Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

1 Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. *Ann Rheum Dis* 2018; **77:** 808–18.

2 Rapkiewicz AV, Mai X, Carsons SE, et al. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: a case series. *EClinicalMedicine* 2020; **24:** 100434.

3 Ridker PM, MacFadyen JG, Everett BM, et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet* 2018; **391:** 319–28.

4 Sterne JAC, Murthy S, Diaz JV, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020; **324:** 1330–41.

5 van Zaane B, Nur E, Squizzato A, et al. Systematic review on the effect of glucocorticoid use on procoagulant, anti-coagulant and fibrinolytic factors. *J Thromb Haemost* 2010; **8:** 2483–93.

Hydroxychloroquine treatment does not reduce COVID-19 mortality; underdosing to the wrong patients?

Published **Online** January 27, 2021 https://doi.org/10.1016/S2665-9913(21)00030-8

Published **Online** January 27, 2021 https://doi.org/10.1016/S2665-9913(21)00031-X

An observational study published in *The Lancet Rheumatology* by Christopher T Rentsch and colleagues[1] showed no association between pre-exposure use of hydroxychloroquine and reduced mortality in patients with COVID-19 who also have systemic lupus erythematosus or rheumatoid arthritis. 138 440 (71·1%) participants were women, and the study population was relatively young, with 50% of the participants younger than 66 years. In a previous study,[2] the death rate in patients younger than 70 years was low, and it was lower for women than men; therefore, the differences in mortality might be very difficult to appreciate in the study by Rentsch and colleagues,[1] in which half of the participants are under 70 years old and more than two thirds are women. Rentsch and colleagues[1] did not reference any of the several large peer reviewed studies showing an association between hydroxychloroquine and lower mortality in patients with COVID-19, or the systematic reviews that have critically appraised and summarised these studies.[3,4] These studies were all disregarded as methodologically weak, and an opportunity to build upon the interesting aspects of previous research was missed. Rentsch and colleagues[1] mentioned that the dose at which hydroxychloroquine is given for systemic lupus erythematosus (SLE) and rheumatoid arthritis is similar to the one used in an ongoing clinical trial (NCT04303507) for prevention of COVID-19 (200–400 mg per day). However, even when hydroxychloroquine is used at maximum dose, patients with SLE or rheumatoid arthritis do not receive doses as high as those used in patients with COVID-19 in studies that showed an association between hydroxychloroquine and reduced mortality (800 mg on day 1 followed by 400 mg a day for four days).[3,4] The large number of studies on hydroxychloroquine that show contradictory results on different outcomes of COVID-19 might reflect the methodological limitations of each study on both sides of the debate. It could mean that hydroxychloroquine might only be beneficial at a certain dose, in specific phase of the disease, or in patients with a particular sociodemographic or clinical profile. Like Rentsch and colleagues,[1] we think that additional studies are required on the potential benefit of hydroxychloroquine, which is economical, has not proven to be harmful at the dose used for COVID-19, and could be prescribed to ambulatory patients right after the diagnosis before they develop respiratory distress.

We declare no competing interests.

**Luis Ayerbe, Carlos Risco-Risco, Iván Núñez-Gil, Maria Perez-Piñar, Salma Ayis*

Lgarcia-morzon@qmul.ac.uk

Centre of Primary Care and Public Health, Queen Mary University of London, London, E1 2AB, UK (LA); Carnarvon Medical Centre, Southend-on-Sea, UK (LA, MP-P); Internal Medicine, Hospital Universitario HM, Madrid, Spain (CR-R); Department of Cardiology, Hospital Universitario Clinico San Carlos, Madrid, Spain (IN-G); and School of Population Health and Environmental Sciences, King's College London, London, UK (SA)

1 Rentsch CT, DeVito NJ, MacKenna B, et al. Effect of pre-exposure use of hydroxychloroquine on COVID-19 mortality: a population-based cohort study in patients with rheumatoid arthritis or systemic lupus erythematosus using the OpenSAFELY platform. *Lancet Rheumatol* 2021; **3:** e19–27.

2 Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; **584:** 430–36.

3 Fiolet T, Guihur A, Rebeaud M, Mulot M, Peiffer-Smadja N, Mahamat-Saleh Y. Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients: a systematic review and meta-analysis. *Clin Microbiol Infect* 2021; **27:** 19–27.

4 Di Castelnuovo A, Costanzo S, Cassone A, Cauda R, de Gaetano G, Iacoviello L. Low dose hydroxychloroquine is associated with lower mortality in COVID-19: a meta-analysis of 26 studies and 44,521 patients. *medRxiv* 2020; published online Nov 4. https://doi.org/10.1101/2020.11.01.20223958 (preprint).

Authors' reply

We thank Luis Ayerbe and colleagues for the opportunity to further discuss our Article.[1] The choice of our study population—individuals with rheumatoid arthritis or systemic lupus erythematosus—was made to minimise the potential for confounding by indication when estimating the effectiveness of hydroxychloroquine use rather than investigating how to prevent severe COVID-19 in this population. The key question is whether our study had sufficient statistical power to detect a real difference in mortality, if one existed? As stated in the Article, the CIs around our key estimate (hazard ratio 1·03 [95% CI 0·80–1·33]) suggested that we could exclude substantial benefit, although a modest benefit or harm on a relative scale could not be ruled out; therefore, trials were warranted. Ayerbe and colleagues suggest that hydroxychloroquine might be differently effective or ineffective in specific demographics: we note that 25% of those in our study were aged over 75 years and, as reported, we found no evidence of effect modification by age.