Safely Administering Potential QTc Prolonging Therapy Across a Large Healthcare System in the COVID-19 Era

Running title: *Saleh et al.; Administering QTc Prolonging Therapy in COVID Era*

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Abstract:

Background - The SARs-CoV-2 coronavirus has resulted in a global pandemic. Hydroxychloroquine ± azithromycin have been widely used to treat COVID-19 despite a paucity of evidence regarding efficacy. The incidence of torsade de pointes (TdP) remains unknown. Widespread use of these medications forced overwhelmed healthcare systems to search for ways to effectively monitor these patients while simultaneously trying to minimize healthcare provider (HCP) exposure and use of personal protective equipment (PPE).

Methods - COVID-19 positive patients that received hydroxychloroquine ± azithromycin across 13 hospitals between March 1st and April 15th were included in this study. A comprehensive search of the electronic medical records was performed using a proprietary python script to identify any mention of QT prolongation, ventricular tachy-arrhythmias and cardiac arrest.

Results - The primary outcome of TdP was observed in 1 (0.015%) out of 6,476 hospitalized COVID-19 patients receiving hydroxychloroquine ± azithromycin. Sixty-seven (1.03%) had hydroxychloroquine ± azithromycin held or discontinued due to an average QT prolongation of 60.5±40.5ms from a baseline QTc of 473.7±35.9ms to a peak QTc of 532.6±31.6ms. Of these patients, hydroxychloroquine ± azithromycin were discontinued in 58 patients (86.6%), while one or more doses of therapy were held in the remaining nine (13.4%). A simplified approach to monitoring for QT prolongation and arrythmia was implemented on April 5th. There were no deaths related to the medications with the simplified monitoring approach and HCP exposure was reduced.

Conclusions - The risk of torsade de pointes is low in hospitalized COVID-19 patients receiving hydroxychloroquine ± azithromycin therapy.

Key words: QT interval electrocardiography; torsade de pointes; telemetry; COVID-19; Hydroxychloroquine; pandemic; Azithromycin

Nonstandard Abbreviations and Acronyms:

AZM – Azithromycin

EMR – Electronic medical record

FDA – Federal drug administration

HCP – Health care provider

HCQ – Hydroxychloroquine

MCOT – Mobile continuous telemetry

NSVT – Non-sustained ventricular tachycardia

PMVT – Polymorphic ventricular tachycardia

PPE – Personal protective equipment

QTc – Corrected QT interval

TdP – Torsade de pointes

VF – Ventricular fibrillation

VT – Ventricular tachycardia

WCT – Wide complex tachycardia

Introduction

The SARs-CoV-2 novel virus, first identified in China, has rapidly spread across the world resulting in over 2.3 million infections and over 150,000 deaths[1]. There are multiple randomized control trials currently underway designed to find an effective therapy to combat the global pandemic. Based on limited in-vitro studies showing viral infection and replication inhibition, and a small study, that was subsequently withdrawn, hydroxychloroquine (HCQ) with and without azithromycin (AZM) was widely promoted to treat COVID-19 patients[2,3]. Of major concern has been the risk of QT prolongation and torsade de pointes (TdP) with the use of these agents individually, and even more so when used in combination. Widespread use of these

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medications created a dilemma as overwhelmed healthcare systems searched for ways to effectively monitor these patients while simultaneously trying to minimize healthcare provider (HCP) exposure and use of personal protective equipment (PPE). Initially, serial electrocardiograms (ECGs) and telemetry were employed. We subsequently utilized mobile continuous telemetry (MCOT) (BioTelemetry, Malvern, PA, USA) patches to expand telemetry capabilities and reduce the need for serial ECGs[4]. In a prospective observational study involving 201 patients, we did not observe any cases of torsade de pointes (TdP) or arrhythmogenic death due to monotherapy with HCQ or when HCQ was combined with AZM[5]. This suggested that a 5-day course of therapy may not warrant monitoring for cardiac arrhythmias in most inpatients with a normal baseline ECG. The findings led us to simplify our approach to monitoring patients treated with these medications; we recommended to only monitor patients with a baseline corrected QT interval (QTc) >500 ms. In this study, we report our evolving experience with monitoring patients receiving HCQ ± AZM and identify the incidence of drug-induced TdP and arrhythmic death due to these medications in a large healthcare network at the epicenter of the US COVID-19 crisis.

Methods

In order to minimize the possibility of unintentionally sharing information that can be used to re-identify private information, a subset of the data generated, and the analytical methods used for this study are available from the corresponding author to other researchers upon reasonable request

This study was approved by the Institutional Review Board of Northwell Health, which waived the requirement for individual informed consent. All patients > 18 years of age with a

polymerase chain reaction test confirmed diagnosis of COVID-19 illness admitted across 13

hospitals within the Northwell Health system that received HCQ ± AZM between March 1st and

April 15th, 2020 were identified. Criteria for initiating HCQ ± AZM within Northwell Health has

been described previously[5]. While there was treatment guidance from the health system, the

treatment regimen was at the discretion of the individual clinician. Prior to initiating treatment,

the QTc interval was optimized by stopping other QTc prolonging medications if possible and

replacing electrolytes. Early on many patients received HCQ+AZM. Over the course of the study

period AZM was dropped from the regimen due to perceived lack of efficacy. In addition,

clinicians were reminded that there was no data supporting the efficacy of HCQ, and there

should therefore be a low threshold for not starting and discontinuing therapy if there was a

competing risk. COVID-19 positive patients that were chronically on HCQ for autoimmune

diseases such as lupus were excluded.

As mentioned above, monitoring over the period of the study evolved. Initially, patients

receiving HCQ ± AZM were monitored via standard telemetry or with serial ECGs. MCOT

patches were then employed to monitor the QTc interval and avoid serial ECGs when telemetry

was not available[4]. The use of MCOTs for this purpose has been previously described[4,5]. Based

on the early experience, a simplified approach to QTc monitoring was instituted system wide on

April 5, 2020 (Figure 1). All patents received a baseline ECG. If the baseline QTc was ≤500 ms,

therapy with HCQ ± AZM was initiated and no further monitoring was performed. This included

not performing serial ECGs. If the baseline QTc was > 500 ms, clinicians were asked to

determine if the risk of an unproven treatment was warranted. If therapy was begun, QTc

monitoring was performed with telemetry if available, or with an MCOT patch if a telemetry bed

was not available. Performing serial ECGs was discouraged in an effort to reduce HCP exposure and PPE usage.

A customized ClinPhen python package was used to identify any mention of QT prolongation, torsade de pointes, non-sustained ventricular tachycardia (NSVT), ventricular tachycardia (VT), ventricular fibrillation (VF), polymorphic ventricular tachycardia (PMVT), wide complex tachycardia (WCT), and cardiac arrest within the electronic medical records (EMR). Different variations of the above terms were utilized to ensure that the search captured all of the events. The ClinPhen python package has been approved as an efficient tool to extract and prioritize patient phenotypes directly from medical records[6]. The box connected the free text content in the EMR notes and broke it into sentences, sub-sentences, and words. The package used a custom rule-based heuristic to match sub-sentences against arrhythmias names and synonyms as defined above. As an example, "prolonged QTc" would be a valid mention of the words "QT prolongation". After the processing with the package, a spreadsheet displaying the key findings, the sub-sentences, essential findings, and original text was created. A subset of these search results was manually validated using the cohort of patients treated with HCQ ± AZM from March 1st to March 23rd in our previous study[5].

An in-depth chart review of all identified arrhythmic events and every case of cardiac arrest was performed. Demographics, comorbidities, duration of therapy with HCQ ± AZM, concomitant use of other QT prolonging agents, electrolyte abnormalities, baseline ECG values including QRS duration, QRS morphology, QT interval duration as well as QT interval duration from the day of the event were collected. Comorbidities were identified from ICD-9 or ICD-10 codes documented on admission. All telemetry strips, ECGs, and MCOT strips were reviewed for patients with arrhythmias or QTc prolongations. All QT intervals were manually measured

regardless of source. Bazett's formula was used to calculate the QTc. QT interval measurement methodology was previously described[5]. Arrhythmic event findings were adjudicated by a senior board-certified cardiac electrophysiologist and a cardiac electrophysiology fellow board certified in cardiovascular disease blinded to duration or course of therapy.

All ECGs performed at the Northwell Heart Hospital (Northshore University Hospital) were tabulated for the 10 days prior to April 5, 2020 and the 10 days after as a marker of healthcare provider exposure and PPE usage. The baseline ECGs for each patient performed in the emergency department were excluded for both time periods.

Outcome measures

The primary clinical outcome of the study was QT prolongation resulting in TdP. Secondary outcomes included QT prolongation resulting in premature discontinuation of HCQ and/or AZM, incidence of ventricular arrhythmias, and arrhythmogenic death.

Statistical Analysis

Continuous variables are reported a mean ± standard deviation and categorical variables are reported a number (percentage). SAS Version 9.4 (Cary, NC) was used to compute descriptive statistics and 95% exact binomial confidence intervals.

Results

Between March 1st and April 15th, there were 6,476 hospitalized patients that were treated for COVID-19 with HCQ ± AZM across 13 hospitals in the Northwell Health system. Three thousand six hundred twenty-nine patients (56%) received AZM in addition to HCQ. The average age of the population was 63.9 ± 15.2 years and 3,980 (61.5%) were men. Complete demographics are displayed in Table 1. The treatment regimens for these medications were as

follows: Hydroxychloroquine: either 400 mg by mouth twice daily or 800 mg by mouth once daily for one day followed by 200 mg by mouth twice daily or 400 mg by mouth once daily for four days. Azithromycin: 500 mg by mouth or intravenous daily for up to five days. Four thousand one hundred and fourteen patients were treated prior to the institution of the simplified monitoring approach and 2,362 patients were treated after.

The primary end point of QTc prolongation resulting in TdP occurred in 1 patient (0.015%, exact 95% Confidence Interval: 0.0-0.09%). The patient's baseline QTc was 514 ms. After receiving two 400mg doses of HCQ and one dose of AZM, the QTc increased to 538ms and a non-sustained, asymptomatic episode of TdP was observed. This patient had also received albuterol and furosemide, which are both known to cause QT prolongation. There were no electrolyte abnormalities associated with the episode. HCQ and AZM were both discontinued and the QTc shortened back to 518 ms. The patient was subsequently discharged home with no further episodes of TdP noted during the hospitalization.

QTc prolongation occurred in 67 patients monitored on HCQ ± AZM. Of these patients, 30 were receiving monotherapy with HCQ and 37 were receiving both HCQ and AZM. Of the 67 patients with a significant prolongation in the QTc, 45 (67.2%) patients had their treatment initiated prior to April 5th and the remaining 22 (32.8%) were treated with HCQ +/- AZM after the simplified monitoring plan was implemented. The average number of other QT prolonging agents received in this subset of patients during the hospitalization was 3.0±1.9. The average baseline QTc for these patients was 473.7±35.9ms and the average maximum QTc was 532.6±31.6ms. The average change in the QTc interval from baseline was 60.5±40.5ms. Of the 67 patients, a majority of patients (n=58, 86.6%) had HCQ ± AZM discontinued as a result of the QT prolongation. The remaining 9 patients (13.4%) had one or more doses of these medications

held, but ultimately were able to finish the course of HCQ ± AZM. Of the 67 patients whose QT prolongation necessitated a change in management, one additional patient (1.5%) was noted to have a ventricular arrhythmia. This patient had ten seconds of monomorphic NSVT at a rate of 190 beats per minute that was not associated with symptoms.

One episode of sustained PMVT in the setting of sustained hypotension occurred in a patient that was made comfort care per the patient's wishes. Four other patients (0.06%) had VF in the setting of myocardial ischemia (n=2) and/or hyperkalemia and severe acidosis (n=2). These rhythms were rapidly identified, and advanced cardiovascular life support was quickly initiated. Five additional patients (0.08%) had sustained monomorphic VT. These episodes were managed with intravenous amiodarone and synchronized direct current cardioversion. Eighteen patients (0.27%) had monomorphic NSVT. A list of the 29 patients (0.45%) who were found to have ventricular arrhythmias while receiving therapy is displayed in Table 2. There were no deaths related to the use of HCQ ± AZM in the entire population.

For the 10-day period prior to instituting the simplified monitoring approach, there were 1,475 ECGs performed (147.5 per day) at the largest hospital in the health system. In the 10-day period following the institution of the simplified approach, 510 ECGs were performed (51 per day). Eliminating the need for serial ECG monitoring in select patients lead to an absolute reduction of 965 ECGs (96.5 per day) and a 65% relative reduction compared with serial monitoring.

Discussion

In this study, involving a large cohort of patients taken from a network of hospitals at the epicenter of the US COVID–19 crisis, we demonstrated that: 1) a simplified approach to

monitoring patients receiving HCQ ± AZM for the treatment of COVID-19 designed to reduce

HCP exposure and PPE use was safe 2) the incidence of life threatening tachy-arrhythmias

associated with the inpatient use of HCQ ± AZM, with baseline screening, was exceedingly low.

The SARs-CoV-2 virus binds and enters human upper and lower respiratory cells through

the viral type I membrane spike glycoprotein and the human ACE-2 receptors[7,8]. Small studies

in-vitro have shown to successfully inhibit viral infection and replication by affecting endosomal

dependent fusion and interfering with the glycosylation of cellular receptors of the virus[2,3].

Incidences of TdP with the use of chloroquine and hydroxychloroquine in COVID-19 patients

have been reported, though remain low[9,10]. The efficacy of the therapy on morbidity and

mortality continues to be controversial, with conflicting and at times unsubstantiated claims

being made. A French study involving 36 patients, which ignited the world's use of

hydroxychloroquine and azithromycin, has since been redacted (https://www.isac.world/news-

and-publications/official-isac-statement). The unprecedented response by some news outlets,

social media, politicians and ultimately the FDA led to the widespread use of these agents.

Subsequent studies showed lack of efficacy and potential harm. A double-blinded, randomized,

phase IIb clinical trial, looking at the use of high vs low dose chloroquine, a sister drug of

hydroxychloroquine, for 10 days in COVID-19 patients reported increased incidence of QT

prolongation and overall death in those receiving the high dose, requiring early termination of

that study arm. Two episodes of ventricular tachycardia resulting in death were reported, though

neither episode was related to TdP[11]. A preprint retrospective study of 368 COVID-19 patients

from the Veterans Administration showed no benefit to the use of HCQ with or without AZM in

reducing the need for mechanical ventilation and suggested a possible overall increase in

mortality with the use of HCQ[12]. It is important to note that the mechanism of death in the study

was not reported, leaving room for debate whether it was arrhythmic or related to some other mechanism. A large multinational COVID-19 registry analysis of the use of HCQ or chloroquine ± a macrolide showed no benefit of either monotherapy or combination therapy on in-hospital outcomes. Moreover, the regiments were associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias[13]. However, the study did not report a breakdown of arrythmias and did not report the incidence of arrhythmic death. Therefore, based on the findings of this study, the excess mortality may be due to a non-arrhythmic cause. The results of this study however have come under great scrutiny and were subsequently retracted after the authors were unable to verify the data set[14]. The FDA has issued a warning against the use of HCQ ± AZM in the outpatient setting or outside of a clinical trial for inpatient use. On April 28th, following the FDA recommendation, the Northwell Health system issued an updated guidance statement recommending against the use of hydroxychloroquine outside of a clinical trial.

The initial widespread use of HCQ ± AZM occurred at a time when hospitals were overwhelmed with COVID-19-positive patients and needed to expand the capacity of both intensive care units and general medical wards. In addition, there was a need to minimize HCP exposure and PPE use. Classical approaches to inpatient monitoring during the initiation of QT prolonging drugs were not possible. There were far too few telemetry beds, and serial ECGs required repeated HCP exposure and use of PPE. The hallmark of managing during the COVID-19 pandemic is innovation and flexibility. To reduce the need for serial ECGs, MCOT patches were utilized to monitor patients in non-telemetry beds[4]. In a prospective observational study of 201 patients treated on average for 5 days with chloroquine/hydroxychloroquine ± azithromycin, no incidence of TdP or arrhythmogenic death was observed despite a statistically significant increase in QTc[5]. This, along with our health system's decision to no longer use AZM in

COVID-19 patients, led us to adopt a simplified approach to monitoring across the health system beginning April 5th (Figure 1).

This study showed that our simplified approach did not result in increased risk of sustained TdP or arrhythmic death related to HCQ ± AZM in a cohort of 6,476 patients. The arrhythmic risk of the therapy was low, with only one episode of non-sustained TdP occurring before our simplified approach to monitoring had been implemented. Had that patient presented after the time when we were using the approach outlined in Figure 1, the patient would still have received monitoring per our simplified approach, given that the baseline QTc was >500 ms. Our algorithm therefore would still have captured the single episode of non-sustained TdP that occurred in the entire cohort, regardless of when that patient was treated. It is important to note that the number of QT prolongation events, and therefore potential TdP episodes, in the study may underestimate the true incidence due to the change in our monitoring approach. QT prolongation occurring in patients not monitored would have not been captured. However, we believe this did not lead to any increased incidence of tachy-arrhythmic death. All in-hospital cardiac arrests in patients receiving HCQ ± AZM were individually reviewed and no instances of TdP were noted in those patients.

Historically, antiarrhythmics have the highest risk of TdP with an incidence of 1-5%. The risk with non-cardiovascular drugs is much lower at 0.001%[15]. Though the risk of developing TdP in this study is tenfold higher compared to historical data (0.015% vs 0.001%), it remains exceptionally low, especially considering that the treatment duration for these medications is five days. The single episode of non-sustained TdP that we observed is distinctly different than what was reported by Mecuro et al. in their cohort of 90 patients. As opposed to our patient, who was actively being treated with HCQ and AZM at the time the event occurred, their case of TdP was

seen in a patient that had discontinued HCQ and AZM three days prior to the event for a QTc of 499 ms. At the time of their patient's TdP event, multiple other concomitant conditions known to prolong the QT and cause TdP were present[9]. Therefore, it is difficult, especially since therapy had been discontinued, to determine how much, if at all, the use of HCQ or AZM contributed to the episode. The results of our study demonstrate that despite the change in our monitoring practice patterns, sudden cardiac death did not increase with the use of this unproven therapy for COVID-19. What is of utmost importance is that by using this simplified approach, we were able to safely deliver this therapy while successfully reducing HCP exposure and PPE use by 65%.

Limitations

Limitations of this study include its retrospective nature and the lack of a control group. Given that a search of the EMR was performed to identify arrhythmic events, the data is also subject to reporting bias. During this pandemic, omissions in documentation due to the surge in volume across the health system may have contributed to a reporting bias. Furthermore, although we validated a subset of patients from a previous study in which a manual chart review was performed, it is possible that our search algorithm failed to identify every arrhythmia in this population. However, as opposed to other events, significant ventricular arrhythmias and/or cardiac arrests would be considered noteworthy and would most likely result in documentation at some level Similarly, due to omissions in documentation and the way comorbidities were collected, the study may underrepresent the true prevalence of certain comorbidities in the cohort. The true number of QT prolongation events after the simplified approach was initiated is larger than reported as only those with a baseline QTc >500 ms would have been captured. It is important to note, despite this we did not see a significant incidence of TdP. Lastly, given that clinicians may have withheld HCQ ± AZM due to a patient having a prolonged QTc at baseline,

and that we did not include patients treated with chloroquine, our results can only be applied to the incidence of TdP and QT prolongation in COVID-19 positive patients who received HCQ ± AZM.

Conclusion

Despite a known increased incidence of QT prolongation in COVID-19 patients receiving HCQ ± AZM, the risk of TdP and arrhythmogenic death with our simplified approach to monitoring the QTc remained exceedingly low. This simplified approach allowed for less HCP exposure and decreased use of PPE. Though the arrhythmic risk appears to be low, no meaningful clinical benefit for the use of HCQ ± AZM in COVID-19 patients has been shown. Given that there is data to suggest increased overall death, unrelated to TdP, caution is advised in their use. Further studies are needed to better evaluate the risk vs benefit of using HCQ ± AZM for the treatment of COVID-19.

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Table 1: Patient Demographics

Characteristics	N=6,476
Age (years)	63.9 ± 15.2
18 to 39	436 (6.7%)
40 to 64	2811 (43.4%)
≥65	3229 (49.9%)
Sex (male)	3980 (61.5%)
Body mass index (kg/m$^{2)}$) †	30.0 ± 7.2
<30	2816 (58.0%)
≥30 to <40	1619 (33.3%)
≥40	421 (8.7%)
Race	
African American	1313 (20.3%)
Asian	770 (11.9%)
White	2151 (33.2%)
Other/Multi-racial	1865 (28.8%)
Unknown/Declined	377 (5.8%)
Hypertension	3184 (49.2%)
Coronary artery disease	588 (9.1%)
Congestive heart failure	242 (3.7%)
Ejection Fraction†	57.4 ± 13.6
Peripheral vascular disease	216 (3.3%)
Diabetes mellitus	2161 (33.4%)
Chronic kidney disease	441 (6.8%)
End stage renal disease	236 (3.6%)
Asthma	452 (7.0%)
Chronic obstructive pulmonary disease	306 (4.7%)
Prior permanent pacemaker	45 (0.7%)
Prior automated implantable cardioverter-defibrillator	34 (0.5%)

*Values listed are represented as means ± standard deviations for continuous variables and numbers (%) for categorical variables.

†Data for body mass index was available for 4,856 patients (75.0%). Data for ejection fraction was available for 312 patients (4.8%).

Table 2: Ventricular Arrhythmias Observed in 6,476 Patients

Arrhythmia	Frequency (percentage)	95% CI	Drug-induced?
Torsade de pointes	1 (0.015%)	(0.00, 0.09%)	Yes
Ventricular fibrillation	4 (0.06%)	(0.02, 0.16%)	No
Sustained polymorphic ventricular tachycardia	1 (0.015%)	(0.00, 0.09%)	No
Non-sustained polymorphic ventricular tachycardia	0	-	-
Sustained monomorphic ventricular tachycardia	5 (0.08%)	(0.03, 0.18%)	No
Non-sustained monomorphic ventricular tachycardia	18 (0.27%)	(0.16, 0.44%)	No
Total	29 (0.45%)	(0.30, 0.64%)	-

Figure Legends:

Figure 1. The simplified approach to monitoring QT interval and arrythmia in hospitalized COVIC-19 patients receiving hydroxychloroquine. Flow chart demonstrating simplified monitoring.

HCQ: Hydroxychloroquine; QTc: Corrected QT interval; MCOT: Mobile continuous telemetry

What is Known:

- In hospitalized COVID-19 patients, the use of hydroxychloroquine and azithromycin significantly increases the corrected QT interval (QTc).

- A QTc greater than 500 ms increases the risk of torsade de pointes by two to three-fold.

- Inpatient telemetry monitoring is warranted for patients at high risk of developing drug related torsade de pointes.
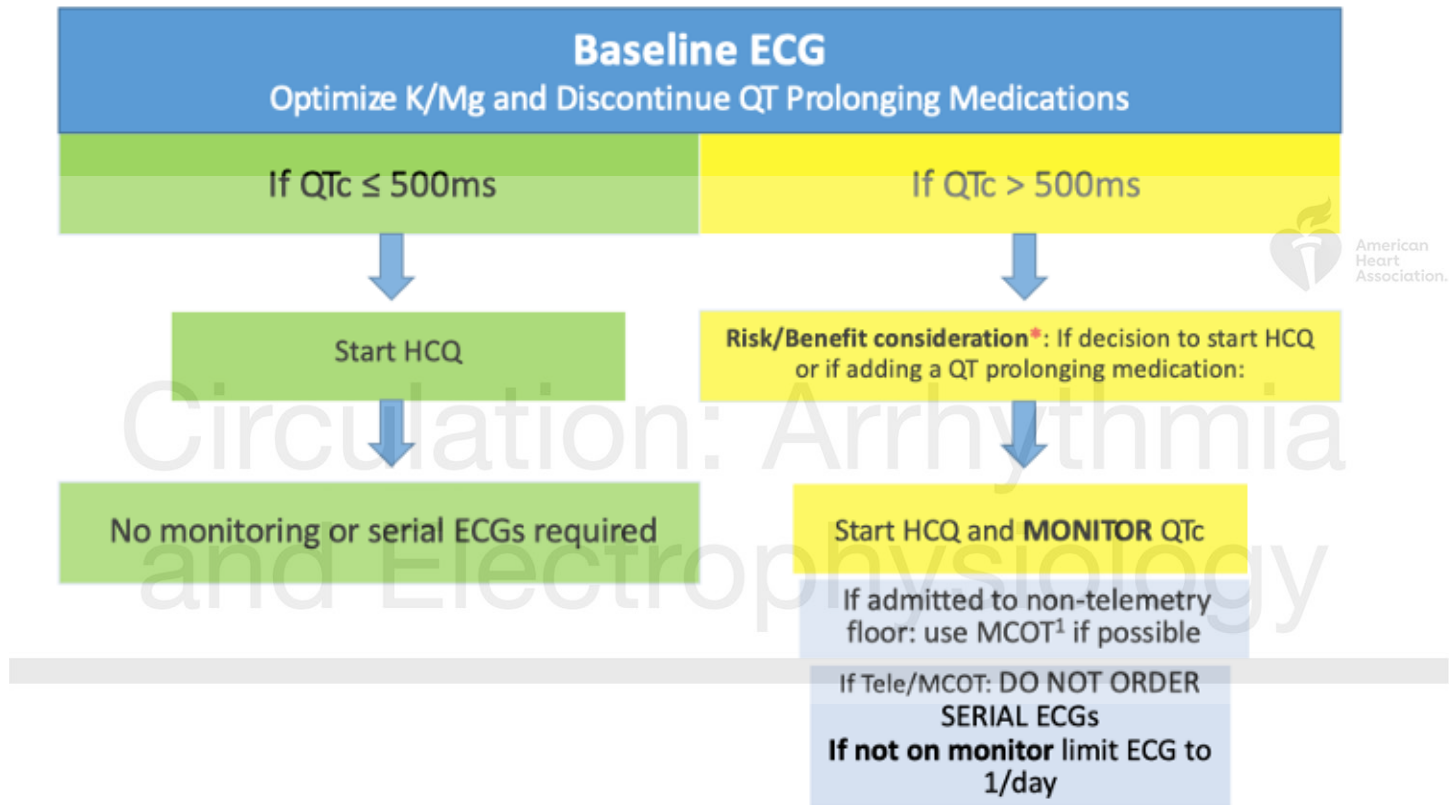
What the Study Adds:

- A simplified approach to monitoring patients receiving hydroxychloroquine ± azithromycin for the treatment of COVID-19 designed to reduce health care provider exposure and personal protective equipment use was safe

- The incidence of life threatening tachy-arrhythmias associated with the inpatient use of hydroxychloroquine ± azithromycin, with baseline screening, was exceedingly low.

Hydroxychloroquine (HCQ) Monitoring for COVID-19*

Baseline ECG
Optimize K/Mg and Discontinue QT Prolonging Medications

If QTc ≤ 500ms	If QTc > 500ms
Start HCQ	**Risk/Benefit consideration***: If decision to start HCQ or if adding a QT prolonging medication:
No monitoring or serial ECGs required	Start HCQ and **MONITOR** QTc

If admitted to non-telemetry floor: use MCOT[1] if possible

If Tele/MCOT: DO NOT ORDER SERIAL ECGs
If not on monitor limit ECG to 1/day

If on telemetry: lead II or derived 12 lead to monitor QTc BID. **DO NOT ORDER SERIAL ECG's**
*HCQ is an unproven therapy: Stop for QTc >550/ventricular arrhythmia or history of LQTS
[1] MCOT = Mobile Continuous Telemetry

American Heart Association.

Circulation: Arrhythmia and Electrophysiology

The risk of torsade de pointes is low in hospitalized COVID-19 patients receiving hydroxychloroquine ± azithromycin therapy

Study population

6,476 COVID-19 positive patients that received hydroxychloroquine ± azithromycin across 13 hospitals between March 1st and April 15th 2020

Monitoring

Initially, patients were monitored via standard telemetry or with serial ECGs

MCOT patches were then employed to monitor the QTc interval and avoid serial ECGs when telemetry was not available

A simplified approach to monitoring only those with a baseline QTc >500 ms was implemented on April 5th

Outcomes

Torsade de pointes was observed in 1 patient (0.015%)

67 patients (1.03%) had hydroxychloroquine ± azithromycin held or discontinued due to QT prolongation

There were no deaths related to the medications with the simplified monitoring approach and HCP exposure was reduced

American Heart Association.

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