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Heather Johnson
Boca Raton Regional Hospital; Christine E. Lynn Women's Health & Wellness Institute,
HJohnson@baptisthealth.net

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Charles H. Hennekens MD, DrPH First Sir Richard Doll Professor & Senior Academic Advisor to the Dean ,
Manas Rane MD Preventive Cardiology Fellow ,
Joshua Solano MD Assistant Professor of Emergency Medicine ,
Scott Alter MD Associate Professor of Emergency Medicine ,
Heather Johnson MD, FACC, FAHA, FASPC Preventive CardiologistCardiologist ,
Shiv Krishnaswamy BS 4th year medical student ,
Richard Shih MD Professor of Emergency Medicine ,
Dennis Maki MD Professor of Medicine and Director ,
David L. DeMets PhD

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Charles H. Hennekens, MD, DrPH (corresponding author)
First Sir Richard Doll Professor & Senior Academic Advisor to the Dean
Charles E. Schmidt College of Medicine, Florida Atlantic University
2800 S. Ocean Blvd. PHA
Boca Raton, FL 33432, USA
Email: chenneke@health.fau.edu
Telephone: 561-393-8845

Manas Rane, MD
Preventive Cardiology Fellow, PGY-5
Harvard Medical School and Brigham and Women's Hospital and
VA Boston Healthcare System

Joshua Solano MD
Assistant Professor of Emergency Medicine,
Charles E. Schmidt College of Medicine, Florida Atlantic University

Scott Alter, MD
Associate Professor of Emergency Medicine,
Charles E. Schmidt College of Medicine, Florida Atlantic University

Heather Johnson, MD, FACC, FAHA, FASPC
Preventive CardiologistCardiologist, Christine E. Lynn Women's Health &Wellness Institute
Boca Raton Regional Hospital/Baptist Health South Florida
Affiliate Clinical Associate Professor, Charles E. Schmidt College of Medicine, Florida Atlantic University

Shiv Krishnaswamy, BS
4th year medical student, Charles E. Schmidt College of Medicine, Florida Atlantic University

Richard Shih MD
Professor of Emergency Medicine,
Charles E. Schmidt College of Medicine, Florida Atlantic University

Dennis Maki MD
Professor of Medicine and Director, COVID-19 Intensive Care Unit
University of Wisconsin School of Medicine & Public Health

David L. DeMets, PhD
Max Halperin Emeritus Professor and former founding Chair of Biostatistics & Medical Informatics,
University of Wisconsin-Madison School of Medicine & Public Health, Madison, Wisconsin

CONFLICTS OF INTEREST

Professor Hennekens reports that he serves as an independent scientist in an advisory role to investigators and sponsors as Chair of data monitoring committees for Amgen, British Heart Foundation, Cadila, Canadian Institutes of Health Research, DalCor, and Regeneron; to the Collaborative Institutional Training Initiative (CITI), legal counsel for Pfizer, the United States Food and Drug Administration, and UpToDate; receives royalties for authorship or editorship of 3 textbooks and as co-inventor on patents for inflammatory markers and cardiovascular disease that are held by Brigham and Women's Hospital; has an investment management relationship with the West-Bacon Group within SunTrust Investment Services, which has discretionary investment authority; does not own any common or preferred stock in any pharmaceutical or medical device company.

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In the prevention and treatment of COVID-19 in the United States (US) 74% trust their health care providers. (1) In 2021 there have been more than 560,000 prescriptions (2) of hydroxychloroquine for the prevention, post-exposure prophylaxis (PEP) and treatment of COVID-19. Last year, the >890,000 prescriptions were 9-fold greater than previous years, leading to major shortages for the approved indications of autoimmune diseases. (3) Biological mechanisms support inhibition of the virus that causes COVID-19. (4) Some case series lacking comparison groups, claims databases, and observational studies, (3) all of which have confounding by indication, reported possible benefits. (5,6) Randomized trials published in high quality peer-reviewed journals, which provide the most reliable evidence to detect the most plausible small to moderate effects, hd shown disappointing results. (3,5,6)

When the totality of evidence is incomplete, it is appropriate for health care providers to remain uncertain. (5) Nonetheless, regulatory authorities are sometimes compelled to act on incomplete evidence. On March 28, 2020, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for hydroxychloroquine in COVID-19. By April 24, 2020, the FDA issued a Drug Safety Communication warning about potentially fatal prolongations of the QTc interval detectable on 12-lead electrocardiograms and risks of other serious cardiac arrhythmias. (3)

In this Commentary we review the recent major randomized, double-blind, placebo-controlled trials of hydroxychloroquine in post-exposure prophylaxis and hospitalized patients, addressing the primary endpoint of SARS-Cov-2 infections, as well as their meta-analyses. We, thus, provide updated perspectives on benefits and risks.

Hydroxychloroquine in Post-Exposure Prophylaxis

One randomized, double-blind, placebo-controlled trial included 821 post-exposure prophylaxis subjects, of whom 107 developed COVID-19 over 14 days. The 49 of 414 (11.8%) assigned hydroxychloroquine and 58 of 407 (14.3%) given placebo resulted in a nonsignificant relative risk (RR) of 0.83 (P=0.35). Overall, 140 of 349 (40.1%) assigned hydroxychloroquine reported a side effect by day five, as compared with 50 of 352 (16.8%) assigned placebo, a highly significant increase. (P<0.001). Nausea, loose stools, and abdominal discomfort were the most common and there were no serious intervention-related adverse effects. (8)

In another study, among 2,314 healthy contacts of 672 Covid-19 index cases, 1,116 were randomized to hydroxychloroquine and 1,198 to usual care. COVID-19 occurred among 5.7% assigned to hydroxychloroquine and 6.2% to usual care, yielding a nonsignificant RR of 0.89 [95% CI, 0.54 to1.46]. Adverse events were significantly higher in hydroxychloroquine (51.6%) compared to usual care (5.9%) but there were no reported cardiac arrhythmias. (9)

In the most recently published trial, 671 households were randomly assigned: 337 (407 participants) to hydroxychloroquine and 334 (422 participants) to the control group. By day 14, there were 53 events in hydroxychloroquine and 45 among usual care yielding a nonsignificant RR= 1.10 [95% CI, 0.73 to 1.66]; P > 0.20). The frequency of participants experiencing adverse

events was significantly higher in the hydroxychloroquine group than the control group (66 [16.2%] versus 46 [10.9%]; *P* = 0.026). (10)

Hydroxychloroquine in Hospitalized patients

One trial was terminated early by the external, independent Data Monitoring Committee due to lack of efficacy and futility. Death within 28 days occurred in 421 patients (27%) in the hydroxychloroquine group and in 790 (25%) in the usual-care group yielding a nonsignificant RR=1.09 (95% CI, 0.97 to 1.23; *P*=0.15). Patients assigned hydroxychloroquine were significantly less likely to be discharged from the hospital alive within 28 days than those in usual care (59.6% vs. 62.9%; RR=0.90; CI, 0.83 to 0.98). Among the patients not dependent on mechanical ventilation at baseline, those in the hydroxychloroquine group had a significantly higher frequency of invasive mechanical ventilation or death (30.7% vs. 26.9%; RR= 1.14; 95% CI, 1.03 to 1.27). There were no significant differences in new major cardiac arrhythmias (11)

At 405 hospitals in 30 countries, of 11,330 patients, 2750 were assigned to remdesivir, 954 to hydroxychloroquine, 1411 to lopinavir (without interferon), 2063 to interferon (including 651 to interferon plus lopinavir), and 4088 to no trial drug. Adherence was 94-96% midway through treatment, with 2-6% crossover. Of 1253 deaths reported, 301 were among those assigned to remdesivir and 303 among its control yielding a nonsignificant RR=0.95 (95% CI, 0.81 to 1.11, *P*=0.50). Further, there were 104 deaths among those assigned hydroxychloroquine and in 84 among its control yielding a nonsignificant RR=1.19 (95% CI, 0.89 to 1.59; P=0.23). There were 148 deaths in patients assigned lopinavir and 146 among its control yielding a nonsignificant RR=1.00 (95% CI, 0.79 to 1.25; *P*=0.9). Finally, there were 243 deaths among patients assigned interferon and 216 receiving its control yielding a nonsignificant RR=1.16

(95% CI, 0.96 to 1.39; *P*=0.11). No drug definitely reduced mortality, overall or in any subgroup, or reduced initiation of ventilation or hospitalization duration. (12)

Meta-analyses of Hydroxychloroquine in Post-Exposure Prophylaxis and COVID-19 Hospitalizations

The quality and usefulness of any meta-analysis depends on the quality and comparability of data from the component trials. Combined trials should have reasonably high adherence and follow-up rates, and use comparable drugs, doses, and outcomes. The characteristics of participants and the magnitude of effects should be qualitatively similar. Such meta-analyses can be hypothesis testing if each component trial was designed *a priori* to test the same issue. In other circumstances such as smaller or heterogeneous trials, meta-analyses are hypothesis generating. Meta-analyses of observational studies are only useful to formulate but not test hypotheses. They reduce the role of chance but always introduce bias as well as uncontrolled and uncontrollable confounding because the individual trials are not randomized. (13)

Our meta-analysis of hydroxychloroquine in post-exposure prophylaxis indicates a nonsignificant RR= 0.90 (95% CI 0.69 to 1.17). Thus, there is a statistically nonsignificant estimated 10% reduction in SARS-CoV-2 infection, but with sufficient precision to rule out as large as 20% reduction.

Our meta-analysis of hydroxychloroquine in hospitalized patients with COVID-19 yields a nonsignificant RR= 1.10 (95% CI 0.99 to 1.23). In hospitalized patients, there is an approximate statistically nonsignificant estimated 10% increase in mortality, but with sufficient precision to rule out as small as a 1% reduction. Further, these data suggest equality, but the point estimate is in the direction of small harm on mortality.

Conclusion

Previously, we recommended a moratorium to healthcare providers concerning prescriptions of hydroxychloroquine. (1) Since that time, no significant benefits have been found in the recent randomized evidence for post-exposure prophylaxis and among hospitalized patients. Regarding risk, hydroxychloroquine derived a reassuring safety profile from decades of prescriptions for autoimmune diseases of greater prevalence in younger and middle-aged women, whose risks of fatal outcomes due to QTc prolongations are very low. In contrast, the risks associated with COVID-19 are much higher because mortality rates for COVID-19 and the side effects of hydroxychloroquine are both highest in older patients and those with comorbidities, both of whom are predominantly men. The current totality of evidence more strongly supports our previous recommendations concerning the lack of efficacy and possible harm of hydroxychloroquine in the treatment and prevention of COVID-19. (3)

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