CARDIOVASCULAR DISEASE PROFILE IN PATIENTS WITH ESTABLISHED RHEUMATOID ARTHRITIS AT KING EDWARD VIII HOSPITAL

DR PREESHA GOVENDER

Student no: 201292945

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As the candidate's supervisor I have/~~have not~~ approved this thesis for submission.

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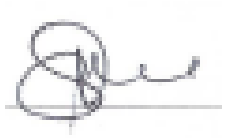
Signed:  Date: 17/11/2018

Dedication

To my mother, whose profound wisdom, laughter and endless conversations are forever etched on my soul…your divine hand I feel on my shoulder every day.

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Overview of thesis

Rheumatoid arthritis (RA) is one of the most common chronic systemic autoimmune inflammatory diseases, which is associated with an increased mortality rate, attributed to premature cardiovascular disease (CVD). Key drivers of mortality from CVD in RA are fuelled by multiple factors.

Rheumatoid arthritis disease profiling, particularly seropositivity, presence of extra-articular disease and high disease activity, confer an increased mortality risk. Traditional CVD risk factors (hypertension, diabetes mellitus, dyslipidaemia, obesity) are influenced by both inflammation inherent to RA, and pharmacodynamics of anti-rheumatic drugs. Notwithstanding the above, the current paradigm shift recognises RA as an independent risk factor for CVD.

Similar to the rest of Africa, local data on the prevalence of CVD in RA are limited. With an increase in non-communicable diseases and longevity, the RA burden in South Africa (SA) is expected to increase. Local studies are needed to stratify practice in cardio-protective strategies and improved long term outcomes in RA. This study aims to determine the prevalence of CVD in RA, describe the prevalence of CVD risk factors in RA and describe the relationship between RA disease activity and CVD.

A retrospective, chart review of all patients with RA according to the American College of Rheumatology 1987/2010 Classification criteria, attending the arthritis clinic in King Edward VIII hospital, a tertiary public healthcare academic teaching hospital in KwaZulu-Natal, SA, during the period August 2017 to March 2018, was undertaken. Patients younger than 18 years of age, or with RA and any other concomitant connective tissue disease or overlap syndrome were excluded. The study group included 150 patients with RA.

The demographic details, duration of the RA disease, traditional CVD risk factors, simplified disease activity index (SDAI) and health assessment questionnaire (HAQ) were documented. In addition, results of electrocardiogram, echocardiogram, haemoglobin, glycated haemoglobin, lipid studies and estimated glomerular filtration rate were recorded.

Cardiovascular disease was found in 16% of the total study cohort, with an age, gender and ethnic differential. Coronary artery disease was the most common CVD finding in RA patients. The burden of traditional CVD risk factors in RA is high, with hypertension, diabetes mellitus, dyslipidaemia, physical inactivity and chronic kidney disease of particular

concern. No significant correlation was observed between RA disease activity, seropositivity and CVD in RA however, extra-articular disease was more common among patients with CVD. Echocardiographic evidence of subclinical cardiac disease in RA is common. Significant disparity was observed between various CVD risk assessment models at different levels of risk, which cautions a comprehensive CVD risk assessment model that stratifies discriminately is needed in patients with RA. The study provides knowledge of CVD burden and risk in RA patients locally, and serves as a foundation for further research in preventative strategies that offer significant survival benefits.

The main limitation in this study is that the study cohort consisted mainly of Black and Indian patients and therefore the findings may not be generalised across all ethnic groups. Furthermore as this was a relatively small study conducted in a single public hospital, which is urban based, conclusions from this study may not be applicable to a rural setting or to all socio-economic classes.

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Literature Review

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease, characterized by a symmetrical, peripheral polyarthritis [1]. The peak age of onset is between 30 and 50 years, and the disease has a predilection for women compared to men (3:1) [2]. It is one of the most common inflammatory arthritis, with a natural history resulting in joint destruction, functional impairment and increased mortality [2]. In addition to the articular disease, extra-articular manifestations are seen in approximately 50% of all patients with RA at some point during the course of disease [1].

The mortality rate amongst RA patients is increased by 70% compared to the general population [3], and the leading cause of death in RA is cardiovascular disease (CVD) [3, 4]. Both traditional and non-traditional factors combine to increase the adverse CVD risk profile in patients with RA, with CVD deaths occurring five to ten years prematurely compared to the general population [4].

Pathogenesis

The exact immuno-pathogenesis of RA remains unknown [5], but it is postulated to involve genetic and environmental factors, with a complex interaction between T-cells, B-cells and pro-inflammatory cytokines. Cytokines act as messengers that activate effector cells causing the local and systemic symptoms associated with this disease [6].

The earliest detectable pre-clinical stage is the breakdown of self-tolerance. In the rheumatoid joint, activation of T-cells stimulate macrophages and synoviocytes to generate pro-inflammatory mediators which eventually destroy cartilage and bone [6]. T-cells help B-cells produce antibodies that promote joint inflammation.

Activated B-cells form plasma cells, which produce rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibodies [7]. Rheumatoid factor contributes to the pathogenic process by forming large immune complexes inside the joint, fixing complement and promoting chemoattractant [7]. In contrast, anti-CCP antibodies are directed against

deiminated peptides and they recognise citrulline containing matrix proteins, which enhance the expression of self-reactivity [7].

The pro-inflammatory cytokine; tumour necrosis factor-alpha (TNF-α), plays a critical role in the pathogenesis of RA [8]. Tumour necrosis factor-alpha together with interleukin (IL) 1, 6 and 17, increases the expression of receptor activator of nuclear factor kappa ligand (RANKL) which stimulates osteoclast differentiation and bone resorption in the joint, thus promoting osteoclastogenesis. Simultaneously, TNF-α also inhibits osteoblast differentiation, thereby actively suppressing new bone formation. Furthermore IL 6, IL 1 and TNF-α together, promote the synthesis of C-reactive protein (CRP) in hepatocytes. In addition to eliminating infection, CRP plays a regulatory role in inflammation and atherosclerotic thrombosis [3, 9]. Since CRP is a direct measure of synovial inflammation, and a by-product of inflammatory reactions in RA, it is therefore a useful marker of disease activity [3, 9]. Emerging evidence supports the role of CRP as a pro-inflammatory bone destructive molecule in the pathogenesis of RA [9].

Persistently elevated CRP levels exacerbate tissue damage, promote lipid metabolism dysregulation and increase the risk of cardiovascular complications [6]. The combined effects of TNF-α, IL-6, acute phase reactants, immune complexes, and pro inflammatory high density lipoprotein (HDL) phenotype, increase endothelial activation and render atheromatous plaques unstable [3, 10]. Cytokine driven insulin resistance of muscle and adipose tissue results in an "inflammatory metabolic" syndrome [10].

Risk factors for rheumatoid arthritis

Several factors influence the development, rate of progression and severity of RA (Figure 1). Although several genetic loci have been described, the epitope of the human leucocyte antigen (HLA)-DRB1*04 cluster has been identified in greater than 80% of patients with RA [11]. Patients expressing the HLA-DRB1*04 cluster inherit a higher risk for nodular disease, major organ involvement and surgery related to joint destruction [6]. Further, strengthening the genetic theory are twin studies that show a concordance rates of 15 to 30% among monozygotic twins and 5% among dizygotic twins [10].

Gene-environment interactions underlie the association of different genotypes in the various geographical and cultural settings [4]. Locally, an urban-rural regional variation of disease,

with a higher prevalence in the South African urban population compared to virtually no cases reported in some rural areas is observed [12-16]. Furthermore, studies also suggest a role for occupational factors, such as exposure to dust, asphalt and silica, resulting in bronchial stress and thereby increasing the risk for anti-CCP antibody positive RA [10].

Seropositive and extra-articular RA is strongly associated with cigarette smoking [4]. Both smoking intensity and duration increases the risk of development of disease. Additionally, citrullination of proteins in broncho-alveolar fluid occurs more often in smokers. The long-term tobacco smoke exposure and citrullination of proteins induce self-reactivity resulting in anti-CCP positive disease, which confers a less favourable prognosis than anti-CCP negative disease [10].

Although there is no clear role for a hormonal influence, it is felt that oestrogen stimulates TNF-α resulting in an increased risk in women, with women usually having a poorer outcome than men [4, 10]. Similarly there is conflicting data on lifestyle and education level, and disease occurrence. Whilst, several studies found a higher prevalence in highly educated, high-income classes, compared with uneducated, lower-income classes, other studies have not confirmed these findings [4].

Infectious agents are increasingly being implicated in the aetiology of RA, on a postulated background of molecular mimicry. The formation of immune complexes during an infection triggers the induction of RF. Possible infectious triggers include Epstein-Barr virus, cytomegalovirus, parvovirus, Proteus species, Escherichia coli and mycoplasma [4, 10]. Additional studies involving clinical bacterial signatures associated with anti-CCP antibody positive RA are emerging [10].

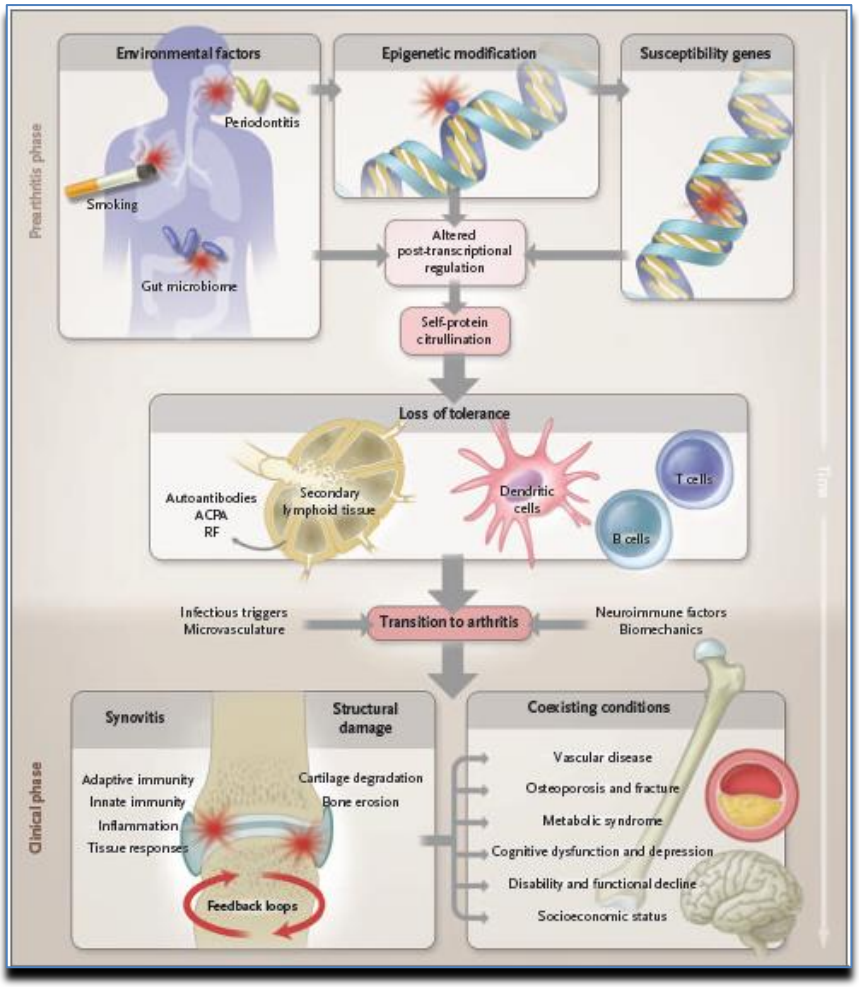

Figure 1. Postulated factors associated with the development of rheumatoid arthritis [10]

Epidemiology

Rheumatoid arthritis is not a recent disease and descriptions of symmetric, chronic polyarthritis with characteristic deformities date back to Rome in 100 BC and India in 500 BC [17].

The epidemiology of RA is well described in developed countries, with estimates from Western Europe and North America reporting a global prevalence of between 0.3% and 1% [18]. In contrast, RA is thought to have a lower prevalence, with a milder disease course in developing countries [12].

The Global Burden of Disease 2010 study, conducted in 187 countries, based on the 1987 American College of Rheumatology (ACR) classification criteria for RA, found a global prevalence of RA of 0.24%, however the true global prevalence of RA remains unknown

[18]. The study used the outdated 1987 ACR classification criteria for RA, which fails to recognize early RA, and hence the use of this classification criteria excluded such patients. Further, since prevalence data was not available for multiple regions, Sub-Saharan Africa included, data was then modelled using a meta-regression tool [18]. This could significantly underestimate the actual burden of disease in African countries, and therefore the true global prevalence of RA.

There is a paucity of prevalence data for RA from Africa and a recent systematic review found an overall prevalence which ranged from 0.13% in Algeria to 2.54% in South Africa (SA) [19]. Differences in urbanisation, cultural and geographical diversity amongst countries contribute to the significant statistical heterogeneity in the overall meta-analysis [12].

Similar to the rest of Africa, local data for prevalence of RA in SA are limited, with environmental factors and the urban-rural gradient contributing to the differences seen in various South African populations [13]. The highest prevalence of 0.9% was found in a mixed urban community in Soweto, followed by the Xhosa of Transkei (0.68%), the Sotho's of Lesotho (0.3%), and the Tswana of Western Transvaal with 0.1% [13], with the lowest (0%) prevalence in rural Venda, a historic district of Northern SA occupied by Venda people, now part of the Limpopo province [12].

In spite of the low prevalence, RA contributes significantly to morbidity and quality of life and a local study found that poor functioning was predictive of substantial functional disability and suboptimal mental health in South African patients with early RA even after 12 months of joint targeted therapy [20].

Clinical expression of disease

The articular expression of disease includes mono-, oligo- or poly-articular symmetrical synovitis, with early morning stiffness lasting more than one hour [7]. Both small and large joints are affected, with untreated or inadequately treated disease progressing to joint deformities [12, 21].

Extra-articular disease occurs in almost 50% of patients with RA, at some point during the course of disease [1]. Risk factors for extra-articular disease include smokers, early onset disability and RF or anti-CCP antibody positive disease. The most frequent extra-articular manifestations include subcutaneous nodules, secondary Sjogren's syndrome, pulmonary nodules and a normochromic, normocytic anaemia [7, 22]. Other manifestations include osteoporosis, scleritis, episcleritis, vasculitis, pulmonary disease (pleural effusions, interstitial lung disease, idiopathic pulmonary fibrosis, pulmonary nodules, pulmonary hypertension), haematological disease (thrombocytopaenia, leucopaenia), neurological disease (mononeuritis multiplex, peripheral neuropathy, nerve entrapment), and cardiovascular disease (cardiomyopathy, pericarditis, valvular heart disease, coronary artery disease (CAD) and atherosclerosis) [7]. Extra-articular disease is associated with an increased mortality due to CVD [22-24].

Diagnostic criteria for rheumatoid arthritis

Prior to 2010, the 1987 ACR classification criteria for RA (Table 1) were used [25, 26]. The criteria included symmetrical small joint involvement, early morning stiffness, radiological disease and a minimum period of six weeks duration of symptoms before a diagnosis could be confirmed [25].

Table 1. The 1987 American College of Rheumatology classification criteria for rheumatoid arthritis [26]

Criterion	Definition
A patient is classified as RA if 4/7 criteria are satisfied. Criteria 1-4 must have been present for ≥6 weeks	
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least an hour before maximal improvement
2. Arthritis of ≥3 joints areas	≥3 joints areas simultaneously have had synovitis observed ay a physician
3. Arthritis of hand joints	At least 1 area swollen in a wrist, MCP or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas on both sides of the body
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, extensor surfaces or juxta-articular regions
6. Serum rheumatoid factor (RF)	Positive RF
7. Radiographic changes	Radiographic changes typical of RA in posteroanterior hand and wrist radiographs

Abbreviations: MCP, metacarpophalangeal; PIP proximal interphalangeal

The above criteria were criticised for lack of sensitivity for early disease, which lead to the 2010 ACR/ European League Against Rheumatism (ACR/EULAR) RA Classification Criteria (Table 2), which is currently used [25, 27]. The revised criteria is more comprehensive, with the inclusion of inflammatory markers and anti-CCP seropositivity, allowing for earlier diagnosis and treatment [25].

Table 2. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis [27]

Target population: **Patients who (i) have at least one joint with clinical synovitis, and (ii) the synovitis not better explained by another disease**	**Score**
Add score of categories A-D, score of ≥6/10 needed to classify patient as having definite RA	
A. Joint involvement (tender/swollen)	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology	
Negative RF /ACPA	0
Low-positive RF/low positive ACPA	2
High positive RF/high-positive ACPA	3
C. Acute phase reactants	
Normal CRP&ESR	0
Abnormal CRP/ESR	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

Large joints refer to shoulders, elbows, hips, knees and ankles

Small joints refer to metacarpophalangeal joints, proximal interphalangeal joints, second through to fifth metatarsophalangeal joints, thumb interphalangeal joints and wrists

Low positive values refer to values less than three times the upper limit of normal

High positive values refer to values greater than three times the upper limit of normal

ACPA, anti-citrullinated protein antibody; ESR, erythrocyte sedimentation rate

Disease activity

Disease severity is a predictor of mortality [4], with premature mortality from CVD related to the number of inflamed joints [28], and persistently elevated inflammatory markers [3]. There are several disease activity scores available [2, 29]. A composite disease activity score is obtained by using a combination of clinical examination of tender and swollen joints, global assessments and laboratory investigations [29]. The ACR core set for disease activity includes the following [2]:

- Tender joint count
- Swollen joint count
- Patient pain assessment
- Patient global assessment
- Doctor global assessment
- Function
- Acute phase reactant
- Radiographic analysis

The twenty eight joint count is most widely used. Function and pain is assessed in a patient-centred health assessment questionnaire (HAQ). The HAQ provides fundamental knowledge about a patient's health, functional status and quality of life from their own personal perspective [30]. The HAQ has been validated in multiple studies, such as prediction of successful aging, inversion of the therapeutic pyramid in RA, and examination of mortality risks in RA, work capacity and performance, occupation and the ability to live independently [30].

Composite scores provide a more accurate reflection of overall state of disease compared to individual measurements. The most widely used composite scores is the Disease Activity Score (DAS) 28, involving tender and swollen 28 joint count together with acute phase reactants and patient global assessment (Table 3) [2]. The Simplified Disease Activity Index (SDAI) combines the sum of tender and swollen 28 joint count, patient and doctor global assessment and acute phase reactants, whilst the Clinical Disease Activity Index (CDAI) is a modification of the SDAI, without the inclusion of acute phase reactants (Table 3) [2]. Acute

phase reactants measured include the CRP or erythrocyte sedimentation rate (ESR). These composite indices are in excellent agreement, correlate with function and radiographic changes, and have been validated in multiple studies [31-34]. It allows for consistency of patient evaluation by multiple physicians, improves patient's understanding of their disease activity by provision of a single number, and facilitates modification of therapeutic decisions, with consequent improved patient outcomes [31, 33].

The score further defines disease activity into remission, low, moderate or high disease activity (Table 3), which identifies poorly controlled patients, and allows for targeted treatment goals to be achieved [29, 35].

Table 3. Composite disease activity scoring system to assess disease activity [29]

Index	Formula	Remission	Disease activity		
			Low	Moderate	High
SDAI	TJC + SJC + PGA (cm) + DGA (cm) + CRP (mg/dL)	≤ 3.3	≤ 11	≤ 26	> 26
CDAI	TJC + SJC + PGA (cm) + DGA (cm)	≤ 2.8	≤ 10	≤ 22	> 22
DAS-28	$0.56 \times \sqrt{TJC} + 0.28 \times \sqrt{SJC} + 0.7 \times \ln(ESR) + 0.014 \times PGA\ (mm)$	≤ 2.6	≤ 3.2	≤ 5.1	> 5.1

SDAI, simplified disease activity index; TJC, tender joint count; SJC, swollen joint counts; PGA, patient global assessment; CRP, C-reactive protein; CDAI, clinical disease activity index; DAS-28, 28-joint disease activity score; ESR, erythrocyte sedimentation rate.

Management of rheumatoid arthritis

The benefits of initiating early, goal directed therapy, where the target is disease remission, has downstream effects of joint preservation and reduced disability [21, 29]. The challenges of rheumatologists managing RA in the developing world are different to those of the developed world. South African Rheumatism and Arthritis Association (SARAA) have developed an algorithmic guideline for management of RA in SA [21]. Disease modifying anti rheumatic drugs (DMARD) play a pivotal immune-modulatory role in RA.

Methotrexate is the first line anchor synthetic DMARD used universally [36]. It inhibits dihydrofolate reductase, an enzyme needed for deoxyribonucleic acid (DNA) synthesis, with resultant downregulation of inflammatory pathways [1]. It has excellent efficacy and tolerability, with a convenient weekly dosing regimen [12]. Leflunomide is an immunomodulatory drug, useful in patients who are unresponsive to, or intolerant of,

methotrexate. However, drug cost has limited its use to the South African private health-care sector and certain provinces in the public health-care sector only.

Hydroxychloroquine, an antimalarial drug, may be used as monotherapy for mild RA, or in combination with methotrexate for moderate to severe disease [29]. In SA, chloroquine rather than hydroxychloroquine is available. Sulphasalazine suppresses lymphocyte and leucocyte functions, with down-regulatory inflammatory actions from enzymatic blockade [1]. It is effective in combination with methotrexate, or as monotherapy in mild RA, and useful in patients in whom methotrexate is contraindicated [21].

Biologic DMARDs are proteins directed against specific cytokines or their cell receptors [21, 29]. They are classified into drugs that inhibit TNF-α (Infliximab, Etanercept, Adalimumab) and drugs targeting cytokines or B-cells other than TNF (Abatacept, Rituximab, Tocilizumab) [21]. Biologic DMARDs are indicated in patients with a poor response to synthetic DMARDs, or in patients with high disease activity, or moderate disease activity with poor prognostic factors (seropositivity, erosive disease, extra-articular disease or functional disability) [21]. Glucocorticoids are potent anti-inflammatory drugs that offer prompt and marked symptomatic relief. When used in combination with DMARD therapy in early RA, they inhibit the development of erosions [37]. All patients with RA are prescribed analgesics including non-steroidal anti-inflammatories (NSAID), on an 'as needed' basis, for symptomatic relief provided there is no contraindication to their use [21, 29].

Cardiovascular disease in rheumatoid arthritis

Epidemiology

Cardiovascular disease carries a higher mortality in developing countries than developed ones [38]. According to the World Health Organisation (WHO) in 2001, CVD accounted for 9.2% of total deaths in Africa, compared to 31% in the developed world [39]. Africa has the lowest global output of cardiovascular research [40], and there is paucity of studies exploring CVD in patients with RA in Africa and SA.

The incidence of cardiovascular events in patients with RA occurs three times more frequently than in the general population [6]. Accelerated coronary artery atherosclerosis is

associated with increased mortality in RA [23]. This excess mortality is more pronounced in studies of RA populations with longer disease duration than in cohorts with early RA [41]. The global Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis Program (QUEST-RA) study, with a cohort of 4363 patients, conducted between 2005-2006, found an overall prevalence of cardiovascular morbidity of 9.3%. There was considerable variation between countries, with the highest prevalence in the United States of America (USA), United Kingdom (UK), Poland and Germany, and the lowest in Argentina and France [23]. These findings were similar to the WHO multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project [42], which found an overall prevalence of lifetime myocardial infarction (MI) of 3.2%, and stroke of 1.9% [23]. Further, cardiovascular events were more prevalent in men than women and occurred approximately a decade earlier in patients with RA, than the general population, suggesting that RA is an independent risk factor for premature ischaemic heart disease (IHD) [22]. In keeping with this, a recent 15-year prospective cohort study, Dutch patients with RA had a 54% higher risk of mortality compared to the general Dutch population, with the last three years of study showing an equal mortality risk between the two groups, a trend likely attributed to effects of treatment intensification in the last decade [43].

Prevalence of traditional cardiovascular risk factors extrapolated from the QUEST-RA study, were hypertension (33%), dyslipidaemia (14%), diabetes mellitus (DM) (8%), smoking (43%), physical inactivity (72%) and obesity (18%). Diabetes mellitus and smoking were both more common in men than women. Additionally, extra-articular disease was significantly associated with cardiovascular morbidity [23].

Rheumatoid arthritis increases the lifetime risk for CAD two fold compared to the general population, and this risk is of equal magnitude to patients with DM [44, 45]. In order to correctly reflect the increased risk of heart disease in patients with RA, the Framingham cardiovascular risk score, is multiplied by a factor of 1.5 in patients with RA [45]. Furthermore, patients with RA have a two-fold increased risk of developing heart failure. Seropositive disease is associated with diastolic dysfunction, with a preserved ejection fraction of more than 50% [44]. The outcome of patients with RA and heart failure is poorer than the general population [44].

A small study found an increased frequency of asymptomatic cardiac involvement in RA patients [46]. Based on echocardiographic findings; 37% had cardiomyopathy, 7% residual abnormalities of an MI, 83% valvular heart disease with mitral regurgitation being the dominant lesion, and 13% had pericarditis. Electrocardiogram abnormalities were found in 63% of patients, which included left ventricular hypertrophy, sequelae of myocardial ischemia, first-degree atrioventricular block, right bundle branch block and right atrial hypertrophy [46].

Traditional cardiovascular risk profile in rheumatoid arthritis

1. Dyslipidaemia

In RA, traditional cardiovascular risk factors are influenced by both inflammation inherent to the disease and the pharmacodynamics of anti-rheumatic drugs. Cholesterol, particularly low density lipoprotein (LDL), forms fatty streaks in coronary arteries, which foster flow-limiting atherosclerotic plaques [47]. When these plaques rupture, thrombosis ensues, leading to blockage of coronary arteries and an MI. Rheumatoid arthritis related dyslipidaemia is characterised by a low total cholesterol and HDL, and elevated triglyceride and small LDL [3]. During periods of high grade inflammation, there is marked suppression of total cholesterol, HDL and LDL levels, yielding an unfavourable pro-atherogenic ratio of total cholesterol to HDL [44].

The total cholesterol to HDL ratio is a better CVD risk predictor in RA than individual lipid components [45], and studies show HDL levels are significantly lower in RA patients compared to matched control subjects [48]. This paradoxical relationship between inflammation and lipid profiles translates into increased CAD risk in RA. Inflammation in RA alters lipoprotein structure and function and the HDL load of serum amyloid A increases with a decrease in apolipoprotein A-I, leading to a shift in the anti-atherogenic effect of HDL to a pro-atherogenic effect [44].

Further, the anti-inflammatory effects of drugs on lipid profiles are inconsistent. While there is evidence that hydroxychloroquine improves atherogenic lipid profiles [49], the role of methotrexate, the gold standard of treatment, is unclear. Tumour necrosis factor-α blockers

elevate both total cholesterol and HDL levels, resulting in a stable atherogenic profile while tocilizumab, an IL-6 inhibitor, elevates total cholesterol and LDL [47].

2. Insulin resistance and diabetes mellitus

Insulin resistance promotes atherosclerosis. Cytokine driven mechanisms make muscle and adipose tissue insulin resistant, resulting in an "inflammatory metabolic" syndrome [10]. Epidemiological studies show a strong association between RA and insulin resistance, and a study in 2004 showed a 54% risk in RA patients compared to 40% in the general population [50]. Furthermore, high grade inflammation is associated with significantly higher levels of insulin resistance. Predictors of insulin resistance included elevated CRP, ESR, IL-6, TNF-α and increased waist circumference [47].

There is a 50% increase in the risk of DM in RA, even after controlling for glucocorticoid use [51]. Studies also show a decrease in insulin resistance with common DMARDs including methotrexate, TNF-α blocker and hydroxychloroquine use [47].

3. Hypertension

Although older studies found no difference in hypertension between RA and control groups [47], more recent studies show that hypertension is commoner in RA [52], with up to 50% of RA patients being underdiagnosed and undertreated (systolic blood pressure greater than 140 mmHg) [44, 52]. There is also a greater prevalence of diastolic hypertension, when compared to non RA community controls [53]. This is probably compounded by inflammation, NSAID and glucocorticoid use which may exacerbate hypertension in RA [44, 47]. Increased arterial wall stiffness seen in patients with RA, suggest a diminished ability of the arterial system to respond to changes in blood volume [47].

4. Obesity

Obesity is defined as a body mass index (BMI) of greater than 29 kg/m^2 by the WHO. In the non RA population, obesity is associated with higher CRP, and an increased cardiovascular

risk [54]. The prevalence of obesity is 54% higher in patients with RA than non RA control groups [47] and a combination of low muscle mass and high fat mass is observed in RA [44].

Adipose tissue releases pro-inflammatory cytokines, IL-6 and adiponectin, thus contributing to low grade inflammation, and furthermore visceral adiposity in RA is associated with hypertension, insulin resistance and metabolic syndrome [44]. Men with RA have higher levels of visceral fat compared to controls, whilst women with RA had increased subcutaneous fat compared to controls, with a similar BMI and waist circumference [47]. Therefore, obesity in RA is associated with higher CRP levels and aggressive articular disease [47].

5. Physical inactivity

Physical activity is an important modifiable risk factor of CVD. Rheumatoid arthritis patients are significantly less physically active than population based controls, due to a combination of uncontrolled inflammation, low muscle mass, increased body fat composition, and limitations of joint movement from poor disease control. Physical inactivity, as in the general population, leads to hypertension and dyslipidaemia, which portends an unfavourable cardiovascular profile [47].

6. Cigarette smoking

Cigarette smoking is one of the most prominent modifiable risk factors for CVD and is also one of the strongest known environmental risk factor for RA [47]. Recent case controlled studies show a higher prevalence of current or past cigarette smoking observed in RA patients [47]. Smoking is associated with higher disease activity, extra-articular disease, accelerated atherosclerosis and multi-vessel coronary artery calcification [55, 56]. The Multiple Risk Factor Intervention Trial (MRFIT) found that smokers had twice the number of coronary heart disease deaths compared to non-smokers. Additionally, a strong association between CRP and subsequent risk of cardiovascular deaths is seen in cigarette smokers independent of the number of cigarettes smoked per day [57].

7. Menopause

Oestrogen has a modulatory effect on endothelial function and vascular tone. It mediates the release of vasodilators (nitric oxide and prostacyclin), and inhibits the production of vasoconstrictors (endothelin and angiotensin II) [58-60]. Further it has an anti-inflammatory effect, and reduces the secretion of TNF-α, a pro-atherogenic cytokine [60].

In a large prospective cohort of pre- and post-menopausal women, the risk of MI was significantly increased in participants with RA compared with those without RA [58]. The risk of CVD increases significantly after menopause due to lower levels of oestrogen, and is the leading cause of morbidity and mortality in these patients [59, 60]. Post menopause, there is a doubling of mortality both for CAD and stroke, for every 20 mmHg systolic and 10 mmHg diastolic blood pressure increase above normal [61]. The risk is higher in women with premature menopause i.e. 40 years and younger [60].

Hormone replacement therapy (HRT) has a cardio-protective effect evident by a reduction in LDL cholesterol, increases in HDL cholesterol, maintenance of endothelial cell integrity and promotion of nitric oxide production [60, 62, 63]. Use of HRT in RA has significant ameliorating effects on inflammation and joint destruction [64], however studies on its influence on CVD risk in RA are unknown.

Rheumatoid arthritis as an independent risk factor for cardiovascular disease

There is mounting evidence that the increased cardiovascular morbidity and mortality in RA is due to the pro-atherogenic changes seen with systemic inflammation rather than it being due to traditional CVD risk factors only (Figure 2) [44, 52, 65, 66]. This has resulted in the recognition of RA as an independent CVD risk factor [23, 67].

Rheumatoid arthritis is associated with a doubling of risk for MI and stroke, and a 30% increase in CVD associated death [67, 68]. In 50% of RA patients with confirmed IHD have clinically silent disease [52]. Further, the 30 day mortality following a MI or stroke is higher amongst patients with RA compared to non RA controls [67]. The relative risk for cardiovascular events in patients with RA is highest among young patients, with an increase

in absolute events greatest amongst older patients [67]. In a case control study of 76 RA and 641 non RA patients, a significantly higher prevalence of CAD, stroke, higher diastolic blood pressure (BP), significantly less HDL cholesterol and higher LDL cholesterol was found in the RA cohort [53, 69].

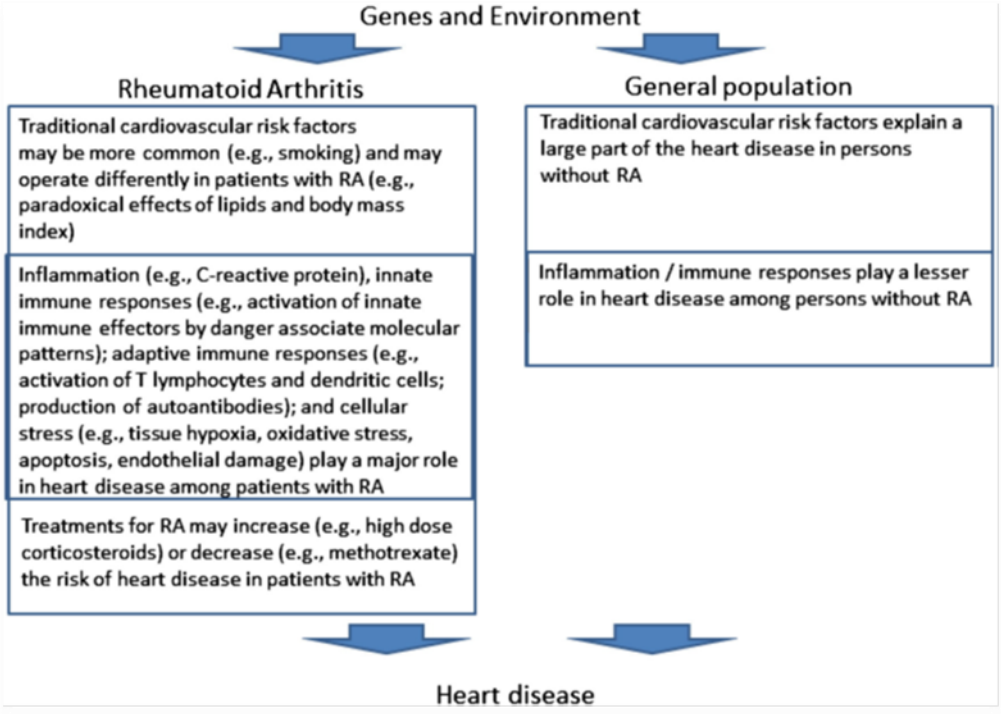

Figure 2. Determinants of heart disease in patients with rheumatoid arthritis compared to the general population [44]

Endothelial dysfunction, an integral step in atherogenesis, is related to inflammation, from chronic cytokine release from inflamed joints in RA [70-72], and HLA-DRB1 expression [73]. Studies show that HLA-DRB1, promotes survival of autoreactive T-cells, which mediate chronic inflammation [44]. These T-cells play a role in atherosclerotic plaque formation by producing cytokines and damaging vascular smooth muscle cells [44]. Therefore the HLA-DRB1 gene is associated with an increased risk of MI and other non-RA associated heart disease [74-76]. Supporting evidence of this effect has been shown in the use of T-cell inhibiting drugs currently used in percutaneous drug eluting stents in CAD, thereby preventing in-stent stenosis [44]. So compelling is atherogenesis a precocious feature in RA, that it is labelled an extra-articular manifestation of the syndrome, and defined in some studies as the ‘rheumatoid vasculopathy’[77, 78].

Studies in the Pima Indians of Arizona, USA who have the highest prevalence of RA in the world, found the presence of swollen, tender joints was a predictor of cardiovascular mortality independent of traditional cardiovascular risk factors [74]. The rheumatoid joint synovial tissue releases in abundance TNF-α, IL-6 and IL-1, which alters the function of adipose tissue and vascular endothelium [3, 79-82]. These changes produce dysregulation in glycaemic control, lipid profiles and endothelial function [3]. The Physicians Health Study, in the general population, found higher IL-6 levels in men who experienced their first MI, compared to those who remained CVD free during a six year follow up [83]. This highlights the atherogenic role of IL-6 [6].

B-cells are important contributors to the immunopathogenesis of RA and RF production. Seropositive disease confers an excess risk in cardiovascular morbidity and mortality [45] and both anti-CCP antibodies and extra-articular disease are independently associated with the development of IHD and an increased mortality from CAD respectively [23, 41]. Dessein et al. showed that in RA patients, a low glomerular filtration rate (GFR) and RF seropositivity were independent predictors of endothelial dysfunction [72]. Autopsy cases showed that in RA patients, the coronary plaque comprised exclusively of B-cells, compared to the general population, where lymphocytic infiltrates in CAD consists exclusively of T-cells [82]. This reinforces the implication that RA is an independent risk factor for CVD.

Higher levels of CRP are risk predictors of CAD and it follows, that chronic inflammation, as occurs in RA, could herald premature atherosclerosis as inflammatory cells have been found in atherosclerotic plaque [79, 80].The role of CRP in clotting and thrombosis is related to its increased activity of tissue factor [81]. A prospective study of subjects without clinical CVD, found that elevated CRP, was an independent predictor of cardiovascular events, both for MI and MI related deaths. This association is stronger in women than men [57].

Carotid artery intima thickness, is a marker of early atherosclerosis, and is increased in patients with RA [84, 85]. Shared mechanisms of immunological disease, systemic endothelial activation and circulating immune complexes lead to increased pro-thrombotic markers and increased arterial stiffness in RA [86]. The prevalence and severity of coronary calcification is increased in patients with established RA, and is associated with elevated inflammatory markers [55].

Studies show a positive relationship between cardiovascular biomarkers and active RA which is associated with consistently reduced HDL levels, leading to an unfavourable lipid profile [87, 88]. Bony erosion, a sequelae of persistent inflammation, occurs in 80% of patients untreated or inadequately treated within one year following diagnosis [10], and predicts cardiovascular events and mortality in RA [41]. Further the QUEST-RA study, supports the association of higher cardiovascular morbidity with severe RA [23] and recent studies suggests CVD risk for patients with RA in remission is similar to non RA controls [89]. Cardiovascular risk increases by 7% for each additional RA acute flare [89, 90]. This highlights the concept of accumulating cardiovascular damage with each acute flare, and possibly explains the excess cardiovascular risk in RA patients compared to non RA controls.

Role of pharmaco-therapeutics in rheumatoid arthritis and effects on cardiovascular risk

Disease modifying anti-rheumatic drugs, apart from their inflammatory ameliorating effects, also decrease atherosclerosis risk and have proven beneficial effects on RA associated CVD [41].

Methotrexate is associated with a 21% reduction in cardiovascular events [44]. In a small study of 22 patients with RA, 14 patients who commenced methotrexate had a decrease in insulin resistance during the first eight weeks [91]. In contrast, other studies show an increased prevalence of homocysteinaemia, an independent risk factor for CVD, in RA patients on methotrexate therapy [92].

Other traditional DMARDs may also decrease cardiovascular risk; hydroxychloroquine improves lipid profiles, with a reduction in LDL, and total cholesterol/HDL ratio [44, 93], and decreases the risk of DM in patients with RA [44]. Newer therapies, example TNF-α inhibitor therapy are associated with reduced risk of all heart disease events [44], and they have a favourable effect on HDL lipid profiles [94], with improved endothelial function and insulin resistance [44].

There is conflicting data on the use of glucocorticoids. Older studies showed that glucocorticoid use resulted in hypertension, decreased insulin sensitivity, elevated lipid

levels, and increased carotid plaque and arterial stiffness [95]. Doses of greater than 7.5 mg per day appear to have twice the risk of heart disease compared to those who did not receive glucocorticoids [96], however, the QUEST-RA study showed that the fundamental effects of lowering inflammatory burden, correlates with an independent association of long-term glucocorticoid use and a reduced risk of all cause cardiovascular events [23]. Additionally, the benefit of reducing high-grade inflammation in an acute flare may counteract the adverse cardiovascular effects of glucocorticoid use [45].

In contrast, both selective and non-selective NSAIDs are known to cause clinically significant hypertension, which may require treatment [97], and even small increases of 5 mmHg in diastolic BP confer a 15% increase in cardiovascular event risk [98].

Cyclooxygenase inhibitors, in particular, through renal prostaglandin inhibition, exacerbate fluid retention and aggravate hypertension [99]. The use of NSAIDs and its association with cardiovascular risk was brought to the fore in the Vioxx Gastrointestinal Outcomes Research (VIGOR) study. An increased risk of heart disease was found with rofecoxib use [100]. A meta-analysis has shown no differences in heart disease events with celecoxib or ibuprofen use, and naproxen conferred the lowest cardiovascular risk [101], with the added benefit of possible aspirin-like antiplatelet cardio-protective effects [102].

Cardiovascular risk assessment in rheumatoid arthritis

There are several validated cardiovascular risk assessment tools available for use, including the Framingham Risk Score (FRS), and the Systematic Coronary Risk Evaluation Score (SCORE), which determines the 10-year risk of fatal CVD (Table 4). Additionally, tools like the Reynolds Risk Score (RRS) takes into account traditional risk factors as well as the added risk of inflammation, in identifying the 10-year risk for a MI or stroke. The QRISK3 score developed in 2017 includes additional CVD risk factors chronic kidney disease, presence of RA and regular glucocorticoid use.

All of these CVD risk models have been developed based on data primarily from white men and women from developed countries, with little validation for multi-ethnic populations [103, 104]. Both the FRS and RRS were developed and validated in USA, SCORE in Europe and

QRISK3 in the UK, and their adaptability to developing countries, particularly an African ethnically diverse population has not been validated [105].

Studies show that traditional risk factors account for only a portion of the overall risk for CVD in RA, with the additional risk attributed to inflammation [65, 66]. Therefore the lack of recognition of inflammatory markers in FRS and SCORE, underestimates the cardiovascular risk in RA. An expert panel convened by EULAR, recommends a multiplier of 1.5 for FRS and SCORE if a patient fulfils two or more of the following: RA disease duration more than 10 years, RF or anti-CCP antibody positivity, or extra-articular manifestations [45, 47].

The most prevalent conventional CVD risk factors reported in limited South African RA studies are hypertension and dyslipidaemia [106]. A local study by Solomon et al. highlighted the need for population specific CVD risk stratification, concluding that individual CVD risk factors are consistently and independently related to atherosclerosis in South African White but not South African Black patients with RA [107]. The impact of urbanisation translates into different evolving CVD risk profiles with consequent altered CVD presentations [108]. Studies in Africa show that obesity is associated with hypertension as well as diastolic heart failure and systemic inflammation [109, 110]. Recent studies in the South African Black population show the prevalence of all major traditional CVD risk factors are high and increasing [111-113], with South African Black women sustaining higher obesity rates than other local South African ethnic groups [114]. Black South Africans with RA smoked less frequently, but had more prevalent hypertension, DM, with lower total cholesterol and HDL cholesterol concentrations compared to other South African ethnic groups with RA [107]. Further, the overall metabolic risk burden was similar in South African Black compared with South African White, Asian and Mixed Ancestry patients with RA [106]. The Framingham score correlated with atherosclerosis in South African White but not Black patients, underscoring the limitations of adequate cardiovascular risk assessment in Africans with RA [107].

With no current national guidelines, CVD risk assessment in clinical practice in SA is extrapolated from models designed in developed countries.

Table 4. Comparison of clinical variables and risk outcomes in the Framingham Risk Score, Reynolds Risk Score and Systematic Coronary Risk Evaluation Score [47]

Clinical variable	FRS	RRS	SCORE
Age	✓	✓	✓
Gender	✓	✓	✓
Tchol	✓	✓	✓
HDL	✓	✓	
Current smoker	✓	✓	✓
Systolic BP	✓		✓
On medication for hypertension	✓		
hsCRP		✓	
Mother or father with heart attack or stroke before age 60		✓	
High-/low-risk European country			✓
Predicted 10-year risk	MI or coronary death	MI or stroke	Fatal CVD

Tchol, total cholesterol; BP, blood pressure; hsCRP, high sensitive C reactive protein

Conclusion

A fundamental principle linking RA to CVD is the shared inflammation. Studies suggest that patients with RA are less likely to receive primary or secondary heart disease screening or preventions [44]. Therefore understanding the cardiovascular risk in a patient with RA requires a revolutionary conceptual model that highlights the overlapping influence of traditional risk factors and inflammation.

In SA, life expectancy has increased to 62 years according to WHO 2015 statistics, and with increased longevity following a decline in communicable diseases (HIV), it is expected that the burden of non-communicable diseases, including RA, will increase [115].

Studies with non RA control groups show that the lifetime risk for CAD in RA patients is of equal magnitude to the general population with DM [44, 45]. In the non RA population, obesity is associated with higher CRP, and an increased cardiovascular risk [54]. Recent studies show that hypertension is commoner in RA compared to community control groups [52]. In developing countries, 46.7% of CVD deaths in the general population occur below the age of 70 years. Case control comparison of incident acute MI cases and age and sex matched controls revealed the most important predictors of acute MI were current smoking, hypertension, DM, and abdominal obesity [38]. The expectations in RA patients, is that these traditional CVD risk factors prevalent in the general population, are common, however, their

CVD risk may be enhanced due to the added deleterious influences of inflammation and effects of joint targeted therapy.

Cardiovascular risk management in patients with RA requires an evaluation of biomarkers, control of traditional risk factors, and RA disease control. Early control of disease activity in RA predicts significant survival benefits. Current therapeutic strategies for the management of RA in SA are outlined by the SARAA [21]. Treatment of dyslipidaemia is based on cardiovascular risk using the Framingham Risk Score [116], with percentage risk multiplied by 1.5 in the setting of RA with seropositivity, extra-articular or established disease [21, 47]. Improved RA disease control, with methotrexate and anti-TNF therapy, decreases CVD risk in RA patients. However, no population specific CVD risk factor surveillance guidelines are currently in use locally.

A robust preventative strategy of CVD in this high-risk group is required. This study will improve our knowledge of CVD burden and risk in RA in our setting, and study results can be applied to developing a framework for risk assessment and health care targets in this specific at-risk group.

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The manuscript

Abstract

Cardiovascular disease (CVD), as a driver of morbidity and mortality in rheumatoid arthritis (RA), is well described in developed countries, with limited studies from developing countries especially Africa.

Objective: To describe the prevalence of CVD and traditional CVD risk factors in patients with established RA, and the relationship between RA disease activity and CVD.

Methods: A retrospective chart review was conducted of all patients diagnosed with RA, according to the American College of Rheumatology classification criteria, attending a regional level arthritis clinic. Demographic data, RA disease profile, Simplified Disease Activity Index (SDAI) and Health Assessment Questionnaire (HAQ) scores, CVD risk factors, electrocardiogram (ECG), echocardiogram and laboratory findings were recorded on a standard data form. Continuous variables were compared using Student T-test, and categorical variables were compared using Pearson Chi Squared test and Fischer's test as appropriate. Relative risk was calculated to determine a difference in prevalence of CVD between age groups and gender. A one way analysis of variance was used to determine the difference between CVD risk assessment scores.

Results: One hundred and fifty patients with RA met the inclusion criteria; of which 24 had CVD. Patients with CVD were older compared to those without CVD (63.4 ± 9.3 years vs 58 ± 11.7 years, $p = 0.02$). Whilst a lower relative risk of CVD was observed in patients younger than 50 years (RR = 0.352), the relative risk of CVD was higher in men compared to women (RR = 2.039). Indian patients were more likely to have CVD compared to both Black ($p = <0.0001$) and White patients ($p = 0.0023$).

No difference in seropositivity ($p = 0.516$), HAQ ($p = 0.349$), SDAI ($p = 0.891$), or radiological involvement was observed. Extra-articular disease was significantly more common among patients with CVD ($p = 0.0002$), whilst in contrast prolonged early morning stiffness was observed significantly more frequently in patients without CVD ($p = 0.0016$). Diabetes mellitus ($p = 0.0018$), dyslipidaemia ($p = 0.0026$) and chronic kidney disease (p =

0.0013) was more common in patients with CVD. Patients without CVD were more physically inactive (p = 0.0001) and obese (p = 0.005), whilst patients with CVD were overweight (p = 0.0293). Women with CVD were more likely menopausal (p = <0.0001), and on hormone replacement therapy (p = <0.0001).

In patients without CVD, subclinical CVD was evident in 25% of 105 ECGs, and 58% of 104 echocardiograms reviewed. Differences between CVD risk assessment scores at different levels of risk were observed (p = <0.0001).

Conclusion: The burden of traditional CVD risk factors in RA is high, and CVD in RA is associated with an ethnic, age and gender differential. Whilst coronary artery disease was the most common CVD in RA patients, echocardiographic evidence of subclinical cardiac disease in RA seems common. No correlation was observed between RA disease activity and CVD in RA. A discriminant CVD risk assessment score is needed in a multi-ethnic South African population with RA.

Keywords: Rheumatoid arthritis, cardiovascular disease, cardiovascular disease risk factors, inflammation

Introduction

Rheumatoid arthritis (RA) is a common chronic systemic autoimmune inflammatory disease, characterized by symmetrical polyarthritis, with extra-articular manifestations [1]. The mortality risk in RA is increased by 70% compared to the general population [2], and the leading cause of death in RA is cardiovascular disease (CVD) [2, 3]. Both traditional and non-traditional factors combine to increase the adverse cardiovascular risk profile in patients with RA, with CVD deaths occurring 5 - 10 years prematurely compared to the general population [4].

The global prevalence of CVD morbidity in RA is 9.3%, with a wide geographic variation; the highest prevalence in Germany (17.8%), followed by Poland (11.8%), and the lowest in France (3.6%) [5]. There are however limited studies on the prevalence of CVD in RA patients from sub-Saharan Africa.

Traditional CVD risk factors (hypertension, diabetes mellitus (DM), dyslipidaemia, obesity, physical inactivity and smoking) play a causal role in 50% of all coronary artery disease (CAD) in the general population [6]. In RA, traditional CVD risk factors are influenced by both inflammation inherent to the disease, and pharmacodynamics of anti-rheumatic drugs, yielding an unfavourable pro-atherogenic profile [7]. Mounting evidence recognises RA as an independent risk factor for CVD [5, 8].

Systemic inflammation results in an "inflammatory metabolic syndrome"[9] and vascular endothelial dysfunction [3], which promote accelerated atherosclerosis [7]. Rheumatoid arthritis seropositivity [10], high disease activity and presence of extra-articular disease confer an excess CVD mortality risk [5]. Disease modifying anti-rheumatic drugs (DMARD), non-steroidal anti-inflammatory drugs (NSAID) and glucocorticoids effect fundamental changes in traditional CVD risk factors and all cause cardiovascular event risk in RA [5, 11].

Several CVD risk assessment tools (Framingham Risk Score (FRS) and the Systematic Coronary Risk Evaluation Score (SCORE)) are validated for CVD risk prediction in the general population [12, 13]. Their performance accuracy in the RA population is poor [14], and recognition of the additional CVD risk attributed to inflammation in RA, has led to the modification of the FRS to be multiplied by 1.5 in RA patients who fulfil two or more of the following: RA disease duration more than 10 years, seropositive disease, or presence of extra-articular manifestations [15]. Other scoring tools recognising the added risk of inflammation includes the Reynolds Risk Score and the QRISK3 score [15]. However these scoring models are country and population specific, with poor reliability in diverse multi-ethnic populations as in South Africa (SA).

There are limited studies describing the cardiovascular profile of patients with RA from SA. Solomon et al. highlighted the need for population specific CVD risk stratification, concluding that individual CVD risk factors are consistently and independently related to atherosclerosis in South African White but not Black patients with RA [16]. The impact of urbanisation translates into different evolving CVD risk profiles with consequent altered CVD presentations [17]. Recent studies in the South African Black population show a high burden of traditional CVD risk factors [18-20], with South African Black women having a much higher rate of obesity than other local South African ethnic groups [21]. A study in Johannesburg found that Black South Africans with RA smoked less frequently, but had more

prevalent hypertension, DM, with lower total cholesterol and high density lipoprotein (HDL) cholesterol concentrations compared to other South African ethnic groups with RA [16]. Overall metabolic risk burden was similar in South African Black compared with South African White, Asian and Mixed Ancestry patients with RA [22]. The Framingham score correlated with atherosclerosis in South African White but not Black patients, underscoring the limitations of adequate cardiovascular risk assessment in non-White Africans with RA [16].

There are limited studies on the prevalence, traditional risk factors and relationship to disease activity of CVD in RA patients from sub-Saharan Africa. With the predicted increase in longevity and non-communicable diseases, it is critical that valid, reliable tools for assessing 10 - year CVD risk be developed to manage CVD risk in RA patients, and thereby favourably influence long term outcomes.

Methods

Ethical approval for the study was granted by the Biomedical Research Ethic Committee of University of KwaZulu-Natal (UKZN) (BREC Ref No.: BE 535/17) and the KwaZulu-Natal (KZN) Provincial Department of Health, King Edward VIII Hospital (KEH) and the arthritis clinic.

A retrospective, descriptive chart review was conducted in the arthritis clinic of KEH, a tertiary public hospital in KZN. The arthritis clinic is a dedicated weekly run rheumatological service, under the stewardship of a team comprising a rheumatologist, general physicians and medical officers. Patients with RA are reviewed on a four monthly basis or sooner if they have complications or are newly commenced on DMARDs. Majority of patients attending the clinic are of Black and Indian ethnicity, reflecting the population demography of KZN, and the majority of the population utilising the public health-care system in KZN.

A chart review of all patients with a clinical diagnosis of RA was conducted between August 2017 and March 2018. Study inclusion criteria were a minimum of six months disease duration, age of 18 years or older, confirmed diagnosis of RA according to the American College of Rheumatology classification criteria 1987/2010 [23, 24] and attendance at the clinic in the last six months. Patients with concomitant connective tissue diseases, or other

forms of arthritis were excluded. A total of 162 files were reviewed, of which 12 were excluded due to missing data and/or a diagnosis of coexisting connective tissue disease. Patients with established cardiovascular disease in this study included CAD, valvular heart disease, cardiomyopathy, dysrhythmia and pericardial disease. Cardiovascular disease was not based on echocardiogram findings.

Demographic data (age, gender, ethnicity, residence, education level, employment history), duration of disease, extra-articular manifestations, underlying cardiovascular risk factors (DM, hypertension, dyslipidaemia, physical activity, smoking history, menopausal status, chronic kidney disease (CKD), history of cerebrovascular accident (CVA) and human immunodeficiency virus (HIV) infection), presence of established CVD, rheumatoid factor (RF)/anti-cyclic citrullinated peptide (ACCP) positivity, health assessment questionnaire (HAQ) score, simplified disease activity index (SDAI), radiological involvement and drug therapy were extrapolated from medical records. Radiographs performed within the preceding twelve months of study were analysed. The presence of osteoporosis was recorded from available dual energy X-Ray absorptiometry (DEXA) scans in medical records. Blood pressure (BP), weight and height as recorded in the last visit, was documented. Weight and height were used to calculate the body mass index (BMI) (weight/height^2), which were categorised according to the World Health Organisation (WHO) classification of obesity viz. underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), obese Class I (30-24.9 kg/m^2), obese Class II (35-39.9 kg/m^2), and obese Class III (> than 40 kg/m^2) [25].

Physical activity was categorised according to the 2016 European Society of Cardiology (ESC) guidelines on CVD prevention in clinical practice [26]. Categories are grouped according to the metabolic equivalent i.e. energy cost of a given activity divided by the resting energy expenditure viz. nil (no physical activity), light (light household work), moderate (cycling or brisk walking) and vigorous (jogging or swimming or running). These categories of physical activity have been validated in several studies, and are incorporated as part of ESC recommendations for CVD prevention [27-29].

The HAQ functional assessment is widely used in RA and has been validated in several studies, such as prediction of successful aging, inversion of the therapeutic pyramid in RA,

and examination of mortality risks in RA, work capacity and performance, occupation and the ability to live independently [30].

The SDAI combines the sum of tender and swollen 28 joint count, patient and doctor global assessment and acute phase reactants. This composite index has been validated in multiple studies in RA, correlating with function and radiographic changes [31-34].

Electrocardiogram (ECG) and echocardiogram findings (performed within the preceding year) were recorded. The annual haemoglobin, estimated glomerular filtration rate, C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) as at last visit, and the glycated haemoglobin (HbA1C) and lipid studies (done within the preceding year) were recorded. It must be noted that a paradoxical relationship between inflammation and lipid profiles occurs in RA which translates into a CAD risk factor. Inflammation in RA alters lipoprotein structure and function and the HDL load of serum amyloid A increases with a decrease in apolipoprotein A-I, leading to a shift in the anti-atherogenic effect of HDL to a pro-atherogenic effect [35].

Deidentified data was entered into an Excel spreadsheet. Data analysis was conducted using SPSS version 25 (IBM SPSS Statistics for Windows, version 24.0. Amonk, NY:IBM Corp.) Continuous variables such as age, disease duration, BMI, amongst others, were summarised as mean (standard deviation (SD)). Categorical variables were summarised using proportions and percentages. Continuous variables were compared using student t-test, and categorical variables were compared using Pearson Chi Squared test and Fischer's test as appropriate. Regression analysis was done to explore independent association of age and gender in relation to CVD. Relative risk was calculated to determine a difference in prevalence of CVD between age groups and gender.

Predicted 10 year CVD risk was calculated for patients without CVD. Algorithm derived scores were divided into three categories viz. low risk (<10%), intermediate (10-19%) and high risk (>20%), stratifying patients who are eligible for blood pressure and lipid lowering therapies [36, 37]. Statins are advised in high risk patients, and conditionally initiated in patients with intermediate risk i.e. low density lipoprotein (LDL) >3.5 mmol/L or apolipoprotein B >1.1 g/L, or men older than 49 years or females older than 59 years with 1

risk factor (low HDL, impaired fasting glucose, increased waist circumference, smoker, or hypertension).

Risk assessment models evaluating different parameters were applied viz. Framingham, modified Framingham, QRisk3 and Reynolds risk score (Table 1).

The Framingham and Reynolds scores have Class I recommendations from the American College of Cardiology and the American Heart Association [38]. The modified Framingham score is a validated RA-specific risk prediction algorithm incorporated in European League Against Rheumatism (EULAR) guidelines on CVD risk management in patients with RA [39, 40]. The QRISK3 score has been validated in comparative prospective cohort studies [41, 42]. A one way analysis of variance (ANOVA) was used to determine if there was a statistical significant difference between various CVD risk assessment scores. In the event of a positive ANOVA, a post hoc test such as Tukeys was used to conduct a pairwise comparison of these scores. Statistical significance was set at $p < 0.05$.

Table 1. Comparison of clinical variables in the Framingham Risk Score, Modified Framingham Risk Score, Reynolds Risk Score and QRISK3 Score [15, 39, 42]

Clinical variable	FRS	Modified FRS	RRS	QRISK3
Age	✓	✓	✓	✓
Gender	✓	✓	✓	✓
Total cholesterol	✓	✓	✓	✓
High density lipoprotein	✓	✓	✓	✓
Current smoker	✓	✓	✓	✓
Systolic blood pressure	✓	✓	✓	✓
On medication for hypertension	✓	✓		✓
C reactive protein			✓	
Mother or father with heart attack or stroke before age 60			✓	✓
Rheumatoid arthritis		✓		✓
Glucocorticoid use				✓
Ethnicity				✓

Diabetes mellitus	✓
Chronic kidney disease	✓
Height	✓
Weight	✓

Results

Demographic profile

The mean age of the study group was 58.9 ± 11.5 years, with a range of 24 to 87 years, and a female to male ratio of 9:1 (Table 1). Majority of patients were Indian 78 (52%), followed by Blacks 63 (42%), with Whites and Coloureds comprising 8 (5.3%) and 1 (0.7%) respectively.

Of the total cohort of 150 patients, CVD was present in 24 patients (16%), with majority having CAD 18 (75%) followed by small numbers having valvular heart disease 2 (8.3%), cardiomyopathy 2 (8.3%), dysrhythmia 1 (4.2%), and pericardial disease 1 (4.2%).

Patients with CVD were significantly older compared to patients without CVD (63.4 ± 9.3 years vs 58.0 ± 11.7 years, p = 0.02). A lower relative risk (RR) of CVD was observed in patients younger than 50 years (RR = 0.352).

Women with CVD, constituted 14.2 % of the total female cohort, and the majority in the CVD cohort (79%), however a higher RR of CVD was observed in men compared to women (RR = 2.039).

Cardiovascular disease was more common in Indian and White patients (p = 0.04, p = 0.07 respectively), and Black patients were less likely to have CVD (p = 0.0015). Albeit a small sample size, Indian patients formed the majority of patients in the CVD group (70.8%) and were significantly more likely to have CVD compared to both Black (p = <0.0001) and White (p = 0.0023) patients.
There was no difference in housing or educational level between patients with and without CVD, however patients who have never been employed were less likely to have CVD, and this approached statistical significance (p = 0.05).

Table 1. Comparison of the demographic profile of rheumatoid arthritis patients with and without cardiovascular disease

Characteristic	Total n=150 n(%)	Presence of CVD n=24 n(%)	Absence of CVD n=126 n(%)	p value
Age, years	58.9 ± 11.5	63.4 ± 9.3	58.0 ± 11.7	0.02
Gender				
Male	16 (10.7)	5 (20.8)	11 (8.7)	0.08
Female	134 (89.3)	19 (79.2)	115 (91.3)	0.08
Ethnicity				
Black	63 (42.0)	3 (12.5)	60 (47.6)	0.0015
Indian	78 (52.0)	17 (70.8)	61 (48.4)	0.04
White	8 (5.3)	4 (16.7)	4 (3.2)	0.007
Coloured	1 (0.7)	0 (0)	1 (0.8)	0.66
Residence				
Urban	146 (97.3)	24 (100.0)	122 (96.8)	0.376
Rural	4 (2.7)	0 (0)	4 (3.2)	-
Level of education*				
None	9 (6.0)	1 (4.2)	8 (6.3)	0.692
Primary school	38 (25.3)	8 (33.3)	30 (23.8)	0.328
High school	89 (59.3)	14 (58.3)	75 (59.5)	0.913
University/College	14 (9.3)	1 (4.2)	13 (10.3)	0.348
Occupation				
Never employed	34 (22.7)	5 (20.8)	29 (42.1)	0.05
Unemployed	38 (25.3)	6 (25.0)	32 (25.4)	0.967
Informal sector	13 (8.7)	1 (4.2)	12 (9.5)	0.399
Formal sector	65 (43.3)	12 (50.0)	53 (42.1)	0.476

Continuous variables presented as mean ± standard deviation

*None = no formal schooling, Primary school = grade 0-7, High school = grade 8-12

Rheumatoid arthritis disease activity

The mean duration of disease in the total cohort was 15.4 ± 10.3 years with no significant difference between the two groups (Table 2). Patients without CVD had significantly longer duration of early morning stiffness compared to patients with CVD (25 ± 19.6 minutes vs 53.7 ± 71.7 minutes, p = 0.0016), however the presence of extra-articular disease was more common in patients with CVD (83.3% vs 41.3%, p = 0.0002). The most common extra-articular features recorded in this study were anaemia 24 (16%), osteoporosis 20 (13.3%), atherosclerosis 19 (12.7%) and subcutaneous nodules 15 (10%), with no significant differences in occurrence of individual extra-articular features between the two groups, probably due to the small sample size. It must be noted that due to limited access to DEXA scans in KZN, not all patients in this study had a DEXA scan. This potentially underestimates the true number of patients with osteoporosis.

Atherosclerosis included all patients known with cerebrovascular accidents, peripheral vascular disease and computed tomography evidence of a calcified aorta and peripheral vascular calcification, and all these conditions were considered an extra-articular feature in this study. Atherosclerosis was present in 50% of RA patients with CVD (12 of 24), compared to 6% (7 of 126) of RA patients without CVD. In isolation, this extra-articular manifestation would bias one to the likelihood of CVD, however in this study, atherosclerosis didn't occur as a lone extra-articular manifestation in many patients, but also other extra-articular features were present eg. nodular disease and anaemia, so it's significance cannot be ascertained with certainty. Additionally due to small sample size, comparison of atherosclerosis between the two groups is limited.

There was no significant difference in seropositivity, disease activity scores (SDAI/HAQ), inflammatory markers (CRP/ESR) and radiological involvement between the two groups (Table 2).

Table 2. Comparison of rheumatoid arthritis disease profile and activity in patients with and without cardiovascular disease

	Total n=150 n(%)	Presence of CVD n=24 n(%)	Absence of CVD n=126 n(%)	p value
Disease duration, years	15.4 ± 10.3	15.3 ± 11.4	15.5 ± 10.1	0.946
Seropositive disease	114 (76.0)	17 (70.8)	97 (77)	0.516
Early morning stiffness, minutes	49.1 ± 67.6	25 ± 29.6	53.7 ± 71.7	0.0016
Extra-articular disease	72 (48.0)	20 (83.3)	52 (41.3)	0.0002
SDAI	16.3 ± 12.9	15.9 ± 14.7	16.4 ± 12.6	0.891
HAQ	0.9 ± 0.8	0.7 ± 0.8	0.9 ± 0.8	0.349
CRP, mg/L	14.6 ± 24.3	22.0 ± 31.6	19.4 ± 19.2	0.6999
ESR, mm/hr	47.0 ± 36.5	49.8 ± 46.7	46.5 ± 34.5	0.746
Radiological involvement				
Normal	26 (17.3)	5 (20.8)	21 (16.7)	0.628
Juxta-articular osteopaenia	88 (58.7)	13 (54.2)	75 (59.5)	0.630
Joint space narrowing	95 (63.3)	15 (62.5)	80 (63.5)	0.926
Erosive disease	88 (58.7)	11 (45.8)	77 (61.1)	0.164
Joint destruction	36 (24.0)	3 (12.5)	33 (26.2)	0.151

Continuous variables presented as mean ± standard deviation, SDAI=simplified disease activity index, HAQ=health assessment questionnaire, CRP=C reactive protein, ESR=erythrocyte sedimentation rate

Pharmaco-therapeutic profile of rheumatoid arthritis patients

The majority of patients in the total cohort were on DMARD therapy (94.7%). Reasons for the eight patients not being on therapy included disease remission and previous drug intolerance with patient preference to remain on NSAIDs only. There was no significant difference in the number of DMARDs patients were on or the use of methotrexate, chloroquine or oral glucocorticoid between patients with or without CVD, however patients using sulphasalazine were more likely to have CVD (Table 3). Traditional NSAIDs were used by 72% of the total cohort.

Table 3. Drug profile of rheumatoid arthritis patients with and without cardiovascular disease

	Total n=150 n(%)	Presence of CVD n=24 n(%)	Absence of CVD n=126 n(%)	p value
DMARD				
None	8 (5.3)	2 (8.3)	6 (4.8)	0.487
Methotrexate	100 (66.7)	12 (50.0)	88 (69.8)	0.060
Sulphasalazine	72 (48.0)	16 (66.7)	56 (44.4)	0.0458
Chloroquine	61 (40.7)	7 (29.2)	54 (42.9)	0.155
Number of DMARDs	64 (42.7)	11 (45.8)	53 (42.1)	0.738
Single	62 (41.3)	9 (37.5)	53 (42.1)	0.676
Double	16 (10.7)	2 (8.3)	14 (11.1)	0.685
Triple				
Oral glucocorticoid	109 (72.6)	18 (75.0)	91 (72.2)	0.779
NSAID	108 (72)	15 (62.5)	93 (73.8)	0.260

DMARD=disease modifying anti-rheumatic drug, NSAID=non steroidal anti-inflammatory drug

Traditional cardiovascular risk factors

Patients with CVD were significantly more likely to have DM, dyslipidaemia and CKD (Table 4). Although hypertension was common in the study population (58.7%), there were no significant differences between the two groups.

An increased BMI was found in 69% of the total cohort. The mean BMI was significantly higher in patients without CVD (25.7 ± 4.1 kg/m^2 vs 28.5 ± 6.2 kg/m^2, p = 0.035) and these patients were significantly more likely to be obese than patients with CVD (38.3% vs 5.3%, p = 0.005). In contrast, patients with CVD were significantly more likely to be overweight than those without CVD (57.9% vs 31.8%, p = 0.0293).

Patients without CVD were significantly more physically inactive than those with CVD (69.8% vs 66.7%, p = 0.0001). There was however no difference in actual measured systolic and diastolic BP, smoking habits, family history of CVD, haemoglobin levels, HbA1C or lipid profiles between the two groups.

Although the majority of women in the total cohort had reached menopause (82%), there was a significantly higher number of post-menopausal women in the group with CVD than those without CVD (89.5% vs 81.7%, p = <0.0001). Furthermore, there was a significantly higher use of hormone replacement therapy (HRT) in this group (p = <0.0001), however these were very small numbers.

Table 4. Traditional cardiovascular risk factors comparison in rheumatoid arthritis patients with and without cardiovascular disease

	Total n=150 n(%)	Presence of CVD n=24 n(%)	Absence of CVD n=126 n(%)	p value
Hypertension	88 (58.7)	17 (70.8)	71 (56.3)	0.188
Blood pressure				
Systolic, mmHg	134.7 ± 20.8	130.3 ± 21.4	135.5 ± 20.7	0.281
Diastolic, mmHg	70.7 ± 13.2	68.6 ± 12.6	71.1 ± 13.3	0.384
Diabetes mellitus	24 (16.0)	9 (37.5)	15 (11.9)	0.0018
Dyslipidaemia	29 (19.3)	10 (41.7)	19 (15.1)	0.0026
Cerebrovascular accident	5 (3.3)	0 (0.0)	5 (4.0)	-
Chronic kidney disease	41 (27.3)	13 (54.2)	28 (22.2)	0.0013
HIV	7 (4.7)	1 (4.2)	6 (4.8)	0.899
Body mass index *				
Underweight	4 (3.2)	1 (5.3)	3 (2.8)	0.574
Normal	35 (27.8)	6 (31.6)	29 (27.1)	0.689
Overweight	45 (35.7)	11 (57.9)	34 (31.8)	0.0293
Obese	42 (33.3)	1 (5.26)	41 (38.3)	0.005
Mean	28.1 ± 6.0	25.7 ± 4.1	28.5 ± 6.2	0.035
Physical activity				
Nil	104 (69.3)	16 (66.7)	88 (69.8)	0.0001
Light	33 (22.0)	6 (25.0)	27 (21.4)	0.697
Moderate	13 (8.6)	2 (8.3)	11 (8.7)	0.949
Vigorous	0 (0.0)	0 (0.0)	0 (0.0)	-
Smoking	29 (19.3)	7 (29.2)	22 (17.5)	0.185
Pack years	14.9 ± 11.7	15.9 ± 10.7	14.6 ± 12.2	0.621
Family history of CVD	21 (14.0)	6 (25.0)	15 (11.9)	0.0911
Haemoglobin	12.4 ± 1.4	12.1 ± 1.7	12.4 ± 1.2	0.416
HbA1C	5.9 ± 1.1	6.3 ± 1.4	5.9 ± 1.0	0.193
Total cholesterol, mmol/L	5.1 ± 1.9	4.8 ± 1.2	5.2 ± 1.2	0.199
Triglycerides, mmol/L	1.4 ± 0.9	1.5 ± 0.8	1.4 ± 0.9	0.511

HDL, mmol/L	1.4 ± 0.4	1.4 ± 0.3	1.5 ± 0.4	0.186
LDL, mmol/L	3.1 ± 1.1	3.1 ± 0.8	3.1 ± 1.2	0.717
Menopause **	111 (82.8)	17 (89.5)	94 (81.7)	<0.0001
Early menopause	24 (21.6)	0 (0.0)	24 (25.5)	-
Received HRT	4 (3.6)	2 (11.8)	2 (2.1)	<0.0001

Continuous variables presented as mean ± standard deviation, *applicable to 126 patients, 19 in the presence CVD group and 107 in the absence of CVD group, **applicable to 134 female patients, 19 in the presence of CVD group and 115 in the absence of CVD group, HbA1C=glycated haemoglobin, HDL=high density lipoprotein, LDL=low density lipoprotein

Electrocardiogram and echocardiogram findings

Only 123 patients of the total study group had an ECG performed within the previous 12 months, of which, 88 (71.5%) were normal. Abnormalities present in the remaining 35 (28.5%) ranged from sinus tachycardia 9 (7.3%), sequelae of ischaemic heart disease (IHD) 6 (4.9%), left axis deviation (LAD) 6 (4.9%), features of right heart disease 5 (4.1%), left ventricular hypertrophy (LVH) 4 (3.3%), left bundle branch block (LBBB) 2 (1.6%), sinus bradycardia 2 (1.6%) and ventricular ectopics 1 (0.8%).

Only 124 patients of the total study group had an echocardiogram performed, of which abnormalities were found in 74 (60%), with valvular heart disease the most common 58 (47%), followed by features of IHD 11 (9%), cardiomyopathy 2 (2%), and the remaining 2% attributed to pulmonary hypertension, dextrocardia and pericardial disease one each respectively.

In CVD-free RA patients, findings of 105 ECGs and 104 echocardiograms are shown (Figure 1 and 2).

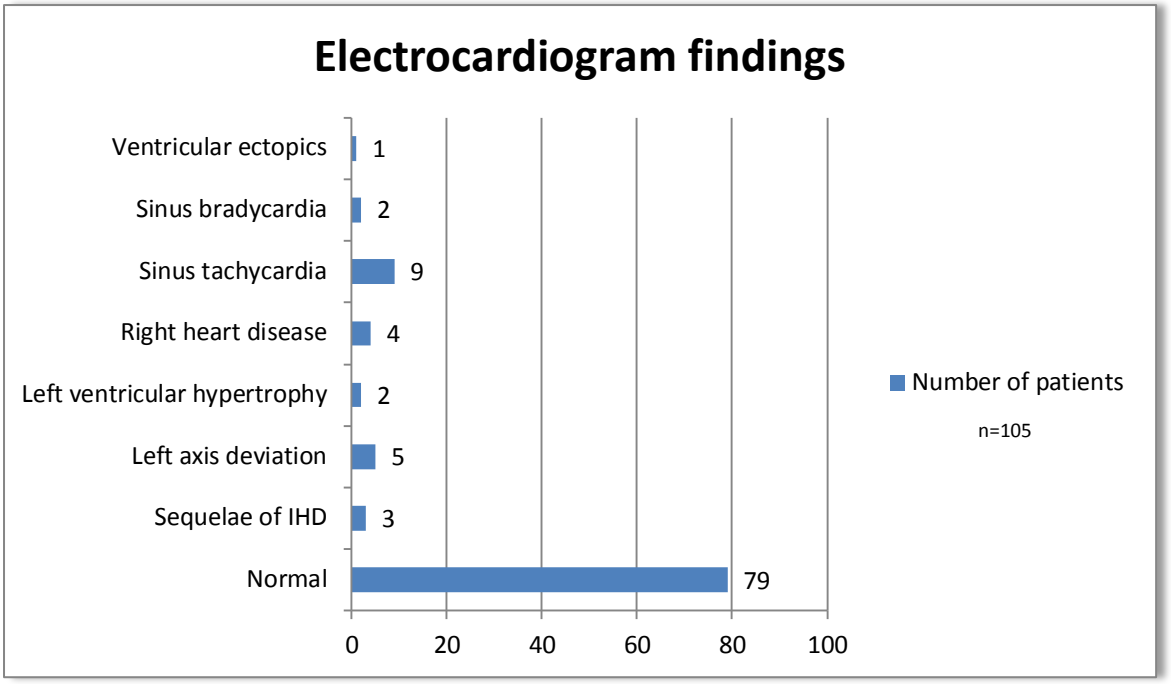

Figure 1. Distribution of electrocardiogram findings in rheumatoid arthritis patients without cardiovascular disease

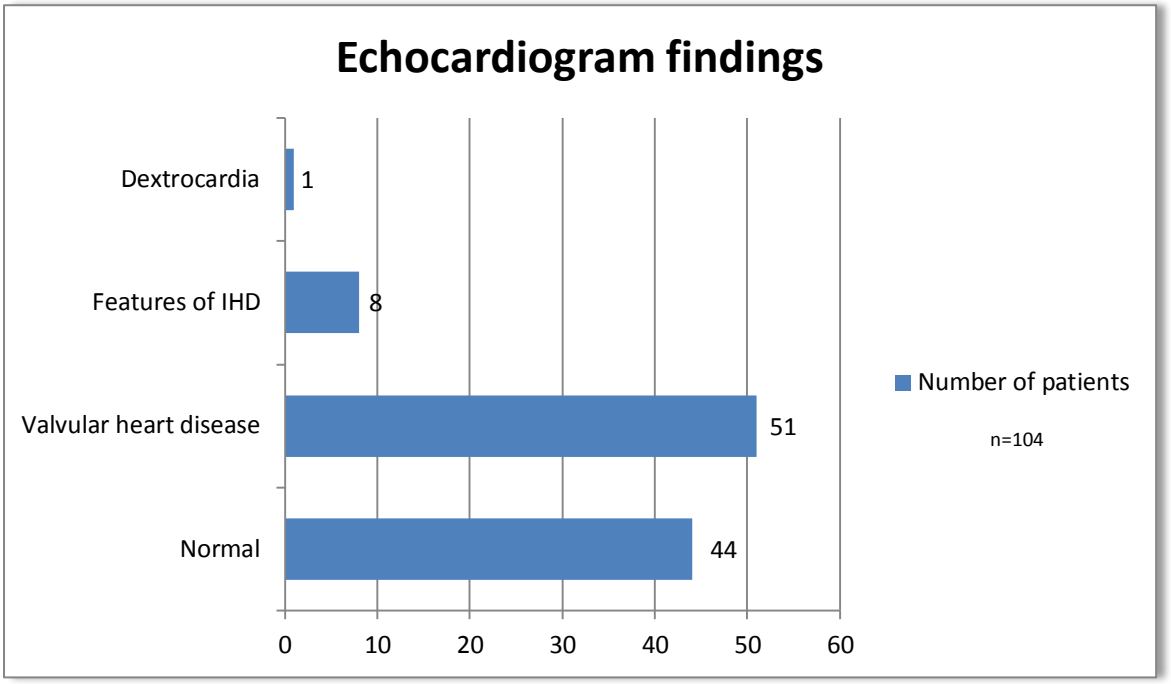

Figure 2. Distribution of echocardiogram findings in rheumatoid arthritis patients without cardiovascular disease

Cardiovascular disease predictive risk assessment

The four most common and validated CVD risk assessment models were applied to 126 patients without CVD and the predicted 10 year risk was calculated (Figure 3).

The risk estimates varied widely between models. Estimated high risk was 24.3%, 47.8%, 34.7% and 5.2% for the Framingham, modified Framingham, QRisk3 and Reynolds CVD models. Estimated intermediate risk was 21.7%, 22.6%, 26.6% and 10.4% respectively. The comparison of different levels of risk between the various scoring models showed a similar distribution of high and intermediate risk observed between the Framingham and QRisk3 score only ($p = 0.07$, $p = 0.37$), with similar distribution of low risk observed between the modified Framingham and QRisk3 score only ($p = 0.1396$).

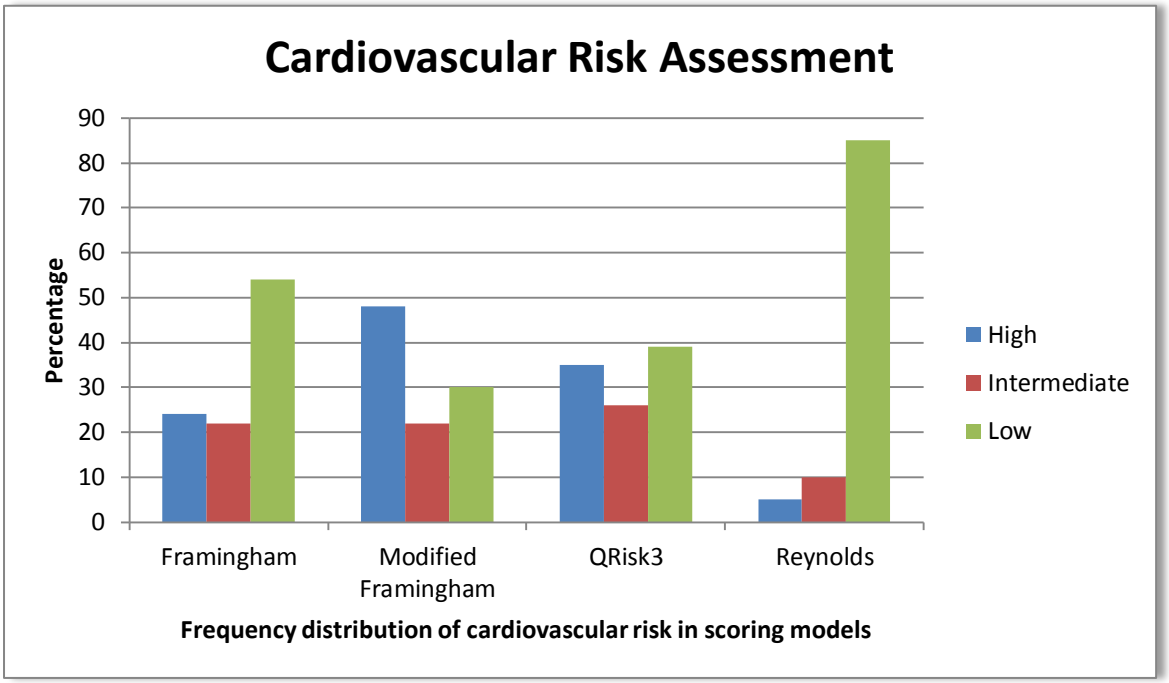

Figure 3. Comparison of cardiovascular risk assessment models

Discussion

With the burden of CVD now shifting to low income or developing countries [22, 43-45], coupled with the well-established excess cardiovascular risk in RA [7], this study, albeit small, is one of few studies from sub-Saharan Africa to describe the relationship between RA and CVD in a predominantly South African Indian and Black population.

The mean age and gender ratio of RA patients in the study were similar to global studies [4, 46-49]. The majority of patients were Black and Indian ethnicity, reflecting the demography of KZN, which is in contrast to a study by Solomon et al. in Johannesburg, SA, where Blacks and Whites were the majority (46.5% and 36.6% respectively), and Indian and Coloured the minority ethnic groups [22]. However, with the absence of a national registry, the true prevalence of RA in South African ethnic subpopulations is unknown, with unclear geographical and socio-demographic differences.

The significantly older age in patients with CVD and long RA disease duration in this study is consistent with studies confirming that CVD prevalence is higher in older patients with established RA, and disease duration in excess of 10 years [5, 47]. Further, mortality trends in recent 15-year prospective cohort study, showed Dutch patients with RA had a 54% higher risk of mortality compared to the general Dutch population, however, in the last three years of study an equal mortality risk between the two groups was shown, a trend likely attributed to treatment intensification in the last decade [50].

Contrary to findings from the multinational Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis Program (QUEST-RA) study which showed a higher independent association of CVD event occurrence in men [5], our study showed a quadruple higher prevalence of CVD in women compared to men, however a higher relative risk of CVD observed in men. These findings could be attributed to the limited number of men in this study, and inferences are guarded.

Indian patients, not unexpectedly, had a higher prevalence compared to both Black and White patients. These findings were consistent with a study by Enas et al. where a 1.5 to 4 fold increase in CVD mortality was observed in Indian migrants to SA compared to indigenous populations [51]. Findings from a door to door survey in India showed the prevalence of RA in India is similar to that reported in developed countries, and is higher than that reported in rural Africa [52].

In contrast to the literature which shows seropositivity is associated with an excess risk in cardiovascular morbidity and a six fold increase risk of CVD mortality [4, 39, 53], no

difference was seen in seropositive or seronegative disease, however extra-articular disease was significantly associated with CVD, consistent with other study findings [5, 11].

Overall, although no difference in functional status, disease activity or radiological involvement was observed between the subgroups, this may be due to small numbers and that both groups were receiving similar level of care. In contrast, CRP and ESR, which are associated with increased cardiovascular risk, and are independent prognostic markers of CVD mortality [4, 49, 54-57], were higher in the CVD group, although this did not reach statistical significance.

Sulphasalazine use was associated with a higher likelihood of CVD, which is in contrast to a study which showed sulphasalazine was associated with significant lower CVD risk compared to patients who are DMARD naïve [58]. However, the majority of patients in this study were on one/multiple DMARDs and therefore the actual effect of DMARD use cannot be determined.

The prevalence of hypertension in Africa ranges between 15 and 30% in adults [59], and is a common co-morbidity in RA [22, 60-62]. Congruent with this, more than half of our study population was treated for hypertension, with no statistical significance between subgroups. Further, a local study by Dessein et al. found a higher prevalence of uncontrolled hypertension among RA patients compared with the general population, with the employment of twice the number of antihypertensive agents in RA patients compared with non RA controls [62]. We did not examine anti-hypertensive medication in detail in this study.

Dyslipidaemia similar to other studies was observed more frequently in the CVD group (3, 8, 11), with lipid studies reflecting more favourable parameters, likely explained by the use of statin therapy as part of secondary CVD prophylaxis in this subgroup.

In a recent meta-analysis of traditional cardiovascular risk factors in RA, an increased prevalence of DM was reported [63]. A local study in an RA population found an increased prevalence of DM in South African Black patients, compared to White, Asians and Mixed ancestry patients [16]. In this study, similarly a significant number of patients were on treatment for DM, with a significantly higher frequency in the CVD subgroup. Although an overall higher HbA1C was observed in patients with CVD, this did not reach statistical

significance (6.3 vs 5.9, p = 0.193), likely secondary to patients in the CVD subgroup being on targeted glucose lowering therapies.

Physical inactivity is a common consequence of RA due to pain or extra-articular cardio-pulmonary disease, with studies showing RA patients walked significantly less than non RA controls [64, 65]. Majority of patients in this study were sedentary, with similar physical activity in both groups, and consequently more than two thirds of the total group had an elevated BMI. This is in agreement with studies observing reduced lean muscle mass and increased body fat accumulation in RA, which translates to an increased metabolic risk [44, 66, 67]. Of note, the extremes of obesity were more common in patients without CVD, while an overweight BMI was more common in patients with CVD. This disparity could be explained by more fervent lifestyle modification in the patient counselled on secondary CVD prophylaxis following the diagnoses of two life altering chronic diseases.

This cluster of the above-mentioned classical cardiovascular risk factors constitutes the metabolic syndrome (MetS), which is associated with a higher CVD risk beyond that attributed by its individual components [68]. In a North African study by Rostom et al. the frequency of MetS was higher in RA compared to the general population [69]. In a local study, the prevalence of MetS in Black women with RA was as high as 30.8% [70]. Although not analysed in this study, the high prevalence of hypertension and obesity, would suggest an associated increased prevalence of MetS.

Owing to the high prevalence of comorbid disease, and majority of patients in the study group using traditional NSAIDs, it isn't surprising to find CKD as a common finding. A significant prevalence of CKD was observed in the CVD group, which is in agreement with a large scale study by Shlipak et al. describing CKD as an independent risk factor for cardiovascular morbidity [71].

Majority of women in the study group were menopausal, and the increased risk of CVD in this group well established [72, 73]. Congruent to this, in our study CVD was more common in menopausal women. The differential cardiovascular effects of HRT are time dependent. Initiating HRT within 10 years of menopause onset is cardio-protective, with improvement in lipid profiles. Conversely, initiating HRT after 10 years post menopause or in the presence of established atherosclerosis has not shown a reduction in CVD events [72]. We found a higher

use of HRT in menopausal women in the CVD group; however these patient numbers were small. Despite the increased cardiovascular risk associated with premature menopause, no differences were observed in this study.

Reported cardiac manifestations in RA are myriad, inclusive of CAD, heart failure, cardiomyopathy, pericarditis, cardiac amyloidosis, coronary vasculitis, dysrhythmia and valve disease [74]. Although pericarditis has been the most common reported abnormality [74, 75], majority of patients with established CVD in this study had CAD, followed by cardiomyopathy, valvular heart disease, dysrhythmia with low numbers of pericardial disease.

Interestingly, in the subgroup without CVD, ECG abnormalities were present in 25% and echocardiogram abnormalities present in 58%, the majority of which was attributed to valvular heart disease, including mitral valve insufficiency, aortic valve insufficiency and tricuspid valve insufficiency, followed by features of IHD in 7.7%. This infers a high proportion of subclinical cardiac disease in RA patients, which is consistent to a small French study of echocardiogram findings in 30 RA patients free of known cardiac disease, demonstrating mitral valve insufficiency (80%), aortic valve insufficiency (33%), tricuspid valve insufficiency (23%), cardiomyopathy (37%) and pericarditis (13%) [48]. Despite a high prevalence of rheumatic heart disease in sub-Saharan Africa, none of the patients in this cohort gave a history of being diagnosed with rheumatic heart disease previously. A prospective control study in this particular cohort of RA patients with subclinical cardiac disease would be of value, to ascertain if these cardiac lesions noted on echocardiogram manifest into clinical disease, as we cannot establish the aetiology currently in this cross sectional study.

Further, in a large study of cardiovascular admissions and mortality in RA patients, between 1981 and 2002, only 42% of patients who died from CVD had any previous admissions related to CVD during the study period, supporting the supposition of undiagnosed, subclinical disease [76]. Maradit-Kremers et al. observed that RA patients are less likely to report symptoms of angina, with unrecognised myocardial infarctions occurring more than 5 times more frequently in RA patients and a doubling of the incidence of sudden cardiac death in RA patients compared with the general population [77]. A prospective study would determine whether our study findings of subclinical cardiac disease herald future CVD events necessitating intervention.

Current CVD risk assessment scores are poorly calibrated for patients with RA, with striking differences between observed and predicted CVD risk [14]. Similarly in this study, statistically significant disparity was observed between scores ($p = <0.0001$) at different levels of risk, with the exception of the Framingham and QRisk3 score which reported similar proportions of high and intermediate risk ($p = 0.07$, $p = 0.37$), and the modified Framingham and QRisk3 score with similar proportions of low risk ($p = 0.1396$). This raises concern, if a substantial proportion of patients with RA at high risk for CVD remaining unidentified depending on the score used. Ultimately, the discriminant usefulness of risk scores in RA patients warrants further research with a prospective cohort design.

The main limitation of this study is that the study was conducted in a single urban regional public hospital consisting mainly of Black and Indian patients and therefore findings may not be generalised across all ethnic or socio-economic groups. The number of males in the total study cohort was small, with remaining gender differences possible.

Conclusion

The study confirms that the burden of traditional CVD risk factors in patients with RA are well established, with hypertension, DM, dyslipidaemia, physical inactivity and CKD of particular concern. Cardiovascular disease in RA was more common in women, older patients, and patients of Indian descent. The most common CVD found was CAD. Although no significant association was observed between RA disease activity or serological status; extra-articular disease was a common finding in RA patients with CVD.

Cardiovascular disease risk management in RA should comprise of appropriate treatment of traditional risk factors as well as tight RA disease activity control. A comprehensive, discriminant CVD risk score is needed to appropriately risk stratify patients with RA, which will guide future treatment algorithms. Therefore, prospective studies in RA cohorts are urgently required.

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Appendix 1: Study protocol

University of KwaZulu-Natal

College of Health Sciences

School of Clinical Medicine

Cardiovascular disease profile in established rheumatoid arthritis

Degree : MMed Internal Medicine

Principal Investigator: Dr Preesha Govender
Student number: 201292945
Department of Internal Medicine
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

Supervisor: Dr. F Paruk
Department of Internal Medicine
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

EXECUTIVE SUMMARY

Rheumatoid arthritis (RA) is a chronic disease which affects both quality of life and life expectancy. The lifespan of a patient with RA is shortened by an average of a decade primarily due to the associated complications of premature cardiovascular disease. A fundamental principle linking RA to cardiovascular disease is inflammation. A combination of both traditional and non traditional factors increase the adverse cardiovascular risk profile in patients with RA.

Studies from developed countries show a higher risk of adverse cardiovascular events in patients with RA compared to the general population, with RA disease activity a predictor of cardiovascular disease. There is a paucity of studies in sub-Saharan Africa reflecting cardiovascular disease and risk profiles in patients with rheumatoid arthritis.

In a resource constrained healthcare system, adopting preventative medicine in everyday practice translates into a far reaching impact on improving functional disability, economic, morbidity and mortality burden. This study expects to improve our knowledge of the cardiovascular burden in RA, and the study results will assist in developing risk assessment and health care targets for this specific group of patients.

CONTENTS

BACKGROUND AND LITERATURE REVIEW

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease, characterized by a symmetrical, peripheral polyarthritis [1]. The peak age of onset is between 30 and 50 years, and the disease has a predilection for women compared to men. It is considered as one of the most common inflammatory arthritis, with a natural history resulting in joint destruction, functional impairment and increased mortality [2]. In addition to the articular disease, extra-articular multi-organ manifestations are seen in approximately 50 percent of all patients with RA at some point during the course of disease [1].

The mortality rate amongst RA patients is increased by 70 percent compared to the general population [3], and the leading cause of death in RA is cardiovascular disease [3, 4]. Both traditional and non- traditional factors combine to increase the adverse cardiovascular (CV) risk profile in patients with RA, with CV deaths occurring five to ten years prematurely compared to the general population [4].

Pathogenesis

The exact immuno-pathogenesis of RA is unknown [5], but it is postulated to involve genetic and environmental factors, with a complex interaction between T cells, B cells, and pro-inflammatory cytokines (Figure 1). The cytokines act as messengers that activate effector cells that cause the local and systemic symptoms associated with this disease [6].

The earliest detectable preclinical stage is the breakdown of self-tolerance. In the rheumatoid joint, resulting in activation of T cells that stimulate macrophages and synoviocytes to generate pro-inflammatory mediators which eventually destroy cartilage and bone. The synovium becomes hyperplastic, and the synovial membrane expands. The destructive osteoclast rich portion of the synovial membrane is termed pannus [6]. T cells help B cells produce antibodies that promote joint inflammation.

Activated B cells form plasma cells, which produce rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibodies [7]. Rheumatoid factor contributes to the pathogenic process by forming large immune complexes inside the joint, fixing complement and promoting chemoattractant [7]. In contrast, anti-CCP antibodies are directed against deiminated peptides and they recognise citrulline containing matrix proteins, which enhance the expression of self-reactivity [7].

The pro-inflammatory cytokine; tumour necrosis factor-alpha (TNF-α), plays a critical role in the pathogenesis of RA [8]. Tumour necrosis factor-alpha together with interleukin (IL) 1, 6 and 17, increases the expression of receptor activator of nuclear factor kappa ligand (RANKL) which stimulates osteoclast differentiation and bone resorption in the joint, thus promoting osteoclastogenesis. Simultaneously TNF- α also inhibits osteoblast differentiation, thereby actively suppressing new bone formation. Additionally IL 6, IL 1 and TNF-α together promote the synthesis of C reactive

protein (CRP) in hepatocytes. In addition to eliminating infection, CRP plays a regulatory role in inflammation and atherosclerotic thrombosis [3, 9]. Since CRP is a direct measure of synovial inflammation and a by-product of inflammatory reactions in RA, and therefore it is a useful marker of disease activity [3, 9]. Emerging evidence supports the role of CRP as a pro-inflammatory bone destructive molecule in the pathogenesis of RA [9].

Persistently elevated C-RP levels exacerbate tissue damage, promote lipid-metabolism dysregulation and increases the risk of cardiovascular complications [6]. The combined effects of TNF-α, IL-6, acute phase reactants, immune complexes, and pro inflammatory high density lipoprotein (HDL) phenotype, increase endothelial activation and render atheromatous plaques unstable. Cytokine driven insulin resistance of muscle and adipose tissue results in an "inflammatory metabolic" syndrome [10].

Risk factors for rheumatoid arthritis

Several factors influence the development, rate of progression and severity of RA (Figure 1). Although several genetic loci have been described, greater than 80% of patients with RA carry the epitope of the human leucocyte antigen (HLA)-DRB1*04 cluster [11]. Patients expressing the HLA-DRB1*04 cluster inherit a higher risk for nodular disease, major organ involvement and surgery related joint destruction [6]. Further strengthening the genetic theory are twin studies that show a concordance rates of 15 to 30% among monozygotic twins and 5% among dizygotic twins [10].

Gene-environment interactions underlie the association of different genotypes in different geographical and cultural settings [4]. Locally, an urban-rural regional variation of disease, with a higher prevalence in the South African urban population compared to virtually no cases reported in some rural areas is observed [12]. Further, studies also suggest a role for occupational factors, such as exposure to dust, asphalt and silica, causing bronchial stress and thereby increasing the risk for anti-CCP antibody positive RA [10].

Cigarette smoking, particularly in seropositive and extra-articular RA is a strong associative factor [4]. Both the smoking intensity and duration increase the risk and additionally citrullination of proteins in broncho-alveolar fluid occurs more often in smokers. The long-term tobacco smoke exposure and citrullination of proteins induce self-reactivity resulting in anti-CCP positive disease, which confers a less favourable prognosis than anti-CCP negative disease [10].

Although there is no clear role for a hormonal influence, it is felt that oestrogen stimulates TNF-α resulting in an increased risk in women. Further women usually have poorer outcomes than men [4, 10]. Similarly there is conflicting data on lifestyle and education level, and disease occurrence. Whilst several studies found a higher prevalence in highly educated, high-income classes, compared with uneducated, lower-income classes others show conflicting results [4].

Infectious agents are increasingly being implicated in the aetiology of RA, on a postulated background of molecular mimicry. The formation of immune complexes during an infection triggers the induction of RF. Possible infectious triggers include Epstein-Barr virus, cytomegalovirus, parvovirus, proteus species, escherichia coli and mycoplasma [4, 10]. Studies involving clinical bacterial signatures associated with anti-CCP antibody positive RA are emerging [10].

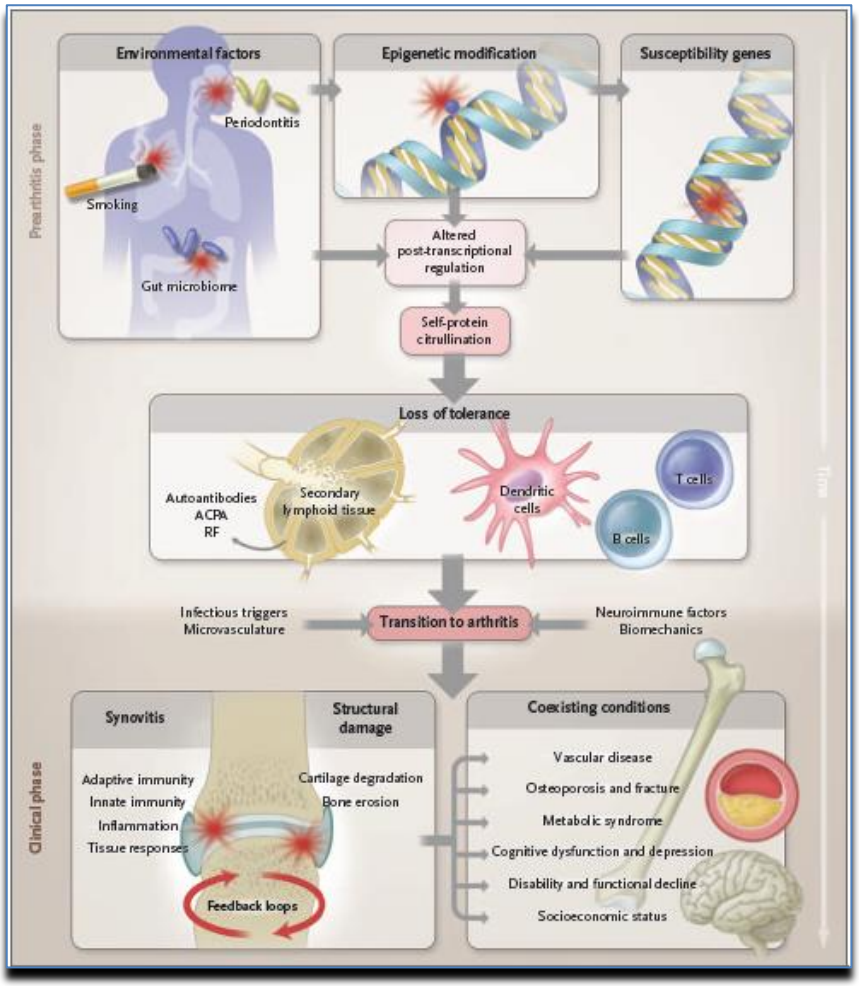

Figure 1. Postulated factors associated with the development of rheumatoid arthritis [10]

Epidemiology

Rheumatoid arthritis is not a recent disease and descriptions of symmetric, chronic polyarthritis with characteristic deformities were described in Rome in 100 BC and India in 500 BC [13].

The epidemiology of RA is well described in developed countries, with estimates from Western Europe and North America reporting a global prevalence of between 0.3% and 1% [14]. In contrast, RA is thought to have a lower prevalence, with a milder disease course in developing countries.

The Global Burden of Disease 2010 study, conducted in 187 countries, based on the 1987 American College of Rheumatology (ACR) classification criteria for RA, found the global prevalence of RA was 0.24% , however the true global prevalence of RA remains unknown [14]. The study used the outdated 1987 ACR classification criteria for RA, which fails to recognize early RA, and hence employment of these classification criteria in this study ignored the mathematical weight of such patients. Further, since prevalence data was not available for multiple regions, Sub-Saharan Africa included, data was then modelled using a meta-regression tool [14]. This could significantly attenuate the actual burden of disease in African countries, and therefore the true global prevalence of RA.

There is a paucity of prevalence data for RA from Africa and a recent systematic review showed an overall prevalence which ranged from 0.13% in Algeria to 2.54% in South Africa (SA) [15]. Variations in urbanisation, cultural and geographical diversity amongst countries contributed to significant statistical heterogeneity in the overall meta-analysis [12].

Similar to the rest of Africa, local data for prevalence of RA in SA are lacking and environmental factors, urban-rural gradient, contribute to the differences seen in various South African populations [16]. The highest prevalence of 0.9% is found in a mixed urban community in Soweto, followed by the Xhosa of Transkei with 0.68%, the Sotho's of Lesotho with 0.3%, and the Tswana of Western Transvaal with 0.1% [16].

Clinical expression of disease

The articular expression of disease includes mono-articular, oligo-articular or poly-articular symmetrical synovitis, with early morning stiffness lasting more than one hour [7]. Both small and large joints are affected, with untreated disease progressing to joint deformities.

Extra- articular disease is found in almost 50% of patients with RA at some point during the course of disease [1]. Patients with RA at risk for extra-articular disease include smokers, early onset disability and RF or anti-CCP antibody seropositive disease. The most frequent manifestations include subcutaneous nodules, secondary Sjogren's syndrome, pulmonary nodules and a normochromic, normocytic anaemia [7]. Other manifestations include osteoporosis, scleritis, episcleritis, vasculitis, pulmonary features of pleural effusions, interstitial lung disease, idiopathic pulmonary fibrosis, pulmonary nodules pulmonary hypertension, haematological features of thrombocytopaenia, leucopaenia, neurological features of mononeuritis multiplex, peripheral neuropathy, nerve entrapment, and cardiovascular features of cardiomyopathy, pericarditis, valvular heart disease, coronary artery disease and atherosclerosis [7].

Diagnostic criteria for rheumatoid arthritis

Prior to 2010, the 1987 ACR classification criteria for RA (Table 1) were used. The criteria looked at seven domains including symmetrical small joint involvement, early morning stiffness, radiological disease and a minimum period of six weeks duration of symptoms before a diagnosis could be confirmed [17].

TABLE 1. The 1987 American College of Rheumatology classification criteria for rheumatoid arthritis [18]

Criterion	Definition
A patient is classified as RA if 4/7 criteria are satisfied. Criteria 1-4 must have been present for ≥6 weeks	
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least an hour before maximal improvement
2. Arthritis of ≥3 joints areas	≥3 joints areas simultaneously have had synovitis observed ay a physician
3. Arthritis of hand joints	At least 1 area swollen in a wrist, MCP or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas on both sides of the body
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, extensor surfaces or juxta-articular regions
6. Serum rheumatoid factor (RF)	Positive RF
7. Radiographic changes	Radiographic changes typical of RA in posteroanterior hand and wrist radiographs

Abbreviations : MCP, metacarpophalangeal; PIP proximal interphalangeal

The above criteria was criticised for the lack of sensitivity for early disease, which lead to the 2010 ACR/ European League Against Rheumatism (ACR/EULAR) RA Classification Criteria (Table 2) , which are currently in use. The revised criteria recognised are more inclusive, with the addition of inflammatory markers, and anti-CCP sero-positivity, allowing for earlier diagnosis and treatment initiation [17].

TABLE 2. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA [19]

Target population: Patients who (i) have at least one joint with clinical synovitis, and (ii) the synovitis not better explained by another disease	Score
Add score of categories A-D, score of ≥6/10 needed to classify patient as having definite RA	
A. Joint involvement (tender/swollen)	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology	
Negative RF /ACPA	0
Low-positive RF/low positive ACPA	2
High positive RF/high-positive ACPA	3
C. Acute phase reactants	
Normal CRP&ESR	0
Abnormal CRP/ESR	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

Large joints refer to shoulders, elbows, hips, knees and ankles
Small joints refer to metacarpophalangeal joints, proximal interphalangeal joints, second through to fifth metatarsophalangeal joints, thumb interphalangeal joints and wrists
Low positive values refer to values less than three times the upper limit of normal
High positive values refer to values greater than three times the upper limit of normal
ACPA, anti-citrullinated protein antibody; ESR, erythrocyte sedimentation rate

Disease activity

Disease severity is a predictor of mortality [4], with premature mortality from cardiovascular disease related to the number of inflamed joints [20], and persistently elevated inflammatory markers [3]. There are several disease activity scores that are used [2, 21]. A composite disease activity score is obtained by using a combination of clinical examination of tender and swollen joints, global assessments and laboratory investigations [21]. The ACR core set for disease activity includes the following [2]:

- Tender joint count
- Swollen joint count
- Patient pain assessment
- Patient global assessment

- Doctor global assessment
- Function
- Acute phase reactant
- Radiographic analysis

The twenty eight joint count is most widely used. Function and pain is assessed in a patient-centred health assessment questionnaire (HAQ). The HAQ provides fundamental knowledge about a patient's health, functional status, satisfaction and quality of life from their own personal perspective [22]. The HAQ has been validated in multiple studies, such as prediction of successful aging, inversion of the therapeutic pyramid in RA, and examination of mortality risks in RA, work capacity and performance, occupation and the ability to live independently [22].

Composite scores provide a more accurate reflection of overall state of disease compared to individual measurements. The most widely used composite scores in current practice are the Disease Activity Score (DAS) 28, involving tender and swollen 28 joint count together with acute phase reactants and patient global assessment [2]. The Simplified Disease Activity Index (SDAI) combines the sum of tender and swollen 28 joint count, patient and doctor global assessment and acute phase reactants and lastly the Clinical Disease Activity Index (CDAI) which is a modification of the SDAI without inclusion of acute phase reactants [2]. Acute phase reactants measured include the CRP or erythrocyte sedimentation rate (ESR).

The score further defines disease activity into remission, low, moderate or high disease activity (Table 3).

TABLE 3. Composite disease activity scoring system to assess disease activity [21]

Index	Formula	Remission	Disease activity		
			Low	Moderate	High
SDAI	TJC + SJC + PGA (cm) + DGA (cm) + CRP (mg/dL)	≤ 3.3	≤ 11	≤ 26	> 26
CDAI	TJC + SJC + PGA (cm) + DGA (cm)	≤ 2.8	≤ 10	≤ 22	> 22
DAS-28	$0.56 \times \sqrt{TJC} + 0.28 \times \sqrt{SJC} + 0.7 \times \ln(ESR) + 0.014 \times PGA\ (mm)$	≤ 2.6	≤ 3.2	≤ 5.1	> 5.1

SDAI, simplified disease activity index; TJC, tender joint count; SJC, swollen joint counts; PGA, patient global assessment; CRP, C-reactive protein; CDAI, clinical disease activity index; DAS-28, 28-joint disease activity score; ESR, erythrocyte sedimentation rate.

Cardiovascular disease in rheumatoid arthritis

Epidemiology

The incidence of cardiovascular events in patients with RA occurs three times more frequently than in the general population [6]. Accelerated coronary artery atherosclerosis is associated with increased mortality in RA [23]. This excess mortality is more pronounced in studies of RA populations with longer disease duration than in cohorts with early arthritis [24]. The global Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis Program (QUEST-RA) study, with a cohort of 4363 patients, conducted in 2005-2006, found an overall prevalence of cardiovascular morbidity of 9.3%. There was considerable variation between countries, with the highest prevalence in the

United States of America (USA), United Kingdom, Poland and Germany, and the lowest in Argentina and Mediterranean countries [23]. These findings were similar to in the World Health Organisation (WHO) multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project [25], which found an overall prevalence of lifetime myocardial infarction of 3.2%, and stroke of 1.9% [23]. Further cardiovascular events were more prevalent in men than women and occurred approximately a decade earlier in patients with RA, than the general population, suggesting that RA is an independent risk factor for premature ischaemic heart disease [23].

Prevalence of traditional cardiovascular risk factors extrapolated from the QUEST-RA study, were hypertension (33%), dyslipidaemia (14%) for, diabetes mellitus (8%), smoking (43%), physical inactivity(72%), and obesity (18%) with diabetes and smoking both being more common in men than women. Additionally extra-articular disease was significantly associated with cardiovascular morbidity [23].

Rheumatoid arthritis increases the lifetime risk for coronary artery disease (CAD) two fold compared to the general population and this risk is of equal magnitude to patients with diabetes mellitus [26, 27]. The increased risk of heart disease in patients with RA is reflected in modification of the Framingham cardiovascular risk score, which requires a multiplication factor of 1.5 in patients with RA. Further patients with RA have a two-fold increased risk of developing heart failure. Seropositive disease is associated with diastolic dysfunction, with a preserved ejection fraction of more than 50% [26]. The outcome of patients with RA and heart failure is poorer than the general population [26].

Further, a small study found an increased frequency of asymptomatic cardiac involvement in RA patients [28]. Based on echocardiographic findings 37% had cardiomyopathy, 7% residual abnormalities of a myocardial infarction, 83% valvular heart disease with mitral regurgitation being the dominant lesion, and 13% had pericarditis. Electrocardiogram abnormalities were found in 63% of patients, which included left ventricular hypertrophy, sequelae of myocardial ischemia, first-degree atrioventricular block, right bundle branch block and right atrial hypertrophy [28].

Traditional cardiovascular risk factor profile in rheumatoid arthritis

1. **Dyslipidaemia**

In RA, traditional cardiovascular risk factors are influenced by both inflammation inherent to the disease, and pharmacodynamics of anti-rheumatic drugs. Cholesterol, particularly low density lipoprotein (LDL), forms fatty streaks in coronary arteries, which foster flow-limiting atherosclerotic plaques [29]. When these plaques rupture, thrombosis ensues, leading to blockage of coronary arteries and myocardial infarction. Rheumatoid arthritis related dyslipidaemia is characterised by low total cholesterol and HDL, and elevated triglyceride and small LDL [3]. During periods of high grade inflammation, there is marked suppression of total cholesterol, HDL and LDL levels, yielding an unfavourable pro-atherogenic ratio of total cholesterol to HDL [26].

The total cholesterol to HDL ratio is a better cardiovascular disease risk predictor in RA than individual lipid components [27] and studies show HDL levels are significantly lower in RA patients compared to matched control subjects [30]. This paradoxical relationship between inflammation and lipid profiles translates into increased CAD risk in RA. Inflammation in RA alters lipoprotein structure

and function and the HDL load of serum amyloid A increases with a decrease in apolipoprotein A-I, leading to a shift in the anti-atherogenic effect of HDL to a pro-atherogenic effect [26].

Further the anti-inflammatory effects of drugs on lipid profiles are inconsistent. While there is evidence that hydroxychloroquine improves atherogenic lipid profiles [31], the role of methotrexate the gold standard of treatment is unclear. Tumour necrosis factor (TNF) α blockers elevate both total cholesterol and HDL levels, resulting in a stable atherogenic profile [29] while tocilizumab, an IL-6 inhibitor, elevates total cholesterol and LDL [29].

2. Insulin resistance and diabetes mellitus

Cytokine driven mechanisms make muscle and adipose tissue insulin resistant, resulting in an "inflammatory metabolic" syndrome [10]. Epidemiological data supports a strong association between RA and insulin resistance, and a study showed that 54% of patients with RA compared to 40% in the general population had insulin resistance [32]. Further significantly higher insulin resistance was seen amongst patients with high-grade inflammation. Predictors of insulin resistance included elevated CRP, ESR, IL-6, TNF-α and increased waist circumference [29]. Additionally studies show a positive association between RA and diabetes mellitus, and a 50% increase in the risk of diabetes mellitus in RA, even after controlling for glucocorticoid use [33]. In contrast, studies on drug effects on insulin resistance, have found a decrease in insulin resistance with common disease modifying drugs including methotrexate, TNF-α blocker and hydroxychloroquine use [29].

3. Hypertension

Although several older studies found no difference in hypertension between RA and control groups [29], studies that are more recent show that hypertension is often underdiagnosed and undertreated in patients with RA [26]. Inflammation and drug effects of non-steroidal anti-inflammatories (NSAID) and glucocorticoids [26, 29] may exacerbate hypertension in RA. Further studies on arterial wall pliability; have found increased arterial wall stiffness in patients with RA, suggesting a diminished ability of the arterial system to respond to changes in blood volume [29].

4. Obesity

Obesity is defined as a body mass index (BMI) of greater than 29 kg/m^2 by the WHO. In the non RA population, obesity is associated with higher CRP, which is associated with an increased cardiovascular risk [34]. The prevalence of obesity is 54% higher in patients with RA than non RA control groups [29] and a combination of low muscle mass and high fat mass is observed in RA [26].

Further visceral adiposity in RA is associated with hypertension, insulin resistance, metabolic syndrome and a greater inflammatory load [26]. Studies also show men with RA have higher levels of visceral fat compared to controls, whilst women with RA had increased subcutaneous fat compared to controls with a similar BMI and waist circumference [29]. Lastly adipose tissue releases pro-inflammatory cytokines, IL-6 and adiponectin, thus contributing to low grade inflammation. Therefore, obesity in RA is associated with higher CRP levels and aggressive articular disease [29].

5. Physical inactivity

Physical activity is an important modifiable risk factor of cardiovascular disease. Studies show that patients with RA are significantly less physically active than population based controls. A

combination of uncontrolled inflammation, low muscle mass, increased body fat composition, and limitations of joint movement from poor disease control, contributes to lack of exercise. This physical inactivity, as in the general population, leads to hypertension and dyslipidaemia, which portends an unfavourable cardiovascular profile [29].

6. Cigarette smoking

Cigarette smoking is one of the most prominent modifiable risk factors for cardiovascular disease. It is also the strongest known environmental risk factor for RA [29]. Smoking is associated with multi-vessel coronary artery calcification [35]. Recent case controlled studies highlight a higher prevalence of current or past cigarette smoking observed in patients with RA [29]. The Multiple Risk Factor Intervention Trial (MRFIT) found twice the number of coronary heart disease deaths in the smokers compared to the non smokers. Additionally the study found a strong association between CRP and subsequent risk of cardiovascular deaths among cigarette smokers that is independent of the number of cigarettes smoked per day [36].

Rheumatoid arthritis as an independent risk factor for cardiovascular disease

There is mounting evidence that the increased cardiovascular morbidity and mortality in RA is due to the pro-atherogenic changes seen with systemic inflammation rather than it being due to traditional cardiovascular risk factors only (Figure 2) [37, 38].This has resulted in the recognition of RA as an independent cardiovascular risk factor [23, 39].

Studies in the Pima Indians of Arizona, USA who have the highest prevalence of RA in the world found the presence of swollen, tender joints was a predictor of cardiovascular mortality independent of traditional cardiovascular risk factors [40]. Further studies show that HLA-DRB1, promotes survival of autoreactive T cells, which mediate chronic inflammation [26]. These T- cells also play a role in atherosclerotic plaque formation by producing cytokines and damaging vascular smooth muscle cells [26]. The HLA-DRB1 gene is associated with an increased risk of myocardial infarction and other non-RA associated heart disease [41, 42]. Supporting evidence of their effects has been shown in the use of T cell inhibiting drugs currently used in percutaneous drug eluting stents in CAD, thereby preventing in-stent stenosis [26].

The rheumatoid joint synovial tissue releases in abundance TNF-α, IL-6 and IL-1, which alters the function of adipose tissue and vascular endothelium [3]. These changes produce dysregulation in glycaemic control, lipid profiles and endothelial function [3]. The Physicians Health Study in the general population found higher IL-6 levels in men who experienced their first myocardial infarction compared to those who remained cardiovascular disease free during a six year follow up [43]. This highlights the atherogenic role of IL-6 in RA [6].

Carotid artery intima thickness, which has been used as a marker of early atherosclerosis, is increased in patients with RA. This correlates with markers of systemic inflammation in patients with RA [44]. Shared mechanisms of immunological disease, systemic endothelial activation and circulating immune complexes lead to increased pro-thrombotic markers and increased arterial stiffness in RA [45]. The prevalence and severity of coronary calcification is increased in patients with established RA, and is associated with elevated inflammatory markers [35].

Studies show a positive relationship between cardiovascular biomarkers and active RA [46]. Bony erosion, a sequelae of persistent inflammation, occurs in 80% of patients untreated or inadequately treated within one year following diagnosis [10] predicts cardiovascular events and mortality in RA [24]. Further the QUEST-RA study supports the association of higher cardiovascular morbidity with severe RA [23]. Recent evidence suggests cardiovascular risk for patients with RA in remission is similar to non RA controls [47]. Cardiovascular risk increases by 7% for each additional RA acute flare [47]. This highlights the concept of accumulating cardiovascular damage with each acute flare, and possibly explains the excess cardiovascular risk in RA patients compared to non RA controls.

Seropositive disease confers an excess risk in cardiovascular morbidity and mortality [27] and anti CCP antibodies are independently associated with the development of ischaemic heart disease [48]. Further extra-articular disease is associated with an increased mortality from CAD [23, 24].

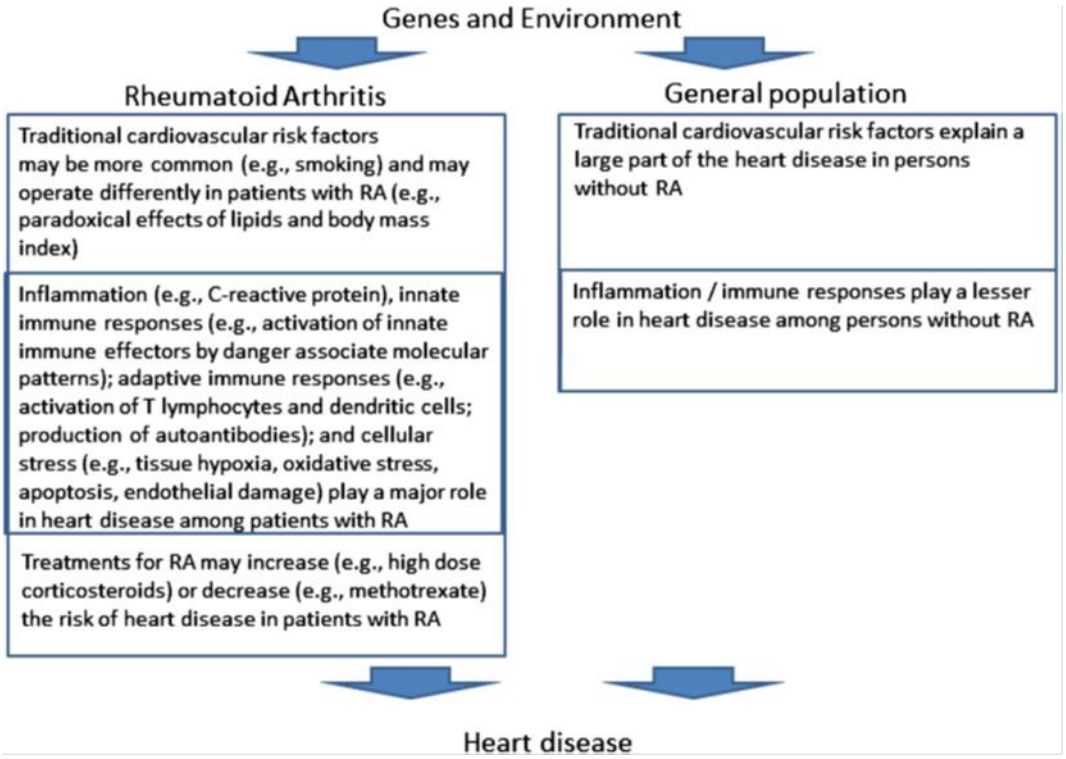

Figure 2. Determinants of heart disease in patients with rheumatoid arthritis compared to the general population [26]

Role of pharmaco-therapeutics in rheumatoid arthritis and effects on cardiovascular risk

Disease modifying anti-rheumatic drugs (DMARD) that target joint inflammation also decrease arthrosclerosis risk and have proven beneficial effects on RA associated cardiovascular disease [24].

Methotrexate, an anchor drug in RA treatment, is associated with a 21% reduction in cardiovascular events [26]. In a small study of 22 patients with RA, 14 patients who commenced methotrexate had a decrease in insulin resistance during the first eight weeks [49]. Tumour necrosis factor-α inhibitor

therapy is associated with reduced risk of all heart disease events [26], further this class of drugs favourably affect HDL lipid profiles [50]. In addition, it improves endothelial function and insulin resistance [26].

Hydroxychloroquine also improves lipid profiles, with a reduction in LDL, and total cholesterol/HDL ratio, and decreases the risk of diabetes mellitus in patients with RA [26].

There is conflicting data on the use of glucocorticoids. Older studies showed that steroid use resulted in hypertension, decreased insulin sensitivity, elevated lipid levels, and increased carotid plaque and arterial stiffness [51]. Patients who are treated with prednisone doses greater than 7.5 mg per day appear to have twice the risk of heart disease compared to those who did not receive steroids [52]. However, recent findings from the QUEST-RA study show that the fundamental effects of lowering inflammatory burden, correlates with an independent association of long-term glucocorticoid use and a reduced risk of all cause cardiovascular events [23]. Further, the benefit of reducing high-grade inflammation in an acute flare may counteract the adverse cardiovascular effects of glucocorticoid use [27].

Both selective and non-selective NSAIDs are known to cause clinically significant hypertension, which may require treatment [53]. The use of NSAID's and its association with cardiovascular risk was brought to the fore in the Vioxx Gastrointestinal Outcomes Research (VIGOR) study. An increased risk of heart disease was found with rofecoxib use [54]. A meta- analysis has shown no differences in heart disease events with celecoxib or ibuprofen use, and naproxen conferred the lowest cardiovascular risk [55].

Cardiovascular risk assessment in rheumatoid arthritis

There are several validated cardiovascular risk assessment tools available for use including the Framingham Risk Score (FRS), and the Systematic Coronary Risk Evaluation Score (SCORE), which determines the 10-year risk of fatal cardiovascular disease (Table 4). Additionally, tools like the Reynolds Risk Score (RRS) takes into account traditional risk factors as well as the added risk of inflammation, in identifying the 10-year risk for a myocardial infarction (MI) or stroke. Studies have illustrated that traditional risk factors account for only a portion of the overall risk for cardiovascular disease in RA, with the additional risk attributed to inflammation [37, 38]. Therefore the lack of recognition of inflammatory markers in FRS and SCORE, underestimates the cardiovascular risk in RA. An expert panel convened by EULAR, recommends a multiplier of 1.5 for FRS and SCORE if a patient fulfils two or more of the following: RA disease duration more than 10 years, RF or ACCP antibody positivity, or extra-articular manifestations [29].

TABLE 4. Comparison of clinical variables and risk outcomes in the Framingham Risk Score, Reynolds Risk Score and Systematic Coronary Risk Evaluation Score [29]

Clinical variable	FRS	RRS	SCORE
Age	✓	✓	✓
Gender	✓	✓	✓
Tchol	✓	✓	✓
HDL	✓	✓	
Current smoker	✓	✓	✓
Systolic BP	✓		✓
On medication for hypertension	✓		
hsCRP		✓	
Mother or father with heart attack or stroke before age 60		✓	
High-/low-risk European country			✓
Predicted 10-year risk	MI or coronary death	MI or stroke	Fatal CVD

Tchol, total cholesterol; BP, blood pressure; hsCRP, high sensitive C reactive protein

Conclusion

A fundamental principle linking RA to cardiovascular disease is the shared inflammation. Further studies suggest that patients with RA are less likely to receive primary or secondary heart disease preventions [26]. Therefore understanding the cardiovascular risk in a patient with RA, requires a revolutionary conceptual model that highlights the overlapping influence of traditional risk factors and inflammation.

From the 2014 World Health Organisation (WHO) statistical profile, life expectancy in South Africa has increased, with life expectancy at birth to be 59 years. With aging populations, the number of people living with RA will increase substantially in the forthcoming decades [56].

Cardiovascular risk management in patients with RA requires an evaluation of biomarkers, control of traditional risk factors, and good RA disease control. Early control of disease activity in RA predicts significant survival benefits. A robust preventative strategy of cardiovascular disease in this high-risk group is required. The study intends to improve our knowledge of RA and cardiovascular profile in our setting, and study results can be applied to developing a framework for risk assessment and health care targets in this specific at-risk group.

Aim

To describe the cardiovascular profile of patients with rheumatoid arthritis in a regional arthritis clinic.

Objectives

1. To determine the prevalence of cardiovascular disease in rheumatoid arthritis.
2. To describe the prevalence of traditional cardiovascular risk factors in RA.
3. To describe the relationship between disease activity and cardiovascular disease in RA.

METHODS

Study design:

This is a retrospective, descriptive chart review of patents with rheumatoid arthritis currently attending the rheumatology clinic at King Edward hospital. The disease activity and cardiovascular risk profile will be reviewed.

Setting:

The study will be conducted at King Edward VIII Hospital, a tertiary care centre in Kwa-Zulu Natal (KZN) Kwa-Zulu Natal is found on the south east coast of South Africa (SA) and is the second most populous South African province, with a population of 10.27 million people, comprising 20% of the total population of SA [57], of which 86.8% is Black African and 7.4% is Indian [58].

King Edward VIII Hospital, opened in 1936, is the second largest hospital in the southern hemisphere. It is a 922 bedded hospital with 360 000 outpatients. It offers a regional and tertiary public healthcare service to Kwa-Zulu Natal. It is an academic teaching hospital linked to the University of Kwa-Zulu Natal Nelson R. Mandela School of Medicine [59]. The hospital's arthritis clinic is a dedicated weekly run rheumatological service, under the stewardship of a team comprising a rheumatologist, general physicians and medical officers.

Study population:

The files of all current patients diagnosed with RA as per 1987 American College of Rheumatology classification criteria or 2010 American College of Rheumatology/European League Against Rheumatism classification criteria, seen in the last six months at King Edward VIII Hospital arthritis clinic will be included.

Inclusion criteria:

- Patients diagnosed with rheumatoid arthritis fulfil :
    1. 1987 American College of Rheumatology classification criteria for rheumatoid arthritis, if clinical presentation prior to 2010

       and/or
    2. 2010 American College of Rheumatology/ European League Against Rheumatism Collaborative Initiative classification criteria for rheumatoid arthritis, if clinical presentation after 2010
- Patients will be 18 years or older

Exclusion criteria

- Patients younger than 18 years
- Patients with RA and who also have any other underlying connective tissue disease or overlap syndrome

Sample size:

This study is a retrospective chart review of all patients attending the arthritis clinic at King Edward VIII Hospital, which includes approximately 120 subjects. All patients are usually reviewed on a two to four monthly basis. As such, over a six month period, every chart will be reviewed.

The following statistical parameters were used to determine an appropriate sample size with a statistical power of 80%. In this binary logistical model, the probability of the presence of CV disease is estimated given a number of independent/predictor risk factors. This means there are two outcomes of this model: presence of cardiovascular disease and absence of cardiovascular disease.

The following statistical parameters were used to arrive at a sample size.

1. Type 1 error (α) = 0.05 (the probability of falsely rejecting null hypothesis)
2. Type 2 error (β) = 0.2 (the probability of falsely accepting null hypothesis)

The assumption is the sample is a good representation of the population from which it came from, with a standard deviation (σ) of 1 and population mean (μ) of 0 (Gaussinal or normal distribution). On the basis of the above, a sample size of 113 was determined. NB. 113 +- 15% padding.

Data Collection:

The following data will be collected from the chart using a structured questionnaire.

- Demographics will include the following:
    1. Age
    2. Gender
    3. Ethnicity
    4. Occupation
    5. Educational level
    6. Area of residence

- Rheumatoid arthritis disease profile
    1. Date of diagnosis
    2. Presence of early morning stiffness and duration
    3. HAQ score (see appendix I)
    4. SDAI (see appendix II)
    5. Serology (Rheumatoid factor and anti-cyclic citrullinated peptide antibody)
    6. Presence of extra-articular features of rheumatoid arthritis
    7. Inflammatory markers at diagnosis and currently (CRP and ESR)
    8. Radiological findings
    9. Dose and duration of drug therapy

- Cardiovascular risk factors :

1. Co morbidities (Diabetes mellitus, hypertension, dyslipidaemia, cerebrovascular accident)
2. Family history of cardiovascular disease and CV risk factors
3. Ambulant arm blood pressure
4. Anthropometry: last recorded
    - Weight
    - Height
    - BMI : According to WHO Classification
        - Obese class I : 30 to 34.99 kg/m^2
        - Obese class II : 35 to 39.99 kg/m^2
        - Obese class III : greater than 39.99 kg/m^2
5. Self reporting of smoking history, stipulated by pack years
6. Self reporting of lifestyle habits including exercise per week
7. If female, menopausal status

- Electrocardiogram findings
- Echocardiogram findings
- Laboratory investigations (Haemoglobin, estimated glomerular filtration rate, glycated haemoglobin, lipid profile, thyroid function)

Data Management:
The ethical integrity of the study will remain within the domains of the strictest confidence held within the sanctum of a doctor/patient relationship. Access to this information will be limited to the principal investigator, the supervisor and the assisting statistician.

Each patient meeting the inclusion criteria will be allocated a study number, to avoid duplication of patients and measurement error. Data will be entered onto a password protected Excel spreadsheet by the principal investigator and only de-identified data will be analysed. Data will be cross checked, validated and captured from source by the principal investigator, to assure reliability of data.

Data analysis:
Descriptive statistics will be used to describe the population frequency and percent to describe categorical variables. Continuous variables will be summarised as mean ± standard deviation; medians and interquartile ranges (IQR) for variables that are highly skewed. Categorical variables will be summarised using proportions and percentages. Proportions and categorical variables will be compared using Pearsons Chi Squared test or Fishers exact test as appropriate.

Binary logistical regression model will be used to identify independent variables that can predict the likelihood of a patient with RA having cardiovascular disease. The level of significance will be set at $p<0.05$.
All statistical analysis will be conducted using SPSS version 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, version 24.0. Amonk, NY:IBM Corp.) and SAS version 9.4 (SAS version 9.4, Copyright 2013 SAS Institute Inc. Cary, NC, USA).

The two groups (RA patients with and without CVS disease) will be compared using the student t-test. Categorical variables will be compared using Pearson's chi square test and Fisher chi square test.

Ethical considerations:

A research protocol will be submitted to the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC) for ethical approval. Permission to conduct the research will be obtained from the medical manager of the hospital concerned after provisional BREC approval. Provincial approval will then be obtained before the study commences. Patient confidentiality will be protected and anonymity ensured by assigning a study number to each patient and by recording patient data on coded data sheets which do not contain patient identifiers. The study holds minimal risk to any patients as there is no intervention.

Social value:

Cardiovascular disease occurs prematurely in patients with rheumatoid arthritis. The knowledge in this study will allow us to gain a South African perspective on the cardiovascular disease risk profile among patients with rheumatoid arthritis. In a resource constrained healthcare system, adopting preventative medicine in our everyday practice translates into far reaching cost-cutting economical gains. This study will serve as a foundation for understanding predictive risk and shaping future improved healthcare targets. This study hopes to serve the ultimate goal of promoting a healthier nation living with a chronic disease with better quality of adjusted life years.

Scientific validity:

Fair selection of participants:

Participants included in this study are adult outpatients to the arthritis clinic. They are selected according to the relevance to the research question. The patient selection process will be exercised strictly within the inclusion and exclusion criteria outlined.

Assessment tools :

The HAQ provides fundamental knowledge about a patient's health, functional status, satisfaction and quality of life from their own personal perspective [22]. The HAQ has been validated in multiple studies, such as prediction of successful aging, inversion of the therapeutic pyramid in RA, and examination of mortality risks in RA, work capacity and performance, occupation and the ability to live independently [22]. The SDAI has been validated in multiple studies globally, particularly in their relationship to radiographic progression, functional decline and mortality risk [2].

Risk/benefit balance:

Data obtained from patients medical records will be handled in the strictest confidence by minimizing the number of people who analyse the data, having all data recorded on password protected documents, and all data recorded will have identifiers removed and replaced with a study number. Patient's anonymity is protected.

Independent ethics review:

A research protocol will be submitted to the University of Kwa-Zulu Natal Biomedical Research Ethics Committee for ethical approval. After obtaining provisional ethics approval, permission to conduct

research will be sought from the medical manager of King Edward VIII Hospital and provincial approval will be sought from the Kwa-Zulu Natal Department of Health.
Patient recruitment will not commence until written ethics approval has been received from the University of Kwa-Zulu Natal registered research ethics committee.

Informed consent:
This study is a retrospective chart review. No informed consent is required.

Ongoing respect for participants:
Hard and electronic copies of data obtained in this study will be destroyed five years following completion of research. All data will have identifiers removed, and replaced with a study number, to protect confidentiality. Reports on the study will be statistically described and the anonymity of participants will be honoured.

METHODOLOGICAL CHALLENGES AND STUDY LIMITATIONS:

Majority of the patients attending this healthcare facility are of Black and Indian ethnicity. It therefore lends a challenge to generalising study findings across all racial backgrounds.

Patients will be assessed from varying points from their rheumatoid arthritis onset, with varying effects of treatment. The clinical records at King Edward VIII Hospital are hard copies. Since a computerised filing system is not active, files including data from the initial clinical presentation, which may have been decades ago, including radiological and laboratory investigations, may be lost.

The patients attending the clinic over many years, would have seen multiple clinicians, with an inter-observer variance in characterisation of disease. This study utilises objective markers as defined by laboratory and radiological data, together with patient reporting of symptoms as categorised by the HAQ score, so as not to be skewed by subjective personal clinician interpretation.

Certain aspects of this study rely on patient self-reporting, and there may be under- or over-reporting.

This is a single study conducted in a single centre, which is urban and hospital based, with most of the patients attending this public healthcare service from low to middle income households. Conclusions from this study may not lend itself to generalisability across the population urban-rural gradient, and all income classes.

Feasibility:

Time lines and project management

1. Literature search : June 2017
2. Protocol preparation, drafting of questionnaire : July 2017
3. Submission of protocol : August 2017
4. Data collection and entry: September 2017 to November 2017
5. Data analysis : December 2017

6. Final write up : January to February 2018

Study team, contributors and authorship:
The study team comprises the principal investigator, the supervisor, and a statistician. Contributions will be made by clinicians at the arthritis clinic and the medical outpatient clinics.
Authorship credit is assigned to Dr P. Govender and Dr F. Paruk.
All data will be collected and entered into an electronic format by the principal investigator.
Statistical analysis will be performed by the statistician, Dr Wilbert Sibanda.
Collating of clinically significant findings and data interpretation will be done by the principal investigator.
There is no conflict of interest.

Study funding :
This study will incur no direct costs to the health facility.

Publication of findings
A scientific report will be submitted to the Department of Internal Medicine, Nelson R. Mandela School of Medicine, University of Kwa-Zulu Natal and the hospital. The results of the study will be submitted for presentation to scientific meetings and publication to local and/or international journals.

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Appendix 2: Guidelines for authorship for the journal selected for submission of the manuscript

South African Medical Journal guidelines for article submission

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text.

Structured abstract

- This should be 250-400 words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to establish
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.

    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc) that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long? Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Appendix 3: Ethical Approval

Department of Health

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
Health Research & Knowledge Management (HKRM)

335 Langalibalele street
Private Bag X9051 PMB, 3200
Tel: 033 395 2805/3189/3123 Fax: 033 394 3782
Email: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference: HRKM453/17
KZ_201711_004

21 November 2017

Dear Dr P Govender
(UKZN)

Subject: Approval of a Research Proposal

1. The research proposal titled '**Cardiovascular disease profile in established rheumatoid arthritis**' was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at King Edward VIII Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facilities before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Ms G Khumalo on 033-395 3189.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 23/11/17

Fighting Disease, Fighting Poverty, Giving Hope

Appendix 3: Ethical Approval

BREC

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

12 December 2017

Dr P Govender 201292945
School of Clinical Medicine
College of Nelson R. Mandela School of Medicine
Govender.preesha@hotmail.com

Dear Dr Govender

PROTOCOL: "Cardiovascular disease profile in established rheumatoid arthritis" Degree: MMed
BREC Ref No: BE 535/17

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 30 August 2017.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 30 November 2017 to BREC correspondence dated 12 October 2017 has been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval** and may begin as from 12 December 2017.

This approval is valid for one year from **12 December 2017.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **13 February 2018.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc postgraduate administrator: konar@ukzn.ac.za
cc supervisor: Dr F Paruk: paruk@ukzn.ac.za

Appendix 3: Ethical Approval

King Edward VIII Hospital

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

OFFICE OF THE HOSPITAL CEO
KING EDWARD VIII HOSPITAL

Private Bag X02, DURBAN, 4013
Corner of Rick Turner (Francois Road) & Sydney Road
Tel.: 031-3003403, Fax:031-2061457, Email: [illegible]
www.kinmedth.gov.za

Ref.: KE 2/7/1(93/2017
Enq.: Mrs. R. Sibiya
Research Programming

19 October 2017

Dr. P. Govender
Department of Internal Medicine
Nelson R. Mandela - School of Medicine
UNIVERSITY OF KWAZULU-NATAL

Dear Dr. Govender

Protocol: "Cardiovascular disease profile in established rheumatoid arthritis"
Degree: MMed; BREC REF. NO. BE535/17

Permission to conduct research at King Edward VIII Hospital is provisionally granted, pending receipt of approval by the Provincial Health Research Committee, KZN Department of Health.

Kindly note the following:-

- The research will only commence once confirmation from the Provincial Health Research Committee in the KZN Department of Health has been received.
- Signing of an indemnity form at Room 8, CEO Complex before commencement with your study.
- King Edward VIII Hospital received full acknowledgment in the study on all Publications and reports and also kindly present a copy of the publication or report on completion.

The Management of King Edward VIII Hospital reserves the right to terminate the permission for the study should circumstances so dictate.

Yours faithfully

SUPPORTED/~~NOT SUPPORTED~~

DR. SA MOODLEY
ACTING SENIOR MEDICAL MANAGER

24/10/17
DATE

Appendix 4: Data Collection Tool

Study Questionnaire

STUDY QUESTIONNAIRE

Study number			Date		
Age			Hospital file number		
Sex	M	F	Place of residence	Peri-urban	Rural
Ethnicity	B	I	Occupation		
Level of education	None	Primary school	High school	University/College	

RHEUMATOID ARTHRITIS DISEASE PROFILE :

Date of diagnosis			
Early morning stiffness duration in minutes			
Serology			
Rheumatoid factor	Positive negative		
Anti citrullinated peptide antibody	Positive negative		
C reactive protein	Initial :	Current :	
Erythrocyte sedimentation rate	Initial :	Current :	

Xrays		HAQ score	
Normal		Tender joint count	
Juxta-articular osteopaenia	Y/N	Swollen joint count	
Joint space loss	Y/N	PGA	
Subchondral erosions	Y/N	MDGA	
Joint destruction	Y/N	SDAI	

Extra articular features of rheumatoid arthritis			
Subcutaneous nodules	Y/N	Vasculitis	Y/N
Scleritis/Episcleritis	Y/N	Osteoporosis	Y/N
Sjogren's syndrome	Y/N		
Pleural effusions	Y/N	Cardiomyopathy	Y/N
Interstitial lung disease	Y/N	Pericarditis	Y/N
Idiopathic pulmonary fibrosis	Y/N	Valvular heart disease	Y/N
Pulmonary nodules	Y/N	Coronary artery disease	Y/N
Pulmonary hypertension	Y/N	Atherosclerosis	Y/N
Anaemia	Y/N	Mononeuritis multiplex	Y/N
Thrombocytopaenia	Y/N	Peripheral neuropathy	Y/N
Leucopaenia	Y/N	Nerve entrapment	Y/N

Drug therapy :	Dose	Duration
Methotrexate		
Chloroquine		
Sulphasalazine		
Prednisone		
Non-steroidal anti-inflammatory drugs		
Other specify		

CARDIOVASCULAR DISEASE :

Presence of cardiovascular disease	
Nature	
Onset	

Drug therapy	
Intervention	

Blood pressure		Smoker	Yes/ No	
Weight		Pack years		
Height		Weekly exercise habits		
Body mass index	25-29 kg/m^2	30-34 kg/m^2	35-39 kg/m^2	>40 kg/m^2
If female, menoapausal		Yes/No		

ECG findings	
Echocardiogram findings	Ejection fraction :
	PAS :
	Abnormality noted :

CO-MORBIDITY AND FAMILY HISTORY :

Co-morbidities		Family history	
Diabetes Mellitus		Rheumatoid arthritis	
Hypertension		Cardiovascular disease	
Dyslipidaemia		Diabetes Mellitus	
Cerebrovascular accident		Hypertension	
Other		Dyslipidaemia	
HIV status		Cerebrovascular accident	

LABORATORY INVESTIGATIONS :

Thyroid function test		Lipogram			
TSH		TC		Triglycerides	
T4		HDL		LDL	
T3		Full blood count			
HbA1C		Hb			
Estimated GFR					

Appendix 4: Data Collection Tools

Health Assessment Questionnaire

HEALTH ASSESSMENT QUESTIONNAIRE (HAQ)[2]

(Subtotal 1	+ Subtotal 2)	÷ No. of answered categories	= HAQ

SCORING

1. Score each item within the 8 categories.
2. Select and add the highest score within each category.
3. Divide the sum of the category scores by the number of answered categories.
4. If the item score is zero but an assistive device is used: score 1. Help from another person is required: score 2. Both a special device and help is required: score 3.

	Without ANY Difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do	Total
1 DRESSING & GROOMING - This past week, were you able to:					
1. Dress yourself, including tying shoelaces and doing buttons?	0	1	2	3	
2. Shampoo your hair?	0	1	2	3	
2 GETTING UP - This past week, were you able to:					
1. Stand up from a chair without armrests?	0	1	2	3	
2. Get in and out of bed?	0	1	2	3	
3 EATING - This past week, were you able to:					
1. Cut up your meat?	0	1	2	3	
2. Lift a full cup or glass to your mouth?	0	1	2	3	
3. Open a new milk carton?	0	1	2	3	
4 WALKING - This past week, were you able to:					
1. Walk outdoors on flat ground?	0	1	2	3	
2. Climb up five steps?	0	1	2	3	
				Subtotal 1	

Please tick any of the following AIDS or EQUIPMENT that you usually use for any of these activities mentioned above:

- Walking stick
- Walking frame
- Crutches
- Wheelchair
- Aids used for dressing (button hook, zip-puller, long-handled shoe horn)
- Specially adapted utensils (such as for eating and cooking)
- Specially adapted chair
- Other (Please Specify)

Please tick any of the following categories for which you usually need HELP FROM ANOTHER PERSON:

- Dressing and Grooming
- Getting up
- Walking
- Eating

	Without ANY Difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do	Total
5 HYGIENE - This past week, were you able to:					
1. Wash and dry your body?	0	1	2	3	
2. Have a bath?	0	1	2	3	
3. Get on and off the toilet?	0	1	2	3	
6 REACHING - This past week, were you able to:					
1. Reach for a 2.5 kg object from just above your head?	0	1	2	3	
2. Bend down to pick up clothing from the floor?	0	1	2	3	
7 GRIPPING - This past week, were you able to:					
1. Open car doors?	0	1	2	3	
2. Open jars that have been previously opened?	0	1	2	3	
3. Turn taps on and off?	0	1	2	3	
8 ACTIVITIES - This past week, were you able to:					
1. Go shopping (supermarket, post office, bank etc.)?	0	1	2	3	
2. Get in and out of a car?	0	1	2	3	
3. Do domestic tasks such as vacuuming or gardening?	0	1	2	3	
				Subtotal 2	

Please tick any of the following AIDS or EQUIPMENT that you usually use for any of the activities mentioned above:

- Raised toilet seat
- Bathtub seat
- Jar opener (for jars previously opened)
- Bath rail
- Long-handled aids for reaching things
- Long-handled aids in bathroom (e.g. a long handled brush for the body)
- Other (Please specify)

Please tick any of the following categories for which you usually need HELP FROM ANOTHER PERSON:

- Hygiene
- Reaching
- Gripping and opening things
- Shopping and domestic tasks

References: [illegible] A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology* 2003; **42**:244-257. **2.** The Health Assessment Questionnaire. Stanford University School of Medicine Division of Immunology and Rheumatology [illegible]. Accessed [illegible].

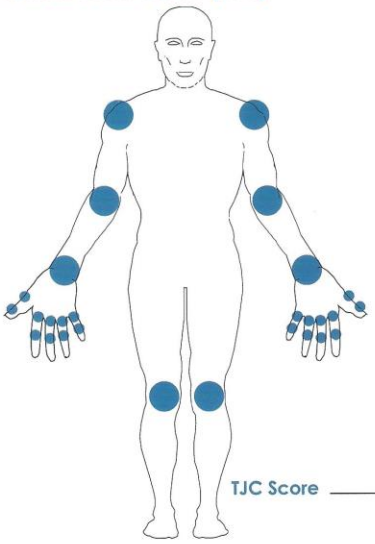
Appendix 4: Data Collection Tool

Simplified Disease Activity Index

SIMPLIFIED DISEASE ACTIVITY INDEX (SDAI)[1]

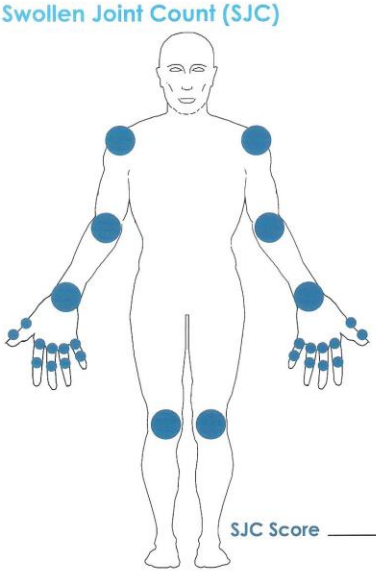
Patient Name: ..... File No: ..... Date: .....

1 Tender Joint Count (TJC)



TJC Score _____

2 Swollen Joint Count (SJC)



SJC Score _____

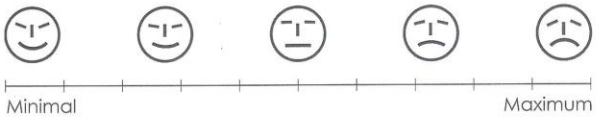
3 Patient Global Assessment (PGA)

Please draw a vertical mark on the line to indicate where you would rate your arthritis and how it affects you today

Minimal Maximum

4 Physician Global Assessment (MDGA)

Please draw a vertical mark on the line to indicate where you would rate your patient's arthritis and how it affects him/her today



Minimal Maximum

5 C-reactive protein (CRP) in mg/dL (where normal <1 mg/dL)

CRP : ..... ÷ 10 = ... mg/dl
Local Score

ESR : .....

Morning stiffness ..... minutes

1	+	2	+	3	+	4	+	5	=	SDAI
TJC		SJC		PGA		MDGA		CRP		

Total Pain

PAIN SCALE (Distance From 0 to vertical mark in cm X 0.2)[2]

0 — Please draw a vertical mark on the line to indicate the degree of pain over this past week — 100

No pain — Severe pain

Total Pain

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