Impact of High-Dose Atorvastatin in Coronary Heart Disease Patients Age 65 to 78 Years

Address for correspondence:
Michael J. Koren, MD
Jacksonville Center for Clinical
Research
4085 University
Boulevard South, Ste. 1
Jacksonville, FL 32216
michaelkoren@jaxresearch.com

Michael J. Koren, MD; Theodore Feldman, MD; Robert A. Mendes, MD

Jacksonville Center for Clinical Research, Jacksonville, Florida (Koren); South Miami Heart Center and Miami Research Associates, Coral Gables, Florida (Feldman); Pfizer Global Pharmaceuticals, Pfizer Inc., New York, New York (Mendes)

ABSTRACT

Background: High-dose statin therapy may be underutilized in aged patients due to doubts about efficacy and safety.

Hypothesis: To investigate outcomes and safety in patients aged 65–78 years compared with patients aged <65 years in the ALLIANCE study.

Methods: A total of 2,442 stable coronary heart disease (CHD) patients with dyslipidemia were randomized to either aggressive treatment (low-density lipoprotein cholesterol titration goal of <80 mg/dL or maximum 80 mg/d of atorvastatin) or usual care (continuation of baseline lipid-lowering therapy, with changes and laboratory analyses directed by treating physicians).

Results: A total of 1,001 patients aged 65–78 years were followed for a median period of 53.9 mo. Older, aggressively treated atorvastatin patients experienced a 27% relative risk reduction for the primary composite endpoint of adverse cardiovascular outcomes (hazard ratio [HR]: 0.73; 95% confidence intervals [CI]: 0.57–0.94; $p = 0.016$). In addition, significant risk reductions were observed for nonfatal myocardial infarction (MI; HR: 0.43; 95% CI: 0.23–0.79; $p = 0.006$), cardiac revascularization (HR: 0.67; 95% CI: 0.48–0.93; $p = 0.017$), and the combined endpoint of cardiac death and nonfatal MI (HR: 0.48; 95% CI: 0.32–0.72; $p = 0.001$). The rate of significant liver transaminase elevations in atorvastatin patients was low and not age related. There were no cases of rhabdomyolysis. The rate of study discontinuations due to serious adverse events was higher in patients aged 65–78 years than in those younger than 65 years, but was similar between the treatment groups.

Conclusions: Our data support the efficacy and safety of aggressive lipid management with atorvastatin in older CHD patients.

Introduction

Cardiovascular disease (CVD) increases precipitously with age.^{1,2} An estimated 83% of all coronary heart disease (CHD) deaths and about 88% of all stroke deaths are experienced by persons aged 65 years and older.³ Despite this concentration of morbidity and mortality in the elderly, the efficacy of treating older patients for hyperlipidemia has been questioned due to the loss of association between elevated cholesterol levels and cardiovascular events with age. These lingering doubts persist despite data from landmark clinical trials that have shown no attenuation of the benefits of statin therapy in older subjects.^{4,5}

Michael Koren serves as an investigator for sponsored research for many companies (including Pfizer, Merck, Merck-Schering, AstraZeneca, and Abbott) and has participated in Advisory Boards for Pfizer. Theodore Feldman has received honoraria from Pfizer, Merck, Schering, AstraZeneca, Abbott, Bristol-Myers Squibb, and Sanofi, and research funding from Merck, Schering, and Bristol-Myers Squibb. Robert Mendes is employed by and has stock interests in Pfizer Inc.

Older CHD subjects have been specifically studied in several clinical trials. In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), which enrolled 5,804 patients aged 70–82 years with a history or high risk of CVD or stroke, treatment with pravastatin 40 mg for an average of 3.2 years reduced major coronary events by 19% and CHD mortality by 24% compared with placebo.⁶ In patients aged 61–86 years in the Study Assessing Goals in the Elderly (SAGE), both pravastatin 40 mg and atorvastatin 80 mg reduced myocardial ischemia based on ambulatory ECG monitoring compared to baseline, but atorvastatin treatment was also associated with a favorable trend in reducing major cardiovascular endpoints and total mortality during this 12-month study.⁷

Because high-dose statin therapy may be currently underutilized in older patients due to safety concerns,⁸ further information on the safety and efficacy of high-dose statin therapy in this population is important. Data from the Treating to New Targets (TNT) study demonstrated a similar safety profile with atorvastatin 80 mg in patients aged older and younger than 65 years,⁹ but this trial included a run-in phase during which subjects received atorvastatin

10 mg daily, perhaps selecting a more statin tolerant population. In contrast, the Aggressive Lipid Lowering Initiation Abates New Cardiac Events (ALLIANCE) study used a real-world design in which CHD patients selected from managed care and Veterans Affairs (VA) clinic databases were immediately randomized to either an aggressive or usual care approach to lipid management. The study demonstrated significant reductions in cardiovascular events with an aggressive atorvastatin treatment strategy compared with usual care.¹⁰ This post hoc analysis of the ALLIANCE study investigates whether previous findings of efficacy and safety of aggressive statin therapy in elderly patients are consistent with those in a study population designed to closely reproduce real clinical practice.

Methods

Study Design

The design of the ALLIANCE study has been described in detail previously.¹⁰ The study was conducted at 16 centers throughout the United States. Participants were limited to established hyperlipidemic CHD patients with health care insurance identified from managed health care organizations or VA facilities databases. Patients were randomized to either aggressive treatment with atorvastatin or usual care by the central laboratory between July 1995 and June 1998. Patients in the atorvastatin group were administered a titrated atorvastatin regimen to achieve an low-density lipoprotein cholesterol (LDL-C) goal of <80 mg/dL, with a maximum dose of 80 mg daily, whereas those in the usual care group continued their baseline lipid-lowering therapy with changes and laboratory analyses as directed by their treating physicians.

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committees or institutional review boards. An independent outcomes committee of 5 cardiologists reviewed and adjudicated all study outcomes. Interim monitoring of study events and serious adverse events were performed by an independent data safety monitoring committee.

Study Population

Subjects eligible for this subanalysis were 1,001 men or women aged 65–78 years at enrollment with CHD defined as a history of acute myocardial infarction (MI), coronary artery bypass graft surgery (CABG), unstable angina (all >3 mo before screening), or percutaneous transluminal coronary angioplasty (PTCA; >6 mo before screening). Inclusion LDL-C levels were between 110 mg/dL (2.8 mmol/L) and 200 mg/dL (5.2 mmol/L) for patients receiving lipid-lowering medication, and between 130 mg/dL (3.4 mmol/L) and 250 mg/dL (6.5 mmol/L) for patients receiving no lipid-regulating therapy. Baseline

laboratory measurements were obtained while subjects continued any lipid-lowering therapy they had utilized prior to randomization.

Patients randomized to atorvastatin had their current lipid-lowering therapy changed to atorvastatin 10 mg/d after baseline laboratory measurements were obtained. The atorvastatin dosage was doubled every 4 wks until an LDL-C level of <80 mg/dL (2.1 mmol/L) was achieved or a maximum dose of 80 mg daily was utilized. Combination lipid-modulating therapy was not allowed. After dose titration was completed, follow-up occurred every 6 months.

Patients randomized to usual care continued the lipid-lowering therapy that they had utilized prior to randomization with changes in therapy occurring only as directed by their treating physicians. Lipid-regulating therapy in patients in the usual care group could include atorvastatin after its approval in 1997. In an attempt to reflect real-world statin utilization and minimize any impact on prescribing or practice patterns for usual care subjects, their follow-up occurred every 6 months and was limited to endpoint assessment and adverse event documentation.

Efficacy and Safety Evaluations

The primary efficacy endpoint was the time from randomization to the first occurrence of a primary cardiovascular event, including cardiac death, nonfatal MI, resuscitated cardiac arrest, cardiac revascularization, and unstable angina requiring hospitalization. Secondary endpoints included noncardiac death, peripheral revascularization, hospitalization for congestive heart failure, and stroke. Although not defined a priori, the commonly used combined endpoint of cardiac death and nonfatal MI was also included in this analysis.

Laboratory analyses for patients in the atorvastatin group at baseline, interim visits, and study completion were performed by Pacific Biometrics (Seattle, Wash.). For usual care patients, laboratory values were measured by the central laboratory at baseline and at the end of study. All other laboratory testing for usual care patients was directed by treating physicians. Rhabdomyolysis was defined based on creatine phosphokinase >10 times the upper limit of normal in the presence of muscle symptoms.

Statistical Analyses

Intention-to-treat analyses were performed on older (65–78 years of age) and younger (<65 years of age) patients. For the primary endpoint analysis, Kaplan-Meier survival curves for the atorvastatin and usual care groups were compared using the log-rank statistic. In addition, each component of the primary endpoint and the composite endpoint of cardiac death and nonfatal MI were examined by a Cox proportional hazards model to assess treatment

differences adjusted for center. The *p* values for heterogeneity were calculated to determine any differential trends between the younger and older cohorts for each endpoint.

Results

Patient Demographics

Of 2,442 patients in the overall ALLIANCE population, 1,001 (41%) were aged 65–78 years, of whom 501 were randomized to atorvastatin and 500 to usual care. A total of 319 atorvastatin and 332 usual care patients in the older cohort completed the study. Others discontinued active study participation prior to an endpoint or 4-year of follow-up for reasons outlined in Figure 1.

Baseline demographics of the older and younger cohorts are shown in Table 1. The mean age of the older cohort was 69.6 ± 3.2 years, of whom 49% were aged 70 years or older; the younger cohort was 55.4 ± 6.3 years. The older compared to the younger cohort tended to have higher systolic blood pressures (139/77 vs 132/80 mm Hg), and a greater likelihood of previous CABG (55% vs 46%) or stroke (9% vs 5%). The younger cohort had a higher mean body weight (91.7 ± 17.8 kg vs 84.4 ± 15.1 kg), were more likely to be current smokers (25% vs 11%), more often had a family history of premature cardiac disease (23% vs 16%), and had a higher prevalence of previous MI (60% vs 55%) or PTCA (44% vs 31%).

Median follow-up of all patients aged 65–78 years was 53.9 months (mean 51.4 months, standard error = 0.55). The mean dose of atorvastatin used in the older aggressively treated group was 36.5 ± 27.4 mg daily. A total of 300 patients (59.9%) were titrated to at least 40 mg daily; 194 older atorvastatin patients (38.7%) were further titrated to 80 mg daily. Those taking 80 mg daily did so for an average of 3.4 years.

Serum Lipid Levels

The mean LDL-C level for the older cohort at baseline was 145.7 mg/dL (3.8 mmol/L) in the atorvastatin group and 144.4 mg/dL (3.7 mmol/L) in the usual care group. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were also similar at baseline (Table 1). Over the course of the trial, both the aggressively treated atorvastatin and usual care older subjects experienced significant reductions in mean LDL-C levels (least squares mean change, 35.5% vs 23.4%, respectively), achieving mean LDL-C levels at the end of the study of 91.0 mg/dL and 107.1 mg/dL, respectively (Figure 2). At the end of the study, National Cholesterol Education Program - Adult Treatment Panel (NCEP-ATP) III goals (LDL-C <100 mg/dL [2.6 mmol/L]) were achieved by more older patients in the aggressively treated atorvastatin group than those receiving usual care (71.7% vs 44.0%, $p < 0.001$).

Figure 1. Disposition of patients aged 65–78 years. *Includes protocol violation, administrative error, investigator decision, laboratory abnormality, and insufficient clinical response.

Cardiovascular Outcomes

A total of 106 patients (21.2%) in the older atorvastatin group compared with 137 patients (27.4%) in the older usual care group experienced a primary cardiovascular event, a 27% relative risk reduction (HR: 0.73; 95% CI: 0.57–0.94; $p = 0.016$; Figure 3). For the composite endpoint of cardiac death and nonfatal MI, aggressive treatment with

atorvastatin was associated with a 52% relative risk reduction in the older cohort (HR: 0.48; 95% CI: 0.32–0.72; $p = 0.001$; Figure 3). These composite endpoint risk reductions were largely attributable to a 57% nonfatal MI relative risk reduction in the atorvastatin treatment arm (HR: 0.43; 95% CI: 0.23–0.79; $p = 0.006$; Figure 3). The nonfatal MI event curves for the older atorvastatin and usual care

Table 1. Demographics and Clinical Characteristics of Patients Aged 65–78 and <65 Years*

Characteristics	Patients Aged 65–78 Years (n = 1,001)		Patients Aged <65 Years (n = 1,441)	
	Atorvastatin (n = 501)	Usual care (n = 500)	Atorvastatin (n = 716)	Usual care (n = 725)
Age, years	69.8±3.1	69.4±3.2	55.0±6.4	55.7±6.3
Age ≥ 70 years, no. (%)	262 (52.3)	225 (45.0)	0	0
Gender, no. (%)				
Male	415 (82.8)	393 (78.6)	585 (81.7)	615 (84.8)
Female	86 (17.2)	107 (21.4)	131 (18.3)	110 (15.2)
Race, no. (%)				
White/Caucasian	443 (88.4)	442 (88.4)	579 (80.9)	584 (80.6)
Black	42 (8.4)	41 (8.2)	97 (13.5)	98 (13.5)
Other	16 (3.2)	17 (3.4)	40 (5.6)	43 (5.9)
Weight, kg	84.7±15.0	84.1±15.2	91.8±18.4	91.6±17.2
CHD risk factors, no. (%)				
Family history of premature CHD	62 (12.4)	97 (19.4)	168 (23.5)	159 (21.9)
Current smoker	60 (12.0)	49 (9.8)	178 (24.9)	188 (25.9)
Diabetes	122 (22.4)	105 (21.0)	160 (22.3)	153 (21.1)
Blood pressure, mm Hg				
Systolic	138.9±18.4	138.3±19.0	130.9±17.4	132.1±17.7
Diastolic	77.1±10.2	77.2±10.1	80.2±10.7	79.7±10.1
Serum lipid levels, mg/dL				
LDL-C	145.7±25.6	144.4±25.5	147.9±26.2	149.1±26.9
HDL-C	41.4±10.8	42.4±11.5	39.5±10.7	39.7±9.8
Total cholesterol	223.3±32.0	224.0±31.3	228.1±33.6	229.1±33.0
Triglycerides	182.2±91.1	187.8±96.1	207.4±116	206.8±121
Medical history, no. (%)				
Myocardial infarction	283 (56.5)	264 (52.8)	449 (62.7)	416 (57.4)
PTCA	152 (30.3)	161 (32.2)	323 (45.1)	316 (43.6)
CABG	281 (56.1)	266 (53.2)	321 (44.8)	342 (47.2)
Unstable angina	106 (21.2)	107 (21.4)	156 (21.8)	145 (20.0)

Table 1. (Continued)

Characteristics	Patients Aged 65–78 Years (n = 1,001)		Patients Aged <65 Years (n = 1,441)	
	Atorvastatin (n = 501)	Usual care (n = 500)	Atorvastatin (n = 716)	Usual care (n = 725)
Congestive heart failure	32 (6.4)	37 (7.4)	39 (5.4)	54 (7.4)
Stroke	46 (9.2)	42 (8.4)	37 (5.2)	37 (5.1)
Peripheral revascularization	24 (4.8)	25 (5.0)	27 (3.8)	17 (2.3)
Other	82 (16.4)	75 (15.0)	107 (14.9)	100 (13.8)

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

*Data are given as means $\pm$ standard deviation unless otherwise indicated. Abbreviations: CABG, coronary artery bypass graft surgery; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PTCA, percutaneous transluminal coronary angioplasty.

Figure 2. Changes in serum lipid levels in patients aged 65–78 and <65 years. Error bars represent the standard error. * $p < 0.0001$ for atorvastatin vs usual care. † $p = 0.013$ for usual care vs atorvastatin. Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

groups separated within months and continued to diverge until the end of the study (Figure 4). Similarly, the event curves for the primary endpoint and for the combined endpoint of cardiac death and nonfatal MI in the older atorvastatin and usual care groups started to diverge at approximately 1 year and continued to do so until the end of the study (Figure 4). Aggressive treatment with atorvastatin was also associated with a 33% relative risk reduction for cardiac revascularization in patients aged 65–78 years (HR: 0.67; 95% CI: 0.48–0.93; $p = 0.017$; Figure 3). The effect of aggressive atorvastatin use on the secondary endpoints of all-cause mortality and stroke in the older cohort is shown in Figure 3.

Compared with younger patients, the older cohort tended to have greater relative risk reductions associated with aggressive treatment, and were significantly greater in

older patients for all-cause mortality and revascularization (Figure 3).

Safety

Adverse events were more common in the older than in the younger group, irrespective of their treatment assignment. However, the incidences of serious adverse events leading to discontinuation were similar between treatment arms for both the younger cohort (6.0% atorvastatin vs 6.1% usual care) and the older cohort (11.6% atorvastatin vs 12.6% usual care).

Protocol-stipulated routine laboratory testing, performed only in the atorvastatin group, demonstrated low rates of significant elevations (>3 times the upper limit of normal) of aspartate aminotransferase levels (0.4% in the younger cohort and 1.0% in the older cohort) or alanine

Figure 3. Effect of atorvastatin and usual care on primary and secondary outcomes in all patients, patients aged 65–78 years, and patients aged <65 years. **p* value for heterogeneity between the older and younger cohorts. †Endpoint not defined a priori. Abbreviations: MI, myocardial infarction.

aminotransferase levels (1.3% in the younger cohort and 1.4% in the older cohort). There were no documented cases of creatine phosphokinase >10 times the upper limit of normal in either atorvastatin age group, and no documented cases of rhabdomyolysis or myopathy in subjects in either treatment arm.

Discussion

This analysis demonstrates that aggressive atorvastatin therapy in stable CHD patients aged 65–78 years is both efficacious and safe compared with usual care. The older population treated with a structured atorvastatin strategy experienced a 27% risk reduction in the primary endpoint, and a 52% risk reduction in cardiac death and nonfatal MI, reflecting a particularly potent impact of an aggressive treatment strategy on the reduction of “hard” cardiovascular endpoints. While it is unclear whether the benefits of intensive lipid lowering is mediated by direct effects of LDL-lowering or anti-inflammatory properties of high-dose statin therapy, our findings are in support of national guidelines for a lower optional LDL-C target in high-risk patients.¹¹

The nature of events differed between younger and older patients—younger patients more likely to have coronary revascularization (19.0% vs 14.8%) and the older patients more likely to suffer a stroke (2.2% vs 4.2%) or

mortality from any cause (7.3% vs 14.3%). Though younger subjects in ALLIANCE benefited from aggressive statin therapy as demonstrated by a significant 37% relative risk reduction in cardiac death and nonfatal MI (*p* = 0.008), older atorvastatin-treated patients experienced even more robust risk reductions for the primary composite outcome, nonfatal MI, and the combination of cardiac death and nonfatal MI. These data suggest that patients aged 65–78 years benefited from the titrated atorvastatin regimen as well as or better than their younger counterparts.

These efficacy results are also noteworthy in that the achieved LDL-C level of 107 mg/dL indicates relatively good care for the usual care cohort, particularly given the time period during which the study was undertaken (1995–2002). In addition, a greater proportion of patients in the older usual care group achieved NCEP ATP III goals than would have been predicted by either the National Health and Nutrition Examination Survey (NHANES) or Lipid Treatment Assessment Project (L-TAP)¹² surveys. Thus, the outcomes realized by the older atorvastatin ALLIANCE population reflect incremental benefits provided by atorvastatin therapy over and above reasonable contemporary usual care.

Reductions in cardiovascular events attributable to aggressive lipid lowering in older patients were achieved

Figure 4. Kaplan-Meier curves for any primary outcome, nonfatal myocardial infarction (MI), and CHD death or nonfatal MI in patients aged 65–78 years. The primary efficacy endpoint was the time from randomization to the first occurrence of a primary cardiovascular event, including cardiac death, nonfatal MI, resuscitated cardiac arrest, cardiac revascularization, and unstable angina requiring hospitalization.

without an increase in the rate of significant elevations of creatine phosphokinase or liver transaminases. There were similar rates of discontinuation due to adverse events in both study arms. This observation, equal tolerance of the intensive and usual care regimens in older patients, is clinically important given that 38.7% received the maximum dose of atorvastatin 80 mg daily. These safety results are particularly impressive considering that ALLIANCE was designed to reflect actual clinical practice and did not utilize a run-in period to preselect patients most likely to tolerate higher doses of atorvastatin.

ALLIANCE supports the recent NCEP-ATP III recommendation that older patients at high risk of CVD should be treated with intensive lipid-lowering therapy.¹¹ Given the high concentration of cardiac deaths, nonfatal MI, and strokes experienced by patients aged 65–78 years, this analysis demonstrates that the risk:benefit ratio favors treating older CHD patients with intensive atorvastatin therapy. The early separation of the Kaplan-Meier curves reinforces the value of treating this population aggressively and is consistent with the early benefits previously demonstrated with atorvastatin in other patient populations.^{13–15} In addition, this analysis may also point to further potential benefits that are left on the table when older subjects are treated with less than optimal aggressiveness. Fewer than 40% of the older atorvastatin patients in ALLIANCE were titrated to 80 mg daily despite the fact that 61% of older atorvastatin subjects failed to achieve the protocol-specified LDL-C goal of 80 mg/dL. In light of the absence of a safety signal, it is reasonable to assume that more frequent use of high-dose statin therapy in the elderly would have generated an even greater benefit than that actually observed.

Conclusion

This ALLIANCE substudy demonstrates that older CHD patients compared to younger CHD patients experience no attenuation of benefit or undue safety issues when treated with an aggressive atorvastatin regimen. These data will hopefully encourage physicians to manage this high-risk population more aggressively to enhance the likelihood that older individuals can enjoy their later years free of disabling health events such as a heart attack or stroke.

Acknowledgements

The authors would like to acknowledge the assistance of Barbara LePetri, MD and Don Luo, PhD (employees of Pfizer Inc. at the time of the data analysis and manuscript preparation) in the development of this article. Editorial support was provided by Richard Hogan and Steve Dobson of Envision Pharma. Funding for the ALLIANCE study and costs attributable to this analysis and publication were provided by Pfizer Inc.

References

1. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, et al.: Heart disease and stroke statistics-2006 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2006;113:e85–e151.
2. Muntner P, Garrett E, Klag MJ, Coresh J: Trends in stroke prevalence between 1973 and 1991 in the US population 25 to 74 years of age. *Stroke*. 2002;33:1209–1213.
3. Kochanek KD, Murphy SL, Anderson RN, Scott C: Deaths: Final data for 2002. *Natl Vital Stat Rep*. 2004;53:1–115.
4. Hunt D, Young P, Simes J, Hague W, Mann S, et al.: Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: Results from the LIPID trial. *Ann Intern Med*. 2001;134:931–940.

5. Miettinen TA, Pyorala K, Olsson AG, Musliner TA, Cook TJ, et al.: Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: Findings from the Scandinavian Simvastatin Survival Study (4S). *Circulation*. 1997;96:4211–4218.
6. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, et al.: Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomised controlled trial. *Lancet*. 2002;360:1623–1630.
7. Deedwania P, Stone PH, Bairey Merz CN, Cosin-Aguilar J, Koylan N, et al.: Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: Results of the Study Assessing Goals in the Elderly (SAGE). *Circulation*. 2007;115:700–707.
8. Allen Maycock CA, Muhlestein JB, Horne BD, Carlquist JF, Bair TL, et al.: Statin therapy is associated with reduced mortality across all age groups of individuals with significant coronary disease, including very elderly patients. *J Am Coll Cardiol*. 2002;40:1777–1785.
9. Wenger NK, Lewis SJ, Herrington DM, Bittner V, Welty FK: Outcomes of using high- or low-dose atorvastatin in patients 65 years of age or older with stable coronary heart disease. *Ann Intern Med*. 2007;147:1–9.
10. Koren MJ, Hunninghake DB: Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: The ALLIANCE study. *J Am Coll Cardiol*. 2004;44:1772–1779.
11. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, et al.: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227–239.
12. Pearson TA, Laurora I, Chu H, Kafonek S: The lipid treatment assessment project (L-TAP): A multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med*. 2000;160:459–467.
13. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, et al.: Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): A multicentre randomised controlled trial. *Lancet*. 2003;361:1149–1158.
14. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, et al.: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685–696.
15. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, et al.: Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504.