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Dyslipidaemia in rheumatic diseases

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DYSLIPIDAEMIA IN RHEUMATIC DISEASES

A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine.

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DECLARATION:

I, Xiaohui Chen, do hereby declare that this research report is my own unaided work. This report is being submitted for the degree of Master of Medicine in the branch of Internal Medicine, at the University of Witwatersrand, Johannesburg. It is being submitted in the publishable format, as recognized by the Faculty of Health Sciences. I further declare that it has not been submitted for any other degree or examination, at this or any other university.



Signed on 15/03/2021

DEDICATION:

To my wonderful mother, Lisa, for the never-ending support, love and understanding throughout my career and life.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS RESEARCH PROJECT:

Nil at the time of submission.

ETHICAL CONSIDERATIONS

Permission for this study was granted by Dr A. Black (Acting Head of Internal Medicine at Helen Joseph Hospital at the time of protocol submission), hospital management, the Medical Advisory Committee (MAC) and the Human Research Medical Ethics Committee at the University of Witwatersrand (clearance certificate no. M181109).

ABSTRACT

Background: It is well established that patients with rheumatic diseases are at high risk of atherosclerosis and cardiovascular disease. Dyslipidaemia is an important modifiable cardiovascular risk factor and in 2018 the Lipid and Atherosclerosis Society of Southern Africa (LASSA) published guidelines with recommended treatment targets for patients with dyslipidaemia.

Objectives: To evaluate the prevalence of dyslipidaemia in patients with rheumatic diseases from a South African population, and identify the proportion of these patients receiving lipid lowering agents (LLAs). The aim was to determine the number of patients on LLAs reaching the low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) targets recommended by LASSA guidelines.

Methods: This was a retrospective cohort study of 200 adult patients attending the Helen Joseph Hospital outpatient rheumatology clinic from 22 August to 12 December 2018. Clinical and laboratory data from patients with a confirmed diagnosis of rheumatic disease(s) and had their lipogram(s) measured since attending the clinic were analysed.

Results: The median age of patients was 54 years (IQR 45-62) with a female predominance of 85.5% (n=171) and the majority 52.5% (n=105) being comprised of black African patients. ***Primary outcomes:*** Of the 200 patients enrolled, 127 (63.5%) met the criteria for dyslipidaemia based on their initial lipograms measured at the clinic but only 59 (46.5%) of these patients were on LLAs. At the time of the audit, 164 (82%) patients were eligible to receive LLAs as recommended by the LASSA guidelines, but only 77 (47.2%) were prescribed LLAs. Of these 77, only 22 (28.6%) met the recommended LDL-C targets for very high risk or high risk groups proposed by LASSA. ***Secondary outcomes:*** There was a high prevalence of cardiovascular risk factors present in 153 (76.5%) of patients – with hypertension being predominant in 132 (86.3%) patients. The majority of patients, 186 (93%), were on disease modifying agents for rheumatic diseases (DMARDs). A low proportion of 23 (11.5%) patients were on corticosteroids.

Conclusion: Despite the high prevalence of dyslipidaemia in patients with rheumatic diseases, the majority of patients did not meet the recommended TC/LDL-C targets suggested

by local guidelines. There is a need to raise awareness amongst healthcare practitioners treating this patient population regarding the pertinent aggressive control of dyslipidaemia. Furthermore, owing to the relationship between inflammation and lipids, rheumatic disease itself should perhaps be considered as an independent cardiovascular risk equivalent to other traditional cardiovascular risk factors.

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LIST OF NOMENCLATURE/ABBREVIATIONS

ACPA	Anti-citrullinated peptide/protein antibody
ACR	American College of Rheumatology
AIDS	Acquired immunodeficiency syndrome
ADM	Amyopathic dermatomyositis
ANA	Antinuclear antibody
Anti-β_2GPI	Anti-β_2 glycoprotein I
Anti-dsDNA	Anti–double-stranded DNA
ART	Antiretroviral therapy
ATV	Atazanavir
AS	Ankylosing spondylitis
AxSpA	Axial spondyloarthritis
BMI	Body mass index
CAD	Coronary artery disease
CRP	C-reactive protein
CTD	Connective tissue disease
CVD	Cardiovascular disease
DECT	Dual-energy computed tomography
DIP	Distal interphalangeal
DISH	Diffuse idiopathic skeletal hyperostosis
DMARDs	Disease-modifying antirheumatic drugs
DNA	Deoxyribonucleic acid
DM	Dermatomyositis
EAS	European Atherosclerosis Society
ELISA	Enzyme-linked immunosorbent assay
ESC	European Society of Cardiology
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
HDL	High density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
IBP	Inflammatory back pain
IgA	Immunoglobulin A

IgG	Immunoglobulin G
IgM	Immunoglobulin M
IIM	Idiopathic inflammatory myopathy
IL	Interleukin
IMNM	Immune-mediated necrotizing myopathy
IQR	Interquartile range
JDM	Juvenile dermatomyositis
LASSA	Lipid and Atherosclerosis Society of Southern Africa
LDL	Low density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LLA	Lipid lowering agent
LLD	Lipid lowering drug
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
JDM	Juvenile dermatomyositis
MCP	Metacarpophalangeal
MI	Myocardial infarct
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MSU	Monosodium urate monohydrate
Nr-axSpA	Non-radiographic axial spondyloarthritis
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
PAD	Peripheral artery disease
PCR	Polymerase chain reaction
PI	Protease inhibitor
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RTV	Ritonavir
SF	Synovial fluid signs
SLE	Systemic lupus erythematosus
SpA	Spondyloarthritis
SSc	Systemic sclerosis

SS	Sjögren's syndrome
TC	Total cholesterol
TG	Triglycerides
TIA	Transient ischaemic attack
VLDL	Very low-density lipoprotein
WHO	World Health Organisation

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CHAPTER 1 PROTOCOL WITH EXTENDED LITERATURE REVIEW

1) Introduction

1.1. Epidemiology

Cardiovascular disease is a major cause of death and disability worldwide. Currently it accounts for over 17 million deaths worldwide annually.[1-3] The term "atherosclerotic cardiovascular disease" incorporates coronary heart disease (angina pectoris, myocardial infarction, heart failure, coronary death), cerebrovascular disease (transient ischaemic attack and stroke), peripheral artery disease (intermittent claudication), aortic atherosclerosis and thoracic or abdominal aortic aneurysm.[4]

According to projections of the global burden of disease and mortality, ischaemic heart disease and cerebrovascular disease will supersede HIV/AIDS as leading causes of death by 2030.[5] Owing to the high burden of communicable diseases, trauma, infant mortality and HIV and AIDS in Sub-Saharan Africa; ischaemic heart disease and cerebrovascular accidents were previously seen as less significant contributors to morbidity and mortality.[6] Upon reaching the 21st century, ischaemic heart disease was found to be the 8th leading cause of death in sub-Saharan Africa.[7]

According to WHO definitions, about 40% of people worldwide have high total cholesterol levels.[8] A study done in South Africa demonstrated that high cholesterol levels caused 59% of deaths related to ischaemic heart disease and 29% of ischaemic stroke.[9] A systematic review and meta-analysis conducted by Karaye and Habib estimated the prevalence of dyslipidaemia to be 38.4% in Sub-Saharan Africa, being most predominant (49.6%) in patients with ischaemic heart disease – which is comparable to that of Western Europe (45-54%).[10]

A cohort study from 2005 done in individuals from Asia, Australia and New Zealand revealed that patients with a high total cholesterol (≥6.25 mmol/L) and systolic blood pressure (≥160 mmHg) had a 7-fold increase in the risk of coronary heart disease and an 8-fold increase in the risk of stroke, compared to patients with a total cholesterol <4.75mmol/L and systolic blood pressure <130mmHg.[11] In patients with premature coronary heart disease,

the presence of dyslipidaemia has been found to be as high as 75-85% versus 40-48% in age-matched patients without coronary heart disease.[12,13]

1.2. Risk factors for dyslipidaemia

In the global INTERHEART study from 2004, 9 potentially modifiable risk factors which accounted for the first episode of an acute myocardial infarction in over 90% of the population were identified: hypertension, diabetes, dyslipidaemia, abdominal obesity, smoking, physical activity, psychosocial factors, alcohol consumption and consumption of fruit and vegetables.[14] The five leading causes believed to be responsible for more than half of cardiovascular disease related deaths include hypercholesterolaemia, hypertension, diabetes, smoking and obesity.[15]

In the INTERHEART study, it was also revealed that dyslipidaemia was responsible for 49% of the population-attributable risk of a first myocardial infarction.[14] It concluded that the two most significant cardiovascular risk factors worldwide were dyslipidaemia and smoking. The INTERHEART Africa study further demonstrated that premature acute myocardial infarctions happen more frequently in sub-Saharan Africa than in any of the other 52 countries involved in the study.[16]

Various non-modifiable risk factors for cardiovascular disease have also been identified. Cardiovascular related morbidity and mortality rates have been shown to be higher in autoimmune rheumatic diseases, mainly due to accelerated atherosclerosis.[17] This can in part be due to traditional risk factors for atherosclerosis and treatment options for these conditions such as corticosteroids, but various inflammatory and autoimmune mechanisms also contribute to this.

Inflammation is characterised by redness (rubor), swelling (tumor), heat (calor), pain (dolor) and loss of function (function laesa).[18] Vascular dilatation and leakiness, followed by secretion of molecules which recruit leukocytes leads to the aggregation of neutrophils, macrophages/monocytes and other inflammatory cells at sites of inflammation – which contribute to the first three characteristics of inflammation.The vascular endothelium plays a crucial role in these events, as vascular endothelial cells attract leukocytes at sites of inflammation and various vascular adhesion molecules recruit different types of cells.[18]

Inflammation is known to play a role in the development of atherosclerosis and atherosclerotic cardiovascular disease. This process is believed to be driven by macrophages – which release a number of inflammatory substances, cytokines and growth factors after taking up oxidized low-density lipoprotein.[19,20]. With the recognition that atherosclerosis is a process of inflammation, certain plasma markers of inflammation have been identified as potential markers for the prediction of coronary event risk.

High sensitivity C-reactive protein (CRP) is one of the inflammatory markers which has been shown to be linked to a higher risk of atherosclerosis and cardiovascular disease, irrespective of cholesterol levels.[21,22] The long term stability of inflammatory marker values such as CRP and erythrocyte sedimentation rate (ESR) have also been found to be similar to blood pressure and total serum cholesterol concentration values.[23] The use of anti-inflammatory medications (such as statins and biologic agents) to lower CRP has been shown to reduce the risk of cardiovascular events, independent of cholesterol lowering.[24,25]

Traditionally (primary) atherosclerosis in the elderly is thought to be partly due to "low grade inflammation" and moderately increased CRP production. Systemic "high grade inflammation" underlying autoimmune rheumatic diseases, on the other hand, appears to be linked with accelerated atherosclerosis and a variety of vasculopathies.[26] Chronic systemic inflammation promotes atherogenic alterations such as endothelial dysfunction, dyslipidaemia, insulin resistance, thrombotic changes and oxidative stress.[27] Ongoing inflammation therefore increases the risk of erosion or rupture of an atherosclerotic lesion.

Even in patients with undifferentiated connective tissue diseases, who typically have milder disease and less major organ involvement [28,29] , chronic inflammation has still been found to have an effect in the microcirculation by impairing nitric oxide-dependent and endothelium independent vasodilatation.[29] This may have clinical implications on the risk of cardiovascular disease as vasodilatation and nitric oxide protects the vessel wall from the development of atherosclerosis and thrombosis.[30] A study by Laczik et al. identified the presence of endothelial dysfunction leading to atherosclerosis, and proposed that high levels inflammatory markers such as CRP in patients with undifferentiated connective tissue diseases contributes to this.[31]

1.3. Dyslipidaemia in rheumatic diseases

Autoimmune rheumatic diseases are commonly associated with traditional risk factors of atherosclerosis including dyslipidaemia, obesity, metabolic syndrome, smoking and the tendency towards systemic inflammation – which all contribute to an increase in cardiovascular morbidity and mortality.[17,32] The contribution of joint deformities in such conditions must also not be overlooked as this can often lead to physical inactivity, immobility and therefore obesity.

Various autoimmune rheumatic diseases have been found to be associated with premature atherosclerosis and therefore an increased risk of cardiovascular disease – these include rheumatoid arthritis (RA), spondyloarthritis, systemic lupus erythematosus (SLE), gout and psoriatic arthritis (PsA).[33] In addition to the risk of premature coronary heart disease, the occurrence of strokes has also been demonstrated to occur more frequently in inflammatory rheumatic disease patients – both of which are thought to be associated with the degree of inflammation.[34] In a Spanish study, the prevalence of cardiovascular disease was found to be highest in patients with SLE, RA and psoriasis – compared to other immune-mediated inflammatory diseases such as Crohn's disease or ulcerative colitis.[35]

1.4. Rheumatoid arthritis

The risk of cardiovascular disease related deaths has been found to be as high as ±50% in patients with rheumatoid arthritis (RA) compared to the general population.[36] The European League Against Rheumatism (EULAR) expert committee has suggested that cardiovascular risk scores e.g. Framingham should be multiplied by 1.5 in certain patients with RA in order to demonstrate the increased risk of cardiovascular disease in such patients.[37] It has also been proposed that the risk of cardiovascular disease in RA patients begins within one year of clinical onset of disease – as patients without clinical features of cardiovascular disease with actively treated RA have been found to have increased carotid intima media thickness (a marker of generalised atherosclerosis) and corresponding mean CRP levels, when compared to healthy controls from the general population .[38]

In a recent South African study of 500 patients with RA, cardiovascular risk factors were noted to be common – notably 70% of patients with co-existing hypertension, 47.4% with hypercholesterolaemia and 15.4% with diabetes mellitus. Despite this, the occurrence of coronary artery disease was found to only be 0.6% and cerebrovascular disease 2.8% in the

population studied; suggesting that some degree of protection is conferred in the black South African RA population.[39] However, in another South African study, the burden of carotid atherosclerosis was found to be identical amongst black and white RA African patients.[40]

In RA patients, there is a term known as the "lipid paradox" when it comes to describing the lipid profiles in these patients. The levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) appear to be reduced in RA, particularly when in the pro-inflammatory state. Despite this reduction, these lowered lipid levels are associated with a higher cardiovascular risk. Anti-inflammatory treatment such as Disease-Modifying Antirheumatic Drugs (DMARDs) and biologic agents, on the other hand, seems to increase these lipid parameters in RA patients – thus also resulting in a possibly higher predisposition to atherogenicity.[41-45] It was subsequently found that lipid ratios (such as TC/HDL or LDL-C/HDL) seem to be less impacted by systemic inflammation, and thus may be a better measure of cardiovascular risk in RA patients[41,43,46]. In comparison to TC and LDL-C, the link between HDL-C and risk of cardiovascular events also seems to be a marker, with higher HDL-C levels correlating with a lower risk for cardiovascular disease.[47-49]

Inflammation in RA is also believed to modify lipid composition and function. The antioxidant activity and cholesterol efflux functions of HDL-C appear to be reduced in RA patients, particularly in inflammatory states. It has been shown that LDL-C from RA patients possessed increased levels of glycated end products and is more frequently oxidized – leading to increased formation of foam cells and further promoting the release of proinflammatory cytokines.[50] These modifications are in turn believed to accelerate the growth of atherosclerotic lesions and the increased rate of plaque progression and rupture in RA. Tight control of inflammation and acute flares therefore has important implications in these patients – as exposure to every acute RA flare has also been found to be associated with a 7% increase in cardiovascular disease risk.[51]

1.5. Systemic lupus erythematosus

Accelerated atherosclerosis and coronary heart disease contribute significantly to the morbidity and premature mortality of SLE patients. The risk of cardiovascular events in this population of patients was found to be increased by 2-2.6 fold in comparison to the general population.[52,53] Young women, a group that usually has a relatively low risk of

atherosclerosis, appear to be most affected[53-55] – with a reported peak of 50-fold increase for myocardial infarction (MI) in those between the ages of 35-44 years.[55] A modified Framingham score where each item is multiplied by 2 has been proposed to be a more accurate reflector to determine coronary artery disease risk amongst SLE patients.[56]

Multiple factors contribute to atherosclerosis in SLE. Universal risk factors for atherosclerosis are prominent and the presence of metabolic syndrome (two or more cardiovascular disease risk factors including hypertension, impaired glucose metabolism, dyslipidaemia, central obesity) appears to occur commonly amongst SLE patients[57,58] – the frequent association of renal impairment and corticosteroid use in SLE may be contributors to this.[59]

In newly diagnosed SLE patients, it was discovered that 36% had hypercholesterolaemia[60], with the prevalence of dyslipidaemia/raised total cholesterol increasing to 65-75% within a 3 year period of diagnosis.[61,62] The lipid profile of SLE patients appears to be related to disease activity. When disease is inactive, levels of very low-density lipoprotein (VLDL) and triglycerides (TG) are found to be increased while HDL-C levels are decreased (known as the "lupus pattern"). During active disease activity, there appears to be a further significant rise in VLDL and TG levels and fall in HDL-C and LDL-C levels (the "active lupus pattern").[63] These observed patterns imply that lipid profile derangements in SLE patients are provoked by degree of disease activity. SLE patients with lupus nephritis have also been shown to have more elevated levels of TC, TG and LDL-C; with subsequent lower levels of HDL-C.[64]

As with RA, inflammatory and immunological mechanisms alter lipid metabolism in SLE. The presence of dysfunctional pro-inflammatory HDL-C once again plays a role in the pathogenesis of altered lipids – being commonly found in SLE patients and leading to accelerated oxidation of LDL, and thus atherosclerosis.[65,66] The activity of lipoprotein lipase, an enzyme which hydrolyzes triglycerides, appears to be reduced in SLE – this causes build-up of chylomicrons and VLDL, which result in increased TG and decreased HDL-C levels.[67] In addition, antibodies against LDL and HDL have been found in SLE patients[68,69], and cell cholesterol efflux is also believed to damaged (independent of HDL)[70]; both further contributing to dyslipidaemia in this population.

1.6. Gout

Hyperuricaemia and gout have been found to be predisposing factors to atherosclerosis. The Framingham study proposed that hyperuricaemia itself is a risk factor for cardiovascular disease, causing up to an excess of 60% of coronary heart disease in men – independent of traditional factors such as hyperlipidaemia, hypertension, diabetes mellitus, obesity or diuretic use.[71] Since then, two other studies have found an estimated 60% increased risk in cardiovascular mortality in gout patients.[72,73] The first study further demonstrated that cardiovascular mortality went up proportionately with concentrations of uric acid, while the second study found the increased risk to predominantly be in men who had previous gout and history of cardiovascular disease.

Inflammation is also thought to play a role in gout. It has been shown that uric acid can prompt CRP expression in vascular endothelial and smooth muscle cells[74], and inflammatory markers (such as CRP, interleukin 6 , neutrophil count) rise with rising serum uric acid levels.[75] During acute gout flares, urate crystals activate inflammatory pathways and promote the generation of pro-inflammatory cytokines such as tumour necrosis factor-α, interleukin 1β (IL-1β) and interleukin 6.[76,77] The presence of active joint synovitis may not always be evident in gout, but low-grade chronic inflammatory activity has been detected in the synovial fluid of gout patients and it is postulated that there is constant, sub-clinical intra-articular inflammation in these patients.[78]

Uric acid levels seem to have an adverse effect on lipid profiles of patients. Total cholesterol triglycerides, LDL-C and TC/HDL-C ratios are found to be increased with the rise of uric acid levels (independent of other cardiovascular risk factors) , while HDL-C has an inverse relationship and tends to fall.[79-82] In a study conducted in the Seychelles, it was discovered that hyperuricaemia had a significant association with various parameters of the metabolic syndrome, and in particular serum triglycerides – with hyperuricaemia leading to hypertriglyceridaemia.[83] In addition, an experimental study showed that a decrease in serum uric acid corresponded with a proportionate decline in TG levels.[84] Even in asymptomatic individuals with hyperuricaemia, lipids have been found to be deranged – with an increase in TC, TG and LDL-C levels.[85]

1.7. Systemic sclerosis

In patients with systemic sclerosis (SSc), it has demonstrated that there is diffuse involvement of the micro- and macrocirculation which predisposes to vascular wall modifications and atherosclerosis.[17,86] The mechanism involves promotion of the inflammatory cascade in SSc, which subsequently promotes oxidation and in turn causes vessel wall inflammation, endothelial injury and cytokine release. This sequence of events thus leads to increased production of inflammatory markers such as CRP, which contributes to atherosclerosis.[17,86]

Vasculature wall stiffness is also increased in SSc, resulting in an increased risk of vascular occlusive diseases – in particular peripheral arterial and carotid artery disease.[87-91]
In the EULAR Scleroderma Trials and Research database, cardiovascular events were found to contribute to 29% of non-SSc-related deaths.[90] Additional studies in the United Kingdom, Australia and United States have noted that the risk for myocardial infarction and stroke is higher in this population of patients when compared to controls.[91-94]

Few studies have examined the relationship between lipids and SS, but it has been suggested that these patients may have higher levels of LDL, lipoprotein(a), homocysteine and CRP – implicating a higher risk of coronary events and an adverse effect on thrombosis.[95,96] A Japanese study by Kodera et al. postulated that the presence of lipoprotein lipase antibodies appears to be elevated in SSc, as found in SLE patients, which then also leads to raised TG levels.[97] Another study found that in SSc patients who have anticentromere antibodies, HDL-C levels seemed to be low.[98] This proposed pattern of increased TG and decreased HDL-C levels in SSc patients was supported by one Chinese study.[99]

1.8. Sjögren's syndrome

Sjögren's syndrome (SS) can present as a primary rheumatic disease or can be associated with other rheumatic diseases – most commonly RA or SLE. Despite this, SS itself has been found to be an independent risk factor for hypertension, hypertriglyceridaemia[100], arterial wall thickening (indicating subclinical atherosclerosis)[101] and subsequently myocardial infarcts and cerebrovascular events.[102-104] In a case control study by De-Lis et al, the prevalence of hypertriglyceridaemia was found to be 1.5 times more common and diabetes mellitus twice as common in SS patients[105]. Lower levels of HDL-C have been detected in SS patients in 2 studies[106,107], and a study by Lodde[106] et al. also noted lower levels of TC

in this population. It has been thought that dyslipidaemia in SS patients appears more often with raised inflammatory markers such as CRP and ESR.[108]

1.9. Osteoarthritis

Osteoarthritis (OA) is a disease which has been commonly found in patients with metabolic syndrome[109-111], with the proposed link between the two conditions being chronic low-grade systemic inflammation. Pro-inflammatory cytokines are also believed to contribute to dyslipidaemia in OA patients – with the belief that adipose tissue is the source of such cytokines and visceral fat the secretor of adipose.[112] A systematic review by Baudart et al found a two times higher risk of dyslipidaemia in OA patients i.e. low HDL-C, high LDL-C, hypercholesterolaemia and hypertriglyceridaemia.[113] Lower limb osteoarthritis has also been linked to obesity[109,114-115], which may be a contributing factor leading to lipid derangements in this population of patients. Despite this association, TC levels have been shown to be raised in OA independent of obesity.[116-118]

Although the exact mechanisms of altered lipid metabolism are unknown, it has been proposed that the cartilage in OA patients has significant amounts of lipid deposits – particularly in the chondrocytes.[119] This study also discovered that total fatty acid and arachidonic acid levels appeared to be drastically raised in OA patients, and correlated with rising incidence and the severity of disease. It has been found that Apolipoprotein A1 (a lipid transport protein which makes up a large component of HDL-C) serum levels are higher in OA patients, but much lower in the synovial fluid of such patients when compared to RA.[120] Oxidized LDL has also been noted to be present in the synovial fluid of OA patients, but appears to have a significant correlation with BMI.[121]

1.10. Ankylosing spondylitis/psoriatic arthritis

In patients with spondyloarthopathies such as ankylosing spondylitis (AS) and psoriatic arthritis (PsA), it has been noted that they are at higher risk of cardiovascular disease versus unaffected individuals, to a degree which possibly approaches the risk of RA patients.[122,123] In two meta analyses, the risk of myocardial infarcts was found to be significantly increased in both AS[124] and PsA[125] patients, and strokes in AS patients when compared with the general population.

A database analysis by Hans et al demonstrated that hyperlipidaemia is more commonly diagnosed in AS patients versus persons without AS.[126] However, a few other studies have found that AS patients had lower levels of TC, HDL-C and TG versus controls.[127-130] It has been shown that lipid dysregulation may be linked to inflammatory markers in AS, and differences between AS and control patients were ameliorated once adjustments for inflammatory markers were made.[131]

PsA patients also appear to decreased levels of TC, LDL-C and HDL-C[132-134], but this pattern was most distinct in patients who had active joint disease – elucidating that there may be an inverse relationship with inflammation. The study by Jones et al [134] supports this relation as a drop in TC and LDL-C was noted particularly in patients with active disease. Furthermore, the Tam et al's study demonstrated that TC/HDL-C ratios are proportional to CRP levels in PsA, while HDL-C is inversely proportional to CRP.[133]

1.11. Polymyositis/dermatomyositis

The risk of coronary artery disease has been found to be at least three times more in patients with idiopathic inflammatory myopathies (IIMs) such as polymyositis and dermatomyositis.[135,136] Three studies noted that metabolic syndrome, dyslipidaemia and abdominal obesity have been shown to occur more commonly in this population of patients[137-139] – yet the one confounding factor is that at least approximately 50% of the patients in all 3 studies were being treated with prednisone.

High level of TGs, low levels of HDL-C and increased TC/HDL-C ratios have been demonstrated in patients with untreated polymyositis and dermatomyositis.[137,139-141] As with other rheumatic diseases, there appears to be an association with inflammation as CRP has been found to be inversely proportional to HDL-C in dermatomyositis patients[140] and to TC in patients with polymyositis.[141] Within the first year of diagnosis of disease, the risk of hospitalisation due to coronary artery disease is already elevated – further suggesting that active inflammation is a powerful driver.[136]

1.12. Undifferentiated connective tissue disease

The term "connective tissue" or "collagen" diseases was traditionally used to describe patients who exhibit clinical and serological features of rheumatic diseases, but do not fulfill the diagnostic criteria or display manifestations of multiple entities.[142,143] Over time, these

patients usually transition into a diagnosis of rheumatic disease. This group of patients was later termed to have “undifferentiated” connective tissue diseases.[144,145]

1.13. Medications used in rheumatic diseases

DMARDs are a group of medications frequently used in the treatment of rheumatic diseases. Their main mechanism of action is mainly to modulate the immune system and thereby suppress inflammation. Traditional DMARDs include methotrexate, leflunomide, hydroxychloroquine and sulfasalazine. Other less frequently used drugs are azathioprine, cyclosporin and mycophenolate mofetil.

Apart from the positive effects of DMARDs on arthritis, these drugs also appear to have an influence on cardiovascular mortality. In a prospective study by Choi et al., methotrexate decreased cardiovascular associated deaths by up to 70% in RA patients, with the suspected mechanism being a reduction in systemic inflammation.[146] Furthermore, a second prospective study demonstrated that methotrexate even improves lipid profiles in RA patients by increasing HDL-C and lowering LDL/HDL levels.[147] Hydroxychloroquine has also been shown to have favourable effects on the metabolic profiles of RA and SLE patients such as reducing glucose levels, lowering TC, LDL-C and TG levels and increasing HDL-C levels.[148-152]

Corticosteroids are a second group of medications commonly used for control of pain and inflammation in rheumatic disease patients. The relationship between corticosteroids and cardiovascular disease is complex. As previously mentioned, cardiovascular risk factors are thought to be driven by inflammation – which is suppressed with the use of corticosteroids. Yet use of corticosteroids leads to an increased risk of development of cardiovascular risk factors such as hypertension, glucose intolerance, central obesity and disturbances in lipid profiles.

In RA patients, it has been demonstrated that ingestion of 5mg-10mg of prednisone or an equivalent drug per day over 2 years led to a body weight gain of 4-8%.[153] Similarly, in SLE patients, a 10mg per day increase in prednisone was shown to cause a rise in blood pressure, body weight and serum cholesterol levels.[154] Yet the combination of steroid and antimalarial use (such as hydroxychloroquine) in SLE patients appears to lower possible steroid induced hypercholesterolaemia, owing to the effects of the antimalarial .[155]

Colchicine, a medication used for the treatment of gout, has been found to lower inflammatory marker levels and seems to be of particular benefit to patients with coronary disease.[156-158] The concomitant use of statins and colchicine appears to be synergistic in reducing inflammation and cardiovascular risk in patients[157], and the combination with atorvastatin specifically has been shown to improve lipid profiles in a rat model.[158] Recent studies have established that treatment with low dose colchicine leads to a lower rate of cardiovascular events in patients who have had a recent myocardial infarction and those with chronic coronary disease.[159,160] Although few studies have been conducted, another commonly used agent in gout treatment allopurinol, has also demonstrated some degree of protection against cardiovascular events – especially myocardial infarction.[161-163]

In a population like South Africa where Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) is a prevalent disease, it is important to take into consideration medications used which may have an effect on lipids. HIV itself has been found to have an adverse effect on lipid profiles of affected patients – with raised TG and reduced HDL-C levels when compared to HIV negative patients.[164]

Protease inhibitors (PIs), a group of drugs used as part of combination antiretroviral therapy (ART) for HIV, and its adverse effects on lipids has been extensively researched. The use of PIs atazanavir (ATV) and ritonavir (RTV) have been shown to significantly increase TC, TG and LDL-C levels.[165,166] RTV boosted PIs, which are often used in the South African setting (such as lopinavir/ritonavir), also appear to negatively influence lipid levels by raising TC and TG levels.[167,168] Furthermore, when administered twice daily, the combination of lopinavir/ritonavir (LPV/r) leads to a greater increase in TC, TG and LDL-C.[169]

1.14. Treatment of dyslipidaemia

Owing to the well-known association between increased cardiovascular disease risk and inflammatory joint disorders, EULAR first published recommendations in 2009 regarding how best to manage such patients. According to the latest 2015/2016 EULAR update, cardiovascular risk assessment is recommended for these patients at least once every 5 years, and needs to be reassessed when there are major changes to antirheumatic treatment.[170] EULAR suggests that as part of cardiovascular risk assessment, laboratory measurements of

lipids should be performed – in particular TC and HDL-C levels. These should also preferentially be done when disease activity is under control or in remission.

The South African Heart Association and the Lipid and Atherosclerosis Society of Southern Africa (LASSA) published a combined statement, the South African Dyslipidaemia Guideline Consensus Statement, in 2018 with recommendations regarding the management of dyslipidaemia in a setting relevant to our population. The guideline proposes screening and tailoring treatment targets for patients based on risk stratification by using tools such as the Framingham risk tables.[171] Patients with autoimmune chronic inflammatory disease would most likely fit appropriately into the moderate to high risk groups, based on their increased cardiovascular risk and common occurrence of co-existing co-morbidities predisposing them to such.

LASSA recommends that when screening for dyslipidaemia, all individuals should have a full lipogram done (TC, TG, HDL-C and LDL-C), or at least a TC or LDL-C level. LDL-C is considered the measurement of choice when trying to determine best treatment for patients and assessing response, as the advantages of reducing this are known and it is correctable with treatment. Once the relationship between LDL-C and on-treatment TC is established, it may be considered appropriate to watch the TC trend only. TC can be measured for assessment of risk, screening and monitoring treatment effects if financial constraints exist or if there is a barrier to obtaining LDL-C levels. In patients where other parameters of the lipid profile (apart from LDL-C) are also increased, a full lipogram is still recommended for follow-up.

LASSA proposes varying target LDL-C levels for patients based on their Framingham cardiovascular risk score. An LDL-C target of <1.8mmol/L is recommended for very high risk groups (secondary prevention or >30% risk for primary prevention), <2.5mmol/L for high risk groups (15-30% risk) and <3mmol/L for those with a moderate to low risk (<15% risk). Equivalent target values for TC have also been established: a TC = 4.5mmol/L is approximately equal to LDL-C of 2.5mmol/L and TC = 4.0mmol/L is roughly equal to LDL-C of 1.8mmol/L. The rationale behind these targets is due to the fact that it has been demonstrated that for every 1mmol/L reduction in LDL-C, there is a 21-24% decline in major coronary artery disease/vascular events and a 12% decrease in overall mortality.[172] In patients with monogenic disorders such as familial hypercholesterolaemia, full treatment is

required regardless of lipogram measurements – as this population of patients are at an extremely high risk of cardiovascular disease.[171]

In 2019, the European Society of Cardiology (ESC)/ European Atherosclerosis Society (EAS) published new guidelines whereby optimal LDL-C targets were lowered even further. A LDL-C level of <1.4mmol/L is recommended in patients with very high cardiovascular risk and LDL-C <1.8mmol/L for high risk patients, coupled WITH at least a 50% reduction in LDL-C from baseline (off lipid lowering agents).[173] In moderate risk individuals, an LDL-C goal level of <2.6mmol/L is suggested and <3.0mmol/L in low risk patients.

Statins are commonly used for the treatment of dyslipidaemia in South African patients. Statins decrease cholesterol production by competitive inhibition of the enzyme HMG-CoA reductase in the liver – the rate-limiting step in cholesterol synthesis. It has been demonstrated that for each 1mmol/L decrease in LDL-C, the risk of major coronary events (myocardial infarctions, coronary revascularisation procedures, coronary deaths) is lowered by ±one quarter – for every year of statin treatment after the 1st year.[174]

Apart from its lipid lowering properties and benefits in cardiovascular mortality, statins also appear to have pleotropic effects which may influence inflammation. It has been shown in vitro that statins have immunomodulatory effects on free radical production, upregulation of adhesion molecules, endothelial adhesion and transmigration, chemokine and pro-inflammatory cytokine secretion and metalloprotease secretion via monocytes/ macrophages.[175,176] They are also believed to down-regulate T cell-mediated immune responses.[177-179] In vivo, statins have been found to reduce circulating levels of pro-inflammatory cytokines such as interleukin-6 and tumour necrosis factor α[180], as well as causing a shift from a pathogenic Th1 response to protective Th2 response.[181-185] They also decrease CRP release from hepatocytes[186] and reduce cardiovascular events in patients with chronically high CRPs.[24] There appears to be no advantage of one statin over another, but intensified statin therapy seems to result in further decreases in CRP.[187] The use of statins in patients with autoimmune conditions may therefore have multiple benefits.

2) Aim

In view that globally, patients with rheumatic diseases are known to be at high risk of atherosclerosis and cardiovascular disease, the aim of this study was to determine whether dyslipidaemia is present in the population of patients at the Helen Joseph Hospital rheumatology clinic. Furthermore, if dyslipidaemia was found amongst these patients, the aim was to determine whether they are on appropriate treatment and achieving treatment goals as recommended by national guidelines.

3) Objectives

3.1. Primary Objectives

3.1.1. To evaluate the presence of dyslipidaemia in patients with rheumatic diseases in the sample population

3.1.2. To analyse the pattern of lipid profiles found in South African patients with rheumatic diseases

3.1.3. To identify the proportion of patients with dyslipidaemia who are on lipid lowering agents

3.1.4. To determine the number of patients on lipid-lowering agents reaching the LDL-C/total cholesterol targets recommended by LASSA

3.2. Secondary Objectives

3.2.1. To describe the study population

3.2.2. To determine the presence of concomitant co-morbidities/risk factors which may predispose to increased atherosclerosis in the study population

3.2.3. To assess the medications used by the study population

4) Methodology

4.1. Study Design

A retrospective cohort study with descriptive and comparative elements

4.2. Study Setting

The rheumatology clinic at Helen Joseph Hospital

4.3. Study Population

Patients over the age of 18 years attending the outpatient Helen Joseph rheumatology clinic

4.3.1. Inclusion criteria

a. Patients with confirmed rheumatic diseases according to the respective classification criteria of each (see Appendices ii-x)

b. Patients who have had their lipogram(s) measured since attending the rheumatology clinic – laboratory measurements of TC, TG, HDL-C and LDL-C were calculated using the Friedewald formula

4.3.2. Exclusion criteria

a. Patients who do not have a confirmed diagnosis of rheumatic disease as per current accepted classification criteria

b. Incomplete or insufficient clinical records for the collection of parameters to be measured, as listed in the data sheet (see Appendix i)

4.4. Sampling Method

A convenience method of sampling was used. The files of patients booked for the rheumatology clinic every week were screened for the inclusion criteria described, until a target sample size of 200 had been reached. This target sample size was expected to be reached within a period of approximately 2-3 months.

4.5. Sampling Size

A sample population of 200 patients who meet the inclusion criteria was chosen from the database at the Helen Joseph Hospital rheumatology clinic

4.6. Sample Selection

Patients with a confirmed diagnosis of rheumatic disease who attended the clinic and had their lipogram(s) measured

4.7. Data Collection

4.7.1. Basic demographic information (age, gender, ethnicity) was obtained from patient files

4.7.2. The following laboratory data were also obtained (if available):

a. lipograms (total cholesterol, triglycerides, HDL-C, LDL-C) \
b. C-reactive protein
c. erythrocyte sedimentation rate
d. uric acid (for patients with gout)
e. HbA1c (if diabetic and where available)
f. Estimated glomerular filtration rate (eGFR) (using MDRD formula) if available
g. Human immunodeficiency (HIV) status if available
h. CD4 count if available in HIV positive patients

4.7.3. The following cardiovascular risk factors were documented:

a. Hypertension
b. Diabetes mellitus
c. Cigarette smoking, past or present
d. Established cardiovascular disease (coronary artery disease, stroke, transient ischaemic attack and/or peripheral artery disease)

4.7.4. The use of the following concomitant medications was noted:

a. Corticosteroids (either intravenous or oral use)
b. Disease Modifying Anti-Rheumatic Drugs
c. Allopurinol
d. Colchicine
e. Lipid lowering agents (statins, fibrates, other)
f. The use of antiretrovirals (specifically protease inhibitors)

4.8. Statistical analysis

The prevalence of dyslipidaemia in the rheumatic diseases was described according to their respective cardiovascular risk, based on the latest LASSA guidelines. Standard descriptive statistics (mean and standard deviation, median and interquartile range) was used to describe the data.

Inferential statistics were used to compare groups. Age, gender and ethnic differences were also compared. Comparisons drawn on patients taking drugs which may lead to

dyslipidaemia, and those not on such agents was performed. The role of co-morbid diseases/risk factors and their effects on lipids were also analysed. The proportion of patients meeting currently recommended lipid targets (based on their respective cardiovascular risk) were determined. A statistician was consulted to assist with the statistical analysis.

4.9. Confounding bias

As this was a retrospective review, not all causes of dyslipidaemia could be screened for. There was thus a potential for missing secondary causes of dyslipidaemia such as (untreated) hypothyroidism and nephrotic syndrome.

5) Timeline

The study commenced once approval had been received from all governing committees concerned. The expected duration was expected to be approximately ten to twelve months.

The following Gant chart shows the proposed timeline of the study:

	Oct 2018	Nov 2018	Dec 2018	Jan 2019	Feb 2019	March 2019	April 2019	May 2019	June 2019	July 2019	August 2019	Sept 2019	Oct 2019
Literature review													
Protocol preparation													
Protocol Assessment													
Ethics application													
Data Collection													
Data Analysis													
Writing up paper													

6) Ethics

- The protocol was submitted for ethics approval to the relevant governing committees i.e. the Human Research Ethics Committee of the University of Witwatersrand and the Postgraduate Committee of the University of Witwatersrand
- Owing to the retrospective nature of the study, with the sample size being randomly

selected from the available data at the rheumatology clinic, individual patient consent was not required

- Consent for use of patient files and data was requested from the Head of Rheumatology, the Head of the Department of Internal Medicine and the Helen Joseph Hospital Ethics and Research Committee
- Each data sheet was assigned only to a study number to maintain patient confidentiality. No patient names or hospital numbers were recorded. Any association between study numbers, identity of patients or patients' initials were kept separately. The data was accessible to the supervisors, statistician and primary researcher

7) Limitations

- Owing to the fact that this was a retrospective study, data collection relied on precision of written notes; thus important data sought may not have been readily available.
- Secondary causes of dyslipidaemia e.g. (untreated) hypothyroidism and proteinuria in disorders such as SLE were not routinely screened for in the study population.
- At the time of patients' lipogram measurements, disease activity was not concomitantly assessed. The possible negative impact of active disease and inflammation on lipograms analysed was thus not taken into account.
- The study population only included patients attending the rheumatology clinic at Helen Joseph Hospital, and thus the sample may not be representative of the entire South African population, with a possible low external validity to the study.

8) Funding

The expected expenses for this project included photocopying of data sheets and travelling costs. These were self-funded. No extra costs were imposed on the hospital or patients.

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CHAPTER 2 STUDY

1) Background

Cardiovascular disease is a major cause of death and disability, accounting for up to 17.3 million deaths worldwide annually.[1-3] Upon reaching the 21st century, ischaemic heart disease was found to be the 8th leading cause of death in sub-Saharan Africa.[4] In the global INTERHEART study, it was revealed that dyslipidaemia was responsible for 49% of the population-attributable risk of a first myocardial infarction.[5] The INTERHEART Africa study further demonstrated that premature acute myocardial infarctions happen more frequently in sub-Saharan Africa than in any of the other 52 countries involved in the study.[6] A systematic review and meta-analysis conducted by Karaye and Habib estimated the prevalence of dyslipidaemia to be 38.4% in Sub-Saharan Africa, being most predominant (49.6%) in patients with ischaemic heart disease – which is comparable to that of Western Europe (45-54%).[7]A study done in South Africa demonstrated that high cholesterol levels cause 59% of deaths related to ischaemic heart disease and 29% of ischaemic stroke in our country.[8]

Patients with rheumatic diseases are known to be predisposed to cardiovascular related morbidity and mortality due to their increased risk of traditional risk factors for atherosclerosis, various inflammatory and autoimmune mechanisms, and medications (e.g. corticosteroids) used in the management of these conditions.[9-11] Dyslipidaemia is one of the important modifiable risk factors identified in the INTERHEART study[5], which is commonly found when analyzing the lipid profiles of patients with rheumatic diseases.[12-30] The lipid profiles in this population usually display a predisposition towards atherogenicity and have been demonstrated in a variety of diseases including RA[12,13], SLE [14,15], gout[16-18], systemic sclerosis (SSc)[19,20], Sjögren's syndrome (SS)[21,22], osteoarthritis (OA)[23,24], spondyloarthopathies such as ankylosing spondylitis (AS) and psoriatic arthritis (PsA)[25-27], and inflammatory myopathies such as polymyositis and dermatomyositis[28-30]. Furthermore, adverse effects on lipids appear to be driven by inflammatory states in rheumatic diseases.[9, 19,27,29-39]

Owing to the well-known association between increased cardiovascular disease risk and inflammatory joint disorders, recommendations have been published by EULAR and the

South African Heart Association and the Lipid and Atherosclerosis Society of Southern Africa (LASSA) regarding how best to manage such patients. As part of cardiovascular risk assessment, both these expert committees recommend the laboratory measurement of lipids – with EULAR suggesting at least once every 5 years in patients with inflammatory joint disorders[40] and LASSA putting an emphasis on checking low-density lipoprotein cholesterol (LDL-C) levels.[41] Varying target LDL-C levels have been proposed for patients by LASSA, based on their Framingham cardiovascular risk score. Patients with autoimmune chronic inflammatory disease would most likely fit appropriately into the moderate to high risk groups, based on their increased cardiovascular risk. In 2019, the European Society of Cardiology (ESC)/ European Atherosclerosis Society (EAS) published new guidelines whereby optimal LDL-C targets have been lowered even further.[42] In patients with a very high cardiovascular risk, a LDL-C level of <1.4mmol/L is now recommended.

Despite the well-known association between rheumatic diseases and accelerated atherosclerosis, to the best of our knowledge no studies in South Africa have thus far been done to analyse the lipid patterns in patients with rheumatic conditions, and whether they are on appropriate therapy. The aim of this study was therefore to determine whether dyslipidaemia is present in our population of patients, at a rheumatology clinic in a South African tertiary hospital. Furthermore, if dyslipidaemia was found to be prevalent amongst these patients, the objective was to determine whether they were on appropriate lipid-lowering agents and achieving treatment targets as recommended by national guidelines.

2) Methodology

2.1. Study design and setting

A retrospective cohort study was conducted at the Helen Joseph Hospital rheumatology clinic, a clinic within a tertiary hospital, in the Gauteng province of South Africa.

2.2. Data collection and sample selection

Data collection commenced on 16th of January 2019 and continued until a sample size of 200 patients meeting the inclusion criteria of the study was reached. The sample size of 200 was reached on 7th November 2019.

2.2.1. Inclusion criteria:

a. Patients over the age of 18 years attending the outpatient Helen Joseph Hospital rheumatology clinic
b. Patients with a confirmed diagnosis of rheumatic disease(s) according to the respective classification criteria of each (see Appendices ii-x)
c. Patients who have had their lipogram(s) measured since attending the rheumatology clinic – laboratory measurements of TC, TG, HDL-C and LDL-C were calculated using the Friedewald formula

2.2.2. Exclusion criteria

a. Patients who did not have a confirmed diagnosis of rheumatic disease as per current accepted classification criteria
b. Incomplete or insufficient clinical records for the collection of parameters to be measured, as listed in the data sheet (see Appendix i)

A convenience method of sampling was used, whereby the files of patients attending the outpatient rheumatology weekly clinic were screened for the inclusion criteria described. Files of patients attending the clinic starting from the last 2018 clinic date i.e. the 12th of December 2018 were screened retrospectively, until patients attending clinic on the 22nd of August 2018 – whereby a sufficient sample population was collected.

Basic demographic information of patients such as age, gender and ethnicity were retrieved from patient files. Laboratory data including lipograms, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), uric acid in patients with gout, HbA1c in diabetic patients if available, estimated glomerular filtration rate (eGFR), human immunodeficiency (HIV) status if available and CD4 count in HIV positive patients were obtained from the results sheets in patient files. The presence of cardiovascular risk factors/co-morbidities including hypertension, diabetes mellitus, smoking and established cardiovascular disease was also noted. Lastly, the use of medications prescribed/documented in the files' prescription charts were noted. These included the use of corticosteroids, Disease Modifying Anti-Rheumatic Drugs (DMARDs), allopurinol, colchicine, lipid lowering agents (statins, fibrates, other) and protease inhibitors in HIV positive patients.

2.3. Statistical analysis

Data was exported into Stata 14.2 for analysis. Descriptive statistics were used to describe demographic characteristics of patients attending the Helen Joseph rheumatology clinic who were enrolled in the study. Median and interquartile ranges were used for continuous variables which frequencies and percentages were used for categorical data. Analysis methods for the primary and secondary objectives are described below:

- To evaluate the prevalence of dyslipidaemia in patients with rheumatic diseases in the sample population: dyslipidaemia was defined as having a total cholesterol (TC) >5mmol/L AND/OR LDL-C >2.5mmol/L AND/ OR triglycerides (TG) >1.7mmol/L – as outlined by the 2018 LASSA guidelines.[39] It was determined as the number of patients who had dyslipidaemia at baseline ÷ total number of patients enrolled and reported as a percentage with a 95% confidence interval.
- Analyse the pattern of lipid profiles found in South African patients with rheumatic diseases: this was determined as the percentages of enrolled patients who had specified lipid abnormalities – high total cholesterol, high triglycerides, high high-density lipoprotein cholesterol (HDL-C) and/or high LDL-C. These were then presented as percentages.
- Identify the proportion of patients with dyslipidaemia who are on lipid lowering agents: the proportion of patients with dyslipidaemia who are on lipid lowering drugs were determined as the number patients with dyslipidaemia who were taking lipid lowering drugs (statins, fibrates other) ÷ total number of patients with dyslipidaemia. This proportion was presented as a percentage with 95% confidence intervals.
- To determine the number of patients on lipid-lowering agents reaching the LDL-C/total cholesterol equivalent targets recommended by LASSA: this was determined as the proportion of patients with dyslipidaemia OR who met LASSA criteria for LDL-C who were taking lipid lowering drugs and had two or more lipograms, whose most recent lipogram met targets recommended by LASSA. This was determined as the number of patients whose most recent lipogram met the LASSA targets ÷ number of patients taking lipid-lowering drugs and had follow up lipograms. The target for

very high-risk individuals was defined as a latest LDL result of <1.8mmol/L and a reduction of at least 50% if baseline LDL-C is between 1.8 and 3.5 mmol/L. The target for high-risk individuals was defined as LDL result of <2.5 mmol/L and reduction of at least 50% if baseline LDL-C is between 2.5 and 5.2 mmol/L.

- For determining the presence of concomitant co-morbidities/risk factors which may predispose to increased atherosclerosis in the study population: descriptive statistics were used to determine the distribution of concomitant comorbidities among enrolled patients. The presence of concomitant comorbidities were determined as proportion of patients with the co-morbidities listed above and presented as percentages.
- Assessment of the medications used by the study population: this was determined using percentages of patients taking any of the medications listed on the data collection sheet.

3) Results

3.1. Patient characteristics

424 Patients' files attending the Helen Joseph Hospital rheumatology clinic between the 22nd of August 2018 until the 12th of December 2018 were reviewed, of which 200 patients had confirmed diagnoses of rheumatic disease(s) and had their lipograms measured since attending the clinic.

Patient demographics and clinical characteristics are summarised in **Table 2.1**. Patients' ages ranged from 23 to 82 years (median age 42) and there was a significantly higher number of female patients with rheumatic diseases than males, 171 (85.5%) vs 29 (14.5%) respectively. The majority of the study population (52.5%, n=105) comprised of black African patients, followed by South African white (31%, n =62) then Indian (12%, n= 24) and coloured (0.5%, n=1) patients. Most of the population group (76.5%, n=153) had underlying co-morbidities/ cardiovascular risk factors.

Less than half of the patients (39%, n=78) had their weights recorded at the rheumatology clinic and no height measurements were available, thus body mass index calculations were not performed. Most patients (81.5%, n=163) have had their HbA1cs measured and the median value was 5.9%. The majority of patients (87%, n=174) had an eGFR of more

than 60 mL/min/1.73m^2. Amongst the HIV positive patients, a median CD4 count of 595cells/μL was recorded in18 (9%) of patients. Inflammatory marker levels such as CRP and ESR were not markedly elevated in the study population group, with a median value of 11mg/L and 21mm/hour respectively. The median uric acid level was also not markedly high at 0.31 mmol/L. Of the 200 patients enrolled, 3 patients did not any have baseline lipid profile parameters (TC or LDL-C) measured at the clinic.

Table 2.1 Patient demographic and clinical characteristics (N=200)

Characteristic	**N**	**Frequency (n, %)**
Age in years (median, IQR)	200	54 (45- 62)
Age ≥ 50 years	200	124 (62)
Female	200	171 (85.5)
Ethnicity	200	
Black		105 (52.5)
White		62 (31.0)
Indian		24 (12.0)
Coloured		1 (0.5)
Non-Indian Asian		8 (4.0)
One or more underlying co-morbidities/risk factors	200	153 (76.5)
Weight in kilograms, (median, IQR)	78	71.2 (62.7- 79.6)
HbA1c in percentages, (median, IQR)	163	5.9 (5.4 - 6.4)
eGlomerular filtration rate (MDRD formula) >60 in mL/min/1.73m^2	200	174 (87.0)
eGlomerular filtration rate (MDRD formula) 30-59 in mL/min/1.73m^2	200	26 (13)
CD4 count in cells/μL, (median, IQR) (median, IQR)	18	595 (402 -850)
C-reactive protein in mg/L, (median, IQR)	200	11 (3.5- 29.5)
Erythrocyte sedimentation rate in mm/hour, (median, IQR)	200	21 (11 – 40)
Highest ESR level in mm/hour		1
Lowest ESR level in mm/hour		140

Uric acid in mmol/L, (median, IQR) (median, IQR)	90	0.31 (0.26 – 0.38)
Total cholesterol in mmol/L, (median, IQR)	197	4.4 (3.7 - 5.3)
Total triglycerides in mmol/L, (median, IQR)	186	1.3 (0.9 - 1.9)
HDL cholesterol in mmol/L, (median, IQR)	187	1.2 (0.9- 1.5)
LDL cholesterol in mmol/L, (median, IQR)	184	2.5 (2.0 - 3.1)

The spectrum of rheumatic diseases seen at the clinic is outlined in **Figure 2.1**, with RA (63.5%, n=127) and SLE (20.5%, n=41) being most common.

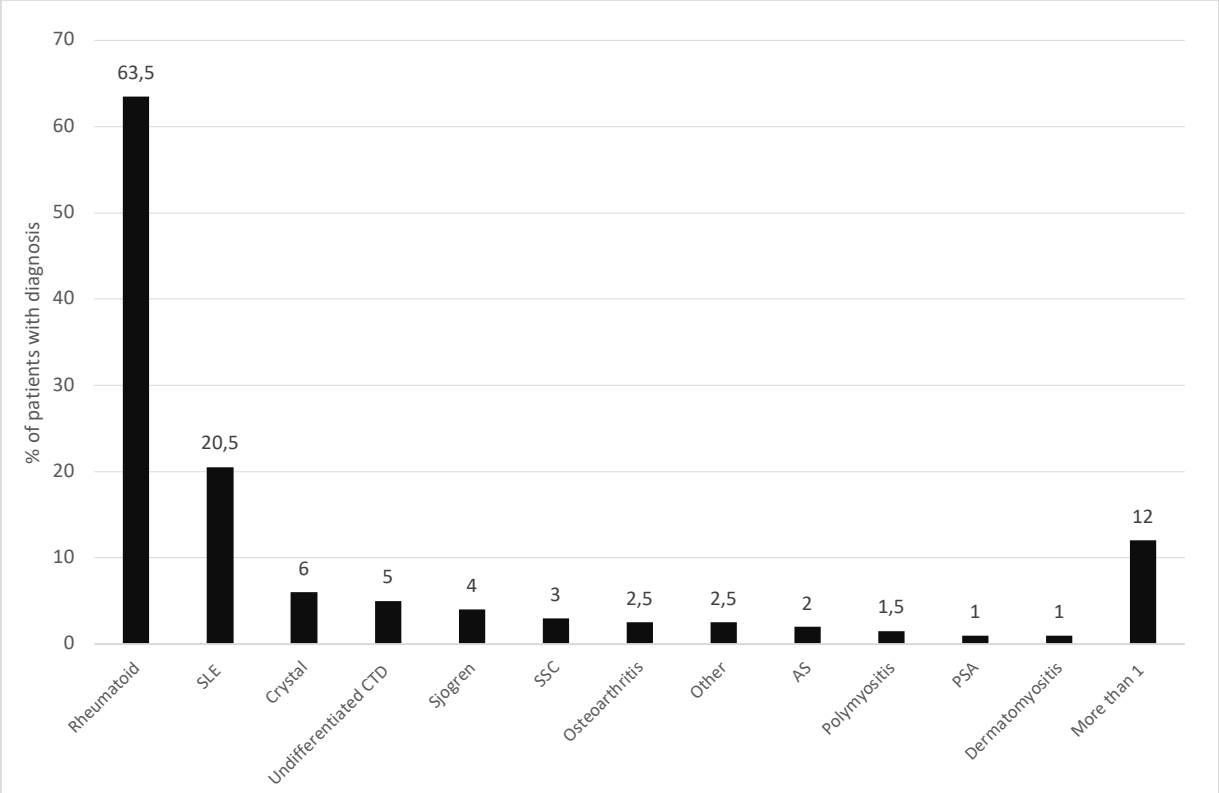

Figure 2.1 Proportion of specific rheumatic diseases among patients attending the Helen Joseph Hospital rheumatology clinic 2018 (N=200)

The prevalence of co-morbidities and/or risk factors which may predispose patients to increased atherosclerosis was common in 153 (76.5%) of patients – these are presented in **Figure 2.2**. Hypertension appeared to be the predominant cardiovascular risk factor found in 132 (86.3%) of patients, followed by smoking in 38 (24.8%) patients and diabetes mellitus in 34 (22.2%) patients. A small proportion (12.4%) of patients were HIV positive

and the majority (9.8%) were on antiretroviral therapy. 7.2% Of the study population already had established cardiovascular disease.

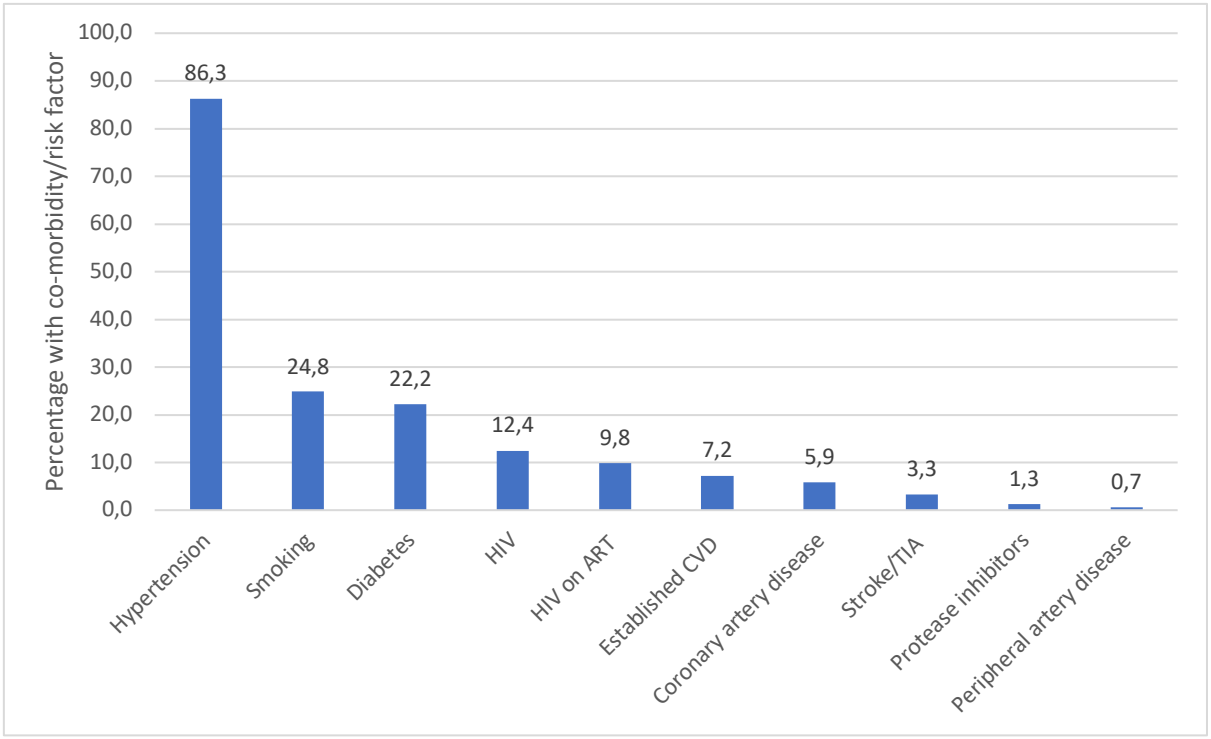

Figure 2.2 Prevalence of co-morbidities among patients with one or more co-morbidities/risk factors attending the rheumatology clinic 2018 (N=153)

The medications used by this population of patients for treatment of their rheumatic diseases and other co-morbidities is shown in **Figure 2.3**. A majority of 186 (93%) patients seemed to be on DMARDs and the most commonly used agents were methotrexate in 131 (65.5%) patients and chloroquine in 53 (26.5%) patients. The use of corticosteroids was uncommon in 23 (11.5%) of patients. In HIV positive patients, only 2 (1%) were on protease inhibitors.

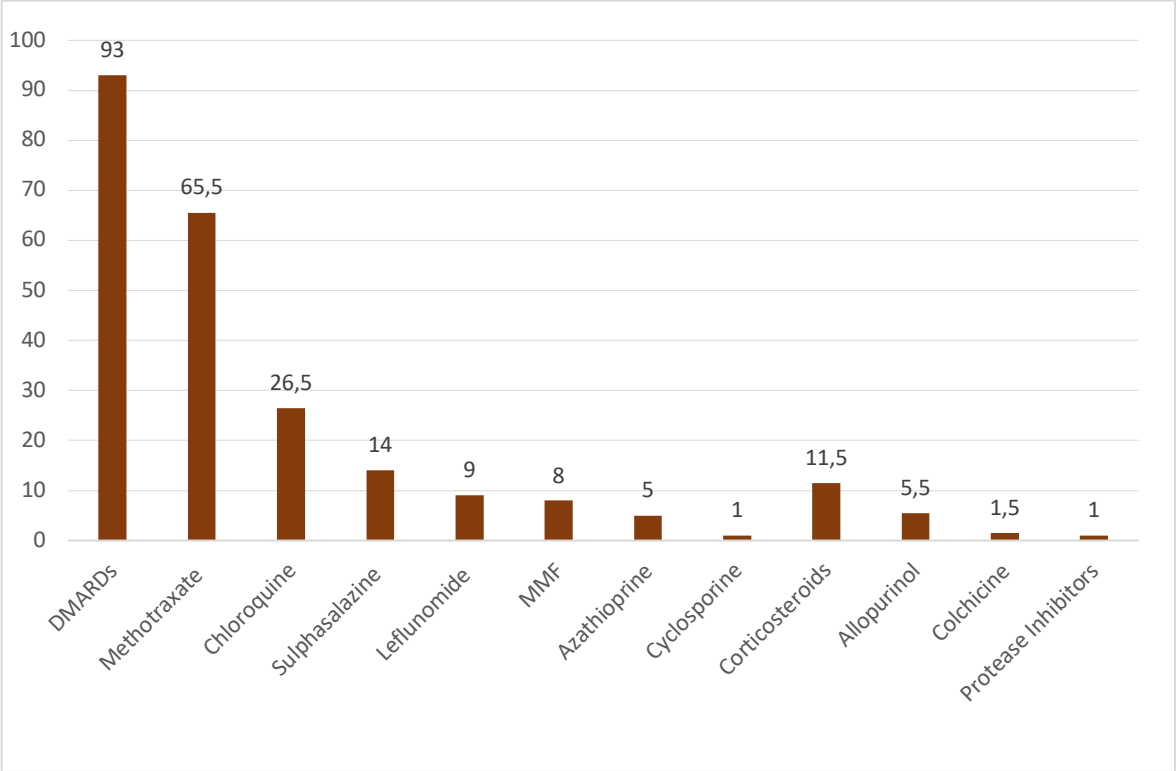

Figure 2.3 Medications used by patients attending the rheumatology clinic (N=200)

3.2. Primary and secondary outcomes

The baseline lipid profiles of patients measured at the rheumatology clinic are displayed in **Table 2.2**. Of the 200 patients enrolled, 127 had dyslipidaemia at baseline. This translated to a prevalence of 63.5% (95% CI 56.5- 69.9%). Dyslipidaemia was defined as having a total cholesterol (TC) >5mmol/L AND/OR LDL-C >2.5mmol/L AND/ OR triglycerides (TG) >1.7mmol/L – as per 2018 LASSA guidelines.[41]

Table 2.2 Baseline lipid profiles among patients attending the rheumatology clinic (N=200)

Total cholesterol levels	n	%	LDL-C levels	n	%
≤4	95	47.5	<1.8	50	25
4.1-4.5	38	19	1.8-2.5	83	41.5
4.5-5	29	14.5	2.51-3	33	16.5
>5	38	19	>3	34	17

A summary of the 200 patients enrolled in the study, those eligible for treatment with lipid lowering drugs (LLDs) and number of patients who have had lipograms measured is displayed in **Figure 2.4**. 164 (82%) Of patients were eligible to receive LLDs at the time of the audit, as recommended by the LASSA guidelines. These patients were risk stratified into very high, high and moderate risk according to Framingham cardiovascular disease risk tables. The majority of patients (97.3%) on LLDs had recent lipograms measured.

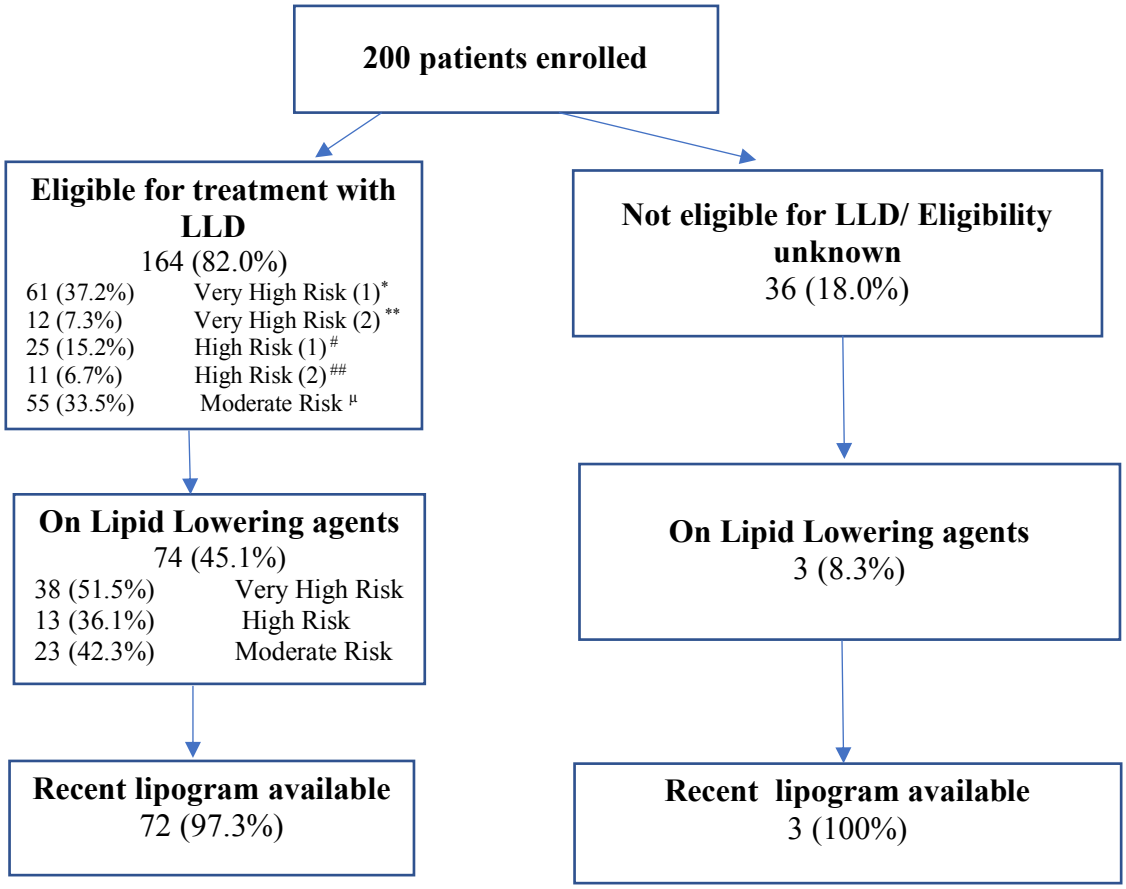

Figure 2.4 Study summary

Based on Framingham cardiovascular disease risk tables[43,44]:

- Very high risk = >30% risk of cardiovascular disease (coronary, cerebrovascular and peripheral arterial disease, heart failure) in 10 years
- High risk = 15-30% risk of cardiovascular disease in 10 years
- Moderate risk = 3-15% risk of cardiovascular disease in 10 years

*Very high risk (1): individuals with any of the following: coronary artery disease (CAD), stroke or transient ischaemia attack (TIA), peripheral artery disease (PAD), diabetes mellitus with smoking, diabetes mellitus with hypertension, diabetes mellitus with age>40 years, baseline TC >7.5mmol/L, first LDL-C >5mmol/l OR GFR<30mL/min/1.73m^2

**Very high risk (2): individuals with Framingham Score≥18 and male gender OR Framingham Score≥20 and female gender

#High risk (1): Framingham Score 13-17 and male gender OR Score 16-19 and female gender

##High risk (2): diabetes mellitus & age<40 years, GFR 30-59 mL/min/1.73m^2

µModerate risk: Framingham Score 4-12, Baseline LDL-C>1.8mmol/L and male gender OR Framingham Score 6-15, Baseline LDL-C>1.8mmol/L and female sex

Figure 2.5 shows the baseline and latest lipid profiles of all patients on LLA.

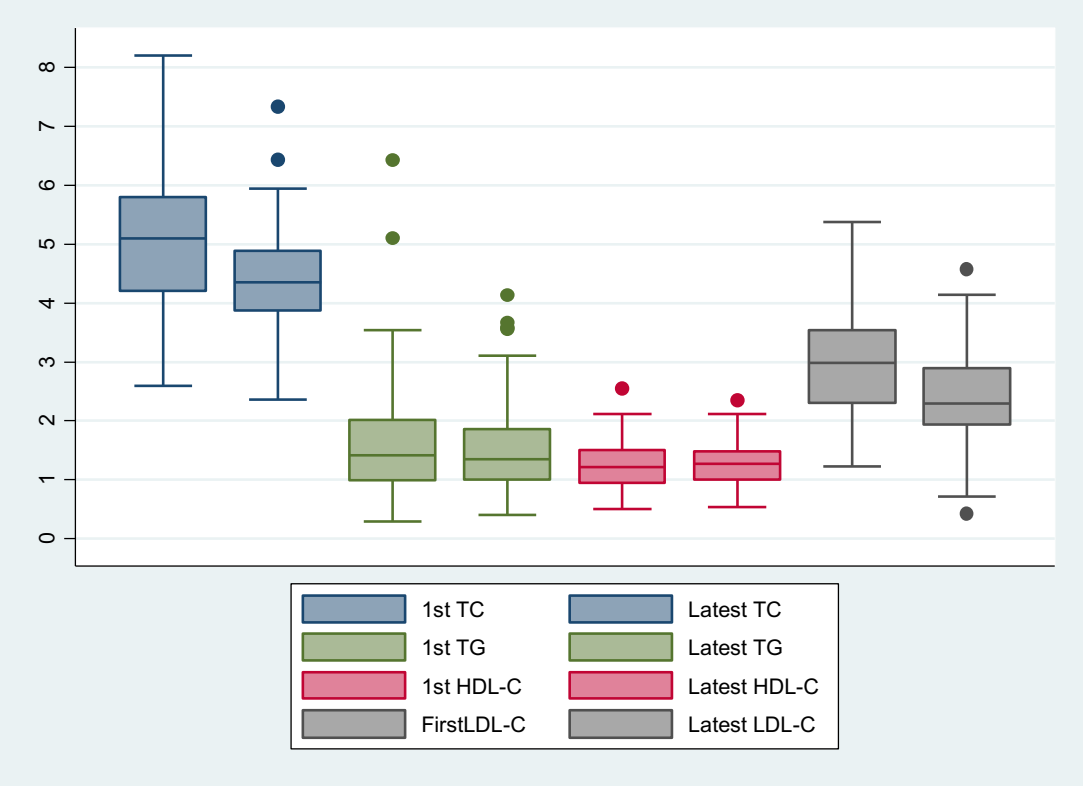

Figure 2.5: Baseline and latest lipid profiles among all patients taking LLAs (N=77)

Of the 127 patients who met criteria for dyslipidaemia at baseline, 59 were on LLAs. This was equivalent to a proportion of 46.5% (95% CI 37.9- 55.2%.) Based on patients' initial lipograms, the highest TC value calculated was 8.20mmol/L and the lowest value 2.40mmol/L. The LDL-C levels ranged from 0.68mmol/L to 5.38mmol/L. At the time of the audit 164 patients were eligible to receive lipid lowering agents (LLAs) as recommended by the LASSA guidelines. Of these, 77 were documented to be receiving LLAs – this was equivalent to a proportion of 47.2% (95% CI 37.8 – 53.2%). The range of TC values at the time of the audit was from 2.01mmol/L to 7.33mmol/L, while LDL-C levels ranged from 0.43mmol/L to 5.02mmol/L.

Overall, of the 77 individuals who were on LLAs, 22 (28.6%) were at the LDL-C target for very high-risk individuals or the LDL-C target for high-risk individuals as per LASSA recommendations. Of the 72 individuals who were considered very high-risk at baseline, 38 (52.8%) were on LLAs and 7 (18.4%) were at the LDL-C targets for very high risk individuals. Of the 36 individuals who were high risk at baseline, 13 (36.1%) were on LLAs and 10 (76.9%) were at the LDL-C target for high risk individuals. These results are displayed in **Figure 2.6**.

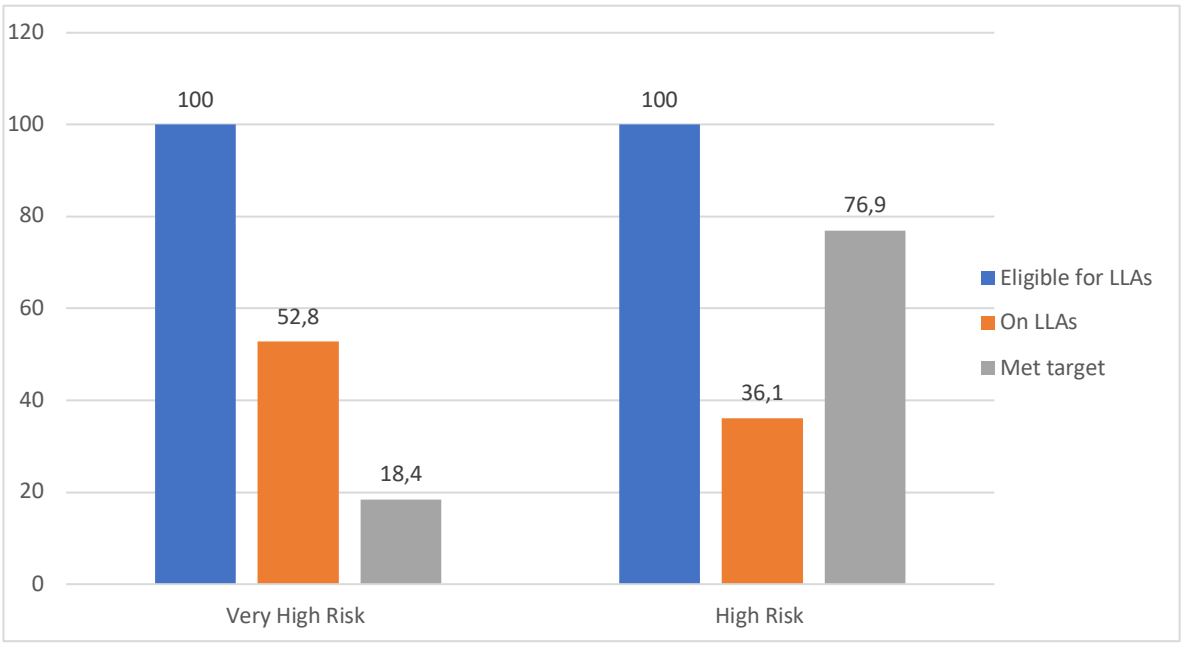

Figure 2.6 Proportions of individuals eligible for LLAs, received LLA and reached LASSA targets (N=72, N=36 for "very high risk" and "high risk" respectively)

Figure 2.7 shows the number of patients on LLAs reaching the LDL-C targets if the latest recommendations by the ESC/EAS were to be used. Of the 77 individuals who were started on LLAs, 5 (6.5%) attained the the ESC/EAS LDL-C targets. Of the 72 individuals who were considered very high-risk individuals at baseline, 38 (52.8%) were on LLAs and 2 (5.3%) reached the ESC/EAS targets. For 36 high-risk individuals, 13 (36.1%) were on LLAs and 1 (7.7%) met the target ESC/EAS LDL-C targets.

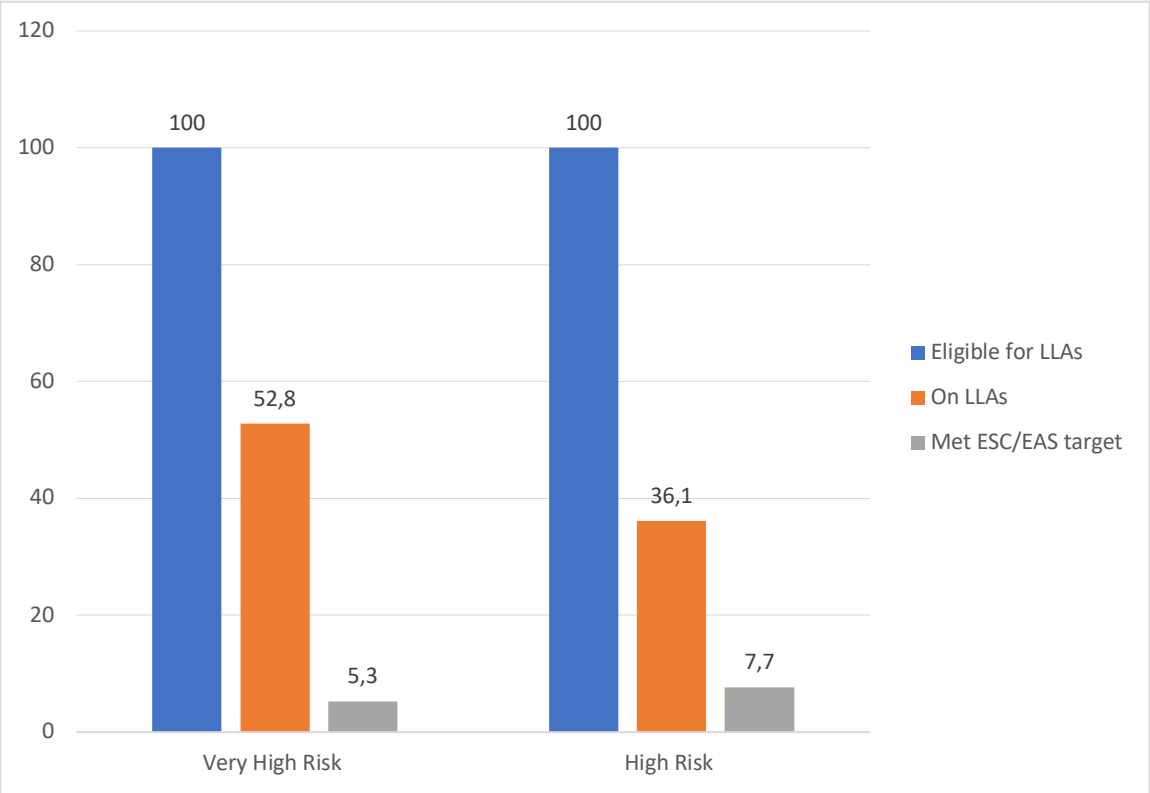

Figure 2.7 Proportions of individuals eligible for LLAs, who received LLAs and reached ESC/EAS targets (LDL<1.4 mmol/L) (N=72, N=36 for "very high risk" and "high risk" respectively)

4) Discussion

In patients with rheumatic diseases attending the Helen Joseph Hospital , dyslipidaemia was a common finding, irrespective of whether patients were on lipid lowering agents or not. This is the first South African study, to our knowledge, to report on the prevalence of dyslipidaemia in rheumatic diseases. The majority of the study population (52.5%, n=105) comprised of black African patients.

This study demonstrated that 63.5% (n=127) of patients had dyslipidaemia based on their initial lipograms measured at the rheumatology clinic, but less than half of these patients (46.5%, n=59) were receiving lipid lowering therapy. Unfortunately, the number of patients with monogenic dyslipidaemia such as familial hypercholesterolaemia were not identified due to insufficient documentation of physical examination findings in patient files, lack of availability of family history and genetic studies.

At the time of the audit, of the 164 patients (82%) who were eligible to receive lipid lowering therapy according to the LASSA guidelines[41], 77 (47.2%) were noted to be on treatment. From the patients who were considered very high risk (n=72) or high risk (n=36) based on their initial lipograms measured/Framingham scores, most did not reach TC/LDL-C targets recommended by LASSA (18.4%-76.9%) or the ESC/EAS (5.3%-7.7%).[42]

The lowering of LDL-C with statin therapy has been found to have benefits in the primary[45-48] and secondary prevention[49-51] of cardiovascular disease, particularly in reducing myocardial infarcts. The recommendation by the ESC/EAS in 2019 regarding the optimal levels of LDL-C to reduce cardiovascular risk demonstrated that further decreases of LDL-C <1.4mmol/L had no adverse effects.[42] In the population of patients, the majority (76.5%, n=153) had underlying co-morbidities which predispose them to cardiovascular disease. According to Framingham risk scores, 66.4% (n=109) of the patients eligible for lipid lowering therapy fell into very high risk or high risk groups based on their co-morbidities. Of these, 7.2% (n=11) patients already had established cardiovascular disease.

Shoenfeld and Sherer et al. noted that autoimmune connective tissue diseases are commonly associated with traditional risk factors of atherosclerosis including dyslipidaemia, obesity, metabolic syndrome, smoking and the tendency towards systemic inflammation.[9,52] It has

been demonstrated that the cardiovascular risk appears to be especially high in patients with RA, SLE, gout and PsA.[53,54] RA (63.5%, n=127), SLE (20.5%, n=41) and gout (6%, n=6) were the most prevalent conditions amongst the study population – which may explain the frequency of cardiovascular risk factors in the study.

In a South African study from 2018, cardiovascular co-morbidities hypertension (70%) and diabetes mellitus (47.4%) were commonly noted in patients with RA.[55] The majority of the study population were females (87%) with RA. The predominant gender in the analysis was also female (85.5%), with hypertension (86.3%) being the most common co-morbidity, followed by smoking (24.8%) and diabetes (22.2%). Similar findings were discovered in another South African study of a predominantly female population (94%) with SLE, where hypertension appeared to be the most frequently occurring co-morbidity at 43.5%.[56]

According to the South African Medical Research Council (MRC) demographic and health survey in 2016, hypertension was present in 46% of women and 44% of men ≥ age 15years.[57] The prevalence of hypertension also increased with age, with 84% of women ≥ 65 years being hypertensive. Blood pressure control was demonstrated to be poor amongst hypertensive patients on medication, with 80% of women and 87% of men displaying uncontrolled hypertension. Metabolic syndrome – a syndrome defined by a clustering of hypertension, insulin resistance, hyperglycaemia, elevated triglycerides, reduced HDL-C levels and central obesity[58], is becoming an increasingly recognised problem in sub-Saharan Africa. A recent systematic review by Faijer-Westerink et al. found the prevalence of metabolic syndrome to be 11.1-23.9%, in this region, depending on various criteria applied. In addition, the highest rates were noted to be in South Africa.[59] The incidence of metabolic syndrome was not sought for in the study population.

HIV, another commonly occurring disease in South Africa, was present in 12.4% of patients in the study, 9.3% of patients in the study by Lala et al[55] and 9.5% of patients in Greenstein et al's study[56] , suggesting that the presence of this disease may not as high in patients with rheumatic diseases when compared to the general population. According to the South African MRC 2016 survey, the prevalence of HIV in adults aged 15-49 years is 21%, being higher in women (27%) than men (14%).[57]

The use of certain medications for the treatment of rheumatic diseases have been shown to have an impact on cardiovascular mortality. In the study population, 93% (n=186) of patients were on DMARDs – with methotrexate (65.5%, n=131) being the most commonly prescribed medication, followed by chloroquine (26.5%, n=53). Methotrexate was found to have favourable effects on lipid profiles and cardiovascular mortality in RA patients from prospective studies[60-61], while hydroxychloroquine has also been shown to have similar benefits in both RA and SLE patients.[62-64] The regular use of DMARDs could possibly account for the low prevalence of established cardiovascular disease (7.2%, n=11) in the patients.

Another group of frequently used medications for the control of pain and inflammation in rheumatic disease patients, corticosteroids, on the other hand have an adverse effect on the metabolic and lipid profiles of patients. The use of corticosteroids was found in a surprisingly low proportion 11.5% (n=23) of the patients, suggesting that physicians are more aware of the adverse effects of long-term steroid use. Corticosteroids are associated with an increased risk of hypertension[65], ischaemic heart disease[66], ischaemic cerebrovascular events[67], hyperglycaemia and cardiovascular mortality overall[68-69] – these adverse effects have been particularly well studied in patients with RA,[65,67,68], which comprised the majority of the study population. Lastly, it is important to take into consideration the number of patients on protease inhibitors – as these have been shown to increase cholesterol levels.[70,71] In the study population, a minority of patients 1% (n=2) were on these antiretroviral drugs. This low incidence was once again most likely due to the fact that HIV disease had a lower prevalence in the study cohort.

Apart from treatments used in rheumatic diseases, the contribution of chronic systemic inflammation to dyslipidaemia and atherosclerotic cardiovascular disease must not be overlooked. Inflammatory marker levels such as CRP (normal value <10mg/L) and ESR (normal value 0-10mm/hour) have been found to correlate with blood pressure and total serum cholesterol values.[72] The median CRP level amongst the patients was 11mg/L (IQR 3.5-29.5) and ESR 21mm/hour (IQR 11-40), suggesting that patient disease activity scores were possibly not very high. Despite this, it has been shown that inflammation in various rheumatic diseases modifies lipid composition and function over time, leading to accelerated atherosclerosis – these include RA[31], SLE[33,73], gout[74], SSc[19,75], SS[35], OA[76], AS/PsA[27,37] and inflammatory myopathies.[29,30]

There are several limitations to the study. Sample selection for this study was reliant on the precision of written notes in patients' files, thus patients fulfilling the inclusion criteria may have been missed owing to poor documentation. The first lipograms of patients measured since attending the Helen Joseph Hospital rheumatology clinic may not have been representative of their baseline lipograms prior to ever starting lipid lowering therapy, as patients may have been initiated on treatment at other medical outpatient/local clinics before – particularly those with multiple concomitant cardiovascular-related co-morbidities. The timing of the follow-up/latest measured lipograms of patients was not noted, making it difficult to interpret whether patients were given reasonable amounts of time to reach cholesterol targets – as the time taken to see full treatment effects of statins can take up to 4 weeks.

In addition, patient disease activity scores were not measured or correlated with the timing of the measurement of lipograms. As mentioned, the lipid profiles of rheumatic disease patients often favour towards atherogenicity[12-30] particularly when disease activity and inflammation are uncontrolled.[9,19,27,29-39] This therefore confounds whether dyslipidaemia in patients was contributed to from poor control of disease activity or as a result of inadequate treatment with LLAs. The study also included a heterogenous group of patients with various rheumatic diseases and it is important to bear in mind that the cardiovascular risk conferred by these diseases is not necessarily equivalent.

As this was a retrospective review, not all causes of dyslipidaemia could be screened for – there was thus a potential for missing secondary causes of dyslipidaemia such as (untreated) hypothyroidism and nephrotic syndrome. Patient adherence to treatment and possible side effects experienced also not recorded, as pill counts were not done and dispensing records not followed. The main cardiovascular risk score calculator used in the study was the Framingham score, which may not be an accurate determinant in a population of Sub-Saharan African patients.

The study population included patients attending the rheumatology clinic at Helen Joseph Hospital only and comprised of a small sample size – and thus may not be representative of the entire South African population. However, this study provided insight into the problem of dyslipidaemia amongst patients with rheumatic diseases, added valuable information to the existing body of knowledge and awareness to healthcare practitioners treating such patients regarding the importance of lipid management. The development of cardiovascular risk

scoring tools and optimal lipid targets based appropriately on individual populations across Sub-Saharan Africa may be an area of future research to explore.

5) Conclusion

The prevalence of dyslipidaemia was high amongst patients with rheumatic diseases attending the Helen Joseph hospital rheumatology clinic, but the majority of patients were not on LLAs and did not meet TC/LDL-C targets recommended by local or international guidelines. Traditional cardiovascular risk related co-morbidities were present in a significant proportion of patients, with hypertension being the most frequently occurring disease – followed by smoking and diabetes mellitus. Although the majority of the study population were on DMARDs and corticosteroids were minimally prescribed, this did not appear to contribute greatly in lowering cardiovascular risks or exerting favourable effects on patient lipid profiles.

Although inflammatory markers such as CRP and ESR levels were not uniformly markedly elevated, it is important to remember that the process of systemic inflammation is chronic and often fluctuates in rheumatic diseases – which in turn leads to lipid modifications and accelerated atherosclerosis over time. It is therefore imperative that clinicians treating rheumatological patients ensure the tight control of inflammation, the driver of adverse lipid derangements, and aggressively treat dyslipidaemia according to national guidelines. Furthermore, owing to the relationship between inflammation and lipids, rheumatic disease itself should perhaps be considered as an independent cardiovascular risk equivalent to other traditional risk factors.

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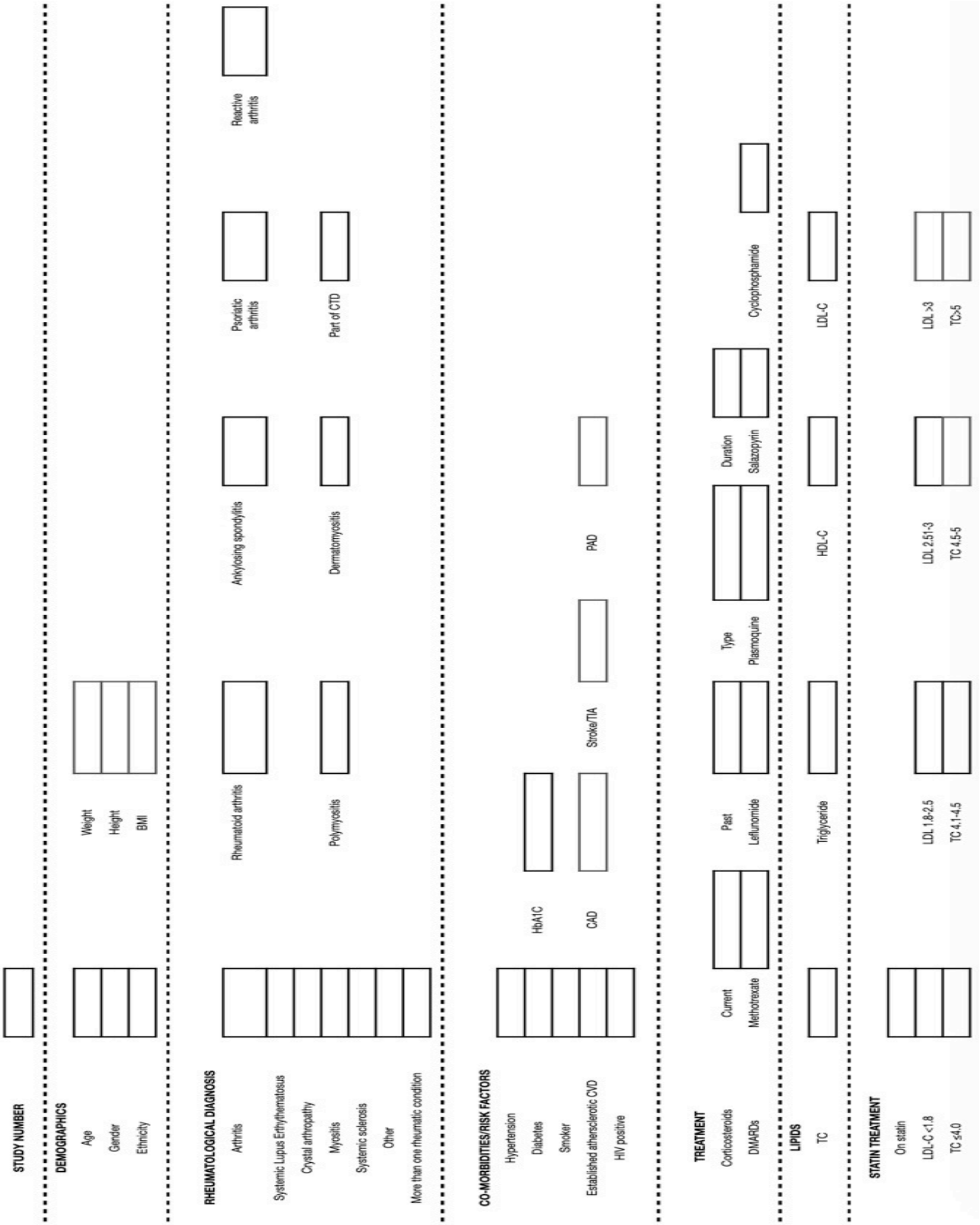
CHAPTER 3: APPENDICES

Appendix i: Data collection sheet



Appendix ii: 2010 ACR/EULAR Classification Criteria for RA

Definite RA is based on:

- The presence of synovitis in at least 1 joint
- The absence of an alternative diagnosis which better explains the synovitis
- A score of ≤6/10 from the domains below

Number and site of joints involved	
1 large joint	0
2-10 large joints	1
1-3 small joints (± involvement of large joints)	2
4-10 small joints (± involvement of large joints)	3
>10 joints + at least 1 small joint	5
Serological markers	
Negative RF + negative ACPA	0
Low positive RF or ACPA (≤ 3 x upper limit of normal)	2
High positive RF or ACPA (>3 x upper limit of normal)	3
Acute phase reactants	
Normal CRP + normal ESR	0
Elevated CRP or elevated ESR	1
Symptom duration	
≤6 weeks	0
≥6 weeks	1

- The above criteria are best used for patients presenting with early disease
- In addition to these criteria, fulfilling the following also classifies a patient as having RA:
  1) Patients with erosions typical of RA with a prior history consistent with fulfilment of the above criteria
  2) Patients with disease of long-standing duration, either active or inactive (with/without treatment), who have previously satisfied the above classification criteria based on retrospectively available data

Appendix iii: 2019 EULAR/ACS Classification Criteria for SLE

- The 2019 EULAR/ACR classification criteria includes a positive ANA at least once as an obligatory entry criterion
- This is followed by additive weighted criteria grouped into 7 clinical and 3 immunologic domains, weighted from 2-10
- Patients require ≥10 points

Entry criterion

Antinuclear antibodies at a titre of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE

If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.

Occurrence of a criterion on at least 1 occasion is sufficient.

SLE classification requires at least 1 clinical criterion and ≥10 points.

Criteria need not occur simultaneously.

Within each domain, only the highest weighted criterion is counted toward the total score*.

CLINICAL DOMAINS AND CRITERIA	WEIGHT	IMMUNOLOGY DOMAINS AND CRITERIA	WEIGHT
Constitutional		**Antiphospholipid antibodies**	
Fever	2	Anti-cardiolipin antibodies OR Anti-β2GP1 antibodies OR Lupus anticoagulant	2
Hematologic		**Complement proteins**	
Leukopenia	3	Low C3 OR low C4 3	3
Thrombocytopenia	4	Low C3 AND low C4	4
Autoimmune hemolysis	4		

Neuropsychiatric Delirium Psychosis Seizure	 2 3 5	**SLE-specific antibodies** Anti-dsDNA antibody OR Anti-Smith antibody	 6
Mucocutaneous Non-scarring alopecia Oral ulcers Subacute cutaneous OR discoid lupus Acute cutaneous lupus	 2 2 4 6		
Serosal Pleural or pericardial effusion Acute pericarditis	 5 6		
Musculoskeletal Joint involvement	 6		
Renal Proteinuria >0.5g/24h Renal biopsy Class II or V lupus nephritis Renal biopsy Class III or IV lupus nephritis	 4 8 10		
Total score			

↓

Classify as Systemic Lupus Erythematosus with a score of ≥10 if entry criterion fulfilled

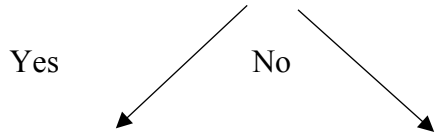
- Note: *additional criteria within the same domain will not be counted

Appendix iv: 2015 ACR/EULAR Gout Classification Criteria

- Classification criteria for gout were developed in 2015 by the ACR/EULAR
- Prior to applying the classification criteria to patients, ACR/EULAR have developed entry and sufficient criteria to first be used in order to identify only those with symptomatic disease:

Entry criterion:

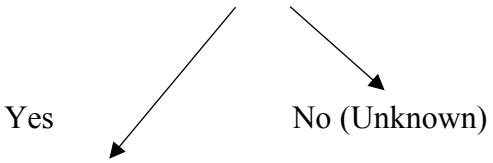
At least 1 episode of swelling, pain or tenderness in a peripheral joint or bursa?



Sufficient Criterion

Presence of MSU crystals in a symptomatic joint/bursa/tophus

Do not score



Subject has gout

Use classification criteria scoring below

- Criteria to be used if sufficient criterion are not met (score ≥8 classified as gout):

Criteria	Categories	Score
CLINICAL CRITERIA		
Pattern of joint/bursa involvement during symptomatic episodes(s) ever	Ankle OR midfoot (as part of monoarticular or oligoarticular episode without involvement of 1st metatarsophalangeal joint)	1

	Involvement of 1st metatarsophalangeal joint (as part of monoarticular or oligoarticular episode)	2
Characteristics of symptomatic episode(s) ever -Erythema overlying affected joint -Can't bear touch/pressure to affected joint -Great difficulty with walking/inability to use affected joint	1 Characteristic	1
	2 Characteristics	2
	3 Characteristics	3
Time course of episode(s) ever -Presence (ever) ≥2, irrespective of anti-inflammatory treatment: Time to maximal pain <24 hours Resolution to symptoms ≤14 days Complete resolution (to baseline) between symptomatic episodes	1 Typical episode	1
	Recurrent typical episodes	2
Clinical evidence of tophus -Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon, bursae, finger pads, tendons	Present	4
LABORATORY		
Serum **urate** -Measured by uricase method	<4mg/dL (<0.24mM)	-4
	6 - <8 mg/dL (0.36- <0.48mM)	2
	8 - <10mg/dL (0.48 - <0.60mM)	3
	≥10mg/dL (≥0.60mM)	4
Synovial fluid examination for **MSU** crystals of a symptomatic (ever) joint/bursa	Negative	-2

IMAGING		
Imaging evidence of **urate deposition** in symptomatic (ever) joint/bursa -Ultrasound evidence OR DECT demonstrating urate deposition	Present (either modality)	4
Imaging evidence of **gout-related joint damage** -Conventional radiography of the hands and/or feet demonstrates at least 1 erosion	Present	4

Appendix v: The 2013 ACR/EULAR Criteria for the Classification of SSc

- If a patient presents with skin thickening of the fingers extending proximal to the metacarpophalangeal joint, it is considered a sufficient criterion and a diagnosis of SSc can be made
- If skin thickening is not present, the criteria below can be used to assist with a diagnosis
- Patients with a total score of ≥9 are considered to have confirmed SSc:

Item	Sub-item(s)	Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)	-	9
Skin thickening of the fingers (only count the higher score)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions (only count the higher score)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease (maximum score 2)	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	-	3
SSc-related autoantibodies (anticentromere, anti-topoisomerase [anti-Sci-70], anti-RNA polymerase III) (maximum score 3)	Anticentromere Anti-topoisomerase I Anti-RNA polymerase III|	3

Definitions of items/sub-items in the ACR/EULAR criteria for the classification of systemic sclerosis

Item	Definition
Skin thickening	Skin thickening or hardening not due to scarring after injury, trauma, etc.
Puffy fingers	Swollen digits – a diffuse, usually nonpitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are tapered distally with the tissues following the contours of the digital bone and joint structures. Swelling of the digits obliterates these contours. Not due to other causes such as inflammatory dactylitis
Fingertip ulcers or pitting scars	Ulcers or scars distal to or at the proximal interphalangeal joint not thought to be due to trauma. Digital pitting scars are depressed areas at digital tips as a result of ischaemia, rather than trauma or exogenous causes
Telangiectasia	Telangiectasiae are visible macular dilated superficial blood vessels, which collapse upon pressure and fill slowly when pressure is released. Telangiectasiae in a scleroderma-like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or are large mat-like telangiectasiae. Distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels
Abnormal nailfold capillary pattern consistent with SSc	Enlarged capillaries and/or capillary loss with or without pericapillary haemorrhages at the nailfold. May also be seen on the cuticle
Pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right-sided heart catheterisation according to standard definitions
Interstitial lung disease	Pulmonary fibrosis seen on high-resolution CT or chest radiography, most pronounced in the basilar portions of the

	lungs, or occurrence of 'Velcro' crackles on auscultation, not due to another cause such as congestive heart failure
Raynaud's phenomenon	Self-reported or reported by a physician, with at least a 2-phase colour change in finger(s) and often toe(s) consisting of pallor, cyanosis, and/or reactive hyperaemia in response to cold exposure or emotion; usually one phase is pallor
SSc-related auto-antibodies	Anticentromere antibody or centromere pattern seen on antinuclear antibody testing, anti–topoisomerase I antibody (also known as anti–Scl-70 antibody), or anti– RNA polymerase III antibody. Positive according to local laboratory standards

Appendix vi: 2016 ACR/EULAR Classification Criteria for Primary Sjögren's syndrome

The classification of primary Sjögren's syndrome applies to anyone who:

1) Fulfills the inclusion criteria
2) Does not have any of the conditions listed in the exclusion criteria
3) Scores ≥4 from 5 criteria items

1) Inclusion criteria

-At least 1 symptom of ocular or oral dryness – defined as a positive response to at least 1 of the following questions:

- Have you had daily, persistent, troublesome dry eyes for more than 3 months?
- Do you have a recurrent sensation of sand or gravel in the eyes?
- Do you use tear substitutes more than 3 times a day?
- Have you had a daily feeling of dry mouth for more than 3 months?
- Do you frequently drink liquids to aid in swallowing dry food?

-OR in whom there is suspicion of Sjögren's syndrome from the EULAR SS Disease Activity Index questionnaire: at least 1 domain with positive item

2) Prior diagnosis of any of the following conditions would exclude the diagnosis of Sjögren's syndrome due to overlapping clinical features or interference with criteria tests:

- History of head and neck radiation treatment
- Active hepatitis C infection (with positive PCR)
- Acquired immunodeficiency syndrome
- Sarcoidosis
- Amyloidosis
- Graft-versus-host disease
- IgG4-related disease

3) Criteria items:

Item	**Weight/score**

Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥1 foci/4 mm^{2*}	3
Anti-Ro/SSA positive	3
Ocular staining score ≥5 (or van Bijsterveld score ≥4) in at least one eye^{+}	1
Schirmer test ≤5 mm/5 minutes in at least one eye^{+}	1
Unstimulated whole saliva flow rate ≤0.1 mL/minute^{+}	1

Of note:

* The histopathologic examination should be performed by a pathologist with expertise in the diagnosis of focal lymphocytic sialadenitis and focus score count (based on number of foci/4mm^2)

$^{+}$ Patients who are normally taking anticholinergic drugs should be evaluated for objective signs of salivary hypofunction and ocular dryness after a sufficient interval without these medications in order for these components to be a valid measure of oral and ocular dryness

Appendix vii: ACR Classification of OA

1986 ACR Classification of OA of the Knee: Idiopathic OA of the Knee

Clinical and laboratory	Clinical and radiographic	Clinical
Knee pain + at least 5 of 9: Age >50 years Stiffness <30 minutes Crepitus Bony tenderness Bony enlargement No palpable warmth ESR<40mm/hour RF<1:40 *SF OA -92% sensitive -75% specific	Knee pain + at least 1 of 3: Age >50 years Stiffness <30 minutes Crepitus + Osteophytes -91% sensitive -86% specific	Knee pain + at least 3 of 6: Age >50 years Stiffness <30 minutes Crepitus Bony tenderness Bony enlargement No palpable warmth -95% sensitive -69% specific Alternative diagnostic. criteria: 4 of 6 of above -84% sensitive -89% specific

*Synovial fluid signs of OA (SF OA): clear, viscous, or white blood cell count <2000/mm^3)

-Reference: R. Altman, E. Asch, D. Bloch, G. Bole, D. Borenstein, K. Brandt, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039-049

1990 ACR Classification of OA of the Hand

Hand pain, aching, or stiffness and 3 or 4 of the following features:

- Hard tissue enlargement of 2 or more of 10 selected joints
- Hard tissue enlargement of 2 or more distal interphalangeal (DIP) joints
- Fewer than 3 swollen metacarpophalangeal (MCP) joints
- Deformity of at least 1 of 10 selected joints

-The 10 selected joints are the second and third DIP, the second and third proximal interphalangeal, and the first carpometacarpal joints of both hands
-This classification method yields a sensitivity of 94% and a specificity of 87%

-Reference: Altman R, Alarcón G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum 1990;33:1601-10

1991 ACR Classification of OA of the Hip: Traditional Format
-Combined clinical (history, physical examination, laboratory) and radiographic classification criteria for OA of the hip
-This classification method yields a sensitivity of 89% and specificity of 91%

Hip pain and at least 2 of the following 3 features:

- ESR<20 mm/hour
- Radiographic femoral or acetabular osteophytes
- Radiographic joint space narrowing (superior, axial, and/or medial)

-Reference: R. Altman, G. Alarcon, D. Appelrouth, D. Bloch, D. Borenstein, K. Brandt, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991;34:505-514.

1991 ACR Classification of OA of the Hip: Tree Format
-Clinical (history, physical examination, laboratory) classification criteria for OA of the hip
-This classification method yields a sensitivity of 86% and specificity of 75%

1. Hip pain

   and

   2a. Hip internal rotation <15°
   and

2b. ESR ≤45mm/hour (if ESR not available, substitute hip flexion <115°)

OR

3a. Hip internal rotation ≥15°
and
3b. Pain on hip internal rotation
and
3c. Morning stiffness of the hip ≤60 minutes
and
3d. Age > 50 years

-Reference: R. Altman, G. Alarcon, D. Appelrouth, D. Bloch, D. Borenstein, K. Brandt, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991;34:505-514.

Appendix viii: The Assessment of SpondyloArthritis international Society (ASAS) Classification Criteria for Spondyloarthritis

- SpA is broadly divided into 2 groups:
  -Axial SpA (axSpA): SpA with predominantly axial involvement. This includes AS with radiographic sacroiliitis on X-rays and axSpA without X-ray evidence of sacroiliitis i.e. non-radiographic axSpA (nr-axSpA)
  -SpA with predominant peripheral involvement is termed "peripheral SpA" and usually comprises mainly symptoms of peripheral enthesitis, peripheral arthritis and/or dactylitis
- There are 2 sets of criteria developed for the classification of SpA – the 2009 ASAS axial SpA criteria and the 2011 ASAS peripheral SpA criteria
- In patients with predominantly axial involvement i.e. back pain ±peripheral manifestations, the ASAS axial SpA criteria should be utilised
- For patients with only peripheral manifestations, the ASAS peripheral SpA criteria are used

Features of criteria	**2009 ASAS axial SpA criteria**	**2011 ASAS peripheral SpA criteria**
Inclusion/entry criteria	≥ 3 months' back pain before age 45 years and either: -sacroiliitis on imaging (radiographs or MRI) + ≥1 other SpA feature (imaging arm) OR -HLA-B27 positive + ≥2 other SpA features (clinical arm)	Arthritis, enthesitis or dactylitis plus: - ≥1 SpA feature marked with [a] OR - ≥2 SpA features marked with [b]
SpA features to be considered		
IBP	√	√[b] (ever)
Arthritis	√	√[b]
Dactylitis	√	√[b]
Enthesitis (heel)	√	√[b]

Good response to NSAIDs	√	x
Psoriasis	√	√[a]
Inflammatory bowel disease	√	√[a]
Uveitis	√	√[a]
Preceding infection	x	√[a]
Positive family history for SpA	√	√[b]
HLA-B27	√	√[a]
Elevated CRP	√	x
Sacroiliitis	Not applicable (part of inclusion/entry criteria)	√[a] (radiographic* or MRI detected)

*Radiographic sacroiliitis is considered present when at least grade 2 bilaterally or grade 3-4 unilaterally

Appendix ix: 2006 ClASsification criteria for Psoriatic ARthritis (CASPAR criteria)

- The original classification criteria for psoriatic arthritis were from Moll and Wright in 1973
- Since then, several other criteria have been proposed but there is no universal consensus regarding which are best
- The CASPAR criteria were developed for the use of clinical research, and are reported to have a specificity of 98.7% and a sensitivity of 91.4%
- A patient is classified as having psoriatic arthritis if he/she has inflammatory articular disease (joint, spinal, enthesal) with ≥3 points from the 5 categories below:

Feature	Point
1. **Evidence** of current **psoriasis**, a personal history of psoriasis, or a family history of psoriasis:	
-Current psoriasis: psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist	2
-Personal history of psoriasis: a history of psoriasis which may be obtained from a patient, family physician, dermatologist, rheumatologist or other qualified healthcare provider	1
-Family history: history of psoriasis in first- or second- degree relative according to patient report	1
2.Typical psoriatic **nail lesions** including oncholysis, pitting and hyperkeratosis noted on current physical examination	1
3. A **negative** test result for the presence of **rheumatoid factor** by any method apart from latex, but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range	1
4. Current **dactylitis** (defined as a swelling of an entire digit) or a history of dactylitis recorded by a rheumatologist	1
5. Radiographic evidence of a **juxta-articular new bone formation**, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand/foot.	1

Appendix x: 2017 EULAR/ACR Classification Criteria for Adult Juvenile Idiopathic Inflammatory Myopathies and Their Major Subgroups

- The EULAR/ACR criteria classify patients as having "definite", "probable" and "possible" disease according to a score and respective probability of disease
- 2 Different scoring systems can be used depending on if a muscle biopsy has been done
- Adult patients who present with pathognomic skin rashes are considered to have dermatomyositis without a muscle biopsy
- A classification tree can be utilised for the subgroups of idiopathic inflammatory myopathy in order to assist in distinguishing between adult and juvenile idiopathic inflammatory myopathy and then subclassify patients into dermatomyositis, polymyositis, amyopathic myositis or inclusion body myositis
- If no better explanation for the signs and symptom exist, the classification criteria below can be used:

Variable	Score points		Definition
	Without muscle biopsy	With muscle biopsy	
Age of onset			
Age of onset of first symptom assumed to be related to the disease ≥18 years and <40 years	1.3	1.5	18 ≤ age (years at onset of first symptom assumed to be related to the disease <40
Age of onset of first symptom assumed to be related to the disease ≥40 years	2.1	2.2	Age (years) at onset of first symptom assumed to be related to the disease ≥40
Muscle weakness			
Objective symmetric weakness, usually progressive, of the proximal upper extremities	0.7	0.7	Weakness of proximal upper extremities as defined by manual muscle testing or other objective strength testing, which is

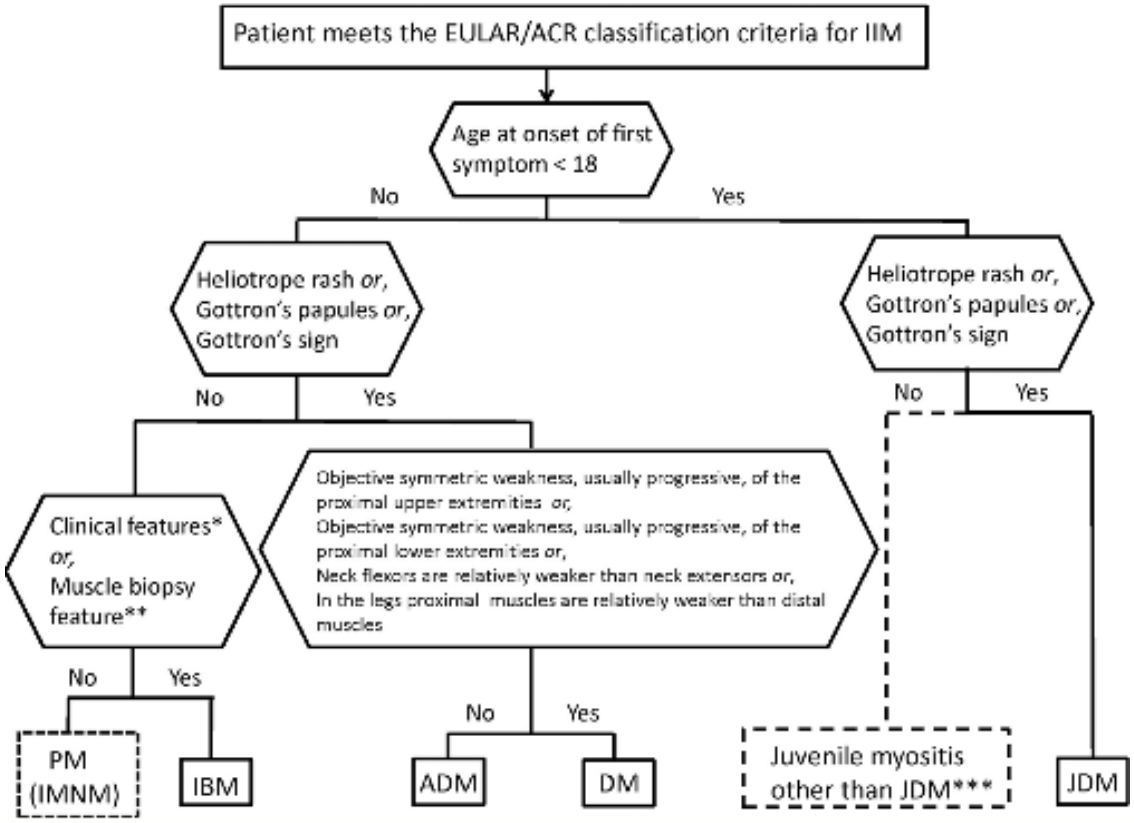
			present on both sides and is usually progressive over time
Objective symmetric weakness, usually progressive, of the proximal lower extremities	0.8	0.5	Weakness of proximal lower extremities as defined by manual muscle testing or other objective strength testing, which is present on both sides and is usually progressive over time
Neck flexors are relatively weaker than neck extensors	1.9	1.6	Muscle grades for neck flexors are relatively lower than neck extensors as defined by manual muscle testing or other objective strength testing
In the legs, proximal muscles are relatively weaker than distal muscles	0.9	1.2	Muscle grades for proximal muscles in the legs are relatively lower than distal muscles in the legs as defined by manual testing or other objective strength testing
Skin manifestations			
Heliotrope rash	3.1	3.2	Purple, lilac-coloured or erythematous patches over the eyelids or in a periorbital distribution, often associated with periorbital oedema
Gottron's papules	2.1	2.7	Erythematous to violaceous papules over the extensor surfaces of joints, which are sometimes scaly. May occur over the finger joints, elbows, knees, malleoli and toes
Gottron's sign	3.3	3.7	Erythematous to violaceous macules over the extensor surfaces of joints, which are not palpable
Other clinical manifestations			

Dysphagia or oesophageal dysmotility	0.7	0.6	Difficulty in swallowing or objective evidence of abnormal motility of the oesophagus
Laboratory measurements			
Anti-Jo-1 (anti-histidyl-transfer RNA synthetase) autoantibody present	3.9	3.8	Autoantibody testing in serum performed with standardized and validated test, showing positive result
Elevated serum levels of creatine kinase (CK)* OR lactate dehydrogenase (LDH)* OR aspartate aminotransferase (ASAT/AST/SGOT)* OR alanine aminotransferase (ALAT/ALT/SGPT)*	1.3	1.4	The most abnormal test values during the disease course (highest absolute level of enzyme) above the relevant upper limit of normal
Muscle biopsy features – presence of:			
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		1.7	Muscle biopsy reveals endomysial mononuclear cells abutting the sarcolemma of otherwise healthy, non-necrotic muscle fibres, but there is no clear invasion of the muscle fibres
Perimysial and/or perivascular infiltration of mononuclear cells		1.2	Mononuclear cells are located in the perimysium and/or located around blood vessels (in either perimysial or endomysial vessels)
Perifascicular atrophy		1.9	Muscle biopsy reveals several rows of muscle fibres, which are smaller in the perifascicular region than fibres more centrally located
Rimmed vacuoles		1.3	Rimmed vacuoles are bluish by haematoxylin and eosin staining and

			reddish by modified Gomori trichrome stain

*Serum levels above the upper limit of normal

- Definite IIM (≥90% probability): total score of ≥7.5 without muscle biopsy and ≥8.7 with muscle biopsy
- Probably IIM (≥55 - <90% probability): score ≥5.5 without muscle biopsy and ≥6.7 with muscle biopsy
- Possible IIM (≥50 - <55% probability): minimum score 5.3 without muscle biopsy and minimum score 6.5 with muscle biopsy
- If a patient meets the classification criteria or probable IIM, he/she can be further subclassified using the classification tree below:



* For inclusion body myositis (IBM) classification, one of the following is required for classification: finger flexor weakness and response to treatment: not improved (∗), or muscle

biopsy: rimmed vacuoles (**). *** = Juvenile myositis other than juvenile dermatomyositis (JDM) was developed based on expert opinion. IMNM and hypomyopathic dermatomyositis were too few to allow subclassification

Appendix xi: Framingham Risk Assessment Chart

Framingham 10-year risk assessment chart for patients without diabetes or severe monogenic disorders (e.g. FH) indicates risk of total CVD (coronary heart disease, stroke, peripheral artery disease or heart failure).

Estimate of 10-year risk of CVD for men

Age (yrs)	Points
30 - 34	0
35 - 39	2
40 - 44	5
45 - 49	6
50 - 54	8
55 - 59	10
60 - 64	11
65 - 69	12
70 - 74	14
75 years or older	15

Total cholesterol (mmol/l)	Points
<4.10	0
4.10 - 5.19	1
5.20 - 6.19	2
6.20 - 7.20	3
>7.20	4

HDL-cholesterol (mmol/l)	Points
≥1.50	-2
1.30 - 1.49	-1
1.20 - 1.29	0
0.90 - 1.19	1
<0.90	2

Systolic BP – untreated (mmHg)	Points
<120	-2
120 - 129	0
130 - 139	1
140 - 159	2
≥160	3

Systolic BP – on antihypertensive treatment (mmHg)	Points
<120	0
120 - 129	2
130 - 139	3
140 - 159	4
≥160	5

Smoker	Points
No	0
Yes	4

Estimate of 10-year risk of CVD for women

Age (yrs)	Points
30 - 34	0
35 - 39	2
40 - 44	4
45 - 49	5
50 - 54	7
55 - 59	8
60 - 64	9
65 - 69	10
70 - 74	11
75 years or older	12

Total cholesterol (mmol/l)	Points
<4.10	0
4.10 - 5.19	1
5.20 - 6.19	3
6.20 - 7.20	4
>7.20	5

HDL-cholesterol (mmol/l)	Points
≥1.50	-2
1.30 - 1.49	-1
1.20 - 1.29	0
0.90 - 1.19	1
<0.90	2

Systolic BP – untreated (mmHg)	Points
<120	-3
120 - 129	0
130 - 139	1
140 - 149	2
150 - 159	4
≥160	5

Systolic BP – on antihypertensive treatment (mmHg)	Points
<120	-1
120 - 129	2
130 - 139	3
140 - 149	5
150 - 159	6
≥160	7

Smoker	Points
No	0
Yes	3

Points total for men

Points total	10-year risk (%)
-3 or less	<1
-2	1.1
-1	1.4
0	1.6
1	1.9
2	2.3
3	2.8
4	3.3
5	3.9
6	4.7
7	5.6
8	6.7
9	7.9
10	9.4
11	11.2
12	13.2
13	15.6
14	18.4
15	21.6
16	25.3
17	29.4
18 or more	>30

Points total for women

Points total	10-year risk (%)
-2 or less	<1%
-1	1.0
0	1.1
1	1.5
2	1.8
3	2.1
4	2.5
5	2.9
6	3.4
7	3.9
8	4.6
9	5.4
10	6.3
11	7.4
12	8.6
13	10.0
14	11.6
15	13.5
16	15.6
17	18.1
18	20.9
19	24.0
20	27.5
20 or more	>30

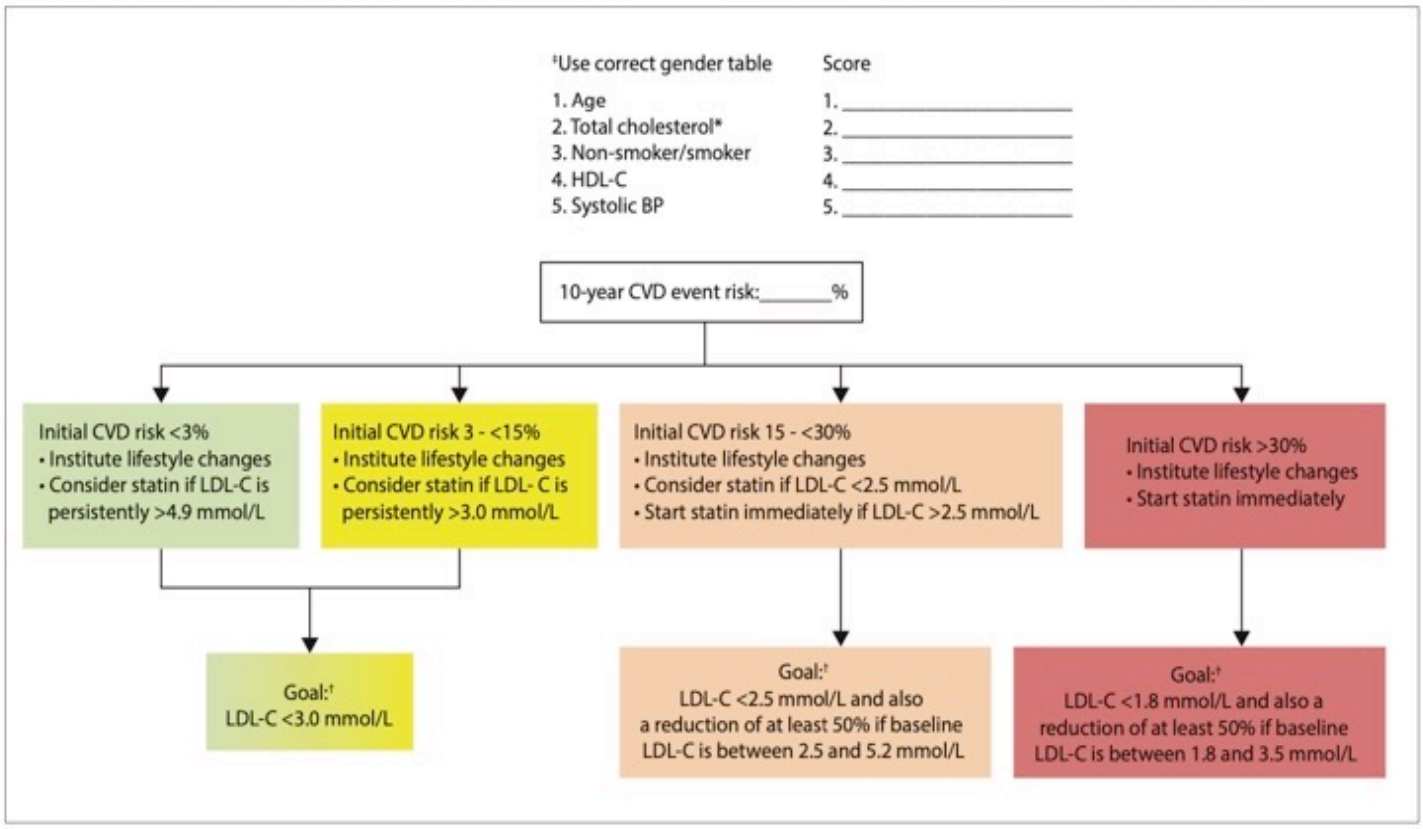
*Point totals indicate the 10-year risk of cardiovascular disease (coronary, cerebrovascular and peripheral arterial disease, and heart failure).

Low risk Moderate risk High risk Very high risk

Adapted from Mosca L., *et al.*, Effectiveness-based guidelines for the prevention of cardiovascular disease in women 2011 update: A guideline from the American Heart Association. Circulation 2011;123:1243-1262[24] and D'Agostino RB, *et al.*, General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743-753.[25]

Appendix xii: Recommended LASSA management and cholesterol goals according to Framingham risk score

Management and cholesterol goals according to Framingham risk score



HDL-C = high-density lipoprotein cholesterol; BP = blood pressure; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

**Total cholesterol level is used to assign risk score and may be used for follow-up cholesterol measurement in patients on drug therapy, but LDL-C remains the target of treatment.*

†Pharmacological treatment is required if LDL-C remains above these levels despite lifestyle modification. At present, statins are first-line drugs for lowering LDL cholesterol.

‡Secondary causes of dyslipidaemia should be excluded before progressing to risk assessment.

§See limitations of Framingham Risk Assessment Score listed below.

§ Limitations of the Framingham Risk Assessment Score Charts

1. Patients who are classified in the very high-risk category do not require further risk scoring for management decisions. Risk will also be underestimated in patients who have a markedly elevated single risk factor (e.g. severe hypertension: systolic BP >180 mmHg and/or diastolic BP >110 mmHg), or associated target organ damage.

2. Severe hypercholesterolaemia and hypertriglyceridaemia: The Framingham Risk Assessment Chart is only accurate up to TC values of 7.25 mmol/L and cannot be used for patients with TC levels above this value. It also does not apply to hypertriglyceridaemia (triglycerides >5 mmol/L).

3. Family history of early atherosclerotic disease is not considered. Clinicians should use their judgement in deciding whether to place a patient with an impressive family history in the high-risk category regardless of their Framingham Score, or avoid calculating risk in these patients.

4. Despite these factors being important risk factors for CVD, impaired glucose tolerance, abdominal obesity and lipoprotein(a) (Lp(a)) >50 mg/dL are not considered in the risk score.

Appendix xiii: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Xiaohui Chen

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M181109

NAME: (Principal Investigator)	Dr Xiaohui Chen
DEPARTMENT:	Internal Medicine Helen Joseph Hospital Dep of Internal Medicine and Rheumatology
PROJECT TITLE:	Dyslipidaemia in Rheumatic Diseases
DATE CONSIDERED:	30/11/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof F. Raal and Dr M. Reddy
APPROVED BY:	Dr. CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	18/12/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore be due in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 18/12/2018

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix xiv: Plagiarism and Turn-it-in report

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Xiaohui Chen (Student number: 348081) am a student registered for the degree of Master of Medicine (MMed) in the academic year 2020.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:  Date: 23/10/2020

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