Original article:

Hydroxychloroquine as Therapeutic Option in COVID-19: Analysis of Suspected Cardiovascular Adverse Drug Events Reported in the VigiBase

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Abstract

Background: Hydroxychloroquine(HCQ), one of the repurposed drugs in COVID-19, has several known cardiovascular(CVS) toxicities. ***Methods:*** VigiBase data were used to analyze the reported ADEs linked to HCQ. The data were analyzed based on age, gender, and seriousness of ADEs at the System Organ Classification level and the individual Preferred Term level. ***Results:*** The majority were above 18 years(91.6%) and from Europe(41.6%). A total of 5,315 ADEs were associated with HCQ use in COVID-19. Of these, 918 ADEs were attributed to CVS and reported from 773 patients. Grossly, CVS ADEs were associated with concomitant use of HCQ and azithromycin(AZM), and only 40 ADEs were solely due to HCQ. The majority were serious (69.3%) and resolved afterward (51%). In CVS ADEs, there were 366 cardiac disorders, 38 vascular disorders, and 514 ADEs under investigation. Among the cardiac disorders, palpitation was the most typical (N=65), followed by bradycardia(N=44) and tachycardia(N=33). Among arrhythmias, QT prolongation (N=469), atrial fibrillation (N=25), and ventricular tachycardia(N=16) were common. The odds of developing serious CVS ADEs increased with age, patients aged 45-64 years(OR=1.75; p= 0.015) and >65 years(OR=1.93, p=0.003) as compared to younger ones. ***Conclusion:*** Hydroxychloroquine with known CVS toxicities and increased risk with co-administering AZM makes physicians cautious while prescribing in COVID-19 patients.

Keywords: Hydroxychloroquine; COVID-19; SARS-COV2; Azithromycin; Cardiovascular; Adverse Events.

Bangladesh Journal of Medical Science Vol. 20 No. 04 October'21. Page : 897-910
DOI: https://doi.org/10.3329/bjms.v20i4.54150

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Introduction

The serious acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is the cause of the current pandemic of coronavirus disease 2019 (COVID-19), which has wreaked havoc on the health systems and economies around the world [1]. As of 16th November 2020, COVID-19 cases worldwide had surged to 54,301,156 with a death toll of 1,316,994 individuals, as reported by the World Health Organization (WHO) [2]. A tremendous effort is being made by physicians, healthcare workers, pharmaceutical giants, and governments to contain the disease. However, there is still no sign of an end to this pandemic anytime soon. In view of no definite treatment or vaccine for COVID-19, many old drugs were being repurposed to find a cure or prophylaxis for this disease, and HCQ is among them [3-5]. An Emergency Use Authorization (EUA) was issued by the Food and Drug Administration (FDA) to allow HCQ use in patients hospitalized with COVID-19. Subsequently, HCQ was revoked from the EUA status by FDA, and later by WHO, because of the insufficient evidence of its benefits in treating COVID-19 and potential risk of cardiac and psychiatric side effects coupled with increased suicide attempts [6-8].

Hydroxychloroquine (HCQ)

Hydroxychloroquine is an aminoquinoline that belongs to the antimalarial class of drugs [9]. It was discovered in 1946 and shown to be about 40% less toxic than chloroquine in preclinical studies [10]. The HCQ was approved to treat malaria and immunological disorders like rheumatoid arthritis and systemic lupus erythematosus [11, 12]. It is also valuable for sarcoidosis, antiphospholipid syndrome, Sjogren's syndrome, and photosensitive dermatosis.[10] When given orally, HCQ is well absorbed with an oral bioavailability of 79 ± 12% and a high apparent distribution volume (525 ± 158 L/kg) [13, 14]. It is slowly released from the tissues and has a prolonged half-life of 1056 (624–1512) hours. The peak plasma concentration is 46 (34–79) ng/mL, and the time taken to reach the peak concentration is 3.2 (2–4.5) hours [14, 15]. HCQ tends to accumulates in the red blood cells (RBCs), and its plasma protein binding is 45 ± 3%. The reported plasma clearance of HCQ is 11.9 ± 5.4 mL/min/kg [14, 15]. As an antimalarial, HCQ acts as a weak base and accumulates in the acidic lysosome-like food vacuoles of the protozoa, leading to protozoa's death through inhibition of heme polymerization and crystallization into hemozoin [11, 16]. The antirheumatic effect of HCQ is postulated to be induced through various mechanisms, such as its interaction with the sulphydryl groups, interference with different cellular enzymes, interaction with DNA binding, stabilization of lysosomal membranes, blocking prostaglandin synthesis, inhibition of neutrophil chemotaxis and phagocytosis, probable decrease in interleukin-1 synthesis from monocytes and blockade of neutrophil superoxide release [17].

Hydroxychloroquine in COVID-19

The major push for the utilization of HCQ in COVID-19 came from the preliminary results of the in-vitro studies showing the inhibitory effect of HCQ on SARS-CoV-2 [18-21]. The mechanisms by which HCQ is hypothesized to be effective in COVID-19 include interference with the entry of SARS-CoV-2 into the host cell, reduced viral replication, suppression of interferon-alpha and other cytokines, reduced immune cell activation, and T cell differentiation which further minimizes the host cellular damage due to inflammation[13, 22]. Specifically, HCQ acts by increasing the medium's acidity in which SARS-CoV-2 spike protein interacts and binds to ACE-2 receptors of the host cells. The acidity turns the medium into a harsh environment for viral survival, thereby degrading the viral spike and reducing the infection rate and spread of COVID-19 [4].

Adverse Drug Events

Based on the use of HCQ in various disorders, ADEs are observed in multiple body systems. Some critical ADEs are related to the cardiovascular system, including palpitation due to various tachyarrhythmias, giddiness, or syncope due to bradyarrhythmias, pulmonary hypertension, sick sinus syndrome, cardiomyopathy, and, very rarely, sudden cardiac death[11, 17]. Electrocardiographic findings may show sinus node dysfunction, various atrioventricular blocks, atrial fibrillation, ventricular tachycardia, QT prolongation, torsades de pointes (TdP), and right or left bundle branch block. Ocular problems, such as blurred vision, difficulty in accommodation, and even irreversible retinal damage on long-term use, have been noted [17]. Dermatological manifestations include worsening of psoriasis and porphyria. Other disorders, such as neuropathy, proximal myopathy, neural and psychiatric events, and hypoglycemia, have been observed [11, 17]. The risk of cardiac ADEs, specifically QT prolongation and TdP, can increase in the presence of drug-drug interactions, for example, interaction with azithromycin, which was also recommended for the management of COVID-19 [23,

[24]. Azithromycin (AZM) was thought to be effective along with HCQ and was used in various trials among COVID-19 patients. As of 8th December 2020, almost 80 registered trials in "ClinicalTrials.gov" pertaining to HCQ and AZM were used in COVID-19 infection [25]. The ADEs associated with HCQ while managing the COVID-19 cases are being reported to the global pharmacovigilance database called VigiBase®, maintained by WHO [23]. Hence, this study assessed the cardiovascular ADEs and ECG changes encountered using HCQ while treating patients with COVID-19 recorded in the VigiBase®.

Materials and Methods

This study was conducted using VigiBase, an extensive database of individual case safety reports (ICSRs) maintained by WHO [26]. VigiBase archives all the suspected ADEs reported by national pharmacovigilance centers from 130 countries worldwide. It stores more than 20 million reports of suspected ADEs compiled since 1968 [26, 27]. The data reported in the VigiBase are sorted by the sociodemographic profile of the patients (age, sex, continent, and country), details of the drug use (date of initiation of therapy, last date of therapy, route of administration, and indications), suspected ADEs (onset date, degree of seriousness, causality, and outcome) and administrative data. VigiBase also permits a facile and flexible extraction and analysis of the stored data over time [27]. The coding of the medicines in the VigiBase is done as per the WHO Drug Dictionary Enhanced, and it also includes the Anatomical Therapeutic Chemical (ATC) classification [28]. The Medical Dictionary for Regulatory Authorities (MedDRA) and WHO Adverse Reaction Terminology were used to code the reported ADEs [29]. International Council constructed the MedDRA for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) [30]. The hierarchical structure used in MedDRA consists of five levels, arranged from very specific to very general, as follows: LTTs (Lowest Level Terms), PTs (Preferred Terms), HLTs (High-Level Terms), HLGTs (High-Level Group Terms), and SOCs (System Organ Classes) [31].

This study was conducted using PTs and SOCs information. PTs are discrete terms for symptoms, manifestations, diagnoses of a disorder, therapeutic uses, investigations, medical or surgical procedures, and medical social or family characteristics. In addition, SOCs are groupings of HLGTSs with specific terms based on etiology (e.g., infections and infestations), area of manifestation (e.g., gastrointestinal disorders), or indication (e.g., surgical and medical procedures) [31, 32]. The analysis of all the suspected cardiovascular ADEs with HCQ use in COVID-19 patients was conducted. Only cardiac ADEs, vascular ADEs, and investigations related to the cardiovascular system were extracted from all reported ADEs. The ADEs were classified according to the MedDRA and categorized under the SOC and individual PT levels.

Statistical Analysis: The data were entered in Microsoft Excel v365 and reported in frequencies and percentages. Descriptive statistics were used for analysis. To explore the predictors of serious CVS ADEs associated with HCQ use, logistic regression models were introduced. Initially, the univariate logistic regression technique was conducted. Explanatory socio-demographic variables (gender, age, and region) were regressed onto the probability of developing CVS ADEs (yes or no) as a response variable. An odds ratio (OR) greater than 1 (or less than 1) indicated a more significant probability (or lower probability) of developing serious ADEs compared to the reference category. A multiple logistic regression model was introduced to identify the independent effects of explanatory variables. The forced entry method of logistic regression was used. The significance level was established as $p \leq 0.05$, and 95% confidence intervals (CI) were used as OR estimates. IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY: IBM Corp. was used to analyze the data. IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY: IBM Corp. was used to analyze the data.

Ethical Approval: The current study was conducted using the WHO's global pharmacovigilance database, and there was no direct involvement of human participants; hence no ethical approval was necessary.

Results

In VigiBase, a total of 430,081 ADEs due to HDQ were reported, out of which 5,315 were directly linked to the use of HCQ in the treatment of COVID-19 infection. Subsequently, after excluding ADEs due to other body systems, 1,254 were attributed exclusively to the cardiovascular system (CVS). Furthermore, following the removal of the duplicated ADEs, a total of 918 CVS ADEs were reported from 773 COVID-19 patients treated with HCQ. Finally, among 918 CVS ADEs verified, 40 were associated

with the typical use of HCQ alone, whereas 878 ADEs were reported following concomitant treatment with AZM and HCQ [Figure 1].

The patients' demographic distribution indicated that most were males (56%) and the largest age group were those aged 65 years and above (46.5%). The highest proportion of the CVS ADEs reported were from Europe [41.6% (382)], followed by the Americas [32.7% (300)], Asia [22.3% (205)], and Africa [3.4% (31)] [Figure 2]. Many CVS ADEs documented were serious (69.3%) and developed while HCQ was taken orally. Further analysis of the outcome indicated that most ADEs (468) resolved, 90 were resolving in due course, 42 did not resolve, 26 were fatal, 98 outcomes were not reported, and 189 outcomes were completely unknown [Figure 3]. Following the dechallenge of HCQ, the ADEs were abated in 53.3% of the cases, and the rechallenge confirmed 27% of the ADEs cases identified [Table 1].

Among the reported 918 CVS ADEs, 366 cardiac disorders, 38 vascular disorders, and 514 were still under investigation. Among the cardiac disorders, palpitation (N=65) was the commonest ADE, followed by bradycardia (N=44), tachycardia (N=33), and atrial fibrillation (N=25). Regarding vascular ADEs, blood pressure abnormalities were the most common (N=21), followed by deep vein thrombosis (N=3). Concerning investigations, an electrocardiogram (ECG) QT prolongation (N=469) was the most common ADE, followed by abnormal ECG (N=11) [Table 2].

Furthermore, the ADEs were broadly reclassified based on the ECG findings into tachyarrythmias and bradyarrhythmias. Among tachyarrythmias, the most common ECG finding was atrial fibrillation (N=25), followed by ventricular tachycardia (VT) [N=16]. Sinus bradycardia (N=13) was the most typical ECG bradyarrhythmia finding. Regarding miscellaneous ECG findings, prolonged QT duration was the most typical (N=502) [Table 3]. Classifying the reported ADEs based on the clinical events revealed that palpitation was the most common clinical event associated with the use of HCQ in COVID-19, followed by vascular disorders [Figure 4].

Male gender, older age, and the European, American, and Eastern Mediterranean regions showed a univariate statistically significant association with the risk of developing serious CVS ADEs associated with HCQ use at $p \leq 0.05$. In the final multiple logistic regression model ($Chi^2 = 142.80$, $p < 0.001$), only age and region were significantly associated with serious ADEs. The odds of developing serious CVS ADEs increased with age, patients aged 45-64 years old [OR = 1.75 (1.11, 2.74), p = 0.015] and 65 years old and above [OR = 1.93 (1.25, 2.99), p = 0.003] were twice as likely to develop serious ADEs associated with HCQ use relative to those aged 45 years old and younger. Only the associations between the risk of developing serious ADEs and the European and Eastern Mediterranean regions have achieved statistical significance. European patients were almost seven times more likely [OR = 6.80 (3.75, 12.31), $p < 0.001$], and patients from Eastern Mediterranean were more than twice more likely [OR = 2.35 (1.06, 5.19), p = 0.036] to develop serious CVS ADEs followed treatment with HCQ than patients from the South East Asian region as the reference group. This model could explain 21.8% of the variation in the probability of developing serious ADEs [Table 4].

Table 1: Characteristics of cardiovascular adverse drug events (918 ADEs reported from 773 individuals) reported for hydroxychloroquine in the WHO database.

Parameter		Frequency (%)
Age	< 18 years	5 (0.5)
	18 – 64 years	414 (45.1)
	≥ 65 years	427 (46.5)
	Not reported	72 (7.8)
Gender	Female	345 (37.6)
	Male	513 (55.9)
	Not reported	60 (6.54)
Report type	Report from the study	95 (10.3)
	Spontaneous	809 (88.1)
	Unknown	14 (1.6)
The seriousness of the adverse event	Serious	636 (69.3)
	Non-serious	282 (30.7)
Route of administration	Oral	734 (79.9)
	Parenteral	9 (0.9)
	Other	26 (2.8)
	Unknown	58 (6.3)
	Not reported	91 (9.9)

Parameter		Frequency (%)
Dechallenge action	Does not changed	73 (8)
	Dose reduced	16 (1.7)
	Drug withdrawn	554 (60.3)
	Not applicable	61 (6.6)
	Unknown	34 (3.7)
	Not reported	180 (19.6)
Dechallenge outcome	Fatal	20 (2.2)
	No effect observed	34 (3.7)
	Reaction abated	489 (53.3)
	Effect unknown	168 (18.3)
	Not reported	207 (22.5)
Rechallenge action	Rechallenge	246 (26.8)
	Not Reported	672 (73.2)
Rechallenge outcome	Effect unknown	212 (23.1)
	Reaction recurred	10 (1.1)
	No recurrence	24 (2.6)
	Not reported	672 (73.2)

Table 2: Cardiovascular Related Adverse Drug Events Suspected to Be Caused by Hydroxychloroquine Use in COVID -19.

Broad Heading	Specific Adverse Drug Events	Total Events	Percentage
Cardiac disorders (n=366)	Acute cardiac event	1	0.11%
	Acute myocardial infarction	1	0.11%
	Arrhythmia	19	2.07%
	Arrhythmia Supraventricular	1	0.11%
	Atrial Conduction Prolongation	1	0.11%
	Atrial Fibrillation	25	2.72%
	Atrial Flutter	6	0.65%
	Atrial Tachycardia	1	0.11%
	Atrioventricular Block	2	0.22%
	Atrioventricular block complete	2	0.22%
	Atrioventricular block first degree	3	0.33%
	Atrioventricular block second degree	1	0.11%
	Bradycardia	44	4.79%
	Brugada syndrome	1	0.11%
	Bundle branch block left	3	0.33%
	Bundle branch block right	4	0.44%
	Cardiac arrest	11	1.20%
	Cardiac disorder	3	0.33%
	Cardiac failure	3	0.33%
	Cardiac failure congestive	1	0.11%
	Cardiac fibrillation	1	0.11%
	Cardio-respiratory arrest	9	0.98%
	Cardiogenic shock	2	0.22%
	Cardiomyopathy	4	0.44%
	Cardiotoxicity	1	0.11%
	Congestive cardiomyopathy	1	0.11%
	Coronary artery occlusion	1	0.11%
	Extrasystoles	3	0.33%
	Long QT syndrome	26	2.83%
	Myocardial infarction	2	0.22%
	Nodal rhythm	1	0.11%
	Palpitations	65	7.08%
	Pulseless electrical activity	1	0.11%
	Sinus bradycardia	13	1.42%
	Sinus tachycardia	3	0.33%
	Stress cardiomyopathy	1	0.11%
	Supraventricular tachycardia	7	0.76%
	Tachyarrhythmia	5	0.54%
	Tachycardia	33	3.59%
	Torsade de pointes	12	1.31%
	Ventricular arrhythmia	11	1.20%
	Ventricular extrasystoles	10	1.09%
	Ventricular fibrillation	3	0.33%
	Ventricular tachycardia	16	1.74%
	Angina pectoris	2	0.22%
Investigations (n=514)	Anticoagulation drug level increased	3	0.33%
	Bleeding time prolonged	1	0.11%
	Blood fibrinogen decreased	1	0.11%
	Blood fibrinogen increased	1	0.11%
	Blood potassium decreased	1	0.11%
	Blood pressure abnormal	1	0.11%
	Blood pressure decreased	3	0.33%
	Blood pressure increased	2	0.22%
	Electrocardiogram abnormal	11	1.20%
	Electrocardiogram PR prolongation	2	0.22%
	Electrocardiogram QRS complex prolonged	2	0.22%

Broad Heading	Specific Adverse Drug Events	Total Events	Percentage
	Electrocardiogram QT interval	2	0.22%
	Electrocardiogram QT interval abnormal	1	0.11%
	Electrocardiogram QT prolonged	469	51.09%
	Electrocardiogram repolarisation abnormality	2	0.22%
	Electrocardiogram ST-T change	1	0.11%
	Electrocardiogram T wave inversion	3	0.33%
	Electrocardiogram U-wave prominent	1	0.11%
	Heart rate decreased	2	0.22%
	Heart rate increased	2	0.22%
	Heart rate irregular	1	0.11%
	Pulse absent	1	0.11%
	Ejection fraction decreased	1	0.11%
Vascular disorders	Deep vein thrombosis	3	0.33%
(n= 38)	Flushing	2	0.22%
	Hematoma	1	0.11%
	Hypertension	12	1.31%
	Hypotension	9	0.98%
	Ischaemia	2	0.22%
	Jugular vein thrombosis	1	0.11%
	Lymphoedema	1	0.11%
	Peripheral arterial occlusive disease	1	0.11%
	Shock	2	0.22%
	Thrombosis	3	0.33%
	Vena cava thrombosis	1	0.11%

Table 3: Analysis of Electrocardiographic Findings Among Reported Adverse Drug Events Associated with Hydroxychloroquine Use in COVID-19.

Electrocardiogram findings		Number of events
Tachyarrhythmias	Sinus tachycardia	3
	Atrial tachycardia	1
	Atrial flutter	6
	Atrial fibrillation	25
	Supraventricular arrhythmia	1
	Supraventricular tachycardia	8
	Ventricular arrhythmias	11
	Ventricular tachycardia	16
	Ventricular fibrillation	3
	Torsades de pointes	12
Bradyarrhythmia's	Sinus bradycardia	13
	Atrial conduction prolongation	3
	First degree AV block	3
	Second degree AV block	1
	Complete AV block	2
	Non-specified AV block	2
	Nodal rhythm	1
Miscellaneous	RBBB	4
	LBBB	3
	Prolonged QT duration	502
Non-Specific	Arrhythmias	19
	Tachycardia	33
	Tachyarrhythmias	5
	Extrasystoles	3
	Bradycardia	44
	Prominent U Wave	1
	Inverted T Wave	3
	ST-T Changes	1
	Cardiac fibrillation	1

Table 4: Predictors of Serious Cardio-Vascular Adverse Drugs Events Associated with Hydroxychloroquine Use Based On Multivariate Regression Analysis.

Serious Adverse Drug Events	Crude		Adjusted	
	OR (95% CI)	p value	OR (95% CI)	p value
Gender:				
Female	1		1	
Male	1.34 (1.00, 1.79)	0.047	1.12 (0.81, 1.55)	0.483
Age:				
< 45 years	1		1	
45 – 64 years	1.91 (1.28, 2.86)	0.002	1.75 (1.11, 2.74)	0.015
≥ 65 years	2.71 (1.86, 3.95)	<0.001	1.93 (1.25, 2.99)	0.003
Region:				
South East Asian	1		1	
Western Pacific	1.08 (0.51, 2.29)	0.844	0.76 (0.34, 1.66)	0.484
of the Americas	2.68 (1.56, 4.61)	<0.001	1.42 (0.79, 2.56)	0.239
Eastern Mediterranean	3.00 (1.38, 6.51)	0.005	2.35 (1.06, 5.19)	0.036
European	9.47 (5.45, 16.45)	<0.001	6.80 (3.75, 12.31)	<0.001

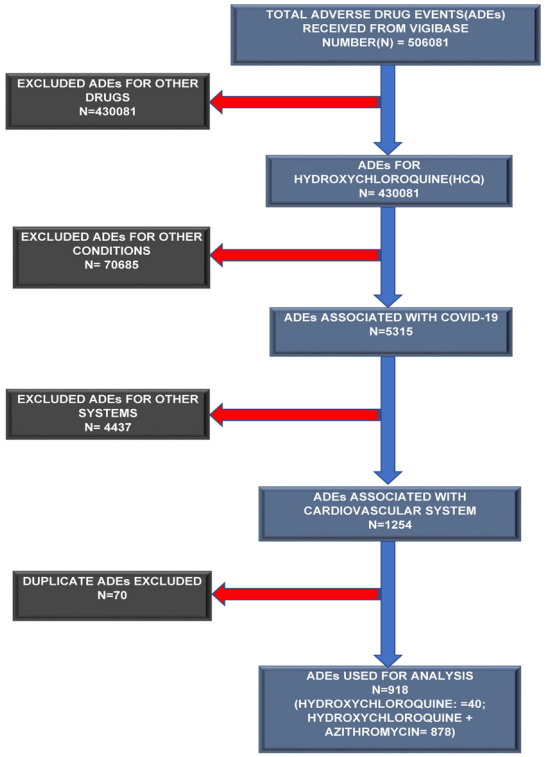

Figure 1: Schematic Diagram of assessment of Adverse Drug Events associated with Hydroxychloroquine in VigiBase database

Discussion

The present study was conducted to analyze the suspected HCQ-associated ADEs reported in the WHO database. Most of the reported ADEs were associated with the concomitant use of HCQ and AZM. Among the CVS ADEs identified, prolonged QT duration was the most prevalent ECG finding, followed by bradycardia, atrial fibrillation, ventricular fibrillation, and torsade de pointes. In the current study, CVS ADEs include palpitation (7.08%), tachycardia (3.6%), cardiomyopathy (0.44%), all types of cardiac failure (0.33%) and congestive cardiac failure (0.11%). A similar study involving COVID-19 patients performed by Gevers et al., in VigiAccess™ reported similar CVS ADEs associated with HCQ [33].

This study recorded 469 events of QT prolongation and 12 events of TdP. A study by Nguyen et al., in Vigibase extracted ADEs associated with HCQ and reported a much lower number of events (53) of QT prolongation but the higher number of events (83) TdP/VT than our study. Also, they found 75 events linked to conduction disorders, such as atrioventricular and bundle-branch blocks, and 203 cases of heart failure. Death due to a high TdP/VT ratio was reported in 8.4% of the cases, and 20.7% of deaths were recorded in the presence of heart failure in patients treated with HCQ [34]. They further noted that concomitant use of AZM and HCQ led to an increased reporting of QT prolongation and/or TdP/VT ratio compared to either drug monotherapy [34].

Montastruc et al., in their study analyzed the serious adverse drug reactions related to HCQ reported in VigiBase before the beginning of its usage in COVID-19 patients, from Jan 2010 to Dec 2019, and revealed that there were 180 events of cardiac arrhythmias, 194 events of shock, 172 events of cardiomyopathy, 158 thromboembolic events, 143 events of cardiac failure, 129 events of arterial hypertension and 86 events of TdP/QT prolongation [35]. Since the pre-COVID-19 period of cardiovascular events reporting was ten years, the overall number of events was higher than in our study. A study conducted by Singh et al., used the FDA adverse event reporting system (FAERS) database from 1998 to 2019. They reported that HCQ was associated with an elevated rate of right ventricular hypertrophy (RVH) [ROR=6.68], left ventricular hypertrophy (LVH) [ROR=3.81], diastolic dysfunction (ROR=3.54), pericarditis (ROR=3.09), TdP (ROR=3.05), congestive cardiomyopathy (ROR=2.98), decreased ejection fraction (ROR=2.41), right ventricular failure (RVF) [ROR=2.40], complete atrioventricular block (ROR=2.30) and QT prolongation (ROR=2.09) [36]. In contrast with current research, Singh et al., analyzed the data on HCQ use in patients with illnesses other than COVID-19; hence the findings can be useful in estimating the probability of HCQ causing CVS in COVID-19 patients. A systematic review conducted by Chatre et al., reported conduction disorders as the most common (80%) cardiac ADE. Other CVS ADEs encountered were LVH (32%), left ventricular hypokinesia (16%), heart failure (36.0%), valvular dysfunction (8.0%), and myocardial infarction (6%) [37]. Literature showed that conditions like LVH and RVH needed chronic administration of the drug but were rare when HCQ was used for a short duration [11].

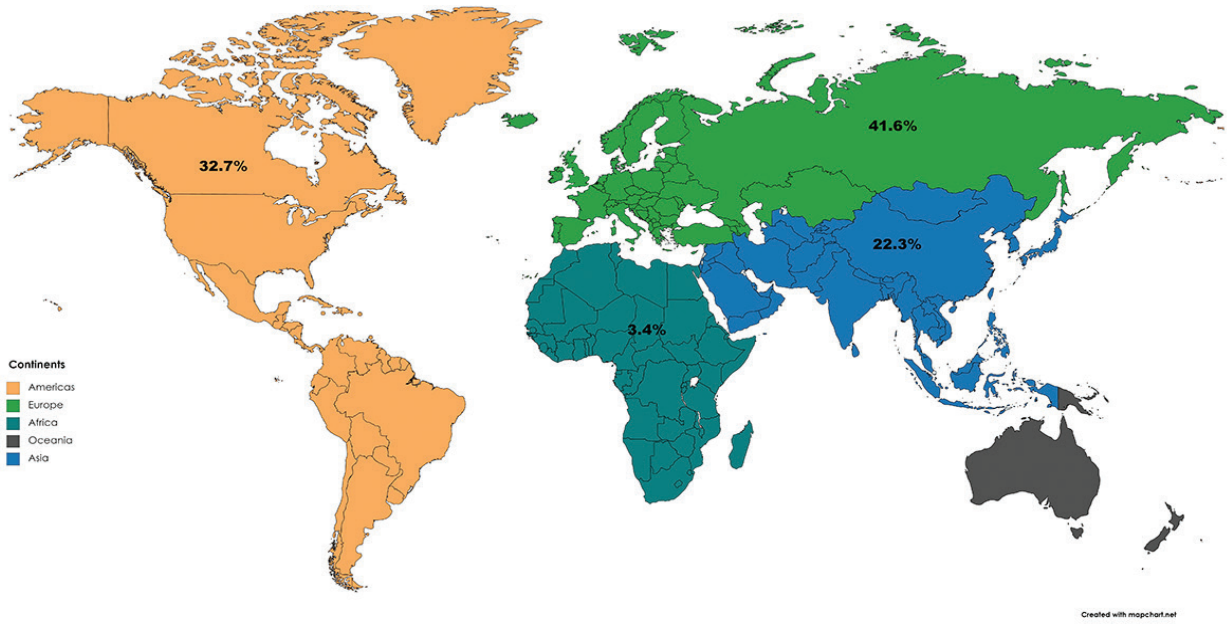

Figure 2: Distribution of Cardiovascular ADEs reported in VigiBase associated with Hydroxychloroquine use in COVID-19 across continents

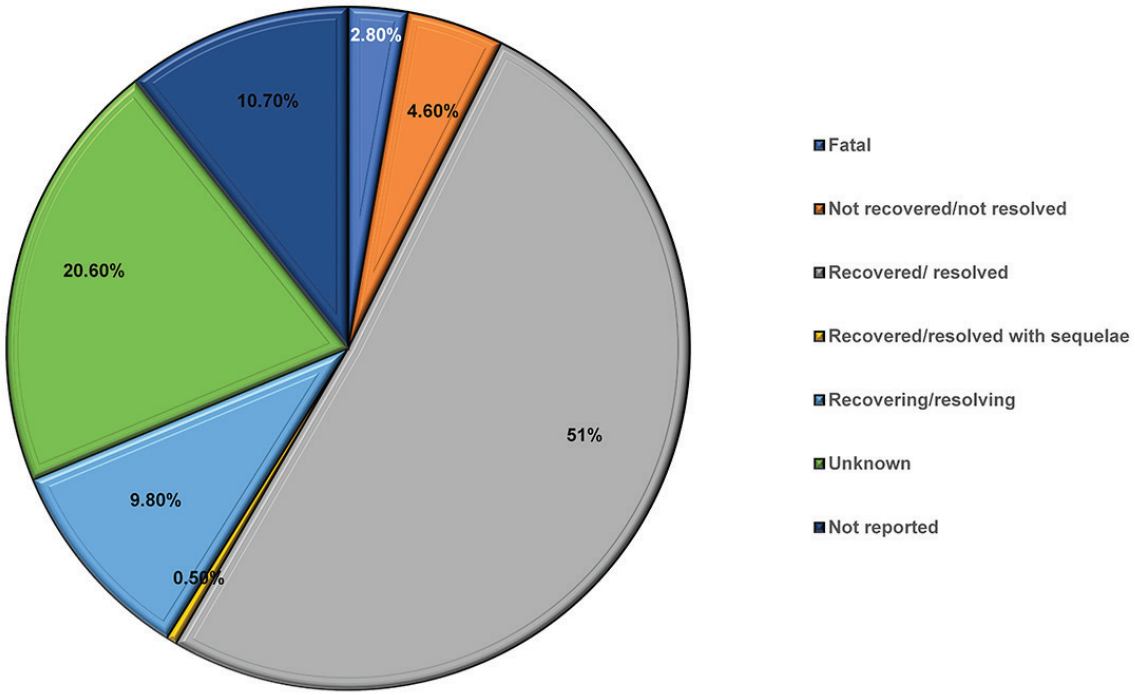

Figure 3: Adverse Drug Event Outcomes of Hydroxychloroquine use in COVID-19

In this research, QT interval prolongation in ECG was the most common (51.1%) CVS ADE associated with HCQ. Diaby et al., in their study, conducted by using the FAERS database to assess the safety signals for QT prolongation and TdP in COVID-19 patients using HCQ with or without AZM. They used disproportionality adjusted analysis and reported significantly increased safety signals for QT prolongation with HCQ [aROR:11.70] and HCQ+AZM [aROR: 75.23]. Similar trend was also noted with TdP signals for HCQ [aROR: 5.62] and HCQ + AZM [aROR: 33.09] [23]. Chorin et al., in their study on 84 COVID-19 patients, reported a significant change in QT duration with HCQ and AZM treatment. The QTc interval was increased by >40 ms in about 30% of the patients and increased by

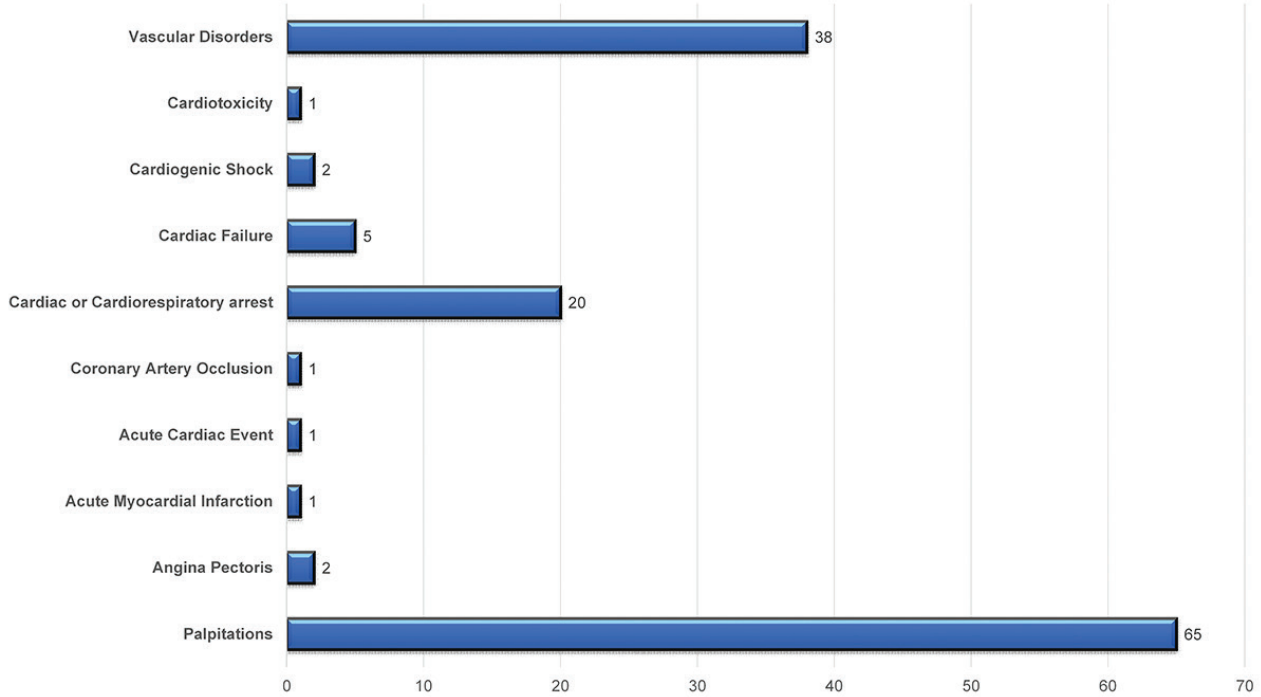

Figure 4: Cardiovascular Clinical Events associated with the use of Hydroxychloroquine in COVID-19

500 ms in about 11% of patients [38]. Magagnoli et al., in their study on COVID-19 patients, reported that mortality in the HCQ group (27.8%) was higher as compared to the HCQ with AZM group (22.1%) and no drug treatment group (11.4%) [39]. However, they did not mention the exact reason for higher mortality with HCQ only group but postulated that it could be due to the effect of HCQ on other vital organs of the body [39]. A study conducted by Voisin et al., reported that 76% of patients presented with alteration of the QTc duration (>30 ms) when treated with HCQ and AZM, and on discontinuation, 12% of patients had normalization of QTc interval [40].

It is obvious from all the evidence available that there is an enhanced risk of cardiotoxicity with HCQ and the risk amplifies when using it combined with AZM. The postulated mechanism for the reported cardiotoxicity is inhibiting lysosomal enzymes like α-galactosidase A, β-galactosidase, and arylsulfatase cardiomyocytes [41]. Microscopic analyses of the damaged cardiomyocytes revealed that vacuolization and Positive periodic acid–Schiff staining showed an accumulation of polysaccharides in the large, granulated myocytes [37]. On ultrastructural microscopy, myelin figures and curvilinear bodies were seen [37]. These cardiomyocyte changes denoted cardiomyopathy associated with biventricular concentric hypertrophy and diastolic dysfunction [37, 42]. Besides, HCQ prolongs the firing of a spontaneous action potential by inhibiting various cardiac channels such as L-type calcium channels (I_{CaL}), rapid delayed rectifier potassium current (I_{kr}), and the funny channels (I_f) leading to various arrhythmias [43, 44].

As per the treatment protocols, HCQ with empirical antimicrobials is added to prevent secondary bacterial or fungal infections in severely ill COVID-19 patients in the hospitals. A few antimicrobials might be responsible for prolonging QT duration, such as AZM, levofloxacin, and azole antifungals [45, 46]. These severe cases are commonly associated with various abnormal biochemical parameters, such as electrolyte abnormalities (hypokalemia and hypomagnesemia) and liver or renal failure, which can further enhance the probability of QT prolongation [44, 47]. The literature revealed that about 30% of COVID-19 patients developed a myocardial injury, and 20–44% tend to develop cardiac complications. including arrhythmias [48, 49]. The use of HCA or AZM in these severely ill patients with injured myocardium can further worsen the scenario and lead to an increase in mortality [36, 48].

Male gender and older age were closely associated with developing serious CVS events, which increased with age. A study done by Simmering et al., reported similar outcomes where patients more than 60 years were more prone to develop CVS ADEs as compared to younger ones [50]. Yang et al., in their study conducted on systemic lupus erythematosus patients on HCQ and reported that patients ≥45 years were associated with an elevated hazard ratio (6.29; 95% CI: 2.83–14.02) for CVS disorders as compared to patients less than 30 years [51].

The terms of the ADEs used in the present study were the same as reported in the VigiBase. Several ADEs reported in the VigiBase, such as blood pressure changes, heart rate changes, cardiotoxicity, and increased anticoagulation drug level were nonspecific. Some of the ADEs were reported with synonymous terms, such as low blood pressure/hypotension and high blood pressure/hypertension, leading to duplicating report of same ADEs under different sections. This issue needs to be addressed and offered more clarity.

Based on the initial experience, HCQ in COVID-19 treatment was recommended with caution and regular ECG monitoring, correction of electrolyte imbalance, hypokalemia, and hypomagnesemia, and avoiding drugs prolong the QT interval [52]. Indian Council of Medical Research, based on the positive results from the case-control study and preclinical evidence, recommended using HCQ in COVID-19 but with restrictions and cautions [53,54]. As of 2nd December 2020, 262 hydroxychloroquine studies registered, including 52 not yet recruiting, 91 recruiting, 10 enrolling by invitation, and 25 active studies. Based on the "Clinicaltrial.gov" website, only five trials had reported their results, and 257 studies were without results. Therefore, the effectiveness of HCQ remains a grey area [55]. However, the CVS ADEs associated with HCQ raise safety issues regarding the use of this drug. Current recommendations are against the use of HCQ or combination therapies in the treatment of COVID-19 [56]. However, with the large number of trials awaiting results and many yet to be started, a common consensus is to be made across the world to decide on the use of HCQ in COVID-19.

Conclusion

The cardiovascular safety analysis of HCQ based on VigiBase pharmacovigilance database analysis denotes that HCQ is associated with a higher risk of cardiotoxicity and increased cardiac ADEs, such as prolongation of QT torsades de pointes, right ventricular hypertrophy, left ventricular hypertrophy, and heart failure, among others. The risk of cardiac ADEs tends to amplify with concomitant use of HCQ and AZM or other drugs with similar cardiotoxicity profiles. Adequate precaution must be observed, and regular patient monitoring instituted by clinicians when recommending treatment with HCQ, especially if combined with AZM among COVID-19 patients.

Article Highlights

- Uncertainty regarding the effective therapy in COVID-19 led to the repurposing of older drugs
- Hydroxychloroquine (HCQ), an age-old antimalarial drug and also valuable for various immunological disorders, was tried in COVID-19
- HCQ has a known cardiotoxicity profile with conduction disorders, arrhythmias, ventricular hypertrophy, and cardiac failure. The co-administration of other drugs, such as azithromycin (AZM), can further increase the chances of cardiovascular adverse events and cardiotoxicity
- Analysis of VigiBase revealed QT prolongation, bradycardia, tachycardia, palpitation, and atrial fibrillation were common ADEs reported
- Although HCQ is being used from decades yet preliminary results of numerous ongoing trials on the use of HCQ and AZM in COVID-19 warrant cautious use, which can be due to enhanced myocardial damage done by SARS-CoV2

Statement of reservations, limitations, and conditions relating to data released from VigiBase

The current study is conducted on the VigiBase, and it is quite well known that it is a WHO global database of ICSRs which receives information on ICSRs from diversified sources, due to which the probability that suspected adverse effects to be drug-related is not always the same in all cases. Further, the data reported in the database does not represent

the opinion of the Uppsala Monitoring Center or the World Health Organization.

Consent for Publication

All authors reviewed and approved the final version and have agreed to be accountable for all aspects of the work, including any issues related to accuracy or integrity

Acknowledgment

We want to acknowledge 'mapchart.net,' a free service used to prepare a map diagram for this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This paper was not funded.

Disclosure

The authors declare that they do not have any financial involvement or affiliations with any organization, association, or entity directly or indirectly with the subject matter or materials presented in this article. This also includes honoraria, expert testimony, employment, ownership of stocks or options, patents or grants received or pending, or royalties.

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