CME

Effect of Rosuvastatin on Repeat Heart Failure Hospitalizations

The CORONA Trial
(Controlled Rosuvastatin Multinational Trial in Heart Failure)

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CME Objective for This Article: After reading this article, the reader should understand: 1) the effect of statin therapy on repeat hospitalization for heart failure; 2) the strengths and limitations of different statistical methodologies to examine repeat events; and 3) the implications of these data related to clinical practice and future research.

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The CORONA Trial (Controlled Rosuvastatin Multinational Trial in Heart Failure)

Objectives	This study sought to examine the effect of statin therapy hospitalizations for heart failure (HFH) in patients in the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial.
Background	HFH is an important, frequently recurrent event. Conventional time-to-first event analyses do not take account repeat events. We used a number of statistical approaches to examine the effect of treatment on first and repeat HFH in the CORONA trial.
Methods	In the CORONA trial, 5,011 patients $\geq$60 years of age with chronic New York Heart Association functional classes II to IV systolic heart failure resulting from ischemia were randomized to receive rosuvastatin or placebo. Poisson, Andersen-Gill, and negative binomial methods (NB) were used to analyze the effect of rosuvastatin on HFH, and the NB and a parametric joint frailty model (JF) were used to examine this effect while accounting for the competing risk of cardiovascular (CV) death. Rosuvastatin/placebo rate ratios were calculated, both unadjusted and adjusted.
Results	A total of 1,291 patients had 1 or more HFH (750 of these had a single HFH only), and there were a total of 2,408 HFHs. The hazard ratio for the conventional time-to-first event analysis for HFH was 0.91 (95% confidence interval [CI]: 0.82 to 1.02, p = 0.105). In contrast, the NB on repeat hospitalizations gave an unadjusted RR (RR) for HFH of 0.86 (95% CI: 0.75 to 0.99, p = 0.030), adjusted 0.82 (95% CI: 0.72 to 0.92, p = 0.001), and after including CV death as the last event, adjusted RR of 0.85 (95% CI: 0.77 to 0.94, p = 0.001). The JF gave an adjusted RR of 0.82 (95% CI: 0.73 to 0.92, p = 0.001). Similar results were found in analyses of all CV hospitalizations and all-cause hospitalizations.
Conclusions	When repeat events were included, rosuvastatin was shown to reduce the risk of HFH by approximately 15% to 20%, equating to approximately 76 fewer admissions per 1,000 patients treated over a median 33 months of follow-up. Including repeat events could increase the ability to detect treatment effects in heart failure trials. (J Am Coll Cardiol HF 2014;2:289–97) © 2014 by the American College of Cardiology Foundation

The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial was designed to examine the effect of statin treatment on the primary composite outcome of cardiovascular death, myocardial infarction, or stroke in patients with chronic heart failure and reduced ejection fraction caused by ischemia (1,2). Rosuvastatin did not reduce the occurrence of this outcome. However, there were few myocardial infarctions or strokes and two-thirds of the primary endpoints were cardiovascular deaths, most of which were sudden (i.e., presumed to be due to a ventricular arrhythmia) (2). Therefore, the number of both nonfatal and fatal events in this composite, amenable to prevention by a statin, was relatively small, and the primary endpoint may thus have been insensitive to the effect of rosuvastatin. Moreover, whereas myocardial infarction and stroke are undoubtedly clinically important, they are, arguably, not as central to the health burden imposed by heart failure, which is much more frequently manifest as worsening of the syndrome leading to unplanned hospital admission (3). Hospitalizations is often recurrent, and there has been recent interest in assessing the effect of treatment on the total number of these events (i.e., first and repeat events) in clinical trials (4–6). Therefore, we have carried out a retrospective analysis of the CORONA trial to explore the effect of rosuvastatin on heart failure hospitalizations (HFH) (a pre-specified secondary outcome of the trial), including both first and repeat admissions.

Methods

Study design and patients. The design and results of CORONA have been published elsewhere (1,2). Briefly, CORONA tested the hypothesis that rosuvastatin would reduce the primary composite outcome of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke in patients with chronic symptomatic systolic heart failure of ischemic origins. A total of 5,011 patients $\geq$60 years of age in New York Heart Association (NYHA) functional class II, III, or IV were randomized to receive either rosuvastatin (10 mg daily) or placebo, in addition to standard therapy. Secondary outcomes included death from any cause, any coronary event, death from cardiovascular (CV) causes and the number of hospitalizations.

Statistical analyses. All analyses were carried out in accordance with the intention-to-treat principle. Baseline characteristics were balanced with respect to treatment group.

Bar plots for the distribution of hospitalizations by treatment group were created separately for HFH, CV hospitalizations that were not heart failure, and non-CV hospitalizations.

Cumulative incidence of HFH. The cumulative incidence of HFH was calculated for each treatment group. The Ghosh and Lin nonparametric method for calculating the cumulative rate of HFH, while adjusting for mortality was also used and compared to the crude estimate, which ignores the competing risk of death (7).

Hospitalization rates. The average number of HFH per 100 patient years was calculated for each treatment group. The HFH rate per patient year was calculated by dividing the total number of HFH in each treatment group by the total number of follow-up years in that group.

Modeling of HFH rates. Recurrent events are typically analyzed using the Poisson, Andersen-Gill, and negative binomial methods (8–10). The Poisson and Andersen-Gill methods assume that all hospitalizations in each treatment group are independent. This assumption is clearly violated, as hospitalizations within individuals are associated. Robust standard errors may be used with the Andersen-Gill method to account for heterogeneity (11). The negative binomial is an attractive method because it accommodates heterogeneity among patients. The negative binomial assumes that each patient has hospitalizations according to his or her own individual, specific event rate through a random effect term which varies according to a gamma distribution. The negative binomial regression model was therefore also used to obtain an estimate of the effect of rosuvastatin in comparison to that of placebo on the rate of HFH.

Because an increase in HFH is associated with an increased risk of subsequent death, any analysis of recurrent admissions should also allow for CV death as a competing risk. The negative binomial method was therefore extended by counting each CV death as an additional event. If a patient died during a HFH, this was counted as a single event. Another method for incorporating the competing risk of death uses a parametric joint frailty model to analyze recurrent HFH and time to CV death simultaneously. This analyses repeat hospitalizations while accounting for the associated mortality risk (6). The joint model specifies distinct distributions for recurrent hospitalizations and for time to CV death. A common frailty term, which can be thought of as an unmeasured indication of the severity of illness that affects both hospitalization rate and hazard for CV death, induces an association between the 2 processes (12).

Rate ratios, 95% confidence intervals (CIs), and p values were also calculated using models adjusted for the following baseline covariates: age, NYHA functional class, ejection fraction, systolic blood pressure, heart rate, angina pectoris, diabetes mellitus, atrial fibrillation, pacemaker implant, low-density lipoprotein, serum creatinine, and N-terminal pro-B type natriuretic peptide. The multivariate model was built using those covariates which had univariate associations with the recurrent HFH at a p value of <0.05. Note that age and sex were included in the multivariate model, regardless of significance. Sensitivity analyses were performed by means of unadjusted models.

Results

The frequencies of hospital admissions, without accounting for differing lengths of follow-up, are presented in Table 1. Of the 5,011 patients randomized, 1,487 (30%) died, and 3,012 (60%) had at least 1 hospitalization for any cause. Of those with at least 1 hospitalization, 2,268 (75%) had at least 1 admission for CV causes, with 1,291 patients (57%) with a CV hospital admission for heart failure (i.e., 43% of all patients admitted were hospitalized for heart failure). There was a total of 7,768 hospitalizations for any cause, with 4,757 (61%) being CV and 2,408 (51%) of those were due to worsening heart failure. This means that 31% of all admissions were HFH.

Including repeat admissions, there were 1,299 HFH in the placebo group and 1,109 in the rosuvastatin group, equating to a HFH rate of 52.0 and 44.1 per 100 patients in the placebo and rosuvastatin groups, respectively, a difference of approximately 8 admissions per 100 patients.

There were 669 patients (27%) in the placebo group and 622 (25%) in the rosuvastatin group, with at least 1 HFH, equating to a relative risk (RR) of 0.92 (95% CI: 0.84 to 1.01, p = 0.097). This compares to a RR of 0.97 (95% CI: 0.86 to 1.08, p = 0.561) for patients with at least 1 "other" CV hospitalization (i.e., excluding admissions for worsening heart failure) and 1.06 (95% CI: 0.93 to 1.22, p = 0.351) for those with at least 1 non-CV hospitalization. Figure 1 shows bar plots for the distributions of the frequencies of hospitalizations for the different hospitalization types.

Baseline variables associated with hospitalization. Several baseline characteristics were significantly associated with the risk of being hospitalized at least once for worsening heart failure (0 vs. ≥1) (Table 2). Patients more likely to be hospitalized were older and had a higher NYHA functional class, heart rate, serum creatinine concentration, N-terminal pro-B type natriuretic peptide level, and high-sensitivity C-reactive protein activity. These patients had a lower ejection fraction, lower systolic blood pressure, diastolic blood pressure, cholesterol level, low-density lipoprotein level, triglyceride level, and estimated glomerular filtration rate (GFR). They were more likely to have a history of diabetes and atrial fibrillation and have a pacemaker implanted. Other baseline characteristics associated with being hospitalized were treatment with a loop diuretic (or a loop or thiazide diuretic), an aldosterone antagonist, digitalis glycoside, antiarrhythmic drug, or anticoagulant therapy. Those baseline characteristics associated with not being hospitalized were treatment with angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, or antiplatelet therapy.

Additionally, several baseline characteristics were associated with the risk of being hospitalized at least twice compared with being hospitalized only once for worsening

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme

ARB = angiotensin-receptor blocker

CABG = coronary artery bypass graft

CV = cardiovascular

GFR = glomerular filtration rate

HFH = heart failure hospitalization

hsCRP = high-sensitivity C-reactive protein

NT-pro-BNP = N-terminal pro-B type natriuretic peptide

NYHA = New York Heart Association

PCI = percutaneous coronary intervention

Table 1	Number of Patients Hospitalized and Number of Hospital Admissions in CORONA	
Parameter	**Placebo**	**Rosuvastatin**
Number of patients	2,497	2,514
Total follow-up years	6,201	6,266
Number of deaths	759	728
Number of CV deaths	593	581
All-cause hospitalizations		
Patients with ≥1 admission	1,523	1,489
Patients with ≥2 admissions	934	883
Number of hospitalizations	4,074	3,694
CV hospitalizations		
Patients with ≥1 admission	1,164	1,104
Patients with ≥2 admissions	589	534
Number of hospitalizations	2,564	2,193
Heart failure hospitalizations		
Patients with ≥1 admission	669	622
Patients with ≥2 admissions	295	246
Number of hospitalizations	1,299	1,109
Patients with number of hospitalizations		
1	374	376
2	153	134
3	63	58
4	32	24
5	16	13
6	14	6
7	12	4
8	1	2
9	1	2
10	1	2
12	0	1
13	1	0
14	1	0

CORONA = Controlled Rosuvastatin Multinational Trial in Heart Failure; CV = cardiovascular.

heart failure. Patients more likely to experience repeat HFH (exactly 1 vs. ≥2) were younger, had a higher heart rate; and higher serum creatinine, N-terminal pro-B type natriuretic peptide, and high-sensitivity C-reactive protein and lower ejection fraction, systolic blood pressure, and cholesterol. They were more likely to be treated with a loop
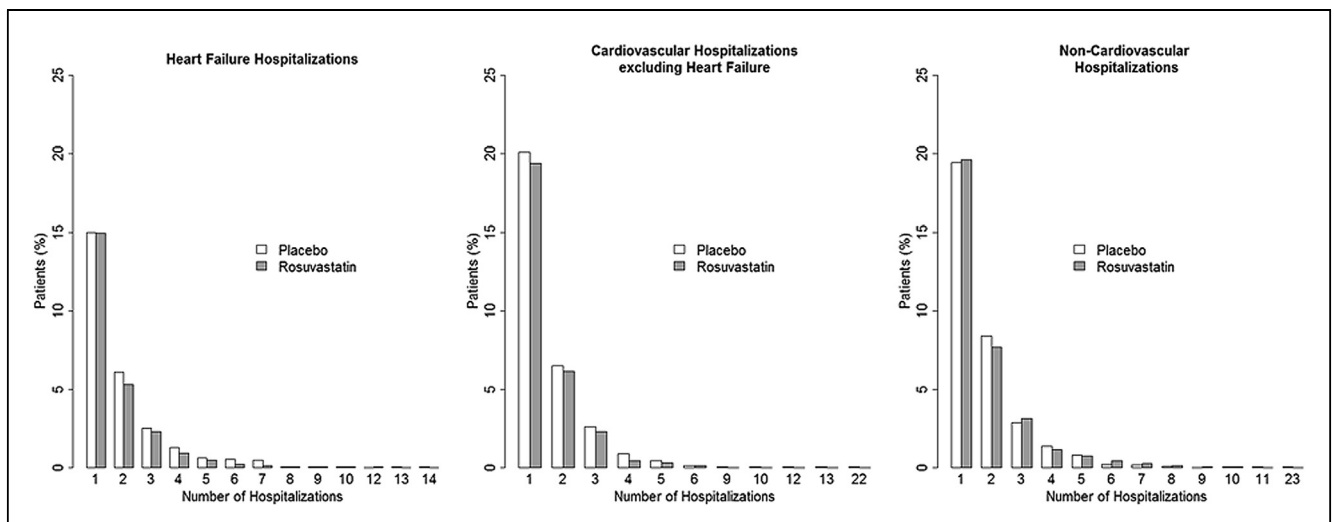

| Figure 1 | Hospitalizations per Person |

Distributions per person of: 1) the number of heart failure hospitalizations; 2) cardiovascular (CV) hospitalizations that were not heart failure; and 3) non-CV hospitalizations.

Table 2	Baseline Characteristics by Hospitalization Status		
	Number of Heart Failure Hospitalizations		
	0	**1**	**≥2**
Age	72.4 ± 7.1	74.0 ± 6.8	72.7 ± 7.3
Females (%)	882 (23.7)	177 (23.6)	121 (22.4)
NYHA functional class (%)			
II	1,494 (40.2)	228 (30.4)	135 (25.0)
III	2,186 (58.8)	505 (67.3)	390 (72.1)
IV	40 (1.1)	17 (2.3)	16 (3.0)
Ejection fraction	0.31 ± 0.1	0.30 ± 0.1	0.29 ± 0.1
Body mass index (kg/m²)	27.2 ± 4.5	27.2 ± 4.7	27.3 ± 4.8
Systolic blood pressure	130 ± 16.3	128 ± 16.6	125 ± 17.0
Diastolic blood pressure	76.6 ± 8.9	75.4 ± 8.8	74.6 ± 8.9
Heart rate	70.8 ± 11.0	73.2 ± 11.4	75.2 ± 11.5
Current smokers (%)	409 (11.0)	72 (9.6)	47 (8.7)
No. with the following medical history (%)			
Myocardial infarction	2,218 (59.6)	444 (59.2)	342 (63.2)
Angina pectoris	2,676 (71.9)	545 (72.7)	417 (77.1)
CABG or PCI	969 (26.0)	188 (25.1)	141 (26.1)
Hypertension	2,341 (62.9)	478 (63.7)	356 (65.8)
Diabetes mellitus	1,010 (27.2)	265 (35.3)	202 (37.3)
Atrial fibrillation	1,399 (37.6)	382 (50.9)	273 (50.5)
Stroke	446 (12.0)	100 (13.3)	78 (14.4)
Pacemaker implanted	357 (9.6)	111 (14.8)	93 (17.2)
Implantable cardioverter-defibrillator	105 (2.8)	17 (2.3)	14 (2.6)
Laboratory measurements			
Cholesterol	5.41 ± 1.1	5.25 ± 1.1	5.09 ± 1.1
Low-density lipoprotein	3.60 ± 0.9	3.47 ± 0.9	3.35 ± 0.9
High-density lipoprotein	1.24 ± 0.3	1.22 ± 0.4	1.21 ± 0.4
ApoB/ApoA-I ratio	0.87 ± 0.2	0.87 ± 0.3	0.87 ± 0.3
Triglycerides	2.03 ± 1.3	1.96 ± 1.2	1.85 ± 1.4
Serum creatinine	114 ± 27.3	118 ± 28.7	123 ± 30.8
Estimated GFR	58.2 ± 14.3	55.5 ± 14.2	53.8 ± 14.6
NT-pro-BNP	173 [88; 231]	173 [154; 386]	199 [173; 512]
hsCRP	3.20 [1.5; 6.9]	4.00 [1.8; 7.9]	5.20 [2.4; 10.3]
No. of patients currently taking the following medications (%)			
Loop diuretic	2,649 (71.2)	640 (85.3)	500 (92.4)
Loop or thiazide diuretic	3,201 (86.0)	693 (92.4)	522 (96.5)
Aldosterone antagonist	1,346 (36.2)	331 (44.1)	288 (53.2)
ACE inhibitor	2,998 (80.6)	596 (79.5)	417 (77.1)
ACE inhibitor or ARB	3,432 (92.3)	683 (91.1)	484 (89.5)
Beta-blocker	2,849 (76.6)	524 (69.9)	393 (72.6)
Digitalis glycoside	1,107 (29.8)	301 (40.1)	240 (44.4)
Antiarrhythmic therapy	425 (11.4)	114 (15.2)	85 (15.7)
Antiplatelet therapy	2,271 (61.0)	409 (54.5)	292 (54.0)
Anticoagulant therapy	1,235 (33.2)	308 (41.1)	224 (41.4)
Antiplatelet or anticoagulant therapy	3,344 (89.9)	683 (91.1)	497 (91.9)

Values are mean ± SD, n (%), or mean [interquartile range].

ACE = angiotensin-converting enzyme; Apo = apolipoprotein; ApoA-I = apolipoprotein A-inhibitor; Apo-ARB = angiotensin-receptor blocker; CABG = coronary artery bypass graft; GFR = glomerular filtration rate; hsCRP = high-sensitivity C-reactive protein; NT-pro-BNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

diuretic (or loop or thiazide diuretic) and an aldosterone antagonist.

A multivariate model was also used to identify independent predictors of admission, as described later (Table 3).

During the trial, 71 patients (31 rosuvastatin/40 placebo) had an acute myocardial infarction preceding a subsequent HFH. Therefore, 1,220 patients (591 rosuvastatin/629 placebo) experienced a HFH that was not preceded by a myocardial infarction during the trial.

Cumulative incidence of HFH. The cumulative crude numbers of HFH per 100 patients in the 2 treatment groups are shown in Figure 2. The cumulative incidence curves did not seem to diverge until approximately 12 months but continued to separate thereafter. To

Table 3	Variables Associated With Heart Failure Hospitalization Rates (Rate Ratio, 95% CI, and p Value) in the Multivariate Negative Binomial Regression Model		
	Rate Ratio	**95% CI**	**p Value**
Rosuvastatin versus placebo	0.815	0.72–0.92	0.001
Age*	1.007	0.94–1.08	0.834
Female	1.083	0.93–1.27	0.316
NYHA class (compared to class II)			
III	1.515	1.32–1.74	<0.001
IV	2.146	1.35–3.40	0.001
Ejection fraction*	0.803	0.75–0.86	<0.001
Systolic blood pressure*	0.853	0.80–0.91	<0.001
Heart rate*	1.268	1.19–1.35	<0.001
Medical history			
Angina pectoris	1.291	1.12–1.49	<0.001
Diabetes mellitus	1.553	1.36–1.78	<0.001
Atrial fibrillation	1.350	1.19–1.54	<0.001
Pacemaker implanted	1.321	1.10–1.59	0.003
Laboratory measurements			
LDL cholesterol*	0.882	0.83–0.94	<0.001
Serum creatinine*	1.213	1.14–1.29	<0.001
NT-pro-BNP*	1.404	1.33–1.48	<0.001

*Rate ratio is per 1-SD increase.

CI = confidence interval; LDL = low-density lipoprotein; NT-pro-BNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association.

incorporate the competing risk of death, the Ghosh and Lin approach was also plotted (Fig. 2). The Ghosh and Lin rates were consistently lower than the cumulative incidence ones, but the separation between the treatment groups appeared to occur at the same time and to the same extent.

Because there were no between-treatment differences in CV death (Fig. 3), use of the Ghosh and Lin approach made a negligible difference to the effect of rosuvastatin on hospitalization. Figure 4 shows the ratio of the crude cumulative numbers of HFH for the rosuvastatin group compared with that of placebo. This ratio remained approximately 1 for the first year before decreasing to
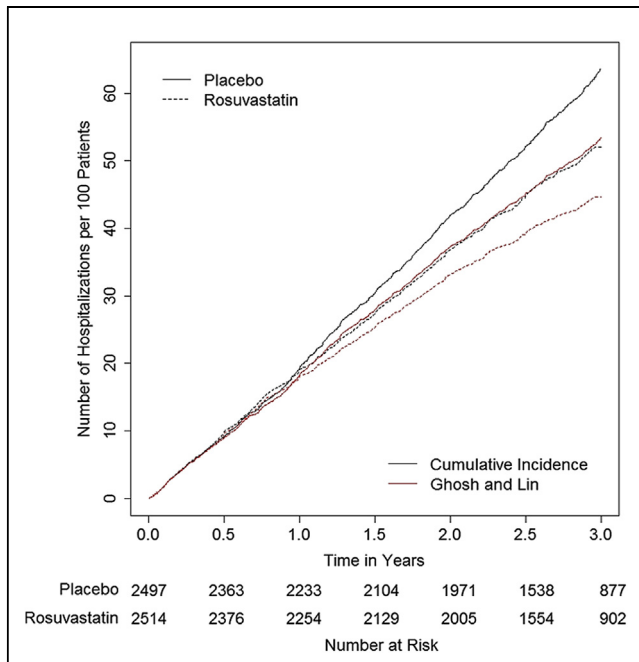

Figure 2   **Rate of Heart Failure Hospitalizations**

Estimated cumulative rate of heart failure hospitalizations per 100 patients over time, by treatment group and statistical method.
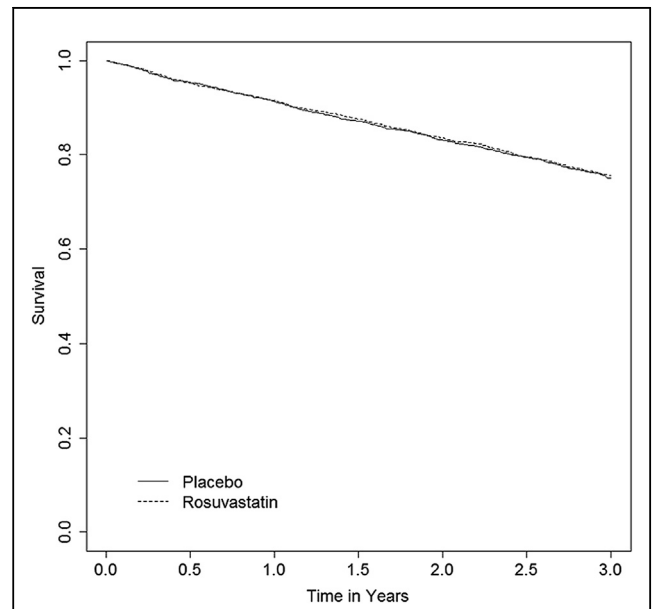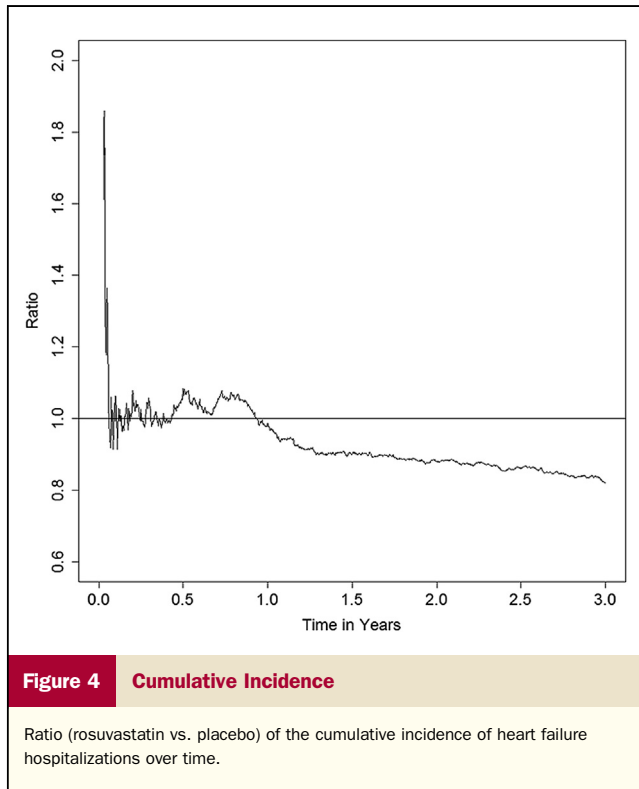

Figure 3   **Cardiovascular Death**

Kaplan-Meier curves for CV death (rosuvastatin vs. placebo).

Figure 4   **Cumulative Incidence**

Ratio (rosuvastatin vs. placebo) of the cumulative incidence of heart failure hospitalizations over time.

Figure 5   **Comparison of Results From Different Methods**

Unadjusted hazard ratio for conventional (Cox) time to first event analyzes of heart failure hospitalization (HFH), as well as rate ratios for the Poisson, Andersen-Gill, and negative binomial analyses of all HFH; negative binomial for the composite of all HFHs and CV (CV) death and the rate ratio for all HFHs from the joint frailty model.

approximately 0.85 by 1.5 years, after which it appeared fairly constant.

Modeling of HFH rates. In the placebo group there were 1,299 HFH over 6,201 years of follow-up, in comparison with 1,109 HFH over 6,266 years of follow-up in the rosuvastatin group. Thus, HFH rates in the placebo and rosuvastatin groups were 21.0 and 17.7 per 100 patient years, respectively, giving a rate ratio of 0.84 (95% CI: 0.78 to 0.92, p < 0.001).

The negative binomial regression model gave an unadjusted rate ratio for HFH in the rosuvastatin group compared with the placebo group of 0.86 (95% CI: 0.75 to 0.99, p = 0.030). Table 3 shows results from the multivariate negative binomial regression model examining the association between baseline covariates and HFH rates. In addition to rosuvastatin treatment, baseline covariates independently associated with increased HFH rates were: being female, history of angina pectoris, diabetes, atrial fibrillation and an implanted pacemaker, higher NYHA functional class, heart rate, serum creatinine and N-terminal pro-B type natriuretic peptide, a lower ejection fraction, lower systolic blood pressure, and lower low-density lipoprotein (LDL) cholesterol. The rate ratio for rosuvastatin, adjusted for baseline covariates, was 0.81 (95% CI: 0.72 to 0.92, p = 0.001).

Rates of CV hospitalizations (both for heart failure and other CV reasons) and hospitalizations for any cause were also analyzed using the negative binomial regression model. The rate ratio for CV hospitalizations for rosuvastatin, as compared with placebo, was unadjusted 0.85 (95% CI: 0.77 to 0.93, p = 0.001) and 0.83 adjusted for the same covariates
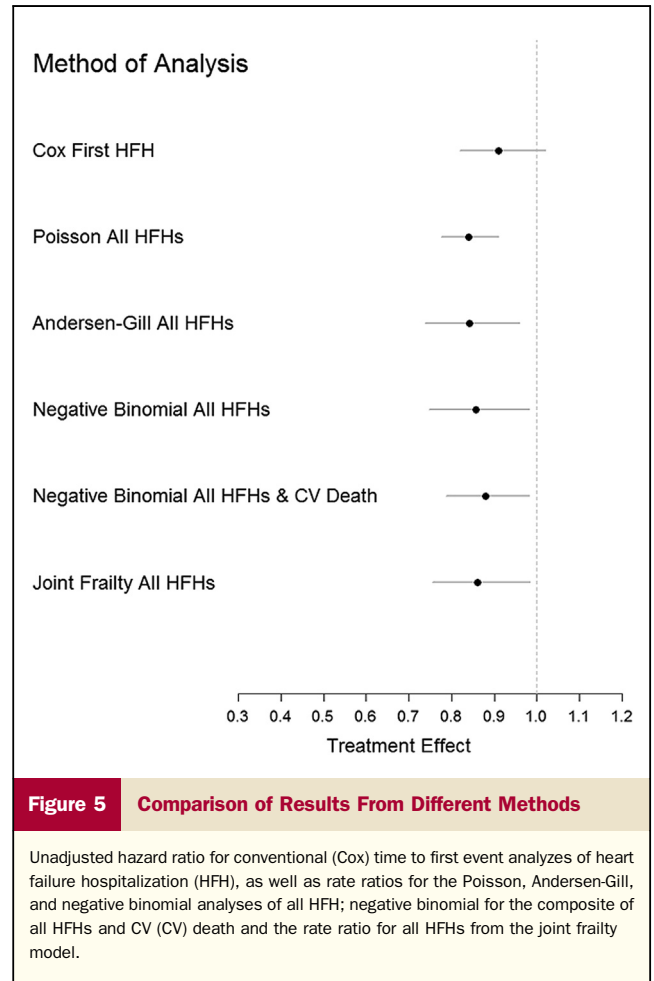
(95% CI: 0.76 to 0.91, p < 0.001). For all-cause hospitalizations, the rate ratio was unadjusted 0.90 (95% CI: 0.83 to 0.97, p = 0.009) and 0.89 adjusted (95% CI: 0.83 to 0.96, p = 0.002).

The negative binomial regression model was also used to analyze the composite of recurrent HFH and CV death, where CV death was treated as an additional event. This gave a rate ratio for rosuvastatin, compared with placebo, of 0.88 (95% CI: 0.79 to 0.98, p = 0.025). An adjusted analysis gave a rate ratio of 0.85 (95% CI: 0.77 to 0.94, p = 0.001).

A joint frailty model was also used to estimate the recurrent HFH rate ratio, taking into account CV death as informative censoring and an estimate for the hazard ratio for CV death taking into account the impact of hospitalizations. This approach gave an estimated rosuvastatin/placebo rate ratio of 0.86 (95% CI: 0.75 to 0.98, p = 0.028) for HFH. The estimated hazard ratio for CV death in the rosuvastatin group, compared with placebo, was 0.99 (95% CI: 0.85 to 1.16, p = 0.890). Analyses adjusted for baseline covariates gave a rate ratio for HFH of 0.82 (95% CI: 0.73 to 0.92, p = 0.001) and a hazard ratio for CV death of 0.94 (95% CI: 0.82 to 1.09, p = 0.423).

In summary, Figure 5 shows the hazard ratio for the conventional time-to-first event analysis for HFH (0.91 [95% CI: 0.82 to 1.02, p = 0.105]) and the rate ratios for the Poisson and Andersen-Gill results for the HFH and negative binomial models for the HFH and the composite of recurrent HFH and CV death, along with the estimated rate ratio from the joint frailty model.

Discussion

In this retrospective analysis, we found evidence that treatment with rosuvastatin causes a highly significant reduction in the overall incidence of hospitalizations for worsening heart failure in the CORONA trial, although the effect size was modest.

As in other recent reports, we showed that first hospitalizations (the only admissions counted in conventional time-to-first analyses) represented just over one-half of such events. Specifically, 1,291 patients had 1 or more admissions for heart failure (750 of these had a single admission only), and there were a total of 2,408 admissions for heart failure. Therefore, 1,291 of 2,408 hospitalizations for heart failure in CORONA (54%) were first admissions, a remarkably similar proportion to that in the SHIFT (56%), EMPHASIS-HF (58%), and CHARM-Preserved (54%) studies (4–6).

The effect of rosuvastatin on second or subsequent hospital admissions was at least as large as on the first admission. This explains why the present analysis of all events (as opposed to just first events) had more power to demonstrate a significant benefit from rosuvastatin. Three other recent analyzes also showed a beneficial effect of the treatments studied (ivabradine, eplerenone, and candesartan) on repeat as well as on first events (4–6).

What was different in the present study was that the benefit of ivabradine, eplerenone, and candesartan was rapid onset, whereas that of rosuvastatin seemed to be delayed for almost a year (4–6). This probably contributed to the modest overall treatment effect size and may also explain why the anticipated benefit on CV mortality (because HFH is associated with an increased risk of death and usually a reduction in the former is associated with a reduction in the latter) was not observed; that is, any beneficial effect on reducing mortality might have been delayed and not demonstrable within the time frame of the CORONA trial.

Although the effect of rosuvastatin was not as large as with the other treatments mentioned, its use in CORONA did prevent approximately 80 fewer admissions for heart failure per 1,000 patients treated over a median of 33 months of follow-up. This compares with 93 admissions (over 23 months), 122 admissions (over 25 months), and 104 admissions (over 37 months) prevented per 1,000 patients treated with ivabradine in SHIFT, eplerenone in EMPHASIS-HF, and candesartan in CHARM-Preserved studies, respectively (4–6).

These findings obviously raise questions about possible mechanisms underlying the effect of rosuvastatin on HFH (and why the effect might take time to become manifest). One obvious explanation is prevention of myocardial infarction (in turn leading to prevention of worsening heart failure). Relatively few patients (n = 71) suffered an endpoint committee-confirmed event of this type, and, although numerically fewer in the rosuvastatin group (n = 31) versus placebo (n = 40), the difference between treatments was not significant and could not have accounted for the difference in HFH observed (2). It is possible, however, that smaller, "subclinical," infarcts were prevented by rosuvastatin. However, rosuvastatin did not reduce troponin levels in a substudy of CORONA (13). Alternatively, there has been much interest in the so-called pleiotropic effects of statins, the best recognized of which is an anti-inflammatory action. Certainly, rosuvastatin reduced plasma hsCRP concentrations in CORONA (2), although in a substudy, it did not affect the levels of other cytokines (14).

Whatever the mechanism of action, the benefit observed, although modest, is clinically worthwhile given that it is incremental (i.e., additional to the benefits of standard treatments), that the treatment in question is a generic and inexpensive one and that statins are very well tolerated in patients with heart failure, with high-quality safety data available from 2 large placebo-controlled randomized trials (2,15). Current guidelines correctly do not recommend statins in heart failure based upon appropriately strict interpretation of the primary analyses of the 2 key randomized trials (16,17). We believe that these new results should lead to further assessment of the role of statins in ischemic, systolic, heart failure.

On a more methodological note, the summary of findings in Figure 5 shows how the use of all HFH (including repeat events) could enhance the ability to detect treatment differences compared with the Cox model using first hospitalization only. The Poisson method should not be used because it naively treats all hospitalizations as equally important and gives a false sense of precision in its estimates of rate ratio by failing to account for the heterogeneity in individual patient risks of repeat events. The other methods (negative binomial, Andersen-Gill with robust standard errors, and joint frailty model) show a consistency of findings, directly accounting for the skewed distribution of hospitalizations and toning down the influence of those patients with many hospitalizations. For future heart failure trials, we would encourage greater use of such repeat event analyses as they enhance statistical power and they capture the total disease burden with regards to HFH.

Study limitations. Our report has a number of limitations. First, we looked at outcomes other than the primary endpoint. Although we believe analysis of repeat events is important, it has not been the standard approach used in most CV trials to date. Although we have shown that rosuvastatin appears to reduce HFH, we do not have a good explanation for this effect (or its time course). All patients in CORONA had systolic heart failure from ischemic causes, and we do not know whether the

treatment effect described would be seen in nonischemic heart failure (and another trial suggests it might not be [15]) or in patients with heart failure and preserved ejection fraction. It should be noted that 3,720 of the 5,011 (74%) patients randomized did not have any HFH during follow-up, resulting in a large number of zeros in the dataset. The negative binomial distribution is commonly used to analyze such skewed distributions as an alternative to zero-inflated models (18).

Conclusions

In older patients with ischemic systolic heart failure, treatment with rosuvastatin led to an approximate RR reduction of 15% to 20% in total HFH, equating to an absolute reduction of approximately 76 fewer admissions for heart failure per 1,000 patients treated over a median of 33 months of follow-up. Although modest, this benefit is potentially clinically worthwhile and should lead to further investigation of the role of statins in ischemic systolic heart failure.

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