Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Chloroquine and hydroxychloroquine are associated with reduced cardiovascular risk: a systematic review and meta-analysis

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Background and aims: Chloroquine (CQ) and hydroxychloroquine (HCQ) are widely used in patients with rheumatic diseases, but their effects on the cardiovascular system remain unclear. We aimed to assess whether CQ/HCQ could reduce the risk of cardiovascular disease (CVD).

Materials and methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, and the ClinicalTrials.gov for studies investigating the association between CQ/HCQ and the risk of CVD from inception to 20 December 2017. We carried out the quality assessment using the Newcastle-Ottawa Quality Assessment Scale (NOS). Random-effects model was used to pool the risk estimates relative ratio (RR), hazard ratio (HR) or odds ratio (OR) with 95% confidence interval (CI) for the outcomes.

Results: A total of 19 studies (7 case-control studies, 12 cohort studies, and no clinical trials) involving 19,679 participants were included in the meta-analysis. Pooled results for HRs or RRs showed that CQ/HCQ was associated with a significantly reduced risk of CVD (pooled RR 0.72, 95% CI 0.56–0.94, p=0.013). Results based on ORs showed a similar tendency towards a reduced risk of CVD with CQ/HCQ (pooled OR 0.41, 95% CI 0.25–0.69, p=0.001).

Conclusion: Our results suggested that CQ/HCQ was associated with a reduced risk of CVD in patients with rheumatic diseases. Randomized trials are needed to confirm the potential of CQ/HCQ in cardiovascular prevention in patients with and without rheumatic diseases.

Keywords: chloroquine, hydroxychloroquine, antimalarials, cardiovascular disease, atherosclerosis, drug repurpose and rheumatic diseases, systematic review

Introduction

The antimalarial agents such as chloroquine (CQ) and hydroxychloroquine (HCQ) are extensively used in the treatment of many rheumatic diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).[1–3] Recently, CQ and HCQ were shown to reduce some traditional cardiovascular risk factors, such as hyperglycemia and hyperlipidemia, in both clinical studies and animal experiments.[4–7] Despite these promising traits, the association between CQ/HCQ and the risk of cardiovascular disease (CVD) is not fully understood. According to the recent systematic review and meta-analysis conducted by Rempenault and colleagues, HCQ has a beneficial effect on metabolic and cardiovascular outcomes in patients with RA, by decreasing modifiable risk factors for CVD, like lipid profile and diabetes incidence. HCQ seemed to decrease the incidence of cardiovascular events, but data were too few for meta-analysis.[8] Besides this, the potential cardiovascular protection by CQ/HCQ was mentioned only in the latest published EULAR recommendations for the management

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of RA,[9] but not other latest guidelines of rheumatic diseases, cardiovascular diseases and diabetes.[10–13]

In the past few decades, several observational studies, either longitudinal or cross-sectional, investigated the association between CQ/HCQ use and cardiovascular outcomes, yielding controversial results.[14–32] Some studies showed that the use of CQ/HCQ reduced the risk of CVD,[15,16,21,24,26,29,31] whereas others reported a neutral effect.[14,17–20,22,23,25,27,28,30,32] Given these inconsistencies among trials, we carried out the current study to assess if CQ/HCQ was associated with a reduced risk of CVD.

Materials and methods

The meta-analysis was conducted in accordance with the Meta-Analyses of Observational Studies (MOOSE)[33] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[34]

Literature search

We conducted a systematic literature search through the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed and Embase for articles published up to 20 December 2017 using the terms "antimalarials" or "hydroxychloroquine" or "chloroquine diphosphate" or "chloroquine" in combination with "heart diseases" or "heart failure" or "heart attack" or "sudden cardiac arrest" or "sudden death" or "ischemic heart disease" or "myocardial infarction" or "myocardial ischemia" or "angina pectoris" or "acute coronary syndrome" or "coronary heart disease" or "coronary artery disease" or "coronary revascularization" or "stroke" or "cardiovascular diseases." The search strategy in PubMed can be seen in Table S1. Results were limited to publications in English. We also searched ClinicalTrials.gov for unpublished data. Reference lists of included articles and relevant systematic reviews were also screened manually to identify potentially eligible publications.

Eligible criteria

Studies were included if they met the following criteria: 1) designed as a randomized controlled trial (RCT), a cohort study or a case-control study; 2) comparing the risk of CVD between CQ/HCQ users and non-users in an RCT or a cohort study or comparing CQ/HCQ prescription ratio in patients with and without CVD in a case-control study; 3) relative risk estimates (relative ratio [RR], hazard ratio [HR] or odds ratio [OR] with 95% confidence interval [CI]) were provided or calculable. For studies of duplicate or overlapping patient populations, only data from the most informative publication with the longest follow-up or with the largest sample size were included. Studies with insufficient data and conference abstracts were excluded.

Data extraction and quality assessment

Paired investigators independently assessed the eligibility of the studies and extracted the following data from every study using a predefined form: first author, year of publication, study design, study population, sample size, country, age, gender, follow-up duration, drug type, definitions of the cardiovascular outcomes, number of events which occurred during the follow-up period, and risk estimates of CVD with their adjusted covariates. The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to evaluate the quality of each included observational study.[35] The NOS score ranges from 0 to 9 points, and a higher score indicates higher study quality. Because no RCT investigating the association between CQ/HCQ and CVD was retrieved in our search, no quality assessment tool for RCTs was used in the current study. Discrepancies were resolved by discussion in group conference.

Statistical analysis

We pooled the risk estimates of outcomes using adjusted ORs, HRs or RRs and their CIs when available. If the adjusted ORs, HRs or RRs were not reported, unadjusted ORs, HRs or RRs and their CIs were employed. When the ORs or RRs with 95% CIs were not shown directly in a publication, they were calculated by a two-by-two frequency table and the following formulas (a, b, c, d, e, f):[36]

$$\mathrm{OR} = \frac{a/c}{b/d} = \frac{ad}{bc} \quad \text{(a)}$$

$$\mathrm{RR} = \frac{a/(a+b)}{c/(c+d)}. \quad \text{(b)}$$

$$\text{Upper 95\% CI} = e^{\ln(\mathrm{OR})+1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}} \quad \text{(c)}$$

$$\text{Lower 95\% CI} = e^{\ln(\mathrm{OR})-1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}} \quad \text{(d)}$$

$$\text{Upper 95\% CI} = e^{\ln(\mathrm{RR})+1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}} \quad \text{(e)}$$

$$\text{Lower 95\% CI} = e^{\ln(\mathrm{RR})-1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}} \quad \text{(f)}$$

where a = number of exposed cases; b = number of exposed non-cases; c = number of unexposed cases; d = number of unexposed non-cases.

To obtain pooled relative risk estimates, we weighted the natural logarithm of the ORs, HRs, and RRs with their 95% CIs for case-control and cohort studies, respectively,

by the inverse of their variance. The statistical heterogeneity was assessed using the chi-square test (significant when $p<0.10$) and quantified by the I^2 statistics (significant when $I^2 \geq 50\%$). Random-effects model was used throughout this meta-analysis in consideration of the clinical heterogeneity. Two subgroup analyses were conducted based on the underlying disease and on whether or not CVD was excluded at baseline. We evaluated potential publication bias by the Begg's test and the Egger's test (significant when $p<0.10$). Two types of sensitivity analyses were performed to evaluate the robustness of the results: 1) by omitting studies in which adjusted risk estimates were not available; 2) by using quality-effects model to pool relative risk estimates.[37] Analyses were performed by STATA statistical software version 12.0 (StataCorp, College Station, TX, USA) and MetaXL version 4.0 (EpiGear International; Wilston, Queensland, Australia).

Results

Study selection

Figure 1 is a summary of the process of study selection. A total of 19,615 potentially eligible papers were identified but 17,754 were excluded by elimination of duplications and screening of the titles and abstracts. After full-text review, another 137 were excluded. Finally, 19 studies involving 19,679 participants were included in this systematic review and meta-analysis.

Study characteristics and quality assessment

No eligible RCT was identified in the literature screening. Seven of the 19 included studies were designed as case-control studies or nesting case-control studies,[16,17,22,23,26,30,31] and 12 were cohort studies.[14,15,18–21,24,25,27–29,32]

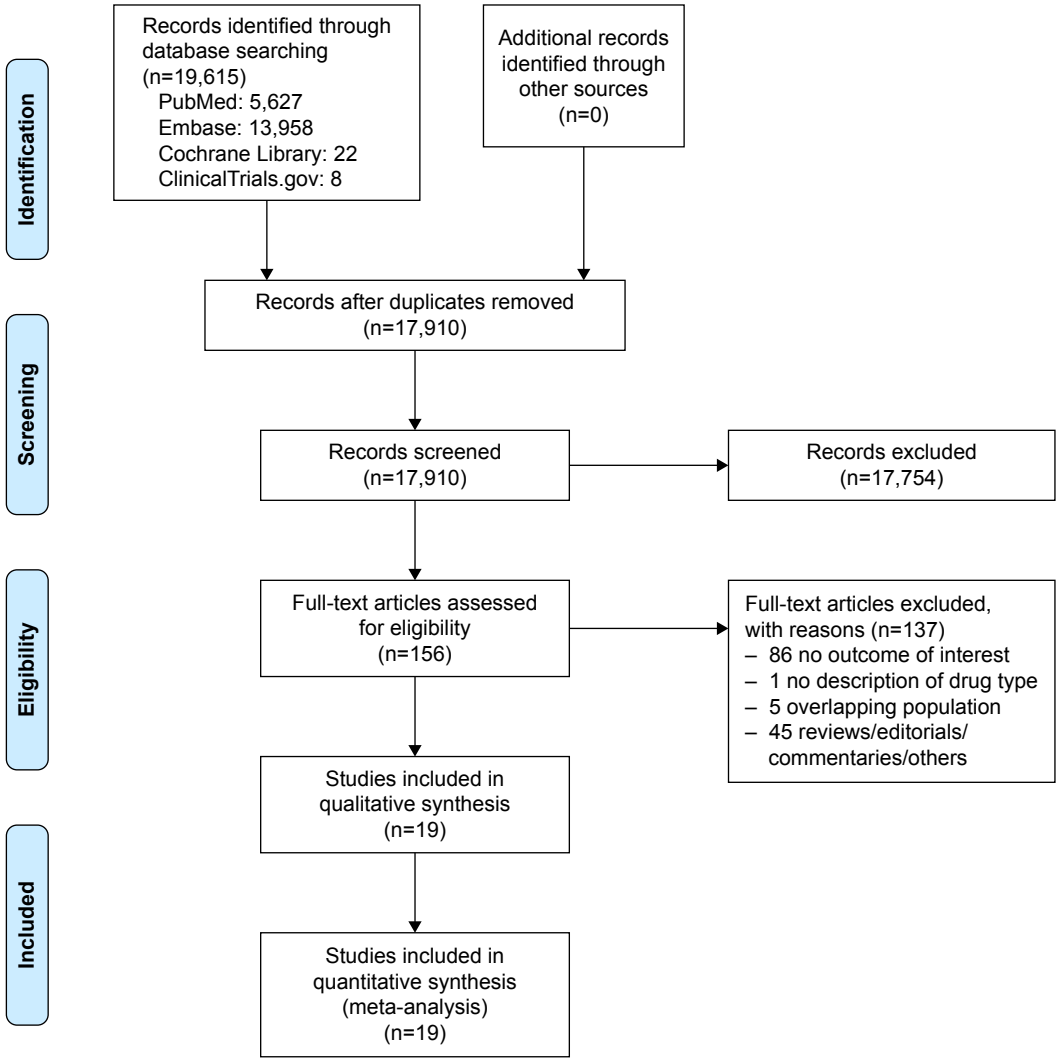

Figure 1 Flow diagram for study identification and inclusion (Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA]).

Table 1 Characteristics of the included cohort studies

Study, year, country	Mean age (years)	No of participants	Male gender, no (%)	Study population	Participants with CVD, excluded or not, at enrollment	Drug type	Follow-up time (years)	Study quality score (NOS)
van Halm et al,[25] 2006, the Netherlands	62 (RA without CVD); 67 (RA with CVD)	613	182 (29.7)	RA	No	HCQ	NA	7
Mok et al,[20] 2007, China	28.8 (LN); 42.7 (PGN)	343	111 (32.4)	LN/PGN	Yes	HCQ	8.1 (mean)	9
Sisó et al,[27] 2008, Spain	31.3	206	21 (10.2)	LN	Yes	HCQ or CQ	12.3 (mean)	8
Becker-Merok et al,[15] 2009, Norway	≥16	158	24 (15.2)	SLE	Yes	HCQ	11.9 (mean)	8
Gustafsson et al,[18] 2009, Sweden	45	182	18 (10)	SLE	Yes	HCQ or CQ	8.3 (mean)	6
Nikpour et al,[21] 2011, Canada	37.1	956	107 (11.2)	SLE	Yes	HCQ or CQ	6.7 (mean)	8
Magder and Petri,[19] 2012, USA	37	1,874	136 (7.3)	SLE	Yes	HCQ	NA	6
Arnaud et al,[14] 2015 Argentina, France, Greece, Italy and Spain	NA	191	NA	SLE	Yes	HCQ	NA	5
Sharma et al,[24] 2016, USA	56.3	1,266	313 (24.7)	Incident RA	Yes	HCQ	6.0 (median)	8
Hsu et al,[28] 2017, China	35.3	3,892	3,404 (87.5)	New-onset SLE	Yes	HCQ	7.4 (mean)	9
Fasano et al,[29] 2017, Italy	33	291	20 (6.9)	SLE	Yes	HCQ	8 (median)	9
Hung et al,[32] 2017, China	53.8	6,260	1,866 (29.8)	RA	Yes	HCQ	5.39 (median)	9

Abbreviations: CQ, chloroquine; CVD, cardiovascular disease; HCQ, hydroxychloroquine; LN, lupus nephritis; NA, not available; NOS, the Newcastle–Ottawa Quality Assessment Scale; PGN, primary glomerulonephritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

The characteristics of included studies are shown in Tables 1 and 2. The NOS score of each study ranged from 5 to 9. The number of subjects in each study ranged from 58 to 6,260. Eleven studies provided mean or median time of follow-up, ranging from 5.39 to 12.3 years.[15,18,20–22,24,27–30,32] All studies were conducted in patients with rheumatic diseases. Four studies recruited patients with RA,[24,25,31,32] 14 studies were conducted in SLE patients,[14–19,21–23,26–30] one included patients with lupus nephritis or non-lupus primary glomerulonephritis,[20] and 13 studies excluded patients with a history of CVD.[14,15,18–22,24,27–30,32]

As shown in Table S2, the CVD investigated was heterogeneous across studies. Variables included for adjustment varied along with the study.

Table 2 Characteristics of the included case-control studies

Study, year, country	Mean age (years) (cases/controls)	No of participants (cases/controls)	Male gender, no (%) (cases/controls)	Study population	Participants with CVD, excluded or not, at enrollment	Drug type	Follow-up time (years)	Study quality score (NOS)
Roman et al,[23] 2003, USA	52/39	73/124	NA	SLE	No	HCQ	NA	8
Bessant et al,[16] 2006, UK	47.7/41.1	29/29	NA	SLE	No	HCQ	NA	7
de Leeuw et al,[17] 2006, the Netherlands	48/40	13/59	1 (7.7)/8 (13.6)	SLE	No	HCQ	NA	7
Pons-Estel et al,[22] 2009, USA	48.1/35.6	43/594	11 (25.6)/54 (9.1)	SLE	Yes	HCQ	6.6 (mean)	7
Yang et al,[26] 2012, China	31.4/31.2	38/38	2 (5.3)/8 (21.1)	SLE	No	HCQ	NA	7
Kao et al,[30] 2013, USA	51.4/43.1	17/375	0 (0)/0 (0)	SLE	Yes	HCQ	8 (mean)	7
Li et al,[31] 2017, China	68.2/53.7	256/1,759	85 (33.3)/336 (19.1)	RA	No	HCQ	NA	7

Abbreviations: CVD, cardiovascular disease; HCQ, hydroxychloroquine; NA, not available; NOS, the Newcastle–Ottawa Quality Assessment Scale; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

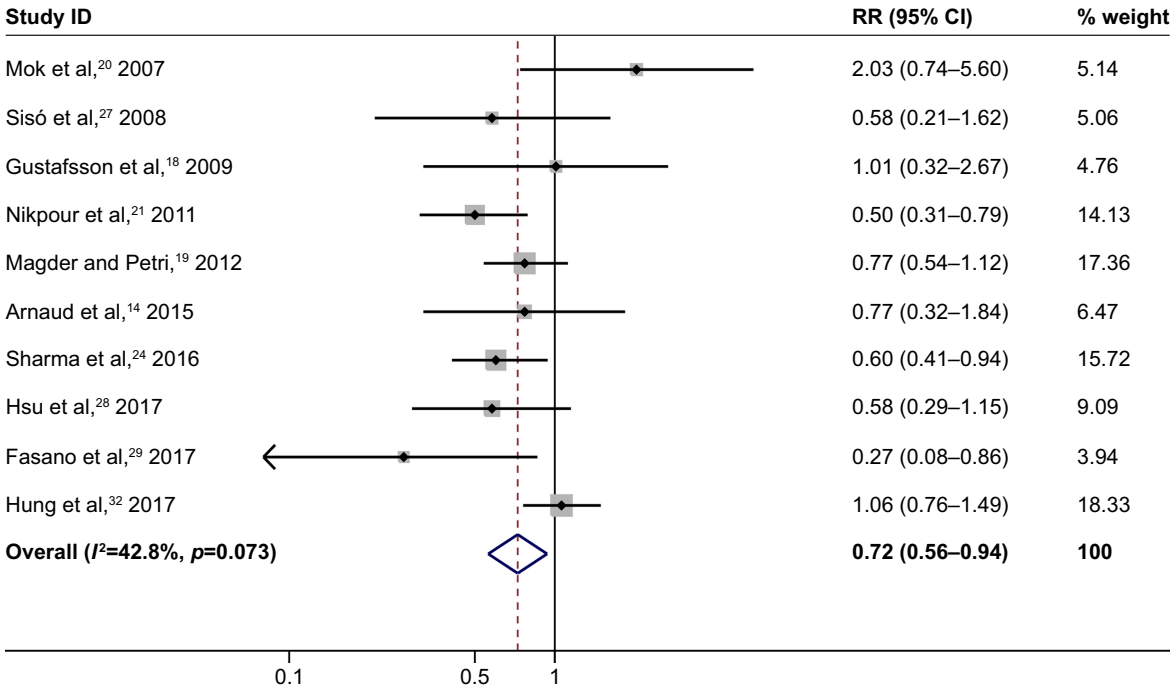

Figure 2 CVD risk in patients receiving CQ/HCQ in HR/RR-reporting studies.
Note: Weights are from random-effects analysis.
Abbreviations: CI, confidence interval; CQ, chloroquine; CVD, cardiovascular disease; HCQ, hydroxychloroquine; HR, hazard ratio; RR, relative ratio.

Overall meta-analysis

Nine of the 19 included studies reported the adjusted HRs or RRs with 95% CIs,[14,18–21,24,28,29,32] four reported the adjusted ORs with 95% CIs,[23,25,26,31] and six provided unadjusted ORs with 95% CIs.[15–18,22,30] In the overall meta-analysis of HRs or RRs, CQ/HCQ use in rheumatic patients was associated with a reduced risk of CVD with statistical significance (pooled RR 0.72, 95% CI 0.56–0.94, p=0.013) (Figure 2). The pooled ORs were 0.41 (95% CI 0.25–0.69, p=0.001) (Figure 3) indicating fewer CQ/HCQ prescriptions in CVD patients.

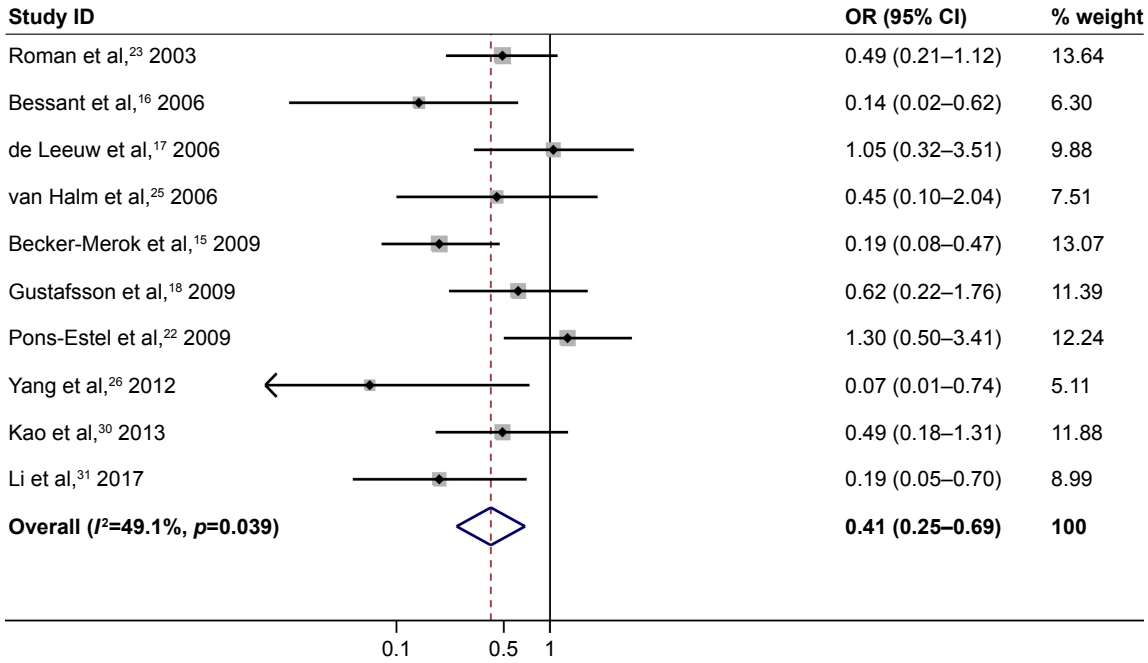

Figure 3 CVD risk in patients receiving CQ/HCQ in OR-reporting studies.
Note: Weights are from random-effects analysis.
Abbreviations: CI, confidence interval; CQ, chloroquine; CVD, cardiovascular disease; HCQ, hydroxychloroquine; OR, odds ratio.

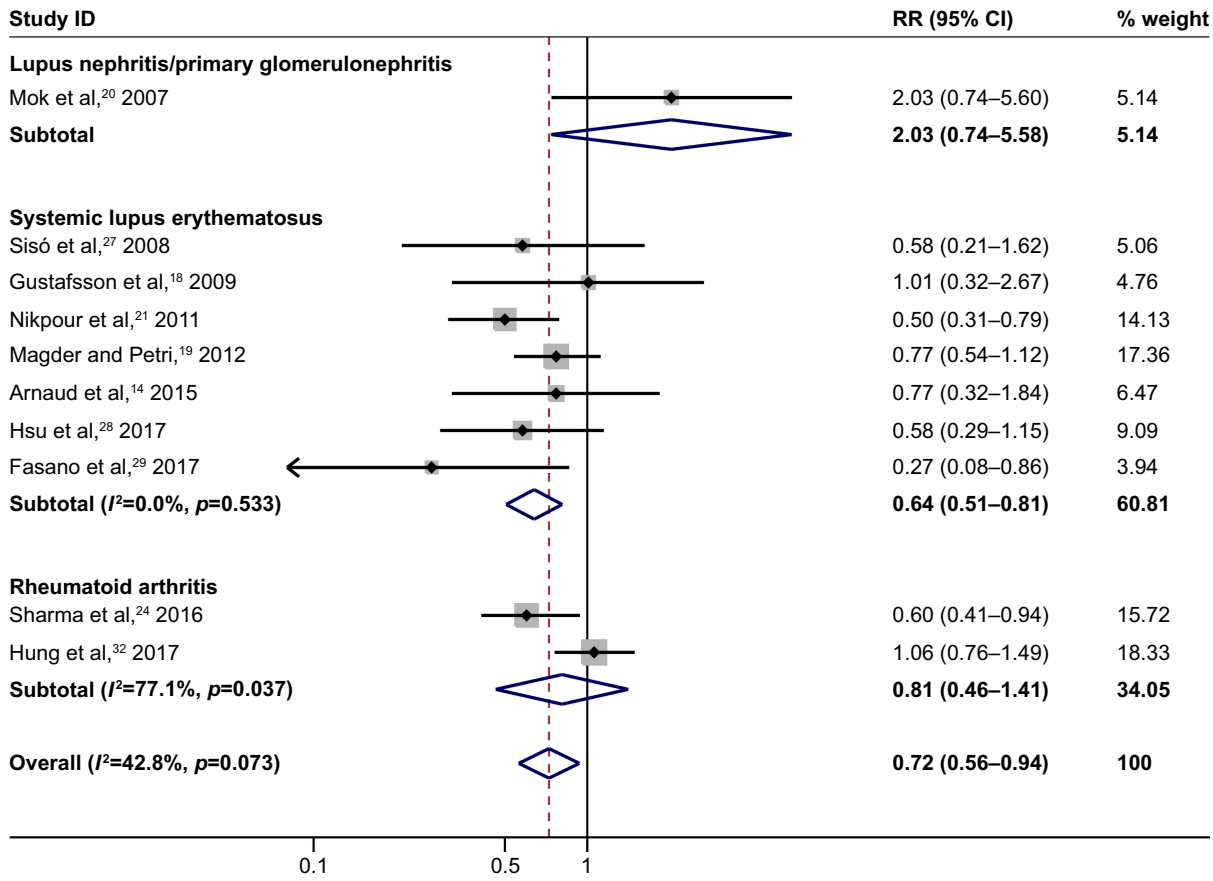

Figure 4 Subgroup analysis based on underlying diseases in HR/RR-reporting studies.
Note: Weights are from random-effects analysis.
Abbreviations: CI, confidence interval; HR, hazard ratio; RR, relative ratio.

Subgroup analyses

Subgroup analyses were performed based on study population in publications reporting HRs (RRs) or ORs, respectively. CQ/HCQ was associated with a reduced risk of CVD in patients with SLE (RR 0.64, 95% CI 0.51–0.81), and a similar trend was seen in patients with RA (RR 0.81, 95% CI 0.46–1.41) but without significant difference. Only one study investigated the association between CQ/HCQ and the risk of CVD in patients with lupus nephritis or non-lupus primary glomerulonephritis (RR 2.03, 95% CI 0.74–5.58) (Figure 4).[20] The pooled ORs (95% CI) of CVD in relation to CQ/HCQ were similar between patients with RA and those with SLE (0.27 [0.10–0.74] and 0.44 [0.24–0.80], respectively) (Figure 5).

The other subgroup analysis showed that the pooled ORs in studies excluding or not excluding prior CVD history were 0.52 (95% CI, 0.23–1.17) and 0.33 (95% CI, 0.16–0.68), respectively (Figure 6). Since all HR/RR-reporting studies excluded patients with prior CVD at baseline, subgroup analysis for pooled RR was not conducted.

Sensitivity analysis

We tested the robustness of our results with sensitivity analyses either by excluding studies without adjusted risk estimates or by using quality-effects model. The pooled risk estimates all remained almost unchanged by these two types of sensitivity analyses (Figures S1–S4).

Publication bias

There was no evidence of publication bias in either the meta-analysis of studies reporting HRs or RRs (Begg's test, p=0.72; Egger's test p=0.67) or in the studies reporting ORs (Begg's test, p=0.21; Egger's test p=0.23). The funnel graphs are shown in Figures S5 and S6.

Discussion

Our systematic review involved 19 observational studies with 19,679 CQ/HCQ treated patients and controls. The pooled results for HRs or RRs indicated that CQ/HCQ was associated with an approximately 30% reduction in the risk of CVD. This effect was comparable to long-term intensive

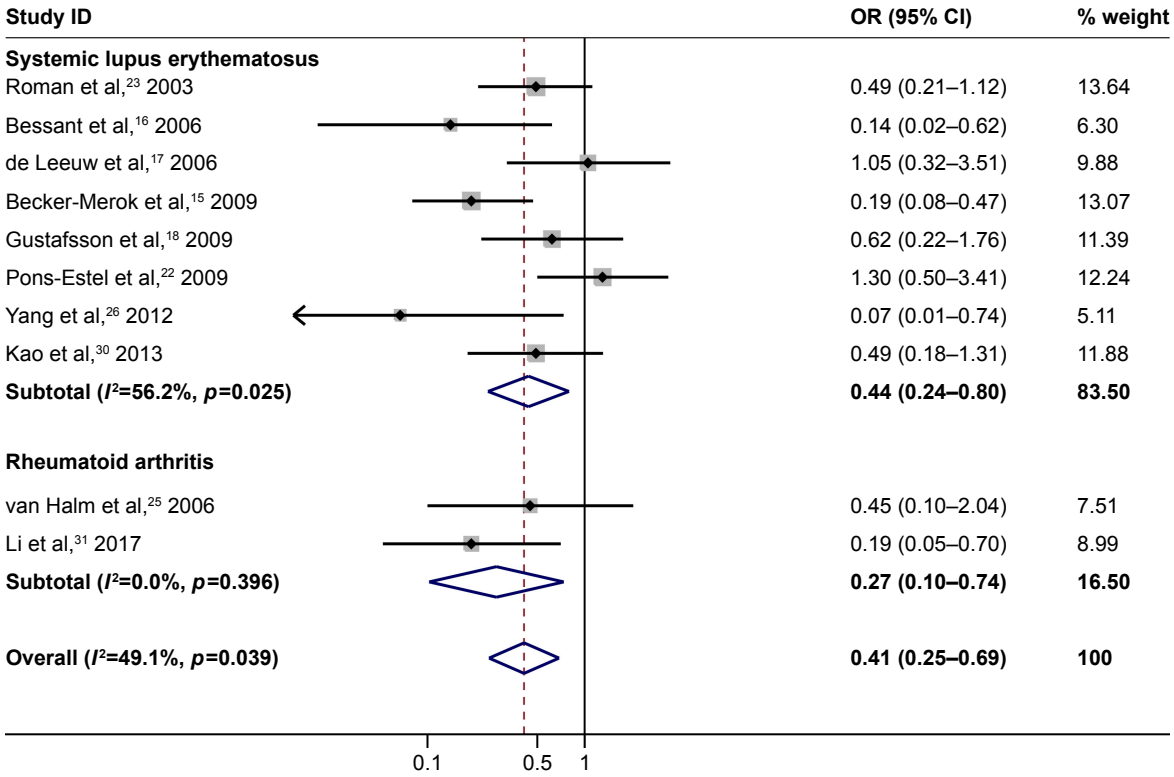

Figure 5 Subgroup analysis based on underlying diseases in OR-reporting studies.
Note: Weights are from random-effects analysis.
Abbreviations: CI, confidence interval; OR, odds ratio.

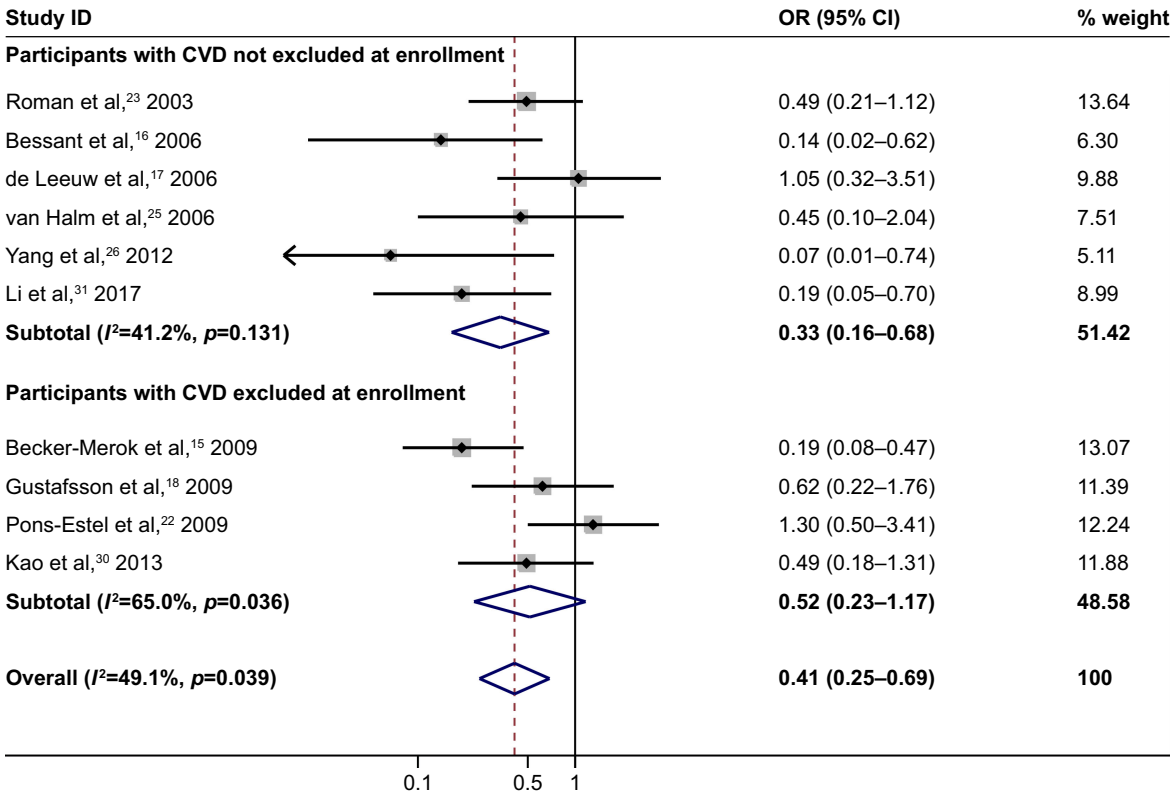

Figure 6 Subgroup analysis based on whether the study excluded the patients with prior CVD at baseline in OR-reporting studies.
Note: Weights are from random-effects analysis.
Abbreviations: CI, confidence interval; CVD, cardiovascular disease; OR, odds ratio.

blood pressure (25% reduction in Systolic Blood Pressure Intervention Trial [SPRINT] study) or glucose control (33% reduction in the United Kingdom Prospective Diabetes Study [UKPDS] study) in large clinical trials and of clinical significance.[38,39] Our study provides more favorable evidence of the preventive effect of CQ/HCQ on CVD based on the current meta-analysis.[8]

Patients with rheumatic diseases are at higher risk of developing CVD and require primary prevention of CVD.[40,41] According to our systematic review, the cardiovascular benefit from CQ/HCQ was promising based on the following considerations: 1) pooled analyses of RR/HR and OR were consistent, and in accordance with the results from most of the included studies; 2) the pooled results were almost unchanged in the sensitivity analyses; 3) no publication bias was found; 4) subgroup analyses showed little difference among different subgroups. Also, the one study excluded from the present meta-analysis, due to not reporting the exact drug, showed results consistent with our analysis.[42] Mok et al's study was the only exception with an opposite result, in which not only patients with lupus nephritis (162 cases) but also those with non-lupus primary glomerulonephritis (181 cases) were enrolled in the cohort study.[20] Compared with other studies included in the current meta-analysis, Mok et al's study considered more covariates in the multivariate analysis. Overadjustment could introduce additional bias, which might help explain this inconsistency.

CQ and HCQ are antimalarial drugs and have been widely used for years as antirheumatic drugs due to their safety, efficacy and low cost, indicating their potential in the primary and secondary prevention of CVD in non-rheumatic patients.[43,44] Adverse events were reported in less than 10% of patients under antimalarials' treatment.[45] Gastrointestinal intolerance and cutaneous manifestations are the commonest adverse effects, but they are usually mild and can be released by dose reduction.[46] CQ/HCQ-associated cardiotoxicity, presenting as hypotension and arrhythmia, could be serious but is very rare with a routine oral dose.[47] It was often associated with high-dose or intravenous CQ/HCQ administration or self-poisoning.[47] Although the mechanism remains unclear, lysosomal disruption and ion channel blockage could be the cause.[48] High dose and long duration of use of CQ is a confirmed but rare cause of toxic retinopathy, with an incremental risk of less than 1% in the first 10 years of therapy under a dose of 5.0 mg/kg.[49] Considering the rarity of cardiotoxicity and retinopathy, and the significantly reduced risk of CVD exhibited in the current study, CQ/HCQ provided more cardiac benefits than potential risks.[50] But, careful monitoring is still needed during treatment. Recently, the American Academy of Ophthalmology recommended an annual screening of retinopathy after 5-year usage of CQ/HCQ in low-risk patients.[49]

Previous studies suggested that CQ/HCQ could reduce some cardiovascular risk factors, such as hyperlipidemia, diabetes mellitus, and thrombosis.[4–6,51,52] Early observations also indicated that HCQ could improve insulin sensitivity, glucose profiles, and glycated hemoglobin (HbA1c) levels in patients with RA and SLE.[53–55] A randomized trial showed that CQ/HCQ could decrease HbA1c level in non-insulin-dependent diabetic patients without rheumatic diseases as well.[56] The underlying mechanism for improving metabolic profiles by CQ/HCQ treatment remains unclear. Possible explanations could be increased affinity of insulin receptors, inhibition of insulin degradation, and increased insulin secretion.[57,58]

CQ/HCQ is also associated with beneficial changes of lipid profiles, including decreased levels of total cholesterol, triglycerides, and low-density lipoprotein-cholesterol (LDL-c), irrespective of concomitant steroid use in RA and SLE patients.[6,59–61] Possible mechanisms behind the lipid-lowering effects of CQ/HCQ include increased lipid clearance rate and expression of LDL receptors.[62]

The use of CQ/HCQ has been shown to be thromboprotective. Recently, the risk of thrombosis was observed to be significantly reduced in patients with lupus and antiphospholipid syndrome under CQ/HCQ treatment when compared with that in patients not receiving CQ/HCQ.[51,63,64] Several plausible mechanisms have been proposed to help explain the antithrombotic effect of CQ/HCQ, including inhibition of platelet aggregation and reduction of red blood cell aggregation.[43,65]

Ataxia telangiectasia mutated (ATM) protein is a nuclear protein involved in DNA repairing and could be activated by CQ/HCQ. In animal experiments, CQ reduced atherosclerotic lesions in apoE$^{-/-}$ mice in an ATM-dependent manner.[7] Our previous study also suggested that polymorphism-enhancing gene expression in the promoter region of ATM (rs189037) was associated with less coronary stenosis.[66] ATM activation is thus a potential molecular mechanism of the anti-atherosclerotic effects of CQ/HCQ, which still requires further clinical and experimental studies to confirm, and additional mechanisms need exploration in future investigations.

Our meta-analysis had several limitations. Firstly, no RCT reporting the risk estimates of CVD under CQ/HCQ treatment was found. Biases and confounders might be introduced by pooling only observational studies. Hence, we combined the adjusted effect sizes when available to minimize

these potential biases and confounders. Secondly, since all included studies were carried out in patients with rheumatic diseases, whether CQ/HCQ could reduce the risk of CVD in the non-rheumatic population remains unknown. Regarding the common mechanisms of cardiovascular prevention, randomized cardiovascular outcome trials in non-rheumatic patients are warranted to further illustrate the CQ/HCQ potentials of primary and secondary CVD prevention.[67] Thirdly, since the metabolic indexes data, such as lipid profiles and blood glucose, are not provided in the included studies, investigating the effect of CQ/HCQ on metabolic outcomes is beyond the scope of our current study.

In conclusion, the present meta-analysis based on observational studies showed that the use of CQ/HCQ was associated with a significantly decreased risk of CVD in patients with rheumatic diseases. Given the widespread clinical use of CQ/HCQ, the potential preventive effect of CQ/HCQ on CVD is worth further exploring through RCTs in patients with and without rheumatic diseases, as the reference of future guidelines. Meanwhile, the safety profiles of CQ/HCQ require further investigations.

Acknowledgments

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Author contributions

YGZ, HT and SL conceived this study. DL and XL performed the literature search and screening. DL, XL and YYZ extracted the study data. DL, JSWK, LL, CX, QL and XS performed the statistical analysis. DL, XL, QL and SL drafted the manuscript. All authors critically revised the manuscript and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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