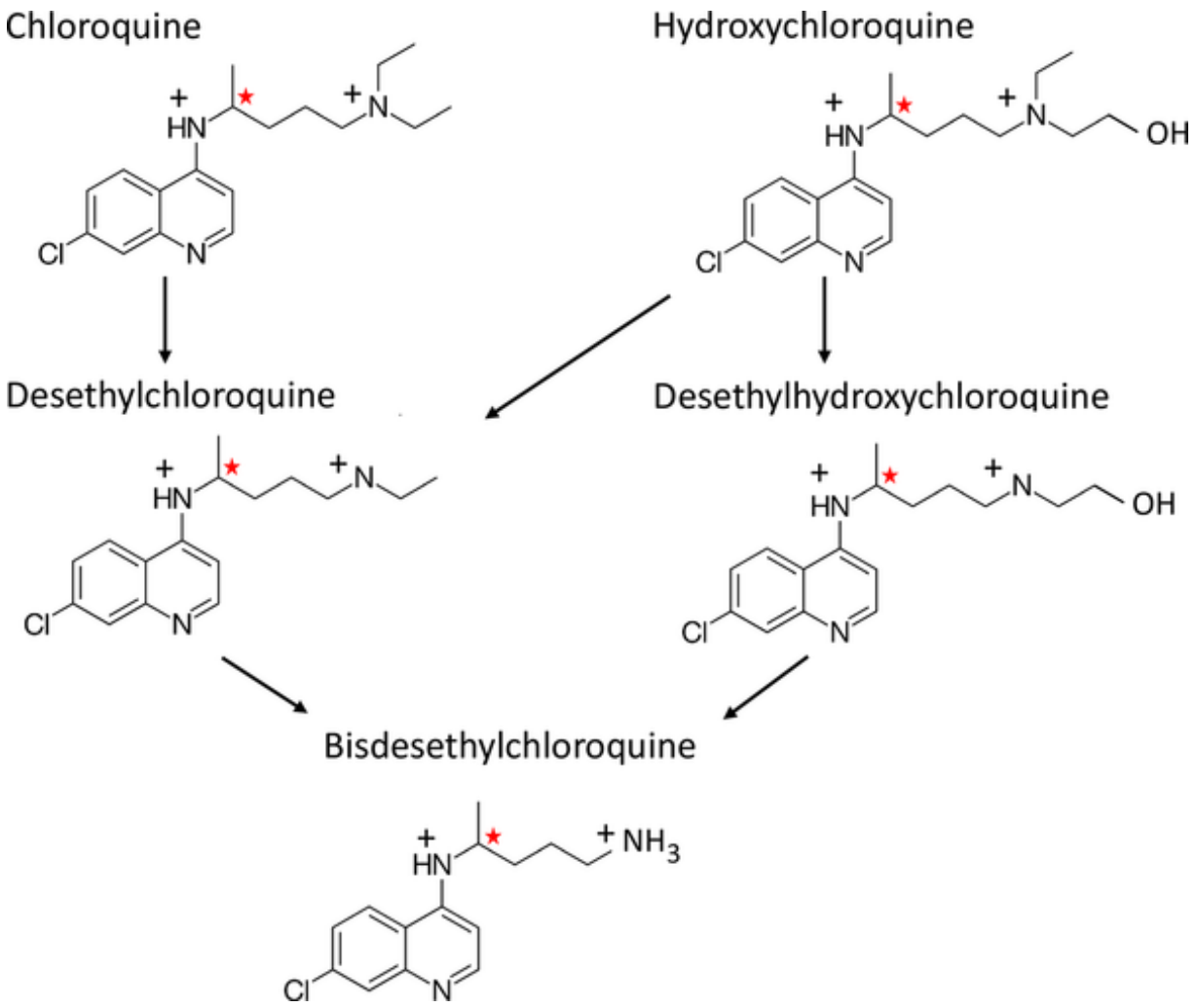
LA TERAPIA CON CLOROCHINA: QUESTIONI APERTE

Fig 1. The metabolism of chloroquine and hydroxychloroquine.



White NJ, Watson JA, Hoglund RM, Chan XHS, Cheah PY, et al. (2020) COVID-19 prevention and treatment: A critical analysis of chloroquine and hydroxychloroquine clinical pharmacology. PLOS Medicine 17(9): e1003252. https://doi.org/10.1371/journal.pmed.1003252
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250MG TABLETS
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Composition
Each film coated tablet contains:
Chloroquine Phosphate 250 mg
Excipients q.s.
Approved colour used.
Dosage: As directed by the physician
Keep in a cool dry place below 25°C
Keep out of reach of children.
10 x 10 Tablets
CHLOROQUINE PHOSPHATE
250MG TABLETS
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Plaquenil 200 mg
Hydroxychloroquini sulfas
30 Filmtabletten / comprimés pelliculés
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Effects of chloroquine on viral infections: an old drug against today's diseases?

Andrea Savarino, Johan R Boelaert, Antonio Cassone, Giancarlo Majori, and Roberto Cauda.

Chloroquine is a 9-aminoquinoline known since 1934. Apart from its well-known antimalarial effects, the drug has interesting biochemical properties that might be applied against some viral infections. Chloroquine exerts direct antiviral effects, inhibiting pH-dependent steps of the replication of several viruses including members of the flaviviruses, retroviruses, and coronaviruses. Its best-studied effects are those against HIV replication, which are being tested in clinical trials. Moreover, chloroquine has immunomodulatory effects, suppressing the production/release of tumour necrosis factor α and interleukin 6, which mediate the inflammatory complications of several viral diseases. We review the available information on the effects of chloroquine on viral infections, raising the question of whether this old drug may experience a revival in the clinical management of viral diseases such as AIDS and severe acute respiratory syndrome, which afflict mankind in the era of globalisation.

Lancet Infect Dis 2003; **3:** 722–27

Chloroquine is a 9-aminoquinoline that has been known since 1934. Specifically synthesised to be used as an antimalarial agent, chloroquine was subsequently shown to have immunomodulatory properties that have encouraged its application in the treatment of autoimmune diseases such as rheumatoid arthritis. For this specific pathology, chloroquine and its hydroxy-analogue hydroxychloroquine have represented a valid contribution to the available pharmacological tools, since they proved able to slow down the progress of the disease while showing limited toxicity.[1]

Unfortunately, chloroquine is being gradually dismissed from antimalarial therapy and prophylaxis, due to the continuous emergence of chloroquine-resistant *Plasmodium falciparum* strains. However, the tolerability, low cost, and immunomodulatory properties of chloroquine/hydroxychloroquine are associated with biochemical effects that suggest a potential use in viral infections, some of whose symptoms may result from the inflammatory response.[2,3] We raise the question of whether this old drug whose parent compound, quinine, was isolated in the late 19th century from the bark of the tropical cinchona tree, may experience a revival in the clinical management of viral diseases of the era of globalisation.

General biochemical and cellular effects of chloroquine

Both chloroquine and hydroxychloroquine are weak bases that are known to affect acid vesicles leading to dysfunction of several enzymes. Extracellularly, chloroquine/hydroxychloroquine is present mostly in a protonated form that, due to its positive charge, is incapable of crossing the plasma membrane. However, the non-protonated portion can enter the intracellular compartment, where, in turn, it becomes protonated in a manner inversely proportional to the pH, according to the Henderson-Hasselbach law. It is thus not surprising that chloroquine/hydroxychloroquine is concentrated within acidic organelles such as the endosome, Golgi vesicles, and the lysosomes, where the pH is low and most chloroquine/hydroxychloroquine molecules are positively charged.[4] Chloroquine/hydroxychloroquine is extruded to the extracellular medium mostly by exocytosis

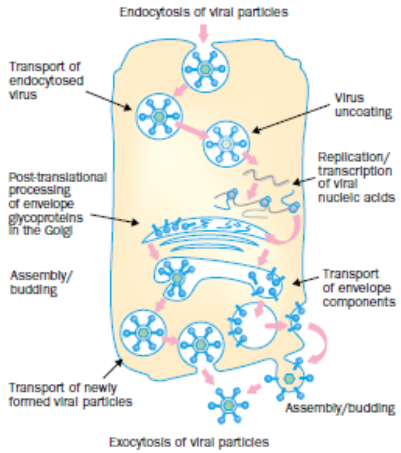


Figure 1. Steps of the replication of different viruses affected by chloroquine (marked by red rectangles). Chloroquine inhibits the replication of different viruses either at the early or late stages of viral replication.

AS and RC are at the Department of Infectious Diseases, Università Cattolica del Sacro Cuore, Rome, Italy; JRB is at the Unit of Infectious Diseases, AZ Sint-Jan, Brugge, Belgium; AC and GM are at the Departments of Infectious Diseases and Parasitology, respectively, Istituto Superiore di Sanità, Rome.

Correspondence: Dr Andrea Savarino, Laboratory of Viral Immunology, Department of Infectious Diseases, Università Cattolica del Sacro Cuore, Largo Agostino Gemelli 8, I-00168 Rome, Italy. Tel +39 06 30155374; fax +39 06 3054519; email asavarino@medscape.com

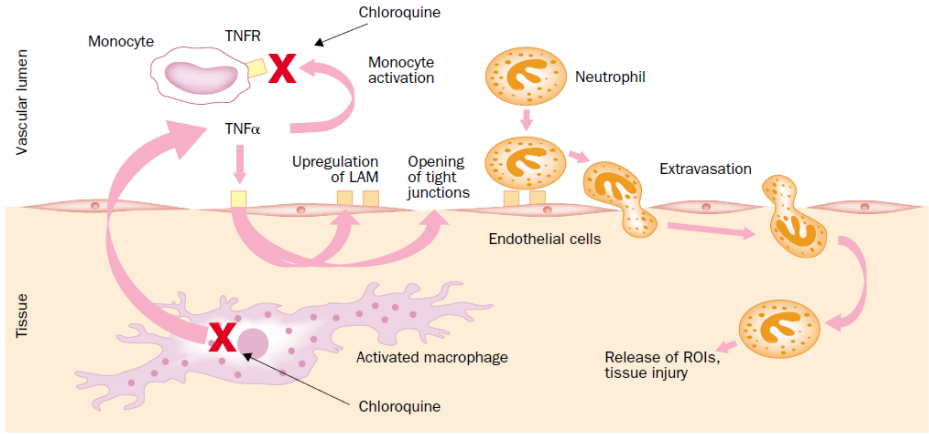
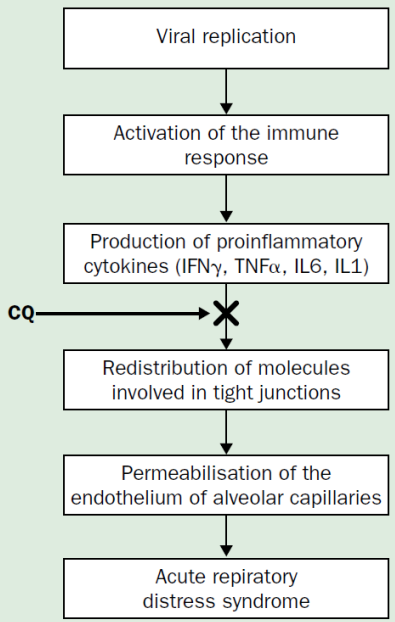


Figure 2. Effects of chloroquine on the immune system. TNFα is produced by activated monocytes/macrophages. Among its multiple functions it helps to activate resting monocytes and favours extravasation of neutrophils by opening tight junctions between human vascular endothelial cells and upregulating leucocyte adhesion molecules (LAM).[26] Chloroquine diminishes TNFα production and downregulates the TNFα receptors 1 and 2 (TNFR) on the monocyte cell surface, which eventually results in decreasedmonocyte activation as well as decreased leucocyte extravasation. Red crosses mark the steps directly inhibited by chloroquine.



Finally, we want to share with the scientific community the speculative hypothesis that chloroquine/hydroxychloroquine, due to its antiviral and anti-inflammatory properties, may have some effect on SARS. We emphasise the need of testing in cell cultures infected with SARS coronavirus the effects of chloroquine, as well as those of other substances possessing in-vitro activity against members of the coronaviridae family. We should remember that the possibility of new outbreaks of SARS cannot be excluded. In the absence of effective inhibitors of SARS coronavirus, the possibility of an inhibition, at least in vitro, of the replication of this virus would represent a breakthrough in the knowledge of SARS.

Acknowledgments

We are grateful to Special Project AIDS, Istituto Superiore di Sanità, Rome, Italy, for financial support.

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Roberto Cauda - Google Sc...

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Journal of antimicrobial chemotherapy 61 (1), 26-38

New insights into the antiviral effects of chloroquine 420 2006
A Savarino, L Di Trani, I Donatelli, R Cauda, A Cassone
The Lancet infectious diseases 6 (2), 67-69

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Effects of chloroquine on viral infections: an old drug against today's diseases

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Autori	Adrea Savarino, John R Boelaert, Antonio Cassone, Giancario Majori, Roberto Cauda
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Descrizione	Chloroquine is a 9-aminoquinoline known since 1934. Apart from its well-known antimalarial effects, the drug has interesting biochemical properties that might be applied against some viral infections. Chloroquine exerts direct antiviral effects, inhibiting pH-dependent steps of the replication of several viruses including members of the flaviviruses, retroviruses, and coronaviruses. Its best-studied effects are those against HIV replication, which are being tested in clinical trials. Moreover, chloroquine has immunomodulatory effects, suppressing the production/release of tumour necrosis factor α and interleukin 6, which mediate the inflammatory complications of several viral diseases. We review the available information on the effects of chloroquine on viral infections, raising the question of whether this old drug may experience a revival in the clinical management of viral diseases such as AIDS and severe acute ...
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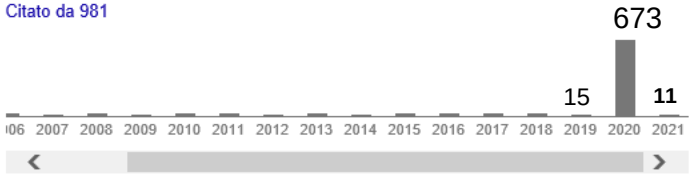

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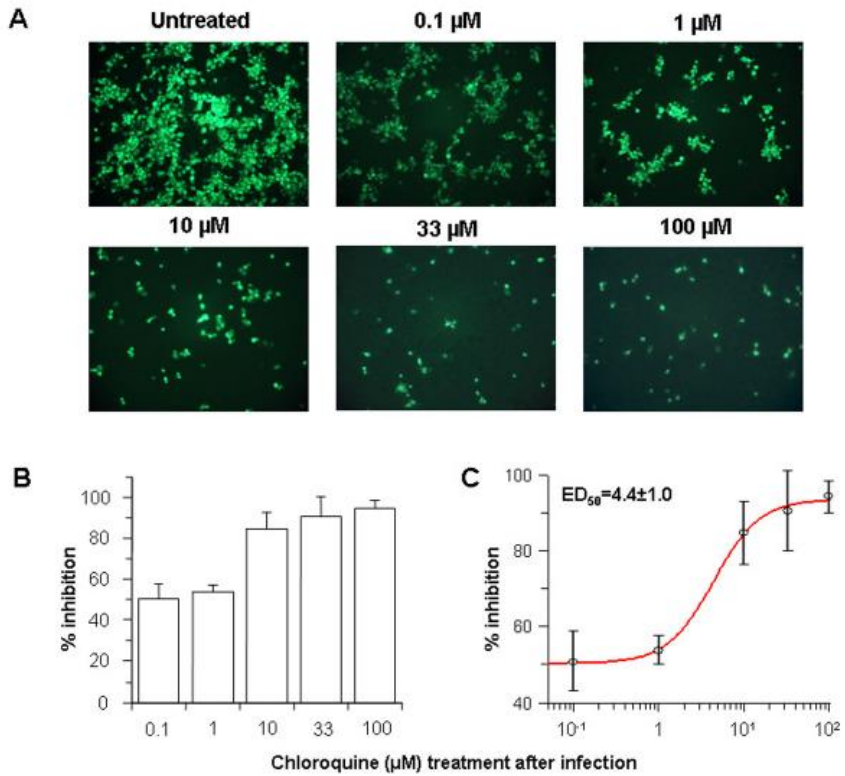

Figure 2
Post-infection chloroquine treatment reduces SARS-CoV infection and spread. Vero E6 cells were seeded and infected as described for Fig. 1 except that chloroquine was added only after virus adsorption. Cells were maintained in Opti-MEM (Invitrogen) containing chloroquine for 16–18 h, after which they were processed for immunofluorescence. **(A)** The concentration of chloroquine is indicated on the top. **(B)** Percent inhibition and SEM were calculated as in Fig. 1B. **(C)** The effective dose (ED_{50}) was calculated using commercially available software (Grafit, version 4, Erithacus Software).

Virology Journal

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Chloroquine is a potent inhibitor of SARS coronavirus infection and spread

Martin J Vincent[1], Eric Bergeron[2], Suzanne Benjannet[2], Bobbie R Erickson[1], Pierre E Rollin[1], Thomas G Ksiazek[1], Nabil G Seidah[2] and Stuart T Nichol*[1]

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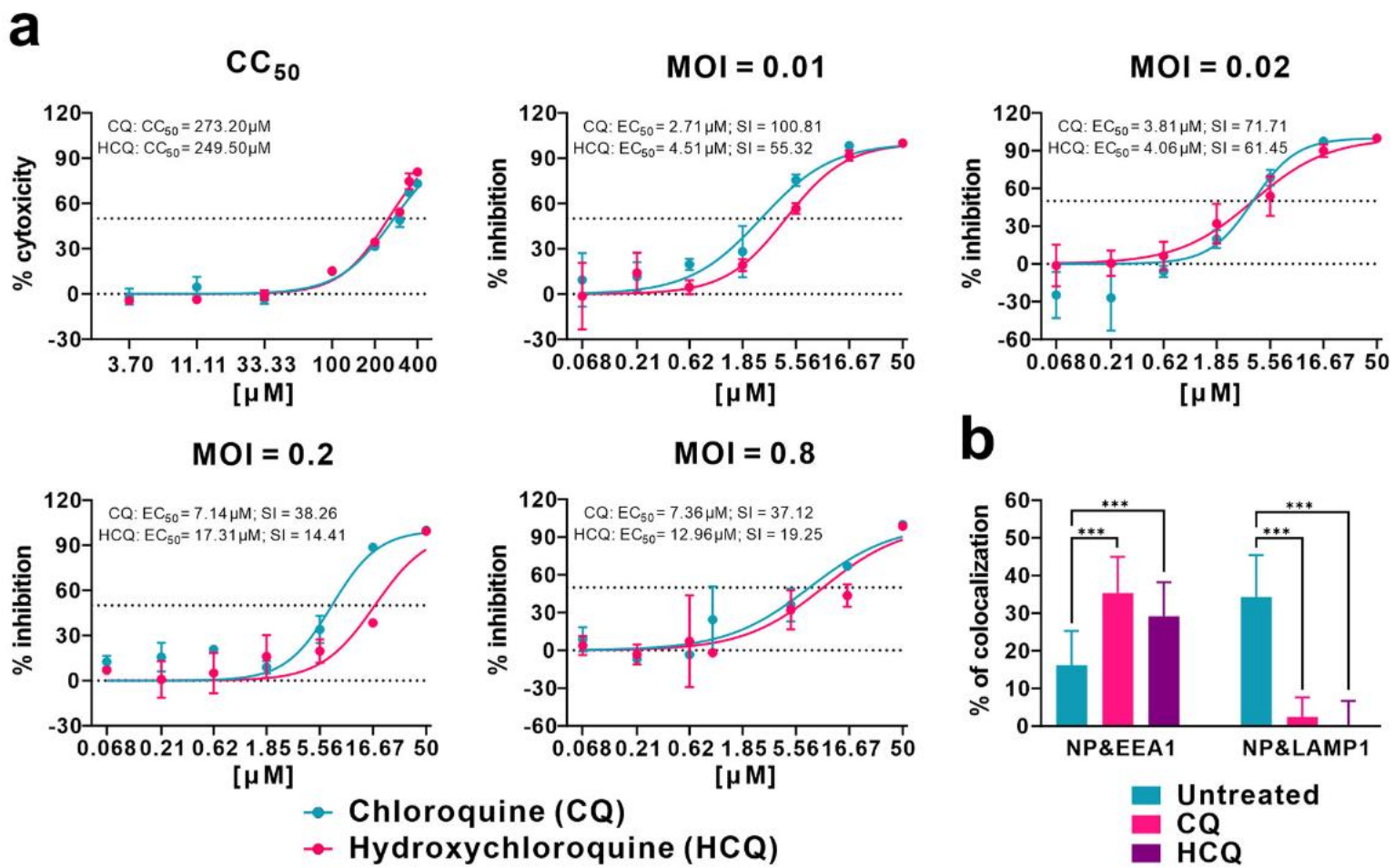
Liu et al. *Cell Discovery* (2020)6:16
https://doi.org/10.1038/s41421-020-0156-0

Cell Discovery
www.nature.com/celldisc

CORRESPONDENCE Open Access

Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro

Jia Liu[1], Ruiyuan Cao[2], Mingyue Xu[1,3], Xi Wang[1], Huanyu Zhang[1,3], Hengrui Hu[1,3], Yufeng Li[1,3], Zhihong Hu[1], Wu Zhong[2] and Manli Wang[1]



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Virus load and virus shedding of **SARS-CoV-2** and their impact on patient outcomes.

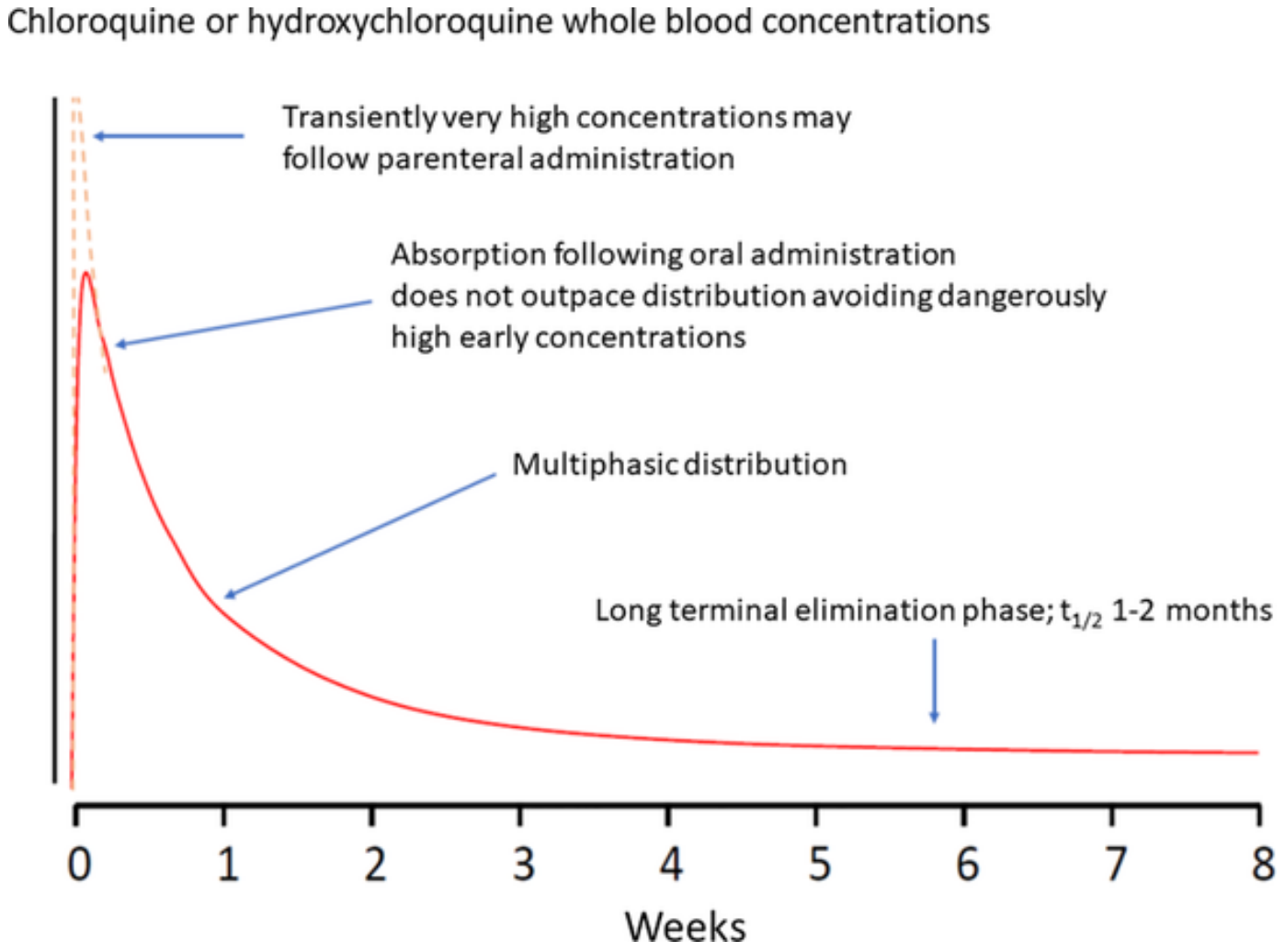
Chen PF, Yu XX, Liu YP, Ren D, Shen M, Huang BS, Gao JL, Huang ZY, Wu M, Wang WY, Chen L, Shi X, Wang ZQ, Liu YX, Liu L, Liu Y.

World J Clin Cases. 2020 Dec 26;8(24):6252-6263. doi: 10.12998/wjcc.v8.i24.6252.

PMID: 33392306 **Free PMC article.**

BACKGROUND: Understanding a virus shedding patterns in body fluids/secretions is important to determine the samples to be used for diagnosis and to formulate infection control measures. AIM: To investigate the **severe acute respiratory syndrome coron** ...

Fig 2. Example of a general whole-blood or plasma concentration-time profile for chloroquine or hydroxychloroquine.



White NJ, Watson JA, Hoglund RM, Chan XHS, Cheah PY, et al. (2020) COVID-19 prevention and treatment: A critical analysis of chloroquine and hydroxychloroquine clinical pharmacology. PLOS Medicine 17(9): e1003252. https://doi.org/10.1371/journal.pmed.1003252
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003252

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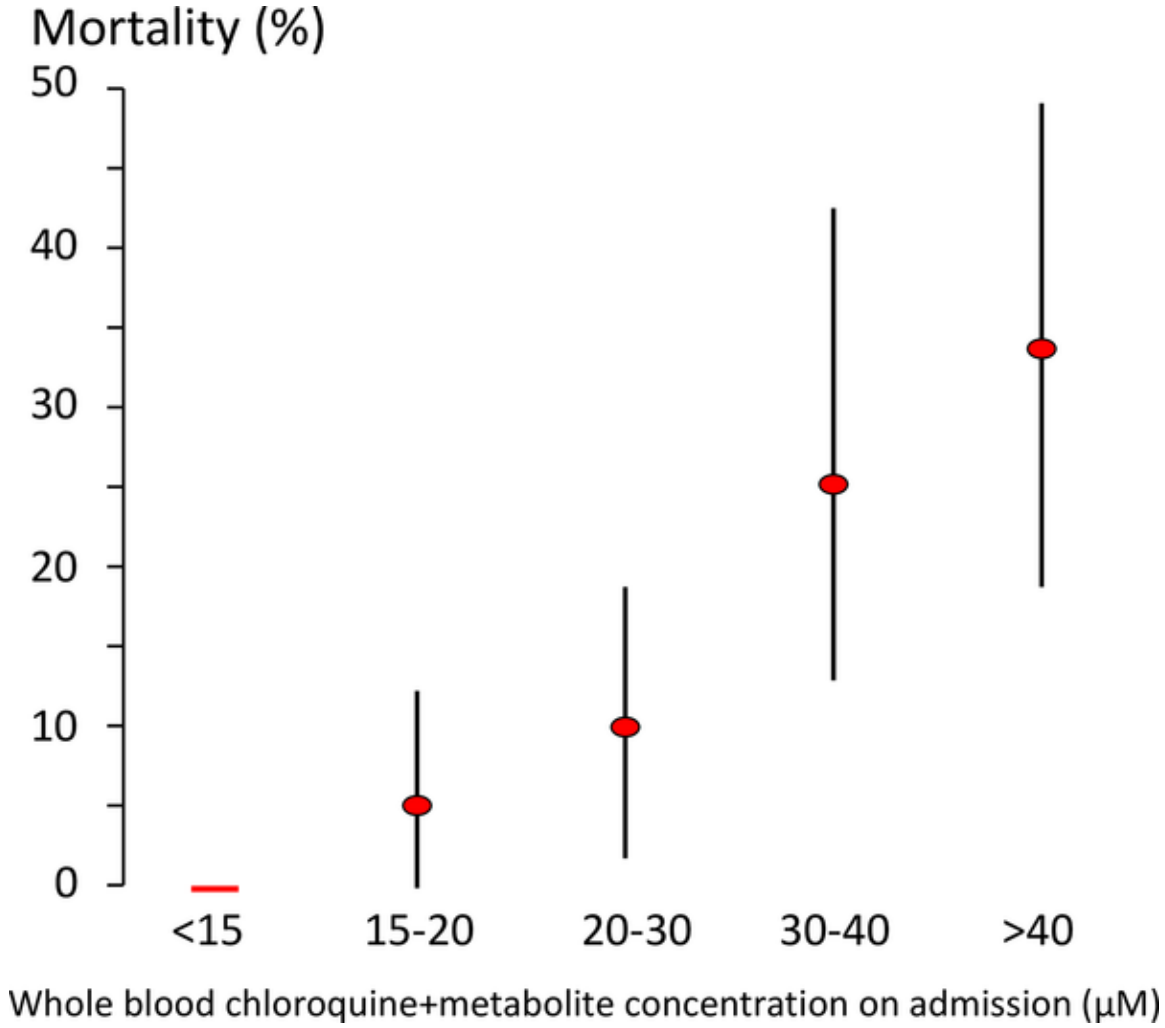
Fig 3. Relationship between whole-blood concentrations of chloroquine + desethyl metabolite (μM) measured by UV-spectrophotometry on admission in self-poisoning, and outcome.



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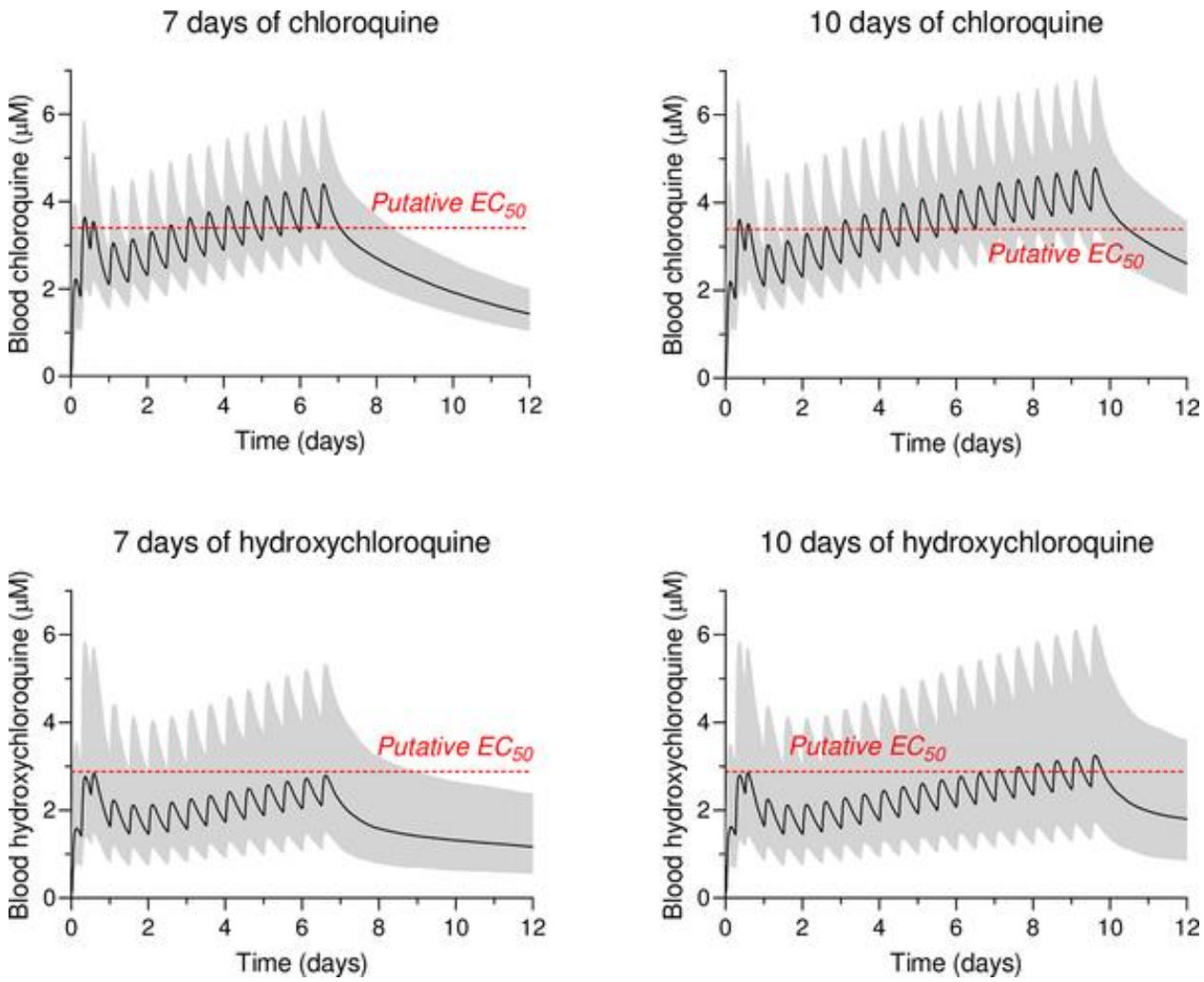
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003252

Fig 4. Pharmacokinetic treatment profiles for a typical 65-kg adult.



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https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003252

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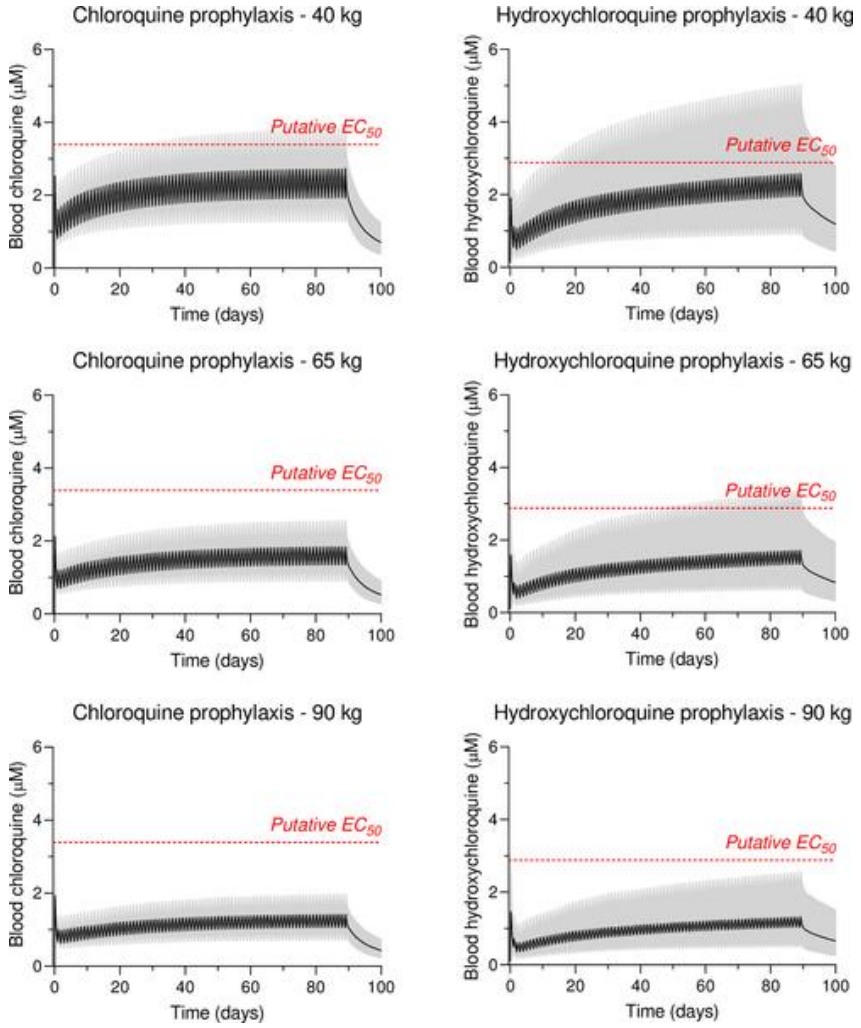
Fig 5. Pharmacokinetic prophylactic profiles of chloroquine and hydroxychloroquine.



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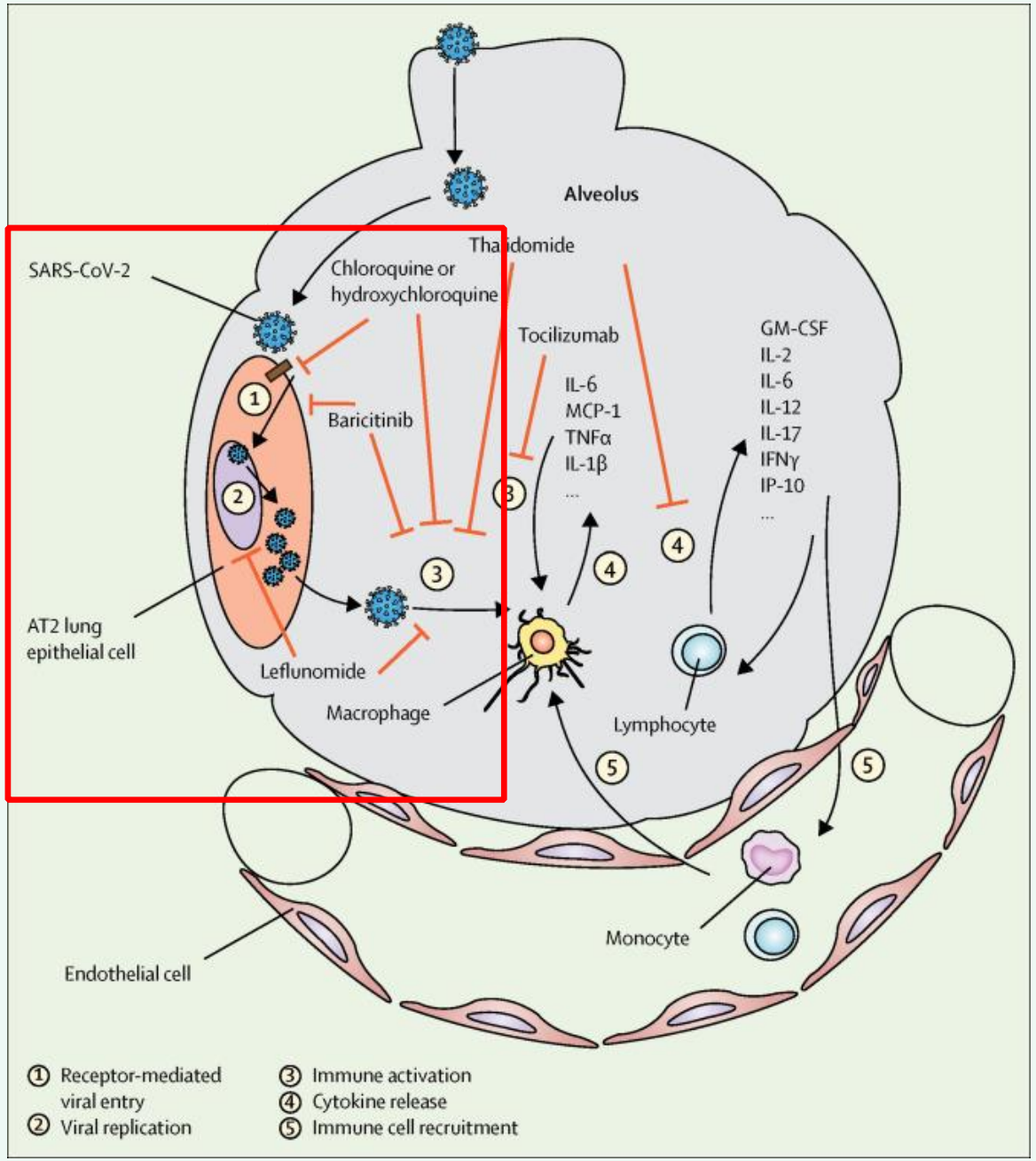

The Lancet Rheumatology 2020 2e428-e436DOI: (10.1016/S2665-9913(20)30120-X)

nature

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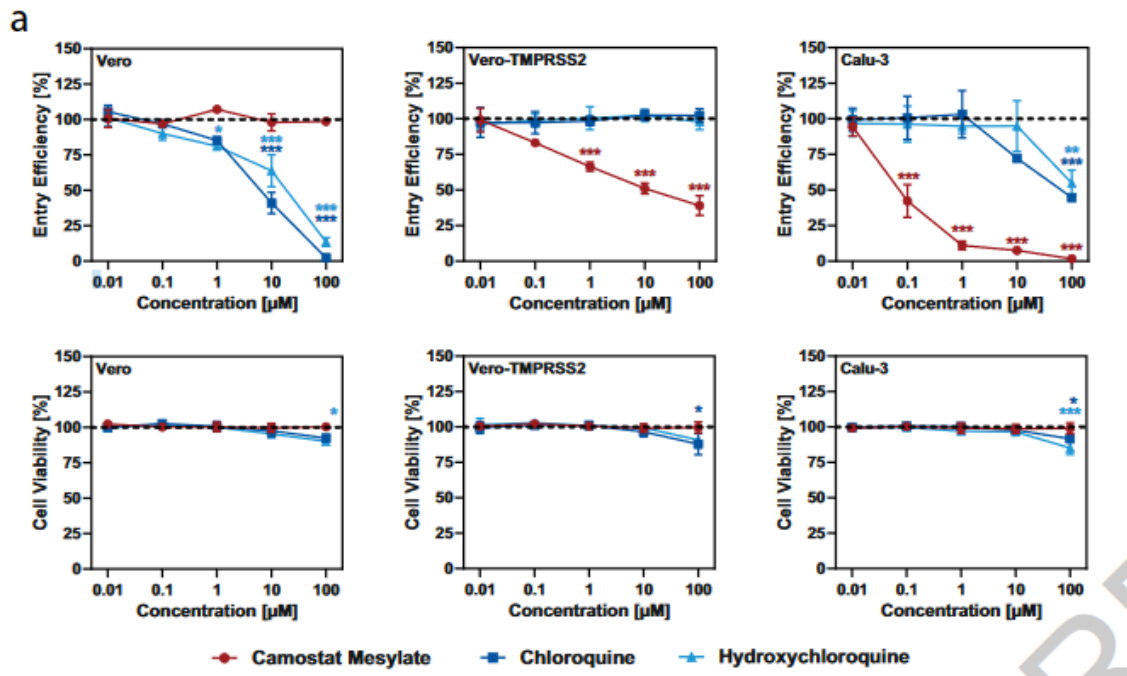
Accelerated Article Preview

Chloroquine does not inhibit infection of human lung cells with SARS-CoV-2

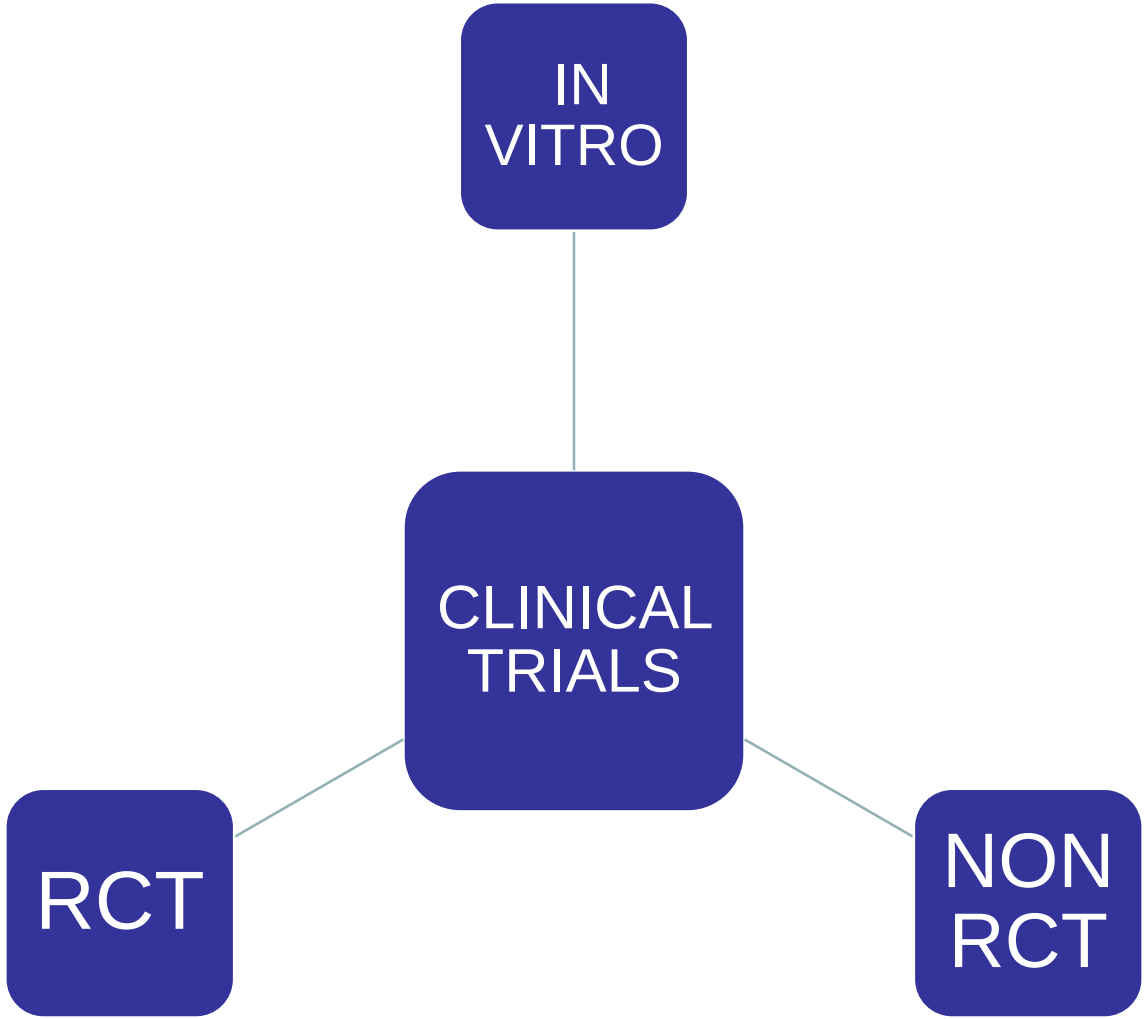
Received: 8 May 2020

Accepted: 16 July 2020

Markus Hoffmann, Kirstin Mösbauer, Heike Hofmann-Winkler, Artur Kaul, Hannah Kleine-Weber, Nadine Krüger, Nils C. Gassen, Marcel A. Müller, Christian Drosten & Stefan Pöhlmann



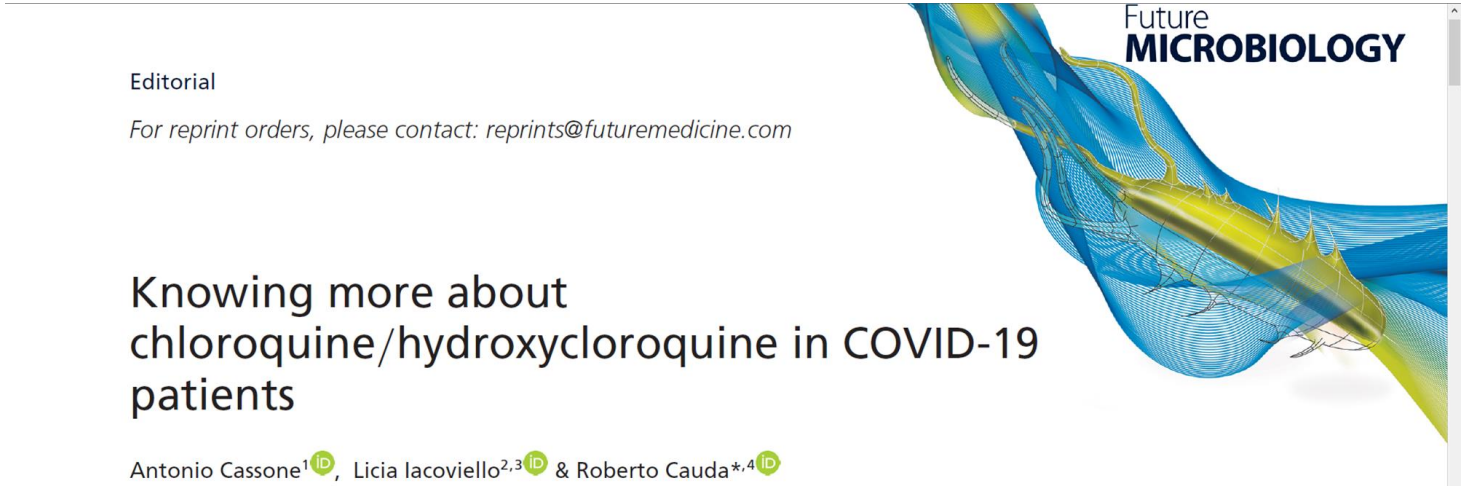
CQ/HCQ



Despite the absence of positive indications from large, well-conducted studies and randomized clinical trials (RCT), these drugs became very popular and widely used by clinicians. Quite inappropriately, they have also been politically-charged, being sponsored as game-changers by important political men and heads of government, and this greatly contributed to unwise use and shortage of CQ/HCQ [14].

One of these studies was subsequently retracted [18], and another one dealing with HCQ prophylaxis had notable limitations, including the lack of consistent diagnosis of SARS-CoV-2 in treated patients [19]. Despite these uncertainties, the results of these studies ingenerated, as a whole, the conclusion that CQ/HCQ were inefficacious as anti-SARS-CoV-2 agents and could be harmful in some patients. It is now a common experience of those performing COVID-19 clinical studies that the editors of major

medical journals have become very reluctant to publish something dealing with CQ/HCQ and COVID-19 unless the conclusion confirms the RCT data, as seen in several recent meta-analyses [20–22]. Nonetheless, interest in these two drugs has remained alive as witnessed by the numerous (more than 100 worldwide), still ongoing clinical trials [23].



INTERVIEW : Pr Andrea Savarino, l'hydroxychloroquine objet d'une bataille politique aux USA

Publié le 03/08/2020 à 18:58 - Mise à jour à 20:56

INTERVIEW : Pr Andrea Savarino, l'hydroxychloroquine objet d'une bataille politique aux USA

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4/01 à 18:20 - Entretiens

Coronavirus: quello che c'è da sapere – 7 ottobre 2020

Sommario

Indice dei grafici e delle tabelle

a cura di Salvatore Curiale - Istituto Nazionale Malattie infettive "Lazzaro Spallanzani" IRCCS – Roma –

a confronto con lo standard di cura per COVID-19, dal momento che l'utilizzo di questi farmaci aveva evidenziato una modesta o nulla riduzione della mortalità nei pazienti COVID-19 ospedalizzati[60].
Alla stessa conclusione - mancanza di evidenza dell'utilità nella riduzione della mortalità - si è giunti anche anche a proposito della clorochina e del suo analogo idrossiclorochina, farmaci comunemente utilizzati per il trattamento della malaria e di alcune malattie reumatiche che avevano mostrato una promettente attività in vitro contro il virus e che, a seguito di alcune esperienze cliniche, sono entrati in numerose sperimentazioni in tutto il mondo (Italia compresa).
L'idrossiclorochina è stata anche al centro di controversie politiche, essendo stata fortemente promossa, senza alcuna evidenza che ne decretasse l'efficacia, dal presidente americano Trump e da quello brasiliano Bolsonaro, nonché di veri e propri colpi di scena editoriali, con ricerche sul suo utilizzo prima pubblicate e poi contestate e ritirate.
Uno studio osservazionale[61] condotto su oltre 96.000 cartelle cliniche di 671 ospedali in sei continenti, dal quale emergeva un aumento di mortalità e di complicanze cardiache associato all'uso del farmaco, è stato ritirato dalla rivista *Lancet* dopo che sono emerse irregolarità nella raccolta dei dati, effettuata da una società che si è rifiutata di fornirli ad un gruppo di esperti indipendenti per la loro valutazione.
Un altro studio[62], condotto utilizzando il farmaco come profilassi post-esposizione su adulti che avevano avuto contatti con casi confermati di COVID-19, non ha evidenziato significative differenze nello sviluppo dei sintomi tra coloro che hanno ricevuto l'idrossiclorochina rispetto a quelli che hanno ricevuto il placebo.
L'utilizzo dell'idrossiclorochina nello studio internazionale SOLIDARITY dell'OMS è stato dapprima sospeso, quindi è ripreso il 3 giugno, quindi nuovamente interrotto il 17 giugno, infine definitivamente chiuso il 4 luglio. L'OMS ha pubblicato una rassegna sulla letteratura disponibile in materia[63], dalla quale emerge che l'utilizzo di questo farmaco, associato o non con un macrolide, non determina allo stato attuale delle conoscenze alcun beneficio apprezzabile nella cura del COVID-19, ed anzi vi è una evidenza, anche se non definitiva, che possa determinare eventi avversi in misura maggiore rispetto allo standard di cura del COVID-19.
In Inghilterra infine i responsabili del trial clinico randomizzato nazionale RECOVERY hanno sospeso l'utilizzo dell'idrossiclorochina, avendo constatato nel corso delle periodiche verifiche che questo farmaco non ha mostrato alcuna superiorità sugli altri trattamenti nella cura dei pazienti ospedalizzati con COVID-19.
In Italia, in considerazione dell'evoluzione della letteratura disponibile e dei trial clinici realizzati in tutto il mondo, l'AIFA ha deciso di sospendere l'autorizzazione all'utilizzo off-label, e la conseguente rimborsabilità a carico del Servizio Sanitario Nazionale, per i seguenti farmaci o combinazioni di farmaci:

- clorochina e idrossiclorochina;
- azitromicina
- darunavir/cobicistat;

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 m[illegible]ide, are b[illegible] widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Although [illegible]erall[illegible]e whe[illegible] used for approved indications such as autoimmune disease or malaria, the safety and bene[illegible] of th[illegible] treatment regimens are poorly evaluated in COVID-19.

Methods We did a multinational registry analysis of the use of hydroxychloroquine [illegible]oquine wit[illegible]thout a macrolide for treatment of COVID-19. The registry comprised data from 671 hosp[illegible]s in [illegible]ntinents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory [illegible]g for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagn[illegible] included in [illegible] of four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychlor[illegible]ine alone, or hydroxychloroquine with a macrolide), and patients who received none of these treatments formed [illegible] control gr[illegible]. Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis o[illegible]ile they w[illegible]on mechanical ventilation, as well as patients who received remdesivir, were excluded. The main outc[illegible] of int[illegible]t were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias ([illegible]tained or [illegible]ed ventricular tachycardia or ventricular fibrillation).

Findings 96 032 patients (mean age 53·8 years, 46·3% women) [illegible]OVID-19 were hospitalised during the study period and met the inclusion criteria. Of tho[illegible] patie[illegible] were in the treatment groups (1868 received chloroquine, 3783 received chloroquine with [illegible]macro[illegible]e, 3016 [illegible]eived hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and [illegible] pati[illegible]s in [illegible]e control group. 10 698 (11·1%) patients died in hospital. After controlling for multiple c[illegible]fou[illegible]ctors (e[illegible] sex, race or ethnicity, body-mass index, underlying cardiovascular disease and its risk fac[illegible] diabetes[illegible]derlying lung disease, smoking, immunosuppressed condition, and baseline disease severity), w[illegible]mpared wi[illegible]ortality in the control group (9·3%), hydroxychloroquine (18·0%; hazard ratio 1·335, 95%[illegible]·2[illegible]·457), hydr[illegible]ychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine (16·4%; 1·365, [illegible]·318–1·531), [illegible]chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were each independently associated [illegible]n an increased [illegible] of in-hospital mortality. Compared with the control group (0·3%), hydroxychloroquine (6[illegible]; 2·36[illegible]·935–2·906), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·983), chloroquine (4·3%; [illegible]·1, [illegible]·0–4·596), and chloroquine with a macrolide (6·5%; 4·011, 3·344–4·812) were independently associate[illegible] an incr[illegible]ed risk of de-novo ventricular arrhythmia during hospitalisation.

Interpretation We [illegible] unable[illegible] confirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macrol[illegible] on in[illegible]spital outcomes for COVID-19. Each of these drug regimens was associated with decreased in-hospital [illegible]i[illegible] [illegible]reased frequency of ventricular arrhythmias when used for treatment of COVID-19.

Funding William[illegible]ey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women's Hospital.

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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,

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Editorial

Hydroxychloroquine/ chloroquine as a treatment choice or prophylaxis for Covid-19 at the primary care level in developing countries: A *Primum non Nocere* dilemma

ARTICLE INFO

Keywords:
Hydroxychloroquine/ chloroquine
Developing countries
Primary care
Bioethics
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ABSTRACT

The Food and Drug Administration (FDA) warned against the use of Hydroxychloroquine or chloroquine for Covid-19 outside of a hospital or a clinical trial setting due to the risk of QT interval prolongation, ventricular tachycardia and the increased risk of these complications when combined with some antibiotics such as azithromycin. Several studies have reported no benefit of Hydroxychloroquine or chloroquine, when used alone or with a macrolide in COVID-19 hospitalized patients.

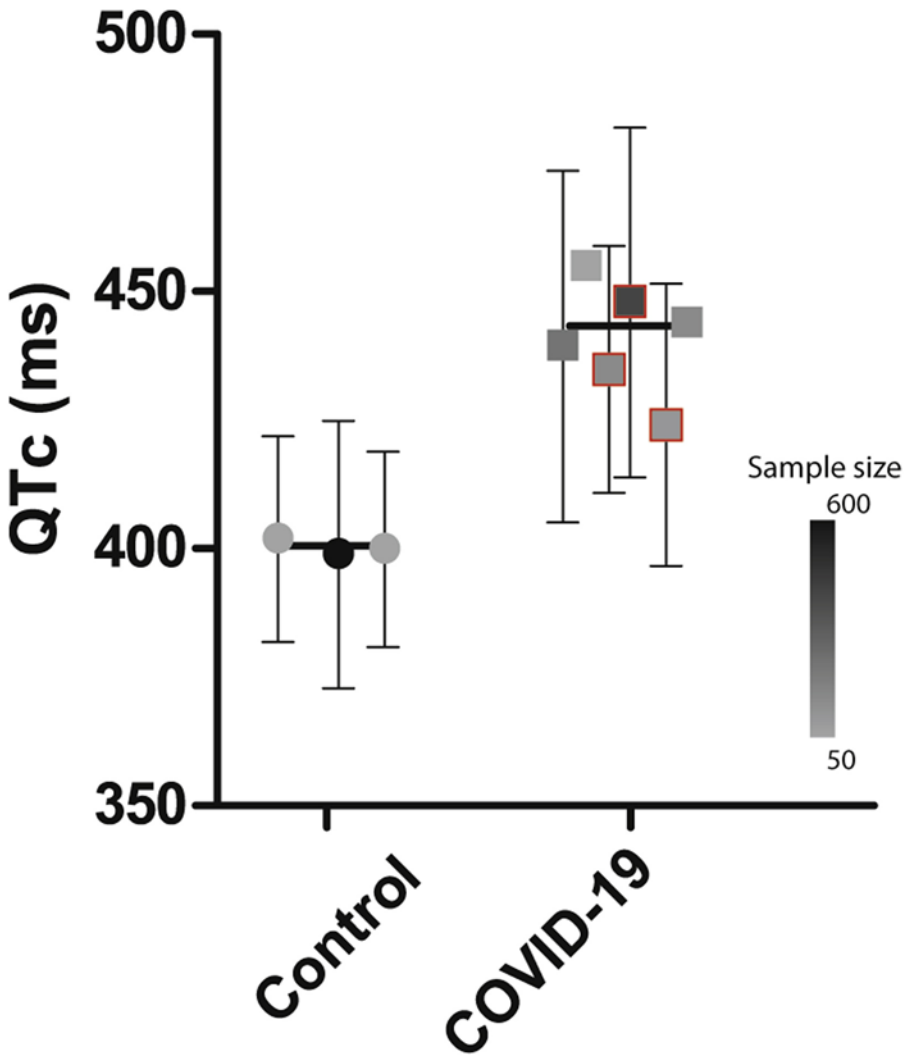
Despite these warnings, in several developing countries the official guidelines for treatment of Covid-19 patients at the primary care level recommend Hydroxychloroquine and azithromycin, among other treatments, as the first-choice for mild symptomatic Covid-19 patients, asymptomatic contacts or for prophylaxis. In our opinion there is a primum non nocere dilemma during this Covid-19 pandemic. In order to solve this bioethical problem, we strongly recommend that a randomized controlled trial in a primary care setting be carried out as a matter of urgency in these areas of the world.

In March 2020 hydroxychloroquine (HC) was reported to have a positive effect in a Covid-19 treatment open-label non-randomized clinical trial [1]. However, in recent Covid-19 observational studies in hospitalized patients, HC was not associated with a reduction in mortality, either alone [2] or in combination with azithromycin [3] and the need for randomized, controlled trials was recommended [2].

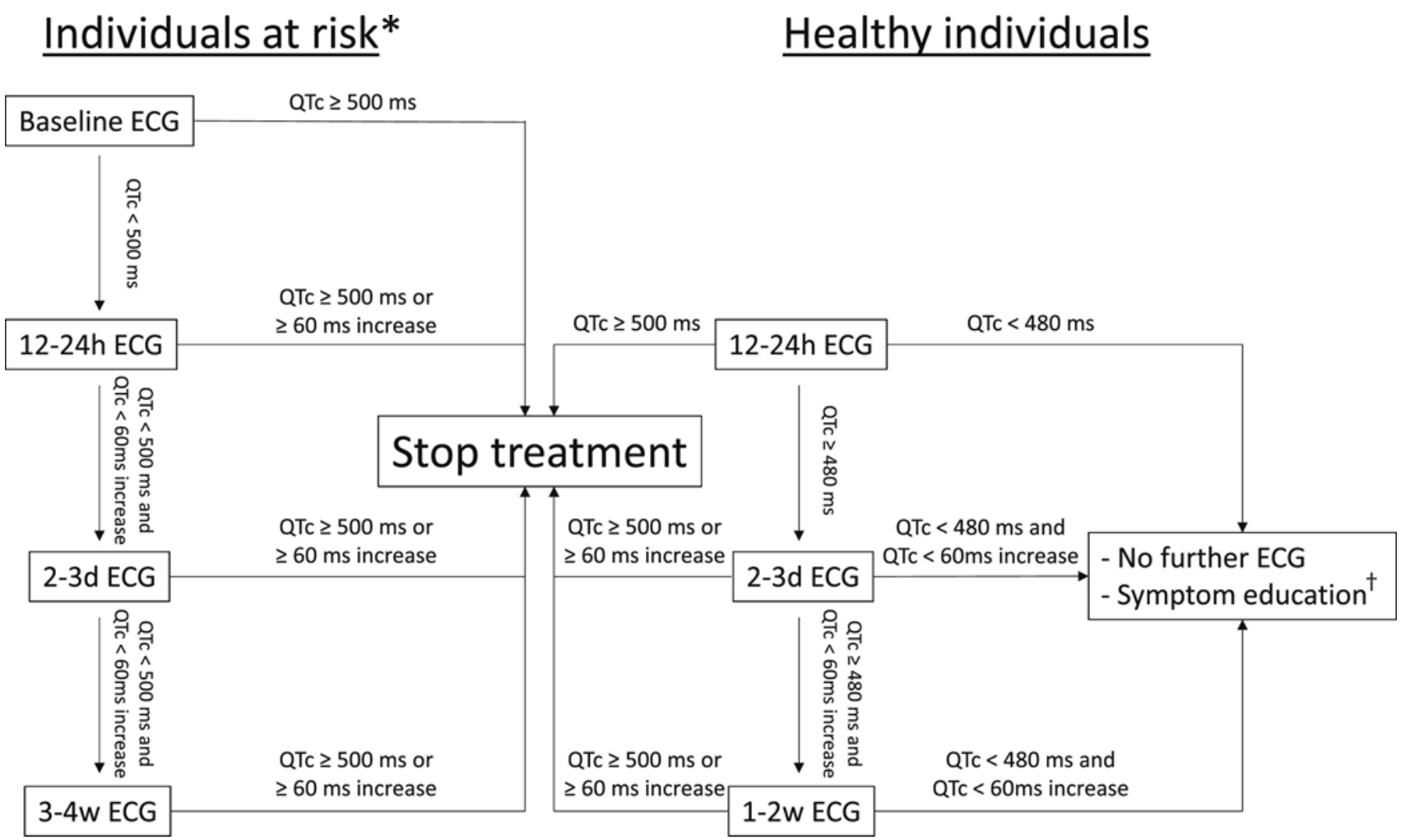
On April 21st 2020, a panel of the United States National Institutes of Health (NIH) recommended that no agent should be used for the treatment of SARS-CoV-2 outside the setting of a clinical trial. At that time no drug had been proven to be safe and effective for treating Covid-19 [4] although Beigel et al. have recently reported that recommendation: 1) Lack of scientific evidence; 2) Increased risk of adverse events, especially cardiac complications; 3) Limited resources to evaluate complications in primary care (e.g, ECG equipment), 4) No consent form required in these guidelines; and 5) Educational issues specific to developing countries.

In our opinion there is a *primum non nocere* dilemma during this Covid-19 pandemic. In order to solve this bioethical problem, we strongly recommend that a randomized controlled trial in a primary care setting be carried out as a matter of urgency in these areas of the world.

Prophylactic (hydroxy)chloroquine in COVID-19: Potential relevance for cardiac arrhythmia risk *Joost A. Offerhaus, MD, Arthur A.M. Wilde, MD, PhD, FHRS, Carol Ann Remme, MD, PhD Heart Rhythm* Volume 17 Issue 9 Pages 1480-1486 (September 2020) DOI: 10.1016/j.hrthm.2020.07.001



Prophylactic (hydroxy)chloroquine in COVID-19: Potential relevance for cardiac arrhythmia risk *Joost A. Offerhaus, MD, Arthur A.M. Wilde, MD, PhD, FHRS, Carol Ann Remme, MD, PhD Heart Rhythm* Volume 17 Issue 9 Pages 1480-1486 (September 2020) DOI: 10.1016/j.hrthm.2020.07.001



Relative frequencies (%)[a] of the most commonly reported suspected adverse drug reactions as registered in the WHO pharmacovigilance database (www.vigiaccess.org) for system organ classes considered relevant to patients with COVID-19 (access date April 9, 2020)

	Chloroquine	Hydroxychloroquine
Cardiac disorders	Tachycardia (1.6%), cardiomyopathy (0.7%), palpitations (0.6%), cardiac arrest 0.6%), atrioventricular block complete (0.5%)	Cardiomyopathy (0.7%), palpitations (0.6%), cardiac failure (0.4%), tachycardia (0.3%), cardiac failure congestive (0.3%)
Gastrointestinal disorders	Vomiting (10.5%), nausea (8.4%), diarrhoea (4.5%), abdominal pain (3.5%), abdominal pain upper (2.5%)	Nausea (5.3%), diarrhoea (3.6%), abdominal discomfort (2.4%), vomiting (2.3%), abdominal pain (1.3%)
Psychiatric disorders	Anxiety (2.1%), depression (2.0%), psychotic disorder (1.5%), hallucination (1.1%), insomnia (1.1%)	Insomnia (0.7%), depression (0.6%), anxiety (0.4%), completed suicide (0.3%), sleep disorder (0.3%)
Nervous system disorders	Headache (7.8%), dizziness (5.2%), seizure (2.8%), balance disorder (1.6%), neuropathy peripheral (1.2%)	Headache (2.8%), dizziness (2.1%), visual field defect (0.6%), paraesthesia (0.6%), hypaesthesia (0.6%)

[a] Relative frequencies (%) were calculated by dividing the absolute number of adverse reaction reports by the total number of adverse reaction reports for each drug. For chloroquine and hydroxychoroquine VigiAccessTM contains a total of 5797 and 22138 records, respectively.

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ESTABLISHED IN 1812 AUGUST 6, 2020 VOL. 383 NO. 6

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

D.R. Boulware, M.F. Pullen, A.S. Bangdiwala, K.A. Pastick, S.M. Lofgren, E.C. Okafor, C.P. Skipper, A.A. Nascene, M.R. Nicol, M. Abassi, N.W. Engen, M.P. Cheng, D. LaBar, S.A. Lother, L.J. MacKenzie, G. Drobot, N. Marten, R. Zarychanski, L.E. Kelly, I.S. Schwartz, E.G. McDonald, R. Rajasingham, T.C. Lee, and K.H. Hullsiek

ABSTRACT

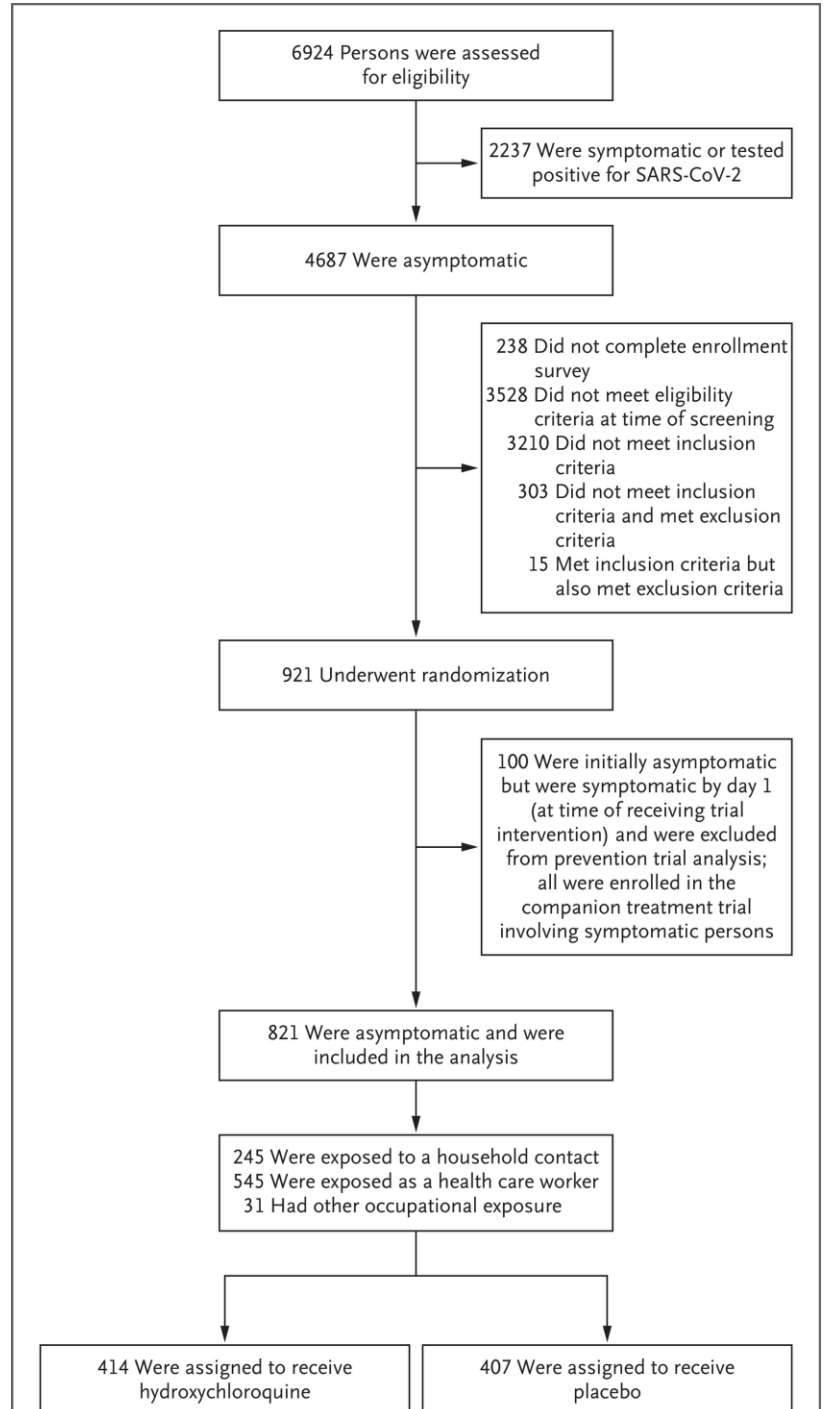


Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Hydroxychloroquine (N=414)	Placebo (N=407)
Median age (IQR) — yr	41 (33–51)	40 (32–50)
Median weight (IQR) — kg	75 (64–86)	76 (64–91)
Female sex — no. (%)†	218 (52.7)	206 (50.6)
Current smoker — no. (%)	15 (3.6)	12 (2.9)
Health care worker — no. (%)	275 (66.4)	270 (66.3)
High-risk exposure — no. (%)‡	365 (88.2)	354 (87.0)
No PPE worn — no. (%)	258 (62.3)	237 (58.2)
Time from exposure to enrollment — no./total no. (%)		
1 day	77/413 (18.6)	63/407 (15.5)
2 days	100/413 (24.2)	106/407 (26.0)
3 days	98/413 (23.7)	117/407 (28.7)
4 days	138/413 (33.4)	121/407 (29.7)
Coexisting conditions — no. (%)		
None	306 (73.9)	290 (71.3)
Hypertension	51 (12.3)	48 (11.8)
Asthma	31 (7.5)	31 (7.6)
Diabetes	12 (2.9)	16 (3.9)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range, and PPE personal protective equipment.

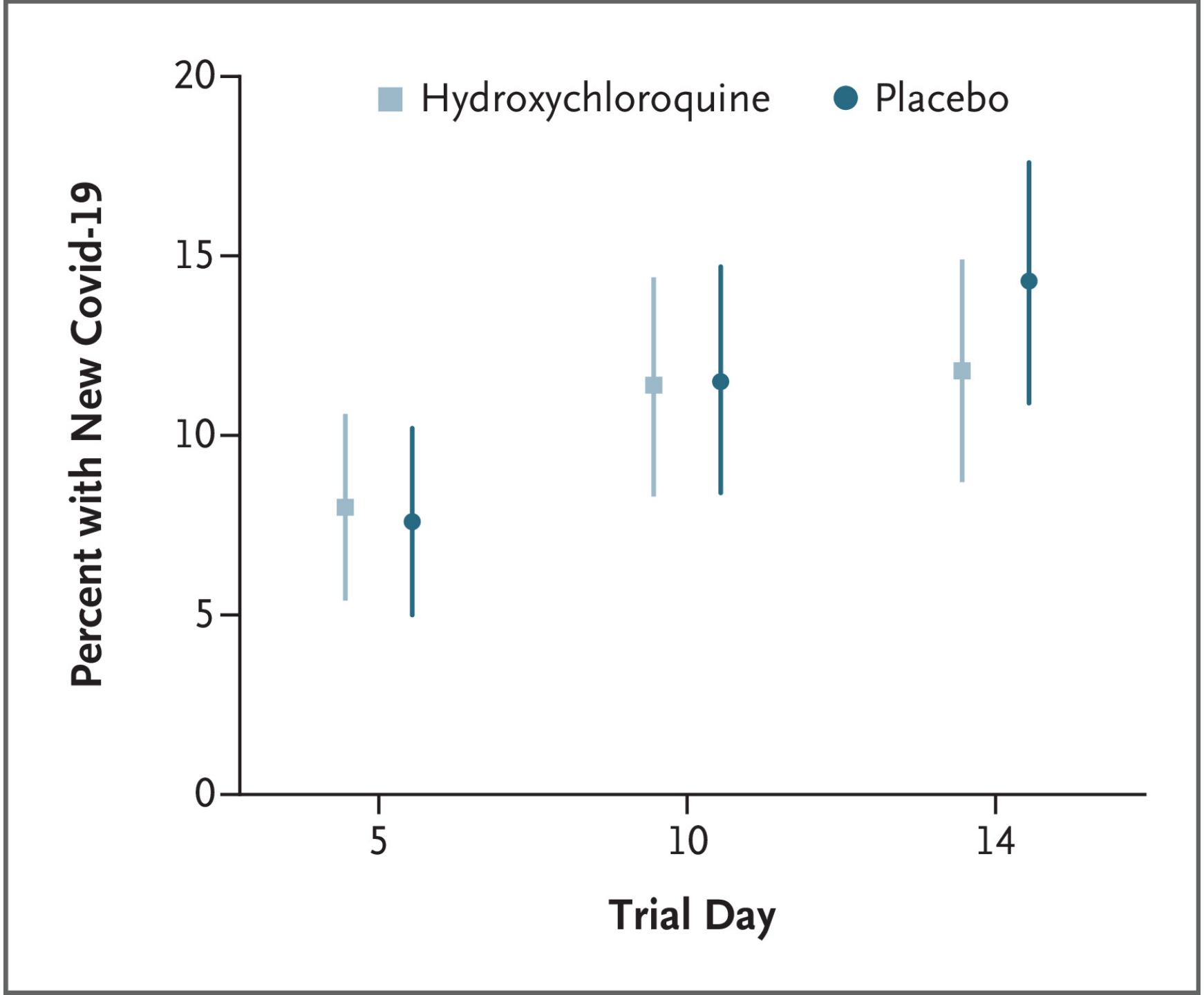
† A total of 0.2% of the women (1 of 424) were pregnant and 1.4% (6 of 424) were breast-feeding at the time of enrollment. One woman (0.2%) reported new pregnancy at day 14.

‡ High-risk exposure was defined as exposure to a person with confirmed coronavirus disease 2019 (Covid-19) at a distance of less than 6 ft for more than 10 minutes while wearing neither a face mask nor an eye shield.

Table 2. Outcomes of Hydroxychloroquine Therapy for Postexposure Prophylaxis against Covid-19.*

Outcome	Hydroxychloroquine (N=414)	Placebo (N=407)	P Value
	number (percent)		
Confirmed or probable Covid-19	49 (11.8)	58 (14.3)	0.35
Laboratory-confirmed diagnosis	11 (2.7)	9 (2.2)	0.82
Symptoms compatible with Covid-19	48 (11.6)	55 (13.5)	0.46
All new symptoms	57 (13.8)	59 (14.5)	0.84
Any hospitalization	1 (0.2)	1 (0.2)	0.99
Death	0	0	—

* Symptoms were adjudicated by four infectious disease physicians, who were unaware of the trial-group assignments, in accordance with U.S. Council of State and Territorial Epidemiologists case definition of probable Covid-19 after an epidemiologic link with a close contact.[15] (Descriptions of the symptom complex are provided in the Supplementary Appendix.) The median number of new symptoms reported in the hydroxychloroquine group was 4 (interquartile range, 2 to 6), as compared with 3 (interquartile range, 2 to 5) in the placebo group.


Hydroxychloroquine
Placebo
Percent with New Covid-19
20
15
10
5
0
5
10
14
Trial Day

EDITORIALS

Hydroxychloroquine for the Prevention of Covid-19 — Searching for Evidence

Myron S. Cohen, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

intended to provide an intervention in the shortest possible time to prevent infection. In a small-animal model of SARS-CoV-2 infection,[8] prevention of infection or more severe disease was observed only when the experimental antiviral agent was given before or shortly after exposure. In the current trial, the long delay between perceived exposure to SARS-CoV-2 and the initiation of hydroxychloroquine (≥3 days in most participants) suggests that what was being assessed was prevention of symptoms or progression of Covid-19, rather than prevention of SARS-CoV-2 infection.

Drugs for the prevention of infections must have an excellent safety profile. When hydroxychloroquine preexposure prophylaxis with hydroxychloroquine, some of which are very large (e.g., the Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine [HERO-HCQ] trial, involving 15,000 health care workers; ClinicalTrials.gov number, NCT04334148)? The results reported by Boulware et al. are more provocative than definitive, suggesting that the potential prevention benefits of hydroxychloroquine remain to be determined.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Institute for Global Heath and Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

METHODS

TRIAL DESIGN

The protocol, which was published previously[3] and is available with the full text of this article at NEJM.org, was designed to involve hundreds of hospitals in dozens of countries. Trial procedures were minimal but rigorous, with data entry through a cloud-based Good Clinical Practice–compliant clinical data management system that recorded demographic characteristics, respiratory support, coexisting illnesses, and local availability of trial drugs before generating the treatment assignment. Written informed consent was provided by patients, or if they were unable to do so, by their legal representatives.[3] Consent forms were retained by signatories and encrypted for records. The enrollment of patients who provided consent took just a few minutes. Eligible patients were 18 years of age or older, were hospitalized with a diagnosis of Covid-19, were not known to have received any trial drug, were not expected to be transferred elsewhere within 72 hours, and, in the physician's view, had no contraindication to any trial drug.

The same cloud-based system was used to report any suspected unexpected serious adverse reaction. It was also used to record death in the hospital or discharge alive (with documentation of respiratory support in the hospital, trial-drug timing, use of nontrial drugs, and probable cause of death). National and global monitors raised or resolved queries (or both) and checked progress and completeness.

available would put that patient into the control group for each of those drugs. Hence, there was partial overlap among the four control groups. Each comparison between a trial drug and its control, however, was evenly randomized (in a 1:1 ratio) and unbiased, because both groups were affected equally by differences between countries or hospitals and by time trends in patient characteristics or the standard of care.

Daily doses were those already used for other diseases, but to maximize any efficacy without undue cardiac risk, the hydroxychloroquine dose was based on that for amoebic liver abscess rather than the lower dose for malaria.[4] (Hydroxychloroquine slightly prolongs the QT interval, and an unduly high dose or rapid administration might cause arrhythmias or hypotension.) Treatments stopped at discharge.

The regimen for remdesivir (intravenous) was 200 mg on day 0 and 100 mg on days 1 through 9. The regimen for hydroxychloroquine (oral) was four tablets at hour 0, four tablets at hour 6, and, starting at hour 12, two tablets twice daily for 10 days. Each tablet contained 200 mg of hydroxychloroquine sulfate (155 mg of hydroxychloroquine base per tablet; a little-used alternative involved 155 mg of chloroquine base per tablet). The regimen for lopinavir (oral) was two tablets twice daily for 14 days. Each tablet contained 200 mg of lopinavir (plus 50 mg of ritonavir, to slow hepatic lopinavir clearance). Other formulations were not provided, so patients who were receiving mechanical ventilation received

ORIGINAL ARTICLE

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

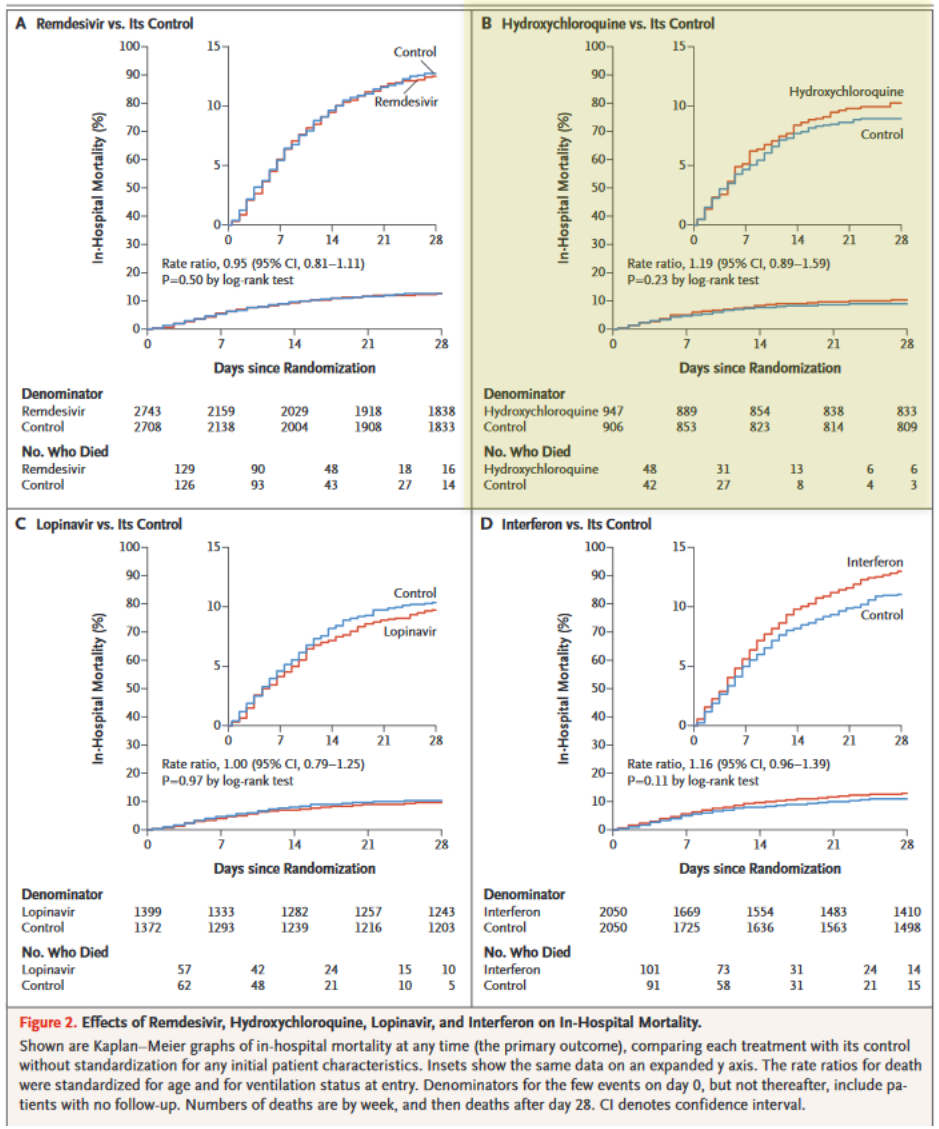


Figure 2. Effects of Remdesivir, Hydroxychloroquine, Lopinavir, and Interferon on In-Hospital Mortality.

Shown are Kaplan–Meier graphs of in-hospital mortality at any time (the primary outcome), comparing each treatment with its control without standardization for any initial patient characteristics. Insets show the same data on an expanded y axis. The rate ratios for death were standardized for age and for ventilation status at entry. Denominators for the few events on day 0, but not thereafter, include patients with no follow-up. Numbers of deaths are by week, and then deaths after day 28. CI denotes confidence interval.

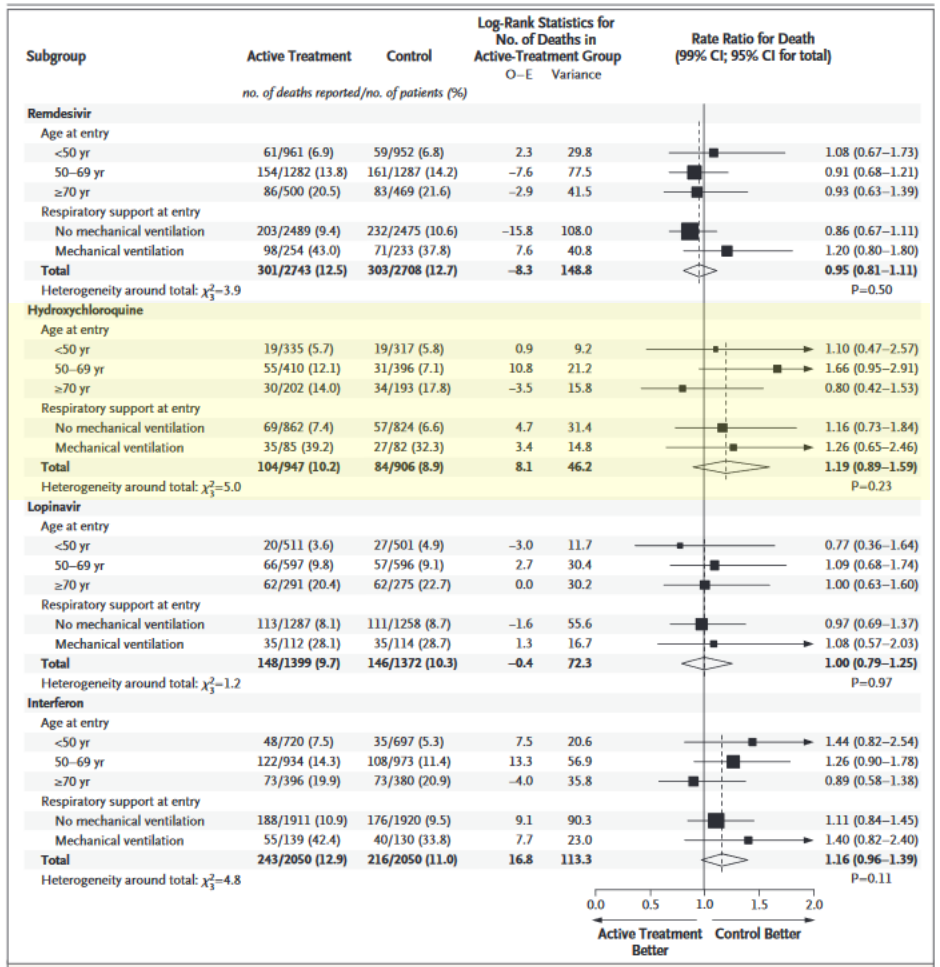


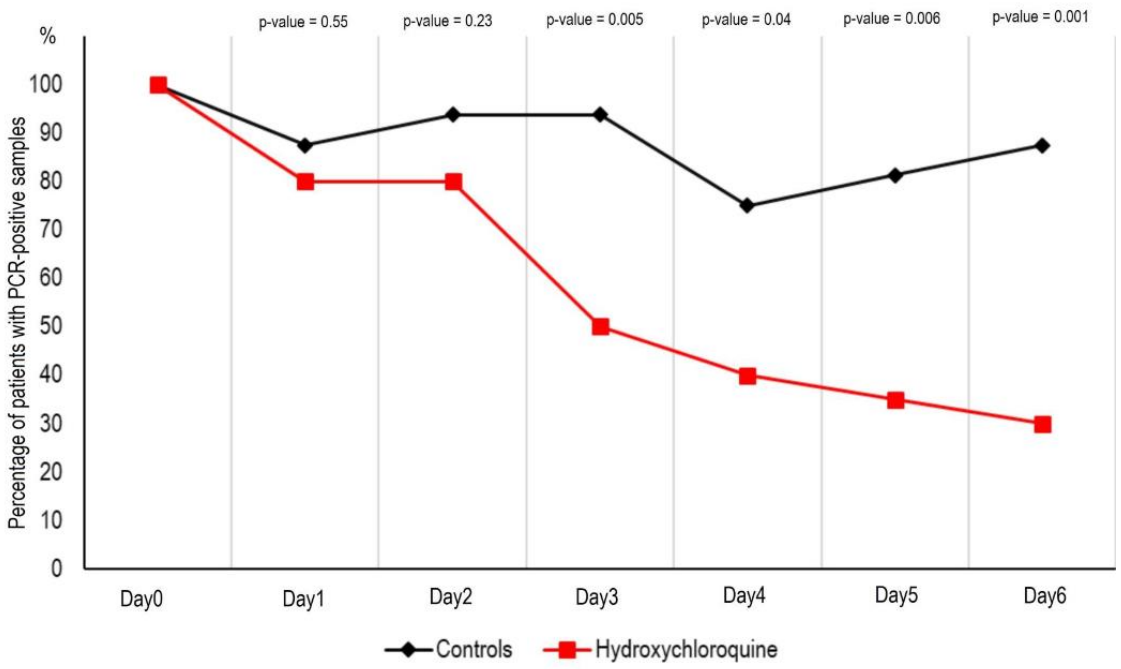
Figure 3. Rate Ratios for In-Hospital Death, Subdivided by Age and Respiratory Support at Trial Entry.

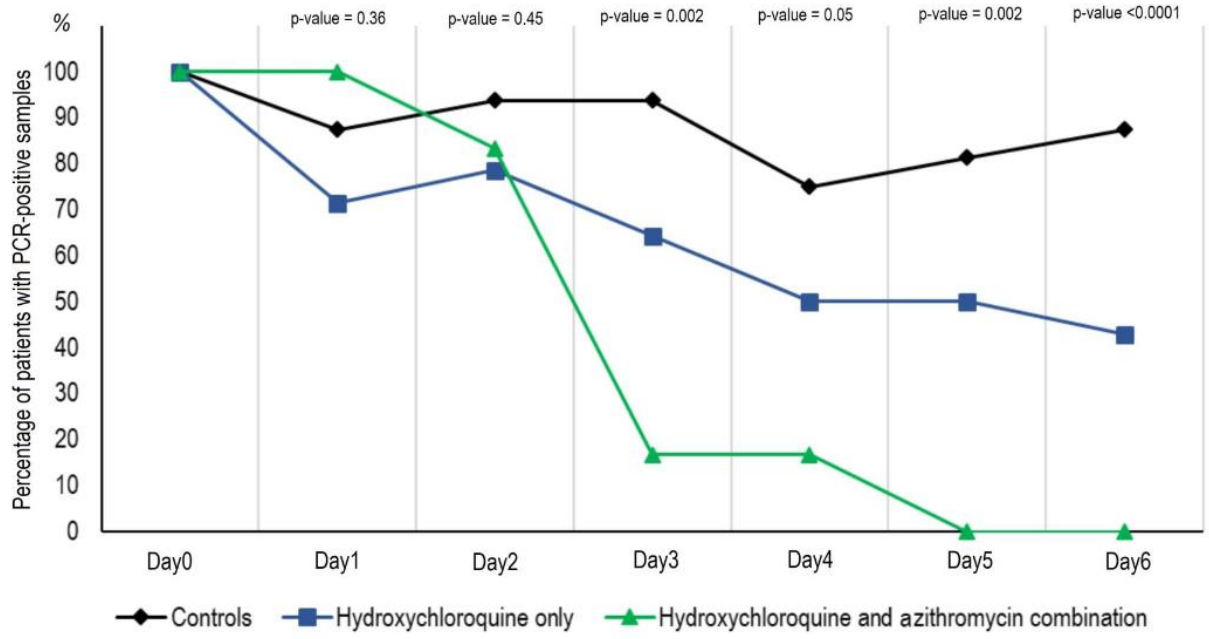
Analyses in subgroups of age are stratified according to respiratory status at trial entry and vice versa, so each total is stratified for both factors. The percentages show Kaplan–Meier 28-day mortality. O–E denotes the observed minus expected number of deaths in patients assigned to active treatment. Diamonds show 95% confidence intervals for treatment effects. Squares and horizontal lines show treatment effects in particular subgroups and their 99% confidence intervals, with an arrow if the upper 99% confidence limit is outside the range shown. The area of each square is proportional to the variance of O–E in the subgroup it describes..

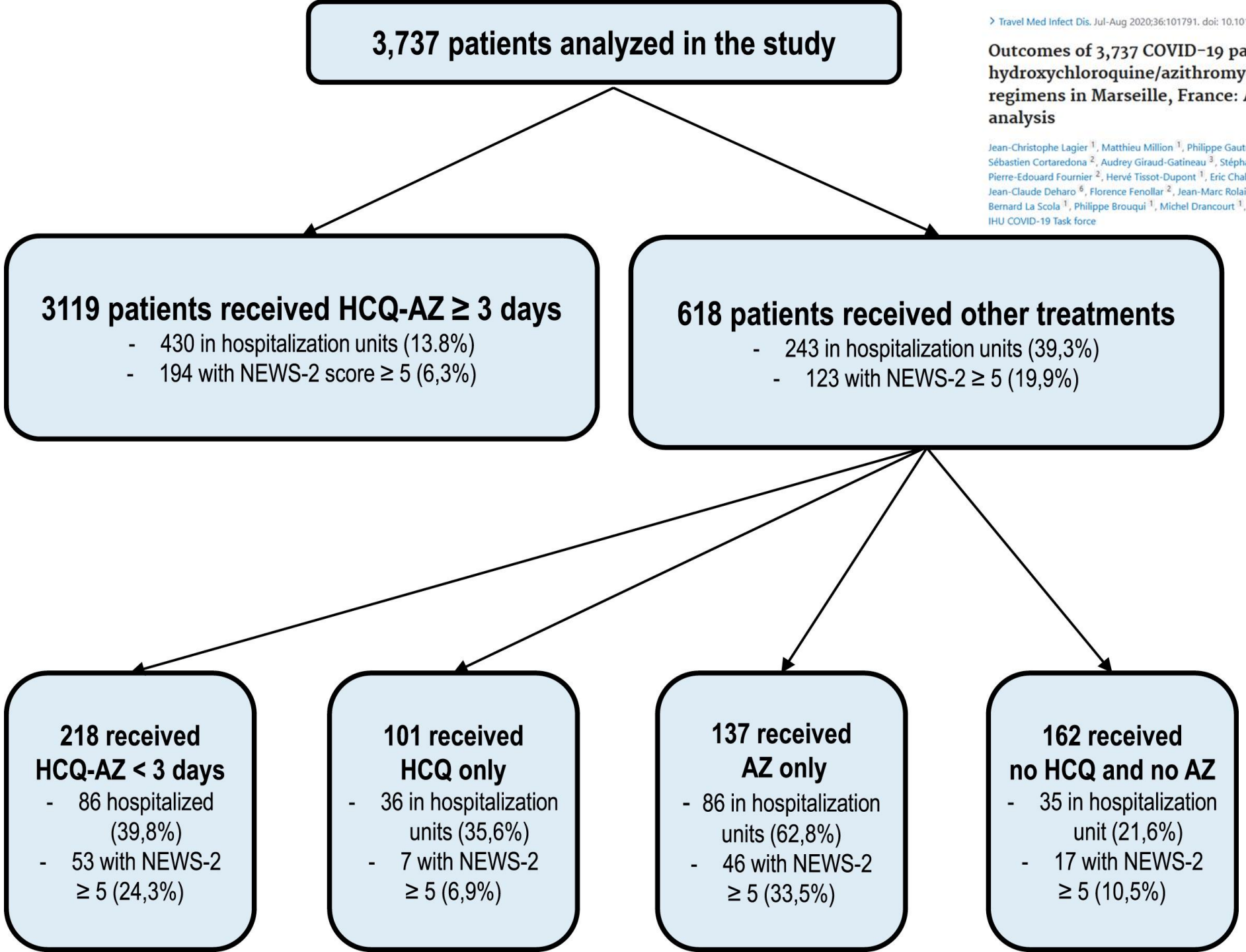
Clinical Trial > Int J Antimicrob Agents. 2020 Jul;56(1):105949.
doi: 10.1016/j.ijantimicag.2020.105949. Epub 2020 Mar 20.

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Philippe Gautret [1], Jean-Christophe Lagier [2], Philippe Parola [1], Van Thuan Hoang [3], Line Meddeb [4], Morgane Mailhe [4], Barbara Doudier [4], Johan Courjon [5], Valérie Giordanengo [6], Vera Esteves Vieira [4], Hervé Tissot Dupont [2], Stéphane Honoré [7], Philippe Colson [2], Eric Chabrière [2], Bernard La Scola [2], Jean-Marc Rolain [2], Philippe Brouqui [2], Didier Raoult [8]



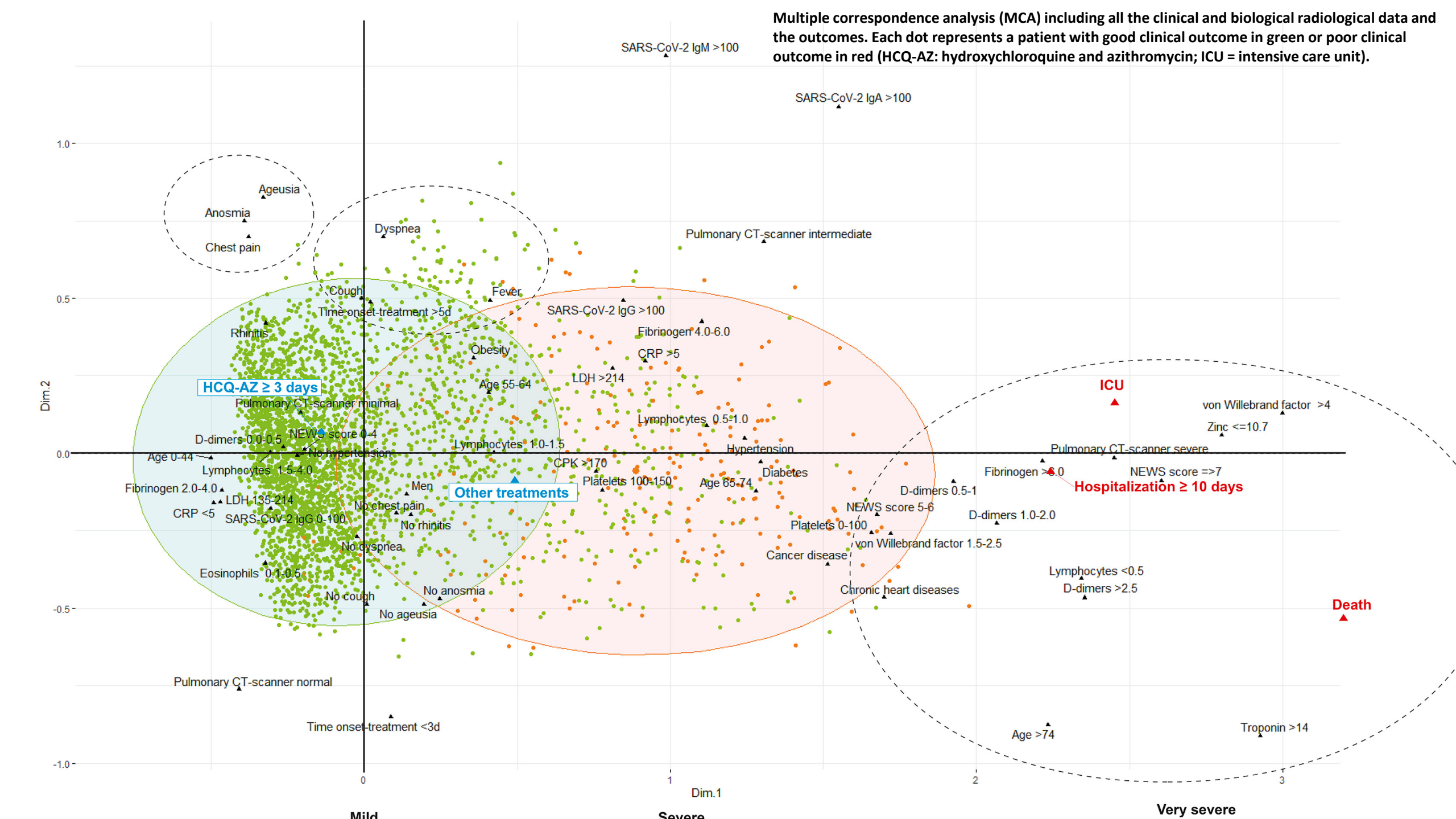


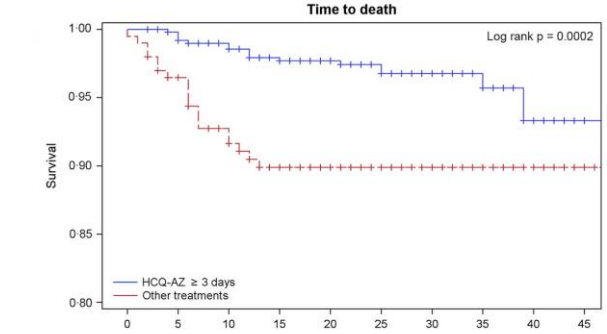


› Travel Med Infect Dis. Jul-Aug 2020;36:101791. doi: 10.1016/j.tmaid.2020.101791. Epub 2020 Jun 25.

Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis

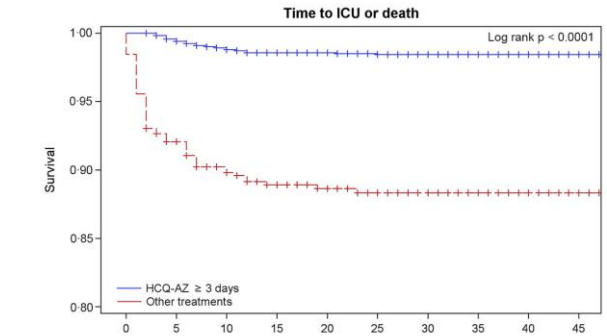
Jean-Christophe Lagier [1], Matthieu Million [1], Philippe Gautret [2], Philippe Colson [1], Sébastien Cortaredona [2], Audrey Giraud-Gatineau [3], Stéphane Honoré [4], Jean-Yves Gaubert [5], Pierre-Edouard Fournier [2], Hervé Tissot-Dupont [1], Eric Chabrière [1], Andreas Stein [1], Jean-Claude Deharo [6], Florence Fenollar [2], Jean-Marc Rolain [1], Yolande Obadia [7], Alexis Jacquier [8], Bernard La Scola [1], Philippe Brouqui [1], Michel Drancourt [1], Philippe Parola [2], Didier Raoult [9], IHU COVID-19 Task force


Multiple correspondence analysis (MCA) including all the clinical and biological radiological data and the outcomes. Each dot represents a patient with good clinical outcome in green or poor clinical outcome in red (HCQ-AZ: hydroxychloroquine and azithromycin; ICU = intensive care unit).
SARS-CoV-2 IgM >100
SARS-CoV-2 IgA >100
Ageusia
Anosmia
Chest pain
Dyspnea
Pulmonary CT-scanner intermediate
Cough
Fever
Time onset-treatment >5d
SARS-CoV-2 IgG >100
Rhinitis
Fibrinogen 4.0-6.0
Obesity
CRP >5
LDH >214
Age 55-64
HCQ-AZ ≥ 3 days
Pulmonary CT-scanner minimal
Lymphocytes 0.5-1.0
D-dimers 0.0-0.5
NEWS score 0-4
Lymphocytes 1.0-1.5
Hypertension
No hypertension
Age 0-44
CPK >170
Diabetes
Lymphocytes 1.5-4.0
Platelets 100-150
Age 65-74
Fibrinogen 2.0-4.0
Men
Other treatments
LDH 135-214
No chest pain
CRP <5
SARS-CoV-2 IgG 0-100
No rhinitis
No dyspnea
Eosinophils 0.1-0.5
No anosmia
No cough
No ageusia
Pulmonary CT-scanner normal
Time onset-treatment <3d
ICU
von Willebrand factor >4
Zinc <=10.7
Pulmonary CT-scanner severe
Fibrinogen >6.0
NEWS score =>7
Hospitalization ≥ 10 days
D-dimers 0.5-1
NEWS score 5-6
D-dimers 1.0-2.0
Platelets 0-100
von Willebrand factor 1.5-2.5
Cancer disease
Lymphocytes <0.5
D-dimers >2.5
Chronic heart diseases
Death
Age >74
Troponin >14
Dim.2
Dim.1
1.0
0.5
0.0
-0.5
-1.0
0
1
2
3
Mild
Severe
Very severe



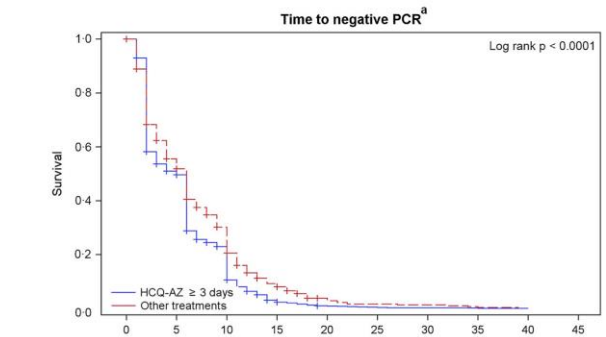
Number at risk Days since inclusion

HCQ-AZ ≥ 3 days	503	494	470	431	373	296	193	91	27	7
Other treatments	199	187	166	143	115	85	55	39	24	9



Number at risk Days since inclusion

HCQ-AZ ≥ 3 days	2365	2317	2212	2046	1785	1431	846	318	86	17
Other treatments	517	463	423	374	322	241	168	123	88	31



Number at risk Days since inclusion

HCQ-AZ ≥ 3 days	3119	1503	643	66	20	8	4	3	1	
Other treatments	618	298	151	40	12	5	4	2	0	

International Journal of Infectious Diseases 101 (2020) 283–289

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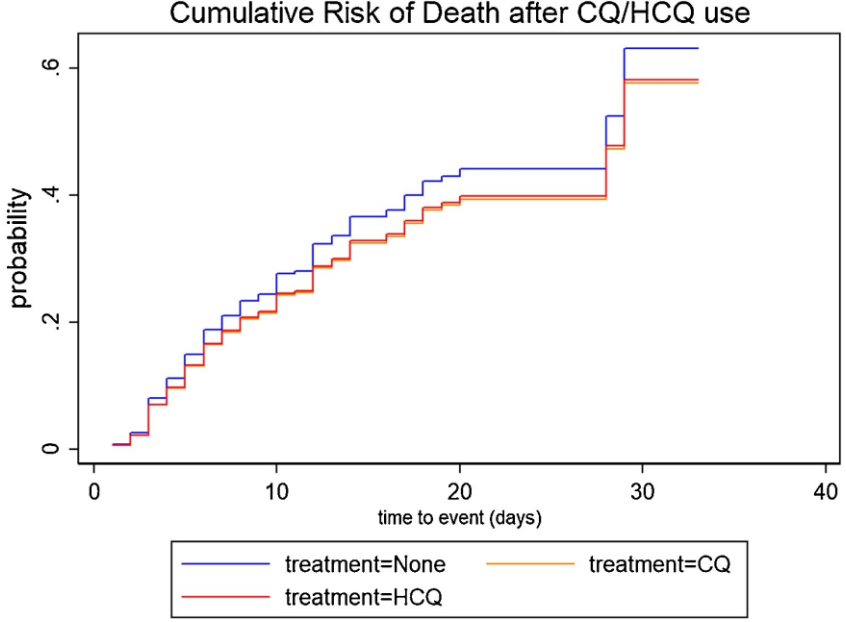
International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Early hydroxychloroquine but not chloroquine use reduces ICU admission in COVID-19 patients

A.J.J. Lammers[a,*,1], R.M. Brohet[b,1], R.E.P. Theunissen[a], C. Koster[a], R. Rood[c], D.W.M. Verhagen[d], K. Brinkman[e], R.J. Hassing[f], A. Dofferhoff[g], R. el Moussaoui[h], G. Hermanides[i], J. Ellerbroek[j], N. Bokhizzou[k], H. Visser[l], M. van den Berge[m], H. Bax[n], D.F. Postma[o], P.H.P. Groeneveld[a]



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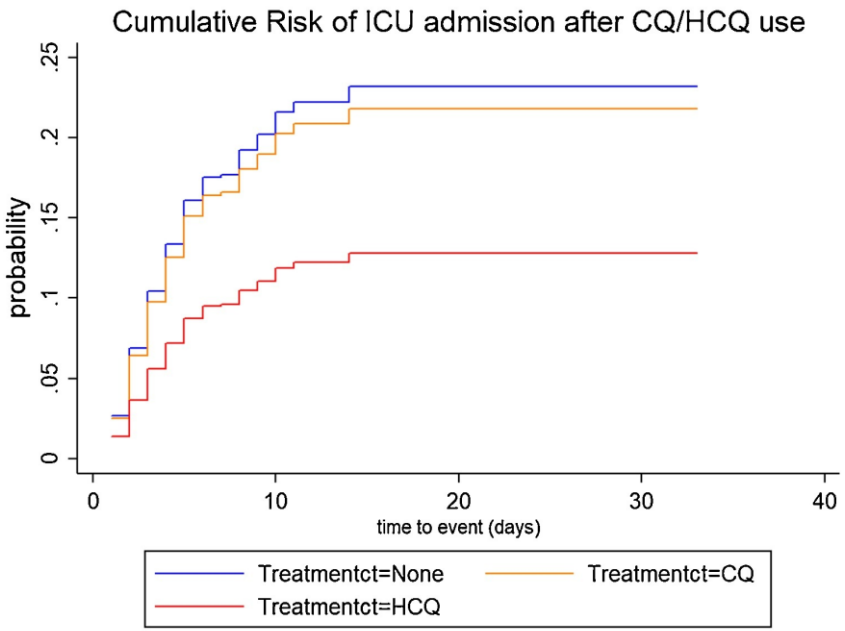


B

European Journal of Internal Medicine 000 (2020) 1–10

Contents lists available at ScienceDirect

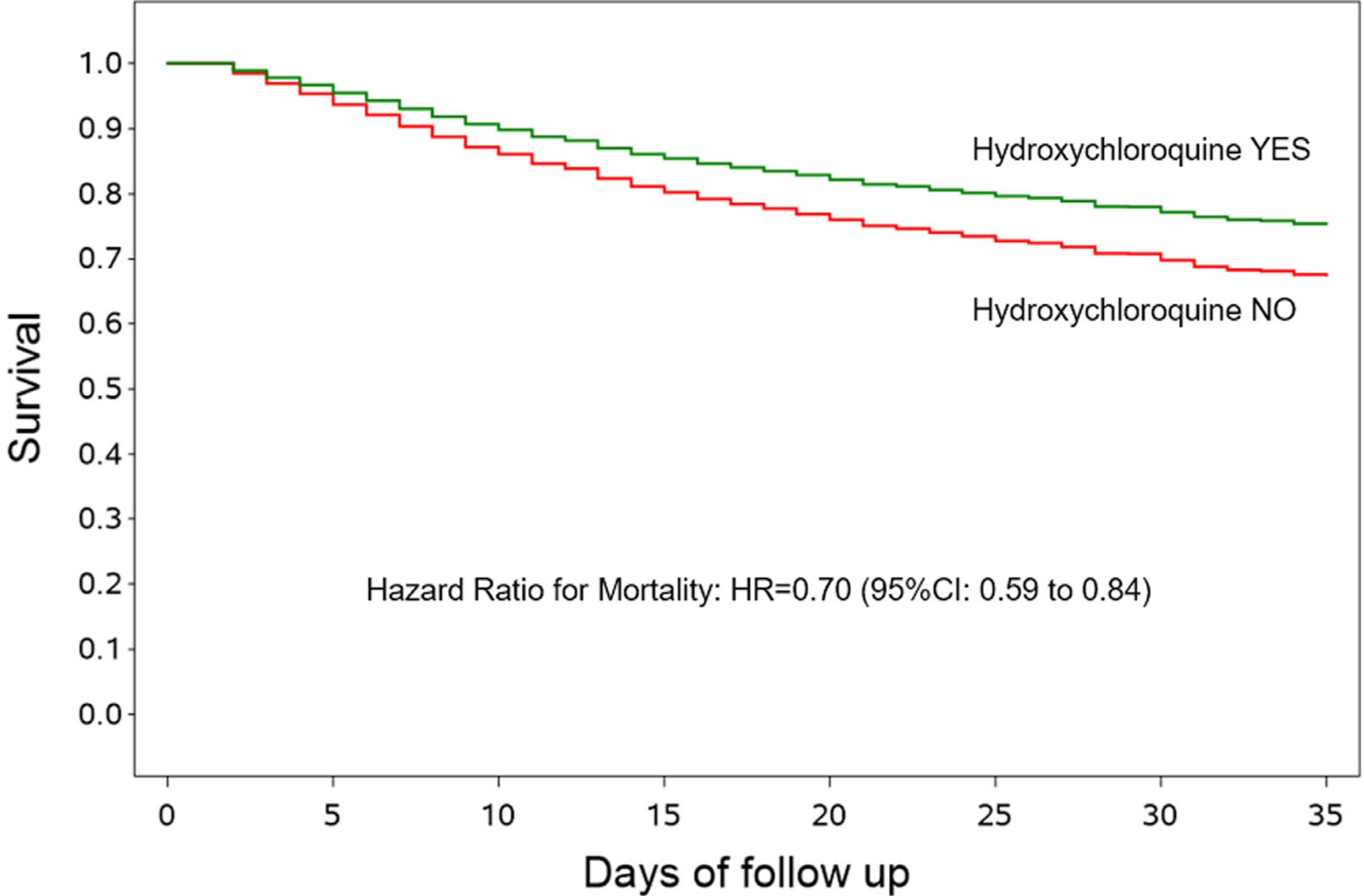
European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejinme

Original article

Use of hydroxychloroquine in hospitalised COVID-19 patients is associated with reduced mortality: Findings from the observational multicentre Italian CORIST study

The COVID-19 RISK and Treatments (CORIST) Collaboration[1,*]


Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Hydroxychloroquine YES
Hydroxychloroquine NO
Hazard Ratio for Mortality: HR=0.70 (95%CI: 0.59 to 0.84)
0
5
10
15
20
25
30
35
Days of follow up

5. Conclusions

Our study, including a large real life sample of patients hospitalized with COVID-19 all over Italy, shows that HCQ use (200 mg twice/day) was associated with a 30% reduction of overall in-hospital mortality. In the absence of clear-cut results from controlled, randomized clinical trials, our data do not discourage the use of HCQ in inpatients with COVID-19. Given the observational design of our study, however, these results should be transferred with caution to clinical practice.

HCQ, une méta-analyse sur 44 521 patients : Le traitement à faible dose entraîne une réduction de la mortalité de 8 à 35%.

Publié le 06/11/2020 à 12:13 - Mise à jour à 12:24

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Low-dose hydroxychloroquine therapy and mortality in hospitalised patients with COVID-19: a nationwide observational study of 8075 participants

Lucy Catteau[a,1], Nicolas Dauby[b,c,d,1,*], Marion Montourcy[a], Emmanuel Bottieau[e], Joris Hautekiet[a,f], Els Goetghebeur[f], Sabrina van Ierssel[g], Els Duysburgh[a], Herman Van Oyen[a,h], Chloé Wyndham-Thomas[a], Dominique Van Beckhoven[a], Belgian Collaborative Group on COVID-19 Hospital Surveillance[2]

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[b] *Department of Infectious Diseases, CHU Saint-Pierre, Brussels, Belgium*
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[d] *Environmental Health Research Centre, Public Health School, Université Libre de Bruxelles (ULB), Brussels, Belgium*
[e] *Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium*
[f] *Department of Applied Mathematics, Computer Science and Statistics, Ghent University, Ghent, Belgium*
[g] *Department of General Internal Medicine, Infectious Diseases and Tropical Medicine, University Hospital Antwerp (UZA), Edegem, Belgium*
[h] *Public Health and Primary Care, Gent University, Gent, Belgium*

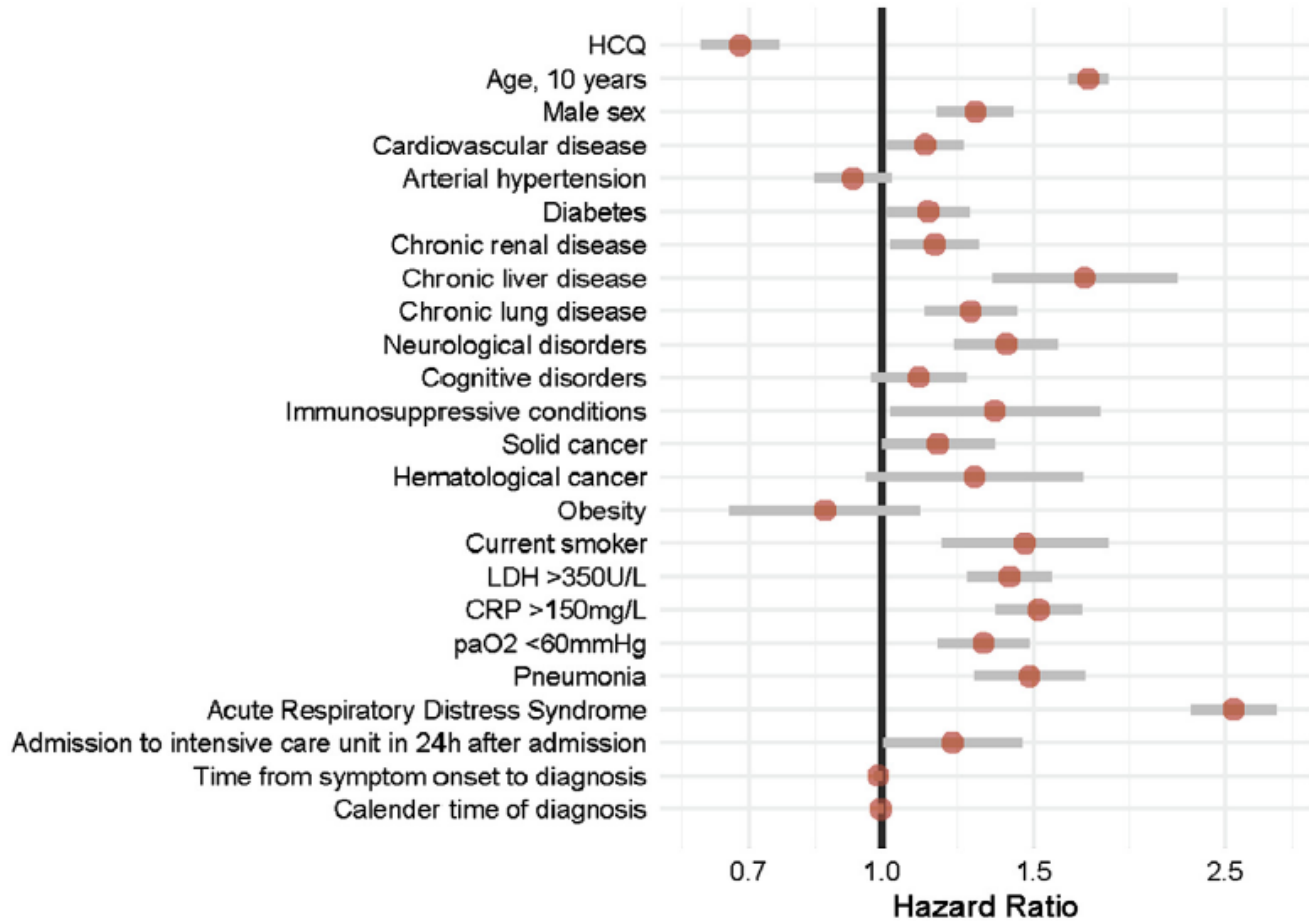


Fig. 2. Independent predictors of in-hospital mortality among 8075 patients with coronavirus disease 2019 (COVID-19). Competing risks proportional hazards regression with robust standard errors analysing in-hospital death competing with alive discharge from hospital. HCQ, hydroxychloroquine; LDH, lactate dehydrogenase; CRP, C-reactive protein; paO_2, partial pressure of oxygen.

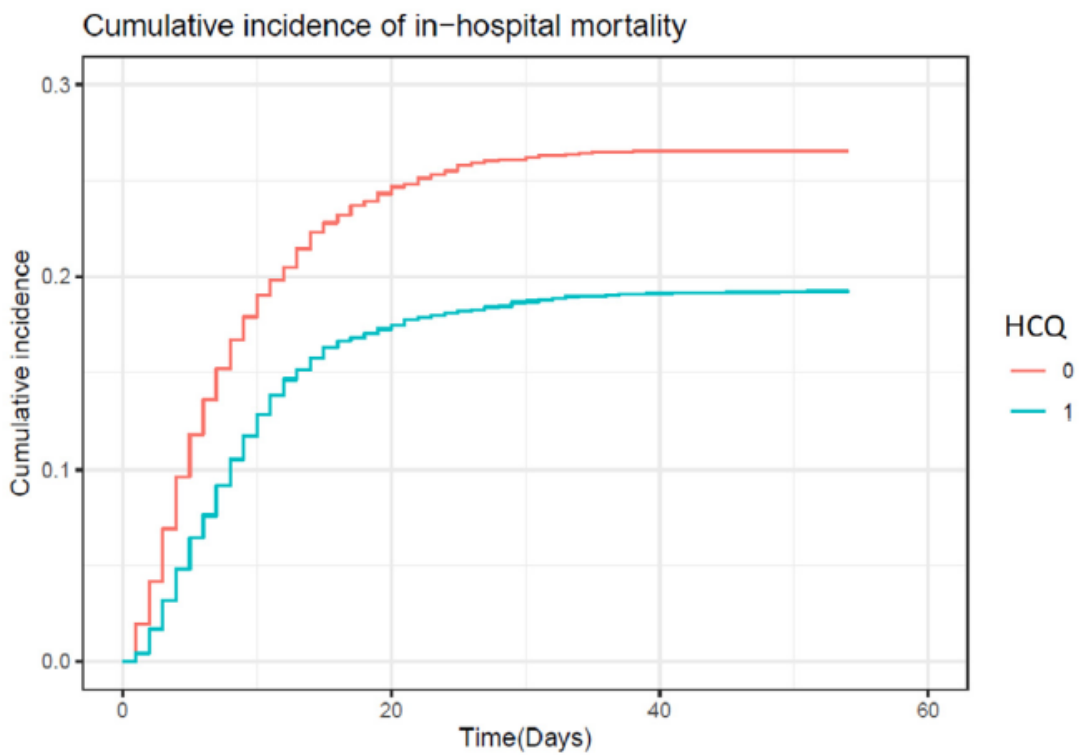


Fig. 3. Cumulative incidence of in-hospital mortality. Inverse propensity-weighted standardised cumulative incidence of in-hospital death according to treatment received: hydroxychloroquine (HCQ) (blue line) versus no-HCQ (red line).

Ram Niwas[1], Aneesa Shahul S[1], M K Garg[2], Vijaya Lakshmi Nag[3], Pradeep Kumar Bhatia[4], Naveen Dutt[1], Nishant Chauhan[1], Jaykaran Charan[5], Shahir Asfahan[1], Praveen Sharma[6], Pankaj Bhardwaj[7], Mithu Banerjee[6], Pawan Garg[8], Binit Sureka[8], Gopal Krishna Bohra[2], Maya Gopalakrishnan[2], Sanjeev Misra[9]

Advances in Respiratory Medicine 2020, vol. 88, no. 6, pages 515–519

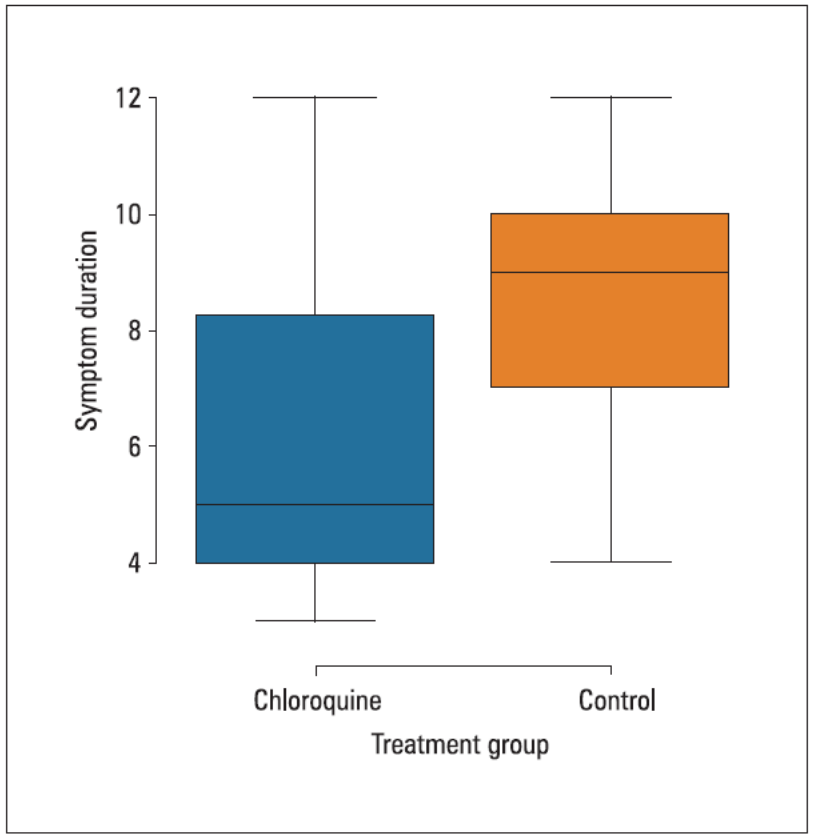


Figure 2. Box-plot showing the distribution of time-to-symptom resolution between the CQ and control arms

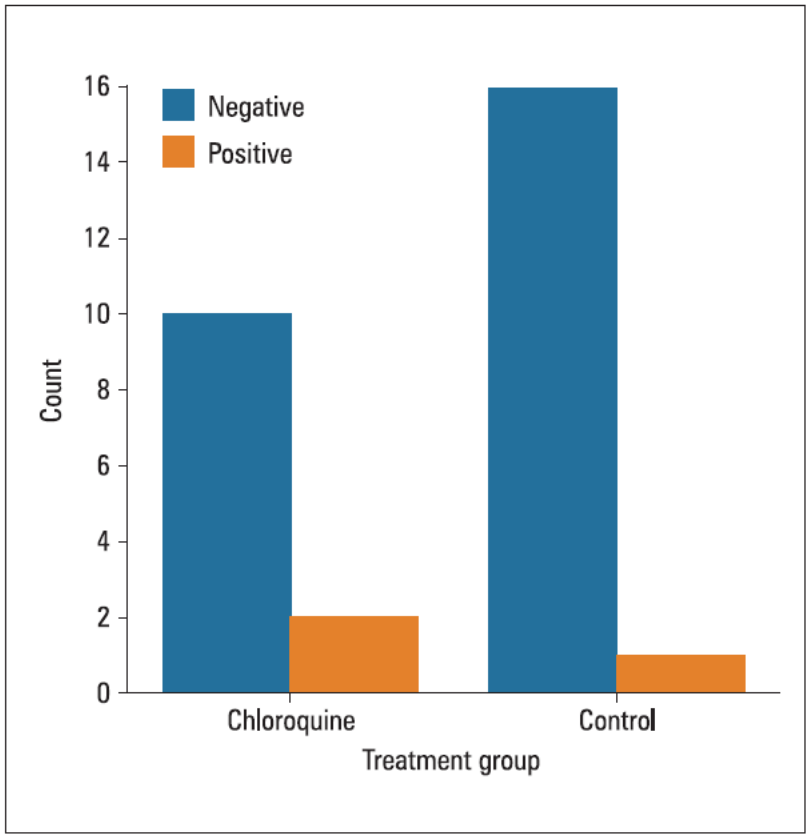


Figure 3. Bar plot showing RT-PCR conversion rate at the end of 2 weeks of hospitalization

Effectiveness of hydroxychloroquine in COVID-19 disease: A done and dusted deal?

A. d'Arminio Monforte et al IJID 2020

Table 1
Unadjusted and adjusted marginal relative hazards of in-hospital mortality

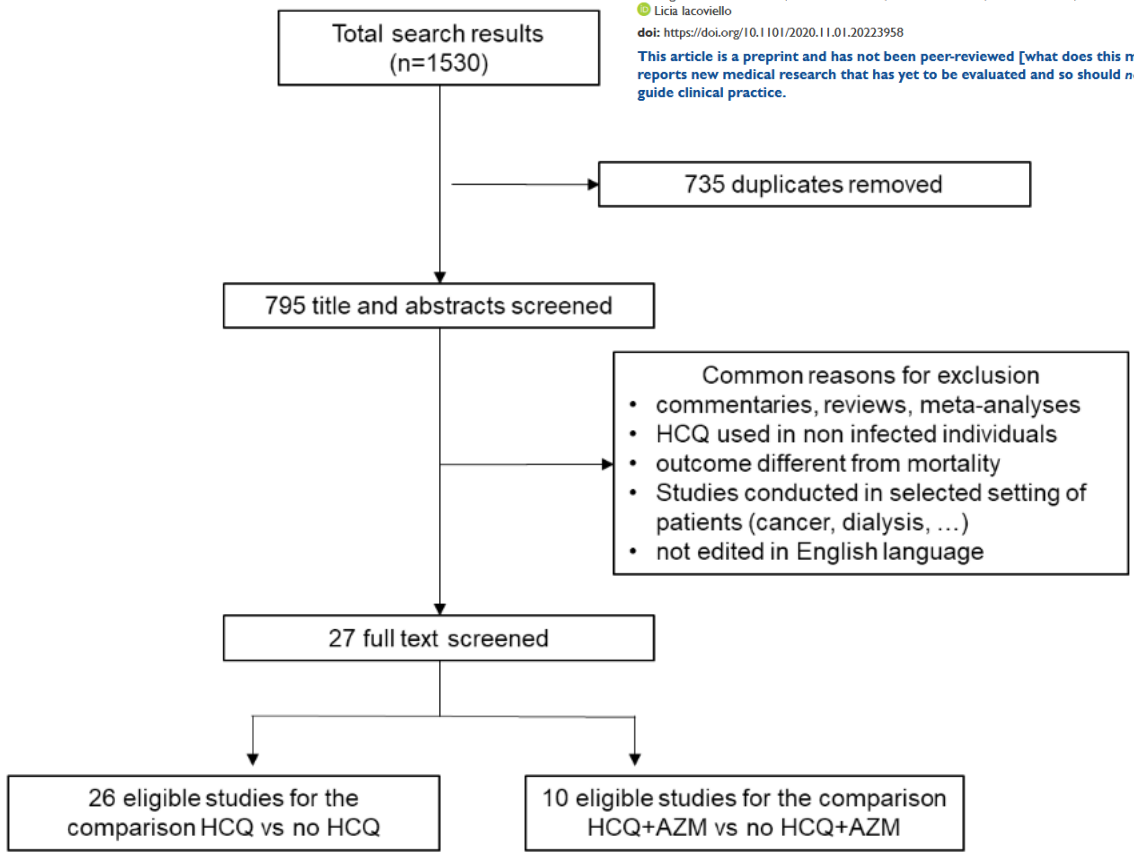
	Unadjusted HR (95% CI)	*p*-Value	Adjusted* £ HR (95% CI)	*p*-Value
	All patients			
Control# (*n* = 92)	1.00		1.00	
Hydroxychloroquine (*n* = 197)	0.43 (0.28, 0.64)	<0.001	0.66 (0.39, 1.11)	0.118
Hydroxychloroquine + Azithromycin (*n* = 94)	0.36 (0.21, 0.60)	<0.001	0.44 (0.24, 0.82)	0.009
	&Baseline PO2/FiO2 0-300			
Control# (*n* = 41)	1.00		1.00	
Hydroxychloroquine (*n* = 83)	0.52 (0.31, 0.87)		0.71 (0.37, 1.35)	
Hydroxychloroquine + Azithromycin (*n* = 28)	0.46 (0.23, 0.93)		0.59 (0.26, 1.35)	
				p-Value for interaction <0.001
	&Baseline PO2/FiO2 300+			
Control# (*n* = 33)	1.00		1.00	
Hydroxychloroquine (*n* = 100)	0.39 (0.15, 0.97)		0.49 (0.15, 1.63)	
Hydroxychloroquine + Azithromycin (*n* = 60)	0.56 (0.21, 1.52)		0.62 (0.19, 1.97)	

* Adjusted for age, gender, number of comorbidities, CVD (yes/no), duration of symptoms, date of admission, CRP and censoring using IPW.
£ The overall estimate was also adjusted for baseline COVID-19 disease severity.
Heparin, immuno-modulatory drugs, HIV antivirals, combinations of these or no drugs at all.
& 45 patients missing baseline PO2/FiO2 not included in the stratified analysis.

http://dx.doi.org/10.1016/j.ijid.2020.07.056

Although unmeasured confounding remains the most likely explanation for the discrepancies, a robust meta-analysis is still lacking, and we believe that hydroxychloroquine should be further tested in randomised trials. When best to start treatment is also a question that needs to be addressed in ad-hoc randomized studies.

Figure 1



HCQ means hydroxychloroquine; AZM means azithromycin

Figure 2

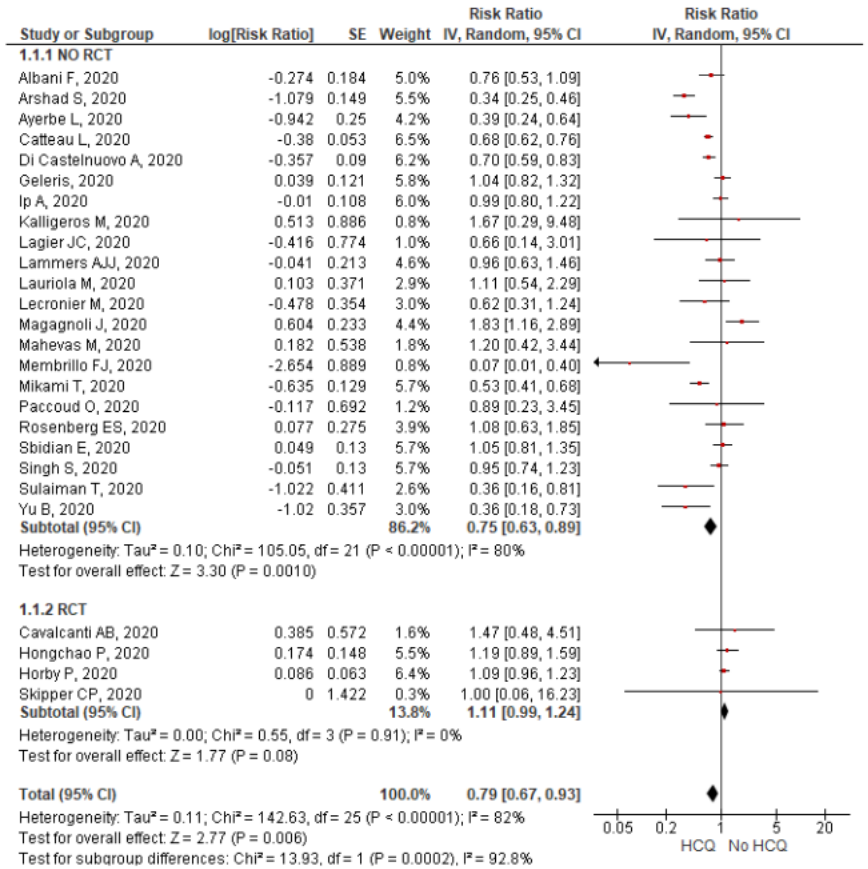
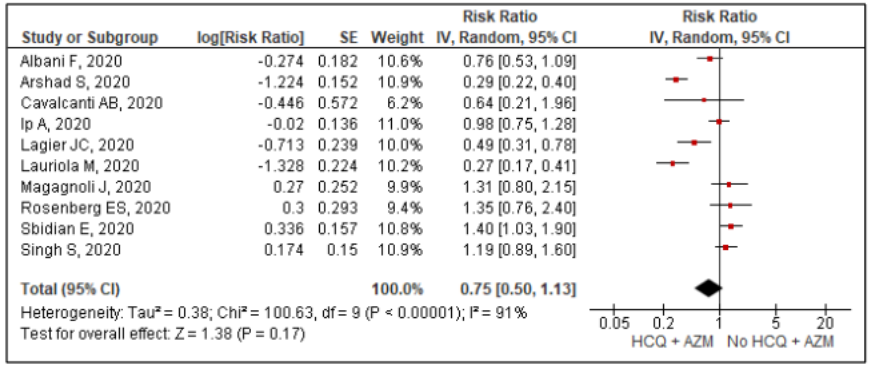


Figure 3

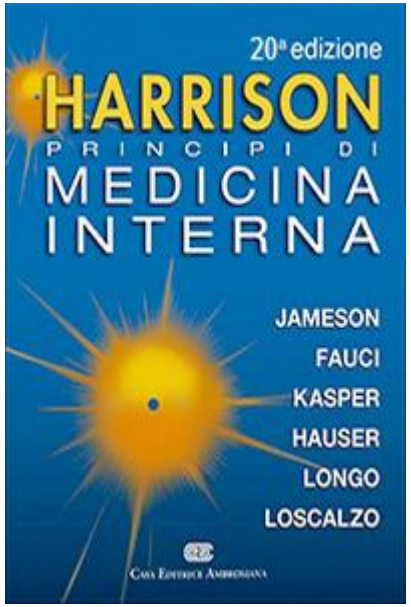


HCQ means hydroxychloroquine; AZM means azithromycin

Conclusions: HCQ use was not associated with either increased or decreased mortality in COVID-19 patients when 4 RCTs only were evaluated, while a 7% to 33% reduced mortality was observed when observational studies were also included. The association was mainly apparent when pooling studies using lower doses of HCQ. These findings can help disentangling the debate on HCQ use in COVID-19.

Le **linee guida IDSA** concludono che la certezza della prova per il trattamento con idrossiclorochina è “moderata” per un rischio di un trend negativo verso l’aumento di mortalità. Lo stesso panel esprime che la certezza della prova è peggiore per l’associazione idrossiclorochina + azitromicina, specie per quanto attiene la sicurezza. Le linee guida IDSA si esprimono contro l’uso di idrossiclorochina da sola e/o in combinazione con azitromicina per il trattamento dei pazienti ospedalizzati per COVID-19. Le **linee guida OMS** non raccomandano (raccomandazione forte) l’uso di idrossiclorochina nei pazienti COVID-19.

Tratto dal paragrafo «Terapia» del Capitolo «COVID-19» redatto da G. Carosi, R. Cauda, G. Antonelli, A. Pession. 2021



AGENZIA ITALIANA DEL FARMACO

Idrossiclorochina nella terapia dei pazienti adulti con COVID-19

Update del 22 dicembre 2020

(precedenti pubblicazioni: 2 aprile 2020; 29 aprile 2020; 29 maggio 2020; 22 luglio 2020; 25 novembre 2020)

Si forniscono di seguito elementi utili ad orientare la prescrizione e a definire un rapporto fra i benefici e i rischi sul singolo paziente.	
Per quali pazienti è raccomandabile?	Alla luce delle evidenze che si sono progressivamente accumulate nell'uso terapeutico su pazienti ricoverati e che dimostrano la completa mancanza di efficacia a fronte di un aumento di eventi avversi, seppur non gravi, AIFA non raccomanda l'utilizzo dell'idrossiclorochina nei pazienti con COVID-19 in ospedale. AIFA inoltre non ritiene utile né opportuno autorizzare nuovi studi clinici nei pazienti ricoverati. Nei pazienti con infezione da SARS-CoV-2 gestiti a domicilio, di bassa gravità e nelle fasi iniziali della malattia, esistono evidenze più limitate che dimostrano la mancanza di efficacia a fronte di un aumento degli eventi avversi, seppur non gravi, pertanto AIFA non raccomanda l'utilizzo dell'idrossiclorochina. Una eventuale prescrizione nei singoli casi si configurerebbe quindi come uso *off label*. In tale setting può ancora essere consentita l'esecuzione di studi clinici randomizzati controllati al fine di rendere conclusive le conoscenze disponibili. Per analogia tale conclusione si intende applicata anche alla clorochina.
A quali dosaggi è preferibilmente prescrivibile e in quali forme?	L'utilizzo di dosi elevate di HCQ aumenta il rischio di eventi avversi. Per tale ragione, anche nell'ambito di eventuali studi clinici, si raccomanda di utilizzare il dosaggio più basso e per il minor tempo possibile (5-7 giorni).

医政医管局

通告公告

关于印发新型冠状病毒肺炎诊疗方案（试行第八版）的通知

发布时间： 2020-08-19 来源: 医政医管局

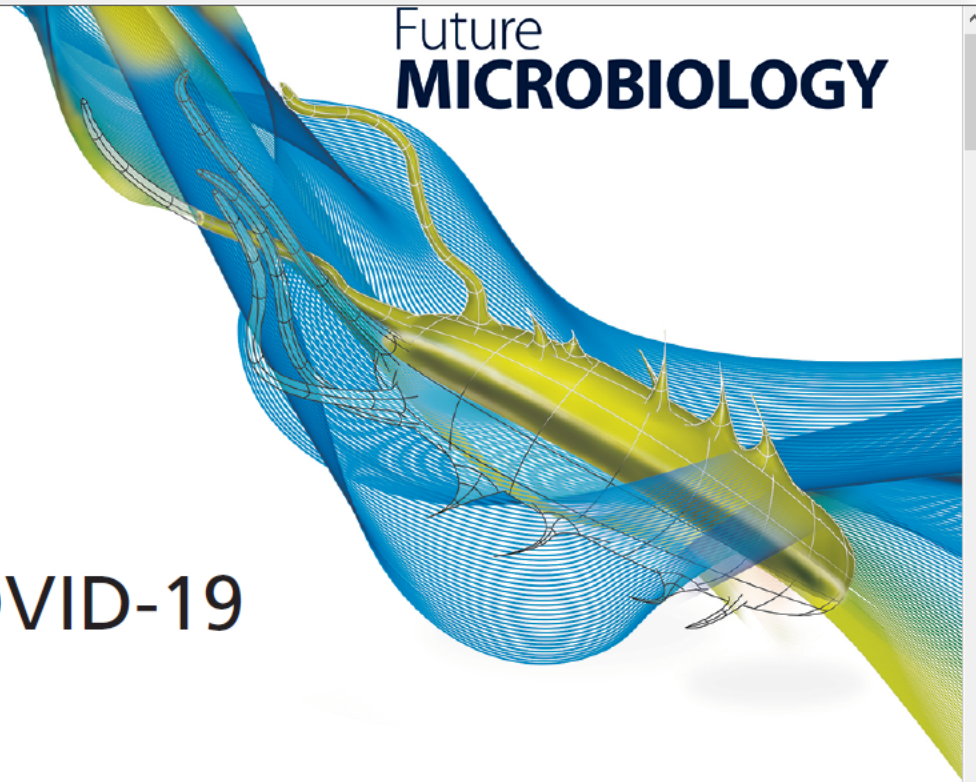
国卫办医函〔2020〕680号

各省、自治区、直辖市及新疆生产建设兵团卫生健康委、中医药管理局:

为进一步做好新型冠状病毒肺炎医疗救治工作，我们组织专家在总结前期新冠肺炎诊疗经验和参考世界卫生组织及其他国家诊疗指南基础上，对诊疗方案进行修订，形成了《新型冠状病毒肺炎诊疗方案（试行第八版）》。现印发给你们，请参照执行。

附件：新型冠状病毒肺炎诊疗方案（试行第八版）

Future MICROBIOLOGY



Editorial

Knowing more about chloroquine/hydroxycloroquine in COVID-19 patients

Antonio Cassone[1], Licia Iacoviello[2,3] & Roberto Cauda*[,4]

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"Overall, the potential therapeutic or prophylactic activity of CQ/HCQ remains undetermined."