

Cardiovascular Toxicities Associated with Hydroxychloroquine and Azithromycin: An Analysis of the World Health Organization Pharmacovigilance Database

Running Title: *Nguyen et al.; Hydroxychloroquine and Azithromycin Cardiotoxicity*

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The data, analytic methods, and study materials are available to other researchers for purposes of reproducing the results or replicating the procedure at <http://www.vigiaccess.org/>.

While hydroxychloroquine and azithromycin, alone or in combination, have been proposed for treatment of COVID-19 patients,¹ their potential cardiovascular toxicities had limited consideration in this new clinical environment. We aimed to determine whether these drugs were associated with an increased reporting of cardiovascular adverse-drug-reactions (CV-ADR) in a real-world population, before start of prescription for COVID-19 in Europe and America.

In this observational, retrospective study, we used VigiBase®,^{2,3} the World Health Organization pharmacovigilance database encompassing over 21 million reports from over 130 countries, to compare CV-ADR reporting in patients who received hydroxychloroquine, azithromycin, or their combination with CV-ADRs reported with all other drugs in the full database (clinicaltrials.gov identifier **NCT04314817**). Association between hydroxychloroquine, azithromycin, and their combination with CV-ADR was assessed using reporting-odds-ratio (ROR) and information component (IC), an indicator value for disproportionate Bayesian reporting that compares observed and expected values to find associations between drugs and ADR).² The lower end of the IC's 95% credibility interval is IC₀₂₅. It is considered significant when above 0.² Reporting-odds-ratio (ROR) were computed to compare ADR frequencies between different exposures, using Chi-2 tests.³ These methods are similar to those used to study CV-ADR related to anticancer and hormonal drugs.^{2,3} For each report, age, sex, time to onset (TTO), fatalities, concurrent ADRs and medications (drugs associated with a known or possible risk of QT prolongation as reported at crediblemeds.org)⁴ were collected. TTO were compared using non-parametric tests. French National Commission for Data Protection and Liberties and institutional review board approved the use of confidential electronically processed patient data.

All CV-ADRs were included, classified by group queries,² according to the Medical Dictionary for Regulatory Activities, between Nov 14, 1967 and March 1, 2020.

We extracted 76,822 ADR cases associated with hydroxychloroquine alone, 89,692 with azithromycin alone, and 607 with the combination of both drugs. The cases were retrieved from 21,275,867 total ADR reports in Vigibase®. Hydroxychloroquine was a suspected (versus concomitantly used) drug in 21,808/76,822 (28.4%) cases and azithromycin in 54,533/89,692 (60.8%) cases.

There was significant greater reporting of prolonged-QT (LQT) and/or ventricular tachycardia including Torsades-de-Pointes (TdP/VT) for each drug individually in suspected cases (n=480 [223 LQT; 257 TdP/VT], IC₀₂₅=1.67 for azithromycin and; n=136 [53 LQT, 83 TdP/VT], IC₀₂₅=1.04 for hydroxychloroquine, **Figure**). Hydroxychloroquine was also associated with conduction disorders (atrioventricular and bundle branch blocks) (n=75, IC₀₂₅=1.04) and heart failure (HF, n=203, IC₀₂₅=0.06). No other CV-ADR (including cardiac ischemia and myocarditis)² were significantly associated with these drugs. The IC values over time, and intersecting cases for significant CV-ADRs associated with hydroxychloroquine or azithromycin are presented in the **Figure**.

Azithromycin monotherapy was associated with a greater reporting of LQT and/or TdP/VT than hydroxychloroquine monotherapy (736/89,085 (0.8%) vs. 263/76,215 (0.3%), respectively; ROR=2.36, 95% CI=2.05-2.71). The combination of azithromycin and hydroxychloroquine was associated with a greater reporting of LQT and/or TdP/VT reporting than either drug in monotherapy (999/165,300 (0.6%) vs. 9/607 (1.5%), ROR=2.48, 95% CI=1.28- 4.79).

Most CV-ADRs reports were in women (516/772, 66.8%). Reporting regions were: mostly Americas (549/851, 64.5%) and Europe (185/851, 21.7%). Reporters were mostly healthcare professionals (674/706, 91.1%). In most cases, ADR was attributed to a single drug (492/844, 58.3%). Concurrent reporting of drugs with a known risk of TdP in TdP/VT cases was 31.5% (81/255) with azithromycin and 16.9% (14/83) with hydroxychloroquine.⁴

Time to onset (TTO) of LQT and/or TdP/VT with azithromycin was shorter compared with hydroxychloroquine (3[IQR=1;7] vs. 51 [IQR=11;113] days, $p<0.01$). With hydroxychloroquine, TTO of LQT and/or TdP/VT was shorter than heart failure (51[IQR=11;113] vs. 348[IQR=91;2016] days, $p=0.027$). This longer TTO observed in hydroxychloroquine may reflect chronic use in lupus or rheumatoid arthritis.

The proportion that resulted in death for TdP/VT cases was 8.4% (7/83) with hydroxychloroquine and 20.2% (52/257) with azithromycin versus 0% (0/53) and 5.4% (12/223) for LQT without TdP/VT with hydroxychloroquine and azithromycin, respectively ($p<0.001$ for both). Corresponding death rate was 20.7% (42/203) for HF associated with hydroxychloroquine. Dose of hydroxychloroquine was higher in HF compared to LQT and/or TdP/VT cases (200[IQR=200;400] vs. 200[IQR=200;200]mg/day, $p=0.033$).

Main limitation is that without data on numbers exposed in Vigibase, this work cannot assess the incidence or risk for QT prolongation with these drugs. However, our results are consistent with the facts that these CV-ADRs are found in the FDA's labels of hydroxychloroquine and azithromycin, and that both drugs are referenced as known-risk of TdP at CredibleMeds website.⁴ These CV-ADRs are important to bear in mind in the setting of COVID-19 with patients presenting additional risk factors of LQT/TdP due to inflammation with



elevated interleukin-6, hypokalemia, numerous interacting drugs, bradycardia and higher hydroxychloroquine dosages.⁵

In conclusion, reports of potentially lethal acute cardiac proarrhythmogenic effects leading to ventricular arrhythmias have been described mainly with azithromycin but also with hydroxychloroquine. Their combination yielded an even stronger signal. Hydroxychloroquine was also associated with potentially lethal HF when exposure was prolonged over several months.

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None.



Disclosures

The supplied data from VigiBase come from various sources. The likelihood of a causal relationship is not the same in all reports. The information does not represent the opinion of WHO. The authors have nothing to disclose related to this study.

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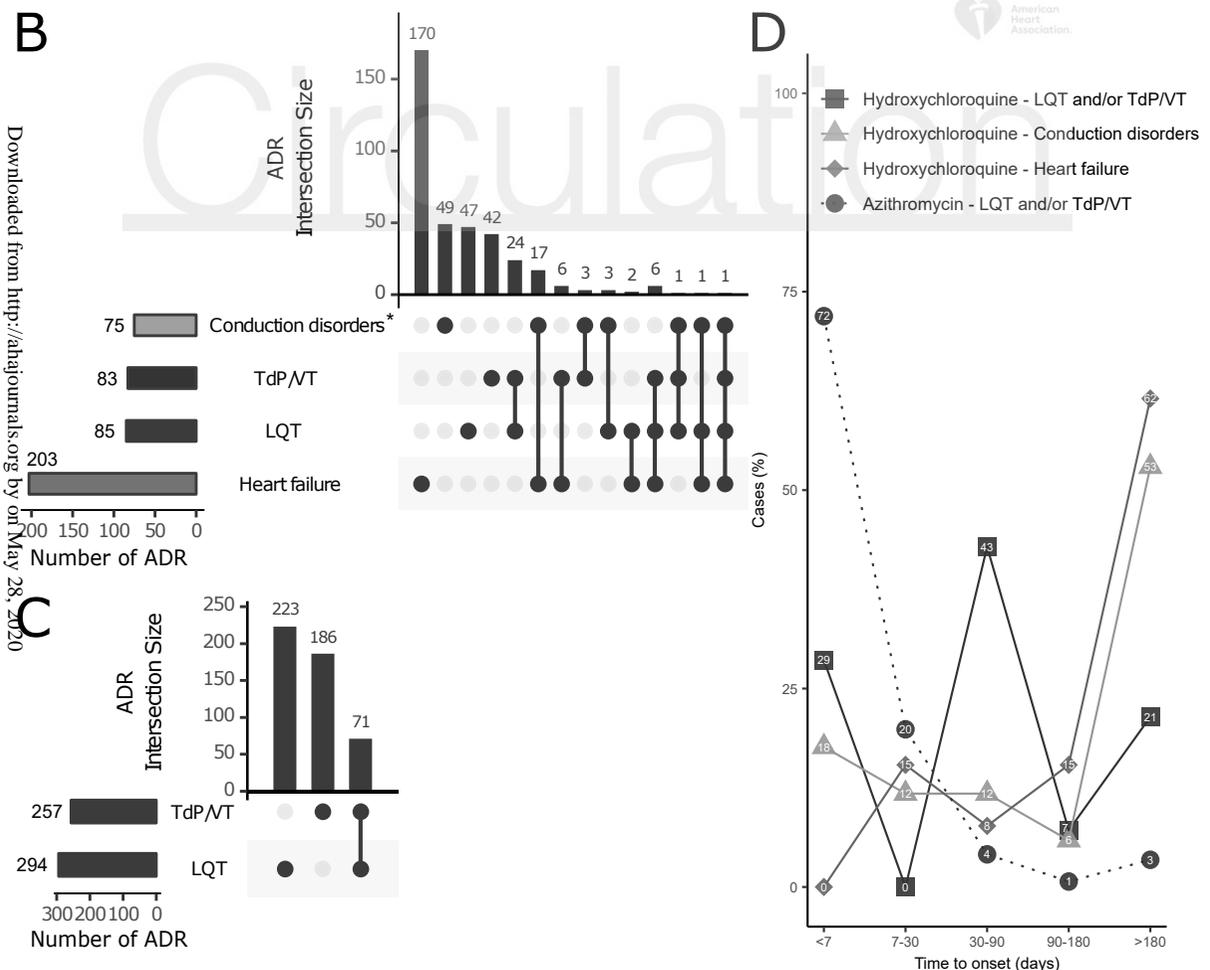
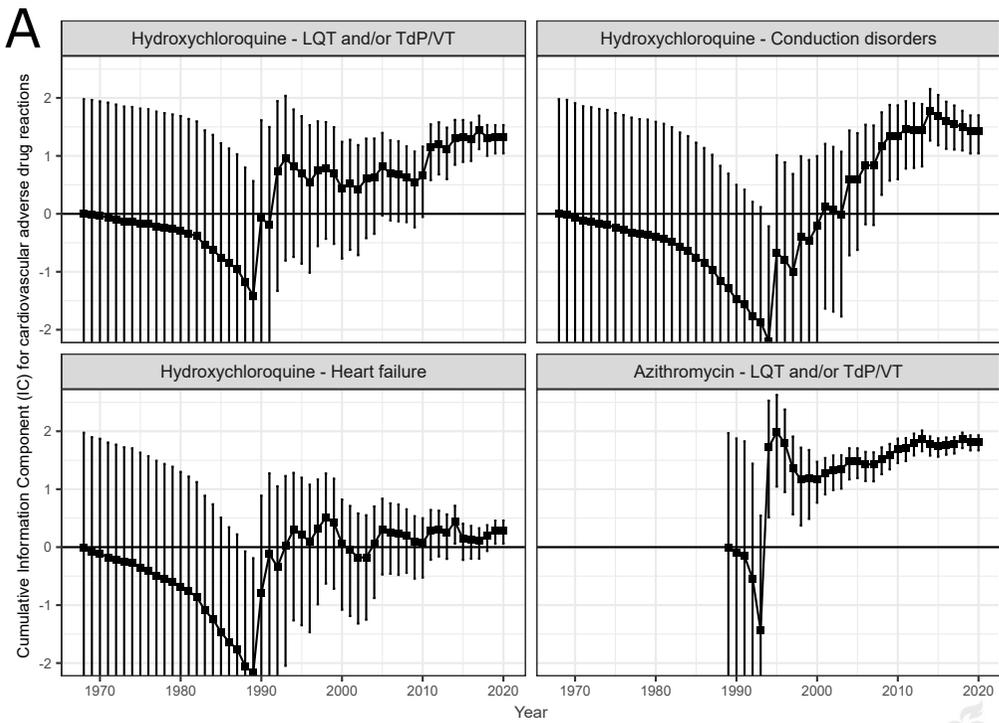
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Figure Legend.

Temporal evolution (last accessed: 03/01/2020) of the information component (IC) for cardiovascular adverse drug reactions (CV-ADR) significantly associated with hydroxychloroquine or azithromycin (see statistics below). Whiskers are IC₀₂₅, IC₉₇₅. IC₀₂₅ and IC₉₇₅ are the lower and upper end of the IC 95% credibility interval, respectively. Significance is IC₀₂₅>0 (black line). LQT: Long QT syndrome, TdP/VT: Ventricular tachyarrhythmias (VT) including Torsades-de-Pointes (TdP). Year of first ADR report within Vigibase for hydroxychloroquine and azithromycin were respectively 1967 and 1989 (**A**). Intersection for selected CV-ADR (IC₀₂₅>0) in case reports from Vigibase, for hydroxychloroquine (**B**) and azithromycin (**C**). Time to onset (in days) between first treatment intake and the CV-ADR associated with hydroxychloroquine or azithromycin (**D**). * Of the conduction disorders (n=75), 50/75 (67%) were atrioventricular blocks, 24/75 (32%) were bundle branch blocks and 1/75 (1%) was a sinus block. Time to onset data are available for hydroxychloroquine and LQT and/or TdP/VT (n=90), for hydroxychloroquine and conduction disorders (n=77), for hydroxychloroquine and heart failure (n=94); and for azithromycin and LQT and/or TdP/VT (n=70)

Statistics:² $IC = \log_2[(N_{\text{observed}} + 0.5)/(N_{\text{expected}} + 0.5)]$, where $N_{\text{expected}} = (N_{\text{drug}} \times N_{\text{reaction}})/N_{\text{total}}$, with N_{expected} being the number of ICSRs expected for the drug-ADR combination; N_{observed} being the actual number of ICSRs observed for the drug-ADR combination; N_{drug} being the number of ICSRs for the drug, regardless of ADR; N_{reaction} being the number of ICSRs for the ADR, regardless of the drug; and N_{total} being the total number of ICSRs in the database. ICSR = individual case safety report.



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