Review

Hydroxychloroquine and the cardiovascular system: lights and shadows

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ABSTRACT

Objective. *To review the dual impact of hydroxychloroquine (HCQ) on the cardiovascular system, focusing on both its cardioprotective effects and potential cardiotoxicity in patients with autoimmune diseases.*

Methods. *A structured narrative review of the literature was conducted using PubMed/MEDLINE up to March 2025. Relevant studies including clinical trials, observational studies, mechanistic research, and reviews were selected to summarise the molecular mechanisms and cardiovascular effects of HCQ.*

Results. *HCQ exerts multiple beneficial cardiovascular effects through anti-inflammatory, antithrombotic, metabolic, and endothelial-protective mechanisms. It reduces cytokine production, oxidative stress, platelet activation, and improves lipid and glucose profiles, contributing to decreased cardiovascular risk in patients with systemic autoimmune diseases. However, HCQ may also induce cardiotoxic effects, particularly with long-term use or high cumulative doses. These include QT interval prolongation, conduction abnormalities, and a rare but severe form of cardiomyopathy related to lysosomal dysfunction and impaired autophagy. The risk is higher in patients with advanced age, renal dysfunction, pre-existing heart disease, or concomitant use of QT-prolonging drugs.*

Conclusion. *HCQ has a complex and context-dependent cardiovascular profile. While generally cardioprotective at standard doses, it may lead to rare but serious cardiac adverse effects in high-risk patients. A risk-adapted monitoring strategy is essential to optimise its benefit-risk balance in clinical practice.*

Introduction

Antimalarial drugs are a class of synthetic compounds originally developed for the prevention and treatment of malaria. Chloroquine (CQ) was first synthesised in the late nineteenth century, and hydroxychloroquine (HCQ), a less toxic derivative, was subsequently introduced to improve tolerability and long-term safety (1). Since the mid-twentieth century, antimalarials have progressively been repurposed for the treatment of immune-mediated and inflammatory diseases, particularly in the field of rheumatology (1, 2).

Beyond their antimalarial properties, these agents exert a wide range of biological effects, which has led to their investigation across multiple therapeutic areas, including autoimmune diseases, infectious diseases, metabolic disorders, and oncology (2, 3). In rheumatology, HCQ has become a cornerstone therapy for systemic lupus erythematosus (SLE) and is widely used in rheumatoid arthritis (RA), undifferentiated and mixed connective tissue diseases, dermatomyositis, Sjögren's disease, and antiphospholipid syndrome (APS) (4-6).

According to recent international recommendations, HCQ should be prescribed to almost all patients with SLE, unless contraindicated, due to its proven efficacy in controlling disease activity, preventing flares, reducing organ damage accrual, and improving long-term survival (4).

Importantly, patients with systemic autoimmune diseases such as SLE and RA exhibit an increased cardiovascular risk, driven by chronic systemic inflammation, endothelial dysfunction, oxidative stress, and prothrombotic mechanisms. Beyond traditional risk factors, immune-mediated vascular injury and persistent type I interferon activation contribute to accelerated atherosclerosis and higher rates of myocardial infarction, stroke, and heart failure in these populations. The increased cardiovascular burden in systemic lupus erythematosus has been extensively

described in recent comprehensive reviews (7) and supported by real-world clinical data (8).

Given its anti-inflammatory, antithrombotic, antioxidant, and metabolic properties, and the association with reduced damage accrual (9), it has been hypothesised that HCQ exerts a protective role on the cardiovascular system.

However, growing evidence has also raised concerns regarding potential electrophysiological alterations and structural cardiotoxicity, particularly in the context of prolonged exposure or high cumulative doses. These seemingly contrasting effects underscore the complex cardiovascular profile of HCQ. In this narrative review, we aim to critically examine both the beneficial and potentially harmful cardiac effects of HCQ, highlighting the 'lights and shadows' of its impact on the heart and discussing the implications for clinical practice.

Methods

A structured narrative literature review was conducted to summarise the current evidence on the mechanisms of action and cardiovascular effects of HCQ. A search of the PubMed/MEDLINE database was performed up to March 2025 using combinations of the following keywords: "hydroxychloroquine", "chloroquine", "mechanism of action", "cardiovascular effects", "cardiotoxicity", "drug toxicity". Original research articles, randomised controlled trials, observational studies, mechanistic studies, and relevant review articles published in English were considered. Given the narrative nature of this review, no formal systematic review protocol or meta-analytic methodology was applied.

General mechanisms of action of hydroxychloroquine

HCQ has multiple pleiotropic effects that contribute to its therapeutic efficacy across diverse clinical conditions: its anti-inflammatory and immunomodulatory properties represent the primary mechanisms underlying its use in autoimmune diseases and are mediated by modulation of innate and adaptive immune responses, including reduced immune cell activation and cytokine production (1, 3).

In addition, HCQ displays significant antithrombotic and endothelial-protective effects, which are particularly relevant in patients with SLE and APS and may contribute to the observed reduction in cardiovascular risk associated with long-term therapy (10-12).

HCQ also exhibits antioxidant properties, limiting the generation of reactive oxygen species (ROS) and reducing oxidative stress, thereby contributing to vascular protection and endothelial function preservation (3).

Metabolic effects have been consistently reported, including improvements in lipid and glucose profiles, possibly mediated by enhanced insulin sensitivity and attenuation of chronic inflammation (12-14). Moreover, CQ and HCQ have been associated with reduced progression of atherosclerosis (14). The underlying mechanisms of these clinical consequences, however, remain largely unknown.

Furthermore, a protection against infections, antiviral and antitumoral activities have been described, largely related to interference with intracellular vesicular trafficking, endosomal function, and autophagy, although their clinical relevance remains context-dependent (3, 15, 16).

Some data suggest that HCQ during pregnancy is protective against the induction of congenital heart block (17-19), possibly owing to a reduction in expression of a type I interferon (IFN) signature (19, 20).

Specific cellular and molecular mechanisms of action

At the cellular level, HCQ interferes with several intracellular pathways involved in immune activation, inflammation, oxidative stress, and thrombosis.

Inhibition of endolysosomal activity

HCQ is a weak base that readily diffuses across cellular membranes and accumulates within acidic intracellular compartments such as lysosomes and endosomes (lysomotropism), where it becomes protonated and trapped (1, 3, 21). By increasing intravesicular pH, HCQ inhibits acid-dependent proteases and enzymes, leading to impaired antigen processing and presentation, as well as inhibition of autophagy (1, 3, 22-24). Inhibition of lysosomal activity may impair lymphocyte function and contribute to the immunomodulatory effects of HCQ (3). Lysosomes and autophagy are involved in MHC class II-mediated autoantigen presentation and immune activation through the increase of pH endosomal compartment (21, 25, 26).

Inhibition of pro-inflammatory signalling

HCQ alters Toll-like receptor (TLR)-mediated signalling by preventing the interaction between nucleic acids and endosomal TLRs, particularly TLR7, TLR8, and TLR9 (3, 27). Indeed, changes in endosomal pH can interfere with TLR9 and TLR7 processing (3, 28). CQ or HCQ can also directly bind to nucleic acids and hence might block TLR9 signalling at the intracellular level by inhibiting TLR-ligand interactions (steric blockade) (27, 29). CQ can also inhibit RNA-mediated activation of TLR7 signalling (3, 30, 31).

HCQ and CQ may further inhibit pro-inflammatory signalling by interfering with cyclic GMP-AMP synthase (cGAS) activity and ligand binding, thereby attenuating activation of the cGAS-STING pathway, a major driver of type I interferon production in inflammatory rheumatic diseases (3, 32). Through reduced cGAMP-mediated STING activation and downstream IRF3 signalling, HCQ may contribute to the suppression of type I IFN responses, a pathway currently under investigation as a therapeutic target in autoimmune inflammation (3, 33, 34).

These mechanisms result in reduced downstream activation of inflammatory cascades and decreased production of pro-inflammatory cytokines (3, 27).

Inhibition of NADPH oxidase-mediated signalling

HCQ also inhibits pro-inflammatory signalling by targeting endosomal NADPH oxidase (NOX2). In human monocytes and MonoMac1 cells, stimuli such as TNF-α, IL-1β, and antiphospholipid antibodies induce assembly of

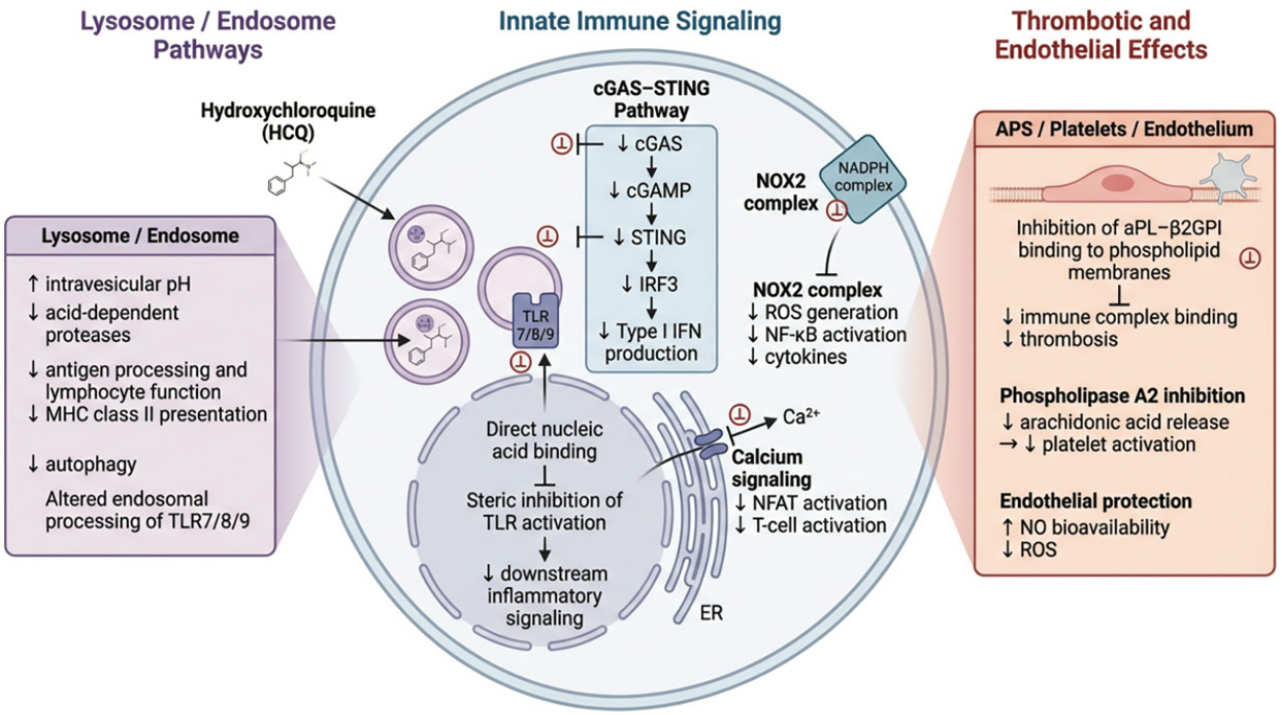

Fig. 1. Molecular mechanisms of hydroxychloroquine.

the active NOX2 complex within early endosomes, leading to reactive oxygen species (ROS) generation and downstream activation of redox-dependent pathways, including NF-κB-mediated gene transcription (35). HCQ dose-dependently suppresses endosomal ROS production by preventing translocation of the catalytic subunit gp91^phox^ to early endosomes, thereby blocking proper NOX2 assembly without interfering with ligand internalisation (35). Functionally, this results in reduced induction of pro-inflammatory genes such as TNF-α, IL-8, and tissue factor, and *in vivo* HCQ prevents NOX2-dependent thrombus formation in a mouse model (35). Collectively, these findings identify inhibition of endosomal NOX2 assembly and ROS-mediated signalling as a central mechanism underlying the anti-inflammatory and antithrombotic effects of HCQ (3).

Modulation of intracellular calcium signalling

HCQ interferes with intracellular calcium signalling following T-cell receptor (TCR) activation. Upon TCR engagement, phospholipase C-γ1 (PLC-γ1) is activated, leading to inositol 1,4,5-trisphosphate (IP_3)-mediated calcium release from the endoplasmic reticulum (ER) and subsequent activation of store-operated calcium entry through calcium release-activated calcium channels. HCQ attenuates both ER calcium release and sustained extracellular calcium influx, thereby reducing activation of calcium-dependent pathways, including the calcineurin-NFAT axis. Given the central role of calcium signalling in T-cell activation and cytokine production, this mechanism further contributes to the immunomodulatory profile of HCQ (3, 26, 36).

Antithrombotic mechanisms in antiphospholipid syndrome

In antiphospholipid syndrome (APS), HCQ inhibits platelet aggregation by preventing the overexpression of the glycoprotein IIb/IIIa (GPIIb/IIIa) complex on the surface of platelets activated by antiphospholipid antibodies, thereby reducing thrombotic risk (10, 11, 37, 38). Beyond its effects on platelet activation, HCQ also exerts a direct antithrombotic action at the molecular level by interfering with the binding of antiphospholipid antibody (aPL)–β2-glycoprotein I (β2GPI) complexes to phospholipid membranes with a dose-dependent and reversible effect, suggesting a direct and non-permanent interference with molecular interactions rather than structural modification of β2GPI or phospholipids (10, 38, 39). CQ seems to inhibit activated phospholipase A2 in Thrombin-stimulated platelets and arachidonic acid liberation from membrane phospholipids (38, 40). Overall, HCQ treatment seems to be associated with improvement in endothelial function (38, 41, 42).

All the molecular mechanisms of HCQ are shown in Figure 1.

From molecular mechanisms to cardiovascular effects

Rheumatic diseases are chronic inflammatory autoimmune disorders associated with a markedly increased risk of cardiovascular events (43), particularly myocardial infarction (44, 45), but also with higher incidence of atherosclerosis and coronary artery disease (46-48). Rheumatological patients have an approximately 1.5- to 3-fold higher incidence of ischaemic heart disease compared with the general population and higher cardiovascular mortality in general (49, 50), but also more risk factors such as arterial hypertension, hyperlipidaemia, diabetes mellitus, and chronic kidney disease (51-54). Persis-

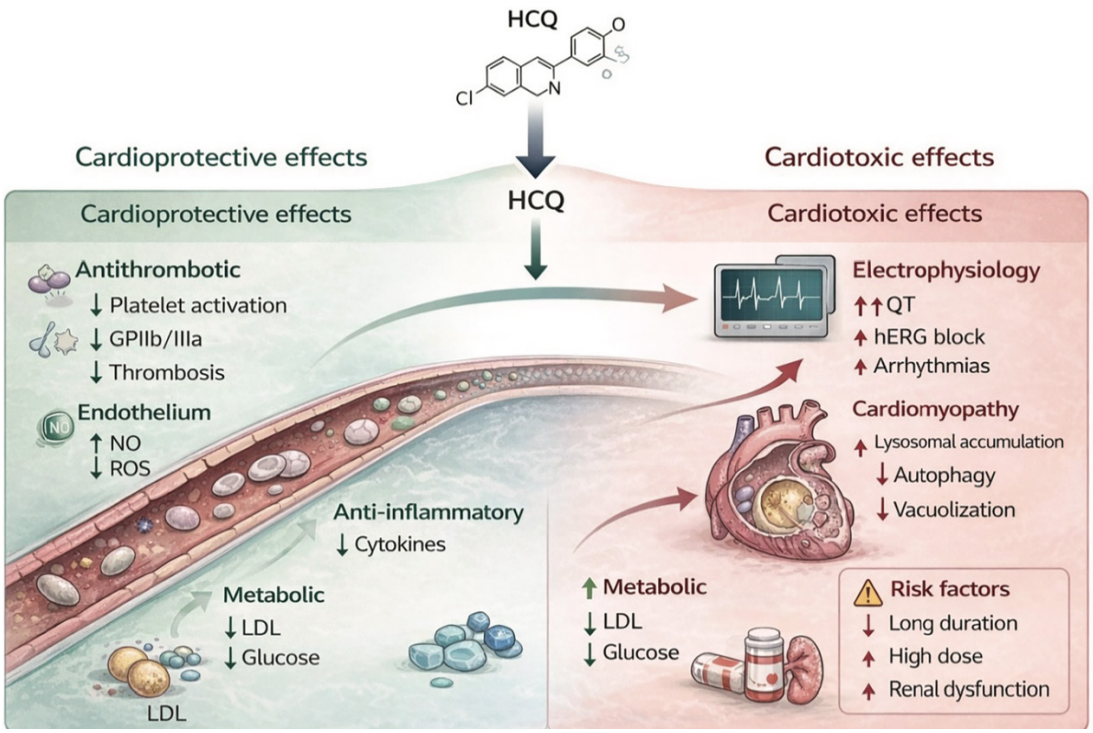

Fig. 2. Cardioprotective *vs*. cardiotoxic effects of hydroxychloroquine.

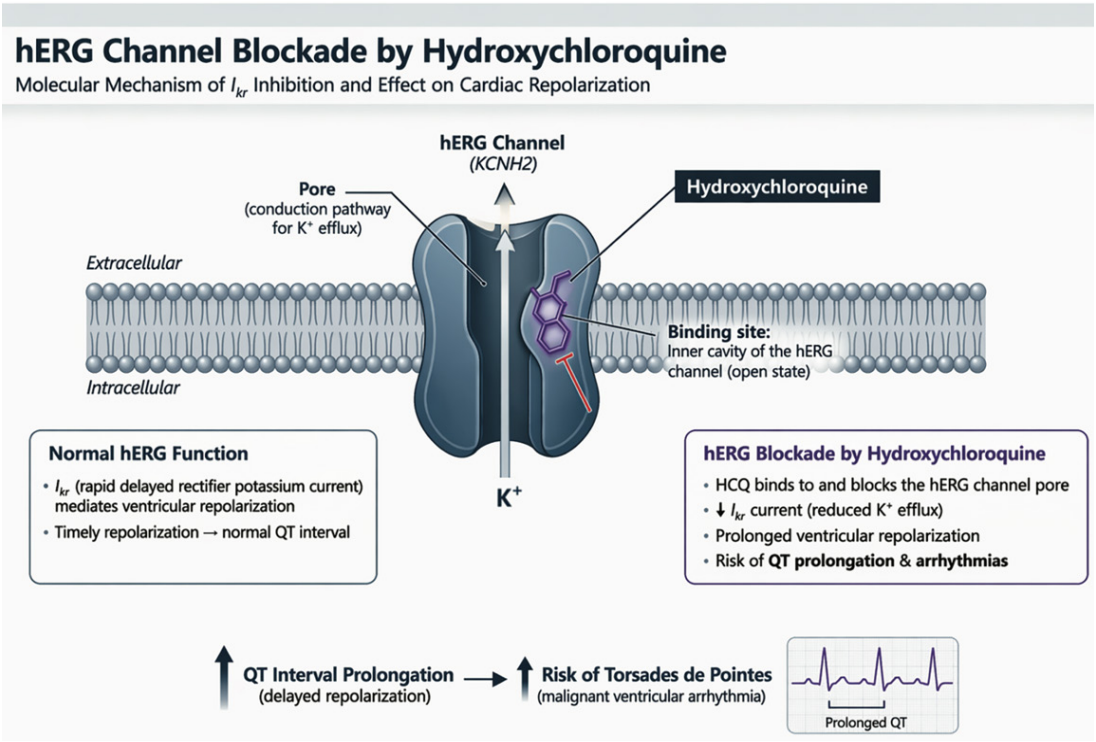

Fig. 3. Hydroxychloroquine effects on potassium channel.

tent inflammation promotes endothelial dysfunction, oxidative stress, and immune-driven vascular injury, thereby accelerating atherosclerosis and plaque destabilisation (55-58). Pro-inflammatory cytokines – including TNF-α, IL-6, and IL-1β – disrupt nitric oxide bioavailability and enhance lipid oxidation, while disease-related autoantibodies further contribute to vascular damage, moreover, chronic microvascular impairment and myocardial fibrosis additionally favour ischaemic cardiac remodelling (44, 47, 55, 59-62).

Antimalarial agents represent a cornerstone therapy in various autoimmune disease and provide several advantages that may directly or indirectly influence cardiovascular disease (CVD) risk and related events (63). It is known that antimalarials are associated with a reduced risk of CVD in the vast majority of observational studies (63-65). Its favourable metabolic actions include

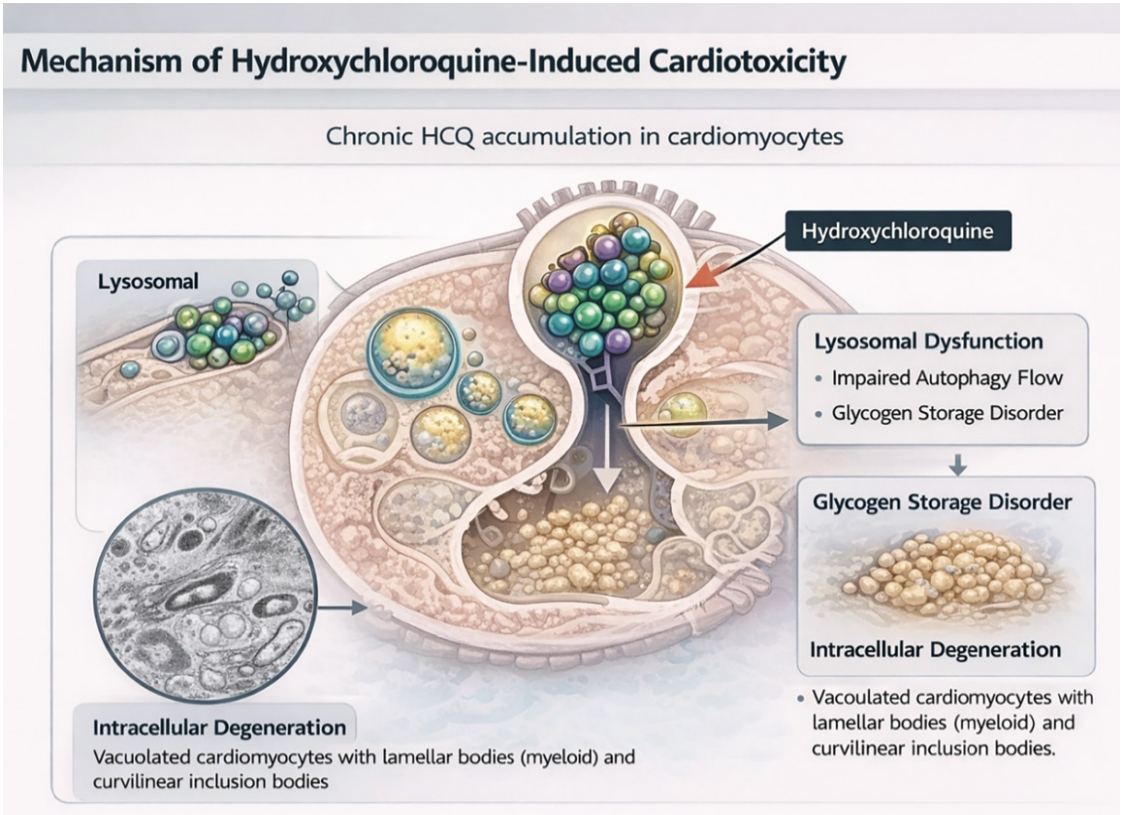

Fig. 4. Mechanism of hydroxychloroquine-induced cardiotoxicity.

reductions in total cholesterol levels , especially in patients receiving corticosteroids (66), as well as improvements in fasting glucose levels (14, 67). Moreover, antimalarial therapy has been linked to a lower incidence of thrombotic complications (68) and improved overall survival (13).

In a large multicentre SLE cohort from the Spanish RELESSER registry, antimalarial therapy was independently associated with a lower risk of chronic heart failure, supporting a potential cardioprotective role of HCQ in routine clinical practice (65).

Early experimental evidence supports a direct endothelial-protective and antiatherosclerotic role of HCQ. In a murine model of systemic lupus erythematosus, HCQ prevented the development of endothelial dysfunction by restoring nitric oxide bioavailability and reducing NADPH oxidase-mediated oxidative stress (39). These vascular effects, together with its antiplatelet activity and favourable modulation of lipid profiles reported in clinical cohorts, provide a mechanistic basis for the reduced atherosclerosis progression observed in patients receiving long-term HCQ therapy.

The molecular and cellular mechanisms described above provide a biological framework to understand the dual impact of HCQ on the cardiovascular system. On one hand, inhibition of inflammatory signalling pathways, reduction of oxidative stress, modulation of endothelial function, and attenuation of platelet activation may collectively contribute to cardiovascular protection (69–72). On the other hand, lysosomal accumulation within cardiomyocytes and interference with ion channel function may underlie rare but potentially severe cardiotoxic effects. These apparently contrasting aspects highlight the complex and context-dependent cardiovascular profile of HCQ (Fig. 2).

Although HCQ is generally considered safe and cardioprotective at standard oral doses, rare but potentially severe cardiac adverse effects have been described, particularly in the context of long-term therapy or high cumulative exposure. Reported manifestations include electrophysiological abnormalities, conduction disturbances, QT interval prolongation (73), and structural cardiomyopathy (74).

Acute toxicity – typically associated with overdose or high-dose intravenous administration – may present with hypotension, malignant arrhythmias, and cardiogenic shock. In contrast, chronic toxicity is usually related to prolonged exposure and is characterised by progressive myocardial dysfunction, often resembling a restrictive or hypertrophic cardiomyopathy (74, 75).

The underlying mechanisms are not fully elucidated but appear to involve lysosomal dysfunction due to drug accumulation within cardiomyocytes and interference with cardiac ion channel function. These mechanisms may coexist and contribute to both structural and electrophysiological abnormalities. The duration of use and cumulative dose appear to be decisive for disease development (75, 76).

Electrophysiological effects: QT prolongation and arrhythmias

HCQ can interfere with cardiac electrophysiology by affecting ion channel function, particularly the potassium current responsible for ventricular repolarisation. Experimental and clinical evidence indicates that HCQ blocks the rapid component of the delayed rectifi-

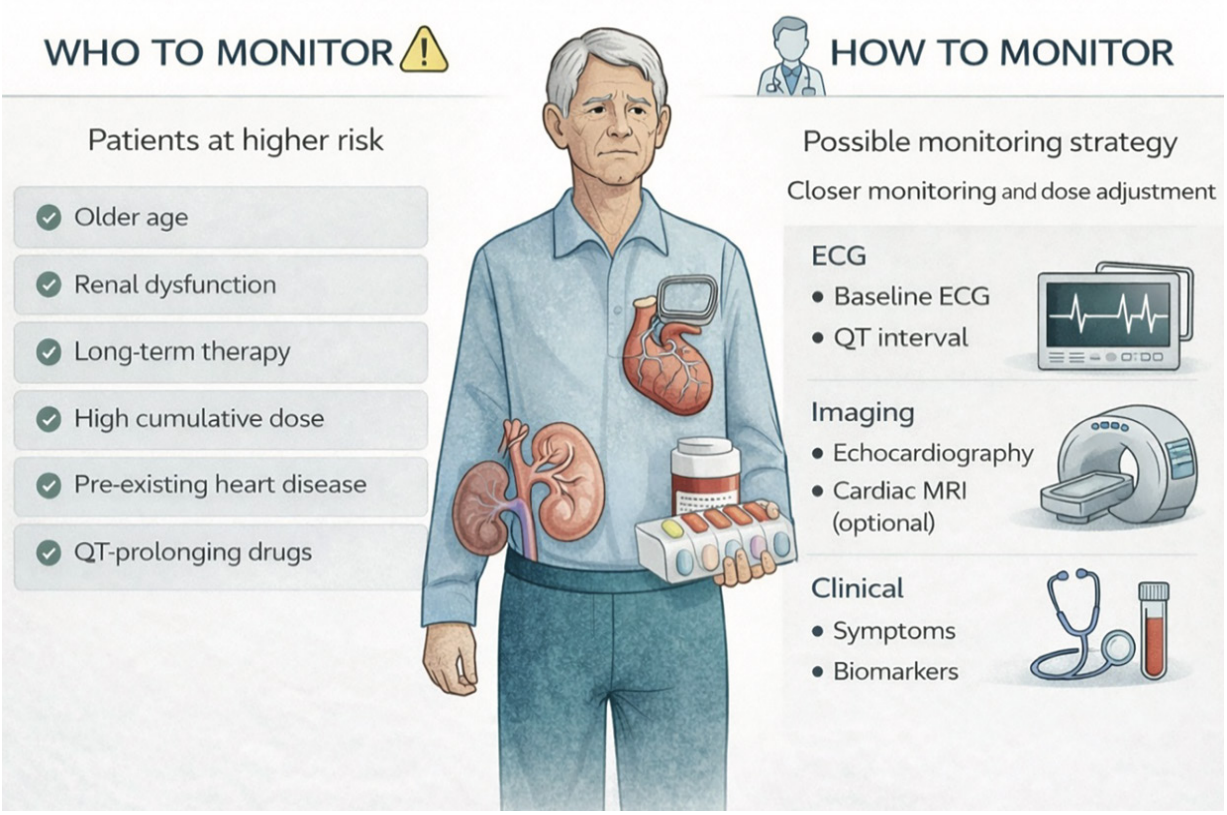

Fig. 5. Proposed strategy for identifying high-risk patients and monitoring hydroxychloroquine cardiotoxicity.

er potassium current, which is mediated by the human ether-a-go-go-related gene (hERG) potassium channel (77, 78). This blockade prolongs the duration of ventricular action potential and leads to lengthening of the QT interval on the electrocardiogram – a sensitive marker of delayed cardiac repolarisation (73, 79-81) (Fig. 3).

Prolongation of the QT interval increases the likelihood of early afterdepolarisations, which can trigger malignant ventricular arrhythmias such as torsades de pointes (TdP) and other polymorphic tachycardias, particularly in susceptible individuals (73, 80, 81).

Although clinically significant QT prolongation and arrhythmias have been most frequently reported in settings of acute high-dose administration (*e.g.* during early COVID-19 treatment protocols), standard rheumatologic doses are generally associated with only modest QTc increases, and severe arrhythmias remain uncommon in stable patients (77, 78, 81, 82).

The arrhythmogenic risk is intensified in the presence of predisposing conditions such as electrolyte imbalances (*e.g.* hypokalaemia, hypomagnesaemia), underlying heart disease, renal dysfunction, female sex, older age, and concomitant use of other QT-prolonging drugs (*e.g.* macrolide antibiotics) (81).

Beyond QT prolongation, HCQ has been associated with additional rhythm disturbances, including sinus bradycardia and conduction abnormalities. Case reports have described HCQ-induced sinus bradycardia (83). Experimental data suggest that HCQ may exert negative chronotropic effects by reducing spontaneous action potential firing in sinoatrial node cells, possibly through inhibitory modulation of the I_f, I_{kf}, and I_{CaL} currents (84). Moreover, HCQ use has been linked to conduction disorders such as right bundle branch block, left anterior fascicular block, and complete atrioventricular (AV) block (85, 86). These abnormalities may precede overt heart failure and can progress gradually from minor conduction delays to advanced AV block (85). Given that older patients may already be at increased arrhythmic risk, careful baseline and follow-up electrocardiographic monitoring has been proposed when initiating HCQ therapy (87).

The dose-effect dependence is demonstrated by an *in vitro* study, in which pluripotent stem cell–derived cardiomyocytes were exposed to HCQ, demonstrating dose-dependent effects. Low concentrations (~20 μM) promoted cell proliferation and had minimal or transient effects on contractile activity, whereas higher concentrations (≥50–100 μM) reduced cell viability and impaired cardiac function, with alterations in beating frequency (80, 88).

Structural cardiotoxicity (cardiomyopathy)

Chronic exposure to HCQ has been linked to a rare, progressive cardiomyopathy that often presents with concentric hypertrophy, restrictive physiology/diastolic dysfunction, conduction disease (AV block, bundle branch block), and heart failure, sometimes mimicking infiltrative or storage disorders (89, 90). The pathogenesis is not completely clear, but the main hypothesis is that at the cellular level, HCQ accumulates within lysosomes, where it disrupts

lysosomal homeostasis and impairs autophagic flux and function, inhibiting lysosomal enzymes, particularly alpha-galactosidase A (23). This can lead to an acquired, drug-induced glycogen storage disorder, and consequently a vacuolar degeneration of cardiomyocytes and the presence of myeloid bodies and curvilinear inclusion bodies on electron microscopy – findings considered highly suggestive/diagnostic of antimalarial cardiomyopathy and frequently demonstrated on endomyocardial biopsy (23, 76, 91) (Fig. 4).

The most common clinical presentation is the congestive heart failure with dyspnea and peripheral oedema (23, 92, 93), less commonly it presents with acute heart failure/pulmonary oedema, syncope or presyncope (94-97). Laboratory finding troponin and brain natriuretic peptide (BNP) can be abnormal (95). The most common findings during HCQ cardiomyopathy were conduction abnormalities, particularly complete AV block (89, 91, 98, 99), second-degree AVB and first-degree AVB (88, 95). Other electrocardiographic presentations are the sick sinus syndrome, right bundle branch block (83, 99).

Echocardiographic findings are impaired systolic function, left ventricular hypertrophy, right ventricular hypertrophy, hypertrophy of the interventricular septum, dilatation of the left and right atrium, but also a restrictive filling pattern of the left ventricle (96, 99, 101).

The evaluation also includes cardiac MRI, that may show increased wall thickness, restrictive filling pattern; late gadolinium enhancement; differential diagnosis includes infiltrative cardiomyopathies (*e.g.* amyloidosis); unlike genetic hypertrophic cardiomyopathy, antimalarial-induced hypertrophy reflects intracellular storage and lysosomal dysfunction rather than sarcomeric disarray (89, 101-105).

Clinically, diagnosis is often delayed because phenotypes overlap with hypertrophic/infiltrative cardiomyopathies; multimodality imaging (echo/CMR) may raise suspicion, but confirmation commonly relies on endomyocardial biopsy with ultrastructural analysis (91, 102). The biopsy shows myocyte hypertrophy, moderate-to-severe vacuolation of cardiomyocytes, intravacuolar lamellar bodies (myeloid) and comma-shaped curvilinear bodies (23, 89, 91, 102).

Importantly, several reports and reviews indicate that early recognition and drug withdrawal may stabilise or partially reverse dysfunction, whereas advanced disease can progress despite discontinuation (89, 90). The treatment is conservative, and rarely heart transplantation was performed (95).

Who is at higher risk of hydroxychloroquine cardiotoxicity?

Available evidence indicates that clinically relevant HCQ cardiotoxicity occurs predominantly in patients with prolonged treatment duration and high cumulative exposure, as consistently reported in systematic reviews and case series of antimalarial-induced cardiomyopathy (89-91). Additional risk factors include older age, renal dysfunction, and pre-existing structural heart disease or baseline conduction abnormalities, which may increase drug accumulation or susceptibility to electrophysiological disturbances (86, 87)

Regarding electrophysiological toxicity, the risk of significant QT prolongation is enhanced by concomitant QT-prolonging medications, electrolyte imbalances (*e.g.* hypokalemia, hypomagnesemia), and acute systemic illness, as highlighted during the COVID-19 experience (73, 81, 106). These observations support a risk-adapted clinical approach, with closer electrocardiographic monitoring and consideration of cardiac imaging in patients with long-standing therapy, impaired renal function, or new-onset conduction abnormalities or unexplained ventricular hypertrophy (89, 90).

Clinical implications/monitoring

The cardiovascular safety of HCQ should be interpreted within the context of its well-established therapeutic benefits in systemic autoimmune diseases. Current international recommendations continue to support long-term HCQ therapy in most patients with SLE, given its favourable benefit-risk profile (4).

Nevertheless, rare cases of antimalarial-induced cardiomyopathy and conduction disease have been reported, particularly in patients with prolonged treatment duration and high cumulative exposure (89, 91, 102). Clinical presentation may include progressive left ventricular hypertrophy, diastolic dysfunction, conduction abnormalities, and heart failure symptoms. Early discontinuation of the drug has been associated with stabilisation or partial reversibility in selected cases (90).

Electrophysiological alterations, including QT interval prolongation, have also been described, especially in the context of high doses or concomitant QT-prolonging medications (106, 107). However, clinically significant arrhythmic events remain uncommon in patients treated with standard rheumatologic regimens.

Based on available evidence, routine systematic cardiac screening in asymptomatic individuals receiving standard doses is not currently recommended. A risk-adapted approach may be reasonable in patients with long treatment duration, renal dysfunction, pre-existing structural heart disease, or unexplained cardiac symptoms.

A more detailed risk-adapted strategy may nevertheless be appropriate in selected patients. Current rheumatologic practice generally recommends maintaining daily HCQ doses below 5 mg/kg/day of actual body weight, primarily to reduce retinal toxicity, although this threshold may also indirectly limit cumulative systemic toxicity (4, 108). Patients with prolonged treatment duration (>5 years), high cumulative exposure (approximately >1000–1500 g), renal dysfunction, pre-existing structural heart disease, baseline conduction abnormalities, or concomitant use of QT-prolonging medications may benefit from closer cardiovascular surveillance (106, 108).

In these higher-risk populations, baseline electrocardiographic evaluation before treatment initiation appears reasonable, followed by periodic ECG reassessment (*e.g.* annually or biennially depending on overall risk profile) (81, 87). Echocardiographic monitoring may be considered every 1–2 years in patients with long-standing exposure

or suggestive symptoms/signs such as dyspnea, conduction disturbances, or unexplained ventricular hypertrophy (81). Cardiac magnetic resonance imaging should be reserved for cases with suspected structural cardiomyopathy, while endomyocardial biopsy remains the diagnostic gold standard in uncertain advanced cases (102, 109).

Although prospective evidence remains limited, such an individualised monitoring approach may facilitate earlier recognition of rare but potentially reversible HCQ-induced cardiotoxicity.

Lessons from the COVID-19 pandemic, during which HCQ was frequently administered at higher doses and often combined with other QT-prolonging agents, further emphasised the importance of individualised arrhythmic risk stratification and electrocardiographic surveillance, particularly in susceptible patients (79, 81, 106, 107).

Figure 5 illustrates a possible schematic overview of patients at higher risk of HCQ cardiotoxicity and potential monitoring strategies.

Conclusions

HCQ represents a paradigmatic example of a drug with a complex and context-dependent cardiovascular profile. On one hand, its anti-inflammatory, antithrombotic, antioxidant, metabolic, and endothelial-protective properties may contribute to meaningful cardiovascular risk reduction in patients with systemic autoimmune diseases, a population intrinsically predisposed to accelerated atherosclerosis and thrombotic events.

On the other hand, its lysosomotropic characteristics and interaction with cardiac ion channels may, in rare cases, lead to electrophysiological alterations and structural cardiotoxicity, particularly in the setting of prolonged exposure or high cumulative doses. HCQ-induced cardiomyopathy, although uncommon, underscores the importance of maintaining clinical vigilance and considering the diagnosis in the presence of suggestive findings.

The cardiovascular effects of HCQ therefore embody both 'lights and shadows': substantial protective potential in inflammatory-driven vascular disease, counterbalanced by rare but potentially severe cardiac adverse events. In most patients treated at standard rheumatologic doses, the benefit–risk profile remains favourable. However, individualised assessment and appropriate monitoring are essential to optimise safety.

Future prospective studies specifically addressing long-term cardiovascular outcomes and risk stratification strategies are warranted to better define this balance. Until more robust data are available, careful clinical judgment remains the cornerstone of safe HCQ therapy.

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