Journal of the American College of Cardiology
© 2009 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 54, No. 25, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.10.005

QUARTERLY FOCUS ISSUE: PREVENTION/OUTCOMES

Reduction in Recurrent Cardiovascular Events With Intensive Lipid-Lowering Statin Therapy Compared With Moderate Lipid-Lowering Statin Therapy After Acute Coronary Syndromes

From the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) Trial

Sabina A. Murphy, MPH, Christopher P. Cannon, MD, Stephen D. Wiviott, MD, Carolyn H. McCabe, BS, Eugene Braunwald, MD

Boston, Massachusetts

Objectives In addition to reducing first events in patients after an acute coronary syndrome (ACS), we hypothesized that high-dose atorvastatin 80 mg would also reduce recurrent cardiovascular events, and therefore total events, compared with pravastatin 40 mg during the 2-year follow-up.

Background In the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial, more intensive lipid lowering with high-dose atorvastatin reduced the first occurrence of the primary end point (death, myocardial infarction, unstable angina requiring rehospitalization, stroke, or revascularization ≥30 days) compared with moderate lipid lowering with pravastatin.

Methods Poisson regression analysis was performed to compare the number of occurrences of the primary end point between high-dose atorvastatin and pravastatin in the PROVE IT–TIMI 22 trial.

Results As previously reported, first primary end point events were reduced by 16% with atorvastatin 80 mg versus pravastatin 40 mg (n = 464 vs. n = 537, respectively; p = 0.005). Additional events were also reduced by 19% with atorvastatin 80 mg (n = 275 vs. n = 340, respectively; p = 0.009). Overall, there were 138 fewer primary efficacy events with atorvastatin 80 mg versus pravastatin 40 mg (n = 739 vs. n = 877, respectively; rate ratio: 0.85, 95% confidence interval: 0.77 to 0.94, p = 0.001).

Conclusions Although analytic techniques commonly used in clinical outcomes trials censor patients who experience a component of the primary composite end point, total cardiovascular events are important to patients, clinicians, and health care payers. Maintaining low levels of low-density lipoprotein cholesterol is central to preventing additional atherosclerotic development and subsequent cardiovascular events. Atorvastatin 80 mg, a more intensive low-density lipoprotein cholesterol lowering agent, reduced both first and subsequent primary end point events compared with pravastatin 40 mg after ACS. (J Am Coll Cardiol 2009;54:2358–62) © 2009 by the American College of Cardiology Foundation

With customary statistical analysis of clinical outcomes trial data using survival methodology, patients who experience a component of a primary composite end point are censored from the analysis after the initial event, despite remaining at risk for additional events during the course of the trial follow-up. Reporting of a composite event only may be less sensitive to the variation of the treatment effect across the

See page 2363

From the TIMI Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. The TIMI Study Group received research grants from Bristol-Myers Squibb to conduct the PROVE IT–TIMI 22 trial. Dr. Cannon receives research grants/support from Accumetrics, AstraZeneca, Bristol-Myers Squibb/Sanofi Partnership, GlaxoSmithKline, Intekrin Therapeutics, Merck, Merck/Schering-Plough Partnership, Novartis, and Takeda; and is a clinical advisor with equity in Automedics Medical Systems. Dr. Wiviott has received speaking honoraria from Pfizer, Merck, AstraZeneca, and Bristol-Myers Squibb; and consulting fees from Bristol-Myers Squibb. Dr. McCabe has received grant support from Bristol-Myers Squibb (for the PROVE IT trial) and Schering-Plough. Dr. Braunwald has received grant support from Bristol-Myers Squibb (for the PROVE IT–TIMI 22 trial), Schering-Plough, and Merck; and has received honoraria and is an advisory board member of Schering-Plough and Merck.

Manuscript received May 7, 2009; revised manuscript received September 30, 2009, accepted October 12, 2009.

individual events, particularly if a treatment reduces the incidence of 1 type of event and increases the incidence of another (1). Additionally, if the events have a different impact on either quality of life or health care costs, it may be important to examine the frequency and treatment effects of the different events (1). Although data on all events occurring during the study are often collected, reporting of such events is generally examined by individual end points rather than by total number of cardiovascular events that occurred. From a clinical perspective, patients and physicians are concerned not only with the initial event a patient may experience but also with subsequent events. We recently examined the impact of more potent antiplatelet therapy on total cardiovascular events (2), but the impact of more intensive lipid-lowering therapy on total cardiovascular events has not been explored.

Compared with moderate lipid lowering using standard-dose pravastatin therapy, intensive lipid lowering with high-dose atorvastatin therapy after acute coronary syndrome (ACS) significantly reduced the first occurrence of the primary end point of death, myocardial infarction (MI), stroke, unstable angina (UA) requiring rehospitalization, or revascularization occurring >30 days after the index ACS event in the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial (3,4). We hypothesized that atorvastatin 80 mg would also reduce recurrent cardiovascular events and therefore total events compared with pravastatin 40 mg during the 2-year follow-up.

Abbreviations and Acronyms

ACS = acute coronary syndrome
CRP = C-reactive protein
LDL-C = low-density lipoprotein cholesterol
MI = myocardial infarction
UA = unstable angina

Methods

The study design and primary results papers for the PROVE IT–TIMI 22 trial have been published previously (3,5). The trial enrolled 4,162 patients with an ACS within the prior 10 days. Patients were randomly assigned to either 80 mg atorvastatin (intensive lipid lowering) or 40 mg pravastatin (moderate lipid lowering). Prior statin use was not an exclusion criterion in the PROVE IT–TIMI 22 trial. Baseline and on-treatment lipid levels and high-sensitivity C-reactive protein (CRP) were

Table 1 Baseline Characteristics of Patients With No Events, a Single Event, or Multiple Events

	No Events (n = 3,161)	Single Event (n = 621)	Multiple Events (n = 380)	p Value
Age, yrs	57 (50–65)	60 (53–69)	59 (50–67)	<0.001
Age ≥65 yrs	27.9%	36.1%	32.6%	<0.001
Male	77.8%	81.0%	76.1%	0.125
White race	90.5%	91.3%	91.8%	0.618
History of diabetes mellitus	15.8%	20.3%	28.7%	<0.001
History of hypertension	47.3%	53.5%	57.5%	<0.001
History of hypercholesterolemia	48.8%	52.5%	58.4%	0.001
Prior MI	16.3%	24.2%	27.1%	<0.001
Prior PCI	13.7%	19.5%	23.2%	<0.001
Prior CABG	9.4%	13.8%	18.4%	<0.001
History of heart failure	2.7%	4.4%	6.6%	<0.001
History of peripheral vascular disease	4.6%	7.9%	12.1%	<0.001
History of renal disease	8.1%	10.6%	14.1%	<0.001
History of stroke	4.9%	6.0%	8.4%	0.013
TIMI risk score				<0.001
0–2	45.4%	36.7%	36.3%	
3–4	49.2%	57.2%	52.9%	
5–6	5.4%	6.1%	10.8%	
Current smoker	37.5%	32.5%	37.1%	0.061
Index event				<0.001
ST-segment elevation MI	35.0%	35.0%	30.0%	
Non–ST-segment elevation MI	37.4%	32.4%	31.6%	
Unstable angina	27.5%	32.6%	38.4%	
Statin use in the 2 weeks before qualifying event	23.7%	28.8%	31.6%	<0.001
Randomized to atorvastatin	51.7%	46.2%	46.6%	0.012
Total cholesterol at baseline, mg/dl	180 (160–204)	180 (157–201)	183 (160–206)	0.320
Low-density lipoprotein cholesterol at baseline, mg/dl	106 (89–127)	105 (85–126)	106 (85–127)	0.465
Triglycerides at baseline, mg/dl	156 (118–210)	151 (114–212)	162 (124–220)	0.044
C-reactive protein at baseline, mg/l	12.0 (4.9–28.3)	13.8 (5.4–34.3)	11.2 (4.5–29.4)	0.051

Values are median (interquartile range) or %.
CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

JACC Vol. 54, No. 25, 2009
December 15/22, 2009:2358–62

measured in central laboratories. Patients were followed up for clinical events for an average of 2 years.

All end points used in the analyses were adjudicated by members of an independent clinical events committee who were blinded to the treatment assignment (5). Fatal events were counted as a single event, not as 2 separate events. For example, if a patient experienced an MI and then had cardiovascular death with the cause of death adjudicated as being due to the MI, the event was considered 1 fatal MI event and was both an MI and cardiovascular death. Patients were to remain on the study drug even if the subject experienced 1 of the nonfatal efficacy end points of the study.

The present analysis was not pre-specified in the primary analytic plan and should be considered exploratory. Baseline clinical characteristics are presented as frequencies for categorical variables and as medians and interquartile ranges for continuous variables. Comparisons between baseline characteristics for patients with no events, a single event, or multiple events were made using the chi-square test for categorical variables and Kruskal-Wallis for continuous variables. Poisson regression analysis was performed to compare the total number of occurrences of the primary end point between all patients in the atorvastatin and pravastatin groups. Analyses were performed using Stata/SE version 9.2 (Stata Corp., College Station, Texas).

Results

Patients who had multiple events had more frequent comorbidities at study entry, including a history of diabetes mellitus, hypertension, and hypercholesterolemia (Table 1). Interestingly, patients who had multiple events were more likely to present with UA as the index event. There was no difference in baseline low-density lipoprotein cholesterol (LDL-C) or total cholesterol among patients who had multiple events compared with patients who had no event or a single event, but triglycerides were higher among patients who had multiple events. Patients having multiple events were more likely to have been statin users before the qualifying event (31.6% for patients with multiple events, 28.8% for patients with single event, 23.7% for patients with no events; $p < 0.001$).

The primary end point of first occurrence of death, MI, stroke, UA requiring rehospitalization, or revascularization occurring >30 days after the index ACS event was significantly reduced among patients randomly assigned to intensive lipid-lowering therapy with atorvastatin 80 mg as compared with moderate lipid-lowering therapy with pravastatin 40 mg (22.4% [n = 464] vs. 26.3% [n = 537], hazard ratio: 0.84, 95% confidence interval: 0.74 to 0.95, $p = 0.005$), as previously reported (3). Thus, by the usual analysis that takes account of only first events, the difference between the 2 treatment arms was 73 events. In addition to the reduction in first events, subsequent events were also reduced in the atorvastatin 80 mg group (n = 275 in the atorvastatin 80 mg group vs. n = 340 in the pravastatin 40 mg group, $p = 0.009$) (Fig. 1), resulting in 138 fewer total primary events during follow-up (total events n = 739 vs. n = 877, rate ratio: 0.85, 95% confidence interval: 0.77 to 0.94, $p = 0.001$). Using a marginal Cox proportional hazards model rather than a Poisson regression analysis produced a hazard ratio of 0.82 ($p = 0.008$) in favor of the atorvastatin 80 mg group. Among the additional events, there were 177 second events in the atorvastatin 80 mg group (8 fatal and 169 nonfatal) versus 203 second events in the pravastatin 40 mg group (12 fatal and 191 nonfatal), and 60 third events in the atorvastatin 80 mg group (3 fatal and 57 nonfatal) versus 74 third events in the pravastatin 40 mg group (3 fatal and 71 nonfatal).

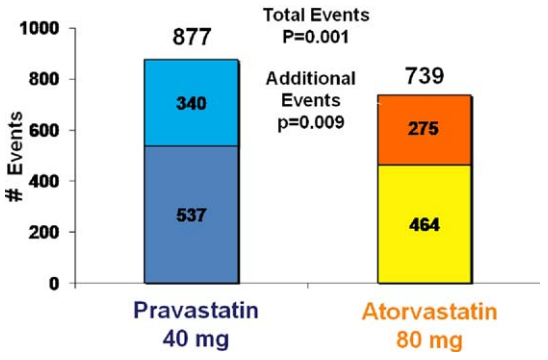

Figure 1 **Total Primary End Point Events by Randomized Therapy**

The atorvastatin 80 mg group had a lower number of first events, additional events, and total events as compared with the pravastatin 40 mg group. Bright blue **(top, left)** = additional events, pravastatin 40 mg; lighter blue **(bottom, left)** = first events, pravastatin 40 mg; orange **(top, right)** = additional events, atorvastatin 80 mg; and yellow **(bottom, right)** = first events, atorvastatin 80 mg.

When examining the individual components of the primary composite end point, the majority of additional events reduced in the atorvastatin 80 mg group were UA events requiring rehospitalization and revascularization, with a similar number of deaths, MI, and strokes (Table 2).

Among patients with a single event or multiple events, cholesterol and CRP levels before the event were compared to those of the final study sample for patients with no events (Table 3). Total cholesterol, LDL-C, and high-density lipoprotein cholesterol were lower and CRP was higher among patients with single and recurrent end point events than among patients without any end point events.

The overall rate of permanent study drug discontinuation within 30 days after the first event was low (3.0%) and did not differ by randomized group (3.3% in the atorvastatin 80 mg group vs. 2.7% in the pravastatin 40 mg group, $p = 0.56$). There were no cases of recurrent myalgia or myositis in the trial in either treatment group. Among patients with no events, compliance was classified as good in 85% of patients at the last contact with available compliance data. Among patients with 1 event, compliance was classified as good in 91% of patients at the contact before the event, whereas 88% of patients with >1 event had compliance classified as good.

Table 2 Primary End Point Events by Randomized Therapy

	Initial Events		Additional Events			Total Events		
	Pravastatin 40 mg	Atorvastatin 80 mg	Pravastatin 40 mg	Atorvastatin 80 mg	p Value	Pravastatin 40 mg	Atorvastatin 80 mg	p Value
Any	537	464	340	275	0.009	877	739	0.001
Death*	49	32	18	15	0.568	67	47	0.053
MI	121	103	64	57	0.472	185	160	0.218
Stroke	14	17	7	8	0.821	21	25	0.529
UA requiring rehospitalization	77	66	46	18	0.001	123	84	0.009
Revascularization >30 days after index ACS event	276	246	205	177	0.127	481	423	0.081

*To avoid double counting, fatal cardiovascular events were counted as a single event, not as 2 separate events.
ACS = acute coronary syndrome; MI = myocardial infarction; UA = unstable angina.

Discussion

This analysis from the PROVE IT–TIMI 22 trial demonstrates that intensive lipid-lowering therapy with high-dose atorvastatin therapy after an ACS prevented not only the first occurrence of the primary end point of death, MI, stroke, UA requiring rehospitalization, or revascularization but also reduced subsequent, and thus the total number of, primary end point events among patients with an ACS. These findings suggest that continued therapy with a regimen that maintains low LDL-C is central to preventing additional atherosclerotic development and cardiovascular events, including recurrent events. Based on the primary end point results from the PROVE IT–TIMI 22 trial, the number of patients needed to treat to prevent the first occurrence of the primary end point is 26. However, when considering total events, the needed-to-treat number to prevent 1 event is much lower, at 14.

Several studies have shown that when compared with placebo, the risk of death and cardiovascular events is lowered by reducing LDL-C levels with statin therapy for both primary and secondary prevention (6). More recent trials, such as the PROVE IT–TIMI 22 study and the TNT (Treating to New Targets) trial, demonstrated that further reductions in LDL-C levels with more intensive statin therapy conferred additional clinical benefit (3,7,8). The JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) trial extended these findings, demonstrating improved outcomes for patients with lipid levels considered optimal under current guidelines but with elevated levels of high-sensitivity CRP (9,10). While these studies have shown improved outcomes with statin therapy to lower LDL-C levels, the primary end point for each trial was time to occurrence of a first major cardiovascular event, the exact definitions of which varied, but all of which were composite end points. The reduction in first event has been consistent across the studies, but total number of events prevented has not been fully reported.

Unexpectedly, the median LDL-C measured before the first event for patients having an event and measured at study end for patients without an event was lower in patients with single and recurrent end point events than in patients without any end point events. While the exact cause of this finding is not known, it is likely confounded by the observation that patients with single or multiple events more frequently presented as statin users before the qualifying event, contributing to the lower LDL-C; thus, the lower LDL-C levels in patients with events may be a spurious finding. It is also possible that the difference may be due to the timing of the LDL-C measurements, which were taken at a median of 2 years, at the time of the final study visit of patients without an event, and at a median of 6 months for patients with an event. Compliance with study drug medication is likely greatest early in the trial when the LDL-C measurement was used for the cohort with a single or multiple event and lower at trial end when the LDL-C measurement was used for the cohort without any events.

Expanded analysis of total events during the course of therapy may warrant more consideration in future trials, given the attention focused on health care resource utilization. Despite the frequent practice of censoring patients

Table 3 Cholesterol and CRP Among Patients With No Events, a Single Event, or Multiple Events*

	No Events (n = 3,002)	Single Event (n = 528)	Multiple Events (n = 317)	p Value
Total cholesterol, mg/dl	160 (134–189)	153 (127–184)	156 (127–188)	<0.001
LDL-C, mg/dl	85 (65–109)	79 (58–106)	83 (61–105)	0.001
HDL-C, mg/dl	42 (35–50)	41 (35–48)	40 (34–48)	0.029
CRP, mg/l	1.7 (0.8–3.8)	1.9 (0.8–4.6)	2.2 (1.0–4.4)	0.005

Values are median (interquartile range). *Final sample used for patients with no events; sample preceding first event used for patients with events; C-reactive protein (CRP) measured only at 30 days, 4 months, and final sample.
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

JACC Vol. 54, No. 25, 2009
December 15/22, 2009:2358–62

who experience a component of the primary composite end point in standard statistical analysis of clinical outcomes trial data, all events occurring during the course of the entire trial are important to patients, clinicians, and payers (11). Multiple ischemic events result in higher mortality and a reduced quality of life (12). Multiple events can also increase costs by requiring more hospitalizations, diagnostic tests, treatments, and physician visits. Another method for analyzing multiple events is to perform a landmark analysis to explore the treatment effect beyond a pre-determined timeframe to evaluate for both early and late benefit. While this type of analysis can be informative, it should be interpreted as a post-randomization analysis because there may be differences among patients who were censored because of the occurrence of a fatal event or differences in concomitant treatments among patients who experienced a nonfatal event during the early part of the trial. Other methods for analyzing multiple events in the presence of a terminal event have also been described by Chen and Cook (1), who propose use of marginal cumulative mean functions between treatment groups and reporting of a global test statistic.

Although cost-effectiveness analyses incorporate total costs when available, including repeat hospitalizations and multiple procedures, multiple events are often not incorporated into the effectiveness component of the analysis (13). From a cost economics perspective, the occurrence of multiple events would have a negative impact on long-term outcomes of both life-years and quality-adjusted life-years. Incorporating the total number of events into cost-effectiveness analyses may provide a more comprehensive estimate of the total cost effectiveness of a given therapy when the agent has been shown to reduce events beyond the first occurrence of the end point.

In a similar analysis of total events in the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcome by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38) study, more potent antiplatelet therapy with the novel thienopyridine prasugrel was shown to reduce first, subsequent, and total occurrences of the primary end point of cardiovascular death, MI, or stroke compared with clopidogrel (2). As with the current analysis, which suggests that continued therapy with a more intensive lipid-lowering agent confers added benefit beyond the first event, the TRITON–TIMI 38 study analysis demonstrated the need for maintaining treatment with continued high levels of platelet inhibition after an ACS.

The National Cholesterol Education Program currently recommends an optional target LDL-C of <70 mg/dl for patients at high risk of cardiovascular events (14–16), including those with an ACS event. Baseline characteristics of patients in the present study were analyzed to identify high-risk characteristics associated with the occurrence of multiple events. Although baseline LDL-C levels did not differ among patients without an event, with a single event, or with multiple events, baseline triglyceride levels were slightly higher in patients who had multiple events. Other established risk factors such as diabetes mellitus and hypertension were most common among patients having multiple events. Presentation with an index event of UA was also more frequent among patients who experienced multiple events.

Reprint requests and correspondence: Dr. Christopher P. Cannon, TIMI Study Group, 350 Longwood Avenue, First Floor, Boston Massachusetts 02115. E-mail: cpcannon@partners.org.

REFERENCES

1. Chen BE, Cook RJ. Tests for multivariate recurrent events in the presence of a terminal event. Biostatistics 2004;5:129–43.
2. Murphy SA, Antman EM, Wiviott SD, et al. Reduction in recurrent cardiovascular events with prasugrel compared with clopidogrel in patients with acute coronary syndromes from the TRITON–TIMI 38 trial. Eur Heart J 2008;29:2473–9.
3. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–504.
4. Wiviott SD, de Lemos JA, Cannon CP, et al. A tale of two trials: a comparison of the post-acute coronary syndrome lipid-lowering trials A to Z and PROVE IT–TIMI 22. Circulation 2006;113:1406–14.
5. Cannon CP, McCabe CH, Belder R, Breen J, Braunwald E. Design of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)–TIMI 22 trial. Am J Cardiol 2002;89:860–1.
6. 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.
7. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol 2006;48:438–45.
8. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425–35.
9. Ridker PM, Fonseca FA, Genest J, et al. Baseline characteristics of participants in the JUPITER trial, a randomized placebo-controlled primary prevention trial of statin therapy among individuals with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. Am J Cardiol 2007;100:1659–64.
10. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.
11. Gold M, Siegel J, Russel L, Weinstein M. Cost-Effectiveness in Health and Medicine. New York, NY: Oxford University Press, 1996.
12. Spertus JA, Radford MJ, Every NR, Ellerbeck EF, Peterson ED, Krumholz HM. Challenges and opportunities in quantifying the quality of care for acute myocardial infarction: summary from the Acute Myocardial Infarction Working Group of the American Heart Association/American College of Cardiology First Scientific Forum on Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke. J Am Coll Cardiol 2003;41:1653–63.
13. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 1996;276:1253–8.
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. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction). J Am Coll Cardiol 2007;50:e1–157.
16. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. J Am Coll Cardiol 2004;44:720–32.

Key Words: statin ■ acute coronary syndrome ■ lipid lowering ■ clinical trial.