Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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An evaluation of co-use of chloroquine or hydroxychloroquine plus azithromycin on cardiac outcomes: A pharmacoepidemiological study to inform use during the COVID19 pandemic

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ABSTRACT

Background: Chloroquine or hydroxychloroquine (chloroquine) plus azithromycin is considered as therapy for COVID-19. With benefit evaluations underway, safety concerns due to potential additive effects on QTc prolongation should be addressed.

Objective: We compared risk of cardiac adverse events between combinations of chloroquine and azithromycin and chloroquine and amoxicillin.

Methods: We conducted a retrospective cohort study using the IBM MarketScan Commercial Claims and Medicare Supplemental Databases, 2005–2018. We included autoimmune disease patients aged ≥18 years initiating azithromycin or amoxicillin for ≥5 days during chloroquine treatment. Patients had continuous insurance coverage ≥6 months before combination use until 5 days thereafter or inpatient death. Two outcomes were sudden cardiac arrest/ventricular arrhythmias (SCA/VA) and cardiac symptoms. We followed patients for up to 5 days to estimate hazard ratios (HR). Covariates were adjusted using stabilized inverse probability treatment weighting.

Results: We identified two SVC/VA events among > 145,000 combination users. The adjusted incidence of cardiac symptoms among azithromycin and amoxicillin users was 276 vs 254 per 10,000 person-years with an adjusted HR of 1.10 (95%CI, 0.62–1.95).

Conclusion: Combination use of chloroquine and azithromycin at routine doses did not show pronounced increases in arrhythmias in this real-world population, though small sample size and outcome rates limit conclusions.

Introduction

The novel coronavirus (COVID-19) is expected to impact millions of people worldwide over the next several months.[1] On April 24, 2020, according to the World Health Organization, there are approximatley 2.6 millions cases and 181 thousand deaths worldwide (81,529 new cases and 6260 new deaths compared to the previous day).[2] Vaccines are projected to not be available until 2021 and no effective antiviral treatment has been identified to-date. Among repurposed medications evaluated as potential therapies to treat COVID-19 is a combination of chloroquine or hydroxychloroquine plus azithromycin, with mixed results from non-controlled case series of COVID-19 patients.[3,4] Moreover, preclinical studies have suggested that chloroquine may also have a potential prophylactic effect on COVID-19 infections.[5] While clinical trials evaluating the efficacy are underway (n = 19; clinicaltrials.gov accessed on 4/22/2020), the U.S. Food & Drug Administration (FDA) has issued an emergency use authorization of chloroquine phosphate from the Strategic National Stockpile to treat adults hospitalized for COVID-19 (04/03/2020).[6] However, given emerging evidence which questions whether treatment has favorable risk-benefit, the FDA recommends against use of chloroquine outside hospital settings or clinical trials for COVID-19 patients because of the known QTc

Abbreviations: CI, confidence interval; COPD, Chronic obstructive pulmonary disease; FDA, U.S. Food & Drug Administration; HR, hazard ratio; SCA/VA, sudden cardiac arrest and ventricular arrhythmias; SIPTW, Standardized inverse probability treatment weighting

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Table 1
Baseline characteristics during six months before index in cohorts for evaluating risk of cardiac symptoms.

Baseline characteristics	Before SIPTW			After SIPTW		
	Azithromycin (N, %) (Total N = 69,473)	Amoxicillin (N, %) (Total N = 72,163)	Absolute standardized difference	Azithromycin (N, %) (Total N = 67,427)	Amoxicillin (N, %) (Total N = 69,866)	Absolute standardized difference
Age						
18–30	3693 (5.3)	4039 (5.6)	0.012	3644 (5.4)	3855 (5.5)	0.005
31–40	8430 (12.1)	8671 (12.0)	0.004	8292 (12.3)	8413 (12.0)	0.008
41–50	15,536 (22.4)	16,150 (22.4)	0	15,181 (22.5)	15,663 (22.4)	0.002
51–65	32,674 (47.0)	34,080 (47.2)	0.004	31,653 (46.9)	33,006 (47.2)	0.006
> 65	9140 (13.2)	9223 (12.8)	0.011	8656 (12.8)	8930 (12.8)	0.002
Male	7927 (11.4)	9467 (13.1)	0.052	8238 (12.2)	8510 (12.2)	0.001
Private insurance only	59,657 (85.9)	62,219 (86.2)	0.01	58,133 (86.2)	60,246 (86.2)	0
Calendar year at index date						
2005–2006	3569 (5.1)	4279 (5.9)	0.035	3716 (5.5)	3845 (5.5)	0
2007–2008	7538 (10.8)	7050 (9.7)	0.036	6973 (10.3)	7204 (10.3)	0.001
2009–2010	12,435 (17.9)	10,746 (14.8)	0.081	11,065 (16.4)	11,450 (16.4)	0.001
2011–2012	15,874 (22.8)	13,493 (18.7)	0.102	14,019 (20.8)	14,456 (20.7)	0.002
2013–2014	12,000 (17.3)	13,209 (18.3)	0.027	11,884 (17.6)	12,336 (17.7)	0.001
2015–2016	10,133 (14.6)	11,978 (16.6)	0.056	10,565 (15.7)	11,001 (15.7)	0.002
2017–2018	7924 (11.4)	11,408 (15.8)	0.129	9205 (13.7)	9576 (13.7)	0.002
Autoimmune diseases during 6 months before index date						
Multiple sclerosis	368 (0.5)	378 (0.5)	0.001	347 (0.5)	358 (0.5)	0
Systemic lupus erythematosus and connective tissue disorders	23,468 (33.8)	24,335 (33.7)	0.001	22,769 (33.8)	23,603 (33.8)	0
Rheumatoid arthritis and related diseases	35,995 (51.8)	36,382 (50.4)	0.028	34,454 (51.1)	35,652 (51.0)	0.001
Systemic sclerosis	1312 (1.9)	1276 (1.8)	0.009	1226 (1.8)	1272 (1.8)	0
Psoriasis	1706 (2.5)	1894 (2.6)	0.011	1706 (2.5)	1770 (2.5)	0
Myasthenia gravis	87 (0.1)	90 (0.1)	0	84 (0.1)	90 (0.1)	0.001
Nephritis	3035 (4.4)	3093 (4.3)	0.004	2899 (4.3)	2979 (4.3)	0.002
Polyarteritis	774 (1.1)	773 (1.1)	0.004	732 (1.1)	760 (1.1)	0
Autoimmune hepatitis	260 (0.4)	273 (0.4)	0.001	253 (0.4)	257 (0.4)	0.001
Iridocyclitis	369 (0.5)	378 (0.5)	0.001	347 (0.5)	374 (0.5)	0.003
Neuropathy	817 (1.4)	1001 (1.4)	0.019	851 (1.3)	880 (1.3	0
Tissue disorder	16,719 (24.1)	18,342 (25.4)	0.031	16,681 (24.7)	17,326 (24.8)	0.001
Infections during 2 weeks before index date						
Pneumonia	1396 (2.0)	524 (0.7)	0.111	865 (1.3)	834 (1.2)	0.008
Tonsillitis	222 (0.3)	387 (0.5)	0.033	294 (0.4)	309 (0.4)	0.001
Acute bronchitis	9688 (13.9)	2845 (3.9)	0.356	5408 (8.0)	5384 (7.7)	0.012
Influenza	656 (0.9)	255 (0.3)	0.074	388 (0.6)	384 (0.5)	0.004
Other upper respiratory infection	25,450 (36.6)	25,647 (35.5)	0.023	25,165 (37.3)	26,308 (37.6)	0.007
Pleurisy	395 (0.6)	250 (0.4)	0.033	300 (0.4)	311 (0.4)	0
Other lower respiratory disease	10,005 (14.4)	5001 (6.9)	0.244	6645 (9.8)	6779 (9.7)	0.005
Other upper respiratory disease	4348 (6.3)	4226 (5.9)	0.017	4152 (6.2)	4296 (6.3)	0
Intestinal infection	70 (0.1)	87 (0.1)	0.006	72 (0.1)	78 (0.1)	0.002
Urinary tract infection	712 (1.0)	1927 (2.6)	0.122	1039 (1.5)	1089 (1.6)	0.001
Skin infection	401 (0.6)	1731 (2.4)	0.151	412 (0.6)	467 (0.7)	0.007
Open wounds	165 (0.2)	740 (1.0)	0.1	165 (0.2)	173 (0.3)	0.001
Eye inflammation/infection	1017 (1.5)	1011 (1.4)	0.005	982 (1.5)	1018 (1.5)	0
Otitis media	1841 (2.6)	3277 (4.5)	0.102	2467 (3.7)	2601 (3.7)	0.003
Other bacterium infections	328 (0.5)	805 (1.1)	0.073	416 (0.6)	466 (0.7)	0.006
Fever	1165 (1.7)	952 (1.3)	0.029	963 (1.4)	1020 (1.5)	0.003
Other clinical characteristics during 6 months before index date						
Drugs related QT prolongation						
Drugs with known risk of QT prolongation	20,909 (30.1)	21,651 (30.0)	0.002	20,253 (30.0)	21,053 (30.1)	0.002
Drugs with possible risk of QT prolongation	37,253 (53.6)	38,958 (54.0)	0.007	36,241 (53.7)	37,587 (53.8)	0.001
Drugs with conditional risk of QT prolongation	38,757 (55.7)	39,975 (55.4)	0.008	37,481 (55.6)	38,903 (55.7)	0.002
Duration of chloroquine/hydroxychloroquine use						
≤30 days	4814 (6.9)	5339 (7.4)	0.018	4977 (7.4)	4860 (7.0)	0.016
31–60 days	4421 (6.4)	5172 (7.2)	0.032	4471 (6.6)	4854.9 (7.0)	0.013
61–90 days	6251 (9.0)	6779 (9.4)	0.014	6245.1 (9.3)	6438 (9.2)	0.002
91–180 days	53,987 (77.7)	54,873 (76.0)	0.04	51,733 (76.7)	53,712 (76.9)	0.004
Respiratory diseases						
Respiratory failure	328 (0.5)	347 (0.5)	0.001	316 (0.5)	339 (0.5)	0.002
Asthma	4547 (6.54	3842 (5.3)	0.052	3990 (5.9)	4136 (5.9)	0
COPD	3942 (5.7)	3342 (4.6)	0.047	3464 (5.1)	3595 (5.2)	0
Others	1474 (2.1)	1611 (2.2)	0.008	1475 (2.2)	1526 (2.2)	0
Cardiovascular related diseases						

(*continued on next page*)

Table 1 (*continued*)

Baseline characteristics	Before SIPTW			After SIPTW		
	Azithromycin (N, %) (Total N = 69,473)	Amoxicillin (N, %) (Total N = 72,163)	Absolute standardized difference	Azithromycin (N, %) (Total N = 67,427)	Amoxicillin (N, %) (Total N = 69,866)	Absolute standardized difference
Coronary atherosclerosis and other heart disease	2775 (4.0)	3035 (4.2)	0.011	2714 (4.0)	2844 (4.1)	0.002
Atrial arrhythmias	1650 (2.4)	1981 (2.7)	0.023	1689 (2.5)	1766 (2.5)	0.001
Congestive heart failure	704 (1.0)	781 (1.1)	0.007	689 (1.0)	722 (1.03)	0.001
Peripheral and visceral atherosclerosis; aneurysms	1388 (2.0)	1578 (2.2)	0.013	1375 (2.0)	1421 (2.0)	0
Acute cerebrovascular disease	478 (0.7)	577 (0.8)	0.013	496 (0.7)	518 (0.7)	0.001
Occlusion or stenosis of precerebral arteries	595 (0.9)	605 (0.8)	0.002	559 (0.8)	569 (0.8)	0.002
Other and ill-defined cerebrovascular disease	301 (0.4)	340 (0.5)	0.006	303 (0.4)	312 (0.4)	0
Transient cerebral ischemia	335 (0.5)	384 (0.5)	0.007	333 (0.4)	352 (0.5)	0.002
Late effects of cerebrovascular disease	175 (0.3)	193 (0.3)	0.003	173 (0.3)	179 (0.3)	0
Hypertension	19,646 (28.3)	20,936 (29.0)	0.016	19,214 (28.5)	19,886 (28.5)	0.001
Obesity	3868 (5.6)	4587 (6.4)	0.033	3986 (5.9)	4143 (5.9)	0.001
Hyperlipidemia	13,707 (19.7)	14,503 (20.1)	0.009	13,378 (19.8)	13,852 (19.8)	0
Diabetes	8059 (11.6)	8942 (12.4)	0.024	7967 (11.8)	8338 (11.9)	0.004
Kidney disease	10,540 (15.2)	11,883 (16.5)	0.036	10,503 (15.6)	10,888 (15.6)	0
Liver disease	2041 (2.9)	2273 (3.2)	0.012	2067 (3.1)	2146 (3.1)	0
Epilepsy	646 (0.9)	711 (1.0)	0.006	644 (0.9)	669 (1.0)	0
Hospitalization	17,229 (24.8)	18,617 (25.8)	0.023	16,964 (25.2)	17,639 (25.3)	0.002
Smoking	1300 (1.9)	1343 (1.9)	0.001	1243 (1.8)	1297 (1.9)	0.001
Surgery	2091 (3.0)	2712 (3.8)	0.041	2252 (3.3)	2344 (3.4)	0.001
Psychiatric conditions						
Substance use disorder	622 (0.9)	771 (1.1)	0.018	653 (1.0)	676 (1.0)	0
Adjustment disorders	1452 (2.1)	1567 (2.2)	0.006	1412 (2.1)	1460 (2.1)	0
Anxiety	5053 (7.3)	5648 (7.8)	0.021	5074 (7.5)	5268 (7.5)	0.001
Depression	6799 (9.8	7551 (10.5)	0.022	6810 (10.1)	7059 (10.1)	0
Bipolar	849 (1.2)	995 (1.4)	0.014	867 (1.3)	911 (1.3)	0.002
ADD/Developmental/childhood disorders	793 (1.1)	955 (1.3)	0.016	821 (1.2)	854 (1.2)	0
Other mental health disorder	2665 (3.8)	2802 (3.9)	0.002	2585 (3.8)	2668 (3.8)	0.001
Parkinson disease	93 (0.1)	89 (0.1)	0.003	84 (0.1)	89 (0.1)	0.001
Other hereditary and degenerative nervous system condition	1333 (1.9)	1487 (2.1)	0.01	1346 (2.0)	1392 (2.0)	0
Nervous system disorder (not related to eye/ear)	10,714 (15.4)	12,122 (16.8)	0.037	10,774 (16.0)	11,178 (16.0)	0.001

Abbreviation: SIPTW: Standardized inverse probability treatment weighting; COPD: Chronic obstructive pulmonary disease.

prolongation risk (04/24/2020).[7]

Although the combination of chloroquine and azithromycin may have potential benefits, each medication is independently associated with an increased risk of QTc prolongation and subsequent death[8]; and the combination of the two medication types may further potentiate this risk. Because severe arrhythmias, the direct consequence of QTc prolongation, are rare, the ongoing clinical trials are unlikely to have sufficient sample size to address whether combination use of hydroxychloroquine or chloroquine and azithromycin may potentiate effects on QTc prolongation and its severe consequences.[8,9] However, as chloroquine and hydroxychloroquine have been used for several decades in patients with autoimmune diseases (e.g., rheumatoid arthritis, lupus), we can use real-world data to evaluate whether combination use with azithromycin potentiates the risk for cardiac adverse events and to inform their use during the COVID-19 pandemic.

Methods

We conducted a retrospective cohort study using the IBM MarketScan Commercial Claims and Medicare Supplemental Databases from 2005 to 2018. These databases provide detailed information on patient healthcare utilization including medical inpatient and outpatient encounters and pharmacy dispensing claims. The University of Florida Institutional Review Board exempted this study from review (IRB201701362, 09/05/2017).

Building on previous work to evaluate drug-drug interactions involving QTc prolongation,[10] we followed patients ≥18 years old with ≥1 diagnosis of autoimmune disease who initiated azithromycin or amoxicillin for ≥5 days during active treatment with chloroquine. Chloroquine and hydroxychloroquine can be used for malaria prophylaxis, resulting in exposure time during travel with limited ability to capture events that occur outside of the country. Thus, we only included patients with at least one diagnosis of autoimmune diseases (including multiple sclerosis, systemic sclerosis, systemic lupus erythematosus and connective tissue disorders, rheumatoid arthritis and related disorders, psoriasis, myasthenia gravis, nephritis, polyarteritis, autoimmune hepatitis, iridocyclitis, neuropathy, tissue disorders, and skin disorders) to mitigate outcome misclassification. Index date was the antibiotics' initiation date during active chloroquine use. Patients had continuous insurance coverage ≥6 months before index date until 5 days thereafter or inpatient death. We excluded patients with history of HIV, cancer, organ transplant, valvular disorders, cardiomyopathy, pregnancy, malaria, study outcomes, or with any azithromycin or amoxicillin prescription filled during the six months before the index date. We allowed patients to contribute to multiple combination use episodes as long as all in-/exclusion criteria were satisfied. The primary endpoint was sudden cardiac arrest or ventricular arrhythmias (SCA/VA) measured by ≥ 1 International Classification of Disease, Ninth

Revision or Tenth Revision, Clinical Modification codes (ICD-9-CM 427.5, 427.1, 427.4, 427.41, 427.42, 798, 798.1, 798.2; ICD-10-CM I46, I46.9, I47.2, I49.0, I49.01, I49.02, R99) as principal diagnosis on emergency department (ED) or hospital encounters.[11] Our secondary endpoint considered ED or inpatient encounters for cardiac symptoms (syncope, tachycardia, or palpitations: ICD-9-CM 780.2, 785.0, 785.1; ICD-10-CM R55, R00.0, R00.2).[10] We followed patients for up to 5 days or until fill of another known QT-prolonging drug[8] and estimated outcome incidence rates per 10,000 person-years and hazard ratios (HR). Covariates (including cardiac and metabolic conditions, type of autoimmune disorder, psychiatric conditions, respiratory conditions, infections, a variety of other chronic conditions, history of hospital admissions, smoking, duration of chloroquine/hydroxychloroquine use, and history of exposure to other QTc prolongation drugs (known, possible, or conditional risk)) were measured during 6 months before the index date. We adjusted for these covariates via exposure propensity scores using stabilized inverse probability treatment weighting. We conducted two sensitivity analyses that restricted to 1) patients with rheumatoid arthritis or lupus and 2) only the first concomitant use episode.

Results

There were 69,743 and 72,163 episodes with chloroquine or hydroxychloroquine and azithromycin combination and chloroquine or hydroxychloroquine and amoxicillin combination, respectively (see Table 1 for detailed baseline characteristics). We identified one SVC/VA event per exposure group. There were 29 azithromycin users and 23 amoxicillin combination users with cardiac symptoms. After adjustment, the incidence (per 10,000 person-years) of cardiac symptoms among azithromycin and amoxicillin combination users was 276 (95%CI, 185–410) versus 254 (95%CI, 168–383) with an adjusted HR of 1.10 (95%CI, 0.62–1.95) (Table 2). The sensitivity analyses showed consistent results (Table 2) as did stratified analyses of the two data sources, though confidence intervals remained wide due to small event rates (Commercial plans versus Medicare supplemental insurance, Table 3).

Discussion

The risk of SCA/VA was rare in our analysis and yielded inconclusive results. Although the incidence of cardiac symptoms among patients who used chloroquine or hydroxychloroquine in combination with azithromycin was slightly higher than among our active comparison group who used combinations with amoxicillin, results were not statistically significant in our primary or sensitivity analyses.

While the low event rates appear encouraging, use of choloroquine and azithromycin combination should still be cautious, especially given other emerging evidence, for a variety of reasons. One recent retrospective cohort study among COVID-19 patients in U.S. Veterans Health Adminstration medical centers found there was no benefits of chlorquine in the reduction of need for mechanical ventilation; however, there was a significantly increased risk of death among chloroquine users as compared to no chloroquine users.[12] Several trials were stopped early due to QTc prolongation related fatalities associated with the use of chloroquine.[4,13]

While controlled evidence on the risk of the combination use is lacking, a recent analysis of the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) data found a signal for QTc prolongation or Torsades de Pointes associated with azithromycin. The analysis found no signal associated with chloroquine or hydroxychloroquine when used alone and a weaker association that did not reach thresholds for a safety signal for the combination with azithromycin.[14] Interestingly, although underreporting of events as well as biases in reporting may obscure causal associations in adverse event reporting data, concerns regarding azithromycin's role in severe arrhythmias are corroborated by previous observational studies. A study in Tennessee Medicaid beneficiaries found that azithromycin users had a 2.5 times higher risk of cardiovascular death (95%CI, 1.4–4.5) and a 2.0 times higher risk of death from any cause compared to amoxicillin users (95%CI, 1.2–3.3).[15] In another case-control study using electrocardiogram results and electronic health records, azithromycin users had 43% increased odds of severe QTc prolongation compared to amoxicillin users (95%CI, 1.13–1.82).[16] In contrast, evidence for adverse cardiac adverse events of chloroquine and hydroxychloroquine consists mostly of case series, and the evidence based on more rigorous observational studies is lacking.[17]

Table 2
Risk of cardiac events following exposure to azithromycin or amoxicillin among chloroquine/hydroxychloroquine users.

Analysis scenarios		Combined result				
		Unadjusted			Adjusted[c]	
		Events/Total episodes	Events/10,000 person-years	HR (95%CI)	Events/10,000 person-years	HR (95%CI)
Main analysis						
SCA/VA[a]	Azithromycin	1/72,529	10 (1–74)	1.01 (0.06–16.14)	11 (1–77)	0.95 (0.06–15.17)
	Amoxicillin	1/75,396	10 (1–74)	Reference	11 (2–76)	Reference
Cardiac symptoms[b]	Azithromycin	29/69,473	317 (221–457)	1.28 (0.74–2.22)	276 (185–410)	1.10 (0.62–1.95)
	Amoxicillin	23/72,163	249 (166–376)	Reference	254 (168–383)	Reference
Excluding patients without lupus or rheumatoid arthritis diagnosis						
SCA/VA	Azithromycin	1/58,168	13 (2–93)	1.00 (0.06–15.94)	14 (2–96)	0.96 (0.06–15.33)
	Amoxicillin	1/59,659	13 (2–93)	Reference	14 (2–96)	Reference
Cardiac symptoms	Azithromycin	22/55,766	300 (197–455)	1.05 (0.58–1.91)	253 (160–402)	0.89 (0.47–1.68)
	Amoxicillin	21/57,151	287 (187–440)	Reference	286 (185–442)	Reference
Restriction to first combination use episode						
SCA/VA	Azithromycin	1/53,512	1 (2–101)	0.99 (0.06–15.86)	14 (2–104)	0.92 (0.06–14.68)
	Amoxicillin	1/54,646	1 (2–102)	Reference	16 (2–105)	Reference
Cardiac symptoms	Azithromycin	21/51,728	308 (201–473)	1.50 (0.76–2.95)	308 (201–473)	1.33 (0.66–2.71)
	Amoxicillin	14/52,782	207 (123–350)	Reference	207 (123–350)	Reference

Abbreviations: SCA/VA: sudden cardiac arrest and ventricular arrhythmias; HR: hazard ratio; CI: confidence interval.

[a] SVC/VA was defined by ≥ 1 code of ICD-9-CM 427.5, 427.1, 427.4, 427.41, 427.42, 798, 798.1, 798.2 or ICD-10-CM I46, I46.9, I47.2, I49.0, I49.01, I49.02, R99.

[b] Cardiac symptom was defined by ≥ 1 code of ICD-9-CM 780.2, 785.0, 785.1 or ICD-10-CM R55, R00.0, R00.2.

[c] Covariates included cardiac and metabolic conditions, autoimmune disorders, psychiatric conditions, respiratory conditions, infections, variety of other chronic conditions, hospital utilization, smoking, duration of chloroquine/hydroxychloroquine, and using of QTc prolongation drugs (known, possible, or conditional risk); detailed coding is available upon request.

Table 3
Risk of cardiac events among chloroquine/hydroxychloroquine-azithromycin and chloroquine/hydroxychloroquine-amoxicillin users stratified by data sources.

Analysis scenarios		Patients with private insurance only					Patients with Medicare and supplemental private insurance				
		Unadjusted			Adjusted[c]		Unadjusted			Adjusted[c]	
		Events/Total episodes	Events/10,000 person-years	HR (95%CI)	Events/10,000 person-years	HR (95%CI)	Events/Total episodes	Events/10,000 person-years	HR (95%CI)	Events/10,000 person-years	HR (95%CI)
Main analysis											
SCA/VA[a]	Azithromycin	1/62,208	12 (2–87)	1.01 (0.06–16.17)	12 (2–90)	0.96 (0.06–15.35)	0/10,321	0	NA	0	NA
	Amoxicillin	1/64,895	12 (2–86)	Reference	13 (11–158)	Reference	0/10,501	0		0	
Cardiac symptoms[b]	Azithromycin	25/59,657	319 (216–472)	1.42 (0.78–2.60)	251 (161–394)	1.16 (0.61–2.21)	4/9816	307 (115–817)	0.80 (0.22–2.97)	317 (119–845)	0.68 (0.17–2.66)
	Amoxicillin	18/62,219	227 (143–361)	Reference	218 (135–353)	Reference	5/9944	484 (202–1163)		468 (209–1049)	
Excluding patients without lupus or rheumatoid arthritis diagnosis											
SCA/VA	Azithromycin	1/49,761	15 (2–109)	1.00 (0.06–15.95)	16 (2–112)	0.97 (0.06–15.43)	0/8407	0	NA	0	NA
	Amoxicillin	1/51,181	15 (2–109)	Reference	16 (2–112)	Reference	0/7478	0		0	
Cardiac symptoms	Azithromycin	19/47,757	303 (193–474)	1.13 (0.59–2.16)	225 (133–383)	0.90 (0.44–1.82)	0/8009	288 (93–892)	0.74 (0.17–3.31)	301 (99–917)	0.66 (0.14–3.14)
	Amoxicillin	17/49,126	271 (169–436)	Reference	253 (153–417)	Reference	4/8025	380 (143–1012)	Reference	456 (184-113)	Reference
Restriction to first combination use episode											
SCA/VA	Azithromycin	1/46,122	16 (2–117)	0.99 (0.06–15.89)	17 (2–121)	0.93 (0.06–14.83)	0/7910	0	NA	0	NA
	Amoxicillin	1/47,276	17 (2–118)	Reference	18 (3–122)	Reference	0/7912	0		0	
Cardiac symptoms	Azithromycin	17/44,602	290 (180–466)	1.55 (0.73–3.31)	262 (158–435)	1.53 (0.71–3.32)	4/7609	396 (149–1055)	1.31 (0.29–5.84)	408 (153–1092)	0.86 (0.18–4.04)
	Amoxicillin	11/45,710	189 (105–341)	Reference	173 (92–324)	Reference	3/7577	306 (98–938)	Reference	476 (190-119)	Reference

Abbreviations: SCA/VA: sudden cardiac arrest and ventricular arrhythmias; HR: hazard ratio; CI: confidence interval.

[a] SVC/VA was defined by ≥ 1 code of ICD-9-CM 427.5, 427.1, 427.4, 427.41, 427.42, 798, 798.1, 798.2 or ICD-10-CM I46, I46.9, I47.2, I49.0, I49.01, I49.02, R99.

[b] Cardiac symptom was defined by ≥ 1 code of ICD-9-CM 780.2, 785.0, 785.1 or ICD-10-CM R55, R00.0, R00.2.

[c] Covariates included cardiac and metabolic conditions, autoimmune disorders, psychiatric conditions, respiratory conditions, infections, variety of other chronic conditions, hospital utilization, smoking, duration of chloroquine/hydroxychloroquine, and using of QTc prolongation drugs (known, possible, or conditional risk).

It should be noted that our findings may not be directly applicable to how chloroquine or hydroxychloroquine are being used in combination with azithromycin. Chronic administration among patients with autoimmune disease cannot replicate physiological responses when both drugs are used acutely in a hospitalized setting, as would be expected for COVID-19 patients. Moreover, doses used in routine care (e.g. for lupus erythematosus, adult dosage is only 125–250 mg chloroquine daily), appear to be lower compared to COVID-19 treatment (1000 mg chloroquine phosphate for day 1 and then 500 mg daily for four to seven days of total treatment),[6] which may suggest an attenuated risk for cardiac adverse outcomes.[18] Additionally, our study was under the guidance of a prescribing clinician and cannot replicate scenarios where patients self-medicate. The desire to benefit from potential prophylactic effects has recently claimed one death when a patient used chloroquine available to clean fish aquariums.[19]

There are a several limitations to mention. First, while we addressed confounding via restriction and statistical adjustment, baseline characteristics suggest that chloroquine users with cardiac history were channeled away from azithromycin, and residual confounding may have masked subtle effects. For example, patients with higher risk for cardiac adverse events may be intentionally prescribed other antibiotics when azithromycin would be on option, thus mitigating the effect. Second, we may have underestimated the actual risk of cardiac adverse events among new users of the chloroquine and azithromycin combination, because our population included patients with long-term chloroquine use who may have been tolerating the drug well. Ideally, patients who initiate both drugs simultaneously, as proposed for COVID-19 treatment, would be studied, but restriction our analysis to such a population was prohibitive in terms of sample size. Third, restriction to patients with autoimmune disorders aimed to exclude chloroquine use for malaria prophylaxis with unknown exposure period and incomplete capture of outcomes during travel, but indications can only be inferred from claims data. Fourth, in an attempt to maximize sample size, we expanded a validated ICD-9-CM code set for SVD/VA[11] to ICD-10-CM codes, which may have missed or mis-specified events after 2015. We tested our crosswalk in our source dataset and found consistent incidence rates of all endpoints across the ICD transition period. While we have found our code set for cardiac symptoms to be sensitive to capture effects of QTc prolongation in previous studies,[10] we are not aware of validation studies.

Conclusion

We conclude that combination use of chloroquine and azithromycin did not show pronounced increases in arrhythmias in this real-world population. We caution however, against encouraging use of this combination for COVID-19, and in particular self-medication, especially among patients with history or risk of QTc prolongation, until appropriate risk-benefit has been established.

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CRediT authorship contribution statement

Scott M. Vouri: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Thuy N. Thai:** Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Almut G. Winterstein:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Supervision.

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