Tropical Journal of Pharmaceutical Research April 2022; 21 (4): 863-870
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i4.25

Original Research Article

Cardiovascular risks and primary interventions among treated rheumatoid arthritis patients: Experience from a tertiary care centre in Kuala Lumpur, Malaysia

Shantini Radhakrishnan[1], Salmi Abdul Razak[1], Mohd Shahrir Bin Mohamed Said[2], Noraida Mohamed Shah[1], Adyani Md Redzuan[1]*

[1]Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, [2]Medical Department, UKM Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Kuala Lumpur, Malaysia

For correspondence: **Email: adyani@ukm.edu.my; **Tel:** +60-392897264*

Sent for review: 27 May 2022 *Revised accepted: 6 March 2022*

Abstract

Purpose: *To investigate the cardiovascular risk among treated rheumatoid arthritis (RA) patients to predict the factors associated with high cardiovascular risk and to determine the presence of pharmacotherapy primary prevention among treated RA patients with high cardiovascular disease (CVD) risk.*
Methods: *The study was a prospective cross-sectional study on adult patients diagnosed and treated for RA and without established heart disease/stroke. Cardiovascular risk scoring was based on Framingham Cardiovascular Disease 10-year risk prediction model (BMI model) x 1.5 factor while descriptive and inferential analyses were done using SPSS.*
Results: *High CVD risk was defined as FRS-CVD cardiovascular risk categories (>20%) and 55.9% of patients were at high CVD risk. Use of Hydroxychloroquine (OR: 0.44; 95 % CI: 0.21- 0.92; p= 0.028) and COX-2 inhibitors (OR: 0.31; 95% CI:0.10- 0.95; p = 0.039) were found to be significantly associated with high CVD risk among treated RA patients. Significant number of high CVD risk patients did receive pharmacotherapy primary prevention (p = 0.001).*
Conclusion: *Hydroxychloroquine and COX-2 inhibitors are independent negative risk predictors associated with high CVD risk among treated RA patients. Baseline cardiovascular risk data may be useful in rational use of medications to treat RA, considering that cardiovascular related mortality is the leading cause of death in RA.*

Keywords: *Cardiovascular risk, Rheumatoid Arthritis, primary prevention, high CVD risk*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by a symmetrical inflammatory polyarthritis but extra-articular features are also common. Almost 50 % of the risk for development of RA is due to genetic factors and smoking is the main environmental risk [1]. The annual incidence of RA is approximately 3 cases per 10,000 population worldwide and the prevalence rate is approximately 1 % [2]. In Malaysia, RA is the

most common form of inflammatory arthritis and is estimated to affect about 1 % of the population [3]. The most common age for the disease to start is between 30 to 50 and women are more commonly affected than men.

Patients with RA have a 1.5 to 2.0-fold increased risk of developing coronary artery disease (CAD) compared with the general population, and similar in magnitude to the risk imparted by diabetes mellitus [4]. Patients with RA also have twice the risk of developing heart failure [5]. RA was associated with a 48 % increased risk of cardiovascular events and a 50 % higher incidence of cardiovascular disease (CVD) related mortality compared with the general population [6].

The aim of this study was to evaluate cardiovascular risk among treated rheumatoid arthritis patients in a tertiary care centre, Kuala Lumpur, Malaysia. Specific objectives were to determine the risk of developing CVD, to predict the factors associated with high CVD risk and to determine the presence of pharmacotherapy primary prevention among treated rheumatoid arthritis patients with high CVD risk.

METHODS

Study design and population

This was a prospective observational study with cross-sectional inclusion of patients. This study was conducted in the Rheumatology Clinic of Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Kuala Lumpur. The target population for this study was treated rheumatoid arthritis patients attending Rheumatology Clinic in UKMMC. The data collection was carried out over a period of 3 months from March 2019 to May 2019. Inclusion criteria for this study were patients diagnosed and treated for RA by a rheumatologist according to the 1987 ACR criteria for RA, and must be at least 30 years old. Patients were excluded if they were diagnosed with ankylosing spondylitis, psoriatic arthritis or systemic lupus erythematous, established cardiovascular disease/history of stroke or patients were diagnosed with RA but currently not receiving any treatment.

Data collection

The tools used in this study consist of data collection form and cardiovascular risk scoring based on Framingham Cardiovascular Disease 10-year risk prediction model [Body Mass Index (BMI) model] x 1.5 factor in RA patients. The cardiovascular risk assessment based on FRS took into account gender, age, systolic blood pressure, treatment of hypertension, BMI, presence of diabetes and smoking status. The data collection form was in English. It consists of five sections, namely demographics of patient, cardiovascular risk assessment, past medical history, RA related variables and finally on patient's drug therapy. Cardiovascular risk assessment was performed by nurses at the rheumatology clinic and researcher (registered pharmacist).

Information on demographic profile, past medical history and smoking status were obtained from the patients. Blood pressure, weight, height and waist circumference were measured at the nursing counter. Other information necessary to fill into the data collection form was gathered from patients' medical record after being seen by a rheumatologist. Information given by patients were counterchecked with patients' medical record. The subject's registration number was recorded to trace lab values and medication records from the UKMMC lab and pharmacy system.

High CVD risk was defined as FRS-CVD cardiovascular risk categories (>20%). Treated to target (low disease activity/ remission) was stated on the patient medical record after being seen by a rheumatologist. Patients' disease activity was measured by a rheumatologist using the disease activity score in 28 joints (DAS28)–ESR score. RA medications were traced from medications prescribed in the UKMMC pharmacy system. They consist of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) namely Methotrexate, Hydroxychloroquine, Sulphasalazine and Leflunamide and Targeted synthetic tsDMARDs such as Tofacitinib. Biological DMARDs include tumour necrosis factor inhibitors TNFi biologics such as adalimumab, etanercept, golimumab or infliximab. Non-TNFi biologics abatacept, rituximab and tocilizumab. Glucocorticoids use include low dose glucocorticoids defined as <10 mg of oral prednisolone/day and high dose glucocorticoids defined as > 10 mg of oral prednisolone/day and up to 60 mg/day with a rapid taper. Short term glucocorticoids are defined as < 3 months treatment [8]. Traditional non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX-2) inhibitors use were included as well.

BMI was calculated as weight (kg) by squared height (m^2) thereafter. BMI was categorized into 4 groups which are underweight (BMI <18.50 kg/m^2), normal (BMI: 18.50-24.99 kg/m^2), overweight (BMI: 25- 29.99 kg/m^2) and obese

(BMI ≥ 30.00 kg/m^2) [9]. Waist circumference (cm) was measured 2 cm above the patients' umbilicus (midway between the lower rib margin and the iliac crest). The lipid profile consisted of TC, LDL-C, HDL-C and TG all in mmol/L. Lipid profile, fasting blood glucose level and HbA1C level were obtained from the UKMMC lab system within the past 6 months if available.

Statistical analysis

IBM® Statistical Package for Social Sciences (SPSS) Desktop version 25 software was used to conduct all statistical analyses in this study. Descriptive statistic was used to analyse demographic data and cardiovascular risk assessment. Categorical data such as gender, ethnic group, family history of heart disease/stroke, BMI by category, past medical history, treat to target (remission/low disease activity), rheumatoid arthritis medications, smoking status and FRS-General CVD scoring were presented as frequency and percentage.

Continuous data such as age, duration of rheumatoid arthritis disease, ESR, CRP, weight, height, waist circumference, blood pressure, lipid profile, fasting blood glucose and HbA1C level were presented as mean ± standard deviation (SD) or median and interquartile range depending on normality distribution. Kolmogorov-Smirnov equation was used to test for normality for all continuous variables in this study.

Multivariate analysis was performed using multiple logistic regression to analyse the association of CV risk factors at baseline for the development of high CVD risk. Factors with a probability value of less than 0.25 at univariate analysis were included in the multivariate analysis. The chi-squared analysis will be used to compare the presence of pharmacotherapy primary prevention (yes/no) with categorical high cardiovascular risk (yes/no) among treated rheumatoid arthritis patients. In this study, pharmacotherapy primary prevention was based on statin use. Anti-hypertensive use was taken into account during CVD risk stratification. $P < 0.05$ was taken as statistically significant and a confidence interval of 95 % was utilised.

Ethical approval

Ethics approval was obtained from the Universiti Kebangsaan Malaysia (UKM) Research Ethic Committee prior to the commencement of the study (approval no. UKM PPI/111/8/JEP-2019-061). All procedures performed in studies were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration.

RESULTS

A total of 161 patients were recruited in this study. All patients were randomly screened and 66 patients were excluded. Reasons for exclusion include the following: 12 patients were wheelchair bound so not able to measure height and weight, 14 patients were walk in patients with other inflammatory joint disease who came in during RA clinic, 4 patients were RA patients who are not treated due to disease remission or defaulted treatment and 36 patients were RA patients with established CVD or history of stroke. Baseline demographics and clinical characteristics are as presented **(**Table 1**)**.

Cardiovascular risk assessments are summarized in (Table 2). Framingham Risk Score (FRS)-General CVD Risk scoring showed 35.4 % of patients having high CV risk (>20 %) followed by 20.5 % patients having very high CV risk (>30 %). 40.4 % and 19.9 % of patients were overweight and obese respectively. High CVD risks are taken as CVD risk score >20 % which is including very high-risk patients. A total of 161 patients; 90 (55.9 %) high CVD risk patients versus 71 (44.1 %) non-high CVD risk patients were included in univariate analysis and further multivariate analysis were conducted to predict any possible factors associated with high CVD risk among treated rheumatoid arthritis patients.

Using chi-squared or Fisher's exact analysis, patients with and without high CVD risk differed significantly with regard to hyperlipidemia (χ^2 = 18.1; p = 0.0001), hydroxychloroquine (HCQ) use (χ^2 = 4.03; p = 0.045) and chronic kidney disease (p = 0.018). Using T-test or Mann Whitney U test patients with and without high CVD risk differed significantly with regard to duration of rheumatoid arthritis disease (U = 2545.5; p = 0.027), TG level (U = 2182; p = 0.004), fasting blood glucose level (U = 1870.1; p = 0.001) and HbA1C level (U = 575.5; p = 0.0001).

Biological DMARDs (p = 0.242), high dose glucocorticoids (p = 0.242), COX-2 inhibitors (χ^2 = 3.27; p = 0.07), and anti-platelet use (p = 0.12), were found to have close probability value of less than 0.25 and thus were included into the multivariate analysis. NSAIDs use (p = 0.282) and treated to target (low disease activity/remission) patients (p = 0.32) were also included into the multivariate analysis considering them as clinically important factors.

Table 1: Baseline demographics and clinical characteristics (n = 161)

Characteristics	Frequency (n %)
Gender (%)	
Male	17 (10.6)
Female	144 (89.4)
Ethnic group (%)	
Malay	84 (52.2)
Chinese	48 (29.8)
Indian	26 (16.1)
Others	3 (1.9)
[a]Age (IQR), year	61 (52-68)
[a] Duration of RA disease (IQR), years	9 (5-16.5)
Family history of heart disease/stroke	
Yes	53 (32.9)
No	108 (67.1)
BMI by Category (%)	
Underweight	9 (5.6)
Normal	55 (34.2)
Overweight	65 (40.4)
Obese	32 (19.9)
Past Medical History (%)	
Hypertension	87 (54)
Diabetes Mellitus	39 (24.2)
Hyperlipidemia	71 (44.1)
Chronic Kidney Disease	7 (4.3)
Thyroid Disease	9 (5.6)
Asthma	12 (7.5)
Concomitant cardiovascular related medications (%)	
Antihypertensives	79 (41.1)
Antiplatelet	16 (9.9)
Statin	73 (45.3)
RA related variables	
[a]ESR (mm/Hr)	41 (28-65.5)
[a]CRP (mg/dL)	0.47 (0.25-1.19)
Remission/Low Disease activity (Treat to target)	109 (67.7)
RA medications (%)	
[b]Conventional Synthetic csDMARDs	159 (98.8)
Methotrexate	104 (64.6)
Hydroxychloroquine	46 (28.6)
Leflunomide	55 (34.2)
Sulphasalazine	40 (24.8)
Targeted Synthetic tsDMARDs	12 (7.5)
Biological DMARDs	7 (4.3)
Glucocorticoids	
Low dose glucocorticoids	87 (54)
High dose glucocorticoids	7 (4.3)
Short Term Glucocorticoids	2 (1.2)
NSAIDS	24 (14.9)
COX-2 Inhibitor	17 (10.6)

Abbreviations: *IQR – Interquartile Range; BMI – Body mass index; ESR–Erythrocyte sedimentation rate; CRP – C-reactive protein; DMARDs – Disease modifying anti-rheumatic drugs; NSAIDs – Non-steroidal anti-inflammatory drugs; COX-2 inhibitor – Cyclooxygenase 2 inhibitor, [a]Median (interquartile range); [b] Use of any one of the four choices (Methotrexate, Hydroxycloroquine, Leflunomide or Sulphasalazine)*

Table 2: Cardiovascular risk factors (n = 161)

Parameter	Mean ± SD or Median (IQR)
[a]Weight (kg)	63 (54.8-74)
Height (cm)	156.8 ± 6.8
BMI by Category (%)	
Underweight	9 (5.6)
Normal	55 (34.2)
Overweight	65 (40.4)
Obese	32 (19.9)
Waist circumference (cm)	98.18 ± 12.43
Male	98.35 ± 11.1
Female	98.16 ± 12.61
Smoking status	
Yes	4 (2.5)
No	157 (97.5)
Blood pressure (mmHg)	
Systolic (mmHg)	137 ± 18
[a]Diastolic (mmHg)	72 (64.5-80)
Lipid profile (n=156)	
[a]Total Cholesterol (mmol/L)	4.88 (4.38-5.68)
LDL-C (mmol/L)	3.04 ± 0.9
HDL-C (mmol/L)	1.47 ± 0.4
Male	1.41 ± 0.40
Female	1.48 ± 0.40
[a]Triglyceride (TG) (mmol/L)	1.09 (0.8-1.45)
[a]Fasting blood glucose (mmol/L) n=149	5.43 (4.82-6.38)
[a]HbA1C (%) n=98	5.7 (5.4-6.6)
FRS-General cvd scoring	**Frequency (n, %)**
Very High CV risk (>30%)	33(20.5)
High CV risk (>20%)	57(35.4)
Intermediate (or Moderate) CV risk (10-20%)	14(8.7)
Low CV risk (<10%)	57(35.4)

Abbreviations: *IQR – Interquartile Range; BMI – Body mass index; LDL-C–Low density lipoprotein cholesterol; HDL-C – High density lipoprotein cholesterol; FRS –Framingham risk score;CV – Cardiovascular; CVD – Cardiovascular disease. [a] Median (Interquartile Range)*

Multivariate analysis **(**Table 3**)**, adjusted for treated to target (remission or low disease activity, HCQ, Biological DMARDs, High dose glucocorticoids, NSAIDs, COX-2 inhibitors and anti-platelet use) revealed that Hydroxychloroquine (odds ratio OR: 0.44; 95 % CI: 0.21- 0.92; p= 0.028) was associated with high CVD risk among treated rheumatoid arthritis patients. This translates to 56 % lower chance of high CVD risk development in treated rheumatoid arthritis patients. Similarly, those who received COX-2 inhibitors were less likely to have high CVD risk by 69 % (odds ratio OR: 0.31; 95 % CI:0.10- 0.95*; p* = 0.039).

Table 3: Multivariate analysis regarding predictors of factors associated with high CVD risk among treated RA patients

Variable	B	*P*-value	OR	95% CI
Treated to target (Remission/Low disease activity)	-0.428	0.253	0.652	0.31-1.36
Hydroxychloroquine	-0.829	0.028*	0.436	0.21-0.92
Biological DMARDs	-1.484	0.118	0.227	0.04-1.46
High Dose Glucocorticoids	-1.163	0.206	0.313	0.05-1.90
NSAIDS	-0.538	0.256	0.584	0.23-1.48
COX-2 inhibitors	-1.18	0.039*	0.307	0.10-0.95
Antiplatelet	1.138	0.075	3.122	0.89-10.91

*Omnibus Test: $p < 0.05$; Hosmer and Lemeshow Test $\chi^2 = 12.293$, $df = 7$, $p = 0.091$. Abbreviations: OR – Odds Ratio; CI – Confidence Interval; *p <0.05 denotes statistical significance*

Using Chi-squared analysis, patients with and without high CVD risk differed significantly with regard to primary prevention ($\chi^2 = 23$; p-value = 0.0001). Based on our findings, patients with high CVD risk were more likely to receive primary prevention therapies.

DISCUSSION

This study gave an overview of cardiovascular risk among treated RA patients in a tertiary teaching hospital. To the best of the author's knowledge, this is the first study done locally on cardiovascular risks and primary interventions among treated RA patients.

In total, 55.9% of our RA population had high CV risk. This percentage is higher compared to a Danish study where systematic screening for cardiovascular risk in patients with rheumatoid arthritis showed 20.2% had high CV risk [10]. This discrepancy might be due to the differences in the tools utilized for the CV risk assessment. Our study used Framingham Cardiovascular Disease 10-year risk prediction model, whereas Primdahl *et al* used Systematic Coronary Risk Evaluation Model (SCORE).

Two independent risk predictors of high CVD risk found in this study were HCQ use and COX-2 inhibitors use. Both factors were found to reduce high CVD risk. HCQ is a csDMARD and is often added to Methotrexate therapy in patients with RA. Many studies have reached similar results that HCQ used as a predictive factor for CV risk reduction. Recent systematic review and meta-analysis showed a similar tendency towards a reduced risk of CVD with HCQ [11,12]. Multinational systematic review with meta-analysis of the metabolic and cardiovascular impact of HCQ in patients with RA showed a positive impact on metabolic and cardiovascular outcomes in patients with RA by decreasing modifiable factors for CVD, namely lipid profile, diabetes incidence, glycosylated haemoglobin level and by decreasing the incidence of cardiovascular events [13]. Our study population are patients without prior CVD events thus HCQ use may be considered by clinicians as an adjunct treatment for RA patients with high CVD risk.

RA patients are at high risk of cardiovascular events from analgesic use. NSAIDs and COX-2 inhibitor use was evident in 14.9% and 10.6% respectively and the majority of patients in this study received Meloxicam (NSAIDs) and Celecoxib (COX-2 inhibitor). The choice of NSAID and COX-2 inhibitor used in this study is a comparatively safe option. This study postulates COX-2 inhibitor use can be considered by clinicians as a safe option of pain killer for RA patients with high cardiovascular risk. In the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial celecoxib was associated with numerically fewer cardiovascular events which resulted in noninferiority p values as compared with two widely used nonselective NSAIDs [14]. Cardiovascular risk is highest with Etoricoxib and lowest with Celecoxib among presently available COX-2 inhibitors. NSAIDs also increase cardiovascular events, the risk is highest with diclofenac and lowest with naproxen. Nevertheless, adverse cardiovascular events can occur within a week of initiation of analgesic treatment [15]. A Cochrane systematic review concluded that there are no studies to guide clinicians on the best choice of analgesic in RA patients with cardiovascular risk factors [16].

It is interesting to observe that the treated-to-target (remission/low disease activity), high dose glucocorticoid use and NSAIDS use found in this study subjects did not emerge as a predictor for high CVD risk. The possible reason for treated-to-target (remission/low disease activity) not emerging as an independent predictor for high CVD risk could be due to cross sectional design of the study in which the effect of disease activity

over time cannot be observed. Since systemic inflammatory process in RA is also responsible for the increased CVD risk, glucocorticoid use might enhance or mitigate the pre-existing CVD risk. Retrospective analysis of exposure to glucocorticoids in a prospective cohort of 350 RA patients highlighted confounding by indication probably distorts the relationship between glucocorticoid exposure and CVD in RA. The adverse cardiovascular effects of glucocorticoids might be balanced by positive effects working through inflammation control [17].

This analysis showed an increased risk for CVD among antiplatelet mostly aspirin (ASA) users but was not statistically significant. Co-prescription of ASA and NSAIDs/COX-2 inhibitors may interfere with the anti-platelet effects of ASA. If a person with RA needs to take low-dose aspirin, healthcare professionals should consider other treatments before adding an NSAIDs if pain relief is ineffective or insufficient [18]. A recent case-crossover study and a propensity score-matched cohort study did not find a protective effect of ASA on myocardial infarction in patients with RA when used as primary prophylaxis [19]. An Italian multicenter retrospective study on low-dose ASA as primary prophylaxis for cardiovascular events in RA found ASA treatment and HCQ treatment as negative predictors for cardiovascular events [20].

Although methotrexate use has been well known predictive factor for the reduction in CV risk, in our study the finding was contrary. This could be due to the proportions of patients on MTX which appeared rather similar in both high and non-high CVD group thus the predictive impact may be less significant. In a meta-analysis of observational studies, methotrexate use among patients with systemic inflammation (mainly RA) was associated with 21% lower CVD risk, with little evidence of between-study heterogeneity [21]. In this study, biologics use was found to be associated with a reduction in CV risk but not statistically significant. This could be due to the proportions of patients of biologics users being relatively small and appeared rather similar in both high and non-high CVD group. Elevated tumor necrosis factor (TNF) may contribute to the excess cardiovascular risk observed in rheumatoid arthritis. The hazard ratio for cardiovascular events for rheumatoid arthritis patients using TNF-a blocking agent compared with nonbiologic DMARDs was reduced by 20% to 29% [22].

This study found a significant number of high-risk patients did receive primary prevention. Rational use of medications plays a role in CVD reduction in high CVD risk RA patients. This study gave an insight into potential of HCQ use as part of treatment in high CVD risk patients. COX-2 inhibitors such as celecoxib may be preferred as pain relief over traditional NSAIDs. Since the current study found that HCQ use and COX-2 inhibitor use act as an independent negative predictive factor associated with high CVD risk in treated RA patients, it will be interesting to explore further on the role of HCQ as primary prevention in high CVD risk RA patients.

Comparative effectiveness studies of various treatment options with a larger sample size, longer follow-up and relatively large subgroups of patients are needed to address this key issue in RA therapy that could possibly influence the choice of the preferred treatment based on baseline CVD risk. A multicenter study can be considered to increase the sample population and study power which allow better generalisation of study outcomes to the nation.

Limitations of the study

This study highlighted the use of HCQ and COX-2 inhibitors as negative predictors for high CVD risk. However, these results should be interpreted cautiously due to few limitations. The RA disease activity reported in this study was obtained at only a single time point. This might not reflect the natural fluctuating course of RA disease. The cross-sectional nature makes it impossible to determine causality. Another limitation was the small number of RA patients recruited in this study, which was mainly due restricted study period. Nevertheless, we would like to highlight that being one of the few public rheumatology centres in the central region of Malaysia which serves a large population, our results are very likely to be representative of the real clinical setting. Since this is a single centre design involving a teaching hospital, the choice of medications used may differ from public rheumatology centers or the private sector due individualized budget constraints and management. Missing data on cardiovascular risk management due to shared care between the treating rheumatologist and the patient's general practitioner may be possible.

CONCLUSION

The findings in this study have provided valuable insight on cardiovascular risks among treated RA patients. A total 55.9 % of RA patients were found to be at high cardiovascular risk with HCQ use and COX-2 inhibitors use being independent negative risk predictors associated with high

CVD risk among treated RA patients. HCQ may benefit as adjunct treatment combined with other DMARDs and COX-2 inhibitors may be preferred over traditional NSAIDs for pain relief in high CVD risk patients. A significant number of high CVD risk patients did receive pharmacotherapy primary prevention. Baseline cardiovascular risk data may be useful in the rational use of medications to treat RA considering cardiovascular-related mortality being the leading cause of death in RA.

DECLARATIONS

Acknowledgement

The authors would like to thank and acknowledge the efforts of UKMMC staffs for assisting in the process of data collection. Special thanks to the patients who participated in this study.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating the content of this article will be borne by authors. Adyani Md Redzuan conceived the original idea, developed the methods, and edited the manuscript. Shantini Radhakrishnan was involved in the data collection, statistical analysis and wrote the manuscript. Noraida Mohamed Shah, Mohd Shahrir Bin Mohamed Said and Salmi Abdul Razak assisted in the data collection process and critically revised the article for intellectual content. All authors read and approved the manuscript for publication.

REFERENCES

1. *Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet. 2010 Sep 25;376(9746):1094-1108. doi: 10.1016/S0140-6736(10)60826-4. PMID: 20870100.*
2. *World Health Organization (WHO) Chronic diseases and health promotion. Chronic rheumatic conditions. [Internet]. [cited 2019 Jul 12]. Available from: from: http://www.who.int/chp/topics/rheumatic/en/*
3. *NATIONAL INFLAMMATORY ARTHRITIS REGISTRY (NIAR) [Internet]. [cited 2019 Jul 23]. Available from: https://app.acrm.org.my/niar/*
4. *Van Halm VP, Peters MJ, Voskuyl AE, Boers M, Lems WF, Visser M, Stehouwer CD, Spijkerman AM, Dekker JM, Nijpels G, et al. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. Ann Rheum Dis. 2009 Sep;68(9):1395-1400. doi: 10.1136/ard.2008.094151. Epub 2008 Aug 12. PMID: 18697775.*
5. *Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV, Gabriel SE. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum 2005; 52(2): 412-420. doi: 10.1002/art.20855. PMID: 15692992.*
6. *Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2012; 71(9): 1524-1529. doi: 10.1136/annrheumdis-2011-200726. Epub 2012 Mar 16. PMID: 22425941.*
7. *Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, Nam J, Ramiro S, Voshaar M, van Vollenhoven R, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017 Jun;76(6):960-977. doi: 10.1136/annrheumdis-2016-210715. Epub 2017 Mar 6. PMID: 28264816.*
8. *Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016 Jan;68(1):1-26. doi: 10.1002/art.39480. Epub 2015 Nov 6. PMID: 26545940.*
9. *Ministry of Health Malaysia (MOH), Health Online Unit [Internet]. [cited 2019 Jul 12]. Available from: http://www.myhealth.gov.my/en/bmi/*
10. *Primdahl J, Clausen J, Hørslev-Petersen K. Results from systematic screening for cardiovascular risk in outpatients with rheumatoid arthritis in accordance with the EULAR recommendations. Ann Rheum Dis. 2013 Nov;72(11):1771-1776. doi: 10.1136/annrheumdis-2013-203682. Epub 2013 Jul 12. PMID: 23852694.*
11. *Liu D, Li X, Zhang Y, Kwong JS, Li L, Zhang Y, Xu C, Li Q, Sun X, Tian H, Li S. Chloroquine and*

hydroxychloroquine are associated with reduced cardiovascular risk: a systematic review and meta-analysis. Drug Des Devel Ther. 2018 Jun 11; 12:1685-1695. doi: 10.2147/DDDT.S166893. PMID: 29928112; PMCID: PMC6001837.

12. *Li C, Wang XR, Ji HJ, Zhang XY, Li XF, Wang LZ, Wang CH, Wang YF, Yang R, Wang GC, et al. Cardiovascular disease in rheumatoid arthritis: medications and risk factors in China. Clin Rheumatol. 2017 May;36(5):1023-1029. doi: 10.1007/s10067-017-3596-7. Epub 2017 Mar 24. PMID: 28342151.*
13. *Rempenault C, Combe B, Barnetche T, Gaujoux-Viala C, Lukas C, Morel J, Hua C. Metabolic and cardiovascular benefits of hydroxychloroquine in patients with rheumatoid arthritis: a systematic review and meta-analysis. Ann Rheum Dis. 2018 Jan;77(1):98-103. doi: 10.1136/annrheumdis-2017-211836. Epub 2017 Sep 25. PMID: 28970215.*
14. *Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, Libby P, Husni ME, Graham DY, Borer JS, Wisniewski LM, Wolski KE, et al. PRECISION Trial Investigators. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med. 2016 Dec 29;375(26):2519-2529. doi: 10.1056/NEJMoa1611593. Epub 2016 Nov 13. PMID: 27959716.*
15. *McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. PLoS Med. 2011 Sep;8(9): e1001098. doi: 10.1371/journal.pmed.1001098. Epub 2011 Sep 27. PMID: 21980265; PMCID: PMC3181230.*
16. *Marks JL, Colebatch AN, Buchbinder R, Edwards CJ. Pain management for rheumatoid arthritis and cardiovascular or renal comorbidity. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD008952. doi: 10.1002/14651858.CD008952.pub2. PMID: 21975789.*
17. *Van Sijl AM, Boers M, Voskuyl AE, Nurmohamed MT. Confounding by indication probably distorts the relationship between steroid use and cardiovascular disease in rheumatoid arthritis: results from a prospective cohort study. PLoS One. 2014 Jan 30;9(1):e87965. doi: 10.1371/journal.pone.0087965. PMID: 24498229; PMCID: PMC3907551.*
18. *National Institute for Health and Care Excellence (2018). Rheumatoid arthritis in adults: diagnosis and management. Available at: https://www.ncbi.nlm.nih.gov/books/NBK519103/*
19. *Durán J, Peloquin C, Zhang Y, Felson DT. Primary Prevention of Myocardial Infarction in Rheumatoid Arthritis Using Aspirin: A Case-crossover Study and a Propensity Score-matched Cohort Study. J Rheumatol. 2017 Apr;44(4):418-424. doi: 10.3899/jrheum.160930. Epub 2017 Mar 1. PMID: 28250138.*
20. *Iacono D, Fasano S, Pantano I, D'Abrosca V, Ruscitti P, Margiotta DPE, Navarini L, Maruotti N, Grembiale RD, Cantatore FP, et al. Low-Dose Aspirin as Primary Prophylaxis for Cardiovascular Events in Rheumatoid Arthritis: An Italian Multicentre Retrospective Study. Cardiol Res Pract. 2019 May 2; 2019: 2748035. doi: 10.1155/2019/2748035. PMID: 31192004; PMCID: PMC6525948.*
21. *Micha R, Imamura F, Wyler von Ballmoos M, Solomon DH, Hernán MA, Ridker PM, Mozaffarian D. Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. Am J Cardiol. 2011 Nov 1;108(9):1362-1370. doi: 10.1016/j.amjcard.2011.06.054. Epub 2011 Aug 17. PMID: 21855836; PMCID: PMC3196048.*
22. *Solomon DH, Curtis JR, Saag KG, Lii J, Chen L, Harrold LR, Herrinton LJ, Graham DJ, Kowal MK, Kuriya B, et al. Cardiovascular risk in rheumatoid arthritis: comparing TNF-α blockade with nonbiologic DMARDs. Am J Med. 2013 Aug;126(8): 730.e9-730.e17. doi: 10.1016/j.amjmed.2013.02.016. PMID: 23885678; PMCID: PMC4674813.*