The impact of nurse-led programme with and without statin treatment base on traditional cardiovascular risk score or carotid ultrasound on addressing cardiovascular risk in patients with arthritis: a prospective, multicentre, randomised, controlled trial

Introduction:

Cardiovascular disease (CVD) risk is elevated in patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) compared with the general population, and is a major source of morbidity and mortality (1, 2). New evidence strengthens the notion that the excess risk of CVD morbidity and mortality in patients with RA is related to both traditional and novel CVD risk factors. In RA, novel risk factors include inflammation, presence of carotid plaques, anticitrullinated protein antibody (ACPA) and rheumatoid factor (RF) positivity (3). In PsA, the prevalence of traditional risk factors is elevated compared with the general population , probably because of the shared inflammatory pathway (4).

CVD risk assessment is recommended for all patients with RA and PsA at least once every 5 years, so that lifestyle advice and CVD preventive treatment can be initiated when indicated (5). Current CVD risk prediction models, for example, Framingham Risk Score (FRS) or the Systematic COronary Risk Evaluation (SCORE) algorithm have been developed for use in the general population. Their performance in patients with RA appears to be suboptimal (6). Therefore, it has been suggested that CVD risk algorithms based solely on traditional risk factors may not be suited for use in the RA population. As a first step towards more accurate CVD risk prediction, it was proposed in the European League Against Rheumatism (EULAR) recommendations for CVD risk management in RA to apply a multiplication factor of 1.5 to the calculated CVD risk by SCORE (modified SCORE [mSCORE]) in selected patients to enhance the risk estimates (7). Nonetheless, a recent study showed that mSCORE do not provide sufficient improvement in risk prediction of future CVD in RA to serve as an appropriate alternative to the original SCORE (8).

Using coronary computer tomography angiogram (CCTA), we and others have found that all types of coronary plaque were more common in RA and PsA patients compared with controls, highlighted the fact that most of these subjects with plaques are having silent ischemia, supporting the notion that more aggressive CV evaluation strategy should be considered in these patients (9, 10). Nonetheless, there are concerns regarding costs and radiation exposure using CCTA or even coronary artery calcium (CAC) as a screening tool. Carotid ultrasound is a noninvasive imaging technique which can identify the presence of carotid plaque and increased intima-media thickness (IMT), representing an unequivocal manifestation of atherosclerosis and serving as a surrogate for CV disease. Other than carotid ultrasound, non-invasive pulse tonometry examination by measuring pulse wave velocity (PWV) and augmentation index (AIx) could evaluate overall aortic stiffness, which is an independent predictor of cardiovascular risk (11). Subclinical carotid atherosclerosis been shown to be more prevalent in RA (12) and PSA (13) then controls, even without classic CV risk factors. Increased IMT significantly correlated with traditional risk factors and disease-related parameters (12, 13).

Screening for asymptomatic atherosclerotic plaques by use of carotid ultrasound has been recommended as part of the CVD risk evaluation in patients with RA (5) as the presence of carotid plaques is associated with poor CVD-free survival and is strongly linked to future acute coronary syndrome (ACS)(14). The presence of bilateral plaque quadrupled the incidence of new ACS independently of any other risk factors compared with patients without carotid plaque (15). Incorporation of carotid ultrasound for patients at intermediate risk for CV disease has been used to further enhance CV risk stratification in the general population (16). Studies have supported the role of carotid ultrasound in re-stratification of CV risk. In RA, severe carotid ultrasound abnormalities were observed in 13% and 63% of patients with low and moderate mSCORE respectively (17). In PSA, our previous study showed that 35% of patients had subclinical atherosclerosis despite having a FRS-based low to moderate CV risk (13). Another study from Toronto also showed that 55.9% of the PsA patients from the FRS-based intermediate risk category were reclassified into an ultrasound-based high-risk category, while 47.1% of the patients in the FRS-based low-risk category were reclassified into a higher US-based risk group (18). Screening this population may help to identify those patients who are optimal candidates for intensive medical treatment. Prior studies suggest that incorporation of carotid ultrasound into treatment algorithms can impact progression of plaque and CV outcomes (19). However, the general applicability of these findings in rheumatology or primary care clinic

settings is not clear. Furthermore, guidelines on the management of patients with identified carotid plaque in RA and PsA have not been formulated.

Despite demonstration of high CV risk by the presence of carotid plaque, implementation of preventive CV services and rates of statin and antiplatelet use in PsA remained low in a recent study (20). “Best practice” electronic referrals were not an effective strategy to increase rates of specialty CV screening, even with a preventive cardiology clinic available in the same institution. It is possible that demonstration of carotid plaque can improve risk stratification but will only be impactful if incorporated into treatment plans by the treating rheumatologists as recommended by EULAR (5).

In RA patients, comorbidities are more common, more severe and less well-managed than in the general population (21). The usefulness of a nurse-led programme for decreasing CV risk has already been shown in a recent study. A single visit with a nurse might facilitate the management of risk factors of CVD by the general practitioner and/or the rheumatologist and demonstrated short-term benefit of a nurse-led programme on RA comorbidity management (22). However, whether the program resulted in changes of surrogate marker of CV endpoint (eg, glycaemia for diabetes, blood pressure for hypertension) remained uncertain because of its short study duration.

In addition to clinical screening, recent studies showed that various biomarker like calprotectin might play a role in detecting subclinical atherosclerosis, which calprotectin was associated with aortic PWV and presence of carotid plaque (23, 24). Our previous study also revealed that miRNA targeting IL-33 gene was associated with presence and progression of subclinical atherosclerosis .

Aim and hypothesis: We hypothesize that CV risk stratification and management in RA and PsA may be improved by incorporation of carotid ultrasound to assess for carotid plaque. This study investigates the impact of a nurse-led programme and initiation of statin treatment decided base on result of traditional CV risk score or carotid ultrasound on CV risk factor control in asymptomatic RA and PsA patients.

Patients and Methods

Subjects

Inclusion criteria

One hundred and forty consecutive patients with RA fulfilled the 2010 ACR/EULAR classification criteria or PsA fulfilled the Classification of Psoriatic Arthritis (CASPAR) criteria attending the outpatient clinics of the Prince of Wales Hospital who are aged between 18 and 75 will be recruited.

Exclusion criteria

Patients will be excluded if they have any one of the followings: a history of overt CVD (ie, symptomatic coronary artery disease [CAD] or ischemic stroke or transient ischemic attack or peripheral vascular disease), had significant co-morbidities including severe renal impairment or severe deranged liver function, female of childbearing potential who are unwilling to use adequate contraception, pregnant or breastfeeding women, and patients who are already taking lipid lowering therapy.

Nurses

Rheumatology nurses will conduct the nurse-led clinic in Prince of Wales Hospital.

Treating rheumatologists

Treating rheumatologists will invite their patients to participate in the study and will be responsible for managing patients with specific instructions given as listed below. Referred patients will then undergo formal screening by the research assistant for interest in the project and eligibility.

Trial design

This is a 1-year prospective, hospital-based, open-label, randomized, controlled trial. The trial comprised two arms. Both group will participate in the nurse-led programme on CV risk screening and carotid ultrasound for carotid plaque assessment. Subjects in group 1 will initiate statin treatment if their Franminham Risk Score >10%; while subjects in group 2 will initiate statin treatment if they had carotid plaque upon carotid ultrasound findings.. (Appendix 1). The method of concealed random allocation will

be used. Simple randomization will be conducted by a computer-generated random list. Randomisation will be centralized for all centres. Information on each patient's allocated treatment will be recorded in the clinical report form (CRF) and also entered into the patient's computerized medical record (CMS) by the nurse. The study will be approved by the respective Ethics Committees of each hospital and all patients will provide written consent.

Clinical assessment

At baseline and then every 3 to 6 months up to 1 year, the following clinical variables and questionnaires will be assessed: erythrocyte sedimentation rate (mm/h^{1st}), CRP (mg/L), number of swollen joints (0–28 for RA, 0-66 for PsA), number of tender joints (0–28 for RA, 0-68 for PsA), number of damaged joints, visual analogue scale (VAS) for pain (0-10=most pain), VAS for patient's global assessment (0-10=worst score), and VAS for physician's global assessment (0-10=worst score). Functional disability will be assessed by the disability index of Health Assessment Questionnaire (HAQ) (0-3=most functional disability). Overall disease activity will be assessed using 28-joint assessment (DAS28) for established RA (symptom onset greater than 2 years), simplified disease activity score (SDAI) for early RA (symptom onset less than 2 years), and Disease Activity in Psoriatic Arthritis (DAPSA), Bath Ankylosing Spondylitis Functional Index (BASFI) Test and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for PsA. Quality of life outcome will also be assessed at baseline and month 12 by Short Form (36) Health Survey and EQ5D. PsA patients will also complete the Dermatology Life Quality Index (DLQI) and Ankylosing Spondylitis Quality of Life (AsQoL) questionnaire.

Cardiovascular assessments

The following anthropomorphic assessment will be performed for all patients at baseline and at the end of the study. Anthropomorphic measurements include body heights, body weight, waist and hip circumferences, two consecutive blood pressure (BP) readings in sitting position and heart rate. Hypertension status is defined as systolic blood pressure (SBP) ≥140mmHg or diastolic blood pressure (DBP) ≥90mmHg or the use of antihypertensive agents. Other data collected at baseline include menopausal status, smoking and drinking habits, social economic status, history of diabetes, hypertension, hypercholesterolemia, dyslipidemia, overt CVD and cerebrovascular diseases, peptic ulcer disease and family history of CVD, diabetes and cerebrovascular diseases in first-degree male relatives <55 years of age or first-degree female relatives <65 years of age. Drug history is retrieved from case notes or elicited during the clinical assessment. Body weight and blood pressure will also be measured during each visit to the rheumatologist.

Laboratory assessment at baseline include fasting blood glucose, fasting lipid profile (total cholesterol [TC], low-density lipoprotein-cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], triglycerides [TG]), fibrinogen, thyroid function test, creatinine kinase and uric acid. Fasting sugar and lipid profile will also be measured at 6 and 12 months. Hemoglobin A1c levels will be measured at baseline and 12 months for patients with known diabetes.

Rationale for choosing FRS and the level of cut off for intervention

Evidence is scarce with regard to the validity of disease specific CVD risk prediction models to accurately predict risk in individual patients with RA and PsA, and it is therefore currently recommended to perform risk evaluation according to general population guidelines. Currently, no national guideline is available in Hong Kong. In our previous study to evaluate the performances of different CV risk scores in detecting high CV risk in PsA patients identified by coronary plaques on CCTA, we categorized patients as having either low or elevated 10-year CV risk using the 10% threshold for the FRS and found that FRS provided better discrimination of PsA patients with significant coronary artery plaque on CCTA than 3 other commonly used risk scores (25). Therefore, FRS was chosen to predict CV risk and a cut off of 10% was chosen to identify high risk individuals for interventions such as lipid-lowering treatment.

Arterial stiffness as alternate CV risk indicator

Apart from FRS, arterial stiffness was suggested to be an alternative measurement of CV risk. An increase in aortic PWV by 1 SD corresponds to an age-, sex- and risk factor-adjusted risk increase of 47%, 47% and 47% in total cardiovascular events, cardiovascular mortality and all-cause mortality, respectively.(26) AIx has emerged as a surrogate marker for CVD. A 10% increase of central AIx is associated with a relative

risk of 1.4 for all-cause mortality.(27) Therefore, arterial stiffness measurement could serve for additional CV risk indication apart from FRS and/or subclinical carotid atherosclerosis by ultrasound.

Intervention of CV risk in the nurse-led clinic

All patients will receive a one-on-one nurse-led intervention at baseline and month 12 including:
(1) Detection of CV risk factors (eg, hypertension, diabetes, hypercholesterolaemia).
(2) Calculation of the FRS. We will follow the recommendation to adapt for patients with RA by a 1.5 multiplication factor (5).
(3) The implementation of the recommendation for the detection (eg, yearly evaluation of CV risk factors) and/or management of such comorbidities at baseline. Nurses will be given a booklet to be used for the systematic identification and assessment of the comorbidities associated with RA and PsA. In case of a detected risk factor (eg, hypertension) and/or a non-optimally managed comorbidity (eg, Hba1c > 7), the nurse reminds the patient the interest of the management of such comorbidity and advises the patient to visit her/his general practitioner and/or rheumatologist to take care of it. In parallel, a report of this visit will be given to the patient to hand-over to the rheumatologist of each evaluated patient during their next clinical visit.
(4) The report of the presence of newly developed CV comorbidities at month 12.
(5) The number of new measures taken against comorbidities at month 12. The following measures against comorbidities are considered for the definition of the secondary objective of the trial: purchase of BP self-measurement devices, attending education class by dietitian and initiation of a diet because of overweight +/- hyperlipidemia, smoking cessation, initiation of lipid-lowering therapy, initiation of antiplatelet therapy, referral to a nephrologist because of renal insufficiency (chronic kidney disease stage IIIb).
(6) adherence of lipid-lowering and antiplatelet therapy at month 12.

Carotid intima-media thickness (IMT) and plaque

All patients will have the carotid intima-media thickness (IMT) and plaque assessed at baseline and 12 months at the Prince of Wales Hospital. Carotid IMT will be measured using a high-resolution B-mode ultrasound machine (Philips EPIQ7). Briefly, duplex carotid ultrasound will be performed by an experienced sonographer blinded to all clinical information using a 30-MHz linear vascular probe (Philips L12-3 broadband linear array transducer). The IMT will be measured offline in the distal common carotid artery (the arterial segment 1 cm proximal to the carotid bulb), bulb, and proximal internal carotid artery (the arterial segment 1 cm distal to the carotid bifurcation) using dedicated software (Philips Xcelera Cardiology Enterprise Viewer Client 4). The values of maximal thickness will be recorded, not including plaques, for the following calculation. Plaque is defined as a localized thickening >1.2 mm that do not uniformly involve the whole artery. The mean and maximal IMT values of 6 arterial segments will be calculated for further analysis. Reproducibility of IMT in our center was 0.97 (13).
A report of this visit will be given to the patient to hand-over to the treating rheumatologist during their next clinical visit. All participating rheumatologist will attend a briefing session on the importance of carotid ultrasound screening and the risk represented by carotid plaque in order to avoid under-appreciation of CV risk. Moreover, while the results of the US scan will be provided to the patient's primary rheumatologist, an interpretation of the findings regarding level of CV risk will also be provided.

Pulse wave velocity (PWV) and pulse wave analysis (PWA)

Arterial stiffness will be measured by baPWV, cfPWV and AIx at baseline and month 12 for all subjects(28). Participants receive PWA examination in the morning, having fasted overnight; having a light meal 4h before measurement and avoid tobacco, alcohol, and caffeine with 3h before measurement. Participants rest in sitting position in a quiet room for at least 10 minutes before examination. BP is measured 3 times at the right brachial artery using a validated oscillometric device (Omron HEM-757 - UK). PWA is performed using the pressure cuff and analog system (VICORDER Version 3.1 - UK). The central aortic arterial pulse wave is transferred from the peripheral arterial pulse wave automatically. Since AIx in an individual patient varies by heart rate, it is standardized to a heart rate of 75 beats-per-minute (b.p.m.) (AIx@75).

Carotid femoral PWV (cfPWV) is a gold standard of arterial stiffness and will be measured by VICORDER system as well. cfPWV will be measured in the supine position by a sphygmomanometer cuff in bilateral carotid and femoral position. The VICORDER machine measures and records results of pulse waveforms

of carotid and femoral arteries automatically. cfPWV is defined as the mean speed of bilateral blood pressure wave traveling between carotid and femoral artery. The distance between sampling points are measured manually.

Brachial-ankle PWV (baPWV) is another measure of arterial stiffness and will be assessed non-invasively in subjects in the supine position by a dedicated tonometry system (Non-Invasive Vascular Profile Device VP-2000; Omron Healthcare, Inc. Bannockburn, Illinois, USA). In brief, this device record PWV, blood pressure, electrocardiogram (ECG), and heart sounds simultaneously. Sphygmomanometer cuffs are applied on both arms just above the level of elbows and on both legs just above the ankles. ECG electrodes are placed on both wrists, and a heart sound microphone is placed on the left sternal border. The machine measures and records results of electrocardiogram, phonocardiogram and blood pressure of limbs as well as pulse waveforms of carotid and limb arteries automatically. baPWV is defined as the speed of the blood pressure wave traveling between brachium and ankle. The distance between sampling points of brachial-ankle PWV are calculated automatically according to the height of the subject. All PWA measurements are made by a single skilled operator. Intra-observer reliability is 0.86 (28). The reports will also be hand over to the attending rheumatologist in their subsequence visit, and to further evaluate the CV risk.

Treatment protocol

There are no formal guidelines on the management of patients with high CV risk or identified carotid plaque in Hong Kong. The following management plan was formulated after a general discussion with practicing rheumatologists and cardiologists locally.

Use of statins

Group 1 patients will be prescribed statin when FRS > 10%; while group patients will be prescribed statin upon presence of carotid plaque as reported from carotid ultrasound. The decision will solely be made base on the randomized group by either FRS>10% or presence of carotid plaque.

We choose atorvastatin 20 mg daily since generic atorvastatin is available in the Hong Kong Hospital Authority drug formulary. Each tablet cost HK $ 0.28 and the yearly cost is HK $ 102.2 (around US $ 13) per person. Atorvastatin 20 mg is recommended as the preferred initial high-intensity statin to use because it is clinically and cost effective for the primary prevention of CVD according to the national institute for Health and Care Excellence (NICE) guideline from the United Kingdom. Nonetheless, similar data is lacking in Hong Kong.

No trials to date that have evaluated effects on CVD events have tested any medication in combination with statins or treatment to specific LDL-C goals, therefore we do not intensify the regimen for any particular level of LDL-C response. Measuring LDL-C response after initiating therapy in this study is mainly to assess adherence. In this primary prevention trial, in patients who do not tolerate statins, no lipid-lowering therapy will be administered. Potential interventions include lifestyle modification and, in higher-risk patients, antiplatelet therapy.

Use of Aspirin

For low-risk patients (ie, men and women whose 10-year absolute risk of a first coronary heart disease event is <10 percent), the absolute benefit of a reduction in CV events is unlikely to exceed the absolute risk of major bleeding. For moderate- and high-risk patients (ie, men and women whose 10-year absolute risk of a first CVD event is ≥10 percent), randomized data on benefits and risks are sparse. Nonsteroidal anti-inflammatory drug (NSAID) therapy combined with aspirin use increases the risk for serious gastrointestinal (GI) bleeding compared with aspirin use alone (29). The gastrointestinal harms may offset the CV benefits in our group of patients on long-term NSAID where the GI risk is high and the CV risk is low. Therefore, aspirin for primary prevention in this trial will be highly individualized based on a benefit/risk ratio assessment for each patient and a clinician-patient discussion regarding potential benefits, potential harms, and patient preferences.

Use of DMARDs

Disease activity should be controlled optimally in order to lower CVD risk in all patients with RA or PsA (5). All participants will receive a 1-year protocolized treatment (Appendix 2 and 3) with the aim to achieve remission. The protocol was developed based on the EULAR recommendations, the Hong Kong Society of Rheumatology recommendation and the Hong Kong guideline for the use of biologics. When patient cannot achieve treatment goal within 3 to 6 months of therapy, the treatment therapy will be escalated to the next step according to the protocol, unless the patient declined or toxic effects preclude this approach.

Toxicity monitoring

To monitor the possible side effect of the NSAID, biologic and synthetic DMARDs, statins and aspirin, patients will be asked about various symptoms (such as myalgias or weakness for statins; coffee ground vomiting, melaena and dyspepsia for NSAID and aspirin). Complete blood count, liver function tests and renal function tests will be performed during every clinic visit. Creatinine kinase will be measured in patients who complain of myalgias or weakness after staring statins. Chest X-rays will be obtained at baseline and at the end of the study. The treating physician record all adverse events and serious adverse events and, if necessary, make treatment adjustments in accordance with the protocol. Serious adverse events are defined as any adverse reaction resulting in any of the following outcomes: a life-threatening condition or death, a significant or permanent disability, a malignancy, hospitalization or prolongation of hospitalization, a congenital abnormality, or a birth defect.

Outcome measures

The primary outcome is the change in FRS. Although this algorithm was developed for prediction of absolute coronary risk among patients without clinical manifestations of CAD, they combine the following major risk factors recognized for coronary and other atherosclerotic CVD (ASCVD): age, sex, high BP, smoking, dyslipidemia, and diabetes status. We use risk scores as a composite measure of change in modifiable major risk factors, rather than as a predictor of risk. This approach has been previously used in evaluating effects of nurse- and dietitian-led case management program to reduce CV risk (30). Baseline age will be applied when calculating the FRS at 12 months.

Secondary end points included

1) Change in arterial stiffness in subjects
2) Change in individual modifiable risk factors (systolic and diastolic BP; TC, LDL-C, HDL-C and TG levels; TC/HDL ratio; and hemoglobin A1c value in patients with diabetes)
3) The number of measures taken against comorbidities.
4) Proportions of patients achieving remission.
5) Changes in IMT and proportion of plaque progression in subjects between 2 groups

The trial will be conducted with compliance to ICH-GCP and Declaration of Helsinki.

Statistical analysis:
Descriptive statistics will be used for demographic and clinical variables included frequencies, percentage, means and standard deviations, median and interquartile range. Comparisons in demographic and clinical characteristics at baseline will be performed using chi-square test, independent samples *t*-test or Mann-Whitney *U* test, depending on distribution of data. We will compare the proportion of participants eligible for statin treatment using FRS >10% vs carotid ultrasound criteria using the McNemar test. The intervention effect on the primary and secondary outcomes will be examined at 12 months on an intention-to-treat basis using a mixed-effects regression model adjusted for baseline FRS. The model will also take into account random effects associated with physicians and clinics in a hierarchical structure. The magnitudes and patterns of missing data will be examined by the randomized group. Missing outcomes at the 12-month follow-up will be imputed using the method of the baseline observation carried forward. The same mixed-effects model will be used for subgroup analyses defined by sex and underlying diseases. All statistical analyses will be conducted using IBM SPSS Statistics Version 23 (IBM, Armonk, NY, USA). A level of significance of p =0.05 is used.

Sample size calculation:
The sample size is estimated by the Power Analysis and Sample Size for Windows software (PASS 2000, NCSS, Utah, USA). All calculations will use a two-sided α of 0.05 and β=0.2 achieving 80% power. From our previous cohort study, standard deviation of FRS was 8. Taking population variance of FRS as 64, and suppose 4 unit drop in FRS is clinically meaningful. A sample size of 63 is required in each group. Assuming a drop-off rate of 10%, a total sample size of 140 (i.e. 70 per arm) would be sufficient.

(G) Purpose and potential for implementation of results

Elevated CVD risk is a significant public health problem that contributes greatly to the increased morbidity and shortened lifespan of individuals with RA and PsA. Over the past decades, there has been great progress into the understanding of the severity of CVD risk in these patients but these risk factors are not well managed. The development of the high-risk strategy is therefore necessary, with more intensive therapy reserved for patients identified as high-risk, e.g. because they have high-risk FRS. However, these risk scores under-estimated CV risk in patients with RA and PsA. An intermediate approach is to use quantification of preclinical vascular disease to further identify high-risk patients. Results from this study will provide clinical implications in terms of detecting and managing cardiovascular morbidity in patients with RA and PsA.

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