Prevention of COVID-19 complications with colchicine

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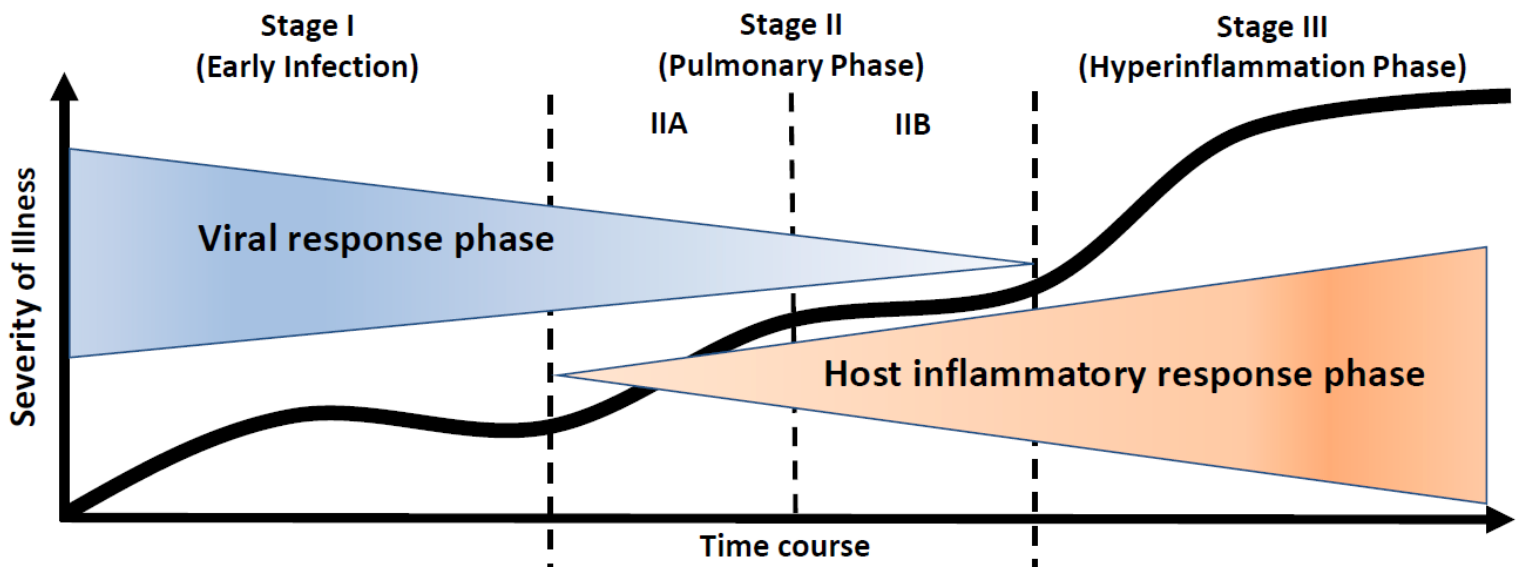
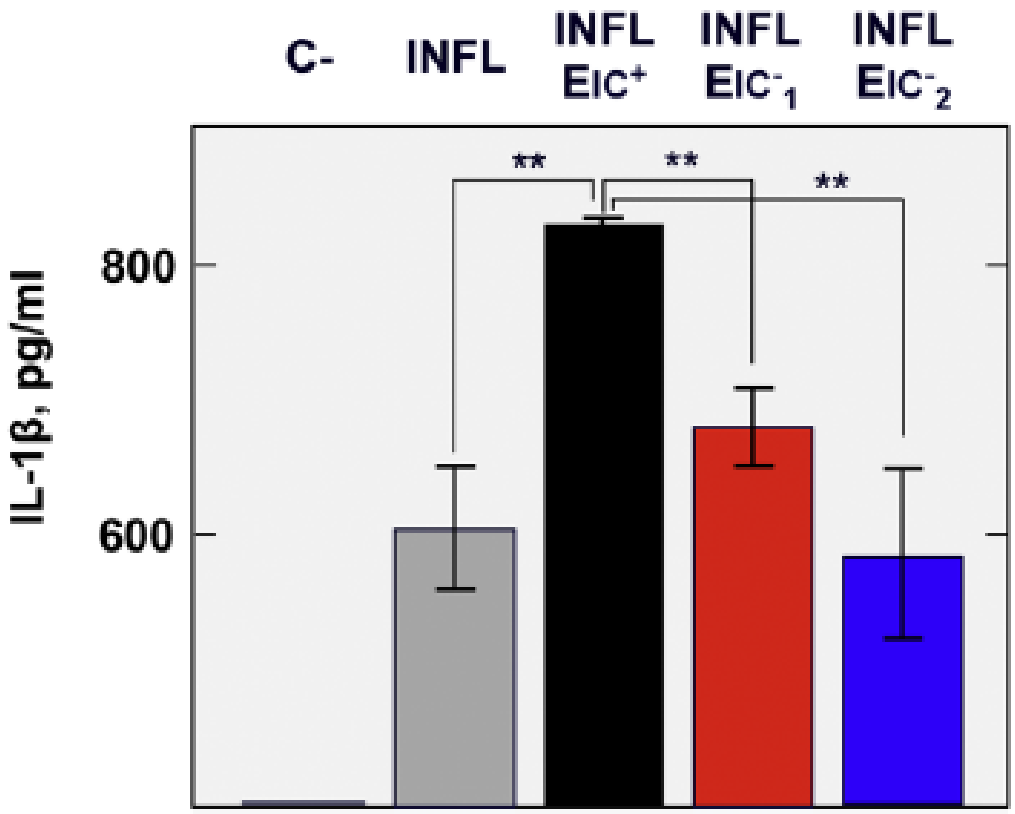
MONTREAL HEART INSTITUTE

Stages of progression of COVID-19



Clinical Symptoms	Mild constitutional symptoms Fever >99.6˚F Dry Cough, diarrhea, headache	Shortness of Breath Hypoxia (PaO2/FiO2≤300mmHg)	ARDS SIRS/Shock Cardiac Failure
Clinical Signs	Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)	Abnormal chest imaging Transaminitis Low-normal procalcitonin	Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation

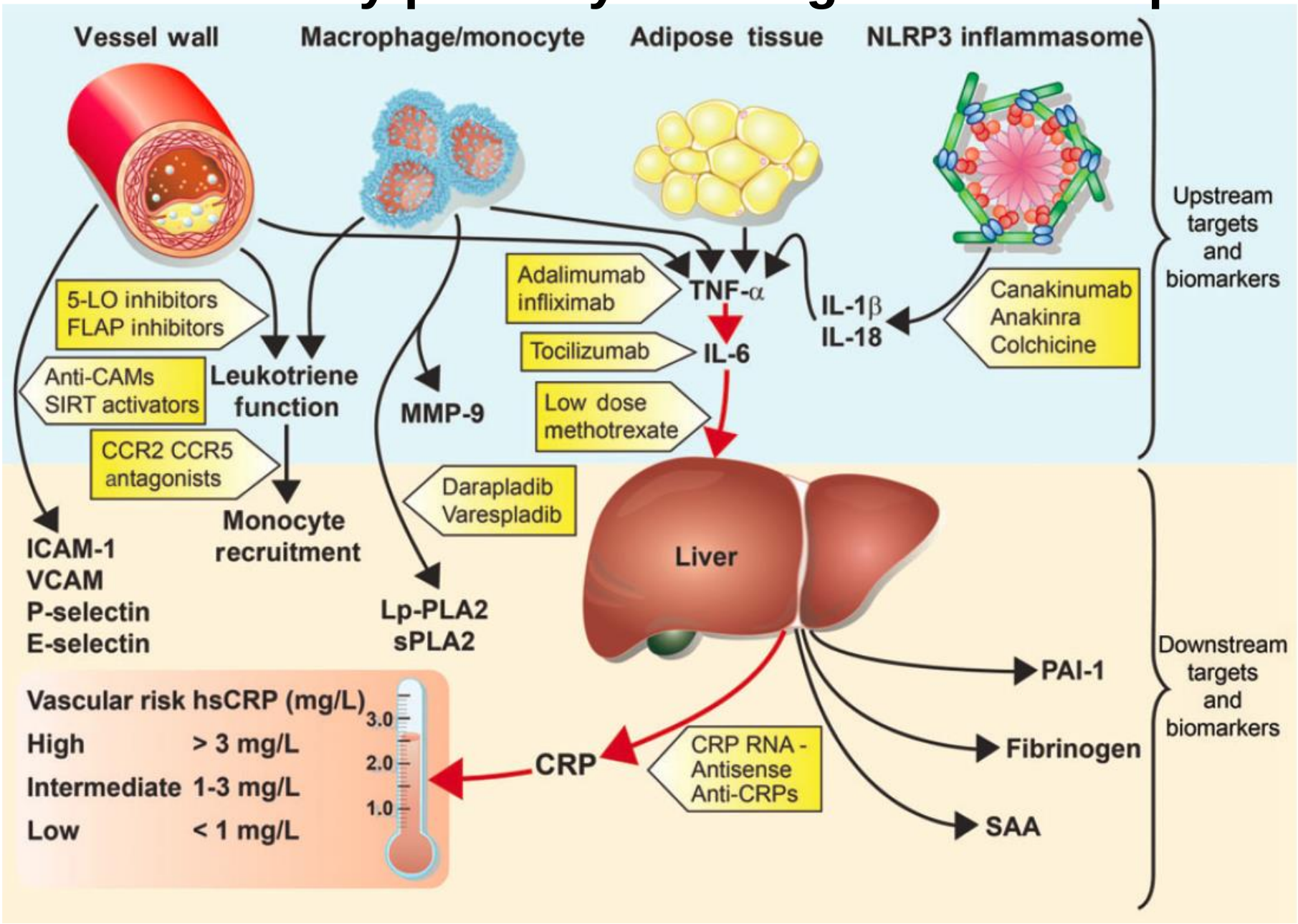
SARS-CoV viroprotein E activates the NLRP3 inflammasome (INFL)



Inflammasome components were transfected in Vero E6 cells, in absence or presence of SARS-CoV E protein with (IC+) or without (IC-) ion channel activity. EIC1- and EIC2- indicate mutants. As a negative control, cells were transfected solely with pro-IL1b (C-).

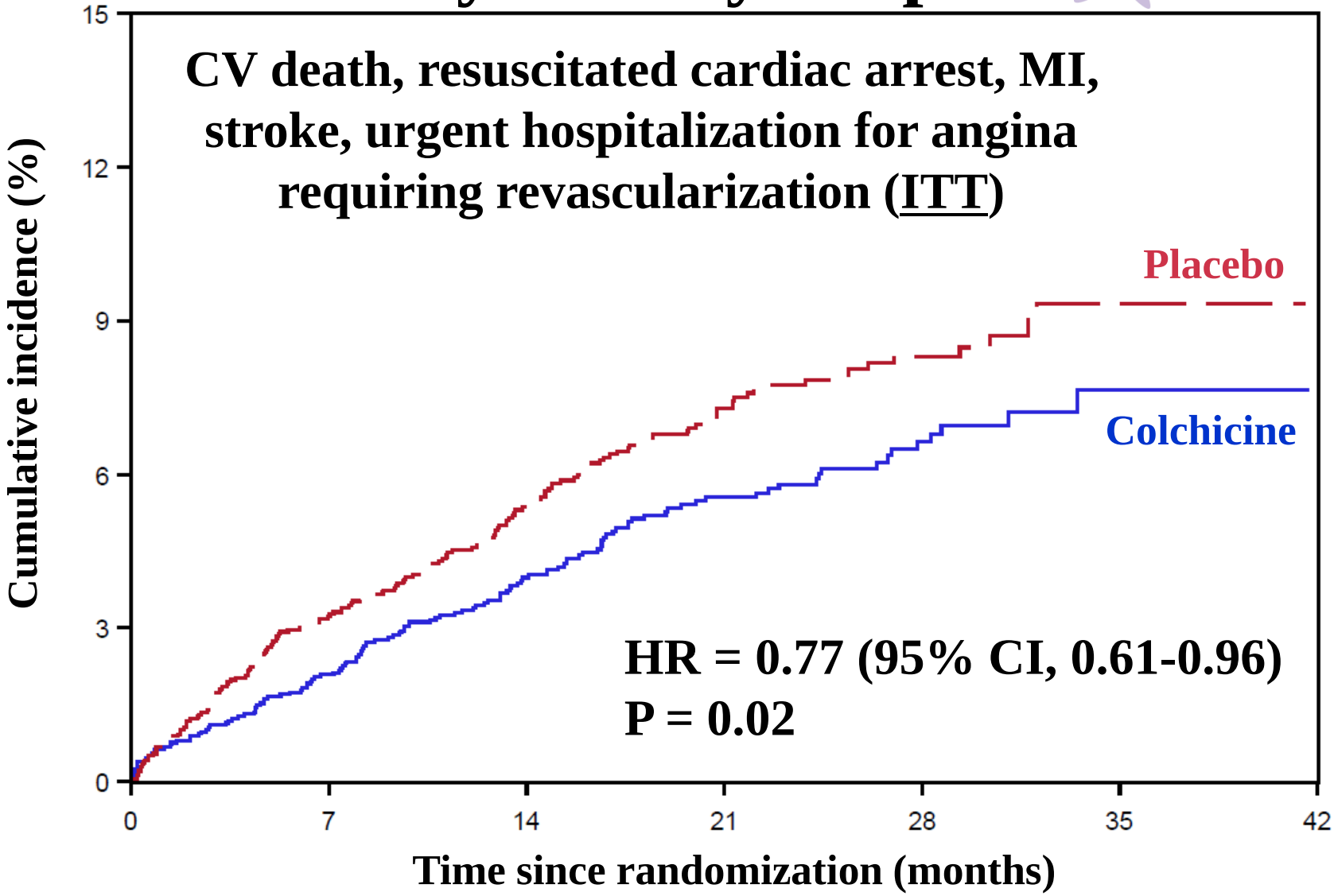
Nieto-Torres JL et al. Virology 2015;485:330-339.

Inflammatory pathways as targets for therapies



Ridker PM, Luscher TF. Eur Heart J 2014;35:1782-1791

Primary efficacy endpoint



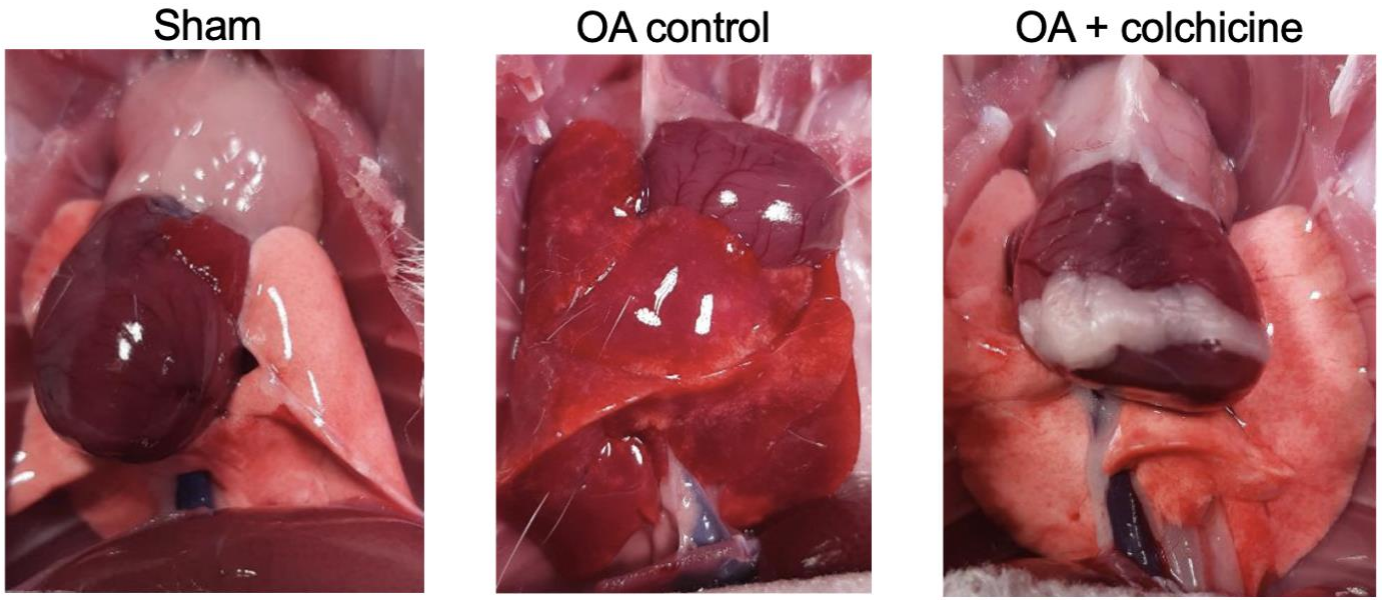
No. at Risk							
Colchicine	2366	2284	1868	1230	628	153	0
Placebo	2379	2261	1854	1224	622	144	0

Tardif et al. N Engl J Med 2019;381:2497-2505.

Adverse events

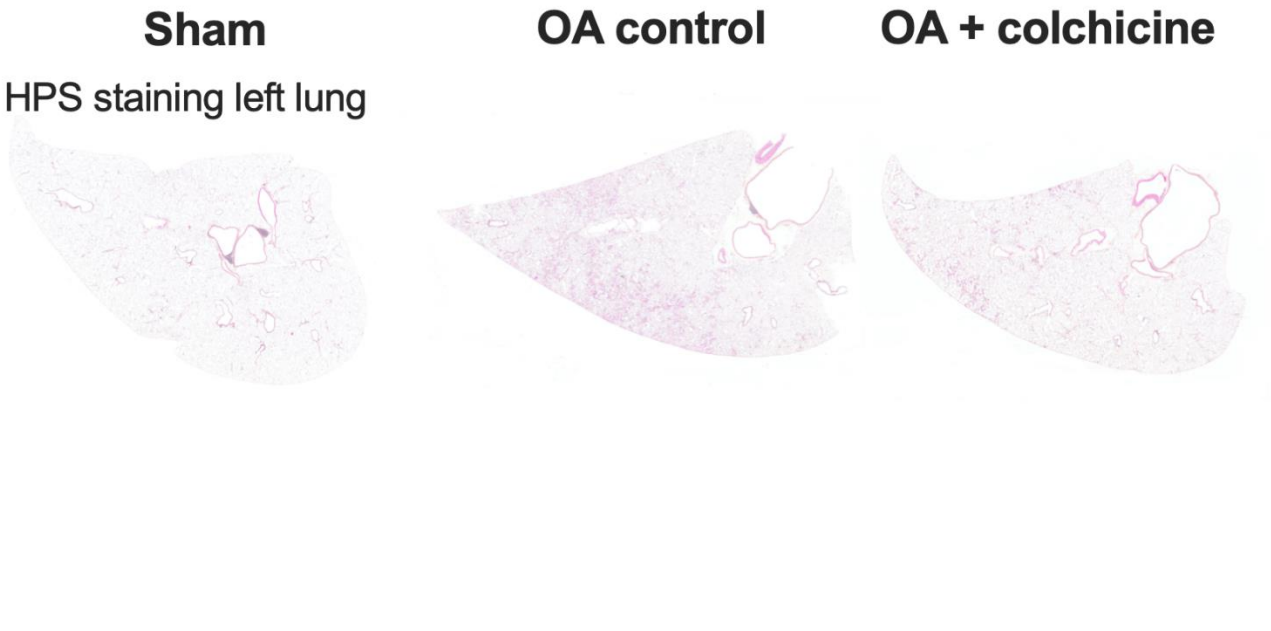
Safety population	Colchicine (N=2330)	Placebo (N=2346)	P Value
Any related AE - no. (%)	372 (16.0%)	371 (15.8%)	0.89
Any SAE - no. (%)	383 (16.4%)	404 (17.2%)	0.47
Gastro-intestinal AE - no. (%)	408 (17.5%)	414 (17.6%)	0.90
Gastro-intestinal SAE – no. (%)	46 (2.0%)	36 (1.5%)	0.25
Diarrhea AE - no. (%)	225 (9.7%)	208 (8.9%)	0.35
Nausea AE - no. (%)	43 (1.8%)	24 (1.0%)	0.02
Flatulence AE - no. (%)	15 (0.6%)	5 (0.2%)	0.02
GI haemorrhage AE - no. (%)	7 (0.3%)	5 (0.2%)	0.56
Infection SAE - no. (%)	51 (2.2%)	38 (1.6%)	0.15
Pneumonia SAE - no. (%)	21 (0.9%)	9 (0.4%)	0.03
Septic shock SAE - no. (%)	2 (0.1%)	2 (0.1%)	0.99
HF hospitalization - no. (%)	25 (1.1%)	17 (0.7%)	0.21
Cancer - no. (%)	43 (1.8%)	46 (2.0%)	0.77
Anemia - no. (%)	14 (0.6%)	10 (0.4%)	0.40
Leukopenia - no. (%)	2 (0.1%)	3 (0.1%)	0.66
Thrombocytopenia - no. (%)	3 (0.1%)	7 (0.3%)	0.21

Colchicine reduces lung injury in ARDS



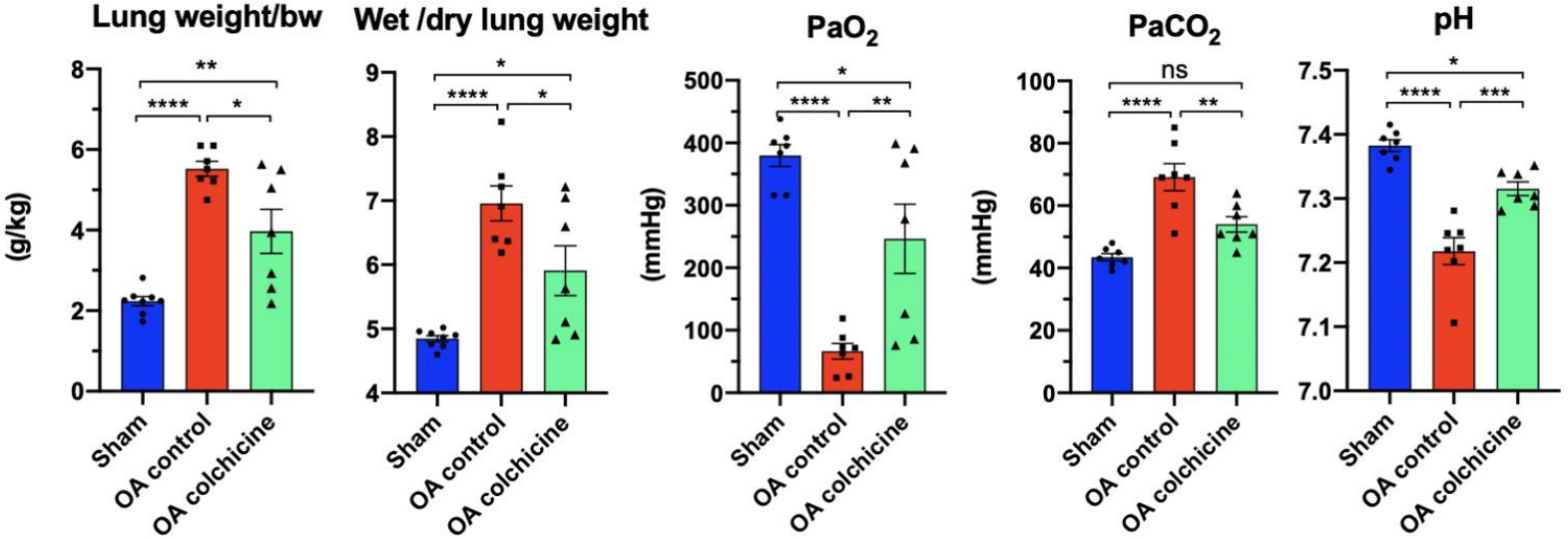
Dupuis J, et al, Tardif JC. Plos One 2020 (in press)

Colchicine reduces lung injury by 61%



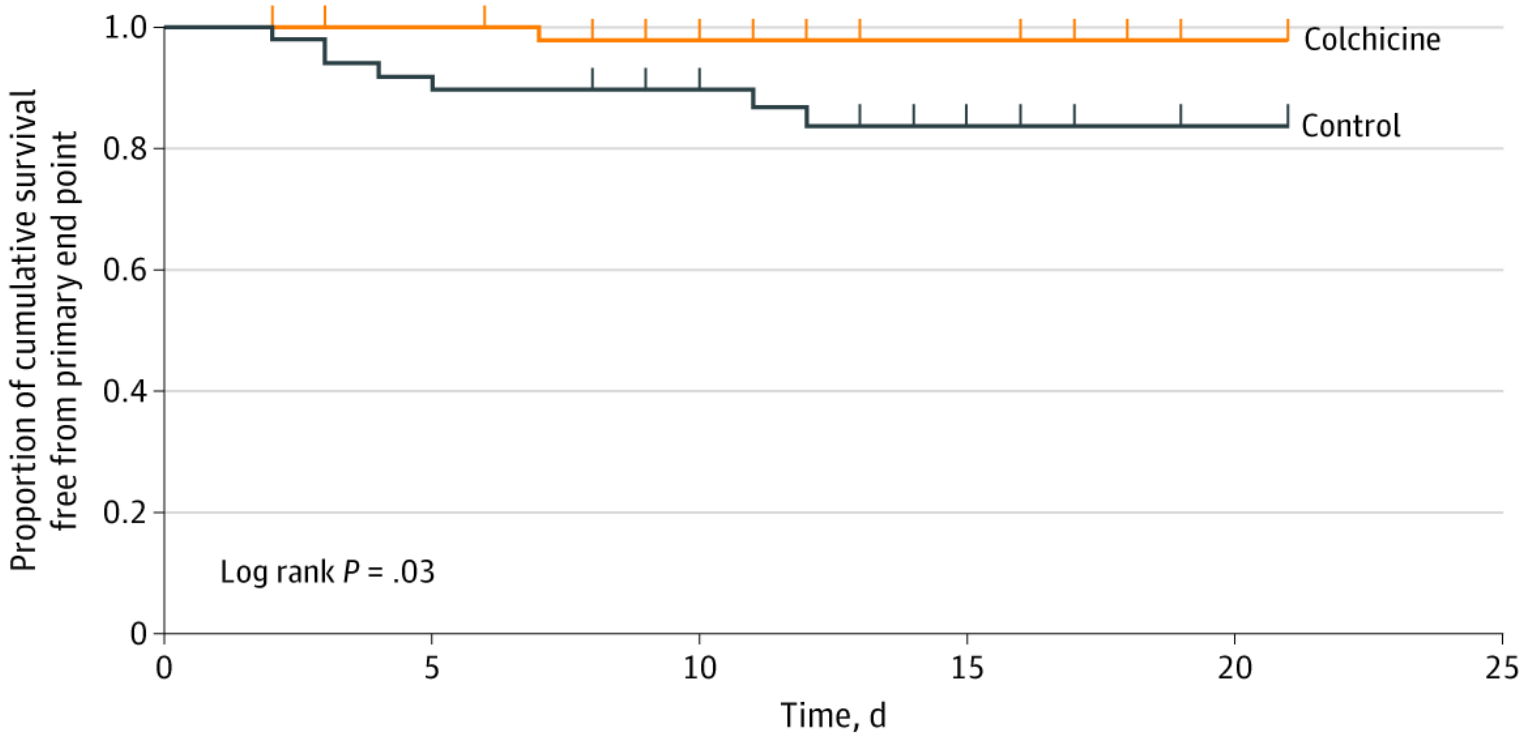
Dupuis J, et al, Tardif JC. Plos One 2020 (in press)

Colchicine reduces lung edema and improves oxygenation and gas exchanges



Dupuis J, et al, Tardif JC. Plos One 2020 (in press)

Colchicine vs standard care on biomarkers and clinical outcomes in patients hospitalized with COVID-19 The GRECCO-19 randomized trial

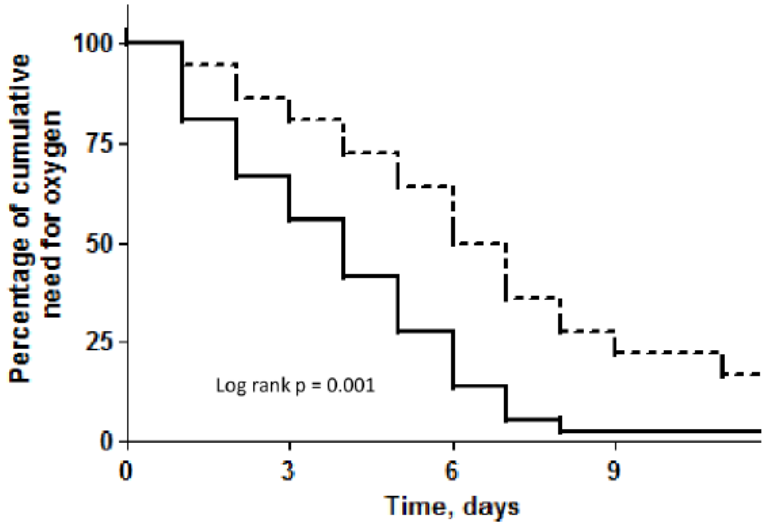


No. at risk					
Colchicine	55	52	26	15	8
Control	50	43	36	15	6

Deftereos SG et al. JAMA Network Open 2020; 3(6)

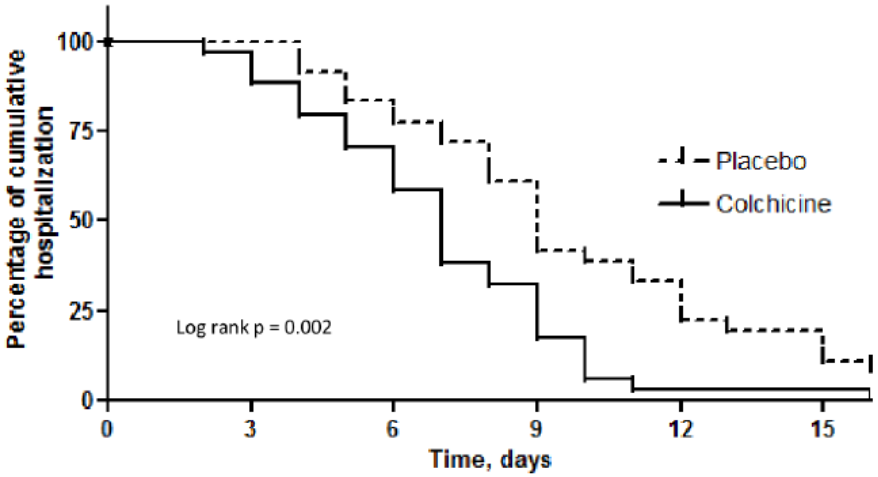
Colchicine in moderate to severe COVID-19
A randomized, double-blind, clinical trial

Need for oxygen therapy



Placebo (n)	36	29	18	8	
Colchicine (n)	36	20	5	1	

Duration of hospitalization



Placebo (n)	36	36	28	15	8	4
Colchicine (n)	36	32	22	6	1	1

Lopes MA et al. Rheumatic and Musculoskeletal Diseases 2021 (in press)

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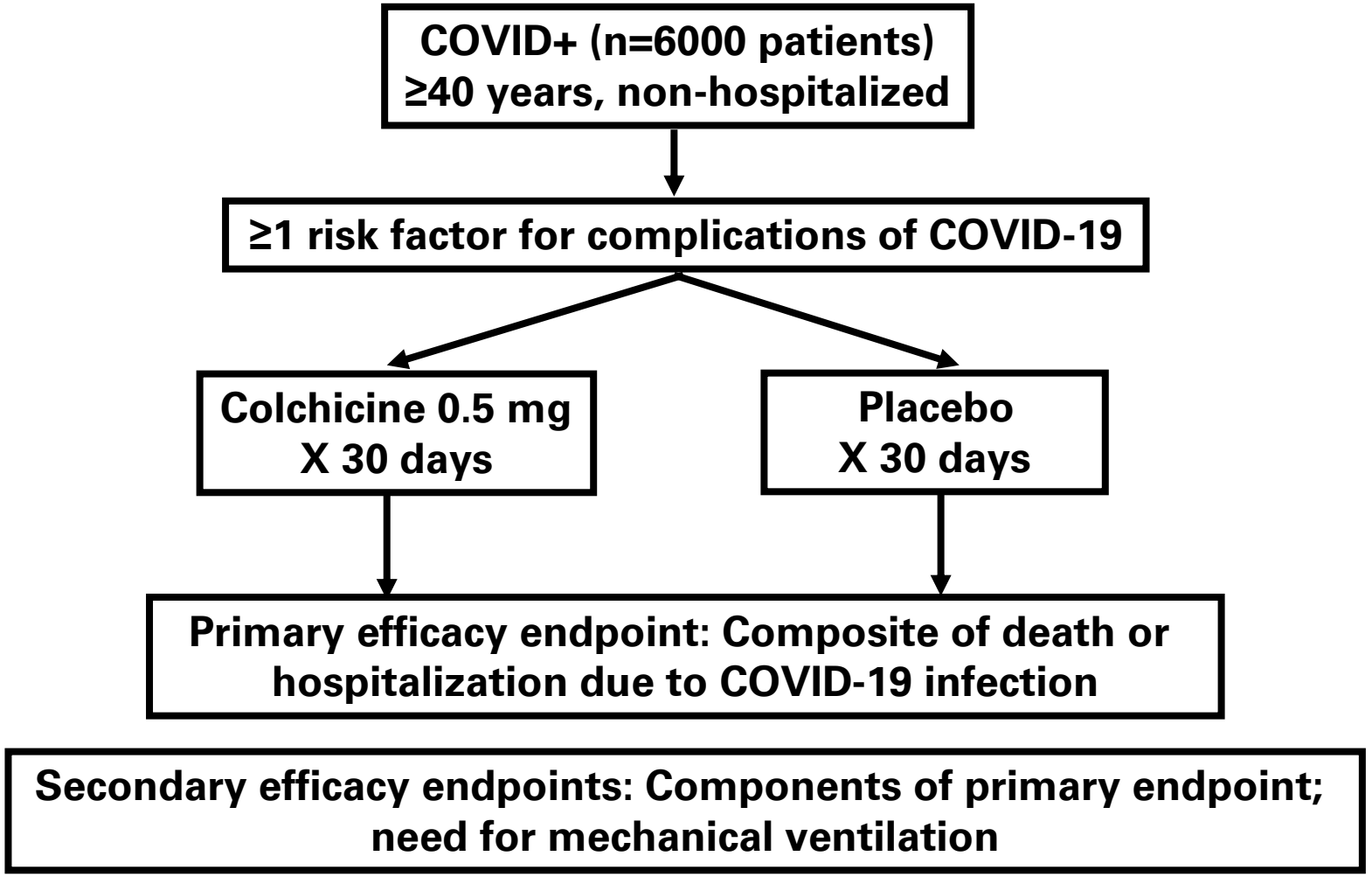
COLCORONA Study Design



Risk factors for complications determining eligibility in COLCORONA

Patient must present ≥1 risk factor for complications:

- Age ≥ 70 years (all patients must be aged ≥40 years)
- Diabetes mellitus
- Body-mass index ≥30 kg/m2
- Uncontrolled hypertension (systolic BP ≥150 mm Hg)
- Known pulmonary disease (including asthma or COPD)
- Known heart failure
- Known coronary disease
- Fever ≥38.4° C in the last 48 hours
- Dyspnea at presentation
- Bicytopenia or pancytopenia
- Combination of high neutrophil count and low lymphocyte count

Diagnosis of COVID-19

• Diagnosis by naso-pharyngeal swab and COVID-19 PCR test, OR

• Diagnosis by epidemiological link with COVID19-compatible symptoms and member of household with positive nasopharyngeal COVID-19 PCR test result, OR

• Probable diagnosis of COVID-19 according to criteria adapted from Public Health of Quebec and European Centre for Disease Prevention and Control

Clinical diagnosis of probable COVID-19 in COLCORONA *

Patient with sudden onset of the following symptoms without an obvious alternative cause:

1- Fever (> 38 degrees C) and cough

OR

2- Fever (> 38 degrees C) or cough with ≥ 1 of the following symptoms:

- shortness of breath
- extreme fatigue
- muscle or joint pains
- Sudden anosmia without nasal obstruction, with or without ageusia

Patient characteristics

	Colchicine (N=2235)	Placebo (N=2253)
Age - years	54.4±9.7	54.9±9.9
Female sex - no. (%)	1238 (55.4%)	1183 (52.5%)
Caucasian - no. (%)	2086 (93.3%)	2096 (93.2%)
Body-mass index - kg/m^2	30.0±6.2	30.0±6.3
Smoking - no. (%)	217 (9.7%)	212 (9.4%)
Hypertension - no. (%)	781 (34.9%)	848 (37.6%)
Diabetes - no. (%)	444 (19.9%)	450 (20.0%)
Respiratory disease - no. (%)	583 (26.1%)	605 (26.9%)
Prior MI - no. (%)	65 (2.9%)	72 (3.2%)
Prior heart failure – no. (%)	24 (1.1%)	18 (0.8%)
Hydroxychloroquine use – n. (%)	7 (0.3%)	5 (0.2%)
Oral anticoagulant use - no. (%)	47 (2.1%)	64 (2.8%)
Aspirin use - no. (%)	195 (8.7%)	235 (10.4%)
Other antiplatelet agent - no. (%)	32 (1.4%)	43 (1.9%)

Rates and Odds Ratios for Major Clinical Outcomes

Clinical Outcome	Colchicine	Placebo	Odds Ratio (95% CI)	P Value
ITT population	N=2235	N=2253		
Primary composite endpoint - no. (%)	104 (4.7%)	131 (5.8%)	0.79 (0.61-1.03)	0.08
Components of primary endpoint:				
Death - no. (%)	5 (0.2%)	9 (0.4%)	0.56 (0.19-1.67)	
Hospitalization for COVID-19 no. (%)	101 (4.5%)	128 (5.7%)	0.79 (0.60-1.03)	
Secondary endpoint:				
Mechanical ventilation - no. (%)	11 (0.5%)	21 (0.9%)	0.53 (0.25-1.09)	
Patients with PCR-proven COVID-19	N=2075	N=2084		
Primary composite endpoint – no. (%)	96 (4.6%)	126 (6.0%)	0.75 (0.57-0.99)	0.04
Components of primary endpoint:				
Death - no. (%)	5 (0.2%)	9 (0.4%)	0.56 (0.19-1.66)	
Hospitalization for COVID-19 no. (%)	93 (4.5%)	123 (5.9%)	0.75 (0.57-0.99)	
Secondary endpoint:				
Mechanical ventilation – no. (%)	10 (0.5%)	20 (1.0%)	0.50 (0.23-1.07)	

Primary Efficacy Composite Endpoint in Prespecified Subgroups

History of diabetes	Colchicine	Placebo	Odds ratio (95% CI)
Yes	27/444 (6.1%)	43/450 (9.6%)	0.61 (0.37-1.01)
No	77/1791 (4.3%)	88/1803 (4.9%)	0.88 (0.64-1.20)
History of hypertension			
Yes	48/781 (6.1%)	64/848 (7.5%)	0.80 (0.54-1.18)
No	56/1454 (3.9%)	67/1405 (4.8%)	0.80 (0.56-1.15)
Smoking			
Non-smoker	59/1279 (4.6%)	71/1270 (5.6%)	0.82 (0.57-1.16)
Previous smoker	38/738 (5.1%)	56/770 (7.3%)	0.69 (0.45-1.06)
Active smoker	7/217 (3.2%)	4/212 (1.9%)	1.73 (0.50-6.01)
Age			
≥ 70 years	18/190 (9.5%)	27/213 (12.7%)	0.72 (0.38-1.36)
< 70 years	86/2045 (4.2%)	104/2040 (5.1%)	0.82 (0.61-1.09)
Sex			
Men	58/997 (5.8%)	90/1070 (8.4%)	0.67 (0.48-0.95)
Women	46/1238 (3.7%)	41/1183 (3.5%)	1.07 (0.70-1.65)
Body-mass index			
≥ 30 kg/m^2	53/1012 (5.2%)	70/1040 (6.7%)	0.77 (0.53-1.11)
< 30 kg/m^2	50/1216 (4.1%)	61/1205 (5.1%)	0.80 (0.55-1.18)
Respiratory disease			
Yes	35/583 (6.0%)	48/605 (7.9%)	0.74 (0.47-1.16)
No	69/1652 (4.2%)	83/1647 (5.0%)	0.82 (0.59-1.14)
Cardiovascular disease			
Yes	6/119 (5.0%)	11/122 (9.0%)	0.54 (0.19-1.50)
No	98/2116 (4.6%)	120/2131 (5.6%)	0.81 (0.62-1.07)
Use of ACEi/ARB			
Yes	37/602 (6.1%)	53/676 (7.8%)	0.77 (0.50-1.19)
No	67/1633 (4.1%)	78/1577 (4.9%)	0.82 (0.59-1.15)

Primary Efficacy Composite Endpoint Based on Risk Score Model*

Risk score	Colchicine	Placebo	Odds ratio (95% CI)
High-risk	56/764 (7.3%)	86/801 (10.7%)	0.66 (0.46-0.94)
Low-risk	39/1305 (3.0%)	40/1277 (3.1%)	0.95 (0.61-1.49)

* Risk score model developed in patients of the placebo group with PCR-proven COVID-19 .

* The c-statistic of this risk score model was 0.72.

* This risk score model has not yet been tested in a second patient cohort.

* P = 0.02 for the comparison of the colchicine and placebo groups in high-risk subgroup.

Preliminary result

Adverse events

Safety population	Colchicine (N=2195)	Placebo (N=2217)	P Value
Any SAE - no. (%)	108 (4.9%)	139 (6.3%)	0.05
Pneumonia SAE - no. (%)	63 (2.9%)	92 (4.1%)	0.02
Pulmonary embolism - no. (%)	11 (0.5%)	2 (0.1%)	0.01
Deep venous thrombosis - no. (%)	0 (0%)	0 (0%)	N/A
Myocardial infarction - no. (%)	0 (0%)	1 (0.0%)	1.00
Dehydration SAE - no. (%)	3 (0.1%)	6 (0.3%)	0.51
Any related AE - no. (%)	532 (24.2%)	344 (15.5%)	<0.0001
Gastro-intestinal AE - no. (%)	524 (23.9%)	328 (14.8%)	<0.0001
Gastro-intestinal SAE - no. (%)	6 (0.3%)	3 (0.1%)	0.34
Diarrhea AE - no. (%)	300 (13.7%)	161 (7.3%)	<0.0001
Nausea AE- no. (%)	43 (2.0%)	47 (2.1%)	0.71
GI haemorrhage AE - no. (%)	1 (0.0%)	0 (0%)	0.50
Rash AE - no. (%)	4 (0.2%)	13 (0.6%)	0.03

Conclusion

• In non-hospitalized patients including those without a mandatory diagnostic test, the effect of colchicine on COVID-19-related clinical events was not statistically significant.

• Among patients with PCR-confirmed COVID-19, colchicine led to a lower rate of the composite of death or hospitalization than placebo.

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