Supplementary Appendix

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

Supplement to: Criner GJ, Connett JE, Aaron SD, et al. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. N Engl J Med 2014;370:2201-10. DOI: 10.1056/NEJMoa1403086

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Section A. List of Collaborators

Collaborators

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Section B. Tables

Table S1. Complete demographics of participants enrolled into STATCOPE

Characteristic	Simvastatin (n=433)	Placebo (n=452)
Age- yrs.	62.2 (8.5)	62.3 (8.4)
Female gender-no. (%)	184 (42.49%)	203 (44.9%)
Hispanic-no. (%)	4 (0.9%)	7 (1.5%)
Race-no. (%)		
White	328 (75.8%)	346 (76.5%)
Black	99 (22.9%)	91 (20.1%)
Other	4 (0.9%)	4 (0.9%)
Multiethnic	2 (0.5%)	11 (2.4%)
Post-bronchodilator FEV_1		
Liters	N=430 1.2 (0.6)	N=449 1.2 (0.6)
% predicted	N=430 41.5% (17.8%)	N=449 41.6% (17.6%)
FEV1/FVC	N=430 44.4% (12.6%)	N=449 44.3% (13.48%)
Gold Stage-no. (%)		
II	142 (33%)	145 (32.3%)
III	142 (33%)	163 (36.3%)
IV	146 (34%)	141 (31.5%)
Smoking history-pack-yr.	50.0 (26.1)	51.2 (28.7)
Current smoker-no. (%)	133 (30.7%)	143 (31.6%)
COPD Medications-no. (%)		
ICS only	14 (3.2%)	12 (2.65%)
LAMAs only	29 (6.7%)	35 (7.7%)
LABAs only	10 (2.3%)	10 (2.2%)
ICS + LAMA	5 (1.15%)	9 (2.0%)
ICS+ LABA	71 (16.4%)	89 (19.7%)
LAMA + LABA	25 (5.8%)	23 (5.1%)
ICS + LAMA + LABA	223 (51.50%)	228 (50.4%)
None	56 (12.9%)	46 (10.2%)
Entry Criteria		
AECOPD < 12 prior mo. Requiring hospitalization or ER visits	216 (49.9%)	238 (52.7%)
Systemic steroids or antibiotics < 12 prior mo.	367 (84.75%)	382 (84.5%)
Long-term oxygen- no. (%)	198 (45.7%)	222 (49.1%)
Long-term oxygen as only criterion- no. (%)	48 (11.1%)	53 (11.7%)

There were no significant differences between simvastatin and placebo groups.

Definition of abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative in Obstructive Lung Disease; ICS, inhaled corticosteroids; LAMAs, long acting muscarinic antagonists; LABAs, long acting beta-2 agonists; AECOPD, acute exacerbations of COPD

Table S2. Effect of Simvastatin on Severity of Acute Exacerbations

Event	Simvastatin		Placebo	
	No. of events	Mean events/ patient yr. (95% CI)	No. of events	Mean events/ patient yr. (95% CI)
AECOPD				
Hospitalizations	205	0.31 [0.24,0.38]	240	0.31 [0.23,0.38]
ER or urgent visits	123	0.17 [0.13,0.22]	138	0.24 [0.16,0.32]
Unscheduled office visits	637	0.85 [0.73,0.97]	639	0.81 [0.70,0.93]
Intubations	12	0.03 [0.00,0.05]	19	0.03 [0.01,0.04]

Definitions of abbreviations: ER, emergency room; AECOPD, acute exacerbations of COPD

Table S3. Effect of Simvastatin on Hospitalizations.

Event	Statin		Placebo		P Value
	No. of events	Mean events/patient yr. (95% CI)	No. of events	Mean events/patient yr. (95% CI)	
All cause Hospitalizations	369	.63 [.49,.76]	414	.67 [.52,.82]	0.539

Table S4. Counts, Rates of Exacerbations (per person-year), by Severity and by Treatment Group: Means ± Standard Deviations

Treatment Group	Mild Exacerbations	Moderate Exacerbations	Severe Exacerbations	Very Severe Exacerbations	*All Exacerbations*
Simvastatin					
Count	1.48 ± 2.15	0.29 ± 0.71	0.45± 0.98	0.03 ± 0.18	2.24 ± 2.75
Rate	0.85 ± 1.25/pyr	0.17 ± 0.47/pyr	0.31 ± 0.75/pyr	0.03 ± 0.23/pyr	1.36 ± 1.61/pyr
Placebo					
Count	1.43 ± 2.21	0.31 ± 0.73	0.49 ± 1.24	0.04 ± 0.23	2.28 ± 2.94
Rate	0.81 ± 1.24/pyr	0.24 ± 0.85/pyr	0.31 ± 0.81/pyr	0.03 ± 0.17/pyr	1.39 ± 1.73/pyr

P-values for differences between groups in rates (negative binomial model):

1. All exacerbations: p = 0.728
2. Moderate or worse exacerbations: p = 0.200
3. Severe or very severe exacerbations: p = 0.420

Table S5. Effect of Simvastatin on Secondary Outcomes Change from Baseline to Last Measure per Person-Year (Median, 10th, 90th percentile) *.

Outcome	Simvastatin	Placebo	P Value
	N=356	N=356	
FVC , % pred.	-0.83 (-7.19, 5.28)	-0.93 (-7.16, 5.40)	.6832
FEV1, % pred.	-0.86 (-11.04, 8.67)	-1.81 (-10.62, 7.10)	.1461
FEV1/FVC	-0.21 (-6.19, 5.47)	-0.21 (-5.04, 5.98)	.3581
SGRQ	N=370	N=383	
Symptom	-0.78 (-17.29, 12.52)	-1.69 (-21.20, 11.62)	.2628
Activity	0.00 (-13.36, 9.56)	0.00 (-12.32, 14.14)	.2205
Impact	0.00 (-12.25, 13.37)	0.00 (-14.41, 13.22)	.9548
Total	-0.18 (-11.01, 9.70)	0.02 (-12.47, 10.73)	.3783
SF-36	N=370	N=382	
Health in last year	0.00 (-19.98, 26.39)	0.00 (-24.48, 24.61)	.7210
Physical function	0.00 (-19.64, 16.01)	0.00 (-16.66, 17.18)	.5585
Role Physical	0.00 (-30.78, 37.20)	0.00 (-33.66, 36.62)	.1359
Role Emotional	0.00 (-32.88, 33.07)	0.00 (-34.01, 33.36)	.3023
Energy	0.00 (-14.13, 15.92)	0.00 (-18.39, 12.06)	.3458
Emotional Wellbeing	0.00 (-12.11, 9.68)	0.00 (-14.05, 11.84)	.7620
Social Function	0.00 (-21.55, 20.50)	0.00 (-24.55, 20.90)	.9167
Pain	0.00 (-20.62, 20.73)	0.00 (-20.07, 17.94)	.4952
Gen Health	0.00 (-14.94, 14.78)	0.00 (-19.43, 15.28)	.5592

Definition of abbreviations: FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; SGRQ, St Georges' Respiratory Questionnaire; SF-36, Medical Outcomes Study 36-item Short Form Health Survey.

* Change was calculated: (last followup-baseline)/ (Time at baseline to Time at last followup /365.25)

The SGRQ has a range of scores from 0-100 with lower scores indicating better functioning and the minimal important clinical difference is considered to be -4 units. The SF-36 is a self-administered general health questionnaire of 36 items that generates scores across 8 health dimensions. Scores range from 0-100; higher levels indicate better health on each dimension. [3]Clinical important changes in SF-36 are 5-10 point increases in specific domains.

Table S6. Reasons for Study Drug Discontinuation by Treatment Assignment.

Category	Statin N=430		Placebo N=447		Total N=877	
	N	%	N	%	N	%
Allergic reaction	1	0.2%	0	0.0%	1	0.1%
Side effects involving muscles (includes myalgias)	10	2.3%	11	2.5%	21	2.4%
Other side effects	5	1.2%	1	0.2%	6	0.7%
MD prescribed incompatible med	17	4.0%	20	4.5%	37	4.2%
Cardiac Event	8	1.9%	6	1.3%	14	1.6%
Diabetes	14	3.3%	14	3.1%	28	3.2%
FDA Guidelines on CCBs	16	3.7%	20	4.5%	36	4.1%
Other Reason	7	1.6%	13	2.9%	20	2.2%
Total	78	18.1%	85	19.0%	163	18.6%

Group	OTHER REASON DETAIL
Placebo	DIFFICULTY FOLLOWING PROTOCOL
Placebo	ELEVATED LIVER ENZYMES AT C24 VISIT
Placebo	DIAGNOSTIC TESTING FOR DVT
Placebo	PT HAS ARTHRITIS FOR YEARS. PI DECIDED BEST TO DISCONTINUE MEDICATION ON CONSULTATION WITH PCP.
Placebo	SUBJECT HAS A HAD A HEALTH DECLINE AND CAN NO LONGER COME TO CLINIC VISITS. HE AGREES TO BE FOLLOWED BY PHONE, BUT FOR SAFETY PURPOSES DRUG WAS DC'D
Placebo	STROKE
Placebo	D.O. DID NOT WANT SUBJECT TO CONTINUE WITH STUDY DRUG.
Placebo	SUBJECT MOVING OUT OF STATE AND NO STUDY SITE WITHIN NEW AREA.
Placebo	BLOOD PRESSURE AND OTHER HEALTH ISSUES
Placebo	SUBJECT HAD AN INCREASE IN HIS ALCOHOL CONSUMPTION THAT WOULD EXCLUDE HIM FROM TAKING THE STUDY DRUG
Placebo	CARDIAC DOCTOR BELIEVED THE STUDY DRUG MAY BE AFFECTING SUBJECT'S BALANCE.
Placebo	ALCOHOL ABUSE
Placebo	THE PRINCIPAL INVESTIGATOR DISCONTINUED MEDICATIONS DUE TO UNRELIABILITY AND NON-COMPLIANCE OF THE SUBJECT AS PER PROTOCOL
Statin	PER PROTOCOL - PERIPHERAL VASCULAR DISEASE
Statin	LUNG TRANSPLANT
Statin	PATIENT WANTED TO PARTICIPATE IN ANOTHER INTERVENTIONAL STUDY AT THIS POINT. AGREES TO BE FOLLOWED BY PHONE.

Statin	INCREASED ALT AND POSSIBLE REACTION
Statin	LUNG CANCER TREATMENT -- CLINICAL TRIAL.
Statin	ELEVATED LIVER ENZYMES LIKELY DUE TO UNDISCLOSED ALCOHOL ABUSE, PER PI.
Statin	SUBJECT WAS DISCHARGED TO LONGTERM CARE, UNAABLE TO ATTEND CLINIC VISITS, CAUSING SUBJECT EXTREME ANXIETY.

Definition of abbreviations: FDA, Food and Drug Administration; MS, medical doctor; CCBs, calcium channel blockers

Table S7. Reasons for Withdrawal

Category	Statin N=430		Placebo N=447		Total N=877	
	N	%	N	%	N	%
Lost Interest	7	1.6%	6	1.3%	13	1.5%
Not willing to follow protocol	0	0%	5	1.1%	5	0.6%
Access to clinic is difficult	1	0.2%	2	0.4%	3	0.3%
Unable to make visits	0	0%	1	0.2%	1	0.1%
Moving out of area	0	0%	1	0.2%	1	0.1%
Medical condition	5	1.2%	3	0.7%	8	0.9%
Doesn't want to be in control group	1	0.2%	0	0.0%	1	0.1%
Adverse event	1	0.2%	1	0.2%	2	0.2%
Other	1	0.2%	1	0.2%	2	0.2%
Total	16	3.7%	20	4.5%	36	4.1%

Table S8. Treatment of Acute Exacerbations with Glucocorticosteroids and Antibiotics in Simvastatin vs. Placebo Groups.

Average Percent of Acute exacerbation Treated with Steroids, p=0.9652 (t-test)

TREATMENT GROUP	NUMBER	MEAN %	STD DEV %
Placebo	292	76.2	35.1
Simvastatin	293	73.2	38.6

Average Percent of AECOPD Treated with Antibiotics, p=0.5464(t-test)

TREATMENT GROUP	NUMBER	MEAN %	STD DEV %
Placebo	292	85.8	28.6
Simvastatin	293	87.2	27.5

Definitions: Average percent of acute exacerbations treated = no. of acute exacerbations treated /no. of acute exacerbations for each person x100, then averaged by group

Table S9: Lipid Levels at baseline and 12 Months by Treatment Group (Mean ± SDEV)

	Placebo (N= 204)			Simvastatin (N=186)				
Variable	Baseline	12 M	12M – BL Diff	Baseline	12 M	12M – BL Diff	Difference between Simvastatin and Placebo in 12-month Change	P-value
Total Cholesterol (mg/dl)	194.2 ± 35.2	190.9 ± 39.4	-3.4 ± 24.9	194.4 ± 35.6	163.2 ± 36.9	-31.2 ± 31.6	-27.8 ± 28.3	<.0001
HDL Cholesterol (mg/dl)	60.5 ± 24.0	60.0 ± 23.5	-0.5 ±10.3	61.3 ± 21.2	63.8 ± 23.9	2.5 ± 12.6	3.0 ± 11.5	.012
Triglycerides (mg/dl)	96.8 ± 54.7	113.6 ± 88.0	16.8 ± 59.2	96.7 ± 54.2	96.1 ± 60.6	-0.7 ± 53.9	-17.4 ±56.7	.0003
LDL Cholesterol (mg/dl)	114.4 ± 27.6	107.8 ± 29.0	-6.6 ± 21.8	113.9 ± 28.2	80.7 ± 30.8	-33.2 ± 28.9	-26.6 ± 25.4	<.0001

Section C. Figures

Figure S1. Effect of Sex on Time to First Exacerbation. Panel A women; Panel B, men. The trend for men randomized to simvastatin to have reduced time to first exacerbation was not significant, p=0.091.

Figure S1. Panel A

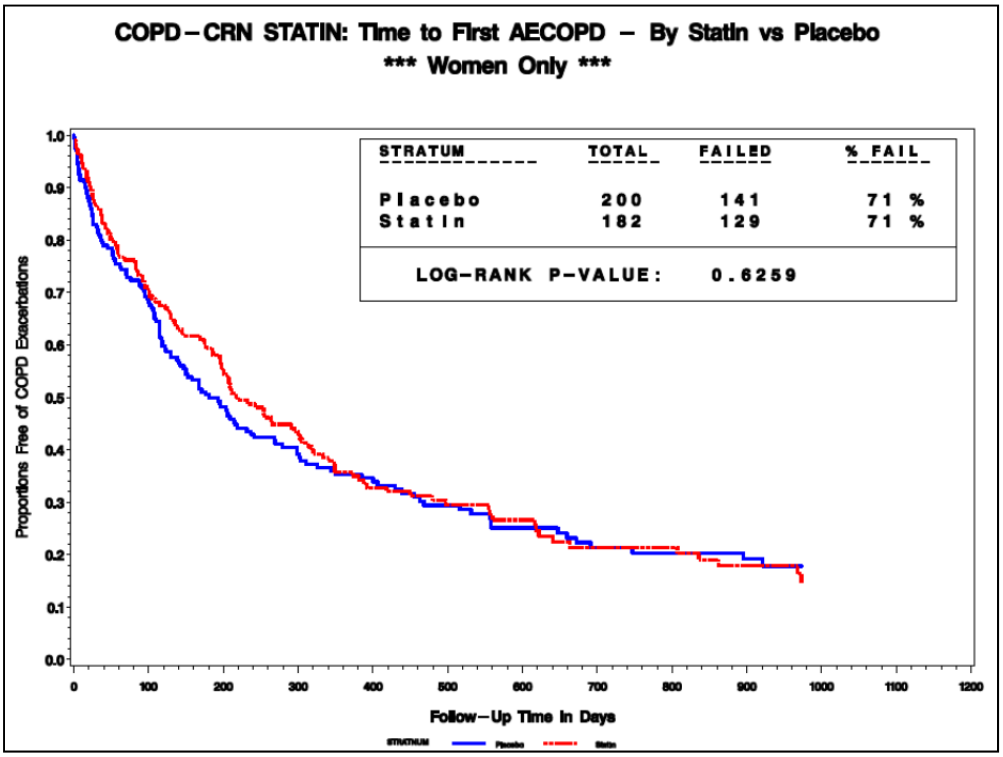

Figure S1. Panel B

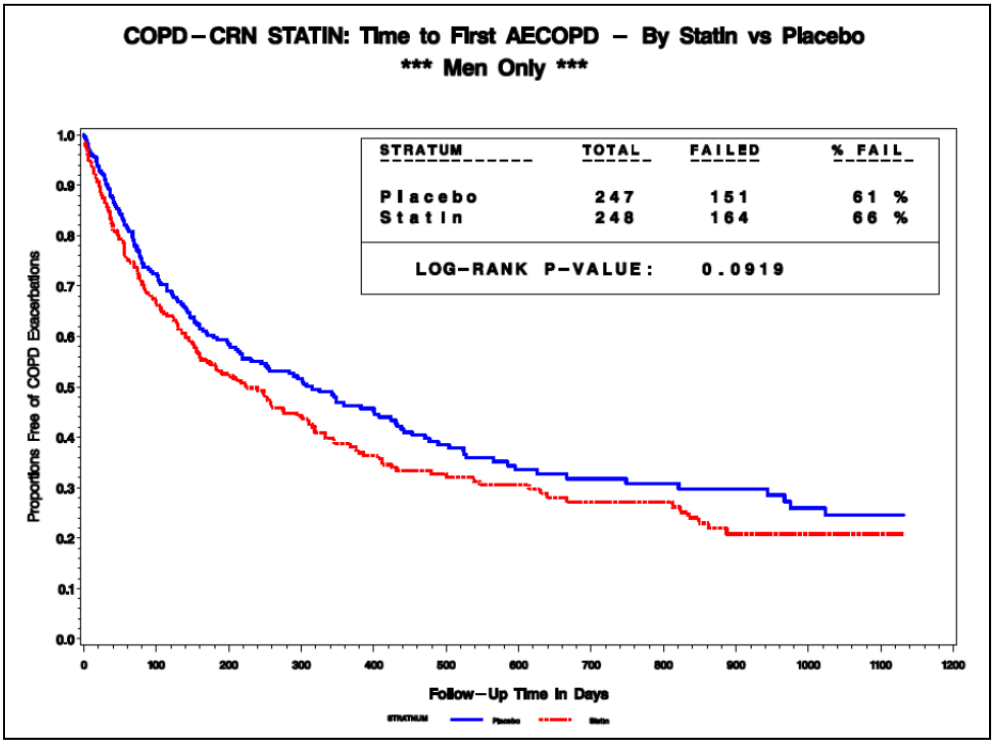

Figure S2. Histogram of Number of Exacerbations per Participant by Study Drug Assignment. Simvastatin had no beneficial effect on participants with frequent and very frequent exacerbations.

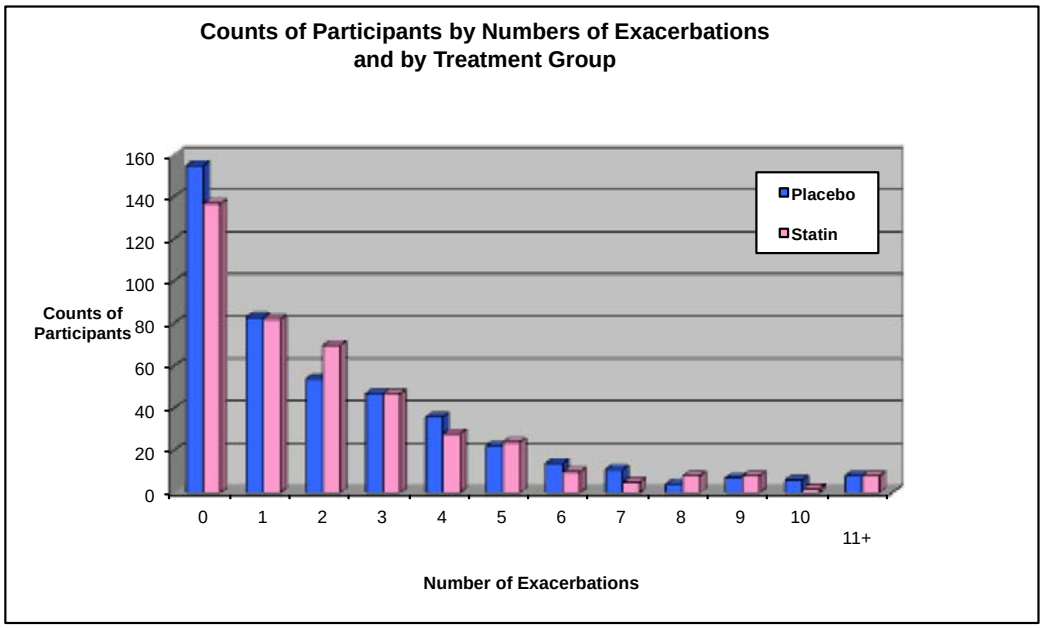

Figure S3. Forest Plot of Influence of GOLD Stage, Age, Whether Prescribed Oxygen or Not, Smoking Status, Gender and Clinical Center on Response to Simvastatin Treatment.