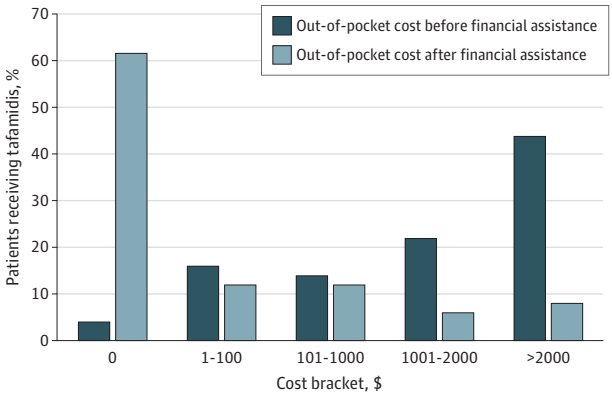
Figure. Tafamidis Out-of-Pocket Costs



Distribution of tafamidis out-of-pocket costs for all patients before any assistance programs were applied to and after 28 patients (56%) received financial assistance.

program, a specialty pharmacy, and a dedicated pharmacist who spent an average of 1 hour per patient to ensure they can afford tafamidis. As such, our experience might not be easily applicable to other health care settings.

Ahmad Masri, MD, MS
Hongya Chen, PharmD
Catherine Wong, MD
Katherine L. Fischer, MSN, RN
Chafic Karam, MD
Walid F. Gellad, MD, MPH
Stephen B. Heitner, MD

Author Affiliations: The Knight Cardiovascular Institute, Oregon Health & Science University, Portland (Masri, Chen, Wong, Fischer, Heitner); Oregon Health & Science University Amyloidosis Center, Portland (Masri, Chen, Wong, Fischer, Karam, Heitner); Department of Neurology, Oregon Health & Science University, Portland (Karam); Center for Pharmaceutical Policy and Prescribing, Division of General Internal Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania (Gellad).

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Corresponding Author: Ahmad Masri, MD, MS, Oregon Health and Science University, 3181 SW Sam Jackson Rd, Mail Code: UHN-62, Portland, OR 97239 (masria@ohsu.edu).

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Author Contributions: Dr Masri had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Masri, Wong, Heitner.
Acquisition, analysis, or interpretation of data: Masri, Chen, Fischer, Karam, Gellad, Heitner.
Drafting of the manuscript: Masri, Heitner.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Masri, Heitner.
Administrative, technical, or material support: Masri, Chen, Fischer, Karam, Heitner.
Supervision: Masri, Chen, Heitner.

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Assessment of QT Intervals in a Case Series of Patients With Coronavirus Disease 2019 (COVID-19) Infection Treated With Hydroxychloroquine Alone or in Combination With Azithromycin in an Intensive Care Unit

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The novel coronavirus disease 2019 (COVID-19) outbreak is an ongoing situation caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Studies in patients with mild to moderate COVID-19 symptoms have suggested benefits of hydroxychloroquine alone or in combination with azithromycin against SARS-CoV-2 and raised hope for treating the disease.[2] As a result, these treatments are increasingly used off-label for patients with COVID-19, including for those in intensive care units (ICUs).[2,3] However, both medications are known to induce QT prolongation via a human Ether-à-go-go-related gene potassium channel blockade, which can promote life-threatening ventricular arrhythmias.[4,5] Safety data for these treatments are largely lacking for patients with COVID-19. This is even more relevant for critically ill patients who are particularly exposed to electrolyte imbalance and/or drugs leading to an increased risk of QT prolongation.[6] Therefore, we aimed to examine the safety of hydroxychloroquine with or without azithromycin regarding QT interval in ICU patients with COVID-19.

Methods | This study was approved by our institutional ethics committee (Comité d'Ethique du CHU de Lyon) with a waiver for informed consent because of the retrospective nature of the study. All consecutive patients with COVID-19 confirmed by positive reverse transcription–polymerase chain reaction results on respiratory samples admitted to the ICU who received hydroxychloroquine (200 mg, twice a day, for 10 days) with or without azithromycin (250 mg, daily, for 5 days) were included. Treatment began in the absence of contraindication, including corrected QT (QTc) intervals greater than 460 milliseconds (Bazett formula). All other drugs (given before or after ICU admission) listed in CredibleMeds (https://crediblemeds.org) with known or possible risk of QT prolongation/torsades de pointes were classified as drugs

Table. Patient Characteristics According to QT Interval Prolongation After Beginning Antiviral Therapy

Variable	No. (%)			*P* value
	Total (N = 40)	QTc ≥500 ms or ΔQTc >60 ms (n = 14)	QTc <500 ms and ΔQTc ≤60 ms (n = 26)	
Demographic characteristics				
Age, median (IQR), y	68 (58-74)	71 (66-75)	66 (56-73)	.35
Women, No. (%)	8 (20)	4 (29)	4 (15)	.42
BMI, median (IQR)	28 (25-33)	32 (27-34)	28 (25-31)	.09
Comorbidities				
Diabetes	16 (40)	8 (57)	8 (30)	.18
Hypertension	23 (57.5)	10 (71.4)	13 (48)	.32
Structural heart disease	8 (20)	4 (28.6)	4 (15.4)	.42
Usual treatments favoring prolonged QT	3 (8)	1 (7)	2 (8)	.62
Treatments favoring prolonged QT in ICU				
Hydroxychloroquine alone	22 (55)	7 (50)	15 (58)	.33
Hydroxychloroquine and azithromycin	18 (45)	7 (50)	11 (42)	.33
Other[a]	20 (50)	8 (57)	12 (46)	.51
Electrocardiograms				
Sinus rhythm	40 (100)	14 (100)	26 (100)	>.99
Baseline heart rate, median (IQR), bpm	78 (72-90)	82 (75-89)	77 (70-89)	.76
QTc before start of antivirals, median (IQR), ms	414 (392-428)	416 (383-440)	415 (401-425)	.88
ΔQTc, median (IQR), ms	35 (10-66)	81 (70-86)	16 (6-29)	<.001
Maximum QTc, median (IQR), ms	454 (420-480)	500 (470-520)	428 (417-448)	<.001
Delay before longest QTc, median (IQR), d	3 (2-5)	5 (2-5)	3 (2-4)	.13
Serum potassium <3.5 mEq/L	11 (28)	5 (36)	6 (23)	.47
Organ support				
Invasive mechanical ventilation	30 (75)	12 (86)	18 (67)	.68
Vasoactive drugs	25 (63)	12 (86)	13 (48)	.04
Renal replacement therapy	7 (18)	2 (14)	5 (19)	.70
SAPS II score, median (IQR), points	35 (26-48)	46 (35-61)	34 (26-37)	.04

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ICU, intensive care unit; IQR, interquartile range; QTc, corrected QT; ΔQTc, difference between maximum QTc and baseline QTc; SAPS II, simplified acute physiology score II.

SI conversion factor: To convert potassium to mmol/L, multiply by 1.

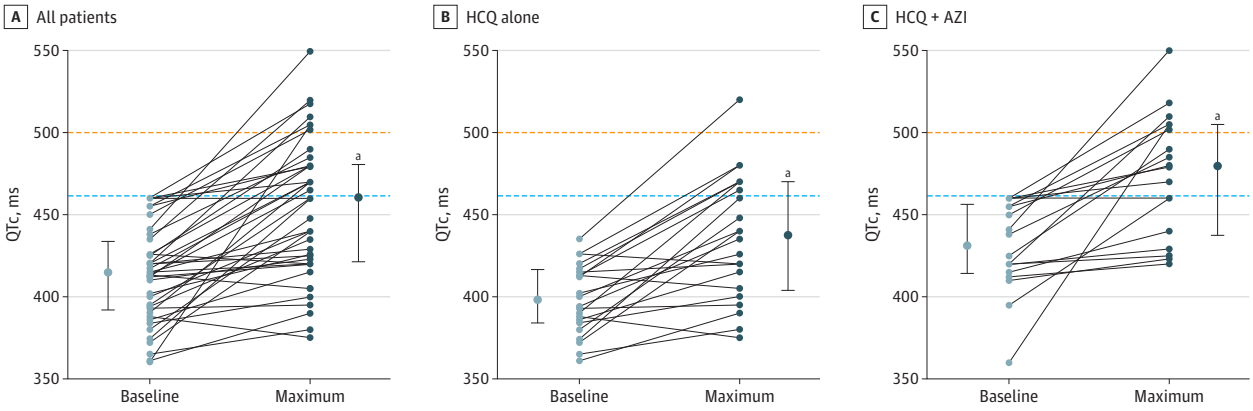
[a] Propofol, amiodarone, ciprofloxacin, and ondansetron.

favoring prolonged QT. The QTc interval was continuously monitored; an electrocardiogram (ECG) was recorded daily. All ECGs were retrospectively reviewed by 2 masked cardiac electrophysiologists. As previously described, prolonged QTc was defined as an increase in QTc intervals of more than 60 milliseconds (ΔQTc >60 milliseconds) compared with baseline or as a QTc of 500 milliseconds or greater.[4] Data, expressed as median (interquartile range [IQR]) and number (percentage), were compared using Mann-Whitney *U*, Wilcoxon matched-pairs signed rank, or Fisher exact tests as appropriate.

Results | Forty patients with COVID-19 (median age, 68 years [IQR, 58-74 years]; 32 men [80%]) were included between March 15 and March 29, 2020 (**Table**). Thirty patients (75%) required invasive mechanical ventilation and 25 (63%) received vasoactive drugs (Table). Hydroxychloroquine with or without azithromycin was given to 18 (45%) and 22 patients (55%), respectively. Twenty patients (50%) also received other treatments favoring QT prolongation in the ICU (Table). Most patients (37 [93%]) showed an increase in QTc after the administration of antiviral therapy (**Figure**). Prolonged QTc was observed in 14 patients (36%) (10 with ΔQTc >60 milliseconds and 7 with QTc ≥500 milliseconds) after a duration of antiviral treatment of 2 to 5 days. No ventricular arrhythmia, including torsades de pointes, was recorded. As shown in the Figure, among patients treated with hydroxychloroquine and azithromycin, 6 of 18 (33%) developed an increase in QTc of 500 milliseconds or greater vs 1 of 22 (5%) of those treated with hydroxychloroquine alone (*P* = .03). The antiviral treatment ceased before completion for 7 patients (17.5%) following ECG abnormalities and in 10 (25%) for acute renal failure.

Discussion | This study raises safety concerns about the use of hydroxychloroquine with or without azithromycin for patients with COVID-19, particularly when both drugs are administered together. There were no baseline clinical factors associated with subsequent QT prolongation. In our cohort, close monitoring of patients (including continuous QTc interval monitoring, daily ECGs, and laboratory tests), which led to an interruption of these drugs for 17 patients (42.5%), may have averted further complications, including drug-induced torsades de pointes. Key limitations of the present case series include a potential lack of generalizability beyond the ICU. However, the finding that QTc intervals increased in more than 90%

Figure. Individual Baseline and Maximal Corrected QT Interval Values in Patients With Coronavirus Disease 2019 (COVID-19) Treated With Hydroxychloroquine and Azithromycin



Individual baseline (pretreatment) and maximal corrected (QTc) interval values are shown for 40 critically ill patients with COVID-19 treated with hydroxychloroquine alone (22 [55.0%]) or in association (18 [45.0%]) with azithromycin. Median and interquartile range values of QTc before and after the start of hydroxychloroquine/azithromycin. Horizontal blue and orange dashed lines represent the upper normal value of the QTc interval (460 milliseconds) and the QTc cutoff value of 500 milliseconds (high risk of ventricular arrhythmia).

[a] $P < .01$.

of patients raises concerns about the widespread use of hydroxychloroquine, with or without azithromycin, to treat COVID-19 in settings where patients cannot be adequately monitored.

Francis Bessière, MD, PhD
Hugo Roccia, MD
Antoine Delinière, MD
Rome Charrière, MD
Philippe Chevalier, MD, PhD
Laurent Argaud, MD, PhD
Martin Cour, MD, PhD

Author Affiliations: Hospices Civils de Lyon, Hôpital Cardiologique Louis Pradel, Service d'électrophysiologie et de Stimulation Cardiaque, Université de Lyon, Lyon, France (Bessière, Delinière, Chevalier); Hospices Civils de Lyon, Hôpital Cardiologique Louis Pradel, Centre de Référence National des Troubles du Rythme Cardiaque d'origine Héréditaire, Lyon, France (Bessière, Delinière, Chevalier, Cour); Hospices Civils de Lyon, Hôpital Edouard Herriot, Médecine Intensive - Réanimation, Lyon, France (Roccia, Argaud); Centre Hospitalier de Valence, Service de Maladies Infectieuses, Valence, France (Charrière).

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Corresponding Author: Martin Cour, MD, PhD, Médecine Intensive-Réanimation, Hôpital Edouard Herriot, 5, Place d'Arsonval, 69437 Lyon Cedex 03, France (martin.cour@chu-lyon.fr).

Author Contributions: Drs Bessière and Cour had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Bessiere, Roccia, Chevalier, Argaud, Cour.
Acquisition, analysis, or interpretation of data: Bessiere, Roccia, Deliniere, Charriere, Chevalier, Cour.
Drafting of the manuscript: Bessiere, Roccia, Chevalier, Cour.
Critical revision of the manuscript for important intellectual content: Bessiere, Roccia, Deliniere, Charriere, Argaud, Cour.
Statistical analysis: Bessiere, Cour.
Supervision: Bessiere, Deliniere, Chevalier, Argaud, Cour.

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COMMENT & RESPONSE

Myocardial Injury in COVID-19—Can We Successfully Target Inflammation?

To the Editor One of the most intriguing issues that rapidly arose in the clinical management of patients with coronavirus disease 2019 (COVID-19) was concurrent myocardial injury with or without corresponding symptoms. Therefore, we read with