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THERAPIES

HEADING: COVID-19

"Off-label" use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: a survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers

Cardiac ADR with hydroxychloroquine, azithromycin, lopinavir and chloroquine in COVID-19.

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Summary

Introduction.- COVID-19 is an unprecedented challenge for physicians and scientists. Several publicized drugs are being used with not much evidence of their efficacy such as hydroxychloroquine, azithromycin or lopinavir-ritonavir. Yet, the cardiac safety of these drugs in COVID-19 deserves scrutiny as they are known to foster cardiac adverse ADRs, notably QTc interval prolongation on the electrocardiogram and its arrhythmogenic consequences. *Methods.*- Since March 27th, 2020, the French Pharmacovigilance Network directed all cardiac adverse drug reactions associated with "off-label" use of hydroxychloroquine, azithromycin and lopinavir-ritonavir in COVID-19 to the Nice Regional Center of Pharmacovigilance. Each Regional Center of Pharmacovigilance first assessed causality of drugs. We performed a specific analysis of these cardiac adverse drug reactions amidst an array of risk factors, reassessed the electrocardiograms and estimated their incidence in

coronavirus-disease-2019. *Results*.- In one month, 120 reports of cardiac adverse drug reactions have been notified, 102 of which associated with hydroxychloroquine alone (85%), or associated with azithromycin (60%). Their estimated incidence is 0.77% to 1.54% of all patients, notwithstanding strong underreporting. Lopinavir-ritonavir came third with 17 reports (14%) and chloroquine fourth with 3 reports (2.5%). There were 8 sudden, unexplained or aborted deaths (7%), 8 ventricular arrhythmias (7 %), 90 reports of prolonged QTc (75%) most of them "serious" (64%), 48 of which proved ≥ 500 ms, 20 reports of severe conduction disorders (17%) and 5 reports of other cardiac causes (4%). Six reports derived from automedication. *Discussion and conclusion*- "Off-label" use of treatments in COVID-19 increases the risk of cardiac ADRs, some of them avoidable. Even if these drugs are perceived as familiar, they are used in patients with added risk factors caused by infection. Precautions should be taken to mitigate the risk, even if they will be proven efficacious.

Abbreviations

ADRs: adverse drug reactions

Keywords: Hydroxychloroquine; Azithromycin; Lopinavir; Cardiac adverse effects; QTc prolongation; Arrhythmia; COVID-19

ANSM: French Drug Agency (*Agence nationale de sécurité des medicaments et des produits de santé*)

AV: atrio-ventricular

AZI: azithromycin

COVID-19: coronavirus disease 2019

CQ: chloroquine

EAD: early after-depolarizations

ECGs: electrocardiograms

EMA: European Medicines Agency

FDA: Food and Drug Administration

FPVD: French Pharmacovigilance database

HCQ: hydroxychloroquine

hERG: human ether-a-go-go related gene

IQR: interquartile range

LQTS: long QT syndrome

LOPI: lopinavir-ritonavir

MedDRA: medical dictionary for regulatory activities

RCPV: Regional Center of Pharmacovigilance

SARS-CoV-2: serious acute respiratory syndrome coronavirus 2

SD: standard deviation

SOC: system organ class

TdP: torsades de pointes

Introduction

As of April 27th, 2020, coronavirus disease 2019 (COVID-19) has been held responsible for 207,885 confirmed deaths worldwide since December 2019 [1] and serious acute respiratory syndrome

coronavirus 2 (SARS-CoV-2) has become a tremendous challenge to the world. Indeed, it rapidly disrupted economies and raised profound societal issues like few other diseases before [2]. Hence the urge for relevant treatments to alleviate COVID-19 symptoms, prevent its worsening and improve its prognosis before any efficient vaccine becomes available. Clinical trials have been launched with antiviral and immunomodulating therapies to evaluate their efficacy and their safety to fight SARS-CoV-2 infection or at least attenuate its pulmonary complications [3, 4].

Based on their experimental properties, chloroquine (CQ) and especially its analog hydroxychloroquine (HCQ) have been suggested [5], often associated with the macrolide antibiotic azithromycin (AZI) for alleged synergistic properties [6]. The anti-HIV protease inhibitor lopinavir, with ritonavir as a booster (LOPI), has also been used in this perspective. Clinical trials and observational studies of all kind have been implemented with these four drugs worldwide [7-10]. Despite inconclusive results about their clinical efficacy in COVID-19, the anxiety about the lack of treatment led patients and some practitioners alike to pharmacies' mongering to a wide extent in order to obtain these treatments, and HCQ in particular. The phenomenon went so far as causing stock-out and disrupting its deliverance to chronic rheumatologic patients, which led health authorities to restrict the delivery of HCQ and LOPI in pharmacies only after instauration in hospitals, or prescription by a specially authorized and listed physician [11].

These four drugs have so far performed poorly, and no robust or convincing data has yet been published about their efficacy in COVID-19. Nevertheless, their safety, related to their propensity to prolong the QT interval of the electrocardiogram, remains challenging [12]. The French Pharmacovigilance system has been among the first to issue an international warning on this topic and to suggest safety measures in order to mitigate the risk [13, 14], soon to be relayed by the European Medicines Agency (EMA) [15] and the Food and Drug Administration (FDA) [16]. A pharmacovigilance national survey has been ordered by French health authorities with a special focus on cardiac safety. Indeed, these drugs are associated with a risk of QT prolongation and "serious" cardiac arrhythmias possibly leading to cardiac arrest and sudden death [17]. In France, each Regional Center of Pharmacovigilance (RCPV), nested within a department of Medical Pharmacology, gathers notifications from a distinct area of France. All RCPV constitute the French Pharmacovigilance network which is unique in Europe to determine how expected –and unexpected- risks associated with drug treatments translate in everyday practice. In return, they provide unique information to health professionals about optimal drug use.

In this study, we aimed to characterize all reports of cardiac adverse drug reactions (ADRs) associated with HCQ, CQ, AZI or LOPI prescribed for COVID-19, as notified in France between March 27th and April 27th to any of the 31 RCPV. We also aimed to characterize the type of ADR by drug, to shed some light on the incidence of spontaneous cardiac reporting of ADRs associated with HCQ alone given its predominance, whether associated with AZI or not.

Methods

The French Pharmacovigilance database (FPVD) [18] centralizes all spontaneous reports of ADR [19], respecting anonymity of both patients and notifiers, in order to accrue the European database EudraVigilance. Such reporting of ADR is deemed mandatory in France for every health professional. The RCPV of Nice-Alpes-Côte d'Azur (RCPV of Nice) was appointed by the French Drug Agency (*Agence nationale de sécurité des medicaments et des produits de santé* [ANSM]) on March 27th, 2020, to investigate all reports of cardiotoxicity reported to any of the 31 RCPVs, associated with HCQ, CQ, AZI, or LOPI used empirically against COVID-19.

Reports were analyzed for causality assessment, validated and a score was associated with each case [20]. Reports were excluded from analysis by each RCPV if chronological and semiological data ruled out the role of the designated drug in the notified effect (i.e. the effect was preexisting before the drug administration). After a first expertise by the RCPV receiver, all notified reports of cardiac ADRs associated with any of the drugs involved were sent consecutively to the RCPV of Nice to be included in this study, since the scope of expertise of that RCPV is precisely drug-induced long QT syndrome.

To assess the completeness of the case-series, an extraction of the FPVD was also done backwards to January 1st, 2020. This extraction involved a research by the treatment indication "coronavirus infection" or "COVID-19" and a research by drugs HCQ, CQ, AZI, LOPI. Reports related to another indication than COVID-19 for these drugs were excluded.

Each transmitted ADR case was reviewed by pharmacovigilants first, to assess for missing data required for expertise, in particular the electrocardiograms (ECGs) before, during and after treatment when necessary. Data on clinical symptoms, patient' characteristics such as sex, age and comorbidities were gathered, as well as drug titrations, prescription dates, ADR time to onset and outcomes, concomitant drugs (and especially those known to induce potential QTc prolongation), kalemia, magnesemia, renal function and any other reported risk factors. Potential automedication and/or overdosage were noted as well. Missing data were requested by pharmacovigilants to the reporting initial health professional.

All ECGs were examined by two residents in clinical pharmacology specializing in pharmacovigilance under the tutelage of a trained cardiologist in the field. All digitized ECGs parameters were measured with help of a digital caliper (Iconico®, CardioCalipers®, www.iconico.com), by classical standard methods [21]. QT intervals were calculated on 3 consecutive complexes, in D2 lead if possible (most of the times) and corrected according to Bazett and Fridericia formulae. ECGs and measurements were triple checked by the Department of Cardiology of the University Hospital of Nice in reports of discrepancy, especially of the corrected QT interval (QTc) value, i.e. in case of the presence of a pacemaker, a complete bundle branch block, or an atrio-ventricular (AV) block. QTc interval durations beyond 450 ms for men and 460 ms for women were deemed abnormal [22]. A QTc ≥500 ms or prolongation thereof (delta QTc) from "baseline" ≥60 ms, after treatment introduction, were deemed "serious". Reports were classified in sudden or unexplained deaths, cardiac arrests, ventricular arrhythmias (including torsades de pointes, syncope and symptoms reflecting such rhythm problems), conduction disorders (associated or not with prolonged QTc), and abnormal/prolonged QTc. ADRs not matching the abovementioned were classified as "other cardiac ADRs". Categories may occur more than once for patient with conduction disorders.

Because of uncertainties in exhaustive reporting or prescription, we aimed to roughly evaluate the incidence of cardiac ADRs associated with HCQ only, because of its frequent use. This drug is marketed in boxes of two blisters containing each 15 tablets impossible to isolate. Standard operating procedures of hospital pharmacies imply that one blister minimum (15 tablets) and 2 blisters (30 tablets) maximum are to be delivered for a complete treatment against COVID-19 infection taking into consideration the various therapeutic regimens proposed. The number of patients treated for COVID-19 in hospitals in March 2020 (outside of a clinical trial) was estimated based on national HCQ consumption data and these considerations.

A query of the FPVD was also performed for reports involving HCQ and the system organ class (SOC) "Cardiac disorders" (according to medical dictionary for regulatory activities [MedDRA] terms) that have been reported since 1985 up to December 2019 (all reports notified to any RCPV since 1985 are registered in that base) [23].

Descriptive statistics are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR). Incidence was calculated with Fisher's exact method (Clopper-Pearson) and results given as point estimates or 95% confidence intervals.

Results

Since March 27th, 2020, 120 cardiac ADR reports of patients mentioning a total of 131 adverse events were notified to the French pharmacovigilance system pertaining to possible unwanted cardiac effects of drugs tested against COVID-19 (Fig. 1A). The vast majority of these reports (91.7%, 110 out of 120) had been considered as "serious" by the original notifiers. The mean age of the patients was 64.3 ± 13.4 [median 65]. Over two thirds were male (66.7%; 92 of 120 patients) [Table 1]. The large majority of ADRs 116/120 (96.7%) occurred in hospital settings. Automedication was noticed in 6 reports (5.0%).

Causality assessment was deemed "likely", "very likely" (11) or "plausible" (66) in two-third of the reports (64%).

Drugs and adverse effects

Out of 120 reports, 103 (85.8%) were associated with the use of HCQ, with about half of which co-treated with AZI. Total AZI reports were 64; LOPI reports were 17 (14.2%) and CQ 2 (1.6%). The median time to onset of ADRs was 3 days (IQR 2-5).

Among the 120 reports, there were 8 sudden or aborted deaths (6.1%), among which 4 (3.0%) of sudden or unexplained deaths, and 4 cardiac arrests (3.3%). There were 8 (6.1 %) ventricular arrhythmias, 90 (68,7%) prolonged QTc, 20 (15,3%) severe conduction disorders and 5 reports (3,8%) qualified as of other cardiac troubles (1 heart failure, 2 supraventricular arrhythmias, 1 chest pain and 1 case of suffocating and palpitation sensations in an asthmatic patient). In 11 reports, both QTc prolongation and conduction disorders were coexisting. Fifty-eight reports (64.4%) of prolonged QTc were deemed "serious", 48 of which had a QTc value ≥500 ms (Fig. 1A and 1B).

In 37 reports (30.8%), patients also received other drugs susceptible to prolong the QTc, such as escitalopram, spiramycin and levofloxacin.

HCQ-associated cardiac adverse drug reactions

Out of the 103 reports reported with HCQ, AZI was associated with 60 of these and LOPI with one. HCQ causality assessment was deemed as "plausible" (66) or "likely"/"very likely" (11) in 76% of the reports. The reports associated with HCQ represented 100% of the reports of sudden, unexplained (4) or aborted deaths (4) and 7% of the 120 reports of ADRs, 75% of the ventricular arrhythmias (6 out of 8; 5% of total reports). There were 67 isolated QTc prolongations representing 86% of this group (56% of total reports). Seventeen notifications reported conduction blocks (85%; 14% of total reports), 7 of which being isolated reports of conduction block (78%; 6% of total reports). Four notifications associated with HCQ (3.3% of total) reported other various cardiac troubles.

Estimated incidence of HCQ related adverse drug reactions reports

The cardiac ADRs reports involving HCQ reported between 1985 up to December 2019 (before the COVID-19 pandemic) add up to 92 reports of cardiac ADRs. The consumption of hydroxychloroquine by French hospitals before the COVID-19 pandemic had been steady over the years for internal medicine. It sharply increased in March 2020. Considering that ~150,000 extra tablets were used to treat COVID-19 infections in hospitals, we estimated this to correspond to 5,000 to 10,000 patients. Since 77 reports were associated with HCQ alone, initiated in March 2020, the estimated hospital incidence is of 0.77 % [0.61-0.96] in case of 10,000 patients to 1.54 % [1.22-1.92] in case of 5,000 patients, notwithstanding underreporting that is common in pharmacovigilance. Corrected by underreporting, such occurrence qualifies them as "frequent" ADRs.

Double check at the RCPV of Nice

After examining the 120 notifications, about two thirds (78 out of 120) had enough supporting documents (ECGs) to confirm the reports and the other 42 were informative enough to be taken into consideration. The close analysis of the 78 reports with complete ECGs pointed out 59 declarations of prolonged QTc. ECG measurements in our department yielded some discrepancies: 12 reports proved normal (absolute value as well as delta QTc), whereas 15 patients whose QTc was notified as normal at baseline QTc were prolonged indeed, putting them at higher risk of rhythm disorders.

Discussion

We provide the first comprehensive survey of the cardiac ADRs associated with HCQ, CQ, AZI or LOPI prescribed for COVID-19 that have been gathered by the French Pharmacovigilance network over one month. Our survey reports 120 reports of cardiac ADRs, which is way more frequent than what had been notified over more than three decades preceding the COVID-19 pandemic in France. For HCQ alone, it represents hundred folds the rate of cardiac notifications, reflecting the recent craze for that drug. The resulting surge of its prescriptions yields over a month a raw incidence of "serious" cardiac ADRs in the range of 0.8 to 2.5%, notwithstanding the strong pharmacovigilance underreporting [24]. Even if the controlled environment of hospital use as well as repeated warnings addressed to physicians since March favors ADR reporting, such notifications are perceived by doctors as cumbersome in COVID-19 intensive care units because health professionals are overwhelmed by their task and most paper files, including ECGs, are also confined in the patients' rooms. Furthermore because of a "regulatory oddity", ADRs occurring in clinical trials are not streamlined by RCPVs, whereas HCQ, AZI, and LOPI are largely used within clinical trials. The incidence of cardiac ADRs with HCQ, from ~ 1 to 2% is in line with what has been recently published

[12], taking note of strong underreporting. Therefore, these 120 hospital reports likely represent "the tip of the iceberg" of cardiac ADRs, hence those linked to prescriptions by city doctors and other heterodox situations (internet, misuse…).

Over 80% of the reports are associated with HCQ, most of the time associated with AZI. This may result from to the wide media diffusion of a possible efficacy of these drugs, even though no conclusive relevant data exists yet [25]. Though, cardiotoxicity of HCQ and CQ is known as they can be considered pharmacologically as "multi-channel blockers". Both drugs inhibit sodium and calcium currents, and HCQ, at least, also blocks the pace-maker current I_f [26]. All four drugs block cardiac voltage-dependent potassium channels, hence their association with QT prolongation which figures in the respective summary of product characteristics of HCQ, CQ, LOPI and AZI. Cardiac action potential is the result of finely tuned voltage-dependent ionic channels, allowing cations to circulate sequentially inward and outward cardiomyocytes. The delayed rectifier current (I_K) and particularly its rapid component I_{Kr} plays a crucial role in outward K^+ conductance leading to repolarization (Fig. 2) [27,28]. By blocking potassium currents, these drugs prolong the cardiac repolarization, thus the duration of the QT interval (Fig. 3A). The latter, as measured on the ECG, reflects the ventricular repolarization by summing all ventricular action potentials. Blockade of potassium channels disrupts the electrical homogeneity required to a proper contraction of the heart and yields therefore an arrhythmogenic substrate. This phenomenon facilitates ventricular arrhythmias which may comprise ventricular extrasystoles (Fig. 3B), ventricular tachycardia and the pathognomonic torsades de pointes (TdP) phenomenon (Fig. 3C). TdP is a life-threatening polymorphic ventricular tachycardia typically triggered by the occurrence of early after-depolarizations (EAD) in a setting of an inhomogeneous repolarization [29].

Patients treated with HCQ associated with AZI bear a significant risk of increased QTc [12], over 10% of whom have a "serious" QTc prolongation (>500 ms). A Brazilian study comparing two doses of HCQ associated with AZI, led to a premature discontinuation of the high dose arm because of cardiac safety concerns [30].

In addition to its ventricular arrhythmogenic effects, HCQ also concurs to bradycardias and AV blocks owing to its inhibiting effect of the hyperpolarization-activated funny current (I_f), which plays a crucial role in the action potential of sinoatrial pacemaker cells [26]. HCQ-induced conduction blocks also occurs because of sodium and calcium channels block [17, 31].

Protease inhibitors such as LOPI are responsible (as a class) for QT prolongation and AV-blocks as well [32]. As HCQ and CQ, they block the ether-a-go-go related gene (hERG) potassium

channel which recapitulates the key potassium current I_{Kr} [33]. If the clinical impact of this effect has been debated in the past [34] our study in novel setting of prescription underlines such a risk again.

Macrolides product labels warn against the risk of QTc prolongation [35-37] and a small absolute increase in cardiovascular deaths has been described in patients with cardiac comorbidities [38]. Azithromycin has been said to block I_{Kr} to a lesser level than erythromycin or clarithromycin, but all three prolong experimentally and clinically the QT interval.

Additional risk factors facilitating cardiac arrhythmias may also play a role in COVID-19. Whether SARS-CoV-2 related cardiomyopathy, co-prescriptions of drugs prolonging the QT interval or inducing bradycardia in patients, they further reduce an ailing repolarization reserve [39, 40]. Renal-induced hypokalemia is frequent in SARS-CoV-2 infected patients [41], and increased incidence of hypomagnesemia should be feared as well through COVID-19-induced diarrhea.

It has been previously stated that a mere 40% of non-cardiologists correctly measure the QTc [42], which may be of concern for "avoidability" of ADRs. Automated interpretation of ECGs should remain complementary to the physician's over-read due to its inherent limitations [43]. Indeed, we observed a significant discordance not only between computer-estimated (machine read) and clinician-estimated QTcs, but also between the clinicians' and our measurements. This led to significant clinical consequences and is illustrated in our study as HCQ was given to a patient with a probable congenital long QT syndrome (LQTS) whose baseline QTc was >500 ms. He suffered from ventricular arrhythmia soon after the second intake of 200 mg oral HCQ and recovered fortunately after cardioversion.

EMA and FDA have restricted the use of HCQ in COVID-19 to solely clinical trials. QTc prolongation and subsequent arrhythmogenic risk is the most worrisome ADR for these drugs in COVID-19 [44]. ECG monitoring is pivotal to mitigate this risk and not only to avoid contra-indications. ECG should be checked 3 to 4 hours after drug intake, and twice a week at least to detect QTc prolongations [14, 45]. Concomitant treatment with other drugs known to increase QTc and/or induce ventricular arrhythmias, such as seen in our study, should be avoided whenever possible and electrolyte disturbances corrected [14].

Like in most pharmacovigilance studies, confounders are present in a significant part of the reports. COVID-19 targets several organs besides the respiratory system, including the heart. Notwithstanding the drugs of this study, underlying myocarditis could have facilitated the emergence of spontaneous arrhythmias and electrolyte disturbances could have precipitated them as well. Subtle

channelopathies might have led to individual susceptibility for some rare patients also. All these elements are limits of our study, as in any pharmacovigilance study.

Conclusions

As of today, no specific drug treatment has proved superior to placebo in treating COVID-19. Yet, HCQ, CQ, AZI and LOPI are frequently used in COVID-19 with its array of inner risk factors. They bear a significant risk of cardiac ADRs [46]. Notwithstanding the need to foster investigation on putative treatments, the safety profile of drugs should not be overlooked. Indeed, spontaneous recovery without hospitalization occurs in 97.4 % of COVID-19 patients [47]. In the uncertain times we are living, it remains paramount to base one's prescription on a clear and positive benefit-risk balance of any chosen drug.

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Disclosures of interest

Authors have no competing interest to declare.

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Table 1. Patients' baseline characteristics

Variable	Value
Male, *n* (%)	92 (76.7)
Median age at notification, year	65 (56;74)
History of ischemic cardiopathy, *n* (%)	18 (15.0)
Medical context, *n* (%)	
Intensive care	55 (45.8)
Hospitalization	61 (50.8)
Ambulatory	4 (3.3)
Automedication, *n* (%)	6 (5)
Other drugs increasing QTc*	27 (22.7)
Mean kalemia, mmol/L	3.9 ± 0.5
<3.5, *n* (%)	15 (20.0)
≥3.5 and <4, *n* (%)	24 (32.0)
≥4 and <5, *n* (%)	35 (46.7)
≥5, *n* (%)	0
Mean glomerular filtration rate, mL/min/1.73m^2	75.1 ± 38.3
Dialysis, *n* (%)	2 (2.5)
<30, *n* (%)	9 (11.4)
≥30 and <60, *n* (%)	17 (21.5)
≥60, *n* (%), *n* (%)	51 (64.6)

Data are shown as mean ± SD, median (interquartile range) or n (%).

* Apart from drugs surveyed against COVID-19 in this study

Figures 1. Spontaneous notifications' profile.

Figure 1A. Cumulative notifications of cardiac adverse drug reactions (ADRs).

Cardiac ADRs accrued from March 27th, 2020, beginning of the survey, till they reached 120 on April 27th, 2020. Insert: ADRs by type.

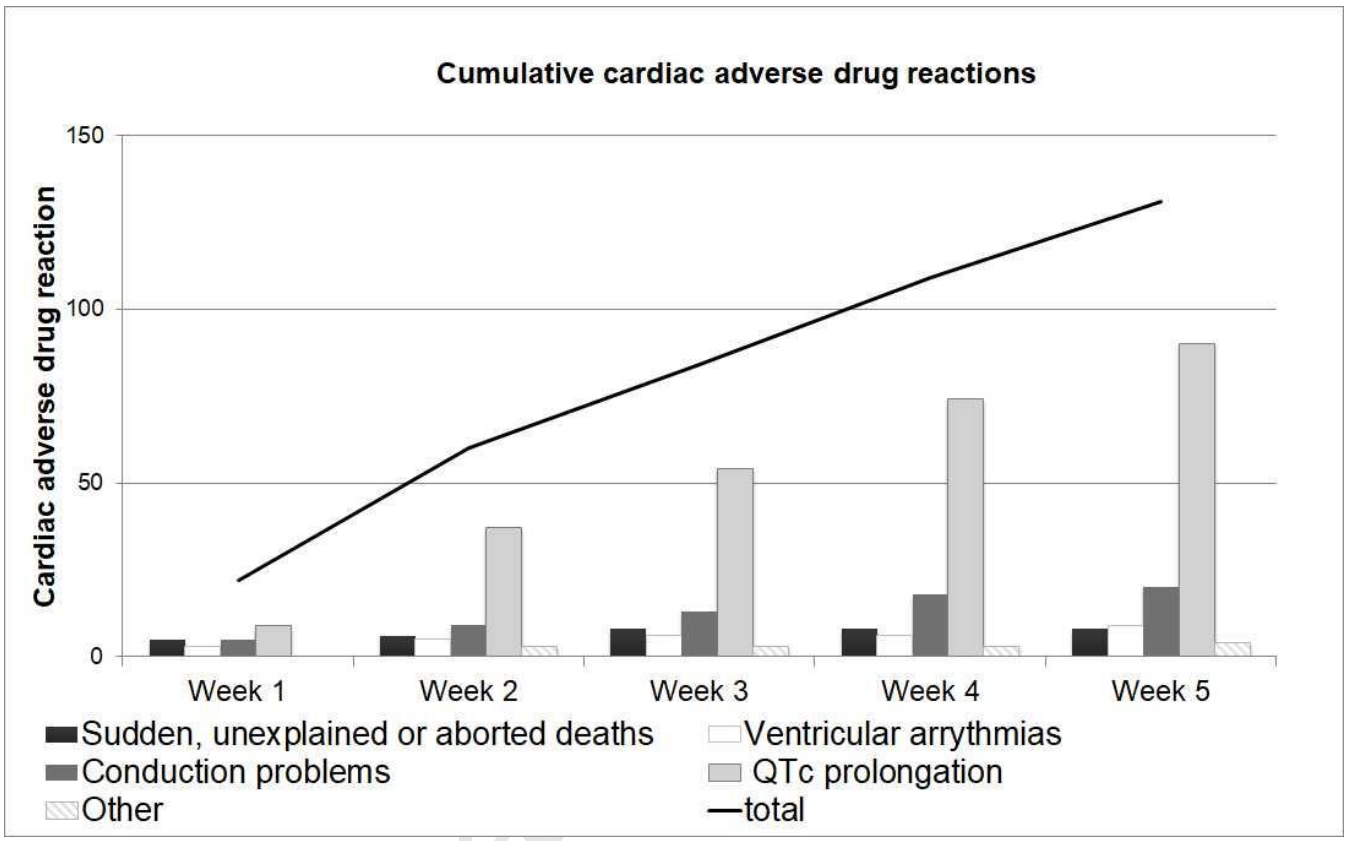


Figure 1B. Cardiotoxicity profile.

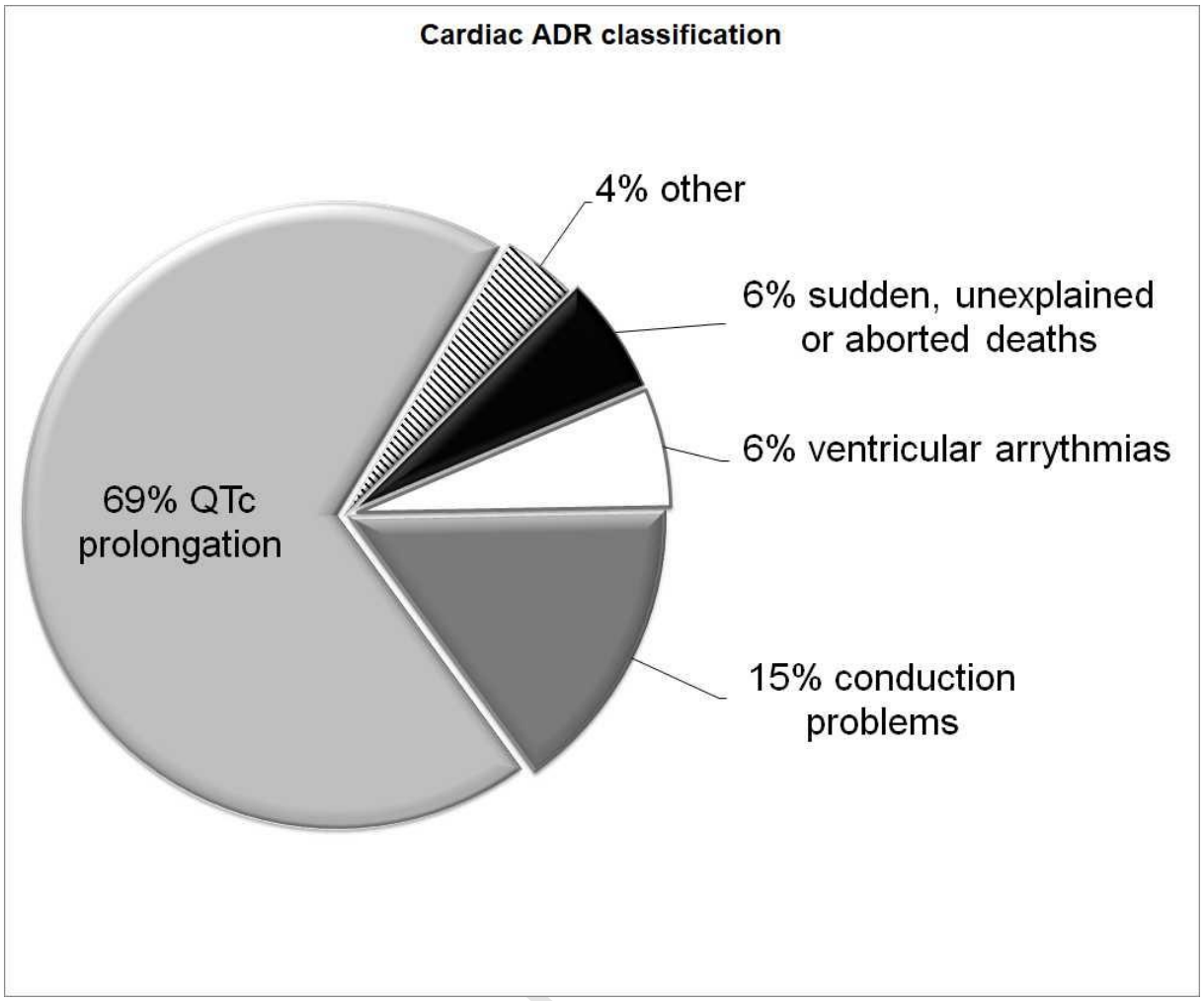
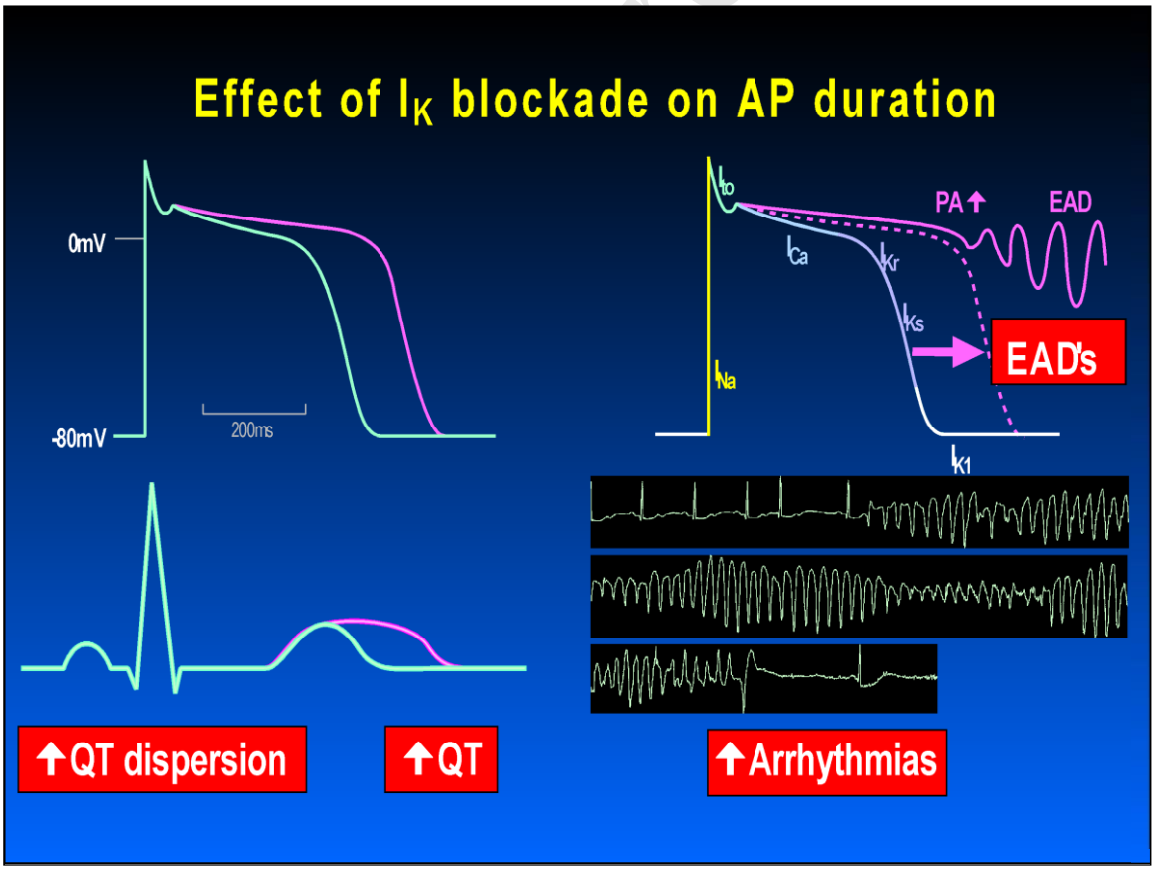


Figure 2. Mechanisms of QT prolongation and TdP

Prolongation of the QT interval on the electrocardiogram results from the prolongation of the action potential duration (APD) of ventricular myocytes, brought in this case by hydroxychloroquine (HCQ), chloroquine (CQ), azithromycin (AZI) or lopinavir-ritonavir (LOPI), hence by their association. They all reduce outward potassium currents during phase 3 of the action potential. Such reduction of net outward current augments the APD which translates in an increased QT interval on the ECG. It also facilitates the development of early afterdepolarizations (EADs) associated with calcium influx, because of the delay in repolarisation and a membrane still relatively electropositive. These EADs can lead to extrasystoles which may trigger complex ventricular reentries such as Torsades de Pointes. The prolonged QT reflects the underlying arrhythmogenic substrate resulting from an increased dispersion of the repolarization. The development of early afterdepolarizations and TdP usually occurs with drugs that block I_{Kr}, the rapid component of the potassium current I_K A factor of particular importance for the genesis of TdP is a particular predisposition of individual patients aggravated by the presence of risk factors (hypokalemia, hypomagnesemia, feminine gender, bradycardia, multiple drugs prolonging the QT…) which reduce the repolarization reserve. [27]



Figures 3. ECG abnormalities associated with hydroxychloroquine (HCQ), azithromycin (AZI) or lopinavir-ritonavir (LOPI) in COVID-19

Figure 3A. Prolonged QTc interval: (lead II) of a 70 y.o. man started on HCQ and AZI for COVID-19. Four days after introduction, the patient had a prolonged QTc (491 ms) which normalized 2 days after treatment discontinuation.

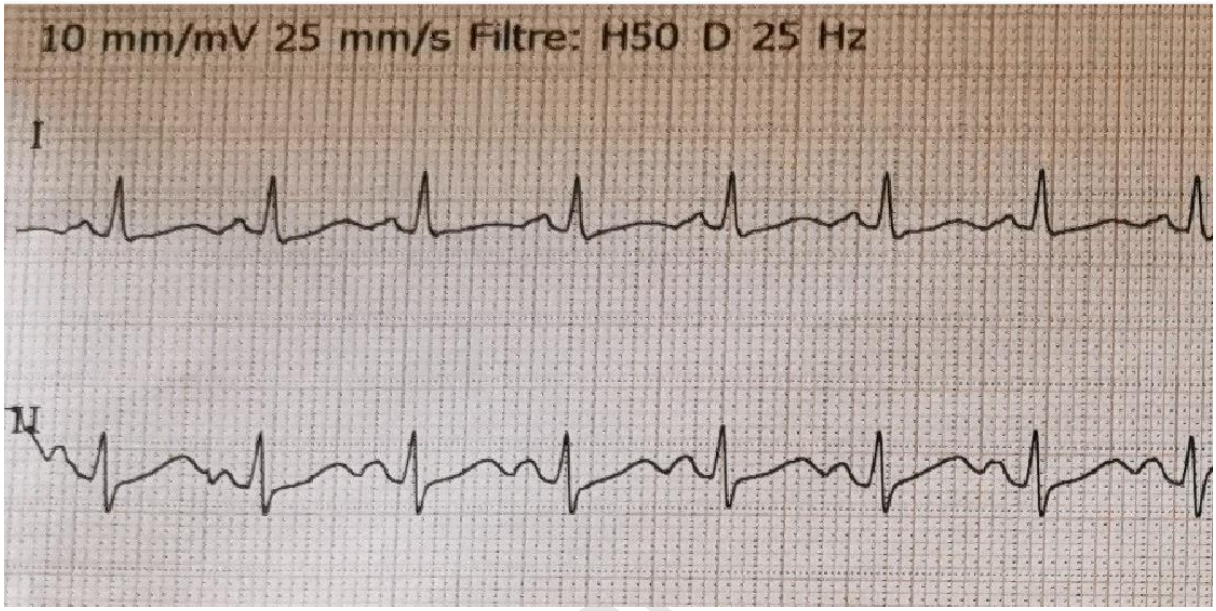


Figure 3B. Bigeminy in an 81 y.o. hypertensive man treated with LOPI 400/100 for COVID-19 in a setting of severe bradycardia. Sudden and "serious" conduction AV conduction and rhythm problems (bigeminy) occurring on the 5th day of treatment. Outcome was favorable after treatment withdrawal.

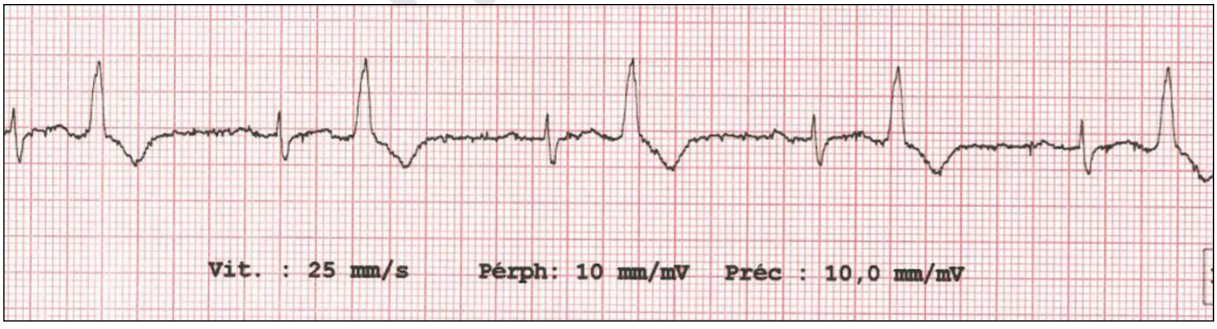


Figure 3C. Torsades de pointes occurring 7 hours after the second and last administration of 200 mg oral HCQ in a 43 y.o. man hospitalized for COVID-19 with a previously undiagnosed long-QT syndrome (baseline Bazett-corrected QT measured at 500 ms). Bazett-corrected QT was 667 ms minutes before the arrhythmia, which required cardioversion. Outcome was favorable after treatment withdrawal.