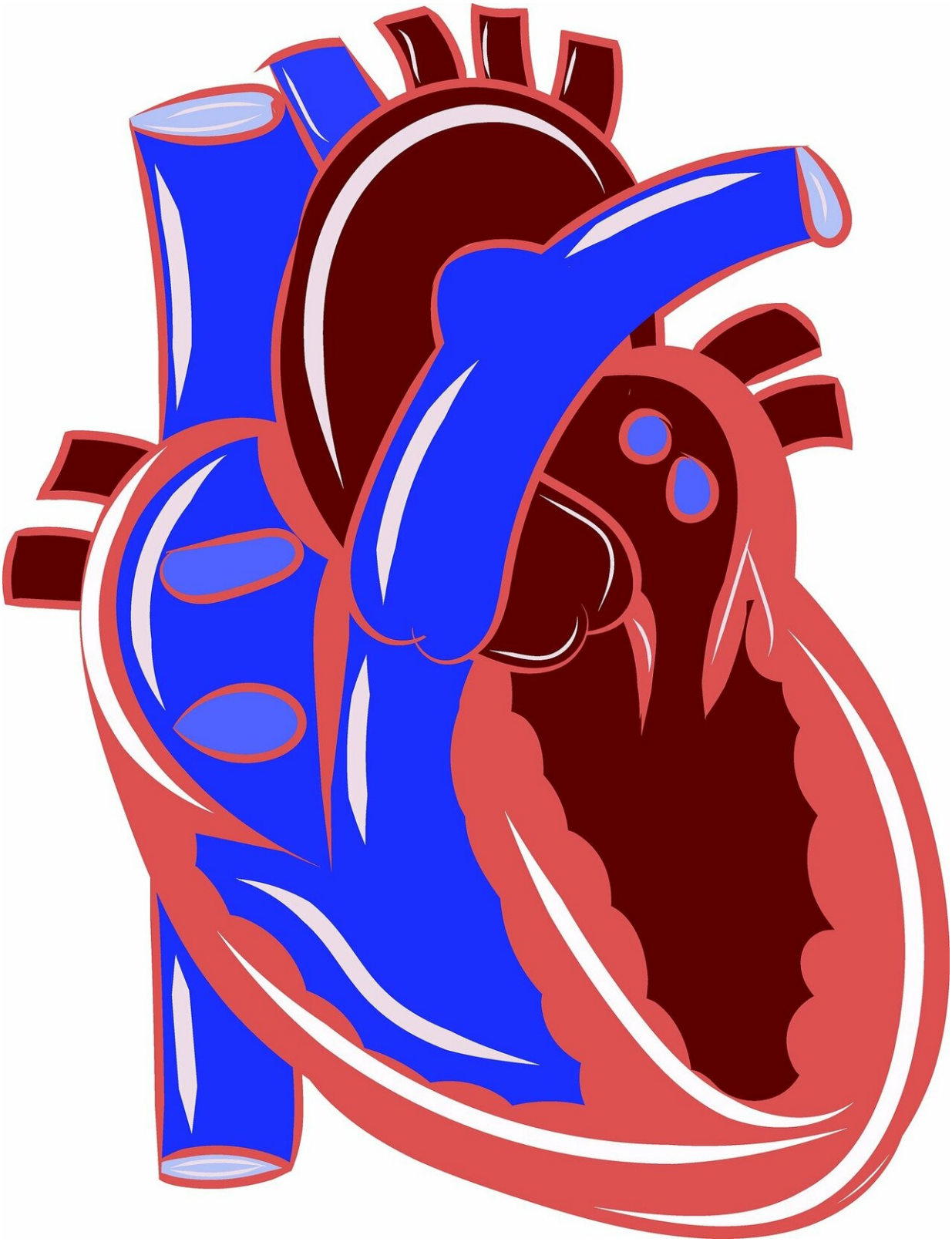
Using hydroxychloroquine and azithromycin together increases cardiovascular risk

August 24 2020



Credit: CC0 Public Domain

The combination of hydroxychloroquine and azithromycin has been linked to significant cardiovascular risks, including mortality, in the largest safety study ever performed comparing hydroxychloroquine treatment to hydroxychloroquine and azithromycin treatment for rheumatoid arthritis patients. Hydroxychloroquine is commonly used to treat rheumatoid arthritis, while azithromycin is a frequently-prescribed antibiotic to treat infections such as pneumonia, chest and sinus infections, etc. This network study, led by the Observational Health Data Sciences and Informatics (OHDSI) community, was recently published in *The Lancet Rheumatology*.

In patients with rheumatoid arthritis, hydroxychloroquine treatment in the short term (30 days) was found to not carry excess risk of complications associated with its use, but hydroxychloroquine treatment in the long term had a 65% relative increase in cardiovascular-related mortality, compared to sulfasalazine, a similar rheumatoid arthritis drug.

Hydroxychloroquine and azithromycin together had a cardiovascular mortality risk that was more than twice (2.19) as high as the comparative treatment even in the short term based on findings from more than 320,000 users of that combination therapy. This treatment also produced a 15-20% increased rate of angina/chest pain and heart failure.

Hydroxychloroquine, a drug commonly used in the treatment of malaria and lupus in addition to rheumatoid arthritis, gained early attention during the pandemic as a potential COVID-19 treatment.

"Hydroxychloroquine, both alone and in combination with azithromycin, gained strong consideration as a potential COVID-19 treatment without a large-scale study of its overall safety profile," said Daniel Prieto-Alhambra, Professor of Pharmaco- and Device Epidemiology at the

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), and co-senior author on this study. "We had access to an unprecedented amount of data on this drug, and we were relieved to find no worrying side effects in the short-term use of hydroxychloroquine. However, when prescribed in combination with azithromycin, it may induce heart failure and cardiovascular mortality and we would urge caution in using the two together."

This is the first published study to be generated from the OHDSI COVID Study-a-thon, a global effort in March to set the foundation for OHDSI efforts to design and execute network observational studies around characterisation, patient-level prediction and population-level effect estimation to inform decision-making around the global pandemic.

The OHDSI community examined more than 950,000 hydroxychloroquine users through de-identified electronic health records and administrative claims data over a 20-year period. Records were collected from 14 different databases spanning six nations (Germany, Japan, Netherlands, Spain, United Kingdom, United States) and then mapped to the OMOP Common Data Model to generate this large-scale analysis.

"At medical school we were taught to 'first do no harm' and to me, our study focuses on this core belief of modern medicine," said Jennifer Lane, MD, NDORMS, who served as co-lead author on this study along with Jamie Weaver, from Janssen Research and Development. "OHDSI has the power to investigate this question in a very thorough way and to go through rigorous steps. We are looking at patients from the general population, which is why it is so important to look at data from multiple countries. There are reasons why you may get bias from one data source, but if we find a signal in the Netherlands, and we find it in Spain, and we find it in the U.S., then we know we have something."

It was first released on MedRxiv and has already made significant impacts in the healthcare community. On April 23, the European Medicines Agency (EMA) cited the study in a warning about the risk of serious side effects with chloroquine and hydroxychloroquine. In July, the EMA again highlighted the study, among other efforts within the OHDSI community, in its eighth revision of The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

"It required a global effort to generate this level of reproducible, reliable real-world evidence to inform decision-making around COVID treatment," said Patrick Ryan, Ph.D., co-senior author on this study. "Our community collaborated for years to develop the high-level analytics which set the course for these studies. Standardizing data for nearly 1,000,000 patients on hydroxychloroquine provides confidence in these findings, and we are pleased to see that this study has already helped make a positive clinical impact as treatment options continue to be evaluated."

More information: Jennifer C E Lane et al. Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study, *The Lancet Rheumatology* (2020). DOI: 10.1016/S2665-9913(20)30276-9

Provided by University of Oxford