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Cardiovascular Disease Screening and Clinical Predictive Models in Axial Spondyloarthropathies

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Summary

This thesis utilizes several approaches to assess cardiovascular disease (CVD) risk in Axial Spondyloarthritis (AxSpA) patients, focusing on the utility of screening tools, imaging, and biomarkers.

1. **ASRI Registry Analysis**: Data from the Ankylosing Spondylitis Registry of Ireland (ASRI) was analysed to assess the prevalence of cardiovascular disease and associated risk factors in a large cohort of AxSpA patients. This provided a comprehensive view of CVD risk in this population, identifying both traditional risk factors and their impact on cardiovascular outcomes.
2. **Literature Review of Cardiovascular Screening Methods**: A thorough review of the literature explored various cardiovascular screening techniques, including imaging modalities and novel biomarkers. The review particularly focused on imaging techniques and biomarkers to assess for subclinical atherosclerosis.
3. **Assessment of Readily Accessible Biomarkers**: While the literature identified novel biomarkers for CVD risk in AxSpA, there was a lack of research on more readily available and cost-effective biomarkers. This led us to investigate the potential association between common biomarkers—such as urate, troponin, BNP, ferritin, fibrinogen, CRP, and ESR—and subclinical atherosclerosis in AxSpA patients.
4. **Carotid Doppler Ultrasound Screening for Subclinical Atherosclerosis**: Based on findings from the literature review, AxSpA patients were screened for subclinical atherosclerosis using carotid Doppler ultrasound. The study assessed how many patients were reclassified into higher cardiovascular risk categories.
5. **Analysis of Demographic and Disease Characteristics**: An in-depth analysis was performed to determine the correlation between demographic data, disease characteristics (such as disease activity and duration), cardiovascular markers, and the biomarkers studied. This analysis aimed to identify significant associations with subclinical atherosclerosis in the AxSpA cohort.

Major Findings

1. **ASRI Findings on Cardiovascular Risk**: The ASRI registry analysis revealed a high prevalence of cardiovascular risk factors in AxSpA patients, with **21.7%** having hypertension, **15.8%** having hyperlipidaemia, and **29%** classified as obese. By comparison, the Healthy Ireland Survey 2023 reported much lower rates in the general population in

Ireland, with 9% having diagnosed hypertension, 5% diagnosed with high cholesterol, and 21% classified as obese. These findings highlight the disproportionately elevated cardiometabolic risk in AxSpA and emphasise the need for more targeted cardiovascular assessment and management strategies.

2. **Literature Review Results**: The literature review identified various useful screening methods, with carotid Doppler ultrasound emerging as the most effective tool for detecting subclinical atherosclerosis in AxSpA patients. Its ability to identify both calcified and non-calcified plaques makes it a superior screening method compared to other imaging techniques. While the literature review revealed ongoing research into novel biomarkers to aid the detection of subclinical atherosclerosis and create CVD prediction models there was a noted lack of research looking at Readily Accessible Biomarkers
3. **Evaluation of Biomarkers:** Despite assessing commonly available biomarkers—urate, troponin, pro-nt-BNP, ferritin, fibrinogen, platelets, Vitamin D ,CRP, and ESR—none showed significant correlation with subclinical atherosclerosis in the AxSpA population. This suggests that more specific biomarkers, which are not yet readily accessible, may be needed to predict cardiovascular risk effectively in this group.
4. **Carotid Doppler Findings**: Screening with carotid Doppler ultrasound revealed that **11%** of patients had detectable carotid plaques. Additionally, 85% patients under the age of 60 were reclassified into higher cardiovascular risk categories using ASE criteria. This reclassification underscores the importance of early cardiovascular screening in AxSpA patients.
5. **Significant Associations in Analysis**: Upon analysing demographic and disease characteristics, it was found that certain cardiovascular markers and disease activity scores correlated with higher cardiovascular risk. However, no significant associations were found between subclinical atherosclerosis and the biomarkers evaluated.

Conclusion

This thesis demonstrates the urgent need for integrating cardiovascular screening into routine care for AxSpA patients. Current tools and biomarkers fall short in detecting subclinical atherosclerosis. Carotid Doppler ultrasound, as highlighted, is a valuable screening tool for identifying patients at higher cardiovascular risk. Additionally, developing AxSpA-specific cardiovascular risk models, incorporating both traditional risk factors and disease-specific markers, is needed for improving early detection and management of cardiovascular disease in this high-risk population.

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List Tables and Figures

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List of abbreviations

10^9/L – Cells per liter

AAU – Acute Anterior Uveitis

AS – Ankylosing spondylitis

ASDAS-CRP – Ankylosing Spondylitis Disease Activity Score - C-reactive Protein

ASE – The American Society of Echocardiography

ASQoL – Ankylosing Spondylitis Quality of Life

ASRI – Ankylosing Spondylitis Registry of Ireland

AxPsA – Axial psoriatic arthritis

AxSpA – Axial spondyloarthritis

BASDAI – Bath Ankylosing Spondylitis Disease Activity Index

BASMI – Bath Ankylosing Spondylitis Metrology Index

bDMARDs – Biological Disease Modifying Antirheumatic Drugs

BMI – Body mass index

BSRBR – British Society for Rheumatology Biologics Register

BSRBR-AS – British Society for Rheumatology Biologics Register in Ankylosing Spondylitis

CAD – Coronary artery disease

CCA – Common carotid artery

CIMT – Carotid intima-media thickness

cIMT – Carotid intima-media wall thickness

CK – Creatinine Kinase

COX – Cyclooxygenase

CR – Conventional radiography

CRP – C-reactive protein

csDMARDs – Conventional synthetic Disease Modifying Antirheumatic Drugs

CVD – cardiovascular disease

DBP – Diastolic blood pressure

ECG – Electrocardiography

EHRs – Electronic health records

EMA – European Medicines Agency

EMMs – Extra-musculoskeletal manifestations

ESC – European Society of Cardiology

ESH – European Society of Hypertension

ESSG – European Spondyloarthritis Study Group registry

EULAR – European League Against Rheumatism

FBC – Full Blood Count

FDA – US Food and Drug Administration

g/L – Grams per liter

GDPR – General Data Protection Regulation

GESPIC – German Spondyloarthritis Inception Cohort

HAQ – Health Assessment Questionnaire

HAQ-S – Health Assessment Questionnaire for Spondyloarthropathies

HbA1c – Hemoglobin A1C

HDL – High-density lipoprotein

hs-CRP – High-sensitivity C-reactive protein

hs-troponin-T – High-sensitivity troponin-T

IBD – Inflammatory bowel disease

IBP – Inflammatory back pain

IHD – Ischemic heart disease

IL-17 – Interleukin-17

IL-23 – Interleukin-23

IQR – Interquartile range

IRDs – Inflammatory rheumatic diseases

IU/L – International units per liter

IXE – Ixekizumab

JAKi – Janus kinase inhibitors

LDL – Low-density lipoprotein

MAI – Mucosal associated invariant

mmol/L – Millimoles per liter

MRI – Magnetic resonance imaging

mSASSS – Modified Stoke Ankylosing Spondylitis Spine Score

NF – Nuclear factor

ng/L – Nanograms per liter

Nr-axSpA – Non-radiographic axial spondyloarthritis

NSAIDs – Non-Steroidal Anti-Inflammatories

NT-proBNP – N-terminal pro b-type natriuretic peptide

OMERACT – Outcome Measures in Rheumatology

PGE2 – Prostaglandin E2

PIP – Proximal interphalangeal

PROs – Patient-reported outcomes

PsA – Psoriatic arthritis

PVD – Peripheral vascular disease

RA – Rheumatoid arthritis

R-axSpA – Radiographic axial spondyloarthritis

RCTs – Randomized controlled trials

RR – Reynolds Risk

SBP – Systolic blood pressure

SCORE – Systematic Coronary Risk Evaluation

SEC – Secukinumab

SLE – Systemic lupus erythematosus

SpA – Spondyloarthritis

STAT3 – Signal transducer and activator of transcription 3

SVT – Society for Vascular Technology of Great Britain and Ireland

TC – Total cholesterol

TG – Triglycerides

TmTNF – Transmembrane tumor necrosis factor

TNFR – Tumor necrosis factor receptors

TNF-α – Tumor necrosis factor-alpha

tsDMARDs – Targeted synthetic Disease Modifying Antirheumatic Drugs

TYK2 – Tyrosine kinase 2

umol/L – Micromoles per liter

VTE – Venous thromboembolism

WHR – Waist-hip ratio

γδ – Gamma delta

List of Outputs

Awards

- Best clinical research oral presentation - Irish Society of Rheumatology 2024

Oral And Poster Presentations

- Significant Indicators Identified for Carotid Doppler Ultrasound Use in Axial Spondyloarthritis Patients Without Conventional Cardiovascular Risk Factors-selected for Poster **Presentation at the American College of Rheumatology Congress 2024-Washington**

- Indicators Identified for Carotid Doppler Ultrasound Use in Axial Spondyloarthritis Patients Without Conventional Cardiovascular Risk Factors- **Oral presentation at Irish Society of Rheumatology 2024**

- Significant Association of HLA-B27 Status on Symptom Onset, Age of Diagnosis, Disease Duration, and Uveitis Incidence in Axial Spondylarthritis- **Poster presentation at 14th International Congress on Spondyloarthritides.**

- Sex Differences in Axial Spondyloarthritis: Higher Incidence of Radiographic Disease in Men, Higher Rates of Uveitis, IBD, Peripheral Arthritis, and Dactylitis in Women- **Poster presentation at 14th International Congress on Spondyloarthritides.**

- Significant Association between Disease Duration in Axial Spondylarthritis and the Occurrence of Uveitis and inflammatory Bowel Disease with no Such Association Found for Psoriasis **– Oral Presentation at British Society of Rheumatology, Liverpool, UK.**

- Insights into Axial Spondyloarthritis in the Irish Population: Demographics, Disease Activity, Comorbidities, and Treatment Patterns. - **Oral presentation at Irish Society of Rheumatology**, Dublin.

Publications

- **"Sex Disparities in Extra musculoskeletal and Peripheral Manifestations in Axial Spondyloarthritis: Higher Incidence of Peripheral Arthritis, Dactylitis, Uveitis, and Inflammatory Bowel Disease in Women, with Comparable Rates of Psoriasis and Enthesitis".**

  Dinneen B, O'shea F sex disparities in extra-musculoskeletal and peripheral manifestations in axial spondyloarthritis: higher incidence of peripheral arthritis, dactylitis, uveitis, and inflammatory bowel disease in women, with comparable rates of psoriasis and enthesitis annals of the rheumatic diseases 2024;83:1751.

- **"Distinct clinical outcomes linked to peripheral arthritis and dactylitis in axial spondyloarthritis: findings from a retrospective Irish cohort**".

  Kenyon, M., Gallagher, P., Dinneen, B. *et al.* Distinct clinical outcomes linked to peripheral arthritis and dactylitis in axial spondyloarthritis: findings from a retrospective Irish cohort. *Rheumatol Int* (2024). Doi:10.1007/s00296-024-05707-0

- **"Significant association between disease duration in axial spondyloarthritis and the occurrence of uveitis and inflammatory bowel disease, with no such association found for psoriasis."**

  Brona Dinneen, Marcus Kenyon, Finbar O'Shea, significant association between disease duration in axial spondyloarthritis and the occurrence of uveitis and inflammatory bowel disease, with no such association found for psoriasis, Rheumatology, Volume 63, Issue Supplement_1, April 2024, keae163.009

- "**The Lingering Health Challenge: Addressing Obesity in Axial Spondylarthritis"**

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- **“Disease Modification in Axial Spondyloarthritis”.**

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- **“Cardiovascular Risk and Screening in Rheumatic Disease”.**

  Dinneen B, O’Shea F. Cardiovascular Risk and Screening in Rheumatic Disease-Hospital Professional News- Musculoskeletal Edition May 2023.

- **“Axial spondyloarthritis: An Update”.**

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  Mindo. Axial spondyloarthritis: An update. Medical Independent. Published February 5, 2024. Accessed.

  https://www.medicalindependent.ie/societies/isr/axial-spondyloarthritis-an-update/#:~:text=In%202022%2C%20the%20European%20Alliance

Chapter 1: Introduction

Axial Spondyloarthritis (AxSpA) is a form of systemic inflammatory arthritis that mainly impacts the axial skeleton and sacroiliac joints (SIJs), potentially resulting in spinal fusion(1). It can also involve peripheral joints and entheses, along with causing extra-musculoskeletal issues such as pulmonary, cardiac, ophthalmic, and neurological complications. In Ireland, AxSpA affects between 0.1% and 0.2% of the population and it is estimated that up to 33,000 suffer from a form of axSpA, while its global prevalence ranges from 0.32% to 0.7% (2,3). This condition can become chronic and disabling, significantly affecting physical and mental health, work productivity, and socioeconomic status (4).

In recent years research has shown a significant link between axSpA and cardiovascular disease (CVD) and highlighted the need to identify patients at risk, particularly early in the disease progression to provide an opportunity for timely intervention, which can subsequently decrease cardiovascular morbidity and mortality as the disease advances. Patients with axSpA are at an increased risk for cardiovascular events, compared to the general population (5). Studies have demonstrated that patients with axSpA have an elevated prevalence of traditional cardiovascular risk factors such as hypertension, dyslipidaemia, and obesity (6). These comorbid conditions further compound the risk of cardiovascular events, contributing to the higher mortality observed in this patient population.

In Ireland, CVD is a major public health issue, accounting for approximately one-third of all deaths each year and remains the leading cause of morbidity and mortality (7). The prevalence of risk factors such as obesity, smoking, and sedentary lifestyles contributes to the high incidence of CVD in the country (8). The burden of CVD on Ireland's health services is profound, with substantial allocations required from hospital and health budgets to manage and treat these conditions (9). The Irish government has recognised the need to address the burden of CVD and has implemented several strategies to mitigate its impact. The Healthy Ireland Framework (2013-2025) emphasizes a whole-of-government approach to improving health outcomes, with a specific focus on reducing the incidence of chronic diseases, including CVD (10,11). Additionally, the National Cardiovascular Health Policy 2010-2019 outlines specific actions to enhance cardiovascular health through prevention, early detection, and improved treatment services (11) .

Despite these initiatives, cardiovascular disease continues to pose a significant public health challenge in Ireland, exerting considerable pressure on hospital resources and health budgets. It is essential to implement strategies for early screening in high-risk patients to enable prompt detection and intervention. These high-risk groups particularly include individuals with inflammatory joint diseases, such as axSpA.

This introduction will discuss axSpA and its association with CVD as well as the current recommendations by the European League Against Rheumatism (EULAR) for screening axSpA patients for CVD. It will review the cardiovascular manifestations of axSpA, the proposed mechanisms behind these associations, and the challenges in their diagnosis and management. Finally, the aims and objectives of this thesis will be outlined.

1.2 Axial Spondyloarthritis

AxSpA serves as the primary form within the spectrum of conditions classified as spondyloarthritis (SpA). In recent developments, axSpA has been divided to cover a wider phenotype, incorporating both radiographic axSpA (r-axSpA), also referred to as ankylosing spondylitis (AS), and non-radiographic axSpA (nr-axSpA), which might indicate early or less severe stages of the disease (Figure 1.1) (12). R-axSpA is characterized by the presence of structural damage in the form of bony erosions, syndesmophytes and new bone formation visible on plain radiographs of the SIJs (13). Nr-axSpA is a form of axial inflammatory arthritis that does not exhibit visible structural or erosions changes on plain radiographs. Despite the lack of radiographic evidence, inflammatory lesions can be detected using magnetic resonance imaging (MRI). This detection capability allows for the identification of nr-axSpA at stages that may otherwise be missed with conventional imaging techniques(14). While patients with nr-axSpA often present with clinical symptoms like those observed in patients with more advanced radiographic progression a subset of patients with nr-axSpA may progress to AS/r-axSpA. A 2023 study found that 16% of non-radiographic axial spondyloarthritis (nr-axSpA) patients progressed to radiographic axial spondyloarthritis (r-axSpA) within 5 years (15).

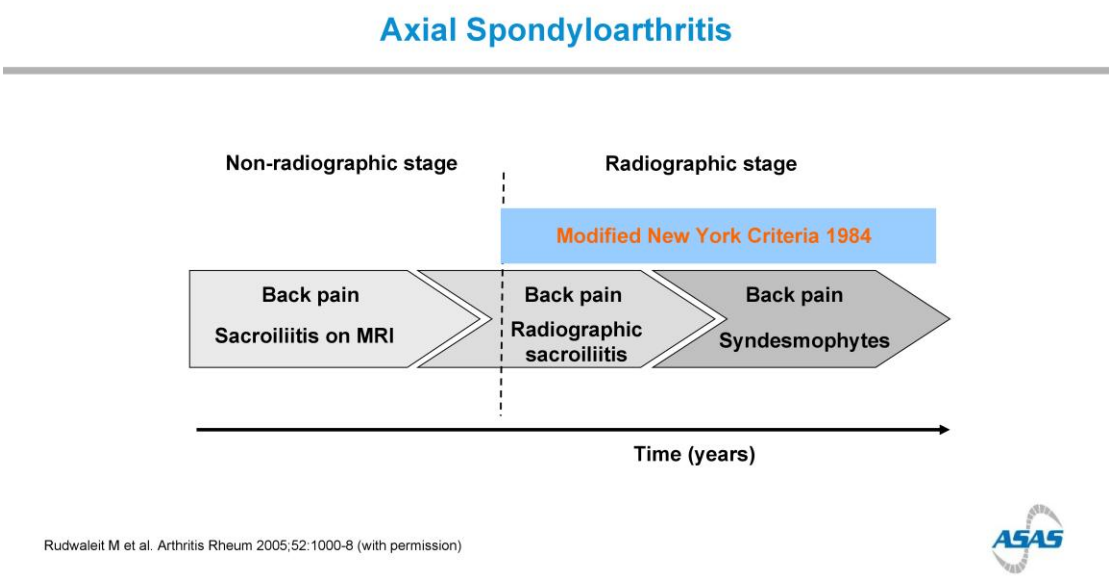

Figure 1.1: Non-Radiographic vs Radiographic AxSpA

1.2.1 Pathogenesis

AxSpA is characterized by inflammatory processes, affecting the entheses, axial skeleton, and peripheral joints which leads to bone and cartilage loss, followed by remodelling with new bone formation (16). This process involves increased bone turnover, resulting in bone loss, osteoporosis, osteitis, erosions, osteosclerosis, and osteoproliferation, which can occur simultaneously or over time in the same patient (17). The pathogenesis of axSpA is complex and to date is not fully understood however research has shown it most likely to be a multifaceted, with hypotheses suggesting genetic factors, misfolding of HLA-B27, arthritogenic peptides, immune system dysregulation, microbiome influence, enthesitis and new bone formation, and environmental factors. Advances in technology, such as next-generation sequencing, single-cell analysis and obtaining tissue samples from

affected areas, such as the axial or peripheral entheses, has allowed for detailed examination of the genetics and immunology involved in axSpA (18–21).

1.2.1.1 HLAB27

The HLA-B27 gene is the most prominent genetic marker associated with the disease as well as being a vital tool in axSpA diagnosis. Approximately 90% of patients with r-AxSpA have been noted to be positive for HLA-B27 in contrast to less than 10% of the general population, however a significant number of axSpA patients do not possess the HLA-B27 allele (22,23). This includes 37.5% of Black patients and 40% of women(24,25) . The exact mechanism by which HLA-B27 contributes to disease pathogenesis is to date not fully understood however the leading theories connecting HLA-B27 to the development of axSpA involves several mechanisms. These include the possibility of arthritogenic peptides being presented by HLA-B27 (26), misfolding of the HLA-B27 protein in the endoplasmic reticulum (27), and the formation of HLA-B27 homodimers which may contribute to an abnormal immune response, particularly involving the interleukin (IL) 23/17 pathway (Figure 1.2) (28,29).

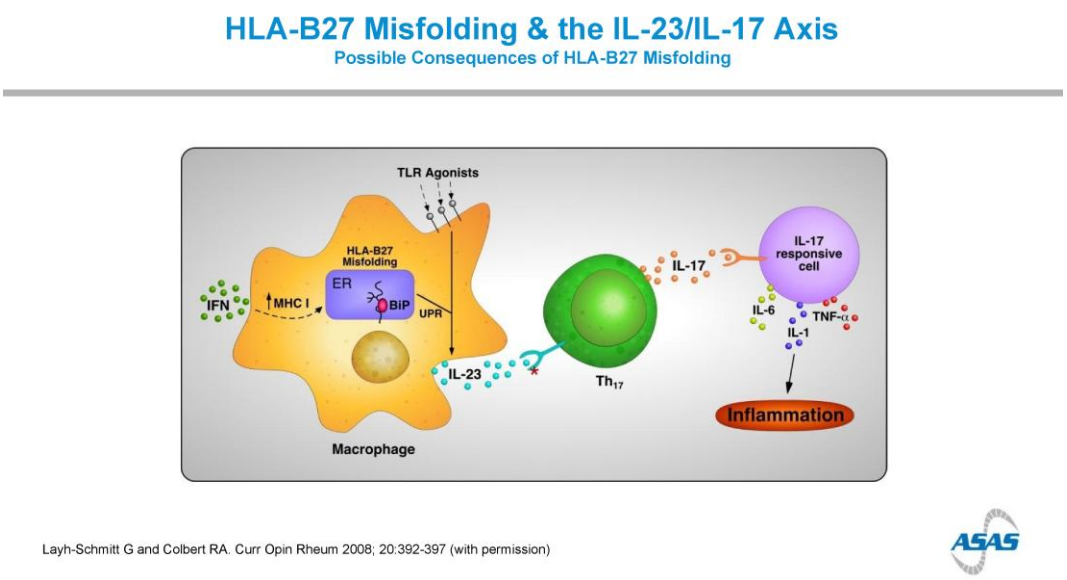

Figure 1.2: Possible Consequences of HLA-B27 Misfolding

1.2.1.2 Microbiome

The connection between axSpA and gut inflammation has long been recognized. Changes in the gut microbiome and barrier function are both causes and consequences of axSpA, contributing to immune system activation. The composition of the gut microbiome is influenced by genetic and environmental factors and shows significant alterations in individuals with axSpA (18). Studies in HLA-B27 transgenic rats have shown that HLA-B27 affects the gut microbiome, suggesting that disruptions in the microbiome, rather than specific pathogens, are associated with inflammation. In humans, microbiome profiling has indicated that HLA-B27 influences the gut microbiome even in healthy individuals, suggesting that dysbiosis precedes the clinical manifestation of the disease and contributes to its risk (30–33). Recent research has linked the mucosal IgA immune

response to the presence of IgA-coated microbes in stool samples from axSpA patients, indicating a potential causal role for dysbiosis in disease development (34).

Gut inflammation in axSpA is characterized by increased intestinal permeability, allowing bacteria and microbial peptides to enter the bloodstream and potentially trigger systemic inflammation (35,36). This loss of gut barrier function is observed in axSpA patients and their healthy relatives, suggesting it may precede or facilitate inflammation. Increased levels of zonulin and bacterial products in the blood, along with invasive bacteria found in ileal biopsies, further support the presence of compromised gut integrity (36,37).

1.2.1.3 Cytokines

Cytokines of the IL-23/IL-17 axis play a critical role in maintaining gut homeostasis and driving inflammation. In axSpA patients, IL-17 produced by innate lymphocytes helps regulate barrier function, while IL-22 induces mucus production (38). Despite increased IL-23 expression in the gut, IL-17 overexpression is not always observed, possibly due to the presence of regulatory T-cells (T-regs) that mitigate pathogenic Th-17 responses (39,40). This indicates a compartmentalized variation in immune responses, with protective effects in the gut contrasting with pathogenic roles in the joints and entheses.

Emerging evidence suggests that immune cells originating from the gut may migrate to joint tissues, contributing to the onset of axSpA. Studies have detected IL-17 and IL-22 producing lymphocytes in the gut, synovial fluid, and inflamed bone marrow of AS patients, indicating a possible gut-joint immune cell trafficking (41). Increased numbers of gut-homing CD8+ T cells and gamma delta (γδ) T-cells in the gut and blood of HLA-B27

positive patients further support this hypothesis (42). These findings suggest that immune cell trafficking from the gut to joints may play a role in axSpA, although the precise mechanisms require further investigation.

1.2.1.4 Enthesitis and New Bone Formation

Enthesitis, the inflammation of entheses, is a key feature of AxSpA affecting both axial and peripheral sites. While mechanical stress leading to microdamage in entheses triggers immune activation and repair in both axSpA patients and healthy individuals, the underlying reasons for the heightened susceptibility in axSpA patients remain unclear (43–45). The role of mechanical strain is underscored by observations that enthesitis is more prevalent in lower limbs, which endure higher strain, and that physical labour involving extensive bending or stretching correlates with greater structural damage in AS patients (43,44,46,47).

In axSpA, inflamed entheses exhibit increased vascularity, CD68+ macrophage infiltration, and disrupted architecture (48). A combination of genetic factors, such as HLA-B27 and IL-23R, and environmental factors, including dysbiosis and loss of barrier function, may lead to chronic entheseal inflammation by activating IL-23 responsive cells. This persistent inflammation can result in further joint damage and new bone formation. The difficulty in obtaining entheseal tissue from axSpA patients has limited direct human studies, making animal models critical for understanding these mechanisms. In these models, IL-23-responsive resident T cells, particularly gamma delta T cells, are major sources of IL-17, driving inflammation (49,50). Monocytes and neutrophils have also been identified as early sources of IL-23 (20). Notably, systemic IL-23 can induce a phenotype resembling

human SpA, although blocking IL-23 post-onset is less effective than pre-emptive intervention, aligning with the limited clinical success of IL-23 inhibitors in axSpA (51).

Research in human tissues has confirmed that normal entheses harbour immune cells linked to Type 3 immunity, including ILC3s, gamma delta T cells, MAIT cells, monocytes, neutrophils, and conventional T cells (20,52–54). These cells can produce IL-17 and other cytokines upon stimulation, suggesting that local immune responses at the entheses contribute significantly to axSpA pathogenesis. Further, the presence of CD14+ myeloid cells in normal human entheses capable of producing IL-23 and TNF upon exposure to microbial adjuvants points to a local initiation of immune responses (55) . Neutrophils in entheseal tissues also contribute to IL-23 production and related inflammatory responses. These findings suggest that local, rather than systemic, IL-23-driven immune activation plays a critical role in the chronic inflammation seen in axSpA.

In recent years, significant advancements have been made in understanding the mechanisms underlying axSpA. The activation of the IL-23/IL-17 pathways, driven by a complex interplay of genetic and environmental factors with immune cells in the gut, skin, and joint tissues, forms the immunological foundation of axSpA. However, direct causal relationships between these observed alterations and the resulting inflammation and structural damage remain to be conclusively demonstrated. An improved understanding of the specific immunological and environmental changes during the disease course in individual patients could guide treatment choices, better targeting pathogenic processes and improving outcomes.

1.2.2 Clinical Manifestations

The onset of symptoms in axSpA typically occur between 20 and 30 years of age (56). Patients tend to present with inflammatory back pain (IBP) that starts before 45 years of age (57). Hallmark features of IBP include, insidious onset, symptom duration of over 3 months, improvement with exercise and Non-Steroidal Anti-Inflammatories (NSAIDS) and early morning wakening secondary to pain (57,58). The sensitivity of IBP is noted to be between 70%–95% for detecting axSpA making it a valuable tool for axSpA screening (59). However, studies have shown that IBP criteria alone lacks specificity for reaching a diagnosis of axSpA with research on referral strategies to rheumatologists revealing that only 17% to 33% of IBP referrals were diagnosed with axSpA (60–62). Previous studies published had found the average time from symptom duration before diagnosis of axSpA to be as long as 13 years however a more recent systematic review by Hay et al. shows a delay in diagnosis from between 2 and 6 years but were unable to identify any variables which influenced the length of delay reported (63). This highlights that despite significant advancements over recent decades, the time it takes for patients to receive a diagnosis of axSpA is still unacceptably lengthy. Early diagnosis and treatment initiation can reduce disease burden and improve quality of life in patients however given the spectrum of disease manifestations, including the presence or absence of peripheral and extra-musculoskeletal manifestations (EMMs), can cause additional delay in reaching a final diagnosis.

1.2.2.1 Extra-musculoskeletal Manifestations

Extra-spinal manifestations are relatively common in AxSpA. They have been divided into peripheral manifestations made up of peripheral arthritis, enthesitis and dactylitis and EMMS which includes uveitis, psoriasis and inflammatory bowel disease (IBD).

Uveitis, often presenting as acute, painful, and unilateral inflammation in the eye's anterior chamber, is characterized by symptoms such as severe pain, light sensitivity, and blurred vision (64). It is the most common EMM in axSpA, affecting up to 30% of patients and is strongly associated with the HLA-B27 gene (65,66). This condition is linked to poorer physical function and increased disease severity in axSpA patients(65). While the precise cause of uveitis is SpA is not fully understood, it appears to stem from a combination of genetic factors, environmental influences like the microbiome or bacterial infections, mechanical stress, and immune system activation leading to inflammation (64).

Psoriasis affects roughly 10% of patients with axSpA (67,68) but the distinctiveness of axial psoriatic arthritis (axPsA) as a separate disease entity remains debated. Although current treatment options are the same, axPsA can present differently from classical axSpA. Notable differences include an onset age that can be over 45 years, a lower rate of HLA-B27 positivity, and typical IBP is reported in only about half of axPsA patients (69–71). Radiographically, axPsA often shows less symmetrical and lower-grade sacroiliitis on MRI, and one-third of axPsA patients may have spondylitis without sacroiliitis. In contrast, sacroiliitis typically occurs before or alongside spondylitis in axSpA (70,71). Psoriasis is common in early axSpA, and patients with both conditions often have more swollen joints and higher use of biologics, but similar disease activity and severity outcomes compared to axSpA patients without psoriasis (72). Improved awareness of these distinctions in

axPsA presentations is crucial for better recognition and management, particularly for patients who do not exhibit classic IBP or SIJ involvement.

IBD which includes Crohn's disease (CD) and ulcerative colitis (UC), is another common EMM associated with axSpA. Abdominal pain and cramping are key symptoms of IBD. Patients often experience diarrhoea, with or without blood or mucus, and rectal bleeding, particularly in UC. Constitutional symptoms are common, such as fever, unintended weight loss and chronic fatigue exacerbated by anaemia and inflammation (73). The link between IBD and axSpA is not well understood, although IBD is clinically evident in 4-14% of axSpA patients (68,74,75), with up to 60% experiencing silent gut inflammation (76–78). AxSpA is more prevalent in Crohn's disease than in ulcerative colitis, with up to 20% of patients with silent inflammation developing Crohn's within five years (77,79). IBD occurs more frequently in axSpA patients than in the general population and is associated with disease severity (80). The overlap of IBD-related spondyloarthritis, a significant yet under-recognized condition, necessitates increased awareness and collaboration between rheumatologists and gastroenterologists for timely diagnosis and treatment.

1.2.2.2 Peripheral Manifestations

Peripheral symptoms include enthesitis, dactylitis, and peripheral inflammatory arthritis. These conditions are associated with poorer quality of life and add to the overall disease burden in axSpA patients. Enthesitis, which is inflammation of the entheses where joint capsule fibres, tendons or ligaments insert into the bone, affects 35% to 60% of axSpA

patients and is linked to higher disease activity and reduced quality of life (68,81,82). Studies show that enthesitis is more frequent among female patients, contributing to greater disease burden despite slower radiographic progression compared to males (83).

Peripheral arthritis demonstrates increased prevalence with prolonged axSpA disease duration. Newly diagnosed patients exhibit a prevalence of 15%-21.3%, which escalates to 37.4%-50% in those with a more extended disease history, indicating the progressive nature of peripheral arthritis (84,85). Patients with this manifestation often experience a higher disease burden, more severe symptoms, and a greater negative impact on overall well-being. Peripheral arthritis is more common in axSpA patients who are older (at least 33 years), non-smokers, and negative for the HLA-B27 antigen. Additionally, these patients are more likely to develop dactylitis and enthesitis (86).

Dactylitis refers to swelling in a digit that extends beyond joint boundaries. This swelling usually appears uniform, resembling a "sausage digit," but can also present as fusiform with emphasis around the proximal interphalangeal (PIP) joints (87). Radiographic imaging often reveals flexor tenosynovitis as the most prominent feature, sometimes accompanied by synovitis in adjacent joints. Additionally, oedema beyond the tendon sheath is common, highlighting the role of enthesitis in the complete phenotype (87). It occurs less frequently than enthesitis and peripheral arthritis but is still significant in contributing to the disease burden. Patients with dactylitis experience severe inflammation and pain, affecting their ability to perform daily activities and reducing their quality of life (74).

1.2.3 Diagnosis

The diagnosis of axSpA is a comprehensive process that integrates a relevant medical history, clinical evaluation, imaging studies, and laboratory tests. Physical examination focuses on detecting tenderness, spinal measurements showing limited range of motion, and signs of inflammation, particularly in the spine and joints. The presence of enthesitis and dactylitis is also evaluated. The modified New York criteria are commonly used to diagnose r-axSpA/AS. These criteria combine clinical and radiographic findings to establish a diagnosis. Clinically, patients must exhibit chronic back pain and stiffness for more than three months that improves with exercise but not with rest, limitation of lumbar spine motion in both sagittal and frontal planes, and decreased chest expansion relative to normal values for age and sex. Radiographically, there must be evidence of sacroiliitis, defined as bilateral grade 2-4 sacroiliitis or unilateral grade 3-4 sacroiliitis on plain radiographs (13). The diagnosis is confirmed if one radiographic criterion is present along with at least one clinical criterion, ensuring a comprehensive assessment of both clinical symptoms and structural changes associated with the disease (Figure 1.3).

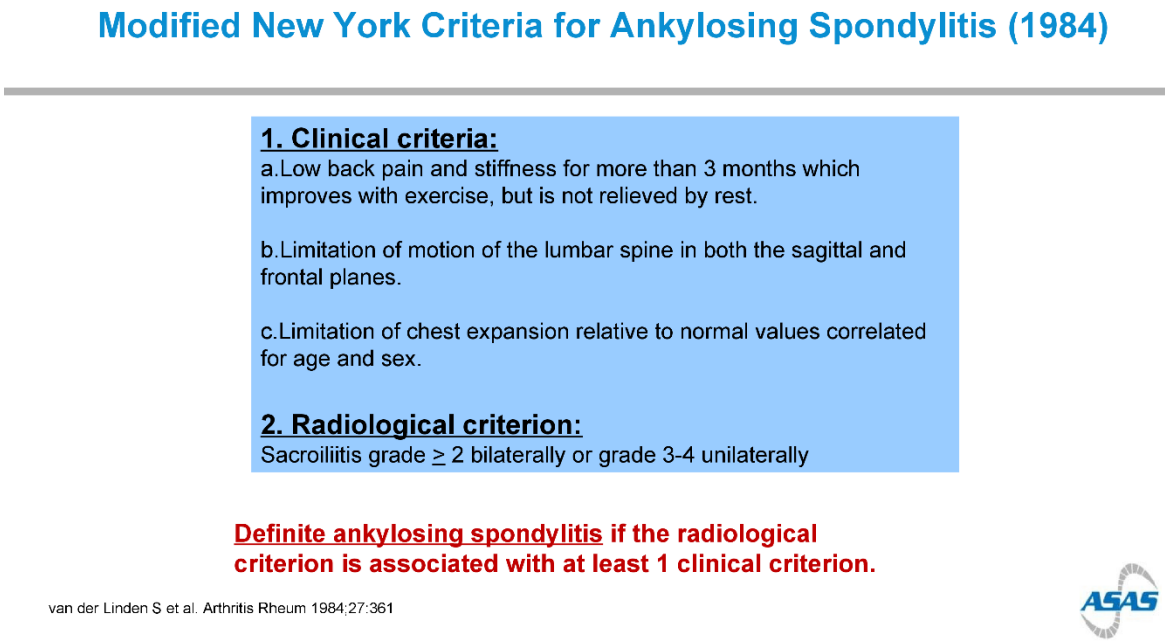

Figure 1.3: Modified New York Criteria for AS

The 2009 classification criteria for axSpA by the Assessment of SpondyloArthritis International Society (ASAS) marked a significant development, particularly for nr-axSpA. These criteria are based on fulfilling one of two arms after meeting the entry requirements of, being under 45 years old and experiencing chronic back pain for more than three months (Figure 1.4) (88,89). The HLA-B27 arm requires a positive HLA-B27 test and two or more SpA features, such as inflammatory back pain, arthritis, heel enthesitis, uveitis, dactylitis, psoriasis, IBD, good response to NSAIDs, family history of SpA, or elevated CRP levels. The imaging arm, on the other hand, allows classification based on a positive MRI or radiographic sacroiliitis combined with one or more of the SpA features. Patients classified as nr-axSpA meet these criteria but do not show radiographic SIJ changes (bilateral grade 2 or unilateral grade 3 or higher). Controversially, nr-axSpA can be diagnosed with a positive MRI or by fulfilling the HLA-B27 arm without objective evidence

of axial inflammatory disease, leading to calls for modifications. Ongoing research, such as the CLASSIC studies by SPARTAN and ASAS, aims to refine these criteria (88,89).

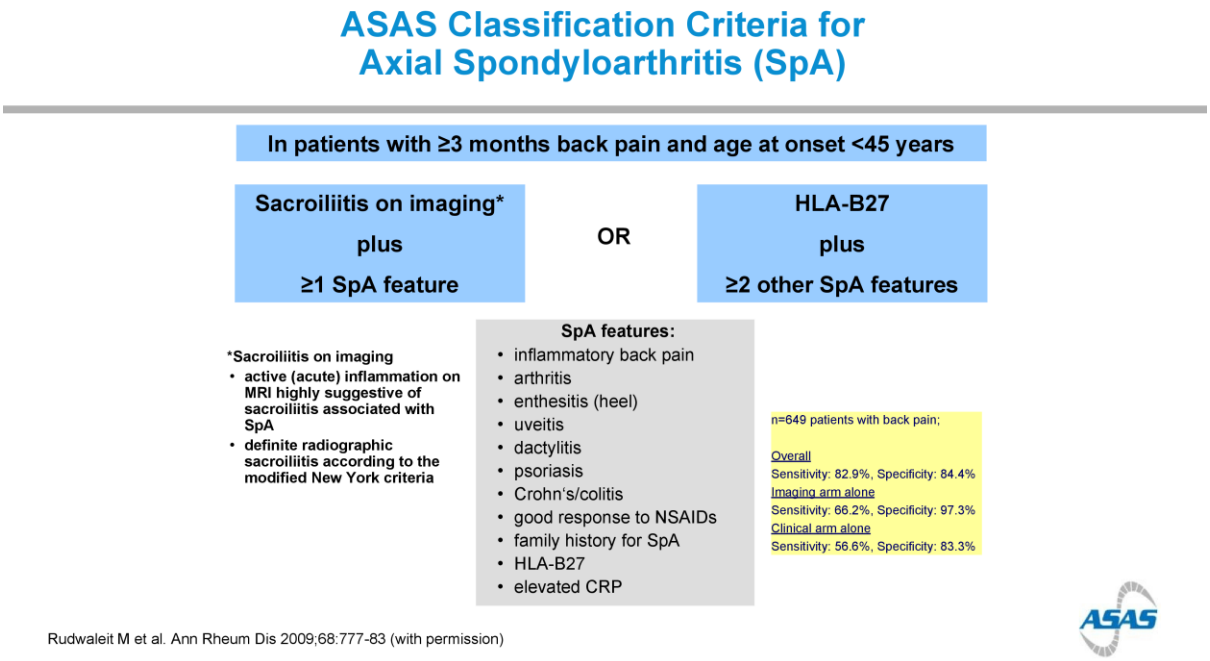

Figure 1.4:2009 ASAS criteria for AxSpA.

1.2.4 Outcome measurements

In the comprehensive management of axSpA, the evaluation of disease activity, functional status, and overall quality of life is paramount. An array of assessment tools has been developed to address these aspects, each serving a unique purpose in both clinical and research settings.

1.2.4.1. BASDAI and ASDAS

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score - C-reactive Protein (ASDAS-CRP) are two crucial tools for assessing disease activity in patients with axSpA. The BASDAI is a self-assessment tool that evaluates the severity of fatigue, spinal pain, joint pain/swelling, areas of localized tenderness, and morning stiffness through six questions (90,91). Each question is scored on a scale from 0 to 10, and the final score is calculated by averaging these individual scores, with weighting given to morning stiffness. This tool helps determine the effectiveness of treatments and monitor disease progression from the patient's perspective (91,92). In contrast, the ASDAS-CRP is a composite index that incorporates both patient-reported outcomes and an objective measure of inflammation, specifically C-reactive protein (CRP) levels. It includes assessments of spinal pain, peripheral pain/swelling, duration of morning stiffness, and a global patient assessment, combined with CRP levels obtained through a blood test. The ASDAS-CRP score is derived from a specific formula that integrates these components, providing a single numerical value representing overall disease activity (93–95). The primary difference between these tools lies in their components and focus. The BASDAI relies solely on patient-reported outcomes, the ASDAS-CRP integrates objective inflammatory markers, offering a more comprehensive assessment of disease activity. This makes BASDAI particularly useful for initial assessments and routine symptom monitoring, whereas ASDAS-CRP is more suitable for evaluating treatment response and longitudinal disease activity.

1.2.4.2 BASFI

The Bath Ankylosing Spondylitis Functional Index (BASFI) measures the impact of the disease on a patient's daily activities and functional status (96). The BASFI consists of ten questions that evaluate a patient's ability to perform various tasks, including activities of daily living and specific functional activities that may be affected in AxSpA. Each question is scored on a visual analogue scale from 0 (easy) to 10 (impossible), and the overall score is calculated by averaging the individual scores, providing a single numerical value that reflects the patient's functional status. The BASFI is particularly useful for both clinical practice and research, as it helps clinicians understand the extent to which the disease affects a patient's functional abilities and daily life. This tool is also valuable for monitoring changes in function over time and assessing the effectiveness of therapeutic interventions (96,97).

1.2.4.3 BASMI

The Bath Ankylosing Spondylitis Metrology Index (BASMI) is used to assess spinal mobility in patients with AxSpA (98). It focuses on measuring the physical limitations imposed by the disease on the spine and related structures. The BASMI consists of five specific tests that evaluate cervical rotation, tragus to wall distance, lumbar side flexion, lumbar flexion with a modified Schober's test, and intermalleolar distance. The scores for each measurement are then added together to get a total out of 50, which is divided by 5 to get the BASMI score (99,100). The primary role of the BASMI is to quantify the extent of spinal stiffness and reduced mobility and provide objective measurements allowing

clinicians monitor disease progression and the effectiveness of therapeutic interventions over time.

1.2.4.4 ASQoL

The Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire is a specialized tool designed to measure the impact of AxSpA on a patient's quality of life, encompassing both physical limitations and emotional concern (101). It captures the subjective experiences and challenges faced by patients, providing insights into how the disease affects their daily living and overall well-being. The ASQoL consists of 18 items, each addressing various aspects of physical, emotional, and social functioning. Patients respond to each item with a simple yes or no, reflecting their agreement or disagreement with statements(102). As it is a patient-reported outcome measure, it captures the patient's perspective on their health status, giving a more comprehensive understanding of the disease's impact on patients.

1.2.4.5 HAQ-S

The Health Assessment Questionnaire for Spondyloarthropathies (HAQ-S) was designed to evaluate the functional status and health-related quality of life in patients with spondyloarthropathies, including AxSpA. The HAQ-S is an adaptation of the original Health Assessment Questionnaire (HAQ) and comprises 20 questions divided into eight categories: dressing, rising, eating, walking, hygiene, reach, grip, and common daily activities. Each item is scored on a scale from 0 (no difficulty) to 3 (unable to do), and the scores are averaged to provide a single disability index. The primary role of the HAQ-S is

to assess the impact of spondyloarthropathies on a patient's ability to perform daily activities and maintain functional independence.

1.2.5 Imaging in AxSpA

Imaging modalities are used in assessing and diagnosing structural changes and progression in axSpA, serving both classification and prognostic purposes (103). Radiological studies provide objective and quantitative data essential for estimating disease progression, which is key for modifying disease outcomes (104). Radiographic progression in axSpA is marked by structural changes such as bone formation, syndesmophyte formation, spinal fusion, ankylosis of the SIJs, sclerosis, and erosions (103). Although typical radiographic changes might not be evident in the early stages, MRI is highly valuable for detecting early signs such as bone marrow oedema, fatty marrow replacement, smaller erosions, and enthesitis (105–107). While MRI offers detailed information on active inflammation and early structural changes, conventional radiography (CR) remains the gold standard for initially assessing structural damage(108).

CR, including anteroposterior views of the SIJs, allows direct visualization of structural changes. Radiographic scoring systems, like the modified New York criteria, quantify radiographic damage by evaluating features such as erosions, sclerosis, joint space narrowing, and ankylosis (109). For the spine, the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) assesses structural changes at the anterior edges of the lumbar and cervical spine (see Figure 1.5). This system scores the vertebral corners for erosion, sclerosis, squaring, syndesmophytes, and bridging syndesmophytes, with higher scores

indicating greater structural damage (110). The mSASSS has proven reliable and sensitive to change, making it the preferred method for scoring spinal damage in axSpA, as endorsed by the ASAS and Outcome Measures in Rheumatology (OMERACT) groups (111,112).

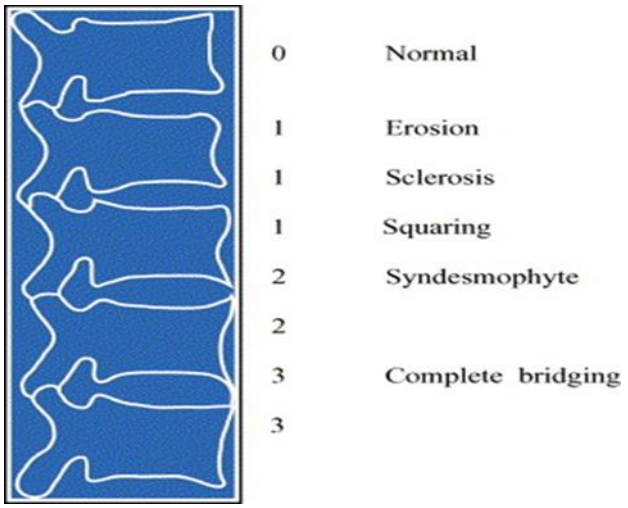

Figure 1.5: mSASSS scoring - range 0-72.

Despite their widespread use, the modified New York criteria and mSASSS have limitations. The former was developed primarily for AS and may not capture the full range of changes in non-radiographic axSpA, while the latter focuses mainly on syndesmophytes and does not account for posterior vertebral changes or facet joint involvement. Both systems, relying on CR, have limited sensitivity for early inflammatory changes. To address these limitations, newer scoring systems incorporate MRI, which enables early detection of sacroiliitis and assesses disease activity through sequences that reveal bone marrow oedema, erosions, and enthesitis. MRI can predict future structural damage by identifying

SIJ ankylosis and fat metaplasia, factors associated with a higher risk of radiographic progression, including syndesmophyte development (113).

Combining inflammation and structural scoring systems could offer a more comprehensive evaluation of radiographic progression in axSpA, aiding in predicting progression and monitoring treatment response. Longitudinal MRI assessments provide valuable insights into disease trajectory and treatment efficacy in controlling inflammation, though the prediction of radiographic progression typically focuses on evaluating structural changes (113).

Currently, the precise mechanisms behind radiographic progression in axSpA remain unclear and necessitate additional research. Factors such as genetic predisposition, high levels of serologic inflammatory markers, the duration of symptoms, and poor control of inflammation and disease activity all contribute to radiographic progression in axSpA. Male gender, the presence of HLA-B27, elevated CRP levels, and smoking have been identified as possible risk factors for more significant radiographic progression, though these findings have not been consistently replicated across all studies (111,114,115). Data on spinal radiographic progression in nr-axSpA are still limited, but recent studies indicate that nr-axSpA patients exhibit less spinal progression compared to those with r-axSpA (111,114,115).

1.2.6 AxSpA Treatment

The primary objective of treatment is to control inflammation, alleviate symptoms, and slow or prevent the progression of structural changes visible on radiology(116). Effective management of axSpA involves a combination of non-pharmacological and

pharmacological interventions and often requires a multidisciplinary approach. In 2022, EULAR and ASAS released updated guidelines for the management of axSpA (see Figure 1.6). These guidelines highlight the need to focus on controlling symptoms and inflammation, improving health-related quality of life, and preventing structural damage over time. Recent advances in treatment have led to more individualized recommendations, taking into account clinical presentations, patient characteristics, comorbid conditions, and psychosocial factors.

Initial recommendations emphasize setting treatment targets and monitoring disease progression. This should encompass patient-reported outcomes (PROs), clinical examinations, laboratory tests, and appropriate imaging. Monitoring frequency should be tailored based on disease activity, severity, clinical manifestations, and the treatment regimen. Like other inflammatory conditions, disease activity scores are crucial for tracking and documenting disease status. The ASDAS which incorporates CRP levels for an objective measure of inflammation, is now recommended for monitoring axSpA patients. The historically used BASDAI remains a viable option as well. Both scores reflect the patient's perspective, but ASDAS includes CRP for a more objective assessment. ASDAS categorizes disease activity into four states: inactive, moderate, high, and very high, with cut-offs at 1.3, 2.1, and 3.0 (116).

Further monitoring in clinical practice includes questionnaires collecting PROs for levels of pain, fatigue, morning stiffness and physical function as well assessing swollen joint counts, EMMs and spinal mobility.

Non-pharmacological management includes patient education, physiotherapy and lifestyle modifications including smoking cessations and regular exercise and this should be discussed at the time of diagnosis (116).

NSAIDs are the first line pharmacological treatment for axSpA and are recommended for use as needed to alleviate pain and stiffness (116). For patients who respond well, continuous use of NSAIDs is favoured, considering the balance of risks and benefits. It is advised that patients try at least two different NSAIDs at the maximum dose over a total period of four weeks to evaluate their effectiveness. Multiple randomized controlled trials (RCTs) have shown that NSAIDs can significantly reduce inflammatory markers (117). These drugs work by inhibiting the cyclooxygenase (COX) activity of prostaglandin E2 (PGE2), thereby reducing inflammation. This inhibition affects macrophages, mast cells, neutrophils, and specific stromal and vascular endothelial cells, facilitating a shift from innate to acquired immune responses through the enhancement of the IL-23/IL-17 axis and the development of regulatory T cells (118). PGE2 influences T-helper (Th)1 and Th17 cells via its EP2 and EP4 receptors, and the effectiveness of COX inhibitors in axSpA may vary due to differences in receptor polymorphisms (119). Consistent use of NSAIDs, as confirmed by ultrasound and X-ray imaging, not only resolves entheseal inflammation and relieves pain but also suppresses vasodilation and slows bone formation, particularly when used regularly rather than intermittently (120,121).

Conventional synthetic DMARDs (csDMARDs), such as methotrexate, leflunomide, and sulfasalazine, play a limited role in treating patients with purely axial disease. However, sulfasalazine can be beneficial for those with peripheral arthritis alongside axial disease (122–124). For patients who do not respond to NSAIDs, additional treatment options

include biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs), such as Janus kinase inhibitors (JAKi).

Patients with an ASDAS of 2.1 or higher, who have not responded to at least two NSAIDs, and who have elevated CRP levels or inflammatory changes in the SIJs observed on MRI or radiographic sacroiliitis, should begin treatment with TNFi or IL-17i (116). TNFi and IL-17i are recommended as the first line of treatment over JAKi due to their greater evidence of efficacy, extensive use in patients with multiple comorbidities, and better-established safety profiles (125–127). If the first bDMARD or tsDMARD fails, switching to another TNFi, IL-17i, or a JAKi should be considered. It is also important to consider considering EMMs or peripheral symptoms when selecting a treatment. For patients with a history of recurrent uveitis or active IBD, a monoclonal antibody against TNF is preferred (128–140), whereas IL-17i may be more suitable for patients with significant psoriasis (141,142).

TNFi have been thoroughly researched for their effectiveness in reducing inflammation and lowering disease activity in axSpA. The exact cellular and molecular mechanisms of TNF in axSpA are not fully understood, but its role in the disease's pathogenesis is supported by substantial evidence and while their primary aim is to alleviate symptoms, TNFi have also been studied for their potential to impact radiographic progression in axSpA (143,144). TNF is a protein with 233 amino acids, existing in two forms: a transmembrane protein (tmTNF) and a soluble molecule (sTNF) created by enzymatic cleavage. Both forms bind to tumour necrosis factor receptors (TNFR) 1 and 2, activating various cellular pathways. These pathways include nuclear factor (NF)-κB, which is involved in cell homeostasis and proliferation, and caspases, which play roles in immune defence and

programmed cell death (143,144). Additionally, tmTNF can act as a ligand by binding to TNF receptors on neighbouring cells and as a receptor itself, transmitting signals that trigger local inflammation in the cells expressing tmTNF (145).

The TNF inhibitors currently approved for treating axSpA include adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. These treatments show similar clinical effectiveness in managing active axSpA, significantly improving symptoms. Approximately 40-50% of patients achieve an ASAS40 response, and up to 50-60% experience a 50% improvement in their BASDAI scores. Additionally, these medications effectively reduce active inflammation, as evidenced by MRI imaging (146–151) .

IL-17i such as secukinumab (SEC) and ixekizumab (IXE), are biologic medications that specifically target IL-17, a pro-inflammatory cytokine implicated in the pathogenesis of axSpA (152). They have been shown to effectively reduce disease activity and alleviate symptoms in axSpA patients. Although their primary purpose is to control inflammation, their impact on radiographic progression has also been studied. IL-17 pro-inflammatory cytokines are produced by various immune cells, including CD8+ T cells, γδ T cells, natural killer (NK) T cells, and mucosal associated invariant (MAI) T cells (153,154). Among these, IL-17A is the most extensively studied, with its expression regulated by inflammatory cytokines such as IL-23. The IL-23/IL-17 axis plays a role in both protecting the host and driving inflammation (155). While the specific role of IL-17A in new bone formation in axSpA remains unclear, evidence suggests that IL-17A promotes osteogenesis by enhancing osteoblast differentiation from local mesenchymal stem cells. Furthermore, IL-17A activates osteoblasts via the JAK2/ Signal transducer and activator of transcription 3

(STAT3) signalling pathway, which is linked to bone formation and have shown promise in slowing down radiographic progression (156–158).

JAKi are a class of medications that target Janus kinase enzymes, specifically JAK1, JAK2, JAK3, and Tyrosine kinase 2 (TYK2), which play a role in the signalling pathways of various pro-inflammatory cytokines such as IL-6, IL-23 and TNF (159,160).By inhibiting JAK activity, these drugs disrupt the signalling pathways of interleukins and interferons, leading to modifications in the immune and inflammatory response. In the context of axSpA, three JAK inhibitors— tofacitinib, upadacitinib, and filgotinib—have been evaluated, each with different selectivities. Currently, tofacitinib and upadacitinib are approved for treating radiographic axSpA/AS, while upadacitinib is also approved for non-radiographic axSpA in some regions. Research on the role of JAK inhibitors in preventing radiographic progression and structural changes is still limited. However, preliminary findings suggest that filgotinib may help reduce structural changes such as erosions in the SIJs (161). Given that JAKi regulate the IL-23/Th17 pathway and suppress the production of IL-17 and IL-22, it is hypothesized that these drugs might slow the development of spinal ossifications (162). Conclusive evidence from dedicated radiographic studies is needed to confirm this.

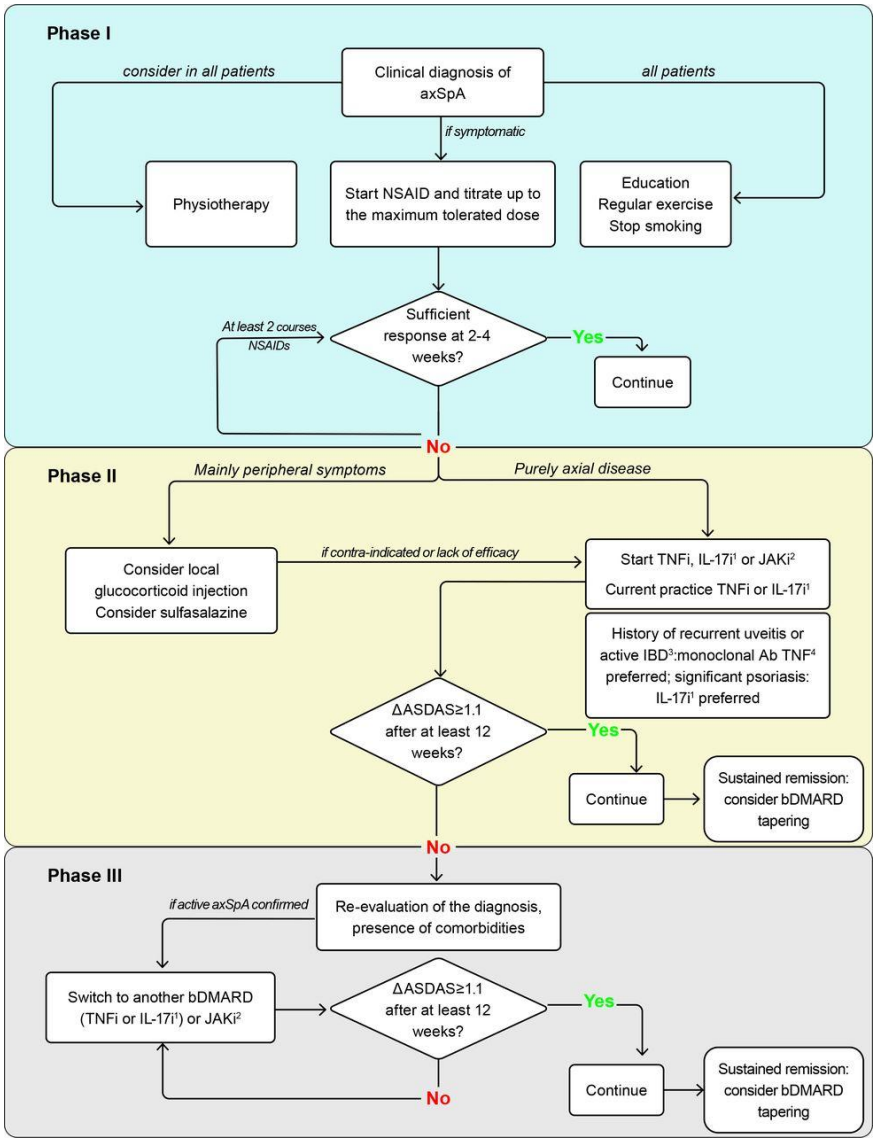

Figure 1.6: Algorithm Based on the ASAS-EULAR Recommendations for the Management of AxSpA

1. 3 Cardiovascular Disease in AxSpA

While CVD remains the main cause of death worldwide, CVD morbidity and mortality is higher in patients with inflammatory rheumatic diseases (IRDs) when compared to the general population (163). Although the relationship between inflammation and increased cardiovascular risk in rheumatic diseases has been widely accepted, the exact

pathogenesis remains unclear and does not appear to be explained by the presence of co-existing traditional cardiovascular risk factors alone (164). CVD is noted to have an increased occurrence across a majority of IRDs and inflammation itself can represent an independent risk factor for development of CVD along with, lifestyle factors in patients with a chronic disabling diseases, such as physical inactivity and certain treatments, namely corticosteroids and NSAIDS (165–168).

CVD can be divided into atherosclerotic events such as ischemic heart disease (IHD), stroke and peripheral vascular disease (PVD) and non-atherosclerotic events including venous thrombosis, heart failure, myocardial and valvular involvement, and arrhythmias. It is now established that atherosclerosis is not solely due to lipid accumulation within the arterial wall, but also as a result of chronic inflammation in response to vascular injury (169). An inflammatory process is seen to prompt the early stages of atherosclerotic development, with both innate and adaptive immune responses playing a key part in this process (170). Previous studies suggest that an increase of certain inflammatory cytokines can be linked with an increased risk of developing cardiovascular diseases, and identification of the key immune cells in this process can potentially lead to new targeted treatment for CVD in the future (171–173).

Patients diagnosed with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic arthritis (PsA), axSpA, and gout all have an increased risk of developing CVD. This risk is partly due to systemic inflammation but there is also a noted increase in the prevalence of traditional cardiovascular risk factors in this patient group, including hypertension and dyslipidaemia (174–176). Over the last decade, the scale of these clinical implications has been increasingly recognised, with ongoing research focusing on further

understanding the pathogenesis of CVD in IRDs, and also into the development of guidelines and screening tools for clinicians.

In 2010 and with an update in 2015/2016, the EULAR recommendations for cardiovascular risk management in patients with RA, axSpA and PsA were published. This recommended that risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor (177). Following European Society of Cardiology (ESC) guidelines, the EULAR task force recommended to perform CVD risk assessment every 5 years for patients found to be at low-to-moderate cardiovascular risk. Screening should be performed more often in patients deemed to have intermediate risk. Patients at high to very high cardiovascular risk will require treatment for noted cardiovascular risks, according to national guidelines. Unfortunately, many IRDs patient's risks remain underestimated as current risk prediction model, that have been developed and used for CVD risk assessment (e.g. Systematic Coronary Risk Evaluation (SCORE), and Framingham are not validated in external cohorts including IRDs patients. These risk assessment models were shown to underestimate risk in these patients and there is still ongoing debate on whether the use of the 1.5 multiplication factor accurately reclassifies the correct patients from intermediate risk into being high risk of CVD and that this method may also be underestimating patient's risk of cardiovascular events (178–180). In 2021 ESC guidelines published the new SCORE2 algorithm to estimates an individual's 10-year risk of fatal and non-fatal CVD events in presumed healthy people between the ages of 40–69 years, with risk factors that have been untreated or have been stable for several years (181). A recent cross sectional multicentre study from Yagensky and Schirmer, looking at cardiovascular risks and risk stratification in inflammatory joint diseases showed, that using the new SCORE2 algorithm, led to the reclassification of patients to a higher risk group in 30%

compared to only 5% when using the original SCORE algorithm. They suggest further longitudinal data could determine whether the new SCORE2 algorithm may be an alternative risk calculator to the 1.5 multiplicators in RA and other inflammatory diseases currently recommended (182).

There are fewer studies investigating CVD in other multisystem autoimmune rheumatic diseases, including systemic sclerosis, Sjogren's syndrome, idiopathic inflammatory myositis, systemic vasculitis and Bechet's, however recent studies have shown, an association with increased risk of premature CVD in these patients. The EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases, including SLE and antiphospholipid syndrome were published in 2022, which emphasise the need for a more tailored therapeutic approach in these patients that strikes a balance between the treatment of the underlying IRD and the patient's individual cardiovascular risks (183). They encourage regular screening and assessment using standard cardiovascular prediction tools, given the lack of validated rheumatic diseases-specific tools and management of modifiable risk factors similar to those used in the general population and focus on adequate disease control. It is important to note, that each IRD carries its own disease characteristics such as manifestations and symptomatology, age of onset, treatment etc. and it could be argued that grouping all IRDs together to discuss their role in the development and progression of CVD as oversimplifying a complex subject matter. Although these guidelines focus mainly on the management of cardiovascular risk factors over risk stratification, they emphasise the need for, increased awareness of the higher risk of CVD, and need for screening in people with IRDs amongst both clinicians and patients.

When discussing cardiovascular risk in patients with IRDs, it is important to discuss the changing landscape of treatments in rheumatic diseases. With more treatment options becoming increasingly available, treatment can now be tailored based on individual patient risk factors and preferences. While certain drugs used to treat rheumatological conditions can increase the risk of developing CVD when used for prolonged periods, such as NSAIDS and corticosteroids, newer steroid sparing, disease modifying treatment can reduce CVD risk by reducing inflammation as seen with methotrexate and TNFi. Certain medications can also be seen to be cardio protective such as hydroxychloroquine in RA und SLE patients and colchicine in gout patients (184–186). There has however been some controversy with newer medication, and their role in cardiovascular events. JAKi indicated in the treatment of RA, PsA, juvenile idiopathic arthritis and AxSpA have recently come under scrutiny for concerns of increased risk of major cardiovascular events, venous thromboembolism (VTE) and death due to any cause, when compared with TNFi. Following the US Food and Drug Administration (FDA) addition of a 'black box warning' on all currently approved JAKi, the European Medicines Agency (EMA) has recommended measures to minimise the risk of serious side effects including the risk of cardiovascular events. While real world evidence does not support the findings of the ORAL surveillance study, these measures include that JAKi should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above and those at increased risk of major cardiovascular problems. It is therefore essential that patients are assessed and screened appropriately for CVD, prior to commencing these medications.

In recent years, there has been an increase in research into methods to identify patients with subclinical atherosclerosis, with the goal of identifying those patients with a higher risk to developing CVD earlier. This has focused on identifying possible biomarkers and the

use of non-invasive imaging. Carotid ultrasound has been utilized to identify patients with subclinical atherosclerosis disease by detecting the presence of carotid plaque and evaluating carotid intima media wall thickness (cIMT). Carotid ultrasound for CVD screening was included in the EULAR recommendations for CVD risk management in patients with IJD 2015/2016 update, as carotid plaques are associated with future ACS in patients with RA (187). There is currently however, an absence of evidence for routine screening of the carotid arteries and the 2021 ESC guidelines on CVD prevention do not recommend the systematic use of cIMT thickness to improve risk stratification as there is currently a lack of methodological standardization. The future role for the use of carotid ultrasound in CVD risk stratification is promising, with newer studies showing increased cIMT can act as a predictor of cardiovascular events, as well as a marker of subclinical atherosclerosis (188–190). It has been used increasingly in IRDS research as an alternative assessment method for identifying subclinical atherosclerosis and more recently as an endpoint, with studies showing notable improvement in cIMT once RA disease activity had been controlled with treatment (190–192). With appropriate development of set cut-off values and standardization need, it is likely that in the future, carotid ultrasound results should be combined as part of a comprehensive cardiovascular assessment to better predict CVD risk.

Studies have shown the prognosis of premature CVD is poorer when coexisting IRDs are present and as this affects a younger population, there are substantial risks of long-term disabilities and health issues causing further strain on the healthcare system (193,194). It is therefore paramount to develop new screening tools to identify those IRDs patients at higher risk of developing CVD, and therefore utilise the most appropriate diagnostic and therapeutic measures that focus on reducing inflammation and atherosclerosis, limiting

CVD development. Identification and validation of modified CVD risk prediction tools, CVD risk biomarkers and vascular imaging in IRDs patients would aid this practical clinical issue. While there are ongoing developments into CVD risk stratification in IRDs, it is important patients are educated on the risks and fully supported with possible lifestyle modifications. Clinicians should perform regular CVD risk assessment along with management of cardiovascular risk factors and cautious prescription of medications including NSAIDS, JAKi and minimal dosages of corticosteroids.

1.3.1 Risk Assessment Algorithms

Cardiovascular risk assessment algorithms play a critical role in preventing and managing CVD by estimating an individual's risk of developing such conditions. Among the widely used algorithms are the SCORE and its updated version, SCORE2, QRISK3, Reynolds Risk Score, and the Framingham Risk Score. These tools utilize various factors, including age, gender, blood pressure, lipid profile, smoking status, and diabetes presence, to predict the likelihood of cardiovascular events. They can assist with the monitoring of intervention effectiveness and allow timely adjustments in treatment plans to address emerging risk factors or changes when needed. Additionally, providing patients with risk scores and information’s enhances their understanding of the importance of managing both their rheumatologic condition and cardiovascular risk factors to aid adherence to treatment plans and lifestyle changes (195).

Each algorithm has unique features and population-specific adaptations which, contributing to their effectiveness and applicability in different clinical settings however,

utilizing cardiovascular risk assessment algorithms in rheumatology patients, particularly those with axSpA can presents several challenges. Firstly, most cardiovascular risk assessment tools were primarily developed and validated in the general population, not specifically for patients with chronic inflammatory diseases (196). Consequently, due to the underlying pathophysiologic mechanism associated with chronic inflammations these tools may underestimate the cardiovascular risk in axSpA especially patients who do not have traditional cardiovascular risk factors. Additionally, these algorithms often do not account for the heightened inflammatory state and the use of immunosuppressive therapy as well use of medications such as instance, NSAIDs and glucocorticosteroids. Inflammatory biomarkers such as CRP and ESR which are routinely used to monitor disease activity, are also not typically included in standard cardiovascular risk models. These omissions can lead to an incomplete risk profile, failing to reflect the true cardiovascular risk in these patients. Another challenge is the heterogeneity of AxSpA patients who have different disease durations, disease severities, and treatment responses, making it difficult to apply a one-size-fits-all approach.

1.3.1.1. SCORE

The SCORE algorithm is designed to estimate the 10-year risk of cardiovascular mortality from a first fatal atherosclerotic even(197) primarily uses data on age, gender, smoking status, systolic blood pressure (SBP), and total cholesterol levels to calculate the risk. The SCORE system is widely used in Europe and provides risk estimates through a risk chart or an online calculator, allowing for easy application in clinical settings. At the international level, two sets of charts are provided: one for high-risk and one for low-risk countries. Countries are classified as high- or low-risk based on their age-standardised cardiovascular

mortality rates, with higher background rates of fatal cardiovascular disease designating a high-risk country and lower rates designating a low-risk country. Low-risk countries include Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, the Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom. High-risk charts should be used for other European countries. Notably, in some of these high-risk regions, the charts may underestimate the risk. These countries include Albania, Algeria, Armenia, Azerbaijan, Belarus, Bulgaria, Egypt, Georgia, Kazakhstan, Kyrgyzstan, Latvia, North Macedonia, Moldova, Russia, Syria, Tajikistan, Turkmenistan, Ukraine, and Uzbekistan. The major limitations to use in axSpA setting are that is designed for adults aged 40-65 without known cardiovascular disease which automatically excludes a large majority of the axSpA patient population.

1.3.1.2 SCORE2

SCORE2 is an updated version of the original SCORE algorithm, designed to improve cardiovascular risk prediction by incorporating more recent and region-specific data. Like SCORE, it estimates the 10-year risk of fatal and non-fatal cardiovascular events but considers other factors, including diabetes status, to refine risk estimates. EULAR currently recommends the use of SCORE as the algorithm of choice in the absence of local or national guidelines and suggests adjustments in the use of the SCORE tool to better reflect the heightened risk in these patients which is the use of the modified SCORE (mSCORE) (183). The mSCORE refers to the SCORE calculation multiplied by 1.5 (198,199)

1.3.1.3 QRESEARCH Risk Estimator Version 3 (QRISK3)

QRISK3 is a cardiovascular risk assessment tool developed in the United Kingdom that estimates the 10-year risk of a heart attack or stroke(200). It incorporates a comprehensive range of variables, including age, gender, smoking status, diabetes, cholesterol levels, blood pressure, body mass index (BMI), family history of heart disease, and other health conditions including RA and SLE. QRISK3 also accounts for factors like ethnicity and socioeconomic status. The updated QRISK3 prediction model was developed and validated to quantify absolute risks of cardiovascular disease in people aged 25 to 84 years. As well as RA and SLE this algorithm accounts for a wider range of risk factors such as an expanded definition of chronic kidney disease, migraine, corticosteroid use, atypical antipsychotic use, severe mental illness, erectile dysfunction and a measure of blood pressure variability (200). There is no need to apply a 1.5 multiplication factor according to the EULAR recommendations because RA is included as a variable however there is no guidelines for axSpA specifically (183).

1.3.1.4 Reynolds Risk Score

The Reynolds Risk (RR) Score is specifically designed to predict cardiovascular risk in women, though it has also been adapted for men. This algorithm includes traditional risk factors such as age, gender, systolic blood pressure, cholesterol levels, and smoking status, as well as high-sensitivity C-reactive protein (hs-CRP) levels and parental history of heart disease before age 60 (201). RR score predicts the probability of a heart attack, stroke, or other significant cardiovascular events over the next ten years in individuals aged 45 to 80

who do not have Diabetes Mellitus or pre-existing cardiovascular disease. Patients are classified as having a higher risk if their calculated score is 10% or higher. While the inclusion of hs-CRP, an inflammatory marker, distinguishes the Reynolds Risk Score from other algorithms by addressing the role of inflammation in cardiovascular disease, previous studies looking at the addition of CRP to the Framingham risk score and QRISK algorithms were not associated with significant improvement in reclassification of CV risk therefore questioning the significance and utility of CRP in current cardiovascular risk assessment algorithms(202).

1.3.1.5 Framingham Risk Score

The Framingham Risk Score is one of the most widely used cardiovascular risk assessment tools, developed from data derived from the Framingham Heart Study. It estimates the 10-year risk of developing coronary artery disease, based on factors such as age, gender, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and smoking status. The Framingham Risk Score is applicable to both men and women and provides a general risk estimate for various populations. When the data from each of the risk factors are entered into a score, they produce an estimated 10-year risk of cardiovascular (CV) death or nonfatal myocardial infarction (MI) (203). The scores are then categorized into low risk (<6% 10-year risk), intermediate risk (6%–20% 10-year risk), and high risk (>20% 10-year risk) of CV death or MI. The Framingham Risk Score, based on older data, may not reflect today's lifestyle factors like diet and smoking (204). It is validated for patients aged 30-79 years without prior coronary heart disease and is not suitable for those with intermittent claudication or diabetes. Its use is limited for younger

adults, certain ethnic groups and patients with chronic inflammatory disease necessitating alternative risk assessment tools (204,205).

The use of cardiovascular risk score algorithms in rheumatology patients remains a topic of considerable debate. It is important to note that the majority of studies on cardiovascular risk assessment in patients with rheumatic conditions have primarily focused on RA and SLE. Consequently, there is a significant need for further research dedicated to risk stratification in axSpA patients to ensure more accurate and effective cardiovascular risk management in this population.

1.4 Aims for the Thesis

1. Assess currently recommended screening tools for cardiovascular disease and subclinical atherosclerosis in the general population.

a) Compare the effectiveness of these tools in the context of axSpA patients, identifying any limitations or areas for improvement.

2. Highlight and Discuss the Importance of Cardiovascular Disease Screening in axSpA Patients:

a) Analyse the prevalence and impact of cardiovascular disease in the axSpA patient population.
b) Provide a detailed discussion on the importance of early detection and management of cardiovascular disease in axSpA patients.
c) Advocate for the integration of cardiovascular screening protocols in the routine clinical management of axSpA patients, supported by evidence from the research findings.

3. Identify Markers for Early Cardiovascular Disease in axSpA Patients:

a) Conduct a comprehensive review of existing literature to compile a list of potential biomarkers and screening tools for early cardiovascular disease in patients with axSpA.

b) Perform study to validate these biomarkers and determine their reliability in predicting early cardiovascular disease in axSpA patients.

4. Identify High-Risk axSpA Patients:

a) Develop a risk stratification model that utilizes identified biomarkers to categorize axSpA patients into various risk levels for developing cardiovascular disease.

b) Test and refine the model using patient data to ensure its accuracy and effectiveness.

5. Develop a Screening Tool for Cardiovascular Disease in axSpA Patients:

a) Evaluate the Functionality of Existing Screening Tools for Cardiovascular Disease:

b) Create a practical and user-friendly screening tool based on the identified biomarkers and risk stratification model.

Chapter 2: Insights into Axial Spondyloarthritis in the Irish Population: Demographics, Disease Activity, Comorbidities, and Treatment Patterns.

2.1 Introduction

Axial spondyloarthritis (AxSpA) is a chronic inflammatory disease that predominantly affects the spine and sacroiliac joints, manifesting with persistent pain, stiffness, and potential structural damage. These symptoms substantially impair the quality of life and functional capacity of those affected. Recent advancements in the understanding of axSpA have underscored the disease's complex and heterogeneous nature, marked by variations in clinical presentation, progression, and treatment response. This chapter provides a comprehensive overview of axSpA as observed in a large Irish cohort, drawing from over a decade of data collected through the Ankylosing Spondylitis Registry of Ireland (ASRI).

Understanding these variations is vital for several reasons. First, the differential presentation of axSpA based on sex and HLA-B27 status can influence the disease trajectory and patient outcomes. For example, previous studies have indicated that female patients tend to exhibit a higher prevalence of peripheral and extra-musculoskeletal manifestations (EMMs), such as enthesitis, psoriasis, and inflammatory bowel disease (IBD), while male patients are more frequently affected by acute anterior uveitis (AAU) (206–209). Similarly, patients without the HLA-B27 gene may experience delays in diagnosis and a higher incidence of EMMs and peripheral symptoms, except for conditions like AAU and dactylitis, which are less prevalent (210–213). By characterizing these differences in the Irish cohort, the study provides a nuanced understanding of how axSpA presents and progresses in diverse patient subgroups.

Moreover, investigating the comorbidities associated with axSpA, including both EMMS and peripheral manifestations, can offer deeper insights into the overall disease burden and management challenges. Comorbid conditions such as IBD, psoriasis, and cardiovascular disease (CVD) often complicate the clinical management of axSpA and contribute to a more significant decline in patient health and quality of life. Thus, identifying these comorbidities and understanding their prevalence in the Irish axSpA population can help clinicians develop more comprehensive and individualized treatment strategies.

By examining real-world data from the ASRI, the study aims to highlight treatment trends and gaps in care, which can inform future clinical guidelines and enhance therapeutic strategies. The use of patient registries in both medicine and research can offer numerous benefits that enhance our understanding and management of various diseases. These organized systems use observational methods to collect uniform data on populations defined by specific diseases, conditions, or exposures, and follow them over time (214). The data captured includes disease demographics, clinical outcomes, and survival rates, providing a comprehensive overview of real-world clinical practice. This information can aid with patient recruitment for clinical research, facilitates the undertaking of studies and clinical trials, and enhances pharmacovigilance efforts (215). Patient registries allow for the monitoring and analysing of outcomes over time, which leads to improved adherence to evidence-based guidelines and personalized patient management.

From a research perspective, patient registries can provide large scale data for observational studies and clinical trials including monitoring the effectiveness and safety of treatments in real-world settings and complementing the findings from RCTs. This

approach is exemplified by registry-based randomized controlled trials, which merge the methodological rigor of RCTs with the practical relevance of observational studies, thereby enhancing the applicability of research outcomes (214). Through research national patient registries can also contribute to informing public health policy. While RCTs are the gold standard for studying medical therapeutics, they lack the extensive data and generalizability offered by clinical registries, which when used appropriately, registries and clinical trials are complementary sources of information, each enhancing the other's value in medical research identifying trends and disparities in healthcare, enabling policymakers to make informed decisions regarding resource allocation and public health interventions.

On an international level patient registry have been combined with electronic health records (EHRs) and this has allowed for further enhancement of their utilisation by streamlining data collection and reducing the administrative burden on healthcare providers. This integration ensures that data are comprehensive and up to date. Unfortunately, in Ireland this is still not the case however the integration of EPRs and other digital health innovations into the Sláintecare initiative will profoundly impact healthcare registries by improving data quality, enhancing interoperability and a multicentre approach allowing Irish registries contribute on a global level.

In more recent years registries have increasingly adopted patient-centred approaches by incorporating patient-reported outcomes and involving patients in the design and governance processes. This ensures that the data collected are reflective of patient experiences and priorities, leading to more relevant and impactful research findings. An example of this is the Swedish Rheumatology Quality Registry which allows both patients

and clinicians to access dashboards displaying longitudinal treatment outcomes and other relevant data, facilitating shared decision-making and more tailored care plans (216).

Despite their evident benefits, the development and maintenance of patient registries can face significant challenges and limitations. Firstly, financial limitations can pose a significant limitation to the establishment and maintenance of a national registry in terms of staffing and infrastructure. Appropriate recruitment and training of staff involved in data collection, entry and storage is necessary to void numerous issues that can arise. This can include issues with data quality and completeness as inconsistencies in data entry and missing information can lead to unreliable datasets (217). Privacy and security are also significant concerns, as ensuring compliance with regulations like General Data Protection Regulation (GDPR) and cyber security can both be resource-intensive and complex. To maintain these standards regulatory compliance requires continuous oversight and adaptation to changing laws which includes regular audits to maintain the registry's integrity. Addressing these multifaceted challenges requires coordinated efforts from healthcare providers, policymakers, and technology developers to maximize the benefits of national healthcare registries.

AxSpA research has been greatly advanced by numerous international studies and registries that have helped to map the demographic, clinical, and genetic landscape of the disease across different populations. Notable among these are the European Spondyloarthritis Study Group (ESSG) registry, the German Spondyloarthritis Inception Cohort (GESPIC), and the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS). These studies have contributed to our understanding of disease

prevalence, variations in clinical features, and the impact of genetic factors such as HLA-B27 status on disease presentation.

In comparison, ASRI provides a unique perspective on axSpA as observed within the Irish population. The ASRI's data allows for a focused analysis of sex differences and comorbidities, which are increasingly recognized as critical factors influencing disease management and patient outcomes. Moreover, the findings from ASRI align with global trends while also revealing distinct characteristics specific to the Irish cohort. This chapter will discuss how these findings contribute to the broader body of knowledge on axSpA and highlight the implications for clinical practice and future research.

In summary, this chapter aims to provide a detailed exploration of axSpA in the Irish population, focusing on critical areas such as demographics, disease activity, comorbidities, and treatment patterns. These insights are not only essential for understanding the disease within this specific cohort but also contribute to the broader global understanding of axSpA. By adding to the global data pool, this study helps to refine clinical approaches and improve outcomes for axSpA patients worldwide, emphasizing the importance of tailoring management strategies to the diverse and heterogeneous nature of the disease.

2.2 Methods

2.2.1 Study design

For this study, data from the Ankylosing Spondylitis Registry of Ireland (ASRI) was used. ASRI is a large, observational, cross-sectional, multicentre cohort study, which is ongoing.

It was established in 2013, with the primary objective to measure the burden of axSpA disease in the Irish population and identify predictors of poor disease outcome. A total of 912 patients with axSpA were enrolled in between January 2013 and November 2022 from 12 different rheumatology centres around Ireland. Patients are invited to partake in ASRI if they are over eighteen years old, have a clinical diagnosis of axSpA which fulfils either the modified New York (mNY) criteria for AS or the International ASAS criteria for axSpA, and have attended secondary or tertiary care in the preceding 3 years. Patients must also be capable of understanding and completing questionnaires and prior to enrolment. Written informed consent was obtained from all subjects.

The study was conducted according to guidelines for good clinical practice in all centres. Ethical approval for ASRI was obtained for all centres from local hospital ethics committees and the Joint Research Ethics Committee for St James' and Tallaght University Hospital. In each centre a trained investigator was responsible for management of data collection. All data was collected and stored in compliance with national data protection legislation.

2.2.3 Patient Assessments

A baseline assessment was performed by a trained investigator for each patient registered. During this assessment baseline clinical data was collected which included, the documented presence of inflammatory back pain, demographics, disease characteristics, clinical measure of disease activity and severity, physical function, peripheral manifestations, EMMs, co morbidities, lifestyle, and current therapies. Baseline anteroposterior pelvic radiographs were taken and assessed by a local radiologist in each

centre. Patients were then classified into radiographic axSpA (r-axSpA) or non-radiographic axSpA (nr-axSpA). This was performed in accordance with the mNY criteria AS which grades sacroiliitis on plain radiographs. Patients were deemed to have r-AxSpA if there was sacroiliitis of grade ≥2 bilaterally or grade ≥3 unilaterally present. Patients were classified as having nr-axSpA if they did not have sacroiliitis on x -rays.

Demographics and disease characteristics included gender, ethnicity, HLA-B27 status, age at onset of symptoms and age of diagnosis. Disease activity was assessed using the BASDAI, while spinal mobility and functionality were assessed using BASMI and BASFI, respectively. Patient reported outcomes (PROs) were assessed using ASQoL and Health Assessment Questionnaire for the HAQ-S.

EMMs included uveitis, psoriasis and IBD defined as ulcerative colitis or Crohn's disease. Peripheral symptoms included dactylitis, enthesitis and peripheral arthritis. Co morbidities assessed included osteoporosis, depression and cardiovascular health (hypertension, hyperlipidaemia, ischaemic heart disease (IHD), diabetes mellitus (DM) type 1 or 2. Lifestyle factors recorded were smoking status, alcohol consumption and employment history and current therapeutic agents were also documented.

2.2.4 Statistical analysis

All baseline data for patients is reported here. Descriptive statistics of baseline demographics and clinical characteristics were performed using Microsoft Excel V. 2304. Medians, IQR and data ranges were also calculated in the Microsoft Excel environment. Any missing or ambiguously recorded data were excluded from the reports. For the

comparison of proportions, exact test analyses were performed using Minitab (Version 21.1). Statistical significance was calculated by Mann Whitney U or chi-square test of two proportions (Fisher's exact). Multiple regression was based on a binary outcome model, using gender, HLA-B27 and AxSpA disease duration as covariates.

2.3 Results

Demographic details were available for 912 patients included at the time of analysis. Table 2.1 shows baseline general characteristics of the ASRI cohort.

Table 2.1: General characteristics of ASRI cohort

Category	**Included n**	**Median (IQR) or n (%)**	**Range**
Demographics and Disease Characterisation			
Gender (male %)	912	75.1	--
Age, median (IQR)	912	44 (36-55)	18 - 85
Age at AxSpA symptom onset, median (IQR)	906	25 (19-33)	7 -78
Age at diagnosis, median (IQR)	906	34 (26-42)	9 -80
Delay to diagnosis in years, median (IQR)	906	6 (2-11)	0 - 52
Disease duration in years, median (IQR)	912	16 (9-27)	0 - 57
ASAS criteria for AxSpA, n (%)	912	912 (100)	--
mNY criteria for AS, n (%)	912	694 (76.1)	--
HLA-B27 positive, n (%)	863	733 (84.9)	--

Clinical Measurements of Disease Activity and Severity			
BASDAI score, median (IQR)	912	3.7 (1.9-5.8)	0.0 - 10.0
BASMI score, median (IQR)	912	3.6 (2.4-5.6)	0.4 - 9.0
BASFI score, median (IQR)	912	3.2 (1.3-5.6)	0.0 - 10.0
AsQoL score, median (IQR)	912	5.0 (1.0-11.0)	0.0 - 18.0
HAQ-s score, median (IQR)	912	0.4 (0.0-0.8)	0.0 - 3.0
Peripheral Manifestations			
Dactylitis, n (%)	897	60 (6.7)	--
Enthesitis, n (%)	894	161 (18.0)	--
Peripheral arthritis, n (%)	894	276 (30.9)	--
Extra-Musculoskeletal Manifestations			
Uveitis, n (%)	895	308 (34.4)	--
Psoriasis, n (%)	895	150 (16.8)	--
IBD1, n (%)	897	96 (10.7)	--
Comorbidities			
Overweight, n (%)	914	338 (37.0)	--
Obese, n (%)	885	257 (29.0)	--
Central obesity, n (%)	912	528 (57.9)	--
Hyperlipidaemia, n (%)	905	143 (15.8)	--
Hypertension, n (%)	905	196 (21.7)	--
Ischaemic heart disease, n (%)	905	34 (3.8)	--
Cerebrovascular disease, n (%)	905	15 (1.7)	--
Diabetes mellitus (type I or II), n (%)	905	46 (5.1)	--
Osteoporosis, n (%)	905	46 (5.1)	--

Depression, n (%)	905	94 (10.4)	--
Lifestyle			
Current smoker, n (%)	912	259 (28.4)	--
Current consumer of alcohol, n (%)	912	657 (72.0)	--
Gainful employment, n (%)	743	531 (71.5)	--
Current Therapies			
Anti-TNF, n (%)	912	531 (58.2)	--
IL-17 pathway inhibitor, n (%)	912	14 (1.5)	--
Methotrexate, n (%)	903	48 (5.3)	--
Sulfasalazine, n (%)	903	33 (3.7)	--
NSAID, n (%)	903	461 (51.1)	--
Multiple therapies, n (%)	912	275 (30.2)	--

2.3.1 Demographics and disease characteristics

The median age of the 912 participants included for analysis was 44 years (IQR 36-55). Among the participants, 75.1% were male. The majority of the participants (694, 76.1%) were diagnosed with r-axSpA based on the mNY criteria. HLA-B27 typing data was available for 863 participants, of which 733 (84.9%) were HLA-B27 positive. The median age at onset of AxSpA symptoms and the age at diagnosis were 25 and 34 years, respectively. The median delay to diagnosis was 6 years (IQR 2-11). The median duration of AxSpA from the onset of the first symptom was 16 years.

2.3.1.1 Clinical Measures of disease activity and severity

The average disease activity of axSpA, as measured by the BASDAI, was 3.7 (IQR 1.9 - 5.8). The severity and functionality of the disease, assessed by the BASMI and the BASFI, respectively, averaged 3.6 (IQR 2.4 - 5.6) and 3.2 (IQR 1.3 - 5.6). The ASQoL and the HAQ-S PROs had average scores of 5.0 (IQR 1.0 - 11.0) and 0.4 (IQR 0 - 0.8), respectively.

2.3.1.2 Extra musculoskeletal manifestations

The most prevalent EMMs reported within the ASRI cohort were uveitis (34.4%), peripheral arthritis (30.9%), psoriasis (16.8%) and IBD (10.7%).

2.3.1.3 Co morbidities

Manifestations directly or indirectly associated with cardiovascular disease were the most observed comorbidities within the ASRI axSpA cohort. DM was reported by 46 (5.1%) patients. In addition to cardiovascular-related comorbidities, other reported comorbidities included depression (10.4%) and osteoporosis (5.1%).

2.3.1.4 Lifestyle

Among the participants, 259 (28.4%) were current smokers, which is significantly higher than the estimated smoking rate among adults in Ireland (18%, P<0.001) (218). Current alcohol consumption was reported by 657 (72%) of the participants, also exceeding the reported rate among the Irish adult population (66%, P<0.001)(218). Engagement in gainful employment was reported by 531 (71.5%) of 743 participants, after the exclusion of retirees, students, and home makers.

2.3.1.5 Current therapies

A total of 785 (86.1%) of participants were receiving therapy at the time of registration, with 275 of them receiving multiple treatments. Among the therapies chosen, bDMARDs were the most frequently used (59.7%), followed by NSAIDs (51.1%). Within the bDMARD therapies, anti-TNF therapies dominated the treatment landscape (58.2%), while only a small number of patients were receiving IL-17 inhibitors (1.5%). Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDS) therapies in use included methotrexate (5.3%) and sulfasalazine (3.7%).

2.3.2 Sex- Associated Differences in Axial Spondyloarthritis

Table 2.2 shows the sex-associated differences in the prevalence of EMMs and peripheral manifestations among individuals with axSpA. The analysis was performed on a cohort comprising 912 individuals, including 686 males and 227 females, with a median age of 46 years for males and 41 years for females.

There were significant differences in disease characteristics between males and females. Males were more likely to meet the Modified New York criteria for AS compared to females (78.8% vs. 67.8%, p = 0.002). This finding was confirmed by multiple regression analysis, which remained significant after adjusting for gender, HLA-B27 status, and disease duration (p = 0.004).

The prevalence of peripheral manifestations such as dactylitis, peripheral arthritis, and enthesitis was also analysed. Dactylitis was significantly more common in females (11.9%) than in males (4.9%), with a p-value of 0.001. This sex difference remained statistically significant in multiple regression analysis (p = 0.001), suggesting that female sex is an independent predictor for the presence of dactylitis among axSpA patients. Similarly, peripheral arthritis was more prevalent in females (37.2%) than in males (28.8%), with a significant p-value of 0.019. This association persisted even after adjustment for confounders in the multiple regression model (p = 0.017). Enthesitis was observed at similar rates between males and females (18.2% vs. 17.4%, respectively), with no significant difference between the sexes (p = 0.841), indicating that enthesitis is equally prevalent among male and female axSpA patients.

Analysis of extra-musculoskeletal manifestations revealed further sex differences. Psoriasis was found to have a similar prevalence in both sexes, with 16.7% of males and 16.9% of females affected ($p = 1.000$). However, uveitis was more commonly reported in females (41.2%) than in males (32.1%), with a significant p-value of 0.015. This difference remained significant after adjusting for potential confounders in the regression analysis ($p = 0.007$), suggesting that females with axSpA are more likely to experience uveitis than males. Inflammatory bowel disease (IBD), which includes ulcerative colitis and Crohn's disease, was significantly more prevalent among females (18.6%) compared to males (8.0%). This finding was highly significant ($p < 0.001$) and remained so in the regression analysis ($p < 0.001$), indicating a strong association between female sex and the occurrence of IBD in axSpA patients.

Overall, the findings of this study highlight significant sex-associated differences in the prevalence of peripheral and extra-musculoskeletal manifestations in individuals with axSpA. Females were more likely to present with dactylitis, peripheral arthritis, uveitis, and IBD compared to males.

Table 2. 2:Sex-Associated Differences in Demographics, Peripheral, and Extra-Musculoskeletal Manifestations among Individuals with AxSpA

Category	Male Median (IQR) or n (%)	Female Median (IQR) or n (%)	P (male vs female)	Multiple regression
Age in years, median (IQR)	46 (37-55)	41 (35-51)	0.005	--
NY criteria for AS, n (%)	540 (78.8)	154 (67.8)	0.002	0.004
Dactylitis, n (%)	33 (4.9)	27 (11.9)	0.001	0.001
Peripheral arthritis, n (%)	193 (28.8)	83 (37.2)	0.019	0.017
Enthesitis, n (%)	122 (18.2)	39 (17.4)	0.841	--
Psoriasis, n (%)	112 (16.7)	38 (16.9)	1	--
Uveitis, n (%)	215 (32.1)	93 (41.2)	0.015	0.007
IBD, n (%)	54 (8.0)	42 (18.6)	<0.001	<0.001

2.3.3 Differences in Demographics and Clinical Features Based on HLA-B27 Status

Table 2.3 summarizes the differences in demographics and clinical features based on HLA-B27 status among patients with axSpA. A total of 863 individuals were included in the analysis, with 733 HLA-B27 positive (B27+) and 130 HLA-B27 negative (B27-) patients.

Demographic characteristics showed notable differences based on HLA-B27 status. The proportion of males was slightly higher in the HLA-B27 positive group (75.9%) compared to the HLA-B27 negative group (70.8%), although this difference was not statistically significant ($p = 0.236$). The median age was lower in the HLA-B27 positive group (44 years, IQR 36-54) compared to the HLA-B27 negative group (48 years, IQR 37-57), with a statistically significant difference ($p = 0.043$). The age at onset of axSpA symptoms was significantly younger in HLA-B27 positive individuals (median 23 years, IQR 19-31) compared to those who were HLA-B27 negative (median 32 years, IQR 24-42), with a highly significant p-value (<0.001). Similarly, the age at diagnosis was significantly younger in the HLA-B27 positive group (median 33 years, IQR 26-40) compared to the HLA-B27 negative group (median 40 years, IQR 31-49), with a p-value of <0.001. Although the delay to diagnosis was slightly longer in HLA-B27 positive patients (median 6 years, IQR 2-12) compared to HLA-B27 negative patients (median 5 years, IQR 2-10), this difference did not reach statistical significance ($p = 0.072$). Disease duration was significantly longer in the HLA-B27 positive group (median 17 years, IQR 10-28) compared to the HLA-B27 negative group (median 11 years, IQR 6-21), with a p-value of <0.001. All patients in both groups met the ASAS criteria for axSpA (100%), and there was no significant difference between

the groups in meeting the modified New York criteria for ankylosing spondylitis (75.2% in HLA-B27 positive vs. 77.7% in HLA-B27 negative, p = 0.527).

Clinical measures of disease severity also revealed differences based on HLA-B27 status. The median BASDAI score was lower in the HLA-B27 positive group (3.6, IQR 1.8-5.7) compared to the HLA-B27 negative group (4.0, IQR 2.2-6.2), with a statistically significant difference (p = 0.032). However, this difference was not significant in the multiple regression analysis (p = 0.764). The BASMI score did not differ significantly between the two groups (median 3.6, IQR 2.4-5.6 in HLA-B27 positive vs. median 3.4, IQR 2.4-5.2 in HLA-B27 negative, p = 0.29). The BASFI score was also similar between the groups, with a median of 3.1 (IQR 1.3-5.4) in HLA-B27 positive patients and 3.7 (IQR 1.4-6.2) in HLA-B27 negative patients (p = 0.074). Quality of life, as measured by the ASQoL score, was significantly lower (indicating better quality of life) in the HLA-B27 positive group (median 5.0, IQR 1.0-11.0) compared to the HLA-B27 negative group (median 7.0, IQR 1.0-13.0), with a p-value of 0.01. The HAQ-s score was also lower in HLA-B27 positive individuals (median 0.4, IQR 0.0-0.8) compared to HLA-B27 negative individuals (median 0.5, IQR 0.1-0.9), with a statistically significant p-value of 0.021, though the difference was not significant in the regression analysis (p = 0.245).

When evaluating peripheral manifestations, no significant differences were observed between HLA-B27 positive and negative patients. The prevalence of dactylitis was similar in both groups (6.4% in HLA-B27 positive vs. 8.5% in HLA-B27 negative, p = 0.343). Similarly, the rates of enthesitis (18.2% in HLA-B27 positive vs. 16.3% in HLA-B27 negative, p = 0.585) and peripheral arthritis (29.9% in HLA-B27 positive vs. 34.4% in HLA-B27 negative, p = 0.328) did not differ significantly between the groups. However, the

prevalence of uveitis was significantly higher in the HLA-B27 positive group (38.3%) compared to the HLA-B27 negative group (15.5%), with a p-value of <0.001. This difference remained significant in the multiple regression analysis (p = 0.03).

Regarding extra-musculoskeletal manifestations, the prevalence of psoriasis did not differ significantly between the two groups (15.4% in HLA-B27 positive vs. 20.9% in HLA-B27 negative, p = 0.15). Similarly, there was no significant difference in the prevalence of inflammatory bowel disease (IBD) between HLA-B27 positive (10.2%) and HLA-B27 negative patients (13.2%, p = 0.363).

In summary, the analysis found HLA-B27 positive patients were younger at symptom onset and diagnosis, had longer disease duration, and showed lower disease activity and better quality of life scores compared to HLA-B27 negative patients. Uveitis was more common in HLA-B27 positive individuals, while no significant differences were found in the prevalence of other peripheral and EMMs.

Table 2. 3: Differences in Demographics and Clinical Features Based on HLA-B27 Status

Category	Description	HLAB27+ Median (IQR) or n (%)	HLAB27- Median (IQR) or n (%)	P (B27+ vs B27-)	Multiple regression
Demographics and disease characterisation	Gender (male %)	75.9	70.8	0.236	--
	Age in years, median (IQR)	44 (36-54)	48 (37-57)	0.043	--
	Age at AxSpA symptom onset, median (IQR)	23 (19-31)	32 (24-42)	**<0.001**	--
	Age at diagnosis, median (IQR)	33 (26-40)	40 (31-49)	**<0.001**	--
	Delay to diagnosis in years, median (IQR)	6 (2-12)	5 (2-10)	0.072	--
	Disease duration in years, median (IQR)	17 (10-28)	11 (6-21)	**<0.001**	--
	ASAS criteria for AxSpA, n (%)	733 (100)	130 (100)	1	--
	mNY criteria for AS, n (%)	551 (75.2)	101 (77.7)	0.527	--
Clinical measures of disease severity	BASDAI score, median (IQR)	3.6 (1.8-5.7)	4.0(2.2-6.2)	0.032	0.764
	BASMI score, median (IQR)	3.6 (2.4-5.6)	3.4 (2.4-5.2)	0.29	--
	BASFI score, median (IQR)	3.1 (1.3-5.4)	3.7 (1.4-6.2)	0.074	--
	AsQoL score, median (IQR)	5.0 (1.0-11.0)	7.0(1.0-13.0)	0.01	--
	HAQ-s score, median (IQR)	0.4 (0.0-0.8)	0.5 (0.1-0.9)	0.021	0.245

Peripheral manifestations	Dactylitis, n (%)	46 (6.4)	11 (8.5)	0.343	--
	Enthesitis, n (%)	131 (18.2)	21 (16.3)	0.585	--
	Peripheral arthritis, n (%)	215 (29.9)	44 (34.4)	0.328	--
Extra-musculoskeletal manifestations	Uveitis, n (%)	276 (38.3)	20 (15.5)	<0.001	0.03
	Psoriasis, n (%)	111 (15.4)	27 (20.9)	0.15	--
	IBD, n (%)	74 (10.2)	17 (13.2)	0.363	--

2.4 Discussion

The findings from ASRI offer a comprehensive overview of axSpA in an Irish cohort, shedding light on the demographic, clinical, and comorbid profiles of the disease. By analysing data from 12 rheumatology centres across Ireland, this study not only reaffirms established characteristics of axSpA but also presents novel insights specific to the Irish population, which are critical for improving patient management and outcomes.

Consistent with global trends, the ASRI cohort shows a male predominance, with 75.1% of the participants being male. This aligns with international findings, where axSpA is generally more prevalent in men. The median age of the Irish cohort was 44 years (IQR 36-55), and the median age at symptom onset was 25 years (IQR 19-33), which is consistent with global data that typically place the onset of axSpA symptoms in the late teens to early thirties. The median age at diagnosis was 34 years, highlighting a diagnostic delay, which

is a common challenge globally due to the nonspecific and often insidious onset of axSpA symptoms.

The study found significant differences in demographics and clinical features based on HLA-B27 status. HLA-B27 positive patients (84.9% of the cohort) were younger at symptom onset (median age 23 years, IQR 19-31) and diagnosis (median age 33 years, IQR 26-40) compared to HLA-B27 negative patients, who had a median symptom onset age of 32 years (IQR 24-42) and diagnosis age of 40 years (IQR 31-49). The younger age at onset and diagnosis in HLA-B27 positive patients may indicate a more aggressive disease course or heightened clinical suspicion leading to earlier detection. Moreover, disease duration was significantly longer in the HLA-B27 positive group (median 17 years, IQR 10-28) compared to the HLA-B27 negative group (median 11 years, IQR 6-21), which could reflect the earlier onset of symptoms in HLA-B27 positive patients and the need for prolonged disease management. These findings are consistent with prior research suggesting that HLA-B27 status is a significant predictor of axSpA onset and progression (210).

In terms of disease activity and severity, the study found differences based on HLA-B27 status. HLA-B27 positive patients reported a lower median BASDAI score of 3.6 (IQR 1.8-5.7) compared to 4.0 (IQR 2.2-6.2) in HLA-B27 negative patients, suggesting less perceived disease activity among HLA-B27 positive patients. However, this difference did not remain significant in the multiple regression analysis, indicating that other factors may also play a role in determining disease activity. Similarly, there were no significant differences in the BASMI and BASFI scores between the two groups, suggesting comparable physical functionality and spinal mobility regardless of HLA-B27 status. Quality of life measures, such as the ASQoL score, were significantly lower in HLA-B27 positive patients (median

5.0, IQR 1.0-11.0) compared to HLA-B27 negative patients (median 7.0, IQR 1.0-13.0), indicating a better quality of life in the HLA-B27 positive group.

The study also highlights sex-associated differences in the prevalence of peripheral and extra-musculoskeletal manifestations. Females in the ASRI cohort were more likely to present with dactylitis (11.9% vs. 4.9% in males) and peripheral arthritis (37.2% vs. 28.8% in males). These differences were statistically significant and suggest that female patients may experience a different clinical phenotype characterized by a higher burden of peripheral joint involvement. Additionally, EMMs such as uveitis were more prevalent in females (41.2%) compared to males (32.1%), which is contrary to some international studies that report a higher prevalence of uveitis among males. Interestingly, IBD was also more common in females (18.6%) than in males (8.0%), further highlighting the need for gender-specific considerations in the clinical management of axSpA. The prevalence of psoriasis in the ASRI cohort was 16.8%, which is on the higher end of the global range (3.1% to 18.9%)(74). The elevated prevalence observed may be influenced by the specific criteria used for psoriasis diagnosis in the ASRI cohort, which might include broader definitions or self-reported cases, as opposed to stricter definitions requiring dermatologist confirmation or biopsy. The variation in psoriasis prevalence across studies highlights the need for standardized diagnostic criteria to improve comparability and enhance our understanding of the disease's clinical spectrum.

Enthesitis, a hallmark feature of axSpA, was observed in 18.0% of the ASRI cohort, a lower prevalence compared to other studies reporting rates between 34% and 74% (219). This discrepancy could be due to differences in the criteria used for diagnosing enthesitis or variations in clinical assessment practices across different settings. Enthesitis significantly

contributes to pain and disability in axSpA, underscoring the importance of including this manifestation in routine assessments to ensure comprehensive patient care.

The study also sheds light on the significant comorbidities associated with axSpA, particularly cardiovascular risk factors and specifically obesity. significant comorbidities in patients with axSpA, particularly in relation to cardiovascular health. Obesity significantly influences the health outcomes of axSpA patients (220). The global obesity crisis, currently affecting over 1 billion people, including 650 million adults, 340 million adolescents, and 39 million children, is anticipated to worsen, with the World Health Organization predicting that by 2025, approximately 167 million individuals will experience health issues related to overweight and obesity (221). Obesity, characterized by an abnormal accumulation of body fat, is commonly assessed using the BMI, a metric that relates weight to height. According to the National Institutes of Health, a BMI under 25 kg/m^2 is considered normal, 25–30 kg/m^2 indicates overweight, and above 30 kg/m^2 signifies obesity (221,222) . Recent research has emphasized the role of BMI in assessing overall health in patients with rheumatic diseases, including axSpA. A previous study from ASRI found that 29.6% of the patients were classified as obese based on BMI, while 41.3% were identified as centrally obese using the WHR (223). This study highlights the limitations of BMI alone in capturing central obesity, a significant risk factor for cardiovascular and metabolic complications, suggesting that WHR should be used alongside BMI for a more comprehensive assessment.

Obesity is a prevalent comorbidity in axSpA, with rates ranging from 14% to 27%, which may be higher than those observed in the general population (220,224,225). Factors such

as gender, socioeconomic status, and age appear to influence these rates. The excess fat tissue in obese individuals can exacerbate inflammatory responses, as adipocytes secrete cytokines like tumor necrosis factor and interleukins, promoting a proinflammatory state that is particularly detrimental in inflammatory diseases like axSpA (226,227). This inflammatory environment is associated with increased disease activity, radiographic progression, and functional impairment, contributing to worse clinical outcomes, including increased pain and reduced spinal mobility (220,223,224).

Moreover, obesity can impair the effectiveness of treatments for axSpA, such as TNFi (228,229). Higher levels of adiposity have been linked to lower drug concentrations, reduced clinical response, and higher rates of treatment discontinuation (228–230). Studies, including those involving the Turkish biologic drug registry (TURKBIO), suggest that certain biologics like secukinumab may not be as affected by obesity, indicating a need for further research to tailor treatment strategies (231) .

Addressing obesity in axSpA patients is crucial for improving disease outcomes. A multidisciplinary approach, involving rheumatologists, physiotherapists, and nutritionists, is recommended. This approach should incorporate lifestyle interventions aimed at weight loss, increased physical activity, and healthier eating habits. Moreover, the socioeconomic challenges associated with obesity, such as limited access to healthy foods and education on nutrition, particularly affect lower-income populations, necessitating public health strategies that target these barriers. The study by Micheroli et al. in a Swiss cohort underscores the significant prevalence of obesity in axSpA patients compared to the

general population, even in countries with relatively low obesity rates (232). This finding highlights the need for targeted public health interventions, such as awareness campaigns and resources to promote weight management and physical activity. Additionally, the study reveals that obese AxSpA patients often exhibit higher disease activity, including increased arthritis, heel enthesitis, and elevated C-reactive protein levels, as well as more pronounced radiographic changes in the sacroiliac joints, indicating more advanced disease stages (232).

Obesity is a critical comorbidity in AxSpA, influencing disease progression, treatment outcomes, and overall patient health. Addressing obesity through comprehensive management strategies is essential for optimizing clinical outcomes and enhancing the quality of life for individuals with AxSpA. Further research is necessary to explore the mechanisms underlying the relationship between obesity and AxSpA and to develop effective therapeutic strategies that consider the unique needs of obese patients with this chronic inflammatory condition.

Obesity was found in 29.6% of patients based on BMI and in 41.3% based on WHR, reflecting a substantial burden of metabolic disease among axSpA patients. This finding is consistent with growing evidence that metabolic syndrome is prevalent in axSpA, potentially exacerbating disease activity and contributing to worse clinical outcomes (220). Additionally, the study reported hypertension in 21.7% and hyperlipidaemia in 15.8% of patients, rates comparable to those seen in other European cohorts (165). These

findings highlight the need for integrated care approaches that address both inflammatory and metabolic aspects of axSpA to optimize patient outcomes.

The study's examination of lifestyle factors and among the participants, 259 (28.4%) were current smokers, which is significantly higher than the estimated smoking rate among adults in Ireland (18%, P<0.001) (218). Current alcohol consumption was reported by 657 (72%) of the participants, also exceeding the reported rate among the Irish adult population (66%, P<0.001)(218). While previous ASRI data did not find a significant association between smoking and disease severity, further longitudinal research is necessary to fully understand the impact of smoking on disease progression and treatment response (233). Given the known detrimental effects of smoking on inflammation and bone health, smoking cessation should be a key component of patient management strategies (234).

In terms of treatment patterns, the study found that 86.1% of patients were receiving therapy at the time of registration, with a substantial proportion (59.7%) on bDMARDS, predominantly anti-TNF therapies. This reflects the current therapeutic landscape where bDMARDs, particularly TNF inhibitors, are a mainstay in the treatment of axSpA. However, with the increasing use of newer biologics such as IL-17 inhibitors and JAK inhibitors, there is potential for improved disease control and patient outcomes in future cohorts. This highlights the importance of ongoing data collection to monitor treatment trends and their impact on disease management and better represent the evolving landscape in axSpA treatment.

2.5 Conclusion

The ASRI study provides a comprehensive analysis of the demographic and clinical characteristics of axSpA patients in Ireland, reflecting both global trends and unique regional variations. The data emphasize the early onset and diagnostic delay associated with axSpA, underscore the moderate disease activity and functional impairment within the cohort, and highlight the significant burden of EMMS peripheral manifestations and cardiovascular comorbidities. These findings underscore the need for a multidisciplinary approach to axSpA management that addresses both inflammatory and metabolic aspects of the disease and incorporates lifestyle modifications to optimize patient outcomes. Ongoing longitudinal data collection will be essential to understand the evolving impact of newer therapies and to ensure that clinical practices remain aligned with the most current evidence. Future research should continue to explore the underlying mechanisms driving these clinical presentations and comorbidities, ultimately aiming to enhance patient care and outcomes in axSpA.

Chapter 3: Impact of Disease Duration on Clinical Manifestations in Axial Spondyloarthritis

3.1 Introduction

Disease duration in axSpA refers to the length of time from the onset of symptoms to the current state of the disease (235). It serves as a key factor in determining disease progression and patient outcomes. In the context of axSpA, longer disease duration has been associated with increased risks of developing EMMs such as inflammatory bowel disease (IBD) and acute anterior uveitis (AAU), but not psoriasis (236). This relationship highlights the role of sustained inflammation and the cumulative burden it places on patients over time. The analysis of large cohort studies, including the (Be)Giant and ASPECT cohorts, has demonstrated that patients with a longer disease duration are at a higher risk of developing AAU and IBD, with a relative risk increase of 20% to 30% per decade of disease duration (236). This association is thought to be due to prolonged exposure to systemic inflammation, as evidenced by elevated CRP levels observed in these patients over time. Notably, this increased risk is not seen with psoriasis, which is less strongly linked to inflammatory burden in axSpA patients, suggesting distinct pathophysiological pathways underlying these different EMMs.

The diagnostic process for axSpA presents significant challenges, often resulting in delayed diagnosis compared to other inflammatory joint diseases such as rheumatoid arthritis or psoriatic arthritis. Delays in diagnosis are primarily due to the absence of specific serological or immunological markers and the reliance on clinical pattern recognition and imaging findings that are not sufficiently sensitive or specific. This has led to variability in

applying classification criteria, such as the modified New York Criteria and the ASAS criteria. Misapplication of these criteria can result in under-diagnosis or over-diagnosis, further complicating the clinical management of axSpA (237). The lack of pathognomonic symptoms in axSpA necessitates a high index of suspicion and careful consideration of differential diagnoses by the clinician, which is needed for early and accurate diagnosis. Early diagnosis is essential to prevent irreversible structural damage to the sacroiliac joints and spine, which can lead to decreased functional capacity and quality of life.

The impact of disease duration on axSpA manifestations extends beyond diagnostic challenges and includes the progression of structural damage. Research indicates that prolonged disease duration is associated with a higher likelihood of transitioning from non-radiographic axSpA (nr-axSpA) to radiographic axSpA (r-axSpA) (12,238). This transition is influenced by several factors, including male sex, HLA-B27 positivity, and smoking status, which are associated with a more severe disease course (239–241). Moreover, patients with longer disease duration exhibit greater radiographic progression, characterized by increased sacroiliitis and spinal damage. This progression is closely linked to high disease activity levels, as measured by CRP and MRI findings of bone marrow oedema, which serve as markers of inflammation (242). Studies have shown that patients with high disease activity levels, particularly in the early stages of axSpA, are more likely to experience accelerated radiographic progression (238,242). This suggests that early and aggressive management of inflammation may be crucial in preventing long-term structural damage and preserving functional capacity.

As discussed previously EMMs are prevalent in axSpA patients, often complicating the disease and adding to the overall burden experienced by individuals. AAU is notably common, with studies indicating a much higher hazard ratio compared to the general population, suggesting that patients with AxSpA are far more likely to develop this manifestation (74). Similarly, IBD is frequently observed in these patients, though psoriasis, while present, is comparatively less impactful in terms of its association with disease progression (74). The central hypothesis of these findings is that patients with AxSpA who develop AAU or IBD are exposed to higher levels of systemic inflammation over time, which may lead to more pronounced structural progression. CRP levels serve as a marker for this inflammation, and their elevation over the course of the disease could reflect a cumulative burden that intensifies the overall impact of axSpA in these patients. In contrast, the presence of psoriasis, with its relatively lower association with inflammation, might indicate a different disease trajectory, one characterized by less aggressive progression.

Despite the clear presence of these manifestations, there has been a gap in understanding their prognostic value over the long term, particularly in relation to disease duration. Most research to date has focused on establishing the baseline characteristics associated with these EMMs, such as elevated CRP levels, hip involvement, HLA-B27 positivity, and inflammation detected through MRI. These characteristics are known to influence the severity and progression of axSpA, but the specific role that EMMs play in this process remains underexplored.

The delay in diagnosis and the subsequent impact on disease progression further complicate the management of axSpA, highlighting the need for early recognition and

intervention. Understanding the role of disease duration in axSpA can inform clinical strategies aimed at reducing the burden of disease, improving patient outcomes, and enhancing quality of life. As we continue to advance our understanding of axSpA, future research should focus on elucidating the mechanisms underlying these associations and developing targeted interventions to mitigate the effects of prolonged disease duration on patient outcomes.

To date there have been few papers looking at the role of axSpA and the development of EMMs and peripheral manifestations in AxSpA. While the (Be)Giant and ASPECT cohorts looked at association between axSpA disease duration and the development of EMMs and concluded that prolonged disease duration is associated with increased risks of developing AAU and IBD, but not psoriasis, there has been no major studies looking at the effects of a prolong disease duration on the development of peripheral manifestations. This chapter aims to investigate the association between axSpA disease duration and the development of peripheral and extra-musculoskeletal manifestations.

3.2 Study Design

This study utilized data from ASRI, an ongoing multicentre, observational study. The inclusion criteria required participants to be aged eighteen or above and to have received a clinical diagnosis of axSpA that meets either the modified New York criteria for AS or the criteria set by the International Assessment of Spondyloarthritis Society (ASAS) for AxSpA. Additionally, participants must have received healthcare at a secondary or tertiary care facility within the three years prior to recruitment and possess the capacity to

comprehend and complete questionnaires. All subjects provided written informed consent prior to their participation in the study. The study was conducted according to good clinical practice guidelines across all centres. Ethical approval for the ASRI was obtained from local hospital ethics committees at all participating centres, including the Joint Research Ethics Committee for St James' and Tallaght University Hospitals. In each centre, a trained investigator was responsible for managing data collection, and all data were collected and stored in compliance with national data protection legislation.

3.3 Patient Assessment

A baseline assessment was performed by a trained investigator for each patient registered in the study. During this assessment, clinical data were collected, including confirmation of axSpA diagnosis according to either the ASAS 2009 or the modified New York criteria. Demographic and disease-related characteristics, such as gender, ethnicity, HLA-B27 status, age at symptom onset, and age at diagnosis, were recorded. For the purpose of this study, disease duration was defined as the time from symptom onset to the time of enrolment.

EMMs including uveitis, psoriasis, and IBD were also documented. IBD was further classified as either ulcerative colitis or Crohn's disease. The presence of these manifestations were confirmed through patient history, retrospective chart review, and diagnosis confirmation by an ophthalmologist, dermatologist, or gastroenterologist, as appropriate. Peripheral symptoms such as dactylitis, enthesitis, and peripheral arthritis were assessed and confirmed by physical examination at the time of enrolment, imaging

confirmation, or documentation by the patient's primary rheumatologist in a retrospective chart review.

3.4 Statistical Analysis

All baseline data for patients are reported in this study. Descriptive statistics of baseline demographics and clinical characteristics were calculated using Microsoft Excel (Version 2304). Medians, interquartile ranges (IQR), and data ranges were also computed within the Excel environment. Any missing or ambiguously recorded data were excluded from the analysis. For the comparison of proportions, exact test analyses were conducted using Minitab (Version 21.1). Statistical significance was determined using the Mann-Whitney U test or the chi-square test for two proportions (Fisher's exact test). Multiple regression analyses were performed using a binary outcome model, with gender, HLA-B27 status, and AxSpA disease duration as covariates.

3.5 Results

Table 3.1 provides an overview of the general characteristics of the ASRI cohort and Table 3.2 presents findings from both univariate and multivariate regression analyses. These analyses explore the association between the disease duration of axSpA and the development of EMMs and peripheral manifestations. The cohort consists of 912 patients, of whom 75.1% are male. The median age of the cohort is 44 years, with the onset of AxSpA symptoms occurring at a median age of 25 years. A median diagnostic delay of 6 years is observed, and the median disease duration is 16 years, with a range extending

from 0 to 57 years. Among the peripheral manifestations, peripheral arthritis is the most commonly observed, affecting 30.9% of patients, followed by enthesitis, which affects 18%. Dactylitis is present in only 6.7% of patients. With respect to extra-musculoskeletal manifestations, uveitis is the most prevalent, affecting 34.4% of the cohort, while psoriasis and IBD are present in 16.8% and 10.7% of patients, respectively.

Table 3.1: General characteristics of the ASRI cohort

Characteristic	**Median (IQR) or n (%)**	**Range**
Gender (male %)	75.1	--
Age, median (IQR)	44 (36 - 55)	18 - 85
Age at AxSpA symptom onset, median (IQR)	25 (19 - 33)	7 - 78
Age at diagnosis, median (IQR)	34 (26 - 42)	9 - 80
Delay to diagnosis in years, median (IQR)	6 (2 - 11)	0 - 52
Disease duration in years, median (IQR)	16 (9 - 27)	0 - 57
Dactylitis, n (%)	60 (6.7%)	--
Enthesitis, n (%)	161 (18.0%)	--
Peripheral arthritis, n (%)	276 (30.9%)	--
Uveitis, n (%)	308 (34.4%)	--
Psoriasis, n (%)	150 (16.8%)	--
IBD1, n (%)	96 (10.7%)	--

The univariate regression analysis reveals a significant association between disease duration and the presence of uveitis ($p < 0.001$), IBD ($p = 0.003$), and peripheral arthritis ($p = 0.002$). Dactylitis and enthesitis, however, do not show significant associations in this analysis.

These findings suggest that the longer the disease duration, the more likely patients are to develop certain EMMs, particularly uveitis and IBD, as well as peripheral arthritis. In the multivariate analysis, which adjusts for covariates such as gender, body mass index (BMI), smoking status, and A-B27 positivity, the association between disease duration and the development of uveitis ($p < 0.001$), IBD ($p = 0.003$), and peripheral arthritis ($p = 0.001$) remains significant. Interestingly, enthesitis, which was not significant in the univariate analysis, becomes significant when controlling for these covariates ($p = 0.041$). Psoriasis and dactylitis remain non-significant in both univariate and multivariate analyses.

Table 3.2: Univariate and multivariate regression of peripheral and extra-musculoskeletal manifestations by axSpA disease duration

Extra-axial manifestation	Univariate P	Multivariate P
Uveitis	<0.001	<0.001
Psoriasis	0.298	0.249
IBD	0.003	0.003
Peripheral arthritis	0.002	0.001
Dactylitis	0.640	0.355
Enthesitis	0.085	0.041

3.6 Discussion

The association between disease duration and the development of EMMs and peripheral manifestations in axSpA has been a growing area of interest in rheumatology. In this study, we confirmed that disease duration plays a significant role in the emergence of certain

extra spinal manifestations, particularly uveitis and IBD. The data suggest that longer disease duration exacerbates the inflammatory burden, leading to increased prevalence of these manifestations. This is consistent with previous findings showing a significant 20–30% increase in the risk of developing uveitis and IBD for each additional 10 years of disease duration (236).Notably, the risk increase was not observed for psoriasis, indicating divergent pathways in the development of different EAMs.

Uveitis, the most common extra-articular manifestation in patients with axSpA was strongly associated with HLA-B27 positivity and longer disease duration in our cohort, reinforcing the relationship between this genetic marker and the inflammatory processes involved in axSpA. This is consistent with the findings from the British Society for Rheumatology Biologics Register (BSRBR) study, which also highlighted a strong association between uveitis and HLA-B27, as well as its inverse association with smoking, further suggesting that genetic predisposition plays a significant role in the disease's progression (241). Additionally, our findings could suggest that disease duration, in conjunction with HLA-B27 positivity, likely contributes to the cumulative inflammatory burden, which may be a key factor in the progression of uveitis in axSpA patients.

IBD similarly showed a significant association with disease duration in this study. IBD is a well-recognized EMM in AxSpA, often manifesting in patients with prolonged disease. The study from the GIANT cohort also supports the notion that gut inflammation is closely linked to sacroiliac joint inflammation in axSpA (236). The association of IBD with both axial and peripheral disease highlights the systemic nature of axSpA, where chronic inflammation in one area of the body may reflect the overall inflammatory state. Additionally, previous studies have demonstrated that IBD, like uveitis, is less common in

HLA-B27-negative patients, suggesting that AxSpA patients without this genetic marker may follow a different disease trajectory(241). However, the exact mechanisms driving the development of IBD in axSpA patients, particularly in the context of cumulative inflammation, warrant further investigation. The increasing use of biologics in treating IBD in axSpA patients has been shown to have variable efficacy, with anti-TNF agents such as adalimumab and infliximab demonstrating greater efficacy compared to etanercept. This suggests that treatment choice may play a role in modifying the course of EMMs over time.

Psoriasis presents a different clinical picture in axSpA. Unlike uveitis and IBD, psoriasis did not show a significant association with disease duration in this study. This finding is consistent with the literature, where psoriasis has been associated with lower MRI inflammation and less radiographic damage in axSpA patients (243). In fact, psoriasis is more frequently associated with peripheral spondyloarthritis and enthesitis, rather than with axial involvement (244). These observations may be linked to the underlying immunopathogenesis of psoriasis, which differs from that of AAU and IBD. Psoriasis has a distinct immunological pathway, with HLA-B27 negativity being more common in patients with psoriasis (219). This further underscores the need to recognize axSpA as a heterogeneous disease, where different EMMs may follow separate inflammatory pathways and progress differently over time.

Another important finding in this study was the significant relationship between disease duration and peripheral manifestations, particularly peripheral arthritis. Peripheral arthritis, along with enthesitis and dactylitis, often indicates a more severe disease course, and its presence may reflect a higher inflammatory burden. While enthesitis did not show a statistically significant association with disease duration in this study, previous research

has suggested that this manifestation may occur earlier in the disease course and may not necessarily progress with longer disease duration (245). This reinforces the idea that different manifestations of axSpA may emerge at different points in the disease trajectory and may be driven by distinct mechanisms.

Interestingly, this study did not find a significant association between disease duration and the development of dactylitis. Dactylitis is a hallmark feature of peripheral spondyloarthritis and has been reported to be more common in patients with concomitant psoriasis (246). The lack of a significant association in this study may be due to the relatively lower prevalence of psoriasis in our cohort, or it may reflect the episodic nature of dactylitis, which may not progress in a linear fashion with disease duration. Future studies with larger sample sizes may be needed to fully explore the relationship between disease duration and dactylitis in axSpA.

The strong association between disease duration and certain EMMs, particularly uveitis and IBD, highlights the importance of early and aggressive management of systemic inflammation in axSpA. Cumulative inflammation, as evidenced by elevated CRP levels over time, has been shown to predict worse outcomes in terms of radiographic progression and structural damage. Therefore, targeting inflammation early in the disease course may help prevent the development of these severe extra-articular manifestations and improve long-term outcomes for axSpA patients. As previously reported the use of biologic therapies such as TNF inhibitors may help reduce the inflammatory burden and prevent the progression of both axial and peripheral disease (247). However, more research is needed to determine the optimal timing and choice of biologic therapy for preventing EMMs in axSpA.

3. 7 Conclusion

This study provides additional insights into the relationship between disease duration and the development of EMMs in axSpA. Using a large cohort from the Ankylosing Spondylitis Registry of Ireland, we observed that longer disease duration is strongly associated with the increased likelihood of developing AAU, IBD, peripheral arthritis, and enthesitis. Psoriasis and dactylitis did not exhibit a statistically significant relationship with disease duration, suggesting that these manifestations may follow different immunopathological pathways compared to uveitis and IBD.

These findings have important clinical implications, suggesting that disease duration should be considered when assessing the risk of developing certain EMMs and peripheral manifestations in axSpA patients. Early identification and targeted management of these manifestations, particularly uveitis and IBD, could improve long-term patient outcomes and reduce disease burden. Future studies should further explore the underlying mechanisms driving these associations and assess the impact of disease-modifying therapies on the progression of both musculoskeletal and extra-articular manifestations in axSpA.

Chapter 4: Cardiovascular Disease Screening and Clinical Predictive Models in Axial Spondyloarthropathies a Literature Review

4.1 Introduction

Cardiovascular disease (CVD) has emerged as a significant comorbidity in patients with axial Spondyloarthropathies (axSpA), which includes Ankylosing Spondylitis (AS) and non-radiographic axSpA (nr-axSpA). These chronic inflammatory conditions are associated with an elevated risk of cardiovascular events, including myocardial infarction, stroke, and peripheral arterial disease (248–250). The chronic systemic inflammation characteristic of axSpA contributes to endothelial dysfunction, accelerated atherosclerosis, and increased arterial stiffness (251–255). AxSpA patients also have a higher prevalence of traditional cardiovascular risk factors such as hypertension, obesity, and hyperlipidaemia, further compounding their cardiovascular risk (256,257). Several studies have demonstrated that inflammation associated with axSpA independently drives cardiovascular risk beyond the presence of these traditional risk factors (257–259).

Mortality data from axSpA, particularly AS, reveals increased cardiovascular-related deaths. Studies show that the standardized mortality ratio (SMR) for cardiovascular complications in AS patients ranges from 1.6 to 1.9, with circulatory diseases being a leading cause of death (256,260,261). These findings highlight the need for proactive cardiovascular management in axSpA patients.

Despite this increased risk, there are no established consensus guidelines specifically addressing cardiovascular screening in axSpA patients. Current screening practices are often extrapolated from those developed for the general population or other

inflammatory diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). However, the unique pathophysiology of axSpA, coupled with its extra-articular manifestations like uveitis, psoriasis, and IBD suggests that these patients may require tailored cardiovascular screening strategies (256). The absence of specific guidelines has resulted in inconsistent screening practices, leaving many axSpA patients without adequate cardiovascular risk assessments, potentially missing opportunities for early intervention.

In clinical practice, cardiovascular screening in axSpA patients is typically limited and often relies on traditional risk assessment tools, such as anthropometric measurements, blood pressure monitoring, and lipid profile evaluations. However, these methods may not accurately capture the cardiovascular burden in axSpA patients, as they do not account for chronic systemic inflammation. Recent studies for example suggest that the total cholesterol to high-density lipoprotein (HDL) ratio, or the use of apolipoproteins, may provide better insight into cardiovascular risk in this population (262–264).

Additionally, the use of non-invasive imaging techniques such as carotid intima-media thickness (CIMT) and carotid Doppler ultrasound remains underutilized, despite their proven effectiveness in detecting subclinical atherosclerosis(178,265–267). Moreover, elevated inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), have been linked to greater cardiovascular risk and may serve as potential biomarkers for assessing subclinical cardiovascular disease in axSpA patients along with an array of new biomarkers currently under investigation (268–272).

Given the lack of specific cardiovascular screening guidelines for axSpA and the reliance on general population screening strategies, there is an urgent need for tailored

cardiovascular risk assessment tools for this patient population. As our understanding of the relationship between chronic inflammation and cardiovascular disease in axSpA evolves, it becomes increasingly clear that traditional risk factors alone may not fully capture the cardiovascular burden. There is a growing consensus that novel predictive models, integrating both traditional cardiovascular risk factors and axSpA-specific elements such as disease duration and inflammation, are needed to better identify high-risk individuals and guide early interventions.

The aim of this chapter is to investigate current and emerging methods for cardiovascular screening in axSpA patients, with a focus on developing clinical predictive models. This review will explore traditional screening methods, imaging modalities and novel biomarkers to identify the most promising tools for predicting cardiovascular risk in axSpA patients. By synthesizing the available evidence, this review aims to provide insights into optimizing cardiovascular screening in axSpA and propose pathways for developing tailored clinical predictive models that incorporate both traditional and disease-specific factors.

4.2 Cardiovascular Risk Assessment in Axial Spondyloarthritis Traditional Risk Factors and Predictive Models

Traditional cardiovascular risk factors, including metabolic abnormalities and hypertension, combined with the systemic inflammatory nature of axSpA, significantly increase the cardiovascular risk in these patients. Cardiovascular risk assessment in axSpA requires careful evaluation of traditional risk factors in combination with emerging methods for screening, including novel biomarkers and advanced imaging techniques. The

aim of this section is to investigate current and emerging methods for cardiovascular screening in axSpA patients, with a focus on developing clinical predictive models based on traditional risk factors such as anthropometric measurements, lipid profiles, diabetes screening, personal and family history, blood pressure, disease activity, and cardiovascular risk algorithms.

Anthropometric measurements, including body mass index (BMI), waist-to-hip ratio (WHR), and waist circumference, are well-established predictors of cardiovascular risk. Studies have shown that axSpA patients exhibit higher levels of central obesity, which contributes to their overall cardiovascular risk (223). It has also been demonstrated that axSpA patients had elevated central obesity compared to the general population, which is closely associated with insulin resistance, hypertension, and dyslipidaemia (273). Waist circumference has been shown to be a stronger predictor of cardiovascular events than BMI alone (274,275). Inflammatory-driven metabolic changes observed in axSpA further exacerbate cardiovascular risks associated with obesity, emphasizing the need for anthropometric measurements to be included in cardiovascular risk assessments (273). It has also been suggested that the relationship between adiposity and inflammation in axSpA is complex, with increased adiposity being linked to higher inflammatory markers such as CRP, which further drives cardiovascular risk (263,276). It could be argued that integrating anthropometric assessments into cardiovascular predictive models can enhance the accuracy of risk stratification in axSpA patients.

Lipid abnormalities, including elevated total cholesterol (TC), low-density lipoprotein (LDL), and triglycerides, alongside reduced high-density lipoprotein (HDL), are frequently observed in axSpA patients, and contribute significantly to cardiovascular disease. It has

been reported that axSpA patients had a higher prevalence of dyslipidaemia, with low HDL and elevated triglycerides contributing to atherosclerosis risk (273). Lipid alterations may be driven by the systemic inflammatory environment characteristic of axSpA, where pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) play a role in modifying lipid metabolism (273). Navarini et al. highlighted that increased CRP levels, combined with dyslipidaemia, compound the cardiovascular risks in axSpA patients, underscoring the need for routine lipid profile assessment as part of cardiovascular screening(277). A pattern resembling the “lipid paradox” described in rheumatoid arthritis has also been noted in axSpA, where inflammation may lower cholesterol levels yet still heighten cardiovascular risk, although more research is required to confirm this. Studies have also confirmed that alterations in the lipid profile are strongly correlated with both disease activity and subclinical atherosclerosis in axSpA, thus making lipid monitoring a critical component of early CVD detection (278,279).

Diabetes screening is another critical element in cardiovascular risk assessment for axSpA patients, given the high prevalence of insulin resistance and impaired glucose tolerance in this population. Systemic inflammation associated with axSpA, particularly elevated levels of CRP and TNF-α, promotes insulin resistance, which exacerbates cardiovascular risk (280). Mok et al. found that fasting glucose levels were elevated in axSpA patients, suggesting an increased prevalence of prediabetes and diabetes with the axSpA cohort (273). In addition, Navarini et al. emphasized the role of persistent inflammation in driving metabolic dysfunction, as prolonged disease activity was associated with higher glucose levels and an increased risk of cardiovascular events (277). Studies conducted have also highlighted the significance of incorporating glucose monitoring into cardiovascular risk models, as impaired glucose metabolism further compounds the cardiovascular risk driven

by chronic inflammation (281). Regular screening for fasting glucose and HbA1c in axSpA patients is, therefore, essential for early identification and intervention in patients at risk for diabetes, which may otherwise go undetected in traditional cardiovascular screening protocols.

Personal and family history of cardiovascular disease is a well-established contributor to cardiovascular risk, particularly in patients with a family history of ischemic heart disease (IHD) or previous cardiovascular events such as myocardial infarction and stroke. Smoking is a major modifiable risk factor for CVD, and axSpA patients who smoke exhibit a further exacerbation of their cardiovascular risk due to both the inflammatory effects of smoking and its detrimental impact on lipid profiles and vascular function (282). In addition to the knowledge of the inflammatory nature of smoking, it has been demonstrated that smoking, combined with a family history of cardiovascular disease, significantly increased the risk of cardiovascular events in axSpA patients (277) . Divecha et al. underscored the contribution of smoking to heightened inflammation in axSpA, leading to greater cardiovascular risks due to the combined effects of disease activity and external cardiovascular insults (283). Therefore, smoking cessation should be a critical component of cardiovascular risk management in axSpA patients, and family history should be routinely assessed as part of potential clinical predictive models.

Hypertension is a common comorbidity in axSpA and represents a significant risk factor for cardiovascular disease (165,175,176,249). Chronic inflammation in axSpA, which contributes to endothelial dysfunction and arterial stiffness, has been closely linked to the development of hypertension. Multiple studies found that the prevalence of hypertension in axSpA patients was significantly higher than in the general population, suggesting that

blood pressure monitoring should be an integral part of cardiovascular screening (273,284,285) with studies also reporting that elevated diastolic blood pressure and the use of antihypertensive medications were strongly associated with cardiovascular events in axSpA patients (277), indicating that aggressive management of blood pressure is required to mitigate cardiovascular risk in this population . Berg et al. also highlighted that hypertension in axSpA patients was often underdiagnosed due to the complex interplay between disease activity and vascular changes, further emphasizing the need for regular blood pressure monitoring in both screening and predictive models (286) .

Disease activity and inflammation play a pivotal role in determining cardiovascular risk in axSpA patients. Persistent systemic inflammation, as measured by CRP, ESR and disease activity scores such as the BASDAI and ASDAS-CRP, is strongly correlated with cardiovascular events (169,170,272,283,287–289). It has been shown that elevated CRP levels and sustained high disease activity significantly increased the likelihood of cardiovascular events in axSpA patients, suggesting that inflammatory markers should be incorporated into cardiovascular risk prediction models (279) with Berg et al emphasizing that the inclusion of disease activity scores, such as ASDAS-CRP and BASDAI, in clinical predictive models significantly improved the accuracy of cardiovascular risk stratification by capturing the impact of chronic inflammation on cardiovascular outcomes (286,290). The close association between inflammatory burden and cardiovascular events in axSpA patients emphasizes the importance of controlling disease activity to reduce cardiovascular risk.

In the context of cardiovascular risk assessment tools, traditional algorithms such as QRISK3, Reynolds Risk Score, SCORE2, and the Framingham Risk Score have been used to

estimate cardiovascular risk in the general population, but their application in axSpA remains challenging due to the lack of integration of disease-specific inflammatory markers and activity scores. It has emphasized throughout the literature that traditional tools tend to underestimate cardiovascular risk in axSpA, where not only persistent inflammation plays a pivotal role but different pathomechanisms across IJD (177,180,183). QRISK3, while accounting for chronic conditions such as RA and SLE, does not include axSpA-specific factors. Similarly, the Reynolds Risk Score, which includes CRP, is more aligned with chronic inflammatory conditions but still lacks sensitivity to axSpA-specific disease activity measures such as BASDAI or ASDAS-CRP, as noted by Ionescu et al. (281). The SCORE2 system, widely used in Europe, and the Framingham Risk Score also exhibit similar limitations in axSpA populations, as they fail to capture the full cardiovascular risk posed by systemic inflammation, as indicated by multiple studies, and only capture limited age and race groups (178,273,283).

4.3 Imaging techniques in Cardiovascular Screening for AxSpA Patient

Two widely used imaging modalities for the assessment of subclinical atherosclerosis are the coronary artery calcium (CAC) score and carotid Doppler ultrasound. These modalities serve different purposes but ultimately aim to identify atherosclerotic disease before it progresses to more severe forms, such as myocardial infarction or strokes. While CAC is more utilized by cardiology focused on coronary atherosclerosis, and carotid Doppler is more routinely used to evaluate plaque buildup in the carotid arteries, providing insight into stroke risk. Here we look at their individual roles in assessing for subclinical atherosclerosis in axSpA patients.

Carotid Doppler ultrasound is emerging as useful tool in cardiovascular screening for assessing the intima-media thickness (IMT) and detecting carotid plaques, both of which are established markers of subclinical atherosclerosis (190,291–293). These parameters provide early indicators of cardiovascular risk, which may not be fully captured by traditional cardiovascular risk factor.

In multiple rheumatology studies IMT in the common carotid artery has been measured and been extensively validated as a surrogate marker for atherosclerosis (178,294). In a cohort of patients with axSpA, carotid Doppler ultrasound has revealed a significantly higher IMT when compared to healthy controls(265,295,296), with Gonzalez-Gay's group demonstrating that axSpA patients had a mean IMT of 0.74 mm compared to 0.67 mm in controls, with a statistically significant difference ($p=0.01$). The same cohort also showed, carotid plaques, which represent more advanced atherosclerotic lesions, were found in 29.7% of axSpA patients compared to only 9.4% of controls ($p=0.03$). These results underscore the importance of carotid Doppler ultrasound in detecting subclinical cardiovascular abnormalities that are not captured by traditional cardiovascular risk assessments.

Carotid doppler ultrasound has proven to be a valuable tool in reclassifying cardiovascular risk in patients with IJD. In axSpA patients, 36% exhibited carotid plaques, leading to 34% of these patients being reclassified into the very high cardiovascular risk category, compared to 25% in controls (267) . It is also worth nothing in a similar study with PsA patients, the prevalence of carotid plaques was 44.4%, significantly higher than the 24.7% observed in controls. This resulted in a higher reclassification rate across six cardiovascular risk algorithms, with PsA patients being reclassified at rates of up to 40.7%, as seen with

the SCORE algorithm, compared to 19.8% in controls (178). These findings highlight the inadequacy of traditional cardiovascular risk models in inflammatory disease populations and suggest that carotid ultrasound should be routinely employed to identify high-risk patients who would otherwise be misclassified by conventional methods.

Looking forward, the role of carotid Doppler ultrasound in cardiovascular screening for axSpA patients is likely to expand, particularly as more emphasis is placed on early detection and intervention. Unlike CAC scoring, which requires exposure to radiation, carotid ultrasound is entirely radiation-free and can be performed repeatedly, making it more suitable for ongoing monitoring.

CAC scoring is typically performed using non-contrast computed tomography (CT). The technique quantifies the calcified plaque in the coronary arteries, with the score reflecting the total burden of calcified atherosclerosis. The use of CAC scoring has become widespread due to its ability to predict coronary heart disease (CHD) and CVD events in asymptomatic individuals. One of the earliest studies to promote the utility of CAC scoring was conducted by Agatston et al., which demonstrated that higher calcium scores are strongly associated with the risk of future heart attacks and other cardiovascular events (297). Like carotid doppler ultrasound CAC scores can be used to reclassify patients who fall into intermediate risk groups based on traditional risk factors. For example, if a patient presents with intermediate risk according to the Framingham Risk Score, a high CAC score could elevate them to a high-risk category, prompting more aggressive preventive measures such as statin therapy (298).

CAC is valuable because it measures calcified plaques, which are considered to be stable but indicative of the presence of atherosclerosis throughout the coronary arteries. It's ability to quantify the degree of coronary calcification allows for nuanced risk stratification beyond that provided by traditional risk factors alone. Studies have confirmed that CAC scoring offers excellent diagnostic and predictive power for coronary artery disease, specifically for primary prevention in asymptomatic patients and those at high risk CVD (298,299) .

There have been conflicting studies regarding whether CAC scoring or carotid Doppler is more effective for screening for subclinical atherosclerotic CVD (298–301). The carotid plaque score and CIMT measurements are predictive of future cardiovascular events, especially in regard to cerebrovascular events. For instance, the study by Gepner et al. demonstrated that while CAC was superior in predicting coronary events, carotid ultrasound was equally predictive of stroke events (300). Carotid ultrasound is particularly useful in populations with high cerebrovascular risk, where assessing plaque in the carotid arteries offers more relevant prognostic information compared to coronary calcification alone. Kim et al. observed that carotid ultrasound was an effective predictor of both primary and secondary prevention of cardiovascular disease, noting that the presence of carotid plaques was strongly associated with an increased risk of stroke and other cerebrovascular events (299). Furthermore, the American Society of Echocardiography consensus supports the use of carotid ultrasound as a method to detect subclinical

vascular disease, advocating its use in patients where traditional risk factors may not fully capture cardiovascular risk (302).

CAC's main advantage lies in its ability to directly quantify calcified atherosclerosis, which is highly correlated with the risk of myocardial infarction and other coronary events. By contrast, carotid ultrasound, while valuable for predicting stroke, does not directly assess the coronary arteries and it can therefore be argued that it is less useful in assessing coronary-specific risk (299,300). Rueda-Gotor et al. noted that in patients with axSpA, carotid ultrasound was more effective in identifying individuals at high cardiovascular risk compared to CAC scoring. The study suggested that in patients with IJD that the inflammatory burden may lead to non-calcified, unstable plaques, which are better detected via carotid ultrasound than by CAC scoring (303).

With the ongoing debate regarding the relative effectiveness of CAC scoring versus carotid Doppler ultrasound for screening subclinical atherosclerotic CVD some have questioned the validity of a combined approach utilizing both modalities for comprehensive cardiovascular risk assessment. While there is no synergistic effect when combining the two methods, using both can provide complementary information—especially in patients at risk of both coronary and cerebrovascular disease (299).

Overall, it appears carotid ultrasound offers greater practical benefits in some clinical settings due to its non-invasive nature, lack of radiation, and ability to detect non-calcified plaques, which may pose a greater risk of rupture and cause stroke (299,303). Additionally, because carotid ultrasound is more readily available and cost-effective in certain regions, it may be used as an alternative screening method in populations where CAC screening is

either unavailable or prohibitively expensive. Moreover, certain researchers have questioned the routine use of CAC in low-risk populations due to the radiation exposure involved. Some guidelines, such as those from the 2013 ACC/AHA, advise using CAC only when the risk-based treatment decision is uncertain following quantitative risk assessment (304).

4.4 Novel Imaging Techniques for Cardiovascular Screening in axSpA Patients

In recent years, there has been newer developments looking at more novel imaging modalities in detecting subclinical cardiovascular involvement in patients with axSpA over more conventional methods such as CAC and carotid doppler ultrasound. Patients with axSpA are at heightened risk for atherosclerosis, myocardial dysfunction, and valvular heart disease, all of which contribute to the increased morbidity and mortality from cardiovascular complications in this population (305–307). The use of advanced imaging techniques such as Cardiac Magnetic Resonance Imaging (MRI) and Strain Imaging, Echocardiography and even Optical Coherence Tomography Angiography (OCT-A) offers new opportunities for early identification and monitoring of these conditions before they manifest clinically, providing critical windows for intervention.

A Turkish study utilized Speckle Tracking Echocardiography (STE**)** to assess left ventricular function in AS patients (308). The study showed that STE was more sensitive than conventional Doppler echocardiography in detecting subclinical left ventricular systolic dysfunction. Despite normal ejection fractions in axSpA patients, STE revealed significant impairments in strain values, particularly in the longitudinal strain of the myocardium. This technique could be beneficial for early identification of myocardial dysfunction before

clinical heart failure manifests. The application of STE in axSpA patients aids in the development of predictive models for early cardiac dysfunction by quantifying strain abnormalities that may not be captured by traditional echocardiographic methods.

Another Turkish study by Caglar et al. looked at Tissue Doppler Echocardiography (TDE) and CIMT measurements were employed to evaluate cardiovascular risk in AxSpA patients (309) . TDE was used to measure atrial electromechanical delay (EMD) and epicardial fat thickness (EFT), both of which were significantly elevated in axSpA patients compared to controls. CIMT was used to detect early signs of atherosclerosis. The findings highlighted that AS patients exhibited increased cardiovascular risk, even in the absence of overt clinical symptoms. These imaging modalities provide an accessible and non-invasive means of screening for subclinical atherosclerosis, contributing to predictive models by quantifying arterial stiffness and cardiac dysfunction.

Rueda-Gotor et al. have published multiple studies focusing on the of carotid ultrasound and its role in detecting subclinical atherosclerotic CVD. However, in a 2018 study they compared the effectiveness of carotid ultrasound with lateral lumbar spine radiography lateral, used to detect abdominal aortic calcification (AAC) (310). The study found that while carotid ultrasound was more sensitive (61.1%) for detecting subclinical atherosclerosis in patients classified as having moderate cardiovascular risk, AAC detected by lateral lumbar spine radiography also provided valuable information, identifying 38.9% of patients in this group. Moreover, 4.7% of AS patients classified as having low cardiovascular risk according to the TC-SCORE system had AAC, further underscoring the usefulness of this imaging modality in improving cardiovascular risk stratification. AAC detected through plain radiography has been recognized as a reliable marker of intimal

atherosclerosis, and in post-mortem studies, it has been shown to correlate with the degree of coronary artery atherosclerosis (311–313). This is particularly relevant in axSpA patients, as it provides a non-invasive and accessible method for assessing cardiovascular risk, especially in settings where advanced imaging techniques may not be readily available. The study found a strong correlation between the presence of AAC and carotid plaques ($r^2 = 0.49$, $p < 0.001$), suggesting that AAC can serve as a useful adjunct to other imaging modalities like carotid ultrasound in identifying axSpA patients at high risk for cardiovascular events (310).

Coronary Computed Tomography Angiography (CCTA) is an advanced imaging technique that provides high-resolution images of coronary arteries, allowing for the detection of both calcified and non-calcified atherosclerotic plaques. In the study by Ozdowska et al, CCTA was employed to assess subclinical coronary atherosclerosis in young patients with axSpA who lacked traditional cardiovascular risk factors (314). The study found that nearly 48.7% of AS patients had detectable atherosclerotic plaques, compared to only 26.3% in the control group. Remarkably, this was observed despite the relatively short disease duration and absence of overt cardiovascular symptoms. Most plaques identified were of low-grade coronary stenosis (<40% narrowing), which, while not immediately clinically significant, indicate a heightened risk of future cardiovascular events. The ability of CCTA to detect non-calcified plaques, which would likely be missed by other methods like the CAC score, emphasizes the role of inflammation in accelerating atherosclerosis in AS. The CAC score, while useful for measuring calcified plaques, does not detect these non-calcified plaques, potentially underestimating cardiovascular risk in young, inflammation-driven patients like those with axSpA (315). Therefore, CCTA offers a more comprehensive evaluation of coronary artery disease, capturing both soft and hard plaques, and is

particularly valuable in AS patients where inflammation plays a critical role in cardiovascular risk beyond traditional risk factors.

More common cardiac imaging modalities such as cardiac MRI and Transthoracic Echocardiography (TTE) can also be used as novel methods to assess for subclinical CVD in axSpA patients. TTE has been used to measure Epicardial Adipose Tissue Thickness (EATT), which was found to be significantly higher in axSpA patients (308,316). Increased EATT has been associated with subclinical atherosclerosis and cardiometabolic risk (317). A study by Ozkaramanli et al. used TTE to utilize strain imaging to assess longitudinal myocardial strain and aortic strain in patients with axSpA (318). The main objective was to evaluate early cardiovascular impairment, which often remains undetected using conventional echocardiographic methods. The study employed strain imaging and pulse wave velocity (PWV) to capture subtle changes in the function of the left ventricle (LV) and the aorta. Results indicated that AS patients exhibited reduced strain values in both the myocardium and aorta compared to healthy controls, suggesting early signs of cardiovascular dysfunction before clinical symptoms became apparent. These studies suggest novel ways in which TTE, a non-invasive technique can be utilized in cardiovascular screening in axSpA patients especially in areas where MRI or CT is not a viable option.

While Cardiac MRI is traditionally utilized in rheumatology to assess for structural heart disease and inflammatory involvement, it is also being used to explore novel applications in assessing subclinical atherosclerosis in axSpA patients. Two studies from Biesbroek et al. highlight the use of Cardiac MRI in axSpA patients for assessing cardiovascular involvement, specifically focusing on aortic stiffness, and LV remodelling. The researchers

employed PWV, an indicator of aortic root stiffness, as well as MRI-based assessment of myocardial hyperenhancement, which is suggestive of fibrosis. The studies found that axSpA patients with increased aortic stiffness had significant associations with reduced LV ejection fraction and myocardial hyperenhancement, indicating early signs of fibrosis and myocardial dysfunction (319,320) . While these findings are interesting in terms of early identification of fibrosis and myocardial dysfunction in axSpA patients, which are often not detectable with conventional methods like TTE, it would not typically be utilized for CVD assessment due to its cost and complexity.

Finally, an interesting approach by van Bentum et al. explored the use of Retinal Imaging, including Fundus Photography and OCT-A, to detect microvascular changes in axSpA patients. Retinal imaging provides a non-invasive window into systemic vascular health and can in fact detect early signs of atherosclerotic CVD (321). The study found that retinal arteriolar narrowing and venular widening were associated with an increased risk of cardiovascular disease (322). An argument for using retinal imaging in axSpA patients could be made given patients' predisposition to uveitis, which involves inflammation of the uveal tract in the eye, and which can cause significant microvascular changes in the retina. Given this predisposition, retinal imaging techniques like Fundus Photography and OCT-A are well-suited for axSpA patients, as they not only help monitor ocular health but also provide insights into systemic microvascular health.

4.5 Novel biomarkers and their role in CVD screening in axSpA patients

While traditional cardiovascular risk factors such as hypertension, hyperlipidaemia, and smoking contribute to CVD, they often do not fully explain the increased cardiovascular burden observed in axSpA patients. As a result, recent research has explored the use of novel biomarkers to identify axSpA patients at heightened cardiovascular risk. These biomarkers reflect underlying processes such as endothelial dysfunction, systemic inflammation, and vascular stiffness, which are all precursors to atherosclerosis.

Biomarkers such as endothelial progenitor cells (EPCs) and inflammatory cytokines like tumour necrosis factor-alpha (TNF-α) have emerged as potential indicators of cardiovascular health in axSpA. These biomarkers could offer clinicians the ability to detect early cardiovascular risk and initiate more aggressive treatment strategies in axSpA patients who may be predisposed to cardiovascular events. Herer explores studies that investigate these biomarkers in axSpA patients and evaluates their potential role in predicting cardiovascular outcomes and their use in routine CVD screening.

One of the most significant findings regarding cardiovascular biomarkers in axSpA is the depletion of EPCs. This has been examined in axSpA patients and it has found that EPCs were significantly depleted in comparison to healthy controls. These findings correlated with increased CIMT, and impaired flow medicated dilation (FMD), a non-invasive test that measures how an artery dilates when blood flow increases, which are markers of subclinical atherosclerosis and endothelial dysfunction, respectively (253,323). Furthermore, EPC depletion was associated with longer disease duration, elevated CRP, and higher TNF-α levels. This highlights the potential of EPCs as an early biomarker for

vascular damage in axSpA patients. In this context, EPCs may serve as both a predictive biomarker and a therapeutic target for preventing cardiovascular disease in axSpA patients by addressing the underlying endothelial dysfunction and chronic inflammation (323).

In a similar study, Baykara et al. investigated the role of visfatin, a pro-inflammatory adipocytokine, in axSpA patients (324). Elevated levels of visfatin were found to correlate with increased CIMT and reduced FMD, indicating that visfatin may play a role in early atherosclerosis development. The study suggests that visfatin could be used as a novel biomarker for identifying axSpA patients at risk of subclinical atherosclerosis. Visfatin, being associated with both metabolic dysfunction and inflammation, underscores the complex interplay between metabolic and inflammatory pathways in the pathogenesis of CVD in axSpA patients (325).

Other biomarkers of interest include osteoprotegerin (OPG) and sclerostin (SCL), which have been studied for their role in vascular calcification. Genre et al. explored the association between these markers and cardiovascular risk in axSpA patients (326). OPG and SCL, which are traditionally linked to bone metabolism, were found to be elevated in axSpA patients and associated with vascular calcification, a key feature of atherosclerosis (327–329). This suggests that the bone-vascular axis may contribute to the increased cardiovascular risk observed in axSpA. Similarly, Sari et al examined fetuin-A, a glycoprotein involved in calcium metabolism and found it to be elevated in axSpA patients. Fetuin-A was positively correlated with inflammatory markers and atherosclerosis, reinforcing the notion that vascular calcification is an important aspect of cardiovascular disease in axSpA (330).

Endothelial dysfunction has also been highlighted as a key contributor to CVD risk in axSpA. Several biomarkers of endothelial dysfunction have been investigated, including von Willebrand factor (vWF), thrombomodulin (sTM), and urotensin-II (UT-II). These biomarkers were elevated in axSpA patients compared to healthy controls, indicating early endothelial damage (255). Elevated levels of vWF, sTM, and UT-II suggest that endothelial dysfunction occurs early in the disease process, which may precede clinically evident cardiovascular disease (255). These findings underscore the potential for using endothelial biomarkers to detect early cardiovascular risk in axSpA patients before irreversible vascular damage occurs.

In the context of inflammatory pathways, Azevedo et al. investigated the levels of VCAM-1 and ICAM-1, which are adhesion molecules involved in endothelial activation, as well as IL-8, a pro-inflammatory cytokine. These biomarkers were evaluated in axSpA patients to assess their association with disease activity and cardiovascular risk. The findings showed that VCAM-1 and ICAM-1 were significantly elevated in axSpA patients and were positively correlated with cardiovascular risk factors like hypertension, dyslipidaemia, and smoking. However, VCAM-1 did not correlate with disease activity scores such as BASDAI, while IL-8 was strongly associated with disease activity, specifically with BASDAI and ASDAS scores, but not with cardiovascular risk factors such as SBP, DBP, or BMI. This suggests that while VCAM-1 and ICAM-1 are more related to cardiovascular risk, IL-8 is more indicative of inflammatory disease activity (331).

However, not all biomarkers studied in axSpA have proven to be effective indicators of cardiovascular risk. Investigations into the neutrophil to lymphocyte ratio, platelet to lymphocyte ratio , and mean platelet volume in axSpA patients but found no significant

association between these markers and cardiovascular risk (332). While these biomarkers have been shown to have utility in other inflammatory conditions, they may not be reliable predictors of cardiovascular disease in axSpA.

Lastly another study from Genre et al. explored biomarkers such as asymmetric dimethylarginine (ADMA), pulse wave velocity (PWV), and FMD, which are linked to endothelial dysfunction and arterial stiffness. Elevated ADMA and increased PWV, along with impaired FMD, were found to be significant indicators of early vascular changes in axSpA patients. These findings suggest that arterial stiffness and endothelial dysfunction are early manifestations of cardiovascular risk in axSpA, driven largely by chronic inflammation (333).

4.6 Discussion

This chapter provides a detailed exploration of current CVD screening tool used in axSpA and the ongoing research in order to create more suitable CVD predictive models for axSpA patients. Several key points and recommendations are discussed in the literature, focusing on the inadequacy of traditional CVD screening methods and the need for tailored approaches to address this unique patient population.

One of the primary findings from the literature is the unique contribution of chronic inflammation in axSpA to cardiovascular risk, independent of traditional factors. As discussed in Chapter 1, the chronic systemic inflammation in axSpA patients leads to endothelial dysfunction, accelerated atherosclerosis, and increased arterial stiffness. Studies confirm that axSpA patients are not only at risk due to traditional factors like

dyslipidaemia and hypertension but also from inflammation-induced metabolic alterations, which significantly increase cardiovascular morbidity and mortality. For example, patients with AS have standardized mortality ratios for cardiovascular complications ranging from 1.6 to 1.9, emphasizing the need for more rigorous cardiovascular management.

The literature notes a significant gap in the current cardiovascular screening methods applied to axSpA patients. The screening practices for cardiovascular disease in axSpA are largely extrapolated from general population guidelines or those developed for other inflammatory diseases such as RA and SLE .The absence of specific screening guidelines for axSpA has resulted in inconsistent cardiovascular assessments, leading to missed opportunities for early intervention and highlighting the need for the development of predictive models that integrate both traditional risk factors and disease-specific elements like chronic inflammation and disease activity.

In this chapter, the discussion also extends to emerging biomarkers and novel imaging techniques that hold promise for better cardiovascular screening in axSpA patients. Novel approaches, such as the use of the apolipoproteins and inflammatory cytokines such as IL-8, are suggested as more accurate predictors of cardiovascular risk.

Moreover, non-invasive imaging techniques like carotid Doppler ultrasound and CAC scoring, which can detect subclinical atherosclerosis, are highlighted as underutilized yet highly effective tools. CIMT, for example, is emerging as a significant predictor of cardiovascular risk, particularly for identifying subclinical disease suggesting carotid doppler ultrasound should be incorporated into clinical predictive models to enhance early detection and intervention in axSpA patients. CAC scoring, while widely used for

coronary artery disease prediction, is somewhat controversial in its effectiveness for axSpA patients due to the risk of underestimating non-calcified plaques driven by inflammation.

Novel imaging techniques such as STE, TDE, and advanced MRI imaging techniques, which may offer more sensitive detection of subclinical cardiovascular issues in axSpA patients. Biomarkers such as EPCs, visfatin, and OPG are also emerging as potential predictors of cardiovascular risk, particularly in their ability to reflect endothelial dysfunction and subclinical atherosclerosis. These biomarkers, combined with advanced imaging techniques, offer an opportunity to develop more refined cardiovascular screening and predictive models.

4.7 Conclusion

In summary, the chapter argues that traditional cardiovascular risk assessment tools may not adequately reflect the true cardiovascular risk in axSpA patients due to their systemic inflammation and disease activity. The review emphasizes the need for novel clinical predictive models that integrate traditional risk factors with disease-specific inflammatory markers, imaging findings, and biomarkers. These tailored tools can offer a more accurate identification of high-risk individuals, ensuring early intervention and better long-term outcomes.

Chapter 5: Cardiovascular Disease Risk Management in Inflammatory Joint Disease: An Audit and Intervention Study

5.1 Introduction

In recent years, axSpA has gained recognition as a condition associated with a significantly elevated risk of cardiovascular disease (CVD) alongside other inflammatory joint disease (IJD). The chronic inflammatory nature of axSpA plays a pivotal role in accelerating atherosclerosis, highlighting the urgent need for effective CVD risk management strategies in this patient population.

Recognizing this, EULAR issued updated recommendations in 2015/2016 for managing CVD risk in IJD focusing on RA, PSA and axSpA. These guidelines underscore the critical importance of clinicians being aware that patients with IJD face a higher risk of CVD compared to the general population. This heightened risk is attributed not only to traditional cardiovascular risk factors but also to the persistent systemic inflammation inherent in these diseases.

To formulate these recommendations, the EULAR task force conducted a comprehensive systematic review of the literature, evaluating the prevalence and impact of CVD in IJD patients. This review encompassed studies on the pathophysiology of cardiovascular risk in IJD, the suitability of traditional CVD risk prediction models for this population, and the efficacy of various therapeutic interventions in mitigating this risk. The recommendations

discussed below were developed based on the strength and quality of the evidence reviewed.

This chapter will delve into these EULAR recommendations, with a particular focus on their application to AxSpA, and will discuss the implications for clinical practice. This section will also include a discussion on a completed audit, conducted to assess whether our department's practices align with these international guidelines. The audit aimed to identify any gaps in the current management of cardiovascular risk factors in our axSpA patient population and to determine the effectiveness of our clinical practices in mitigating this elevated cardiovascular risk.

Below are the EULAR recommendations that outline the essential steps for integrating comprehensive cardiovascular risk assessments and management strategies into the routine care of patients with inflammatory joint disorders, including axSpA, RA, and PsA.

1. Rheumatologists are tasked with ensuring that CVD risk management is integrated into the routine care of patients with AxSpA. This responsibility includes conducting regular risk assessments and coordinating care with other healthcare professionals as necessary.
2. The recommendations also advise that the use of NSAIDs and corticosteroids should be guided by specific treatment protocols, given their potential to exacerbate cardiovascular risk.

3. Controlling disease activity in axSpA is essential for reducing CVD risk, as persistent inflammation has been linked to an increased risk of atherosclerosis. Evidence suggests that effective management of axSpA, particularly through DMARDs can mitigate this risk.
4. EULAR recommends that patients with axSpA undergo CVD risk assessment at least once every five years, with reassessment following significant changes in antirheumatic therapy. It is important to note that this is only advised for patients who are deemed low risk, and this approach aligns with broader cardiovascular guidelines, acknowledging that more frequent assessments may not substantially reduce CVD morbidity or mortality in this population. These guidelines stop short on stating specify time frames for follow-up in intermediate- and high-risk patients. While they emphasize that higher-risk patients should be monitored more closely and that re-assessment should occur more frequently than in low-risk patients, they do not provide specific intervals for these patient cohort.
5. Traditional CVD risk models, such as the SCORE system, are not fully accurate for patients with inflammatory joint disorders due to the additional risk posed by chronic inflammation. EULAR suggests using a 1.5 multiplication factor when applying these models to patients with RA, a practice that could also theoretically be considered for axSpA however this adjustment remains debated, as the evidence is less robust compared to RA studies.
6. The EULAR guidelines emphasize the importance of regular lipid profile assessments in patients with IJD, recommending the measurement of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides. Among these, the Total

Cholesterol to HDL Cholesterol (TC:HDL ratio is highlighted as a particularly important marker for cardiovascular risk, with higher ratios indicating an elevated risk of atherosclerosis and cardiovascular events. The guidelines also recognize that chronic inflammation inherent in IJD can alter lipid metabolism, sometimes resulting in lipid profiles that appear less atherogenic—such as lower total cholesterol or LDL levels—but which still carry significant cardiovascular risk due to the underlying inflammatory burden.

7. Lifestyle modifications, including smoking cessation, regular physical activity, and a healthy diet, are strongly advocated by EULAR as fundamental components of CVD risk management.
8. A significant addition to the 2015/2016 EULAR recommendations is the consideration of carotid ultrasound as part of the cardiovascular risk evaluation in patients with RA. This imaging modality is advocated for detecting asymptomatic atherosclerotic plaques, which are strongly predictive of future cardiovascular events. The presence of carotid plaques, as identified through doppler ultrasound, is associated with a heightened risk of acute coronary syndromes (ACS) in patients with inflammatory joint disorders. Consequently, carotid ultrasound can play a pivotal role in reclassifying patients into higher CVD risk categories, prompting more aggressive preventive measures such as the initiation of statin therapy.

Despite the EULAR guidelines emphasizing the importance of CVD screening in patients with IJD, first introduced in 2011 and updated nearly a decade ago to advocate for screening these patients as rigorously as those with type 2 diabetes, the question persists as to whether IJD patients in Ireland are being appropriately screened for CVD in accordance with these international recommendations. This audit was conducted to

identify any potential gaps in the current management of cardiovascular risk factors in our IJD patient population and to assess whether our clinical practices align with the EULAR guidelines.

Clinical audits are essential tools for assessing and improving healthcare practices. By systematically comparing current practices against established standards, audits identify gaps in care and inform necessary changes. The audit cycle is completed when these changes are implemented, and a re-audit is conducted to evaluate the effectiveness of the interventions. This study employed this method to evaluate CVD risk management practices in a cohort of IJD patients, followed by the establishment of a clinician-led CVD screening clinic for AxSpA patients.

5.2 Methods

5.2.1 Initial Audit Design

The initial audit was conducted retrospectively from August to October 2023, involving 150 patients diagnosed with IJD including RA, PSA and AxSpA. Data were extracted from patient medical records using a standardized audit proforma (Appendix 3.1). This form collected detailed information on demographics, diagnosis, documented CVD conditions, and screening practices for CVD risk factors. The parameters evaluated included:

1. Blood pressure (BP)
2. Lipid profiles
3. Glucose levels
4. Smoking status

5. Use of corticosteroids and NSAIDs
6. Disease activity scores
7. Documentation of lifestyle advice including exercise, diet and smoking cessation.

5.2.2 Implementation of a Clinician-Led CVD Screening Clinic

Following the audit, the results were discussed in a departmental meeting, which led to the establishment of a dedicated CVD screening clinic for AxSpA patients. The clinic's protocol was designed to align with the 2015/2016 EULAR guidelines and included comprehensive assessments of CVD risk factors. A significant difference to EULAR guidance however was the choice of cardiovascular risk prediction model. The Q-Risk 3 cardiovascular risk prediction model was chosen over the SCORE model, which is typically recommended by EULAR, particularly with the advised adjustment of multiplying the SCORE by 1.5 for patients with RA. The decision to use Q-Risk 3 was influenced by several factors that make it more appropriate for our patient population, particularly those with AxSpA. While the SCORE model, with its 1.5 multiplier, is recommended specifically for RA, it does not account for the broader spectrum of IJDs, nor does it include direct adjustments for chronic inflammation outside of RA. Moreover, Q-Risk 3 considers a broader set of risk factors beyond those included in SCORE, such as chronic kidney disease (CKD), corticosteroid use, and other inflammatory conditions like RA and SLE are specifically noted, providing a more comprehensive and tailored cardiovascular risk

assessment. The SCORE model is also primarily designed for middle-aged individuals, typically between the ages of 40-65, limiting its applicability to younger and older patients.

5.3 Objectives

The primary objective of this pilot study is to evaluate the feasibility and utilization of such a specialized clinic within the context of routine rheumatology care. The pilot will assess whether a dedicated CVD clinic is necessary for this patient population, or if CVD risk management should be more effectively integrated into general rheumatology clinics. As part of this pilot, patients will undergo a comprehensive, once-off CVD assessment at the specialized clinic, with subsequent follow-up and ongoing management to be conducted in the general rheumatology clinic. This approach allows for the evaluation of the clinic's impact on patient care and outcomes, while also determining the practicality of implementing such a model in broader clinical practice The secondary objectives of this clinic is to reduce cardiovascular events in axSpA patients through early identification and proactive management of CVD risk factors and to ensure that care provided adheres strictly to EULAR guidelines, particularly focusing on disease activity control, lifestyle modification, and appropriate use of pharmacologic interventions.

5.4 Patient Eligibility

Patients eligible for inclusion in the study must have a diagnosis of axSpA, be 18 years of age or older, and provide consent for cardiovascular screening. Patients will be excluded if

they have been diagnosed with other inflammatory joint diseases, such as RA and PsA or if they demonstrate non-compliance with clinic visits or management plans.

5.5 Baseline Assessment Protocol

1. Medical History: Comprehensive review including axSpA disease activity, traditional CVD risk factors including smoking, hypertension, diabetes mellitus and family history of CVD.
2. Physical Examination: Includes measurements of BP, BMI, and WHR, as well as assessment of peripheral pulses and signs of vascular disease.
3. Laboratory Tests: Lipid profile including total cholesterol (TC), high-density lipoprotein cholesterol (HDL), Low-density lipoprotein cholesterol (LDL), Triglycerides (TG) and TC:HDL ratio. Diabetic screen to include random blood glucose and HbA1c, and inflammatory markers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]).
4. Disease Activity Assessment: Utilize BASDAI and ASDAS-CRP
5. Medication Review: Evaluation of current medications, particularly NSAIDs and corticosteroids, with adjustments made to minimize CVD risk.
6. Risk Stratification: Application of the Q-risk 3 and classification of patients into low, moderate, or high CVD risk categories.

5.6 Management Plan

1. Disease Activity Control: Optimize therapy to achieve low disease activity or remission.
2. Lifestyle Modifications: Provide personalized recommendations on diet, physical activity, and smoking cessation.
3. Pharmacologic Interventions: Initiate or adjust antihypertensive, lipid-lowering, or antidiabetic medications as appropriate or consult GP to do same where appropriate. Consider cardiology review in high-risk patients if deemed appropriate.
4. Corticosteroids and NSAIDs: Minimize corticosteroid use and initiate tapering when possible. Prescribe NSAIDs cautiously, particularly in patients with high CVD risk.

Plan for Follow-Up Visits

1. Reassess disease activity and adjust treatments accordingly.
2. Monitor BP, BMI, waist-hip ratio, lipid profile, and glucose levels.
3. Reinforce lifestyle recommendations and ensure adherence to prescribed medications.
4. Update CVD risk stratification and revise management plans as guided by recommendations.
5. Comprehensive re-evaluation of all baseline assessment components.

5.7 Quality Improvement

The clinic will engage in continuous quality improvement through periodic reviews of clinical outcomes and adherence to protocols. Feedback from patients will be solicited to identify potential gaps in service delivery. Ongoing education and training for clinic staff will ensure alignment with the latest guidelines and best practices in CVD risk management for AxSpA patients.

5.8 High Value Definitions for Use in Clinical Practice

Blood Pressure (BP)

- Systolic Blood Pressure (SBP): Greater than 130 mmHg
- Diastolic Blood Pressure (DBP): Greater than 80 mmHg

Waist-Hip Ratio (WHR)

- Females: Greater than 0.85
- Males: Greater than or equal to 0.90

Body Mass Index (BMI)

- Underweight: BMI less than 18.5
- Normal weight: BMI 18.5 to 24.9
- Overweight: BMI 25.0 to 29.9
- Obesity Class I (Moderate): BMI 30.0 to 34.9
- Obesity Class II (Severe): BMI 35.0 to 39.9

- Obesity Class III (Very severe or Morbid obesity): BMI 40.0 and above

HbA1C

- Pre-diabetic range: Greater than or equal to 42 mmol/mol
- Diabetic range: Greater than or equal to 48 mmol/mol

Random Glucose

- High: Greater than or equal to 11.1 mmol/L

Lipid Profile

- **Total Cholesterol:**
  - Borderline: 5.17–6.18 mmol/L
  - High: Greater than 6.18 mmol/L
- **LDL Cholesterol:**
  - Borderline: 3.37–4.11 mmol/L
  - High: Greater than or equal to 4.14 mmol/L
- **HDL Cholesterol:**
  - Low for Males: Less than 1.04 mmol/L
  - Low for Females: Less than 1.29 mmol/L
- **Triglycerides:**
  - Borderline: 1.70–2.26 mmol/L
  - High: Greater than 2.27 mmol/L
- **TC: HDL Ratio:**
  - High risk: Greater than or equal to 5

5.9 Results

5.9.1 Findings from Initial Audit

The initial audit highlighted significant deficiencies in the screening and documentation of CVD risk factors among the 150 IJD patients reviewed. The key findings are summarized in Table 5.1 and 5.2 below:

Table 5.1: CVD screening results from Initial Audit

Screening	PSA	RA	AxSpA	Total N=150 (%)
BP	0	0	0	0 (0)
Lipids	12	3	2	17 (11.33%)
Glucose	4	0	1	5 (3.33%)
Smoking Status	7	7	12	26 (17.33%)
Steroid Use	25	21	3	29 (19.33%)
NSAID use	21	17	34	73 (48.67%)
Disease Activity	49	48	47	144 (96%)
CVD RPM	0	0	0	0 (0%)

Table 5.2: Lifestyle Advice results from initial audit

Lifestyle Advice	PSA	RA	AxSpA	Total N=150 (%)
Exercise	2	2	14	16 (10.67%)
Diet	2	1	0	3(2 %)

The initial audit results showed a notable lack of comprehensive screening and documentation for CVD risk factors across all patient groups. BP a fundamental marker of cardiovascular risk, was not recorded for any of the 150 patients included in the audit. This

omission represents a critical gap in routine clinical practice, given that hypertension is a well-established risk factor for CVD and is easily measurable in clinical settings.

Lipid profiles, essential for assessing dyslipidaemia—a key modifiable risk factor—were documented in only 11.33% of patients. This low rate of screening is particularly concerning in a population already at heightened risk due to chronic systemic inflammation. Similarly, glucose levels were recorded in just 3.33% of patients, further highlighting the inadequate assessment of CVD risk factors.

Smoking status, another significant risk factor, was documented in only 17.33% of cases. This suggests missed opportunities for smoking cessation interventions, which are crucial for reducing cardiovascular risk. Although disease activity was monitored in 96% of patients, the complete absence of cardiovascular risk prediction models in clinical practice is alarming. These models are critical for identifying high-risk patients and guiding appropriate interventions, and their omission could result in missed opportunities for necessary risk factor modifications.

While disease activity was recorded in 96% of patients, indicating a good level of monitoring for disease-related factors, no cardiovascular risk prediction models were applied in any case. The absence of cardiovascular risk prediction models' usage is particularly concerning, as these models are crucial for estimating a patient's overall risk of cardiovascular events and guiding appropriate interventions. Without the application of these models, clinicians may miss opportunities to identify high-risk patients who could benefit from more aggressive risk factor modification.

Moreover, the provision of lifestyle advice was notably lacking, with only 10.67% of patients receiving exercise recommendations and a mere 2% receiving dietary guidance. This suggests a broader issue of insufficient focus on lifestyle modifications, which are essential components of managing cardiovascular risk. The lack of emphasis on these interventions reflects a gap in clinician awareness of their role in comprehensive patient management and the importance of empowering patients to actively manage their cardiovascular health.

5.9.2 Prevalence of Cardiovascular Disease

Table 5.3 and 5.4 show the prevalence of various CVD conditions among patients with PSA, RA and AxSpA and the extent to which these conditions were documented correctly in the clinic.

Table 5.3: Official Prevalence of CVD in IJD patients

CVD	PsA	RA	AxSpA	Total	Prevalence %
IHD	2	9	3	14	9.33%
Stroke	0	0	1	1	0.67%
PVD	0	0	1	1	0.67%
DM	4	3	1	8	5.33%
HTN	14	17	10	41	27.33%
Dyslipidaemia	13	11	6	30	20%

Table 5.4: CVD Conditions Documented in IJD Patients.

CVD	PSA	RA	AxSpA	Total	Documented correctly %
IHD	1	2	1	4	29
Stroke	0	0	0	0	0
PVD	0	0	1	1	100
DM	4	1	1	6	75
HTN	10	8	4	22	53.65
Dyslipidaemia	12	3	3	18	60

The audit also documented the noting or documentation of various CVD conditions within the cohort, revealing that 9.33% of patients had IHD, 0.67% had experienced a stroke, 0.67% had peripheral vascular disease (PVD), 5.33% had diabetes mellitus (DM), 27.33% had hypertension (HTN), and 20% had dyslipidaemia. These findings highlight the significant burden of CVD in this patient population, reinforcing the need for more rigorous screening and management practices.

The audit revealed significant variability in the accuracy of documentation for CVD conditions among patients with IJD. IHD was documented correctly in only 29% of cases, despite a high prevalence of 9.33% within the cohort. This under-documentation suggests a substantial gap in the recognition or recording of this serious condition, which could lead to inadequate management and increased patient risk. No stroke cases were documented however this had a low prevalence of 0.67% similar PVD which had a documentation accuracy of 100%.

DM had a relatively high documentation rate of 75%, yet the 25% under-documentation still presents a concern, especially given its strong link to CVD. HTN despite being the most common condition in the cohort, was correctly documented in only 53.65% of cases, highlighting a significant gap in accurate record-keeping. Similarly, dyslipidaemia was properly documented in just 60% of cases, leaving 40% unrecorded. These levels of under-documentation across key risk factors represent major deficiencies in patient care, potentially undermining the effective management of CVD risk in this population.

These findings underscore the need for improved screening and documentation practices in clinical settings. Accurate documentation is essential not only for the effective management of individual patients but also for understanding broader trends and risks within patient populations. The discrepancies between the official prevalence and documented cases suggest that many patients may not be receiving the appropriate level of care and intervention required to manage their cardiovascular risk effectively. To address these issues, routine and systematic screening for CVD risk factors, improved clinician training on the importance of accurate documentation, and the integration of standardized cardiovascular risk assessments into routine care for IJD patients are recommended.

5.9.3 Re-Audit Results Following Clinic Implementation

After the establishment of the clinician-led CVD screening clinic, a re-audit was conducted focusing on 30 AxSpA patients who underwent the new comprehensive assessment protocol. The results are summarized in Table 5.5 below:

Table 5.5: Re-Audit Results Following Clinic Implementation

Parameter	n (%)
Review AxSpA disease activity	30 (100)
Medications review	30 (100)
Steroid and NSAID use review	30 (100)
Assess traditional CVD risk factors	30 (100)
Record family history of CVD	30 (100)
BP	30 (100)
BMI	30 (100)
WHR	30 (100)
Assess peripheral pulses	30 (100)
TC	30 (100)
LDL	30 (100)
HDL	30 (100)
TC:HDL ratio	30 (100)
Triglycerides	30 (100)
HBA1c	30 (100)
Random glucose	30 (100)
CRP	30 (100)
ESR	30 (100)
Apply the Q-risk 3 CVD risk prediction model	30 (100)
Classify patient into CVD risk category	30 (100)

The re-audit results demonstrate a remarkable improvement in the management and documentation of CVD risk factors among axSpA patients. Unlike the initial audit, which revealed significant gaps in screening and documentation, the re-audit shows 100% compliance across all evaluated parameters. This includes the review of axSpA disease activity, medication use (including steroids and NSAIDs), assessment of traditional CVD risk factors, and the recording of critical measurements such as BP, BMI, WHR, lipid profiles, glucose levels, and inflammatory markers. Additionally, the Q-risk 3 CVD risk prediction model was applied to all patients, and each patient was appropriately classified into a CVD risk category.

Table 5.6 shows the Demographics and Disease Characteristics of 30 axSpA patients included in the specialised CVD screening clinic. The cohort is predominantly male, with 73.33% of the participants being men, and has a mean age of 40 years, indicating a relatively young population. The average disease duration is 12.4 years, reflecting a group with long-standing chronic disease. Disease activity scores, including the ASDAS-CRP with a mean of 2.26 and BASDAI with a mean of 3.60, suggest moderate disease activity.

The Q-risk 3 classification indicates that 97% of the patients are at low risk for cardiovascular events, which aligns with the younger age and relatively well-controlled traditional risk factors in this population. Despite this, there are modifiable risk factors that warrant attention. The mean SBP is 130 mmHg and DBP is 81 mmHg, both within the high-normal range, suggesting a need for ongoing monitoring and potentially early intervention to prevent hypertension. The mean BMI of 27.20 kg/m² places the group, on average, in

the overweight category, which is associated with an increased risk of cardiovascular disease.

Inflammatory markers, such as the ESR and CRP, show means of 9.6 mm/hr and 5.30 mg/dl, respectively, indicating low to moderate systemic inflammation. risk.

The lipid profile is generally within acceptable limits, with a mean total cholesterol (TC) of 4.70 mmol/L, LDL cholesterol of 2.78 mmol/L, and HDL cholesterol of 1.39 mmol/L, resulting in a TC:HDL ratio of 3.52. This ratio is slightly above the ideal, indicating a need for careful monitoring, as it may suggest a borderline cardiovascular risk. Triglycerides average 1.25 mmol/L, which is within the normal range, and the HbA1c mean of 36.62 mmol/mol reflects good glycaemic control. The random glucose level, with a mean of 4.96 mmol/L, also supports this, indicating that most patients in the cohort are maintaining healthy blood glucose levels.

Table 5.6: Demographics and CVD characteristics of axSpA patients included in the specialised CVD screening clinic.

Parameter n=30	Mean (SD)
Male n (%)	22 (73.33)
QRisk -3 Low risk classification	29 (97)
Age	40 (7.59)
Disease Duration(years)	12.4 (6.5)
ASDAS-CRP	2.26 (1.18)
BASDAI	3.60 (2.34)
SBP mmHg	130 (16.25)

DBP mmHg	81 (9.45)
BMI kg/m2	27.20 (5.90)
WHR	0.93 (0.09)
ESR mm/hr	9.6 (14.54)
CRP mg/dl	5.30 (10.76)
TC mmol/L	4.70 (1.01)
LDL mmol/L	2.78 (0.86)
HDL mmol/L	1.39(0.35)
TC:HDL ratio	3.52(1.06)
Triglycerides	1.25(1.00)
HBA1c	36.62 (3.51)
Random glucose	4.96 (0.82)

While the results displayed in Table 5.6 provide an overview of the general characteristics of the axSpA patient cohort, Table 5.7 table delves deeper into how many patients met specific diagnostic criteria for CVD risk factors as defined in the clinic protocol. This analysis reveals the extent to which modifiable risk factors are present within the group, even among those generally classified as low risk by standard models such as Q-risk 3.

BP measurements were concerning, with 31% of patients exhibiting a SBP greater than 130 mmHg, while 44.8% had a DBP exceeding 80 mmHg. These elevated levels of blood pressure highlight the potential for increased cardiovascular events, even in patients without recognized risk factors. The data suggest the importance of vigilant monitoring

and early intervention strategies to manage blood pressure effectively within this population.

The waist-hip ratio (WHR), an important marker of central obesity, was elevated in 75.9% of the patients, surpassing the threshold of 0.85 for females or 0.90 for males. This finding underscores a high prevalence of central obesity, which is strongly linked to an increased risk of cardiovascular complications. Obesity, as measured BMI, was also prevalent in this cohort, with 34.5% of patients classified as obese (BMI of 30 or greater. Given this, there is a clear need for targeted weight management and lifestyle interventions to reduce cardiovascular risk in axSpA patients.

In terms of glycaemic control, 10.3% of the patients had elevated HbA1C levels (≥ 42 mmol/mol), indicating impaired glucose regulation. However, none of the patients had HbA1C levels indicative of overt diabetes (≥ 48 mmol/mol), and random glucose levels remained below the threshold for concern (≥ 11.1 mmol/L). While significant dysglycemia was not widespread, the presence of elevated HbA1C in a subset of patients suggests that glucose metabolism should still be carefully monitored as part of a comprehensive CVD risk assessment.

Lipid profile analysis revealed notable abnormalities. TC levels were borderline elevated in 13.8% of patients, with another 13.8% presenting with high TC levels. LDL cholesterol was borderline elevated in 24.1% of patients, although none had critically high LDL levels. Notably, 30% of patients had low HDL cholesterol, a condition associated with increased cardiovascular risk. Additionally, 10.3% of the cohort had borderline elevated TG levels, with 6.9% exhibiting high TG levels. The TC:HDL ratio, an indicator of atherogenic

dyslipidaemia, was elevated in 10.3% of patients, further pointing to a significant lipid-related cardiovascular risk.

Table 5.7: Prevalence of Diagnostic Criteria for Cardiovascular Disease Risk Factors in AxSpA Patient

Parameter	n (%)
SBP > 130 mmHg	9 (31.0%)
DBP > 80 mmHg	13 (44.8%)
WHR > 0.85 (F) or >= 0.90 (M)	22 (75.9%)
BMI >= 30	10 (34.5%)
HbA1C >= 42 mmol/mol	3 (10.3%)
HbA1C >= 48 mmol/mol	0 (0.0%)
Random Glucose >= 11.1 mmol/L	0 (0.0%)
Total Cholesterol 5.17-6.18 mmol/L (Borderline)	4 (13.8%)
Total Cholesterol > 6.18 mmol/L (High)	4 (13.8%)
LDL Cholesterol 3.37-4.11 mmol/L (Borderline)	7 (24.1%)
LDL Cholesterol >= 4.14 mmol/L (High)	0 (0.0%)
Low HDL Cholesterol	9 (31.0%)
Triglycerides 1.70-2.26 mmol/L (Borderline)	3 (10.3%)
Triglycerides > 2.27 mmol/L (High)	2 (6.9%)
TC:HDL Ratio >= 5	3 (10.3%)

5.10 Conclusion

These findings highlight a critical disparity between the general cardiovascular risk classification and the actual presence of significant modifiable risk factors in this cohort of AxSpA patients. The specialized CVD clinic played an essential role in uncovering these risk factors that may have been overlooked in a general rheumatology setting, where the primary focus is often on managing disease activity rather than systematically addressing cardiovascular risk.

The high prevalence of elevated blood pressure, central obesity, and lipid abnormalities in a cohort largely classified as low risk by traditional models emphasizes the need for early and proactive cardiovascular management. This clinic has demonstrated the importance of comprehensive cardiovascular screening in AxSpA patients, revealing that even those categorized as low risk can harbour significant risks for future cardiovascular events.

The clinic's focused approach has not only identified these risks but also provided a structured framework for ongoing management, which is crucial for improving long-term cardiovascular outcomes in this high-risk population. The transition of care back to general rheumatology clinics, with continued monitoring and management based on the findings from this clinic, will be essential in sustaining the benefits of this once-off comprehensive assessment. This pilot study underscores the necessity of integrating cardiovascular risk management into routine care for axSpA patients, ensuring that modifiable risk factors are identified and addressed promptly to prevent future cardiovascular events. Future audits will be essential to evaluate the effectiveness of this intervention and to ensure continuous improvement in CVD risk management across all IJD patient groups. Additionally,

expanding similar clinics to other IJD populations, such as RA and PsA patients, could further enhance cardiovascular outcomes in these vulnerable groups.

Chapter 6: Integrating Cardiovascular Risk Assessment in Axial Spondyloarthritis: A Pathway for Utilizing Carotid Doppler Ultrasound in Low-Risk and Asymptomatic Patients

6.1 Introduction

In patients with IJD there is a well-established increased risk of developing atherosclerosis, driven by chronic systemic inflammation that accelerates the atherosclerotic process. This heightened risk necessitates effective strategies for the early detection and management of subclinical atherosclerotic disease within this population. Carotid Doppler ultrasound, a non-invasive imaging technique, has been proposed as a valuable tool for assessing subclinical atherosclerosis by measuring carotid intima-media thickness (CIMT) and detecting carotid plaques. The 2015/2016 EULAR guidelines for cardiovascular risk management in patients with inflammatory joint diseases recommend carotid Doppler ultrasound screening, reflecting a growing recognition of its potential utility in detecting early atherosclerotic changes and stratifying cardiovascular risk.

In recent years carotid ultrasound has become a newer method in detecting subclinical atherosclerosis, particularly among patients with IJD. The use of carotid ultrasound is based on its capability to provide a non-invasive, detailed evaluation of vascular changes that precede the clinical onset of CVD. Recent research has consistently demonstrated its value in identifying early markers of atherosclerosis, such as increased carotid intima-media thickness and the presence of carotid plaques, which serve as indicators of heightened cardiovascular risk however its use in clinical practice to date has not been

utilized (334–337). Alonso Blanco-Morales et al. developed a risk scoring system, AROSpA, incorporating factors like age, CRP levels, waist circumference, sex, and systolic blood pressure to predict the presence of subclinical atherosclerosis in SpA patients (337). In 2015, their research suggested that patients exceeding a certain score threshold were more likely to exhibit abnormal carotid findings. However, since then, there seems to be a lack of further studies aimed at developing pathways or methods to identify patients who could benefit from carotid doppler ultrasound for detecting subclinical atherosclerosis.

Previous studies have also examined the relationship between cardiovascular disease biomarkers and vascular changes in axSpA patients (336). These have emphasized the role of carotid ultrasound in detecting early vascular alterations, such as increased CIMT and arterial stiffness, which were more pronounced in axSpA patients than in healthy controls. These findings suggest that such vascular changes correlate strongly with disease duration and systemic inflammation, highlighting the need for early and regular cardiovascular monitoring using carotid ultrasound in this patient group (336).

The technology and methodology of carotid ultrasound have been refined to improve diagnostic accuracy. High-resolution B-mode ultrasound remains the standard technique for measuring CIMT and detecting plaques, offering a clear depiction of the arterial walls and enabling the identification of early atherosclerotic changes (338). Additional techniques, such as applanation tonometry for measuring pulse wave velocity, further enhance the detection of subclinical vascular abnormalities (302). Studies looking at the role of carotid ultrasound in assessing subclinical atherosclerotic disease in IJD such have

demonstrated that using automated software-guided radiofrequency techniques can improve the consistency and reliability of CIMT measurements, thereby refining cardiovascular risk stratification processes (334,335). However, there are several downsides to these automated approaches. Firstly, the effectiveness of these systems is highly dependent on the quality of the ultrasound images meaning that poor image quality can lead to inaccurate CIMT measurements this can also be due to the fact that automated systems lack the flexibility that experienced sonographers or radiologists possess, which is required when dealing with unique anatomies or complex cases (339) . There is also a risk of over-reliance on technology which may lead to lack of training and experience of trained personnel available to perform manual measurements, potentially compromising patient care. Moreover, issues related to software calibration and validation can arise, as different systems may use varying algorithms, leading to discrepancies between measurements and complicating comparisons between studies (340). The cost and accessibility of automated systems can be prohibitive, particularly in low-resource settings, and the underlying algorithms may introduce biases if they have been trained on limited datasets. Automated systems also lack the ability to integrate clinical context or detect incidental findings that could influence clinical decisions beyond CIMT measurements (340). Furthermore, these systems are prone to measurement artifacts, particularly in the presence of arterial calcification or plaques, which can lead to incorrect CIMT values (339,340). These limitations suggest that while automated software-guided techniques can improve the utilization of carotid doppler ultrasound for CVD risk stratification and may be beneficial for research purposes or for use by untrained sonographers, such as rheumatologists, they cannot replace the precision and accuracy of a trained professional sonographer or radiologist. Without a standardized approach where

every hospital uses the same machine with identical software there is no guarantee of consistent, accurate measurements across all patients, leading to potential disparities in assessments and compromising the reliability of cardiovascular risk stratification.

Carotid ultrasound findings frequently lead to the reclassification of cardiovascular risk. Rueda-Gotor et al. showed that axSpA patients are often reclassified into a very-high cardiovascular risk category following carotid ultrasound, primarily due to the detection of carotid plaques and increased CIMT (335). Such reclassification carries significant clinical implications, potentially prompting more aggressive cardiovascular preventive measures, including lifestyle changes, pharmacotherapy, and closer patient monitoring.

The body of evidence supports the role of carotid ultrasound in the early detection of subclinical atherosclerosis among patients with inflammatory conditions, allowing for timely intervention and potentially reducing the long-term cardiovascular burden in these high-risk groups. There is a growing consensus on the need to integrate carotid ultrasound into routine cardiovascular risk assessments for patients with conditions such as axSpA. Current research highlights the potential of carotid ultrasound to provide valuable insights into the early stages of atherosclerosis, facilitating a more proactive approach to preventing cardiovascular disease in clinical practice.

CIMT is recognized as a significant marker of atherosclerotic risk, though it does not always equate to subclinical atherosclerosis. An increase in IMT may also result from

nonatherosclerotic processes such as smooth muscle cell hyperplasia and fibrocellular hypertrophy, leading to medial hypertrophy and compensatory arterial remodelling (341). While IMT is an important marker of atherosclerotic risk, it should not be considered a direct risk factor requiring treatment.

Several guidelines provide recommendations for evaluating IMT. The European guidelines on cardiovascular disease prevention recommend IMT measurement for asymptomatic individuals with a 10-year risk of fatal cardiovascular disease between 1% and 5%, especially middle-aged adults at moderate cardiovascular risk (342). For hypertensive individuals at moderate risk, the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) suggest IMT measurement to detect asymptomatic vascular damage, defined as IMT greater than 0.9 mm or the presence of plaque (343). The American Society of Echocardiography (ASE) recommends carotid ultrasound scanning for patients at intermediate risk, including those with a family history of premature cardiovascular disease or severe abnormalities in a single risk factor (302).However, the American College of Cardiology (ACC) and American Heart Association (AHA) guidelines do not recommend routine vascular ultrasound for risk assessment of a first atherosclerotic cardiovascular disease event. IMT is measured as the distance between the lumen-intima and media-adventitia interfaces on a longitudinal view of the common carotid artery (CCA).

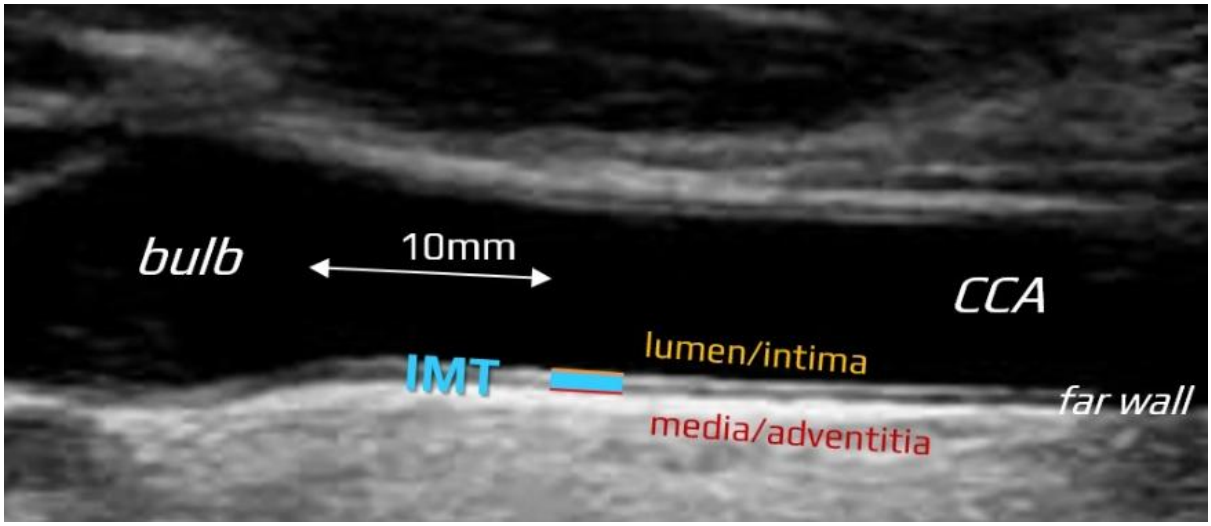

Figure 7:cIMT Measurement by Carotid Doppler Ultrasound

Accurate measurement requires a 10-mm straight arterial segment free of atherosclerotic plaque with clearly defined boundaries(344). The American Society of Echocardiography (ASE) recognises that normal IMT values increase with age and are higher in men than in women, and age- and sex-adjusted reference ranges are often used (345–347). The ASE guidelines suggest IMT values at or above the 75th percentile is generally considered high and indicative of increased cardiovascular risk (Table 6.1) (302). For instance, normal common carotid artery IMT values for men under 30 range from 0.39 to 0.48 mm on the right and 0.42 to 0.49 mm on the left, with values increasing progressively with age in both men and women. This understanding of IMT helps clinicians reclassify intermediate cardiovascular risk patients into lower or higher risk categories, aiding in more precise management strategies. Challenges in interpreting IMT results arise due to differences in measurement methodologies, such as defining the investigated carotid segment, using mean or maximal IMT, and including or excluding plaques. To mitigate these discrepancies, standardized methods for IMT measurement have been established, emphasizing the use

of high-resolution B-mode systems, specific equipment settings, and guidelines for conducting and measuring observations.

Table 6.1: Normal IMT Values According to ASE guideline

Age	P25 Right	P50 Right	P75 Right	P25 Left	P50 Left	P75 Left
Men <30	0.39	0.43	0.48	0.42	0.44	0.49
Men 31-40	0.42	0.46	0.50	0.44	0.47	0.57
Men 41-50	0.46	0.50	0.57	0.50	0.55	0.61
Men >50	0.46	0.52	0.62	0.53	0.61	0.70
Women <30	0.39	0.40	0.43	0.30	0.44	0.47
Women 31-40	0.42	0.45	0.49	0.44	0.47	0.51
Women 41-50	0.44	0.48	0.53	0.46	0.51	0.57
Women >50	0.50	0.54	0.59	0.52	0.59	0.64

This chapter will explore how carotid Doppler ultrasound can be instrumental in reclassifying patients into appropriate cardiovascular risk categories and in identifying low-risk individuals who could benefit from such screening. By examining the existing literature and evidence, the aim is to develop a pathway for incorporating carotid Doppler

ultrasound into clinical practice for better cardiovascular risk management in patients with axial spondyloarthritis and similar conditions. This approach seeks to refine risk stratification strategies and optimize preventive care, thereby improving overall patient outcomes.

6.2 Methods

This study included patients aged 25 to 60 years who had no previous history of CVD or known cardiovascular risk factors, renal disease, and could understand and consent to the study. Patients must also be able to lie in a supine. Individuals who were ex-smokers were eligible if they had abstained from smoking for at least five years. A family history of cardiovascular disease was also allowed. Participants were recruited from a specialty axSpA clinic at St. James's Hospital. Out of 115 patients screened, 35 met the inclusion criteria for the study. Written and oral informed consent was obtained from all participants prior to their involvement in the study.

All patients were assessed by the same rheumatology fellow to ensure consistency in evaluation. Each participant underwent a comprehensive clinical review that included a detailed medical history, medication review, and assessment of sleep and exercise patterns, as well as social history. The evaluation also covered disease manifestations, including extra-musculoskeletal and peripheral features, as well as radiographic versus non-radiographic disease classification and HLA-B27 status. Disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing

Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP). Patient-reported outcomes, including the Bath Ankylosing Spondylitis Functional Index (BASFI) and the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire, were also recorded. Full spinal measurements were conducted to determine the Bath Ankylosing Spondylitis Metrology Index (BASMI).

Anthropometric measurements, including weight, height, waist, and hip circumference, were obtained to calculate the waist-hip ratio and body mass index (BMI). Blood pressure was measured three times during the visit, and the average systolic (SBP) and diastolic blood pressure (DBP) were recorded. Blood tests to assess CVD risk factors included a fasting lipid profile (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], non-HDL cholesterol, total cholesterol/HDL ratio, and triglycerides), glycated hemoglobin (HbA1c), random glucose levels, high-sensitivity troponin-T, and N-terminal pro b-type natriuretic peptide (NT-proBNP). Additional novel biomarkers such as ferritin, fibrinogen, urate, creatine kinase (CK), and vitamin D levels were also measured. Inflammatory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), as well as a full blood count (FBC) to record platelet levels, were also obtained.

In this study, all patients underwent carotid doppler ultrasound and CIMT measurement at the common carotid artery (CCA) level to assess the presence of subclinical atherosclerosis. Patients were positioned supine with the head tilted slightly away from the side being examined to provide optimal access to the carotid arteries. The neck was extended, and ultrasound gel was applied to enhance the quality of the ultrasound

images. A high-resolution B-mode ultrasound machine with a transducer frequency of 7.5 to 15 MHz was used to obtain the images. Imaging settings, including gain and depth, were adjusted to clearly visualize the intima-media complex without artifacts, with the focal zone set at the level of the CCA.

All CIMT measurements were performed by the same senior vascular physiologist to ensure consistency and reduce variability. Measurements were conducted at three standardized locations (M1, M2, M3) along a 1 cm segment of both the right and left common carotid arteries, specifically 1 cm proximal to the carotid bulb. Manual measurements were taken during end-diastole to minimize variability due to arterial wall motion, with the end-diastolic phase identified through ECG gating or visual observation of arterial wall movement. The far wall of the CCA was targeted for measurement to maintain consistency across patients.

For each patient, three measurements were obtained on both the right and left CCAs. The mean of these three measurements for each side was calculated to derive an average CIMT value for the right and left CCAs. The CIMT values were considered abnormal if they exceeded 0.9 mm, as per the ESC criteria, or if they were greater than the 75th percentile based on age and sex, according to the ASE guidelines. In this study, a plaque was defined as a focal structure that encroaches into the arterial lumen by at least 0.5 mm or 50% of the surrounding intima-media thickness (IMT) or demonstrates a thickness of greater than 1.5 mm as measured from the media-adventitia interface to the intima-lumen interface. This definition was used to differentiate between diffuse intima-media thickening and

localized atherosclerotic changes, ensuring consistent identification and assessment of atherosclerotic plaques across all patients.

To minimize inter- and intra-observer variability, all measurements were performed by the same experienced vascular physiologist using consistent ultrasound settings and measurement techniques throughout the study. Data was documented meticulously, with CIMT measurements recorded along with patient identifiers and securely stored in accordance with local data protection guidelines. In Ireland, the Strandness criteria for carotid stenosis, as recommended by the Society for Vascular Technology of Great Britain and Ireland (SVT), is the standard practice for assessing carotid artery stenosis. These criteria were adhered to in the interpretation of the ultrasound findings for this study.

The statistical analysis was conducted using Microsoft Excel to explore the relationship between carotid plaques and various cardiovascular risk factors. Data were organized into columns for each variable. The Pearson correlation coefficient was likely used to measure the strength and direction of the linear relationship between each independent variable (e.g., age, disease duration) and the dependent variable (abnormal CIMT). Correlation coefficients range from -1 to +1, where values close to 0 suggest weak or no linear relationship. p-values were calculated to determine the statistical significance of each correlation coefficient. A p-value less than 0.05 typically indicates that the correlation is statistically significant. In this analysis, all p-values are above 0.05, indicating no significant associations were found.

6.3 Results

6.3.1 Cohort Demographics and Disease Characteristics

The study cohort consisted of 35 individuals with general characteristics shown in Table 6.2. Mean age was 40.97 years, 71.43% of participants were male and 94.29% were Caucasian. The cohort had an average disease duration of 12.46 years (SD = 6.55), suggesting a long-term presence of axSpA. A significant portion (62.86%) of the cohort had a diagnosis of R-axSpA, while 82.86% were HLA-B27 positive. Family history of CVD was reported in 22.85% of participants.

Table 6.2: General Characteristics of Patients Undergoing Carotid Doppler Ultrasound

Characteristic	Value
Age, mean (SD)	40.97 (9.34)
Male, n (%)	25 (71.43)
Caucasian, n (%)	33 (94.29)
Disease Duration in Years, mean (SD)	12.46 (6.55)

Characteristic	Value
Family History of CVD, n (%)	8 (22.85)
R-AxSpA, n (%)	22 (62.86)
HLA-B27 Positive, n (%)	29 (82.86)
Employed, n (%)	29 (82.86)
Ex-Smoker, n (%)	14 (48.85)
Sleep > 7 hours a night, n (%)	14 (40)
Moderate exercise (3+ days/week), n (%)	28 (80)

6.3.2 Medication Use and Treatment Patterns

Medication usage (shown in Table 6.3) within the cohort was varied, with 42.85% of participants having used NSAIDS previously, and 25.71% currently using NSAIDs. Steroid use was low, with only 2.85% of the cohort on current steroid therapy. There was no cumulative NSAID, or steroid dose calculated for patients. The use of bDMARDS was significant, with 75.43% of participants on bDMARDS and 57.14% specifically on a TNFi.

Table 6.3: Medication Use Among Study Cohort

Medication Use	n (%)	Medication Use	n (%)
NSAID Use		**DMARDS**	
Previous NSAID Use	14 (42.85)	csDMARDs	0 (0)
Current NSAID Use	9 (25.71)	bDMARDs	25 (75.43)
Never NSAID Use	3 (8.5)	**Biologic Therapies**	
As Needed NSAID Use	8 (22.5)	TNFi	20 (57.14)
Steroid Use		IL-17i	2 (5.7)
Current Steroid Use	1 (2.85)	JAKi	0 (0)
Previous Steroid Use	10 (28.57)	IL-12/23i	3 (8.5)
Never Steroid Use	24 (68.57)		

6.3.3 Cardiovascular Risk Factors and Clinical Measurements

The cohort's cardiovascular risk profile was evaluated through various clinical measurements and risk assessments and is summarized in Table 6.4. The cohort consists of individuals with no previous cardiovascular risk factors, as indicated by their categorization into low-risk groups according to Q-risk 3 scores (100%). The mean SBP is 128.45 mmHg (SD 11.30), and the mean DBP is 79.77 mmHg (SD 7.15), suggesting generally controlled blood pressure levels within this cohort. The average BMI is 27.10 kg/m² (SD 5.12), which falls within the overweight range.

Waist and hip circumferences have median values of 96 cm (IQR 86.5–105.0) and 103 cm (IQR 99.5–113.5), respectively, with a median waist-to-hip ratio of 0.9 (IQR 0.855–0.96), indicating a central fat distribution that may suggest an emerging risk profile. Lipid profile analysis shows a TG level of 1.07 mmol/L (IQR 0.56) and a mean non-HDL cholesterol level of 3.12 mmol/L (SD 0.96), along with a mean TC/HDL Ratio of 3.34 (SD 0.86), which are generally within acceptable ranges for a low-risk population.

Overall, while the cohort is categorized as low risk for cardiovascular disease and had no previous diagnosis of CVD risk factors, there are indicators such as elevated BMI and central adiposity that could suggest early risk factors potentially impacting future cardiovascular health.

Table 6.4: Cardiovascular Risk Factors and Clinical Measurements

Measurement	Mean (SD) or Median (IQR)
SBP (mmHg)	128.45 (11.30)
DBP (mmHg)	79.77 (7.15)
BMI (kg/m²)	27.10 (5.12)
Waist Circumference (cm)	96 (86.5–105.0)
Hip Circumference (cm)	103.0 (99.5–113.5)
Waist/Hip Ratio	0.9 (0.855–0.96)
TG (mmol/L)	1.07(0.56)
Non-HDL Cholesterol (mmol/L)	3.12 (0.96)

Measurement	Mean (SD) or Median (IQR)
TC/HDL Ratio	3.34 (0.86)
HbA1c	96 (86.5–105.0)
Random glucose	103.0 (99.5–113.5)
Q-risk 3 - Low-Risk Group, n (%)	35 (100)

6.3.4 Disease Activity

Disease activity scores was assessed using the BASDAI and ASDAS-CRP in this cohort with resulted shown Table 6.5. The BASDAI median score was 3.7 (IQR: 1.8–5.0), indicating moderate disease activity. Functional impairment was relatively low, with a BASFI median score of 1.8 (IQR: 1.2–2.9). AsQoL median score was 4.0 (IQR: 2.0–9.0), reflecting a moderate impact on the quality of life.

Table 6.5: Disease Activity Scores in cIMT cohort

Score Type	Median (IQR)
BASDAI	3.7 (1.8-5.0)
BASFI	1.8 (1.2-2.9)
BASMI	1.7 (1.05-3.35)
ASDAS-CRP	2.15 (1.41-2.55)
AsQoL	4.0 (2.0-9.0)

6.3.5 Carotid Artery Ultrasound Assessments

Carotid Doppler ultrasound assessments revealed mean cIMT measurements highlighted in Table 6.6. The mean right CCA IMT was 0.63 mm (SD = 0.12), and the left CCA IMT was 0.67 mm (SD = 0.15). Additionally, carotid plaques were present in 11% of the cohort.

Table 6.6: Carotid Doppler Ultrasound Measurements

Measurement	Mean (SD) or n (%)
Right CCA-IMT (mm)	0.63 (0.12)
Left CCA-IMT (mm)	0.67 (0.15)
Right ICA-IMT (mm)	0.66 (0.31)
Left ICA-IMT (mm)	0.60 (0.21)

6.3.6 Potential CVD Biomarkers

Table 6.7 presents the various biomarkers measured in the study cohort. Evaluating these values against clinically established normal ranges provides insight into the inflammatory status, cardiovascular risk, and overall health of the patients with axSpA.

Table 6.7: Potential CVD Biomarkers in cIMT Cohort

Biomarker	Median	IQR Range	Biomarker	Median	IQR Range
Urate (umol/L)	289.0	251.75 - 326.25	Vit D (nmol/L)	65	48.75 – 81.25
PRO-nt-BNP (ng/L)	27.0	12.5 - 41.5	CRP (mg/L)	1.7	0.65 – 2.75
CK (IU/L)	94.0	46.25 - 141.75	ESR (mm/Hr)	2.0	0 - 5.0
Fibrinogen (g/L)	2.8	2.36 - 3.24	Ferritin	63.6	34.58 – 92.63
Platelets (10-9/l)	257	234 - 280			

Urate levels within the cohort have a median of 289.0 umol/L, falling within the normal range for both men and women. This suggests that the patients do not exhibit hyperuricemia, a condition associated with gout and increased cardiovascular risk. The IQR range (251.75 - 326.25 umol/L) indicates that most patients have urate levels within a healthy range, aligning with typical population levels.

Troponin levels were measured in all patients within the cohort. All patients had levels below 14 ng/L, indicating that troponin was consistently low across the group. This uniform finding demonstrates that troponin levels were not a relevant marker in this study for assessing CVD risk, as all patients exhibited levels below the threshold typically associated with cardiac injury or increased CVD risk. Consequently, troponin was not considered a significant finding for the purposes of this analysis.

The median PRO-nt-BNP level is 27.0 ng/L, well below the threshold that typically indicates heart failure (<125 ng/L for individuals under 75 years of age). This low level of PRO-nt-BNP suggests that there is no overt cardiac dysfunction or significant cardiac stress within the cohort. Given the median falls well within the normal range, this biomarker provides reassurance regarding the cohort's overall cardiovascular health status, particularly concerning left ventricular function.

CK is a marker of muscle damage or inflammation, for this cohort the median CK value is 94.0 IU/L, which again falls within the normal range (26 - 192 IU/L). Normal levels suggest that there is no significant muscle injury or inflammatory myopathy in the cohort. The IQR (46.25 - 141.75 IU/L) supports this finding, as most patients have CK levels within the expected range, indicating stable muscular health in the context of AxSpA.

The median fibrinogen level of 2.8 g/L is within the normal range (2.0 - 4.0 g/L). Fibrinogen is an acute-phase reactant that increases in response to systemic inflammation. The fact that the median and IQR (2.36 - 3.24 g/L) fall within normal limits suggests that, on average, the cohort does not have elevated systemic inflammation. This aligns with the disease activity scores, which suggest moderate disease activity in AxSpA without significant inflammatory exacerbation.

Platelets are crucial in blood clotting and have been linked to atherosclerosis, a major cause of CVD. Elevated platelet counts can indicate increased thrombotic risk, which may contribute to cardiovascular events. The median platelet counts of 257.0 falls within the normal range of 150-400 x 10^9/L, suggesting no significant platelet-related risk in this cohort. The IQR shows a narrow variability (234.0 to 280.0), indicating that most patients

have platelet levels well within the normal range, with no signs of thrombocytosis or thrombocytopenia that might impact CVD risk.

Vitamin D deficiency has been associated with various adverse health outcomes, including increased risk of CVD. Vitamin D plays a role in cardiovascular health by influencing calcium metabolism, inflammation, and endothelial function. The median level of 65.0 nmol/L in this cohort is within the range often considered sufficient (50-125 nmol/L), although on the lower end. The IQR (48.75 to 81.25) suggests that some individuals may have levels nearing deficiency, which could potentially contribute to an increased risk of CVD. Sufficient Vitamin D levels are also important for reducing inflammation, and maintaining adequate levels could help mitigate inflammation-related cardiovascular risks.

CRP is a well-known marker of inflammation and is used in clinical practice to assess systemic inflammation levels. Elevated CRP levels have been strongly associated with an increased risk of CVD, as inflammation plays a critical role in the development of atherosclerosis. The median CRP level of 1.7 mg/L falls within the range that might be considered low-grade inflammation (1-3 mg/L). The IQR (0.65 to 2.75 mg/L) shows some variability, but generally, most patients have CRP levels within a range that does not indicate high inflammatory activity. This suggests that systemic inflammation, as measured by CRP, is not a significant concern for CVD risk in this cohort.

ESR is another marker of inflammation, although less specific than CRP. It measures the rate at which red blood cells sediment in a period of one hour and can be elevated in a

range of inflammatory, infectious, and malignant conditions. The median ESR in this cohort is 2.0 mm/Hr, which is within the normal range for most adults (0-20 mm/Hr). The IQR from -1.0 to 5.0 suggests minimal variability, and the values are well within normal limits, indicating that systemic inflammation levels are low in this cohort. Given the low levels of ESR, it is unlikely that inflammation, as measured by ESR, contributes significantly to CVD risk in this group.

Elevated Ferritin levels may reflect inflammation or iron overload, both of which can be associated with increased CVD risk. The median ferritin level of 63.6 falls within the normal range (20-250 ng/mL for men and 20-150 ng/mL for women), suggesting adequate iron stores in the cohort. The IQR (34.58 to 92.63) indicates some variability but remains within normal limits. The absence of elevated ferritin levels supports the conclusion that inflammation, as measured by this biomarker, is not a prevalent concern in this cohort and is unlikely to be a contributing factor to increased CVD risk.

The biomarker results for this cohort of AxSpA patients are mostly within normal clinical ranges, suggesting that these patients generally do not exhibit high systemic inflammation or significant cardiovascular risk as measured by these specific biomarkers. Overall, these findings support the notion that while axSpA patients may have moderate disease activity, they do not necessarily present with elevated cardiovascular or inflammatory markers, at least as captured by these commonly measured biomarkers.

The cohort studied demonstrated a moderate disease activity with a generally low to moderate cardiovascular risk profile. The presence of subclinical atherosclerosis and specific cardiovascular risk factors among this AxSpA cohort underscores the importance

of integrating cardiovascular risk assessments into routine clinical practice. The findings highlight the potential utility of carotid Doppler ultrasound as a non-invasive tool to monitor cardiovascular risk in low-risk and asymptomatic AxSpA patients. Close monitoring and tailored interventions are recommended to manage both disease progression and cardiovascular risk effectively.

6.4 Evaluating the Efficacy of Q-Risk 3 in Cardiovascular Risk Stratification of AxSpA Patients: A Comparison with Carotid Doppler Ultrasound Findings

All patients (n=35) in this study were initially classified as low risk for cardiovascular events according to the QRisk3 score. Table 6.8 shows the reclassification of patients to a higher CVR group after undergoing Carotid Doppler Ultrasound examination. Reclassification of CVR group was observed based on the criteria from the ASE and ECS for identifying subclinical atherosclerosis.

Table 6.8: Reclassification of Cardiovascular Risk in AxSpA Patients Based on Carotid Doppler Ultrasound Findings

Finding	Number of Patients (n)	Percentage (%)
Plaques Present	4	11.0
ASE-Abnormal Right Common Carotid Artery	30	85.7
ASE-Abnormal Left Common Carotid Artery	24	68.6
ECS-Abnormal Right Common Carotid Artery	1	2.8
ECS-Abnormal Left Common Carotid Artery	2	5.7

The data shows that a substantial number of patients were reclassified as having abnormal CIMT when evaluated using the ASE criteria. Specifically, 85.7% of patients had an abnormal right CCA and 68.6% had an abnormal left CCA. Additionally, 11% of patients presented with plaques, indicating potential subclinical atherosclerosis.

In contrast, the reclassification rates were significantly lower when applying the ECS criteria. Only 2.8% of patients were found to have an abnormal right CCA, and 5.7% had an abnormal left CCA.

These findings highlight a considerable discrepancy between the initial QRisk3 assessments and the subsequent CDU findings. The high reclassification rates using the ASC criteria suggest that the QRisk3 may underestimate the presence of subclinical atherosclerosis in patients with axSpA. Therefore, incorporating additional screening tools such as Carotid Doppler Ultrasound could enhance the accuracy of cardiovascular risk stratification in this patient population. Given that Carotid Doppler Ultrasound is a

resource-intensive procedure requiring specialized equipment and trained personnel, it would be necessary to identify patients who may have a heightened risk of subclinical atherosclerosis and could benefit from more intensive CVD screening. Therefore, we explored potential markers that could help identify patients at increased risk and prioritize them for further evaluation, potentially leading to their reclassification.

6.5 Factors Associated with Abnormal CIMT in Axial Spondyloarthritis Patients based on ASE guidelines.

Table 6.9 shows results on exploring potential associations between various clinical and demographic factors with abnormal CIMT as defined by the ASE in patients with axSpA. None of the variables analysed showed a statistically significant association with abnormal CIMT, as indicated by all p-values being greater than 0.05. This means there is no strong evidence to suggest that any of these factors have a meaningful impact on CIMT in this patient population and showed no Significant Associations

The correlation coefficients for all variables range from -0.185 to 0.170, suggesting that any relationships between the variables and CIMT are weak at best. Positive correlations indicate a direct relationship, while negative correlations indicate an inverse relationship. However, all correlations are close to zero, reinforcing the lack of strong relationships.

Table 6.9: Demographic and Clinical Factors Associated with Abnormal CIMT as per ASE Guidelines

Variable	Correlation Coefficient	P-Value
Disease Duration	0.0811	0.6431
Age	0.0959	0.5838
HLAB27 Status	0.1634	0.3483
Radiographic Disease Status	-0.0956	0.5849
EMMS	-0.0059	0.9733
Peripheral Manifestations	0.1704	0.3278
NSAIDs Usage	-0.124	0.478
Steroids Usage	-0.185	0.286
Biological DMARDs	-0.134	0.444
Sleep Quality	-0.02	0.911
Exercise	-0.104	0.554
Employment Status	0.154	0.377

The study also examined the correlation between disease activity and quality of life measures with abnormal cIMT summarized in Table 6.10. The variables analysed included the BASDAI, BASFI, BASMI, ASDAS-CRP and AsQoL

Table 6.10: Disease Activity and Quality of Life Measures Associated with Abnormal CIMT as per ASE Guideline

Score	Correlation Coefficient	p-value
BASDAI	-0.0391	0.823546
BASFI	0.094745	0.588244
BASMI	0.101044	0.563565
ASDAS-CRP	-0.01033	0.953054
AsQoL	0.209213	0.22775

The results indicated that none of these measures had a statistically significant correlation with abnormal CIMT, as all p-values were greater than 0.05. This suggests that within this cohort, disease activity and quality of life indices do not significantly predict abnormal CIMT, indicating a limited relationship between these measures and cardiovascular risk as reflected by CIMT.

Table 6.11 shows the correlation between various lipid profile variables and the likelihood of having abnormal CIMT as per ASE guideline in axSpA patients. The lipid profile variables considered were TC, HDL, Non-HDL Cholesterol, TG, TC/HDL Ratio and LDL. The results indicated that only LDL levels showed a statistically significant correlation with abnormal CIMT. This finding suggests that as LDL levels increase, the likelihood of abnormal CIMT as per the ASE definition also increases.

Table 6.11: Correlation of Lipid Profile Variables with Abnormal ACS in Axial Spondyloarthritis Patients

Variable	Correlation Coefficient	P-Value
TC	0.228	0.187
HDL	-0.096	0.584
Non-HDL Cholesterol	0.224	0.196
Triglycerides	-0.228	0.188
TC: HDL Ratio	0.229	0.185
LDL	**0.345549**	**0.042036**

In assessing CVR factors associated with abnormal CIMT, anthropometric measures and blood pressure readings were analysed to determine their correlation with abnormal CIMT. The variables examined included Waist Circumference, Hip Circumference, WHR, BP and BMI. The analysis found that none of these variables showed a statistically significant correlation with abnormal CIMT, as all p-values were above the standard significance threshold of 0.05. This indicates that within this dataset, measures of body composition and blood pressure do not significantly predict the likelihood of abnormal CIMT in patients. Table 6.12 summarizes the findings for anthropometric and blood pressure variables, showing no significant association with abnormal CIMT in this cohort.

Table 6.12: Correlation of Anthropometric and Blood Pressure Variables with Abnormal CIMT

Variable	Correlation Coefficient	P-Value
Waist Circumference	0.012	0.945
Hip Circumference	0.054	0.759
Waist-Hip Ratio	0.060	0.734
Body Mass Index	-0.264	0.125
Systolic Blood Pressure	0.015	0.933
Diastolic Blood Pressure	0.103	0.556

Table 6.13 shows biomarkers associated with CVD were analysed for their correlation with abnormal CIMT as per ASE guidelines. The biomarkers studied included Urate, PRO-nt-BNP, Platelets, Vitamin D, Ferritin, CRP, ESR and Fibrinogen.

Table 6.13: Correlation of Biomarkers with Abnormal CIMT as per ASE

Biomarker	Correlation Coefficient	P-Value
Urate	0.198334	0.260828
PRO-nt-BNP	0.02056	0.908116
Platelets	-0.15245	0.389386
Vit D	-0.0109	0.951216
Ferritin	0.104293	0.557215
CRP	0.057635	0.746115
ESR	-0.15788	0.372503
Fibrinogen	0.005229	0.976585

The results indicated that none of these biomarkers showed a statistically significant correlation with abnormal CIMT, as all p-values were above the standard significance threshold of 0.05. This finding suggests that these biomarkers do not have a significant predictive value for abnormal CIMT in this patient cohort.

6.6 Factors Associated with Abnormal CIMT in Axial Spondyloarthritis Patients based on ECS guidelines.

We also investigated the association between clinical and demographic factors and abnormal CIMT in accordance with the guidelines set forth by the European Society of Cardiology guidelines.

Table 6.14 shows that most clinical and demographic factors, such as disease duration, age, HLAB27 status, radiographic disease, extra-musculoskeletal manifestations, peripheral manifestations, NSAID use, bDMARD use, and employment status, exhibited weak correlations with abnormal cIMT in axSpA patients. The low correlation coefficients and high p-values (all $p > 0.05$) suggest a lack of significant association. However, sleep quality and exercise showed a modest positive correlation with abnormal cIMT, with correlation coefficients of 0.29407 ($p = 0.086398$) and 0.29698 ($p = 0.083184$), respectively. Although these correlations were not statistically significant at the conventional alpha level of 0.05, they approached significance, suggesting a potential trend that may warrant further investigation in larger patient cohorts.

Table 6.14: Correlation Between Clinical and Demographic Factors and Abnormal CIMT in Axial Spondyloarthritis Patient as per ESC guidelines

Variable	Correlation Coefficient	P-Value
Disease Duration	-0.07468	0.669823
Age	-0.02536	0.885018
HLAB27 Status	-0.11198	0.521891
Radiographic Disease	-0.18924	0.276247
EMMS	-0.13679	0.43328
Peripheral Manifestations	-0.11677	0.504101
NSAIDS	-0.19544	0.260529
bDMARD	0.166031	0.340479
Sleep quality	0.294071	0.086398
Exercise	0.296984	0.083184
Employment status	-0.10566	0.545782

In accordance with the ECS guidelines, the study evaluated the correlation between disease activity, quality of life measures, and abnormal cIMT (Table 6.15).

Table 6.15: Disease Activity and Quality of Life Measures Associated with Abnormal CIMT as per ESC Guidelines.

Variable	Correlation Coefficient	P-Value
BASDAI	-0.0176	0.920071
BASFI	0.024916	0.887021
BASMI	0.085204	0.626502
ASDAS-CRP	-0.03842	0.826569
AsQoL	0.066812	0.702953

The findings revealed that none of these variables demonstrated a statistically significant correlation with abnormal CIMT, as all p-values were well above the threshold of 0.05. This suggests that measures of disease activity and quality of life in this cohort do not significantly correlate with abnormal CIMT, indicating a limited role of these measures in predicting cardiovascular risk based on CIMT.

Table 6.16 highlights the correlation between lipid profile components and abnormal CIMT as per ESC guidelines. The findings indicate that most components of the lipid profile, including total cholesterol, HDL, non-HDL cholesterol, triglycerides, and LDL, showed weak correlations with abnormal cIMT, with correlation coefficients ranging from -0.26825 to 0.26752 and p-values all greater than 0.05, indicating a lack of significant associations.

However, the TC/HDL ratio demonstrated a moderate positive correlation with abnormal cIMT (r = 0.50154, p = 0.00214), which was statistically significant.

Table 6.16: Correlation Between Lipid Profile Components and Abnormal cIMT as per ESC guidelines

Lipid Profile	Correlation Coefficient	P-Value
TC	0.161757	0.353228
HDL	-0.26825	0.119217
Non-HDL	0.267518	0.120268
Triglycerides	0.216309	0.212008
TC: HDL Ratio	**0.501542**	**0.002145**
LDL	0.214534	0.215874

Anthropometric and blood pressure variables were analysed for their correlation with abnormal cIMT as per ESC guideline (Table 6.17). The results indicated that Waist circumference (r = 0.485, p = 0.003), Hip circumference (r = 0.399, p = 0.018), (r = 0.346, p = 0.042), and DBP (r = 0.392, p = 0.020) were significantly positively correlated with abnormal CIMT, suggesting that higher values of these variables are associated with increased CIMT. In contrast, WHR and SBP did not show a significant correlation (p > 0.05), indicating no substantial association with abnormal CIMT.

Table 6.17: Correlation Between Anthropometric and Blood Pressure Variable and Abnormal CIMT as per ESC Guidelines

Measurement	Correlation Coefficient	P-Value
Waist Circumference	0.485363	**0.003122**
Hip Circumference	0.398582	**0.01771**
Waist/ Hip Ratio	-0.03829	0.827131
BMI	0.345714	**0.041932**
SBP	0.288128	0.093251
DBP	0.392031	**0.01985**

Table 6.18 shows results looking at the selected biomarkers to determine their correlation with abnormal cIMT as per. The results showed that none of the biomarkers had a statistically significant correlation with abnormal CIMT, as all p-values were greater than 0.05. This indicates that in this patient cohort, these biomarkers do not have a significant association with abnormal CIMT, suggesting limited predictive value for cardiovascular risk based on these measures.

Table 6.18: Correlation of Biomarkers with Abnormal CIMT as per ESC guidelines

Biomarker	Correlation Coefficient	P-Value
Urate	0.049602	0.780566
PRO-nt-BNP	-0.1333	0.452301
Platelets	-0.13679	0.440458
Vit D	0.01353	0.939464
Ferritin	-0.12806	0.470455
CRP	-0.0154	0.931101
ESR	-0.0828	0.64156
Fibrinogen	0.082266	0.6437

6.7 Results- Factors Associated with the Presence of Atherosclerotic Plaques in Axial Spondyloarthritis Patients

This study investigates the factors associated with carotid plaque formation in a cohort of patients, where 4 out of 25 individuals were identified with plaques. A carotid plaque, as defined by ultrasound imaging, refers to a focal structure that encroaches into the arterial lumen by at least 0.5 mm or 50% of the surrounding intima-media thickness or has a thickness of more than 1.5 mm from the intima-lumen interface (348). To determine the potential associations, a comprehensive analysis of clinical and demographic data, discussed above, was performed with the aim was to identify any correlations that could

indicate risk factors contributing to the development of carotid plaques, which are significant predictors of cardiovascular event.

The analysis identified several significant associations shown in Table 6.19. Peripheral manifestations, demonstrated a significant negative correlation with plaque presence This finding suggests that patients exhibiting peripheral manifestations are less likely to develop atherosclerotic plaques, potentially indicating a differential risk profile within this subgroup.

Additionally, BMI was significantly positively correlated with the presence of atherosclerotic plaques. This suggests that higher BMI is associated with an increased likelihood of plaque formation, underscoring the importance of managing weight to reduce cardiovascular risk in this patient population. Waist Circumference (cm) also showed a significant positive correlation ($p = 0.036$), indicating that patients with larger waist circumferences are more prone to atherosclerotic plaque development. This highlights central adiposity as a relevant risk factor for cardiovascular morbidity.

Moreover, HDL levels were found to have a significant negative correlation with plaque presence ($p = 0.011$), suggesting that lower HDL cholesterol levels are associated with a higher risk of atherosclerosis in this cohort. The Total Cholesterol to HDL Ratio exhibited a significant positive correlation ($p = 0.008$), indicating that a higher TC/HDL ratio is linked to an increased likelihood of atherosclerotic plaque formation.

These findings underscore the role of metabolic and anthropometric factors, such as BMI, waist circumference, HDL levels, and the TC ratio, in the development of atherosclerotic plaques among patients with Axial Spondyloarthritis. The inverse association with

peripheral manifestations further suggests potential differences in cardiovascular risk stratification within this patient group.

Table 6.19: Factors Associated with Atherosclerotic Plaques in Axial Spondyloarthritis Patients

Variable	Coefficient	P-Value
Peripheral Manifestations	-0.369	**0.029**
BMI	0.347	**0.041**
Waist Circumference	0.356	**0.036**
HDL	-0.427	**0.011**
TC: HDL Ratio	0.441	**0.008**

6.8 Discussion

Carotid Doppler ultrasound has emerged as a valuable tool in identifying subclinical atherosclerosis in patients with axSpA, who are often misclassified as low risk based on traditional cardiovascular risk assessments. The results of this study underscore the limitations of standard risk assessment tools, such as, QRisk3, in accurately capturing the atherosclerotic burden in this population. Despite all patients being categorized as low risk according to QRisk3, carotid Doppler ultrasound findings revealed a substantial proportion of patients with subclinical atherosclerosis. Specifically, 85.7% of patients had abnormal findings in the right common carotid artery (CCA), 68.6% had abnormalities in the left CCA according to the ASE criteria, and 11% of patients presented with detectable carotid plaques. These findings suggest that many patients with axSpA, even those deemed low

risk by conventional methods, harbour a considerable atherosclerotic burden that is not being captured by standard cardiovascular risk scores.

The findings from this study highlight the critical role of carotid Doppler ultrasound in cardiovascular risk stratification among axSpA patients. Given the high rate of reclassification to a higher cardiovascular risk category following Doppler ultrasound examination, it is clear that carotid ultrasound can uncover significant subclinical disease that may otherwise go undetected. This is particularly important in axSpA patients, who may be at heightened risk for atherosclerosis due to chronic systemic inflammation associated with their condition. By identifying subclinical atherosclerosis early, carotid Doppler ultrasound allows for timely intervention, potentially reducing the long-term cardiovascular burden in these patients through more aggressive risk management strategies, including lifestyle modifications, pharmacotherapy, and closer monitoring.

The lack of significant correlations between traditional cardiovascular risk factors —such as age, BMI, blood pressure, and lipid profiles—and abnormal CIMT as per the ASE guidelines, in this study further highlights the inadequacy of these conventional risk factors in assessing cardiovascular risk in axSpA patients. The only exception was a significant correlation between LDL levels and abnormal CIMT, suggesting that while traditional lipid measures may provide some indication of risk, they do not fully account for the cardiovascular risk in this specific patient population. This underscores the potential utility of carotid Doppler ultrasound in providing a more accurate assessment of cardiovascular risk by directly visualizing subclinical atherosclerotic changes, rather than relying solely on indirect markers.

Additionally, when considering the European Society of Cardiology (ESC) guidelines, several more factors were found to have a significant correlation with abnormal CIMT. These include waist circumference, hip circumference, BMI, and diastolic blood pressure. The positive correlations between these factors and abnormal CIMT suggest that body composition and blood pressure management are crucial for preventing subclinical atherosclerosis in axSpA patients. The total cholesterol to HDL ratio also showed a significant correlation, emphasizing the importance of lipid management in this population.

Furthermore, the study identified several factors associated with the presence of carotid plaques, which are significant predictors of future cardiovascular events. Peripheral manifestations of axSpA were found to have a significant negative correlation with plaque presence, suggesting that patients with these manifestations might be at a lower risk for developing atherosclerotic plaques. Conversely, higher BMI and greater waist circumference were positively correlated with plaque presence, indicating that patients with higher levels of adiposity are more likely to develop subclinical atherosclerosis. Additionally, lower levels of HDL cholesterol and a higher total cholesterol to HDL ratio were significantly associated with an increased likelihood of plaque formation. These findings underscore the importance of managing metabolic risk factors, such as obesity and dyslipidaemia, to reduce cardiovascular risk in axSpA patients.

The role of carotid Doppler ultrasound in cardiovascular risk stratification is also supported by the 2015/2016 EULAR guidelines for cardiovascular risk management in patients with IJD. These guidelines recognize the potential utility of carotid ultrasound for detecting

early atherosclerotic changes and stratifying cardiovascular risk. However, as rheumatologists, there is still uncertainty about what constitutes an abnormal CIMT that would necessitate reclassification or increased frequency of screening in patients. The question remains whether to follow the ESC or ASE guidelines or to focus solely on the presence of plaques. This ambiguity calls for further clarification and consensus on standardized thresholds for CIMT and plaque detection to guide clinical decision-making and ensure consistent patient management.

In selecting the biomarkers for this study, consideration was given to their accepted roles in both inflammation and potential contributions to cardiovascular disease and risk. These included standard known risk factors such as lipid profiles, diabetes, BMI, smoking history, and blood pressure. The choice of these biomarkers was based on their established relevance to both inflammatory processes and cardiovascular health. Interestingly, despite their cost-effectiveness and ease of measurement, none of the biomarkers showed a significant correlation with abnormal CIMT in this cohort. This finding suggests a potential avenue for future research to explore novel and emerging biomarkers that might better identify axSpA patients at higher risk for early cardiovascular disease or subclinical atherosclerosis. By expanding our understanding of biomarkers beyond the traditional ones, we may enhance our ability to predict and prevent cardiovascular events in this vulnerable population.

6.9 Conclusion

The findings of this study support the integration of carotid Doppler ultrasound into cardiovascular risk assessment protocols for axSpA patients. This approach not only allows for a more accurate assessment of cardiovascular risk but also facilitates early detection and intervention for subclinical atherosclerosis. Future research should focus on developing standardized protocols for the use of carotid ultrasound in clinical practice, as well as exploring its utility in broader patient populations beyond those with inflammatory joint diseases. Additionally, investigating novel biomarkers could provide further insight into identifying axSpA patients at higher risk for cardiovascular disease, ultimately improving patient outcomes and reducing the cardiovascular burden in this high-risk group.

Chapter 7: Conclusions & Clinical Implications

7.1. Introduction

Cardiovascular disease (CVD) remains the leading cause of death globally, particularly among patients with chronic inflammatory conditions like axSpA. This thesis investigates the cardiovascular risks in axSpA patients, highlighting gaps in screening practices, the role of carotid Doppler ultrasound in detecting subclinical atherosclerosis, and the ongoing need for standardized cardiovascular screening protocols. By utilizing data from the Ankylosing Spondylitis Registry of Ireland (ASRI) and a specialized cardiovascular screening clinic, we identified significant cardiovascular risks frequently underestimated by traditional cardiovascular risk models like QRisk3. This chapter consolidates these findings and emphasizes the importance of incorporating novel imaging techniques and addressing modifiable risk factors early in the disease process for improved cardiovascular risk management in axSpA.

7.2. Cardiovascular Risk in AxSpA: Current Landscape

Studies highlight that axSpA patients face an elevated risk of cardiovascular disease, influenced by systemic inflammation and traditional risk factors such as hypertension, dyslipidaemia, and obesity. Data from the ASRI reveals that 21.7% of patients had hypertension, 15.8% had hyperlipidaemia, and 29% were classified as obese. In the study cohort, 31% of patients had systolic blood pressure above 130 mmHg, 34.5% had a BMI over 30, and 28.4% were active smokers. Despite the significant prevalence of these

cardiovascular risk factors, many of these patients may remain undetected for early cardiovascular risks. These findings highlight the need for more proactive and comprehensive screening strategies that can identify cardiovascular risks earlier, addressing both traditional risk factors and inflammation-related mechanisms specific to axSpA.

By capturing real-world data from a large cohort of patients, ASRI provides valuable insights into the prevalence and management of CVD within the axSpA population. The data from ASRI highlights significant rates of cardiovascular comorbidities, mirroring global trends and emphasizing the heightened cardiovascular risk associated with axSpA.

ASRI's contribution to research goes beyond the identification of traditional cardiovascular risk factors. It allows for a more nuanced understanding of the intersection between systemic inflammation and cardiovascular health, offering insights that can help refine screening practices and guide future research. Furthermore, registries like ASRI are instrumental in identifying treatment gaps and enabling long-term studies that assess the effectiveness of interventions aimed at reducing cardiovascular risk in AxSpA patients.

Chapter 4 explores previous studies and how traditional cardiovascular risk factors contribute to the screening of subclinical atherosclerosis in AxSpA patients. While traditional cardiovascular risk factors remain crucial, they alone do not sufficiently capture the full extent of cardiovascular risk in axSpA patients. The review highlights the importance of integrating inflammation-driven mechanisms into cardiovascular screening models, as markers like CRP and disease activity scores (BASDAI, ASDAS-CRP) are closely linked to cardiovascular outcomes.

Additionally, the review underlines the limitations of commonly used cardiovascular risk assessment tools, such as SCORE, QRISK3 and the Framingham Risk Score, which tend to underestimate the cardiovascular risk in axSpA patients by failing to account for inflammation and disease activity. Moving forward, predictive models must incorporate both traditional factors and AxSpA-specific inflammatory markers to provide a more accurate assessment of cardiovascular risk.

The current approach to cardiovascular risk assessment in axSpA primarily focuses on identifying traditional risk factors and modifiable comorbidities, which are essential but insufficient for patients with inflammatory conditions like axSpA. To improve early detection and better manage cardiovascular risk in this population, it is essential to go beyond traditional assessments and focus on identifying subclinical atherosclerosis, particularly through advanced screening techniques.

7.2. Subclinical Atherosclerosis and its Detection

Chapter 4's literature review examined several imaging modalities for detecting subclinical atherosclerosis in axSpA patients, including coronary artery calcium (CAC) scoring, computed tomography (CT) angiography, and carotid Doppler ultrasound. While each method has its strengths, carotid Doppler ultrasound emerged as the most practical and effective for routine use in rheumatology, particularly for early cardiovascular risk detection in patients with inflammatory conditions.

CAC scoring, while commonly used for general cardiovascular risk assessments, is limited in axSpA patients due to its inability to detect non-calcified plaques, which are common in early atherosclerosis. Additionally, the radiation exposure associated with CAC scoring

makes it less ideal for regular monitoring. CT angiography offers detailed imaging of both calcified and non-calcified plaques, but its high cost, need for contrast agents, and radiation exposure limit its utility in routine clinical practice for rheumatology.

Carotid Doppler ultrasound, by contrast, is non-invasive, cost-effective, and easily accessible. It effectively detects both calcified and non-calcified plaques, making it particularly valuable for identifying early cardiovascular risk in patients with inflammatory joint diseases like axSpA. Non-calcified plaques, which are often present in axSpA patients, serve as early indicators of cardiovascular disease and can be easily identified using this method. Moreover, carotid intima-media thickness (CIMT) measurements from Doppler ultrasound correlate well with cardiovascular outcomes, enhancing its utility for routine cardiovascular risk assessment.

Given the findings of the literature review, carotid Doppler ultrasound stands out as the preferred imaging modality for detecting subclinical atherosclerosis in AxSpA patients. Its ability to identify early disease, combined with its accessibility and lack of radiation exposure, makes it an ideal tool for ongoing cardiovascular health monitoring in patients with chronic inflammatory diseases like axSpA.

Chapter 6 discusses the use of carotid Doppler ultrasound in axSpA patients demonstrated the significant role of this imaging modality in identifying subclinical atherosclerosis. The findings revealed that 85.7% of patients had abnormal CIMT in the right common carotid artery (CCA) and 68.6% in the left CCA when using the American Society of Echocardiography (ASE) guidelines. Additionally, 11% of patients had detectable carotid plaques, further confirming the utility of this method for identifying cardiovascular risks that conventional tools like QRisk3 overlook.

The lack of significant correlations between traditional risk factors—such as age, disease duration, and inflammatory markers—and subclinical atherosclerosis challenges the reliance on conventional cardiovascular screening methods. None of the evaluated factors, including systemic inflammation measured by CRP or disease activity, showed significant associations with abnormal CIMT. This may suggest that subclinical atherosclerosis may develop with additional pathomechanisms other than inflammation and other traditional risk factors, necessitating better markers and imaging modalities for early detection.

One of the significant challenges highlighted in Chapter 6 is the absence of standardized guidelines for the use of carotid Doppler ultrasound in axSpA patients. The variability between the American Society of Echocardiography (ASE) and the European Society of Cardiology (ESC) thresholds for abnormal CIMT complicates clinical decision-making. ASE criteria, which provide tailored thresholds based on age and sex, may offer a more realistic framework for cardiovascular risk assessment in axSpA patients, given the heterogeneity of the population.

7.3 Novel Biomarkers for Cardiovascular Risk in AxSpA

Chapter 4's literature review explored various emerging biomarkers with potential to improve cardiovascular risk stratification in axSpA patients. While the review identified promising novel biomarkers such as endothelial progenitor cells (EPCs), visfatin, and osteoprotegerin (OPG), it was noted that there were very few publications looking at more readily available and cost-effective biomarkers traditionally associated with inflammation and cardiovascular disease. Given this gap, we chose to investigate whether there was a

link between more accessible biomarkers—urate, ferritin, fibrinogen, platelets, and Vitamin D—and subclinical atherosclerosis. These biomarkers have historically been associated with both inflammation and cardiovascular risk in other populations, making them a practical option for routine screening. However, our study did not yield statistically significant findings in relation to subclinical atherosclerosis, suggesting that these traditional markers may not be effective predictors in the axSpA population.

In contrast, the literature highlighted novel biomarkers with greater potential for identifying subclinical atherosclerosis. For instance, EPC depletion was significantly correlated with increased CIMT and impaired flow-mediated dilation (FMD), both of which are indicators of subclinical atherosclerosis and endothelial dysfunction. Other markers of endothelial dysfunction, such as VCAM-1, ICAM-1, and IL-8, also emerged as promising targets for further research, though their associations with cardiovascular risk in axSpA remain variable.

The absence of significant correlations between traditional inflammation markers and subclinical atherosclerosis underscores the need for novel biomarkers that can more accurately capture the early stages of atherosclerosis driven by non-inflammatory mechanisms. Identifying these biomarkers will be crucial not only for the early detection of subclinical atherosclerosis but also for understanding the underlying pathomechanisms that contribute to early cardiovascular disease in axSpA patients.

7.4 Recommendations for Clinical Practice

The findings of this thesis underscore the importance of integrating cardiovascular screening into routine rheumatology care for axSpA patients. Rheumatologists must adopt a more proactive role in addressing traditional cardiovascular risk factors.

Chapter 5 discusses an audit conducted as part of this thesis which revealed significant gaps in the screening and management of cardiovascular risk factors in axSpA patients. Basic screening for modifiable risk factors, such as blood pressure, lipid profiles, and glucose levels, was lacking in a large proportion of patients. These findings highlight the urgent need for more comprehensive cardiovascular risk assessments in routine clinical practice.

The pilot study of a specialized cardiovascular screening clinic demonstrated a significant improvement in detecting modifiable cardiovascular risk factors. During the pilot, 34% of patients were newly diagnosed with cardiovascular risk factors that had not been previously identified, including hypertension, dyslipidaemia, and glucose intolerance. This highlights the effectiveness of dedicated screening efforts in improving cardiovascular risk management for axSpA patients.

While it may not be feasible to implement specialized cardiovascular clinics for all IJD patients, the success of the pilot study emphasizes the importance of routine cardiovascular screening in this population. These screenings should ideally be conducted by physician- or nurse-led clinics within rheumatology settings. Early identification of modifiable risk factors can enable timely intervention, reducing the long-term cardiovascular burden in axSpA patients.

Furthermore, screening needs to start early, as evidenced by the reclassification of many patients under the age of 60 into higher cardiovascular risk categories based on the ASE guideline for abnormal CIMT. Early and consistent cardiovascular screening is critical for preventing the progression of subclinical atherosclerosis and reducing the risk of future cardiovascular events. Rheumatology practices should prioritize these screenings to ensure that cardiovascular disease is addressed as part of comprehensive axSpA care.

7.5 Final Discussion and Future Directions

This thesis highlights the substantial cardiovascular risk associated with axSpA, a risk often overlooked by traditional assessment models. Carotid Doppler ultrasound, an underutilized tool, has proven effective in detecting subclinical atherosclerosis and reclassifying patients who would otherwise be considered low risk. The lack of correlation between inflammation markers and subclinical atherosclerosis in our study could point to the involvement of alternative pathways—likely metabolic or endothelial—in the development of CVD in axSpA patients.

Future research should focus on exploring novel biomarkers and advanced imaging techniques, such as endothelial biomarkers and strain imaging, to improve early detection of cardiovascular risk. It is essential to develop axSpA-specific cardiovascular risk models that integrate traditional risk factors with inflammatory disease activity scores, such as BASDAI and ASDAS-CRP, to provide a more accurate and comprehensive assessment of cardiovascular risk.

In conclusion, early and precise cardiovascular screening is critical for preventing long-term cardiovascular complications in axSpA patients. By incorporating advanced imaging, novel biomarkers, and disease-specific risk factors into routine clinical practice, rheumatologists can significantly enhance the management of cardiovascular health and reduce the burden of cardiovascular disease in this high-risk population.

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Appendices

Appendix 1: Ethics Approval

Tallaght University Hospital | Ospidéal Ollscoile Thamhlachta

An Academic Partner of Trinity College Dublin

Research Office

Ospidéal San Séamas – Seirbhís Dé agus A Phobail

Project ID: 3610

Dr Brona Dinneen,

St James's hospital

Approval Date: 19 March 2024

Submission Number: 3364

Submission Title: ASRI (Ankylosing Spondylitis Registry of Ireland)
Submission Date: 15.Feb.2024 15:17

Dear Dr Dinneen,

On behalf of the Chair and members of the SJH/TUH Joint Research Ethics Committee I wish to inform you that your study has received **FULL APPROVAL.** Your study can now proceed.

The following documents were reviewed and approved:

Document Type	File Name	Date	Version
Participant Information Leaflet	PIL and Consent version 5 dated 14th February 2023- Clean		
Participant Consent Form	PIL and Consent version 5 dated 14th February 2023- Clean		
Amended Documents	Ethics standard application form clean-dated 30th January 2023		

Please note that ethical approval for this study is only active under the following conditions:

1. *Applicants must submit an annual report for ongoing projects.*
2. *Applicants must submit an end of study declaration/end of study report upon completion of the study.*

3. *All adverse events must be reported to the JREC.*
4. *All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.*

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Dr Sadhbh O'Neill

Research Ethics & Clinical Trials Manager,

SJH/TUH Joint Research Ethics Committee

The SJH/TUH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Appendix 2: Patient Information Leaflet and Consent Form

Ankylosing Spondylitis Registry of Ireland (ASRI)

Patient Information and Consent

Title of study

Subclinical cardiovascular disease screening and clinical predictive models in Axial Spondyloarthropathies.

Principal Investigator:
Prof. Barry O'Shea

Introduction:

You are invited to participate in a research study at St James Hospital. Thank you for taking time to read this. Before you decide whether or not you wish to take part, you should read the information provided in this leaflet carefully. Take time to ask questions – don't feel rushed or under pressure to make a quick decision. You should understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. You may wish to discuss it with your family, friends or GP.

You should be satisfied that all your questions concerning this study are answered and that you understand your rights as a study patient.

Purpose of the study:

The purpose of this study is to investigate the potential association between subclinical cardiovascular disease and Axial Spondyloarthropathies/Ankylosing Spondylitis (axSpA). "Subclinical" refers to a stage of a disease or condition that is not yet severe enough to cause noticeable symptoms or to be clinically diagnosed and through screening can be diagnosed early.

Research in axSpA has traditionally focused on musculoskeletal manifestations however, emerging evidence suggests a possible link between these conditions and development of cardiovascular disease. This study aims to develop screening techniques to assess for early signs of cardiovascular disease in individuals with axSpA, particularly those who may not exhibit overt cardiovascular symptoms.

Through this research we hope to gain further understanding into the connection between cardiovascular disease and axSpA, and to develop effective screening tools for early detection and possible treatment of cardiovascular disease in patients with axSpA and other rheumatic disorders.

Why am I being asked to take part?

You are being asked to participate in this study as you have a diagnosis of Ankylosing Spondylitis (AS) and have no history of cardiovascular disease or risk factors associated with cardiovascular disease. This includes: high blood pressure (hypertension), high cholesterol (hyperlipidaemia), smoking or diabetes.

Do I have to take part?

Your participation is voluntary. You don't have to take part in this study. If you decide not to take part it won't affect your current or future medical care. You can change your mind about taking part in the study and opt out at any time even if the study has started. If you decide to opt out, it won't affect your current or future medical care and you will continue to be seen in the specialist clinic for AS. You don't have to give a reason for not taking part or for opting out.

If you wish to opt out, please contact Dr Barry O'Shea or a member of the Rheumatology team – 01 4162551 who will be able to organize this for you.

How will the study be carried out?

Your study visits will take part in the Rheumatology outpatients department at St James's hospital and vascular and each visit will take approximately two hours or less.

What will happen to me if I agree to take part?

You are asked to carefully read this information leaflet and consent form. The doctor or research nurse will ask you if you understand all aspects of the study and what is involved for you. If you agree to participate, you will be asked to sign the attached consent form. You will be seen by Dr Barry O'Shea or a member of the Rheumatology team assigned by him.

- You will have a physical examination consistent with routine clinical practice.
- You will be asked to give a once off blood sample of approximately (3 tablespoon) of blood to screen to detect for cardiac failure and to assess for risk factors associated with cardiovascular disease in your system
- You will be asked to complete some questionnaires to assess your pain level, your disease activity, cardiovascular risk factors, medications, diet, lifestyle, and your physical function.
- We will also collect your medical details, as part of your routine consultations with the doctor on your first visit and all subsequent visits to the rheumatology clinic. The data we collect will be stored with no identifying details (this is called pseudonymised) on a secure database. This will allow us to match detailed

medical assessment with the information gained from the samples we have collected from you. You will be aware of all the information that is collected about you.

- **Investigations and Procedures:** You may be asked to have an ECG and carotid artery doppler (ultrasound of arteries in the neck)

- **Body Composition measurements** may be taken which include: Mid upper arm circumference, Waist Hip ratio. These are standard measurements to measure fat composition in your body.

Benefits:

There is no direct benefit to you in participating in this study but the knowledge gained from this study may be of help to other patients in the future.

Risks:

There will be no risks other than those associated with taking blood from a vein in your arm, which you would be having as part of your standard care. These are discomfort, pain or bruising. No additional risks to you are foreseen from participating in this study.

Will I be told the outcome of the study? Will I be told the results of any tests or investigations performed as part of this study that relate to me?

You will not be told the outcome of the study and you will not be given individual results **unless requested or intervention/treatment required** – anonymised results will be published in medical journals and will be presented at peer groups. Data is published in an aggregated form only (as a group as opposed to individual results) and the information obtained may provide further knowledge of this condition.

DATA Protection:

What information about me (personal data) will be used as part of the study? Will my medical records be assessed?

Your identity will remain confidential. A study number will identify you. Your name will not be published or disclosed to any party other than the Co-Principal Investigators and their staff.

It is a requirement that your involvement in this study is noted in your medical records. Direct access to your records by medical staff of St James's Hospital will be needed to check the information collected for the study.

By signing this consent form you authorise access to this confidential information by the medical staff of St James's Hospital for the purpose of this study.

The confidentiality of your medical records will be maintained to the extent permitted by the applicable laws. If results of the study are published your identity will remain confidential.

You have the right of access to and the right to rectification of your medical records upon written request to one of the Principal/ Co- Investigators at the Department of Rheumatology at St James's Hospital.

What will happen my personal data?

All your data and samples will be coded and rendered pseudonymous (you can be identified by a number only) once collected. A unique study number will be assigned to this data. The personnel involved in collecting samples and the data will be responsible for safeguarding anonymity. All pseudonymised data will be kept as long as the registry is active. This is a safeguard to avoid duplication.

Your research blood samples will be processed at St James's Hospital laboratory and the Carotid Ultrasound will take place in the vascular department of St James's Hospital.

Who will access and use my personal data as part of this study?

The Principal Investigator and personnel assigned by him are allowed to access the data.

We use a third party service provider to provide a database to store your information. This data base is hosted on a virtual server owned by Ankloysing Spondylitis Ireland (ASRI).This server will be protected by using SSL, a protocol for encrypting information over the internet. All data entered into the database will be pesudoanymised and only the Principal Investigator or his staff can identify you.

Will my personal data be kept confidential? How will my data be kept safe?

St James Hospital operates and uses appropriate technical and physical security measures to protect your personal data.

We have in particular taken appropriate security measures to protect your data from accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access, in connection with this research study. Access is only granted on a need –to – know basis to those people whose roles require them to process your personal data.

In addition our service providers are also selected carefully and required to us appropriate protective measures.

What is the lawful basis to use my personal?

The processing of your personal data will be in compliance with the Data Protection Acts 1988 to 2018 (as amended) and the General Data Protection Regulation (the "Data Protection Legislation") Article 6 & Article 9.

Will it cost me anything if I agree to take part?

Your participation in this study will not cost you any additional money. You will not receive any payment for participation in this study

Your study doctors are covered by a standard clinical indemnity scheme.

Who is funding this study? Will the study results be used for commercial purposes?

The overall study is organised by Dr Barry O'Shea, Consultant Rheumatologist. There is a nominal fee paid to each Investigator participating to cover administration costs**. The overall project is presently being funded by a grant from Abbvie Pharmaceuticals and Pfizer Pharmaceuticals.** In the future if an opportunity arises to conduct further research projects with a pharmaceutical company, you will be contacted and consented for that study separately.

The registry (ASRI) will not be disclosing results for commercial purposes but may collaborate with commercial organisations who are for profit organisation. All donations to the registry from commercial organisations will be directly used to support work within ASRI.

Stopping the study:

You understand that your doctor may stop your participation in the study at any time without your consent.

Has the study been approved by a Research ethics Committee?

SJH / AMNCH RESEARCH ETHICS COMMITTEE, have reviewed and approved this study.

Contact Details : TUH/SJH REC OFFICER:

Dr. Sadhbh O'Neill
Email: ResearchEthics@tuh.ie/ Sadhbh.ONeill@tuh.ie
Phone: 01-414 2199

No persons carrying out the research have a link to the committee or the Institution behind the committee.

Initial Approval was granted on 19th June 2013 with an amendment granted in April 2023

What if I wish to make a complaint?

If you wish to make a complaint in relation to the study- please contact Patient experience office at St James's hospital on 014284248

You will only be contacted if there is a change to the protocol or to the data we collect. You will be asked to resign a consent form if we make a change that affects you or wish to seek any further information.

Further information:

For further information,

Please contact the following

Principal Investigator: Dr Barry O'Shea 014162551 from 0900-1700 (Monday to Friday)

Data Controller: St James's hospital and Dr Barry O'Shea

Data Processor: Dr Barry O'Shea and research staff assigned by him

Data Protection Officer**:**

Cathal Kinsella

Freedom of Information Officer

St. James's Hospital

Dublin 8

Phone: +353 1 416 2463

Title of research study:

Subclinical cardiovascular disease screening and clinical predictive models in Axial Spondyloarthropathies

CONSENT FORM

STUDY TITLE

To be completed by the **PARTICIPANT**:

I have read and understood the information leaflet.	YES ☐	NO ☐
I have had the opportunity to discuss the study, ask questions about the study and I have received satisfactory answers to all my questions.	YES ☐	NO ☐
I have received enough information about this study.	YES ☐	NO ☐
I understand that I am free to withdraw from the study at any time without giving a reason and this will not affect my future medical care.	YES ☐	NO ☐
I agree to allow the researchers use my information (personal data) as part of this study as outlined in the information leaflet.	YES ☐	NO ☐
I agree to allow the researchers access my medical records as part of this study.	YES ☐	NO ☐
I agree to be contacted by researchers as part of this study for the purpose of data clarification.	YES ☐	NO ☐
I agree to give blood samples as described in the patient information leaflet as part of this study.	YES ☐	NO ☐
I agree to have imaging performed as described in the patient information leaflet as part of this study.	YES ☐	NO ☐
I agree to take part in the study.	YES ☐	NO ☐
Future research I agree that the samples I have given, and the Information gathered about me can be Pseudonymised and stored in the St James's Hospital, for use in future projects relating to Ankylosing Spondylitis	YES ☐	NO ☐

without further consent being required and subject to the research being approved by a Research Ethics Committee.		

Participant's Name (Block Capitals):	
Participant's Signature:	
Date:	

To be completed by the **RESEARCHER**:

I have fully explained the purpose and nature (including benefits and risks) of this study to the participant in a way that he/she could understand. I have invited him/her to ask questions on any aspect of the study.	YES □	NO □
I confirm that I have given a copy of the information leaflet and consent form to the participant.	YES □	NO □

Researcher's Name (Block Capitals):	
Researcher's Title & Qualifications:	
Researcher's Signature:	
Date:	

Appendix 3: Protocols

Appendix 3.1: Audit Data Collection Proforma

Cardiovascular disease in inflammatory Rheumatic Diseases Audit

MRN: _____

AGE: _____

Gender: _____

IRD Diagnosis

AxSpA	
SLE	
RA	
PsA	

Treatment -Name

csDMARD	bDMARD/tsDMARD

Past medical history	Yes	NO	On treatment	Documented	Treatment
IHD					
Stroke					
PVD					
DM					
Hypertension					
Hyperlipidaemia					

Screening	Recorded	Date recorded	**Action Taken GP vs treatment started**	Lifestyle	Recorded	Date recorded
BP				Exercise		
Lipids				Diet		
BMI				Smoking cessation		
Blood Glucose						

Smoking status				SCORE/CVD RPM		
Steroid use						
NSAID use						
Disease activity						

Appendix 3.2 – Clinical Information Leaflet

Ankylosing Spondylitis Registry of Ireland

Name: _____ Study Number: _____MRN: _____

Date: _____ Age: _____Disease Duration: _____

Cardiovascular risk factors:

	YES	NO	Don't know
Previous heart attack			
Previous stroke			
Peripheral vascular disease			
Previous coronary stents			
Previous blood clot			
Diabetes			
Heart failure			
High blood pressure			
High cholesterol			
Family history of ischaemic heart disease			
Cardiac arrhythmia			
Pacemaker			

Medications

	Current	Past	As Needed
Anti-inflammatories			
Steroids			

	Yes	No	Previously
Simponi			
Adalimumab			
Etanercept			
Cimzia			
Xeljanz			
Rinvoq			
Cosentyx			

Taltz			
Salazopyrine			
Methotrexate			
Infliximab			

	Yes	No	Previously
Aspirin			
Plavix			
Statin			
Antihypertensive			

Lifestyle

	Yes	No	Don't know
Do you sleep more than 8 hours a night			
Do you sleep between 7-8 hours a night			
Do you sleep between 5-6 hours a night			
Do you sleep <4 hours a night			
Current smoker > 20 cigarettes a day			
Current smoker < 20 cigarettes a day			
Ex-smoker			
Never smoker			
Never drinks alcohol			
Drinks alcohol > 3 drinks daily or > 21 units a week			
Drinks alcohol >2 drinks a day 0r > 14 units a week			
Drinks alcohol 1 drink daily or 7 units a week			
Moderate exercise(20mins) < once a week			
Moderate exercise once per week			
Moderate exercise 2-3 times a week			
Moderate exercise 4-5 time a week			
Moderate exercise >5 days a week			

Employed			
Unemployed			
Retired			
Disability			

Co-Morbidities

	YES- New since baseline questionnaire	Yes- Recorded on baseline questionnaire	No
Asthma			
Bronchiectasis			
Emphysema			
Pulmonary fibrosis			
Tuberculosis			
Osteoporosis			
Peptic ulcer disease			
Depression			
Hip replacement surgery			
Knee replacement surgery			
Spinal corrective surgery			
Fibromyalgia			
Malignancy			

REST TO BE COMPLETED BY DOCTOR

SpA features

	YES	NO	DON'T KNOW
Uveitis			
Colitis			
Enthesitis			
Dactylitis			
Psoriasis			
Peripheral Arthritis			
HLAB27 Positive			
Radiographic			
Non radiographic			

Measurements

BP	
Height (cm)	
Weight (kg)	
BMI	
Waist circumference (cm)	
Hip circumference (cm)	
Waist hip ratio	

Disease Activity Scores

BASDAI	
BASFI	
BASMI	
ASDAS	
AsQoL	

Spinal measurements

Tragus to wall	
Lumbar side flexion – total	
Modified Schober's	
Cervical rotation – total	
Intermalleolar	
Chest expansion	

Biomarkers

Urate	
Troponin	

NT- PRO-BNP	
CK	
Fibrinogen	
Platelets	
CRP	
ESR	
Ferritin	
Vit D	
Total cholesterol	
HDL	
LDL	
Triglycerides	
TC:HDL ratio	
Non-HDL Cholestrol	
HbA1c	
Random Glucose	
Creat	
Urea	

Algorithms

Framingham –Lipids	
ASCVD	
Qrisk3	
SCORE2	

Carotid Dopplers

Site	Average	Philips Epic IMT average
Right CCA		
Left CCA		
Right ICA		
Left ICA		
Plaques		

Appendix 3.3 – Back Questionnaire

NAME:_____ DATE:_____ VISIT #: _ _ SITE #: ___
STUDY # : _____

Questionnaire 4: BACK QUESTIONNAIRE

1. PAIN

Please tick the box that represents your answer (i.e. ~~10~~).

1.1. Nocturnal Back Pain

Based on your assessment, please indicate what is the amount of **back pain at night** that you experienced **during the last week**?

0	1	2	3	4	5	6	7	8	9	10

no pain **most severe pain**

1.2. Total Back Pain

Based on your assessment, please indicate what is the amount of **back pain at any time** that you experienced **during the last week**?

0	1	2	3	4	5	6	7	8	9	10

no pain **most severe pain**

2. PATIENT GLOBAL DISEASE ACTIVITY

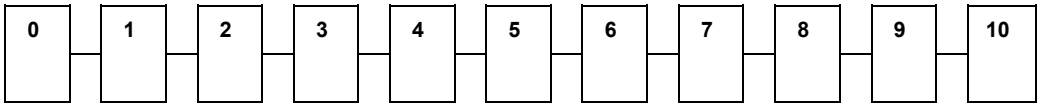
2.1. Tick a box to indicate your overall assessment of your disease activity **during the last week?**

0	1	2	3	4	5	6	7	8	9	10

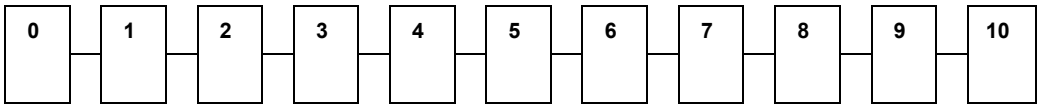
none **severe**

3. BAS - G

3.1. Tick a box to indicate the effect your disease has had on your well-being over **the last week**?



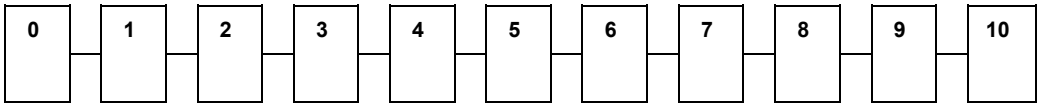
3.2. Please indicate the effect your disease has had on your well-being over the l**ast six months**.



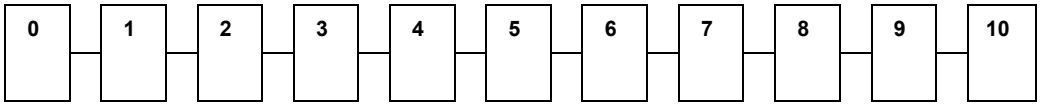
4. BASDAI

Please tick the box that represents your answer. (i.e. 10). All questions refer to the **last week**.

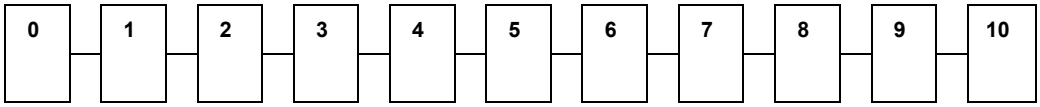
4.1. How would you describe the overall level of fatigue / tiredness you have experienced?



4.2. How would you describe the overall level of AS **neck, back or hip** pain you have had?

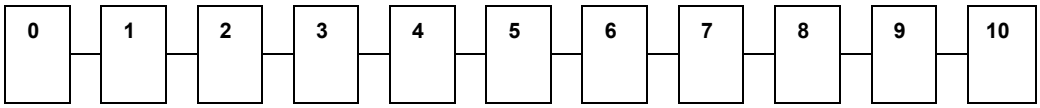


4.3. How would you describe the overall level of pain / swelling in joints **other than** neck, back or hips you have had?



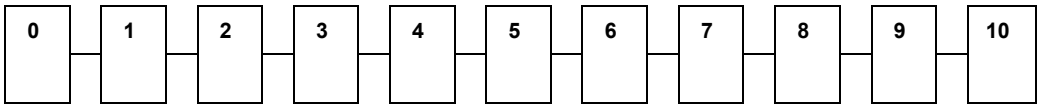
none very severe

4.4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?



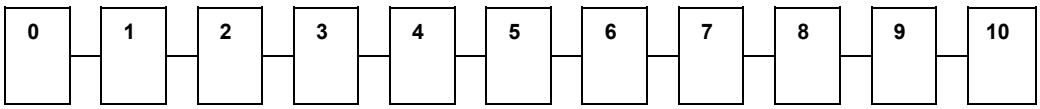
none very severe

4.5. How would you describe the overall level of morning stiffness you have had from the time you wake up?



none very severe

4.6. How long does your morning stiffness last from the time you wake up?



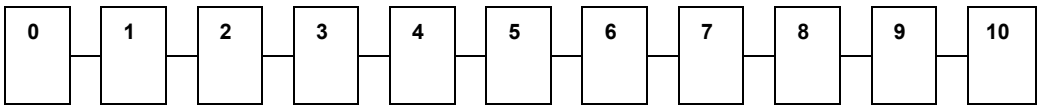
0 hr **1 hr** **2 or more hrs**

5. BASFI

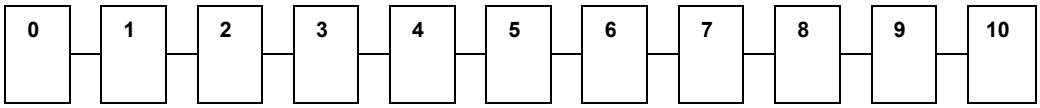
Please indicate your level of ability with each of the following activities during the last week.

(i.e. ~~10~~). An aid is a piece of equipment which helps you to perform an action or movement.

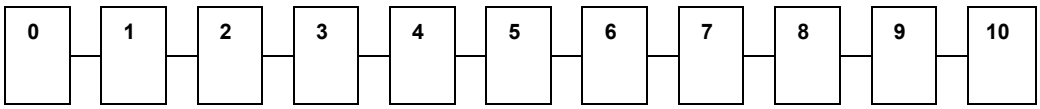
5.1. Putting on your socks or tights without help or aids (e.g. sock aid).



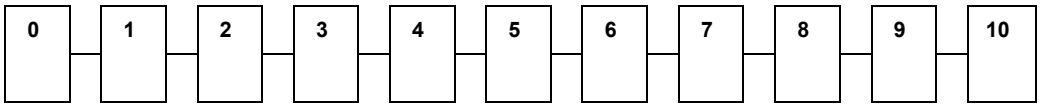
5.2. Bending forward from the waist to pick up a pen from the floor without an aid.



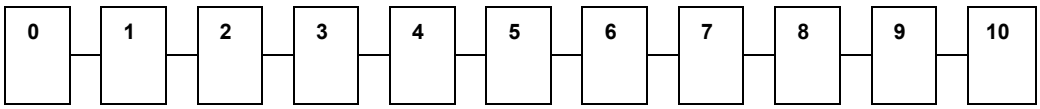
5.3. Reaching up to a high shelf without help or aids (e.g. helping hand).



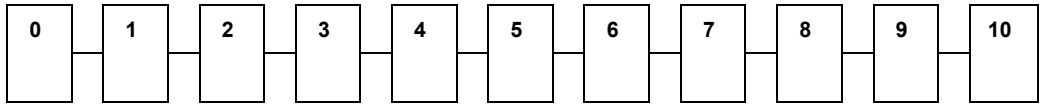
5.4. Getting up out of an armless dining room chair without using your hands or any other help.



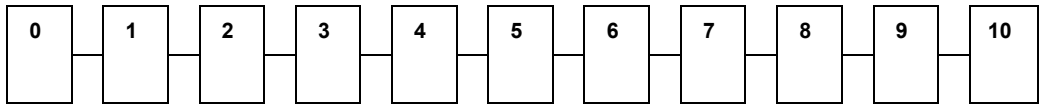
5.5. Getting up off the floor without help from lying on your back.



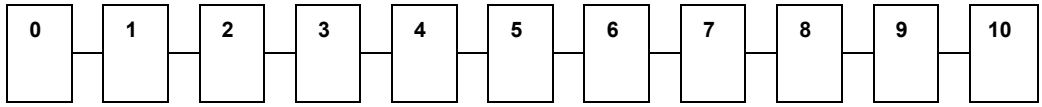
5.6. Standing unsupported for 10 minutes without discomfort.



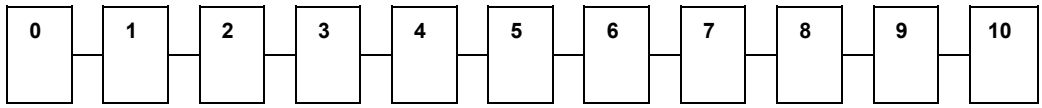
5.7. Climbing 12-15 steps without using a handrail or walking aid. One foot at each step.



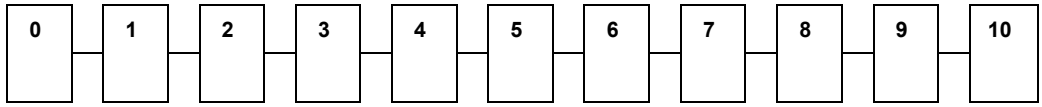
5.8. Looking over your shoulder without turning your body.



5.9. Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports).



5.10. Doing a full days activities, whether it be at home or at work.



Please read each statement carefully. We would like you to tick ‘yes’ if the statement applies to you, and tick ‘no’ if it does not.

Tick the **one** response that applies best to you **at the moment**.

6.1. My condition limits the places I can go. □ No □ Yes

6.2. I sometimes feel like crying. □ No Yes

6.3. I have difficulty dressing. □ No Yes

6.4.	I struggle to do jobs around the house.	□ No	Yes
6.5.	It's impossible to sleep.	□ No	Yes
6.6.	I am unable to join in activities with my friends / family.	□ No	Yes
6.7.	I am tired all the time.	□ No	Yes
6.8.	I have to keep stopping what I am doing to rest.	□ No	Yes
6.9.	I have unbearable pain.	□ No	Yes
6.10.	It takes a long time to get going in the morning.	□ No	□ Yes
6.11.	I am unable to do jobs around the house.	□ No	Yes
6.12.	I get tired easily.	□ No	Yes
6.13.	I often get frustrated.	□ No	Yes
6.14.	The pain is always there.	□ No	Yes
6.15.	I feel I miss out on a lot.	□ No	Yes
6.16.	I find it difficult to wash my hair.	□ No	Yes
6.17.	My condition gets me down.	□ No	Yes
6.18.	I worry about letting people down.	□ No	Yes

Appendix 3.4: Carotid Doppler Ultrasound Clinical Information Leaflet

NAME:
DATE:
MRN:

RIGHT
COMMON CAROTID ARTERY – IMT
M1
M1
M3
AVERAGE
MAX
PHILIPS EPIC IMT AVERAGE

INTERNAL CAROTID ARTERY
M1
M2
M3
AVERAGE
MAX
PHILLIPS EPIC IMT AVERAGE

LEFT
COMMON CAROTID ARTERY – IMT
M
M2
M3
AVERAGE
MAX
PHILLIPS EPIC IMT AVERAGE

INTERNAL CAROTID ARTERY
M1
M2
M3
AVERAGE
MAX
PHILLIPS EPIC IMT AVERAGE