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Coronary Artery Disease

Statin Use in Patients With Extremely Low Low-Density Lipoprotein Levels Is Associated With Improved Survival

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Background—Aggressive lipid management has recently become the standard of care for patients with coronary heart disease. The safety and effectiveness of statin usage for patients with extremely low low-density lipoprotein (LDL) levels are less clear, however. The aim of this study was to investigate the safety and clinical outcomes of statin treatment in patients with LDL cholesterol levels below 60 mg/dL.

Methods and Results—A total of 6107 consecutive patients with LDL levels less than 60 mg/dL were identified from a tertiary care medical center or affiliated community clinic. Statin therapy was defined as a prescription during the 150 days after the low LDL value was obtained. The propensity to be treated with a statin was used to adjust the association of statin therapy and survival. A total of 4295 patients (70%) had at least 1 prescription for any medication during the 150-day observation period after the low LDL value. Their mean age was 65 years, 43% had prior ischemic heart disease, and 47% had diabetes mellitus. Statins were prescribed in 2564 patients (60%) after the low LDL value was observed. During a mean follow-up of 2.0 ± 1.4 years after the observation period, there were 510 deaths. After controlling for the propensity to receive a statin, statin therapy was associated with improved survival (hazard ratio [HR], 0.65; 95% CI, 0.53 to 0.80). This lower mortality was also observed for subgroups of patients already taking statins at baseline (HR, 0.58; 95% CI, 0.38 to 0.88), those with extremely low LDL levels (<40 mg/dL, n=623; HR, 0.51; 95% CI, 0.33 to 0.79), and those without a history of ischemic heart disease (n=2438; HR, 0.58; 95% CI, 0.42 to 0.80). Statin use was not associated with an increase in malignancy, transaminase elevation, or rhabdomyolysis.

Conclusions—Statin therapy in the setting of a very low LDL level appears to be safe and is associated with improved survival. (***Circulation***. 2007;116:613-618.)

Key Words: statins ■ lipids ■ stroke ■ morbidity ■ mortality

An extensive body of evidence now supports the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in patients with significant cardiac risk factors or known coronary artery disease. Recently, research has focused on identifying the optimal level to which lipids should be reduced. In a large meta-analysis, a near-linear relationship between cholesterol reduction and improvement in cardiovascular outcomes was described for cholesterol levels from 73.1 to 150.4 mg/dL.[1] Post–acute coronary syndrome patients were found to benefit from an aggressive statin regimen in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) study, as were patients with stable atherosclerotic vascular disease in the Treating to New Targets (TNT) study, both with calculated low-density lipoprotein (LDL) goals of 70 mg/dL or less (actual mean LDL achieved: 65 to 77 mg/dL).[2,3]

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These studies have led to a recent paradigm shift in lipid management, and many clinicians have adopted a more aggressive treatment strategy. Although the safety profile of high-dose statin use appears acceptable preliminarily,[4–6] an association between very low cholesterol levels and adverse outcomes such as noncardiac mortality and malignancy has also been reported.[7–9] In addition, aggressive therapy frequently results in LDL reductions well below the new goal of 70 mg/dL, and the long-term safety of statin usage in these patients remains unclear. It was our aim to investigate the safety and clinical outcomes associated with statin therapy in patients with very low LDL levels (below 60 mg/dL).

Methods

Study Population

We identified 6107 consecutive patients seen at the Palo Alto VA Medical Center in Palo Alto, Calif, or 1 of 7 affiliated community clinics between 1998 and 2004 with LDL cholesterol levels below 60 mg/dL. For patients with more than 1 LDL cholesterol value below 60 mg/dL, we used the earliest value to determine the index date. To limit the cohort to patients with follow-up with the VA Palo Alto Health Care System, patients were excluded if they had no prescriptions during the 150 days after the low LDL cholesterol value.

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TABLE 1. Baseline Characteristics

Characteristic	Statin (n=2564)	No Statin (n=1731)	P
Age, y (SD)	67.9 (10.5)	61.4 (13.3)	<0.001
Females, n (%)	75 (4.3)	63 (2.5)	0.001
Creatinine greater than 1.5 mg/dL, n (%)	579 (23.1)	272 (16.2)	<0.001
LDL level, mg/dL (SD)	49.9 (9.3)	48.2 (10.4)	<0.001
HDL level, mg/dL (SD)	40.8 (12.4)	44.5 (19.7)	<0.001
Prior malignancy, n (%)	522 (20.4)	300 (11.9)	0.01
Ischemic heart disease, n (%)	1466 (57.2)	391 (22.6)	<0.001
Prior myocardial infarction (troponin >0.1), n (%)	104 (4.1)	134 (2.3)	0.001
Peripheral arterial disease, n (%)	119 (4.6)	50 (2.9)	0.004
Hypertension, n (%)	2185 (85.2)	1060 (61.2)	<0.001
Congestive heart failure, n (%)	463 (18)	194 (11.2)	<0.001
Diabetes, n (%)	1420 (55.4)	617 (35.6)	<0.001
Stroke, n (%)	338 (13.1)	131 (7.6)	<0.001
Chronic obstructive pulmonary disease, n (%)	689 (26.9)	477 (27.6)	0.62
Alcohol dependence, n (%)	222 (8.7)	422 (24.4)	<0.001
ACE inhibitors/ARBs, n (%)	1929 (63)	924 (30.3)	<0.001
β-Blockers, n (%)	1516 (49.5)	750 (24.6)	<0.001

HDL indicates high-density lipoprotein; ACE, angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.

Comorbid conditions were defined as present at baseline if documented with an *International Classification of Diseases,* 9th Revision, Clinical Modification (*ICD*-9-CM) code in a patient encounter during the 5 years before the index date: coronary artery disease (410–414), cerebrovascular disease (433–436), peripheral arterial disease (440–441), heart failure (428), diabetes mellitus (250), hypertension (401–405), malignancy (140–208), chronic obstructive pulmonary disease (490–496), liver disease (570–571), and alcohol dependence or abuse (303 or 305). The following laboratory abnormalities were defined as present at baseline if recorded within 12 months before the index date: troponin I > 0.1 ng/mL, creatinine >1.5 mg/dL, hemoglobin <10 g/dL, alanine aminotransferase >126 IU/L (3 times the upper limit of normal), hemoglobin A1c >7%, and triglycerides >200 mg/dL. Baseline use of statins, fibrates, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers was defined as a filled prescription within 12 months before the index date. The study was approved by the institutional review board at Stanford University.

Statin Therapy

Subsequent statin therapy was defined as any statin prescription within the 150 days after the initial low LDL laboratory value.

Outcome

Follow-up began after the 150-day observation period to determine the use of statins. The primary end point was total mortality. Secondary end points included ischemic heart disease hospitalization, congestive heart failure hospitalization, myocardial infarction, cerebrovascular accident, de novo malignancy, rhabdomyolysis, liver dysfunction, and renal failure. Mortality data were gathered from VA records and the Social Security Death Index. Subjects were followed up for a mean of 2.0±1.4 years.

Statistical Analysis

Pearson χ^2 analysis was used to evaluate categorical variables, and *t* tests were used to evaluate differences in continuous variables between those treated with and without a statin. Kaplan-Meier survival analysis for the mortality end point was performed for patients taking and not taking statin therapy.

Propensity Score

Logistic regression was used to determine the propensity to receive statin. This nonparsimonious model included all available patient characteristics, medication use, and laboratory values. Cox proportional hazards analyses were then used to evaluate the association between statin use and total mortality after adjustment for the propensity to receive a statin. Logistic regression was used to compare the association between statin use and secondary end points, with adjustment for the propensity to receive a statin. The propensity score was incorporated into these analyses both as a continuous variable and by stratified categorical quartiles. A probability value less than 0.05 was considered statistically significant. Statistical analyses were performed with STATA (College Station, Tex) version 9.0.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics

Of the 6107 subjects initially identified, 4295 (70%) survived 150 days and continued to receive care in the healthcare system (defined as at least 1 subsequent prescription for any medication). This group formed the cohort for analysis. The baseline characteristics of these subjects are shown in Table 1. They had a mean age of 65 years (±12 years); 43% had documented ischemic heart disease, 47% were diabetic, and 15% had documented heart failure. A total of 138 subjects (3.2%) were female. Prior malignancy was reported in 19% and prior stroke in 11%, and 8% had renal dysfunction. The average LDL cholesterol value was 49.3±9.8 mg/dL, and 57% were being treated with a statin at baseline. Overall, 72% (3087/4295) had coronary disease, diabetes mellitus, cerebrovascular disease, heart failure, or peripheral arterial disease.

After the index low LDL value, 2564 patients filled a prescription for a statin (59.7%). This group was notably

TABLE 2.   Clinical Outcomes

End Point	Statin (n=2564)	No Statin (n=1731)	P
Death, n (%)	258 (10.0)	252 (14.6)	<0.001
IHD event (MI or unstable angina admission), n (%)	317 (12.4)	139 (8.03)	<0.001
MI, n (%)	67 (2.61)	19 (1.1)	0.001
Heart failure hospitalization, n (%)	120 (4.7)	88 (5.1)	0.55
Cerebrovascular accident, n (%)	33 (1.3)	15 (0.9)	0.19
Creatinine >1.5 mg/dL, n (%)*	603 (26)	276 (19)	0.01
Rhabdomyolysis, n (%)	0 (0)	0 (0)	n/a
AST >3× normal, n (%)†	7 (0.3)	3 (0.2)	0.66
De novo malignancy, n (%)	23 (1.1)	19 (1.3)	0.59

IHD indicates ischemic heart disease; MI, myocardial infarction; and AST, alanine aminotransferase.

*Number with measured creatinine (2281 statin, 1424 no statin).

†Number with measured AST (2424 statin, 2425 no statin).

sicker than patients not prescribed a statin (Table 1), with significantly higher rates of ischemic heart disease, heart failure, hypertension, malignancy, diabetes mellitus, renal insufficiency, and stroke ($P<0.05$ for all conditions). Those prescribed a statin were also significantly more likely to take β-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers ($P<0.000$). Interestingly, patients with a history of alcohol abuse or dependence were significantly less likely to be prescribed a statin ($P<0.000$).

Clinical Outcomes

The mean follow-up was 2.0 ± 1.4 years, during which time 510 deaths occurred (12%). The mean LDL achieved for those taking a statin in the first year was 73.6 ± 26 mg/dL, consistent with a regression toward the mean. The combined end point of ischemic heart disease admission or death at 1 year occurred in 301 subjects (7%). There were 267 myocardial infarctions (6%) and 208 hospitalizations for heart failure (5%). There were also 48 admissions for stroke (1.1%), 271 cases of newly diagnosed renal failure (creatinine >1.5 mg/dL; 6%), 42 de novo malignancies (1.0%), and 10 subjects with new hepatic transaminase elevation greater than

3 times normal (0.2%). No rhabdomyolysis was observed at any point during follow-up.

Statin Use, LDL Levels, and Associated Clinical Outcomes

The clinical outcomes are summarized by use of statin in Table 2. Survival status according to statin use is shown in Figure 1. Unadjusted proportional hazards show that statin use was associated with a significantly lower mortality (hazard ratio [HR] 0.81, 95% CI 0.68 to 0.96). After adjustment for baseline demographics, comorbidities, medication use, and laboratory findings, the association between statin use and decreased mortality was stronger (HR, 0.65; 95% CI, 0.53 to 0.80). This association persisted both when the propensity to take a statin was considered as a continuous variable and when it was studied as a categorical value. No interaction between quartile of propensity score and actual statin use was observed ($P=0.34$). Patients taking a statin had more ischemic events and a trend toward more strokes (Figure 2). However, after adjustment for observed variables described above, a trend was noted for reduced admission for ischemic events (adjusted OR, 0.79; 95% CI, 0.60 to 1.05)
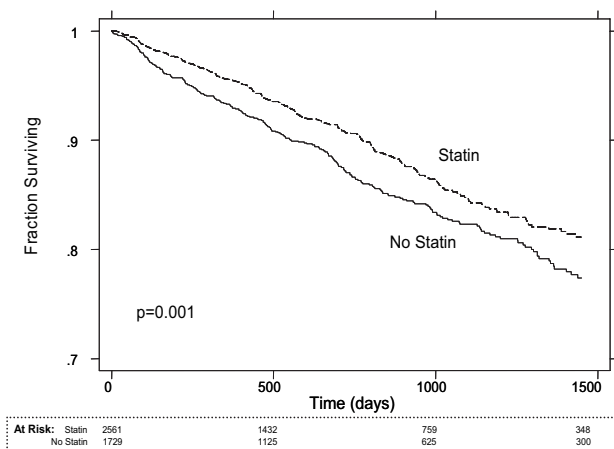

Figure 1. Kaplan-Meier survival curve. Statin use in subjects with very low LDL levels is associated with significantly improved survival at 4.1 years.
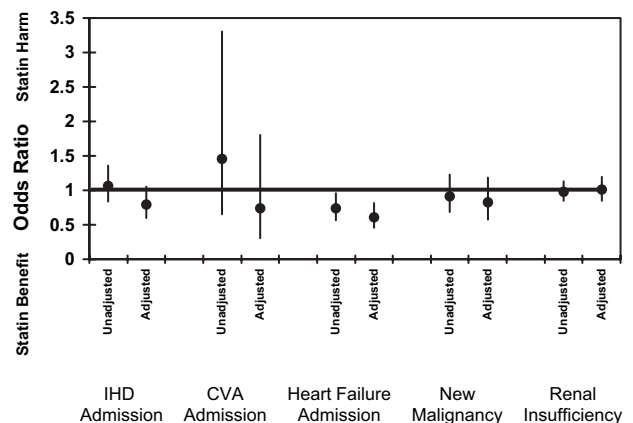

Figure 2. Secondary end points. Statin use is not associated with any harm and was associated with reduced congestive heart failure admissions. These findings were strengthened after adjustment for the propensity to receive statin therapy. IHD indicates ischemic heart disease; CVA, cerebrovascular accident.
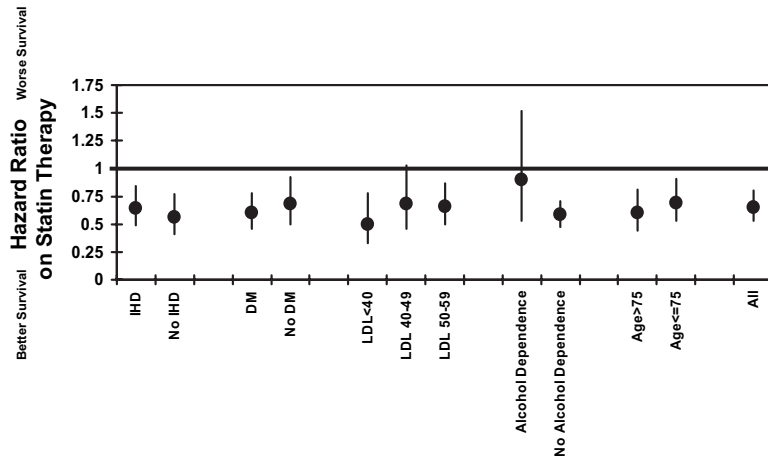
Figure 3. Subgroup analysis. Statin use is associated with an adjusted survival benefit across several subgroups. IHD indicates ischemic heart disease; DM, diabetes mellitus.

and stroke (OR, 0.74; 95% CI, 0.30 to 1.80), and a significant decrease in heart failure admissions was observed (OR, 0.61; 95% CI, 0.46 to 0.82). Statins were not associated with renal dysfunction or new malignancy.

Subgroup analysis found that statin use in these subjects was associated with a significant survival benefit in the elderly (age >75 years; mortality HR, 0.62; 95% CI, 0.46 to 0.85), those with diabetes mellitus (mortality HR, 0.58; 95% CI, 0.44 to 0.76), and those with ischemic heart disease (mortality HR, 0.66; 95% CI, 0.51 to 0.87; Figure 3). It is important to note that this protective association even extended to patients without a history of ischemic heart disease (mortality HR, 0.58; 95% CI, 0.42 to 0.80). Furthermore, there was no evidence of harm when a statin was prescribed to subjects with alcohol dependence and low LDL values (mortality HR, 0.91; 95% CI, 0.54 to 1.56). Patients treated with a statin at baseline had better survival if their statin use was continued (mortality HR, 0.58; 95% CI, 0.38 to 0.88). Although not significant, even the 295 subjects with LDL values below 60 mg/dL who were not taking a statin at baseline demonstrated a trend toward better survival when a statin was added to their medical regimen (mortality HR, 0.79; 95% CI, 0.54 to 1.17).

The survival benefit associated with statins also extended across all LDL levels. When considered by descending absolute LDL value (Figure 4), those taking statin therapy had improved mortality rates. Even subjects with extraordinarily low LDL values (ie, <40 mg/dL), who otherwise had the worst survival rates, were found to live significantly longer when prescribed a statin. This cohort derived the greatest absolute mortality benefit from therapy of any subgroup studied (unadjusted mortality rate 12.0% versus 20.6%, *P*=0.004; adjusted mortality HR, 0.51; 95% CI, 0.33 to 0.79).

Statin therapy was not associated with an increase in any adverse event in the present study. No cases of rhabdomyolysis were found for those undergoing statin therapy, nor was there a difference in the risk of developing hepatic transaminase elevation (0.32% versus 0.23%, *P*=0.66). As noted above, statin usage was not associated with an increase in de novo malignancy or renal insufficiency (Figure 2).

Discussion

Aggressive statin therapy has rapidly become the standard of care for patients with heart disease and recent myocardial infarctions. As a result of several recent trials demonstrating the incremental benefit of progressively lower lipid levels, the National Cholesterol Education Program amended its treatment guidelines in 2004 by offering an optional, more aggressive LDL goal of 70 mg/dL for patients believed to be at very high risk of atherosclerotic heart disease.[10] In a pooled analysis of 4 large randomized trials of intensive versus standard statin therapy, however, the mean LDL achieved was only 75 mg/dL (range 65 to 81 mg/dL), and the effect of achieving significantly lower values has not been described prospectively.[11] These studies have all included subjects with clear cardiovascular disease or recent acute coronary syndromes, whereas patients without documented coronary artery disease have been omitted. Furthermore, although a clear cardiovascular benefit can be attributed to statin therapy, total mortality is not clearly reduced by aggressive lipid management, and a trend toward increased noncardiovascular mortality was described in the TNT trial.[3] By extension, it is possible that an even more aggressive statin regimen might be associated with significantly more noncardiac death.
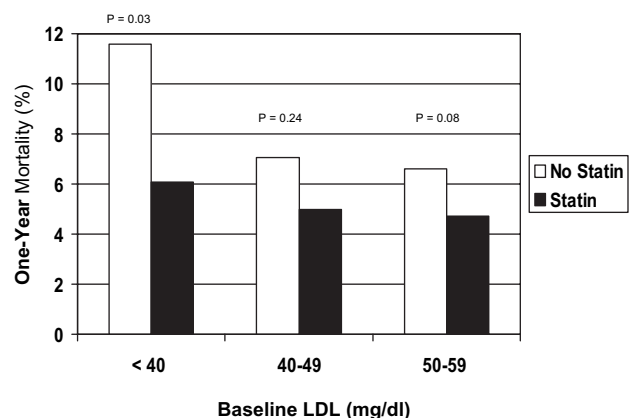

Figure 4. Mortality rates by LDL value. Statin use is associated with improved survival in subjects with LDL values below 40 mg/dL. Number of subjects by LDL level: <40 mg/dL: 247 taking a statin, 242 not on a statin; 40 to 49 mg/dL: 382 taking a statin, 355 not taking a statin; and 50 to 59 mg/dL: 1105 taking a statin, 772 not taking a statin.

Physicians are increasingly using higher starting doses of statin therapy as opposed to the previous escalating-dose paradigm[12] and frequently encounter patients with lipid levels far below the new LDL target of 70 mg/dL. Management of this cohort and the long-term implications of continued statin therapy have not been clearly defined. Thus, the safety and efficacy of antilipid therapy in patients with extremely low LDL levels, its effect on overall mortality, and its utility in those without coronary artery disease are of interest. The results of the present study suggest that statin therapy can safely be prescribed to subjects with very low LDL levels (<60 mg/dL) and that treatment is associated with a survival benefit even when the LDL level is below 40 mg/dL. Similarly, statin therapy was both safe and associated with improved mortality for patients without documented coronary artery disease.

Because those patients taking a statin comprised a notably sicker cohort, it is not surprising that the protective association with a statin became more robust after we controlled for the propensity to take a statin. This trend of greater statin benefit with adjustment suggests that the association would be even stronger if perfect adjustment for covariates were possible.

Lower rates of death with a statin occurred without an increase in observed rhabdomyolysis, hepatic dysfunction, malignancy, or stroke, all of which have previously been reported to occur more frequently in subjects with such low cholesterol levels. Rates of heart failure admission were significantly reduced for those taking a statin, and a trend toward lower stroke admissions was found as well. The cohort of patients with LDL values below 40 mg/dL not taking antilipid therapy had the worst long-term prognosis, but prescription of a statin to this group was associated with the greatest improvement in survival observed in the present study. Alcoholics, who may have low cholesterol levels due to malnutrition, appear to be unaffected by statin use, although few subjects with alcohol dependence were included. No subgroup in the present study derived harm from prescription of a statin.

A recent post hoc analysis of the PROVE IT-TIMI 22 trial also reported a favorable safety profile for a subgroup of patients who achieved an LDL level below 60 mg/dL while undergoing intensive statin therapy.[6] Although they reported a trend toward a reduction in cardiac events for progressively lower cholesterol levels achieved, they did not find a significant difference in their primary end point with greater LDL reductions. The results of the present study complement their findings by confirming the low incidence of side effects at very low LDL levels and demonstrating a significant association between overall mortality benefit and statin usage for patients with LDL levels below 60 mg/dL. Furthermore, this difference was noted in a more representative older cohort of consecutive patients both with and without documented ischemic heart disease.

The mechanism by which therapy improves survival in patients with very low cholesterol levels is unclear. Although continued plaque stabilization and prevention of atheroma development are possible, other unmeasured effects of the drug may be responsible for the present findings. [13,14] Further

in vivo and prospective studies are warranted to investigate the mechanism of benefit.

Study Limitations

The present study was an observational study designed primarily to evaluate associations between statin use in patients with very low cholesterol levels and clinical outcomes. Because the trial was not randomized, unmeasured clinical factors may have affected the physician's decision to prescribe or not prescribe the drug. For example, statin therapy may have been withheld from sicker patients and therefore would have artificially inflated the protective effects ascribed to the statin therapy. Nevertheless, our propensity score adjustment argues against this scenario in that the adjustment for all observable covariates increased the beneficial effect of statins. Additionally, effects of fibrate and bile acid sequestration agents were not investigated, and the present results only apply to statin therapy. Specific drugs were not studied individually, and additional investigation is indicated to confirm a class effect, especially given the divergent potency and high-density lipoprotein effects of various statin drugs.[15] With the exception of mortality and renal failure, adverse outcomes were uncommon, and the present study had little power to detect differences between therapy groups. The study consisted predominantly of male patients, and the results are not necessarily applicable to women. Finally, hospitalizations that occurred outside the healthcare system could not be captured; however, this was not true for the primary outcome of death, which was evaluated with the Social Security Death Index.

The strengths of the study include the evaluation of a population not previously evaluated, ie, those with LDL <60 mg/dL. Furthermore, we evaluated all patients during the study time period. Thus, the present cohort included many patients who would not have been enrolled in randomized trials, including the very elderly and those with severe comorbidities.

In summary, statin use in patients with very low LDL levels (<60 mg/dL) appears to be safe and is associated with significantly improved survival. The survival benefit was consistent across multiple subgroups, including those with LDL values below 40 mg/dL and even those without documented coronary artery disease. The results herein extend the benefit with intensive statin therapy observed in recent randomized trials and suggest that even lower LDL goals may additionally prolong life. Prospective randomized studies should be performed in patients with very low LDL values to confirm these findings.

Disclosures

None.

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CLINICAL PERSPECTIVE

Several recent clinical trials have led to a dramatic paradigm shift in the field of lipid management. Studies such as Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) and Treating to New Targets (TNT) have led clinicians to employ a much more aggressive approach to statin therapy in the cardiovascular patient. What is not clear, however, is the long-term safety and efficacy of this approach in the patient with extremely low cholesterol levels. Herein, we investigated the outcomes of patients undergoing statin therapy who had low-density lipoprotein values below 60 mg/dL. We found that therapy is not associated with any adverse outcome and is actually associated with significantly improved survival. This beneficial association was also noted for patients without documented coronary artery disease. Remarkably, statin use was associated with improved outcomes at all levels of low-density lipoprotein, even in subjects with values below 40 mg/dL. Although these findings were retrospective in nature and confirmatory studies are required, this report suggests that statins can safely be used in patients with extremely low low-density lipoprotein levels and may lead to improved survival.