Supplemental document 1.

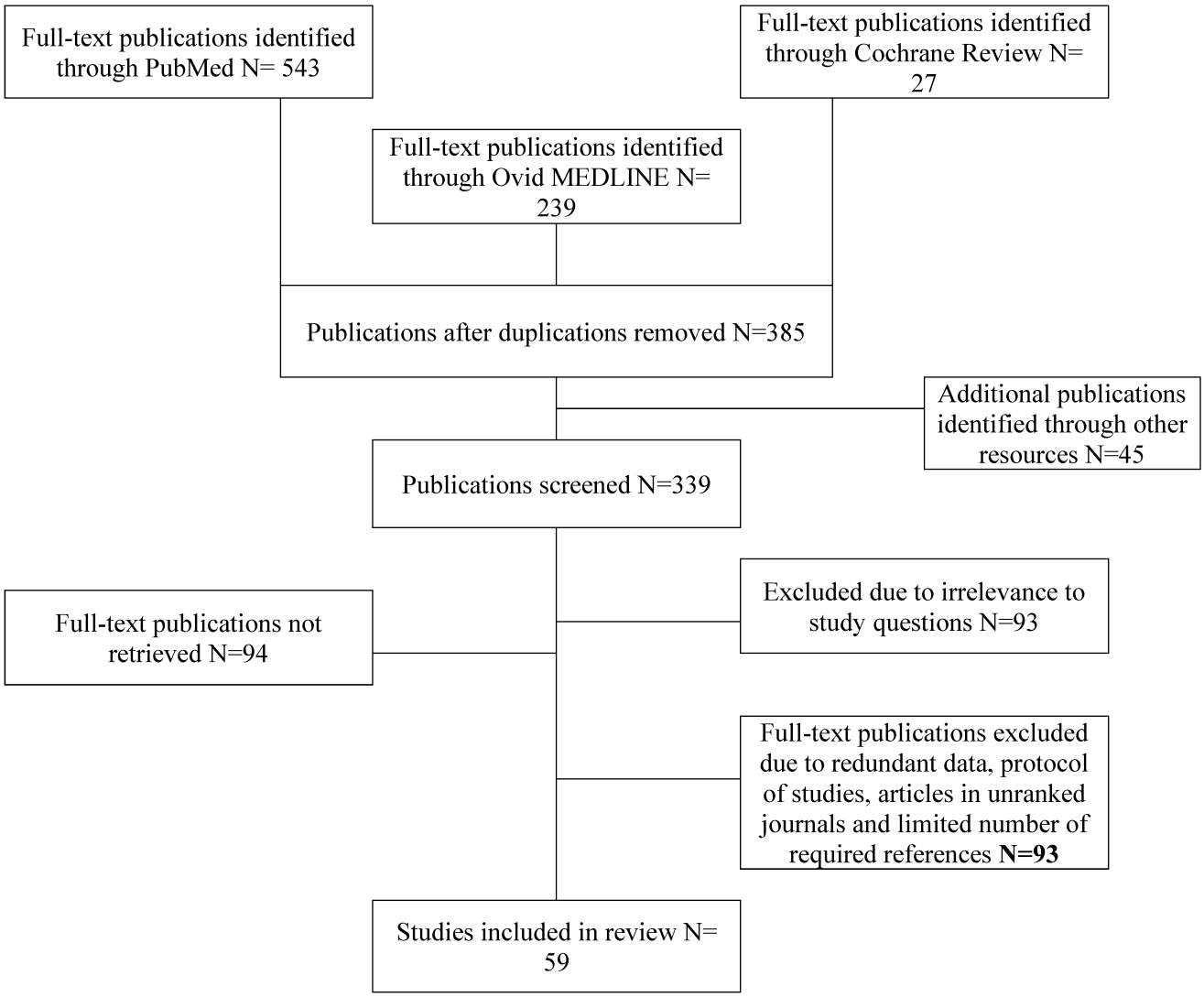
Aspirin review search strategy overview

Question(s):	1	What is the current understanding of COVID-19 pathophysiology and its relationship to thrombus formation?
	2	What research is available regarding COVID-19 and aspirin use?
	3	What are the current guidelines or evidence supporting aspirin use for primary prevention of systemic diseases?

Date of search:	1/1/2016-1/1/2021	
PubMed Search Strategy:		
No.	**Query results**	Results
#1	(COVID-19 or coronavirus disease 2019 or SARS-CoV-2[MeSH Major Topic]) AND (thombosis[Title] OR thromboembolism[Title] OR thromboembolic[Title] OR vascular endothelialitis[Title] OR endotheliopathy[Title] OR clot[Title] OR hypercoagulability[Title] OR coagulopathy[Title]) limit to (full text and journal article or meta-analysis or randomized control trial or review or systematic review and yr= "01/01/2016 -01/01/2020")	311
#2	(aspirin or ASA or acetylsalicylic acid[MeSH Major Topic]) AND (coronavirus disease 2019[Title] OR COVID-19[Title] OR SARS-CoV-2[Title]) limit to (full text and journal article and yr= "01/01/2016 -01/01/2020")	83
#3	(aspirin or ASA or acetylsalicylic acid[MeSH Major Topic]) AND (prevention[Title] OR guideline[Title] OR consensus[Title]) limit to (full text and guideline or meta-analysis or systematic review or consensus development conference and yr= "01/01/2016 -01/01/2020")	149
	Total	543
MEDLINE Search Strategy:		
No.	**Query results**	Results
#1	((coronavirus disease 2019 or COVID-19 or SARS-CoV-2) and (thombosis or thromboembolism or thromboembolic or vascular endothelialitis or endotheliopathy or clot or hypercoagulability or coagulopathy)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease	198

	supplementary concept word, unique identifier, synonyms] limit to (english language and full text and yr="2016 -2021")	
#2	((coronavirus disease 2019 or COVID-19 or SARS-CoV-2) and (aspirin or ASA or acetylsalicylic acid)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] limit to (english language and full text and yr="2016 -2021")	21
#3	((aspirin or ASA or acetylsalicylic acid) and (prevention or guidelines or consensus)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] limit to (english language and full text and "review articles" and "core clinical journals (aim)" and yr="2016 -2021")	20
	Total	239
Cochrane Review Library Search Strategy		
No.	**Query results**	Results
#1	(coronavirus disease 2019 or COVID-19 or SARS-CoV-2):kw AND (thombosis or thromboembolism or thromboembolic or vascular endothelialitis or endotheliopathy or clot or hypercoagulability or coagulopathy):kw	15
#2	(coronavirus disease 2019 or COVID-19 or SARS-CoV-2):kw AND (aspirin or ASA or acetylsalicylic acid):kw	0
#3	(aspirin or ASA or acetylsalicylic acid):ti,ab,kw AND (prevention or guidelines or consensus):kw limit to (Cochrane Reviews and Heart&Circulation and yr = 2016 -Current")	12
	Total	27
	Cummulative total	809
	Additional resources	45
	Total	854

Search strategy flow sheet



Data extraction table for included studies

	Title	Type of article	Journal	Obtained through	First author	Peer review ?	Publication date	Topic	Key findings
1	Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health.	Guidelines/Consensus		https://www.covid19treatmentguidelines.nih.gov/.	COVID-19 Treatment Guidelines Panel.		2020	Treatment guideline	
2	Effects of Aspirin on Endothelial Function and Hypertension.	Review	Curr Hypertens Rep	doi:10.1007/s11906-016-0688-8.	Dzeshka MS	Yes	2016	Aspirin effects	
3	Antiviral activity of aspirin against RNA viruses of the respiratory tract-an in vitro study.	Experimental study	Influenza Other Respir Viruses.	doi:10.1111/irv.12421.	Glatthaar-Saalmüller B	Yes	2017	Antiviral activity of aspirin	
4	COVID-19 as an Acute Inflammatory Disease.	Review	J Immunol	doi:10.4049/jimmunol.2000413.	Manjili RH	Yes	2020	Pathogensis	
5	Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19.	Series of case reports	N Engl J Med.	doi:10.1056/NEJMc2007575.	Zhang Y	Yes	2020	Pathogensis	
6	An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study.	Observational cohort study	Lancet.	doi:10.1016/S0140-6736(20)31103-X.	Verdoni L	Yes	2020	Epidemiology of Kawasaki-like disease	
7	The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system.	Review	Cytokine Growth Factor Rev.	doi:10.1016/j.cytogfr.2020.05.003.	Coperchini F	Yes	2020	Pathogensis	
8	COVID-19: consider cytokine storm syndromes and immunosuppression.	Correspondence	Lancet.	doi:10.1016/S0140-6736(20)30628-0.	Mehta P	Yes	2020	Pathogensis	

9	COVACTA trial raises questions about tocilizumab's benefit in COVID-19.	News	Lancet Rheumatol.	doi:10.1016/S2665-9913(20)30313-1.	Furlow B		2020	Pathogensis	
10	COVID-19: the vasculature unleashed.	Comment	Nat Rev Immunol.	doi: 10.1038/s41577-020-0343-0.	Teuwen LA	Yes	2020	Pathogensis	
11	Endothelial cell infection and endotheliitis in COVID-19.	Case reports	Lancet.	doi:10.1016/S0140-6736(20)30937-5.	Varga Z	Yes	2020	Pathogensis	
12	Endothelial Dysfunction and Thrombosis in Patients With COVID-19-Brief Report.	Case reports	Arterioscler Thromb Vasc Biol.	doi:10.1161/ATVBAHA.120.314860.	Nagashima S	Yes	2020	Pathogensis	
13	Aspirin with or without statin in the treatment of endotheliitis, thrombosis, and ischemia in coronavirus disease.	Case series	Rev Soc Bras Med Trop.	doi: 10.1590/0037-8682-0472-2020.	Florêncio FKZ	Yes	2020	Aspirin in COVID-19	
14	ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic	Guidance		https://www.escardio.org/Education/COVID-19-and-Cardiology/ESCCOVID-19-Guidance	ESC		2020	Prevention	
15	Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement	Guidelines/Consensus	*Ann Intern Med*	doi:10.7326/M16-0577	Bibbins-Domingo K	Yes	2016	CVD Prevention	

16	2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)	Guidelines/Consensus	*Atherosclerosis*	doi:10.1016/j.atherosclerosis.2016.05.037	Authors/Task Force Members	Yes	2016	CVD Prevention	
17	Standards of Medical Care in Diabetes-2020 Abridged for Primary Care Providers	Guidelines/Consensus	*Clin Diabetes*	doi:10.2337/cd20-as01	American Diabetes Association	Yes	2020	CVD Prevention	
18	Canadian Stroke Best Practice Recommendations, seventh edition: acetylsalicylic acid for prevention of vascular events	Guidelines/Consensus	*CMAJ*	doi:10.1503/cmaj.191599	Wein T	Yes	2020	CVD Prevention	
19	2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in Circulation	Guidelines/Consensus	*Circulation*	doi:10.1161/CIR.0000000000000678	Arnett DK	Yes	2019	CVD Prevention	
20	Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages.	Review	Nat Rev Immunol.	doi: 10.1038/s41577-020-0331-4.	Merad M	Yes	2020	Pathogensis	

21	Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy.	Retrospective cohort study	Thromb Res.	doi:10.1016/j.thromres.2020.04.024.	Lodigiani C	Yes	2020	Epidemiology of COVID-9 complications	
22	Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System.	Letter	JAMA	doi: 10.1001/jama.2020.13372.	Bilaloglu S	Yes	2020	Epidemiology of COVID-9 complications	In a health system in New York, where most patients were treated with low dose of anticoagulation, the incidence of arterial and venous thrombosis in 829 ICU patients were 18.6% and 13.6% respectively, and among 2505 non-ICU patients, the incidence of arterial and venous thrombosis were 8.4% and 3.6% respectively
23	Venous thrombosis epidemiology, pathophysiology, and anticoagulant therapies and trials in severe acute respiratory syndrome coronavirus 2 infection.	Review	J. Vasc. Surg. Venous Lymphat. Disord.	doi: 10.1016/j.jvsv.2020.08.030.	Obi AT	Yes	2020	Epidemiology of COVID-9 complications	21% to 69% incidence rate of venous thromboembolism (VTE) in critically ill patients with COVID-19. In addition to deep venous thrombosis (DVT) and acute pulmonary embolism (APE), patients developed circuit clotting of continuous renal replacement therapy and ECMO. They also described ‘breakthrough VTE’ where VTE develops despite receiving

									prophylactic or therapeutic doses of anticoagulation
24	Incidence of venous thromboembolism in hospitalized patients with COVID-19.	Single-center cohort study	J Thromb Haemost.	doi: 10.1111/jth.14888.	Middeldorp S	Yes	2020	Epidemiology of COVID-9 complications	A cohort study of 198 hospitalized patients with COVID-19 in Amsterdam, where all patients had received prophylactic anticoagulation, the cumulative risk for developing VTE at 7, 14 and 21 days was 16%, 33%, and 42% respectively, with a higher incidence in ICU patients than non-ICU patients
25	Incidence of thrombotic complications in critically ill ICU patients with COVID-19.	Descriptive study	Thromb Res.	doi: 10.1016/j.thromres.2020.04.013.	Klok FA	Yes	2020	Epidemiology of COVID-9 complications	A Dutch study reported the frequency of arterial thrombosis (ischemic stroke, myocardial infarction or systemic thromboembolism) as 3.7% in 184 ICU patients
26	Acute pulmonary embolism in non-hospitalized COVID-19 patients referred to CTPA by emergency department.	Retrospective study	Eur Radiol.	doi: 10.1007/s00330-020-06977-5.	Gervaise A	Yes	2020	Epidemiology of COVID-9 complications	18% of non-hospitalized patients with COVID-19 who were evaluated by computed tomography pulmonary angiography (CTPA) in the emergency department were found to have APE

27	Multiple Thrombotic Events in a 67-Year-Old Man 2 Weeks After Testing Positive for SARS-CoV-2: A Case Report.	Case study	Am J Case Rep.	doi:10.12659/AJCR.925786.	Shawkat A	Yes	2020	Epidemiology of COVID-9 complications	
28	The unique characteristics of COVID-19 coagulopathy.	Review	Crit Care.	doi:10.1186/s13054-020-03077-0.	Iba T	Yes	2020	Pathogensis	
29	Emerging evidence of a COVID-19 thrombotic syndrome has treatment implications.	Review	Nat Rev Rheumatol.	doi:10.1038/s41584-020-0474-5.	Merrill JT	Yes	2020	Pathogensis	
30	Aspirin Bioactivity for Prevention of Cardiovascular Injury in COVID-19.	Opinion article	Front Cardiovasc Med.	doi: 10.3389/fcvm.2020.562708.	Diaz T	Yes	2020	Pathogensis	
31	New insights into the mechanisms of action of aspirin and its use in the prevention and treatment of arterial and venous thromboembolism.	Review	Ther Clin Risk Manag.	doi:10.2147/TCRM.S92222.	Mekaj YH	Yes	2015	Pathogensis	
32	COVID-19 pneumonia: different respiratory treatments for different phenotypes?	Editorial	Intensive Care Med	doi:10.1007/s00134-020-06033-2.	Gattinoni L	Yes	2020	Pathogensis	
33	Pathways in the Pathophysiology of Coronavirus 19 Lung Disease Accessible to Prevention and Treatment.	Review	Front Physiol.	doi:10.3389/fphys.2020.00872.	Eisenhut M	Yes	2020	Pathogensis	
34	Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19.	Case reports	N Engl J Med.	doi: 10.1056/NEJMoa2015432.	Ackermann M	Yes	2020	Pathogensis	
35	Aspirin as a potential treatment in sepsis or acute respiratory distress syndrome.	Review	Crit Care.	doi:10.1186/s13054-015-1091-6.	Toner P	Yes	2015	Aspirin and sepsis	

36	Antiplatelet Therapy After Percutaneous Coronary Intervention in Patients With COVID-19: Implications From Clinical Features to Pathologic Findings.	Perspective	Circulation.	doi:10.1161/CIRCULATIONAHA.120.046988.	Zhou X	Yes	2020	Aspirin and ARDS and its sequuale	
37	Kawasaki-like diseases and thrombotic coagulopathy in COVID-19: delayed over-activation of the STING pathway?	Review	Emerg Microbes Infect.	doi:10.1080/22221751.2020.1785336.	Berthelot JM	Yes	2020	Pathogensis	
38	TMEM173 Drives Lethal Coagulation in Sepsis.	Experiments	Cell Host Microbe.	doi: 10.1016/j.chom.2020.02.004.	Zhang H	Yes	2020	Pathogensis	
39	Fibrinolytic abnormalities in acute respiratory distress syndrome (ARDS) and versatility of thrombolytic drugs to treat COVID-19.	Review	J Thromb Haemost.	doi:10.1111/jth.14872.	Whyte CS	Yes	2020	Pathogensis	
40	Does Ibuprofen Worsen COVID-19?	Editorial	Drug Saf.	doi:10.1007/s40264-020-00953-0.	Moore N	Yes	2020	Aspirin safety	
41	Acute Respiratory Infection and Use of Nonsteroidal Anti-Inflammatory Drugs on Risk of Acute Myocardial Infarction: A Nationwide Case-Crossover Study.	A Nationwide Case-Crossover Study	J Infect Dis.	doi:10.1093/infdis/jiw603.	Wen YC	Yes	2017	Aspirin safety	
42	Risk of stroke associated with use of nonsteroidal anti-inflammatory drugs during acute respiratory infection episode.	A population-based study	Pharmacoepidemiol Drug Saf.	doi:10.1002/pds.4428.	Wen YC	Yes	2018	Aspirin safety	population-based cohort study in Denmark involved 9236 patients with confirmed COVID-19, among them NSAID users were 248 (2.7%). They found that use of NSAIDs was not associated with 30-day mortality, hospitalization, ICU

									admission, mechanical ventilation, or renal replacement therapy in Danish patients who tested positive for COVID-19
43	Risks Related to the Use of Non-Steroidal Anti-Inflammatory Drugs in Community-Acquired Pneumonia in Adult and Pediatric Patients.	Two cohort studies	J Clin Med.	doi:10.3390/jcm8060786.	Voiriot G	Yes	2019	Aspirin safety	
44	Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs who tested positive for SARS-CoV-2: A Danish nationwide cohort study.	Population cohort study	PLoS Med.	doi:10.1371/journal.pmed.1003308.	Lund LC	Yes	2020	Aspirin safety	
45	Mortality and pre-hospitalization use of low-dose aspirin in COVID-19 patients with coronary artery disease.	Retrospective cohort	J Cell Mol Med.	doi: 10.1111/jcmm.16198. Epub ahead of print.	Yuan S	Yes	2020	Aspirin	
46	Clinical Effectiveness and Safety of Aspirin for Venous Thromboembolism Prophylaxis After Total Hip and Knee Replacement: A Systematic Review and Meta-analysis of Randomized Clinical Trials.	A nationwide cohort study	JAMA Intern Med.	doi:10.1001/jamainternmed.2019.6108.	Matharu GS	Yes	2020	Aspirin	
47	Lessons Learned: Using the Caprini Risk Assessment Model to Provide Safe and Efficacious Thromboprophylaxis Following Hip and Knee Arthroplasty.	Review	Clin Appl Thromb Hemost.	doi: 10.1177/1076029620961450.	Krauss ES	Yes	2020	Aspirin	

48	Association Between Prior Aspirin Use and Acute Respiratory Distress Syndrome Incidence in At-Risk Patients: A Systematic Review and Meta-Analysis.	A Systematic Review and Meta-Analysis	Front Pharmacol.	doi:10.3389/fphar.2020.00738.	Liang H	Yes	2020	Aspirin	
49	The preventive effect of antiplatelet therapy in acute respiratory distress syndrome: a meta-analysis.	A meta-analysis	Crit Care.	doi:10.1186/s13054-018-1988-y.	Wang Y	Yes	2018	Antiplatelet	
50	Enhanced platelet inhibition treatment improves hypoxemia in patients with severe Covid-19 and hypercoagulability. A case control, proof of concept study.	Clinical trial	Pharmacol Res.	doi:10.1016/j.phrs.2020.104950.	Viecca M	Yes	2020	Antiplatelet in ARDS	
51	Potential therapeutic effects of dipyridamole in the severely ill patients with COVID-19.	Cohort study	Acta Pharm Sin B.	doi:10.1016/j.apsb.2020.04.008.	Liu X	Yes	2020	Dipyridamole in COVID-19	
52	New (re)purpose for an old drug: purinergic modulation may extinguish the COVID-19 thromboinflammatory firestorm.	Perspective	JCI Insight.	doi:10.1172/jci.insight.140971.	Kanthi Y	Yes	2020	Aspirin	
53	Aspirin use is associated with decreased mechanical ventilation, ICU admission, and in-hospital mortality in hospitalized patients with COVID-19.	Retrospective cohort	Anesth. Analg.	doi: 10.1213/ANE.0000000000005292.	Chow JH	Yes	2020	Aspirin in COVID-19	The results of a multi-center cohort study of 412 COVID-19 patients in the USA were released that support the potential adjunctive therapeutic role of aspirin in COVID-19. The authors found that after adjustment for confounding variables, aspirin use was

									independently associated with a lower risk of mechanical ventilation (adjusted HR 0.56, 95% CI 0.37-0.85, p=0.007), ICU admission (adjusted HR 0.57, 95% CI 0.38-0.85, p=0.005), and in-hospital mortality (adjusted HR 0.53, 95% CI 0.31-0.90, p=0.02)
54	Kawasaki disease in siblings and a review of drug treatment.	Case report	Drugs Context.	doi:10.7573/dic.2020-4-1.	Loo SK	Yes	2020	Aspirin in Kawasaki disease	
55	Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement.	Guideline	Ann Intern Med.	doi:10.7326/M14-1884.	LeFevre ML	Yes	2014	Prevention of preeclampsia	
56	Gestational Hypertension and Preeclampsia.	Guideline	Obstet Gynecol.	doi:10.1097/AOG.0000000000003018.	ACOG	Yes	2019	Prevention of preeclampsia	
57	Why we should not stop giving aspirin to pregnant women during the COVID-19 pandemic.	Comment	Ultrasound Obstet Gynecol.	doi:10.1002/uog.22049.	Kwiatkowski S	Yes	2020	Prevention of preeclampsia in COVID-19	
58	Should we stop aspirin prophylaxis in pregnant women diagnosed with COVID-19?	Comment	Ultrasound Obstet Gynecol.	doi:10.1002/uog.22063.	Gavillet M	Yes	2020	Prevention of preeclampsia in COVID-19	

59	Is Acetylsalicylic Acid a Safe and Potentially Useful Choice for Adult Patients with COVID-19?.	Review	Drugs	doi: 10.1007/s40265-020-01365-1.	Bianconi V	Yes	2020	Aspirin safety in COVID-19	

Grey Literature Collection

No.	Title	Type of article	Organization/Journal/Clinical Trial Registries	Obtained through	First author	Peer review?	Publication date	Topic
1	Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health.	Guideline	National Institutes of Health	https://www.covid19treatmentguidelines.nih.gov/.	COVID-19 Treatment Guidelines Panel.		2020	Prevention
14	ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic	Guidance	European Society of Cardiology	https://www.escardio.org/Education/COVID-19-and-Cardiology/ESCCOVID-19-Guidance	ESC		2020	CVD Prevention
9	COVACTA trial raises questions about tocilizumab's benefit in COVID-19.	News	Lancet Rheumatol.	doi:10.1016/S2665-9913(20)30313-1.	Furlow B		2020	Pathogensis
	Study of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients: Sarilumab, Azithromycin, Hydroxychloroquine Trial - CORIMUNO-19 - VIRO (CORIMUNO-VIRO)	Trial registration	NCT04341870					

14 studies on clinical trials website, including ten randomized trials

1	Aggrenox To Treat Acute Covid-19 (ATTAC-19)		NCT04410328
2	Coronavirus Response - Active Support for Hospitalised Covid-19 Patients (CRASH-19)		NCT04343001
3	COVID-19 Positive Outpatient Thrombosis Prevention in Adults Aged 40-80		NCT04498273
4	Hemostasis in COVID-19: an Adaptive Clinical Trial		NCT04466670
5	The LEAD COVID-19 Trial: Low-risk, Early Aspirin and Vitamin D to Reduce COVID-19 Hospitalizations (LEAD COVID-19)		NCT04363840
6	Ivermectin, Aspirin, Dexamethasone and Enoxaparin as Treatment of Covid 19 (IDEA)		NCT04425863
7	Protective Effect of Aspirin on COVID-19 Patients (PEAC)		NCT04365309
8	Anti-Coronavirus Therapies to Prevent Progression of Coronavirus Disease 2019 (COVID-19) Trial (ACTCOVID19)		NCT04324463
9	Preventing Cardiac Complication of COVID-19 Disease With Early Acute Coronary Syndrome Therapy: A Randomised Controlled Trial. (C-19-ACS)		NCT04333407
10	Prevention and Treatment for COVID -19 (Severe Acute Respiratory Syndrome Coronavirus 2 SARS-CoV-2) Associated Severe Pneumonia in the Gambia (PaTS-COVID)		NCT04703608
11	Australasian COVID-19 Trial (ASCOT) ADAptive Platform Trial (ASCOT ADAPT)		NCT04483960
12	Randomised Evaluation of COVID-19 Therapy (RECOVERY)		NCT04381936
13	Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP)		NCT02735707
14	Evolution of COVID-19 in Anticoagulated or Antiaggregated Patients (CORONA Study) (CORONA)		NCT04518735