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

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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 (18·0%; hazard ratio 1·335, 95% CI 1·223–1·457), hydroxychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine (16·4%; 1·365, 1·218–1·531), and chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were each independently associated with an increased risk of in-hospital mortality. Compared with the control group (0·3%), hydroxychloroquine (6·1%; 2·369, 1·935–2·900), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·983), chloroquine (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 de-novo ventricular arrhythmia during hospitalisation.

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.[1,2] These drugs have been shown in laboratory conditions to have antiviral properties as well as immunomodulatory effects.[3,4] 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.[5,6] The combination of hydroxychloroquine with a second-generation macrolide, such as azithromycin (or clarithromycin), has also been advocated,

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 arrythmia 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.

despite limited evidence for its effectiveness.[7] Previous studies have shown that treatment with chloroquine, hydroxychloroquine, or either drug combined with a macrolide can have the cardiovascular adverse effect of prolongation of the QT interval, which could be a mechanism that predisposes to ventricular arrhythmias.[8,9]

Although several multicentre randomised controlled trials are underway, there is a pressing need to provide accurate clinical guidance because the use of chloroquine or hydroxychloroquine along with macrolides is widespread, often with little regard for potential risk. Some countries have stockpiled these drugs, resulting in a shortage of these medications for those that need them for approved clinical indications.[10] The purpose of this study was to evaluate the use of chloroquine or hydroxychloroquine alone or in combination with a macrolide for treatment of COVID-19 using a large multinational registry to assess their real-world application. Principally, we sought to analyse the association between these treatment regimens and in-hospital death. Secondarily, we aimed to evaluate the occurrence of de-novo clinically significant ventricular arrhythmias.

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

See **Online** for appendix

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 health-care 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. COVID-19 was diagnosed, at each site, on the basis of WHO guidance.[11] Patients who did not have a record of testing in the database, or who had a negative test, were not included in the study. Only one positive test was necessary for the patient to be included in the analysis. Patients who received either hydroxychloroquine or a chloroquine analogue-based treatment (with or with-out a second-generation macrolide) were included in the treatment group. Patients who received treatment with these regimens starting more than 48 h after COVID-19 diagnosis were excluded. We also excluded

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.

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
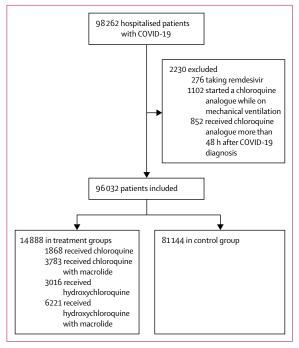

Figure 1: Study profile

	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 (5·1)	31·8 (6·4)	<0·0001
Obese, BMI >30 kg/m²	22 992 (26·9%)	6518 (60·9%)	<0·0001
Sex			
Female	40 169 (47·1%)	4257 (39·8%)	<0·0001
Male	45 165 (52·9%)	6441 (60·2%)	<0·0001
Race or ethnicity			
White	57 503 (67·4%)	6717 (62·8%)	<0·0001
Black	7219 (8·5%)	1835 (17·2%)	<0·0001
Hispanic	4948 (5·8%)	1030 (9·6%)	<0·0001
Asian	12 657 (14·8%)	862 (8·1%)	<0·0001
Native American	1023 (1·2%)	56 (0·5%)	<0·0001
Other	1984 (2·3%)	198 (1·9%)	0·0019
Comorbidities at baseline			
Coronary artery disease	9777 (11·5%)	2360 (22·1%)	<0·0001
Congestive heart failure	1828 (2·1%)	540 (5·0%)	<0·0001
Arrhythmia	2700 (3·2%)	681 (6·4%)	<0·0001
Diabetes	10 963 (12·8%)	2297 (21·5%)	<0·0001
Hypertension	21 948 (25·7%)	3862 (36·1%)	<0·0001
Hyperlipidaemia	26 480 (31·0%)	3718 (34·8%)	<0·0001
COPD	2603 (3·1%)	574 (5·4%)	<0·0001
Current smoker	7972 (9·3%)	1516 (14·2%)	<0·0001
Former smoker	14 681 (17·2%)	1872 (17·5%)	0·45
Immunocompromised	2406 (2·8%)	462 (4·3%)	<0·0001
Medications			
ACE inhibitor	7521 (8·8%)	428 (4·0%)	<0·0001
Statin	8506 (10·0%)	739 (6·9%)	<0·0001
Angiotensin receptor blocker	5190 (6·1%)	659 (6·2%)	0·75
Antiviral	35 189 (41·2%)	3738 (34·9%)	<0·0001
Disease severity			
qSOFA <1	71 457 (83·7%)	7911 (73·9%)	<0·0001
SPO₂ <94%	7188 (8·4%)	2129 (19·9%)	<0·0001
Treatment group			
Chloroquine alone	1561 (1·8%)	307 (2·9%)	<0·0001
Chloroquine with macrolide*	2944 (3·4%)	839 (7·8%)	<0·0001
Hydroxychloroquine alone	2473 (2·9%)	543 (5·1%)	<0·0001
Hydroxychloroquine with macrolide*	4742 (5·6%)	1479 (13·8%)	<0·0001
Outcomes			
De-novo ventricular arrhythmia	839 (1·0%)	400 (3·7%)	<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)	9·4 (10·6)	<0·0001
Total length of stay, days	11·1 (7·3)	19·2 (14·4)	<0·0001
Mechanical ventilation	4821 (5·6%)	4533 (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.

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

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

medications (angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers, and statins) or use of antiviral therapy other than the drug regimens being evaluated. The initiation of hydroxychloroquine or chloroquine during hospital admission was recorded,

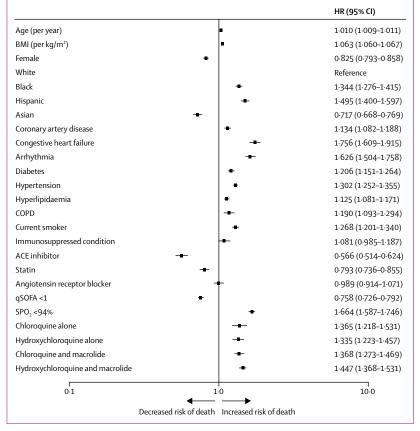|	Control group (n=81144)	Chloroquine (n=1868)	Chloroquine with macrolide* (n=3783)	Hydroxychloroquine (n=3016)	Hydroxychloroquine with macrolide* (n=6221)
Age, years	53·6 (17·6)	55·1 (18·0)	54·9 (17·7)	55·1 (17·9)	55·2 (17·7)
BMI, kg/m²	27·4 (5·4)	27·8 (6·1)	28·2 (5·8)	28·4 (5·9)	28·5 (5·9)
Sex					
Female	37716 (46·5%)	845 (45·2%)	1718 (45·4%)	1388 (46·0%)	2759 (44·3%)
Male	43428 (53·5%)	1023 (54·8%)	2065 (54·6%)	1628 (54·0%)	3462 (55·7%)
Race or ethnicity					
White	54403 (67·1%)	1201 (64·3%)	2418 (63·9%)	2074 (68·8%)	4124 (66·3%)
Black	7519 (9·3%)	203 (10·9%)	369 (9·8%)	287 (9·5%)	676 (10·9%)
Hispanic	4943 (6·1%)	108 (5·8%)	273 (7·2%)	194 (6·4%)	460 (7·4%)
Asian	11504 (14·2%)	301 (16·1%)	603 (15·9%)	366 (12·1%)	745 (12·0%)
Native American	922 (1·1%)	19 (1·0%)	37 (1·0%)	33 (1·1%)	68 (1·1%)
Other	1853 (2·3%)	36 (1·9%)	83 (2·2%)	62 (2·1%)	148 (2·4%)
Comorbidities					
Coronary artery disease	10076 (12·4%)	284 (15·2%)	515 (13·6%)	421 (14·0%)	841 (13·5%)
Congestive heart failure	1949 (2·4%)	50 (2·7%)	103 (2·7%)	78 (2·6%)	188 (3·0%)
Arrhythmia	2861 (3·5%)	63 (3·4%)	126 (3·3%)	108 (3·6%)	223 (3·6%)
Diabetes	11058 (13·6%)	258 (13·8%)	584 (15·4%)	447 (14·8%)	913 (14·7%)
Hypertension	21437 (26·4%)	560 (30·0%)	1095 (28·9%)	891 (29·5%)	1827 (29·4%)
Hyperlipidaemia	25538 (31·5%)	607 (32·5%)	1164 (30·8%)	941 (31·2%)	1948 (31·3%)
COPD	2647 (3·3%)	55 (2·9%)	144 (3·8%)	111 (3·7%)	220 (3·5%)
Current smoker	7884 (9·7%)	190 (10·2%)	428 (11·3%)	342 (11·3%)	644 (10·4%)
Former smoker	14049 (17·3%)	321 (17·2%)	648 (17·1%)	509 (16·9%)	1026 (16·5%)
Immunocompromised	2416 (3·0%)	53 (2·8%)	122 (3·2%)	90 (3·0%)	187 (3·0%)
Baseline disease severity					
qSOFA <1	67316 (83·0%)	1530 (81·9%)	3051 (80·7%)	2477 (82·1%)	4994 (80·3%)
SPO₂ <94%	7721 (9·5%)	209 (11·2%)	413 (10·9%)	323 (10·7%)	651 (10·5%)
Outcomes					
De-novo ventricular arrhythmia	226 (0·3%)	81 (4·3%)	246 (6·5%)	184 (6·1%)	502 (8·1%)
Non-ICU length of stay, days	9·1 (6·4)	8·8 (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	11·7 (8·4)	13·2 (9·1)	13·8 (11·0)	13·2 (9·3)	13·8 (10·7)
Mechanical ventilation	6278 (7·7%)	403 (21·6%)	814 (21·5%)	616 (20·4%)	1243 (20·0%)
Mortality	7530 (9·3%)	307 (16·4%)	839 (22·2%)	543 (18·0%)	1479 (23·8%)
Ventilator or mortality	10703 (13·2%)	531 (28·4%)	1288 (34·0%)	877 (29·1%)	2120 (34·1%)

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.

Table 2: **Patient demographics and characteristics by treatment group**

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

	HR (95% CI)
Age (per year)	1·010 (1·009–1·011)
BMI (per kg/m²)	1·063 (1·060–1·067)
Female	0·825 (0·793–0·858)
White	Reference
Black	1·344 (1·276–1·415)
Hispanic	1·495 (1·400–1·597)
Asian	0·717 (0·668–0·769)
Coronary artery disease	1·134 (1·082–1·188)
Congestive heart failure	1·756 (1·609–1·915)
Arrhythmia	1·626 (1·504–1·758)
Diabetes	1·206 (1·151–1·264)
Hypertension	1·302 (1·252–1·355)
Hyperlipidaemia	1·125 (1·081–1·171)
COPD	1·190 (1·093–1·294)
Current smoker	1·268 (1·201–1·340)
Immunosuppressed condition	1·081 (0·985–1·187)
ACE inhibitor	0·566 (0·514–0·624)
Statin	0·793 (0·736–0·855)
Angiotensin receptor blocker	0·989 (0·914–1·071)
qSOFA <1	0·758 (0·726–0·792)
SPO₂ <94%	1·664 (1·587–1·746)
Chloroquine alone	1·365 (1·218–1·531)
Hydroxychloroquine alone	1·335 (1·223–1·457)
Chloroquine and macrolide	1·368 (1·273–1·469)
Hydroxychloroquine and macrolide	1·447 (1·368–1·531)

0·1   1·0   10·0

← Decreased risk of death   Increased risk of death →

Figure 2: **Independent predictors of in-hospital mortality**
Age and BMI are continuous variables. The 95% CIs have not been adjusted for multiple testing and should not be 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.

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, 7555 (7·9%) from Asia, 4402 (4·6%) from Africa, 3577 (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, 3177 (3·3%) had COPD, 2868 (3·0%) had an underlying immunosuppressed condition, 16 553 (17·2%) were former smokers, and 9488 (9·9%) were current smokers. In terms of pre-existing cardiovascular disease, 12 137 (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 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 (2·0). 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 1). 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

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
96 032 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 1). All included patients completed their hospital course (discharged or died) by April 21, 2020. Patients

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 arrythmia 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 1·935–2·900), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·983), chloroquine alone (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 de-novo ventricular arrhythmia during hospitalisation.

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 1·5 to tip this analysis to non-significance at the 5% level. For a comparison with the observed confounders in this study, if congestive heart failure (which has an HR of 1·756) were left out of the model, it would need to have a prevalence of approximately 30% in the population to lead to confounding in the analysis.
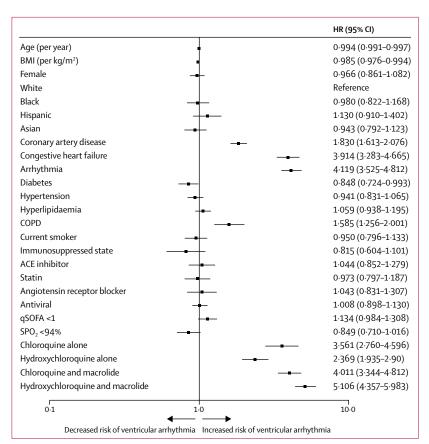

	HR (95% CI)
Age (per year)	0·994 (0·991–0·997)
BMI (per kg/m²)	0·985 (0·976–0·994)
Female	0·966 (0·861–1·082)
White	Reference
Black	0·980 (0·822–1·168)
Hispanic	1·130 (0·910–1·402)
Asian	0·943 (0·792–1·123)
Coronary artery disease	1·830 (1·613–2·076)
Congestive heart failure	3·914 (3·283–4·665)
Arrhythmia	4·119 (3·525–4·812)
Diabetes	0·848 (0·724–0·993)
Hypertension	0·941 (0·831–1·065)
Hyperlipidaemia	1·059 (0·938–1·195)
COPD	1·585 (1·256–2·001)
Current smoker	0·950 (0·796–1·133)
Immunosuppressed state	0·815 (0·604–1·101)
ACE inhibitor	1·044 (0·852–1·279)
Statin	0·973 (0·797–1·187)
Angiotensin receptor blocker	1·043 (0·831–1·307)
Antiviral	1·008 (0·898–1·130)
qSOFA <1	1·134 (0·984–1·308)
SPO₂ <94%	0·849 (0·710–1·016)
Chloroquine alone	3·561 (2·760–4·596)
Hydroxychloroquine alone	2·369 (1·935–2·90)
Chloroquine and macrolide	4·011 (3·344–4·812)
Hydroxychloroquine and macrolide	5·106 (4·357–5·983)

Decreased risk of ventricular arrhythmia ← → Increased risk of ventricular arrhythmia

***Figure 3:* Independent predictors of ventricular arrhythmias during hospitalisation**
Age and BMI are continuous variables. The 95% CIs have not been adjusted for multiple testing and should not be 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.

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 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, had it not been adjusted for in the Cox proportional hazards model.

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,

uncontrolled studies, which suggested that the combination of hydroxychloroquine with the macrolide azithromycin was successful in clearing viral replication.[7] On March 28, 2020, the FDA issued an emergency use authorisation for these drugs in patients if clinical trial access was unavailable.[12] Other countries, such as China, have issued guidelines allowing for the use of chloroquine in COVID-19.[13] Several countries have been stock-piling the drugs, and shortages of them for approved indications, such as for autoimmune disease and rheumatoid arthritis, have been encountered.[10] 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.[14] 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.[15] 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,[16] which lengthens ventricular repolarisation and the duration of ventricular action potentials. Under specific conditions, early after-depolarisations can trigger ventricular arrhythmias.[9] 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.[17,18] Furthermore, individuals with cardiovascular disease represent a vulnerable population that experience worse outcomes with COVID-19.[19,20] Pathological studies have pointed to derangements in the vascular endothelium and a diffuse endotheliitis noted across multiple organs in COVID-19.[21] 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.[22] The use of chloroquine or hydroxychloroquine in combination with a macrolide is designed to use their antimicrobial properties in a synergistic manner.[23] Macrolides, such as azithromycin and clarithromycin, are antibiotics with immunomodulatory and anti-inflammatory effects.[24] However, these drugs prolong the QT interval and increase the risk of sudden cardiac death.[8,9] In a preliminary analysis, Borba and colleagues[25] 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[26] 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 arrythmias. 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.[27,28] 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,[20] 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.[21]

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

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 pointes). 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, but 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.

References
1 Principi N, Esposito S. Chloroquine or hydroxychloroquine for prophylaxis of COVID-19. *Lancet Infect Dis* 2020; published online April 17. https://doi.org/10.1016/S1473-3099(20)30296-6.
2 Perricone C, Triggianese P, Bartoloni E, et al. The anti-viral facet of anti-rheumatic drugs: lessons from COVID-19. *J Autoimmun* 2020; published online April 17. DOI:10.1016/j.jaut.2020.102468.
3 Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov* 2020; 6: 16.
4 Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents* 2020; published online March 12. DOI:10.1016/j.ijantimicag.2020.105938.
5 Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients mainly with mild to moderate COVID-19: an open-label, randomized, controlled trial. *medRxiv* 2020; published online May 7. DOI:10.1101/2020.04.10.20060558 (preprint).
6 Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. *J Zhejiang Univ (Med Sci)* 2020; 49: 215–19.
7 Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020; published online March 20. DOI:10.1016/j.ijantimicag.2020.105949.
8 Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012; 366: 1881–90.
9 Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc-prolonging and torsadogenic potential of possible pharmacotherapies for coronavirus disease 19 (COVID-19). *Mayo Clin Proc* 2020; published online April 7. DOI:10.1016/j.mayocp.2020.03.024.
10 Peschken CA. Possible consequences of a shortage of hydroxychloroquine for patients with systemic lupus erythematosus amid the COVID-19 pandemic. *J Rheumatol* 2020; published online April 8. DOI:10.3899/jrheum.200395.
11 WHO. Clinical management of severe acute respiratory infection (SARI) when novel COVID-19 disease is suspected: interim guidance. March 13, 2020. https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf (accessed April 24, 2020).
12 US Food and Drug Administration. Emergency use authorization: coronavirus disease 2019 (COVID-19) EUA information. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#covidtherapeutics (accessed May 15, 2020).
13 Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020; 14: 72–73.
14 Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19. *medRxiv* 2020; published online April 23. DOI:10.1101/2020.04.16.20065920 (preprint).
15 Mahevas M, Tran V-T, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalised for COVID-19 infection with oxygen requiremenr: results of a study using routinely collected data to emulate a target trial. *medRxiv* 2020; published online April 14. DOI:10.1101/2020.04.10.20060699 (preprint).
16 Traebert M, Dumotier B, Meister L, Hoffmann P, Dominguez-Estevez M, Suter W. Inhibition of hERG K+ currents by antimalarial drugs in stably transfected HEK293 cells. *Eur J Pharmacol* 2004; 484: 41–48.
17 Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020; published online March 25. DOI:10.1001/jamacardio.2020.0950.
18 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.
19 Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. *JAMA Cardiol* 2020; published online March 27. DOI:10.1001/jamacardio.2020.1105.
20 Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in COVID-19. *N Engl J Med* 2020; published online May 1. DOI:10.1056/NEJMoa2007621.
21 Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; 395: 1417–18.
22 Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Heart Lung Transplant* 2020; 39: 405–07.

23 Nakornchai S, Konthiang P. Activity of azithromycin or erythromycin in combination with antimalarial drugs against multidrug-resistant *Plasmodium falciparum* in vitro. *Acta Trop* 2006; **100:** 185–91.

24 Lee N, Wong CK, Chan MCW, et al. Anti-inflammatory effects of adjunctive macrolide treatment in adults hospitalized with influenza: a randomized controlled trial. *Antiviral Res* 2017; **144:** 48–56.

25 Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open* 2020; **3:** e208857.

26 Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; published online May 1. DOI:10.1001/jamacardio.2020.1834.

27 Lavie CJ, Arena R, Alpert MA, Milani RV, Ventura HO. Management of cardiovascular diseases in patients with obesity. *Nat Rev Cardiol* 2018; **15:** 45–56.

28 Sanchis-Gomar F, Lavie CJ, Mehra MR, Henry BM, Lippi G. Obesity and outcomes in COVID-19: when an epidemic and pandemic collide. *Mayo Clin Proc* 2020; published online May 19. DOI:10.1016/j.mayocp.2020.05.006.