients who died or who were treated at our hospital were analyzed. Other institutions that admitted patients provided details and causes of death.

2.5. Statistical analysis

Continuous variables are expressed as means ± SD. Data from two independent groups were compared using a t-test or the Wilcoxon rank-sum test and intra-group data were analyzed using a paired t-test or the Wilcoxon signed-rank test. Categorical data were tabulated as frequencies and percentages and compared using the χ^2 test or Fisher's exact test. Event-free survival probabilities for MACCE were estimated using the Kaplan–Meier method and group differences were assessed using a log-rank test. Unadjusted hazard ratios for variables, namely early statin therapy, age, gender, body mass index, hypertension, diabetes, smoking, prior coronary artery disease and baseline LDL-C values, were calculated using the Cox proportional hazards model. We also computed adjusted hazard ratios with the multivariate Cox hazard model including all the above variables. This model did not identify significant interaction between early statin administration and the important variables described above for MACCE. A two-sided p-value of <0.05 was considered significant. All data were analyzed using JMP version 7.0 for Windows (SAS Institute, Cary, NC).

3. Results

All 180 patients who participated in the Extended-ESTABLISH trial between November 2001 and July 2005 were followed up. Consequently, the Extended-ESTABLISH trial was completed because sufficient IVUS data were collected. Ninety patients each were randomly assigned to receive either atorvastatin (atorvastatin group) or standard care (control group) (Fig. 1A). Demographic and clinical characteristics at ACS onset were similar between the two groups (Table 1). All patients were implanted with bare metal stents to treat ACS. The mean values for total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglyceride among all of the patients were 184.5, 117.6, 42.0 and 102.0 mg/dL, respectively. The LDL-C values in the atorvastatin and control groups at follow-up decreased to mean values of 72.2 ± 36.7 (median,

Table 1
Baseline characteristics at ACS occurrence.

	Atorvastatin ($n = 89$)	Control ($n = 89$)	p value
Age (y)	62.3 ± 10.4	62.8 ± 10.4	0.714
Male, n (%)	79 (88.8)	70 (78.6)	0.103
Body mass index (kg/m^2)	24.2 ± 3.5	24.1 ± 3.2	0.781
Hypertension, n (%)	57 (64.0)	52 (58.4)	0.491
Diabetes, n (%)	33 (37.1)	33 (37.1)	0.953
Smoker, n (%)	59 (66.3)	54 (60.7)	0.483
Prior CAD, n (%)	11 (12.4)	10 (11.2)	0.867
Family history of CAD, n (%)	24 (27.0)	29 (32.6)	0.477
Classification of ACS			0.338
AMI, n (%)	52 (58.4)	58 (65.2)	
Unstable angina, n (%)	37 (41.6)	31 (34.8)	
Maximum CPK (IU/L)	1662.5 ± 2274.7	1440.2 ± 1661.8	0.864
Use of ACE inhibitor, n (%)	34 (38.2)	42 (47.2)	0.139
Use of AT1 antagonist, n (%)	43 (48.3)	39 (43.8)	0.443
Use of β-blocker, n (%)	44 (49.4)	48 (53.9)	0.528

CAD, coronary artery disease; ACS, acute coronary syndrome; AMI, acute myocardial infarction; CPK, creatine phosphokinase; ACE, angiotensin converting enzyme; AT1, angiotensin receptor type 1. Values are means ± SD. $p < 0.05$ was considered to indicate statistical significance.

Please cite this article in press as: Dohi T, et al. Early intensive statin treatment for six months improves long-term clinical outcomes in patients with acute coronary syndrome (Extended-ESTABLISH trial): A follow-up study. Atherosclerosis (2009), doi:10.1016/j.atherosclerosis.2009.12.001

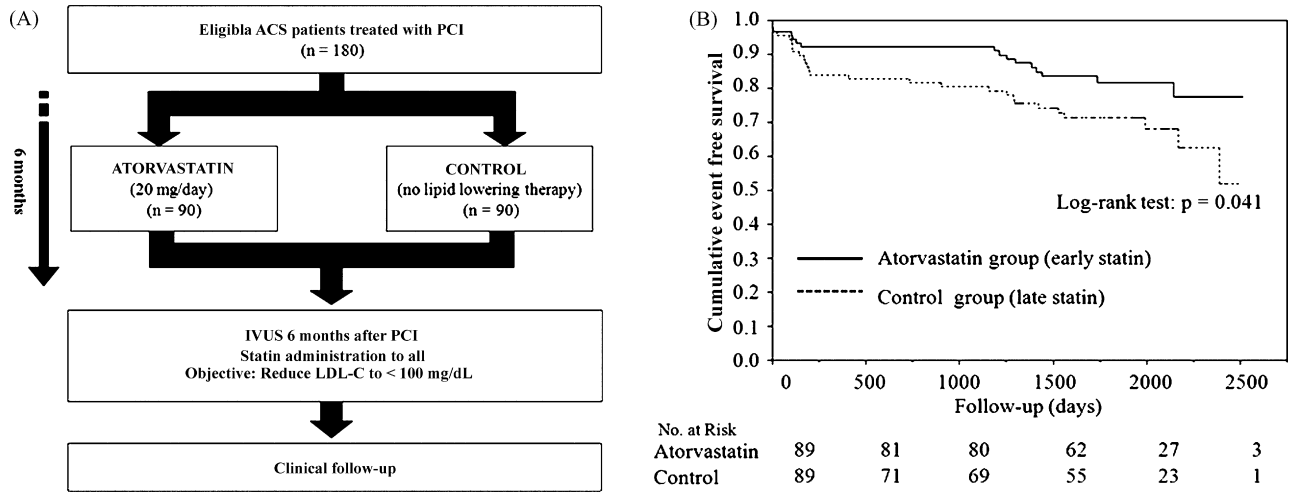

Fig. 1. (A) Summary of follow-up study of Extended-ESTABLISH trial. (B) Kaplan–Meier estimates of incidence of MACCE. Cumulative event-free survival is significantly higher in atorvastatin, than control group (log-rank test, $p = 0.041$).

68.8 mg/dL; $p < 0.001$) and 111.2 ± 38.2 (median, 119.6 mg/dL; $p = 0.930$), respectively, and the percent changes from baseline were −33.8 ± 38.2% and 5.8 ± 37.1%, respectively ($p = 0.001$). The ratio of LDL-C/HDL-C was significantly lower in the atorvastatin group than in the control group (1.7 ± 0.8 vs 2.6 ± 1.1; $p < 0.001$). Mean high-sensitivity-CRP (hs-CRP) values in the atorvastatin and controls fell to 1.3 ± 1.8 and 1.8 ± 3.0 mg/L ($p = 0.889$) (Table 2). None of the patients in the atorvastatin group was withdrawn from the study due to the development of adverse events. The statin was changed to another type such as pitavastatin, pravastatin, simvastatin and fluvastatin, or the dose of atorvastatin was reduced depending on the lipid profiles of some patients in the atorvastatin group at 6 months after ACS onset. On the other hand, statins (including atorvastatin, pitavastatin, pravastatin, simvastatin and fluvastatin) were started in all patients in the control group from 6 months after ACS onset. Subsequently, all patients in both groups were treated and the dose and type of statin was appropriately changed for optimal lipid management. One year after ACS onset, statins were administered to both groups at the same frequency (91.1% vs 89.3%; $p = 0.727$). At that time, the mean LDL-C values in the atorvastatin (early statin) and the control (late statin) groups were 85.5 ± 22.8 and 96.1 ± 20.3 mg/dL, respectively ($p = 0.025$).

3.1. Clinical events and multivariate analysis

Prognostic data were fully documented during the entire follow-up period (mean duration, 1538 ± 707 days, 4.2 ± 1.9 years), during which MACCE developed in 16 (death, $n = 4$; ACS, $n = 10$; stroke = 2) patients in the atorvastatin group and 27 (death, $n = 6$; ACS, $n = 18$; stroke, $n = 3$) in the control group. Cumulative event-free survival was significantly higher in the atorvastatin, than in the control group ($p = 0.041$; log-rank test; Fig. 1B). However, cumulative incidence rates of MACCE did not significantly differ between the atorvastatin and control groups at 6 months as well as at 1 year after ACS onset (7.8% vs 11.1%; $p = 0.445$, 7.8% vs 15.6%; $p = 0.104$, respectively).

Both the unadjusted and multivariate Cox proportional hazards models revealed that early statin treatment was a significant predictor for MACCE (hazard ratio: 0.53; 95%CI 0.28–0.97; $p = 0.040$ and hazard ratio: 0.46; 95%CI 0.23–0.86; $p = 0.015$, respectively; Table 3). We also conducted a sub-group analysis separate from the presence of hypertension and diabetes, class of ACS, baseline median LDL-C (118 mg/dL) and hs-CRP (3.0 mg/L) values for non-fatal cardiovascular events (recurrent ACS and stroke). As a result, a high baseline LDL-C value amplified the beneficial effect of early statin therapy on non-fatal cardiovascular events (Fig. 2).

Table 2
Blood parameters of patients at baseline and follow-up at 6 months.

	Baseline			Follow-up		
	Atorvastatin ($n = 89$)	Control ($n = 89$)	p value	Atorvastatin ($n = 85$)	Control ($n = 84$)	p value
Total cholesterol (mg/dL)	183.1 ± 36.6	191.1 ± 38.7	0.174	148.1 ± 32.1*	190.6 ± 30.1	<0.001
Reduction in TC (%)				28.1 ± 32.1*	−2.6 ± 25.3	<0.0001
HDL-C (mg/dL)	45.8 ± 13.0	43.4 ± 12.2	0.107	48.1 ± 13.2	47.9 ± 17.6	0.567
Triglyceride (mg/dL)	110.2 ± 67.7	127.3 ± 59.7	0.247	130.5 ± 96.8*	139.2 ± 97.1	0.261
LDL-C (mg/dL)	115.3 ± 33.6	122.3 ± 36.3	0.114	72.2 ± 36.7**	111.2 ± 38.2	<0.0001
Reduction in LDL-C (%)				33.8 ± 38.2**	5.8 ± 37.1	<0.0001
LDL/HDL ratio	2.8 ± 1.1	2.9 ± 1.2	0.476	1.7 ± 0.8	2.6 ± 1.0	<0.001
Lipoprotein(a) (mg/dL)	21.9 ± 16.2	23.3 ± 15.8	0.316	23.2 ± 20.6	26.0 ± 19.3	0.228
Apolipoprotein A1 (mg/dL)	113.0 ± 21.3	108.0 ± 21.1	0.355	126.3 ± 23.5	122.7 ± 21.6	0.438
Apolipoprotein B (mg/dL	86.3 ± 19.6	93.7 ± 21.2	0.067	68.9 ± 20.1**	96.1 ± 19.3	<0.001
Apolipoprotein E (mg/dL)	3.84 ± 0.84	3.88 ± 0.95	0.945	3.32 ± 0.93	4.37 ± 1.25	<0.001
HbA1C (%)	5.9 ± 1.4	6.0 ± 1.5	0.938	5.6 ± 0.8	5.6 ± 1.0	0.429
Insulin (μU/mL)	12.2 ± 10.2	11.0 ± 9.9	0.374	7.7 ± 4.3**	6.7 ± 4.5*	0.113
hs-CRP (mg/L)	9.5 ± 17.8	8.5 ± 18.3	0.244	1.3 ± 1.8**	1.8 ± 3.0**	0.889

TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein. Values are means ± SD. $p < 0.05$ was considered statistically significant.
* $p < 0.05$ (baseline versus follow-up).
** $p < 0.01$ (baseline versus follow-up).

Please cite this article in press as: Dohi T, et al. Early intensive statin treatment for six months improves long-term clinical outcomes in patients with acute coronary syndrome (Extended-ESTABLISH trial): A follow-up study. Atherosclerosis (2009), doi:10.1016/j.atherosclerosis.2009.12.001

Table 3
Results of Cox proportional hazards regression analysis.

Variables	Proportional hazards model					
	Unadjusted model			Adjusted model[a]		
	HR	95%CI	*p* value	HR	95%CI	*p* value
Early statin therapy—yes	0.53	0.28–0.97	0.040	0.46	0.23–0.86	0.015
Age (1 year increase)	1.02	0.99–1.06	0.097	1.04	1.01–1.07	0.033
Male—yes	1.34	0.61–3.53	0.497	1.53	0.63–4.30	0.358
Body mass index (1—increase)	0.97	0.89–1.07	0.577	0.98	0.88–1.09	0.721
Hypertension—present	1.62	0.86–3.23	0.135	1.58	0.81–3.22	0.179
Diabetes—present	1.40	0.76–2.55	0.275	1.00	0.51–1.90	0.997
Smoking—present	1.72	0.88–3.68	0.116	1.82	0.90–4.01	0.095
Prior CAD—present	2.21	0.99–4.42	0.052	2.04	0.88–4.32	0.089
Baseline LDL-C—high (>median)	0.91	0.49–1.66	0.764	0.90	0.47–1.72	0.759

CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol. Values of $p < 0.05$ were considered statistically significant.

[a] Multivariate Cox hazard model included the following variables: early statin therapy, age, gender, body mass index, hypertension, diabetes, smoking, prior coronary artery disease and baseline LDL-C value.

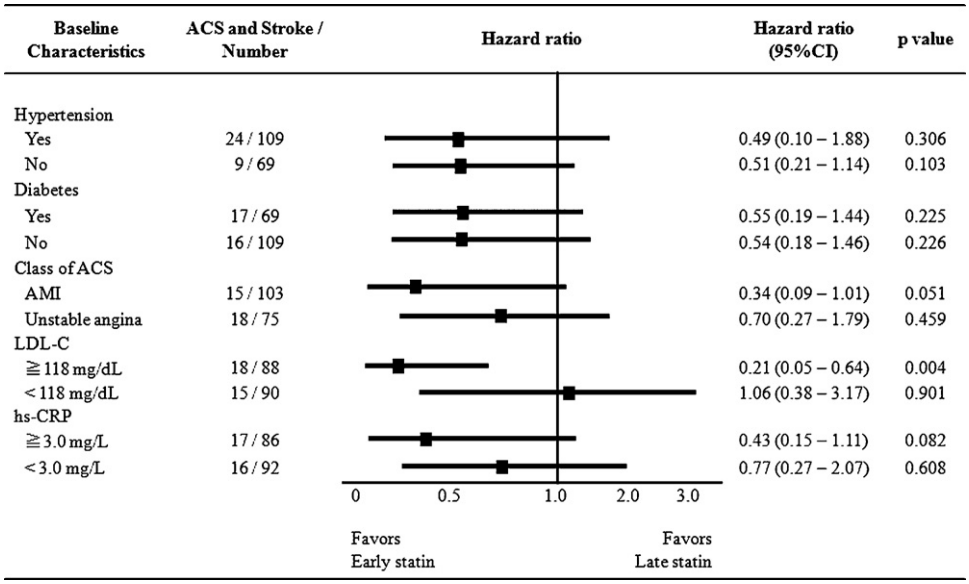

Fig. 2. Estimates of hazards ratios for recurrent ACS and stroke in groups given statin early (atorvastatin group) and late (control group).

4. Discussion

The present study demonstrated that starting statin therapy within 48 h of ACS onset followed by intensive lipid-lowering therapy for 6 months was associated with reduced incidence of long-term cardiovascular events in patients with ACS after PCI. The results also showed that a high baseline LDL-C value amplified the beneficial effect of early statin therapy on non-fatal cardiovascular events.

The present findings were consistent with those of several clinical studies that have shown benefits of statin therapy with respect to cardiovascular events among patients with ACS. Among randomized trials of statin therapy versus control ACS patients, the landmark MIRACL trial (for the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study) showed that early atorvastatin administration resulted in a significantly (16%) lower rate of major cardiac events at 4 months of follow-up [15]. However, patients for whom coronary revascularization therapy was planned within 24–96 h of ACS onset were excluded from the MIRACL trial. The omission of this large subpopulation of patients was a critical limitation for clinical practice because early revascularization is an important therapeutic strategy for treating ACS. We thus designed the present study to more closely resemble actual practice. Revascularization reduced the risk of future ischemic events, whereas medical treatment including statins reduced mortality and morbidity among patients with cardiovascular disease [16–18]. The present study extends and strengthens the benefits of statins with respect to long-term outcomes among ACS patients after revascularization. We believe that this is the first long-term follow-up study of ACS patients after revascularization.

Recent advances in basic sciences have established a fundamental role for inflammation in mediating all stages of atherosclerosis, from initiation through progression to plaque formation and ultimately plaque rupture and subsequent thrombotic complications leading to ACS [19,20]. Therefore, we postulated that the process of plaque rupture is in fact an acute inflammatory response or reaction. Some clinical studies have shown that groups of patients with ACS accompanied by significant inflammation have a poor prognosis [21,22]. Thus, to control systemic inflammation from the early stage of ACS occurrence is important. We consider that the anti-inflammatory properties of statins play an important role in the long-term benefits conferred upon hospital inpatients by administration soon after ACS. We also consider that CRP is an important marker of inflammation in atherosclerotic disease. Furthermore, several studies have suggested that hs-CRP levels upon admission can predict early and late outcomes in patients with ACS [22–24]. However, hs-CRP values did not significantly differ between the atorvastatin and control groups at 6 months. In addi-

Please cite this article in press as: Dohi T, et al. Early intensive statin treatment for six months improves long-term clinical outcomes in patients with acute coronary syndrome (Extended-ESTABLISH trial): A follow-up study. Atherosclerosis (2009), doi:10.1016/j.atherosclerosis.2009.12.001

tion, our data did not show a prognostic significance of hs-CRP in unadjusted and adjusted Cox proportional hazard models (HR 0.96; 95%CI 0.78–1.11; $p = 0.698$ and HR 1.01; 95%CI 0.81–1.17; $p = 0.955$, respectively).

The reduction in MACCE conferred by early statin treatment was already apparent at 6 months after starting therapy, although this benefit was not statistically significant. The early separation of clinical event curves also revealed a continued long-term benefit of early statin therapy. Our findings suggest that patients with ACS who receive early and intensive lipid-lowering for 6 months continue to derive benefit in the chronic phase even if the intensity of lipid-lowering therapy is reduced after 6 months. We also thought that an important reason to start statin therapy during the early phase of ACS is to ensure that patients receive this critical component of secondary prevention and to improve long-term compliance by taking advantage of a moment when the attending physician and patients are most motivated. Thus, we would like to emphasize the significance of the early initiation of intensive lipid-lowering therapy with statins and at least 6 months of continued administration for patients with ACS.

The influence of the pre-treatment LDL-C value on the clinical benefits of statin therapy remains controversial [4,25–28]. Our data showed that the benefits of atorvastatin over controls deteriorated from higher to lower baseline LDL-C values. Definitive explanations for the reduced benefit of intensive statin therapy in patients with lower baseline LDL-C have not been elucidated. Since the relationship between LDL-C levels and cardiovascular events was linear, the benefit of aggressive LDL-C reduction should be greater in patients with higher baseline LDL-C. However, the greater reduction in LDL-C induced by atorvastatin in patients with higher baseline values might have partially contributed to the difference in the benefit. The absolute difference in LDL-C achieved at 6 months with control versus atorvastatin significantly increased from the group with a lower to a higher LDL-C value. We also consider that patients with ACS and low baseline LDL-C should be managed more strictly for other coronary risk factors such as diabetes, hypertension and negative lifestyle habits. The benefit of lipid therapy in these groups of patients is still underestimated, although it is generally a confirmative strategy. More careful intervention, such as multifactorial treatment, might be required because other risks for cardiovascular events would be considerably influenced.

Several limitations are associated with the present study. Firstly, the study population comprised only Japanese patients, whereas the principal data regarding statin treatment for ACS were generated from large-scale studies in European and American countries. We considered that 20 mg/day of atorvastatin would be sufficient to intensively lower lipid values among this Asian population. The administration of 80 mg/day of atorvastatin decreased the mean LDL-C value to 72 mg/dL in the MIRACL study of ACS among mostly European and North American patients [15]. Our values after statin treatment support the findings of that study. Therefore, the LDL-C results and the other effects of statins might differ from those of other populations. However, we believe that the significance of early statin treatment for ACS provides valuable information about long-term outcomes, regardless of race. Secondly, the scale of this study cohort was small and the advantages conferred by this study design will be difficult to replicate. Considerable positive evidence about statin treatment for coronary artery disease has recently been publicized, and finding untreated patients for future comparisons with statin-treated patients with ACS will therefore be challenging. We feel that this factor outweighs the issue of the study cohort size.

5. Conclusions

The findings of this clinical follow-up study of the Extended-ESTABLISH trial suggest that the incidence of MACCE is decreased by the early, rather than the late initiation of statin treatment for ACS. Moreover, 6 months of intensive lipid-lowering therapy for patients with ACS improved long-term clinical outcomes after PCI even when the intensity of the therapy was reduced thereafter. We postulate that early statin therapy is warranted for all patients with ACS even under the current guidelines, as the likely outcome can be predicted primarily from lipid profiles.

Conflict of interest

None declared.

Acknowledgements

The authors are grateful to the staff of the Department of Cardiovascular Medicine at Juntendo University. We also thank Natsuko Yamamoto for IVUS data analysis, Hisamaro Suso for data collection, as well as Yumi Nozawa for secretarial assistance.

References

[1] Wallentin L, Lagerqvist B, Husted S, et al. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. FRISC II Investigators. Fast Revascularisation during Instability in Coronary artery disease. Lancet 2000;356:9–16.
[2] Granger CB, Weaver WD. Reducing cardiac events after acute coronary syndromes. Rev Cardiovasc Med 2004;5(Suppl. 5):S39–46.
[3] Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and other Societies on coronary prevention. Eur Heart J 1998;19:1434–503.
[4] Baseline serum cholesterol and treatment effect in the Scandinavian Simvastatin Survival Study (4S). Lancet 1995;345:1274–5.
[5] Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996;335:1001–9.
[6] Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med 1998;339:1349–57.
[7] Waters D, Schwartz GG, Olsson AG. The Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL) trial: a new frontier for statins? Curr Control Trials Cardiovasc Med 2001;2:111–4.
[8] Fonarow GC. In-hospital initiation of statin therapy in acute coronary syndromes: maximizing the early and long-term benefits. Chest 2005;128:3641–51.
[9] Lenderink T, Boersma E, Gitt AK, et al. Patients using statin treatment within 24 h after admission for ST-elevation acute coronary syndromes had lower mortality than non-users: a report from the first Euro Heart Survey on acute coronary syndromes. Eur Heart J 2006;27:1799–804.
[10] Sakamoto T, Kojima S, Ogawa H, et al. Effects of early statin treatment on symptomatic heart failure and ischemic events after acute myocardial infarction in Japanese. Am J Cardiol 2006;97:1165–71.
[11] Hulten E, Jackson JL, Douglas K, et al. The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. Arch Intern Med 2006;166:1814–21.
[12] Briel M, Schwartz GG, Thompson PL, et al. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. JAMA 2006;295:2046–56.
[13] Okazaki S, Yokoyama T, Miyauchi K, et al. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH Study. Circulation 2004;110:1061–8.
[14] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
[15] Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA 2001;285:1711–8.
[16] Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. JAMA 2005;293:2908–17.
[17] Bavry AA, Kumbhani DJ, Rassi AN, et al. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. J Am Coll Cardiol 2006;48:1319–25.
[18] Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–78.
[19] Lusis AJ. Atherosclerosis. Nature 2000;407:233–41.

Please cite this article in press as: Dohi T, et al. Early intensive statin treatment for six months improves long-term clinical outcomes in patients with acute coronary syndrome (Extended-ESTABLISH trial): A follow-up study. Atherosclerosis (2009), doi:10.1016/j.atherosclerosis.2009.12.001

[20] Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135–43.
[21] Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005;352:20–8.
[22] Liuzzo G, Biasucci LM, Gallimore JR, et al. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. N Engl J Med 1994;331:417–24.
[23] Ferreiros ER, Boissonnet CP, Pizarro R, et al. Independent prognostic value of elevated C-reactive protein in unstable angina. Circulation 1999;100:1958–63.
[24] Morrow DA, Rifai N, Antman EM, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in myocardial infarction. J Am Coll Cardiol 1998;31:1460–5.
[25] Giraldez RR, Giugliano RP, Mohanavelu S, et al. Baseline low-density lipoprotein cholesterol is an important predictor of the benefit of intensive lipid-lowering therapy: a PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) analysis. J Am Coll Cardiol 2008;52:914–20.
[26] Ridker PM, Rifai N, Pfeffer MA, et al. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. Circulation 1999;100:230–5.
[27] Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). Circulation 1998;97:1440–5.
[28] MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7–22.

Please cite this article in press as: Dohi T, et al. Early intensive statin treatment for six months improves long-term clinical outcomes in patients with acute coronary syndrome (Extended-ESTABLISH trial): A follow-up study. Atherosclerosis (2009), doi:10.1016/j.atherosclerosis.2009.12.001