Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Rosuvastatin for Sepsis Associated Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network

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This document supplements the information contained in the manuscript entitled **"Rosuvastatin for Sepsis Associated Acute Respiratory Distress Syndrome. "**

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Figure S1

Log Day 6 CRP vs log Peak Rosuvastatin, R=0.29, P value=0.0005
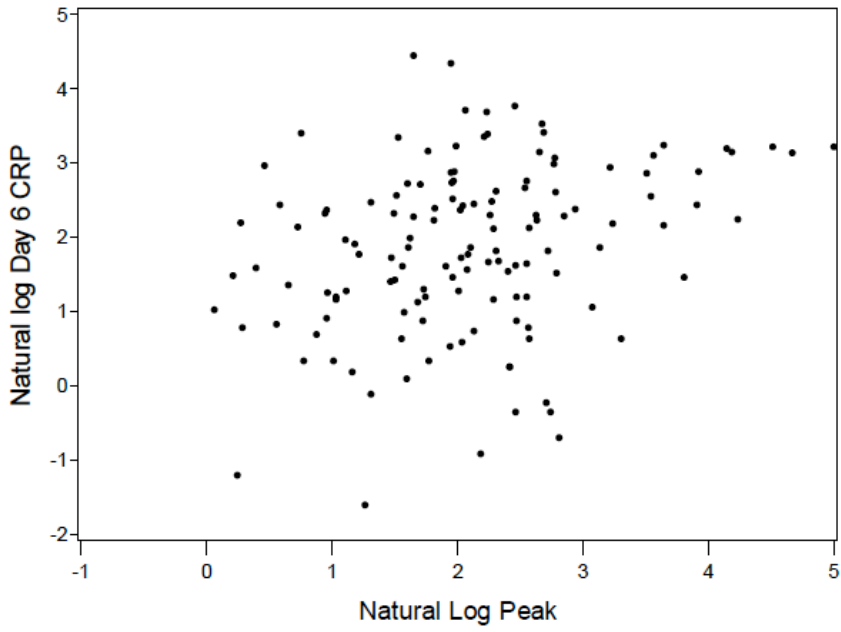
Figure S2

Log Day 6 CRP vs log Trough Rosuvastatin, R=0.27, P value=0.0008
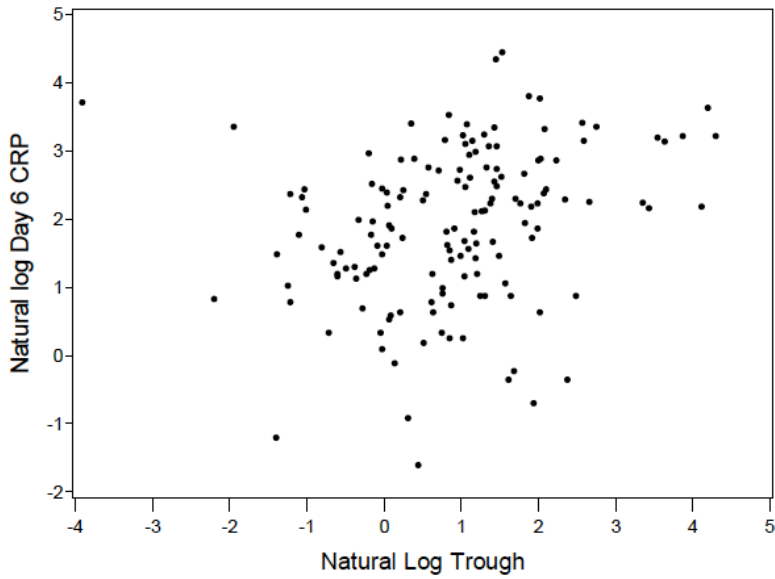
Table S1: Other exclusions referred to in Figure 1

711 Other exclusions in Figure 1	Number
Receiving niacin, fenofibrate, cyclosporine, gemfibrozil, lopinavir, ritonavir or planned use of oral contraceptives or estrogen therapy during the ICU stay	105
Diffuse alveolar hemorrhage from vasculitis	104
Chronic respiratory failure defined as PaCO2 > 60 mm Hg in the outpatient setting	88
Allergy or intolerance to statins	71
Intraparenchymal CNS bleed within 6 months	71
Home mechanical ventilation (noninvasive ventilation or via tracheotomy) except for CPAP/BIPAP used solely for sleep-disordered breathing	62
Pregnancy or breast feeding	50
Cardiac disease classified as NYHA class IV	47
Unwillingness or inability to utilize the ARDS network 6ml / kg PBW ventilation protocol	44
Physician insistence on AVOIDANCE of statins during the current hospitalization	32
Burns > 40% total body surface area	19
Age less than 18 years	9
Diagnosis of hypothyroidism and not on thyroid replacement therapy	9

Table S2: Expanded table of baseline characteristics

Baseline Characteristics	All Patients		Prior Statin Users	
Characteristic	Rosuvastatin (N =379)	Placebo (N =366)	Rosuvastatin (N =54)	Placebo (N =55)
Age, y	54.2 ± 17.1	54.1 ± 15.6	64.3 ± 14.6	62.7 ± 12.5
Women, No. (%)	195 (52)	185 (51)	25 (46)	27 (49)
White, No. (%)	301 (83)	289 (81)	49 (93)	45 (85)
Hispanic or latino, No. (%)	46 (12)	40 (11)	4 (7)	6 (11)
Medical ICU, No. (%)	330 (87)	317 (87)	51 (94)	52 (95)
Primary cause of lung injury, No. (%)				
Pneumonia	267 (71%)	260 (71%)	38 (72%)	37 (67%)
Non-pulmonary infection	72 (19%)	73 (20%)	9 (17%)	13 (24%)
Aspiration	26 (7%)	23 (6%)	4 (8%)	3 (6%)
Other	7 (2%)	4 (1%)	2 (4%)	2 (4%)
Multiple Transfusion	3 (1%)	1 (0%)		
Trauma	2 (1%)	4 (1%)		

Baseline Characteristics	All Patients		Prior Statin Users	
Characteristic	Rosuvastatin (N =379)	Placebo (N =366)	Rosuvastatin (N =54)	Placebo (N =55)
Weight, kg	88.4 ± 29.9	86.7 ± 30.8	93.2 ± 23.9	91.6 ± 29.6
BMI +	31.0 ± 9.9	30.4 ± 10.1	32.5 ± 7.8	31.9 ± 8.7
APACHE III score †	92.1 ± 28.4	94.8 ± 27.9	94.6 ± 24.2	94.4 ± 25.8
Diabetes, No. (%)	84 (22)	86 (24)	26 (48)	22 (40)
Chronic renal failure requiring dialysis, No. (%)	5 (1)	10 (3)	1 (2)	2 (4)
Baseline shock, No. (%) ¦	173 (46)	166 (45)	29 (54)	28 (51)
Prerandomization fluid intake, mL/24 h	3970 ± 2386	4149 ± 2839	3341 ± 2021	4208 ± 2530
Prerandomization fluid balance, mL/24 h	2128 ± 2635	2227 ± 3136	1513 ± 2286	2144 ± 3418
Mean arterial pressure, mm Hg	76.5 ± 13.5	77.0 ± 13.9	77.1 ± 16.1	77.5 ± 12.7
Central venous pressure, mm Hg	12.3 ± 4.9	11.2 ± 4.8*	12.0 ± 5.2	12.1 ± 5.0
Tidal volume, mL/kg predicted body weight	6.6 ± 1.1	6.8 ± 1.3**	7.0 ± 1.6	6.7 ± 1.3
Minute ventilation, L/min	10.7 ± 3.1	10.8 ± 3.2	10.7 ± 3.6	11.0 ± 3.4
Inspiratory plateau pressure, cm H2O	23.4 ± 6.6	23.6 ± 6.6	21.2 ± 5.1	22.6 ± 5.6
PEEP, cm H2O	9.2 ± 3.7	9.2 ± 3.9	8.3 ± 2.9	8.4 ± 3.8
PaCO2, mm Hg	39.9 ± 9.9	40.7 ± 11.7	41.0 ± 12.2	41.6 ± 13.5
$PaO_2:FIO_2$ ratio mm Hg	170 ± 71	170 ± 67	179 ± 63	178 ± 78
$PaO_2:FIO_2$ ratio <= 200, No. (%)	267 (72)	253 (70)	32 (62)	33 (60)
Oxygenation index cm H_2O/mm Hg †	10.8 ± 6.9	11.2 ± 8.2	9.3 ± 5.9	11.1 ± 9.6
BUN, mg/dL ‡	28 ± 21	28 ± 20	33 ± 21	38 ± 20
Creatinine, mg/dL ‡	1.6 ± 1.3	1.5 ± 1.1	1.9 ± 1.5	1.8 ± 1.3
Creatine kinase, U/L	224 ± 417	214 ± 396	207 ± 288	196 ± 224
Alanine aminotransferase, U/L	37 ± 37	36 ± 34	35 ± 26	38 ± 35
Aspartate aminotransferase, U/L	54 ± 69	50 ± 44	49 ± 45	44 ± 28
Hours from intubation to randomization, No. (%)				
<=24 Hrs	124 (33%)	129 (35%)	17 (32%)	26 (47%)
24<time<=48 Hrs	204 (54%)	192 (53%)	26 (48%)	21 (38%)
48<time<=72 Hrs	41 (11%)	31 (9%)	9 (17%)	4 (7%)
>72 Hrs	10 (3%)	13 (4%)	2 (4%)	4 (7%)

Baseline Characteristics	All Patients		Prior Statin Users	
Characteristic	**Rosuvastatin (N =379)**	**Placebo (N =366)**	**Rosuvastatin (N =54)**	**Placebo (N =55)**
Unknown	0 (0%)	1 (0%)		
Hours from meeting ARDS criteria to randomization, No. (%)				
<=24 Hrs	192 (51%)	200 (55%)	26 (48%)	30 (55%)
24-48 Hrs	184 (49%)	162 (44%)	28 (52%)	25 (46%)
>48 Hrs	3 (1%)	4 (1%)		

Table S2. Baseline Characteristics (All patients and Prior Statin Users)
Plus–minus values are means ±SD. Race was assigned by the coordinators on the basis of hospital records or information from the next of kin. Because of rounding, not all percentages total 100. PEEP denotes positive end-expiratory pressure, PaO_2 partial pressure of arterial oxygen, $PaC0_2$ partial pressure of arterial carbon dioxide, FiO_2 fraction of inspired oxygen, and BUN blood urea nitrogen. Enrolled patients with non-pulmonary infections were classified as having sepsis as the primary cause of lung injury.
*P= 0.02 ** p=0.04
+Body Mass Index, Calculated as weight in kilograms divided by height in meters squared.
†APACHE III denotes Acute Physiology, Age, and Chronic Health Evaluation.
Scores can range from 0 to 299, with higher scores indicating more severe illness.
¦Shock was defined as a mean arterial pressure below 60 mmHg or the use of vasopressors as previously described[27].
†Oxygenation Index, calculated as mean airway pressure x (FiO_2/PaO_2) x 100 (cm H_2O/mm Hg).
‡To convert the levels for blood urea nitrogen to millimoles per liter, multiply by 0.357. To convert the levels for creatinine to micromoles per liter, multiply by 88.4.

Table S3: Percent having 10mg on-study dose

Day	Placebo Percent ± SE	N	Rosuvastatin Percent ± SE	N	Overall Percent ± SE	N	P [1]
1	4.7% ± 1.1%	362	8.3% ± 1.4%	372	6.5% ± 0.9%	734	0.05
2	5.1% ± 1.2%	355	7.7% ± 1.4%	364	6.4% ± 0.9%	719	0.15
3	4.3% ± 1.1%	345	7.6% ± 1.4%	353	6.0% ± 0.9%	698	0.07
4	3.8% ± 1.0%	339	5.0% ± 1.2%	339	4.4% ± 0.8%	678	0.44
5	2.8% ± 0.9%	323	6.8% ± 1.4%	325	4.8% ± 0.8%	648	**0.02**
6	2.7% ± 0.9%	299	6.3% ± 1.4%	300	4.5% ± 0.8%	599	**0.04**
7	2.6% ± 1.0%	266	6.1% ± 1.4%	279	4.4% ± 0.9%	545	0.06
8	3.9% ± 1.3%	231	7.8% ± 1.7%	243	5.9% ± 1.1%	474	0.07
9	6.5% ± 1.7%	201	7.5% ± 1.8%	213	7.0% ± 1.3%	414	0.67
10	3.9% ± 1.4%	180	3.7% ± 1.4%	191	3.8% ± 1.0%	371	0.92
11	6.8% ± 2.0%	161	4.9% ± 1.7%	164	5.8% ± 1.3%	325	0.46
12	4.1% ± 1.6%	146	4.1% ± 1.6%	146	4.1% ± 1.2%	292	0.95
13	3.8% ± 1.7%	130	4.8% ± 1.9%	124	4.3% ± 1.3%	254	0.63
14	2.6% ± 1.5%	116	4.6% ± 2.0%	109	3.6% ± 1.2%	225	0.43
15	3.8% ± 1.9%	104	3.2% ± 1.8%	94	3.5% ± 1.3%	198	0.78
16	2.4% ± 1.7%	83	4.9% ± 2.4%	82	3.6% ± 1.5%	165	0.42
17	2.7% ± 1.9%	73	7.2% ± 3.1%	69	4.9% ± 1.8%	142	0.23
18	1.6% ± 1.6%	62	7.6% ± 3.3%	66	4.7% ± 1.9%	128	0.12
19	3.4% ± 2.4%	58	8.2% ± 3.5%	61	5.9% ± 2.2%	119	0.25
20	3.6% ± 2.5%	55	6.9% ± 3.3%	58	5.3% ± 2.1%	113	0.38
21	6.0% ± 3.4%	50	6.1% ± 3.4%	49	6.1% ± 2.4%	99	1.00
22	4.4% ± 3.1%	45	4.4% ± 3.1%	45	4.4% ± 2.2%	90	0.69
23	4.9% ± 3.4%	41	7.7% ± 4.3%	39	6.3% ± 2.7%	80	0.81
24	5.3% ± 3.6%	38	10.8% ± 5.1%	37	8.0% ± 3.1%	75	0.43
25	2.9% ± 2.8%	35	13.3% ± 6.2%	30	7.7% ± 3.3%	65	0.14
26	2.9% ± 2.9%	34	14.8% ± 6.8%	27	8.2% ± 3.5%	61	0.12
27	3.4% ± 3.4%	29	11.5% ± 6.3%	26	7.3% ± 3.5%	55	0.25
28	3.6% ± 3.5%	28	12.5% ± 6.8%	24	7.7% ± 3.7%	52	0.26

[1] p-value from linear model stratified over possible patient types

Rosuvastatin subjects were more likely to receive 10 mg study drug dose on study days 5 and 6. Dose is reduced to 10 mg from 20 mg for serum creatinine ≥ 2.8 mg/dL, provided patient not receiving renal replacement therapy.   Missed doses and deaths may also impact percentages

Table S4: Percent having 20mg on-study dose

Day	Placebo Percent ± SE	N	Rosuvastatin Percent ± SE	N	Overall Percent ± SE	N	P [1]
1	90.3% ± 1.6%	362	85.5% ± 1.8%	372	87.9% ± 1.2%	734	**0.04**
2	89.6% ± 1.6%	355	84.3% ± 1.9%	364	86.9% ± 1.3%	719	**0.04**
3	87.8% ± 1.8%	345	81.0% ± 2.1%	353	84.4% ± 1.4%	698	**0.01**
4	85.8% ± 1.9%	339	82.0% ± 2.1%	339	83.9% ± 1.4%	678	0.17
5	87.3% ± 1.9%	323	81.2% ± 2.2%	325	84.3% ± 1.4%	648	**0.03**
6	86.0% ± 2.0%	299	80.0% ± 2.3%	300	83.0% ± 1.5%	599	0.05
7	83.8% ± 2.3%	266	79.2% ± 2.4%	279	81.5% ± 1.7%	545	0.16
8	79.7% ± 2.6%	231	74.5% ± 2.8%	243	77.0% ± 1.9%	474	0.18
9	77.6% ± 2.9%	201	74.6% ± 3.0%	213	76.1% ± 2.1%	414	0.48
10	77.8% ± 3.1%	180	77.0% ± 3.0%	191	77.4% ± 2.2%	371	0.87
11	73.9% ± 3.5%	161	75.0% ± 3.4%	164	74.5% ± 2.4%	325	0.81
12	77.4% ± 3.5%	146	70.5% ± 3.8%	146	74.0% ± 2.6%	292	0.19
13	74.6% ± 3.8%	130	72.6% ± 4.0%	124	73.6% ± 2.8%	254	0.77
14	74.1% ± 4.1%	116	68.8% ± 4.4%	109	71.6% ± 3.0%	225	0.40
15	70.2% ± 4.5%	104	69.1% ± 4.8%	94	69.7% ± 3.3%	198	0.88
16	67.5% ± 5.1%	83	67.1% ± 5.2%	82	67.3% ± 3.7%	165	0.99
17	64.4% ± 5.6%	73	58.0% ± 5.9%	69	61.3% ± 4.1%	142	0.47
18	61.3% ± 6.2%	62	56.1% ± 6.1%	66	58.6% ± 4.4%	128	0.57
19	60.3% ± 6.4%	58	57.4% ± 6.3%	61	58.8% ± 4.5%	119	0.75
20	61.8% ± 6.6%	55	62.1% ± 6.4%	58	61.9% ± 4.6%	113	0.98
21	58.0% ± 7.0%	50	63.3% ± 6.9%	49	60.6% ± 4.9%	99	0.58
22	53.3% ± 7.4%	45	55.6% ± 7.4%	45	54.4% ± 5.2%	90	0.79
23	53.7% ± 7.8%	41	53.8% ± 8.0%	39	53.8% ± 5.6%	80	0.94
24	55.3% ± 8.1%	38	51.4% ± 8.2%	37	53.3% ± 5.8%	75	0.70
25	54.3% ± 8.4%	35	50.0% ± 9.1%	30	52.3% ± 6.2%	65	0.72
26	55.9% ± 8.5%	34	44.4% ± 9.6%	27	50.8% ± 6.4%	61	0.36
27	55.2% ± 9.2%	29	46.2% ± 9.8%	26	50.9% ± 6.7%	55	0.47
28	46.4% ± 9.4%	28	33.3% ± 9.6%	24	40.4% ± 6.8%	52	0.26

[1] p-value from linear model stratified over possible patient types

Rosuvastatin subjects were less likely to receive 20 mg study drug dose on study days 1,2,3,5. Dose is reduced to 10 mg from 20 mg for serum creatinine ≥ 2.8 mg/dL, provided patient not receiving renal replacement therapy. Missed doses and deaths may also impact percentages.

Table S5: Peak and Trough Analysis

	PEAK (n=171)	TROUGH (n=187)	Half life in days (n=170)	Half life in hours (n=170)
Mean	13.38	5.09	0.84	20.10
Stdev	19.21	10.07	1.00	24.00
Median	7.31	2.37	0.56	13.40
Interquartile Range	8.67	3.56	0.43	10.42
Range	147.48	73.18	7.11	170.57
Percentile				
100% Max	148.00	73.20	7.22	173.35
90%	33.30	8.17	1.38	33.13
75% Q3	13.10	4.54	0.83	19.97
50% Median	7.31	2.37	0.56	13.40
25% Q1	4.43	0.98	0.40	9.55
10%	2.08	0.47	0.32	7.61
0% Min	0.52	0.02	0.12	2.78

Six patients had rosuvastatin values trough>peak.
Their trough values were included in the analysis but peak values were not.

A total of 171 patients had peak rosuvastatin measurements with a mean of 13.38 ng/ml;187 had trough measurements with a mean of 5.09 ng/ml. Log transformed trough rosuvastatin levels are positively associated with log highest on-study CK (p=0.014). Both log peak and log trough rosuvastatin levels are positively associated with log day 6 CRP and a change in the log day 6 CRP (please see the following plots). Neither peak nor trough rosuvastatin levels were associated with on-study ALT. The terminal elimination half life was calculated using peak/trough ratio (http://www.fvet.uba.ar/equinos/8313/half-life.pdf).

Table S6: Secondary Outcomes

Outcome	Placebo Percent of Patients ± SE	N	Rosuvastatin Percent of Patients ± SE	N	Overall Percent of Patients ± SE	N	P [1]
Arrhythmias	8.4% ± 1.5%	359	9.0% ± 1.5%	367	8.7% ± 1.0%	726	0.75
Bowel Ischemia	1.9% ± 0.7%	360	1.4% ± 0.6%	367	1.7% ± 0.5%	727	0.55
MI	0.6% ± 0.4%	360	0.5% ± 0.4%	367	0.6% ± 0.3%	727	0.99
Myopathy	8.9% ± 1.5%	360	6.8% ± 1.3%	367	7.8% ± 1.0%	727	0.30
Ischemic Stroke	0.3% ± 0.3%	360	0.3% ± 0.3%	367	0.3% ± 0.2%	727	0.99
VTE	6.9% ± 1.3%	360	6.3% ± 1.3%	367	6.6% ± 0.9%	727	0.72

[1] p-value from linear model stratified over possible patient types

Table S7: On Study Tidal Volume (ml/kg PBW)

Day	Placebo Mean ± SD	N	Rosuvastatin Mean ± SD	N	Overall Mean ± SD	N	P [1]
1	6.4 ± 1.1	246	6.3 ± 1.0	250	6.4 ± 1.1	496	0.13
2	6.4 ± 1.1	196	6.3 ± 1.1	198	6.3 ± 1.1	394	0.20
3	6.5 ± 1.4	171	6.2 ± 0.8	163	6.4 ± 1.2	334	0.06
4	6.4 ± 1.2	145	6.3 ± 1.0	130	6.3 ± 1.1	275	0.39
7	6.4 ± 1.6	91	6.3 ± 0.9	82	6.4 ± 1.3	173	0.74
12	6.7 ± 1.8	38	6.4 ± 0.7	24	6.6 ± 1.4	62	0.41
21	6.4 ± 1.5	17	6.4 ± 0.9	8	6.4 ± 1.3	25	0.98
28	5.9 ± 1.2	10	6.5 ± 1.1	6	6.2 ± 1.2	16	0.35

[1] p-value from linear model stratified over possible patient types

Table S8: On Study PEEP (cm H_2O)

Day	Placebo Mean ± SD	N	Rosuvastatin Mean ± SD	N	Overall Mean ± SD	N	P [1]
1	8.8 ± 3.9	354	8.6 ± 3.6	363	8.7 ± 3.7	717	0.39
2	8.1 ± 3.8	307	7.9 ± 3.5	308	8.0 ± 3.7	615	0.53
3	8.1 ± 3.6	259	7.9 ± 3.9	260	8.0 ± 3.8	519	0.66
4	7.9 ± 3.6	220	7.6 ± 3.4	223	7.7 ± 3.5	443	0.35
7	7.2 ± 3.1	144	7.5 ± 3.4	140	7.3 ± 3.2	284	0.42
12	7.3 ± 3.5	71	7.1 ± 2.6	47	7.2 ± 3.1	118	0.76
21	6.9 ± 2.7	29	6.4 ± 2.5	20	6.7 ± 2.6	49	0.91
28	6.8 ± 2.5	19	6.7 ± 2.6	12	6.8 ± 2.5	31	0.67

[1] p-value from linear model stratified over possible patient types

Table S9: On Study Fluid Balance (ml)

Day	Placebo Mean ± SD	N	Rosuvastatin Mean ± SD	N	Overall Mean ± SD	N	P [1]
1	1279.9 ± 2875.5	364	1480.8 ± 2326.1	377	1382.2 ± 2610.6	741	0.29
2	357.6 ± 2600.5	361	182.2 ± 2553.3	370	268.8 ± 2576.5	731	0.37
3	-128.7 ± 2214.9	349	-393.7 ± 2224.3	359	-263.1 ± 2222.1	708	0.12
4	-419.1 ± 2204.3	329	-515.3 ± 2266.3	333	-467.4 ± 2234.5	662	0.59
5	-230.4 ± 1999.0	306	-410.2 ± 1944.7	311	-321.0 ± 1972.3	617	0.25
6	-166.1 ± 1813.9	274	-118.1 ± 2079.7	286	-141.6 ± 1952.6	560	0.77
7	-219.0 ± 1776.6	246	-131.5 ± 2692.4	264	-173.7 ± 2294.9	510	0.68

[1] p-value from linear model stratified over possible patient types

Table S10: On Study PaO$_2$/F$_I$O$_2$ (mm Hg)

Day	Placebo Mean ± SD	N	Rosuvastatin Mean ± SD	N	Overall Mean ± SD	N	P [1]
1	192.3 ± 81.1	279	183.4 ± 77.0	277	187.9 ± 79.2	556	0.18
2	201.4 ± 131.9	239	208.8 ± 99.8	238	205.1 ± 117.0	477	0.48
3	199.6 ± 89.0	190	193.6 ± 77.0	197	196.5 ± 83.0	387	0.47
4	195.9 ± 79.8	166	201.2 ± 82.1	171	198.6 ± 80.9	337	0.56
7	207.8 ± 84.1	102	193.4 ± 69.2	92	201.0 ± 77.6	194	0.20
12	194.4 ± 78.8	52	215.7 ± 76.2	32	202.5 ± 78.1	84	0.28
21	221.2 ± 102.2	15	230.1 ± 93.6	12	225.2 ± 96.7	27	0.60
28	194.9 ± 133.3	6	290.4 ± 66.2	5	238.3 ± 114.5	11	0.08

[1] p-value from linear model stratified over possible patient types

Table S11: On Study Oxygenation Index (cm H$_2$O/mm Hg)

Day	Placebo Mean ± SD	N	Rosuvastatin Mean ± SD	N	Overall Mean ± SD	N	P [1]
1	9.9 ± 7.5	271	10.2 ± 8.0	267	10.1 ± 7.7	538	0.58
2	8.8 ± 5.7	226	8.9 ± 9.9	222	8.8 ± 8.0	448	0.95
3	9.0 ± 6.3	178	9.0 ± 6.2	185	9.0 ± 6.2	363	0.91
4	9.1 ± 6.6	153	8.5 ± 6.7	154	8.8 ± 6.6	307	0.45
7	7.6 ± 5.4	90	9.2 ± 8.0	84	8.4 ± 6.8	174	0.12
12	9.9 ± 9.7	46	8.2 ± 6.6	27	9.3 ± 8.7	73	0.44
21	8.0 ± 10.0	13	8.0 ± 7.6	11	8.0 ± 8.8	24	0.65
28	12.9 ± 12.8	5	4.0 ± 0.9	4	8.9 ± 10.2	9	0.10

[1] p-value from linear model stratified over possible patient types

Table S12: On Study Plateau Pressure (cm H$_2$O)

Day	Placebo Mean ± SD	N	Rosuvastatin Mean ± SD	N	Overall Mean ± SD	N	P [1]
1	21.9 ± 6.2	230	22.5 ± 6.4	224	22.2 ± 6.3	454	0.30
2	21.9 ± 6.5	184	22.1 ± 6.2	171	21.9 ± 6.3	355	0.87
3	22.5 ± 5.5	152	22.0 ± 6.8	144	22.3 ± 6.2	296	0.48
4	22.0 ± 5.9	137	21.8 ± 6.7	119	21.9 ± 6.3	256	0.92
7	22.4 ± 5.4	72	22.4 ± 7.4	67	22.4 ± 6.4	139	0.90
12	24.5 ± 8.3	32	22.5 ± 6.4	20	23.8 ± 7.6	52	0.38
21	23.4 ± 6.4	12	23.0 ± 8.7	5	23.3 ± 6.9	17	0.91
28	22.7 ± 6.7	9	23.0 ± 1.4	2	22.7 ± 6.0	11	0.85

[1] p-value from linear model stratified over possible patient types

Table S13: On Study Cstat (ml/cm H₂O)

Day	Placebo Mean ± SD	N	Rosuvastatin Mean ± SD	N	Overall Mean ± SD	N	P [1]
1	38.3 ± 45.0	200	35.6 ± 28.0	205	36.9 ± 37.3	405	0.41
2	35.8 ± 39.3	166	34.7 ± 20.9	157	35.3 ± 31.6	323	0.68
3	31.0 ± 14.7	136	33.7 ± 20.6	130	32.3 ± 17.8	266	0.21
4	34.1 ± 20.9	116	35.2 ± 22.8	107	34.6 ± 21.8	223	0.84
7	35.6 ± 47.2	67	32.3 ± 16.4	61	34.0 ± 35.9	128	0.64
12	28.3 ± 15.2	26	32.1 ± 21.0	20	30.0 ± 17.9	46	0.50
21	28.5 ± 11.8	11	40.1 ± 20.1	4	31.6 ± 14.6	15	0.24

[1] p-value from linear model stratified over possible patient types

Table S14: On Study Minute Ventilation (l/min)

Day	Placebo Mean ± SD	N	Rosuvastatin Mean ± SD	N	Overall Mean ± SD	N	P [1]
1	10.6 ± 3.2	348	10.6 ± 3.1	358	10.6 ± 3.1	706	0.93
2	10.7 ± 3.4	300	10.3 ± 3.2	297	10.5 ± 3.3	597	0.22
3	10.5 ± 3.4	257	10.3 ± 3.5	258	10.4 ± 3.5	515	0.49
4	10.6 ± 3.5	213	10.4 ± 3.3	218	10.5 ± 3.4	431	0.61
7	10.6 ± 3.6	138	10.4 ± 3.5	141	10.5 ± 3.5	279	0.73
12	10.1 ± 2.8	67	10.8 ± 3.7	48	10.4 ± 3.2	115	0.23
21	10.5 ± 3.8	28	11.3 ± 5.1	19	10.8 ± 4.3	47	0.53
28	10.5 ± 3.0	18	9.0 ± 2.6	11	9.9 ± 2.9	29	0.17

[1] p-value from linear model stratified over possible patient types

Table S15: On Study PaCO2 (mm Hg)

Day	Placebo Mean ± SD	N	Rosuvastatin Mean ± SD	N	Overall Mean ± SD	N	P [1]
1	40.6 ± 11.2	279	40.7 ± 9.8	277	40.6 ± 10.5	556	0.89
2	41.7 ± 10.8	239	42.4 ± 12.5	238	42.1 ± 11.7	477	0.48
3	42.1 ± 10.3	191	42.7 ± 10.6	197	42.4 ± 10.5	388	0.56
4	44.0 ± 10.8	167	44.1 ± 11.2	173	44.1 ± 11.0	340	0.85
7	44.8 ± 11.4	102	46.6 ± 22.5	93	45.6 ± 17.6	195	0.46
12	46.0 ± 11.4	52	43.5 ± 9.3	32	45.0 ± 10.7	84	0.30
21	50.9 ± 15.2	15	50.8 ± 13.7	12	50.9 ± 14.3	27	0.86
28	47.3 ± 15.2	6	46.2 ± 8.2	5	46.8 ± 11.9	11	0.79

[1] p-value from linear model stratified over possible patient types

Table S16: On Study Arterial pH

Day	Placebo Mean ± SD	N	Rosuvastatin Mean ± SD	N	Overall Mean ± SD	N	P [1]
1	7.38 ± 0.08	280	7.37 ± 0.09	277	7.37 ± 0.09	557	0.65
2	7.39 ± 0.08	239	7.39 ± 0.08	238	7.39 ± 0.08	477	0.83
3	7.40 ± 0.08	191	7.41 ± 0.08	197	7.40 ± 0.08	388	0.07
4	7.40 ± 0.07	167	7.41 ± 0.08	173	7.41 ± 0.08	340	0.26
7	7.41 ± 0.09	102	7.41 ± 0.08	93	7.41 ± 0.09	195	0.91
12	7.40 ± 0.07	52	7.39 ± 0.10	32	7.40 ± 0.08	84	0.76
21	7.38 ± 0.07	15	7.32 ± 0.12	12	7.35 ± 0.10	27	0.15
28	7.43 ± 0.03	6	7.39 ± 0.05	5	7.41 ± 0.04	11	0.22

[1] p-value from linear model stratified over possible patient types

Table S17: Baseline and On Study CRP (mg/dL)

Day	Placebo Mean ± SD (N)	Rosuvastatin Mean ± SD (N)	Total Mean ± SD (N)	P
0	25.1 ± 24.13 (338)	27.7 ± 36.42 (361)	26.4 ± 31.10 (699)	0.26
1	19.9 ± 12.55 (55)	25.7 ± 25.00 (76)	23.3 ± 20.84 (131)	0.12
2	20.1 ± 12.49 (11)	23.0 ± 11.31 (17)	21.9 ± 11.65 (28)	0.54
3	10.7 ± 8.50 (25)	14.8 ± 10.37 (27)	12.8 ± 9.65 (52)	0.13
4	11.5 ± 7.93 (17)	15.2 ± 15.61 (18)	13.4 ± 12.45 (35)	0.38
5	10.5 ± 8.47 (25)	14.4 ± 22.06 (31)	12.7 ± 17.34 (56)	0.40
6	9.5 ± 10.97 (239)	11.6 ± 13.28 (239)	10.6 ± 12.21 (478)	0.07
7	10.2 ± 8.73 (34)	12.5 ± 11.84 (38)	11.4 ± 10.49 (72)	0.35
8	9.6 ± 7.37 (19)	6.4 ± 6.61 (11)	8.4 ± 7.17 (30)	0.24
9	6.0 ± 3.96 (13)	13.5 ± 15.18 (7)	8.6 ± 9.81 (20)	0.10
10	11.6 ± 16.31 (19)	22.5 ± 36.19 (5)	13.9 ± 21.36 (24)	0.32
14	8.4 ± 10.80 (115)	6.7 ± 7.32 (122)	7.5 ± 9.20 (237)	0.14
21	8.2 ± 6.06 (13)	9.5 ± 8.02 (10)	8.7 ± 6.84 (23)	0.68

Day 0 is baseline and pre-randomization.

Table S18: On Study CRP Change from Baseline (mg/dL)

Day	Placebo Mean ± SD (N)	Rosuvastatin Mean ± SD (N)	Total Mean ± SD (N)	P
1	-9.8 ± 39.07 (48)	0.9 ± 25.45 (70)	-3.5 ± 31.99 (118)	0.07
2	-4.2 ± 14.42 (11)	-0.0 ± 10.83 (17)	-1.7 ± 12.28 (28)	0.39
3	-14.9 ± 29.65 (23)	-4.7 ± 13.94 (26)	-9.5 ± 23.04 (49)	0.12
4	-11.1 ± 10.66 (17)	-13.3 ± 14.87 (16)	-12.1 ± 12.72 (33)	0.63
5	-22.7 ± 48.24 (23)	-10.5 ± 25.10 (31)	-15.7 ± 36.87 (54)	0.23
6	-15.1 ± 23.26 (229)	-12.9 ± 27.79 (229)	-14.0 ± 25.62 (458)	0.36
7	-13.5 ± 17.90 (31)	-18.2 ± 14.89 (36)	-16.0 ± 16.40 (67)	0.24
8	-15.6 ± 12.07 (19)	-22.3 ± 14.68 (11)	-18.1 ± 13.25 (30)	0.19
9	-23.4 ± 7.72 (13)	-8.7 ± 15.97 (6)	-18.8 ± 12.65 (19)	0.01
10	-25.1 ± 42.18 (18)	-9.6 ± 10.62 (3)	-22.9 ± 39.43 (21)	0.54
14	-14.8 ± 26.28 (110)	-19.8 ± 31.23 (115)	-17.3 ± 28.96 (225)	0.19
21	-12.7 ± 11.26 (13)	-18.4 ± 20.41 (9)	-15.1 ± 15.47 (22)	0.41

Day 0 is baseline and pre-randomization.

Table S19: Outcomes by PaO₂/FᵢO₂ (mm Hg) and baseline shock

Characteristic	Rosuvastatin	Placebo	Difference (95% CI)	P value
All Patients				
60-day Mortality				
200<PaO2/FᵢO₂<=300	26/105 (24.9%)	27/108 (25.0%)	-0.1 (-11.8, 11.5)	0.94
PaO2/FᵢO₂<=200	79/267 (29.6%)	61/253 (24.1%)	5.5 (-2.1, 13.1)	0.13
SAILS-Baseline P/F interaction				0.43
Ventilator-free days @d28				
200<PaO2/FᵢO₂<=300	16.9 ± 10.2	17.0 ± 11.0	-0.0; (-2.9, 2.8)	0.98
PaO2/FᵢO₂<=200	4.5 ± 11.0	14.4 ± 11.0	0.0; (-1.9, 1.9)	0.99
SAILS-Baseline P/F interaction				0.98
Patients with baseline shock				
60-day Mortality				
200<PaO2/FᵢO₂<=300	14/47 (30%)	25/48 (31.3%)	-1.2 (-19.8, 17.4)	0.87
PaO2/FᵢO₂<=200	48/125 (38/4%)	37/116 (31/9%)	6.5 (-5.5, 18.5)	0.26
SAILS-Baseline P/F interaction				0.49
Ventilator-free days @d28				
200<PaO2/FᵢO₂<=300	14.9 ± 10.2	15.3 ± 11.2	-0.4; (-4.8, 4.0)	0.85
PaO2/FᵢO₂<=200	11.2 ± 11.0	12.4 ± 11.1	-1.2; (-4.0, 1.6)	0.42
SAILS-Baseline P/F interaction				0.78
Patients without baseline shock				
60-day Mortality				
200<PaO2/FᵢO₂<=300	2/58 (20.7%)	12/60 (20.0%)	0.7 (-13.8, 15.2)	0.95
PaO2/FᵢO₂<=200	31/142 (21.8%)	24/137 (17.5%)	4.3 (-5.0, 13.6)	0.33
SAILS-Baseline P/F interaction				0.68
Ventilator-free days @d28				
200<PaO2/FᵢO₂<=300	18.6 ± 9.9	18.3 ± 10.6	0.3; (-3.5, 4.1)	0.87
PaO2/FᵢO₂<=200	17.3 ± 10.2	16.2 ± 10.6	1.1; (-1.3, 3.6)	0.38
SAILS-Baseline P/F interaction				0.73

Table S20: Baseline CK and On Study Natural Log CK (Log IU/L) Change from Baseline

Day	Placebo Mean ± SD (N)	Rosuvastatin Mean ± SD (N)	Total Mean ± SD (N)	P
0	214.22 ± 396.30 (365)	224.00 ± 417.46 (378)	219.20 ± 406.96 (743)	0.74
1	-0.03 ± 0.71 (357)	-0.00 ± 0.77 (360)	-0.02 ± 0.74 (717)	0.58
2	0.01 ± 1.20 (72)	0.04 ± 1.10 (67)	0.03 ± 1.15 (139)	0.88
3	-0.28 ± 1.11 (308)	-0.14 ± 1.16 (316)	-0.21 ± 1.14 (624)	0.15
4	-0.40 ± 1.60 (54)	0.19 ± 1.46 (57)	-0.10 ± 1.55 (111)	0.05
5	-0.32 ± 1.31 (47)	0.27 ± 1.65 (47)	-0.02 ± 1.51 (94)	0.06
6	-0.48 ± 1.18 (260)	-0.23 ± 1.34 (260)	-0.35 ± 1.27 (520)	0.03
7	-0.29 ± 1.33 (40)	0.03 ± 1.88 (46)	-0.12 ± 1.64 (86)	0.37
8	0.04 ± 1.94 (24)	0.12 ± 2.16 (28)	0.08 ± 2.04 (52)	0.89
9	-0.57 ± 2.05 (30)	0.53 ± 2.03 (35)	0.02 ± 2.10 (65)	0.03
10	-0.56 ± 1.47 (131)	-0.23 ± 1.65 (144)	-0.39 ± 1.57 (275)	0.08
14	-0.67 ± 1.23 (125)	-0.31 ± 1.73 (127)	-0.49 ± 1.51 (252)	0.06
21	-0.93 ± 1.28 (57)	-0.67 ± 1.70 (59)	-0.79 ± 1.51 (116)	0.36

Day 0 is baseline and pre-randomization.
When the numbers are small (close to 0), they approximate the percent change.

Table S21: Baseline ALT and On Study Natural Log ALT (Log IU/L) Change from Baseline

Day	Placebo Mean ± SD (N)	Rosuvastatin Mean ± SD (N)	Total Mean ± SD (N)	P
0	35.69 ± 34.00 (366)	36.88 ± 36.65 (379)	36.30 ± 35.35 (745)	0.65
1	0.06 ± 0.57 (362)	0.02 ± 0.41 (368)	0.04 ± 0.49 (730)	0.27
2	0.20 ± 0.84 (135)	0.12 ± 0.70 (138)	0.16 ± 0.77 (273)	0.36
3	0.10 ± 0.74 (326)	0.17 ± 0.63 (329)	0.14 ± 0.69 (655)	0.21
4	0.22 ± 0.88 (110)	0.20 ± 0.72 (127)	0.21 ± 0.80 (237)	0.90
5	0.35 ± 0.84 (103)	0.30 ± 0.80 (126)	0.32 ± 0.82 (229)	0.66
6	0.18 ± 0.79 (265)	0.31 ± 0.82 (281)	0.25 ± 0.81 (546)	0.07
7	0.24 ± 0.95 (96)	0.33 ± 0.92 (112)	0.29 ± 0.93 (208)	0.51
8	0.26 ± 0.88 (84)	0.40 ± 1.03 (85)	0.33 ± 0.96 (169)	0.37
9	0.14 ± 0.85 (64)	0.54 ± 1.07 (77)	0.36 ± 1.00 (141)	0.02
10	0.38 ± 0.81 (77)	0.42 ± 0.94 (88)	0.40 ± 0.88 (165)	0.77
14	0.27 ± 0.83 (130)	0.31 ± 0.91 (134)	0.29 ± 0.87 (264)	0.68
21	0.23 ± 0.74 (66)	0.12 ± 0.85 (66)	0.17 ± 0.80 (132)	0.45

Day 0 is baseline and pre-randomization.
When the numbers are small (close to 0), they approximate the percent change.

Table S22: Baseline AST and On Study Natural Log AST (Log IU/L) Change from Baseline

Day	Placebo Mean ± SD (N)	Rosuvastatin Mean ± SD (N)	Total Mean ± SD (N)	P
0	49.65 ± 44.25 (364)	53.99 ± 68.53 (379)	51.86 ± 57.93 (743)	0.31
1	0.01 ± 0.48 (85)	0.03 ± 0.56 (98)	0.02 ± 0.52 (183)	0.84
2	0.08 ± 0.55 (32)	0.08 ± 0.57 (41)	0.08 ± 0.56 (73)	0.99
3	-0.04 ± 0.56 (76)	0.10 ± 0.61 (86)	0.04 ± 0.59 (162)	0.14
4	-0.18 ± 0.45 (25)	-0.02 ± 0.62 (38)	-0.08 ± 0.56 (63)	0.26
5	-0.16 ± 0.50 (24)	0.17 ± 0.91 (39)	0.05 ± 0.80 (63)	0.11
6	-0.04 ± 0.62 (63)	0.14 ± 0.80 (80)	0.06 ± 0.73 (143)	0.16
7	-0.15 ± 0.55 (29)	0.22 ± 0.81 (39)	0.06 ± 0.73 (68)	0.04
8	-0.08 ± 0.58 (19)	0.21 ± 0.75 (29)	0.09 ± 0.70 (48)	0.16
9	-0.00 ± 0.56 (21)	0.22 ± 0.84 (27)	0.12 ± 0.73 (48)	0.30
10	-0.05 ± 0.59 (24)	0.21 ± 0.81 (31)	0.10 ± 0.73 (55)	0.20
14	-0.18 ± 0.51 (39)	0.03 ± 0.80 (41)	-0.07 ± 0.67 (80)	0.17
21	-0.26 ± 0.56 (20)	-0.31 ± 0.89 (22)	-0.28 ± 0.74 (42)	0.83

Day 0 is baseline and pre-randomization.
When the numbers are small (close to 0), they approximate the percent change.