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Chloroquine or hydroxychloroquine for COVID-19: why might they be hazardous?

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The 4-aminoquinoline antimalarials chloroquine and hydroxychloroquine have been promoted and sometimes used in the treatment of COVID-19, alone or combined with azithromycin, based on their immunomodulatory and antiviral properties, despite an absence of methodologically appropriate proof of their efficacy. The global community awaits the results of ongoing, well powered randomised controlled trials showing the effects of chloroquine and hydroxychloroquine on COVID-19 clinical outcomes. These drugs, however, might be associated with cardiac toxicity. Macrolides[1] and 4-aminoquinolines[2] prolong ventricular repolarisation, as evidenced by QT interval prolongation corrected for heart rate (QTc) on the electrocardiogram. QTc prolongation can be associated with a specific ventricular arrhythmia called torsade de pointes, which, although often self-terminating, can degenerate into ventricular tachycardia or fibrill leading to death. Torsade de pointes is a ra event with an estimated annual crude incidence million population; the incidence is al st dou in women compared with men and i ses with a Drug-induced torsade de pointe most curs in the presence of several risk fac s, including h drug concentration, simultan s ex osure to ultiple QTc-prolonging drugs, rona eart disease, heart failure, hypokalaemia, bra dia, or genital long-QT syndrome, thers.

In *The La*, Mand p Mehra nd colleagues[5] report the largest ery y published to date on the effects of oquine or hydroxychloroquine, with or without a macr in 96 032 hospitalised patients (mean age 53·8 years, 46·3% women) who tested positive for severe acute respiratory syndrome coronavirus 2. Verified data from an international registry comprising 671 hospitals in six continents were used to compare patients with COVID-19 who received chloroquine (n=1868), hydroxychloroquine (n=3016), chloroquine with a macrolide (n=3783), or hydroxychloroquine with a macrolide (n=6221) within 48 h of COVID-19 diagnosis, with 81 144 controls who did not receive these drugs. The primary outcome was in-hospital mortality and the occurrence of de-novo non-sustained or sustained ventricular tachycardia or vent fibrillation was also analysed. A Cox proportio hazard model accounting for many confounding riables, including age, sex, ethnicity, comorbidi , othe edi-cations, and COVID-19 severity, sh ed a signif increase in the risk of in-hospital tality th the fou treatment regimens compar wit control oup (hazard ratios [HRs] of 1 [95% C 23 57] to 1·447 [1·368–1·531]) ar using pro sity score matching by treatment grou pported this result. The increased h-hospital m lity was similar in men (1·293 178–1·420] to 1·408 [1·309–1·513]) and women (1·3 [1·169–1·] to 1·494 [1·334–1·672]). The incidence f repet e ventricular arrhythmias r from 4·3% 1% in patients treated with a 4- inoq line, compared with 0·3% in the control gro p 001).

Des limitations inherent to the observational nature this study, Mehra and colleagues should be nded for providing results from a well designed and controlled study of the effects of chloroquine or hydroxychloroquine, with or without a macrolide, in a very large sample of hospitalised patients with COVID-19. Their results indicate an absence of benefit of 4-aminoquinoline-based treatments in this population and suggest that they could even be harmful. It is tempting to attribute the increased risk of

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in-hospital deaths to the higher observed incidence of drug-induced ventricular arrhythmias, given that these drugs are known to prolong QTc and provoke torsade de pointes. However, the relationship between death and ventricular tachycardia was not studied and causes of deaths (ie, arrhythmic *vs* non-arrhythmic) were not adjudicated. Although not all ventricular arrhythmias might have been detected, the number of deaths in the treatment groups was much greater than the number of patients who had ventricular arrhythmias. The risk of death associated with 4-aminoquinolines alone or combined with a macrolide was similar, whereas it would be expected that the combination of two QTc-prolonging drugs would increase their proarrhythmic potential.[6] The HRs for death w similar in men and women, whereas women h a higher sensitivity to drug-induced QTc prolong on[7] and a higher risk of drug-induced torsade de poi than men. The study therefore do t suggest that the increased risk of death with 4-a noq es was due to a proarrhythmic mecha n. Another hypothesis to explain the sed r of death with 4-aminoquinoline s that their an iral and immunomodulatory pr ties n COVID-19 severity in some ients. ertheless, the increased incidence of ricular ar mias is intriguing. Chloroquin hydr chloroquine,[9] and azithromycin[10] have so m channe cking properties that might cont ute to proarrhyth ia[11] and heart failure in the c xt o yocardial injury and hypoxia present in COV .[12] This h othesis remains to be tested.

The fi om Mehra and colleagues' study add prelimi y reports suggesting that regimens of chloroquine or hydroxychloroquine, alone or with azithromycin, are not useful and could be harmful in hospitalised patients with COVID-19.

We declare no competing interests.

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1 Mason JW icrobi d QT prolonga on. *J Antimicrob Chemother* 2017; **72:** 12
2 Whi Cardio y of antim al drugs. *Lancet Infect Dis* 2007; 7 –58.
3 s G, Garbe E, Ki Hering RC, Bronder E, Haverkamp W. Epid gy of symptom ic drug-induced long QT syndrome and torsade intes in Germany. *Europace* 2014; **16:** 101–08.
4 Vlachos K, poulos S, Efremidis M, Sideris A, Letsas KP. An update on risk factors fo -induced arrhythmias. *Expert Rev Clin Pharmacol* 2016; **9:** 117–27.
5 a MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or c oquine with or without a macrolide for treatment of COVID-19: a tinational registry analysis. *Lancet* 2020; published online May 22. s://doi.org/10.1016/S0140-6736(20)31180-6.
Frommeyer G, Fischer C, Ellermann C, et al. Additive proarrhythmic effect of combined treatment with QT-prolonging agents. *Cardiovasc Toxicol* 2018; **18:** 84–90.
7 Darpo B, Karnad DR, Badilini F, et al. Are women more susceptible than men to drug-induced QT prolongation? Concentration-QTc modelling in a phase 1 study with oral rac-sotalol. *Br J Clin Pharmacol* 2014; **77:** 522–31.
8 Vicente J, Zusterzeel R, Johannesen L, et al. Assessment of multi-ion channel block in a phase I randomized study design: results of the CiPA phase I ECG biomarker validation study. *Clin Pharmacol Ther* 2019; **105:** 943–53.
9 Ten Broeke R, Mestrom E, Woo L, Kreeftenberg H. Early treatment with intravenous lipid emulsion in a potentially lethal hydroxychloroquine intoxication. *Neth J Med* 2016; **74:** 210–14.
10 Yang Z, Prinsen JK, Bersell KR, et al. Azithromycin causes a novel proarrhythmic syndrome. *Circ Arrhythm Electrophysiol* 2017; **10:** e003560.
11 Roden DM, Anderson ME. Proarrhythmia. *Handb Exp Pharmacol* 2006; **171:** 73–97.
12 Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; published online March 27. DOI:10.1001/jamacardio.2020.1017.