Hydroxychloroquine exposure reduces the risk of cardiovasular disease events in patients with hypertension or diabetes mellitus

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Abstract

Objective

To investigate the association of hydroxychloroquine (HCQ) with the risk of cardiovascular disease (CVD) events in patients with traditional risk factors, hypertension (HTN) or diabetes mellitus (DM).

Methods

We conducted a retrospective cohort study from 1 January, 2010 to 30 September, 2022. There was a total of 1007585 patients from a hospital-based population. In this cohort, 146862 patients had newly diagnosed HTN or DM. Among these patients, 1903 patients had HCQ exposure and 136396 patients had no HCQ exposure after exclusion of previous CVD events or invasive cardiovascular procedures. The risk of developing CVD events, a composite of acute myocardial infarction (AMI) and ischaemic stroke was evaluated.

Results

The patients with HCQ exposure had reduced risk of CVD events [HR (hazard ratio)=0.67 95%CI: 0.55-0.83], AMI (HR=0.61, 95%CI: 0.41-0.90) and ischaemic stroke (HR=0.74, 95%CI:0.59-0.93), when compared with non-HCQ exposure, after adjusting for age, sex, rheumatic diseases, comorbidities and medications. Specifically, reduced risk for CVD events (HR=0.67, 95%CI: 0.54–0.83), including AMI (HR=0.67, 95%CI: 0.44-1.00) and ischaemic stroke (HR=0.71, 95%CI: 0.55-0.90) were observed in older patients (age ≥50 yrs) with HCQ exposure, and reduced risk for AMI also observed in younger patients (age <50 yrs) (HR=0.28, 95%CI: 0.08-0.97). Reduced risk for CVD events (HR=0.63, 95%CI: 0.48-0.82) and ischaemic stroke (HR=0.63, 95%CI: 0.47–0.85) were observed particularly in female patients with HCQ exposure. Reduced risk for AMI was observed particularly in male patients with HCQ exposure (HR=0.44, 95%CI: 0.22–0.87).

Conclusion

HCQ has protective effect on CVD events, including both AMI and ischaemic stroke in the patients with traditional risk factors. The protective effect of HCQ on CVD events is prominent in older patients.

Key words

hydroxychloroquine, cardiovascular disease, acute myocardial infarction, ischaemic stroke, hypertension, diabetes mellitus

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Introduction

Hydroxychloroquine (HCQ) is initially used as an antimalarial drug, and is now widely used to treat many rheumatic diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) (1-5). In particular condition, HCQ is used for the therapy of primary Sjögren's syndrome (pSS) (6) and antiphospholipid syndrome (APS) (7). The effects of HCQ on the rheumatic diseases is through its anti-inflammatory and immunomodulatory properties. HCQ interferes with endolysosomal function, blocks Toll-like receptors (TLRs) activation, inhibits autophagy, decreases T-cell proliferation, and reduces production of pro-inflammatory cytokines from blood peripheral mononuclear cells, including IFN-α, IFN-γ, TNF-α, IL-1, IL-6 and IL-2 (8, 9). HCQ inhibits TLRs activation within endosome in macrophage, monocytes and T helper cells by its base property to impair endosomal acidification (10). In addition, HCQ blocks activation of endosomal TLRs by directly interacting with nucleic acids and preventing their binding to endosomal TLRs, thus inhibiting subsequent signal transduction pathway (8-10).

HCQ reduces disease activity, flaring up, organ damage, steroid dose and mortality in SLE patients (4, 11, 12). It also improves disease activity and functional ability in RA patients (13). HCQ demonstrates the protective effect on thrombosis in SLE patients (14-17). HCQ has been associated with 30% reduction in the risk of cardiovascular disease (CVD) in patients with SLE and RA (18). HCQ decreases antiphospholipid antibodies levels (19), inhibits platelet aggregation (20) and reduces the incidence of thrombosis in patients with primary APS.

Traditional cardiovascular disease (CVD) risk factors include increasing age, male sex, hypertension (HTN), diabetes mellitus (DM), hypercholesterolaemia, physical inactivity, smoking and obesity (21-23). HCQ has been shown to reduce some traditional CVD risk factors, including improve glucose metabolism and lipid profiles in patients with rheumatic diseases (24-26). HCQ may have the potential in improving CVD risk factors in patients without rheumatic diseases. To our knowledge, whether HCQ has the protective effect on CVD as compared to general population has not yet been reported. We aim to investigate the association of HCQ with the risk of CVD in patients with traditional risk factors from a hospital-based population. The study was carried out to assess if HCQ exposure can reduce risk of CVD in patients with traditional CVD risk factors from the patient database in Taipei Tzuchi Hospital, Taiwan. HTN and DM are the common risk factors of CVD. The CVD was focused on the acute events of coronary artery disease (CAD) and thrombotic cerebrovascular accident, including acute myocardial infarction (AMI) and ischaemic stroke.

Materials and methods

Data source

We conducted a retrospective cohort study using the patient database in a quasi-medical center, Taipei Tzuchi Hospital, Taiwan. The database consists of all records in health care, including patient demographic characteristics, out-patient medical visits, hospitalisation, emergency care, details of disease diagnoses, drug prescriptions and medical procedures. There was a total of 1007585 patients included in the database from 1 January, 2010 to 30 September, 2022. International Classification of Diseases-9th revision-Clinical Modification (ICD-9-CM) system was used to code the disease diagnosis. Patient data in the database were encrypted, and this study was approved by the Institutional Review Board of Taipei Tzuchi Hospital, Taiwan (11-XD-104).

Study population and HCQ exposure

The study population consisted of patients with newly diagnosed HTN (ICD-9-CM = 401) or DM (ICD-9-CM = 250), aged 20 years or more, from 1 January, 2010 to 30 September, 2022. There was a total of 146862 patients with HTN or DM (HTN/DM). These patients with HTN/DM were divided into two groups with or without exposure to HCQ. Exposure to HCQ after HTN/DM diagnosis was necessary for inclusion as the HCQ exposure group.

Exposure to HCQ after HTN/DM diagnosis was excluded as the non-HCQ exposure group. A total of 1996 patients with HCQ exposure, and 144866 patients without HCQ exposure were included. To confirm the new-onset CVD events, we excluded the patients with a history of previous CVD events [including old myocardial infarction (ICD-9-CM=412) and late effects of cerebrovascular disease (ICD-9-CM=438.0, 438.11, 438.12, 438.19, 438.2, 438.3, 438.4, 438.5, 438.8, 438.9)], which was diagnosed before the index date. The patients who had accepted invasive medical procedure with percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass grafting (CABG) before the index date were also excluded. Therefore, a total of 1903 patients with HCQ exposure, and 136396 patients without HCQ exposure were included after exclusion of previous CVD events, PTCA or CABG. The index date was the first date of diagnosis of HTN/DM in both the HCQ exposure group and the non-HCQ exposure group. The outcome variables were defined as a diagnosis of CVD events, a composite of AMI (ICD-9-CM=410) and ischaemic stroke (ICD-9-CM=433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.11, 434.91). Patients were followed-up until the earliest of the occurrence of CVD events, the date 30 September, 2022 was reached, or the withdrawal from the patient database. The study flow chart to identify the HTN/DM patients with or without exposure to HCQ is shown in Figure 1. The baseline characteristics of this study population included age, sex, and the presence of common rheumatic and skin diseases, including SLE (ICD-9-CM=710.0), RA (ICD-9-CM=714.0), pSS (ICD-9-CM=710.2), vasculitis (ICD-9-CM=437.4, 446.0, 446.2, 446.4, 446.5, 447.6), inflammatory myositis (ICD-9-CM=710.3, 710.4), systemic sclerosis (ICD-9-CM=710.1), palindromic rheumatism (ICD-9-CM=719.3), APS (ICD-9-CM=286.5), urticaria (ICD-9-CM=708), and comorbidities, including hyperlipidaemia (ICD-9-CM=272.0, 272.1, 272.2, 272.3, 272.4), chronic renal disease (ICD-9-CM=585, 586, V45.1), chronic obstructive pulmonary disease (COPD) (ICD-9-CM=491.2, 493.2, 496) and gout (ICD-9-CM=274.0, 274.9). Those rheumatic diseases and comorbidities were defined as occurring before and within one year of the index date. The medication use of corticosteroids (prednisolone or methylprednisolone), anti-platelet drugs (aspirin or clopidogrel), methotrexate and azathioprine after the index date during the study period were included as the covariates. The adverse effects of HCQ on electrocardiographic abnormalities were evaluated among the patients with HTN/DM. The risk of new-onset cardiac arrhythmia (ICD-9-CM=426, 427.0, 427.1, 427.4, 427.6, 427.8, 427.9, 794.31) was assessed in this population during the study period.

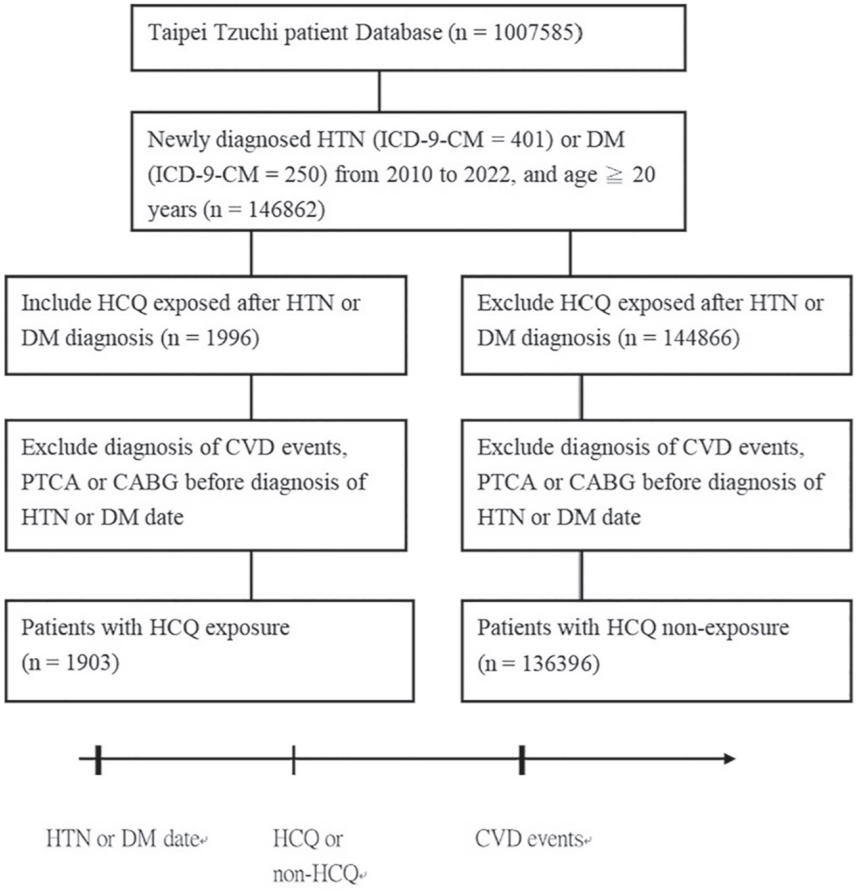

Fig. 1. Study flow chart of the HTN/DM patients with or without HCQ exposure.
HTN: hypertension; DM: diabetes mellitus; HCQ: hydroxychloroquine; CVD: cardiovascular disease; PTCA: percutaneious transluminal coronary angioplasty; CABG: coronary artery bypass grafting

Statistical analysis

Continuous variables were described as mean ± standard deviation (SD.). Student t-test was used for continuous variables, and Pearson's Chi-squared test was used for categorical variables. Kaplan-Meier analysis was used to estimate the cumulative incidence of CVD events across the study period, and the log-rank test was used to evaluate the statistical significance. Cox proportional hazard model was used to estimate the hazard ratio (HR) of CVD events in relation to HCQ exposure and was adjusted for potential confounding variables. A *p*-value less than 0.05 was considered as significant. The statistical analysis was supported by the computer programme software (ASUS LUMOS v. 3.3) in Taipei Tzuchi Hospital, Taiwan.

Results

Patient characteristics

A total of 1903 patients with HCQ exposure and 136396 patients without HCQ exposure were included in this cohort study. The HCQ exposure group had a higher number of female

Table I. Clinical characteristics of HTN or DM patients with or without exposure to HCQ.

Characteristic	HCQ exposure	HCQ exposure percentage (%)	Non-HCQ exposure	Non- HCQ exposure percentage (%)	*p*-value
Patient count	1903		136396		
Age (mean ± SD) yr	62 ± 13		62 ± 15		0.53
Sex (male)	448	24	65839	48	<0.001*
Sex (female)	1455	76	70557	52	<0.001*
SLE	184	10	79	0	<0.001*
RA	387	20	292	0	<0.001*
pSS	479	25	533	0	<0.001*
Vasculitis	33	2	90	0	<0.001*
Systemic sclerosis	25	1	11	0	<0.001*
Inflammatory myositis	33	2	949	1	<0.001*
Palindromic rheumatism	24	1	34	0	<0.001*
APS	1	0	0	0	<0.001*
Urticarira	130	7	2473	2	<0.001*
Hyperlipidaemia	640	34	42176	31	<0.05*
Chronic renal failure	168	9	9554	7	<0.01*
COPD	92	5	5563	4	0.1
Gout	114	6	6116	4	<0.01*
Corticosteroids	1113	58	17108	13	<0.001*
Methotrexate	376	20	336	0	<0.001*
Azathioprine	190	10	268	0	<0.001*
Antiplatelet drugs	617	32	29400	22	< 0.001*

Values are shown as mean ± standard deviation or patient number (%).
Subjects with missing age or sex data were excluded.
HCQ: hydroxychloroquine; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; pSS: primary Sjögren's syndrome; APS: antiphospholipid syndrome; COPD: chronic obstructive pulmonary disease. Antiplatelet drugs: aspirin, clopidogrel. *Significance.

patients than the non-HCQ exposure group (76% *vs*. 52%, $p<0.001$). The percentage of patients with common rheumatic and skin diseases, including SLE, RA, pSS, vasculitis, inflammatory myositis, systemic sclerosis, palindromic rheumatism, APS, and urticaria were higher in the HCQ exposure group than the non-HCQ exposure group (all $p<0.001$). Comorbidities with hyperlipidaemia, chronic renal failure and gout were higher in the HCQ exposure group than the non-HCQ exposure group (all $p<0.05$). The percentage of patients who use the medication: corticosteroids, methotrexate, azathioprine and antiplatelet drugs, were higher in the HCQ exposure group than the non-HCQ exposure group (all $p<0.001$). The demographic characteristics of patients with and without HCQ exposure are shown in Table I.

Higher HR of CVD events in patients with male sex, older age, SLE, chronic renal failure, corticosteroids and antiplatelet drug use

The risks of CVD events in the HTN/DM patients with different conditions are shown in Table II. Higher HR for developing CVD events were observed in patients with male sex, older age, SLE and chronic renal failure (male sex: HR=1.23, 95% CI: 1.24–1.36; age: HR = 1.03, 95% CI: 1.02–1.03; SLE: HR=2.12, 95% CI: 1.32–3.42, chronic renal failure: HR=1.45, 95% CI: 1.36–1.55), after adjusting for age, sex, rheumatic diseases, comorbidities and medication use. Higher HR for developing CVD events were observed in patients with corticosteroids (HR=1.19, 95% CI: 1.13–1.25) and antiplatelet drugs use (HR=14.89, 95% CI: 13.89–15.96). In contrast, reduced HR for developing CVD events were observed in patients with COPD (HR=0.9, 95% CI: 0.82–0.99) and hyperlipidaemia (HR=0.95, 95% CI: 0.91–1.00). There was no significant difference in the risk of CVD events in patients with RA, pSS, vasculitis, systemic sclerosis, inflammatory myositis, palindromic rheumatism, APS, urticaria, gout, or with methotrexate and azathioprine use.

Decreased HR for CVD events, AMI and ischaemic stroke in patients with HCQ exposure

The HR for CVD events in the HTN/DM patients exposed to HCQ is shown in Table III. Patients with HCQ exposure had significant reduction in HR of developing CVD events when compared with non-HCQ exposure (HR=0.67 95% CI: 0.55–0.83), after adjusting for age, sex, rheumatic diseases, comorbidities and medication use (Table III). Moreover, patients with HCQ exposure had significant reduction in HR of developing AMI (HR=0.61, 95% CI: 0.41–0.90) and ischaemic stroke (HR=0.74, 95% CI: 0.59–0.93) when compared with non-HCQ exposure, after adjusting for age, sex, rheumatic diseases, comorbidities and medication use.

The HRs for CVD events, AMI, and ischaemic stroke between patients with and without HCQ exposure, stratified by age or sex are shown in Table IV.

Significant CVD events protection of HCQ in female patients or aged ≥50 years old

When the age of patients was less than 50 years old, there was no significantly different HR for CVD events between HCQ exposure and non-HCQ exposure groups. However, a significant reduction of HR for CVD events was observed in patients aged 50 years old and above in the HCQ exposure group when compared with non-HCQ exposure group (HR = 0.67, 95% CI: 0.54–0.83) (Table IV). In the female subgroup, significant reduction of HR for CVD events was observed in patients with the HCQ exposure group when compared with non-HCQ exposure group (HR=0.630, 95% CI: 0.48–0.82).

Significant AMI protection of HCQ in male patients

There were significant reduced HR for AMI observed in patients aged less than 50 years old (HR=0.28, 95% CI: 0.08–0.97) or 50 years old and above (HR=0.67, 95% CI: 0.44–1.00) in the HCQ exposure group when compared with non-HCQ exposure group (Table IV). Significant AMI protection of HCQ was observed in both younger and older patients. Only in the male subgroup, significant reduction of HR for AMI was observed in patients with the HCQ exposure group when com-

Table II. HRs of developing CVD events according to age, sex, rheumatic diseases, comorbidity, drug usage in patients with HTN or DM.

Name	Crude HR	95% CI (Lower)	95% C. (Upper)	*p*-value	Adjusted HR	95% CI (Lower)	95% CI (Upper)	*p*-value
Male	1.39	1.33	1.46	<0.001*	1.23	1.24	1.36	<0.001*
Age	1.05	1.04	1.05	<0.001*	1.03	1.02	1.03	<0.001*
SLE	1.30	0.84	2.02	0.24	2.12	1.32	3.42	<0.01*
RA	0.69	0.48	1.00	0.05	1.01	0.68	1.51	0.95
pSS	0.67	0.51	0.90	<0.01*	0.82	0.61	1.12	0.21
Vasculitis	1.29	0.64	2.58	0.48	1.14	0.57	2.29	0.71
Systemic sclerosis	2.23	0.84	5.95	0.11	1.56	0.57	4.24	0.39
Inflammatory myositis	0.40	0.25	0.66	<0.001*	0.68	0.42	1.12	0.13
Palindromic rheumatism	0.69	0.22	2.14	0.52	1.18	0.38	3.67	0.78
APS	0.00	0.00	1.3E+122	0.96	0.00	0.00	2.6E+195	0.97
Urticarira	0.93	0.80	1.09	0.37	0.92	0.78	1.08	0.29
Hyperlipidaemia	1.01	0.96	1.06	0.67	0.95	0.91	1.00	<0.05*
Chronic renal failure	2.63	2.47	2.81	<0.001*	1.45	1.36	1.55	<0.001*
COPD	1.82	1.66	1.99	<0.001*	0.90	0.82	0.99	<0.05*
Gout	1.34	1.23	1.47	<0.001*	1.07	0.98	1.18	0.15
Corticosteroids	1.79	1.70	1.88	<0.001	1.19	1.13	1.25	<0.001*
Methotrexate	0.79	0.59	1.06	0.12	1.04	0.76	1.44	0.79
Azathioprine	0.85	0.60	1.22	0.39	0.84	0.57	1.22	0.35
Antiplatelet drugs	18.37	17.17	19.66	<0.001*	14.89	13.89	15.96	<0.001*

Cardiovascular disease (CVD) events: a composite of acute myocardial infarction (AMI) and ischaemic stroke.
Adjusted HR: adjusted for age, sex, SLE, RA, pSS, vasculitis, systemic sclerosis, inflammatory myositis, palindromic rheumatism, APS, urticaria, hyperlipidaemia, chronic renal failure, COPD, disease, gout, corticosteroids, methotrexate, azathioprine and antiplatelet drugs.
HR: hazard ratio; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; pSS: primary Sjögren's syndrome; APS: antiphospholipid syndrome; COPD: chronic obstructive pulmonary disease. Antiplatelet drugs: aspirin, clopidogrel. *Significance.

Table III. HRs of cardiovascular disease events among HTN or DM patients with HCQ exposure as compared to non-HCQ exposure.

	no. of patients	no. of events	Observed person-years	Incidence rate (per 1000 person-years)	*p*-value	Crude HR	95% CI (Lower)	95% CI (Upper)	*p*-value	Adjusted HR	95% CI (Lower)	95% CI (Upper)	*p*-value
CVD events													
Non-HCQ	136396	7322	542162.9	13.51		1				1			
HCQ	1903	124	11777.12	10.53	0.06	0.85	0.71	1.01	0.06	0.67	0.55	0.83	<0.001*
AMI													
Non-HCQ	136396	2070	562290.1	3.68		1				1			
HCQ	1903	34	12175.13	2.79	0.15	0.78	0.55	1.09	0.15	0.61	0.41	0.90	<0.05*
Ischaemic stroke													
Non-HCQ	136396	5594	548073	10.21		1				1			
HCQ	1903	99	11890.16	8.33	0.29	0.90	0.74	1.10	0.29	0.74	0.59	0.93	<0.01*

Cardiovascular disease (CVD) events: a composite of acute myocardial infarction (AMI) and ischaemic stroke.
Adjusted HR: adjusted for age, sex, SLE, RA, pSS, vasculitis, systemic sclerosis, inflammatory myositis, palindromic rheumatism, APS, urticaria, hyperlipidaemia, chronic renal failure, COPD, disease, gout, corticosteroids, methotrexate, azathioprine and antiplatelet drugs.
HR: hazard ratio, HCQ: hydroxychloroquine *Significance.

pared with non-HCQ exposure group (HR=0.44, 95% CI: 0.22–0.87).

Significant ischaemic stroke protection of HCQ in female patients or aged ≥50 years old

When the age of patients was less than 50 years old, there was no significant different HR for ischaemic stroke between HCQ exposure and non-HCQ exposure groups. However, a significant reduction of HR for ischaemic stroke was observed in patients aged 50 years old and above in the HCQ exposure group when compared with non-HCQ exposure group (HR=0.71, 95% CI: 0.55–0.90) (Table IV). In the female subgroups, there was significant reduction of HR for ischaemic stroke observed in patients with the HCQ exposure group when compared with non-HCQ exposure group (HR=0.63, 95% CI: 0.48–0.82).

Patients with HCQ exposure had significant increased incidence of arrhythmia when compared with non-HCQ exposure [number of patients, number of events, observed person-years, incidence rate [(per 1000 person-years) = 1751, 205, 10335.93, 19.83 *vs*. 127714, 7276, 495619.6, 14.68, $p<0.001$)]. Patients with HCQ exposure had increased risk of arrhythmia when compared with non-HCQ exposure, but did not show significance after adjusting for age, sex, CVD events, rheumatic diseases, comorbidities and medication use (HR=1.06, 95% CI: 0.90–1.25). The study showed that HCQ exposure

Table IV. HRs of cardiovascular disease events, AMI, ischaemic stroke among HTN or DM patients with HCQ exposure as compare to non-HCQ exposure, stratified by age and sex.

	no. of patients	no. of events	Observed person-years	Incidence rate (per 1000 person-years)	*p*-value	Crude HR	95% CI (lower)	95% CI (upper)	*p*-value	Adjusted HR	95% CI (lower)	95% CI (upper)	*p*-value
CVD events													
Age 20-50 yr													
Non-HCQ	30069	743	130712.5	5.68		1				1			
HCQ	340	17	2280.95	7.45	0.18	1.39	0.86	2.24	0.18	0.75	0.42	1.35	0.34
Age ≧50 yr													
Non-HCQ	108883	6677	423660.6	15.76		1				1			
HCQ	1599	109	9724.83	11.21	<0.01*	0.77	0.64	0.93	<0.01*	0.67	0.54	0.83	<0.001*
Male													
Non-HCQ	65839	4038	253389.5	15.94		1				1			
HCQ	448	45	2655.14	16.95	0.33	1.16	0.86	1.55	0.33	0.76	0.55	1.05	0.1
Female													
Non-HCQ	70557	3284	288773.4	11.37		1				1			
HCQ	1455	79	9121.98	8.66	0.07	0.82	0.65	1.02	0.07	0.63	0.48	0.82	<0.001*
AMI													
Age 20-50 yr													
Non-HCQ	30069	254	132925.9	1.91		1				1			
HCQ	340	4	2337.06	1.71	0.81	0.89	0.33	2.39	0.81	0.28	0.08	0.97	<0.05*
Age ≥50 yr													
Non-HCQ	108883	1852	441882.2	4.19		1				1			
HCQ	1599	31	10070.71	3.08	0.12	0.76	0.53	1.08	0.12	0.67	0.44	1.00	<0.05*
Male													
Non-HCQ	65839	1262	264211.9	4.78		1				1			
HCQ	448	10	2828.38	3.54	0.4	0.76	0.41	1.42	0.4	0.44	0.22	0.87	<0.05*
Female													
Non-HCQ	70557	808	298078.2	2.71		1				1			
HCQ	1455	24	9346.75	2.57	0.83	0.96	0.64	1.43	0.83	0.76	0.47	1.23	0.27
Ischaemic stroke													
Age 20-50 yr													
Non-HCQ	30069	516	131669.5	3.92		1				1			
HCQ	340	14	2294.53	6.10	0.05	1.69	0.99	2.87	0.05	1.16	0.62	2.16	0.65
Age ≥50 yr													
Non-HCQ	108883	5146	428746.8	12.00		1				1			
HCQ	1599	86	9827.87	8.76	< 0.05*	0.80	0.65	0.99	< 0.05*	0.71	0.55	0.90	<0.01*
Male													
Non-HCQ	65839	2961	257504.6	11.50		1				1			
HCQ	448	38	2689.04	14.13	0.06	1.36	0.99	1.88	0.06	0.96	0.67	1.36	0.81
Female													
Non-HCQ	70557	2633	290568.4	9.06		1				1			
HCQ	1455	61	9201.12	6.63	0.07	0.79	0.62	1.02	0.07	0.63	0.47	0.85	<0.01*

Cardiovascular disease (CVD) events: a composite of acute myocardial infarction (AMI) and ischaemic stroke.
Adjusted HR: adjusted for age, sex; SLE; RA: pSS, vasculitis, systemic sclerosis, inflammatory myositis, palindromic rheumatism, APS, urticaria, hyperlipidaemia, chronic renal failure, COPD, disease, gout, corticosteroids, methotrexate, azathioprine and antiplatelet drugs.
HR: hazard ratio, HCQ: hydroxychloroquine. *Significance.

did not result in a significant increase in electrocardiographic abnormalities among the patients with HTN/DM.

Discussion

Our study compared 1903 HCQ exposed with 136396 non-HCQ exposed HTN/DM patients from the patient database in a single hospital centre from year 2010 to 2022 in Taiwan. The results showed that HCQ was associated with a 33% reduction in the risk of developing CVD events, which included AMI and ischaemic stroke, in the HTN/DM patients. Moreover, HCQ was associated with a 33% reduction in the risk of developing CVD events in patients aged 50 and above, and a 37% risk reduction in female patients. This finding suggested that HCQ has significant protection effect on CVD events in patients with traditional risk factors. A recent study showed that HCQ was associated with an approximately 30% reduction in the risk of CVD in patients with SLE and RA (18).

Our study found that HCQ was associated with a 39% reduction in the risk of developing AMI in the HTN/DM patients. Specifically, HCQ was associated with a 72% risk reduction of developing AMI in patients less than 50 years old, and a 33% risk reduction in patients aged 50 years old and above. HCQ was associated with reduced risk of developing AMI regardless of age,

and a 56% risk reduction of developing AMI in male patients. The protective effect of HCQ on developing AMI was observed in male patients, but not in female patients. Previous studies have reported a decreased risk of developing CAD in pSS and SLE patients with higher usage and cumulative dose of HCQ (27, 28).

Our study showed that HCQ was associated with a 26% reduction in the risk of developing ischaemic stroke in the HTN/DM patients. In patients aged 50 years old and above, HCQ was associated with a 29% risk reduction of developing ischaemic stroke. Moreover, HCQ was significantly associated with a 37% reduction in the risk of developing ischaemic stroke in female patients. These findings suggested that HCQ has protective effect on ischaemic stroke in female or older patients. However, previous studies have showed that HCQ did not have a protective effect on ischaemic stroke in patients with SLE and RA (28, 29). The protective effect of HCQ on ischaemic stroke may be predominantly observed in older patients.

Most of the HTN/DM patients with exposure to HCQ have some kind of rheumatic diseases, such as RA, SLE, pSS, vasculitis, systemic sclerosis, inflammatory myositis, palindromic rheumatism and APS, while most of the patients without exposure to HCQ did not have rheumatic diseases in our study. Patients with inflammatory rheumatic diseases, including RA, SLE, pSS, ankylosing spondylitis and psoriatic arthritis have an increased risk of fatal and nonfatal CVD when compared with the general population. Active disease and its complications are major risk factors for CVD in patients with RA, SLE and pSS (30-32). Additionally, immune mediated vascular thrombosis events were observed to be increased in SLE patient (14-16), while the risk of unstable plaques is higher in RA patients than in the control group (32). Cardiac manifestations are the leading cause of an increased morbidity and mortality in inflammatory rheumatic diseases, particularly due to an increased atherosclerotic process (33, 34). Inflammation and traditional risk factors, including older age, male sex, HTN, DM, hypercholesterolaemia and smoking, combine together to accelerate the development of atherosclerosis in CVD in patients with RA and SLE (30). The reduced risk of CVD events in the HTN/DM patients with exposure to HCQ indicated that HCQ could reverse the higher risk of CVD in patients with inflammatory rheumatic diseases. HCQ could even lead to lower risk of CVD in patients with rheumatic diseases compared to the general population.

The properties of HCQ on reducing inflammation, preventing thrombosis, improving glucose and lipid profiles could contribute to the protective effects on CVD events. HCQ has been demonstrated to reduce the levels of antibodies to cardiolipin and beta-2 glycoprotein 1 in patients with primary APS (19). HCQ can reverse platelet activation induced by antiphospholipid antibodies, and reduce platelet aggregation by reducing formation of antiphospholipid-β2-glycoprotein complexes on monocytes surfaces (35). HCQ could decrease vascular inflammation and endothelial dysfunction in a murine model of APS (36).

HCQ has been shown to lower the risk of incident DM and metabolic syndrome in RA patients (24, 25, 37). HCQ could reduce the risk of incident DM in a dose-dependent manner in SLE patients (38). The usage of HCQ was associated with a greater reduction in HbA1c as compared with methotrexate in DM patients with rheumatic disease (26). HCQ increased the serum insulin level in pre-diabetic patients, and improved insulin sensitivity in obese non-diabetic individuals (39, 40). HCQ was associated with lower fasting glucose in women with SLE or RA and also lower insulin resistance in SLE patients (41). The glucose-lowering properties of HCQ have multifaceted effects that include improving insulin sensitivity, increasing insulin secretion and reducing hepatic insulin clearance (42). HCQ could improve lipid profiles, including a decreased level of total cholesterol, low-density cholesterol and triglycerides, as well as an increased level of high-density cholesterol in patients with RA and SLE (43, 44).

Our results demonstrated that higher HRs for developing CVD events was observed in the HTN/DM patients with older age, male sex, SLE, chronic renal failure, corticosteroids and antiplatelet drugs use. Older age and male sex are traditional CVD risk factors (21-23). Patients with chronic kidney disease are at an increased risk for CVD and death (45). During the disease course of SLE and RA, glucocorticosteroids and immunosuppressive agents may be used to control the disease activity. A higher dose of glucocorticosteroid exposure was associated with increased CVD risk in SLE and RA patients (46, 47). These results may confirm the impact of inflammation on CVD events, and imply that patients with higher risks were given antiplatelet drugs for prophylaxis of CVD, such as aspirin and clopidogrel.

The side effects of HCQ include cutaneous maculopapular and erythematous rash, skin hyperpigmentation, acute generalised exanthematous pustulosis, gastrointestinal disturbance, headache, retinopathy, myopathy, cardiomyopathy, neuromyopathy and peripheral polyneuropathy (11, 12, 48). Retinopathy is one of the main adverse events related to HCQ. It is not reversible and can cause permanent visual loss (42). Early recognition is important to prevent a central visual loss. The 2016 revised American Academy of Ophthalmology recommendations on screening for chloroquine and HCQ retinopathy recommended a maximum daily HCQ use of ≤5.0 mg/kg real weight. At the recommended doses, the risk of toxicity up to 5 years is under 1% and up to 10 years is under 2%, but it rises to almost 20% after 20 years. After 20 years, a patient without toxicity has only a 4% risk of converting in the subsequent year. Major risk factors for retinopathy include high dose, long duration of HCQ, chronic kidney disease, use of tamoxifen and preexisting retinal disease (49). A baseline fundus examination and annual screening after 5 years should be performed for patients on acceptable doses and without major risk factors (50).

HCQ has a half-life of around 50 days, with half of the drug excreted from

kidney (21). The drug reaches 95% of its steady-state concentration by about 6 months of therapy, and if objective improvement does not occur within six months, the drug should be discontinued (52). High daily dose and long duration of HCQ use may have several and irreversible adverse effects and could be a limitation of long-term use for preventing CVD events either in the patients with rheumatic or non-rheumatic diseases.

Our study has some limitations; first, our cohort is from a single hospital, thus our results cannot be extrapolated to patients from a general population. Second, the exposure of HCQ did not include the daily dosage, cumulative dosage, and duration of usage, the dosage effect of HCQ on CVD events could not be demonstrated in this study. Third, the disease duration and disease activity of rheumatic diseases at the time of the CVD event may have impacted the cardiovascular outcome, but are not available in the database. Finally, this is a retrospective cohort analysis, a further prospective cohort study is needed to investigate the protective effect of HCQ on CVD events, and evaluate the balance between the benefits and cost of side effects.

In conclusion, HCQ exposure has a protective effect on CVD events, including AMI and ischaemic stroke in the patients with HTN or DM. HCQ exposure has a protective effect on AMI, particularly in male patients. The protective effect of HCQ on CVD events is prominent in older patients with traditional risk factors. HCQ is widely used in patients with rheumatic diseases and has rare severe adverse effects. Adequate use of HCQ for disease control and CVD protection is encouraged to patients with rheumatic diseases, particularly with cardiovascular risk factors.

Further investigation of the protective effect of HCQ on the non-rheumatic patients with cardiovascular risk factors is recommended.

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