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ORIGINAL ARTICLE

Cardiovascular disease in rheumatoid arthritis: medications and risk factors in China

Chun Li[1] · X. R. Wang[2] · H. J. Ji[1] · X. Y. Zhang[1] · X. F. Li[3] · L. Z. Wang[3] · C. H. Wang[3] · Y. F. Wang[4] · Rong Yang[4] · G. C. Wang[5] · Xin Lu[5] · Ping Zhu[6] · L. N. Chen[6] · H. T. Jin[7] · J. T. Liu[7] · X. Y. Liu[8] · Lin Sun[8] · H. Y. Chen[9] · Ping Wei[9] · J. X. Wang[9] · L. F. Cui[10] · Rong Shu[10] · B. L. Liu[10] · Z. L. Zhang[11] · G. T. Li[11] · Z. B. Li[12] · Jing Yang[12] · J. F. Li[13] · Bin Jia[13] · F. X. Zhang[14] · J. M. Tao[14] · S. L. Han[2] · J. Y. Lin[15] · M. Q. Wei[15] · X. M. Liu[16] · Dan Ke[16] · S. X. Hu[17] · Cong Ye[17] · X. Y. Yang[18] · Hao Li[18] · C. B. Huang[19] · Ming Gao[19] · Bei Lai[19] · X. F. Li[20] · L. J. Song[20] · Yi Wang[21] · X. Y. Wang[21] · Y. D. Tang[22] · Yin Su[1] · Rong Mu[1] · Z. G. Li[1]

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Abstract This study aims to assess the risk factors of cardiovascular disease (CVD) and to determine the association of traditional and biologic disease-modifying anti-rheumatic drugs (DMARDs) with risk for CVD in Chinese rheumatoid arthritis (RA) patients. A cross-sectional cohort of 2013 RA patients from 21 hospitals around China was established.

✉ Rong Mu
murong@pkuph.edu.cn

✉ Z. G. Li
li99@bjmu.edu.cn

[1] Department of Rheumatology and Immunology, Peking University People's Hospital, 11 South Xizhimen Street, Beijing 100044, China

[2] Department of Rheumatology and Immunology, Peking University Shougang Hospital, 9 Jinyuanzhuang Street, Beijing 100144, China

[3] Department of Rheumatology and Immunology, The Second Affiliated Hospital Shanxi Medical University, 382 Wuyi Road, Taiyuan 030001, China

[4] Department of Rheumatology and Immunology, The First Affiliated Hospital, Baotou Medical College, 41 Linyin Road, Baotou 014010, China

[5] Department of Rheumatology and Immunology, China-Japan Friendship Hospital, 2 Yinghua Dongjie, Beijing 100029, China

[6] Department of Rheumatology and Immunology, Xijing Hospital, 15 Changle Road, Xian 710032, China

[7] Department of Rheumatology and Immunology, The Second Hospital of Hebei Medical University, 215 West Heping Road, Shijiazhuang 050000, China

[8] Department of Rheumatology and Immunology, Peking University Third Hospital, 49 North Garden Rd, Beijing 100191, China

[9] Department of Rheumatology and Immunology, The Third Hospital of Hebei Medical University, 139 Ziqiang Rd, Shijiazhuang 050000, China

[10] Department of Rheumatology and Immunology, Kailuan Hospital of North China Coal Hospital, 57 West Xinhua Rd, Tangshan 063000, China

[11] Department of Rheumatology and Immunology, Peking University First Hospital, 8 Xishiku Road, Beijing 100034, China

[12] Department of Rheumatology and Immunology, Peace Hospital, 398 West Zhongshan Rd, Shijiazhuang 050082, China

[13] Department of Rheumatology and Immunology, Hebei Handan Central Hospital, 311 Heping Rd, Handan 056001, China

[14] Department of Rheumatology and Immunology, Hebei People's Hospital, 348 West Heping Rd, Shijiazhuang 050051, China

[15] Department of Rheumatology and Immunology, The People's Hospital of Guangxi Zhuang Autonomous Region, 6 Taoyuan Rd, Nanning 530021, China

[16] Department of Rheumatology and Immunology, Beijing Shunyi Hospital of China Medical University, 3 South Guangming Rd, Beijing 101300, China

[17] Department of Rheumatology and Immunology, Tongji Medical College Huazhong University of Science and Technology, 1095 Jie Fang Avenue, Wuhan 430030, China

[18] Department of Rheumatology and Immunology, First Affiliated Hospital of Sun Yat-sen University, 58 Second Zhongshan Rd, Guangzhou 510080, China

[19] Department of Rheumatology and Immunology, Beijing Hospital, 1 Dahua Rd, Beijing 100730, China

[20] Department of Rheumatology and Immunology, Qilu Hospital of Shandong University, 107 Jinan Culture Road, Jinan 250012, China

Medical history of CVD was documented. The patients' social background, clinical manifestations, comorbidities, and medications were also collected. Of the 2013 patients, 256 had CVD with an incidence of 12.7%. Compared with non-CVD controls, RA patients with CVD had a significantly advanced age, long-standing median disease duration, more often male and more deformity joints. Patients with CVD also had higher rates of smoking, rheumatoid nodules, interstitial lung disease, and anemia. The prevalence of comorbidities, including hypothyroidism, diabetes mellitus (DM), hypertension, and hyperlipidemia, was also significant higher in the CVD group. In contrast, patients treated with methotrexate, hydroxychloroquine (HCQ), and TNF blockers had lower incidence of CVD. The multivariate analysis showed that the use of HCQ was a protective factor of CVD, while hypertension, hyperlipidemia, and interstitial lung disease were independent risk factors of CVD. Our study shows that the independent risk factors of CVD include hypertension, hyperlipidemia, and interstitial lung disease. HCQ reduces the risk of CVD in patients with RA.

Keywords Cardiovascular disease · Rheumatoid arthritis · Risk factor

Introduction

Rheumatoid arthritis (RA) is a common autoimmune disease characterized by chronic inflammation of synovial joints. Mortality in RA patients is 1.5–1.6-fold higher than that in the general population, and approximately 40% of all deaths in RA is attributed to cardiovascular disease (CVD), including ischemic heart disease and stroke [1, 2]. However, traditional cardiovascular risk factors such as family cardiac history, hypertension, dyslipidaemia, body mass index, and hypertension imparted significantly less risk for the development of cardiovascular disease in RA [3].

RA itself is recognized as an independent risk factor due to persistent inflammation [4]. The heightened inflammatory state and traditional cardiovascular risk factors interact to accelerate atherosclerosis in RA [5]. Recently, the European League Against Rheumatism (EULAR) made a conservative recommendation for a multiplication factor of 1.5 to the calculated CVD risk by Systematic Coronary Risk Evaluation (SCORE) if the RA patient had two or more of the following: disease duration >10 years, rheumatoid factor/anti-citrullinated protein antibody positivity, or extra-articular manifestations [6]. However, this modified SCORE (mSCORE) still cannot identify substantial proportion of RA patients at high risk for CVD [7–9]. Adequate stratification of CV risk in patients with RA is far from being completely established.

Conversely, treatments aimed at reducing disease activity in RA may have diverse impact on CVD risk. Disease-modifying anti-rheumatic drugs (DMARDs), especially methotrexate (MTX), and/or biologic agents, such as anti-TNF agents, have been reported to link with reduced risk for CVD by lessening the burden of systemic inflammation [10–12]. In contrast, patients treated with high-dose steroids (>7.5 mg/day prednisone) appear to have twice the risk of heart disease compared with those who do not receive steroids [13]. However, the pattern of drug usage may have been affected by indication bias in daily practice. For example, physicians may not describe high-dose steroids to patients with risk factors of CVD. The relationship between DMARDs and CVD needs to be validated in the real-world setting.

The present study had two major objectives. The first was to evaluate the prevalence of CVD and its risk factors in Chinese RA patients. The second was to determine the effect of DMARDs and other medications commonly used in RA on risk of CVD in a representative population sample in China.

Materials and methods

Patients This was an observational, cross-sectional, multicenter study. Two thousand thirteen subjects that fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA were consecutively recruited from 21 tertiary care hospitals across 10 provinces in China between July 2009 and December 2014. The study was approved by the Ethics Committee of Peking University People's Hospital, and informed written consents were obtained from all study participants (FWA00001384).

Data collection Data were collected by physician interview with patients face to face. We collected information on demographic characteristics and clinical profile of each patient, including the age of RA onset, disease duration, extra-articular manifestations, tender joint counts (TJCs), swollen joint counts (SJCs), and deformity joint counts (DJCs). Traditional CV risk factors, such as hypertension, diabetes mellitus (DM), and hyperlipidemia, were also recorded. The patient's medications associated with RA, such as DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticoid and biologic agents, were recorded in detail.

Cardiovascular disease and risk factors Cardiovascular disease was defined as a verified medical history of coronary, cerebral, or peripheral arterial disease [10]. Ischemic heart disease (IHD) included acute coronary syndromes and chronic

[21] Department of Rheumatology and Immunology, Second Hospital of Lanzhou University, 82 Cuiyingmen Rd, Lanzhou 730030, China

[22] Department of Cardiology, Fuwai Hospital, North Lishi Road, Beijing 100037, China

coronary heart disease. IHD was confirmed if any of the following criteria were satisfied: a recorded diagnosis of ischemic cardiopathy (CT), acute myocardial infarction or unstable angina, the presence of pathological Q waves in the electrogram with chest pain, and coronary images showing >50% stenosis of at least one coronary vessel [14]. Cerebral arterial disease included ischemic and hemorrhagic stroke as defined by clinical documentation of the diagnosis with confirmatory finding on computed tomography, magnetic resonance imaging, or autopsy. Peripheral arterial disease was defined as peripheral arterial reconstructive surgery, limb amputation, or an ankle brachial pressure index (ABPI) <0.50 [15].

Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg [16] or there was a physician's diagnosis in the medical record or an anti-hypertensive medication was prescribed. DM was diagnosed if the fasting blood glucose ≥7 mmol/L or a 2-h plasma glucose ≥11.1 mmol/L following a glucose load [17] or if the patient had diagnosed in the medical record or taken anti-diabetic medications. Hyperlipidemia involved abnormally elevated levels of any or all lipids and/or lipoproteins in the blood. Height and weight were measured at the time of visit, and body mass index (BMI) (kg/m^2) was calculated. Obesity was defined as BMI ≥27 kg/m^2, or overweight ≥23 kg/m^2, and ≤27 kg/m^2 on the revised criteria for Asian populations [18]. The diagnosis of interstitial lung disease (ILD) in RA patients was based on the findings of chest radiography or CT images.

Statistics Characteristics of the populations with a normal distribution were presented as means with standard deviations or as absolute numbers with percentages of the total. For variables with skewed distribution, the data are presented as medians and interquartile ranges (IQRs). The patients of our cohort were divided into RA with CVD (RA-CVD group) and RA without CVD group (RA-non-CVD group). Comparisons between the RA-CVD group and the RA-non-CVD group was performed using Student's *t* tests and Mann-Whitney *U* tests for continuous variables and Pearson's chi-squared tests for dichotomic variables.

To explore the relationship between DMARDs and CVD, the dataset was categorized into groups according to the use of hydroxychloroquine (HCQ), biologic agents, or MTX, either as monotherapy or as combinations of these drugs. The comparison also consisted of patients who never used any of DMARDs.

Logistic regression modeling was used to calculate the odds ratios (ORs) and 95% confidence intervals (95% CIs) of CVD for traditional risk factors, various manifestations, and medications of RA. These ORs were then adjusted for age and gender. *P* value <0.05 was considered statistically significant. SPSS 22.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used for all analyses.

Results

Descriptive characteristics of study population Among the 2013 RA subjects, 79.1% were women. All subjects were Chinese with mean age of 55.5 years (range 11.0–97.0 years). The median disease duration was 6.0 years (IQR 2.0–14.0 years). The median numbers of SJCs and TJCs were 3.0 (IQR 1.0–9.0) and 5.0 (IQR 2.0–14.0), respectively. The positive rate of anti-cyclic citrullinated peptide (CCP) antibody and rheumatoid factor (RF) were 81.5 and 80.0%. The prevalence of CVD was 12.7% (256/2013) in patients with RA.

Differences of clinical characteristics between RA subjects with and without CVD Table 1 presents the clinical characteristics of the RA patients with and without CVD. Compared with RA-non-CVD controls, the RA-CVD group had a significantly advanced age (68.2 ± 9.0 vs 53.7 ± 13.6 years, $P = 0.000$), long-standing median disease duration (IQR 10.0 vs 6.0 years, $P = 0.000$), and more often male (33.3 vs 19.1%, $P = 0.000$). The CVD group also had higher rates of diabetes mellitus, hypertension, hyperlipidemia, and smoking (Table 1). Furthermore, patients with CVD had more deformity joints (IQR 2 vs 0, $P = 0.000$). No significant differences were observed in BMI, TJCs, SJCs, prevalence of anti-CCP antibody, RF, levels of erythrocyte sedimentation rate (ESR), and CRP ($P > 0.05$).

The prevalence of rheumatoid nodules (15.3 vs 4.2%, $P = 0.000$), ILD (22.0 vs 10.3%, $P = 0.000$), hypothyroidism (4.3 vs 1.8%, $P = 0.000$), and anemia (21.3 vs 12.5%, $P = 0.000$) was higher in the CVD group (Table 1). RA patients in these two groups had similar frequencies of pleural effusion, pericardial effusion, cutaneous vasculitis, ophthalmitis, thrombocythemia, and renal involvement (Table 2).

Medications and CVD The percentage of DMARD naive patients was significantly higher in the RA-CVD group than the RA-non-CVD group (Table 2). Lower percentage of patients with CVD used HCQ (9.4 vs 19.7%, $P = 0.000$), MTX (37.0 vs 43.9%, $P = 0.038$), and TNF blockers (5.5 vs 13.8%, $P = 0.000$). The percentages of patients treated with HCQ or TNF blockers combined with other DMARDs were also lower in the CVD group (Table 2). However, no significant differences were observed in the treatment of SSZ, LEF, celecoxib, and prednisone.

Risk factors for CAD in RA patients To analyze the risk factors of CVD in RA, multivariate Cox regression tests were conducted using the following data: gender; age; disease duration; age of RA onset; hypertension; DM; smoking; hyperlipidemia; TJCs, SJCs, and DJCs; ESR; CRP; ILD; rheumatoid nodules; anemia; anti-CCP antibody and the use of HCQ,

Table 1 Characteristics of RA patients with or without CVD

	Total ($N = 2013$)	RA-CVD ($N = 256$)	RA-non-CVD ($N = 1759$)	P
Demographic features				
Age (years)[a]	55.5 ± 14.0	68.2 ± 9.0	53.7 ± 13.6	0.000*
Sex male *n* (%)	421 (20.9)	85 (33.3)	336 (19.1)	0.000*
Disease duration[a], IQR	6.0 (2.0–14.0)	10.0 (5.0–20.0)	6.0 (2.0–12.0)	0.000*
CAD-related variables				
Smoking, *n* (%)[b]	298 (15.6%)	62 (24.6%)	239 (14.3%)	0.000*
BMI (kg/m^2)[a]	22.9 ± 3.7	23.2 ± 4.3	22.9 ± 3.6	0.176
DM, *n* (%)[b]	216 (10.8%)	71 (27.8%)	147 (8.4%)	0.000*
Hypertension, *n* (%)[b]	500 (25.4%)	159 (62.4%)	350 (20.1%)	0.000*
Hyperlipidemia, *n* (%)[b]	119 (6.1%)	76 (29.8%)	43 (2.6%)	0.000*
RA-related variables				
No. of tender joint[a], IQR	5.0 (2.0–14.0)	6.0 (1.0–16.0)	5.0 (2.0–14.0)	0.275
No. of swollen joint[a], IQR	3.0 (1.0–9.0)	3.0 (0–11.0)	3.0 (1.0–9.0)	0.249
No. of deformity joint[a], IQR	0 (0–4.0)	2.0 (0–11.0)	0 (0–4.0)	0.000*
Rheumatoid factor (RF)	1102 (1378, 80.0%)	110 (148, 74.3%)	992 (1230, 80.7%)	0.069
Anti-CCP antibody	834 (1023, 81.5%)	76 (96, 79.2%)	758 (927, 81.8%)	0.532
ESR (mm/h)	49.2 ± 32.8	49.7 ± 32.7	49.1 ± 32.8	0.823
CRP (mg/L)	30.2 ± 46.6	32.1 ± 81.0	29.9 ± 39.6	0.726
Rheumatoid nodules, *n* (%)[b]	113 (5.6%)	39 (15.3%)	74 (4.2%)	0.000*
Pleural effusion, *n* (%)[b]	19 (1.0%)	3 (1.2%)	16 (0.9%)	0.725
Pericardial effusion, *n* (%)[b]	3 (0.2%)	1 (0.4%)	2 (0.1%)	0.334
Cutaneous vasculitis, *n* (%)[b]	12 (0.6%)	0	12 (0.7%)	0.382
Anemia, *n* (%)[b]	274 (13.6%)	54 (21.3%)	220 (12.5%)	0.000*
Ophthalmitis, *n* (%)[b]	47 (2.3%)	7 (2.8%)	40 (2.3%)	0.636
Hypothyroidism, *n* (%)[b]	42 (2.1%)	11 (4.3%)	31 (1.8%)	0.008*
Renal involvement, *n* (%)[b]	38 (1.9%)	5 (2.0%)	33 (1.9%)	0.808
Interstitial lung disease, *n* (%)[b]	236 (11.7%)	56 (22.0%)	180 (10.3%)	0.000*

CVD cardiovascular disease, *RA* rheumatoid arthritis, *DM* diabetes mellitus, *BMI* body mass index

*$P < 0.05$

[a] Data are presented as mean (SD)

[b] Data are presented as *n* (%)

MTX, celecoxib, prednisone, biologics; and patients who never use DMARDs. Hypertension, hyperlipidemia, and ILD were independently associated with CVD. In contrast, the use of HCQ conferred a protective effect for CVD in RA (Table 3).

Discussion

This study suggests that the prevalence of diabetes mellitus, hypertension, smoking, hyperlipidemia, and deformity joint was significantly higher in RA patients with CVD than those without. Multivariate regression tests showed that hypertension, hyperlipidemia, and ILD appeared to be independent risk factors for CVD in RA.

The prevalence of CVD was 12.7% in Chinese RA patients. Previous study based on Western population has shown that the prevalence of CVD in RA is 12.9% and is at least comparable to that of type 2 diabetes (DM) [15]. The increased CVD risk in RA is partly related to the high frequency of traditional CVD risk factors, such as hypertension [19–21]. In our study cohort, the prevalence of cardiovascular risk factors, such as hypertension and hyperlipidemia, was also increased. A meta-analysis concluded that RA was associated with an abnormal lipoprotein pattern, principally low levels of high-density lipoprotein (HDL) cholesterol [22]. Classic CVD

Table 2 The association of drugs and CVD

	RA with CVD ($N = 256$)	RA without CVD ($N = 1759$)	P
Never DMARDs, *n* (%)	87 (34.4%)	480 (27.7%)	0.028*
MTX ever, *n* (%)	94 (37.0%)	760 (43.9%)	0.038*
HCQ ever, *n* (%)	24 (9.4%)	342 (19.7%)	0.000*
LEF ever, *n* (%)	111 (43.7%)	838 (48.4%)	0.165
SSZ ever, *n* (%)	26 (10.2%)	242 (14.0%)	0.103
Prednisone ever, *n* (%)	97 (38.2%)	586 (33.9%)	0.174
Celecoxib ever, *n* (%)	12 (4.7%)	75 (4.3%)	0.774
Biologics ever, *n* (%)	14 (5.5%)	240 (13.8%)	0.000*
Current MTX + other DMARDs, *n* (%)	45 (17.8%)	387 (22.4%)	0.099
Current HCQ + other DMARDs, *n* (%)	19 (7.5%)	231 (13.3%)	0.009*
Current prednisone + other DMARDs, *n* (%)	38 (15.0%)	209 (12.1%)	0.195
Current biologics + DMARDs, *n* (%)	6 (2.4%)	119 (6.9%)	0.006*

Data are presented as *n* (%)

CVD cardiovascular disease, *RA* rheumatoid arthritis, *DMARDs* disease-modifying anti-rheumatic drugs, *HCQ* hydroxychloroquine, *MTX* methotrexate, *LEF* leflunomide, *SSZ* sulfasalazine

*$P < 0.05$

Table 3 Risk factors for CVD in RA, as determined using multivariate analysis

Variable	OR (95% CI)	P
Gender	0.567 (0.243–1.320)	0.188
Age	1.027 (0.928–1.137)	0.605
Disease duration	1.087 (0.989–1.196)	0.085
Smoking	1.830 (0.758–4.416)	0.179
Age of RA onset	1.067 (0.969–1.175)	0.188
SJCs	0.990 (0.946–1.035)	0.644
TJCs	0.995 (0.963–1.029)	0.782
DJCs	1.026 (0.987–1.066)	0.197
ESR	1.009 (0.999–1.019)	0.076
CRP	0.993 (0.984–1.002)	0.145
Anti-CCP antibody	0.980 (0.373–2.573)	0.967
Hypertension	4.073 (2.091–7.931)	0.000*
Hyperlipidemia	15.114 (5.962–38.314)	0.000*
DM	1.155 (0.512–2.603)	0.729
Interstitial lung disease	2.942 (1.281–6.758)	0.011*
Anemia	2.316 (0.846–6.341)	0.102
Rheumatoid nodules	1.390 (0.393–4.913)	0.609
The use of HCQ	0.192 (0.052–0.705)	0.013*
The use of MTX	0.799 (0.379–1.685)	0.555
The use of prednisone	0.785 (0.386–1.594)	0.503
The use of celecoxib	0.183 (0.017–1.977)	0.183
The use of biologics	0.348 (0.081–1.504)	0.158
Never DMARDs	0.708 (0.338–1.483)	0.361

SJCs swollen joint counts, *TJCs* tender joint counts, *DJCs* deformity joint counts, *CVD* cardiovascular disease, *RA* rheumatoid arthritis, *DM* diabetes mellitus, *HCQ* hydroxychloroquine, *MTX* methotrexate, *OR* odd ratio

*$P < 0.05$

risk factors appear to predict the progression of carotid plaque [21] and associate with vascular function and morphology in patients with RA [23]. Recent study has shown that higher blood pressure is associated with coronary artery calcium (CAC) [24], which implies a higher risk of coronary artery disease. All the results suggest that established CV risk factors play an important role in the CV morbidity that occurs in RA, as they do in the general population. Aggressive screening and controlling blood pressure and lipids are helpful in RA patients with high risk of CVD.

This is the first study to show that ILD is an independent risk factor for CVD in patients with RA. ILD is related to both disease activity and anti-CCP antibodies and served as a poor prognosis marker [25]. This gained support to the role of inflammation in the development of CVD in RA. RA patients with ILD should be assessed for CVD due to their high risk of developing CVD.

In the present study, we confirmed that the use of HCQ was a protective factor of CVD in the real world. Hydroxychloroquine (HCQ) is an anti-malarial medication used as a basic DMARD in the treatment of RA. Previous studies have indicated several potential mechanisms why HCQ reduced the risk of CVD. First, the use of HCQ is independently associated with a significant decrease in low-density lipoprotein (LDL), total cholesterol, LDL/HDL, and total cholesterol/HDL [26]. Second, HCQ may have potential benefits on lowering blood pressure [27], providing one substitutive reason for HCQ reducing the risk for CVD. Third, HCQ could reduce the risk of CVD by improving glycemic control in patients with RA [28]. Abdominal obesity, antihypertensive therapy, disease activity, and use of

glucocorticoids affect glucose metabolism in RA [29]. Conversely, HCQ has the beneficial effects on glucose metabolism and insulin sensitivity [30, 31], thus reduces the risk of developing diabetes in RA by around 77% [32]. Fourth, HCQ reduces the risk of CVD by the anti-inflammatory effect. Epidemiological, clinical, and laboratory investigations have shown that the immune system and inflammation play a major role in all stages of atherosclerosis and contribute considerably to the increased cardiovascular risk [33]. It is likely that the beneficial effect on CVD is conferred by controlling systemic inflammation in RA. However, it cannot be ruled out that there might be some other mechanisms by which HCQ use could influence the risk for CAD.

In our study, patients treated with TNF blockers had lower incidence of CVD. Several studies have shown that TNF blockers are associated with a decreased risk of all cardiovascular events [34, 35]. Different biologic drugs have different effects on the risk of CVD in patients with RA. Treatment with tocilizumab (TCZ) results in elevations in mean lipid levels. Although such elevations are also found in the treatment with anti-TNF blockers, they are of greater magnitude [36, 37]. However, a recent study has shown that greater reduction in RA disease activity during TCZ therapy were associated with a statistically significantly lower risk of major adverse cardiovascular event [38]. Abatacept, another biologic, has been implicated to improve whole-body insulin sensitivity [39], thus may reduce the risk of CVD in rheumatoid arthritis. The effects of rituximab remain inconclusive [36, 40]. In summary, biologics should not be banned in patients with high risk of CVD when weighing the risks versus benefits of these medications.

Some potential limitations should be considered when interpreting our results. First, it was a cross-sectional retrospective study. The pattern of drug usage may have been affected by indication bias. Second, family history is a risk factor of CVD, but it is not available in our study. Third, it is important to screen the CV disease in female RA patients. Male gender is a traditional risk factor and important variable in Framingham Risk Score (FRS), Reynolds Risk Score (RRS), and the SCORE for CVD [41]. So CVD may be more likely to be suspected in men and less diagnosed in women. Although we screened the symptoms and history of CVD carefully in our study, underdiagnosis in female RA patients might be possible. Prospective studies are warranted. However, it is one of the largest real-world studies on CVD and its risk factors in patients with RA in China. And this cross-sectional, multicenter study reflects the actual drug use in Chinese patients with RA.

In conclusion, this is the first study showing the prevalence of CVD and risk factors in Chinese RA patients. Our study demonstrates that concomitant with hypertension, hyperlipidemia and ILD increase the risk for CVD, while HCQ plays a protective role for the risk of CVD in RA patients. Adequate control of disease activity, extra-articular manifestations, and traditional CV risk factors, such as hypertension and hyperlipidemia, are of main importance to successfully reducing CVD in RA patients. The findings of this study support the potential benefit of HCQ in CVD. Along with its excellent safety profile and low cost, HCQ is a beneficial first-line or adjunct therapy for RA patients, especially in those with established CVD and risk factors.

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Compliance with ethical standards The study was approved by the Ethics Committee of Peking University People's Hospital, and informed written consents were obtained from all study participants (FWA00001384).

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