Colchicine in COVID-19

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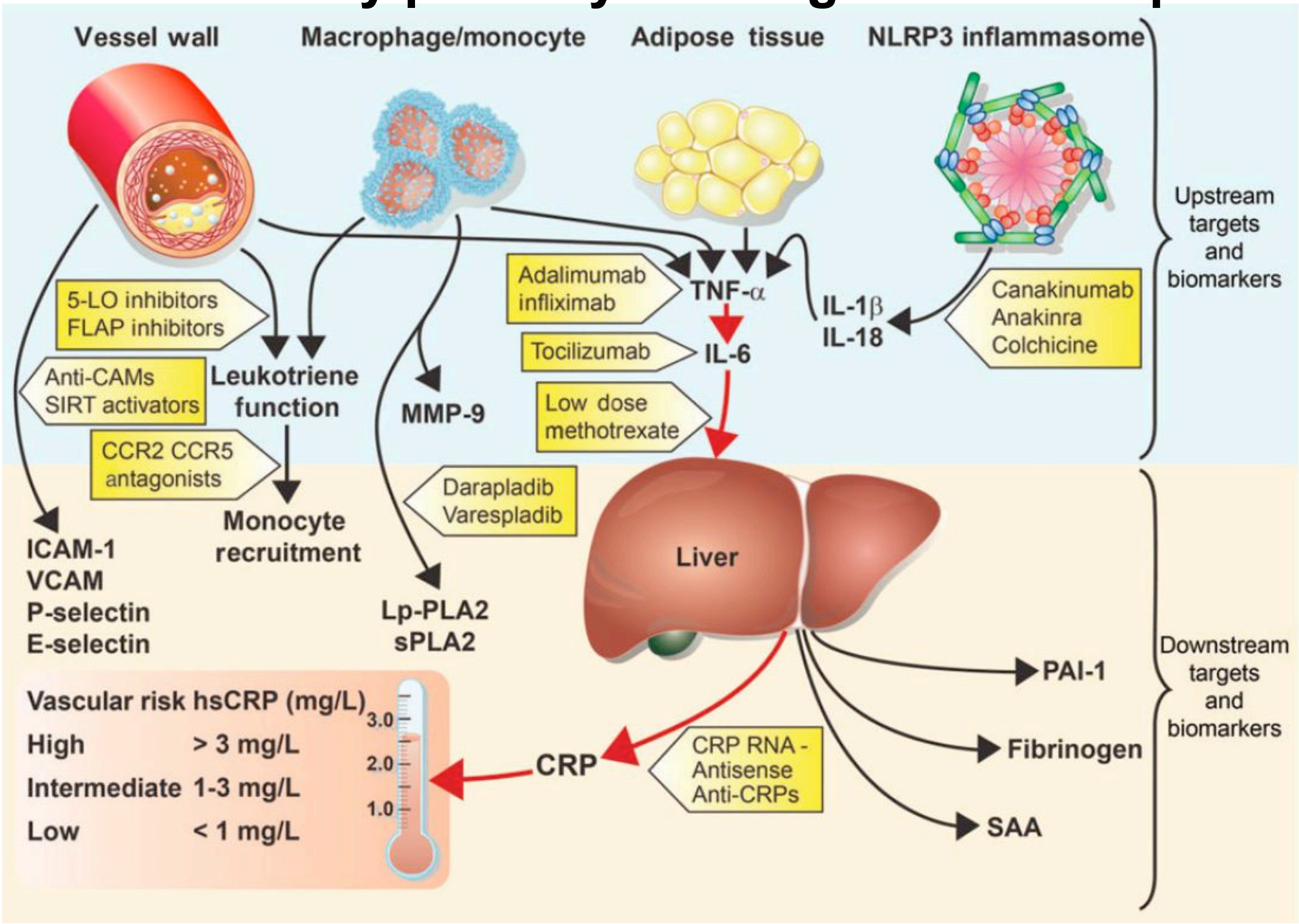
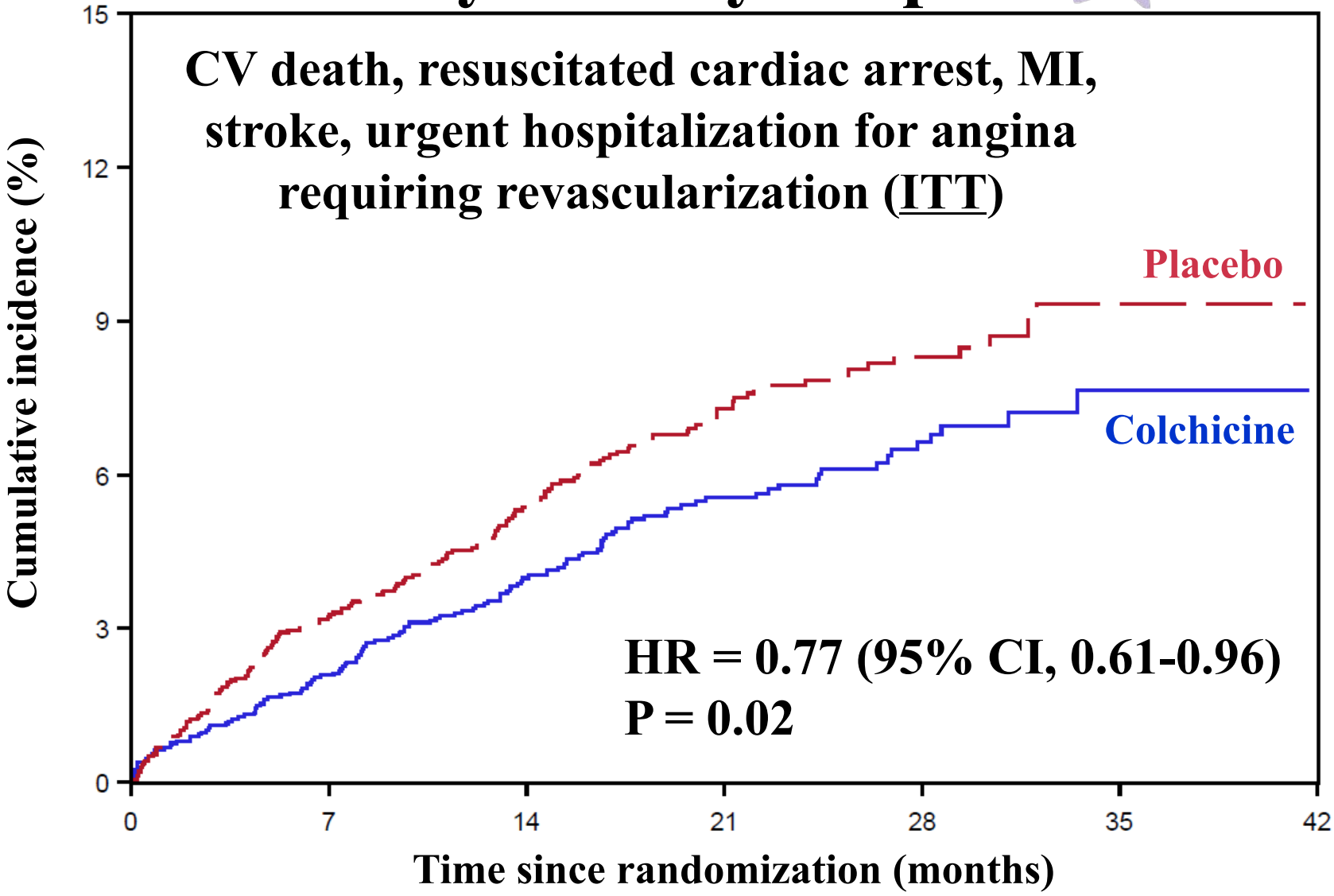
MONTREAL HEART INSTITUTE

Inflammatory pathways as targets for therapies



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

Primary efficacy endpoint

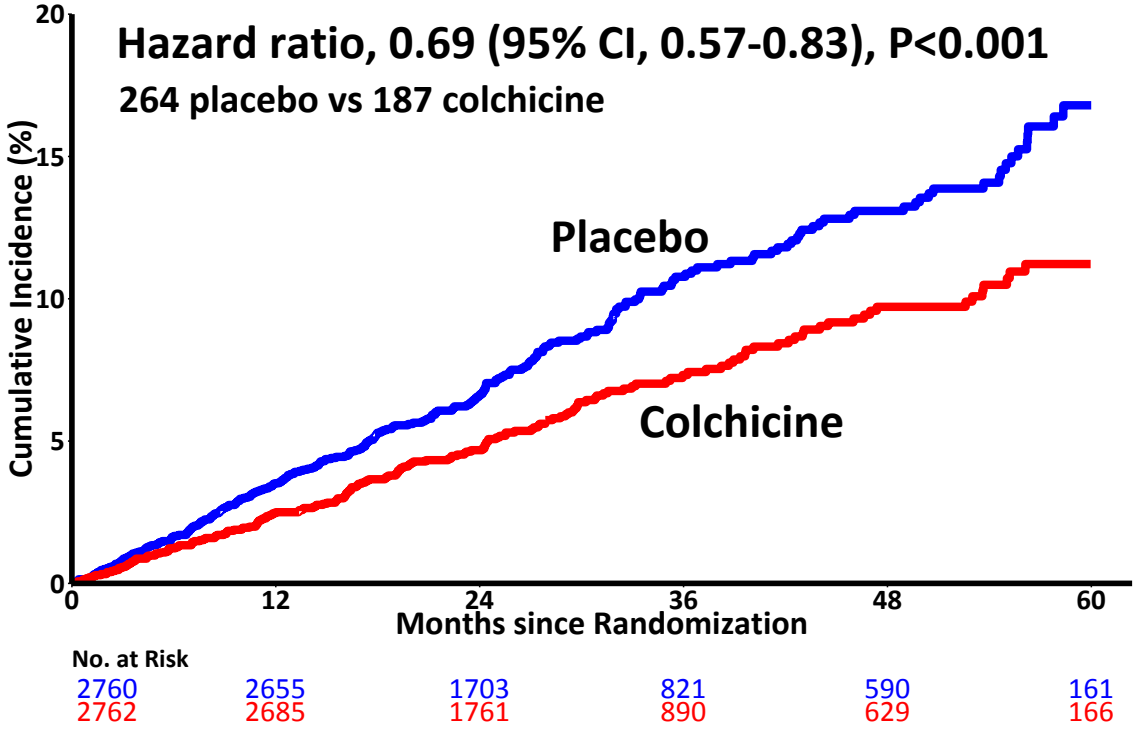


No. at Risk							
Colchicine	2366	2284	1868	1230	628	153	0
Placebo	2379	2261	1854	1224	622	144	0

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

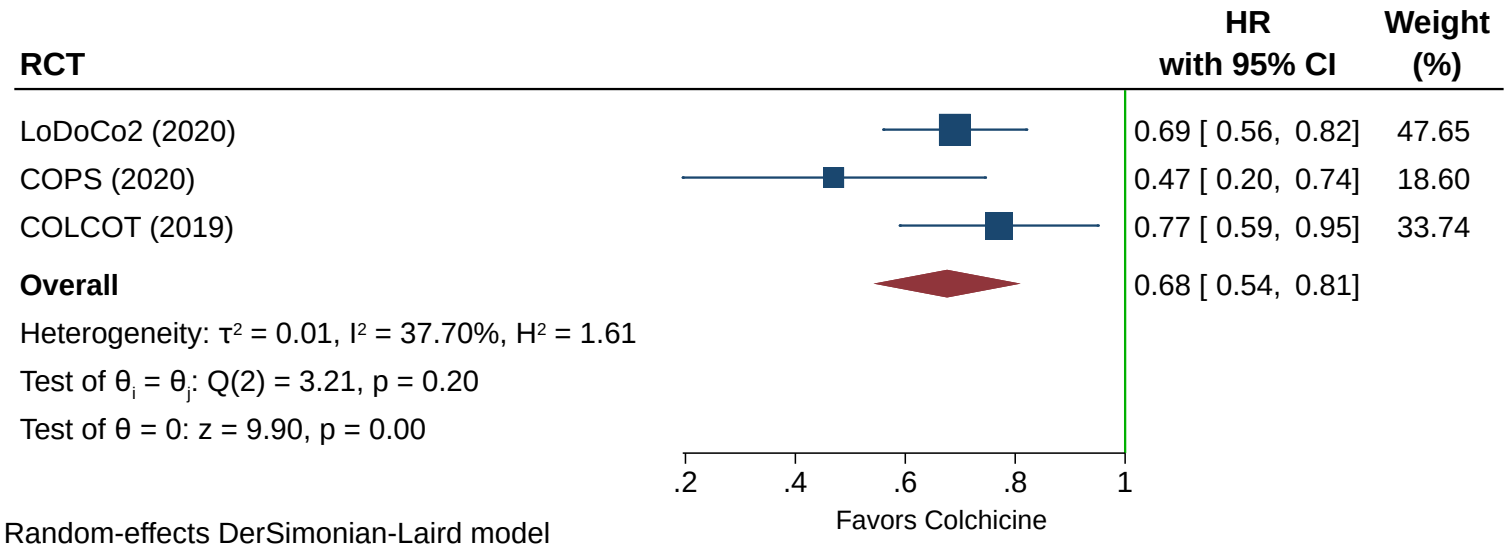
Primary endpoint

Cardiovascular death, myocardial infarction, ischemic stroke or ischemia-driven coronary revascularization



Nidorf SM et al. N Engl J Med 2020 Aug 31

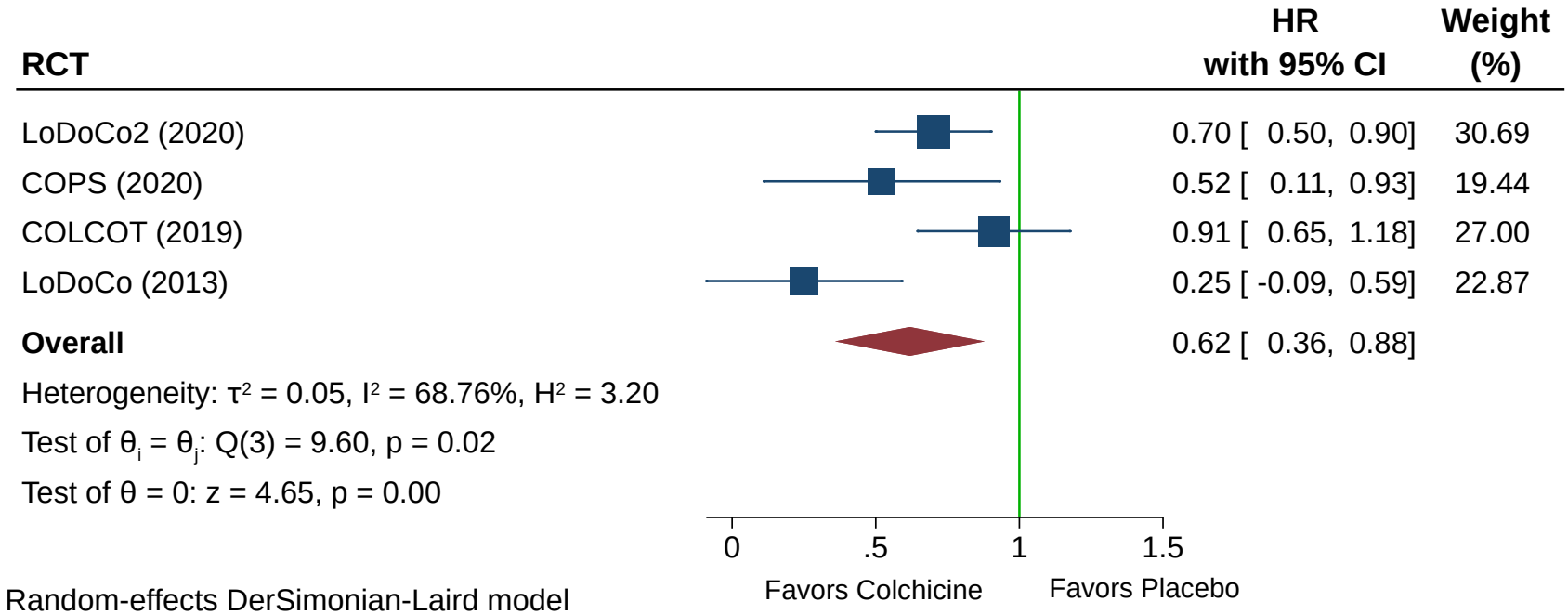
Meta-analysis of colchicine studies in CAD Primary composite endpoint



*Primary composite endpoint includes cardiovascular mortality, myocardial infarction, ischemic stroke, and urgent coronary revascularization

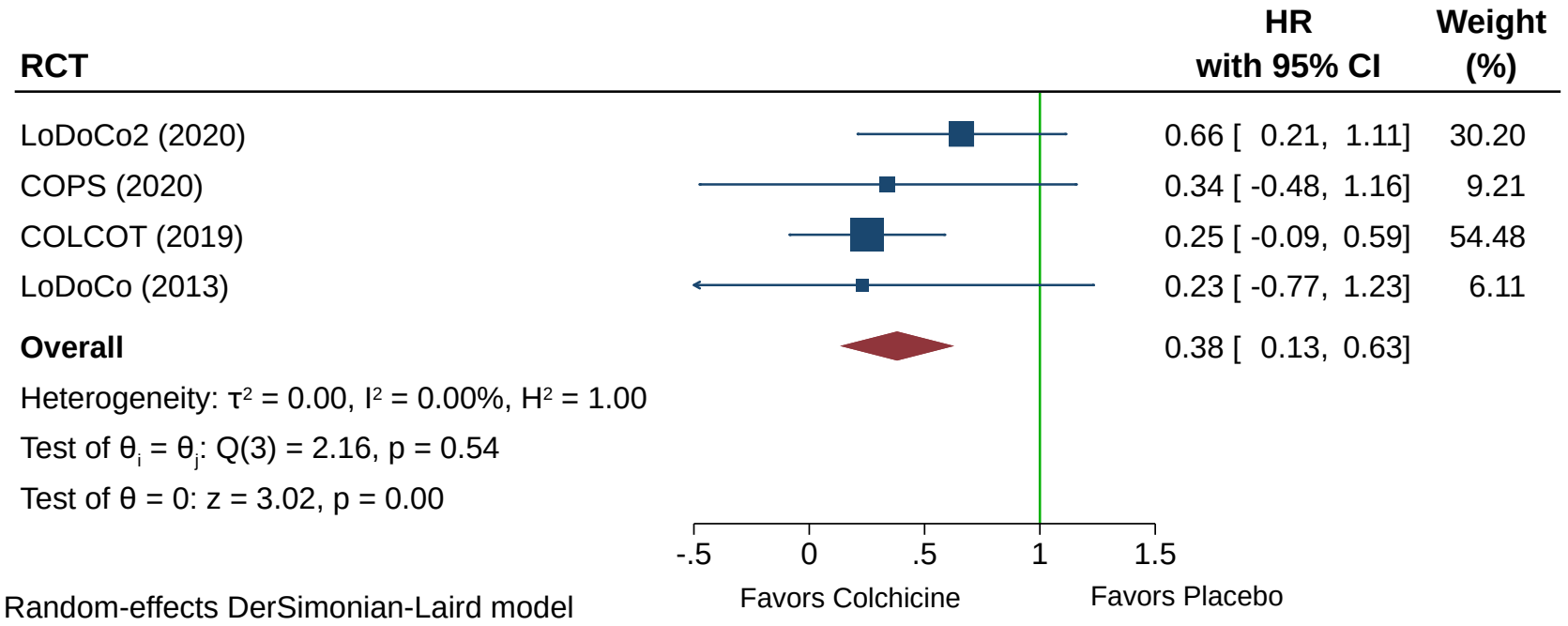
Samuel M, Tardif JC, et al. Can J Cardiol 2020 (in press)

Meta-analysis of colchicine studies in CAD
Myocardial infarction



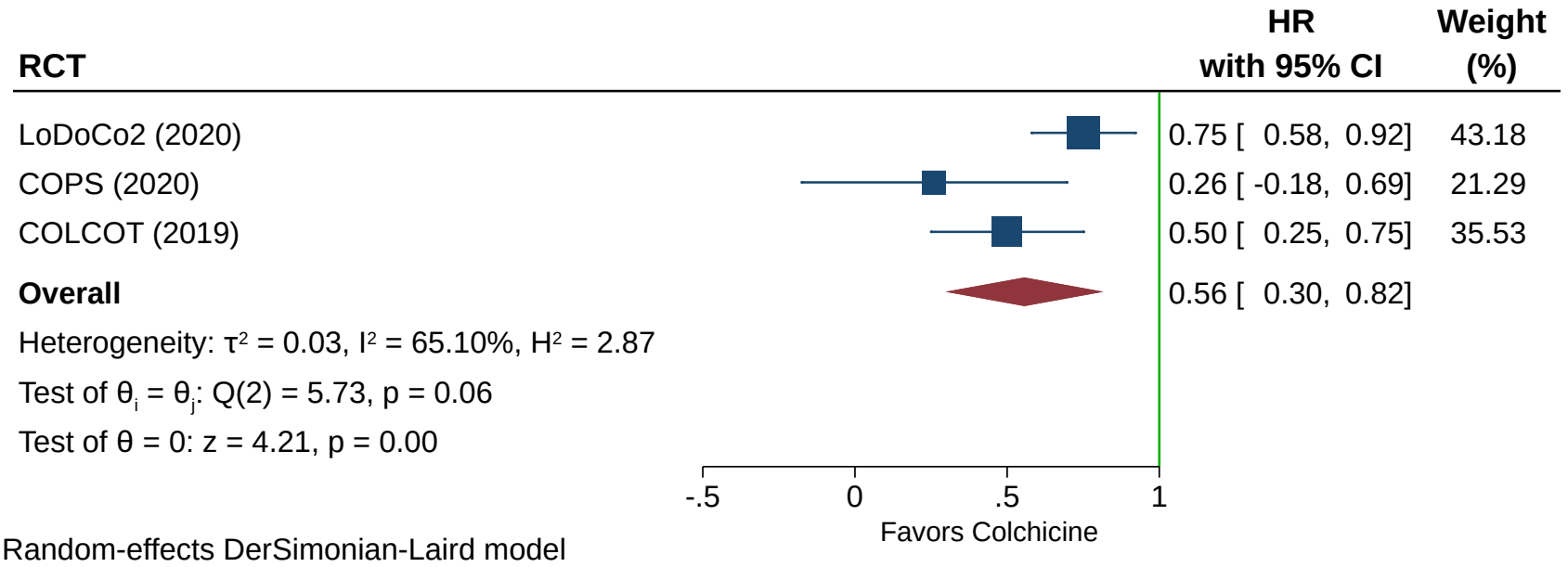
Samuel M, Tardif JC, et al. Can J Cardiol 2020 (in press)

Meta-analysis of colchicine studies in CAD Ischemic stroke



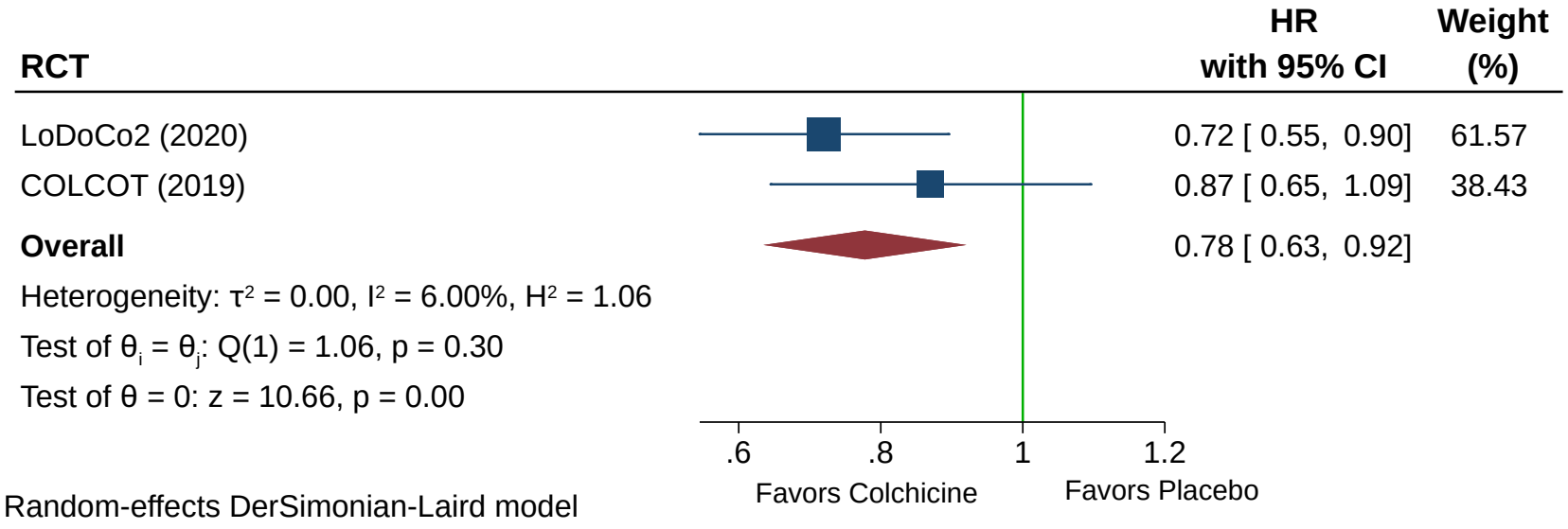
Samuel M, Tardif JC, et al. Can J Cardiol 2020 (in press)

Meta-analysis of colchicine studies in CAD
Urgent coronary revascularization



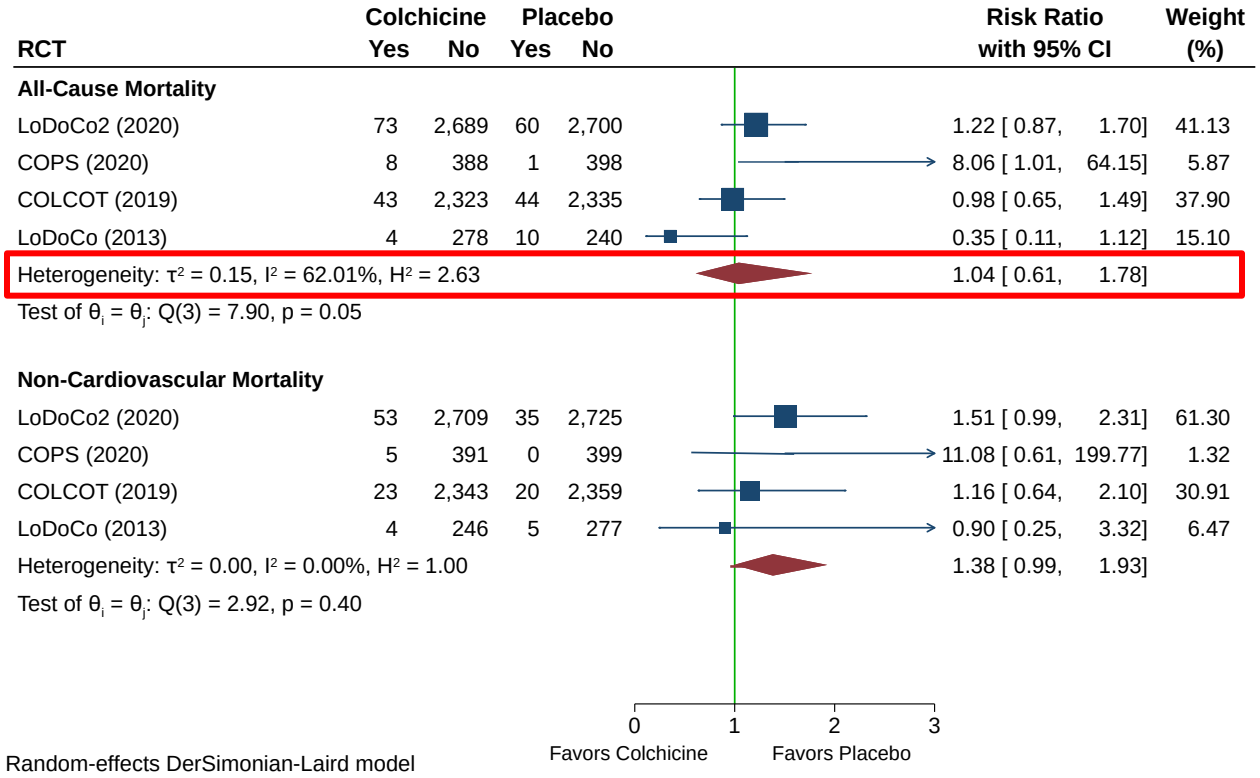
Samuel M, Tardif JC, et al. Can J Cardiol 2020 (in press)

Meta-analysis of colchicine studies in CAD CV death, MI and ischemic stroke



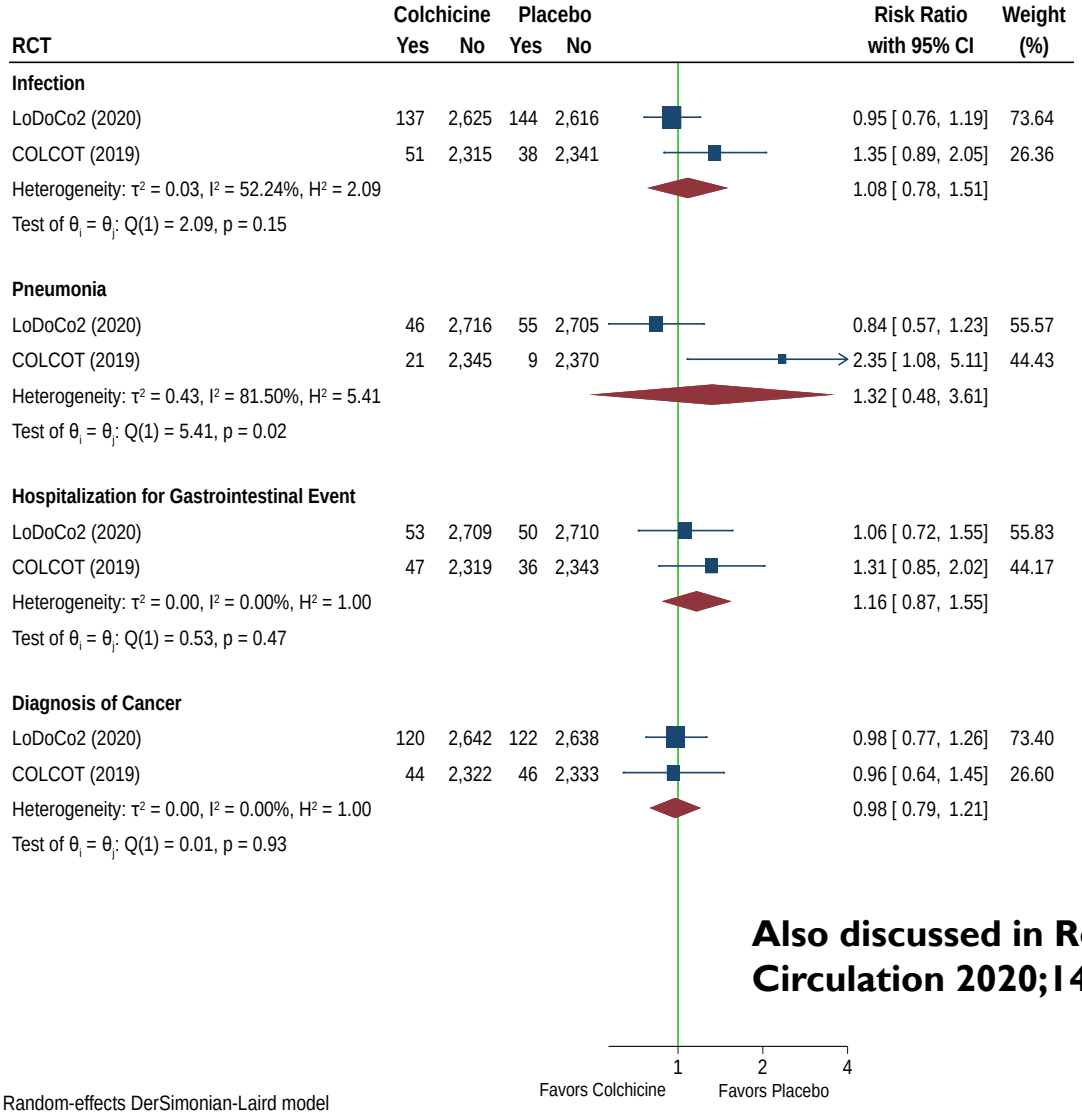
Samuel M, Tardif JC, et al. Can J Cardiol 2020 (in press)

Meta-analysis of colchicine studies in CAD
All-cause and non-CV mortality



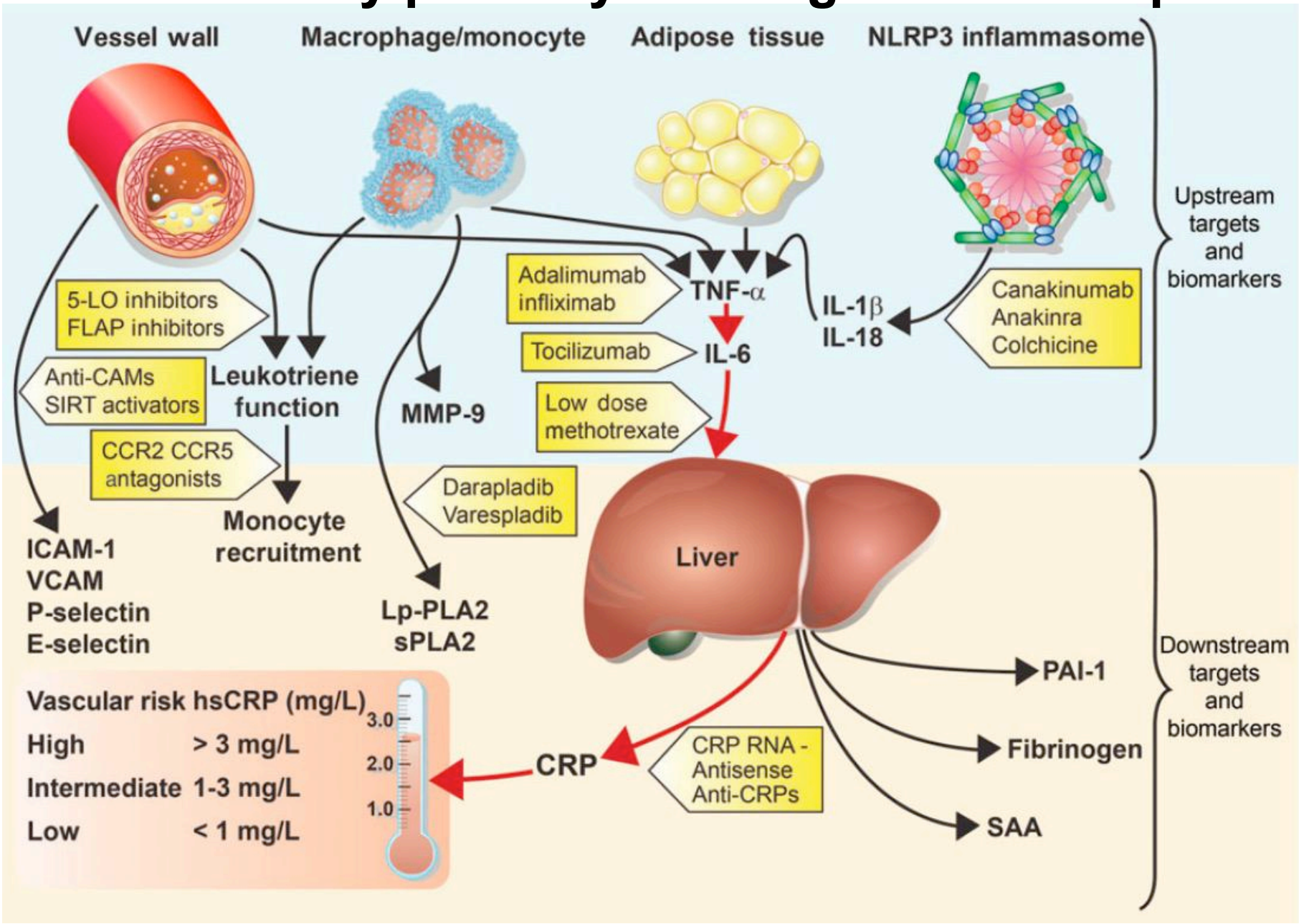
Samuel M, Tardif JC, et al. Can J Cardiol 2020 (in press)

Meta-analysis of colchicine studies in CAD Safety outcomes



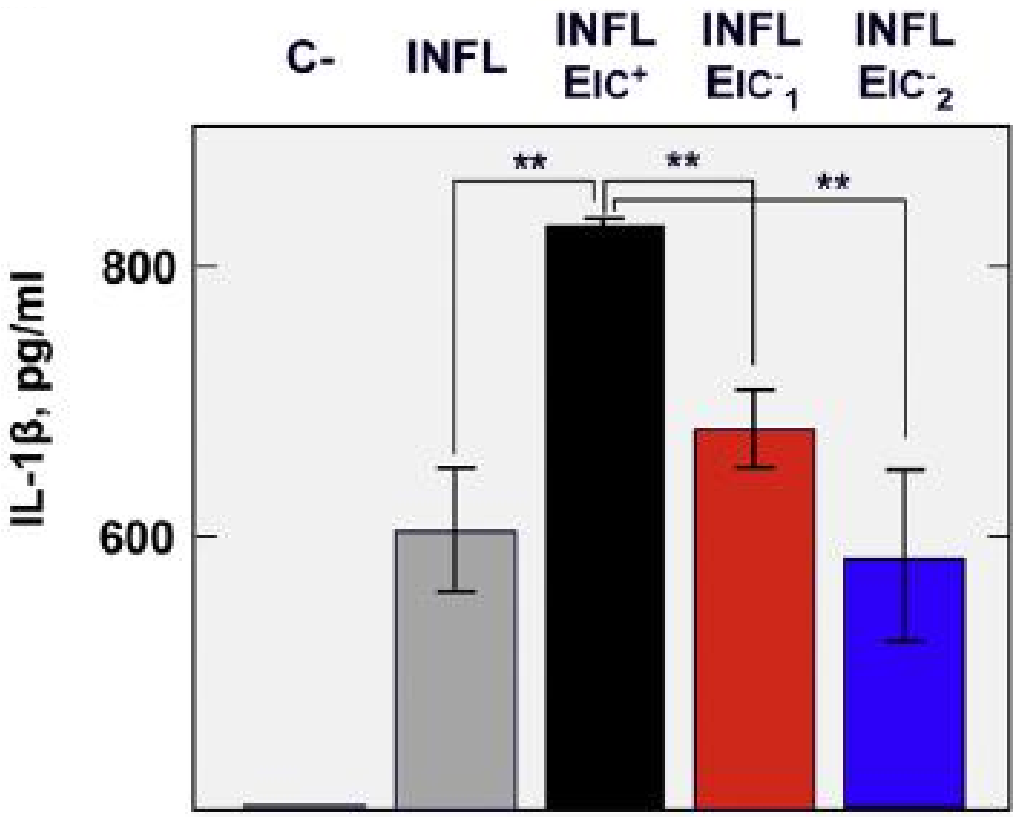
Also discussed in Roubille F, Tardif JC. Circulation 2020;142:1901-1904

Inflammatory pathways as targets for therapies



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

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.

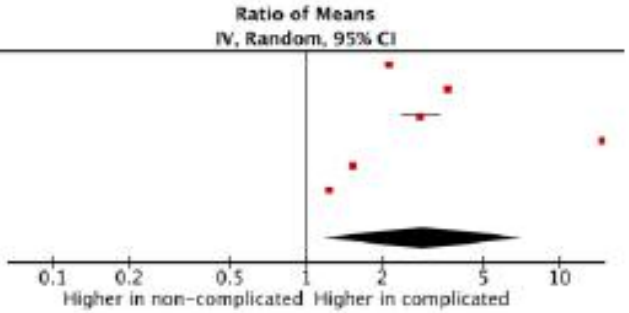
IL-6 in COVID-19: Systematic Review and Meta-Analysis

Figure 2. Meta-Analysis of Serum IL-6 Levels in COVID-19

Panel A. Patients with Complicated COVID-19 versus Non-Complicated

Study or Subgroup	log[Ratio of Means]	SE	Complicated Total	Non-Complicated Total	Weight	Ratio of Means IV, Random, 95% CI
Chen et al. 2020a	0.75030559	0.01700847	14	15	16.7%	2.12 [2.05, 2.19]
Diao et al. 2020	1.2861085	0.01523892	20	479	16.7%	3.62 [3.51, 3.73]
Huang et al. 2020a	1.03489647	0.08752466	13	28	16.6%	2.81 [2.37, 3.34]
Liu 2020	2.69261639	0.00539448	69	11	16.7%	14.77 [14.61, 14.93]
Qin et al. 2020	0.42527895	0.0036103	286	166	16.7%	1.53 [1.52, 1.54]
Wu et al. 2020	0.20490848	0.00385624	84	117	16.7%	1.23 [1.22, 1.24]
Total (95% CI)			**486**	**816**	**100.0%**	**2.90 [1.17, 7.19]**

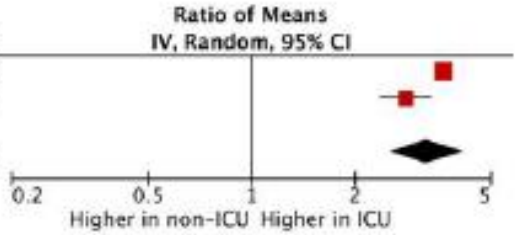
Heterogeneity: $Tau^2 = 1.28$; $Chi^2 = 158694.72$, df = 5 ($P < 0.00001$); $I^2 = 100\%$
Test for overall effect: Z = 2.30 (P = 0.02)



Panel B. Patients Requiring ICU Admission versus Not Requiring ICU Admission

Study or Subgroup	log[Ratio of Means]	SE	Complicated Total	Non-Complicated Total	Weight	Ratio of Means IV, Random, 95% CI
Diao et al. 2020	1.2861085	0.01523892	20	479	55.9%	3.62 [3.51, 3.73]
Huang et al. 2020a	1.03489647	0.08752466	13	28	44.1%	2.81 [2.37, 3.34]
Total (95% CI)			**33**	**507**	**100.0%**	**3.24 [2.54, 4.14]**

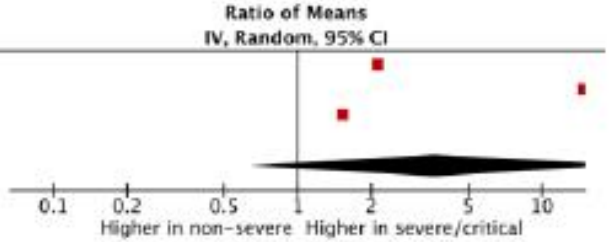
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 8.00$, df = 1 ($P = 0.005$); $I^2 = 87\%$
Test for overall effect: Z = 9.42 ($P < 0.00001$)



Panel C. Patients with Severe or Critical COVID-19 versus Mild COVID-19

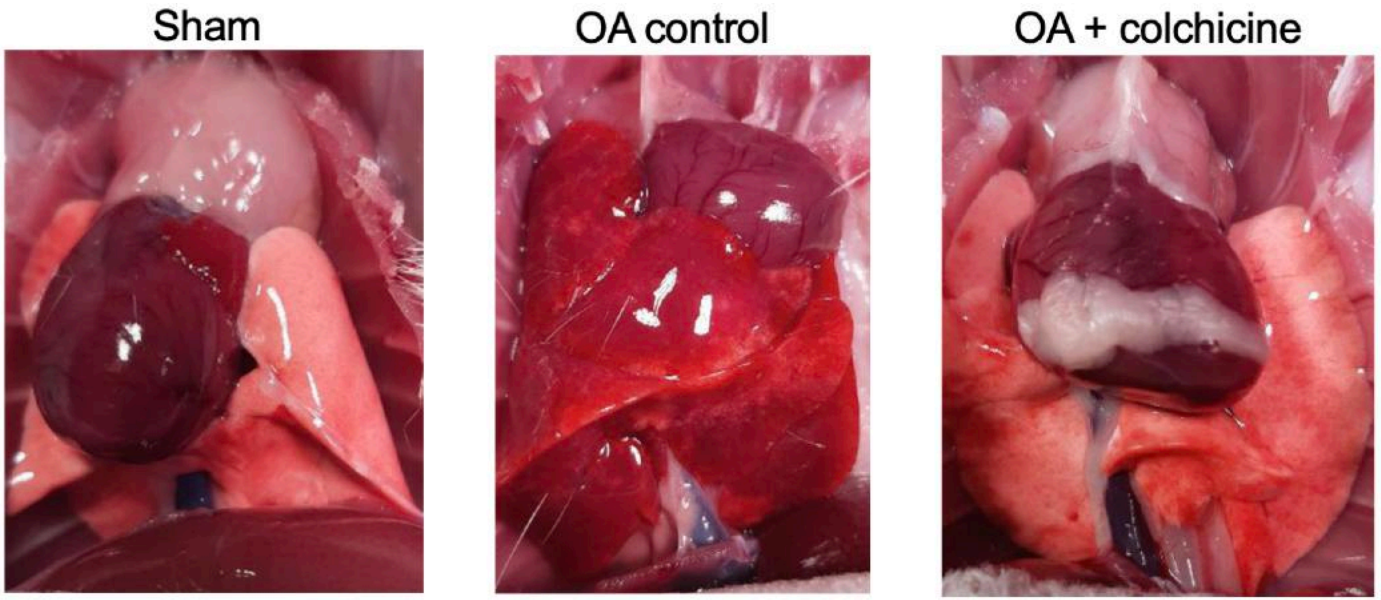
Study or Subgroup	log[Ratio of Means]	SE	Complicated Total	Non-Complicated Total	Weight	Ratio of Means IV, Random, 95% CI
Chen et al. 2020a	0.75030559	0.01700847	14	15	33.3%	2.12 [2.05, 2.19]
Liu 2020	2.69261639	0.00539448	69	11	33.3%	14.77 [14.61, 14.93]
Qin et al. 2020	0.42527895	0.0036103	286	166	33.3%	1.53 [1.52, 1.54]
Total (95% CI)			**369**	**192**	**100.0%**	**3.63 [0.65, 20.37]**

Heterogeneity: $Tau^2 = 2.32$; $Chi^2 = 122484.25$, df = 2 ($P < 0.00001$); $I^2 = 100\%$
Test for overall effect: Z = 1.47 (P = 0.14)



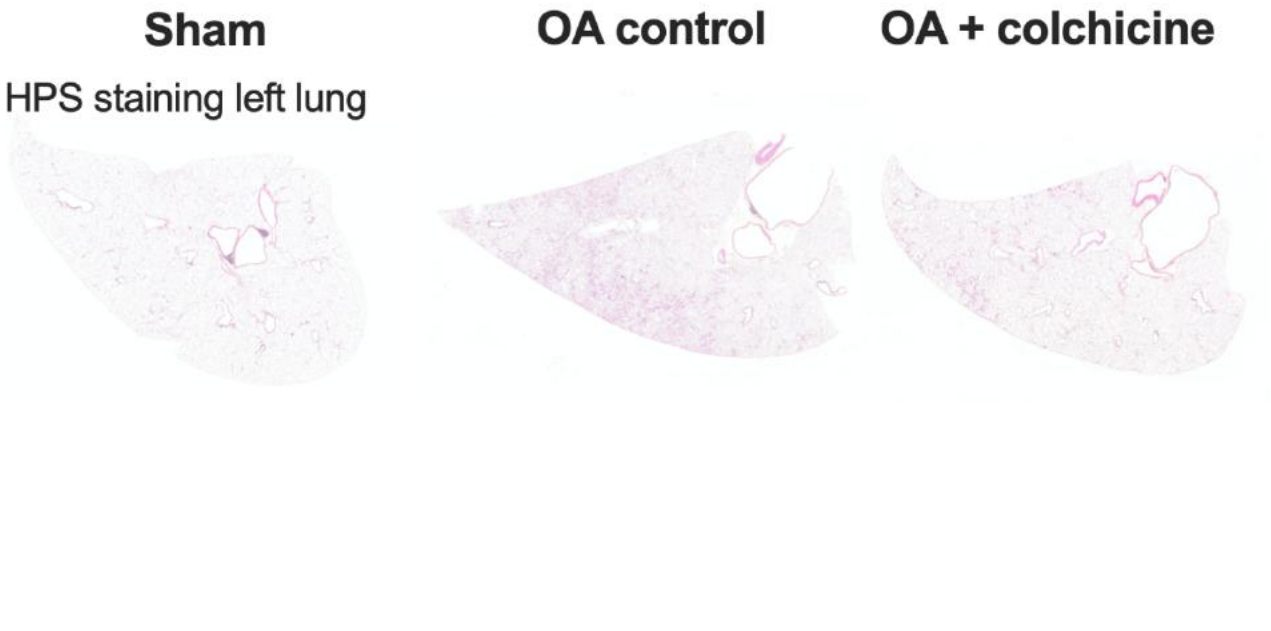
Coomes EA, Haghbayan H. *medRxiv*, 2020.2003.2030.20048058, doi:10.1101/2020.03.30.20048058 (2020).

Colchicine reduces lung injury in ARDS



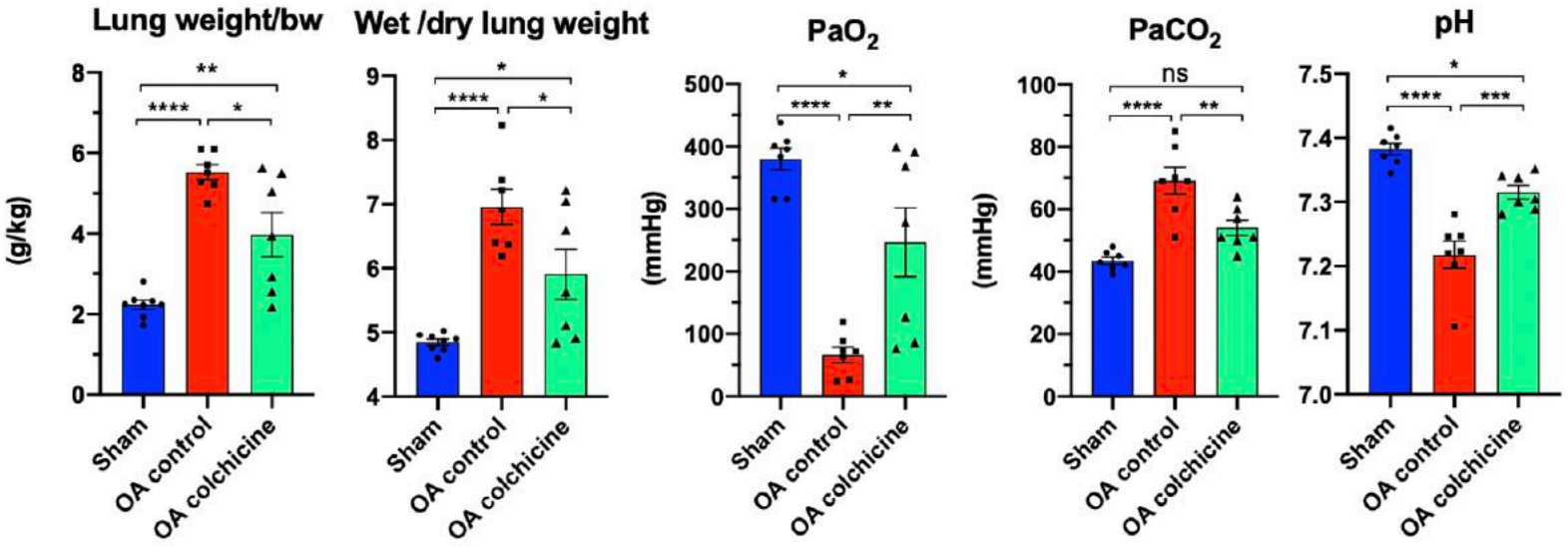
Dupuis J, et al, Tardif JC. Can J Cardiol 2020 (in press)

Colchicine reduces lung injury by 61%



Dupuis J, et al, Tardif JC. Can J Cardiol 2020 (in press)

Colchicine reduces lung edema and improves oxygenation and gas exchanges

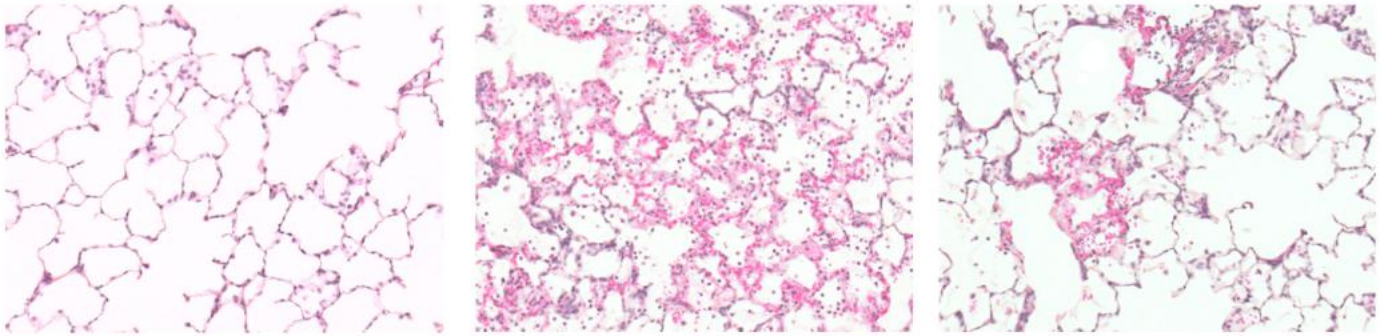


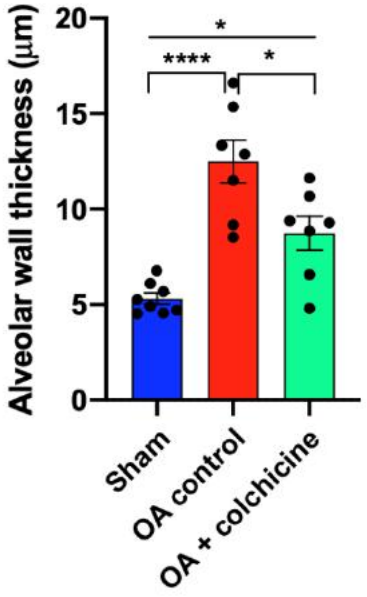
Dupuis J, et al, Tardif JC. Can J Cardiol 2020 (in press)

Colchicine reduces alveolar wall thickness

Sham **OA control** **OA + colchicine**

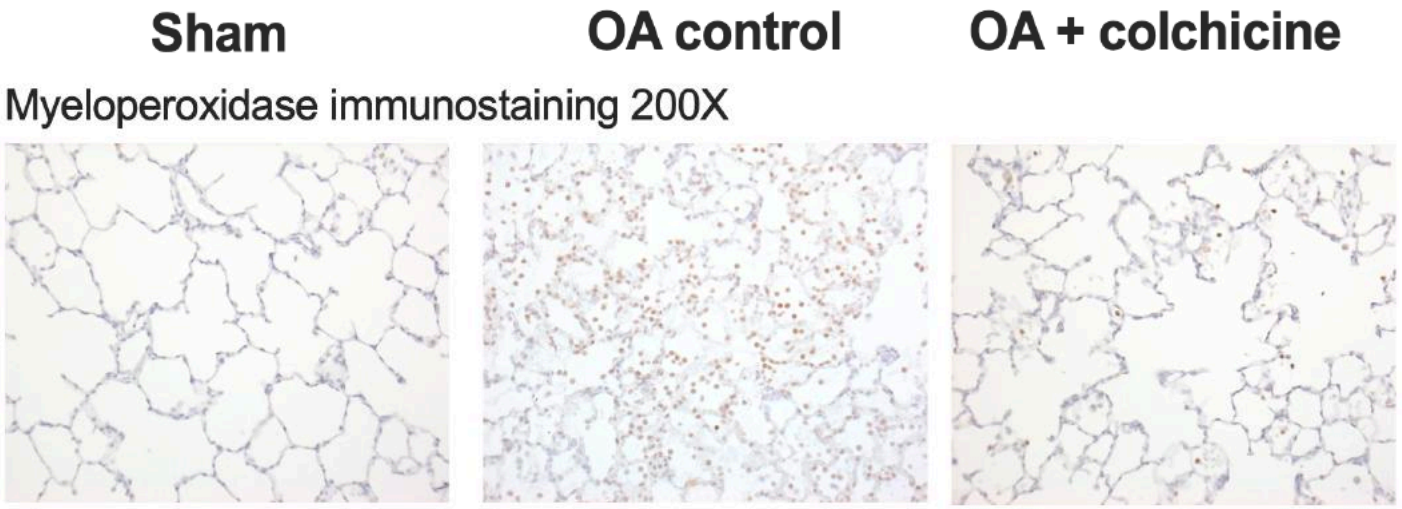
HPS staining 200X

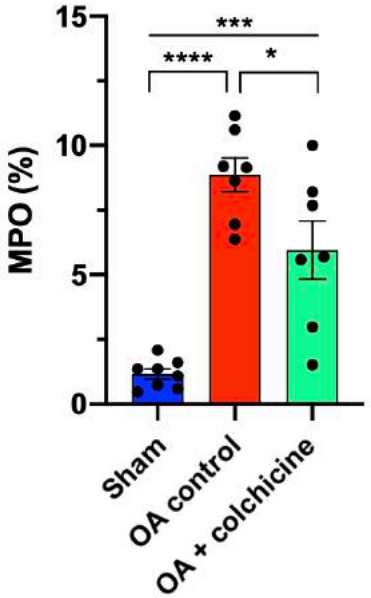




Dupuis J, et al, Tardif JC. Can J Cardiol 2020 (in press)

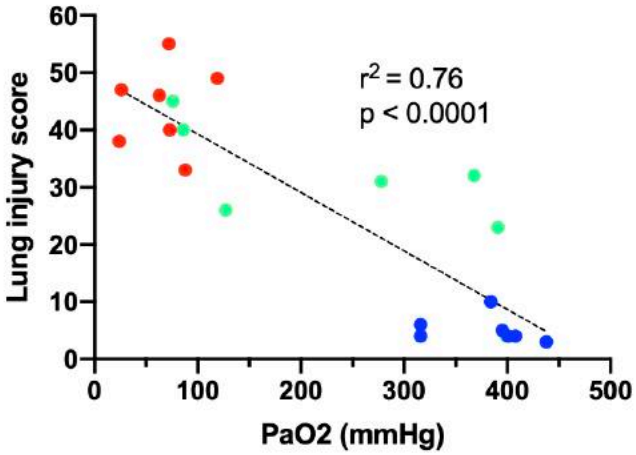
Colchicine reduces lung neutrophil recruitment

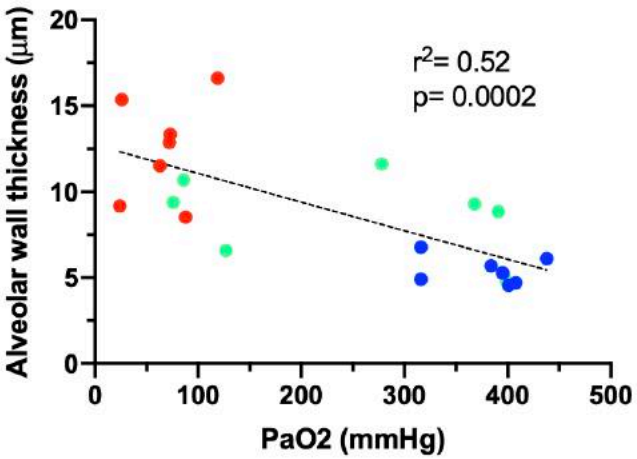


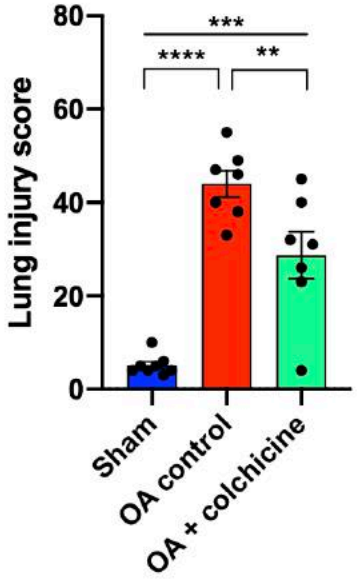


Dupuis J, et al, Tardif JC. Can J Cardiol 2020 (in press)

Colchicine reduces lung injury score, correlating with improved oxygenation

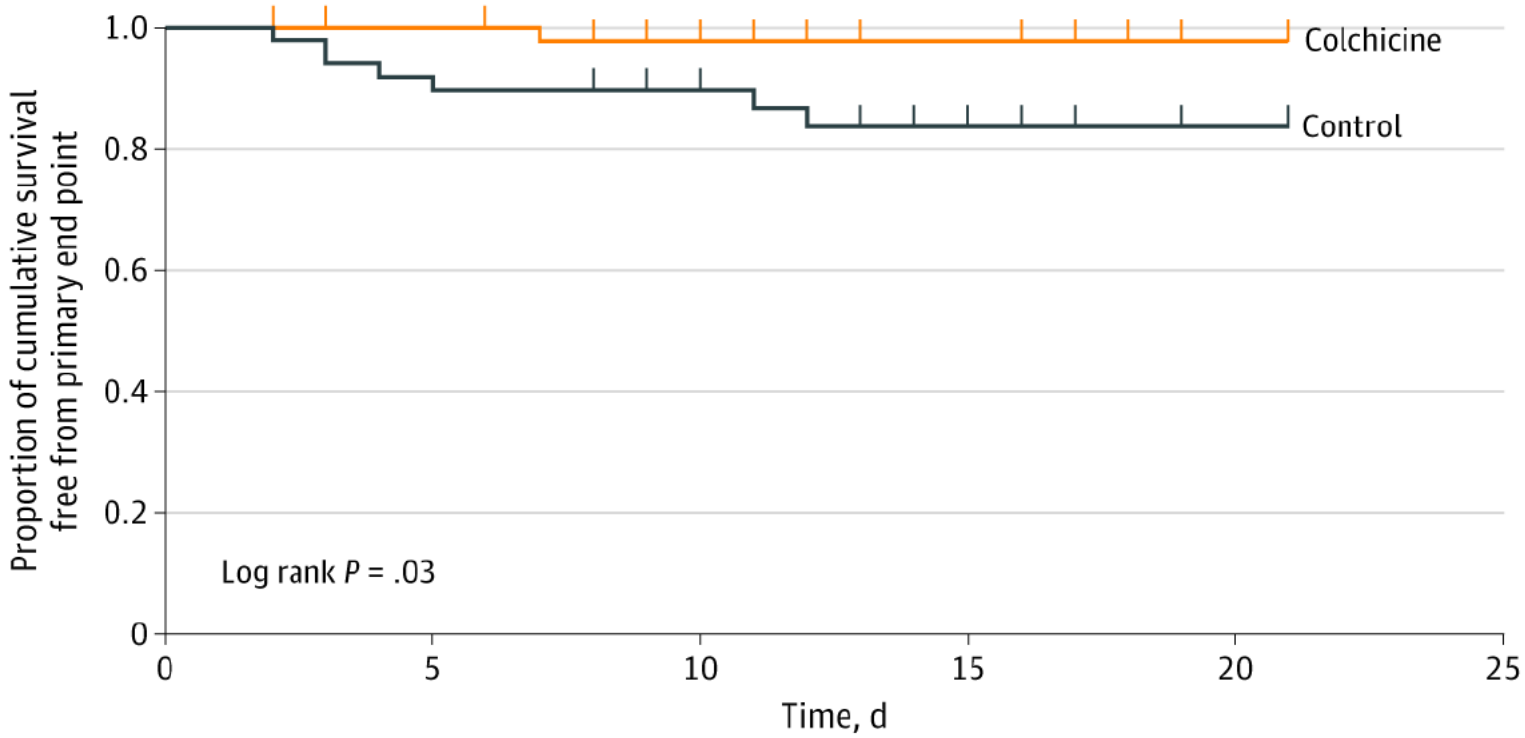






Dupuis J, et al, Tardif JC. Can J Cardiol 2020 (in press)

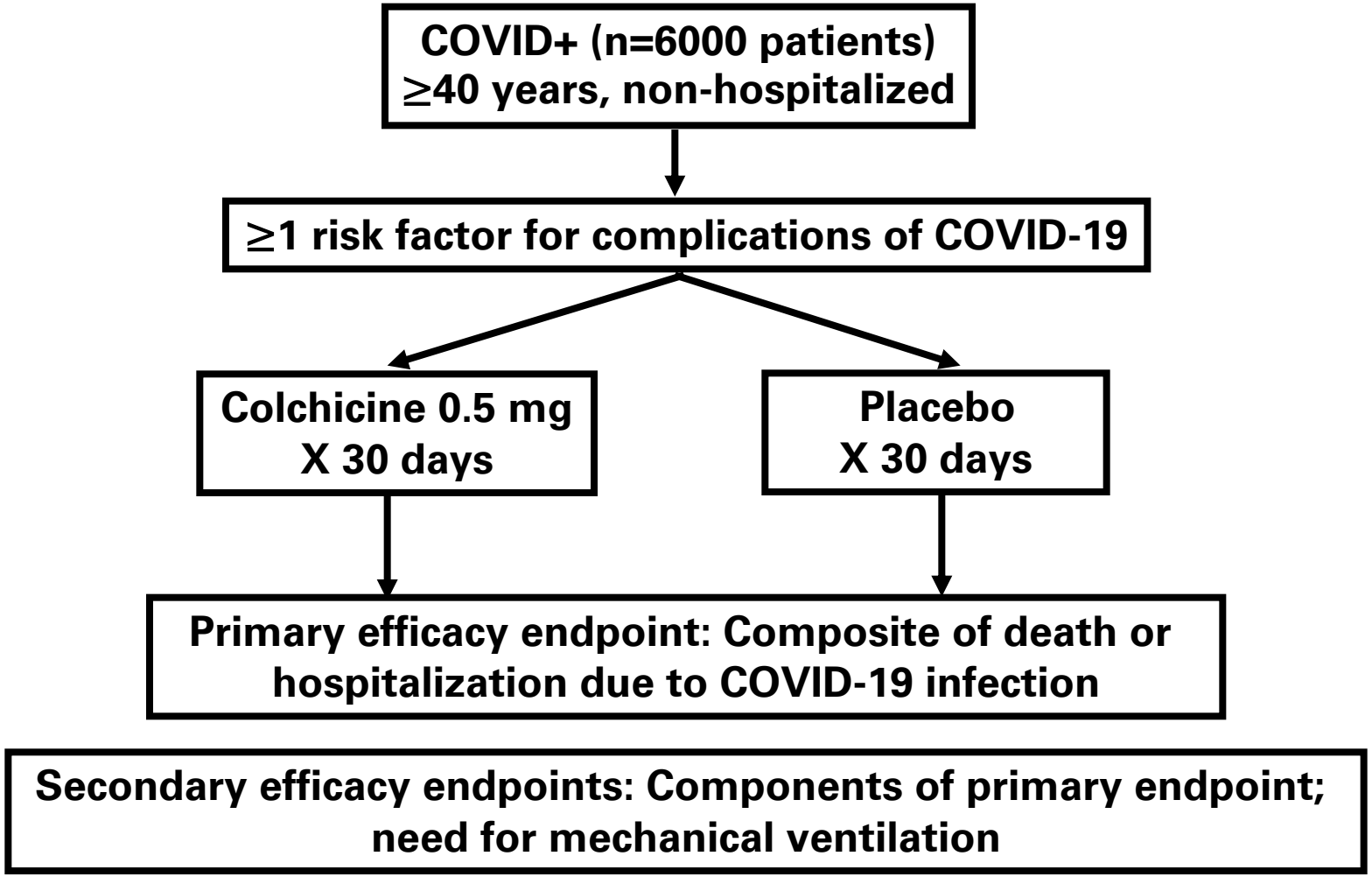
Colchicine vs standard care on biomarkers and clinical outcomes in patients hospitalized with COVID-19 The GRECCO-19 randomized trial



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)

COLCORONA Study Design*



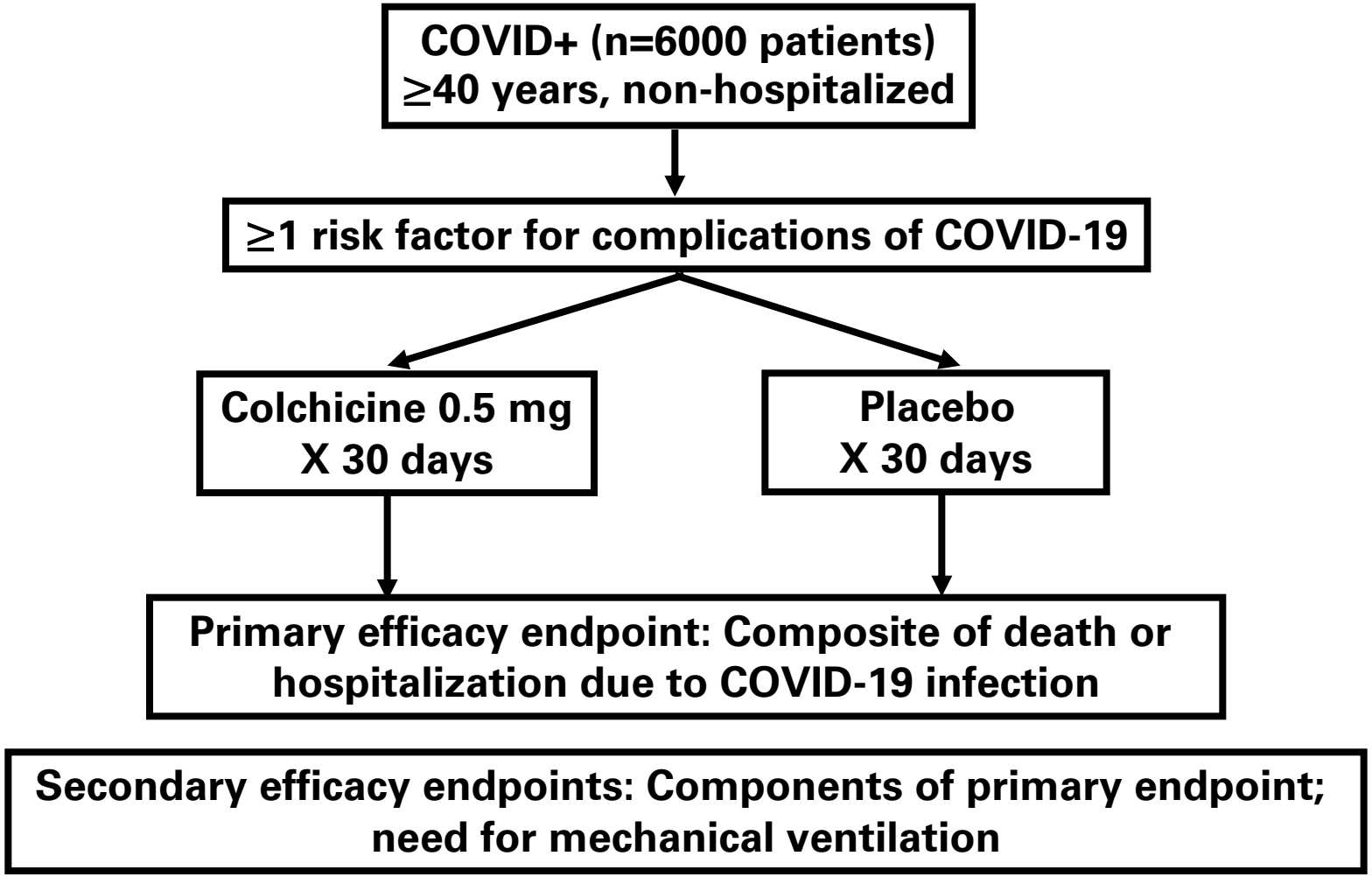
* funded by the Government of Québec, the US NIH and the Gates Foundation

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

COLCORONA Study Design*



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