

Electronic Supplementary Material

Supplement to:

Drugs - Real World Outcomes

Serious Cardiovascular Adverse Events Associated with Hydroxychloroquine/chloroquine Alone or with Azithromycin in Patients with COVID-19: A pharmacovigilance analysis of FDA Adverse Event Reporting System (FAERS)

Running title: Hydroxychloroquine with Azithromycin in COVID-19 Patients

Ying Zhao^{*1}, MS; Jingru Zhang^{*2}, MS; Kai Zheng³, PharmD; Sydney Thai⁴, MS; Ross J Simpson Jr⁵, MD, PhD; Alan C. Kinlaw^{6,7}, PhD; Yang Xu⁸, PhD; Jingkai Wei⁹, PhD; Xiangli Cui¹, PhD; John B Buse⁵, MD, PhD; Til Stürmer⁴, MD, PhD; Tiansheng Wang⁴, PharmD

* Y.Z. and J.Z. contributed equally to this work.

ORCID: Ying Zhao, <https://orcid.org/0000-0003-2563-7211>

¹ Department of Pharmacy, Beijing Friendship Hospital, Capital Medical University, Beijing, China

² Department of Biostatistics, University of North Carolina at Chapel Hill Gillings School of Global Public Health, North Carolina, USA

³ Department of Pharmacy, Beijing Cancer Hospital, Beijing, China

⁴ Department of Epidemiology, University of North Carolina at Chapel Hill Gillings School of Global Public Health, North Carolina, USA

⁵ Department of Medicine, University of North Carolina at Chapel Hill School of Medicine, North Carolina, USA

⁶ Department of Pharmaceutical Outcomes and Policy, University of North Carolina School of Pharmacy, North Carolina, USA

⁷ Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill, North Carolina, USA

⁸ Peking University Clinical Research Institute, Peking University First Hospital, Beijing, China

⁹ Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, USA

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Table S1. Medication names

ATC Code	Generic names	Brand names
P01BA02	Hydroxychloroquine	PLAQUENIL
P01BA01	Chloroquine	ARALEN
J01FA10	Azithromycin	AZASITE, AZITHROMYCIN, ZITHROMAX, ZMAX
J01CA04 J01CR02	Amoxicillin Amoxicillin with clavulanate potassium	AMOXIL, DISPERMOX, LAROTID, MOXATAG, POLYMOX, TRIMOX, UTIMOX, WYMOX, AUGMENTIN, AUGMENTIN XR
J05AR10	Lopinavir/ritonavir, Lopinavir and ritonavir	Kaletra
Unknow	Remdesivir	Remdesivir-GS-5734, VEKLURY

Abbreviations: ATC, Anatomical Therapeutic Chemical

Table S2. Medical Dictionary for Regulatory Activities (MedDRA) terms used to identify serious cardiovascular adverse events (SCAEs) (cases)*

Outcome	MedDRA term
Cardiac arrest	Cardiac arrest, Cardiac death, Sudden cardiac death,
Ventricular arrhythmia	Ventricular arrhythmia, Ventricular tachyarrhythmia, Ventricular tachycardia, Ventricular asystole, Ventricular fibrillation, Ventricular flutter,
Atrial fibrillation	Atrial fibrillation
Bradyarrhythmia	Bradyarrhythmia, Atrioventricular block second degree, Atrioventricular block complete, Sinoatrial block, Sinus arrest, Sinus bradycardia,
QTc prolongation	Electrocardiogram QT prolonged, Long QT syndrome
Myocardial infarction	Myocardial infarction, Acute myocardial infarction, ECG signs of myocardial infarction, Silent myocardial infarction, Coronary artery occlusion
Stroke	Cerebrovascular accident, Stroke, Stroke in evolution, Basal ganglia stroke, Brain stem stroke, Cerebellar stroke, Embolic stroke, Thrombotic stroke, Haemorrhagic stroke, Ischaemic stroke, Lacunar stroke, Haemorrhagic transformation stroke, Basal ganglia infarction, Brain stem infarction, Cerebral infarction, cerebral infarct, Ischaemic cerebral infarction, Migrainous infarction, Lacunar infarction, Pituitary infarction,
Cardiac failure	Cardiac failure, Cardiac failure congestive, Cardiac failure acute, Cardiac failure high output, Ventricular failure, Acute left ventricular failure, Acute right ventricular failure, Left ventricular failure, Right ventricular failure, Cardiopulmonary failure, myocardial failure
Coronary ischemia	Myocardial ischaemia, ECG signs of myocardial ischaemia, Subendocardial ischaemia
Torsade de pointes	Torsade de pointes

* Additional terms in sensitivity were highlighted by underline.

Table S3. Torsade de pointes/QTc prolongation searched by Standardized MedDRA Queries (SMQ)

Outcome	SMQ term
Torsade de pointes/QT prolongation	Torsade de pointes, Ventricular arrhythmia, Ventricular fibrillation, Ventricular tachyarrhythmia, Syncope, Sudden death, Electrocardiogram QT prolonged, Long QT syndrome, Electrocardiogram QT interval abnormal, Ventricular tachycardia, Cardiac fibrillation, Cardiac arrest, Cardiac death, Cardio-respiratory arrest, Loss of consciousness, Multiple organ dysfunction syndrome, Sudden cardiac death

Table S4. MedDRA terms used to identify comorbidities of identified diseases

Diseases	MedDRA term
Indication of hydroxychloroquine/chloroquine	
COVID-19	coronavirus disease 2019, COVID-19, coronavirus, corona virus, SARS-CoV-2, 2019-nCoV
Precipitating factors for serious cardiovascular adverse event	
Cardiac failure	Cardiac failure, Cardiac failure congestive, Cardiac failure acute, Cardiac failure high output, Ventricular failure, Acute left ventricular failure, Acute right ventricular failure, Left ventricular failure, Right ventricular failure, Cardiopulmonary failure, myocardial failure, <u>Cardiogenic shock</u>
Hypertension	Hypertension, Blood pressure increased , Orthostatic hypertension, Supine hypertension, Accelerated hypertension, Congenital pulmonary hypertension, Endocrine hypertension, Essential hypertension, Gestational hypertension, Labile hypertension, Malignant hypertension, Malignant renal hypertension, Neurogenic hypertension, Pulmonary arterial hypertension, Pulmonary hypertension, Renal hypertension, Renovascular hypertension, Right ventricular hypertension, Secondary hypertension, Systolic hypertension, Withdrawal hypertension
Hyperlipidemia	Hyperlipidemia , Acquired mixed hyperlipidaemia, Autoimmune hyperlipidaemia, Type IIb hyperlipidaemia, Type IIa hyperlipidaemia, Type II hyperlipidaemia, Type IIa hyperlipidaemia, Hyperlipidaemia, Type V hyperlipidaemia, Remnant hyperlipidaemia, Type I hyperlipidaemia, Type II hyperlipidaemia, Type IIa hyperlipidaemia, Type IIb hyperlipidaemia, Type III hyperlipidaemia, Type IV hyperlipidaemia, Type V hyperlipidaemia
Left ventricular hypertrophy	Left ventricular hypertrophy
Severe renal disease	End stage renal disease, Chronic kidney disease, Diabetic end stage renal disease, Dialysis, Renal failure
Diabetes	Diabetes, Diabetes mellitus , Gestational diabetes, Acquired lipotrophic diabetes, Cystic fibrosis related diabetes, Diabetes complicating pregnancy Diabetes mellitus inadequate control, Diabetes with hyperosmolarity, Fulminant type 1 diabetes mellitus, Insulin resistant diabetes, Insulin-requiring type 2 diabetes mellitus, Ketosis-prone diabetes mellitus, Latent autoimmune diabetes in adults, Monogenic diabetes, Pancreatogenous diabetes, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Type 3 diabetes mellitus
Sepsis	Sepsis
Obesity	Obesity, Overweight
Hypokalemia	Hypokalemia
Hypomagnesemia	Hypomagnesemia
Hypocalcemia	Hypocalcemia

Table S5. Generic/brand names identify concomitant QTc prolonging medications that may induce SCAEs of identified cases

ATC Code	Generic names	Brand names
Quinolones (levofloxacin, moxifloxacin, ciprofloxacin)		
J01MA12, S01AE05	Levofloxacin	IQUIX, LEVAQUIN, QUIXIN
J01RA05	Levofloxacin and ornidazole	
J01MA14, S01AE07	Moxifloxacin	AVELOX, MOXEZA, VIGAMOX
J01MA02, S01AE03, S02AA15, S03AA07	Ciprofloxacin	CETRAXAL, CILOXAN, CIPRO, CIPRO XR, OTIPRIO, PROQUIN XR
J01RA10	Ciprofloxacin and metronidazole	
J01RA12	Ciprofloxacin and ornidazole	
J01RA11	Ciprofloxacin and tinidazole	
	Ciprofloxacin, combinations	CIPRO HC, CIPRODEX, OTOVEL
Macrolide (erythromycin, clarithromycin)		
D10AF02, J01FA01, S01AA17	Erythromycin	BRISTAMYCIN, E-BASE, E-MYCIN, E-MYCIN E, ERY-PED, ERYPED, ERY-TAB, ERYC, ERYC 125, ERYC SPRINKLES, ERYPAR, ERYTHROCIN, ERYTHROCIN STEARATE, WYAMYCIN, WYAMYCIN E, WYAMYCIN S, ERYZOLE, ETHRIL, ETHRIL 250, ETHRIL 500, ILOSONE, ILOSONE SULFA, ILOTYCIN, PCE, PEDIAMYCIN, PEDIAZOLE, PFIZER-E, R-P MYCIN, ROBIMYCIN
D10AF52	Erythromycin, combinations	
J01FA09	Clarithromycin	BIAXIN, BIAXIN XL
A02BD07	Lansoprazole, amoxicillin and clarithromycin	PREVPAC
A02BD05	Omeprazole, amoxicillin and clarithromycin	OMECLAMOX
A02BD06	Esomeprazole, amoxicillin and clarithromycin	
A02BD04	Pantoprazole, amoxicillin and clarithromycin	
A02BD11	Pantoprazole, amoxicillin, clarithromycin and metronidazole	
A02BD12	Rabeprazole, amoxicillin and clarithromycin	
A02BD14	Vonoprazan, amoxicillin and clarithromycin	
A02BD09	Lansoprazole, clarithromycin and tinidazole	
Azole antifungals (fluconazole, itraconazole, ketoconazole, posaconazole)		

D01AC15, J02AC01	Fluconazole	DIFLUCAN
J02AC02	Itraconazole	ONMEL, SPORANOX, TOLSURA
D01AC08, G01AF11, J02AB02	Ketoconazole	EXTINA, KETOZOLE, NIZORAL, NIZORAL A-D, XOLEGEL
J02AC04	Posaconazole	NOXAFIL
Tricyclics (amitriptyline, clomipramine, desipramine, doxepin, imipramine)		
N06AA09	Amitriptyline	AMITID, AMITRIL, ELAVIL, ENDEP
N06CA01	Amitriptyline and psycholeptics	ETRAFON, LIMBITROL, TRIAVIL
N06AA04	Clomipramine	ANAFRANIL
N06AA01	Desipramine	NORPRAMIN, PERTOFRANE
D04AX01, N06AA12	Doxepin	SILENOR, SINEQUAN, ZONALON
N06AA02,	Imipramine	JANIMINE, PRAMINE, PRESAMINE, SURMONTIL, TOFRANIL, TOFRANIL-PM
SSRI (citalopram, escitalopram)		
N06AB04	Citalopram	CELEXA
N06AB10	Escitalopram	LEXAPRO
5-HT3 antagonist (ondansetron, palonosetron, granisetron, dolasetron)		
A04AA01	Ondansetron	ZOFran, ZOFran ODT, ZOFran PRESERVATIVE FREE, ZUPLENZ
A04AA05	Palonosetron	ALOXI
A04AA55	Palonosetron, combinations	AKYNZEO
A04AA02	Granisetron	GRANISOL, KYTRIL, SANCUSO, SUSTOL
A04AA04	Dolasetron	ANZEMET
Antipsychotics (haloperidol, droperidol, thioridazine, aripiprazole, asenapine, clozapine)		
N05AD01	Haloperidol	HALDOL, HALDOL SOLUTAB
N05AD08	Droperidol	INAPSINE, INNOVAR
N05AC02	Thioridazine	MELLARIL, MELLARIL-S
N05AX12	Aripiprazole	ABILIFY, ABILIFY MAINTENA KIT, ABILIFY MYCITE KIT, ARISTADA, ARISTADA INITIO KIT
N05AH05	Asenapine	SAPHRIS, SECUADO
N05AH02	Clozapine	CLOZARIL, FAZACLO ODT, VERSACLOZ
Loop diuretics (furosemide, torsemide, bumetanide, ethacrynic acid)		
C03CA01	Furosemide	LASIX
C03CB01	Furosemide and potassium	
C03EB01	Furosemide and potassium-sparing agents	
C03CA04	Torsemide (torasemide)	DEMADEX
C03CA02	Bumetanide	BUMEX
C03CB02	Bumetanide and potassium	
C03EB02	Bumetanide and potassium-sparing agents	
C03CC01	Ethacrynic acid (etacrynic acid)	EDECRIN
Class Ia antiarrhythmic agents (Disopyramide, Quinidine, Procainamide)		
C01BA03	Disopyramide	NORPACE, NORPACE CR

C01BA01	Quinidine	CARDIOQUIN, CIN-QUIN, DURAQUIN, QUINACT, QUINAGLUTE, QUINALAN, QUINATIME, QUINIDEX, QUINORA
C01BA51	Quinidine, combinations excl. Psycholeptics	NUEDEXTA
C01BA71	Quinidine, combinations with psycholeptics	
C01BA02	Procainamide	
Class III antiarrhythmic agents (Amiodarone, Dronedarone, Sotalol, Ibutilide, Dofetilide)		
C01BD01	Amiodarone	CORDARONE, NEXTERONE, PACERONE
C01BD07	Dronedarone	MULTAQ
C07AA07	Sotalol	BETAPACE, BETAPACE AF, SORINE, SOTYLIZE
C07FX02	Sotalol and acetylsalicylic acid	
C07BA07	Sotalol and thiazides	
C01BD05	Ibutilide	CORVERT
C01BD04	Dofetilide	TIKOSYN
Methadone		
N07BC02	Methadone	WESTADONE, DOLOPHINE
N02AC52	Methadone, combinations excl. Psycholeptics	
Donepezil		
N06DA02	Donepezil	ARICEPT, ARICEPT ODT,
N06DA52	Donepezil and memantine	NAMZARIC

Table S6. Two by two tables for disproportionality analysis and calculation of ROR*

	Drug of interest	Comparators
Events of interest	a	b
All other events	c	d

Abbreviation: ROR, reporting odds ratio.

* ROR is a measure of disproportionality for signal detection in spontaneous report databases for adverse drug reactions [1]. It was chosen in our study for its advantages of enabling to estimate relative risk (RR) and more deliberate elimination of biases over the proportional reporting ratio (PRR, another frequently used measure for disproportionality analysis in spontaneous report databases) [2]. Generally, a signal is considered when the lower limit of the 95% confidence interval (CI) of the ROR is greater than one. A significant signal was defined as a ROR of ≥ 2 .

ROR and 95% CI can be calculated by [1]:

$$ROR = \frac{(a/c)}{(b/d)} = \frac{ad}{bc}$$

$$95\%CI = e^{\ln(ROR) \pm 1.96 \sqrt{\left(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}\right)}}$$

Number of events (a, b, c, and d) were counted to calculate ROR.

1. van Puijenbroek EP, Bate A, Leufkens HG et al. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf.* 2002;11(1):3-10.
2. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiol Drug Saf.* 2004;13:519-23.

Table S7. Chi-square values for all RORs

Comparison	Chi-square value	P value
Primary outcome: SCAEs		
HCQ/CQ+Azithromycin vs HCQ/CQ+Amoxicillin	0.0001	0.9910
HCQ/CQ+Azithromycin vs HCQ/CQ	34.1055	<.0001
HCQ/CQ+Azithromycin vs Lopinavir/ritonavir	41.0489	<.0001
HCQ/CQ+Azithromycin vs Remdesivir	154.3779	<.0001
HCQ/CQ+Azithromycin vs Other	336.4805	<.0001
HCQ/CQ vs Lopinavir/ritonavir	23.9447	<.0001
HCQ/CQ vs Remdesivir	104.1279	<.0001
HCQ/CQ vs Other	264.9377	<.0001
Secondary outcome 1: TdP/QTc prolongation		
HCQ/CQ+Azithromycin vs HCQ/CQ+Amoxicillin	1.0170	0.3132
HCQ/CQ+Azithromycin vs HCQ/CQ	24.2998	<.0001
HCQ/CQ+Azithromycin vs Lopinavir/ritonavir	36.0236	<.0001
HCQ/CQ+Azithromycin vs Remdesivir	438.5642	<.0001
HCQ/CQ+Azithromycin vs Other	368.0848	<.0001
HCQ/CQ vs Lopinavir/ritonavir	22.1466	<.0001
HCQ/CQ vs Remdesivir	347.6868	<.0001
HCQ/CQ vs Other	278.7012	<.0001
Secondary outcome 2: Ventricular arrhythmia		
HCQ/CQ+Azithromycin vs HCQ/CQ+Amoxicillin	0.9502	0.3297
HCQ/CQ+Azithromycin vs HCQ/CQ	20.5666	<.0001
HCQ/CQ+Azithromycin vs Lopinavir/ritonavir	68.9509	<.0001
HCQ/CQ+Azithromycin vs Remdesivir	41.2938	<.0001
HCQ/CQ+Azithromycin vs Other	179.0576	<.0001
HCQ/CQ vs Lopinavir/ritonavir	24.4844	<.0001
HCQ/CQ vs Remdesivir	17.7121	<.0001
HCQ/CQ vs Other	89.6281	<.0001
Secondary outcome 3: Cardiac arrest		
HCQ/CQ+Azithromycin vs HCQ/CQ+Amoxicillin	0.2349	0.6279
HCQ/CQ+Azithromycin vs HCQ/CQ	0.2896	0.5905
HCQ/CQ+Azithromycin vs Lopinavir/ritonavir	1.4384	0.2304
HCQ/CQ+Azithromycin vs Remdesivir	30.0242	<.0001
HCQ/CQ+Azithromycin vs Other	1.1129	0.2915
HCQ/CQ vs Lopinavir/ritonavir	0.2231	0.6367
HCQ/CQ vs Remdesivir	69.2789	<.0001
HCQ/CQ vs Other	1.7959	0.1802
Secondary outcome 4: TdP/QTc prolongation by SMQ terms		
HCQ/CQ+Azithromycin vs HCQ/CQ+Amoxicillin	0.0136	0.9071
HCQ/CQ+Azithromycin vs HCQ/CQ	51.1703	<.0001
HCQ/CQ+Azithromycin vs Lopinavir/ritonavir	79.1822	<.0001
HCQ/CQ+Azithromycin vs Remdesivir	200.9187	<.0001
HCQ/CQ+Azithromycin vs Other	425.5920	<.0001
HCQ/CQ vs Lopinavir/ritonavir	27.6970	<.0001
HCQ/CQ vs Remdesivir	125.9908	<.0001
HCQ/CQ vs Other	262.0245	<.0001

Abbreviations: CQ, chloroquine; HCQ, hydroxychloroquine; SCAE, serious cardiovascular adverse event; SMQ, standardized MedDRA Queries; TdP, torsade de pointes. Other, other medications used by patients with COVID-19 except for HCQ/CQ, azithromycin, lopinavir/ritonavir, and remdesivir (e.g., insulin, simvastatin, etc.).

Table S8. Descriptive characteristics of SCAE case reports listing use of HCQ/CQ±azithromycin and Remdesivir desivir in COVID-19 cases reported to FAERS from 1 January 2020 to 31 December 2020

Characteristics	HCQ/CQ±azithromycin (N=571)*	Remdesivir desivir (N=275)*
Age, year	434 reported	272 reported
Mean (SD)	64.1 (17.8)	64.9 (16.2)
Sex	440 reported	274 reported
Female	133 (30.2)	117 (42.7)
Weight, kg	148 reported	249 reported
Mean	85.1 (18.4)	95.3 (37.6)
Precipitating factors†		
Hypertension	36 (6.3)	2 (0.7)
Heart failure	8 (1.4)	0
Diabetes	17 (3.0)	3 (1.1)
Sepsis	1 (0.2)	0
Female sex	133 (30.2)	117 (42.7)
Advanced age >65	248/434 (57.1)	144/272 (52.9)
Concurrent QTc prolonging medications may induce SCAEs‡		
Lopinavir/ritonavir	111 (19.4)	1 (0.4)
Quinolones	17 (3.0)	6 (2.2)
Macrolide	2 (0.4)	0
Azole antifungals	5 (0.9)	3 (1.1)
Tricyclics	7 (1.2)	2 (0.7)
Selective serotonin reuptake inhibitors (SSRI)	6 (1.1)	1 (0.4)
5-HT3 antagonist	6 (1.1)	12 (4.4)
Antipsychotics	7 (1.2)	1 (0.4)
Loop diuretics	34 (6.0)	51 (18.5)
Class Ia antiarrhythmic agents	0	1 (0.4)
Class III antiarrhythmic agents	22 (3.9)	26 (9.5)
Donepezil	1 (0.2)	6 (2.2)
Serious cardiac adverse events§		
QTc prolongation	350 (61.3)	8 (2.9)
Ventricular arrhythmia	69 (12.1)	27 (9.8)
Atrial fibrillation	47 (8.2)	45 (16.4)
Torsade de pointes	27 (4.7)	3 (1.1)
Cardiac arrest	25 (4.4)	125 (45.5)
Heart failure	22 (3.9)	10 (3.6)
Stroke	11 (1.9)	27 (9.8)
Myocardial infarction	10 (1.8)	17 (6.2)
Bradyarrhythmia	10 (1.8)	13 (4.7)
Serious outcomes	564 reported	262 reported
Hospitalization	129 (22.9)	26 (9.9)
Life-threatening	102 (18.1)	34 (13.0)
Death	109 (19.3)	174 (66.4)
Other serious events	365 (64.7)	116 (44.3)

Abbreviations: COVID-19, coronavirus disease 2019; CQ, chloroquine; HCQ, hydroxychloroquine; SCAE, serious cardiovascular adverse event; SD, standard deviation.

* Values are numbers (percentage) of events unless otherwise noted. † Precipitating factors included heart failure, hypertension, hyperlipidemia, left ventricular hypertrophy, severe renal disease, diabetes, female sex, advanced age >65, sepsis, hypokalemia, hypomagnesemia, hypocalcemia, and obesity. For those with zero or missing values were not listed; ‡ Individual drug of each group was shown in Table S5 in the Electronic Supplementary Material. § SCAEs was predefined as composite endpoint including cardiac arrest, ventricular arrhythmia, atrial fibrillation,

bradyarrhythmia, QTc prolongation, myocardial infarction, stroke, cardiac failure, coronary ischemia, and torsade de pointes. For those with zero or missing values were not listed.

Table S9. Descriptive characteristics of SCAE case reports listing use of HCQ/CQ±azithromycin and lopinavir/ritonavir in COVID-19 cases reported to FAERS from 1 January 2020 to 31 December 2020

Characteristics	HCQ/CQ±azithromycin (N=458)*	Lopinavir/ritonavir (N=137)*
Age, year	336 reported	128 reported
Mean (SD)	63.4 (18.7)	67.5 (15.5)
Sex	342 reported	129 reported
Female	106 (31.0)	34 (26.4)
Weight, kg	131 reported	59 reported
Mean	86.2 (18.5)	82.9 (16.9)
Precipitating factors†		
Hypertension	33 (7.2)	7 (5.1)
Heart failure	8 (1.7)	12 (8.8)
Diabetes	14 (3.1)	6 (4.4)
Sepsis	1 (0.2)	0
Female sex	106 (31.0)	34 (26.4)
Advanced age >65	144/336 § (42.9)	83/128 § (64.8)
Concurrent QTc prolonging medications may induce SCAEs‡		
Quinolones	14 (3.1)	22 (16.1)
Macrolide	2 (0.4)	1 (0.7)
Azole antifungals	5 (1.1)	0
Tricyclics	7 (1.5)	0
Selective serotonin reuptake inhibitors (SSRI)	4 (0.9)	6 (4.4)
5-HT3 antagonist	5 (1.1)	0
Antipsychotics	5 (1.1)	0
Loop diuretics	31 (6.8)	13 (9.5)
Class III antiarrhythmic agents	21 (4.6)	9 (6.6)
Donepezil	1 (0.2)	0
Serious cardiac adverse events§		
QTc prolongation	276 (60.3)	78 (56.9)
Ventricular arrhythmia	66 (14.41)	3 (2.19)
Atrial fibrillation	20 (4.37)	20 (4.37)
Torsade de pointes	27 (5.9)	3 (2.2)
Cardiac arrest	23 (5.02)	9 (6.57)
Heart failure	16 (3.49)	11 (8.03)
Stroke	10 (2.18)	0
Myocardial infarction	10 (2.18)	1 (0.73)
Bradyarrhythmia	20 (4.37)	6 (4.38)
Serious outcomes	451 reported	136 reported
Hospitalization	101 (22.4)	17 (12.5)
Life-threatening	93 (20.6)	30 (22.1)
Death	80 (17.8)	34 (25.0)
Other serious events	281 (62.3)	85 (62.5)

Abbreviations: COVID-19, coronavirus disease 2019; CQ, chloroquine; HCQ, hydroxychloroquine; SCAE, serious cardiovascular adverse event; SD, standard deviation.

* Values are numbers (percentage) of events unless otherwise noted. † Precipitating factors included heart failure, hypertension, hyperlipidemia, left ventricular hypertrophy, severe renal disease, diabetes, female sex, advanced age >65, sepsis, hypokalemia, hypomagnesemia, hypocalcemia, and obesity. For those with zero or missing values were not listed; ‡ Individual drug of each group was shown in Table S5 in the Electronic Supplementary Material. § SCAEs was predefined as composite endpoint including cardiac arrest, ventricular arrhythmia, atrial fibrillation, bradyarrhythmia, QTc prolongation, myocardial infarction, stroke, cardiac failure, coronary ischemia, and torsade de pointes. For those with zero or missing values were not listed.

Table S10. Descriptive characteristics of SCAE case reports listing use of HCQ/CQ±azithromycin and other medications in COVID-19 cases reported to FAERS from 1 January 2020 to 31 December 2020

Characteristics	HCQ/CQ±azithromycin (N=394)*	Other medications (N= 213)*
Age, year	289 reported	184 reported
Mean (SD)	63.7 (18.0)	64.1 (17.3)
Sex	299 reported	191 reported
Female	100 (33.4)	60 (31.4)
Weight, kg	116 reported	71 reported
Mean	86.2 (17.8)	77.9 (22.3)
Precipitating factors†		
Hypertension	26 (6.6)	14 (6.6)
Heart failure	5 (1.3)	0
Diabetes	8 (2.0)	10 (4.7)
Female sex	100 (33.4)	60 (31.4)
Advanced age >65	83/289 (28.7)	98/184 (53.3)
Concurrent QTc prolonging medications may induce SCAEs‡		
Lopinavir/ritonavir	43 (10.9)	94 (44.1)
Quinolones	5 (1.3)	13 (6.1)
Macrolide	2 (0.5)	1 (0.5)
Azole antifungals	5 (1.3)	0
Tricyclics	7 (1.8)	1 (0.5)
Selective serotonin reuptake inhibitors (SSRI)	4 (1.0)	7 (3.3)
5-HT3 antagonist	4 (1.0)	1 (0.5)
Antipsychotics	2 (0.5)	0
Loop diuretics	23 (5.8)	12 (5.6)
Class III antiarrhythmic agents	12 (3.0)	11 (5.2)
Donepezil	1 (0.3)	0
Serious cardiac adverse events§		
QTc prolongation	256 (65.0)	96 (45.1)
Ventricular arrhythmia	56 (14.2)	5 (2.4)
Atrial fibrillation	15 (3.8)	33 (15.5)
Torsade de pointes	25 (5.7)	0
Cardiac arrest	13 (3.3)	38 (17.8)
Heart failure	12 (3.1)	11 (5.2)
Coronary ischemia	0	1 (0.5)
Stroke	4 (1.0)	14 (6.6)
Myocardial infarction	9 (2.3)	11 (5.2)
Bradyarrhythmia	4 (1.0)	4 (1.9)
Serious outcomes	387 reported	212 reported
Hospitalization	92 (23.8)	28 (13.2)
Life-threatening	83 (21.5)	39 (18.4)
Death	59 (15.3)	92 (43.4)
Other serious events	246 (63.6)	136 (64.2)

Abbreviations: COVID-19, coronavirus disease 2019; CQ, chloroquine; HCQ, hydroxychloroquine; SCAE, serious cardiovascular adverse event; SD, standard deviation.

* Values are numbers (percentage) of events unless otherwise noted. † Precipitating factors included heart failure, hypertension, hyperlipidemia, left ventricular hypertrophy, severe renal disease, diabetes, female sex, advanced age >65, sepsis, hypokalemia, hypomagnesemia, hypocalcemia, and obesity. For those with zero or missing values were not listed; ‡ Individual drug of each group was shown in Table S5 in the Electronic Supplementary Material. § SCAEs was predefined as composite endpoint including cardiac arrest, ventricular arrhythmia, atrial fibrillation,

bradyarrhythmia, QTc prolongation, myocardial infarction, stroke, cardiac failure, coronary ischemia, and torsade de pointes. For those with zero or missing values were not listed.