

ORIGINAL ARTICLE

Rosuvastatin in Older Patients
with Systolic Heart Failure

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ABSTRACT

BACKGROUND

Patients with systolic heart failure have generally been excluded from statin trials. Acute coronary events are uncommon in this population, and statins have theoretical risks in these patients.

METHODS

A total of 5011 patients at least 60 years of age with New York Heart Association class II, III, or IV ischemic, systolic heart failure were randomly assigned to receive 10 mg of rosuvastatin or placebo per day. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcomes included death from any cause, any coronary event, death from cardiovascular causes, and the number of hospitalizations.

RESULTS

As compared with the placebo group, patients in the rosuvastatin group had decreased levels of low-density lipoprotein cholesterol (difference between groups, 45.0%; $P < 0.001$) and of high-sensitivity C-reactive protein (difference between groups, 37.1%; $P < 0.001$). During a median follow-up of 32.8 months, the primary outcome occurred in 692 patients in the rosuvastatin group and 732 in the placebo group (hazard ratio, 0.92; 95% confidence interval [CI], 0.83 to 1.02; $P = 0.12$), and 728 patients and 759 patients, respectively, died (hazard ratio, 0.95; 95% CI, 0.86 to 1.05; $P = 0.31$). There were no significant differences between the two groups in the coronary outcome or death from cardiovascular causes. In a prespecified secondary analysis, there were fewer hospitalizations for cardiovascular causes in the rosuvastatin group (2193) than in the placebo group (2564) ($P < 0.001$). No excessive episodes of muscle-related or other adverse events occurred in the rosuvastatin group.

CONCLUSIONS

Rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in older patients with systolic heart failure, although the drug did reduce the number of cardiovascular hospitalizations. The drug did not cause safety problems. (ClinicalTrials.gov number, NCT00206310.)

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ALTHOUGH A HIGH PROPORTION OF patients with heart failure caused by left ventricular systolic dysfunction have coronary artery disease, reported rates of myocardial infarction have been low in previous clinical trials.¹⁻⁴ Therefore, the potential value of statins has been questioned because their benefit is largely due to the prevention of myocardial infarction. In addition, in this population of patients, low levels of total cholesterol are common and are associated with worse outcomes.¹⁻⁶ Lipoproteins may remove endotoxins that enter the circulation through the intestinal wall, which may be edematous and leaky in patients with heart failure.⁷

Statins could also be harmful in these patients because they reduce the synthesis of coenzyme Q10 (a cofactor in the mitochondrial electron-transport chain and an antioxidant) and the production of selenoprotein, which could lead to skeletal and cardiac myopathy.^{1,2,8,9} Conversely, autopsy studies have suggested that unrecognized acute coronary syndromes are common underlying causes of sudden death and even death from pump failure. If this hypothesis is correct, it would indicate that statins could play an important role in patients with heart failure.^{10,11}

The pleiotropic actions of statins, including improvement of endothelial function and antiinflammatory activity, could be of benefit in heart failure.¹⁻⁴ Many nonrandomized studies have suggested that the use of statins is associated with better outcomes in patients with heart failure, and several small, prospective studies in patients with ischemic and nonischemic heart failure^{1-4,12,13} have shown beneficial effects on left ventricular function and clinical status.^{1-4,14-16} Unfortunately, results of previous large, randomized trials do not clarify which of these perspectives is accurate. Patients with heart failure were excluded from all but two placebo-controlled trials, and neither of these studies enrolled patients with severe heart failure, described the ejection fraction, or reported whether heart failure was present at baseline.^{17,18}

Consequently, in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA),³ we hypothesized that the beneficial effects of rosuvastatin would outweigh any theoretical hazards and improve survival, reduce morbidity, and increase well-being in patients with chronic, symptomatic, systolic, ischemic heart failure.

METHODS

PATIENTS

Patients who were at least 60 years of age and who had chronic New York Heart Association (NYHA) class II, III, or IV heart failure of ischemic cause (as reported by investigators) and an ejection fraction of no more than 40% (no more than 35% in patients in NYHA class II) were eligible, provided that the investigator thought they did not need treatment with a cholesterol-lowering drug.³

Patients had to be stable on optimal treatment for at least 2 weeks before randomization. Criteria for exclusion included the following: previous statin-induced myopathy or hypersensitivity reaction; decompensated heart failure or a need for inotropic therapy; myocardial infarction within the past 6 months; unstable angina or stroke within the past 3 months; percutaneous coronary intervention (PCI), coronary-artery bypass grafting (CABG), or the implantation of a cardioverter-defibrillator or biventricular pacemaker within the past 3 months or a planned implantation of such a device; previous or planned heart transplantation; clinically significant, uncorrected primary valvular heart disease or a malfunctioning prosthetic valve; hypertrophic cardiomyopathy; acute endomyocarditis or myocarditis, pericardial disease, or systemic disease (e.g., amyloidosis); acute or chronic liver disease; levels of alanine aminotransferase or thyrotropin of more than 2 times the upper limit of the normal range; a serum creatinine level of more than 2.5 mg per deciliter (221 μ mol per liter); chronic muscle disease or an unexplained creatine kinase level of more than 2.5 times the upper limit of the normal range; previous treatment with cyclosporine; any other condition that would substantially reduce life expectancy or limit compliance with the protocol; or the receipt of less than 80% of dispensed placebo tablets during the run-in period.

STUDY PROCEDURES

The trial was approved by the ethics committee at each of the participating hospitals, and patients provided written informed consent. Eligible patients were treated with single-blind placebo for 2 to 4 weeks before randomization to demonstrate compliance. Randomization was based on an op-

timal assignment procedure (minimization method), with a random element included. An optimally balanced allocation was achieved with the use of a score that included age; ejection fraction; NYHA class; the presence or absence of diabetes, myocardial infarction, or hypertension; the use of beta-blockers; and total cholesterol level.³

Patients were randomly assigned to receive 10 mg of rosuvastatin or matching placebo once daily with the use of a centralized interactive Web-based response system (ClinPhone). All investigators who were connected with the trial were unaware of study-group assignments except for those on the data and safety monitoring board.

Patients were seen at 6 weeks and 3 months after randomization and every 3 months there-

after. NYHA class was assessed by investigators at each visit. Patients completed the McMaster Overall Treatment Evaluation questionnaire¹⁹ every 6 months and at the last visit. In a protocol amendment that was adopted on December 20, 2004, the data and safety monitoring board requested that a questionnaire on muscle symptoms be added at each visit. Starting from that date, creatine kinase and creatinine were measured at 6 and 15 months and then yearly, as well as at the last study visit. Alanine aminotransferase was measured 3 months after randomization and then yearly and at the last visit. If the serum creatinine level was more than 2.5 mg per deciliter, additional measurements of creatinine, creatine kinase, and alanine aminotransferase were made within 2 weeks. All

Table 1. Characteristics of the Patients.*

Variable	Placebo (N=2497)	Rosuvastatin (N=2514)	P Value
Age			
Mean — yr	73±7.0	73±7.1	0.99
≥75 yr — no. (%)	1029 (41)	1035 (41)	0.98
Female sex — no. (%)	587 (24)	593 (24)	0.95
NYHA class — no. (%)			
II	918 (37)	939 (37)	
III	1540 (62)	1541 (61)	
IV	39 (1.6)	34 (1.4)	
Ejection fraction	0.31±0.07	0.31±0.07	0.94
Body-mass index	27±4.6	27±4.5	0.54
Blood pressure — mm Hg			
Systolic	129±17	129±17	0.52
Diastolic	76±8.9	76±8.8	0.12
Heart rate — beats/min	72±11	72±11	0.61
Current smoker — no. (%)	206 (8)	224 (9)	0.41
Medical history — no. (%)			
Myocardial infarction	1494 (60)	1510 (60)	0.87
Past or current angina pectoris	1807 (72)	1831 (73)	0.71
CABG or PCI	638 (26)	660 (26)	0.57
Hypertension	1581 (63)	1594 (63)	0.95
Diabetes mellitus	734 (29)	743 (30)	0.90
Current atrial fibrillation or flutter on ECG	585 (23)	609 (24)	0.51
Stroke	309 (12)	315 (13)	0.87
Pacemaker	299 (12)	262 (10)	0.08
Implantable cardioverter-defibrillator	64 (2.6)	72 (2.9)	0.51

Table 1. (Continued.)			
Variable	Placebo (N=2497)	Rosuvastatin (N=2514)	P Value
Laboratory measurements			
Cholesterol — mmol/liter			
Total	5.35±1.06	5.36±1.11	0.77
Low-density lipoprotein	3.56±0.93	3.54±0.95	0.60
High-density lipoprotein	1.23±0.34	1.24±0.36	0.23
ApoB:ApoA-I ratio	0.87±0.24	0.87±0.25	0.60
Triglycerides — mmol/liter			
	1.99±1.23	2.01±1.33	0.65
Serum creatinine			
Mean	115±28	115±28	0.66
>130 μ mol/liter — no. (%)	593 (24)	570 (23)	0.35
Estimated GFR			
Mean	58±15	58±15	0.99
<60 ml/min/1.73 m ² — no. (%)	1432 (57)	1418 (57)	0.98
NT-pro-BNP — pmol/liter†			
Median	166	180	0.13
Interquartile range	71–350	74–384	
hsCRP — mg/liter			
Median	3.5	3.5	0.68
Interquartile range	1.6–7.8	1.6–7.2	
Current medication — no. (%)			
Loop diuretic	1875 (75)	1914 (76)	0.39
Loop or thiazide diuretic‡	2185 (88)	2231 (89)	0.18
Aldosterone antagonist	979 (39)	986 (39)	0.99
ACE inhibitor	2010 (80)	2001 (80)	0.42
ACE inhibitor or ARB	2307 (92)	2292 (91)	0.12
Beta-blocker	1879 (75)	1887 (75)	0.88
Digitalis glycoside	803 (32)	845 (34)	0.27
Antiarrhythmic therapy	289 (12)	306 (12)	0.51
Antiplatelet therapy	1502 (60)	1470 (59)	0.23
Anticoagulant therapy	857 (34)	910 (36)	0.16
Antiplatelet or anticoagulant therapy	2251 (90)	2273 (90)	0.75

* Plus–minus values are means \pm SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. CABG denotes coronary-artery bypass grafting, PCI percutaneous coronary intervention, Apo apolipoprotein, GFR glomerular filtration rate estimated with use of the modified diet in renal disease equation, NT-pro-BNP N-terminal pro-B-type natriuretic peptide, hsCRP high-sensitivity C-reactive protein, ACE angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

† Measurements were performed in 1820 patients in the placebo group and 1844 patients in the rosuvastatin group.

‡ This category includes thiazide-like diuretics.

Figure 1. Kaplan–Meier Estimates for the Primary Outcome, Death from Any Cause, and Any Coronary Event.

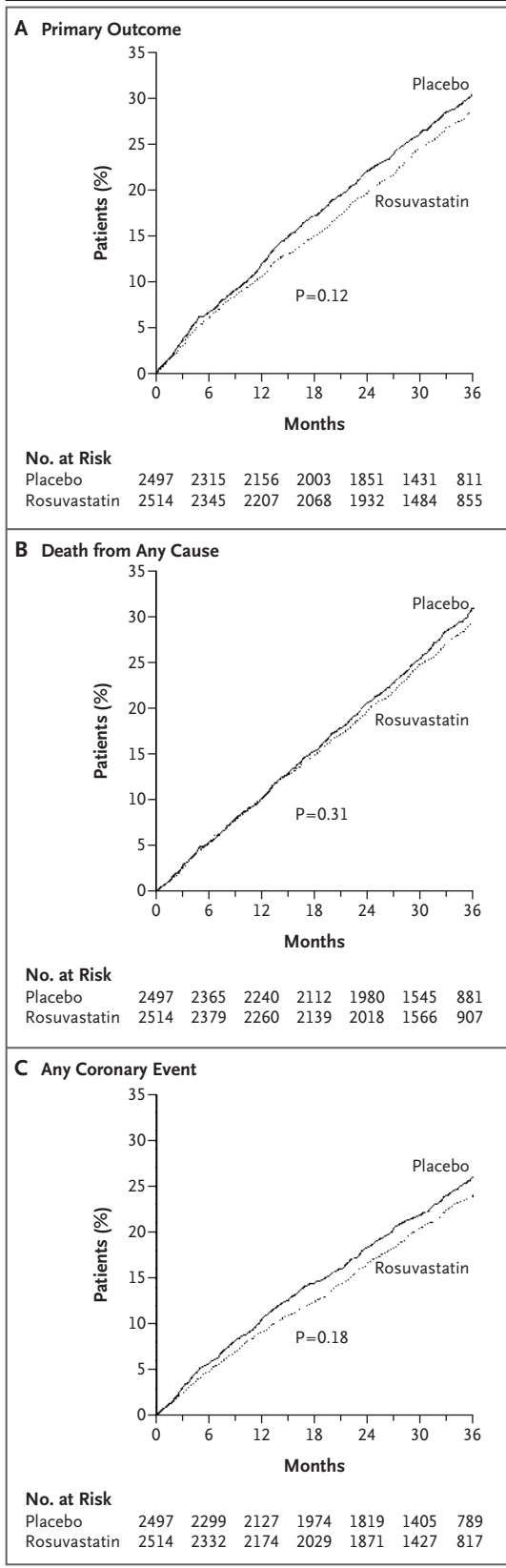
For patients in the the rosuvastatin group, the hazard ratio for the combined primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke) was 0.92 (95% CI, 0.83 to 1.02) (Panel A); for death from any cause, the hazard ratio was 0.95 (95% CI, 0.86 to 1.05) (Panel B); and for any coronary event (including sudden death, fatal myocardial infarction, resuscitation after cardiac arrest, ventricular defibrillation by an implantable cardioverter–defibrillator, nonfatal myocardial infarction, hospitalization for unstable angina, CABG, or PCI), the hazard ratio was 0.92 (95% CI, 0.82 to 1.04) (Panel C).

blood samples were obtained without a fasting requirement and analyzed at a central laboratory (Medical Research Laboratories).

The steering committee designed the trial and supervised its conduct in collaboration with representatives of the study’s sponsor, AstraZeneca. The sponsor collected the trial data, which then were analyzed at the Statistical Data Analysis Center at the University of Wisconsin, Madison, independently of the sponsor, according to a predefined statistical analysis plan. The sponsor performed the same analyses, separately, with identical results. The manuscript was prepared and submitted for publication by the steering committee, which had unrestricted access to the study data and vouches for the accuracy and completeness of the reported analyses.

STUDY OUTCOMES AND DEFINITIONS

The primary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, analyzed according to the time to the first event. The secondary outcomes were death from any cause, any coronary event (defined as sudden death, fatal or nonfatal myocardial infarction, the performance of PCI or CABG, ventricular defibrillation by an implantable cardioverter–defibrillator, resuscitation after cardiac arrest, or hospitalization for unstable angina), death from cardiovascular causes (with an additional analysis of cause-specific death from a cardiovascular cause), and the number of hospitalizations for cardiovascular causes, unstable angina, or worsening heart failure. Tertiary objectives included evaluation of the effects of rosuvastatin on outcomes (both NYHA class and results on the McMaster Overall Treatment



Evaluation questionnaire), as reported by either physicians or patients,¹⁹ newly diagnosed diabetes, and overall tolerability and safety of rosuvastatin.

Hospitalization was defined as care at an acute hospital lasting for at least 24 hours. Hospitalization for heart failure required documentation that worsening heart failure was the principal reason for hospitalization, and if competing reasons were judged to be of equal importance, heart failure received preference. Deaths were classified as due to cardiovascular causes unless a definite noncardiovascular reason was identified (except in patients who withdrew consent, in which case the cause was classified as unknown). For all patients, a single cause of death or hospitalization was stated. All serious adverse events were adjudicated by an independent committee to identify study outcomes according to prespecified definitions.

STATISTICAL ANALYSIS

We anticipated that there would be a mean yearly hazard rate of 10.4% for the primary outcome in the placebo group. It was assumed that rosuvastatin would have no effect for 10 months but after that time would reduce the risk of the primary outcome by 22%, resulting in a mean overall reduction of 16.1% (i.e., to 8.7%), taking into account withdrawals from randomized treatment. To provide a statistical power of 90% to detect such a reduction in risk with a two-sided alpha of 0.05, 1422 patients with the primary outcome were needed. To achieve this result, we estimated that 4950 patients would be needed on the basis of a recruitment period of 16 months and a follow-up of 35 months.

All data were analyzed in the intention-to-treat population, which was defined as all patients who received a bottle of a study drug. The main analyses were performed with the use of the log-rank test for the comparison of the study groups and an unadjusted Cox proportional-hazards model to calculate hazard ratios and 95% confidence intervals (SAS software, version 8.2). Cox analyses of the primary outcome were performed to explore for an unfavorable outcome in prespecified risk groups, provided that more than 260 events occurred in the subgroup. Risk subgroups were defined as either the third of a given group that was at highest risk (e.g., the oldest or with the lowest ejection fraction) or as a

subgroup with the presence of a condition (e.g., previous diabetes).²⁰

The number of hospitalizations and changes in NYHA class and score on the McMaster Overall Treatment Evaluation questionnaire were analyzed with the use of a permutation test. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

The trial was monitored by an independent data and safety monitoring board supported by the Statistical Data Analysis Center. Three planned interim analyses were performed when 25%, 50%, and 75% of the total expected primary events and deaths had occurred, with appropriate adjustment of the overall significance level.

RESULTS

PATIENTS

From September 15, 2003, to April 21, 2005, a total of 5459 patients entered the placebo run-in period, and 5011 patients underwent randomization at 371 sites in 19 European countries, Russia, and South Africa. Of those patients, 2514 were assigned to receive rosuvastatin and 2497 to receive placebo. The study was stopped, as planned, on the date that 1422 primary events were anticipated (May 20, 2007). The median follow-up time was 32.8 months. In total, 6290 patient-years accumulated in the rosuvastatin group and 6219 in the placebo group.

The two groups had similar characteristics at study entry (Table 1). The patients had a mean age of 73 years, and 41% of them were at least 75 years old. There was a high prevalence of previous or current hypertension, diabetes mellitus, and chronic kidney disease. They had been well treated for heart failure, and most had been treated with an antiplatelet agent or anticoagulant. During follow-up, 69 patients who were assigned to the rosuvastatin group and 120 patients who were assigned to the placebo group received open-label treatment with a statin.

LIPIDS AND C-REACTIVE PROTEIN

Levels of low-density lipoprotein (LDL) cholesterol declined from 137 mg per deciliter (3.54 mmol per liter) at baseline to 76 mg per deciliter (1.96 mmol per liter) at 3 months in the rosuvastatin group (−43.8%) but did not change significantly in the placebo group, in which levels were 136 mg per deciliter (3.52 mmol per liter) at baseline and 138

mg per deciliter (3.57 mmol per liter) at 3 months (+1.2%), an absolute difference of 45.0% between groups ($P<0.001$). Levels of high-density lipoprotein (HDL) cholesterol increased from 48 mg to 50 mg per deciliter (1.24 mmol to 1.29 mmol per liter) in the rosuvastatin group and remained at 47 mg per deciliter in the placebo group, an absolute difference of 5.0% between groups ($P<0.001$).

Triglyceride levels decreased from 178 mg to 138 mg per deciliter (2.01 mmol to 1.56 mmol per liter) in the rosuvastatin group and increased from 176 mg to 178 mg per deciliter (1.99 mmol to 2.01 mmol per liter) in the placebo group, an absolute difference of 20.5% between groups ($P<0.001$).

Median levels of high-sensitivity C-reactive

protein decreased from 3.1 mg per liter at baseline to 2.1 mg per liter at the last visit in the rosuvastatin group (−31.6%) and increased from 3.0 mg to 3.3 mg per liter in the placebo group (+5.5%, $P<0.001$), an absolute difference of 37.1% between groups.

PRIMARY OUTCOME

The primary composite outcome occurred in 692 patients in the rosuvastatin group (11.4 per 100 patient-years of follow-up) and in 732 patients in the placebo group (12.3 per 100 patient-years), with a hazard ratio in the rosuvastatin group of 0.92 (95% confidence interval [CI], 0.83 to 1.02; $P=0.12$) (Fig. 1). The components of the primary

Table 2. Prespecified Composite Cardiovascular Outcomes and Fatal and Nonfatal Events.*

Variable	Placebo (N=2497)		Rosuvastatin (N=2514)		Hazard Ratio (95% CI)	P Value
	No. of Patients	Event Rate	No. of Patients	Event Rate		
Outcome						
Primary outcome	732	12.3	692	11.4	0.92 (0.83–1.02)	0.12
Death from cardiovascular causes	487		488			
Nonfatal myocardial infarction	141		115			
Nonfatal stroke	104		89			
Secondary outcome						
Death from any cause†	759	12.2	728	11.6	0.95 (0.86–1.05)	0.31
Any coronary event‡	588	10.0	554	9.3	0.92 (0.82–1.04)	0.18
Fatal event						
Death from cardiovascular causes§	593	9.6	581	9.3	0.97 (0.87–1.09)	0.60
Sudden death	327	5.3	316	5.0	0.96 (0.82–1.12)	0.57
In primary outcome	284		284			
In coronary events	283		272			
Worsening heart failure	191	3.1	193	3.1	1.00 (0.82–1.22)	1.00
In primary outcome	157		161			
Myocardial infarction¶	9	0.2	15	0.2		
In primary outcome	8		9			
In coronary events	8		9			
Stroke§¶	32	0.5	35	0.6		
In primary outcome	11		14			
Pulmonary embolism	8	0.1	2	<0.1		
In primary outcome	7		1			
Aortic aneurysm	5	<0.1	0			
In primary outcome	5		0			
Other	21	0.3	20	0.3		
In primary outcome	15		19			

Table 2. (Continued.)

Variable	Placebo (N=2497)		Rosuvastatin (N=2514)		Hazard Ratio (95% CI)	P Value
	No. of Patients	Event Rate	No. of Patients	Event Rate		
Death from noncardiovascular cause	159	2.6	138	2.2		
Infection	68	1.1	54	0.9		
Cancer	50	0.8	52	0.8		
Any organ failure	11	0.2	10	0.2		
Liver failure	2		1			
Renal failure	1		6			
Multiorgan failure	8		3			
Suicide or accident	10	0.2	8	0.1		
Gastrointestinal bleeding	9	0.2	1	<0.1		
Other	11	0.2	13	0.2		
Unknown cause	7	0.1	9	0.1		
Nonfatal event						
Myocardial infarction§	145	2.4	116	1.9		
In coronary events	126		96			
Stroke¶	106	1.7	91	1.5		
CABG	28	0.4	32	0.5		
In coronary events	15		15			
PCI	76	1.2	87	1.4		
In coronary events	40		48			
Resuscitation after cardiac arrest	62	1.0	56	0.9		
In coronary events	46		47			
Ventricular defibrillation by ICD**	4	<0.1	6	<0.1		
In coronary events	4		6			
Unstable angina	71	1.2	65	1.1		
In coronary events	66		61			

* The event rate is the number of events per 100 patient-years of follow-up. The hazard ratio is for the rosuvastatin group. CABG denotes coronary-artery bypass grafting, PCI percutaneous coronary intervention, and ICD implantable cardioverter-defibrillator.

† Vital status was determined for all patients who underwent randomization. One death that occurred in the placebo group on August 27, 2006, was not included in this analysis, since it could not be determined whether the patient died before or after the study closing date at the time the randomization code was broken.

‡ The total number of events in each composite can be calculated by adding the components described as occurring “in primary outcome” or “in coronary events.” Events included sudden death, fatal or nonfatal myocardial infarction, PCI, CABG, ventricular defibrillation by an ICD, resuscitation after cardiac arrest, and hospitalization for unstable angina.

§ The total numbers of patients with either fatal or nonfatal myocardial infarction or stroke were 264 in the placebo group and 227 in the rosuvastatin group (hazard ratio for the rosuvastatin group, 0.84; 95% CI, 0.70 to 1.00; P=0.05). These numbers included nonfatal myocardial infarction in 141 patients in the placebo group and 115 in the rosuvastatin group, nonfatal stroke in 104 patients in the placebo group and 89 in the rosuvastatin group, fatal myocardial infarction in 8 patients in the placebo group and 9 in the rosuvastatin group, and fatal stroke in 11 patients in the placebo group and 14 in the rosuvastatin group.

¶ Of all strokes included in the primary outcome, 90 in the placebo group and 73 in the rosuvastatin group were ischemic, 9 in the placebo group and 15 in the rosuvastatin group were hemorrhagic, and 16 in the placebo group and 15 in the rosuvastatin group were unclassifiable.

|| In a masked retrospective review of these cases by the adjudication committee, none was attributed to a study drug.

** These events were confirmed by printout from the ICD showing ventricular fibrillation followed by new rhythm (not including defibrillation of ventricular tachycardia).

outcome are listed in Table 2. The effect of treatment was consistent across all subgroups of patients with prespecified risks, with no indication of harm in any subgroup (Fig. 2).

TOTAL MORTALITY

There were 728 deaths (11.6 per 100 patient-years) in the rosuvastatin group and 759 deaths (12.2 per 100 patient-years) in the placebo group, with a hazard ratio of 0.95 in the rosuvastatin group (95% CI, 0.86 to 1.05; $P=0.31$) (Fig. 1 and Table 2).

CORONARY OUTCOME

A coronary event occurred in 554 patients in the rosuvastatin group (9.3 per 100 patient-years) and in 588 patients in the placebo group (10.0 per 100 patient-years). This resulted in a hazard ratio in the rosuvastatin group of 0.92 (95% CI, 0.82 to 1.04; $P=0.18$) (Fig. 1 and Table 2).

HOSPITALIZATION

There were significantly fewer hospitalizations of any type (including for cardiovascular causes and heart failure) in the rosuvastatin group than in the placebo group. There was no difference in the number of hospitalizations for unstable angina or for a noncardiovascular cause (Table 3).

OTHER OUTCOMES

Rosuvastatin had no effect, as compared with placebo, on the NYHA class or on the score on the McMaster Overall Treatment Evaluation questionnaire. Newly diagnosed diabetes was reported in 100 patients in the rosuvastatin group and in 88 patients in the placebo group ($P=0.40$).

ADVERSE EVENTS

Premature, permanent discontinuation of a study drug was more common overall (including because of adverse events) in the placebo group. Most categories of adverse events were less common in the rosuvastatin group (Table 4). Reports of muscle-related symptoms (as sought by active questioning or reported as an adverse event) and elevations in levels of creatine kinase and alanine aminotransferase (more than 3 times the upper limit of the normal range for the latter) were not more common in the rosuvastatin group.

From baseline to the last visit, serum creatinine levels increased from 1.30 mg to 1.41 mg per deciliter (115 μmol to 125 μmol per liter) among

Figure 2 (facing page). Primary Outcome in Subgroups of Patients with Prespecified Risks.

Risk groups were defined as either the third of the population that was at the highest risk (e.g., the oldest patients or those with the lowest ejection fraction) or as a subgroup with a specific condition (e.g., a history of diabetes). The lower-risk group is presented above the higher-risk group in all cases. Numbers refer to the number of events divided by the number of patients in the subgroup. Rates refer to events per 100 patient-years of follow-up. Heart rate was measured from the study-entry pulse. Hazard ratios are indicated by a solid square, and the horizontal line represents the 95% confidence interval. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. NYHA denotes New York Heart Association, LDL low-density lipoprotein, Apo apolipoprotein, HDL high-density lipoprotein, GFR glomerular filtration rate estimated with use of the modified diet in renal disease equation, NT-pro-BNP N-terminal pro-B-type natriuretic peptide, and hsCRP high-sensitivity C-reactive protein. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129.

1619 patients in the rosuvastatin group and from 1.30 mg to 1.45 mg per deciliter (115 μmol to 128 μmol per liter) among 1553 patients in the placebo group. There were no excessive episodes of a doubling of the serum creatinine level during follow-up at any time after randomization in the rosuvastatin group.

DISCUSSION

Despite having favorable effects on lipids (a reduction in levels of LDL cholesterol and triglycerides and an increase in the level of HDL cholesterol) and on high-sensitivity C-reactive protein, a daily dose of 10 mg of rosuvastatin did not reduce the primary composite cardiovascular outcome or death from any cause when the drug was added to extensive background pharmacologic therapy in this previously unstudied population of older patients with moderate to severe ischemic systolic heart failure. Rosuvastatin reduced the number of hospitalizations for cardiovascular causes (154 fewer admissions per 1000 patients treated for a median follow-up of 2.7 years) and, as a result, reduced the total number of hospital admissions for any cause. Although we studied elderly patients who had renal impairment and muscle fatigue and who were at risk for hepatic congestion, we found that rosuvastatin was

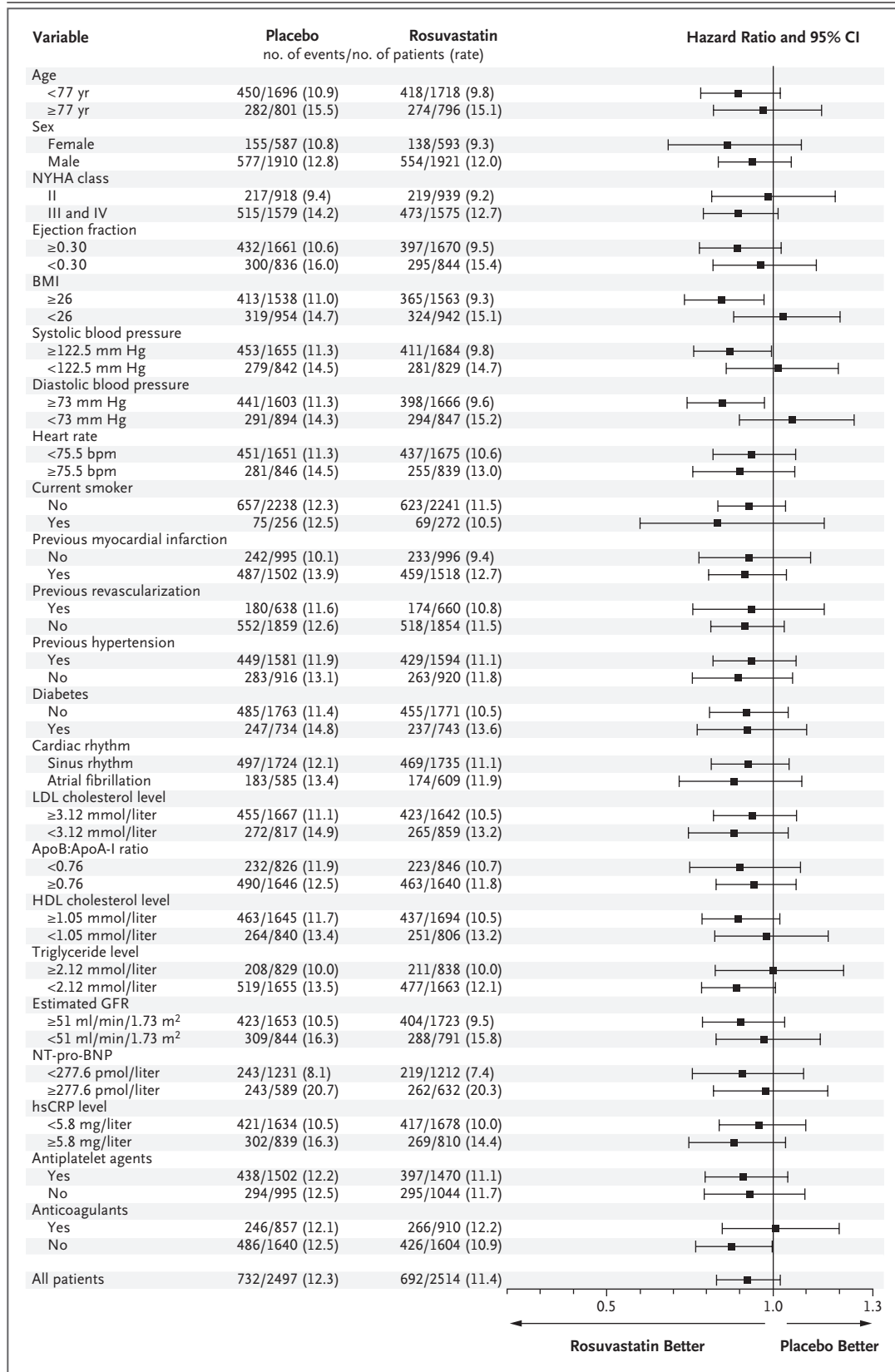


Table 3. Patients Who Had at Least One Hospitalization and the Total Number of Hospitalizations.*

Variable	Placebo (N = 2497)		Rosuvastatin (N = 2514)		Hazard Ratio (95% CI)	P Value
	No.	Event Rate	No.	Event Rate		
For any cause						
Patients	1523	38.0	1489	35.6	0.94 (0.88–1.01)	0.09
Hospitalizations	4074		3694			0.007
For a cardiovascular cause						
Patients	1164	25.0	1104	22.9	0.92 (0.85–0.99)	0.04
Hospitalizations	2564		2193			<0.001
For worsening heart failure†						
Patients	669	12.3	622	11.3	0.91 (0.82–1.02)	0.11
Hospitalizations	1299		1109			0.01
For unstable angina						
Patients‡	71	1.2	65	1.1	0.91 (0.66–1.27)	0.56
Hospitalizations	90		74			0.30
For a noncardiovascular cause						
Patients	840	16.5	839	16.2	0.98 (0.89–1.08)	0.72
Hospitalizations	1510		1501			0.82

* The event rate is the number of events per 100 patient-years of follow-up.

† The numbers of patients who died from any cause or were hospitalized for worsening heart failure were 1116 in the placebo group (20.5 per 100 patient-years) and 1064 in the rosuvastatin group (19.2 per 100 patient-years), with a hazard ratio for the rosuvastatin group of 0.94 (95% CI, 0.86 to 1.02; P=0.12).

‡ These numbers do not include five patients (three in the placebo group and two in the rosuvastatin group) who were deemed to have unstable angina by the outcome adjudication committee, since the events occurred during a hospitalization but were not the cause of the hospital admission.

not associated with an excessive number of adverse events, a conclusion supported by the consistent finding of fewer primary events in the rosuvastatin group than in the placebo group in most high-risk subgroups.

We do not know exactly why rosuvastatin did not reduce the frequency of the primary composite outcome. Nonfatal myocardial infarction and stroke were relatively uncommon in this population, and death from cardiovascular causes accounted for the majority of primary events (and sudden death for the majority of deaths from cardiovascular causes). Rosuvastatin had no effect on the rates of death from cardiovascular causes or sudden death.

In previous trials involving different populations of patients, statins reduced the rate of sudden death, probably by preventing the rupture of coronary plaques and preventing myocardial ischemia and infarction.²¹⁻²³ On the basis of previous autopsy studies showing that approximately half of sudden deaths in patients with heart

failure were due to plaque rupture and coronary occlusion,^{10,11} we hypothesized that rosuvastatin therapy might also reduce the risk of sudden death in patients with ischemic heart failure. Why it did not is uncertain. In heart failure, sudden death may be caused by a primary electrical event that is related to ventricular dilatation and scarring. The patients in our trial were also treated extensively with other drugs known to reduce the risk of sudden death, including angiotensin-converting-enzyme inhibitors, beta-blockers, and aldosterone antagonists. In a similar way, although autopsy studies have suggested that acute coronary disease can be identified in up to a third of patients who have died from pump failure, rosuvastatin had no effect on death from heart failure in our trial.

An alternative explanation for the lack of treatment benefit is that rosuvastatin caused harm in a subgroup of patients, which offset a larger benefit in the remainder. This seems unlikely, since no such effect was identified in any of the sub-

Table 4. Side Effects and Adverse Events.*

Variable	Placebo (N=2497)	Rosuvastatin (N=2514)
Patients who discontinued study drug — no.†	546	490
Adverse event‡	302	241
Patient unwilling to continue	162	187
Other reason	82	62
All adverse events — no.	13,635	13,258
All serious adverse events — no.§	5,536	5,146
Patients with any serious adverse event — no.§	1,672	1,626
Cardiac	1,065	1,005
Infection	370	344
General disorder	294	285
Nervous system	272	247
Respiratory	226	208
Gastrointestinal	223	171
Vascular	164	160
Neoplasms	144	156
Injury or procedural complications	140	154
ALT >3× ULN after randomization — no. of patients¶		
At least 1 episode	24	25
>1 episode	5	3
Doubling of serum creatinine — no. of patients	32	23
Muscle-symptom questionnaire — no. of patients		
Muscle pain since last visit	125	132
Current muscle pain at visit**	93	84
Muscle adverse events — no. of patients††	155	170
Classification of event		
Serious adverse event	11	3
Nonserious adverse event	144	167
Maximum intensity		
Severe (incapacitating)	8	4
Moderate	61	58
Mild (easily tolerated)	86	108
Any muscle symptom — no. of patients‡‡	207	225
Creatine kinase level — no. of patients		
>10× ULN§§	3	1
>10× ULN with muscle symptoms¶¶	1	0
Any muscle symptom or creatine kinase level >10× ULN — no. of patients	209	226

* ALT denotes alanine aminotransferase, and ULN upper limit of the normal range.

† The hazard ratio for the rosuvastatin group was 0.88 (95% CI, 0.78 to 0.99; P=0.03).

‡ The hazard ratio for the rosuvastatin group was 0.78 (95% CI, 0.66 to 0.92; P=0.004).

§ Listed are the number of patients who had at least one serious adverse event with a frequency of >5% in the rosuvastatin group. All serious adverse events were referred to the outcome adjudication committee.

¶ The numbers of samples that underwent analysis after randomization were 8173 from patients in the placebo group and 8297 from patients in the rosuvastatin group.

|| To be included in this category, a patient needed to have both a doubling of the baseline level and a level above the ULN.

** At each visit, patients were asked whether they had had muscle pain since the last visit. If the answer was yes, they were asked whether they had pain during the present visit. If the answer was yes, investigators were asked to report it as an adverse event as well and to send a sample to the central laboratory for analysis of creatine kinase.

†† Included in this category were the following preferred terms from the *Medical Dictionary for Regulatory Activities*: musculoskeletal chest pain, musculoskeletal chest discomfort, musculoskeletal pain, myalgia, intercostal myalgia, and myositis.

‡‡ Included are the cumulative number of patients who reported having the symptom as a result of active questioning or for whom the symptom was reported as an adverse event.

§§ Levels were more than 1200 IU per liter. Creatine kinase was analyzed after randomization in 5468 samples from patients in the placebo group and 5602 samples from patients in the rosuvastatin group.

¶¶ One patient in the placebo group reported having muscle symptoms after the initiation of physiotherapy.

groups of patients with prespecified risks that we examined and because there were fewer hospitalizations in the rosuvastatin group. Another possibility is that we did not follow patients long enough to see a beneficial effect of treatment.

We found that rosuvastatin reduced the total number of hospitalizations for heart failure, perhaps because the drug prevented the development of acute coronary disease that would have contributed to such episodes. An alternative explanation is that rosuvastatin reduced myocardial ischemia by improving endothelial or microvascular function or by a direct or indirect effect on cardiomyocytes, through the suggested pleiotropic effects of these drugs.¹⁻⁶ Such data on hospitalizations and changes in the NYHA class and scores on the McMaster Overall Treatment Evaluation questionnaire refute previous speculation that statins might lead to a worsening of heart failure.¹⁻⁹ In addition, there was no significant excess in the number of muscle-related symptoms or elevations in creatine kinase levels in patients receiving rosuvastatin than in those receiving placebo. These findings suggest that the hypothetical detrimental effects of statins on the function of skeletal and cardiac muscle (and other physiological processes) do not result in important clinical consequences,¹⁻⁹ nor was there any suggestion of the hypothetical risk of further reduction in LDL cholesterol in patients with already low levels.¹⁻⁹

There were also no more episodes of a significant elevation in liver aminotransferase levels, a worsening of renal function, or infections in the rosuvastatin group than in the placebo group. There were fewer treatment discontinuations and fewer deaths from noncardiovascular causes in the rosuvastatin group than in the placebo group.

Our trial had some limitations. We studied older patients with moderate-to-severe heart failure who were in NYHA class III or IV (or who had an ejection fraction of $\leq 35\%$ in NYHA class II) and whose physicians had not recommended that they should receive a statin. Since these patients

may have had atherosclerotic or myocardial disease that was too advanced to modify, rosuvastatin might have had a different effect in patients with milder heart failure. We did not investigate two other important groups of patients with heart failure: those with nonischemic heart failure and those with a preserved ejection fraction. Such patients have been enrolled in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico trial, comparing rosuvastatin with placebo and n-3 polyunsaturated fatty acids with placebo in 6975 patients, with 4574 assigned to participate in the rosuvastatin portion of the study.²⁴ The two primary outcome measures are the time to death and the time to either death or hospitalization for cardiovascular causes. This trial is expected to be completed in 2008.

In summary, we found that daily treatment with 10 mg of rosuvastatin did not reduce the composite outcome of death from cardiovascular causes or nonfatal myocardial infarction or stroke in vulnerable, elderly patients with ischemic, systolic heart failure who had already received extensive treatment with drugs for cardiovascular disease. However, rosuvastatin reduced the number of hospitalizations for cardiovascular causes, in addition to effectively reducing levels of LDL cholesterol and high-sensitivity C-reactive protein.

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APPENDIX

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