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.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 25, 2020

PUBLISHED BY ELSEVIER

THE PRESENT AND FUTURE

CARDIOVASCULAR MEDICINE AND SOCIETY

COVID-19, Clinical Trials, and QT-Prolonging Prophylactic Therapy in Healthy Subjects

First, Do No Harm

Michael H. Gollob, MD

A mere 6 months ago, our lives were relatively calm and routine. The thought of a novel, infectious, worldwide pandemic threatening the lives of hundreds of thousands of individuals seemed the storyline of a fictional Hollywood script. The rapid surge and toll of coronavirus disease-2019 (COVID-19) infection has been sobering, already claiming the lives of >330,000 people and projected to potentially reach a death toll of 1 million individuals globally.

Compared with other viral pandemics of recent times, SARS (severe acute respiratory syndrome coronavirus) (2003; 800 deaths) and H1N1 (2009; 18,000 deaths), COVID-19 has provoked an unprecedented level of concern, appropriately leading to major government-mandated preventative measures. Consequently, the disruption to the general population has been extreme, with loss of employment, separation of family and friends, on top of the loss of loved ones. Anxiety levels are high, and the impact of COVID-19 has stirred a near urgent pressure on the scientific community to identify effective lifesaving therapies. To this end, the National Institutes of Health alone received a rapid stimulus of funds boosting the COVID-19-dedicated research budget to $1.8 billion. Together with the large available funding has been the call from a multitude of government and national research funding agencies globally for "urgent," "rapid," and "emergency" proposals to combat the COVID-19 crisis. This has been coupled with promises of facilitated institutional protocol reviews to assist in rapid implementation of research studies. Although the intentions of expediting research interventions are well-meaning, such an approach may limit the necessary scrutiny of proposed interventions to minimize risk to research subjects.

CLINICAL TRIALS INVOLVING HEALTHY SUBJECTS FOR COVID-19 PREVENTION

At present, >1,000 studies on COVID-19 have been registered on ClinicalTrials.gov, a National Institutes of Health web-based resource describing ongoing clinical studies, including description of the research protocol. These studies vary widely in the targeted research subjects and in specific inclusion/exclusion criteria for enrollment. No doubt, in studies proposing interventions in the sickest and most rapidly deteriorating patients with a high probability of mortality, the nature of intervention reasonably requires less scrutiny, and even desperation therapies outside of approved clinical indications or trials may be justified. More concerning, however, are the dozens of "prophylactic" studies proposed in asymptomatic, COVID-19-negative subjects,

From the Inherited Arrhythmia and Cardiomyopathy Program, Arrhythmia Service, Division of Cardiology, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada; and the Department of Physiology, University of Toronto, Toronto, Ontario, Canada. The author has reported that he has no relationships relevant to the contents of this paper to disclose.
The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

Manuscript received April 23, 2020; revised manuscript received May 1, 2020, accepted May 5, 2020.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2020.05.008

predominantly health care professionals considered to be at increased risk of infection. These studies are motivated by the observation that >1,000 of our colleagues around the world have succumbed during their valiant efforts to serve COVID-19 patients. The loss of lives of these true heroes warrants consideration of evidence-based preventative measures best obtained through randomized, double-blinded clinical trials. However, in trials involving a previously well, asymptomatic cohort, the premise of maleficence, or "first, do no harm," must be at the forefront of trial design.

As of April 30, 2020, 155 randomized trials currently registered on ClinicalTrials.gov propose the use of chloroquine or hydroxychloroquine, known QT-prolonging drugs. A major theme of these studies is prophylactic treatment of predominantly healthy, asymptomatic health care workers for the purpose of preventing COVID-19 infection, cumulatively enrolling >170,000 participants. Some studies propose a combination therapy with azithromycin, compounding concerns of the effect of potential QT-prolongation and arrhythmic risk. Overall, it can be expected that >85,000 asymptomatic individuals will be randomized to active therapy and be exposed to these drugs. Surprisingly, only 6 small studies stipulate exclusion based on measured QTc from the resting 12-lead electrocardiogram (ECG), whereas the remaining randomized studies do not require resting ECG upon enrollment or consider enrollment exclusion based on resting QTc. *What does this mean for the risk of adverse events for the >85,000 asymptomatic research subjects randomized to QT-prolonging drugs?*

RECOGNIZING THE RISK FOR DRUG-PROVOKED CARDIAC EVENTS IN HEALTHY SUBJECTS

Congenital long QT syndrome has a prevalence of 1 of 2,000 in the general population, is commonly asymptomatic or unknown to the affected individual, and often presents for the first time with a fatal event, frequently drug-provoked (1). Additionally, not all healthy subjects are created equally in regards to QT-prolonging drug response and risk of drug-provoked torsades de pointes. Well-recognized genetic risk variants, collectively present in up to 4% of the population, and are well known to create a vulnerability to QT-provoked arrhythmic events and sudden death (2–6). Most common among these risk variants is *KCNE1*-D85N, carried by 2% of the general population and by 5% of individuals of Ashkenazi Jewish decent (2,4,5). Taken together, >3,400 asymptomatic, healthy research subjects will be at an elevated risk of a drug-provoked cardiac event. Although the majority will survive unscathed, it can be certain that the absence of ECG screening and monitoring will result in the sudden death of previously healthy subjects during these studies. This risk might be justified if it was expected that mortality from COVID-19 in these prophylactic studies of asymptomatic cohorts was measurably much greater. However, it would be anticipated that the age for most participants, given the emphasis on health care personnel in most studies, would not be in the high-risk range for COVID-19 fatalities. Assuming drug efficacy might exist, the most relevant question is whether a competing event rate could be similar and offset from drug-provoked events or deaths.

ABBREVIATIONS AND ACRONYMS

COVID-19 = coronavirus disease-2019

ECG = electrocardiogram

EXCLUSION CRITERIA FOR CLINICAL TRIALS OF QT-PROLONGING DRUGS IN HEALTHY SUBJECTS

Randomized drug trials to prevent COVID-19 infection in frontline health care providers or COVID-19-exposed individuals are needed. Preserving the health of our colleagues and preventing a rapid decline in personnel to care for the sick is essential. This need should not, however, supersede a thoughtful and safe research protocol to ensure the safety of research subjects, particularly when enrolling previously healthy participants.

HOW SHOULD RESEARCH SUBJECTS BE PROTECTED IN THESE QT-DRUG PROLONGING DRUG STUDIES?

First and foremost, exclusion criteria based on a measured QTc from resting 12-lead ECG should be required. As the risk of arrhythmic events begins to escalate for QTc intervals in excess of 490 ms, and as QTc prolongation should be expected in those randomized to active drug, exclusion to trial enrollment is most reasonable for individuals with a resting QTc of >450 ms. This is the common QTc exclusion range in efficacy studies of known QT-prolonging drugs to ensure curtailing of adverse torsadogenic events (7,8). Chorin et al. (9) have shown that even healthy subjects may be drug-provoked to maximal QTc increases of 20 to 30 ms on average, depending on the provoking agent used. These effects are more notable in women, and greatly exaggerated in patients harboring long QT syndrome genetic mutations (9). Most recently, it has been reported that 30% of very ill COVID-19 patients who received empiric hydroxychloroquine/azithromycin combination therapy had a QTc increase in excess of 40 ms, and 11%

were drug-provoked to a QTc in excess of 500 ms (10). Importantly, broad ranges of drug-provoked QTc prolongation was observed in both studies, highlighting the unpredictability of drug response in most individuals. These data further mandate the need for follow-up ECG on day 1 and intermittently thereafter, with discontinuation of subject enrollment if QTc exceeds 480 ms. Although this may seem like a conservative value for subject withdrawal from a study, in studies of a prophylactic nature involving healthy subjects where maleficence should be of primary concern, this is a prudent QTc cut-off, particularly when the severity of the adverse event, sudden death, may be worse than the study endpoint. Last, the medication history of prospective participants should be thoroughly vetted to minimize a synergistic effect on QTc that might occur with the concomitant use of electrolyte-depleting drugs or other QT-prolonging agents.

Those who have stepped up and have worked many hours organizing COVID-19 randomized trials and other research during these challenging times deserve to be applauded. This commentary is not a criticism to our hard-working colleagues, but rather a reminder of the need to consider potential risk to previously healthy and asymptomatic research volunteers as the field moves quickly to find successful evidence-based treatments. First, do no harm.

ADDRESS FOR CORRESPONDENCE: Dr. Michael H. Gollob, Toronto General Hospital, 200 Elizabeth Street, Toronto, Ontario M5G 2C4, Canada. E-mail: michael.gollob@uhn.ca. Twitter: @UHN_Research.

REFERENCES

1. Vincent GM, Schwartz PJ, Denjoy I, et al. High efficacy of beta-blockers in long-QT syndrome type 1: contribution of noncompliance and QT-prolonging drugs to the occurrence of beta-blocker treatment "failures. Circulation 2009;119:215–21.

2. Roden D, Viswanathan PC. Genetics of acquired long QT syndrome. J Clin Invest 2005;115:2025–32.

3. Schwartz PJ, Woosley RL. Predicting the unpredictable: drug-induced QT prolongation and torsades de pointes. J Am Coll Cardiol 2016;67:1639–50.

4. Kääb S, Crawford DC, Sinner MF, et al. A large candidate gene survey identifies the *KCNE1* D85N polymorphism as a possible modulator of drug-induced torsades de pointes. Circ Cardiovasc Genet 2012;5:91–9.

5. Adler A, Novelli V, Abiusi E, et al. An international, multicentered, evidence-based reappraisal of genes reported to cause congenital long QT syndrome. Circulation 2020;141:418–28.

6. Roberts JD, Krahn AD, Ackerman MJ, et al. Loss-of-function *KCNE2* variants: true monogenic culprits of Long-QT syndrome or proarrhythmic variants requiring secondary provocation? Circ Arrhythm Electrophysiol 2017;10:e005282.

7. Pritchett ELC, Page RL, Connolly SJ, Marcello SR, Schnell DJ, Wilkinson WE. Antiarhythmic effects of azimilide in atrial fibrillation: efficacy and dose-response. J Am Coll Cardiol 2000;36:794–802.

8. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med 2011;365:689–98.

9. Chorin E, Hochstadt A, Granot Y, et al. Grapefruit juice prolongs the QT interval of healthy volunteers and patients with long QT syndrome. Heart Rhythm 2019;16:1141–8.

10. Chorin E, Dai M, Shulman E, et al. The QT interval in patients with SARS-CoV-2 infection treated with hydroxychloroquine/azithromycin. medRxiv 2020 Apr 3 [E-pub ahead of print].

KEY WORDS clinical trials, COVID-19, genetics, QT interval, sudden cardiac death