Indian Pacing and Electrophysiology Journal 21 (2021) 36–43

Contents lists available at ScienceDirect

Indian Pacing and Electrophysiology Journal

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

Hydroxychloroquine and QTc prolongation in patients with COVID-19: A systematic review and meta-analysis

Sourabh Agstam [a], Ashutosh Yadav [b], Praveen Kumar-M [c], Ankur Gupta [d, *]

[a] Department of Cardiology, VMMC & Safdarjung Hospital, New Delhi, India
[b] Department of Cardiology, Fortis Hospital, Mohali, Punjab, India
[c] Department of Pharmacology, Post Graduate Institute of Medical Education and Research, Chandigarh, India
[d] Department of Cardiology, Advanced Cardiac Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India

ARTICLE INFO

Article history:
Received 5 August 2020
Received in revised form
11 September 2020
Accepted 15 October 2020
Available online 16 October 2020

Handling editor: Narayanan Namboodiri

Keywords:
COVID-19
Coronavirus
SARS-CoV-2
Hydroxychloroquine
Chloroquine
Aminoquinoline
QTc prolongation
Torsades de pointes

ABSTRACT

Background: Among many drugs that hold potential in COVID-19 pandemic, chloroquine (CQ), and its derivative hydroxychloroquine (HCQ) have generated unusual interest. With increasing usage, there has been growing concern about the prolongation of QTc interval and Torsades de Pointes (TdP) with HCQ, especially in combination with azithromycin.

Aims: This meta-analysis is planned to study the risk of QTc prolongation and Torsades de pointes (TdP) by a well-defined criterion for HCQ, CQ alone, and in combination with Azithromycin in patients with COVID-19.

Methods: A comprehensive literature search was made in two databases (PubMed, Embase). Three outcomes explored in the included studies were frequency of QTc > 500 ms (ms) or ΔQTc > 60 ms (Outcome 1), frequency of QTc > 500 ms (Outcome 2) and frequency of TdP (Outcome 3). Random effects method with inverse variance approach was used for computation of pooled summary and risk ratio.

Results: A total of 13 studies comprising of 2138 patients were included in the final analysis. The pooled prevalence of outcome 1, outcome 2 and outcome 3 for HCQ, CQ with or without Azithromycin were 10.18% (5.59–17.82%, I^2 – 92%), 10.22% (6.01–16.85%, I^2 – 79%), and 0.72% (0.34–1.51, I^2 – 0%) respectively. The prevalence of outcome 2 in subgroup analysis for HCQ and HCQ + Azithromycin was 7.25% (3.22–15.52, I^2 – 59%) and 8.61% (4.52–15.79, I^2 – 76%), respectively. The risk ratio (RR) for outcome 1 and outcome 2 between HCQ + Azithromycin and HCQ was 1.22 (0.77–1.93, I^2 – 0%) & 1.51 (0.79–2.87, I^2 – 13%), respectively and was not significant. Heterogeneity was noted statistically as well clinically (regimen types, patient numbers, study design, and outcome definition).

Conclusion: The use of HCQ/CQ is associated with a high prevalence of QTc prolongation. However, it is not associated with a high risk of TdP.

1. Introduction

The World Health Organization has declared coronavirus disease 2019 (COVID-19), a pandemic on March 11, 2020 [1]. In the absence of a specific and effective therapy against the disease, currently the treatment remains supportive. COVID-19 is caused by a novel beta coronavirus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [2]. Among many proposed antiviral therapies, an anti-malarial Hydroxychloroquine (HCQ) has been suggested to be of potential benefit in patients with COVID-19 based on in-vitro and small clinical studies [3–5]. The most serious adverse event associated with the use of HCQ is QTc prolongation which can lead to fatal polymorphic ventricular tachycardia known as Torsades de pointes (TdP) [6].

The prominent mechanism of QTc prolongation by HCQ is by blocking the delayed rectifier potassium current (I_{Kr}), which is involved in final rapid repolarization phase (phase 3) of the action

Abbreviations: COVID-19, Coronavirus disease2019; CQ, Chloroquine; EAD, Early afterdepolarization; ECG, Electrocardiography; HCQ, Hydroxychloroquine; HERG, human ether-a-go-go-related gene; ICU, Intensive care unit; RCT, Randomized control trial; RR, Risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SA, Sinoatrial; TdP, Torsades de pointes; VT, Ventricular tachycardia; WHO, World Health organization.

* Corresponding author.
E-mail address: ag_pgi@yahoo.com (A. Gupta).

Peer review under responsibility of Indian Heart Rhythm Society.

https://doi.org/10.1016/j.ipej.2020.10.002

potential (Fig. 1) [6]. A human ether-a-go-go related gene (HERG, alpha subunit) potassium channel underlies I_{Kr} and HCQ specifically inhibits this subunit of I_{Kr}. The blockade of the HERG channel lengthens the ventricular repolarization, and this is reflected on the surface electrocardiogram as a prolonged QTc interval. It may also result in the reactivation of inward, mainly calcium, depolarizing currents, thereby generating early afterdepolarizations and can trigger TdP [7,8]. Macrolides antibiotics such as erythromycin, azithromycin also block these HERG channels and prolong QTc interval [9]. Another overlooked mechanism of QTc prolongation by HCQ is its bradycardic action on sinoatrial cells. In animal study of HCQ, HCQ slowed the rate of spontaneous action potential firing in the sinoatrial node through multichannel inhibition, including L-type calcium channels (I_{CaL}), rapid delayed rectifier potassium current (I_{kr}), and most importantly, funny channels (I_f) [10].

Given the widespread use of HCQ in COVID-19, we did this meta-analysis to provide the evidence on the safety of HCQ along with azithromycin regarding QTc prolongation and the risk of TdP in patients with COVID-19 disease.

2. Methods

Searches were made in two databases namely PubMed and Embase from inception to May 24, 2020. The key terms used for searching include COVID-19, Coronavirus, SARS-CoV-2, hydroxychloroquine, aminoquinoline, HCQ, Chloroquine, and Azithromycin. A detailed search strategy is given in the supplementary file. Clinical studies either evaluating HCQ, chloroquine (CQ), either alone or in combination with Azithromycin were included for full-text analysis.

Among the selected studies, studies reporting ECG parameters were taken for data extraction. The studies which reported QTc prolongation, defined as QTc > 500 ms (ms) or increase in QTc >60 ms from baseline (ΔQTc) or TdP were included for final metanalysis. QT prolongation was taken into account and QRS prolongation was not assessed in the metanalysis. Both screening and data extraction were conducted by two investigators (SA and AY) and were matched with conflicts resolved by a third investigator (AG). Three outcomes were extracted from the included studies namely.

1. Outcome 1 – Frequency of QTc prolongation defined as QTc > 500 ms or ΔQTc > 60 ms out of total patient evaluated.
2. Outcome 2 - Frequency of QTc prolongation defined as QTc > 500 ms out of total patient evaluated.
3. Outcome 3 - frequency of TdP out of total patient evaluated.

Studies not providing a clear definition of QTc prolongation were omitted. We took the number of patients rather than the number of events when both the information was provided. When the authors did not distinguish between the events and patients, it was presumed to be patients. If a study had taken the patients which were included in the previous study, only the study with the largest sample size was included. Studies including patients with structural heart diseases in which ECG may be influenced by underlying diseases were excluded. Also, the minimum number of patients in a study required for inclusion into the metanalysis was kept as 10. In case of queries, electronic mail (e-mail) communication was made to the author for clarification.

Besides the study design, the severity of included patients,

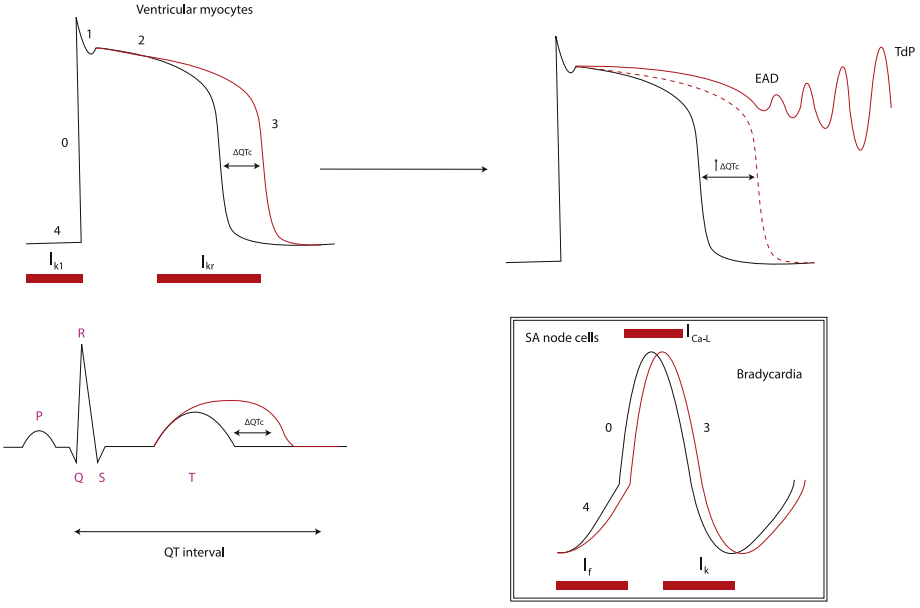

Fig. 1. Mechanism of QT prolongation and Torsades de Pointes (TdP) by Hydroxychloroquine (HCQ). The red bar represents the currents blocked by HCQ/CQ. At ventricular and atrial myocytes, HCQ blocks inward rectifier potassium channels involved in the action potential. Potassium channels are involved in outward currents in the cellular membranes at phase 3 and phase 4. HCQ blocks the human ether-a-go-go related gene (HERG), which is responsible for potassium current (I_{Kr}), prolongs phase 3 repolarization, thereby predisposing to the development of TdP [8]. The prolongation of ventricular action potential is reflected on the surface ECG as a prolonged QT interval. Further, HERG blockade facilitates the reactivation of inward, mainly calcium depolarizing currents, thereby generating early afterdepolarizations (EAD) [7,8]. Under the right spatial and temporal heterogeneity of refractoriness in ventricular cardiomyocytes, EAD's can trigger TdP [11]. Chloroquine additionally blocks potassium channel current (IK_1), which are involved in maintaining phase 4 diastolic depolarization of cardiac myocytes [12]. In addition, HERG channels are also blocked by azithromycin, and antivirals lopinavir/ritonavir [13]. Combination of multiple QTc prolonging drugs, bradycardia, female sex, dyselectrolytemia (hypokalemia, hypocalcemia, and hypomagnesemia) reduces the repolarization reserve and precipitates TdP [8]. Furthermore, at sinoatrial node (SA node) cells (Inset) HCQ predominantly blocks funny channels, along with potassium channels and long-acting calcium channels in animal studies [10]. Funny channel current (I_f) is involved in generating phase 4 depolarization, potassium channel current (I_K) is involved in generating phase 3 repolarization phase of sinoatrial nodal action potential, and calcium channel current (I_{Ca-L}) is involved in generating phase 0 rapid depolarization. The blockade of these current prolongs the action potential of the SA node, reduces automaticity, and causes bradycardia [14]. The bradycardia prolongs QT interval [8].

dosing regimen, and any special cardiovascular-related information either in terms of monitoring or outcomes were extracted and tabulated.

2.1. Statistical analysis

The analysis was conducted using R (version 3.6.2) and meta-package was used in addition to the base package [15,16]. Logit transformations were made in proportion before computing the summary. Clopper-Pearson confidence interval was used for individual studies. The summary pooled prevalence was computed using a random effect model along with an inverse variance approach. The risk ratio (RR) was computed for the comparison between the frequency between the two interventions. The

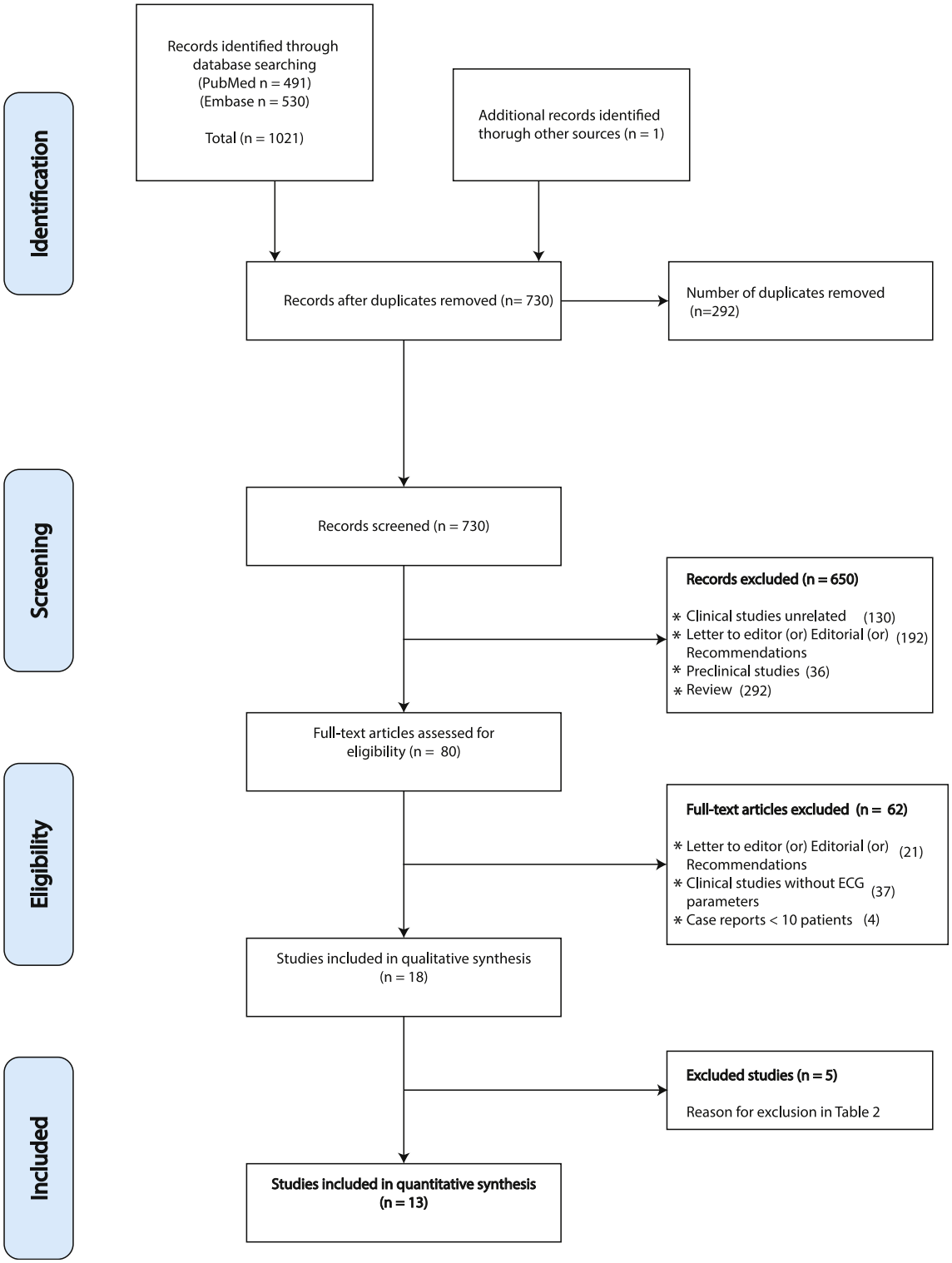

Fig. 2. PRISMA flowchart showing the flow of study selection.

summary effect of the risk ratio was also computed by the random effect model and inverse variance approach. DerSimonian-Laird estimator was used for tau^2 and Jackson method for the confidence interval of tau^2. The heterogeneity was computed by calculation of I^2 and p value of heterogeneity ($p < 0.10$ was kept for significance). If the value of I^2 is >50%, then it represents that the studies included in the meta-analysis are heterogenous and if the value of I^2 is <50%, then the studies included in the meta-analysis are homogenous. Generally, if heterogeneous, the random effect model is used for the computation of summary, and if homogenous, the fixed-effect model is used for the computation of summary. But we have used random-effects irrespective of the I^2 value, as the characteristics of the studies included in the metaanalysis varied in terms of sample size, study design, geographical location, the patient population included, and methodology of conduct. Continuity correction of 0.5 was applied for studies with zero cell frequencies.

3. Results

Eighteen studies have evaluated ECG parameters, out of which 13 were included in the metanalysis and 5 were excluded [17–34]. The flow of study inclusion is shown in Fig. 2. In Saleh et al. study, we took HCQ/CQ as a single group (HCQ) as the author has not reported distinct outcome between HCQ/CQ and the number of patients of CQ was only 10 [28]. The characteristics of the included studies for metanalysis for any of the outcomes is shown in Table 1. The reasons for excluding clinical studies reporting ECG parameters are shown in Table 2.

Out of 11 studies reporting HCQ with or without Azithromycin, 2 followed regimen 1 (HCQ 200 mg twice daily for 10 days and azithromycin 250 mg for 5 days), 4 followed regimen 2 (HCQ 400 mg twice daily for day 1 followed by 200 mg twice daily for next 4 days), 5 followed regimen 3 (HCQ 200 mg three times a day for 10 days, and azithromycin 500 mg single dose followed by 250 mg OD for day 2–5). 2 studies of CQ with or without azithromycin gave either (high dose CQ 600 mg twice daily for 10 days versus low dose 450 mg twice daily on day 1 followed by 450 mg OD for the next 4 days). For analysis, drug-specific outcomes were explored, irrespective of the regimen.

Out of the 13 studies (2138 patients) which evaluated either HCQ or CQ alone or with a combination of Azithromycin for outcome 1 (QTc >500 ms or ΔQTc > 60 ms), the prevalence varied between 0 and 35% with a pooled prevalence of 10.18% (5.59%–17.82%, I^2 – 92%) (Fig. 3A). Similarly, 10 studies (1926 patients) which explored the same drugs with outcome 2 (QTc >500 ms), the prevalence varied between 0 and 23.16% with a pooled prevalence of 10.22% (6.01%–16.85%, I^2 – 79%) (Fig. 3B). I^2 showed heterogenous results for both the QTc prolongation outcome ($I^2 > 50\%$). For consideration of outcome 3 i.e., frequency of TdP with the same group of drugs, 12 studies reported a prevalence between 0 and 1.11% with a pooled prevalence of 0.72% (0.34%–1.51%, I^2 – 0%) (Fig. 3C). The results were homogenous among studies for TdP ($I^2 < 50\%$).

Exploration of prevalence for HCQ and HCQ + Azithromycin for

Table 1
Characteristics of included studies.

Study, Country	Study Design	Number of Patients	Criteria (All values in msec)	Dosing regimen	Treatment Groups (n)	Illness severity
Bessiere et al. [17], France	Retrospective study	40	QTc >500 ms or ΔQTc 60 ms	Regimen 1	HCQ (n = 22) vs.HCQ + Azithromycin (n = 18)	Severe, ICU admitted patients
Borba et al. [18], Brazil	Randomized double-blind study	81	QTc >500 ms	CQ	High dose CQ (600 mg BD ×10 days) vs. low dose (450 mg BD on day 1 followed by 450 mg OD for next 4 days All azithromycin)	Severe, Hospitalized patients
Chang et al. [19], USA	Prospective observational study	117	QTc >500 ms	Regimen 2	HCQ (n = 66) vs. HCQ + Azithromycin (n = 51)	Hospitalized, Non-ICU
Chorin et al. [20], USA, Italy	Retrospective study	251	QTc >500 ms or ΔQTc 60 ms or JTc >410 ms	Regimen 2	HCQ + Azithromycin	Hospitalized patients
Ciprani et al. [21], Italy	Prospective observational study	22	QTc >500 ms	Regimen 1	HCQ + Azithromycin (minimum for 3 days)	Hospitalized patients, room air
Gautret et al. [22], France	Prospective observational study	80	QTc > 500 ms	Regimen 3	HCQ+ Azithromycin	Hospitalized patients, mild-moderate illness
Mahevas et al. [23], France	Retrospective observational study	181	QTc >500 ms or ΔQTc 60 ms	Regimen 3	HCQ (n = 84) Azithromycin (n = 15) vs.standard of care (n = 89)	Hospitalized patients, requiring oxygen
Million et al. [24], France	Retrospective observational study	1061	QTc >500 ms or ΔQTc 60 ms	Regimen 3	HCQ + Azithromycin	Mild illness
Mercuro et al. [25], USA	Retrospective observational Study	90	QTc >500 ms or ΔQTc 60 ms	Regimen 2	HCQ (n = 37) vs. HCQ + Azithromycin (n = 53)	Hospitalized patients
Molina et al. [26], France	Prospective observational study	11	QTc >500 ms or ΔQTc 60 ms	Regimen 3	HCQ +Azithromycin	Hospitalized patients, requiring oxygen
Perinal et al. [27], France	Prospective cohort study	13	QTc >500 ms	Regimen 3	HCQ alone	Hospitalized ICU patients
Saleh et al. [28], USA	Prospective observational study	201	QTc > 500 ms	Regimen 2	CQ (n = 10) HCQ (72) HCQ + Azithromycin (n = 119)	Hospitalized ICU severe patients
Broek et al. [29], Netherlands	Retrospective observational study	95	QTc >500 ms	CQ	CQ 600 mg loading dose followed by 300 mg BD for next 5 days started after 12 h of loading dose	Hospitalized patients

Regimen 1- HCQ 200 mg twice daily for 10 days and azithromycin 250 mg for 5 days,
Regimen 2- HCQ 400 mg twice daily for day 1 followed by 200 mg twice daily for next 4 days, Azithromycin 500 mg daily for 5 days,
Regimen 3- HCQ 200 mg three times a day for 10 days, and azithromycin 500 mg single dose followed by 250 mg OD for day 2–5.
CQ dose has been mentioned inside the table due to variable doses.

Table 2
Description of excluded studies along with the reason of exclusion.

Study name	Type of study	Number of patients	Antiviral regimen	Reason for exclusion
Alberici et al. [30], Italy	Retrospective observational	94	Lopinavir/ritonavir with HCQ (dose adjusted according to kidney function)	QTc not defined for prolonged QT
Jain et al. [31], USA	Observational comparative study	415	HCQ dose not defined	QTc prolongation criteria was >470 ms
Rosenberg et al. [32], USA	Retrospective Observational	1438	Variable HCQ dose 4 groups HCQ (n = 271) HCQ +Azithromycin (n = 735) Azithromycin (n = 211) No drug (221)	QTc not defined for prolonged QT
Louhaichi et al. [33], Tunisia	Retrospective observational	15	HCQ+ Azithromycin HCQ 200 mg TDS X 10 days, AZT 500 mg single dose followed by 250 mg OD for day 2–5	QTc prolongation criteria was > 480 ms
Tang et al. [34], China	Open labelled RCT	150.	HCQ + standard of care (n = 75) vs. standard of care alone (n = 75) HCQ administrated at a loading dose of 1200 mg daily for three days followed by a maintenance dose of 800 mg daily	QTc not defined for prolonged QT

the outcome 1 showed the pooled prevalence of 13.11% (6.9%–23.52%, I^2 – 67%) and 8.2% (3.26%–19.13%, I^2 –93%), respectively, with combined prevalence of 9.87% (5.39%–17.40%, I^2 – 89%) (Fig. 4A). The number of studies (HCQ – 6; HCQ + Azithromycin – 10), the maximum (HCQ- 82, HCQ+ Azithromycin – 1061) and minimum (HCQ – 13, HCQ + Azithromycin – 11) sample size were different between the two agents, thereby making them directly not comparable. Similarly, the prevalence of HCQ and HCQ + Azithromycin for the outcome 2 showed a pooled prevalence of 7.25% (3.22%–15.52%, I^2 – 59%) and 8.61% (4.52%–15.79%, I^2 – 76%), respectively, with combined prevalence of 8.25% (5.07%–13.15%, I^2 – 71%) (Fig. 4B). Again, the number of studies, the maximum and minimum sample sizes were different, thereby making the results, not comparable based on prevalence. The two studies reporting TdP were from HCQ + Azithromycin arm. Since the number of studies was less for all outcomes for CQ and CQ + Azithromycin, its prevalence was not computed.

Five studies had a direct comparison of HCQ and HCQ + Azithromycin for outcome 1 and outcome 2. In those studies, the RR for outcome 1 and outcome 2 were 1.22 (0.77–1.93, I^2 – 0%) & 1.51 (0.79–2.87, I^2 – 13%) and both were not significant (Fig. 5A and B).

4. Discussion

Multiple studies on HCQ in COVID 19 patients have focussed upon the efficacy of the drug without clearly defining the methodology used for QTc prolongation [30–34], 13 studies which laid down the criteria for QTc prolongation reported a pooled prevalence of 10.18% taking either HCQ or CQ alone or in combination with Azithromycin for outcome 1 and 10.22% for outcome 2. We had to exclude one of the biggest studies of Rosenberg et al. [32], consisting of 1438 patients as the criteria for QTc prolongation was not defined. Another study of 524 patients by Jain et al., had to be excluded as they had taken the criteria for QTc prolongation dependent upon the QRS duration (QTc >470 ms for QRS < 120 ms, QTc > 500 ms for QRS > 120 ms) without mentioning the absolute numbers in each group [31]. An attempt was made to get the data via e-mail for the 5 excluded studies, however, the same could not be obtained (except Louhaichi et al. [33] where QTc criteria were informed as >480 ms, hence excluded). The pooled prevalence must be taken in the context of other associated factors causing QTc prolongation in these patients which include and are not limited to concomitant medications including various anti-viral drugs, electrolyte disturbances, structural heart disease, channelopathies, and advanced age. This QTc prolongation prevalence of 10% matches with the recently published review by Jankelson et al. [35]. The high prevalence of QTc prolongation with these drugs reiterates that the clinicians should be proactive in monitoring of QTc interval by doing daily ECGs in these patient population.

11 out of 13 studies included in our meta-analysis included HCQ and only 2 studies used CQ. It is commonly believed that the addition of Azithromycin to HCQ in COVID 19 patients significantly increases the risk for QTc prolongation [9]. Interestingly, in our meta-analysis the pooled prevalence in patients taking only HCQ versus HCQ and Azithromycin for outcome 1 was 13.11% and 8.20%, respectively and for outcome 2 was 7.25% and 8.61%, respectively. The RR of QTc prolongation in patients taking both HCQ and Azithromycin as compared to HCQ alone was also not significant. These results are predominantly influenced by the study of Million et al., who reported significantly lower events (9 out of 1061) in patients taking both HCQ and Azithromycin and mostly included patients with mild disease [24]. The heterogeneity among the included studies for outcome 1 and outcome 2 can be explained by the variability in the dosing regimen, variability in the severity of COVID-19 among the included patients, confounding factors such as associated comorbidity and medications, variability between the study design, number of patients and study settings.

Another important observation from our meta-analysis was the relatively low pooled prevalence (0.72%) of TdP which occurred in only 2 out of 2021 patients taking aminoquinoline with or without macrolides. The prevalence of TdP must be considered in the background of the following factors: only 2 studies reported the events, the number of patients varied between studies, and continuity correction of 0.5 was applied for computing the summary effect. This may be compared to the risk of around 2.5% of TdP associated with oral sotalol use [36]. This increased risk with sotalol may be attributed to the chronic use and the fact that the majority of the patients had underlying structural heart disease. It is important to note that the ventricular arrhythmia in TdP is a polymorphic ventricular tachycardia. The underlying cardiovascular diseases in COVID 19 patients may predispose these patients to VT which may not be polymorphic and may not be related to HCQ usage. Therefore, patients in which polymorphic ventricular tachycardia was not explicitly mentioned were not considered to have TdP in this meta-analysis. Very low chances of developing TdP

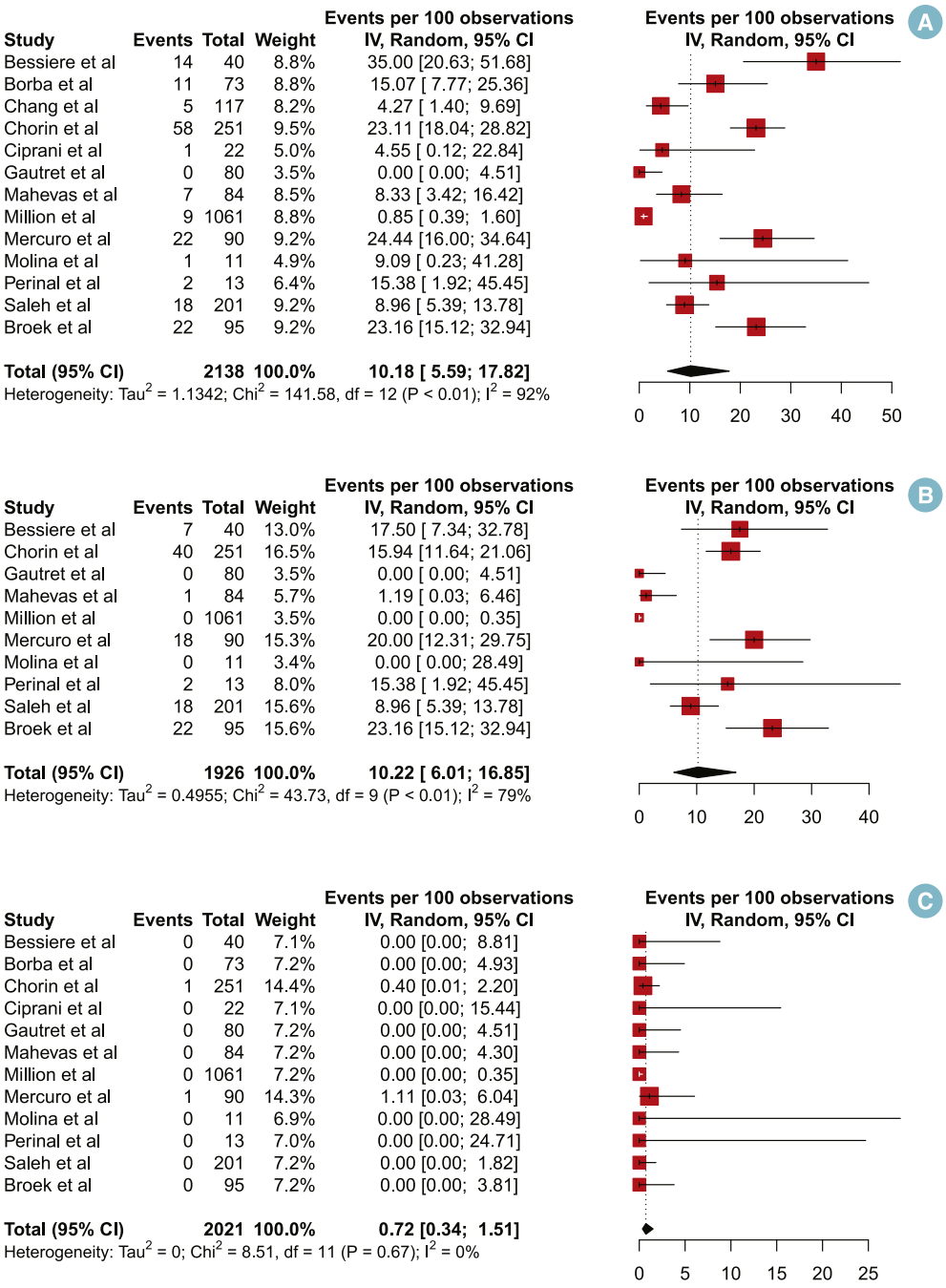

Fig. 3. Overall prevalence of HCQ and CQ alone with or without azithromycin for three outcomes are shown: Fig. 3A: Outcome 1 (QTc >500 ms or ΔQTc > 60 ms); Fig. 3B: Outcome 2 (QTc >500 ms); Fig. 3C: Outcome 3 (Torsades de Pointes -TdP). The summary was computed by a random effect. The heterogeneity was assessed by I^2 and p-value of heterogeneity ($p < 0.10$). C.I. stands for confidence interval.

in hospitalized COVID 19 patients with QTc prolongation, which on the contrary should be at a higher risk, suggests that there is a missing link between QTc prolongation and the risk of developing TdP. This is further strengthened by the fact the TdP has been reported in COVID 19 patient taking HCQ with a QTc interval of <500 ms [25]. In a malaria-endemic country like ours, HCQ is commonly prescribed and sudden unexpected deaths are unheard of. Even, WHO second this notion [6]. Not all the drugs that prolong QTc interval, significantly increase the risk of TdP. Proarrhythmic potential also depends upon prolongation of transmural dispersion of repolarization across the myocardium as proposed by El-Sherif and co-workers where re-entry causes a short-long-short initiating pattern of TdP [11]. For this, the coupling interval of the initiating premature ventricular contraction is important and needs to be studied in this patient subset. In the presence of many confounders, a clear cause and effect relationship cannot be established between HCQ and TdP, data from large randomized studies are awaited and will make us wiser. Till then, caution is advised and the use of HCQ/CQ can only be recommended in the setting of a clinical trial with close monitoring of QTc.

The greatest limitation of this metanalysis was the marked heterogenicity among the studies. Apart from different dosages of

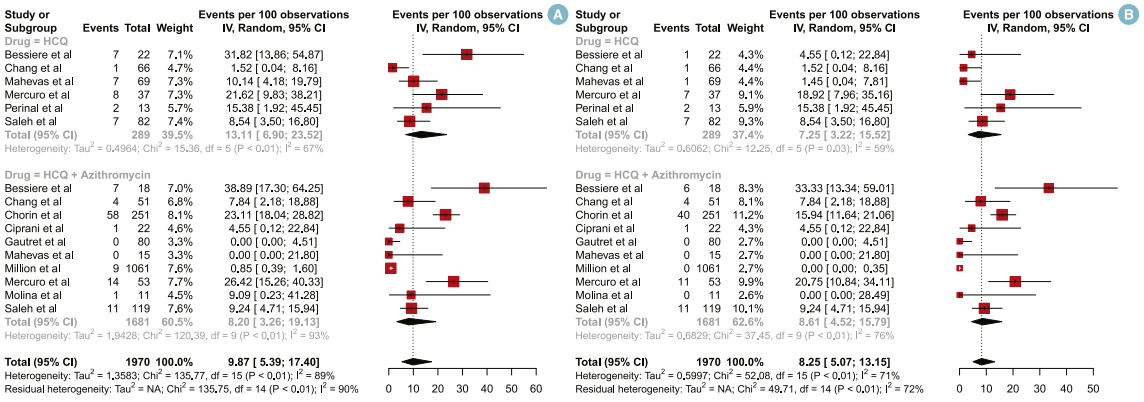

Fig. 4. Subgroup based prevalence of HCQ and HCQ + azithromycin for two outcomes are shown: Fig. 4A: Outcome 1 (QTc >500 ms or ΔQTc > 60 ms); Fig. 4B: Outcome 2 (QTc >500 ms). The summary was computed by a random effect method. The heterogeneity was assessed by I^2 and p-value of heterogeneity ($p < 0.10$). C.I. stands for confidence interval.

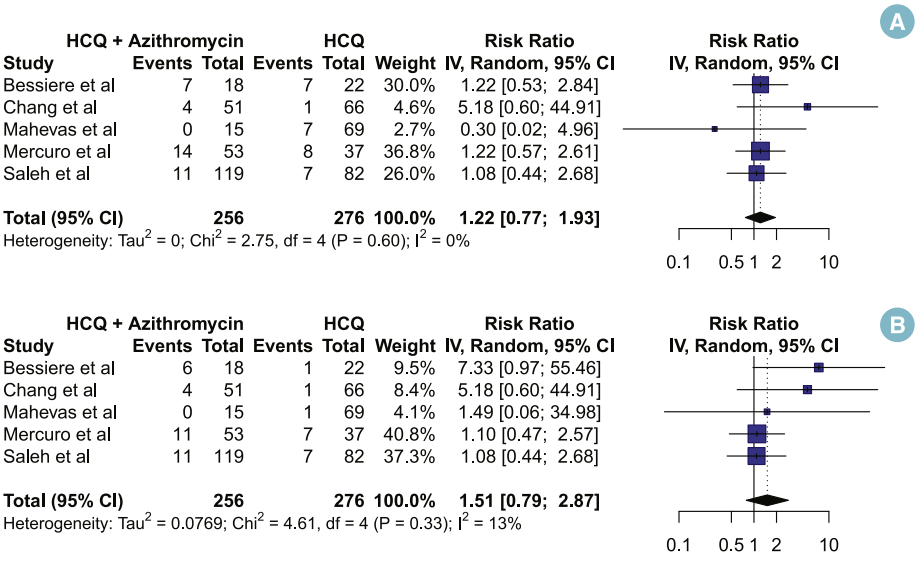

Fig. 5. Risk ratio (RR) between HCQ + azithromycin and HCQ for two outcomes are shown: Fig. 5A: Outcome 1 (QTc >500 ms or ΔQTc > 60 ms); Fig. 5B: Outcome 2 (QTc >500 ms). The summary was computed by a random effect method. The heterogeneity was assessed by I^2 and p-value of heterogeneity ($p < 0.10$). C.I. stands for confidence interval.

HCQ used in these studies, there were few studies in which other QTc prolonging drugs like Lopinavir/Ritonavir were used and underlying dyselectrolemia was present. The QTc prolonging effect attributable to HCQ is difficult in the presence of so many confounding factors. For better comprehension, we tabulated the dosage of HCQ into three different regimens. Another important limitation is the difference in the severity of the disease amongst patients in the absence of a well-defined definition of disease severity and admission criteria.

5. Conclusion

The risk of QTc prolongation associated with HCQ/CQ with or without Azithromycin is significant; however, very few patients develop TdP.

Funding

No funding was involved.

Declaration of competing interest

None.

References

[1] Report of the WHO-China joint mission on coronavirus disease 2019. COVID-19, https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf.
[2] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. J Am Med Assoc 2020 Feb 7;323(11):1061–9. https://doi.org/10.1001/jama.2020.1585. Epub ahead of print.
[3] Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis. 2003;3(11):722–7.
[4] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020 Mar;30(3):269–71. https://doi.org/10.1038/s41422-020-0282-0. Epub 2020 Feb 4.
[5] Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov 2020 Mar 18;6. 16.
[6] World Health Organization. The cardiotoxicity of antimalarials: World Health organization malaria policy advisory committee meeting. Published March 22, 2017. Accessed, https://www.who.int/malaria/mpac/mpac-mar2017-erg-cardiotoxicity-report-session2.pdf. [Accessed 22 April 2020].
[7] Roden DM. Taking the "idio" out of "idiosyncratic": predicting torsades de pointes. Pacing Clin Electrophysiol. 1998;21(5):1029–34.
[8] Roden DM, Drici MD. Drug-induced sudden death. In: Priori SG, Zipes DP, editors. Sudden cardiac death: a handbook for clinical practice. (USA): Wiley; 2005, ISBN 978-1-405-13292-3. 177—88.
[9] Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart. 2003;89(11):1363–72.

[10] Capel RA, Herring N, Kalla M, Yavari A, Mirams GR, Douglas G, et al. Hydroxychloroquine reduces heart rate by modulating the hyperpolarization-activated current If: novel electrophysiological insights and therapeutic potential. Heart Rhythm 2015 Oct;12(10):2186–94.
[11] El-Sherif N, Turitto G, Boutjdir M. Acquired long QT syndrome and electrophysiology of torsade de Pointes. Arrhythmia Electrophysiol Rev 2019;8(2):122–30.
[12] Rodríguez-Menchaca AA, Navarro-Polanco RA, Ferrer-Villada T, Rupp J, Sachse FB, Tristani-Firouzi M, et al. The molecular basis of chloroquine block of the inward rectifier Kir 2.1 channel. Proc Natl Acad Sci U S A 2008 Jan 29;105(4):1364–8. https://doi.org/10.1073/pnas.0708153105.
[13] Gérard A, Romani S, Fresse A, Viard D, Parassol N, Granvuillemin A, , et alFrench Network of Pharmacovigilance Centers. Off-label" use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: a survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers. Therapie 2020 May 7;S0040–5957(20):30091–3.
[14] DiFrancesco D. The role of the funny current in pacemaker activity. Circ Res 2010;106(3):434–46.
[15] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019. URL, https://www.R-project.org/.
[16] Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Base Ment Health 2019 Nov 1;22(4):153–60.
[17] Bessière F, Roccia H, Delinière A, Charrière R, Chevalier P, Argaud L, et al. 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. JAMA Cardiol 2020 May1:e201787. https://doi.org/10.1001/jamacardio.2020.1787 [Epub ahead of print].
[18] Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. JAMA Netw Open 2020 Apr 1;3(4):e208857.
[19] Chang D, Saleh M, Gabriels J, Ismail H, Goldner B, Willner J, et al. Inpatient use of ambulatory telemetry monitors for COVID-19 patients treated with hydroxychloroquine and/or azithromycin. J Am Coll Cardiol 2020 Apr 18;(20). S0735–109735009-9.
[20] Chorin E, Wadhwani L, Magnani S, Dai M, Shulman E, Nadeau-Routhier C, et al. QT interval prolongation and torsade de pointes in patients with COVID-19 treated with hydroxychloroquine/azithromycin. Heart Rhythm 2020 May 11;S1547–5271(20). 30435-5.
[21] Cipriani A, Zorzi A, Ceccato D, Capone F, Parolin M, Donato F, et al. Arrhythmic profile and 24-hour QT interval variability in COVID-19 patients treated with hydroxychloroquine and azithromycin. Int J Cardiol 2020 May 19;S0167–5273(20). 32223-3.
[22] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. Trav Med Infect Dis 2020 Mar-Apr;34. 101663.
[23] Mahévas M, Tran VT, Roumier M, Chabrol A, Paule R, Guillaud C, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. BMJ 2020 May 14;369. m1844.
[24] Million M, Lagier JC, Gautret P, Colson P, Fournier PE, Amrane S, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: a retrospective analysis of 1061 cases in Marseille, France. Trav Med Infect Dis 2020 May 5. 101738.
[25] Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCoy CM, Zimetbaum PJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020 May 1:e201834.
[26] Molina JM, Delaugerre C, Le Goff J, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Maladies Infect 2020 Jun;50(4). 384.
[27] Perinel S, Launay M, , Botelho-Nevers É, Diconne É, Louf-Durier A, Lachand R, et al. Towards optimization of hydroxychloroquine dosing in intensive care unit COVID-19 patients. Clin Infect Dis 2020 Apr 7. ciaa394.
[28] Saleh M, Gabriels J, Chang D, Kim BS, Mansoor A, Mahmood E, et al. The effect of chloroquine, hydroxychloroquine and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. Circ Arrhythm Electrophysiol; 2020 Apr 29.
[29] van den Broek MPH, Möhlmann JE, Abeln BGS, Liebregts M, van Dijk VF, van de Garde EMW. Chloroquine-induced QTc prolongation in COVID-19 patients. Neth Heart J 2020 Apr 29:1–4.
[30] Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, et al. A report from the Brescia Renal COVID Task Force on the clinical characteristics and short-term outcome of hemodialysis patients with SARS-CoV-2 infection. Kidney Int 2020 May 8;(20). https://doi.org/10.1016/j.kint.2020.04.030. S0085–253830508-1[Epub ahead of print].
[31] Jain S, Workman V, Ganeshan R, Obasare ER, Burr A, DeBiasi RM, et al. Enhanced ECG monitoring of COVID-19 patients. Heart Rhythm 2020 May 5;S1547–5271(20):30421–5.
[32] Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. J Am Med Assoc 2020 May 11:e208630.
[33] Louhaichi S, Allouche A, Baili H, Jrad S, Radhouani A, Greb D, et al. Features of patients with 2019 novel coronavirus admitted in a pneumology department: the first retrospective Tunisian case series. Tunis Med 2020 Apr;98(4):261–5.
[34] Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020 May 14;369. m1849.
[35] Jankelson L, Karam G, Becker ML, Chinitz LA, Tsai MC. QT prolongation, torsades de pointes and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: a systematic review [published online ahead of print, 2020 May 10]. Heart Rhythm 2020;S1547–5271(20):30431–8.
[36] MacNeil DJ, Davies RO, Deitchman D. Clinical safety profile of sotalol in the treatment of arrhythmias. Am J Cardiol 1993;72(4):44A–50A.