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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 \( \geq \) 18 years initiating azithromycin or amoxicillin for \( \geq \) 5 days during chloroquine treatment. Patients had continuous insurance coverage \( \geq \) 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 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.\textsuperscript{4} On April 24, 2020, according to the World Health Organization, there are approximately 2.6 million cases and 181 thousand deaths worldwide (81,529 new cases and 6260 new deaths compared to the previous day).\textsuperscript{5} 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 COVID19 patients.\textsuperscript{6,7} Moreover, preclinical studies have suggested that chloroquine may also have a potential prophylactic effect on COVID-19 infections.\textsuperscript{8} 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).\textsuperscript{9} 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.

| Calendar year at index date | Before SIPTW | After SIPTW | Absolute standardized difference |
|-----------------------------|--------------|-------------|---------------------------------|
| 2005–2006                   | 3569 (5.1)   | 4279 (5.9)  | 0.035                           | 3715 (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           |

Autimmune 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 erythematos 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

| Navratri |
|----------|
| 1312 (1.9) | 1276 (1.8) | 0.009          | 1226 (1.8) | 1272 (1.8) | 0               |

Mycostosias

| Grinostas |
|----------|
| 87 (0.1) | 90 (0.1) | 0              | 84 (0.1)  | 90 (0.1)  | 0.001           |

Nephritis

| Nephritis |
|----------|
| 3035 (4.4) | 3093 (4.3) | 0.004          | 2899 (4.3) | 2979 (4.3) | 0.002           |

Polyarteritis

| Polyarteritis |
|-------------|
| 774 (1.1) | 773 (1.1) | 0.004          | 732 (1.1)  | 760 (1.1)  | 0               |

Autoimmune hepatitis

| Autoimmune hepatitis |
|----------------------|
| 260 (0.4) | 273 (0.4) | 0.001          | 253 (0.4)  | 257 (0.4)  | 0.001           |

Indocycloisis

| Indocycloisis |
|--------------|
| 369 (0.5) | 378 (0.5) | 0.001          | 347 (0.5)  | 374 (0.5)  | 0.003           |

Neuropathy

| Neuropathy |
|------------|
| 817 (1.4) | 1001 (1.4) | 0.019          | 851 (1.3)  | 880 (1.3)  | 0               |

Tissue disorder

| Tissue disorder |
|-----------------|
| 16,719 (24.1) | 18,342 (25.4) | 0.031       | 16,681 (24.7) | 17,326 (24.8) | 0.008           |

Infections during 2 weeks before index date

| Pneumonia |
|----------|
| 1396 (2.0) | 524 (0.7) | 0.111          | 865 (1.3)  | 834 (1.2)  | 0.008           |

Skin infection

| Skin infection |
|----------------|
| 35,995 (51.8) | 36,382 (50.4) | 0.028       | 34,454 (51.1)| 35,652 (51.0)| 0.001           |

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 |
| 4314 (6.9) | 5339 (7.4) | 0.018 | 4977 (7.4) | 4860 (7.0) | 0.016 |

| 31–60 days |
| 4241 (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 |
|----------------------|
| Asthma |
| 389 (5.9) | 4136 (5.9) | 0 |

| COPD |
| 344 (5.1) | 3595 (5.2) | 0.002 |

| Others |
| 1474 (2.1) | 1611 (2.2) | 0.008 | 1475 (2.2) | 1526 (2.2) | 0 |

Cardiovascular related diseases

(continued on next page)
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 this risk. Because severe arrhythmias, the direct consequence of QTc 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 this risk. Because severe arrhythmias, the direct consequence of QTc prolongation, are rare, the ongoing clinical trials are unlikely to have this risk. Because severe arrhythmias, the direct consequence of QTc prolongation, are rare, the ongoing clinical trials are unlikely to have this risk.

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

### Table 1 (continued)

| Baseline characteristics | Before SIPTW | After SIPTW |
|--------------------------|-------------|------------|
|                           | Azithromycin (N, %) | Amoxicillin (N, %) | Absolute standardized difference | Azithromycin (N, %) | Amoxicillin (N, %) | Absolute standardized difference |
|                           | (Total N = 69,473) | (Total N = 72,163) | | (Total N = 67,427) | (Total N = 69,866) | |
| 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 preclinical 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) | 413 (5.9) | 0.001 |
| Hyperlipidemia | 13,707 (19.7) | 14,503 (20.1) | 0.024 | 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) | 0.024 | 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 | 622 (0.9) | 771 (1.1) | 0.018 | 653 (1.0) | 676 (1.0) | 0 |
| Substance use disorder | 1452 (2.1) | 1567 (2.2) | 0.006 | 1412 (2.1) | 1460 (2.1) | 0 |
| Adjustment disorders | 5053 (7.3) | 5648 (7.8) | 0.021 | 5074 (7.5) | 5268 (7.5) | 0.001 |
| Anxiety | 6799 (9.8) | 7551 (10.5) | 0.022 | 6810 (10.1) | 7059 (10.1) | 0 |
| Depression | 849 (1.2) | 995 (1.4) | 0.014 | 867 (1.3) | 911 (1.3) | 0.002 |
| Bipolar | 793 (1.1) | 955 (1.3) | 0.016 | 821 (1.2) | 854 (1.2) | 0 |
| AIDs/Developmental/childhood disorders | 2665 (3.8) | 2802 (3.9) | 0.002 | 2585 (3.8) | 2668 (3.8) | 0.001 |
| Other mental health disorder | 93 (0.1) | 89 (0.1) | 0.003 | 84 (0.1) | 89 (0.1) | 0.001 |
| Parkinson disease | 1333 (1.9) | 1487 (2.1) | 0.01 | 1346 (2.0) | 1392 (2.0) | 0 |
| Other hereditary and degenerative nervous system condition | 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.
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 146, 146.9, 147.2, 149.0, 149.01, 149.02, R99) as principal diagnosis on emergency department (ED) or hospital encounter.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 drug11 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 chloroquine 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 Administration medical centers found there was no benefits of chloroquine 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<sup>2</sup> |
|                    | Events/Total episodes | Events/10,000 person-years | HR (95%CI) | Events/10,000 person-years | HR (95%CI) |
| **Main analysis** |            |                       |            |                          |            |
| SCA/VA<sup>a</sup> | 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<sup>b</sup> | 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<sup>a</sup> | 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<sup>b</sup> | 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<sup>a</sup> | 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<sup>b</sup> | 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.
<sup>a</sup> 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 146, 146.9, 147.2, 149.0, 149.01, 149.02, R99.
<sup>b</sup> Cardiac symptoms was defined by ≥ 1 code of ICD-9-CM 780.2, 785.0, 785.1 or ICD-10-CM R55, R00.0, R00.2.
<sup>c</sup> 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.

2015
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<sup>c</sup> | Unadjusted | Adjusted<sup>c</sup> | Unadjusted | Adjusted<sup>c</sup> |
|                    | Events/Total episodes | Events/10,000 person-years | HR (95%CI) | Events/Total episodes | Events/10,000 person-years | HR (95%CI) | Events/Total episodes | Events/10,000 person-years | HR (95%CI) |
| Main analysis       |            |                          |            |                        |            |                          |            |                        |            |                          |
| SCA/VA<sup>a</sup>  |            |                          |            |                        |            |                          |            |                        |            |                          |
| 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 | NA | 0 | NA |
| Cardiac symptoms<sup>b</sup> | 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 | 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 |
| SCA/VA<sup>a</sup>  | 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 | 288 (93–892) | 0.74 (0.17–3.31) | 301 (99–917) | 0.66 (0.14–3.14) |
| Cardiac symptoms<sup>b</sup> | 301 (193–674) | 1.13 (0.59–2.16) | Reference | 225 (133–383) | 0.99 (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) | 456 (184–113) | Reference |
| Restriction to first combination use episode | 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 |
| SCA/VA<sup>a</sup>  | 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 | 396 (149–1055) | 1.31 (0.29–5.86) | 408 (153–1092) | 0.86 (0.18–4.04) |
| Cardiac symptoms<sup>b</sup> | 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 (0.29–5.86) | 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) | 476 (190–119) | Reference |

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

<sup>a</sup> 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.

<sup>b</sup> Cardiac symptom 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.

<sup>c</sup> 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), which may suggest an attenuated risk for cardiac adverse outcomes. 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.

There are 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我们的 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 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, 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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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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References

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA. February. 2020. https://doi.org/10.1001/jama.2020.2648.
2. World Health Organization. Coronavirus Disease 2019 (COVID-19) Situation Report - 95. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports; April 2020.
3. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. March. 2020:105949. https://doi.org/10.1016/j.ijantimicag.2020.105949.
4. Molina J, Delauregne C, Goff J, 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 Mal Infect. March. 2020. https://doi.org/10.1016/j.medmal.2020.03.006.
5. Shah S, Das S, Jain A, Maira DP, Negi VS. A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in Coronavirus Disease-19 (COVID-19). Int J Rheum Dis. April. 2020. https://doi.org/10.1111/1756-185X.13842.
6. U.S. Food & Drug Administration. FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF CHLOROQUINE PHOSPHATE SUPPLIED FROM THE STRATEGIC NATIONAL STOCKPILE FOR TREATMENT OF COVID-19 IN CERTAIN HOSPITALIZED PATIENTS. April. 2020; April 2020https://www.fda.gov/media/136535/download.
7. U.S. Food & Drug Administration. FDA Cautions against Use of Hydroxychloroquine or Chloroquine for COVID-19 outside of the Hospital Setting or a Clinical Trial Due to Risk of Heart Rhythm Problems. April; April 2020https://www.fda.gov/media/137250/download.
8. Woolsey R, Heise C, Romero K. QD Drugs list. March 2020 https://www.crediblemeds.org/.
9. Cuomo AM. Video, Audio, Photos & Rush Transcript: Amid Ongoing COVID-19 Pandemic, Governor Cuomo Accepts Recommendation of Army Corps of Engineers for Four Temporary Hospital Sites in New York. 2020; 2020 Albany, New York; https://www.governor.ny.gov/news/video-audio-photos-rush-transcript-amid-ongoing-covid-19-pandemic-governor-cuomo-accepts.
10. Alrwisan AA, Wei Y-JJ, Brumback BA, Antonelli PJ, Winterstein AG. Concomitant use of quinolones and stimulants and the risk of adverse cardiovascular symptoms: a retrospective cohort study. Pharmacotherapy. 2019;39(12):1167–1178. https://doi.org/10.1002/phar.2343.
11. Hennessey S, Leonard CE, Freeman CP, et al. Validation of diagnostic codes for out-patient-originating sudden cardiac death and ventricular arrhythmia in Medicaid and Medicare claims data. Pharmacoepidemiol Drug Saf. 2018;19(6):555–562. https://doi.org/10.1002/pds.1869.
12. Magagnoli J, Narendran S, Perezin F, et al. Outcomes of Hydroxychloroquine Usage in United States Veterans Hospitalized with Covid-19. https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v2; April 2020.
13. Borba M, de Almeida Val F, Sampaio S, et al. Chloroquine Diphosphate in Two Different Dosages as Adjunctive Therapy of Hospitalized Patients with Severe Respiratory Syndrome Coronavirus 2 Infection. A Retrospective Study in the Context of Coronavirus (SARS-CoV-2) Infection: Preliminary Safety Results of a Randomized, Double-Blinded, Phase IIb Clinical Trial (CloroCov-19 Study). April 2020; April 2020https://www.medrxiv.org/content/10.1101/2020.04.07.20056424v2.
14. Sarayani A, Cicali B, Heinzkera C, Brown J. Safety signals for QT prolongation or Torsades de Pointes associated with azithromycin with or without chloroquine or hydroxychloroquine [published online ahead of print, 2020 Apr 19]. Res Soc Adm Pharm. 2020. https://doi.org/10.1016/j.sapharm.2020.04.016.
15. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med. 2012;366(20):1881–1890. https://doi.org/10.1056/NEJMc1003833.
16. Choi Y, Lim H-S, Chung D, Choi J-G, Yoon D. Risk evaluation of azithromycin-induced QT prolongation in real-world practice. Biomed Res Int. 2018;2018:1574806. https://doi.org/10.1155/2018/1574806.
17. Charte C, Roubille F, Verheye H, Jorgensen C, Pers Y-M. Cardiac complications attributed to chloroquine and hydroxychloroquine: a systematic review of the literature. Drug Saf. 2018;41(10):919–931. https://doi.org/10.1007/s40264-018-0669-4.
18. Clinical Pharmacology [Database Online]. Tampa, FL: Gold Standard, Inc.; 2020http://www.clinicalpharmacology.com.
19. U.S. Food & Drug Administration. FDA Letter to Stakeholders: Do Not Use Chloroquine Phosphate Intended for Fish as Treatment for COVID-19 in Humans. https://www.fda.gov/animal-veterinary/product-safety-information/fda-letter-stakeholders-do-not-use-chloroquine-phosphate-intended-fish-treatment-covid-19-humans; March 2020.