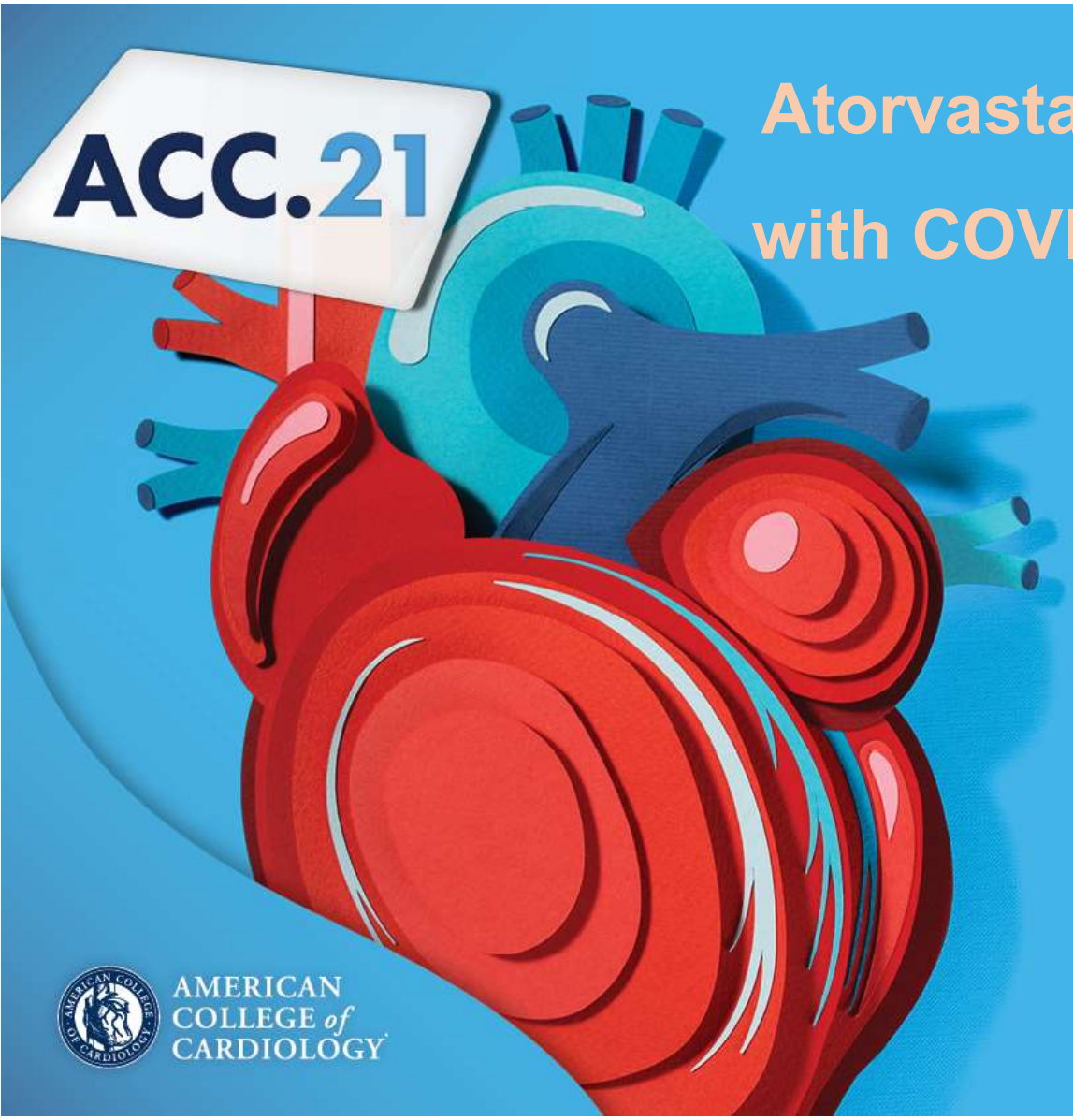

Atorvastatin vs Placebo in Patients with COVID-19 Admitted to the ICU: The INSPIRATION-S Trial

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For the INSPIRATION-S Investigators

HARVARD MEDICAL SCHOOL

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Cardiovascular Research Foundation

CENTER FOR OUTCOMES RESEARCH AND EVALUATION
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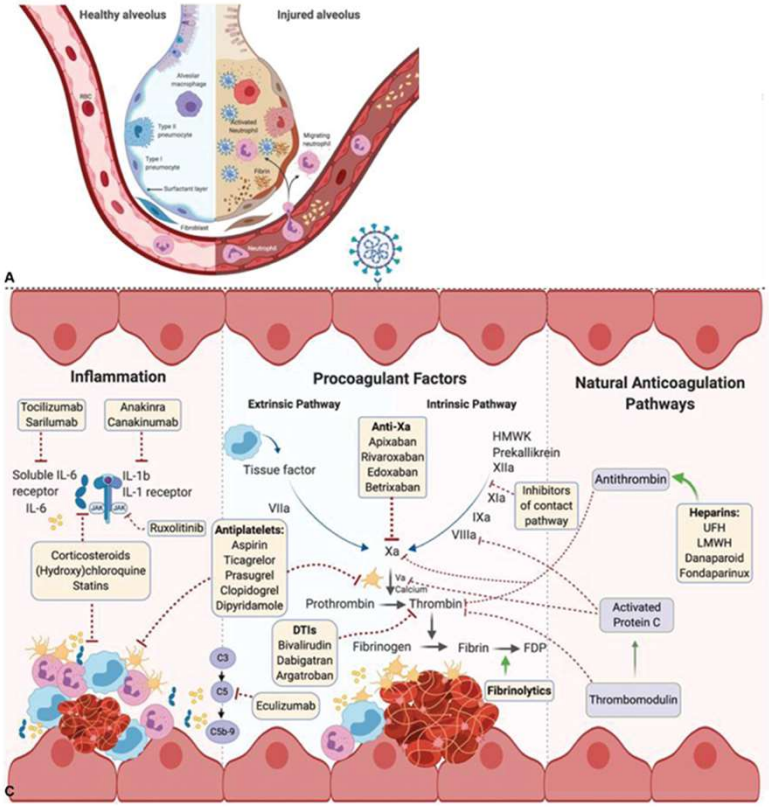
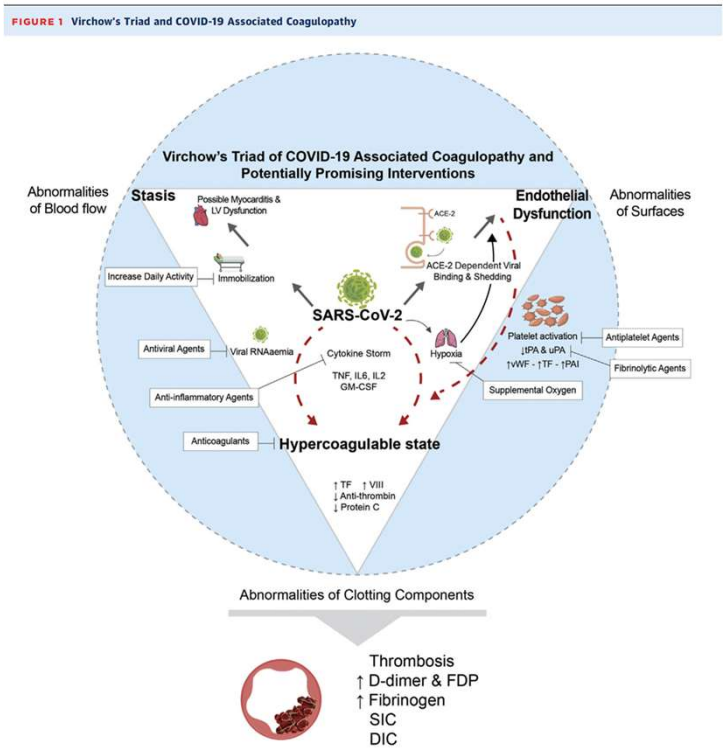
Disclosures

- Project support: RIETE (Bayer Pharma and Sanofi Spain)
- T-32 salary support (NHLBI, 2017-2018)
- Consulting expert (on behalf of the plaintiff) for litigation related t two brand models of IVC filters
- INSPIRATION-S funding: Rajaie Cardiovascular Medical and Research Center –no personal fees or salary support.

COVID-19: Inflammation and Thrombosis



Bikdeli B, et al. Thromb Haemost. 2020; 120: 1004-1024.



Talasaz AH, et al… Bikdeli B. J Am Coll Cardiol. 2021; 77: 1903-1921.

Statins in ARDS, and COVID-19

- Anti-inflammatory and antithrombotic properties.
- HARP-2 trial: neutral results in the full population of patients with ARDS.
- In hyperinflammatory sub-type of ARDS: ↓ mortality with simvastatin vs. placebo (32% vs. 45%)
- Antecedent statin use in COVID-19 associated with reduced mortality in hospitalized patients.
- Limited high-quality evidence in COVID-19.

Mcauley DF, et aal. N Engl J Med 2014; 371:1695-1703.
Gupta A, et al. Nat Commun. 2021;12: 1325.
Calfee CS, et al. Lancet Respir Med. 2018; 6: 691-698.

INSPIRATION AND INSPIRATION-S

Research question:

- Would atorvastatin, compared with placebo, confer benefit in ICU patients with COVID-19?

- **INtermediate versus Standard-dose Prophylactic anticoagulation In cRitically-ill pATIents with COVID-19: An opeN label randomized controlled trial (INSPIRATION) trial**

- **Second randomization to statin therapy vs. placebo (INSPIRATION-S)**

INSPIRATION-S: Trial Design

- Multicenter randomized clinical trial with a 2x2 factorial design in 11 hospitals in Iran
- Patients with RT-PCR-confirmed COVID-19 admitted to ICU, with estimated survival >24h, and meeting the eligibility criteria
- Intervention: Double-blind assignment to atorvastatin 20mg once daily versus placebo

Study eligibility criteria

Inclusion Criteria for the Statin Hypothesis

- Patients enrolled for the anticoagulation randomization
- Willingness to participation in the study and providing informed consent

Exclusion Criteria for the Statin Hypothesis

- Baseline liver function tests>6 times upper normal limits
- Total creatine kinase>500 U/L
- Active liver disease (LFT>3 times upper normal limit plus histologic finding including cirrhosis or inflammation or necrosis)
- Routine use of statins prior to the index hospitalization
- Previous documented statin intolerance

Bikdeli B, et al. Thromb Res. 2020 Dec;196:382-394.

Outcomes

Primary efficacy outcome:	Composite of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation (ECMO), or mortality within 30 days
Secondary efficacy outcomes:	Individual components of the primary efficacy outcome, ventilator-free days
Main safety outcomes:	Rise in liver enzymes > x3 times upper normal limit. Clinically-diagnosed myopathy
Additional safety outcomes:	BARC 3 or 5 bleeding, CRNMB, severe thrombocytopenia

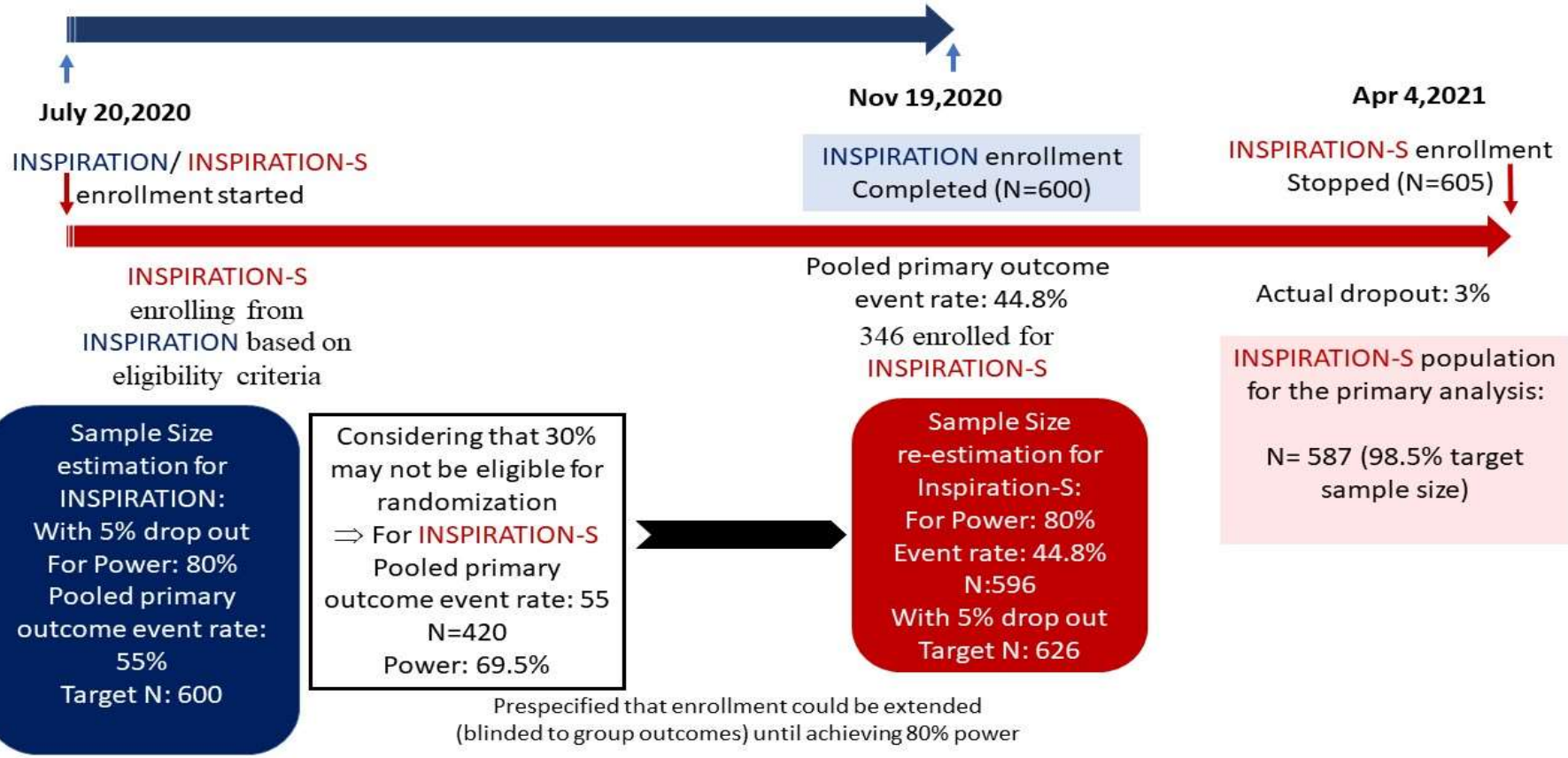
Bikdeli B, et al. Thromb Res. 2020 Dec;196:382-394.

July 20,2020

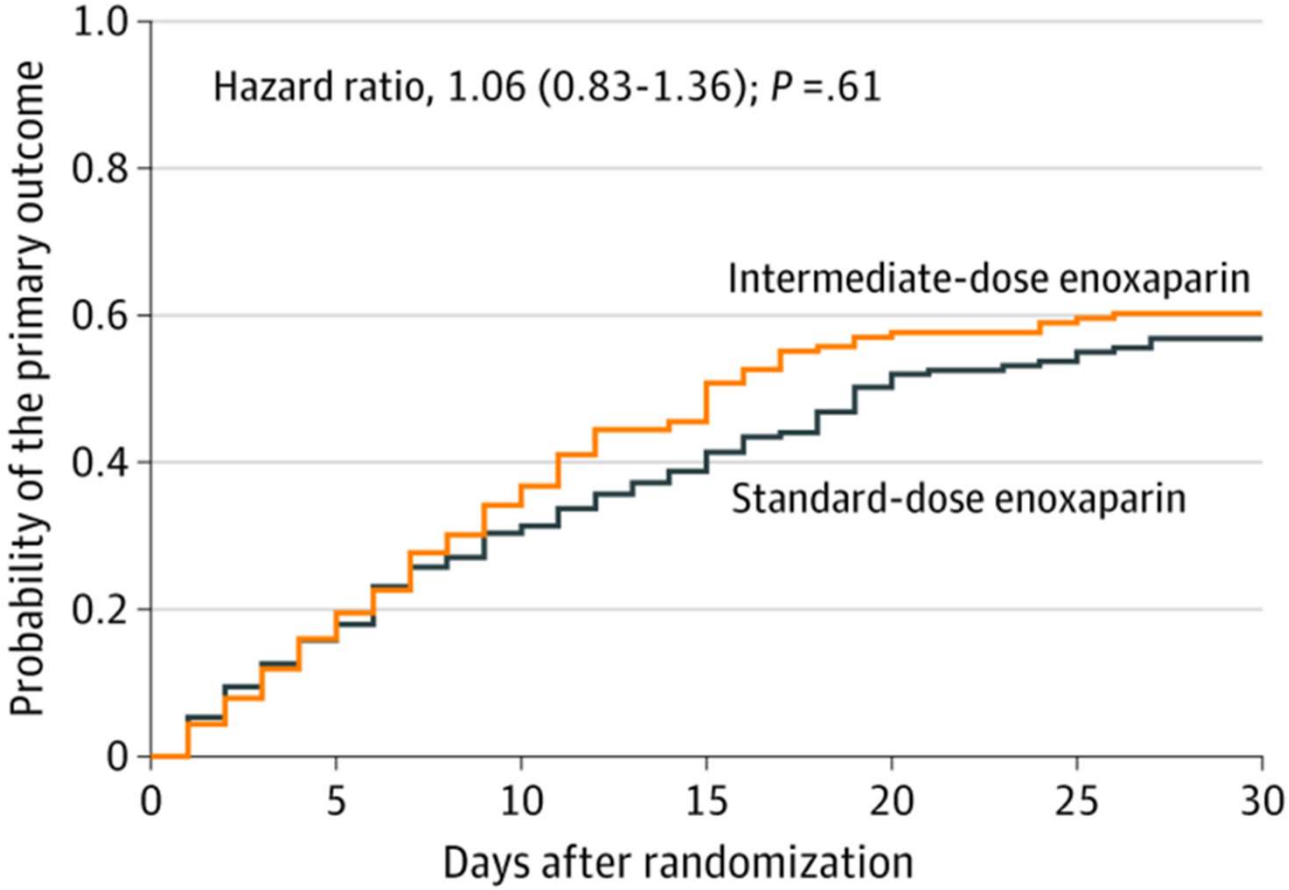
INSPIRATION/ INSPIRATION-S enrollment started

INSPIRATION-S enrolling from INSPIRATION based on eligibility criteria

Sample Size estimation for INSPIRATION:
With 5% drop out
For Power: 80%
Pooled primary outcome event rate: 55%
Target N: 600


July 20,2020
INSPIRATION/ INSPIRATION-S enrollment started
Nov 19,2020
INSPIRATION enrollment Completed (N=600)
Apr 4,2021
INSPIRATION-S enrollment Stopped (N=605)
INSPIRATION-S enrolling from INSPIRATION based on eligibility criteria
Pooled primary outcome event rate: 44.8%
346 enrolled for INSPIRATION-S
Actual dropout: 3%
INSPIRATION-S population for the primary analysis:
N= 587 (98.5% target sample size)
Sample Size estimation for INSPIRATION:
With 5% drop out
For Power: 80%
Pooled primary outcome event rate: 55%
Target N: 600
Considering that 30% may not be eligible for randomization
⇒ For INSPIRATION-S
Pooled primary outcome event rate: 55
N=420
Power: 69.5%
Sample Size re-estimation for Inspiration-S:
For Power: 80%
Event rate: 44.8%
N:596
With 5% drop out
Target N: 626
Prespecified that enrollment could be extended
(blinded to group outcomes) until achieving 80% power

Anticoagulation hypothesis

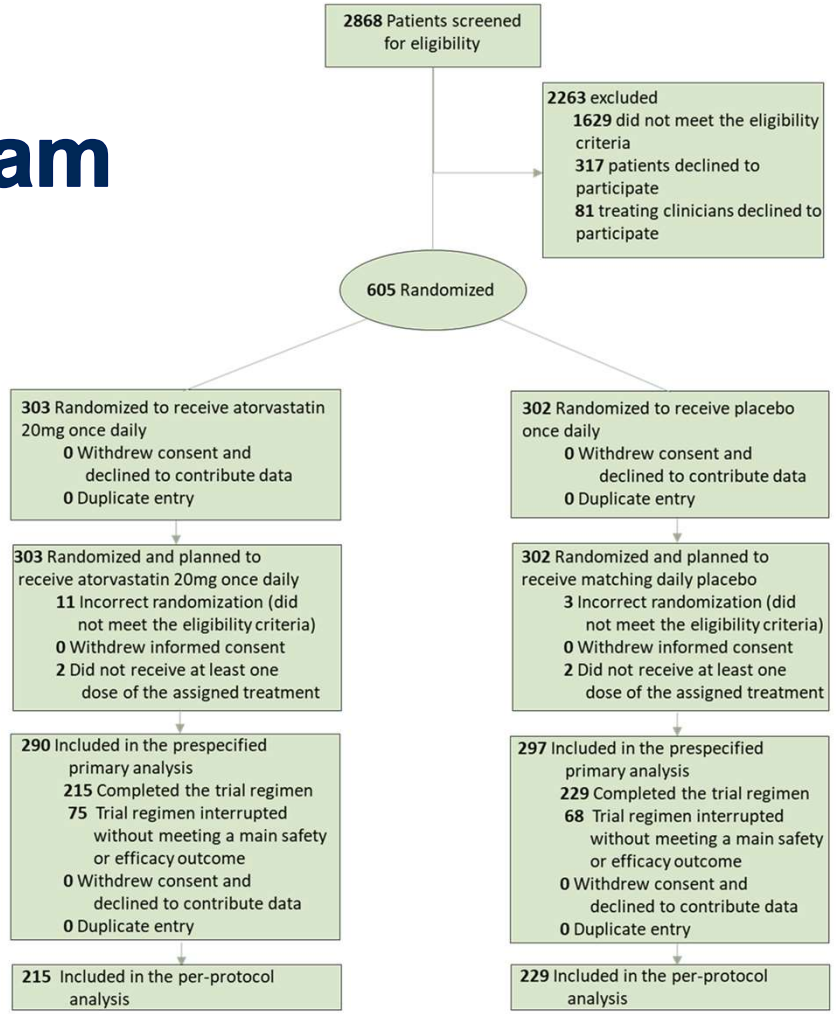


Sadeghipour P, et al... Bikdeli B. JAMA. 2021; 325: 1620-1630.

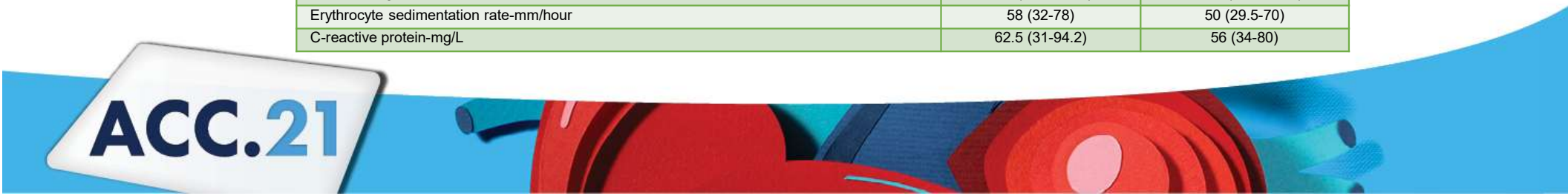
Statin hypothesis statistical considerations

- No treatment interaction observed with the anticoagulant treatment assignment.
- Mixed effects models with random intercept for enrolling sites.
- P<0.05 for the primary hypothesis as significant. All others considered exploratory.

Study flow diagram



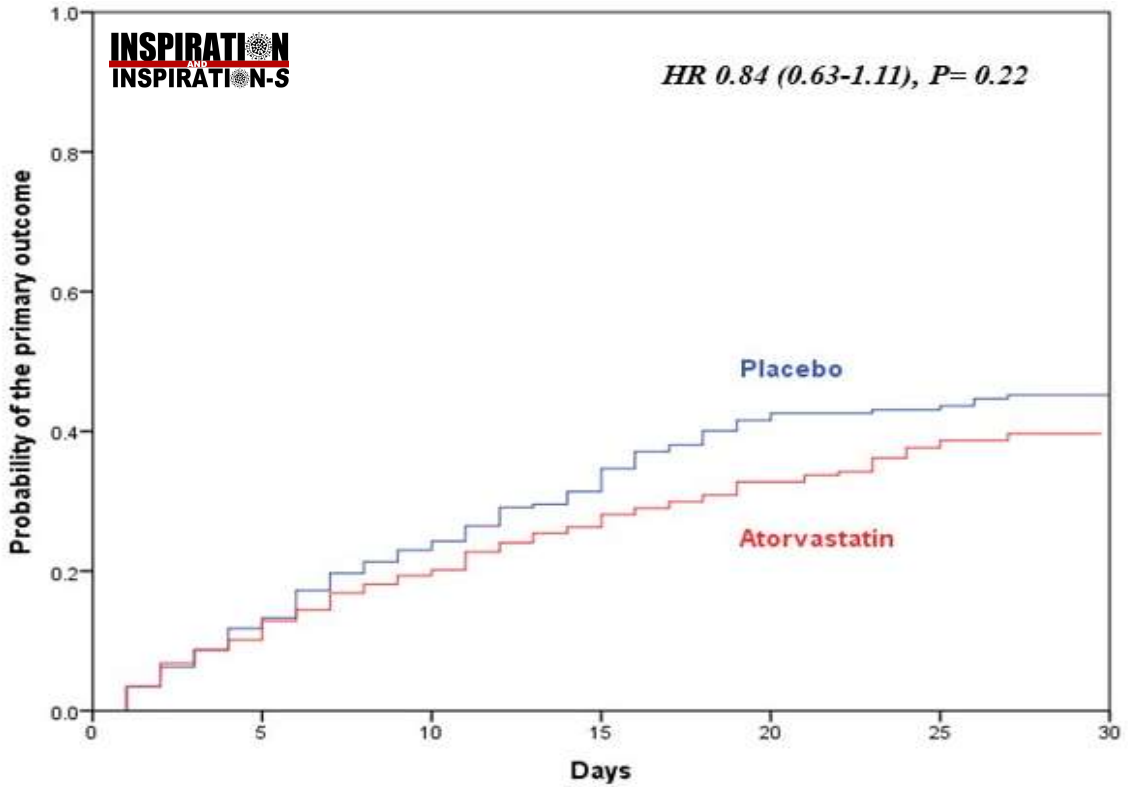
Baseline characteristics		
	Atorvastatin (n=290)	**Placebo (n=297)**
Age— years	57 (45-67)	57 (45-68)
Women — no. (%)	125 (43.1)	131 (44.1)
Body, mass index [b] — kg/m²	27 (24-29)	27 (24-30)
Coexisting conditions— no. (%)		
Diabetes	49 (16.8)	49 (16.4)
Hypertension	89 (30.7)	96 (32.3)
Coronary artery disease	0	0
Obstructive airway disease	24 (8.3)	23 (7.7)
Systolic blood pressure <100mmHg at the time of randomization — no. (%)	29 (10.0)	27 (9.0)
Vasopressor agent support within 72-hour of enrollment— no. (%)	35 (12.0)	49 (16.4)
Fraction of inspired oxygen>50% at the time of randomization — no. (%)	125 (43.1)	133 (44.7)
Acute respiratory support at the time of enrollment— no. (%)		
Nasal cannula	28 (9.6)	30 (10.1)
Face or reservoir mask	131 45.2)	122 (41.1)
High flow nasal cannula	10 (3.4)	9 (3.0)
Non-invasive positive pressure ventilation	87 (30.0)	91 (30.6)
Invasive positive pressure ventilation (endotracheal intubation)	34 (11.7)	45 (15.2)
Drug history— no. (%)		
Aspirin	72 (24.8)	85 (28.6)
Antiviral therapy	233 (80.3)	237 (79.8)
Corticosteroids	268 (92.4)	280 (94.3)
Tocilizumab	43 (14.8)	42 (14.1)
Median laboratory values at baseline[e]		
Plasma creatinine— mg/dL	1.0 (0.8-1.2)	1.0 (0.9-1.2)
Hemoglobin level—g/dL	13.5 (11.8-14.7)	13.4 (12-14.7)
D-dimer—ng/mL	800 (401-1,565)	1,000 (520-1,943)
Erythrocyte sedimentation rate-mm/hour	58 (32-78)	50 (29.5-70)
C-reactive protein-mg/L	62.5 (31-94.2)	56 (34-80)



Efficacy outcomes

Outcome	Atorvastatin (n=290)	Placebo (n=297)	Odds ratio (95% CI)	P value
Composite of adjudicated VTE, arterial thrombosis, treatment with ECMO, or all-cause mortality	95 (32.7)	108 (36.3)	0.84 (0.58-1.21)	0.35
All-cause mortality	90 (31.0)	103 (34.6)	0.84 (0.58-1.22)	0.39
Adjudicated venous thromboembolism	6 (2.0)	9 (3.0)	0.71 (0.24-2.06)	0.53
Ventilator-free days (median, Q1, Q3)	30 (10-30)	30 (4-30)		0.08
Objectively clinically-diagnosed type I acute myocardial infarction	0	0		
Objectively clinically-diagnosed stroke	0	1 (0.3)		0.32

Primary efficacy outcome



Atorvastatin	**Patients at risk**	290	262	239	223	209	199	195
	Primary outcome	0	28	23	16	14	10	4
	All-cause mortality	0	25	23	15	13	10	4
	VTE	0	3	1[a]	1	1	0	0
	Ischemic stroke	0	0	0	0	0	0	0
Placebo	**Patients at risk**	297	264	236	217	196	193	189
	Primary outcome	0	33	28	19	21	3	4
	All-cause mortality	0	28	27	19	22	3	4
	VTE	0	4[a]	3[a]	1	1[a]	0	1[a]
	Ischemic stroke	0	1[b]	0	0	0	0	0

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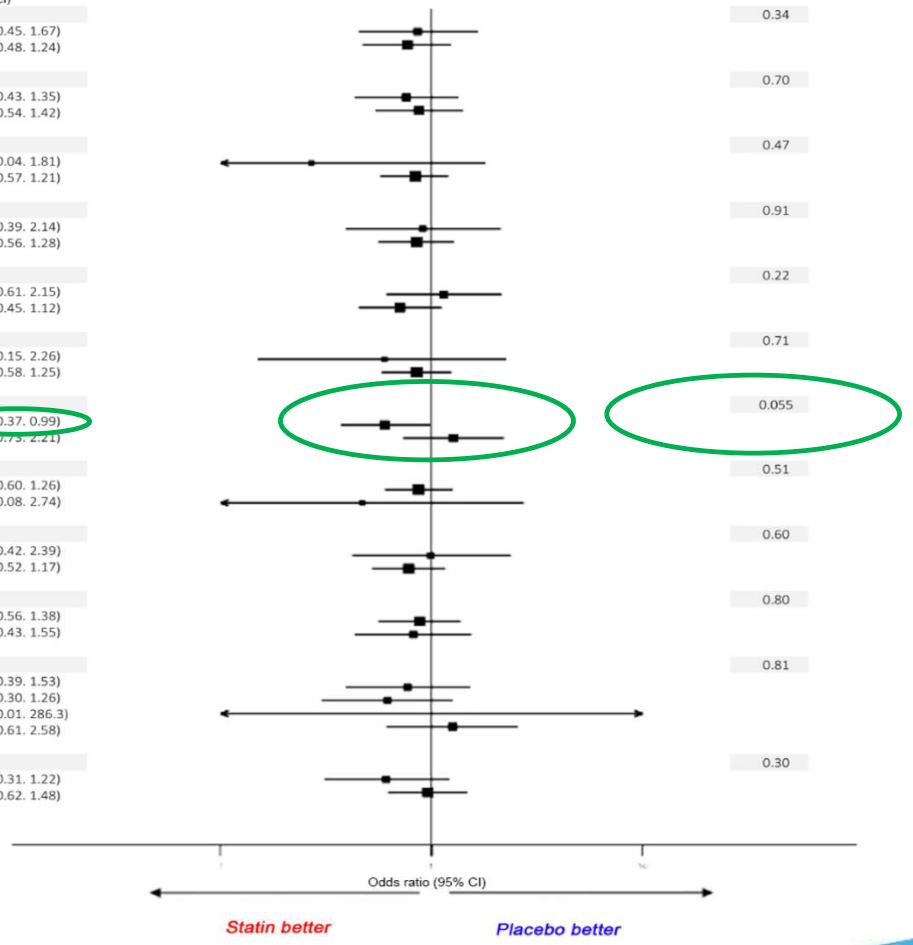
Safety Outcomes

Outcome	Atorvastatin (n=290)	Placebo (n=297)	Odds ratio (95% CI)	P value
Safety outcomes				
Fatal bleeding (BARC 5)	2 (0.6)	2 (0.6)	1.02 (0.14-7.32)	0.98
Major bleeding (BARC 3 or 5)	11 (3.7)	5 (1.6)	2.30 (0.78-6.73)	0.12
Clinically-relevant non-major bleeding (BARC 2)	6 (2.0)	8 (2.6)	0.77 (0.26-2.27)	0.64
Clinically-diagnosed myopathy	0	0		
Rise in liver enzymes	5 (1.7)	6 (2.0)	0.85 (0.25-2.81)	0.79

Subgroup	Atorvastatin No./total No. (%)	Placebo No./total No. (%)	Odds ratio (95% CI)	P value
Age				0.34
Age ≥ 65 (186)	46/89 (51.6)	56/97 (57.7)	0.86 (0.45. 1.67)	
Age <65 (401)	49/201 (24.3)	52/200 (26.0)	0.77 (0.48. 1.24)	
Sex				0.70
Female (256)	38/125 (30.4)	44/131 (33.5)	0.76 (0.43. 1.35)	
Male (331)	57/165 (34.5)	64/166 (38.5)	0.87 (0.54. 1.42)	
Current smoker				0.47
Yes (41)	13/31 (41.9)	6/10 (60.0)	0.27 (0.04. 1.81)	
No (546)	82/259 (31.6)	102/287 (35.5)	0.84 (0.57. 1.21)	
Diabetes				0.91
Yes (98)	23/49 (46.9)	24/49 (48.9)	0.91 (0.39. 2.14)	
No (489)	72/241 (29.8)	84/248 (33.8)	0.85 (0.56. 1.28)	
HTN				0.22
Yes (185)	40/89 (44.9)	38/96 (39.5)	1.14 (0.61. 2.15)	
No (402)	55/201 (27.3)	70/201 (34.8)	0.71 (0.45. 1.12)	
Obstructive airway disease				0.71
Yes (47)	8/24 (33.3)	11/23 (47.8)	0.60 (0.15. 2.26)	
No (540)	87/266 (32.7)	97/274 (35.4)	0.85 (0.58. 1.25)	
Symptom Onset				0.055
Symptom onset≤7 (342)	53/171 (30.9)	69/171 (40.3)	0.60 (0.37. 0.99)	
Symptom onset>7 (245)	42/119 (35.2)	39/126 (30.9)	1.27 (0.73. 2.21)	
Corticosteroid use at baseline				0.51
Yes (548)	90/268 (33.5)	102/280 (36.4)	0.87 (0.60. 1.26)	
No (39)	5/22 (22.7)	6/17 (35.2)	0.47 (0.08. 2.74)	
RAAS blocker use at baseline				0.60
Yes (99)	24/51 (47.1)	21/48 (43.0)	0.99 (0.42. 2.39)	
No (488)	71/239 (29.7)	87/249 (34.9)	0.78 (0.52. 1.17)	
BMI				0.80
<30 (413)	65/211 (30.8)	69/202 (34.1)	0.88 (0.56. 1.38)	
≥30 (174)	30/79 (37.9)	39/95 (41.0)	0.82 (0.43. 1.55)	
Prophylactic anticoagulation regimen				0.81
≥80% Standard-dose (175)	31/79 (39.2)	41/96 (42.7)	0.77 (0.39. 1.53)	
≥80% Intermediate-dose (144)	25/68 (36.7)	37/76 (48.6)	0.62 (0.30. 1.26)	
≥80% Therapeutic-dose (16)	7/8 (87.5)	7/8 (87.5)	1.58 (0.01. 286.3)	
Others (252)	32/135 (23.7)	23/117 (19.6)	1.26 (0.61. 2.58)	
Aspirin use at baseline				0.30
Yes (157)	26/72 (36.1)	40/85 (47.0)	0.61 (0.31. 1.22)	
No (430)	69/218 (31.6)	68/212 (32.0)	0.96 (0.62. 1.48)	



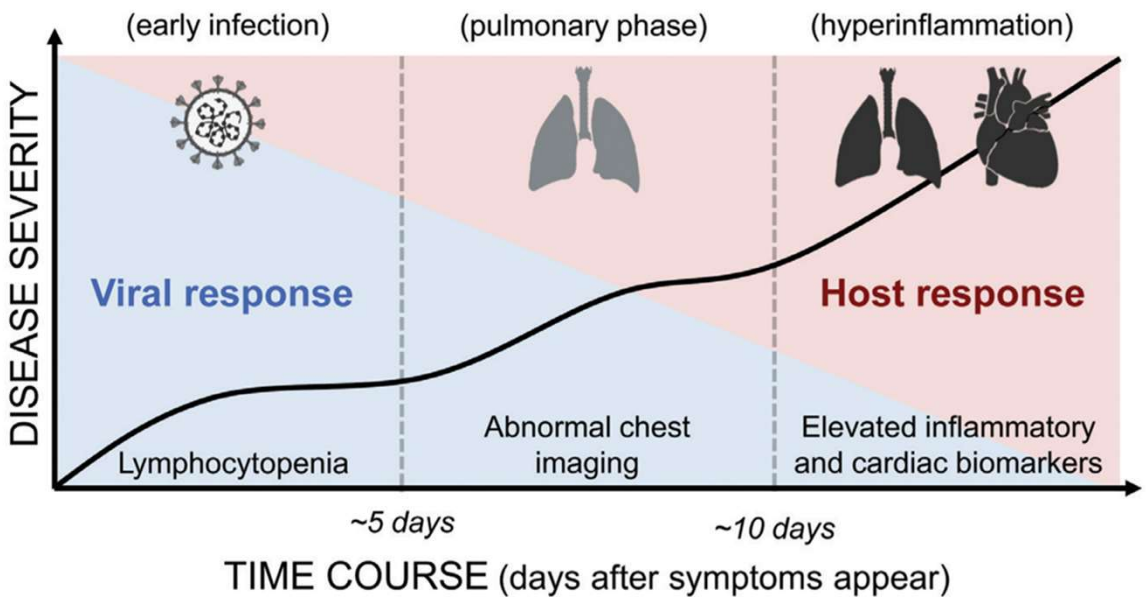
Discussion

- In patients with COVID-19 admitted to ICU, atorvastatin 20mg/d compared with placebo, did not result in significantly reduced risk of the primary outcome, a composite of adjudicated venous or arterial thrombosis, treatment with ECMO, or all-cause mortality.

- Consistent findings within most subgroups and in sensitivity analyses (not shown).

Discussion

- Potential treatment effect in those presenting within 7 days? Hypothesis-generating.



Akhmerov A, et al. Circ Res. 2020;126:1443-1455.

Limitations

1. Cannot exclude a smaller treatment effect.

2. Rate of thrombotic events lower than expected. However, many patients were tested (according to clinicians' suspicions).

3. Other ongoing RCTs should address the effects of statins in other patient groups.

RCTs of Statin Therapy in ICU Patients with COVID-19

Study Name	Inclusion Criteria (Brief*)	Exclusion Criteria (Brief*)	Sample Size	Study Arms	Duration of Administration	Patient Enrollment Setting†	Liver Disease Consideration	DDI Consideration	Primary Outcomes	Primary Outcome Follow-up Duration
INSPIRATION-S NCT04486508	Age 18 years, PCR confirmed COVID-19, estimated survival>24 hours	Pregnancy, antecedent statin use, weight <40 Kg, exclusion from anticoagulation randomization (recent bleed, stroke, trauma, surgery, platelets <50,000/fL), elevated LFTs or liver disease	600	Atorvastatin [20 mg] Placebo	30			-	Composite clinical endpoint	30
NCT04813471	Age 18-99 years, PCR confirmed COVID-19	Pregnancy, lactation, antecedent statin or nicorandil use, concomitant use of levodopa, PDE-5 inhibitors, riociguat, pulmonary edema, active liver disease, elevated LFTs	70	Atorvastatin [40 mg] SOC	14 days or until DC				Clinical Improvement	28
NCT04359095	Age 18 years, PCR confirmed COVID-19	Pregnancy, cirrhosis or elevated LFTs, GFR < 30mL/min, advanced or metastatic cancer, FRAIL score of fragility >3	1200	Rosuvastatin [40 mg]+ Colchicine Rosuvastatin[40 mg]+ Colchicine+ Truvada SOC	14 (Truvada for 10 days)			-	Mortality	28
MEDIC-LAUMC NCT04631536	Age 18 years, PCR confirmed COVID-19 admitted for inpatient treatment.	Pregnancy, lactation, antecedent beta-blocker, statin, nicorandil, PDE5 inhibitor or riociguat use, myocarditis, shock, bradycardia (<50 bpm), >1st degree heart block, decompensated heart failure, active liver disease, elevated LFTs	80	Atorvastatin [40 mg] Placebo	14 (or until DC or death)				Clinical improvement	30

Talasaz AH, et al… Bikdeli B. Under Review.

Conclusions

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- In patients with COVID-19 admitted to ICU, atorvastatin 20mg/d compared with placebo did not result in significantly reduced risk of the primary outcome, a composite of adjudicated venous or arterial thrombosis, treatment with ECMO, or all-cause mortality.
- A smaller treatment effect and findings within specific subgroups warrant additional investigation.

Acknowledgements

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Diagnostic Tests for VTE

	Atorvastatin	Placebo	Total
Venous doppler ultrasound performed	40	41	81
Confirmed deep venous thrombosis	3	6	9
CT pulmonary angiogram performed	17	17	35
Confirmed pulmonary emboli	3	3	6