Cardiac Complications Attributed to Hydroxychloroquine: A Systematic Review of the Literature Pre-COVID-19

Georgi Fram¹, Dee D. Wang¹,* , Kelly Malette¹, Pedro Villablanca¹, Guson Kang¹, Kent So¹, Mir B. Basir¹, Arfaat Khan², John E. McKinnon³, Marcus Zervos³ and William O’Neill¹

¹Center for Structural Heart Disease, Henry Ford Health System, Detroit, Michigan, MI 48202, USA; ²Section of Cardiac Electrophysiology, Henry Ford Health System, Detroit, Michigan, MI 48202, USA; ³Division of Infectious Disease, Henry Ford Health System, Detroit, MI 48202, USA

Abstract: Introduction: Hydroxychloroquine has been used for rheumatological diseases for many decades and is considered a safe medication. With the COVID-19 outbreak, there has been an increase in reports associating cardiotoxicity with hydroxychloroquine. It is unclear if the cardiotoxic profile of hydroxychloroquine is previously underreported in the literature or is it a manifestation of COVID-19 and therapeutic interventions. This manuscript evaluates the incidence of cardiotoxicity associated with hydroxychloroquine prior to the onset of COVID-19.

Methods: PubMed, EMBASE, and Cochrane databases were searched for keywords derived from MeSH terms prior to April 9, 2020. Inclusion eligibility was based on appropriate reporting of cardiac conditions and study design.

Results: A total of 69 articles were identified (58 case reports, 11 case series). The majority (84%) of patients were female, with a median age of 49.2 (range 16-92) years. 15 of 185 patients with cardiotoxic events were in the setting of acute intentional overdose. In acute overdose, the median ingestion was 17,857 ± 14,873 mg. 2 of 15 patients died after acute intoxication. In patients with long-term hydroxychloroquine use (10.5 ± 8.9 years), new onset systolic heart failure occurred in 54 of 155 patients (35%) with median cumulative ingestion of 1,493,800 ± 995,517 mg. The majority of patients improved with the withdrawal of hydroxychloroquine and standard therapy.

Conclusion: Millions of hydroxychloroquine doses are prescribed annually. Prior to the COVID-19 pandemic, cardiac complications attributed to hydroxychloroquine were uncommon. Further studies are needed to understand the impact of COVID-19 on the cardiovascular system to understand the presence or absence of potential medication interactions with hydroxychloroquine in this new pathophysiological state.

Keywords: Clinical cardiology, hydroxychloroquine, infectious disease, COVID-19, cardiac complications, SLE.

1. INTRODUCTION

The antimalarial medication Hydroxychloroquine (HCQ) has an established safety profile in the long-term use for rheumatological conditions, such as Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA) [1]. For connective tissue disorders, HCQ has been demonstrated to improve clinical symptoms, decrease SLE renal involvement, and decrease the rate of thrombotic events in patients [1, 2]. It has also been commonly prescribed for the prevention and treatment of malaria in adults and children who are planning on traveling to areas where malaria transmission occurs [3]. HCQ has been approved by the United States Food and Drug Administration (FDA) since 1955 [3]. Although HCQ has been in widespread use for decades, recent retrospective database reviews of HCQ administration in patients infected with the novel coronavirus (SARS-CoV-2) has cast doubt on the safety profile of HCQ [4, 5].

Given the recent outbreak of the novel severe respiratory distress syndrome coronavirus (SARS-CoV-2) and early reports of the possible therapeutic benefit of HCQ in its management, a national spotlight has been shone on the medication. Until recently, HCQ-related cardiac adverse events (AE) have been infrequently reported, despite its regular usage for about seven decades. Since the onset of the SARS-CoV-2 pandemic, there is speculation regarding the acuity of side effects, with some publications suggesting the incidence of arrhythmias in the acute to a sub-acute setting, requiring closer monitoring [6].

However, it currently remains unclear if there is a specific cumulative dosage, duration of therapy, or vulnerable patient population at risk of toxicity with HCQ administration. The aim of this study is to perform a systematic review of...
the literature regarding the cardiac AE related to HCQ prior to the onset of SARS-CoV-2 to help elucidate if HCQ was previously not well-studied or if SARS-CoV-2 is exacerbating cardiac manifestations with HCQ use.

2. METHODS

2.1. Data Sources and Literature Searches

A systematic review was conducted by performing a systematic electronic search in MEDLINE of PubMed, EMBASE, and Cochrane Databases, including all articles published prior to April 9, 2020. This search utilized a variety of relevant keywords according to the MeSH terms for heart disease with subcategories such as cardiomyopathy, heart failure, cardiac toxicity, and arrhythmias (“hydroxychloroquine”[MeSH] AND (“QT”[MeSH] OR “QT prolongation”[MeSH] OR “arrhythmia”[MeSH] OR “torsades”[MeSH] OR “ventricular tachycardia”[MeSH] OR “ventricular fibrillation”[MeSH] OR “atrioventricular block”[MeSH] OR “cardiomyopathy”[MeSH] OR “heart failure”[MeSH] OR “cardiac toxicity”[MeSH]). After the removal of duplicate studies, one author (DDW) initially screened the potentially relevant manuscripts based on titles and abstracts, with the final selection of articles performed independently by two authors (GF, KM) based on the full-text evaluation. The consensus was obtained between the authors to resolve any article discrepancies.

2.2. Study Selection

As demonstrated in Fig. (1), all studies reporting patients who experienced cardiac complications while taking hydroxychloroquine, were included. Duplicate articles were excluded after review, as were articles that did not describe cardiac adverse effects. Articles were also excluded that described the use of HCQ as therapy for autoimmune conditions with cardiac manifestations.

2.3. Data Extraction

Using a standardized data form, two reviewers independently extracted study characteristics from the remaining articles. The data collected for each patient included: age, sex, median daily dose, median cumulative dose, the median duration of therapy, underlying disease, cardiac disorders, ECG and echocardiogram findings, and evolution of clinical course over time.

2.4. Statistical Analysis

Qualitative variables were described by frequencies. Quantitative variables were expressed as the mean with standard deviation, median, and minimum/maximum values.

3. RESULTS

The literature search identified a total of 69 manuscripts for review, attributing HCQ to cardiac disorders. Of these articles, 11 were case studies and 58 were case reports [7-73]. Baseline patient characteristics are summarized in Table 1. The majority of patients were female (84%), with a median age of 49.2 ± 18.7 years old (range 16–92 years old). Most patients were being treated for SLE, representing 52% of our review, with rheumatoid arthritis (RA) the next most frequent entity treated.

![Fig. (1). Article review.](image)

In the cohort of patients admitted for HCQ overdose after acute intoxication, 15 patients presented with adverse cardiac events. Adverse cardiac events in any patient were defined as sudden cardiac death, atrioventricular heart block, new bundle branch block, atrial fibrillation, atrial flutter, QT prolongation, ventricular tachycardia, ventricular fibrillation, torsades de pointes, QRS prolongation, new-onset left or right heart failure, or new-onset valvular disorder. Acute overdose was defined as the intentional ingestion of multiple tablets with purposeful intent to go beyond standard FDA approved dosing regimens. The median dose ingested during acute intoxication prior to hospital presentation was 17,857 ± 14,873 milligrams (mg), with minimum-maximum of 4,000 – 60,000 mg, with details described in Table 2.

There were no documented episodes of sudden cardiac death after an acute intentional overdose of HCQ. Seven patients had a manifestation of QTc prolongation, three patients developed unstable ventricular tachycardia requiring attempted defibrillation, three patients developed ventricular fibrillation, one developed a prolonged QRS, and one patient developed torsades de pointes. Two patients expired after arrival to the emergency department, one developed ventricular fibrillation and the other pulseless ventricular tachycardia.
Table 1. General characteristics.

| Sex n, (%)       | Results   |
|------------------|-----------|
| Female           | 156 (84)  |
| Male             | 29 (16)   |
| Median age, years ± SD | 49.2 ± 18.7 |
| Age range, years (min - max) | 16-92 |
| Diseases involved, n (%) | - |
| Systemic lupus erythematosus | 94 (52) |
| Rheumatoid arthritis | 39 (20) |
| Discoid lupus | 3 (2) |
| Sjogren syndrome | 4 (2) |
| Mixed connective tissue disease | 2 (1) |
| Scleroderma | 4 (2) |
| Other | 45 (24) |

Abbreviations: SD – standard deviation.

Amongst patients whose intoxication was after long-term chronic usage, the median duration of therapy with HCQ was approximately 10.5 years, with a range of 0.25 – 31 years. The median lifetime cumulative dose was approximately 1,493,800 mg with a range of 16,000 – 3,212,000 mg.

Compared to the acute intoxication arm, patients with long-term HCQ cumulative usage over 10 years, had more literature documentation of arrhythmias and cardiomyopathies. Incidence of atrial fibrillation, bundle branch block, QT prolongation, and left-sided heart failure were more pronounced in long-term intoxication case series compared to acute intoxication case reports.

The data revealed the most common cardiac AE associated with acute HCQ overdose was QT prolongation (7/15 patients). There were no cardiomyopathies reported in acute HCQ overdose. In patients who were using HCQ in the 10.5 ± 8.9-year long-term setting, the most common cardiac adverse event was left-sided heart failure. Table 3 summarizes findings of cardiac adverse events.

4. DISCUSSION

A meta-analysis was performed to evaluate the cardiac adverse events profile of the HCQ pre-COVID pandemic. The findings demonstrated time-dependent variable and cumulative dosage response to the manifestation of adverse cardiovascular outcomes. In acute HCQ overdose, the most common adverse cardiac events were QT prolongation (7 patients), followed by ventricular tachycardia or ventricular fibrillation (3 patients each, respectively). Of the 7 out of 15 patients presenting with adverse cardiac events following acute intoxication, the presence of ventricular tachycardia or ventricular fibrillation is suggestive of an underlying mechanism of significant QT prolongation secondary to massive overdose. Acute HCQ intoxication was successfully treated in the majority of reported cases.

Long-term hydroxychloroquine use in publications demonstrate less common arrhythmic events and more association with structural cardiac abnormalities. After over 10 years of HCQ usage, with cumulative dosage levels exceeding 1,400,000 milligrams, there were sixty reports of new left-sided heart failure felt to be secondary to HCQ administration and 7 reported cases of right-sided heart failure.

To date, it is not well understood if the cardiomyopathy identified with chronic decade use of HCQ is attributable to the medication or progression of underlying autoimmune and connective tissue disease. When HCQ toxicity is suspected, it is standard of care to withdraw the medication and initiate pharmacotherapy for the specific cardiovascular process. There is evidence of high rates of recovery, replicated in our review, when this treatment regimen is enacted. However, further complicating the diagnosis of HCQ-related cardotoxicity, the underlying inflammatory disorder may cause similar disease processes, independent of HCQ usage [74, 75]. This may lead to poor patient outcomes due to the unnecessary withdrawal of HCQ when toxicity is suspected. Although there are well-established pharmacotherapies for the most common cardiac complications, the underlying autoimmune disease may progressively worsen with the discontinuation of HCQ.

The overwhelming majority of cases of HCQ-related cardotoxicity occurred at very high cumulative doses of the medication, with once or twice daily dosing over several years. In these chronic-HCQ patients, intoxication often presented with progressive onset of symptoms over many months. As stated above, excluding acute intoxication events, the average duration of therapy of patients with cardotoxicity was greater than 10 years, with an average cumulative dose of over 1,400 grams. SLE and RA are widely prevalent diseases, with SLE estimated to affect 1.4 million people in North America alone, and RA having a worldwide incidence estimated at 16 million [76, 77]. HCQ is often first- or second-line therapy in a large number of these patients, yet there are only a few reports of cardiac AE. Our data reinforces that patients taking their medication appropriately are at very low risk of experiencing cardiac AE, particularly with short term administration and at the onset of therapy. Of the 69 manuscripts included in this review, only three identified patients experienced cardotoxicity within
Table 2. Cardiac complications with all HCQ-toxicity.

| Dose                        | Acute Intoxication (n=15) | Long-term Intoxication (n=170) |
|-----------------------------|---------------------------|--------------------------------|
| Median daily (mg±SD)        | -                         | 377 ± 98.2                     |
| Median cumulative (mg±SD)   | 17,857 ± 14,873           | 1,493,800 ± 995,517            |
| Median duration (years±SD)  | -                         | 10.5 ± 8.9                     |
| Post-withdrawal change, n   | -                         | -                              |
| Improvement                 | 13                        | 77                             |
| Death                       | 2                         | 35                             |
| Stable                      | -                         | 6                              |
| Pacemaker placement         | -                         | 9                              |
| Heart transplant            | -                         | 1                              |
| Cardiac disorder, n         | -                         | -                              |
| 1st or 2nd degree AV block  | -                         | 9                              |
| Complete AV block           | -                         | 7                              |
| New left or right BBB       | 1                         | 23                             |
| Atrial fibrillation/ flutter| -                         | -                              |
| QTc prolongation            | *7                        | 14                             |
| Ventricular tachycardia     | 3                         | ^4                             |
| Ventricular fibrillation    | **3                       | 1                              |
| Torsades de pointes         | *1                        | ^2                             |
| Widened QRS                 | 1                         | -                              |
| Sudden cardiac death        | -                         | 1                              |
| New left sided heart failure| -                         | 60                             |
| LVEF                        | -                         | -                              |
| < 40%                       | -                         | 45                             |
| 40 – 60%                    | -                         | 21                             |
| > 60%                       | -                         | 7                              |
| New right sided heart failure| -                        | 7                              |
| New valve disorder          | -                         | -                              |

Note: * patient had QT prolongation and torsades de pointes. ** case 1 occurred in setting of HCQ, bromazepam, zolpidem, & paroxetine overdose. *** case 2 occurred in setting of rapid correction of hypokalemia. ^ patient had torsades that degenerated into ventricular tachycardia. Abbreviations: SD – standard deviation.

one year of therapy initiation, making it difficult to elucidate any pattern of susceptible patient populations.

Acute intoxication certainly poses a separate yet equally important threat of toxicity to the cardiovascular system. The most common finding in acutely intoxicated patients appears to be QT prolongation, possibly leading to other, more life-threatening arrhythmias. The average dose of patients presenting with acute HCQ-toxicity was ingestion of approximately 17,000 milligrams, demonstrating a high dosage needed in a short timeframe to cause these life-threatening abnormalities.

While there are well-established guidelines for monitoring of more common HCQ-related AE, there remains debate over periodic cardiac monitoring in patients taking the medication. This literature review did not reveal a single study which incorporated a formal screening protocol in any patient that was initiated on the medication or long term follow up. In 2018, Chatre et al. proposed monitoring intervals for cardiotoxicity, with heart screening occurring one month after onset of therapy and biennially thereafter [1]. To date, there is no widespread adoption of monitoring guidelines for HCQ-related cardiotoxicity.

Since its creation, HCQ has had multiple mechanisms of action, allowing its versatility as a medication primarily blocking toll-like receptors in addition to the prevention of stimulation of B cell antigen receptors, thus acting as an anti-inflammatory agent [78]. The proposed mechanism of action of HCQ, as it relates to SARS-CoV-2, involves its ability to prevent membrane fusion, disrupting the viruses’ ability to enter cells and begin replication [79, 80]. The underlying pathophysiology of SARS-CoV-2 contributes to cardiac complications in the population it infects, with estimates ranging from 20-40% incidence [81, 82]. Proposed SARS-CoV-2 mechanisms of injury involve a direct injury via viral infiltration into the myocardial tissue, leading to inflammation [83]. Additionally, respiratory failure may lead to systemic inflammation, causing further damage to the myocardium. While SARS-CoV-2 patients will be at high risk of cardiotoxicity, this is due to the inherent nature of the virus, and the question remains if the addition of HCQ to their therapy is associated with an increased risk of cardiac AE [84].
Table 3. Acute intoxication case characteristics.

| Age (Years) | Gender | Dose Ingested (mg) | Pills Ingested (n) | Adverse Event | Therapy | Survival |
|-------------|--------|--------------------|-------------------|---------------|---------|---------|
| 16 [53]     | Female | 12,000             | 60                | QTc 600 ms    | BCB, vasopressor | Yes     |
| 16 [50]     | Female | 20,000             | 100               | QTc 520 ms    | BCB, vasopressor, inotropic support, KCl | Yes     |
| 16 [40]     | Female | *                  | *                 | RBBB          | IVF, dopamine, GL, KCl | Yes     |
| 17 [69]     | Female | 22,000             | 110               | V-tach        | BCB, IVF, GL, AC, MgS | Yes     |
| 18 [32]     | Female | 20,000             | 100               | QTc 564 ms    | GL, AC, vasopressor, KCl, MgS | Yes     |
| 19 [41]     | Female | 6,000              | 30                | V-fib         | KCl **     | Yes     |
| 20 [19]     | Female | 36,000             | 180               | QTc 563 ms    | AC, BCB, MgS, KCl | Yes     |
| 20 [47]     | Female | 60,000             | 300               | QTc 600 ms, TdP | GL, KCl, MgS, ILE | Yes     |
| 28 [72]     | Male   | 20,000             | 100               | V-tach        | IVF, diazepam, vasopressor | No |
| 29 [73]     | Male   | 14,000             | 70                | V-fib         | GL, AC, BCB, MgS, diazepam, vasopressor | No |
| 30 [18]     | Male   | 4,000              | 20                | V-tach        | GL, vasopressor ** | Yes |
| 39 [43]     | Female | 12,000             | 60                | QTc 474 ms    | ILE, vasopressor, KCl | Yes     |
| 47 [73]     | Female | 4,000              | 20                | QRS prolongation | IVF, vasopressor, clonazepam, atropine | Yes |
| 49 [37]     | Male   | 8,000              | 40                | QTc 492 ms    | Vasopressor, KCl | Yes     |
| 55 [16]     | Female | 12,000             | 60                | QTc 474 ms    | ILE, vasopressor, KCl | Yes     |

Note: * case reported “handful of 200 mg HCQ tablets”, unable to determine exact final dose; ** incomplete treatment regimen provided.

Abbreviations: ms - milliseconds, RBBB - right bundle branch block, GL - gastric lavage, BCB - bicarbonate infusion, KCl - potassium chloride, IVF - intravenous fluids, V-Tach - ventricular tachycardia, AC- activated charcoal, MgS- magnesium sulfate, V-fib - ventricular fibrillation, TdP - torsades de pointes, ILD - intravenous lipid emulsion, ECMO - extracorporeal membrane oxygenation, [Ref] - Reference number.

Several recent publications have mentioned the use of HCQ at variable doses without significant cardiac toxicity. The RECOVERY trial administered a total of 2400mg of HCQ in the first 24 hours, followed by 800mg per day thereafter for 9 days for a total of 9600mg HCQ in the study arm [85]. A total of 1542 patients were randomized to hydroxychloroquine and compared with 3132 patients randomized to usual standard of care, and upon an urgent internal review of the trial by their safety committee following the publication of the now-retracted LANCET manuscript [4, 86], the Committee found no reasons to suspend the trial due to safety concerns over HCQ [85]. Subsequent analysis by the investigators found no significant difference in 28-day mortality between patients in the HCQ arm versus the usual care arm (p=0.10) [85]. Publications by Didier et al. have demonstrated efficacy in the treatment of COVID-19 patients with early HCQ + Azithromycin + Zinc therapy [84, 87]. When administered within 72 hours of symptom onset in COVID-19 patients, there was a decreased risk of hospitalization, shorter duration of viral shedding, decreased transfer to the ICU, and lower incidence of death. Out of 3,737 patients, 25 (0.67%) experienced QT prolongation requiring cessation of HCQ in 3 cases. The duration and cumulative dosing of HCQ therapy for SARS-CoV-2 patients did not exceed the thresholds described in our review when cardiotoxic risk begins to become prominent.

There are multiple prospective, randomized clinical trials evaluating the safety of hydroxychloroquine. The United Kingdom’s “Solidarity Trial” is an adaptive prospective randomized trial comparing different treatments against COVID-19 syndrome, of which one arm evaluates hydroxychloroquine [88]. This trial was initially stopped on May 27th, 2020, following safety concerns surrounding hydroxychloroquine raised by Mehra et al.’s LANCET publication, and then restarted on June 4th, 2020, after the LANCET study by Mehra et al. was retracted by the authors due to serious concerns on data integrity [4, 86, 89]. A second randomized clinical trial, the “COVOCOY” study by the Mahidol Oxford Tropical Medicine Research Unit, is ongoing and prospectively enrolling 40,000 frontline healthcare workers and staff, evaluating if chloroquine or hydroxychloroquine is able to prevent COVID-19 in the healthcare setting [90]. To date, three smaller randomized clinical trials investigating hydroxychloroquine for outpatient use as pre-exposure prophylaxis, post-exposure prophylaxis, and early treatment have completed data safety monitor board review and reported no ventricular arrhythmias and no sudden deaths [91].

COVID-19 syndrome has been established to trigger a biphasic response in patients infected with SARS-CoV-2, an early viral replication stage, and a subsequent hyperimmune response, cytokine storm. Cardiac complications of cytokine storm have been well documented to involve fatal cardiac dysrhythmias and acute systolic heart failure [92, 93]. Prior to the COVID-19 pandemic, this systematic review demonstrates no literature for acute intoxication of HCQ and sudden cardiac death. From April 2020, till present, numerous publications have been released, describing electrocardiographic QT prolongation in COVID-19 patients attributed to the use of HCQ. Most recently, Kawasaki’s disease has been reported in adult and pediatric survivors of COVID-19 [94, 95]. As the world’s supply of personal protection equipment starts to get replenished, the implementation of cardiac imaging studies is allowing increased discovery of pericardial effusions, new cardiomyopathies, stent thrombosis, and myocarditis in the setting of acute COVID-19 infection, independent of HCQ administration [92, 93, 96-100].
CONCLUSION

The cardiotoxic AE of HCQ, including atrial and ventricular arrhythmias, ECG changes, and HF, is not a common occurrence. It most often presents with high cumulative doses after many years of therapy or in the setting of a purposeful acute intoxication. It is exceedingly rare for patients to develop cardiac AE while taking recommended doses within the first year of therapy, particularly under the supervision of a cardiologist. There is a divergence in the proliferation of literature pre and post COVID-19 pandemic on the safety of HCQ in patients. The question remains, did the medication change after 70 years, or could there be a different pathophysiology associated with COVID-19 warranting more scientific evaluation of the impact of SARS-CoV-2 on cardiac structure and function. It is important to study and understand the 3 distinct COVID-19 patient groups in the evaluation of the efficacy of medical interventions, such as hydroxychloroquine. In summary, the reported increased arrhythmic events in the COVID-19 era appear to be more related with the direct inflammatory effect of the virus (myocarditis) or the concomitant administration of multiple drugs capable of prolonging QT intervals rather than to hydroxychloroquine itself [91, 101]. Given the dynamic pathophysiology of the COVID-19 syndrome, larger studies are needed to understand the role and impact of hydroxychloroquine in pre-exposure, early post-exposure, and late post-exposure therapeutics.

CONSENT FOR PUBLICATION

Not applicable.

STANDARD OF REPORTING

PRISMA guidelines & methodologies were followed.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Chatre C, Rouhielle F, Vernhet H, Jorgensen C, Pers YM. Cardiac complications attributed to chloroquine and hydroxychloroquine: A systematic review of the literature. Drug Saf 2018; 41(10): 919-31. http://dx.doi.org/10.1007/s40264-018-0689-4 PMID: 29858838
[2] Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken) 2012; 64(6): 797-808. http://dx.doi.org/10.1002/acr.21664 PMID: 22556106
[3] CDC. Medicines for the prevention of malaria while traveling hydroxychloroquine. plaquenil 2020. Available from: https://www.cdc.gov/malaria/resources/pdf/6p/drugs/hydroxychloroquine.pdf
[4] Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet 2020.
[5] Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. Med 2020; 1(1): 114-27
[6] Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc-Prolonging and Torsadogenic potential of possible pharmacotherapies for coronavirus disease 19 (COVID-19). Mayo Clin Proc 2020; 95(6): 1213-21. http://dx.doi.org/10.1016/j.mayocp.2020.03.024 PMID: 32359771
[7] Abbasi S, Tarter L, Farzaneh-Far R, Farzaneh-Far A. Hydroxychloroquine: A treatable cause of cardiomyopathy. J Am Coll Cardiol 2012; 60(8): 786. http://dx.doi.org/10.1016/j.jacc.2011.12.060 PMID: 22898072
[8] Abbi B, Patel SN, Blanco I, Kunthekar A, Schwartz D. A growing concern: Cardiomyopathy with long term hydroxychloroquine use. J Invest Med 2019; 67: 807.
[9] Azimian M, Gultekin SH, Hata JL, et al. Fatal antimalarial-induced cardiomyopathy: report of 2 cases. J Clin Rheumatol 2012; 18(7): 363-6. http://dx.doi.org/10.1097/RHU.0b013e31826852db PMID: 23047537
[10] Bae SM, Jung HO, Ihm SM, et al. Hydroxychloroquine-induced cardiomyopathy that presented as pulmonary hypertension: a newly noted complication. Cardiology 2012; 123(3): 197-200. http://dx.doi.org/10.1159/000343142 PMID: 23154245
[11] Chang A, Stohl G, Fan J, et al. Hypertrophic cardiomyopathy in a lupus patient: a case of hydroxychloroquine cardiotoxicity. ESC Heart Fail 2019; 6(6): 1326-30. http://dx.doi.org/10.1002/ehf2.12508 PMID: 31493341
[12] Chang ICY, Bois JP, Bois MC, Maleszewski JJ, Johnson GB, Grogan M. Hydroxychloroquine-mediated cardiotoxicity with a false-positive “Technetium-Labeled Pyrophosphate scan for transthyretin-related cardiac amyloidosis. Circ Cardiovasc Imaging 2018; 11(1): 11. http://dx.doi.org/10.1161/CIRCIMAGING.117.007059 PMID: 29288196
[13] Chatre C, Filippi N, Roubille F, Pers YM. Heart involvement in a woman treated with hydroxychloroquine for systemic lupus erythematosus revealing fabry disease. J Rheumatol 2016; 43(5): 997-8. http://dx.doi.org/10.3899/jrheum.151357 PMID: 27134281
[14] Chen CY, Wang FL, Lin CC. Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia. Clin Toxicol (Phila) 2006; 44(2): 173-5. http://dx.doi.org/10.1080/155636505014558 PMID: 16615675
[15] Choi HC, Jung YO, Jo SH, Kim HA. Three cases of fatal lupus cardiomyopathy clinical features and outcomes. J Clin Rheumatol 2015; 21(7): 379-81. http://dx.doi.org/10.1097/RHU.0000000000000307 PMID: 26398476
[16] Cole JB, Stellpflug SJ, Smith SW. Refractory hypotension and “ventricular fibrillation” with large uwaves after overdose. JAMA Intern Med 2016; 176(7): 1007-9. http://dx.doi.org/10.1001/jamainternmed.2016.2065 PMID: 27272338
[17] Cotronne J, Sleik KM, Rene Rodriguez E, Klein AL. Hydroxychloroquine-induced restrictive cardiomyopathy: Correlation between clinical, Echocardiographic and pathologic findings. Eur J Echocardiogr 2007; 8: 247-51. http://dx.doi.org/10.1002/ejeu.2006.02.002
[18] de Jong-Straková Z, Blaauw AA, van der Linden SJ, Ferwerda J. A patient with acute hydroxychloroquine poisoning; recommendation for treatment. Ned Tijdschr Geneeskd 1990; 134(50): 2445-6.
[19] de Olano J, Howland MA, Su MK, Hoffman RS, Biary R. Toxicokinetics of hydroxychloroquine following a massive overdose. Clin Toxicol 2018; 56: 530-1.
[20] de Olano J, Howland MA, Su MK, Hoffman RS, Biary R. Toxicokinetics of hydroxychloroquine following a massive overdose. Am J Emerg Med 2019; 37: 2264-6.9. http://dx.doi.org/10.1016/j.ajem.2019.158387
Hydroxychloroquine and Cardiac Manifestations

[21] Dogar MU, Shah NN, Ishtiaq S, et al. Hydroxychloroquine-induced restrictive cardiomyopathy: A case report. Postgrad Med J 2018; 94(1109): 185-6.

[22] Fakhrri S, Lee H, Lublin B, Rudofsky E, Gupta A. The heart aches for what the joint wants. Am J Respir Crit Care Med 2019; 199.

[23] Faridani V, Shamim S, Awad A. Systemic lupus erythematosus induced non-ischemic cardiomyopathy. J Hosp Med 2012; 7: S317-8.

[24] Frustaci A, Morgante E, Antuzzi D, Russo MA, Chimienti C. Inhibition of cardiomyocyte lysosomal activity in hydroxychloroquine cardiomyopathy. Int J Cardiol 2012; 157(1): 117-9.

[25] Ghinacea A, Allsop J, Groves DW, Rizeq M, Revelo MP, Raghasan V. A failing heart: A new diagnosis of heart failure due to hydroxychloroquine-induced cardiomyopathy. J Gen Intern Med 2019; 34: 840.

[26] Gosche E, Odeyemi O, Altmann N. The MRI may lie biopsies confirmed hydroxychloroquine-induced cardiomyopathy without late gadolinium enhancement on mri in a patient with heart failure with preserved ejection fraction. J Am Coll Cardiol 2020; 75: 2333.

[27] Grzeskowiak M, Pu D. Hydroxychloroquine toxicity leading to cardiac arrest in a 23-year-old. J Gen Intern Med 2019; 34: S551-2.

[28] Hamilton A, Langerman F. Two for the price of one: Simultaneous hepatic and cardiac toxicity from hydroxychloroquine. J Hosp Med 2012; 7: S193.

[29] Hartmann M, Meek LL, van Houwelingen GK, et al. Acute left ventricular failure in a patient with hydroxychloroquine-induced cardiomyopathy. Neth Heart J 2011; 19(11): 482-5.

[30] Hawkins AM, Jesuthasan LSB, Vardesh DL. Case of severe acute lupus myocarditis and multiple-organ failure. BMJ Case Reports 2018; 2018.

[31] Imran TF, Laklouk I, Eberhardt R, Asery E, Pinmental D. The issue is the cause: A rare pharmacologic cause of potentially fatal cardiomyopathy. J Am Coll Cardiol 2020; 75: 2564.

[32] Jordan P, Brookes JG, Nikolic G, Le Couteur DG. Hydroxychloroquine overdose: toxicoekinetics and management. J Toxicol Clin Toxicol 2011; 49(10): 1047-51.

[33] Joyce E, Fabre A, Mahon N. Hydroxychloroquine cardiotoxicity presenting as a rapidly evolving biventricular cardiomyopathy: key diagnostic features and literature review. Eur Heart J Acute Cardiovasc Care 2013; 2(1): 77-83.

[34] Kandan SR, Saha S. Severe primary hypothyroidism presenting with tordas de pointes. BMJ Case Rep 2012; 2012; bcr1220115306.

[35] Keating RJ, Bhatta S, Amin S, Williams A, Sinak LJ, Edwards WD. Hydroxychloroquine-induced cardiotoxicity in a 39-year-old woman with systemic lupus erythematosus and systolic dysfunction. J Am Soc Echocardiogr 2005; 18(9): 981.

[36] Lau E, Sakhuja R, Januzzi J. Lost in translation: New cardiomyopathy in a 49-year-old spanish-speaking man with systemic lupus erythematosus and lungs nephritis. Circulation 2017; 136.

[37] Ling Ngan Wong A, Tsu Fung Cheung I, Graham CA. Hydroxychloroquine overdose: Case report and recommendations for management. Eur J Emerg Med 2006; 13(1): 16-8.

[38] Malchair P, Labori M, Rubio-Rivas M, Salazar-Mendiguchia J, Baixeras N, Corbella X. Hydroxychloroquine myocardial toxicity in a patient with systemic lupus erythematosus. Eur J Case Rep Intern Med 2015; 2(3)

[39] Manohar VA, Modet KG, Edwards WD, Klarich K. Restrictive cardiomyopathy secondary to hydroxychloroquine therapy. J Rheumatol 2009; 36(2): 440-1.

[40] Marquardt K, Albertson TE. Treatment of hydroxychloroquine overdose. Am J Emerg Med 2001; 19(5): 420-4.

[41] Mongan ND, Patel SV, Dvorkina O. Suspected hydroxychloroquine-associated QT-interval prolongation in a patient with systemic lupus erythematosus. J Clin Rheumatol 2013; 19(5): 286-8.

[42] Morgan ND, Patel SV, Dvorkina O. Suspected hydroxychloroquine-associated QT-interval prolongation in a patient with systemic lupus erythematosus. J Clin Rheumatol 2013; 19(5): 286-8.

[43] Muthukrishnan P, Roukoz G, Hafertan J, Collin-A-Dams M. Hydroxychloroquine-induced cardiomyopathy: a case report. Curr Heart Fail 2011; 4(2): e7-8.

[44] Nandagudi A, Jury EC, Alonzi D, Butters TD, Hughes S, Isenberg DA. Heart failure in a woman with SLE, anti-phospholipid syndrome and Fabry’s disease. Lupus 2013; 22(10): 1070-6.

[45] Nandagudi A, Jury EC, Alonzi D, Butters TD, Hughes S, Isenberg DA. Heart failure in a woman with SLE, anti-phospholipid syndrome and Fabry’s disease. Lupus 2013; 22(10): 1070-6.

[46] Nandagudi A, Jury EC, Alonzi D, Butters TD, Hughes S, Isenberg DA. Heart failure in a woman with SLE, anti-phospholipid syndrome and Fabry’s disease. Lupus 2013; 22(10): 1070-6.

[47] Nandagudi A, Jury EC, Alonzi D, Butters TD, Hughes S, Isenberg DA. Heart failure in a woman with SLE, anti-phospholipid syndrome and Fabry’s disease. Lupus 2013; 22(10): 1070-6.

[48] Nandagudi A, Jury EC, Alonzi D, Butters TD, Hughes S, Isenberg DA. Heart failure in a woman with SLE, anti-phospholipid syndrome and Fabry’s disease. Lupus 2013; 22(10): 1070-6.

[49] Nandagudi A, Jury EC, Alonzi D, Butters TD, Hughes S, Isenberg DA. Heart failure in a woman with SLE, anti-phospholipid syndrome and Fabry’s disease. Lupus 2013; 22(10): 1070-6.

[50] Nguyen T, Reveley C. Intentional overdose in an adolescent with depression: Important considerations when prescribing for adolescents. J Paediatr Child Health 2019; 55(4): 472-6.

[51] Newton-Cheh C, Lin AE, Baggish AL, Wang H. Case records of the Massachusetts General Hospital. Case 11-2011. A 47-year-old man with systemic lupus erythematosus and heart failure. N Engl J Med 2011; 364(15): 1450-60.

[52] Newton-Cheh C, Lin AE, Baggish AL, Wang H. Case records of the Massachusetts General Hospital. Case 11-2011. A 47-year-old man with systemic lupus erythematosus and heart failure. N Engl J Med 2011; 364(15): 1450-60.

[53] Negoescu A, Thornback A, Wong E, Ostor AJ. Long QT and hydroxychloroquine; a poorly recognised problem in rheumatology patients. Arthritis Rheum 2013; 65: S872.

[54] Negoescu A, Thornback A, Wong E, Ostor AJ. Long QT and hydroxychloroquine; a poorly recognised problem in rheumatology patients. Arthritis Rheum 2013; 65: S872.

[55] Negoescu A, Thornback A, Wong E, Ostor AJ. Long QT and hydroxychloroquine; a poorly recognised problem in rheumatology patients. Arthritis Rheum 2013; 65: S872.

[56] Negoescu A, Thornback A, Wong E, Ostor AJ. Long QT and hydroxychloroquine; a poorly recognised problem in rheumatology patients. Arthritis Rheum 2013; 65: S872.
Reveille JD. Associated factors and impact of myocarditis in patients with SLE from LUMINA, a multiethnic US cohort (LV). [corrected]. Rheumatology (Oxford) 2008; 47(3): 362-7.  
http://dx.doi.org/10.1093/rheumatology/kem371 PMID: 18250089

García MA, Alarcón GS, Boggio G, et al. Primary cardiac disease in systemic lupus erythematosus patients: protective and risk factors - data from a multi-ethnic Latin American cohort. Rheumatology (Oxford) 2014; 53(8): 1431-8.  
http://dx.doi.org/10.1093/rheumatology/keu011 PMID: 24633413

Rees F, Doherty M, Grainge MJ, Lanyon P, Zhang W. The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review and epidemiological studies. Rheumatology (Oxford) 2017; 56(11): 1945-61.  
http://dx.doi.org/10.1093/rheumatology/kex260 PMID: 28968809

Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014; 73(7): 1316-22.  
http://dx.doi.org/10.1136/annrheumdis-2013-204627 PMID: 24550173

Leadbetter EA, Rifkin IR, Hohlbaum AM, Beaudette BC, Shlomchik MJ, Marshak-Rothstein A. Chromatin-IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. Nature 2002; 416(6881): 603-7.  
http://dx.doi.org/10.1038/416694a PMID: 11948342

Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov 2020; 6: 16.  
http://dx.doi.org/10.1038/s41421-020-0156-0 PMID: 32194981

Yao X, Ye F, Zhang M, et al. In vitro Antimalarial Activity and Prediction of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020; 71(15): 732-9.  
http://dx.doi.org/10.1093/cid/ciaa237 PMID: 32150618

Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020; 5(7): 802-10.  
http://dx.doi.org/10.1001/jamacardio.2020.0733 PMID: 3252591

Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020; 46(5): 846-8.  
http://dx.doi.org/10.1007/s00134-020-05991-x PMID: 32125452

Akhmerov A, Marbán E. COVID-19 and the Heart. Circ Res 2020; 126(10): 1443-55.  
http://dx.doi.org/10.1161/CIRCRESAHA.120.317055 PMID: 32252591

Risch HA. Early outpatient treatment of symptomatic, high-risk COVID-19 patients that should be ramped-up immediately as key to the pandemic crisis. Am J Epidemiol 2020; 189(11): 1218-26.  
http://dx.doi.org/10.1093/aje/kwa903 PMID: 32458969

Randomised evaluation of COVID-19 therapy. RECOVERY 2020. Available from: Clinicaltrials.gov

Watson J. On the behalf of 201 signatories. An open letter to the Lancet (Version 4) Zenodo 2020. http://dx.doi.org/10.105281/zenodo3862788

Raoul D. Early Diagnosis and Management of COVID-19 Patients: a real-life cohort study of 3,737 patients, Marseille, France. Mediterranee Infection 2020. COVID-IHU #15

WHO. “Solidarity” clinical trial for COVID-19 treatments. World Health Organization 2020.

The Lancet Editors. Expression of concern: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: A multinational registry analysis. Lancet 2020; 395(10240): e102.  
http://dx.doi.org/10.1016/S0140-6736(20)31290-3 PMID: 32504543

Network MTH COCPOV at a glance 2020. Available from: http://www.tropmedres.ac/covid-19/copecov

Lofgren SMM, Nicol MR, Bangdiwala AS, et al. Safety of hydroxychloroquine among outpatient clinical trial participants for COVID-19. Open Forum Infectious Diseases 2020; 7(11): ofaa500.  
http://dx.doi.org/10.1093/ofid/ofaa500

Kim I-C, Kim YJ, Kim HA, Han S. COVID-19-related myocarditis in a 21-year-old female patient. Eur Heart J 2020; 41(19):
Hydroxychloroquine and Cardiac Manifestations

Aghagoli G, Gallo Marin B, Soliman LB, Sellke FW. Cardiac involvement in COVID-19 patients: Risk factors, predictors, and complications: A review. J Card Surg 2020; 35(6): 1302-5. http://dx.doi.org/10.1111/jocs.14538 PMID: 32306491

Viner RM, Whittaker E. Kawasaki-like disease: emerging complication during the COVID-19 pandemic. Lancet 2020; 395(10239): 1741-3. http://dx.doi.org/10.1016/S0140-6736(20)31129-6 PMID: 32410759

Harahsheh AS, Dahdah N, Newburger JW, et al. Missed or delayed diagnosis of Kawasaki disease during the 2019 novel coronavirus disease (COVID-19) pandemic. J Pediatr 2020; 222: 261-2. http://dx.doi.org/10.1016/j.jpeds.2020.04.052 PMID: 32370951

Dabbagh MF, Aurora L, D’Souza P, Weinmann AJ, Bhargava P, Basir MB. Cardiac tamponade secondary to COVID-19. JACC Case Rep 2020; 2(9): 1326-30. http://dx.doi.org/10.1016/j.jaccas.2020.04.009 PMID: 32328588

Paul J-F, Charles P, Richaud C, Caussin C, Diakov C. Myocarditis revealing COVID-19 infection in a young patient. Eur Heart J Cardiovasc Imaging 2020; 21(7): 776. http://dx.doi.org/10.1093/eurheartj/ehaa288 PMID: 32282027

Ali-Ahmed F, Dalgaard F, Al-Khatib SM. Sudden cardiac death in patients with myocarditis: Evaluation, risk stratification, and management. Am Heart J 2020; 220: 29-40. http://dx.doi.org/10.1016/j.ahj.2019.08.007 PMID: 31765933

Prieto-Lobato A, Ramos-Martínez R, Vallejo-Calcerrada N, Corbi-Pascual M, Córdoba-Soriano JG. A case series of stent thrombosis during the COVID-19 pandemic. JACC Case Rep 2020; 2(9): 1291-6. http://dx.doi.org/10.1016/j.jaccas.2020.05.024 PMID: 32835270

Mahmoud-Elsayed HMM, Bradlow WE, William ME. Echocardiographic findings in COVID-19 pneumonia. Can J Cardiol 2020; 36(8): 1203-7. http://dx.doi.org/10.1016/j.cjca.2020.05.030 PMID: 32474111

Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020; 5(11): 1265-73. http://dx.doi.org/10.1001/jamacardio.2020.3557 PMID: 32730619