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Statin Therapy Is Associated With Reduced Mortality Across All Age Groups of Individuals With Significant Coronary Disease, Including Very Elderly Patients

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OBJECTIVES This study evaluated the effect of statin therapy on mortality in individuals with significant coronary artery disease (CAD) stratified by age.

BACKGROUND Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) significantly reduce morbidity and mortality in individuals with CAD. Unfortunately, the large statin trials excluded individuals over 80 years old, and it is therefore unknown whether very elderly individuals benefit from statins as do younger individuals.

METHODS A cohort of 7,220 individuals with angiographically defined significant CAD (≥70%) was included. Statin prescription was determined at hospital discharge. Patients were followed up for 3.3 ± 1.8 years (maximum 6.8). Patients were grouped by age (<65, 65 to 79, and ≥80 years) to determine whether statin therapy reduced mortality in an age-dependent manner.

RESULTS Average age was 65 ± 12 years; 74% were male; and 31% had a postmyocardial infarction status. Overall mortality was 16%. Elderly patients were significantly less likely to receive statins than younger patients (≥80 years: 19.8%; 65 to 79 years: 21.1%; <65 years: 28.0%; $p < 0.001$). Mortality was decreased among statin recipients in all age groups: ≥80 years: 29.5% among patients not taking a statin versus 8.5% of those taking a statin (adjusted hazard ratio [HR] 0.50, $p = 0.036$); 65 to 79 years: 18.7% vs. 6.0% (HR 0.56, $p < 0.001$); and <65 years: 8.9% vs. 3.1% (HR 0.70, $p = 0.097$).

CONCLUSIONS Statin therapy is associated with reduced mortality in all age groups of individuals with significant CAD, including very elderly individuals. Although older patients were less likely to receive statin therapy, they received a greater absolute risk reduction than younger individuals. More aggressive statin use after CAD diagnosis may be indicated, even in older patients. (J Am Coll Cardiol 2002;40:1777–85) © 2002 by the American College of Cardiology Foundation

Although individuals of all ages are affected by coronary artery disease (CAD), most new coronary events occur in older persons, and about 85% of people who die from CAD are age 65 or older (1). A variety of landmark clinical trials have demonstrated the ability of hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) therapy to significantly decrease myocardial infarction (MI), stroke, and cardiovascular mortality among patients with CAD (2–4). Likewise, it has since been demonstrated that the application of these trial findings to clinical practice can result in significant reductions in death and MI in a wide range of patients with CAD (5).

However, despite this extensive evidence of a clinical benefit of statin therapy, derived from studies of tens of thousands of patients with CAD, the question still remains of whether statins benefit elderly patients. This is largely due to the historical exclusion of older individuals from major lipid trials. For the most part, major lipid trials have excluded older patients, with only those younger than 75 years of age included in the Cholesterol And Recurrent Events (CARE) study and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study (<70 years in the Scandinavian Simvastatin Survival Study [4S]) (2–4) and those younger than 80 years of age included in the Heart Protection Study (6). In addition, subgroup analyses highlighting the efficacy of statins in older subpopulations have only recently been published (7–9), but these still did not include patients older than 75 years of age.

Studies demonstrating differences in the relationship between cholesterol and risk between younger and older individuals have further justified the question of statin therapy efficacy among elderly individuals. For instance, clinical studies have not been able to show a direct relationship between mortality and elevated cholesterol in elderly individuals (2,10), even though demonstrations of such a correlation have been made in pooled data of a broad age range of subjects (11). Most recently, the Honolulu Heart Study demonstrated that it was actually those with low cholesterol who had a significant association with mortality (12), clearly opposite of the results from studies of the

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Abbreviations and Acronyms

CABG	= coronary artery bypass graft surgery
CAD	= coronary artery disease
CHF	= congestive heart failure
CI	= confidence interval
CK-MB	= creatine kinase-MB fraction
HR	= hazard ratio
MI	= myocardial infarction
PCI	= percutaneous coronary intervention

relationship between cholesterol and mortality in younger individuals.

As a result, statins continue to be less utilized in older patients with CAD. Observational results cite utilization rates in elderly individuals that lag well behind the statin prescription rates in younger individuals (13). A significant percentage of patients with CAD are older than 80 years of age (1); therefore, it is important to determine whether statin therapy is warranted in this group of patients.

METHODS

Study objectives. The objective of this study was to determine the effect of statin therapy on mortality in three age groups of patients with angiographically defined significant CAD: <65, 65 to 79, and ≥80 years.

Study population. The study consisted of a cohort of 7,220 patients who were found to have angiographically defined significant CAD (≥70% stenosis in at least one major coronary vessel). Study participants were selected among a consecutive cohort of 13,529 patients who had been admitted with symptoms or clinical findings suggestive of CAD and underwent coronary arteriography between October 1993 and December 1999 at the LDS Hospital (Salt Lake City, Utah) (14). Subjects were of unrestricted age and gender who gave written, informed consent for blood to be drawn at angiography for use in confidential blood bank studies approved by the hospital's institutional review board and who survived the hospital period. Patients were stratified into three age categories: <65, 65 to 79, and ≥80 years. Age categories were chosen to coincide with cut-points from previous clinical trials.

Clinical variables. Patient information was entered into a computerized database, as previously described (15). These data included age, gender, hyperlipidemia, hypertension, smoking, family history of coronary heart disease, renal failure, diabetes, congestive heart failure (CHF), previous MI, previous stroke, presenting diagnosis, number of diseased vessels, and type of treatment. Hyperlipidemia was reported by the physician and determined by a serum cholesterol value >240 mg/dl (6.2 mmol/l) or current antihyperlipidemic treatment. Hypertension was reported by the physician and defined as a history of systolic blood pressure >160 mm Hg, a diastolic blood pressure >90 mm Hg, or use of antihypertensive therapy. Tobacco use was considered present in subjects who were active smokers or who had a smoking history of >10 pack-years. Family history was considered positive if a first-order relative had a cardiovascular death, MI, or coronary revascularization before age 65 years. Renal failure was considered present if reported by the physician or if the serum creatinine level was >2.0 mg/dl. Diabetes was determined by the presence of a diagnosis, fasting blood glucose >126 mg/dl, or use of antidiabetic medication. Congestive heart failure was determined by the physician report and by linking International Classification of Diseases (ICD-9) codes in the patient's medical record. Previous stroke was determined by linking ICD-9 codes in the patient's medical record. Previous MI was reported by the physician at the time of angiography. The clinical presentation at index hospitalization was categorized as stable angina (stable exertional symptoms only), unstable angina (progressive symptoms or symptoms at rest), or MI (creatine kinase-MB fraction [CK-MB] >6 mg/dl and CK-MB index >3%). For initial management, patients were stratified into those receiving, during the initial hospital period, either coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PCI), or medical therapy alone. Prescription of beta-blocker, angiotensin-converting enzyme inhibitor, and statin therapy was determined at hospital discharge. Assessment of CAD was made by a review of the coronary angiogram by the patient's cardiologist, and the number of diseased vessels was determined from this review. All data were entered into the catheterization laboratory database in a format modified after the Coronary Artery Surgery Study protocol (16).

Follow-up and determination of outcomes. Patients were followed to determine the incidence of all-cause mortality; their mean follow-up was 3.3 ± 1.8 years (maximum 6.8). Death was determined from the Social Security death registry, death certificates, and/or telephone interviews with a family member. Essentially, 100% follow-up was attained by these methods.

Statistical analysis. The chi-square test was used for categorical variables, and Student *t* test for continuous variables, to estimate the univariate association of each variable to mortality. The chi-square test, Fisher exact test, or *t* testing was used, as appropriate, to compare co-variates with statin status in each of the age groups. Graphical estimation of age group–specific survival based on statin status was performed by Kaplan-Meier methods.

Univariate and multivariate statistics for statin status were determined using Cox proportional hazards regression (SPSS version 10.0), and potential confounding of statin therapy was determined by inclusion of individual co-variates in bivariate and multivariate analyses. Age-specific models of the mortality risk associated with statin use were built for each age stratum, with adjustment for the co-

Table 1. Baseline Characteristics of the Three Age-Stratified Groups

Characteristic	Age <65 Years		Age 65–79 Years		Age ≥80 Years	
	No Statin	Statin	No Statin	Statin	No Statin	Statin
Statin prescription	72.0%	28.0%	78.9%	21.1%	80.2%	19.8%
Demographics						
Age (yrs)	54.4 ± 7.3	53.6 ± 7.3*	71.8 ± 4.2	71.7 ± 4.1	82.9 ± 2.9	83.3 ± 3.2
Gender (female)	19%	19%	28%	30%	39%	54%*
Cardiac risk factors						
Diabetes	16%	8%†	16%	9%†	11%	5%‡
Family history	36%	47%†	31%	42%†	22%	33%*
Hypertension	51%	52%	57%	68%†	58%	72%*
Hyperlipidemia	51%	71%†	44%	74%†	35%	65%†
Smoking	37%	37%	19%	22%	12%	7%
Renal failure	2.2%	0.4%†	1.0%	1.9%	2.7%	0.8%
CHF	8%	6%	15%	10%†	21%	12%‡
Stroke history	1.3%	1.1%	2.0%	2.4%	3.4%	12.3%†
MI history	23.9%	26.8%	23.1%	25.3%	18.7%	30.0%*
Presentation						
Stable angina	45%	32%	52%	38%	49%	25%
Unstable angina	22%	23%	24%	30%	21%	29%
Acute MI	32%	46%†	24%	33%‡	30%	47%†
Coronary anatomy						
One vessel	46%	51%	34%	36%	29%	28%
Two vessels	27%	27%	27%	26%	27%	36%
Three vessels	27%	23%*	39%	38%	45%	36%
Treatment type						
Medical only	36%	20%	41%	30%	48%	29%
PCI	41%	65%	30%	50%	31%	61%
CABG	24%	15%‡	29%	20%	21%	11%
Concomitant medications						
ACE inhibitor	35.4%	75.0%†	38.4%	75.7%†	45.3%	81.4%†
Beta-blocker	22.0%	58.5%†	20.2%	53.0%†	23.3%	59.7%†

Statistical comparisons are within the age group for statin versus no statin. For presentation of CAD, coronary anatomy, and treatment type, p values are shown for the trend across the three categories. *$p < 0.01$; †$p < 0.001$; ‡$p < 0.05$.

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; MI = myocardial infarction; PCI = percutaneous coronary intervention.

variates noted earlier. Models were built using conditional, stepwise regression and were refined, using forced entry of co-variates to build the final models. An additional analysis was performed with multivariate Cox regression of the overall population to evaluate any interaction between statin therapy and age on mortality. Two-tailed p values are presented, and the threshold for significance was $p < 0.05$.

RESULTS

Patient characteristics. Of the 7,220 patients included in this study, 45% (n = 3,256) were <65 years old, 46% (n = 3,309) were 65 to 79 years old, and 9% (n = 655) were 80 or older. Ages ranged from 19 to 97 years. Table 1 summarizes the baseline patient characteristics for each age category based on statin status. Overall, the patients' average age was 65 ± 12 years; 75% (n = 5,399) were male, and 25% (n = 1,821) were female. Thirty-one percent (n = 2,256) had a post-MI status.

Statin therapy. Statins were prescribed to 24.1% (n = 1,741) of study patients at discharge from the index hospitalization. Table 1 shows the proportion of patients discharged on statins by age category. In each of the three age groups, individuals with a history of hyperlipidemia were more likely to receive a statin, and those with diabetes or CHF were less likely to receive a statin. Among individuals ≥80 years old, those with a previous MI or stroke were more likely to receive statin therapy. In general, statin therapy was more often prescribed in younger patients and decreased in older groups ($p < 0.001$). Statin prescription rates changed little with age for those <65 years old; however, after an individual reached 65 years of age, there was an abrupt drop-off in the percentage of those receiving statin therapy.

Clinical follow-up. In analysis by age groups, the effect of statin therapy was not diminished by age. All-cause mortality was significantly reduced in each age group in those receiving statin therapy, compared with those not receiving statin therapy, and the absolute benefit from statin therapy was greatest for the very old (Fig. 1). Death rates were

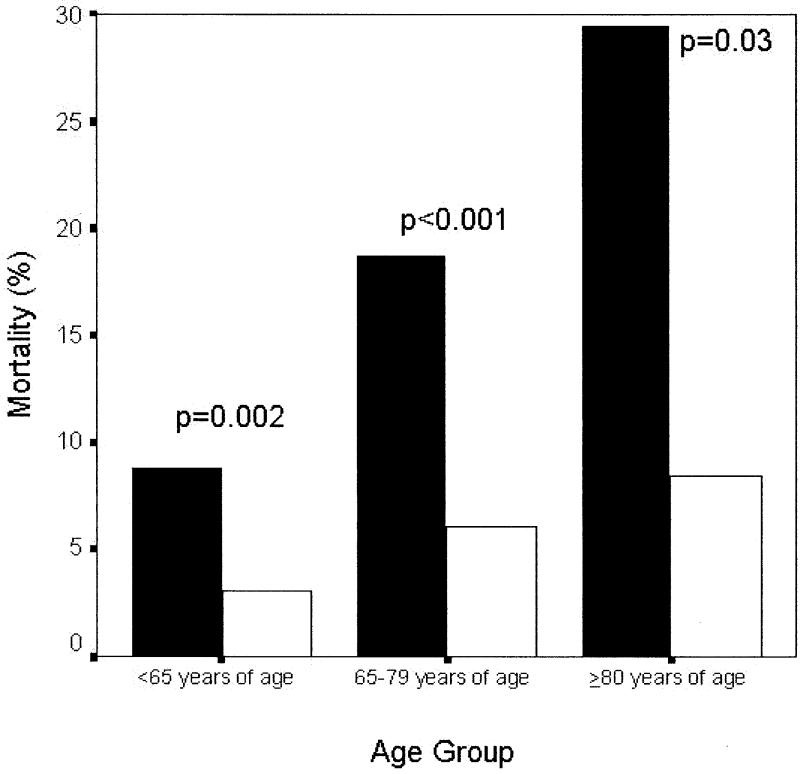

Figure 1. Bar graph of mortality for patients using statins **(open bars)** and not using statins **(solid bars)** by age groups.

reduced by absolute amounts of 5.8%, 12.7%, and 21.0% in individuals <65 years, 65 to 79 years, and ≥80 years, respectively. Univariate Kaplan-Meier survival curves are shown in Figure 2. In univariate Cox regression entering only statin status, all three age groups showed significant benefit from statins. Hazard ratios (HRs) from univariate survival analyses are summarized in Table 2 (age <65 years: HR 0.52, 95% confidence interval [CI] 0.35 to 0.79; age 65 to 79 years: HR 0.53, CI 0.38 to 0.73; age >80 years: HR 0.49, CI 0.26 to 0.93).

Survival analysis and multivariate adjustment. In multivariate Cox regression analysis controlling for demographic data, risk factors, and clinical variables, statins retained a clinically profound benefit regardless of age group. Kaplan-Meier survival curves based on statin status in each age group are shown in Figure 3, along with the adjusted hazard ratio estimates and p values for statins.

In Cox regression among patients <65 years of age, statins had a 30% adjusted risk reduction (HR 0.70, CI 0.46 to 1.07, p = 0.097). This reduction, however, was not statistically significant in the final regression model, which included statin therapy, diabetes, renal failure, beta-blocker therapy, age, male gender, hypertension, CHF, coronary anatomy, and treatment type (PCI or CABG) (Table 2).

Cox regression among patients 65 to 79 years of age showed that statins reduced the adjusted risk of death by 44% (HR 0.56, CI 0.41 to 0.77, p < 0.001). As mentioned earlier, diabetes reduced the significance of statins, but renal failure did not. Other variables included in the final regression model included age, hypertension, CHF, coronary anatomy, type of treatment, presentation (unstable angina MI), previous stroke, and smoking (Table 2).

Among patients age 80 years or older, statins remained a statistically significant and clinically important protective factor in preventing death. Statins reduced the risk of mortality by more than 50% in this age group (HR 0.50, CI 0.26 to 0.96, p = 0.036). This risk estimate was essentially unchanged by controlling for other co-variates, and the effect of statins in this very elderly age group remained greater than the risk estimates in the younger two groups. Other co-variates that were contained in the final regression model for the 80-and-over age group included age, renal failure, CHF, coronary anatomy, and smoking (Table 2).

Interestingly, in the older two age groups, smoking was predictive of mortality among these patients with developed CAD but was not predictive in the younger group. In the oldest age group, a history of diabetes did not predict increase in the risk of death, and male gender, hypertension, and treatment type were no longer protective.

Analysis of the full population for an interaction between statins and age showed that, in a model entering the main

Table 2. Final Multiple Variable Cox Regression Model Showing the Independent Protective Effect of Statins

Risk Factor	Hazard Ratio (CI)
<65 years old	
Statins	0.70 (0.46–1.07)
CHF	3.3 (2.5–4.5)
Renal failure	4.2 (2.5–6.8)
Diabetes	2.2 (1.6–3.0)
CABG	0.53 (0.37–0.76)
Coronary anatomy (per vessel)	1.3 (1.1–1.6)
Age (per decade)	1.34 (1.09–1.61)
Beta-blocker	0.54 (0.34–0.86)
PCI	0.73 (0.53–0.99)
Gender (male)	0.75 (0.55–1.01)
Hypertension	0.77 (0.57–1.0)
65–79 years old	
Statins	0.56 (0.41–0.77)
Age (per decade)	2.0 (1.6–2.5)
CABG	0.62 (0.53–0.72)
CHF	2.6 (2.2–3.1)
Coronary anatomy (per vessel)	1.3 (1.1–1.4)
Diabetes	1.9 (1.5–2.3)
Renal failure	3.3 (2.1–5.3)
Previous stroke	2.5 (1.5–4.0)
PCI	0.81 (0.72–0.90)
Smoking	1.5 (1.2–1.8)
Hypertension	0.78 (0.65–0.93)
Acute MI	1.25 (1.13–1.39)
Unstable angina	1.1 (1.01–1.2)
≥80 years old	
Statins	0.50 (0.26–0.96)
Age (per decade)	2.6 (1.6–4.3)
CHF	2.4 (1.7–3.4)
Smoking	1.8 (1.1–2.7)
Coronary anatomy (per vessel)	1.2 (0.98–1.4)

For each age group, statins are listed first, followed by co-variates according to the level of significance.
CI = 95% confidence interval; other abbreviations as in Table 1.

effects variables and the interaction variable, the interaction was not significant ($p = 0.72$ for interaction).

DISCUSSION

The key finding of our study is that all age groups of patients with CAD, even very elderly patients, receive a clinical benefit from statin therapy. Relative risk reductions in mortality reached 50% for those ≥80 years, compared with 44% and 30% for individuals 65 to 79 years old and those <65 years old, respectively, even after adjusting for various potentially confounding factors. The proportionate mortality risk was similarly reduced by statins in all age groups, as evidenced by a nonsignificant interaction term between statin usage and age.

Study results demonstrating a survival benefit for elderly patients with CAD receiving statin therapy may seem to contradict the findings of the Honolulu Heart Study (12). In that cohort of elderly Japanese-American men (ages 71 to 93 years), low total cholesterol levels were correlated with an increased risk of all-cause mortality, and reducing cholesterol to low concentrations in elderly patients was questioned. However, no direct evaluation was made regarding cholesterol-lowering therapy itself.

Our study shows that among elderly patients with CAD, a strong association does exist between statin therapy and mortality benefit. In fact, because more events occurred in older patients, the absolute benefit from statin therapy was actually greatest among the very elderly participants. Our results are similar to results from previous studies also demonstrating an increased absolute benefit for elderly patients despite similar proportionate risk reductions for all ages. For example, both the CARE and LIPID subanalyses demonstrated an increased clinical benefit from statin therapy among older patients (8,9). However, compared with our study, which included patients up to 97 years of age, no individuals older than 75 years of age were included in these randomized trials.

Like previous reports on the underutilization of statins in elderly patients (13), older patients were also significantly less likely to receive a statin than younger individuals in this study cohort. Although the overall rate of statin prescription at hospital discharge in this study, which was initiated before publication of the earliest statin trials (2), was quite low, it was especially low in elderly patients and decreased abruptly after 65 years of age. This is an important area of focus, as elderly patients comprise a significant proportion of patients with CAD and may potentially derive the greatest benefit from statin therapy.

In addition to the positive effect of statin therapy on all-cause mortality demonstrated in this study and others, previous randomized trials have shown an association between statin therapy and reductions in a variety of other end points, including stroke and CHF, which are prevalent among older individuals. In the 4S trial, which excluded individuals with CHF at enrollment, statin therapy was associated with a decreased incidence of heart failure (17). Among patients 65 to 75 years old who were enrolled in the CARE trial, a trend toward reduced CHF was observed among those receiving statin therapy (9). An association between statin therapy and reduced stroke rates has also been shown, both among patients with CAD (18) and among those at risk of CAD (19). Because stroke and CHF rates nearly double for each successive age decade (1), this observation reinforces the contention that the potentially greatest public health impact of statin therapy may be among very elderly individuals.

Study limitations. Our study has several limitations. First, because our study is observational, there may be uncontrolled confounding factors. Despite statistical adjustments to decrease any effect due to confounders, unmeasured differences in the study groups may persist. Next, cause-specific mortality was not available, and we were unable to

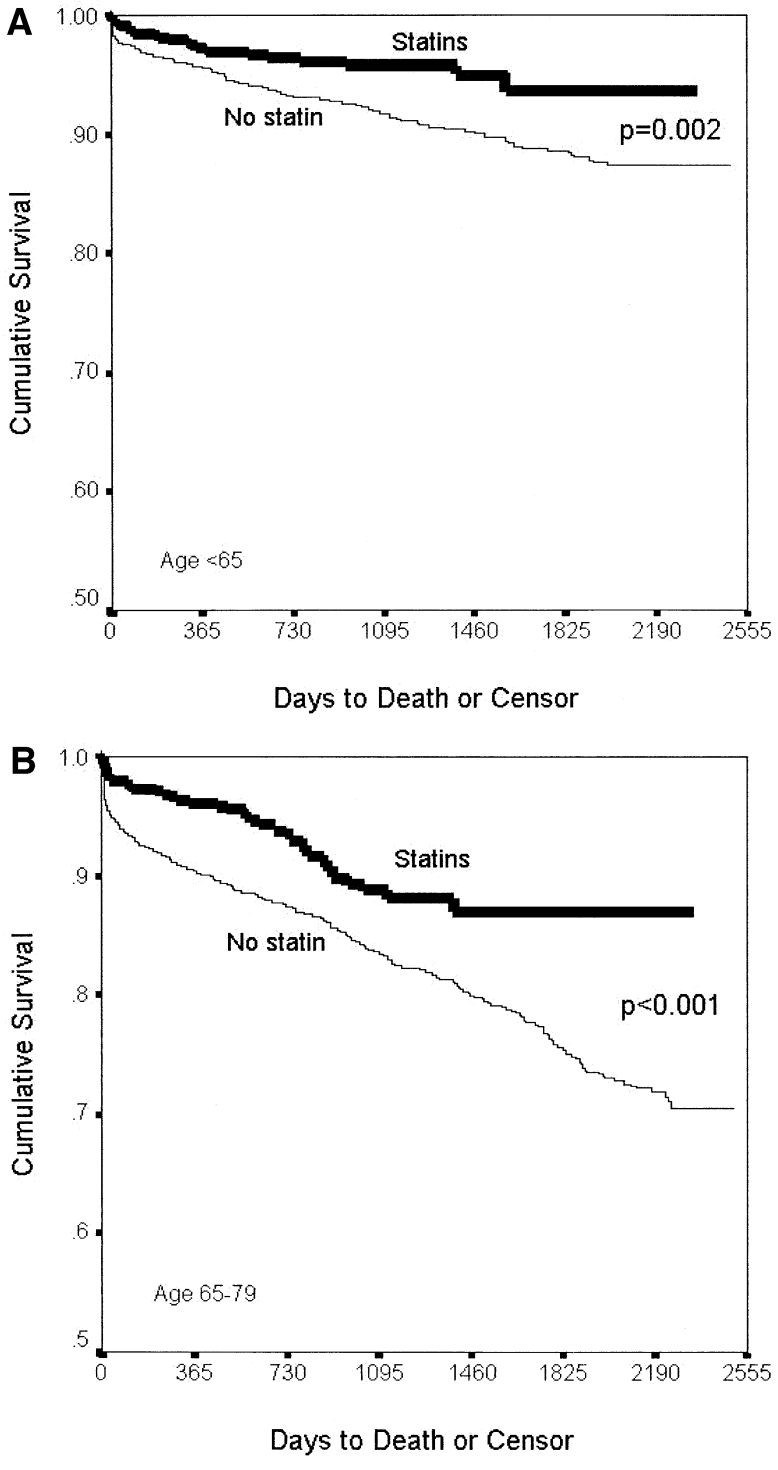

Figure 2. Univariate Kaplan-Meier survival curves for statin users and nonusers among three age groups: **(A)** younger patients <65 years old; **(B)** older patients 65 to 79 years old; and **(C)** very elderly patients 80 years of age or older. *Continued on next page.*

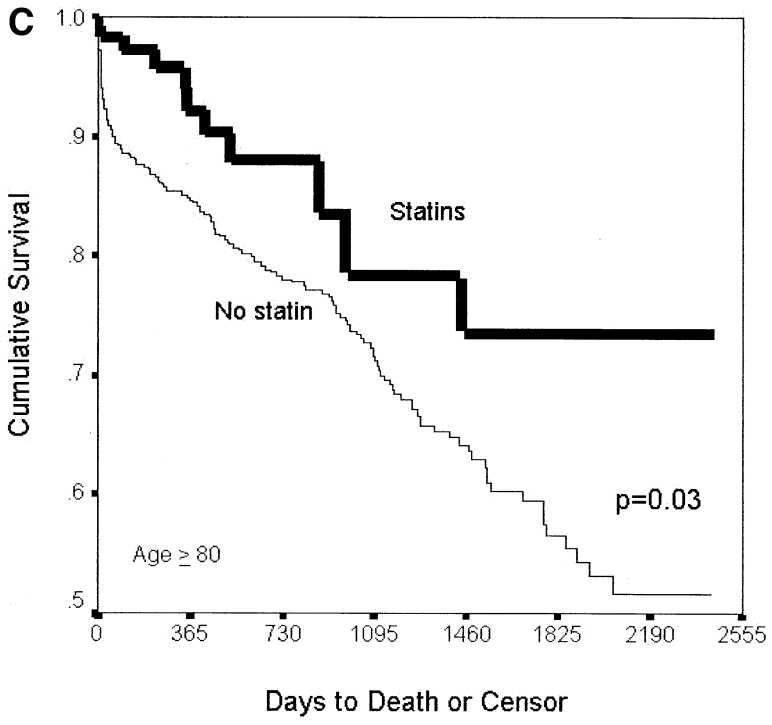

Figure 2 Continued.

determine whether those not receiving statin therapy were more likely to die of non-cardiovascular co-morbidities. This is especially relevant, as those receiving statins may be healthier patients, which was evident in this study population in that significantly fewer patients had diabetes and CHF among those receiving statins. A potential bias, due to the fact that there is a greater percentage of individuals with CHF among non–statin users, may exist in all age groups, but it may have the greatest effect among the ≥80-years age group, which includes the highest prevalence of CHF. The percentage of patients with diabetes, however, was fairly constant in all age groups, suggesting that any diabetes-related bias toward an increased benefit from statins would be similar for all ages. Other risk factors, such as previous stroke and MI, though similarly distributed among statin users and non–statin users <80 years old, were actually more prevalent among those ≥80 years old who received statin therapy.

In addition, statin therapy was ascertained at the time of hospital discharge, and follow-up compliance data were not available for the entire population. We have previously demonstrated, however, that a majority of patients prescribed a statin at hospital discharge remain on long-term statin therapy (20). Likewise, individuals who do not receive a statin at hospital discharge are not likely to receive one during a follow-up period. However, if the actual drop-in/drop-out rates are high, this would have actually decreased the apparent benefit from statin therapy observed in our study.

Finally, cholesterol levels were not available for the majority of participants, and we did not correlate statin therapy and the subsequent risk of mortality with the dose of drug or degree of cholesterol lowering. Studies that may be nearing completion and/or are in publication, including the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) (21) and Heart Protection Study (6), will provide additional information about the relationship between statin therapy, degree of cholesterol lowering, and subsequent outcomes in patients with preexisting vascular disease or a high cardiovascular risk.

Conclusions. Based on this large observational study, we conclude that statin prescription at hospital discharge is associated with similar proportionate reductions in all age groups of patients with known CAD, including very elderly patients. Indeed, there was an increased absolute risk reduction among elderly patients due to an overall increased risk at baseline. Hence, more aggressive use of statins among patients with diagnosed CAD, including elderly patients, appears to be indicated. Because this study focused on patients with established CAD, future studies of statin usage among elderly patients are required to assess their potential for primary prevention of CAD.

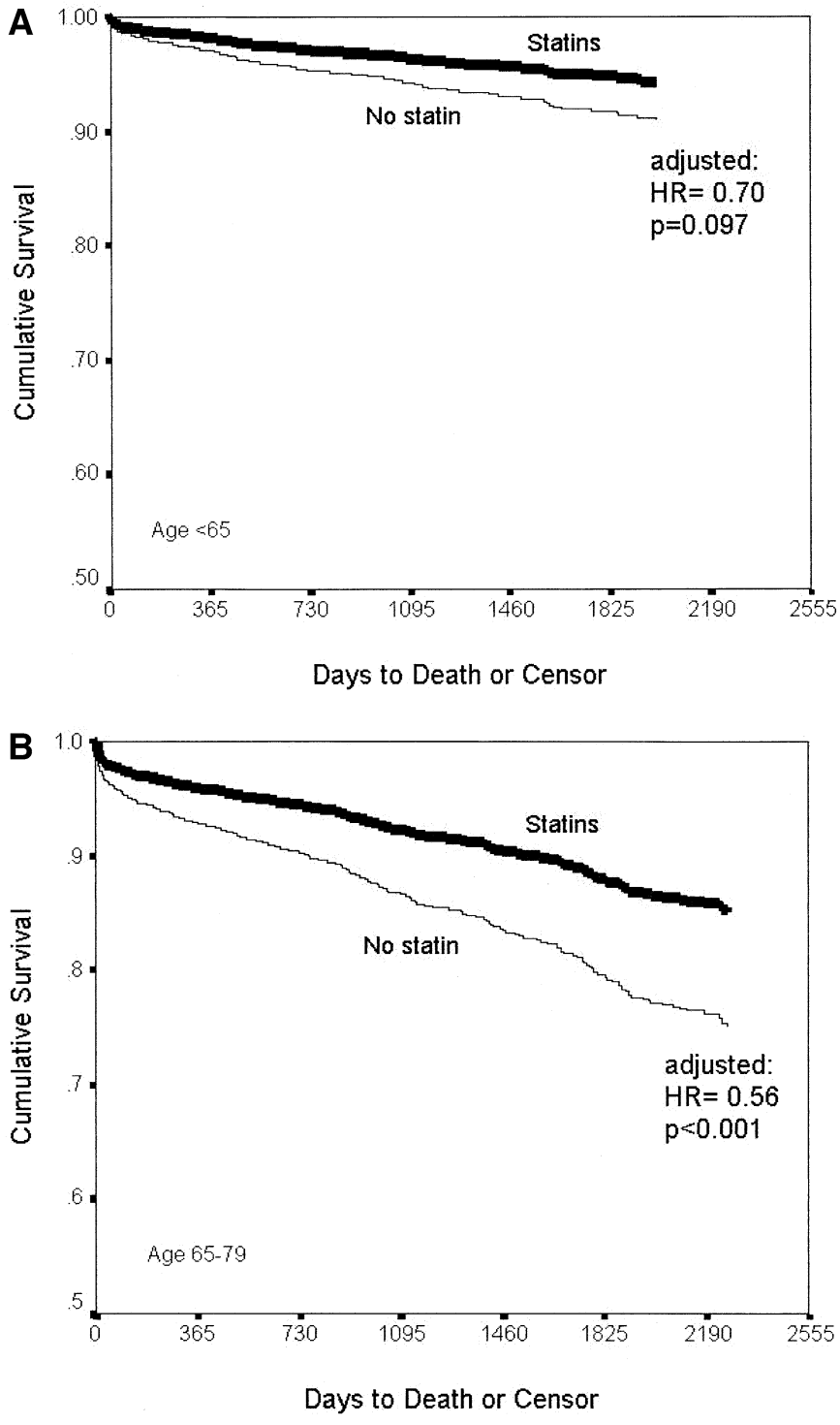

Figure 3. Multivariate adjusted Kaplan-Meier survival curves for statin users and nonusers among the age groups: **(A)** younger patients <65 years old; **(B)** older patients 65 to 79 years old; and **(C)** very elderly patients 80 years of age or older. Although the absolute survival rates differed substantially across the age groups, statins had clinically profound benefits for all age groups of patients with coronary artery disease. HR = hazard ratio. *Continued on next page.*

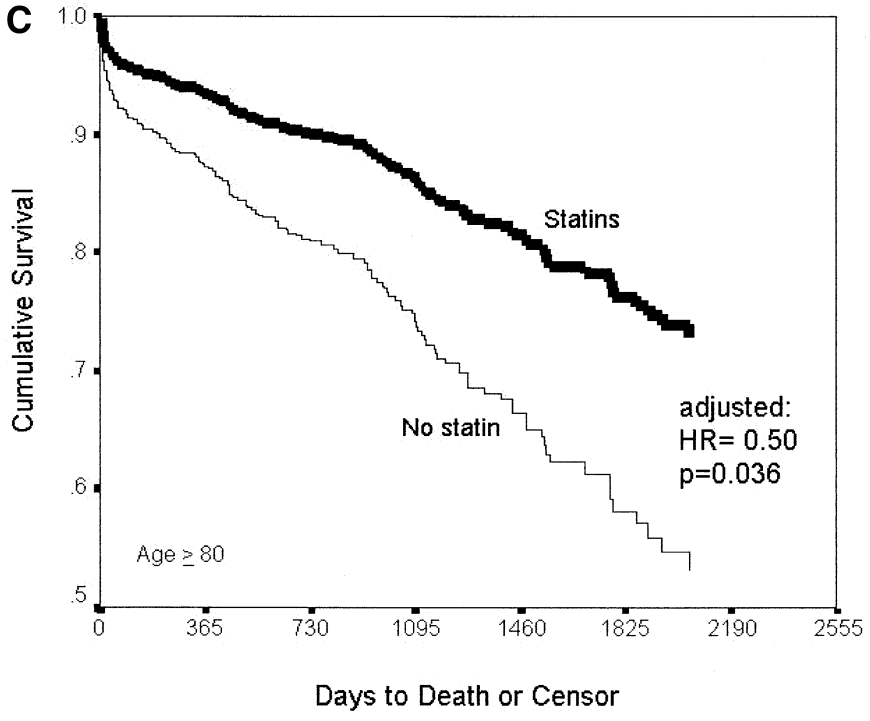

Figure 3 Continued.

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