

Supplementary table 1 Detailed search strategy in Pubmed

Search	Query	Items
Pubmed (up to 20 December 2017)		
1	("antimalarials"[Pharmacological Action] OR "antimalarials"[MeSH Terms] OR "antimalarials"[All Fields])	81666
2	("hydroxychloroquine"[MeSH Terms] OR "hydroxychloroquine"[All Fields])	3977
3	("chloroquine diphosphate"[Supplementary Concept] OR "chloroquine diphosphate"[All Fields])	530
4	("chloroquine"[MeSH Terms] OR "chloroquine"[All Fields])	22064
5	1 OR 2 OR 3 OR 4	86811
6	("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields])	218047
7	("death, sudden"[MeSH Terms] OR ("death"[All Fields] AND "sudden"[All Fields]) OR "sudden death"[All Fields] OR ("sudden"[All Fields] AND "death"[All Fields]))	54212
8	("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields] OR ("heart"[All Fields] AND "attack"[All Fields]) OR "heart attack"[All Fields])	233673
9	("myocardial ischaemia"[All Fields] OR "myocardial ischemia"[MeSH Terms] OR ("myocardial"[All Fields] AND	448821

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- "ischemia"[All Fields]) OR "myocardial ischemia"[All Fields] OR
"coronary artery disease"[MeSH Terms] OR ("coronary"[All
Fields] AND "artery"[All Fields] AND "disease"[All Fields]) OR
"coronary artery disease"[All Fields] OR ("myocardial"[All
Fields] AND "ischemia"[All Fields]))
- 10 ("heart diseases"[MeSH Terms] OR ("heart"[All Fields] AND 1107971
"diseases"[All Fields]) OR "heart diseases"[All Fields])
- 11 ("acute coronary syndrome"[MeSH Terms] OR ("acute"[All 26741
Fields] AND "coronary"[All Fields] AND "syndrome"[All Fields])
OR "acute coronary syndrome"[All Fields])
- 12 ("death, sudden, cardiac"[MeSH Terms] OR ("death"[All Fields] 30984
AND "sudden"[All Fields] AND "cardiac"[All Fields]) OR
"cardiac sudden death"[All Fields] OR ("sudden"[All Fields] AND
"cardiac"[All Fields] AND "arrest"[All Fields]) OR "sudden
cardiac arrest"[All Fields])
- 13 ("ischaemic heart disease"[All Fields] OR "myocardial 463593
ischemia"[MeSH Terms] OR ("myocardial"[All Fields] AND
"ischemia"[All Fields]) OR "myocardial ischemia"[All Fields] OR
("ischemic"[All Fields] AND "heart"[All Fields] AND
"disease"[All Fields]) OR "ischemic heart disease"[All Fields] OR
"coronary artery disease"[MeSH Terms] OR ("coronary"[All
Fields] AND "artery"[All Fields] AND "disease"[All Fields]) OR
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	"coronary artery disease"[All Fields] OR ("ischemic"[All Fields]	
	AND "heart"[All Fields] AND "disease"[All Fields]))	
14	("coronary disease"[MeSH Terms] OR ("coronary"[All Fields]	297136
	AND "disease"[All Fields]) OR "coronary disease"[All Fields] OR	
	("coronary"[All Fields] AND "heart"[All Fields] AND	
	"disease"[All Fields]) OR "coronary heart disease"[All Fields])	
15	("angina pectoris"[MeSH Terms] OR ("angina"[All Fields] AND	48337
	"pectoris"[All Fields]) OR "angina pectoris"[All Fields])	
16	(("heart"[MeSH Terms] OR "heart"[All Fields] OR "coronary"[All	33749
	Fields]) AND revascularization [All Fields])	
17	("stroke"[MeSH Terms] OR "stroke"[All Fields])	280971
18	("cardiovascular diseases"[MeSH Terms] OR	2217214
	("cardiovascular"[All Fields] AND "diseases"[All Fields]) OR	
	"cardiovascular diseases"[All Fields])	
19	6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR	2436156
	16 OR 17 OR 18	
20	5 AND 19	5627

Supplementary table 2 Detailed outcomes of studies on chloroquine/hydroxychloroquine and cardiovascular disease (CVD)

Study	All CVD		Adjusted factors in multivariate analysis	Definitions of CVD
	Events occurred during follow-up period	RR (95% CI) (or OR [95% CI])		
Mok, 2007, China²⁰	42	2.03 (0.74-5.60)	Age, gender, smoking, hypertension, diabetes mellitus, obesity, hypercholesterolemia, chronic renal insufficiency, SLE; and use of high-dose prednisolone cyclophosphamide, azathioprine, mycophenolate mofetil, calcineurin inhibitors, aspirin, statins, angiotensin-converting enzyme inhibitors, and angiotensin II-receptor blockers	Cerebrovascular accident (CVA or stroke), transient ischemic attack, angina pectoris, acute myocardial infarction, digital gangrene, intermittent claudication, amaurosis fugax or retinal artery occlusion
Siso, 2008, Spain²⁷	28	0.58 (0.21-1.62)	Unadjusted	Cardiovascular events, including cerebrovascular accident or ischemic heart disease
Gustafsson, 2009, Sweden¹⁸	24	1.01 (0.32-2.67)	Age	Myocardial infarction, angina pectoris, cerebral infarction, transitory ischemic attacks, intermittent claudication or peripheral arterial thrombosis/embolus, death due to myocardial infarction, heart failure, sudden death, cerebral infarction, generalized atherosclerosis as stated by death certificate
Nikpour, 2011, Canada²¹	86	0.50 (0.31-0.79)	Age, gender, disease duration, disease-activity score, anti-phospholipid antibodies, diabetes, smoking and medications including corticosteroids,	Coronary artery disease events including angina pectoris, myocardial infarction, and sudden cardiac death

Study	All CVD		Adjusted factors in multivariate analysis	Definitions of CVD
	Events occurred during follow-up period	RR (95% CI) (or OR [95% CI])		
Magder, 2012, USA¹⁹	134	0.77 (0.54-1.12)	immunosuppressives, antihypertensives, and lipid-lowering therapy (statins) Age, gender, year before 1993, blood pressure, serum cholesterol, diabetes mellitus, SELENA-SLEDAI, anti-dsDNA, serum creatinine, low hematocrit, history of hemolytic anemia, history of lupus anticoagulant and current corticosteroid dose	Myocardial infarction, thrombotic stroke, clinically definite angina, percutaneous coronary intervention, a coronary bypass procedure, or claudication
Arnaud, 2015, Argentina, France, Greece, Italy and Spain¹⁴	-	0.77 (0.32-1.84)	Center effect	Arterial thrombosis
Sharma, 2016, USA²⁴	102	0.60 (0.41-0.94)	Age, gender, body mass index, low-density lipoprotein, smoking, diabetes, hypertension, anti-cyclic citrullinated peptide antibodies, rheumatoid factor, erythrocyte sedimentation rate, methotrexate, and tumor necrosis factor α inhibitor use	A composite of Coronary artery disease (myocardial infarction, unstable angina, or cardiac revascularization procedure), sudden death due to cardiac etiology, stroke, transient ischemic attack or peripheral arterial disease with arterial revascularization procedure
Hsu, 2017, China²⁸	35	0.58 (0.29-1.15)	Propensity score matching (age, gender, comorbidities, medications, overlapping immune diseases, number of admissions due to SLE and year of index date)	Acute coronary syndrome

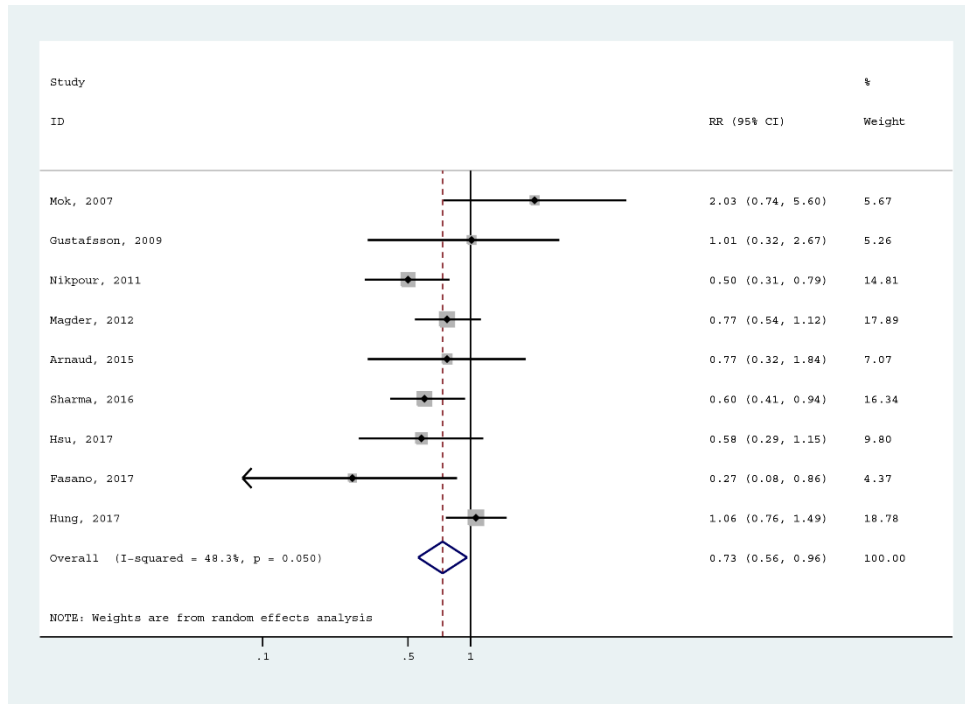
Study	All CVD		Adjusted factors in multivariate analysis	Definitions of CVD
	Events occurred during follow-up period	RR (95% CI) (or OR [95% CI])		
Fasano, 2017, Italy²⁹	16	0.27 (0.08-0.86)	ASA treatment, hypertension, aPL positivity, cumulative damage at last visit, hypercholesterolaemia	Angina, myocardial infarction, heart failure, transient ischaemic attack, stroke or peripheral arterial thrombosis
Hung, 2017, China³²	1253	1.06 (0.76-1.49)	Age, sex or the preexisting cardiovascular comorbidities (hypertension, diabetes, hyperlipidemia)	Acute myocardial infarction, other acute and subacute forms of ischaemic heart disease, old myocardial infarction, angina pectoris, other forms of chronic ischemic heart disease
Roman, 2003, USA²³	-	0.49 (0.21-1.12)	Age, the age at diagnosis, the duration of disease, the damage-index score, the presence of anti-Sm antibodies and significant treatment variables	Atherosclerosis (carotid plaque)
Bessant, 2006, UK¹⁶	-	0.14 (0.02-0.62)	Unadjusted	Myocardial infarction, angina, cerebral infarction, or peripheral vascular disease
de Leeuw, 2006, Netherlands¹⁷	-	1.05 (0.32-3.51)	Unadjusted	Ischemic heart disease, cerebrovascular accidents or peripheral vascular disease
Van-Halm, 2006, Netherlands²⁵	-	0.45 (0.10-2.04)	Age, gender, smoking, rheumatoid arthritis duration, hypertension, diabetes and hypercholesterolemia	Coronary artery disease (myocardial infarction, a coronary artery by-pass graft procedure, a percutaneous transluminal coronary angioplasty or ischemic abnormalities on ECG), cerebral arterial disease (cerebral vascular accident, a transient ischemic attack or a carotid endarterectomy),

Study	All CVD		Adjusted factors in multivariate analysis	Definitions of CVD
	Events occurred during follow-up period	RR (95% CI) (or OR [95% CI])		
Becker-Merok, 2009, Norway¹⁵	44	0.19 (0.08-0.47)	Unadjusted	peripheral arterial disease (aneurysm of the thoracic and/or abdominalis aorta, a peripheral arterial by-pass operation or amputation of the (lower) leg) Myocardial infarction, angina pectoris, intermittent claudication or cerebrovascular accident
Gustafsson, 2009, Sweden¹⁸	24	0.62 (0.22-1.76)	-	-
Pons-Estel, 2009, USA²²	43	1.30 (0.50-3.41)	Unadjusted	Angina, coronary artery bypass surgery, heart failure or myocardial infarction
Yang, 2012, China²⁶	-	0.067(0.01-0.73)	Reduced levels of C4, the presence of anti-Sm antibody, proteinuria, elevated levels of AST and serum creatinine	Myocardial infarction, angina, cerebral infarction, peripheral atherosclerosis, pulmonary arterial hypertension or valvular heart disease
Kao, 2013, USA³⁰	17	0.49 (0.18-1.31)	Unadjusted	Myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, fatal cardiac arrest, and/or cerebrovascular accident
Li, 2017, China³¹	256	0.19(0.05-0.71)	Age, gender, disease duration, age of RA onset,	Acute coronary syndromes, chronic coronary heart

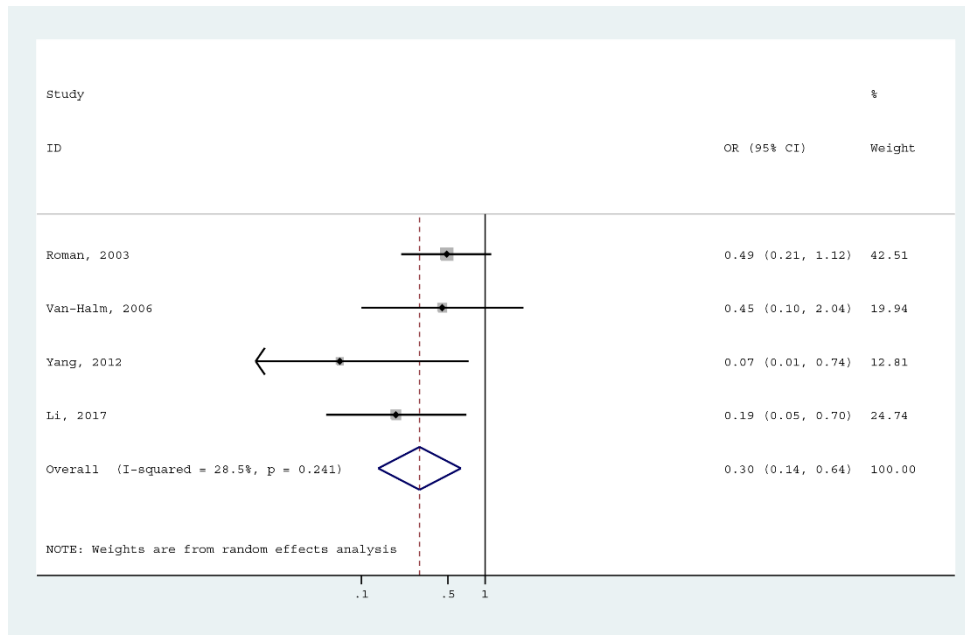
Study	All CVD		Adjusted factors in multivariate analysis	Definitions of CVD
	Events occurred during follow-up period	RR (95% CI) (or OR [95% CI])	hypertension, diabetes mellitus, smoking, hyperlipidemia, rheumatoid nodules, anemia	disease, ischemic and hemorrhagic stroke, peripheral arterial reconstructive surgery, limb amputation, or an ankle brachial pressure index (ABPI) <0.50

Abbreviations: aPL, antiphospholipid antibodies; AST, aspartate transaminase; CI, confidence interval; C4, complement component 4; CVD, cardiovascular disease; OR, odds ratio; RA, rheumatoid arthritis; RR, relative risk; SELENA, safety of estrogens in lupus erythematosus national assessment; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index instrument score.

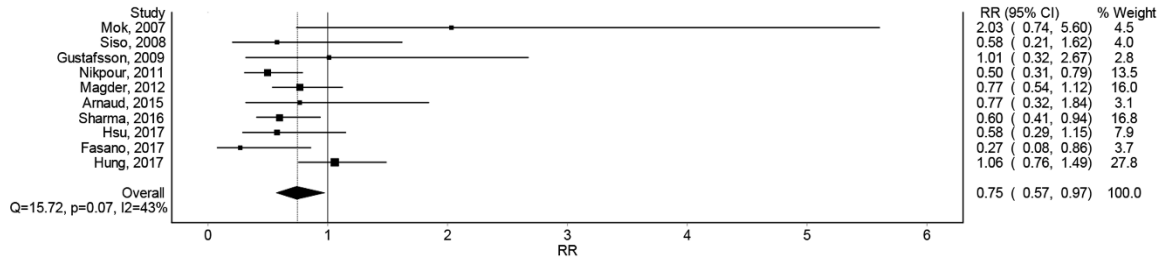
Supplementary figure 1. Sensitivity analysis excluding unadjusted RR in HR/RR-reporting studies.



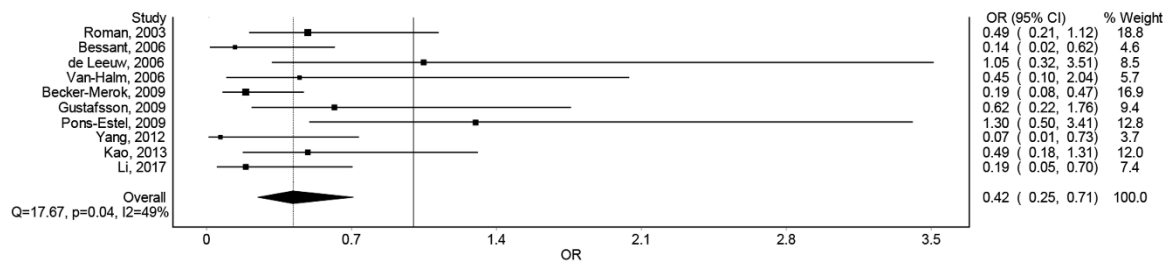
Supplementary figure 2. Sensitivity analysis excluding unadjusted OR in OR-reporting studies.



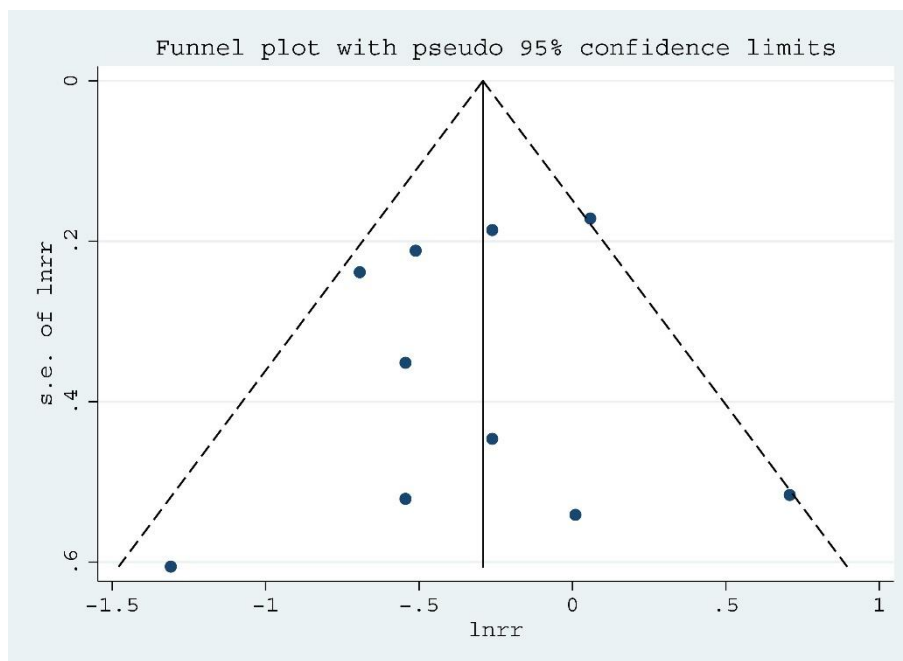
Supplementary figure 3. Sensitivity analysis using quality-effects model in HR/RR-reporting studies.



Supplementary figure 4. Sensitivity analysis using quality-effects model in OR-reporting studies.



Supplementary figure 5. Funnel graph in HR/RR-reporting studies.



Supplementary figure 6. Funnel graph in OR-reporting studies.

