Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

Summary

Background Hydroxychloroquine or chloroquine, often in combination with a second-generation macrolide, are being widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Although generally safe when used for approved indications such as autoimmune disease or malaria, the safety and benefit of these treatment regimens are poorly evaluated in COVID-19.

Methods We did a multinational registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19. The registry comprised data from 671 hospitals in six continents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory finding for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagnosis were included in one of four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychloroquine alone, or hydroxychloroquine with a macrolide), and patients who received none of these treatments formed the control group. Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis or while they were on mechanical ventilation, as well as patients who received remdesivir, were excluded. The main outcomes of interest were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias (non-sustained or sustained ventricular tachycardia or ventricular fibrillation).

Findings 96 032 patients (mean age 53·8 years, 46·3% women) with COVID-19 were hospitalised during the study period and met the inclusion criteria. Of these, 14 888 patients were in the treatment groups (1868 received chloroquine, 3783 received chloroquine with a macrolide, 3016 received hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and 81 144 patients were in the control group. 10 698 (11·1%) patients died in hospital. After controlling for multiple confounding factors (age, sex, race or ethnicity, body-mass index, underlying cardiovascular disease and its risk factors, diabetes, underlying lung disease, smoking, immunosuppressed condition, and baseline disease severity), when compared with mortality in the control group (9·3%), hydroxychloroquine (4·3%; 3·561, 2·760–4·596), and chloroquine with a macrolide (6·5%; 4·011, 3·344–4·812) were independently associated with an increased risk of in-hospital mortality. Compared with the control group (9·3%), hydroxychloroquine (18·0%; hazard ratio 1·335, 95% CI 1·223–1·457), hydroxychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), and chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were each associated with increased in-hospital survival and an increased frequency of ventricular arrhythmias when used for treatment of COVID-19.

Interpretation We were unable to confirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-hospital outcomes for COVID-19. Each of these drug regimens was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias when used for treatment of COVID-19.

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Introduction

The absence of an effective treatment against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has led clinicians to redirect drugs that are known to be effective for other medical conditions to the treatment of COVID-19. Key among these repurposed therapeutic agents are the antimalarial drug chloroquine and its analogue hydroxychloroquine, which is used for the treatment of autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis.12 These drugs have been shown in laboratory conditions to have antiviral properties as well as immunomodulatory effects.14 However, the use of this class of drugs for COVID-19 is based on a small number of anecdotal experiences that have shown variable responses in uncontrolled observational analyses, and small, open-label, randomised trials that have largely been inconclusive.15 The combination of hydroxychloroquine with a second-generation macrolide, such as azithromycin (or clarithromycin), has also been advocated.
Articles

Research in context

Evidence before this study
We searched MEDLINE (via PubMed) for articles published up to April 21, 2020, using the key words “novel coronavirus”, “2019-nCoV”, “COVID-19”, “SARS-CoV-2”, “therapy”, “hydroxychloroquine”, “chloroquine”, and “macrolide”. Moreover, we screened preprint servers, such as Medrxiv, for relevant articles and consulted the web pages of organisations such as the US National Institutes of Health and WHO. Hydroxychloroquine and chloroquine (used with or without a macrolide) are widely advocated for treatment of COVID-19 based on in-vitro evidence of an antiviral effect against severe acute respiratory syndrome coronavirus 2. Their use is based on small uncontrolled studies and in the absence of evidence from randomised controlled trials. Concerns have been raised that these drugs or their combination with macrolides could result in electrical instability and predispose patients to ventricular arrhythmias. Whether these drugs improve outcomes or are associated with harm in COVID-19 remains unknown.

Added value of this study
In the absence of reported randomised trials, there is an urgent need to evaluate real-world evidence related to outcomes with the use of hydroxychloroquine or chloroquine (used with or without macrolides) in COVID-19. Using an international, observational registry across six continents, we assessed 96 032 patients with COVID-19, of whom 14 888 were treated with hydroxychloroquine, chloroquine, or their combination with a macrolide. After controlling for age, sex, race or ethnicity, underlying comorbidities, and disease severity at baseline, the use of all four regimens was associated with an increased hazard for de-novo ventricular arrhythmia and death in hospital. This study provides real-world evidence on the use of these therapeutic regimens by including a large number of patients from across the world. Thus, to our knowledge, these findings provide the most comprehensive evidence of the use of hydroxychloroquine and chloroquine (with or without a macrolide) for treatment of COVID-19.

Implications of all the available evidence
We found no evidence of benefit of hydroxychloroquine or chloroquine when used either alone or with a macrolide. Previous evidence was derived from either small anecdotal studies or inconclusive small randomised trials. Our study included a large number of patients across multiple geographic regions and provides the most robust real-world evidence to date on the usefulness of these treatment regimens. Although observational studies cannot fully account for unmeasured confounding factors, our findings suggest not only an absence of therapeutic benefit but also potential harm with the use of hydroxychloroquine or chloroquine drug regimens (with or without a macrolide) in hospitalised patients with COVID-19.

Methods
Registry features and data acquisition
We did a multinational registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19. The registry comprised 671 hospitals located in six continents (appendix p 3). The Surgical Outcomes Collaborative (Surgisphere Corporation, Chicago, IL, USA) consists of de-identified data obtained by automated data extraction from inpatient and outpatient electronic health records, supply chain databases, and financial records. The registry uses a cloud-based health-care data analytics platform that includes specific modules for data acquisition, data warehousing, data analytics, and data reporting. A manual data entry process is used for quality assurance and validation to ensure that key missing values are kept to a minimum. The Surgical Outcomes Collaborative (hereafter referred to as the Collaborative) ensures compliance with the US Food and Drug Administration (FDA) guidance on real-world evidence. Real-world data are collected through automated data transfers that capture 100% of the data from each health-care entity at regular, predetermined intervals, thus reducing the impact of selection bias and missing values, and ensuring that the data are current, reliable, and relevant. Verifiable source documentation for the elements include electronic inpatient and outpatient medical records and, in accordance with the FDA guidance on relevance of real-world data, data acquisition is performed through use of a standardised Health Level Seven-compliant data dictionary, with data collected on a
prospective ongoing basis. The validation procedure for the registry refers to the standard operating procedures in place for each of the four ISO 9001:2015 and ISO 27001:2013 certified features of the registry: data acquisition, data warehousing, data analytics, and data reporting.

The standardised Health Level Seven-compliant data dictionary used by the Collaborative serves as the focal point for all data acquisition and warehousing. Once this data dictionary is harmonised with electronic health record data, data acquisition is completed using automated interfaces to expedite data transfer and improve data integrity. Collection of a 100% sample from each healthcare entity is validated against financial records and external databases to minimise selection bias. To reduce the risk of inadvertent protected health information disclosures, all such information is stripped before storage in the cloud-based data warehouse. The Collaborative is intended to minimise the effects of information bias and selection bias by capturing all-comer data and consecutive patient enrolment by capturing 100% of the data within electronic systems, ensuring that the results remain generalisable to the larger population. The Collaborative is compliant with the US Agency for Healthcare Research and Quality guidelines for registries. With the onset of the COVID-19 crisis, this registry was used to collect data from hospitals in the USA (that are selected to match the epidemiological characteristics of the US population) and internationally, to achieve representation from diverse populations across six continents. Data have been collected from a variety of urban and rural hospitals, academic or community hospitals, and for-profit and non-profit hospitals. The data collection and analyses are deemed exempt from ethics review.

Study design
We included all patients hospitalised between Dec 20, 2019, and April 14, 2020, at hospitals participating in the registry and with PCR-confirmed COVID-19 infection, for whom a clinical outcome of either hospital discharge or death during hospitalisation was recorded. A positive laboratory finding for SARS-CoV-2 was defined as a positive result on high-throughput sequencing or reverse transcription-quantitative PCR assay of nasal or pharyngeal swab specimens, and this finding was used for classifying a patient as positive for COVID-19.

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Data collection
Patient demographics, including age, body-mass index (BMI), sex, race or ethnicity, and continent of origin were obtained. Underlying comorbidities (based on International Classification of Diseases, tenth revision, clinical modification codes) present in either the inpatient or outpatient electronic health record were collected, which included cardiovascular disease (including coronary artery disease, congestive heart failure, and history of a cardiac arrhythmia), current or previous history of smoking, history of hypertension, diabetes, hyperlipidaemia, or chronic obstructive pulmonary disease (COPD), and presence of an immunosuppressed condition (steroid use, pre-existing immunological condition, or current chemotherapy in individuals with cancer). We collected data on use of medications at baseline, including cardiac data from patients for whom treatment was initiated while they were on mechanical ventilation or if they were receiving therapy with the antiviral remdesivir. These specific exclusion criteria were established to avoid enrolment of patients in whom the treatment might have started at non-uniform times during the course of their COVID-19 illness and to exclude individuals for whom the drug regimen might have been used during a critical phase of illness, which could skew the interpretation of the results. Thus, we defined four distinct treatment groups, in which all patients started therapy within 48 h of an established COVID-19 diagnosis: chloroquine alone, chloroquine with a macrolide, hydroxychloroquine alone, or hydroxychloroquine with a macrolide. All other included patients served as the control population.

Study profile
We included all patients hospitalised between Dec 20, 2019, and April 14, 2020, at hospitals participating in the registry and with PCR-confirmed COVID-19 infection, for whom a clinical outcome of either hospital discharge or death during hospitalisation was recorded. A positive laboratory finding for SARS-CoV-2 was defined as a positive result on high-throughput sequencing or reverse transcription-quantitative PCR assay of nasal or pharyngeal swab specimens, and this finding was used for classifying a patient as positive for COVID-19.

COVID-19 was diagnosed, at each site, on the basis of a positive laboratory finding for SARS-CoV-2. A positive laboratory finding for SARS-CoV-2 was defined as a positive result on high-throughput sequencing or reverse transcription-quantitative PCR assay of nasal or pharyngeal swab specimens, and this finding was used for classifying a patient as positive for COVID-19.

Figure 1: Study profile
including the time of initiation. The use of second-generation macrolides, specifically azithromycin and clarithromycin, was similarly recorded. A quick sepsis-related organ failure assessment (qSOFA) was calculated for the start of therapy (including a scored calculation of the mental status, respiratory rate, and systolic blood pressure) and oxygen saturation (SPO₂) on room air was recorded, as measures of disease severity.

### Outcomes

The primary outcome of interest was the association between use of a treatment regimen containing chloroquine or hydroxychloroquine (with or without a second-generation macrolide) when initiated early after COVID-19 diagnosis with the endpoint of in-hospital mortality. The secondary outcome of interest was the association between these treatment regimens and the occurrence of clinically significant ventricular arrhythmias (defined as the first occurrence of a non-sustained [at least 6 sec] or sustained ventricular tachycardia or ventricular fibrillation) during hospitalisation. We also analysed the rates of progression to mechanical ventilation use and the total and intensive care unit lengths of stay (in days) for patients in each group.

### Statistical analysis

For the primary analysis of in-hospital mortality, we controlled for confounding factors, including demographic variables, comorbidities, disease severity at presentation, and other medication use (cardiac medications and other antiviral therapies). Categorical variables are shown as frequencies and percentages, and continuous variables as means with SDs. Comparison of continuous data between groups was done using the unpaired t-test and categorical data were compared using Fisher’s exact test. A p value of less than 0·05 was considered significant. Multiple imputation for missing values was not possible because for disease and drug variables, there were no codes to indicate that data were missing; if the patient’s electronic health record did not include information on a clinical characteristic, it was assumed that the characteristic was not present.

Cox proportional hazards regression analysis was done to evaluate the effect of age, sex, race or ethnicity (using white race as a reference group), comorbidities (BMI, presence of coronary artery disease, presence of congestive heart failure, history of cardiac arrhythmia, diabetes, or COPD, current smoker, history of hypertension, immunocompromised state, and history of hyperlipidaemia), medications (cardiac medications, antivirals, and the treatment regimens of interest), and severity of illness scores (qSOFA <1 and SPO₂ <94%) on the risk of clinically significant ventricular arrhythmia (using the time from admission to first occurrence, or if the event did not occur, to the time of discharge) and mortality (using the time from admission to inpatient mortality or discharge). Age and BMI were treated as continuous data between groups was done using the unpaired t-test and categorical data were compared using Fisher’s exact test. A p value of less than 0·05 was considered significant. Multiple imputation for missing values was not possible because for disease and drug variables, there were no codes to indicate that data were missing; if the patient’s electronic health record did not include information on a clinical characteristic, it was assumed that the characteristic was not present.

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### Table 1: Demographics and comorbidities of patients by survival or non-survival during hospitalisation

| Demographic/Comorbidity | Survivors (n=85 334) | Non-survivors (n=10 698) | p value |
|--------------------------|----------------------|--------------------------|---------|
| **Age, years**           | 53·1 (17·5)          | 60·0 (17·6)              | <0·0001 |
| **BMI, kg/m²**           | 27·0 (5·4)           | 31·8 (6·4)               | <0·0001 |
| **Obese, BMI >30 kg/m²** | 22·992 (26·9%)       | 65·182 (60·9%)           | <0·0001 |
| **Sex**                  |                      |                          |         |
| Female                   | 40·169 (47·1%)       | 42·579 (39·8%)           | <0·0001 |
| Male                     | 45·165 (52·9%)       | 64·441 (60·2%)           | <0·0001 |
| **Race or ethnicity**    |                      |                          |         |
| White                    | 57·503 (67·4%)       | 67·172 (62·8%)           | <0·0001 |
| Black                    | 72·19 (8·4%)         | 18·35 (17·2%)            | <0·0001 |
| Hispanic                 | 49·48 (5·8%)         | 10·90 (9·6%)             | <0·0001 |
| Asian                    | 12·652 (14·8%)       | 86·82 (8·1%)             | <0·0001 |
| **Comorbidities at baseline** |                      |                          |         |
| **Coronary artery disease** | 97·777 (11·5%)     | 23·60 (22·3%)           | <0·0001 |
| **Congestive heart failure** | 18·281 (2·1%)       | 54·02 (6·9%)            | <0·0001 |
| **Arrhythmia**           | 27·02 (3·8%)         | 681·4·4%                 | <0·0001 |
| **Diabetes**             | 10·962 (12·8%)       | 22·97 (21·5%)            | <0·0001 |
| **Hypertension**         | 21·948 (25·7%)       | 38·62 (36·1%)            | <0·0001 |
| **Hyperlipidaemia**      | 26·480 (31·0%)       | 37·28 (34·8%)            | <0·0001 |
| **COPD**                 | 26·02 (3·1%)         | 57·48 (5·4%)             | <0·0001 |
| **Current smoker**       | 79·72 (9·3%)         | 15·16 (14·2%)            | <0·0001 |
| **Former smoker**        | 14·685 (17·2%)       | 18·72 (17·5%)            | 0·45    |
| **Immunocompromised**    | 24·06 (2·8%)         | 46·42 (4·3%)             | <0·0001 |
| **Medications**          |                      |                          |         |
| **ACE inhibitor**        | 7·521 (8·8%)        | 42·40 (4·0%)             | <0·0001 |
| **Statin**               | 85·06 (10·0%)        | 73·9 (6·9%)              | <0·0001 |
| **Angiotensin receptor blocker** | 5·190 (6·1%) | 65·96 (6·2%)             | 0·75    |
| **Antiviral**            | 35·189 (42·1%)       | 37·38 (34·9%)            | <0·0001 |
| **Disease severity**     |                      |                          |         |
| **qSOFA <1**             | 71·457 (83·7%)       | 79·11 (73·9%)            | <0·0001 |
| **SPO₂ <94%**            | 71·88 (8·4%)         | 21·29 (19·9%)            | <0·0001 |
| **Treatment group**      |                      |                          |         |
| **Chloroquine alone**    | 15·61 (1·8%)         | 30·72 (2·9%)             | <0·0001 |
| **Chloroquine with macrolide*** | 29·444 (3·4%) | 83·982 (8·7%)             |         |
| **Hydroxychloroquine alone** | 24·732 (2·9%)       | 54·32 (5·1%)             |         |
| **Hydroxychloroquine with macrolide*  ** | 4·747 (5·6%)  | 14·79 (13·8%)            | <0·0001 |
| **Outcomes**             |                      |                          |         |
| **De-novo ventricular arrhythmia** | 83·9 (1·0%)  | 400 (3·3%)               | <0·0001 |
| **Non-ICU length of stay, days** | 9·0 (6·2)   | 9·8 (7·4)                | <0·0001 |
| **ICU length of stay, days** | 2·1 (3·7)    | 9·0 (10·6)               | <0·0001 |
| **Total length of stay, days** | 11·1 (7·3)  | 19·2 (14·4)              | <0·0001 |
| **Mechanical ventilation** | 48·215 (5·6%) | 453·3 (42·4%)            | <0·0001 |

Data are mean (SD) or n (%); BMI=body mass index; COPD=chronic obstructive pulmonary disease; ACE=angiotensin-converting enzyme; qSOFA=quick sepsis-related organ failure assessment; SPO₂=oxygen saturation; ICU=intensive care unit. *Macrolides include only azithromycin or clarithromycin.
continuous variables and all other data were treated as categorical variables in the model. From the model, hazard ratios (HRs) with 95% CIs were estimated for included variables to determine their effect on the risk of in-hospital mortality (primary endpoint) or subsequent mechanical ventilation or death (composite endpoint). Independence of survival times (or time to first arrhythmia for the ventricular arrhythmia analysis) was confirmed. Proportionality between the predictors and the hazard was validated through an evaluation of Schoenfeld residuals, which found \( p > 0.05 \) and thus confirmed proportionality.

To minimise the effect of confounding factors, a propensity score matching analysis was done individually for each of the four treatment groups compared with a control group that received no form of that therapy. For each treatment group, a separate matched control was identified using exact and propensity-score matched criteria with a calliper of 0.001. This method was used to provide a close approximation of demographics, comorbidities, disease severity, and baseline medications between patients. The propensity score was based on the following variables: age, BMI, gender, race or ethnicity, comorbidities, use of ACE inhibitors, use of statins, use of angiotensin receptor blockers, treatment with other antivirals, qSOFA score of less than 1, and SPO2 of less than 94% on room air. The patients were well matched, with standardised mean difference estimates of less than 10% for all matched parameters. Additional analyses were done to examine the robustness of the estimates initially obtained. Individual

| Control group (n=81144) | Chloroquine (n=1868) | Chloroquine with macrolide* (n=3783) | Hydroxychloroquine (n=3016) | Hydroxychloroquine with macrolide* (n=6221) |
|-------------------------|----------------------|--------------------------------------|-----------------------------|--------------------------------------------|
| Age, years 53±17 (6-7) 55±18 (6-9) 54±17 (7-7) 55±17 (7-9) 55±2 (7-7) | | | | |
| BMI, kg/m² 27±5 (4-8) 27±8 (4-7) 28±5 (4-7) 28±5 (4-7) 28±5 (4-5) | | | | |
| Sex                       | | | | |
| Female                   | 37±31 (46±5) 84±5 (45±2) 17±18 (45±4) 13±88 (46±0) 37±9 (44±3) | | | |
| Male                     | 43±42 (53±5) 102±5 (43±8) 20±65 (54±0) 16±28 (54±0) 34±62 (55±7) | | | |
| Race or ethnicity         | | | | |
| White                    | 54±40 (67±1) 120±1 (64±2) 24±18 (63±9) 20±74 (68±8) 4±12 (66±3) | | | |
| Black                    | 7±51 (9±3) 20±3 (10±9) 3±69 (9±8) 2±87 (9±5) 6±76 (9±9) | | | |
| Hispanic                 | 4±43 (6±1) 10±5 (5±8) 2±73 (7±2) 1±94 (6±4) 4±60 (7±4) | | | |
| Asian                    | 1±10 (4±2) 3±0 (16±1) 6±03 (15±9) 3±66 (12±1) 7±45 (12±0) | | | |
| Native American          | 9±2 (1±1) 1±9 (1±0) 3±7 (1±0) 3±3 (1±1) 6±8 (1±1) | | | |
| Other                    | 1±85 (2±3) 3±6 (1±9) 8±3 (2±2) 6±2 (2±1) 1±48 (2±4) | | | |
| Comorbidities            | | | | |
| Coronary artery disease  | 10±07 (12±4) 2±84 (15±2) 5±15 (13±6) 4±21 (14±0) 8±41 (13±5) | | | |
| Congestive heart failure | 19±49 (2±4) 5±0 (2±7) 1±03 (2±7) 7±28 (2±6) 1±88 (3±0) | | | |
| Arrhythmia               | 2±86 (3±5) 6±3 (3±4) 1±26 (3±3) 1±08 (3±6) 2±23 (3±6) | | | |
| Diabetes                 | 11±05 (13±6) 2±58 (13±8) 5±84 (15±4) 4±47 (14±8) 9±13 (14±7) | | | |
| Hypertension             | 2±14 (2±6) 5±0 (3±0) 1±09 (5±8) 8±91 (29±5) 1±82 (29±4) | | | |
| Hyperlipidaemia          | 2±53 (3±5) 6±07 (3±5) 1±16 (3±0) 9±41 (31±2) 1±94 (31±3) | | | |
| COPD                     | 2±64 (3±3) 5±5 (2±9) 1±44 (3±8) 1±11 (3±7) 2±20 (3±5) | | | |
| Current smoker           | 7±88 (9±7) 1±90 (10±2) 4±28 (11±3) 3±42 (11±3) 6±44 (10±4) | | | |
| Former smoker            | 1±4 (9±7) 3±21 (17±2) 6±48 (17±1) 5±09 (16±9) 1±026 (16±5) | | | |
| Immunocompromised        | 2±41 (6±0) 5±3 (2±8) 1±22 (3±2) 9±0 (3±0) 1±87 (3±0) | | | |
| Baseline disease severity| | | | |
| qSOFA <1                | 6±31 (83±0) 1±53 (81±9) 3±051 (80±7) 2±477 (82±1) 4±994 (80±3) | | | |
| SPO2 ≤94%              | 7±72 (9±5) 2±09 (11±2) 4±23 (10±9) 3±23 (10±7) 6±51 (10±5) | | | |
| Outcomes                | | | | |
| De-novo ventricular arrhythmia | 22±6 (0±3) 8±1 (4±3) 2±46 (6±5) 1±84 (6±1) 5±02 (8±1) | | | |
| Non-ICU length of stay, days | 9±1 (6±4) 8±1 (6±2) 9±0 (6±6) 8±9 (6±2) 9±1 (6±7) | | | |
| ICU length of stay, days | 2±6 (5±0) 4±3 (6±8) 4±9 (8±1) 4±3 (6±8) 4±7 (7±8) | | | |
| Total length of stay, days | 1±17 (8±4) 1±3 (9±1) 1±3 (11±0) 1±3 (9±3) 1±3 (10±7) | | | |
| Mechanical ventilation   | 6±27 (7±7) 4±0 (21±6) 8±14 (21±5) 6±16 (20±4) 1±243 (20±0) | | | |
| Mortality               | 7±50 (9±3) 3±07 (14±6) 8±39 (22±2) 5±43 (18±0) 1±479 (23±8) | | | |
| Ventilator or mortality  | 1±07 (12±3) 5±31 (28±4) 1±288 (34±0) 8±77 (29±1) 1±210 (34±1) | | | |

TABLE 2: Patient demographics and characteristics by treatment group

Data are mean (SD) or n (%). BMI = body mass index. COPD=chronic obstructive pulmonary disease. qSOFA=quick sepsis-related organ failure assessment. SPO2=oxygen saturation. ICU=intensive care unit. *Macrolides include only clarithromycin and azithromycin.
analyses by continent of origin and sex-adjusted analyses using Cox proportional hazards models were performed. A tipping-point analysis (an analysis that shows the effect size and prevalence of an unmeasured confounder that could shift the upper boundary of the CI towards null) was also done. All statistical analyses were done with R version 3.6.3 and SPSS version 26.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author and co-author ANP had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
96032 hospitalised patients from 671 hospitals were diagnosed with COVID-19 between Dec 20, 2019, and April 14, 2020 and met the inclusion criteria for this study (figure I). All included patients completed their hospital course (discharged or died) by April 21, 2020. Patients who were hospitalised during the study period without a completed course were unable to be analysed. The study cohort included 63,315 (65.9%) patients from North America, 16,574 (17.3%) from Europe, 7,553 (7.9%) from Asia, 4,402 (4.6%) from Africa, 3,577 (3.7%) from South America, and 609 (0.6%) from Australia (details of the number of hospitals per continent are presented in the appendix, p 3). The mean age was 53.8 years (SD 17.6), 44,426 (46.3%) were women, mean BMI was 27.6 kg/m² (SD 5.5; 29.510 [30.7%] were obese with BMI ≥30 kg/m²), 64,220 (66.9%) were white, 9054 (9.4%) were black, 5978 (6.2%) were Hispanic, and 13,519 (14.1%) were of Asian origin (appendix p 4). In terms of comorbidities, 30,198 (31.4%) had hyperlipidaemia, 25,810 (26.9%) had hypertension, 13,260 (13.8%) had diabetes, 3773 (3.8%) had COPD, 2868 (3.0%) had an underlying immunosuppressed condition, 16,557 (17.2%) were former smokers, and 9488 (9.9%) were current smokers. In terms of pre-existing cardiovascular disease, 12,317 (12.6%) had coronary artery disease, 2368 (2.5%) had a history of congestive heart failure, and 3381 (3.5%) had a history of arrhythmia. The mean length of stay in hospital was 9.1 days (SD 6.4), with an overall in-hospital mortality of 10,698 (11.1%) of 96,032. The use of other antivirals was recorded in 38,927 (40.5%) patients as treatment for COVID-19. The most common antivirals were lopinavir with ritonavir (12,304 [31.6%]), ribavirin (7904 [20.3%]), and oseltamivir (5101 [13.1%]). Combination therapy with more than one of these antiviral regimens was used for 6782 (17.4%) patients.

The treatment groups included 1868 patients who were given chloroquine alone, 3016 given hydroxychloroquine alone, 3783 given chloroquine with a macrolide and 6221 given hydroxychloroquine and a macrolide. The median time from hospitalisation to diagnosis of COVID-19 was 2 days (IQR 1–4). The mean daily dose and duration of the various drug regimens were as follows: chloroquine alone, 765 mg (SD 308) and 6.6–6.6 days (2–4); hydroxychloroquine alone, 596 mg (126) and 4.2 days (1–9); chloroquine with a macrolide, 790 mg (320) and 6.8 days (2–5); and hydroxychloroquine with a macrolide, 597 mg (128) and 4.3 days (2–6). Additional details of the study cohort are provided in the appendix (pp 4–5).

Demographic variables and comorbidities were compared among survivors and non-survivors (table I). Non-survivors were older, more likely to be obese, more likely to be men, more likely to be black or Hispanic, and to have diabetes, hyperlipidaemia, coronary artery disease, congestive heart failure, and a history of arrhythmias. Non-survivors were also more likely to have COPD and to have reported current smoking.

The distribution of demographics, comorbidities, and outcomes between the four treatment groups are shown in table 2. No significant between-group differences were found among baseline characteristics or comorbidities. Ventricular arrhythmias were more common in the
treatment groups compared with the control population. Mortality was higher in the treatment groups compared with the control population (p<0·0001; appendix pp 15–18).

Independent predictors of in-hospital mortality are shown in figure 2. Age, BMI, black race or Hispanic ethnicity (versus white race), coronary artery disease, congestive heart failure, history of arrhythmia, diabetes, hypertension, hyperlipidaemia, COPD, being a current smoker, and immunosuppressed condition were associated with a higher risk of in-hospital death. Female sex, ethnicity of Asian origin, use of ACE inhibitors (but not angiotensin receptor blockers), and use of statins was associated with reduced in-hospital mortality risk. Compared with the control group (9·3%), hydroxychloroquine alone (18·0%; HR 1·335, 95% CI 1·223–1·457), hydroxychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine alone (16·4%; 1·365, 1·218–1·531), and chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were independently associated with an increased risk of in-hospital mortality. The multivariable Cox regression analyses by continent are shown in the appendix (pp 6–11), as well as data from the sex-adjusted multivariable logistic regression analyses (pp 12–13) and a separate Cox regression analysis for the combined endpoint of mechanical ventilation or mortality (p 14).

Independent predictors of ventricular arrhythmia are shown in figure 3. Coronary artery disease, congestive heart failure, history of cardiac arrhythmia, and COPD were independently associated with an increased risk of de-novo ventricular arrhythmias during hospitalisation. Compared with the control group (0·3%), hydroxychloroquine alone (6·1%; HR 2·369, 95% CI 2·001–2·800), hydroxychloroquine with a macrolide (2·900, 95% CI 1·223–1·531), hydroxychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine alone (16·4%; 1·365, 1·218–1·531), and chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were independently associated with an increased risk of in-hospital mortality. The multivariable Cox regression analyses by continent are shown in the appendix (pp 6–11), as well as data from the sex-adjusted multivariable logistic regression analyses (pp 12–13) and a separate Cox regression analysis for the combined endpoint of mechanical ventilation or mortality (p 14).

Analyses using propensity score matching by treatment group are shown in the appendix (pp 15–18). The results indicated that the associations between the drug regimens and mortality, need for mechanical ventilation, length of stay, and the occurrence of de-novo ventricular arrhythmias were consistent with the primary analysis.

A tipping point analysis was done to assess the effects of an unmeasured confounder on the findings of significance with hydroxychloroquine or chloroquine (appendix pp 19–20). For chloroquine, hydroxychloroquine, and chloroquine with a macrolide, a hypothetical unobserved binary confounder with a prevalence of 50% in the exposed population would need to have an HR of 2·0 to tip this analysis to non-significance at the 5% level. Again, congestive heart failure (which has an HR of 1·756) would need to have a prevalence of approximately 50% in the population to lead to confounding in the analysis.

Similarly, for hydroxychloroquine with a macrolide, a hypothetical unobserved binary confounder with a prevalence of 37% in the exposed population would need to have an HR of 1·5 to tip this analysis to non-significance at the 5% level. Again, congestive heart failure (which has an HR of 1·756) would need to have a prevalence of approximately 50% in the population to lead to confounding in the analysis, had it not been used to infer definitive effects. ACE=angiotensin-converting enzyme. BMI=body mass index. COPD=chronic obstructive pulmonary disease. HR=hazard ratio. qSOFA=quick sepsis-related organ failure assessment. SPO2=oxygen saturation.

Discussion

In this large multinational real-world analysis, we did not observe any benefit of hydroxychloroquine or chloroquine (when used alone or in combination with a macrolide) on in-hospital outcomes, when initiated early after diagnosis of COVID-19. Each of the drug regimens of chloroquine or hydroxychloroquine alone or in combination with a macrolide was associated with an increased hazard for clinically significant occurrence of ventricular arrhythmias and increased risk of in-hospital death with COVID-19.

The use of hydroxychloroquine or chloroquine in COVID-19 is based on widespread publicity of small,
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However, these drugs prolong the QT interval and outcomes with COVID-19. Pathological studies have represented a vulnerable population that experience worse prognosis, independent of the use of cardiotoxic drug combination, consistent with our previous findings in a study population could partially explain the observed risk of increased cardiovascular toxicity with the use of chloroquine or hydroxychloroquine, especially when used in combination with macrolides. In this investigation, consistent with our previous findings in a smaller cohort of 8910 patients, we found that women and patients being treated with ACE inhibitors (but not angiotensin receptor blockers) or statins had lower mortality with COVID-19. These findings imply that drugs that stabilise cardiovascular function and improve endothelial cell dysfunction might improve prognosis, independent of the use of cardiotoxic drug combinations.

Our study has several limitations. The association of decreased survival with hydroxychloroquine or chloroquine treatment regimens should be interpreted cautiously. Due to the observational study design, we cannot exclude the possibility of unmeasured confounding factors, although we have reassuringly noted consistency between the primary analysis and the propensity score matched analyses. Nevertheless, a cause-and-effect relationship between drug therapy and survival should not be inferred. These data do not apply uncontrolled studies, which suggested that the combination of hydroxychloroquine with the macrolide azithromycin was successful in clearing viral replication. On March 28, 2020, the FDA issued an emergency use authorisation for these drugs in patients if clinical trial access was unavailable. Other countries, such as China, have issued guidelines allowing for the use of chloroquine in COVID-19. Several countries have been stockpiling the drugs, and shortages of them for approved indications, such as for autoimmune disease and rheumatoid arthritis, have been encountered. A retrospective observational review of 368 men with COVID-19 treated at the US Veterans Affairs hospitals raised concerns that the use of hydroxychloroquine was associated with a greater hazard of death; however, the baseline characteristics among the groups analysed were dissimilar and the possibility of bias cannot be ruled out. Another observational study in 181 patients from France reported that the use of hydroxychloroquine at a dose of 600 mg per day was not associated with a measurable clinical benefit in patients with COVID-19 pneumonia. Our large-scale, international, real-world analysis supports the absence of a clinical benefit of chloroquine and hydroxychloroquine and points to potential harm in hospitalised patients with COVID-19.

Chloroquine and hydroxychloroquine are associated with concerns of cardiovascular toxicity, particularly because of their known relationship with electrical instability, characterised by QT interval prolongation (the time taken for ventricular depolarisation and repolarisation). This mechanism relates to blockade of the hERG potassium channel, which lengthens ventricular repolarisation and the duration of ventricular action potentials. Under specific conditions, early after-depolarisations can trigger ventricular arrhythmias. Such propensity for arrhythmia provocation is more often seen in individuals with structural cardiovascular disease, and cardiac injury has been reported to occur with high frequency during COVID-19 illness. Furthermore, individuals with cardiovascular disease represent a vulnerable population that experience worse outcomes with COVID-19. Pathological studies have pointed to derangements in the vascular endothelium and a diffuse endothelitis noted across multiple organs in COVID-19. Whether patients with underlying cardiovascular disease and those that experience de-novo cardiovascular injury have a greater predilection to ventricular arrhythmias with chloroquine or its analogues remains uncertain but plausible. COVID-19 is exemplified by initial viral replication followed by enhanced systemic inflammation. The use of chloroquine or hydroxychloroquine in combination with a macrolide is designed to use their antimicrobial properties in a synergistic manner. Macrolides, such as azithromycin and clarithromycin, are antibiotics with immunomodulatory and anti-inflammatory effects. However, these drugs prolong the QT interval and increase the risk of sudden cardiac death.

In a preliminary analysis, Borba and colleagues reported a double-blind, randomised trial with 81 adult patients who were hospitalised with severe COVID-19 at a tertiary care facility in Brazil. This study suggested that a higher dose of chloroquine represented a safety hazard, especially when taken concurrently with azithromycin and oseltamivir. In another cohort study of 90 patients with COVID-19 pneumonia, Mercuro and colleagues found that the concomitant use of a macrolide was associated with a greater change in the corrected QT interval. Our study did not examine the QT interval but instead directly analysed the risk of clinically significant ventricular arrhythmias. We showed an independent association of the use of either hydroxychloroquine or chloroquine with the occurrence of de-novo ventricular arrhythmias. We also note that the hazard of de-novo ventricular arrhythmias increased when the drugs were used in combination with a macrolide.

In our analysis, which was dominated by patients from North America, we noted that higher BMI emerged as a risk marker for worse in-hospital survival. Obesity is a known risk factor for cardiac arrhythmias and sudden cardiac death. The most commonly reported arrhythmias are atrial fibrillation and ventricular tachycardia. Although age, race, and BMI were predictive of an increased risk for death with COVID-19 in our analysis, they were not found to be associated with an increased risk of ventricular arrhythmias on our multivariable regression analysis. The only variables found to be independently predictive of ventricular arrhythmias were the four treatment regimens, along with underlying cardiovascular disease and COPD. Thus, the presence of cardiovascular comorbidity in the study population could partially explain the observed risk of increased cardiovascular toxicity with the use of chloroquine or hydroxychloroquine, especially when used in combination with macrolides. In this investigation, consistent with our previous findings in a smaller cohort of 8910 patients, we found that women and patients being treated with ACE inhibitors (but not angiotensin receptor blockers) or statins had lower mortality with COVID-19. These findings imply that drugs that stabilise cardiovascular function and improve endothelial cell dysfunction might improve prognosis, independent of the use of cardiotoxic drug combinations.
to the use of any treatment regimen used in the ambulatory, out-of-hospital setting. Randomised clinical trials will be required before any conclusion can be reached regarding benefit or harm of these agents in COVID-19 patients. We also note that although we evaluated the relationship of the drug treatment regimens with the occurrence of ventricular arrhythmias, we did not measure QT intervals, nor did we stratify the arrhythmia pattern (such as torsade de points). We also did not establish if the association of increased risk of in-hospital death with use of the drug regimens is linked directly to their cardiovascular risk, nor did we conduct a drug dose-response analysis of the observed risks. Even if these limitations suggest a conservative interpretation of the findings, we believe that the absence of any observed benefit could still represent a reasonable explanation.

In summary, this multinational, observational, real-world study of patients with COVID-19 requiring hospitalisation found that the use of a regimen containing hydroxychloroquine or chloroquine (with or without a macrolide) was associated with no evidence of benefit, instead was associated with an increase in the risk of ventricular arrhythmias and a greater hazard for in-hospital death with COVID-19. These findings suggest that these drug regimens should not be used outside of clinical trials and urgent confirmation from randomised clinical trials is needed.

Contributors
The study was conceived and designed by MRM and ANP. Acquisition of data and statistical analysis of the data were supervised and performed by SSD. MRM drafted the manuscript and all authors participated in critical revision of the manuscript for important intellectual content. MRM and ANP supervised the study. All authors approved the final manuscript and were responsible for the decision to submit for publication.

Declaration of interests
MRM reports personal fees from Abbott, Medtronic, Janssen, Mesoblast, Portola, Bayer, Baim Institute for Clinical Research, NupulseCV, FineHeart, Levitexus, Roivant, and Triple Gene. SSD is the founder of Surgisphere Corporation. FR has been paid for time spent as a committee member for clinical trials, advisory boards, other forms of consulting, and lectures or presentations; these payments were made directly to the University of Zurich and no personal payments were received in relation to these trials or other activities. ANP declares no competing interests.

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