Subclinical Cardiovascular Disease in early Rheumatoid Arthritis and established Giant Cell Arteritis: Insights from Cardiovascular Magnetic Resonance Imaging

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Intellectual property and publication statements

The candidate confirms that the work submitted is his own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapter 4 includes content from the following peer-reviewed publication:

Erhayiem B, Pavitt S, Baxter P, *et al*. Coronary Artery Disease Evaluation in Rheumatoid Arthritis (CADERA): study protocol for a randomized controlled trial. Trials. 2014;15:436. doi:10.1186/1745-6215-15-436.

SP, PDB, JA, JPG, MHB and SVP participated in the design of the study and helped to draft the manuscript. BE participated in the co-ordination of the study and drafted the manuscript. MHB and SVP conceived the study. All authors read and approved the final manuscript.

Chapter 1 includes content used from my MD transfer report. Chapter 7 includes content that is undergoing peer-review for publication, but is yet accepted nor in press by any journal.

Publications arising from this work

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Erhayiem B, Bissell L-A, McDiarmid AK, *et al*. Abnormal left ventricular geometry is prevalent in asymptomatic patients with established rheumatoid arthritis compared with those with early disease and healthy controls. Journal of Cardiovascular Magnetic Resonance. 2015;17(Suppl 1):P297. doi:10.1186/1532-429X-17-S1-P297.

Erhayiem B, McDiarmid AK, Swoboda PP, *et al*. Dilatation of the thoracic aorta and increased arterial stiffness is common in patients with giant cell arteritis - preliminary findings from a cardiac magnetic resonance study. Journal of Cardiovascular Magnetic Resonance. 2015;17(Suppl 1):P407. doi:10.1186/1532-429X-17-S1-P407.

Erhayiem B, Kidambi A, Ripley DP, *et al*. Quantification of septal and whole slice myocardial blood flow by myocardial perfusion CMR is similar in healthy volunteers. Journal of Cardiovascular Magnetic Resonance. 2014;16(Suppl 1):P12. doi:10.1186/1532-429X-16-S1-P12.

Erhayiem B, Pavitt S, Baxter P, *et al*. Coronary Artery Disease Evaluation in Rheumatoid Arthritis (CADERA): study protocol for a randomized controlled trial. Trials. 2014;15:436. doi:10.1186/1745-6215-15-436.

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Abstract

Immune-mediated inflammatory diseases (IMID) are a group distinguished by specific pathways of immune-dysregulation that lead to inflammation, organ damage and dysfunction, of which Rheumatoid Arthritis (RA) and Giant Cell Arteritis (GCA) are two examples. An increased risk of cardiovascular disease (CVD) is observed in patients with IMID. Inflammation plays an important role in atherosclerosis. The inflammatory process has confounding effects on lipid and glucose metabolism, blood pressure and haemostatic factors. RA is a chronic inflammatory arthritis and one of the most common systemic autoimmune diseases affecting approximately 1% of the UK population. In RA, the risk of myocardial infarction (MI) is independent of, and incremental to, traditional CVD risk factors. CVD, as a direct result of the IMID process and independent of atherosclerosis can be an additional insult and seen in GCA. GCA is associated with an increased mortality mainly due to CVD, including aortic syndromes. Aortic involvement in GCA may manifest clinically as a syndrome of systemic inflammation without specific symptoms, or even be asymptomatic until aortic dissection or rupture supervenes with life-threatening consequences.

The early identification of disease can benefit patients clinically by initiation of earlier disease modifying therapy, potentially reducing morbidity and mortality. Determining disease phenotype is important to develop effective screening strategies. This thesis aims to identify subclinical cardiovascular (CV) change using cardiovascular magnetic resonance (CMR) in the IMIDs of RA and GCA. It is also tested whether therapeutic interventions can modulate surrogate markers of CV outcomes in RA.

Using CMR, this thesis demonstrates the presence of CV abnormalities in early RA (ERA) and established GCA. Changes in vascular function, myocardial tissue composition and ventricular geometry/performance are present in ERA, inferring an increased risk of CVD at the earliest stages of the RA disease continuum. There are thoracic aortic structural changes in established, treated, GCA. Dilatation of the thoracic aorta is common in GCA, with polymyalgic symptoms a possible risk factor. Patients with GCA also had increased aortic arterial stiffness than controls.

This thesis also discusses interventional data that evaluates if early aggressive control of newly diagnosed RA can reduce subclinical CV pathology at 1 year from treatment initiation. It is explored whether tumour necrosis factor inhibitor (TNFi) offers any additional benefit over and above conventional synthetic disease modifying anti-rheumatic drugs (DMARDs) in the burden of subclinical CV pathology. Increased arterial stiffness, by measure of aortic distensibility, can be modulated and improved after 1 year of disease modifying therapy using a methotrexate (MTX) treat-to-target (MTX TTT) regimen or early biological therapy with etanercept (ETN). Patients with higher baseline C-reactive protein (CRP) appear to improve arterial stiffness the most.

CMR is able to detect subclinical CV change in asymptomatic ERA and established GCA patients without known CVD. Surrogate markers of CV events can be modulated in ERA with early aggressive RA therapy and CMR can identify silent aortic dilatation, associated with adverse outcomes, in GCA. CMR can aid the early and appropriate diagnosis of disease and complications, and potentially identify those at the highest risk of adverse outcomes.

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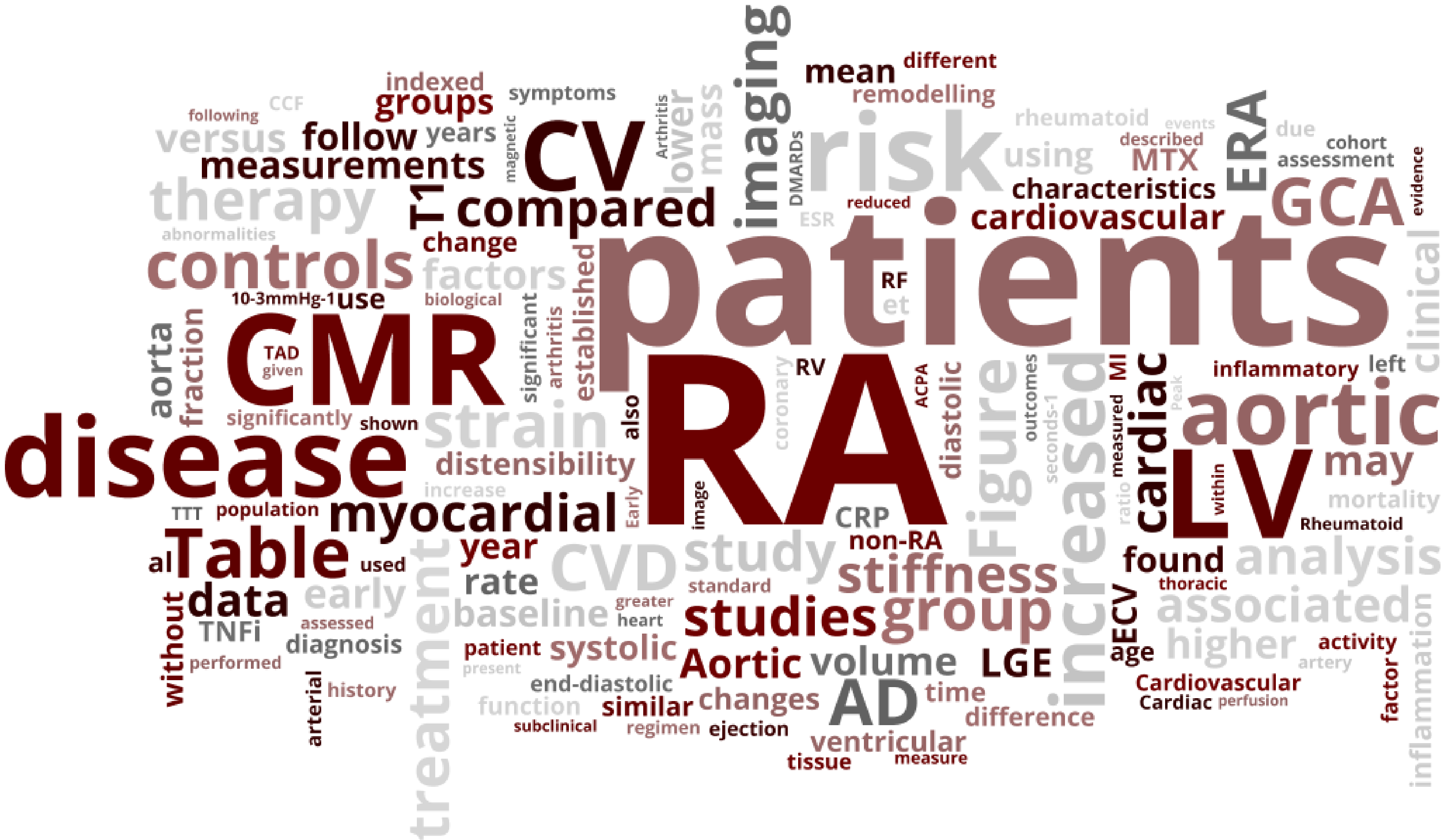
Abbreviations

AA	Amyloid A
ACC	American College of Cardiology
ACEi	Angiotensin-converting-enzyme inhibitor
ACPA	Anti-citrullinated peptide antibody
ACR	American College of Rheumatology
ACS	Acute coronary syndrome
AD	Aortic distensibility
AF	Atrial fibrillation
AHA	American Heart Association
AR	Aortic regurgitation
ARB	Angiotensin receptor blocker
AsAo	Ascending aorta
BB	Beta-blocker
bDMARD	Biological disease modifying anti-rheumatic drug
BLAST	Broad-use Linear Acquisition Speed-up Technique
BP	Blood pressure
BSA	Body surface area
bSSFP	Balanced steady state free precision
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CADERA	Coronary Artery Disease Evaluation in Rheumatoid Arthritis trial
CCF	Congestive cardiac failure
CCS	CT coronary artery calcium scoring
CI	Confidence interval
CIMT	Carotid intimal-media thickness
CK	Creatine kinase
CMR	Cardiovascular magnetic resonance
CoV	Coefficient of variability
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease

CT	Computed Tomography
CTD	connective tissue disease
CXR	Chest radiograph
DAS	Disease activity score
DM	Diabetes mellitus
DMARD	Disease modifying anti-rheumatic drug
DsAo	Descending aorta
ECG	Electrocardiogram
ECV	Extra-cellular volume
EDSR	Early diastolic strain rate
EDV	End-diastolic volume
EF	Ejection fraction
EMB	Endomyocardial biopsy
ESC	European Society of Cardiology
ERA	Early RA
ESR	Erythrocyte sedimentation rate
ETN	Etanercept
EULAR	The European League Against Rheumatism
EUROSCORE	European System for Cardiac Operative Risk Evaluation
FDG-PET/CT	^{18}fluorodeoxyglucose-PET/CT
GCA	Giant cell arteritis
hsCRP	High sensitivity CRP
IACON	Inflammatory Arthritis disease CONtinuum study
IDEAL	Incremental Decrease in Endpoints through Aggressive Lipid-lowering trial
IHD	Ischaemic heart disease
IL-6	Interleukin-6
LDSR	Late diastolic strain rate
LGE	Late gadolinium enhancement
LMBRU	Leeds musculoskeletal biomedical research unit
LV	Left ventricle
LVV	Large vessel vasculitis
LVM	LV mass

LVSD	LV systolic dysfunction
MBF	Myocardial blood flow
MDT	Multi-disciplinary team
MESA	Multi-Ethnic study of atherosclerosis
MI	Myocardial infarction
MOLLI	Modified look-locker inversion
MTX	Methotrexate
MVA	Multivariate linear regression analysis
NICE	National Institute for Health and Care Excellence
NRES	National Research Ethics Service
NASID	Non steroidal anti inflammatory drug
NSTE-ACS	Non ST elevation-ACS
NT-pro BNP	N-terminal prohormone of B-type natriuretic peptide
NYHA	New York Heart Association
PA	Pulmonary artery
PCI	Percutaneous intervention
PET	Positron emission tomography
PMR	Polymyalgia rheumatica
PWV	Pulse wave velocity
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
REC	Research Ethics Council
RF	Rheumatoid factor
RV	Right ventricle
SD	Standard deviation
SPAMM	Spatial modulation of magnetization
SPECT	Single-photon emission computed tomography
TAA	Thoracic aorta aneurysm
TAD	Thoracic aorta dilatation
TE	Echo time
Tn	Troponin
TNF	Tumour necrosis factor

TNFi	Tumour necrosis factor inhibitor
TOE	Trans-oesophageal echocardiography
TR	Repetition time
TRACE RA	UK Trial of Atorvastatin for the primary prevention of CV Events in RA
TTE	Transthoracic echocardiography
TTT	Treat to target
UK	United Kingdom
UVA	Univariate analysis
VEDERA	Very Early versus Delayed Etanercept in Rheumatoid Arthritis trial
VENC	Velocity encoding
VHD	Valvular heart disease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AD
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difference
Cardiovascular
Cardiac
perfusion
subclinical
regimen
ejection
ventricular
tissue
measure

1 Introduction

1.1 Immune-mediated inflammatory disease

Immune-mediated inflammatory diseases (IMID) are a group distinguished by specific pathways of immune-dysregulation that lead to inflammation, organ damage and dysfunction[1]. This thesis focuses on CV changes in IMID as assessed by CMR. During my time as a Clinical Research Fellow in CMR at the University of Leeds, I was *primarily* involved in projects and collaborations involving one IMID, RA; by means of studying ERA in the Coronary Artery Disease Evaluation in Rheumatoid Arthritis (CADERA) trial and established RA in the Inflammatory Arthritis Continuum (IACON) studies. With interest in heart failure and IMID, further projects and collaborations allowed me opportunity to study GCA in the UK GCA Consortium study, systemic sclerosis in the ELectrophysiology and CArdiac imaging in SclerodermA (ELCASA) study and Systemic Lupus Erythematosus (SLE) in the CONnective tissue and VASculitis (CONVAS) registry. They all share a common ground of being IMIDs with links to CV morbidity and mortality. I chose to focus my thesis on two IMIDs; principally on RA, with an additional study on GCA. RA is one of the most common autoimmune diseases affecting approximately 1% of the UK population[2]. A chronic, systemic, inflammatory arthritis with increased mortality largely due to premature CVD[3]. GCA is the commonest primary systemic vasculitis affecting older people[4]. It is also associated with an increased early mortality mainly due to CVD, including aortic syndromes[5].

1.2 Inflammation and atherosclerosis

Inflammation plays an important role in atherosclerosis. CRP has been well studied, with its presence known about in atherosclerotic lesions. Immune cells and intermediate factors also found in atheroma further implicate inflammatory mechanisms[6]. Advances in cell biology research allowed testing of specific molecules supporting immune mechanisms for atherosclerotic formation[7]. When arterial wall endothelial cells are activated by inflammation, they can express adhesion molecules to attract white cells. Monocytes are the most abundant and chemokine stimuli allow them to enter the vessel intima. There they mature into macrophages and engulf modified lipoprotein particles giving the typical

appearance of foam cells[8]. Inflammation is further accelerated by release of growth factors and cytokines.

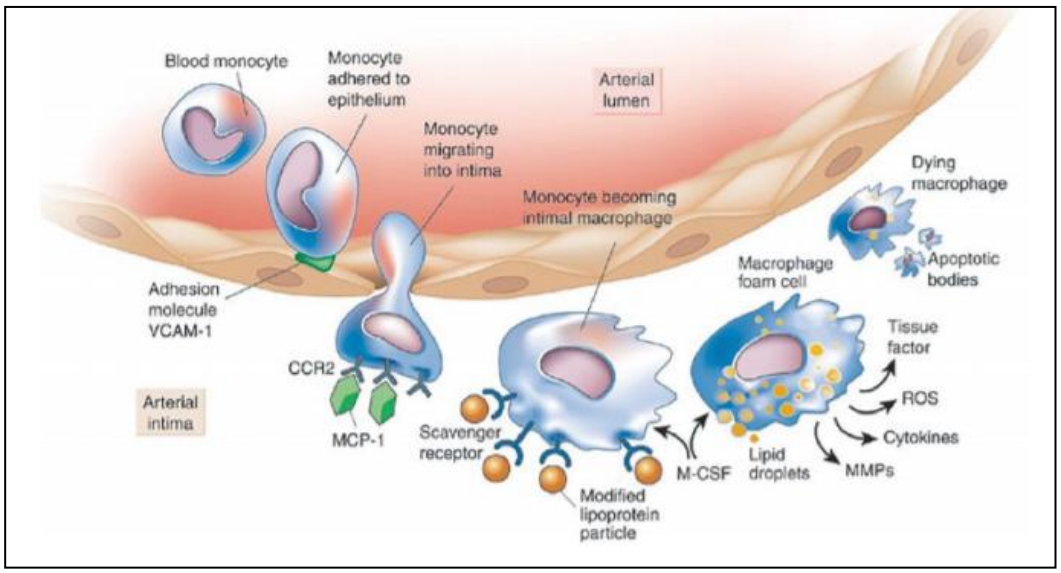


Figure reproduced from Libby *et al*. Inflammation in atherosclerosis: transition from theory to practice. Circ J. 2010 Feb;74(2):213-20[8].

Plaque rupture causes most cases of fatal myocardial infarction and inflammation regulates the fibrous cap rupture and subsequent thrombosis[9]. T-lymphocytes play an important role in this step and enter the intima in response to various chemokine signals, ligands and proteins[10]. Activated T-lymphocytes further secrete pro-inflammatory cytokines and pro-coagulants[11]. Inflammation reduces the strength of plaque fibrous caps by way of interferon-γ, which inhibits collagen production by smooth muscle cells[12]. There are inflammatory contributions in atherosclerosis from the formation of atherosclerotic plaques, their evolution, and the reduction of stability to the final conclusion of rupture and thrombosis. There is much interest with the development of drugs to target the inflammatory cascade at various levels. Higher high-sensitivity CRP (hsCRP) has been shown to predict CV events[13]. Statins can lower hsCRP levels, largely in an LDL independent way[14]. It has been shown that rosuvastatin in healthy persons without hyperlipidemia and higher hsCRP reduces the incidence of major cardiovascular events[15]. Very recently, presented at the European Society of Cardiology meeting in Barcelona and published online in the New England Journal of Medicine, the phase III study CANTOS (Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease) was presented. Canakinumab is a monoclonal antibody that targets the interleukin-1β innate

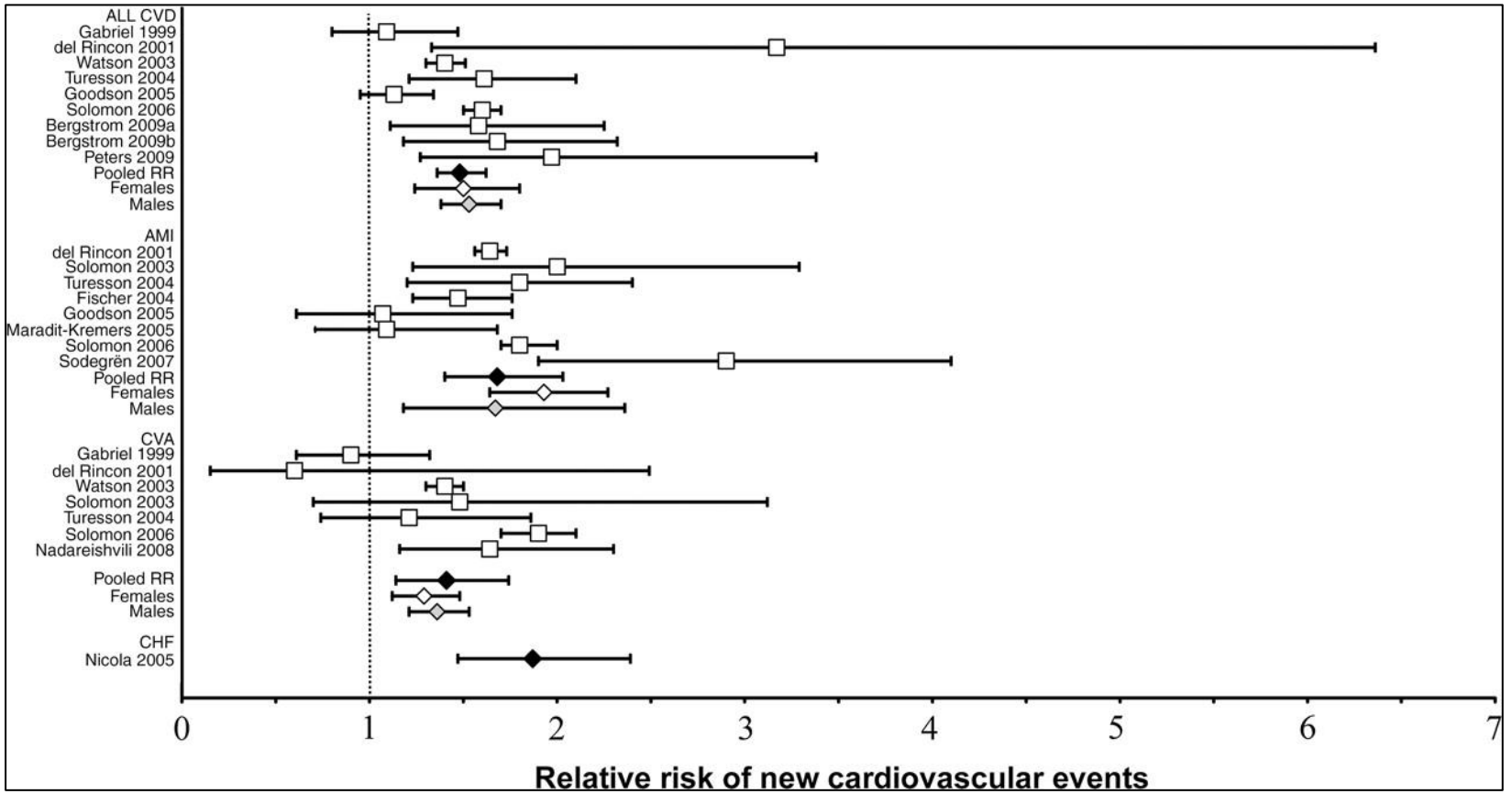
immunity pathway. This was a randomized, double-blind trial and recruited around 10,000 patients with prior MI and raised hsCRP. Independent of lipid-lowering, a 150mg dose every 3 months led to a significantly lower rate of recurrent CV events than placebo[16].

1.3 Rheumatoid arthritis

RA is a chronic inflammatory arthritis and one of the most common systemic autoimmune diseases affecting approximately 1% of the UK population[2]. It is associated with circulating rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA), and if not adequately controlled can lead to joint damage with subsequent impairment of function. Mortality is increased in RA patients, compared to the general population, with premature CVD and heart failure constituting up to 40% of mortality compared to 15% in the general UK population[3]. It has been compared to the risk of other established CV risk factors such as type 2 diabetes mellitus (DM)[17].Figure 1-1, taken from a meta-analysis by Avina-Zubieta *et al*, shows the overall and cause-specific CVD in patients with RA.

It is accepted that CVD risk in RA is independent of, and incremental to, traditional CVD risk factors[18] with the likely predominant pathological process being immune dysregulation leading to systemic inflammation[19]. The inflammatory process has confounding effects on lipid and glucose metabolism, blood pressure and haemostatic factors[20]. Markers of RA severity are strongly associated with adverse CV outcomes in RA[21] and reduced time-average disease activity is associated with fewer CV events[22]. Arterial stiffness is associated with an increased risk of CV events in a range of co-morbidities[23]. In patients with established RA without traditional CV risk factors, aortic pulse wave velocity (PWV) is higher than in controls[24] and correlates with age, mean arterial pressure and CRP. RA patients have a greater carotid intimal-media thickness (CIMT), a direct measure of the status of the vascular wall and measure of atherosclerotic and arteriosclerotic processes[25], than controls[26]. These findings are consistent with the concept of microvascular pathology and accelerated atherosclerosis due to systemic inflammation in RA, which may contribute to the effects of coronary artery disease (CAD).

Figure 1-1 - Overall and cause-specific cardiovascular disease in patients with Rheumatoid Arthritis



Reproduced from Avina-Zubieta JA, et al. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2012;71(9):1524-9[27].

1.4 Giant Cell Arteritis

GCA is the commonest primary systemic vasculitis affecting older people[4]. In the elderly, GCA is even more common than rheumatoid arthritis (incidence in the over-70s is 53/100,000/year[28, 29] and yet it receives relatively little research attention. For example, in the 5 years to September 2010 there had been 432 articles on GCA available on Pubmed, compared with 7,910 on rheumatoid arthritis. Polymyalgia rheumatica (PMR), characterised by inflammatory limb-girdle pain with early morning stiffness and a systemic inflammatory response, demonstrated by elevation in inflammatory markers erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and/or plasma viscosity (PV). Approximately 10% of patients with PMR will go on to develop late GCA[30] and approximately half of all patients presenting with GCA also have symptoms of PMR. Most individuals with GCA also have a systemic inflammatory response. Although several different sets of classification criteria exist, there is still no universally-agreed set of core outcome measures for clinical characterisation of PMR which will be necessary for genetic association studies[31]. Like GCA, patients with PMR may experience complications related to long-term steroid treatment. Although GCA and PMR appear closely related, it remains unclear whether GCA and PMR are the same disease, or separate diseases which may share common pathogenetic features[32]. Major sequelae of GCA include:

- Ischaemic manifestations (usually at onset of disease)
- Complications of steroid treatment
- Arterial aneurysm

1.5 Causes of GCA

The cause of GCA remains unknown. There are some data to suggest that hypertension or atherosclerosis may predispose to ischaemic features[33, 34]. Social deprivation may also be of importance, with a gradient of incidence highest in the affluent South-East of England and lower moving further north[28], which contrasts with the general pattern of a higher incidence at more northern latitudes within Europe. There may be a complex interplay of genetic, constitutional and environmental (e.g. ultraviolet light exposure, diet, psychosocial stress, infections including periodontal infection), and social factors. Studies from Europe and America

have demonstrated genetic associations, particularly with HLA-DBR1*04, but this finding was not universal, not being observed either in an Italian GCA cohort, or in many PMR cohorts[33, 34].

1.6 Aortic involvement in GCA

Classical descriptions focus on involvement of the superficial cranial arteries, but with modern imaging techniques it is increasingly recognised that aortic involvement is common and may lead to serious complications, such as aortic aneurysm[2]. Aortic involvement in GCA may manifest clinically as a syndrome of systemic inflammation without specific symptoms, or even be asymptomatic until aortic dissection or rupture supervenes with life-threatening consequences[35]. Even if asymptomatic, thoracic aortic aneurysm (TAA) may require corrective surgery in up to 40% to prevent such complications of dissection or rupture[36]. GCA with large-vessel vasculitis (LVV-GCA), or involvement of the large extracranial arteries has a younger, female preponderance and may spare the temporal artery, such that the temporal artery biopsy may be negative[37]. It has been suggested that glucocorticoid doses sufficient to suppress clinical symptoms of GCA may not be adequate to suppress inflammation in the wall of the larger arteries[38].

GCA is associated with an increased early mortality mainly due to CVD, including aortic syndromes, during the first 2 years of diagnosis[5]. GCA patients are older and so the definition of 'early mortality' from CVD is not well refined. Aortic imaging may reveal thoracic aortic dilatation (TAD), presumed to be a precursor to TAA. Previously-described associations of TAA/TAD development in GCA include aortic regurgitation (AR), dyslipidaemia, CAD[35], hypertension, higher acute phase markers[39], male sex and smoking[40]. Greater aortic uptake of ^{18}F-deoxyglucose (^{18}FDG) tracer on positron emission tomography (PET) imaging is associated with greater subsequent aortic diameter[37]. The question whether aortic imaging should be routinely carried out in unselected patients with GCA is important. Older patients, with increasing frequency of co-morbidity, inherently have greater surgical risk, which should be considered before looking for TAD. The timing and frequency of imaging is also uncertain without further longitudinal studies to determine the natural history of aortic structural changes.

Much is unknown about the mechanism of TAD in GCA. Dilatations might occur from direct inflammation-related damage to elastin; alternatively dilatation might arise proximal or distal to a relatively stiff aortic segment[41]. In the general population, aortic stiffness caused by age-related loss of aortic elasticity is associated with CV risk. In diseases such as PMR and GCA, however, additional stiffening may relate to the inflammatory disease itself and be improved with glucocorticoid therapy[42].

1.7 Screening of thoracic aorta dilatation in GCA

Various guidelines and recommendations have been proposed for TAA screening and monitoring in GCA[43]. Current UK guidelines suggest a chest radiograph every 2 years[44] but this is insensitive compared to computed tomography or CMR of the aorta. It has been estimated that 5 to 10 GCA patients would need aortic imaging to detect a previously unknown TAA/TAD but this was based on small, heterogeneous datasets[40]. Furthermore this did not seem to fit with clinical experience: although thoracic contrast computed tomography (CT) is now performed for a multitude of indications, aortic aneurysm in patients with GCA seems to be rarely discovered incidentally. In large-scale routinely-collected clinical data the frequency of any aortic aneurysm diagnosis in patients with GCA was only 1%, compared with 0.7% of those without GCA[45]. Because of this, and bearing in mind the costs and burdens of sophisticated imaging tests used to screen for asymptomatic pathology, there is still no consensus amongst clinicians regarding the clinical utility of routine aortic imaging in patients with GCA.

1.8 Cardiovascular disease risk in the asymptomatic rheumatoid arthritis patient

1.8.0 Assessment of cardiovascular risk

CVD risk in RA is independent of, and incremental to, traditional CV risk factors[18]. Although the exact mechanisms continue to remain unclear, the predominant pathological process is likely to be immune dysregulation leading to systemic inflammation[19].

Figure 1-2 - Interplay between CV risk, inflammation and traditional CV risk factors

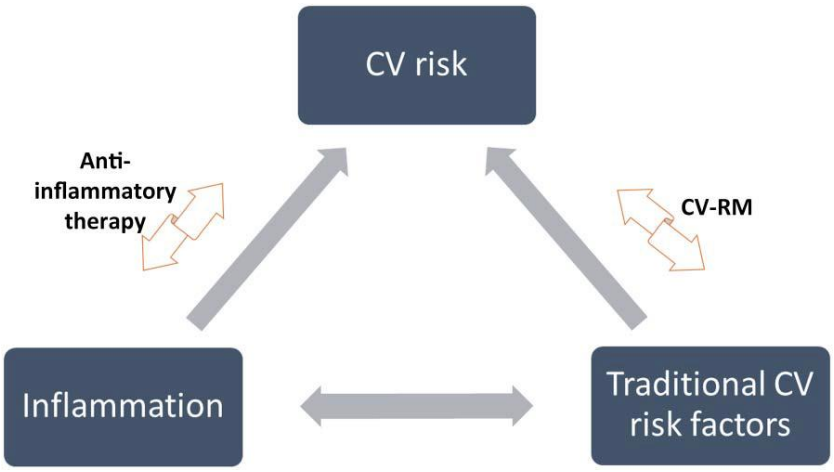
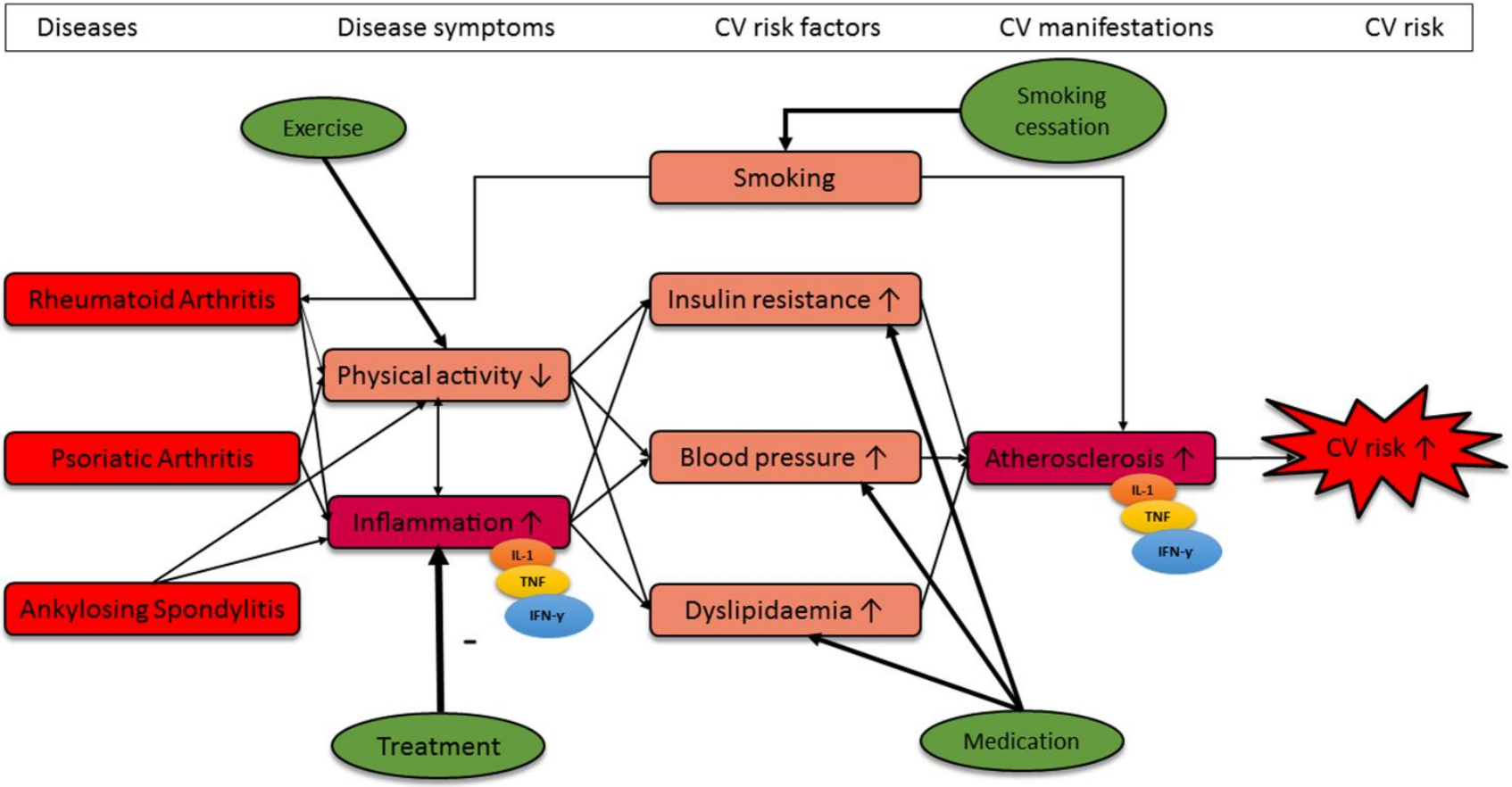


Figure reproduced from Agca R, et al. Atherosclerotic cardiovascular disease in patients with chronic inflammatory joint disorders. Heart 2016;102:790–795[46]

The inflammatory process is linked to atherosclerosis and plaque rupture and has synergistic effects on lipid and glucose metabolism, blood pressure and haemostatic factors[20]. While it appears that long-term inflammation in RA contributes to this increased CV risk, traditional CV co-morbidities play an important role. Patients with RA have been shown to have increased insulin resistance, abnormal fat distribution, increased cigarette smoking and decreased amount of aerobic physical activity - with dyslipidaemia, DM and hypertension rates also at an increased prevalence[47].

Figure 1-3 - A model of immune-mediated inflammatory joint disorders, including RA, and CV risk



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The European League Against Rheumatism (EULAR) has published recommendations for CV risk management in patients with RA (Table 1-1). Annual CV risk assessment should be offered to RA patients with established cardiac risk score models being adapted for patients with RA by introducing a 1.5 multiplication factor if not already included in the model. Previously, in the 2009 guidelines, the multiplication factor was used when two of the following three criteria are met; a) disease duration of more than 10 years, b) RF or ACPA positivity or c) presence of certain extra-articular manifestations[48], given that markers of RA severity are associated with adverse CV outcomes[21]. In contrast, the 2015/2016 EULAR guideline update states the presence of RA-specific criteria are no longer mandatory to the multiplication factor, given some evidence of increased CV mortality and atherosclerosis in seropositive patients with recent-onset/early inflammatory polyarthritis[21, 49].

Despite the evidence of increased CVD risk in RA and guidelines attempting to mitigate this risk, RA patients may not get a level of scrutiny for CVD risk assessment, as do other traditional CV risk factors such as DM. The first population-based, cross-sectional observational study that looked at RA co-morbidity and management was published in October 2013 and analysed 3920 patients over 17 countries from rheumatology clinics. History of CVD was 6% with CV risk factors of hypertension, hyperglycaemia and hyperlipidaemia at 11.2%, 3.3% and 8.3% respectively[50]. Although prevalence of traditional CV risk factors differed from country to country, it confirmed previous studies[51] that management of cardiac disease, risk assessment and adherence to available guidelines was variable and suboptimal in 30-50% of RA patients. The under-recognition of excess CV risk in RA further exists in primary care[52].

In a 2014 update of national guidelines, for CV primary prevention strategies, the United Kingdom National Institute for Health and Care Excellence (NICE) recommend using the QRISK®2 assessment tool to assess the 10 year risk of developing CVD in the general population. Previously, NICE has asked primary care physicians to decide on whichever CVD risk calculator to use themselves, including the Framingham scoring tool. The QRISK®2 calculator is the only calculator that takes into account RA as a separate CVD risk factor. It takes into account ethnicity, age, smoking status, sex, systolic blood pressure, total cholesterol, HDL cholesterol, BMI, family history, postal code, anti-hypertensive therapy, rheumatoid arthritis, chronic kidney disease, diabetes, and atrial fibrillation[53]. QRISK®2 corresponds to the

populations in England and Wales as it not validated for international populations. The tool is used if the patient is *not* in any of the following groups: established CVD; type I diabetic; have chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) <60mL/min/1.73m2 and/or a urinary albumin:creatinine ratio (ACR) greater than 3 mg/mmol; aged 85 years or older. The assessment is repeated every five years, but earlier if any significant medical changes occur in personal or family history. QRISK®2 has been specifically developed by doctors and academics for use in the UK. Published in 2007, the original research underpinning QRISK® was performed using the electronic health records of 550 general practices using the Egton Medical Information Systems (EMIS) clinical computer system. 2 million contributed to the database. More recently, the QRISK®3 CVD risk calculator has included further factors than QRISK®2. These include further disease and treatment history associated with inflammation, in that regular corticosteroid use and Systemic Lupus Erythematosus (SLE) are now part of the calculator. Other additions include: CKD, including stage 3; history of migraines; use of atypical antipsychotics; history of severe mental illness; history of erectile dysfunction and; systolic blood pressure variability. By including history of regular corticosteroid use, IMIDs may be included and raise the risk of CVD, but so far it is only RA and SLE that are specifically mentioned diseases in the QRISK®3 risk calculator. QRISK®3 will be the standard version of QRISK® shipped in software development kits during 2018.

Table 1-1 - The EULAR overarching principles and recommendations for CVD risk management in patients with RA

	Level of evidence	Strength of recommendation	Level of agreement (SD)
Overarching principles A. Clinicians should be aware of the higher risk for CVD in patients with RA compared with the general population. This may also apply to AS and PsA. B. The rheumatologist is responsible for CVD risk management in patients with RA and other IJD. C. The use of NSAIDs and corticosteroids should be in accordance with treatment-specific recommendations from EULAR and ASAS			
Recommendations			
1. Disease activity should be controlled optimally in order to lower CVD risk in all patients with RA, AS or PsA	2b-3	B	9.1 (1.3)
2. CVD risk assessment is recommended for all patients with RA, AS or PsA at least once every 5 years and should be reconsidered following major changes in antirheumatic therapy	3–4	C	8.8 (1.1)
3. CVD risk estimation for patients with RA, AS or PsA should be performed according to national guidelines and the SCORE CVD risk prediction model should be used if no national guideline is available	3–4	C–D	8.7 (2.1)
4. TC and HDLc should be used in CVD risk assessment in RA, AS and PsA and lipids should ideally be measured when disease activity is stable or in remission. Non-fasting lipids measurements are also perfectly acceptable	3	C	8.8 (1.2)
5. CVD risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor, if this is not already included in the model	3–4	C	7.5 (2.2)
6. Screening for asymptomatic atherosclerotic plaques by use of carotid ultrasound may be considered as part of the CVD risk evaluation in patients with RA	3–4	C–D	5.7 (3.9)
7. Lifestyle recommendations should emphasise the benefits of a healthy diet, regular exercise and smoking cessation for all patients	3	C	9.8 (0.3)
8. CVD risk management should be carried out according to national guidelines in RA, AS or PsA, antihypertensives and statins may be used as in the general population	3–4	C–D	9.2 (1.3)
9. Prescription of NSAIDs in RA and PsA should be with caution, especially for patients with documented CVD or in the presence of CVD risk factors	2a-3	C	8.9 (2.1)
10. Corticosteroids: for prolonged treatment, the glucocorticoid dosage should be kept to a minimum and a glucocorticoid taper should be attempted in case of remission or low disease activity; the reasons to continue glucocorticoid therapy should be regularly checked	3–4	C	9.5 (0.7)

AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; CVD, cardiovascular disease; EULAR, European League against Rheumatism; HDLc, high-density lipoprotein cholesterol; IJD, inflammatory joint disorder; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SCORE, Systematic Coronary Risk Evaluation; TC, total cholesterol.

Table reproduced from Agca R, et al. Atherosclerotic cardiovascular disease in patients with chronic inflammatory joint disorders. Heart 2016;102:790–795[46]

1.8.1 A summary of the effect of rheumatoid arthritis therapy on the risk of cardiovascular disease

The TTT use of conventional DMARDs is internationally recommended practice[54]. In a 2011 systematic review and meta-analysis, MTX was associated with 21% lower risk of total CVD and 18% lower risk of myocardial infarction (MI)[55]. Studies that controlled for underlying disease severity and medication use were associated with 36% and 27% lower CVD risk respectively compared with studies that did not[55]. Biologic DMARD (bDMARD) treatments are highly effective therapy that can be used to achieve remission and have improved outcomes in RA. TNFi, the first bDMARDs, have demonstrated particularly high rates of remission induction in ERA, with similar or slightly greater efficacy than conventional DMARDs, but with superior structural benefits and the ability to achieve drug-free remission[56-62]. There may be benefit of bDMARD therapy in reducing CV morbidity and mortality given improvement of surrogate markers of CVD[63, 64] but as TNFi treatment is reserved for established, MTX-refractory disease, observational studies are inherently limited by a selection bias. A large prospective study of 3529 etanercept (ETN) treated patients and 2864 on conventional DMARDs, with notable baseline differences, found no evidence of adverse outcome from long-term exposure to ETN, such as serious infections, but there was evidence of improved survival and reduced CV events[65]. In patients with resistant disease and mean disease duration of 7.1 years given infliximab, another TNFi, left ventricular ejection fraction (LVEF) measured by transthoracic echocardiography (TTE) increased from 59% before treatment to 63% after, with significant reduction in biochemical markers of heart failure[66]. ETN has also been shown to be associated with a significant decrease in adverse left ventricle (LV) remodelling with medium-term treatment[67] supporting experimental studies that tumour necrosis factor (TNF) may induce adverse LV remodelling[68]. The CV benefit of TNFi treatment appeared to be strongest in RA patients over 65 years old in an observational study of 8656 new users of conventional DMARDs versus 11587 on TNFi, with the study showing an overall reduced risk of CV events in bDMARDs[69].

A recent, large extended report by Low *et al*[70] aimed to review the relationship between exposure to TNFi therapy and incidence and severity of MI in patients with RA. Their analysis looked at RA patients recruited to the British Society for Rheumatology Biologics Register for RA between 2001 and 2009. They found a total of 252 first MIs in which 194 were receiving TNFi

(out of 11,200 patients) and 58 were receiving conventional DMARDs (out of 3,058 patients). They found that a lower risk of MI in the TNFi, by means of propensity score decile adjusted hazard ratio of TNFi to conventional DMARD of 0.61 (95% confidence interval [CI] 0.41 to 0.89). They did not find any significant differences between treatment groups of the severity of the MI or the CV mortality over this medium term analysis.

Further well conducted experimental studies and randomized clinical trials are needed to determine mechanisms, supporting the inflammatory hypothesis of atherothrombosis or not, and investigate true causality of disease activity, CV risk factors, DMARD therapy and CV outcomes. Studies at present continue to suggest that a direct treatment of inflammation in RA may reduce risk of CVD.

1.9 The rheumatoid arthritis patient with cardiac symptoms

1.9.0 Typicality of ischaemic cardiac symptoms

RA can be associated with atypical cardiac symptoms. The United Kingdom National Institute for Health and Care Excellence (NICE) and European Society of Cardiology (ESC) have published guidance that aims to define the typicality of symptoms for angina pectoris. They summarise anginal pain as; a) a constricting discomfort in the front of the chest, or in the neck, shoulders, jaw, or arms, b) precipitated by physical exertion and c) being relieved by rest or GTN within about 5 minutes. All three features present are defined as typical angina with two features defined as atypical angina. One or none of the features above are defined as non-anginal chest pain[71]. The typicality of the symptoms coupled with age, sex and clinical risk factors give a pre-test likelihood of having CAD[72].

A retrospective cohort, by Maradit-Kremers *et al*, of 603 age/sex matched patients found that, along with the increased risk of developing CVD, RA patients were significantly more likely to have unrecognised MI and less likely to have a history of angina prior to a cardiac event[73]. Typicality of symptoms prior to cardiac events and/or revascularisation was assessed using guidance for diagnosis of angina or case-note documentation of clinical diagnosis. A smaller cohort of 43 RA patients already selected to undergo percutaneous intervention (PCI) for coronary revascularisation found that typicality and frequency of symptoms, as well as CAD distribution, were similar in treatment and outcomes to well-matched non-RA patients[74]. This study differed significantly to the Maradit-Kremers *et al* study, however this may be predicted given the smaller cohort and that these patients were all already selected out to undergo PCI.

Atypical cardiac symptoms have been described in other chronic diseases, such as end-stage renal failure and DM[75]. Possible explanations include the attribution of cardiac ischaemia to musculoskeletal pain due to their RA[73] and differences in pain perception[75]. Inflammatory hypotheses state that a higher production of anti-inflammatory cytokines with lower expression of CD11b/CD18 adhesion molecules on phagocytes can be present among patients and contribute to asymptomatic ischaemia[76]. Atypical symptoms may be a factor in the observed increase of unrecognised MI and sudden cardiac deaths in RA. There are observations that RA patients without recognised CAD have higher prevalence and extent of coronary plaque and so

the role of inflammation on plaque destabilisation causing an acute occlusion, without existing focal, severe stenoses, may be a factor for cardiac events without preceding typical symptoms[77].

1.9.1 Differential diagnoses of ischaemia: pericarditis, myocarditis and coronary vasculitis

1.9.1.1 Pericarditis

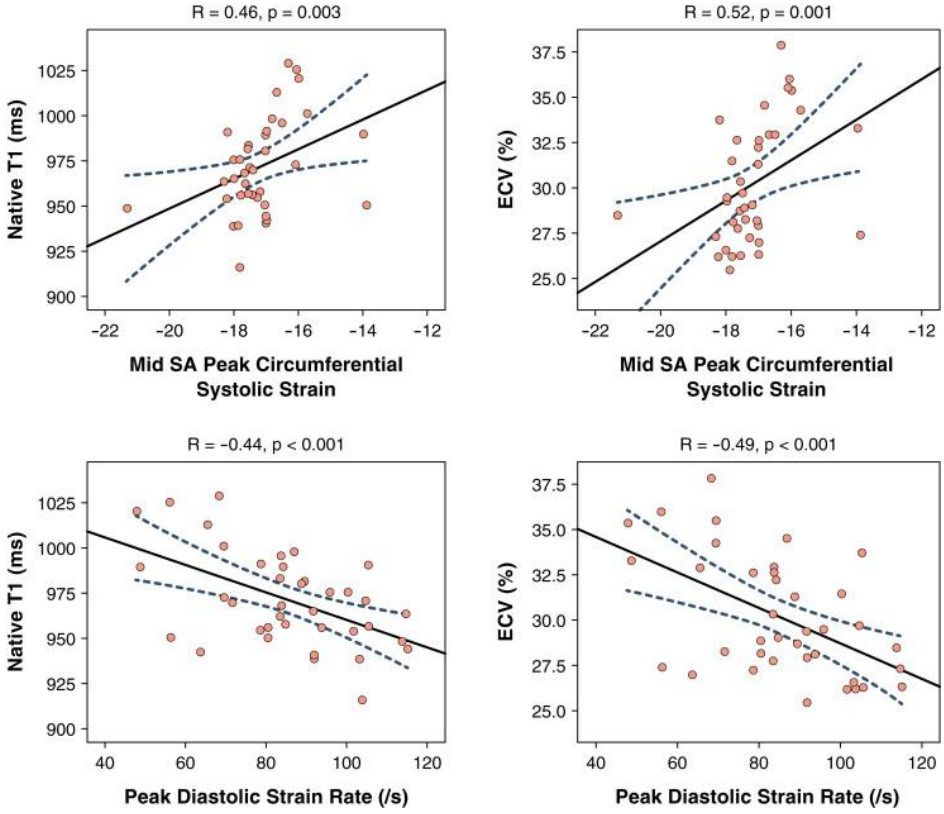
Evidence of pericardial inflammation in RA patients with a prevalence of 30-50% in older post-mortem studies of the 1970s[78]. An autopsy-based study in 2013 found increased prevalence of pericarditis in 369 RA patients between 1952 to 1991 (23% versus 8% in non-RA controls) but found little difference in reported symptoms or diagnoses of pericarditis during lifetime[79]. Within clinical practice, there appears to be a low symptom presentation of typical pericarditis compared to post-mortem prevalence. An hospital based study in 1986 found an annual incidence of pericarditis of 0.34% in females and 0.44% in males. The diagnosis was by clinical examination, ECG signs and using chest radiograph as the radiological test. The study did support previous work stating associations of pericarditis with positive RF, rheumatoid nodules, pleurisy and that it occurred more frequently in patients over 40 years old[80]. A 2012 retrospective community based study with diagnosis of pericarditis made by TTE, ECG and clinical judgement again only found an incidence of 1.5%[81].

The clinical significance of RA pericarditis is sparse in the contemporary literature, perhaps as a result of improved anti-inflammatory regimens. It is unknown whether pericarditis is causal to increased morbidity or reflection of inflammatory burden[82]. Two contemporaneous CMR studies found no pericardial abnormalities in 75 patients with RA on non-contrast CMR[83] and 18 patients using contrast-enhanced CMR [84]. Given the higher sensitivity and specificity of CMR to detect pericardial abnormalities over ECG, TTE and CXR, these studies require fewer patients and it is perhaps that pericardial disease is not an important or common CV manifestation currently.

1.9.1.2 Myocarditis

Non-infectious causes of myocarditis are on the whole more uncommon but are an important differential diagnosis in RA populations for the substantial morbidity and the potential for specific immunosuppressive treatments[85]. Extra-articular features in RA are associated with an increased incidence of non-ischemic cardiomyopathy, including myocarditis, estimated to be as high as 39%. A significant prevalence of myocarditis at autopsy is not associated with symptoms or diagnosis of myocarditis during lifetime[79]. These data were acquired in the 1980s and, similar to incidence of pericarditis, the decreased rate seen today may be due to the increased use of DMARDs[86]. Sub-clinical myocardial abnormalities and myocarditis exists in established RA. Established RA patients with higher disease activity scores (DAS) have been found to have sub-clinical non-ischaemic myocardial scar/fibrosis patterns on CMR[84]. Tissue characterisation techniques of myocardial extra-cellular volume (ECV) by T1 mapping show diffuse myocardial fibrosis and inflammation and association with impaired strain and RA disease activity[87], Figure 1-4.

Figure 1-4 - Correlation Between Myocardial Involvement in RA as Detected by Using T1 Parameters and LV Systolic and Diastolic Strains



ECV, extra-cellular volume; LV, left ventricle; RA, rheumaroid arthritis; s, seconds; SA, short-axis. Reproduced from Ntusi *et al*. Diffuse Myocardial Fibrosis and Inflammation in Rheumatoid Arthritis: Insights From CMR T1 Mapping. JACC Cardiovasc Imaging. 2015 May;8(5):526-36[87]..

1.9.1.3 Coronary vasculitis

Coronary vasculitis due to RA is a rare manifestation with seldom case reports published. This may be because differentiation between it and CAD is difficult, even with coronary arteriography, and both can co-exist. Additionally, it may never become clinically apparent unless resulting in a MI with frequent cases found in older autopsy series[88, 89]. The importance of remembering this differential diagnosis becomes apparent when considering the immunosuppressive treatment that is required to potentially reverse a life-threatening vasculitis rather than only using conventional therapy for MI[90].

1.9.2 Arrhythmias

Cardiac arrhythmia in RA could be due to ischaemia, fibrosis, congestive cardiac failure (CCF) or AA Amyloidosis[78]. Antibodies to cardiac conducting tissue have been found to be significantly higher in RA patients with right bundle branch block[91] but atrio-ventricular block remains rare in RA and hasn't been shown to respond to anti-inflammatory or immunosuppressive treatment[92]. International guidelines for pacemaker implantation should be followed without specific considerations named for RA patients in them[93]. Complex ventricular arrhythmias and sudden cardiac death have been described with prolonged QT interval in RA[94]. Prolonged QT interval has been linked to raised CRP[95] with a recent prospective study finding QT prolongation associated with CRP levels in RA patients and that a 50ms increase in corrected QT interval associated with a doubling of the hazard for all-cause mortality[96]. A 2012 Danish longitudinal cohort study over 15 years found a 40% higher risk of atrial fibrillation (AF) with a 30% higher risk of stroke in RA patients[97], however these results were not corroborated with a 2013 retrospective USA study that adjusted for a number of AF risk factors compared with non-RA patients[98]. There may be interplay between inflammation and specific antibodies with arrhythmias in RA that are for future study but no specific recommendations or differing management can be extrapolated at this time. Awareness of the possibility of increased arrhythmia in RA should continue with vigilance in looking for evidence on them on routine clinical reviews.

1.10 Myocardial Infarction in rheumatoid arthritis

1.10.0 Diagnosis

Clinical diagnosis of MI requires observation of a rise in cardiac biomarkers with typical electrocardiographic features, a new regional wall-motion abnormality, thrombus identified on coronary arteriogram or history of cardiac symptoms attributable to a coronary event[99]. Presence of traditional CV risk factors alert the physician to a differing diagnostic threshold and suspicion but is the patient with RA being assessed or treated differently? Troponin (Tn) is the primary biomarker of myocardial injury and care has to be taken in the interpretation when requested in the asymptomatic patient with RA or indeed any patient. An incidental false-positive level can occur in patients with high RF titres without an acute coronary syndrome (ACS) due to molecular mechanisms in certain manufacturer assays. If clinical reassurance is required in suspicious cases with raised Tn levels and high RF titres, nonlinear results after serial sample dilutions, using an alternative assay or using creatinine kinase (CK) measurement may be useful[100].

1.10.1 Corticosteroid use in myocardial infarction

Active glucocorticoid use is common in inflammatory conditions and presentation with MI whilst undergoing a course is a clinical situation encountered not infrequently. Management will be based on the clinical scenario and specific indication for the glucocorticoid prescription. Physicians may choose to; (a) stop glucocorticoids if only just initiated and the bleeding risk outweighs clinical benefit, (b) continue the current dosing regimen or (c) increase the maintenance dose in the short-term to account for a possible impaired/blunted stress response during acute MI. Glucocorticoid use is associated with a 68% increased risk of MI in RA with dosing, cumulative duration of use and cumulative dosing also being factors to the increased risk[101]. A large cohort study with nested case-control analysis presented an adjusted odds ratio (OR) for MI with existing corticosteroids use of 1.42 compared to non-users. This population included other non-RA indications for corticosteroid use such as asthma and chronic obstructive pulmonary disease. The risk was greater with prednisolone-equivalent doses greater than 10mg/day[102]. Glucocorticoids could exhibit an immediate as well as long-term effect on the risk of MI. The interplay of acute and chronic inflammation and the pathogenesis

of MI has been the subject of trials of corticosteroids as adjunctive treatment in MI. A meta-analysis of 11 trials with 2,646 patients did suggest a possible mortality decrease with corticosteroids but the benefit was no longer statistically significant when the analysis was limited to randomised control trials. Importantly, there was no conclusive evidence of a detrimental effect of corticosteroid adjunctive therapy during acute MI[103].

1.10.2 Management and outcomes

Increased mortality in RA following MI is commonly reported[104]. It is unlikely that there will ever be RCTs to compare effectiveness of secondary prevention therapy in MI specifically in patients with RA, with the evidence base primarily being retrospective/prospective cohorts and explorative sub-study analyses. Antecedent medical illnesses or surgical events can be more common in patients with RA presenting with MI and, along with atypical/delayed presentations, could provide explanations as to why acute reperfusion, especially in the thrombolysis era, was reduced when compared to matched-controls[105]. These studies looked at the RA population as a whole after hospitalisation following first MI and did not select out patients who were revascularised as a distinct group on their own. Differing management could also be as a result of the observation that RA patients may be likely to have diffuse, multivessel and microvascular disease[106]. A meta-analysis of 11 longitudinal studies between 1955 to 1995 found that although mortality after MI has reduced it still remained higher when compared to the general population using incidence and standardised mortality rates[107]. Explanations offered to the higher morbidity and mortality in RA patients following MI include a higher risk population, such as in DM[108], with evidence supporting higher overall mortality despite the same reported management[109]. In a small population-based cohort in Minnesota of 77 patients by McCoy *et al*, although the same management, secondary prevention and short-term outcomes were similar, RA patients still seemed to have worse long-term outcomes with respect to mortality and recurrent ischaemia[110]. Figure 1-5 and Figure 1-6, taken from Low *et al*[70], show the differences between RA patients on TNFi therapy and conventional DMARDs, and the severity of MI and early to medium mortality. Although, as mentioned above, there appears to be a lower CVD risk and incident MI with TNFi use in RA, in pooled observational studies, this hasn't gone on to clearly show decreased mortality.

Figure 1-5 - Severity of MI between RA patients treated with conventional DMARDs and TNFi.

Number of verified first MIs with additional MINAP data	Group 1 (sDMARD), n=35	Group 2 (on TNFi at the time of or within 90 days prior to MI), n=108	Group 3 (exposure to TNFi more than 90 days prior to MI), n=55	p Value
Proportion of patients with STEMI, n (%)	16 (46)	53 (49)	27 (49)	0.32
Cardiac arrest, n (%)	3 (9)	5 (5)	5 (9)	0.48
Median peak CK, IU/L (IQR)	290 (172, 1598)	691 (150, 1293)	286 (125, 660)	0.19
Median peak troponin I, µg/L (IQR)	5.0 (1.3, 7.2)	7.4 (1.1, 22.8)	7.6 (1.5, 29.0)	0.46
Median peak troponin T, µg/L (IQR)	0.7 (0.3, 2.3)	0.9 (0.2, 2.3)	0.8 (0.2, 2.1)	0.95
Median length of hospital stay, days (IQR)	6 (5, 9)	6 (4, 8)	6 (4, 11)	0.46

CK, creatine kinase; MI, myocardial infarction; MINAP, Myocardial Ischaemia National Audit Project; sDMARD, synthetic disease modifying anti-rheumatic drug; STEMI, ST-elevation myocardial infarction; TNFi, tumour necrosis factor α inhibitor.

Figure 1-6 - Medium term mortality in RA patients following first MI

	Group 1 (sDMARD)	Group 2 (on TNFi+90 days lag at time of MI)	Group 3 (exposure to TNFi more than 90 days prior to MI)
Total number of verified first MIs identified from BSRBR-RA and/or MINAP	58	194	82
Deaths within 6 months, n (%)	12 (21)	25 (13)	40 (48)
Unadjusted OR (95% CI)	Referent	0.61 (0.28 to 1.31)	2.84 (1.33 to 6.04)
OR adjusted for age and gender (95% CI)		0.68 (0.31 to 1.47)	3.07 (1.42 to 6.62)
Number of verified first MIs with MINAP data (% total verified MIs)	35 (60)	108 (56)	55 (67)
Deaths within 6 months, n (%)	2 (6)	3 (3)	11 (20)
Median MG score (IQR)	108 (81 to 131)	100 (84 to 120)	112 (93 to 129)
Unadjusted OR (95% CI)	Referent	0.47 (0.08 to 2.94)	4.13 (0.86 to 19.89)
OR adjusted for age and gender (95% CI)		0.51 (0.08 to 3.21)	4.07 (0.82 to 20.07)
OR adjusted for MG score (95% CI)		0.47 (0.06 to 3.45)	5.40 (0.93 to 31.18)

BSRBR-RA, British Society for Rheumatology Biologics Register for Rheumatoid Arthritis; MG score, modified Global Registry of Acute Coronary Events score; MI, myocardial infarction; MINAP, Myocardial Ischaemia National Audit Project; sDMARD, synthetic disease modifying anti-rheumatic drug; TNFi, tumour necrosis factor α inhibitor.

Both figures taken from Low ASL, et al. Relationship between exposure to tumour necrosis factor inhibitor therapy and incidence and severity of myocardial infarction in patients with rheumatoid arthritis[70].

1.10.3 Secondary prevention measures

Clinical trials of therapy in RA are challenging because of the relatively small number of hard clinical endpoints[111] and the UK Trial of Atorvastatin for the primary prevention of CV Events in RA (TRACE RA) had recruited over 3000 patients but was stopped early due to this reason[112]. Reduced initiation of secondary prevention measures have been hypothesised as a factor in unfavourable outcomes. One such cohort of 66107 patients in Denmark found that, of 877 RA patients, the immediate and short-term initiation of aspirin, beta-blockers (BB) and statins were significantly lower. Angiotensin converting enzyme inhibitors (ACE-i), angiotensin receptor blocker (ARB) and clopidogrel prescriptions showed a trend for under-prescription that did not reach significance. The adherence to statin therapy following MI was lower compared to the non-RA group[113] with discontinuation of statin therapy possibly leading to further increased risk of MI[114]. An explorative analysis from the Incremental Decrease in Endpoints through Aggressive Lipid-lowering (IDEAL) trial[115] found similar lipid-lowering effects and rate of CV events between RA and non-RA patients following MI with lipid reductions comparable between atorvastatin 80mg daily or simvastatin 20-40mg daily. It was noted that RA patients began with lower baseline cholesterol levels[116]. Current EULAR guidelines[48] for CV risk management in primary prevention in RA, as well as established international guidelines[117, 118], should continue to be followed.

1.11 Heart Failure in rheumatoid arthritis

1.11.0 Left ventricular systolic dysfunction: prevalence, risk and effect of RA therapy

Cardiac dysfunction in RA can exist in several and potentially overlapping sub-groups of cardiomyopathy. Dysfunction from ischaemia, with or without previous MI, can occur and hypertensive heart disease is a further cause secondary to uncontrolled systemic hypertension. Within contemporary classifications of *non-ischaemic* secondary cardiomyopathy[119], RA is considered autoimmune in aetiology causing dilatation and/or impairment or as a result from chronic inflammation causing restrictive cardiomyopathy from AA amyloidosis[78, 120]. RA is associated with abnormal LV remodelling on TTE with significance continuing compared to controls after adjustment for CVD and CV risk[121]. TTE of 226 non-matched RA outpatients found a prevalence of 5.3% with LVEF <40% with 1 in 9 having a concurrent abnormal resting ECG[122]. Any level of systolic dysfunction by TTE was found in around 18% of a cohort and was associated with RF, ACPA levels and duration of disease. No adjustments for CVD risk factors were made compared to controls but the RA cohort that had LV systolic dysfunction (LVSD) had increased prevalence of existing ischaemic heart disease (IHD), DM or dyslipidaemia[123].

In contrast to previous TTE studies that showed increased LV mass but not decreased LVEF[124], CMR studies give evidence that patients with RA have differing LV remodelling to what was previously described. A large study of 75 patients showed reduced LV mass as well as LVEF[83]. Patterns of CMR findings in 45 patients post-coronary angiogram with RA and New York Heart Association (NYHA) class I/II congestive cardiac failure (CCF) found 4 different patterns; myocarditis (33%), dilated cardiomyopathy (33%), IHD (22%) and/or diffuse subendocardial fibrosis (11%). Chronic versus acute myocarditis was 18% and 16% respectively with endomyocardial biopsy supporting CMR diagnosis. Late-gadolinium enhancement positively correlated with CRP, erythrocyte sedimentation rate (ESR) and disease activity[125].

Typicality of CCF symptoms and likelihood of referral for TTE are reduced in RA patients. This may institute a delay to diagnosis/therapy. After adjustment of differences to controls, RA patients are more likely to have CCF with preserved LVEF and also have an increased mortality

at one year[126]. Prescription rates for ACEi and BB have been seen to be lower in RA patients with CCF but there is a difficulty in comparing unadjusted treatment options compared to non-RA for potential confounding indications[126]. An attempt to remove traditional CV risk factors and causes for CCF with respect to IHD and hypertension continued to find an excess risk of CCF in a population-based inception cohort of 575 matched RA patients[127]. Nicola *et al* calculated that patients with RA have twice the risk of developing CCF compared to non-RA sex and age matched controls with this not being explained solely with CVD and CV risk factors[128]. CCF may contribute more to excess mortality when compared to IHD/MI alone[129]. Adjusting for CV risk factors and IHD, the risk of developing CCF in RA is also associated with positive RF, severe extra-articular disease and corticosteroid use[130].

1.11.1 Acute decompensation of congestive cardiac failure

Preceding inflammation may have a role in the development or exacerbation of CCF in RA. Significantly raised ESR has been found in the preceding 6 months to diagnosis of new-onset CCF without correlation of ESR with HTN or DM diagnosis timings[131]. An independent impact of RA on CCF that can be further modified by conventional DMARDs has been observed with an apparent protective effect of MTX[130]. In a case-control design within a retrospective cohort of RA patients, the use of DMARDs was associated with a reduction in the risk of hospitalisation for CCF with the use of the COX-II inhibitor rofecoxib associated with an increase[132]. TNF is considered as part of the pathophysiology of CCF but trials of TNFi have shown harmful deterioration of CCF with higher doses of different agents[133, 134]. These studies did enrol more patients with NYHA IV CCF. Current recommendations in RA do not support the use of TNFi in NYHA III/IV CCF, with caution being exercised in NYHA I/II CCF and discontinuation if there is worsening whilst on treatment[135, 136]. TNFi use in patients over 65 is also associated with risk of CCF exacerbation and hospitalisation but without residual confounders being ruled out[137]. There have not been adequately powered trials to observe CCF risk when adjusted for established CVD and risk factors, TNFi naivety and appropriate used clinical dosing. In 2013, attempts to overcome some previous limitations were made in a large US cohort. Solomon *et al* concluded that TNFi use following initial MTX use in TNFi-naive RA patients was not associated with an increased risk of CCF admissions compared to conventional DMARDs[138]. Severity of RA as well as CCF development/exacerbation isolated to community care was not examined and a highlighted limitation. Listing *et al* found that the reduction of inflammatory activity of RA

with TNFi is more likely to be beneficial with regard to the risk of CCF, especially without simultaneous use of corticosteroids or COX-II inhibitors[139]. There continues to be a need for RCTs looking into development and/or deterioration of LVSD with exacerbation of CCF with TNFi in RA but until then it is hard to contest current avoidance of bDMARDs in LVSD with poor NYHA status[140].

1.11.2 Diastolic dysfunction and B-type natriuretic peptide

Diastolic dysfunction can result in the clinical syndrome of CCF and has been described in RA populations by TTE[141, 142] but with conflicting data. Some studies describe a prevalence of 31%-47.2%[123, 143, 144] with others giving mixed findings of no significance in prevalence when compared to matched controls as a whole[143] or within certain diastolic severities[144]. The use of DMARDs does not seem to affect its presence[145] as well as traditional CVD or duration of RA, implying that different mechanisms may underlie the pathophysiology in contrast to LVSD[146]. B-type natriuretic peptide (BNP) has been implemented as part of the diagnostic algorithm in heart failure guidelines in recent years for systolic and diastolic dysfunction[147]. BNP is released from the myocardium in response to pressure and/or volume loading and is thought to be more of a specific cardiac biomarker[148]. The levels of BNP have been found to be raised in RA and related to inflammation but not associated with LV abnormalities[149]. The implication of this in diastolic dysfunction has been looked in RA populations, where it has been found that BNP is a poor screening tool for LV diastolic dysfunction without clinical evidence of CVD[150]. There is difficulty in knowing how to manage diastolic heart failure in the cardiology community as opposed to the multiple treatments and large evidence base for systolic heart failure. It is not unreasonable to control risk factors and fluid management in RA patients, as is the practice in non-RA, until further research helps guide future management.

1.11.3 Cardiac amyloidosis

Secondary AA amyloidosis due to RA is a rarer cause of CCF by restrictive cardiomyopathy. This is caused by cardiac deposition of circulatory serum amyloid A protein derived from RA inflammation[151]. AA Amyloidosis differs from AL amyloidosis, where early mortality in AL Amyloidosis is very high from cardiac death following the diagnosis of CCF. In AA Amyloidosis,

death is usually from renal failure or sepsis after a survival of 4-5 years[151, 152]. Retrospective autopsy findings have shown a frequency of cardiac amyloid similar to the prevalence of renal amyloid. Secondary AA amyloidosis is diagnosed in 37% of patients before death and correlated with a longer disease duration and disease activity[153]. Prospective studies have supported this retrospective work on subclinical AA amyloidosis in RA using Congo red staining on abdominal fat aspiration biopsy finding a prevalence of 21.5% to 29% and having associations with longer time to diagnosis, extra-articular disease, proteinuria and lack of MTX use[154, 155]. The cornerstone of treatment of secondary AA amyloidosis in RA is to control disease activity aggressively with DMARDs in an attempt to cease the production of serum amyloid A protein deposition created from RA inflammation. ETN has been found to be more effective than cyclophosphamide therapy[156].

1.12 The rheumatoid arthritis patient undergoing invasive procedures

1.12.0 Peri-operative cardiovascular assessment and risk in non-cardiac operations

Three key areas of perioperative care in rheumatic diseases have been suggested by Veetil *et al* in a 2012 review on the subject; the management of CV risk, immunosuppression and altered coagulation states[157]. Altered coagulation states in the form of anti-phospholipid syndromes are an entity more pronounced in SLE but the first two areas are of importance in RA. The position that a cardiologist, surgeon, anaesthetist and rheumatologist hold in discussion with the rest of the multi-disciplinary team is not to simply accept/decline an RA patient for a procedure but to offer a peri-procedural risk and if acceptable to attempt augmentation of that to be as low as possible. The ESC has produced clear recommendations on perioperative cardiac risk and evidence base for management that are endorsed by the European Society of Anaesthesiology.[158] The ACC/AHA have produced similar documents[159] and all societies do not include any specific risk assessment or recommendations for the patient with RA. It can be accepted from various cardiac risk algorithms that if (1) the condition is a life-threatening emergency, (2) there are no active cardiac conditions, (3) the surgery is low risk or (4) there is good functional capacity, then surgery can usually go ahead. However, when this is not the case clinical risk factors are taken into account along with level of risk the surgery itself holds before further assessment and surgery is considered.

Despite the increased and widespread use of bDMARDs and conventional DMARDs, orthopaedic surgery remains an important intervention to improve quality of life for RA patients. Hip, knee and other large joint arthroplasty occur in 24% of RA patients over their lifetime with more aggressive disease making this more likely[160]. ESC guidelines place arthroplasty as an intermediate-risk procedure at 1% to 5% risk of serious cardiac events[158]. As discussed in previous sections, CVD in RA patients has been demonstrated to be sub-clinical with risk estimates of clinical disease developing at the same rates as DM[161]. Adding RA as a clinical risk factor in peri-operative risk assessment, as suggested by Veetil *et al*, may change existing algorithms by introducing a decision whether to proceed with planned surgery along with heart rate control or to consider stress testing if it could change management[157]. In a

general orthopaedic population the risk of post-operative MI can be around 6.4% if a patient has pre-existing CV risk factors[162]. In comparison to arthroplasty in patients with osteoarthritis, if RA is the *only* risk factor in elective surgery there is support that short-term CV events are not increased but the risk of repeat/redo surgery is[163]. Given that some patients with functional limitations may not be able to exercise to maximal predicted physiological stress on treadmill or bike, non-invasive stress testing with pharmacological agents in adherence to peri-operative guidelines can be considered.

With respect to immunosuppression, current literature focuses on peri-operative flares of RA and infectious complications that are focussed on the surgical site. No data are available for cardiac complications with differing immunosuppressive regimens peri-operatively but it is important to note that pre-existing CAD has been independently associated with increased post-operative infection in RA[164]. Type-II MI, defined as MI secondary to ischaemia due to either increased oxygen demand or decreased supply, can be caused by sepsis and tends to occur in patients with impaired functional levels[165]. There are no specific guidelines with respect to type-II MI but these patients are less likely to receive coronary intervention, guideline-directed medical therapy and have increased morbidity and mortality[165]. There is a wealth of information on MTX throughout the peri-operative period and multi-national guidelines in 2009 recommend their continued use[166]. Further recommendations from systematic reviews and meta-analyses state that the use of conventional DMARDs could continue only in the absence of other risk factors relating to post-operative complications[167, 168]. With respect to bDMARDs, there are conflicting datasets and case-series[169, 170] regarding their influence on post-operative infections, and wound healing in particular, but no RCT data[171]. From observation, the literature leans towards increased infection and discontinuation of the drugs but it is necessary to judge each patient on a case-by-case basis with respect to their increased morbidity and potential serious complication if they had a RA flare due to drug cessation[157]. Limiting peri-operative corticosteroid exposure is well recognised to be an important factor in reducing post-operative complications and patients should ideally be on 10mg per day prednisolone equivalent with more than 15mg per day recognised as a significant contributor to increased risk[164].

1.12.1 Percutaneous coronary intervention

The modern era of early invasive management with percutaneous coronary intervention (PCI) of non ST elevation-ACS (NSTE-ACS) and ST elevation MI (STEMI) could well be in favour of the RA patient in comparison to previous decades of thrombolysis and medical therapy. One would hypothesise that given the observation of worse outcomes in MI as a whole in patients with RA, coupled with the observation of more microvascular disease, that coronary intervention may, with coronary artery bypass grafting (CABG) or percutaneous intervention, have increased in-hospital mortality or peri-procedural complications. Paradoxically, opposite findings have been published. Outcomes in US groups, where the likelihood of PCI as a primary treatment option in MI is higher, show RA patients have an in-hospital survival advantage compared to non-RA patients[104, 172]. A smaller retrospective cohort of 43 RA patients (matched on age, sex and revascularisation history) who underwent PCI were analysed with respect to presentation, coronary anatomy and treatment. Traditional CV risk factors were similar in both groups. Mode of presentation was predominantly as an ACS in both RA and non-RA groups and there were similar distributions of multi-vessel CAD. The prescription of standard cardiac medications was also similar between the 2 groups apart from higher ARB/ACE-i use in the RA group. In short term follow-up, there was no difference in mortality or procedural complications[74]. Larger numbers in Taiwan of 240 RA patients, which were not differentiated with respect to severity of RA, undergoing non-stenting PCI matched to 1200 non-RA patients again failed to find a difference in outcomes with respect to in-hospital, 90-day and 1 year mortality or readmission[173]. Cross-sectional analysis into mortality of RA patients after coronary revascularisation, by CABG or PCI, further found that there was a survival advantage as well as reduced hospitalisation[174]. As always with observational data, it cannot be concluded that RA would continue to have a protective effect once patients are in an RCT and, furthermore, LV function, coronary anatomy and use of medications were not adjusted for. As all MDTs put patients forward for intervention based on a consensus opinion that it would be in the patients' favour, the findings above between intervention in RA and non-RA populations show there are grounds for further investigation and, at present, it can be considered there should be little trepidation in putting forward patients with RA for PCI with respect to short/medium-term mortality, hospital days and procedural complications.

1.12.2 Cardiac surgery

Historically, it is known that cardiac surgery in IMID can present with it difficulties include suture detachment, valvular dehiscence, impaired wound healing, friable tissues and progression of vascular lesions following surgery[175]. Outcomes and surgical approaches in these patients have been looked at emphasising the importance in assessing the systemic features of each patient, albeit with small case series and reports[176]. The logistical European System for Cardiac Operative Risk Evaluation (EUROSCORE) is a common risk scoring calculator used to predict peri-operative complication in cardiac surgery. It does not take inflammatory diseases into account although reference is made to patients with DM on insulin. Peri-operative inflammation in cardiac surgery patients is a complex process involving humeral and cellular mechanisms with cytokines produced during cardiopulmonary bypass[177, 178].

1.12.2.1 Coronary artery bypass grafting

Given the apparent worse outcomes in MI and increased microvascular disease in RA, with increased peri-operative inflammation after cardiac surgery it would not be surprising to observe increased complications but some data suggests otherwise. To complement their findings, with respect to PCI outcomes in RA patients, Varghese *et al* found that RA patients undergoing CABG had a 31% increase of in-hospital survival advantage with reduced days of hospitalisation compared to non-RA patients[174]. A retrospective cohort of 44 patients with IMID, that included 35 patients with RA and 35 month mean follow up, described an overall survival and freedom from re-intervention at 3 years were 89% and 75% respectively[179]. They concluded that CABG is an acceptable treatment modality in IMID with reasonable early to mid-term results. In established RA, the use of arterial conduits for CABG have been shown histopathologically to have expected and acceptable atherosclerotic changes[180]. There are no further large data specific to CABG outcomes specifically in patients with RA and the observations are so far mixed. Hypotheses for reduction in some complications following CABG in RA patients include the RA therapy immunomodulation that can work against the cardiopulmonary bypass inflammatory insult. This hypothesis from Varghese *et al* seems less substantial given improvements also described in their PCI cohort. No further satisfactory pathophysiological explanation has been put forward in attempt to corroborate the findings in these small observational studies.

1.12.2.2 Heart valve surgery

Rheumatoid valvular heart disease (VHD), whether caused by valvulitis, vasculitis or nodule/amyloid deposition leaves variable degrees of valvular regurgitation and rarely stenosis. Presentations can be of acute regurgitation in the cases of nodule rupture or of clinically overt syndromes such as peripheral embolism or Libman-Sacks-like vegetation. A trans-oesophageal echocardiography (TOE) study of 34 RA patients found no correlation between VHD and duration, clinical subtypes or RA therapy other than it was a common finding compared to controls and that valve nodules and thickening are distinctive features[181]. In taking a mixed cohort of different subtypes of VHD, a small case series showed short and medium term morbidity and mortality of RA patients at 1 month and 1 year post valvular replacement is approximately 2–3 times higher than that of non-RA patients[182]. Aortic valve regurgitation in RA necessitating valve replacement is uncommon and data over 40 years is limited to case reports in patients with variable presentations and without long-term follow up[183-186]. The difficulty of procedures are seemingly higher in the patient with aortic incompetence and aortitis, with experienced authors wanting to ensure active disease is treated with immunosuppressant to make the procedure technically easier, with respect to suturing tissue that is less inflamed[187]. Mitral valve pathology described in a retrospective surgical series of 36 RA patients between 1978 and 2005 found that severe MR had similar mechanisms of regurgitation to that of non-RA patients. On having mitral valve repair, they had decreased survival and freedom from reoperation at 8 years, but when compared to matched RA patients without severe MR they had similar survival at 5 years[188]. The disease itself rather than surgical specific issues were thought to contribute to these findings and the conclusion being that mitral valve repair is safe and durable with the interesting note that this cohort found no clear pathology characteristic of involvement with rheumatoid VHD. The short-term mortality and length of stay was shown to be similar to non-RA patients in a series between 2005 and 2008 and it wasn't apparent that RA appeared to be an additional risk factor for adverse outcome following isolated mitral valve surgery. They did find that conversion to mitral valve replacement rather than repair was higher but within the RA subset, hospital mortality rates were similar[189]. Given that RA patients may need corticosteroids and NSAID medications for their articular disease, it would be presumed unfavourable in the long-term if anticoagulation was enforced with metallic valve replacement. As CVD is accelerated in RA, younger patients may present and the difficult decision of earlier life tissue valve replacement with anticipated

re-intervention 10-15 years later have to be weighed up. RA patients with isolated VHD disease selected for surgery appear to have similar survival compared to the RA patient without severe VHD and with surgical technique being acceptable and durable - especially in mitral valve disease and aortic disease without aortitis. In the longer term, it may be that morbidity and mortality is higher but whether this is directly due to having VHD versus progression of systemic disease and other CVD is less straightforward to conclude.

2 Non-invasive cardiovascular imaging modalities

2.1 Introduction

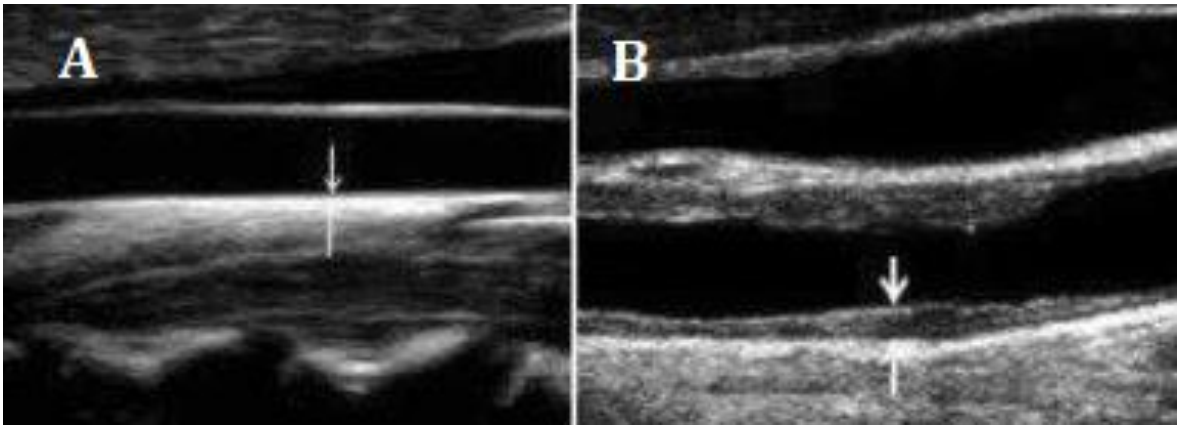
Common clinical and research cardiovascular imaging modalities used to assess for CVD are ultrasound, TTE, single-photon emission computed tomography (SPECT), positron emission tomography (PET), computed tomography (CT) and CMR[190]. TTE is safe and low-cost. It can assess cardiac structure and function, providing information on ischaemia when combined with stress protocols. Poor acoustic windows may be a problem due to individual body habitus or acoustic shadowing from lungs. Reproducibility is a further weakness due to measurement & reporting variability. PET is the gold standard for quantifying myocardial blood flow but is hindered by high cost and reduced availability. SPECT is commonly used and has been established over many years for ischaemia testing but, similar to PET, it cannot assess cardiac anatomy and exposes patients to ionising radiation[191]. CMR is a safe, sensitive, reproducible and comprehensive non-invasive imaging test to detect CVD with the ability to assess cardiac anatomy and function. Utilisation is limited by cost, claustrophobia and the inability to scan certain metallic implants.

2.2 Carotid Ultrasound

Ultrasound may directly demonstrate atherosclerotic plaque in the carotid artery as well as measure the intima-media thickness. This common carotid intima-media thickness (CIMT) is a surrogate measure of CVD and is well validated. In the general population, for every 0.1mm increase in CIMT measurement there is a relative risk of MI of 1.15 and of stroke was 1.18 after age and sex adjustment[192]. An absolute CIMT of greater than 0.9cm above the 75th centile confers a high risk of CVD [193]. There is a large evidence base supporting use in the general population and given the simple, rapid and reproducible measurements (along with the lack of ionising radiation) they have been used as endpoints in clinical trials assessing therapies for lipid management and hypertension. One of the larger CIMT studies in RA (meta-analysis of 1384 RA patients) found that compared to controls the overall mean CIMT difference was greater in RA by 0.09mm (95% CI 0.07, 0.11mm)[26]. However, there are questions over applicability to an RA population, which do not share a similarly large evidence based or

randomised clinical trial endpoints. Furthermore, a targeted ultrasound assessment of CIMT negates being able to assess additional CV manifestations of RA in the heart and larger arteries.

Figure 2-1 - Ultrasound examination of the carotid intima media thickness



CIMT = distance between arrows. Panel A: Normal CIMT. Panel B: Increased CIMT.
Image reproduced from Erkocoglu et al, Carotid intima media thickness in adolescents with increased risk for atherosclerosis. Turk J Pediatr. 2013 Sep-Oct;55(5):510-8[194].

Carotid ultrasound is incorporated into recent guidelines (Table 1-1 - The EULAR overarching principles and recommendations for CVD risk management in patients with RA, statement 6) when assessing CVD risk in RA patients. This is largely when a risk estimate is at an intermediate level with an annual CVD risk of 1-4%. When there are high-risk features with an abnormal ultrasound, then the physician may consider initiating primary CVD prevention therapy as per RA patients with a >5% annual CVD risk as per modified SCORE risk estimation. If the carotid ultrasound suggests low-risk, then the RA patient should continue as per <1% annual CVD risk and continue yearly CVD risk assessment and lifestyle modification[195, 196].

2.3 Transthoracic Echocardiography

TTE shares much of the technical advantages of carotid ultrasound given they are based on the same technology and physics. It is similarly relatively low-cost, widespread in availability and free from ionising radiation. The largest CV imaging modality used to assess cardiac structure and function in RA is with TTE at present time. Individual studies have shown changes in cardiac structure with increased left ventricular mass and function with lower left ventricular ejection fraction. Although meta-analysis of TTE studies continued to show the finding of left ventricular mass changes, no difference in systolic performance by ejection fraction existed when studies were combined[197]. The intra-observer and inter-study variability is less attractive than CIMT measurement and CMR[198].

2.4 Cardiac Computed Tomography

Cardiac computed tomography is commonly utilised for two major clinical assessments. The first is to assess for burden of coronary artery calcium and the second is for anatomical assessment of the epicardial coronary arteries. Due to the marked X-ray attenuation properties of calcium, CT coronary artery calcium scoring (CCS) provides good visualisation of vascular calcification and effective ionising radiation dosing for CCS is 1mSv[199]. In the Multi-Ethnic study of atherosclerosis (MESA), absolute scores alone were considered sufficient for quantification of coronary plaque burden over further stratification to age, sex and ethnicity[200]. Guideline recommended CCS Agaston scoring categories and their interpretation are given in the adapted table from Rumberger JA *et al* in Table 2-1.

Table 2-1 - Recommended calcium score guidelines

Calcium score	Plaque burden	Probability of significant CAD#	Implications for CV risk
0	No identifiable atherosclerotic plaque	Very low generally <5%	Very low
1-10	Minimal identifiable plaque burden	Very unlikely, <10%	Low
11-100	Definite, at least mild atherosclerotic plaque burden	Mild or minimal, coronary stenoses likely	Moderate
101-400	Definite, at least moderate atherosclerotic plaque burden	Nonobstructive CAD highly likely, although atherosclerotic obstructive disease possible	Moderately high
>400	Extensive atherosclerotic plaque burden	High likelihood of at least one significant stenosis (≥90%)	High

CAD: Coronary artery disease, CV: Cardiovascular, CVD: Cardiovascular disease

Adapted from Rumberger JA, Brundage BH, Rader DJ, Kondos G. Electron beam computed tomographic coronary calcium scanning: A review and guidelines for use in asymptomatic persons. Mayo Clin Proc 1999;74:243-52[201].

There are very limited research data of the use of CCS in RA. This is likely due to options and evidence-base of non-ionising radiation imaging modalities. In 2014, Løgstrup BB *et al*[202] investigated RA disease activity, ACPA status and CCS in 53 treatment-naive ERA (30 women), along with left ventricular systolic function by TTE. They found CCS showed no correlation with TTE, disease duration or any rheumatologic parameters. The mean CCS calculated from this study was 65, and when applied to online MESA calculators would lie on the 30th to 60th centile for age, ethnicity and sex.

CT coronary angiography (CTCA) studies in RA are similarly as sparse as studies utilising CCS. The typical radiation dose is 1-3mSv for a prospective ECG-gated CTCA (step and shoot and fast helical acquisition) and 7-12mSv for a retrospective ECG-gated CTCA with ECG-correlated mA pulsing[203] A 2016 study by Hromádka *et al*[204] prospectively recruited 44 women with RA, (of at least 1 year disease duration on biological therapy), to be examined using CTCA and compared to biomarker parameters of atherosclerosis and the EULAR guideline recommended Classical CV Systematic Coronary Risk Evaluation (SCORE and modified SCORE) CVD risk scoring

system. 9% of RA patients had severe coronary stenoses (defined as >70%). High-sensitivity troponin I level was the only marker found to be associated with severe coronary stenosis (OR 6.37; 95% CI 1.53 − 26.48; P = 0.01). The SCORE system had no correlation in predicting severe stenoses (P ≥ 0.49) in this asymptomatic cohort without known CVD. High-sensitivity troponin I is therefore a biomarker for further study, in larger populations and including males, to investigate these preliminary findings further. High sensitivity Troponin I may be used to predict possible flow-limiting CAD in RA patients with established RA disease and no known CVD or cardiac symptoms.

In a CT imaging study [41], Prieto-Gonzalez *et al* identified active thoracic aortitis in 65% of in newly-diagnosed GCA patients, with TAD already present in 15%. Our rate of TAD of 66%, after a mean of 65 months of disease, is similar to their initial large-vessel vasculitis (LVV) prevalence. Even after one year of therapy, they found persistent aortic wall thickening in 68%. In a follow-up study of 54 GCA patients with a median disease-length of 5.4 years[36], 22.2% were reported to have TAD/TAA.

2.5 Single-photon emission computed tomography

Nuclear perfusion imaging with single-photon emission computed tomography (SPECT) imaging is widely available and well-established with a body of research and trial outcome data in the diagnosis of reversible ischaemia in the evaluation of patients with coronary artery disease. A patient-based analysis demonstrates a pooled sensitivity of 88% and specificity of 61% for the diagnosis of obstructive coronary artery disease[205]. There is a paucity of data specifically of SPECT study use in RA. Perhaps the largest study utilising SPECT in RA was in a 2004 study that evaluated 62 patients, that were consecutively recruited from an outpatients clinic, for the presence of ischaemic heart disease and compared to circulating autoantibodies[206]. Increased levels of antibodies to cytokeratin 18 were found in the RA patients with ischaemic heart disease as defined by positive defects seen by adenosine stressed thallous-210 chloride SPECT. Dipyridamole Thallium-201 scintigraphy was carried out in an older study by Momose *et al* in 1995, where 27 of 54 established RA patients without CV symptoms had perfusion defects. Higher ESR, CRP and IgM/IgG rheumatoid factor levels were observed in the group with perfusion defects. In 12 of the cases, cardiac histological samples were obtainable through

autopsy and of 7/12 microvasculitis and microthrombosis was seen without myocardial infarction[207].

2.6 Positron Emission Tomography

PET imaging may be utilised as a tool for the evaluation of myocardial blood flow by the detection of emitted positrons from radionuclides/labelled radiotracers. The PET radiotracers that are used currently to assess myocardial blood flow are ^{15}Oxygen-water, ^{13}Nitrogen-ammonia and ^{82}Rubidium[208]. Quantification by ^{15}Oxygen-water in absolute terms (millilitres per gram per minute) by PET imaging has been considered the gold standard[209] but this is for whole heart coverage and not regional cardiac uptake, as the weakness of ^{15}Oxygen-water is that there is free diffusion of the radiotracer between target tissue and the background. This does not make it clinically applicable to look for regional differences for ischaemia testing or for regional hibernating myocardium assessment. ^{13}Nitrogen-ammonia and ^{82}Rubidium both have characteristics of active extraction uptake mechanisms with reasonable half-lives, which allows for relative perfusion imaging and, therefore, ischaemia testing. The overall characteristics of the radiotracers are given in Table 2-2. Although PET can be used to assess people for suspected angina, and is incorporated into international guidelines given further usefulness in predicting CV mortality in those with CAD[210], several factors have limited widespread use. These include the cost and radiotracer availability. Furthermore, an assessment of cardiac structures and regional function cannot be performed with nuclear imaging. There have been no studies specifically utilising PET for myocardial blood flow quantification in patients with RA but there have been in some mixed IMID populations. PET in patients with IMID without CAD shows lower myocardial blood flow reserve compared to controls with an inverse correlation to disease duration[211].

Table 2-2 - Basic characteristics of common cardiac PET radiotracers

Characteristic	$Rubidium^{82}$	N^{13}-ammonia	O^{15}-water
Supplied	Generator	Cyclotron	Cyclotron
Half-life	76 s	9:96 min	2.09 min
Uptake mechanism	Active extraction	Active extraction	Freely diffusible
Positron range in water	1.6 mm	0.28 mm	0.5 mm
Image quality	Very good	Excellent	Uninterpretable
Radiotracer uptake characteristics	Adequate	Very good	Excellent

Taken from Al Badarin et al, Assessment of myocardial blood flow and coronary flow reserve with positron emission tomography in ischemic heart disease: current state and future directions. Heart Fail Rev. 2017 Jul;22(4):441-453. doi: 10.1007/s10741-017-9625-4 [208].

PET has been utilised in a few studies in patients with RA by assessment of vascular inflammation. Mäki-Petäjä *et al*, in 2012, used ^{18}fluorodeoxyglucose-PET/CT (FDG-PET/CT) imaging in 17 patients with established RA before and after 8 weeks of TNFi therapy[212]. They demonstrated that the RA patients had increased aortic uptake of the radiotracer, implying aortic inflammation, in comparison with 34 non-RA patients with stable CVD. There was also increased arterial stiffness by measure of pulse wave velocity. After 8 weeks of the TNFi therapy, there were improvements in tracer uptake that correlated with improved arterial stiffness. In 2016, Haavisto *et al* looked at the ^{18}FDG uptake in the carotid artery in 15 patients with recently diagnosed, ERA prior to DMARD therapy[213]. They reported that after 1 month of DMARD therapy, carotid artery inflammation was reduced.

2.6.0 Cross-sectional imaging in GCA

Diagnostic performance of large-vessel vasculitis (LVV) by cross-sectional imaging is well-described and can be performed with CT and CMR using wall thickness measurements with or without the of gadolinium-based contrast agents[214]. The lack of a gold standard creates problems in calculating sensitivity and specificity. Hybrid ^{18}F-FDG PET-CT may also be utilised if initial cross-sectional imaging is non-diagnostic[215], however, the utility for routine disease monitoring in GCA is not yet realised. Normal wall aortic thickness does not rule out active inflammation and, conversely, it may take time for increased wall thickness to respond to therapy and regress[216]. There is an emerging role for hybrid PET-CT/CMR and CMR with gadolinium-based contrast in indeterminate cases of relapse/response. Hybrid PET-CMR may aid management of GCA with reduced radiation exposure compared with PET-CT[217].

2.7 Cardiovascular Magnetic Resonance

2.7.0 Introduction

As this thesis presents data on the use of CMR in RA and GCA, I have presented information here of greater detail than other imaging modalities described above. Further information into specific sequences, settings and analysis methodology is described in the methods sections later. CMR is a safe, sensitive, reproducible and comprehensive non-invasive imaging test to detect CVD with the ability to assess cardiac anatomy and function. LV mass and function can be measured more accurately than with any other imaging method[218]. Vascular function assessment using aortic distensibility and pulse-wave velocity can be reliably measured from the ascending and descending aorta[219]. Myocardial deformation characteristics using tissue-tagging or cine image feature tracking provide measurements of regional and global myocardial strain as early markers of contractile dysfunction[220, 221]. CMR has been shown to detect myocardial ischaemia with greater sensitivity than nuclear perfusion imaging[222] and dynamic contrast enhanced methods can be used to estimate myocardial blood flow at rest and during hyperaemic stress[223]. Late-gadolinium enhancement (LGE) imaging in CMR is used to detect myocardial scar tissue and fibrotic tissue and is recognised as the in-vivo gold standard to do so[224]. Secondary AA amyloidosis due to RA is a rarer cause of CCF by restrictive cardiomyopathy. The classic LGE pattern on CMR imaging is that of diffuse myocardial fibrosis, with subendocardial involvement in non-coronary artery territory patterns, as well LV hypertrophy, biatrial enlargement and ventricular impairment. The myocardial fibrosis in Amyloidosis may be so involved and diffuse that there is difficulty finding the optimum inversion time to ‘null’ the myocardium to observe where normal areas of myocardium are compared to LGE[120]. T1 mapping methods using contrast agents are used to measure the extent of the extracellular matrix in the heart, which expands in response to inflammation and fibrosis[225, 226]. CMR has no harmful effects and all measurements can be combined in a single imaging protocol[219].

2.7.1 A summary of CMR physics

There are three types of magnetic field used in CMR;

- B_0, a static field created by the superconducting solenoid
- A gradient field, that is switched on/off quickly
- B_1, a radiofrequency (RF) field, resonating hydrogen nuclei in different states with pulses.

Hydrogen nuclei in free water/adipose tissue align with B_0, with a small net magnetisation (M) in one direction. The hydrogen nuclei resonate at 127.74MHz at 3Tesla magnet strength, termed the Larmor frequency. This emits a small, clinically ineffective, RF signal governed by a number of variables including B_0, M, hydrogen nuclei density and body temperature. For measureable and useful signal generation, an external RF pulse 'flipping' the hydrogen nuclei is applied. Once a pre-determined flip angle has been reached, the RF pulse is switched off and equilibrium occurs. This release in energy, or 'free induction delay', is detected as an RF signal from the hydrogen nuclei. The echo-time is time from RF pulse to maximum amplitude of echo. Those generated by gradient-induced dephasing and rephasing are called gradient echoes. Those generated using refocussing RF pulses are spin echoes. T1 relaxation time corresponds to longitudinal relaxation following an external RF pulse. Fat has the shortest T1 relaxation time, followed by muscle, with fluid being the longest. T2 relaxation time corresponds to transverse relaxation and occurs quicker than T1 relaxation. T2 measures the interaction of adjacent hydrogen nuclei protons. Denser structures, like muscle, aid interaction and so have shorter T2 relaxation times compared with fluid. Fat demonstrates intermediate T2 relaxation times. There are two major forms of gradient echo; spoiled gradient echo and balanced steady state free precession (bSSFP). bSSFP is now predominantly used to create moving cine imaging. bSSFP sequences ensure that transverse magnetisation is fully re-phased prior to next RF pulse. This allows it to culminate and a steady-state of transverse magnetisation allowing for a more powerful signal. The imaging contrasts relies on T2/T1 ratio from the tissue and so fluid and fat have a higher ratio and appear bright compared to muscle. This is, therefore, useful in cardiac cine imaging as it allows for increased endocardial to blood-pool definition aiding cardiac volumetric analysis, which is consistent through the cardiac cycle. Every data sample is stored as a data point in an image space file named k-space. The image point data within k-space

equates to a specific frequency across the field of view and *not* specific *position*. The position of that frequency from k-space translating to location within the subject is related to the strength of when each gradient was applied, from when it was applied to when it was measured for any particular point measurement. Fast Fourier transformation mathematically interprets this k-space data for digital transformation into interpretable imaging.

2.7.2 Cardiac volume analysis

A continuous stack of gradient echo imaging along an axis of a cardiac chamber with subsequent measurement of the multiple end-diastolic and end-systolic areas forms the backbone of assessment in CMR. These multiple contoured 2D areas allow for the calculation of end-diastolic volume, end-systolic volume and epicardial contours. This is turn allows calculation of ejection fraction, stroke volume and mass. The convention for left ventricular measurement is a series of short-axis stacks covering the length of the left ventricle from base to apex. Methodology for this is explained later in this thesis. Different stacks can also be applied, such as transverse stacks onto the right ventricle. As well as length of the ventricle, the number of breath-holds required depends on slice thickness and gap. CMR measurement of ventricular volumes has excellent reproducibility and is superior to 2D echocardiography[198]. 87 patients are required to detect a 3% change in left ventricular ejection fraction with 2D echocardiography but as few as 11 patients are necessary by CMR. Similarly, to identify a 10g change in left ventricular mass by 2D echocardiography 132 subjects would be required in contrast to 13 by CMR[198]. Scanning time may be reduced with acceleration techniques. These include sensitivity encoding (SENSE), simultaneous acquisition of spatial harmonics (SMASH) and generalized auto-calibrating partially parallel acquisitions (GRAPPA). Acceleration techniques may worsen signal-to-noise ratio, spatial or temporal resolution[227].

2.7.3 Cardiac strain

Strain is the amount of myocardial shortening divided by the pre-contraction length and is another measure of systolic function in addition to ejection fraction. Strain rate incorporates the time taken for the shortening to take place. CMR tissue-tagging sequences allow measurement of cardiac strain. The tissue-tagging sequence employs a selective RF saturation pulse prior to cine imaging to create tag lines in the heart muscle, which persist through the

cardiac cycle[220]. Depending on the orientation the acquisition is made, strain can be measured in any direction i.e radial, circumferential or longitudinal. Tissue-tagging sequences are also utilised to measure the mechanics of left ventricular twisting motion. Typically, the left ventricular base rotates clockwise in early systole and apex rotates anti-clockwise later. This motion generates maximal force at end-systole[228]. Twist is defined as apical minus basal rotation, (measured in degrees). Torsion is a correction taking into account the different lengths and diameters of ventricles and so allowing the comparisons of measurements between studies[229]. CMR derived left ventricular strain, twist and torsion have good inter-study reproducibility[230].

2.7.4 Phase-contrast imaging

Blood flow can be quantitatively timed and flow measured using velocity-encoded gradient echo imaging (VENC), or phase-contrast imaging. This sequence measures the phase shift of hydrogen nuclei as they pass through the magnetic field. The usual clinical utilities of this are to qualitatively assess the path of blood flow through cardiac chambers and vessels and to quantitatively assess blood flow at pre-specified regions of interest. The common pathologies that this is useful for are, but not limited to, cardiac valvular stenoses, regurgitations and assessment of shunts. The sequence is also implemented for measurement of aortic pulse-wave velocity (PWV), where the timing between peak flows at two regions of interest in the aorta can be measured with known distance between them to calculate blood flow at metres per second. PWV is a biomarker for arterial stiffness, clinically assessed by applanation tonometry (AT), and there is good intra- and inter-observer variability compared to AT. This is also the case for less experienced CMR operators using freely available research tools[231]. For VENC image measurements, an imaging plane is selected perpendicular to the path of blood flow. A cine is formed by creating VENC images for multiple phases of the cardiac cycle. Time-velocity or time-flow curved can be calculated by post-processing software once a region of interest has been applied by the operator.

2.7.5 Myocardial tissue characterisation

2.7.5.1 Late gadolinium enhancement imaging

Gadolinium-based contrast agents, which shorten T1 relaxation times, are of large molecular size and exclusively extra-cellular. The length of time it remains in the blood-pool and differing tissue types are variable before renal excretion. These properties are utilised for imaging during first-pass perfusion and early/late gadolinium enhancement imaging. When there is abnormal myocardial tissue, gadolinium kinetics are altered and so the contrast agent persists in the tissue, giving lower T1 values. T1 weighted LGE imaging is acquired using an inversion time where 'normal' remote myocardium appears normal/black. This is called nulling. Usually, LGE images are acquired at least five minutes following contrast[232]. Abnormal myocardium therefore appears brighter/white on LGE imaging.

2.7.5.2 T1 Mapping and extracellular volume fraction

The presence of normal myocardium is needed for effective LGE imaging, therefore diffuse, subtle, global processes can be under appreciated and missed. These processes can be categorised as 'normal', artefactual or indeed subjective descriptions of 'haze' could be used. LGE imaging limitation in diffuse processes may be improved upon with T1 mapping. T1 mapping allows a pixel-by-pixel point measurement of the T1 relaxation time. Signal is sampled at time-points along the tissue recovery curve following an inversion/saturation pulse. The time-points are modelled so that the pixel T1 relaxation time can be estimated[233]. This can then be encoded into a colour or grayscale image[234]. There are several T1 mapping acquisitions and at time of my studies at the University of Leeds, we used a Modified Look-Locker Inversion Recovery (MOLLI) sequence for acquisition on our Phillips CMR scanners at 3T[19]. I will go into the MOLLI sequence in some greater detail but other sequences, some specific to other vendors, are in use for T1 relaxation time measurement. These include Shortened Modified Look-Locker Inversion recovery (ShMOLLI), Saturation recovery single-shot acquisition (SASHA) and Saturation Pulse Prepared Heart Rate Independent Inversion Recovery (SAPPHIRE). The initial MOLLI sequence was a 3(3b)3(3b)5 scheme and is what is used in my studies. This is described in the methods section later. The nomenclature above describes the number of samples of the sequence after an inversion pulse (3, 3 and 5, totalling 11) and the recovery period is in brackets (3b = 3 beats).

Native T1, as in T1 relaxation time without presence of gadolinium contrast agent, is more prolonged with increasing water content[235]. An increased native T1 is seen in a variety of diseases that include acute myocardial infarction and myocarditis of any aetiology[236]. A lower native T1 value can be seen in Fabry's and diseases that cause myocardial iron deposition, such as haemochromatosis[237]. The specific nature of gadolinium-based contrast agents being extra-cellular can be utilised in T1 mapping to provide an estimated calculation of extra-cellular volume (ECV) fraction. This can be calculated by using further acquired T1 maps following contrast administration. The formula for this requires T1 values of blood pool and the subject's haematocrit value. This is described in greater detail in my methods section. As per native T1 maps, ECV maps can be created in colour and gray-scale to display the data, rather than just take numerical values, once a defined scale is applied. Raised ECV and T1 have been correlated to myocardial tissue fibrosis[16] leading to its use as a surrogate in research and clinical studies. The danger of this generalisation is that there are other factors that could account for differing extra-cellular space and water content that aren't fibrosis i.e. oedema, haemorrhage, fat, infiltration, capillary dilation etc. A current issue with T1 is that it is affected by scanner field strength, in-homogeneity and the mapping sequence employed. Therefore, there are no strict cut-offs for values applicable between vendors, sites and field strengths. The requirement of blood sampling may be negated as there is good correlation with synthetic ECV calculation using derived haematocrit values[238]. It is imperative that image acquisition between native T1 maps and post-contrast T1 maps is as exact as possible to ensure the same myocardium is being assessed. Colour/gray-scale maps cannot be fitted if there is movement, differing breath-holds or new artefact.

2.7.5.3 T2 imaging

T2 imaging was not employed for any of my studies and during 2013 and 2015 we were not developing sequences with exploratory measures on my studies. I have presented T2 imaging briefly here, for completeness of common techniques to describe tissue characterisation and awareness of them. As described briefly in the physics summary, T2 imaging is created from spin echo sequences. Two major sequences used in clinical applications are turbo spin-echo and short-TI triple inversion recovery prepared fast spin echo (STIR)[239]. A brighter signal on T2 imaging may imply acute myocardial oedema from a range of conditions such as myocarditis

and acute myocardial infarction and correlates with histological specimens[240]. The technique is subjective and hampered with higher intra-observer variability, artefacts from slow moving blood at the endocardium (giving a higher intensity signal) and field in-homogeneity. There are two main areas of quantification of T2 values, T2* mapping and native T2 mapping. T2* is shorter than T2, and is more established in clinical practice[241]. It is most clinically useful in assessment of myocardial iron loading and correlates with biopsy specimens and improved survival when therapy is based on the measurement[242]. There is active sequence development in native T2 mapping for development of pixel-by-pixel T2 values, not unlike T1 mapping. This may help provide less subjectivity and more quantification of any potential pathology[243].

2.7.6 CMR studies in RA

The following tables present a summary of all the CMR studies in RA. A Pubmed search was performed with the keywords; Cardiac, Cardiovascular, CMR, MRI, Rheumatoid. Some studies have solely investigated RA and some studies are a mixture of IMID, where RA was one of the diseases investigated. Table 2-3 presents the studies that are solely on RA and Table 2-4 presents studies with a mixture of diseases.

There have not been any randomised control trials for RA therapy using CMR for any endpoints, despite the knowledge that fewer numbers are required to power for CV changes on CMR. All the studies presented in Table 2-3 and Table 2-4 present patients with established RA disease and have a variety of previous therapies including bDMARDs and conventional DMARDs. They are mainly cross-sectional heterogeneous RA populations, with a few retrospective and prospective studies, however, none are randomised trials or true case-control studies.

CMR is increasingly used to demonstrate subclinical cardiac involvement in IMID[244, 245]. Protocols, however, vary and the amount of data describing the disease phenotype is minimal. Studies differ in the CMR imaging endpoints as well as recruitment homogeneity of the clinical characteristics of the disease population. A larger study of 75 RA patients demonstrated a reduced LV mass compared to 225 matched controls, correlating with ACPA titre and use of bDMARDs[83]. Smaller studies have shown subclinical changes in myocardial deformational characteristics, vascular function and regional LV dysfunction in asymptomatic RA patients and

that the cardiac abnormalities due to RA appear to be independent and incremental to those due to traditional CV risk factors[246] with disease activity scores proposed to be independent risk factors for myocardial involvement[247]. Ntusi *et al* in 2015, utilised T1 mapping CMR techniques to demonstrate evidence of diffuse myocardial fibrosis in patients with established RA. 39 established RA patients were assessed compared to matched controls with evidence of increased myocardial extra-cellular space fraction. Despite the heterogeneous group of established RA with respect to medication use and length of disease, impaired LV strain was associated with RA disease activity[87]. The use of LGE has demonstrated different patterns of enhancement in patients with CCF and RA[125] with presence of LGE also correlating with disease activity and disease duration but not qualitative stress perfusion defects[84]. No previous trial studies have combined macrovascular, microvascular and detailed myocardial assessment by CMR in RA, such that the full potential of CMR for a comprehensive multi-parametric and quantitative evaluation of CVD in RA has not yet been realised.

The presence of abnormalities by CMR have a wide prevalence and it would be difficult to ascertain a true prevalence of sub-clinical CV change given the differences and wide range of disease duration, CV symptoms, age and RA therapy. Looking at the 'purpose' column in both tables, the questions the community are asking are not being refined and simply collecting further large amounts of CMR data with cross-sectional studies does not advance progress sufficiently enough to attempt a clinical change and outcome for RA patients. It is time to focus on *when* CV risk occurs, *how* it occurs and *if* specific therapy can change disease and outcome.

Table 2-3 - Summary findings of CMR studies in RA

Population	Year	Type	Purpose	CVD disease	Number	CMR details	Main findings	Ref.
Japan	2017	CS	LV function and morphology between RA patients treated with bDMARDs versus conventional DMARDs.	Asymptomatic	84 female RA 20 Controls	LV volumes	DAS28 was significantly higher in the conventional DMARD group than in the bDMARD group. conventional DMARD group showed had higher (by 18%) LVMI and lower EF (by 15%). There were no significant differences in LVMI/EF between the control and bDMARD groups. 30% of RA patients in conventional DMARD group showed eccentric hypertrophy and 4% showed concentric remodelling. The bDMARD group showed normal LV morphology. The LVMI and EF were both significantly correlated with DAS28 ($r = 0.545$, $p < 0.001$ and $r = 0.333$, $p < 0.002$, respectively). The bDMARD group had a significantly lower DAS28, higher EF, and lower LVMI than the conventional DMARD group.	[248]
Japan	2016	CS	To model association between RA characteristics and NT-proBNP levels with LGE and T2-weighted imaging.	No known CVD or CV risk factors	60 RA	3T LV volumes LGE T2-imaging	LGE present in 19 (32%) and T2-weighted imaging in 7 (12%). Higher odds of LGE with each swollen joint (odds ratio [OR] 1.87, P = 0.008), each log unit higher CRP level (OR 3.36, P = 0.047), and each log unit higher NT-proBNP (OR 20.61, P = 0.009). NT-proBNP higher (135%) with T2-weighted imaging than in those without T2-weighted imaging or LGE. Higher LVMI and LV remodelling in those with T2-weighted imaging than in those without. LVEF was not reduced in those with either LGE or T2-weighted imaging.	[249]

Finland	2016	CS	CMR in active RA without CVD	Asymptomatic	60 female RA 21 controls	1.5T and 3T LV/RV volumes T1 times LGE	With 1.5T, T1 time 1011ms in 20 patients with RA vs. 976ms in 10 control subjects (p=0.045). With 3T CMR, T1 time 1173ms in 29 RA patients vs. 1053ms in 9 control subjects (p=0.002). Myocardial LGE was detected in 55% of the RA patients. LV ejection fraction averaged 58% vs. 66% (p<0.001) in the RA (n=60) and control groups (n=21). The end-diastolic volumes of either ventricle were enlarged in RA compared to the control group (p<0.05 for both).	[250]
Japan	2016	PC	Tocilizumab (TCZ) effects on LV function.	No clinical diagnosis of CVD	13 RA 10 controls	Radial LV strain by feature tracking	DAS28-ESR lower at 52 weeks than at baseline. Mean peak Err at baseline was lower than in normal subjects (P = 0.03). Mean peak Err was significantly higher at 52 weeks than at baseline (P = 0.028).	[251]
UK	2015	CS	Assess myocardial fibrosis and oedema in RA	No clinical diagnosis of CVD	39 RA 39 controls	1.5T LV/RV volumes Tagging T2-weighted T1 mapping LGE ECV imaging	Focal LGE in 46% of RA patients compared with none of the control subjects. Focal myocardial edema 10% vs. 0%, higher native T1 values (973ms v 961ms; p=0.03), expansion of ECV (30.3% v 27.9%; p<0.001). LV volumes, mass, and EF similar between RA patients and control subjects. Peak systolic circumferential strain (-16.9 v -18.7; p<0.001) and peak diastolic circumferential strain rate (83s(-1) v 112s(-1); p<0.001) impaired in RA patients. Myocardial T1 and ECV correlated myocardial strain and RA disease activity.	[252]
Japan	2014	PC	Tocilizumab	No clinical	20 RA	LV volumes	RA baseline LVEF lower (-3.7%) and LVMI higher (+9.2%) compared with	[253]

			(TCZ) effects on LV function.	diagnosis of CVD	20 controls		controls. TCZ treatment resulted in decrease in disease activity after 52 weeks of treatment, paralleling a significant increase in LVEF (+8.2%) and a significant decrease in LVMI (-24.4%). The percentage change in LVMI correlated strongly with the percentage change in disease activity (r = -0.63, p=0.0028).	
Japan	2014	CS	bDMARD (TCZ and IFX) and MTX effects on regional LV function.	No clinical diagnosis of CVD	41 RA 10 controls	Radial LV strain by feature tracking	24, 7, and 10 received MTX, MTX plus IFX, or TCZ, respectively. DAS28 was higher in the MTX group than bDMARDs (4.5 v 2.9; p=0.002). Mean peak Err in the MTX group was significantly lower than in the control group (p = 0.014). No significant difference in mean peak Err between the bDMARDs and the control group (p = 0.424). Mean peak Err was significantly higher in the TCZ group than the MTX group (p = 0.036). Abnormal peak Err in patients with RA was significantly associated with longer disease duration (r = –0.69, p=0.001), and was mildly correlated to ESR (r = –0.44, p=0.36).	[254]
Greece	2013	CS	CMR in recent diagnosis of CCF in patients with RA	Clinical diagnosis of congestive cardiac failure	45 RA 45 controls	1.5 T. LV volumes Acute and chronic lesions were assessed by T2>2 with positive LGE and T2<2 with positive LGE, respectively.	4 patterns detected: Epi/endomyocardial LGE (myocardial inflammation): 33% Transmural DE (LGE): 22% (all RF+ve) Dilated cardiomyopathy: 33% (no inflammation/fibrosis present) Diffuse subendocardial fibrosis: 11% LGE positively correlated with disease activity, CRP and ESR.	[125]

Japan	2010	CS	CMR in RA	No clinical diagnosis of CVD	18 RA	1.5T Stress perfusion LGE	7 had LGE and 2 perfusion defects DAS28 higher if had LGE (4.77 vs. 3.44 without, p=0.011). Trend for correlation for CRP and ESR with LGE	[84]
USA	2010	CS	CMR in RA	No clinical diagnosis of CVD	75 RA 225 controls	1.5T LV volumes	Mean LV mass lower in RA (18% difference), along with LVEF, CO, SV. Lower LV mass and SV correlated with higher ACPA titre and use of biologics.	[83]

CS, cross sectional; PS, prospective cohort; RC, Retrospective cohort.

Table 2-4 - Summary findings of CMR studies in immune-mediated inflammatory disease that have included RA

Population	Year	Type	Purpose	CVD disease	Number	CMR details	Main findings	Ref.
Greece	2017	CS	CMR can detect occult lesions at CTD diagnosis	Asymptomatic	12 RA 66 CTD	1.5T Acute and chronic lesions were assessed by T2>2 with positive LGE and T2<2 with positive LGE, respectively.	In 9/12 RA, the T2 ratio was higher compared to normal. Myocarditis was identified in 1 RA. Diffuse, subendocardial fibrosis in 1 RA patient. Subendocardial myocardial infarction in 2 RA patients.	[255]
Israel	2016	CS	Evaluate aortic stiffness in female patients with RA	Asymptomatic. Presence of CV risk factors including diabetes	31 RA 30 SLE 53 controls	1.5T Aortic distensibility Aortic pulse wave velocity	Mean PWV higher in comparison to controls (6.2 ± 2.3 vs. 5.4 ± 1.7, p = 0.04). Aortic distensibility lower (4.4 ± 4.6 vs. 5.8 ± 4.9 kPa(-1) × 10(-3), p = 0.04). PWV and age (r = 0.67, p < 0.001), Framingham risk score (r = 0.61, p < 0.001), waist to hip ratio (r = 0.45, p < 0.001), systolic blood pressure (r = 0.37, p = 0.01), diabetes (r = 0.32, p = 0.001) and dyslipidemia (r = 0.32, p = 0.001).	[256]
Greece	2015	CS	Imaging patterns of CV lesions in patients with CTD and CV symptoms.	Mixed CV symptoms	5 RA 17 CTD	1.5T LV volumes Adenosine perfusion LGE	Positive CMR in 1 RA patient No correlation between disease duration and/or inflammatory indices and cardiac lesions was identified	[257]
Greece	2014	CS	CMR in CTD with LBBB on ECG	Mixed CV symptoms	6 RA 20 CTD 26 controls	1.5T LV volumes Acute and chronic lesions were assessed by T2>2 with positive LGE and T2<2 with positive LGE, respectively.	2/6 RA had transmural LGE in intra-ventricular septum consistent with myocardial infarction	[258]

Greece	2014	RS	CMR in CTD with normal TTE	Mixed CV symptoms	35 RA 211 CTD	1.5T LV volumes Acute and chronic lesions were assessed by T2>2 with positive LGE and T2<2 with positive LGE, respectively.	Abnormal CMR identified in 32% and 15% of patients with typical and atypical CV symptoms, respectively. 10/10 RA patients had LGE. 3 diff subendocardial, 4 sub-epicardial, 1 intra-myocardial, 2 transmural.	[244]

CS, cross sectional; PS, prospective cohort; RC, Retrospective cohort.

2.8 Conclusion

Transthoracic echocardiography remains the cornerstone of first-line testing. There is utilisation of carotid ultrasound in current guidelines for an attempt to assess intermediate risk patients, in a similar way that CT coronary calcium score has been used in the general, asymptomatic population. However, for symptomatic patients and accurate CV assessment, structural and functional non-invasive imaging should be utilised. It is recommended that future trials and studies adopt a multi-parametric CMR protocol with defined outcomes. This would help assess subclinical myocardial and vascular disease, allow lower patient numbers to be recruited given the excellent reproducibility and accuracy, and be able to assess multiple CV pathologies in one examination and relate them to future hard clinical endpoints and biochemical parameters.

Table 2-5 - The advantages and disadvantages of non-invasive imaging modalities

Imaging technique	Cost	Availability	Expertise	Radiation	Inflammation
Echo	Low	Yes	Yes	No	No
Nuclear	High	No	Yes	Yes	No
CT	High	No	No	Yes	No
CMR	High	No	No	No	Yes

Imaging technique	Ischemia	Scar	Vasculitis	Coronary arteries
Echo	Yes ± no	Yes ± no	Yes ± no	No
Nuclear	Yes ± no	Yes ± no	Yes ± no	No
CT	No	Yes ± no	No	Yes
CMR	Yes	Yes	Yes	Yes ± no

Adapted from Mavrogeni et al, Heart involvement in rheumatoid arthritis: multimodality imaging and the emerging role of cardiac magnetic resonance. Semin Arthritis Rheum. 2013 Dec;43(3):314-24[190].

Table 2-6 - Summary of characteristics of non-invasive functional imaging modalities

	Stress echo	Stress nuclear	Stress CMR
Limitations	Poor acoustic window	Inability to detect small perfusion defects	CMR contraindications
Scar detection	Indirect, through wall motion changes	Inability to detect small or subendo-cardial scars	High
Cost	Low	High	High
Availability	High	High	Low
Spatial resolution	Low	Low	High
Artifacts	High	High	Low
Operator dependency	High	Low	Low
Radiation	No	Yes	No

Adapted from Mavrogeni et al, Cardiovascular magnetic resonance in rheumatology: Current status and recommendations for use. Int J Cardiol. 2016 Aug 15;217:135-48 [259]

3 Thesis aims and hypotheses

Patients with RA have a variety of clinical presentations with overlapping CV pathology that need to be recognised by first-line healthcare professionals, cardiology and rheumatology teams. The most notable presentation is the earlier and increased incidence of IHD and CCF. There is recent formal adoption of RA into the UK CVD risk calculators with QRISK®2 and the update of QRISK®3 in 2018. There is support that the use of contemporary medical and interventional therapy in cardiac disease is as valuable in patients with RA compared to those without but it is with intrigue and anticipation whether we learn that early use of conventional DMARDs and bDMARDs significantly alters the risk of developing premature CVD and altering CV mortality.

As with RA, GCA is another IMID distinguished by specific pathways of immune-dysregulation that lead to inflammation, organ damage and dysfunction[1]. GCA is the commonest primary systemic vasculitis affecting older people[4] and, like RA, is associated with an increased early mortality mainly due to CVD. There are inflammatory contributions in atherosclerosis from the formation of atherosclerotic plaques, the development, the reduction in their stability to the final conclusion of rupture and thrombosis. The additional CV mortality that GCA is associated with includes aortic syndromes[5].

Much of the data summarised in my introduction around RA is in patients with established disease on a variety of disease-modifying therapy. What has not been adequately answered in the literature is precisely when along the RA disease continuum do CV changes start and when can they be measured using standard clinical tools. Furthermore, it may be important to realise if CV changes are present at the time of diagnosis, when the inflammatory cascade is already in force with clinical joint and systemic effects, if they can be modulated with therapy.

The data surrounding aortic change in GCA is hampered with differences in cross-sectional imaging modalities, inclusion criteria in studies and definitions of aortic dilatation. The prevalence and scale of effect of aortic dilatation is not well documented in the literature by any specific cross-sectional imaging tool.

3.1 Aims

The primary aim of this thesis is to characterise subclinical cardiovascular changes by CMR in patients with immune-mediated inflammatory disease, namely RA and GCA. The patient populations are refined in attempt to answer specific questions about CV change in their disease continuums. Namely:

1. The study of CV structural and functional change by CMR in patients with early RA (ERA) that have not begun any disease-modifying therapy, in attempt to see if already present at diagnosis or not.

2. The study of CV change, specifically of the thoracic aorta, in GCA patients with established disease. To contribute data surrounding prevalence of clinically important aortic dilatation and aid relevant screening assessment and monitoring.

Furthermore, with the assessment of CV change in ERA, the thesis has further aims in assessing if disease-modifying RA therapy modulates any CV changes seen at baseline CMR assessment. The studies aim to provide guidance for rheumatologists and reassurance to the patient group whether early biologic treatment in patients with early RA can reduce CVD burden - the leading cause of mortality in RA patients and thus a central consideration in daily rheumatology practice.

3.2 Hypotheses

The hypotheses in these studies are that, using multi-parametric CMR;

- Subclinical CV pathology exists in patients with early, treatment-naive RA. These data will be presented in chapter 5. I hypothesised that patients with ERA would have evidence of subclinical CVD compared to healthy controls.

- Early, aggressive control of RA can reduce this subclinical CV pathology at 1 year from treatment initiation. These data will be presented in chapter 6.

- TNFi may offer additional benefit over and above conventional DMARD in burden of subclinical CV pathology. These data will also be presented in chapter 6.

- GCA patients would have a higher prevalence of thoracic aorta dilatation, both when compared to controls without GCA, and when compared to population-derived CMR normal ranges. These data will be presented in chapter 7.

3.3 Statistical considerations

As per recommendations for good practice within pilot studies[260], 30 healthy controls were prospectively recruited. Statistical analysis are performed using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY). Continuous variables are expressed as mean ±SD with normality of distribution determined with Kolmogarov-Smirov testing. Categorical variables are expressed as N(%) and non-parametric variables as median[inter-quartile range]. Correlation was assessed with Pearson's correlation co-efficient. Differences between groups were evaluated using Students *t*-test for normally distributed data and the Mann-Whitney or Wilcoxon signed-rank test on non-parametric data for independent groups and pairwise comparisons respectively. The Chi-squared and Fisher-exact tests were used for comparing categories of data. A two sided $P<0.05$ is considered statistically significant. Multivariate linear regression analysis (MVA) is used for variables with statistical significance from univariate analysis (UVA) ($p<0.1$) and CMR measurements are adjusted for age, sex and CV risk factors. CV risk factors are defined as: hypertension (history of hypertension or anti-hypertensive agent), dyslipidaemia (history of dyslipidaemia or on lipid-lowering medication), ever smoked and family history of premature CVD (all y/n categories).

Furthermore, with the GCA study, potential predictors of ascending (AsAo) and descending aortic (DsAo) diameter within the GCA patients (age, sex and prior diagnosis of atherosclerotic vascular disease) and features at onset of GCA ischaemic manifestations, acute-phase markers and polymyalgic features) were explored by linear regression in univariable analysis. These variables are defined in a previous publication[261]. Features at onset of GCA that were significant on univariable analysis were adjusted for age, sex and prior diagnosis of

atherosclerotic vascular disease) in multivariable linear regression and residuals were plotted to assess model fit.

I am aware of the limitations of multiple testing, considering a set of statistical inferences simultaneously. The more inferences that are made, the more likely an erroneous inference may occur. There are several statistical techniques and simple corrections in attempt to prevent this from happening, such as Bonferroni and Holm's method. These techniques require a stricter significance threshold for individual comparisons, so as to compensate for the number of inferences being made. However, there are limitations with statistical correction techniques such as Bonferroni. Type I errors cannot decrease (the main point of Bonferroni) without increasing type II errors. Type II errors are no less false than type I errors, therefore Bonferroni adjustments do not assure a cautious interpretation of data. Several CMR derived CV measurements are closely linked in their production, therefore I will carefully report when this is present, so as not inflate any potential significant results.

3.4 Chapter summaries

Chapter 4 is the methodology of cardiovascular magnetic resonance assessment of cardiovascular changes in early Rheumatoid Arthritis and measurement of the effect of early biological therapy. Further study design, including the CMR protocol and image analysis, are described in detail here.

The results data on this ERA population are presented in chapter 5 and chapter 6. The data presented between chapters 5 and 6 are split with respect to the hypotheses of assessing i) the presence of sub-clinical CV pathology in early, treatment-naive RA, and ii) the effects of RA therapy.

Chapter 5 presents the results of the first component of the RA study and evaluates the presence of CV abnormalities in ERA. The CMR findings of a cohort of ERA patients are compared to non-RA controls and their baseline clinical characteristic data are explored.

Chapter 5 reports on the entire cohort at baseline and all completed recruitment and data analysis under my full-time supervision in the capacity as Clinical Research Fellow in CMR at the University of Leeds from 2013.

Chapter 6 presents the second component of the RA study and evaluates if early aggressive control of RA can reduce subclinical CV pathology at 1 year from treatment initiation and whether tumour necrosis factor inhibitor (TNFi) offers additional benefit over and above conventional synthetic disease modifying anti-rheumatic drugs (DMARDs) in the burden of subclinical CV pathology. Chapter 6 reports on the interim follow-up analysis on patients that had undertaken their 1 year follow up CMR before September 2015, marking the end time-point of my full-time supervision in the capacity as Clinical Research Fellow in CMR at the University of Leeds. Data analysis was undertaken once all the recruited CADERA patients had completed their 1 year CMR in November 2016.

In chapter 7, I sought to characterise thoracic aortic structural change in patients with established GCA. There were some differences in the CMR sequence protocol between the RA studies of chapters 5 and 6 and the GCA study in chapter 7. This is because assessing aortic structural change in GCA was the focus, above-and-beyond detailed myocardial change. The differences in CMR sequences are described in detail in a separate methods addition in chapter 7.

Chapter 8 is a summary of the results chapters presented in 5 to 7 with some comments on future work.

4 Cardiovascular magnetic resonance assessment of cardiovascular changes in early Rheumatoid Arthritis and measurement of the effect of early biological therapy

4.1 Abstract

4.1.0 Background

The incidence of CVD in RA is increased compared to the general population. Immune dysregulation and systemic inflammation are thought to be associated with this increased risk. Early diagnosis with immediate treatment and tight control of RA forms a central treatment paradigm. It remains unclear however whether using TNFi to achieve remission confer additional beneficial effects over standard therapy, especially on the development of CVD.

4.1.1 Methods

This prospective CV imaging study from the CADERA (Coronary Artery Disease Evaluation in Rheumatoid Arthritis) trial bolts onto an existing single-centre, randomised controlled trial, VEDERA (Very Early versus Delayed Etanercept in Rheumatoid Arthritis). VEDERA aims to recruit 120 patients with early, treatment-naïve RA, randomized to TNFi therapy ETN combined with MTX or therapy with MTX +/- additional synthetic DMARDs with escalation to ETN following a TTT regimen. Patients recruited undertook a comprehensive multi-parametric CMR assessment for a complete CV functional and structural assessment including; cine imaging, rest/stress adenosine perfusion, tissue-tagging, aortic distensibility, T1 mapping and late-gadolinium imaging. The primary objective is to detect the prevalence and change of CV abnormalities by CMR between TNFi and standard therapy over a 12 month period.

4.1.2 Discussion

This chapter describes the methodology for this CMR study describing CV abnormalities in early, treatment-naïve RA patients with assessment of changes at 1 year between early bDMARD therapy and conventional DMARD therapy.

4.2 Introduction

RA is one of the most common autoimmune diseases affecting approximately 1% of the UK population[2]. A chronic, systemic, inflammatory arthritis, if not adequately controlled, RA can lead to significant joint damage and subsequent functional impairment. Mortality is increased compared to the general population largely due to increased frequency of premature CVD, which constitutes up to 40% of mortality in RA patients[3] and is as high as that of patients with other major CVD risk factors such as Type 2 diabetes mellitus[17]. It is accepted that CVD risk in RA is independent of, and incremental to, traditional CVD risk factors[18] with the likely predominant pathological process being immune dysregulation leading to systemic inflammation[19]; although the exact mechanisms remain unclear. The inflammatory process, mediated through pro-inflammatory cytokines such as tumour necrosis factor (TNF), is linked to atherosclerosis and plaque rupture and has confounding effects on lipid and glucose metabolism, blood pressure and haemostatic factors[20]. Markers of RA severity are strongly associated with adverse CV (CV) outcomes in RA[21] and reduced time-average disease activity is associated with fewer CV events[22]. Atherosclerosis itself being increasingly viewed as an inflammatory-mediated process[262].

Arterial stiffness is associated with an increased risk of CV events with a range of co-morbidities[23]. In patients with established RA without traditional CV risk factors, aortic pulse wave velocity is higher than in controls[24] and correlates with age, mean arterial pressure and CRP. Echocardiography studies have shown that patients with RA have high rates of diastolic dysfunction[144], heart failure[128, 129] and heart failure with preserved ejection fraction[126]. Positron emission tomography (PET) in patients with rheumatic diseases without coronary artery disease (CAD) shows lower myocardial blood flow (MBF) reserve compared to controls with an inverse correlation to disease duration[211]. In a meta-analysis of 22 studies, RA patients had a greater carotid intimal-media thickness (CIMT), a direct measure of the status of the vascular wall and measure of atherosclerotic and arteriosclerotic processes[25], than controls[26] with emerging evidence that CIMT is abnormal even in early disease[263]. These findings are consistent with the concept of microvascular pathology and accelerated atherosclerosis due to systemic inflammation in RA, which may precede and contribute to the effects of CAD.

The assessment of left ventricular (LV) mass and geometry provides incremental prognostic information regarding CV outcomes[264]. LV hypertrophy (LVH) and concentric geometry has been described in established RA echocardiography studies[121] with diastolic dysfunction seen in ERA[265]. CMR studies in established RA have conversely shown that patients have reduced LV mass and ejection fraction (EF)[83] with lower LV mass associated with seropositivity and the use of biological bDMARDs[266]. Recent CMR studies in established RA have found diffuse myocardial fibrosis as measured by expansion of the myocardial extra-cellular volume (ECV) using CMR T1 mapping[87]. As well as presence of focal fibrosis on CMR, as imaged by late-gadolinium enhancement (LGE), ECV expansion is associated with poorer outcomes in patients with a range of co-morbidities[267]. Without symptomatic cardiac disease, established RA patients with higher disease activity scores have been found to have sub-clinical LGE and non-ischaemic perfusion defect patterns on adenosine stress imaging[84].

Early diagnosis of RA and immediate intervention with conventional DMARDs in a TTT approach with remission the goal of treatment is an internationally recommended, established practice[54]. bDMARD treatments, first introduced at the turn of the century, are highly effective tools to achieve this and have revolutionised outcomes in RA. TNFi were the first bDMARD agents to be introduced. First-line TNFi studies in ERA have demonstrated particularly high rates of remission induction, similar or slightly greater than conventional DMARD but with superior structural benefits and the ability to achieve drug-free remission[56-62]. TNFi treatment has been shown to improve arterial stiffness[63]. In addition, reports have suggested wider benefits of bDMARD therapy including reduction in biomarkers associated with CVD[63, 64]. Recent pilot data have shown that tocilizumab treatment over 1 year significantly increased LVEF and decreased LVMI associated with disease activity[266].

CV clinical trials of TNFi treatments in RA are challenging because under-powering and the small number of hard clinical CV mortality endpoints in study populations[111], which also means being unable to adjust for important confounders that differentiate between CV events that follow other pathophysiological pathways[268]. As TNFi treatment is reserved for patients with established, MTX-refractory disease, observational studies are inherently limited by a selection bias. Although aggressive treat to target approaches with conventional DMARDs are associated with impressive remission rates, the use of bDMARD may offer a “window of opportunity” in

ERA by interrupting progression along the disease continuum with the additional potential to impact CVD.

4.3 Methods

4.3.0 Study design

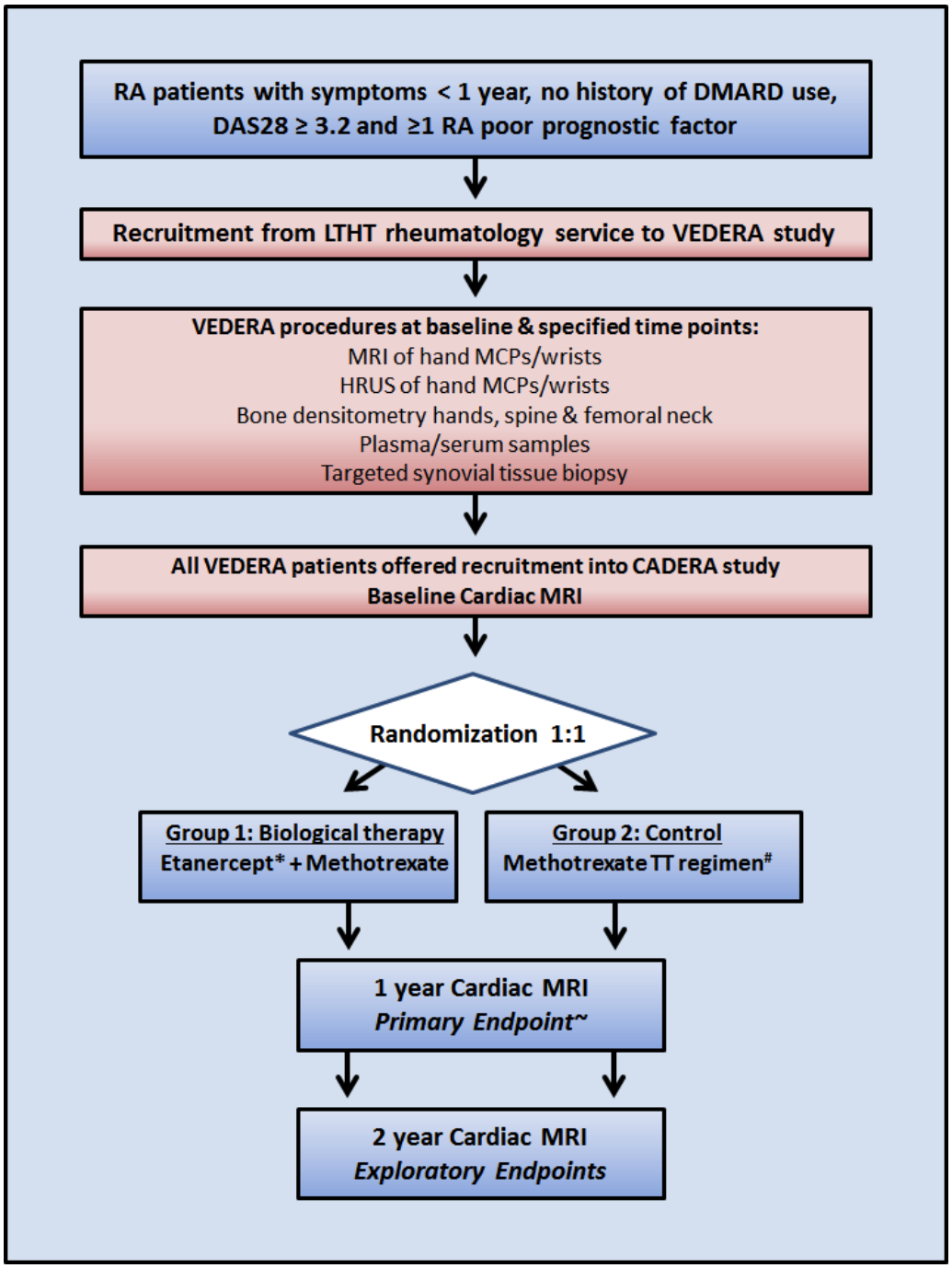
The CADERA study and experiments bolt on to the VEDERA (Very Early versus Delayed Etanercept in Rheumatoid Arthritis) trial, a prospective parallel cohort intervention study of patients with ERA, randomly allocated to either first-line TNFi therapy (etanercept, ETN) and MTX or optimal synthetic DMARD therapy. VEDERA is an investigator-initiated Research (IIR) study based at the Leeds Institute of Rheumatic & Musculoskeletal Medicine and is funded by an unrestricted educational grant that is part of an IIR agreement with Pfizer. The aim of VEDERA is to assess for the depth of remission (clinical and imaging) and immunological normalisation induced by the treatment arms as well as to identify predictors of remission. CADERA specifically is reporting on CV changed by CMR assessment.

The patients undergo CMR at baseline (prior to treatment) as well as after 1 year and 2 years of treatment. I present the baseline data in chapter 5 and the interim, follow-up results at 1 year in chapter 6. Study flow chart is presented in Figure 4-1.

4.3.1 Ethics

The National Research Ethics Service (NRES) Committee Yorkshire & The Humber – Leeds West approved the study protocol and other relevant documentation (Research Ethics Committee (REC) reference: 10/H1307/138).

Figure 4-1 - Study flow diagram



**Etanercept non-responders or intolerance managed at physician's discretion. #Methotrexate for duration of study, addition of other DMARDs at week 8 if not in remission and escalated to etanercept at week 24 if not in remission. ~Etanercept discontinued at the primary endpoint unless clinically indicated and at physician's discretion. DAS=disease activity score, DMARD=disease modifying anti-rheumatic drug, HRUS=high resolution ultrasound, LTHT=Leeds Teaching Hospitals NHS Trust, MCP=metacarpophalangeal, RA=rheumatoid arthritis, TT=treat to target.*

4.3.2 Enrolment criteria

Patients eligible for VEDERA were recruited from the Leeds Teaching Hospitals NHS Trust Rheumatology service. The recruitment period was between February 2012 until November 2015. All patients recruited to VEDERA were offered inclusion into the CADERA CMR study. All the CMR scans were performed and analysed at Leeds General Infirmary. The study was performed in accordance with the Declaration of Helsinki (October 2000), with all patients providing informed written consent.

Inclusion criteria: patients diagnosed with RA according to the 2010 ACR/EULAR criteria (Table 4-1), who have not yet received therapy with DMARDs, have early (symptoms for less than 1 year) active disease (clinical or imaging evidence of synovitis and DAS28-ESR ≥ 3.2).

Exclusion criteria: previous treatment with DMARDs, known CVD, contraindications to TNFi therapy (or severe co-morbidity that would in the clinician's opinion be associated with unacceptable risk of receiving TNFi therapy) and contraindications to CMR, (which include renal failure (eGFR<30 ml/min/1.73m2), known allergy to gadolinium-based contrast agents and contraindications to adenosine (asthma or high grade heart block)).

As per recommendations for good practice within pilot studies[260], 30 non-RA controls were prospectively recruited matched by age/sex to the first 30 ERA patients. Healthy controls were sought through existing departmental ethics approval. Interest was received through local University of Leeds information bulletins for volunteer recruitment as well as word-of-mouth through trial participants. Adherence to the exclusion criteria above was strictly observed.

Table 4-1 - The 2010 ACR/EULAR classification criteria for rheumatoid arthritis

JOINT DISTRIBUTION	**Score**
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (at least one small joint)	5
SEROLOGY	
Negative RF **AND** negative ACPA	0
Low positive RF **OR** low positive ACPA	2
High positive RF **OR** high positive ACPA	3
SYMPTOM DURATION	
<6 weeks	0
≥6 weeks	1
ACUTE PHASE REACTANTS	
Normal CRP **AND** normal ESR	0
Abnormal CRP **OR** abnormal ESR	1

A score ≥6 = definite RA. Requires that the patient has at least one joint with definite synovitis and that the synovitis is not better explained by another disease. The score may be retrospective or prospective. RF, rheumatoid factor; ACPA, anti-citrullinated peptide antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

4.3.3 Outcome measures

The primary outcome measure for the CADERA trial is aortic distensibility. Aortic distensibility is a measure of how much an arterial vessel wall can expand; lower values signify stiffer arteries [269]. It is measured and quantified at baseline and at 1 year in each arm of the study. Increased arterial stiffness is associated with an increased risk of CV events[23]. It can be measured by pulse wave velocity or as distensibility of the aorta. It has shown utility in the prediction of CV events in the general population[270]. There are few studies assessing aortic distensibility in RA but it appears to be reduced when compared to controls[271, 272]. It has previously been shown that aortic distensibility relates to clinical outcome and that TNFi improve aortic distensibility[63].

A pilot study was performed in 10 patients with RA (disease duration 20±9.6 years) and matched by age and sex to 10 asymptomatic subjects without RA. Aortic distensibility was significantly different in RA patients with a mean and standard deviation of 1.83±0.4cm^2 versus 2.6±0.6cm^2 in controls. LV volumes and mass were similar between groups and LV strain and twist showed trends towards a reduction in RA patients, but without reaching statistical significance. Our pilot data therefore suggested CV abnormalities in patients with RA in several quantitative CMR parameters with aortic distensibility reaching statistically significant difference even in the small sample size. It has previously been shown (with other imaging modalities) that aortic distensibility relates to clinical outcome and that TNF alpha blockade improves aortic distensibility. From the directly measured aortic area on CMR imaging, AD, strain, compliance and stiffness index are further derived and inter-related outcome measures. The formulae and image analysis methods are described in this chapter.

Further outcome measures derived directly from CMR image analysis are LV strain, LV twist, LV/RV volumes, LV mass and LV myocardial T1 relaxation time. From these directly measured outcomes, further data are created including LVEF, LV torsion, LV strain rates, myocardial ECV and indexed values to BSA of the above parameters. LGE and qualitative perfusion defects are further outcome measures I will be assessing. These outcome measures will be a comprehensive functional and structural description of CV change by CMR.

Significant differences (expressed as p<0.05) of CV abnormalities detected by CMR between the two treatment arms will be presented and the magnitude of this difference will be expressed as a 95% confidence interval.

4.3.4 Sample size calculation

Powering is based on scaling of effect sizes reported by Ikonomidis *et al*[64]. We had contacted the author and obtained confirmation of the data they presented. Our effect size of 2.46 cm^2 $dyne^{-1}10^{-6}$ represented the smallest detectable difference above measurement error. We proposed 2.46 as an effect size in our power calculation (representing 75% of the difference between treated and non-treated RA patients of Ikonomidis *et al*., 2008).

Our pilot and initial patient data gave a standard deviation of 1.6 from 50 treatment naïve patients. The upper limit of a 95% confidence interval for the standard deviation based on these data is 2.5 (representing a conservative estimate of the variability in this patient group). With a revised standard deviation of 2.5, a 5% significance level in a two-tailed independent samples t-test at 90% power, 25 patients would be required per group - biologic therapy versus standard conventional therapy - (adjusting for 10% drop-out).

4.3.5 Statistical considerations

Both treatment arms are compared with primary outcome aortic distensibility from baseline to 1 year follow up, as well as other outcome measures. As per recommendations for good practice within pilot studies[260], 30 non-RA controls were prospectively recruited matched by age/sex to the first 30 ERA patients. Statistical analysis are performed using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY). Continuous variables are expressed as mean ±SD with normality of distribution determined with Kolmogarov-Smirov testing. Categorical variables are expressed as N(%) and non-parametric variables as median[inter-quartile range]. Correlation was assessed with Pearson's correlation co-efficient. Differences between groups were evaluated using Students *t*-test for normally distributed data and the Mann-Whitney or Wilcoxon signed-rank test on non-parametric data for independent groups and pairwise comparisons respectively. The Chi-squared and Fisher-exact tests were used for comparing categories of data. A two sided P<0.05 is considered statistically significant. Multivariate linear regression analysis (MVA) is

used for variables with statistical significance from univariate analysis (UVA) ($p<0.1$) and CMR measurements are adjusted for age, sex and CV risk factors. CV risk factors are defined as: hypertension (history of hypertension or anti-hypertensive agent), dyslipidaemia (history of dyslipidaemia or on lipid-lowering medication), ever smoked and family history of premature CVD (all y/n categories).

4.3.6 Missing data

The numbers of patients with missing data for CMR measurements, and the number of un-interpretable images, are reported.

4.3.7 CMR investigation details

Our group has well-established multi-parametric protocols that have been validated in other populations[273]. CMR is performed on a dedicated 3T Philips Achieva system equipped with a 32-channel coil, vectorcardiographic triggering and multi-transmit technology. Patients will be asked to avoid caffeine for 24 hours prior to the scan. The CMR protocol (Figure 4-7) lasts approximately 60 minutes and comprises:

1. Low resolution survey, reference scans and localisers, Figure 4-2. Following survey and reference scans, the heart's short axis, vertical long axis and horizontal long axis will be defined with a series of cine images (balanced steady state free precession acquisition [bSSFP], echo time (TE) 1.48ms, repetition time (TR) 3.0ms, flip angle 45^{o}, field of view 320 – 420mm according to patient size, slice thickness 10mm and 30 phases per cardiac cycle).

Figure 4-2 - Low resolution survey imaging and reference scans

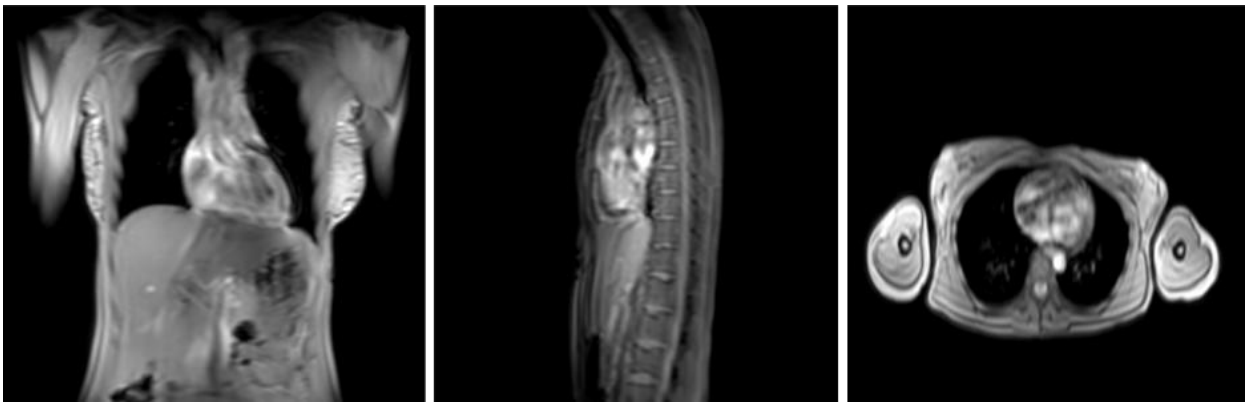
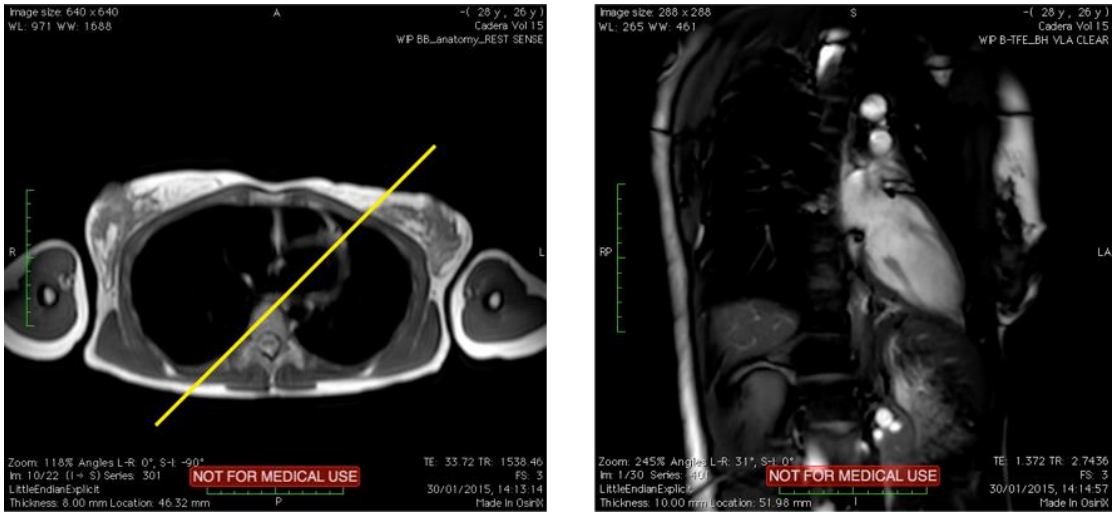
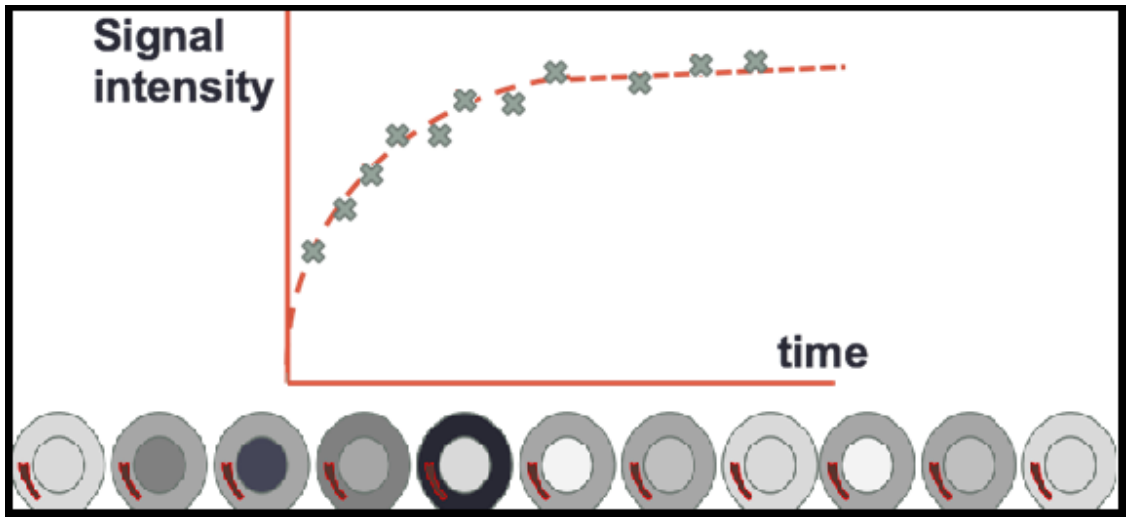


Figure 4-3 - A vertical long axis cut through black-blood imaging enabling the cine image



2. Baseline T1 mapping. 1 slice will be acquired at the LV short axis using an ECG-triggered modified Look-Locker inversion (MOLLI) method, Figure 4-4, to acquire 11 images (3-3-5 acquisition with 3x R-R interval recovery epochs) in a single end-expiratory breath hold (voxel size 1.7x2.14x10mm^3 Trigger delay at end-diastole, flip angle 35^o, field of view 320 – 420mm)[233, 274].

Figure 4-4 - Diagrammatic representation of MOLLI T1 Mapping scheme



A septal region of interest (red contour) will be selected, carefully avoiding blood pool, for T1 relaxation values.

3. Adenosine stress first-pass myocardial perfusion imaging (spoiled Turbo Gradient Echo, 5x k-t Broad-use Linear Acquisition Speed-up Technique (BLAST), 11 training profiles, 1.31x1.32x10mm³ acquired resolution, pre-pulse delay 100ms, acquisition shot 123ms/slice, three short axis slices)[275]. Intravenous adenosine will be administered at 140mcg/kg/min for 3 minutes under continuous ECG monitoring. Adequate haemodynamic response is assessed by either;

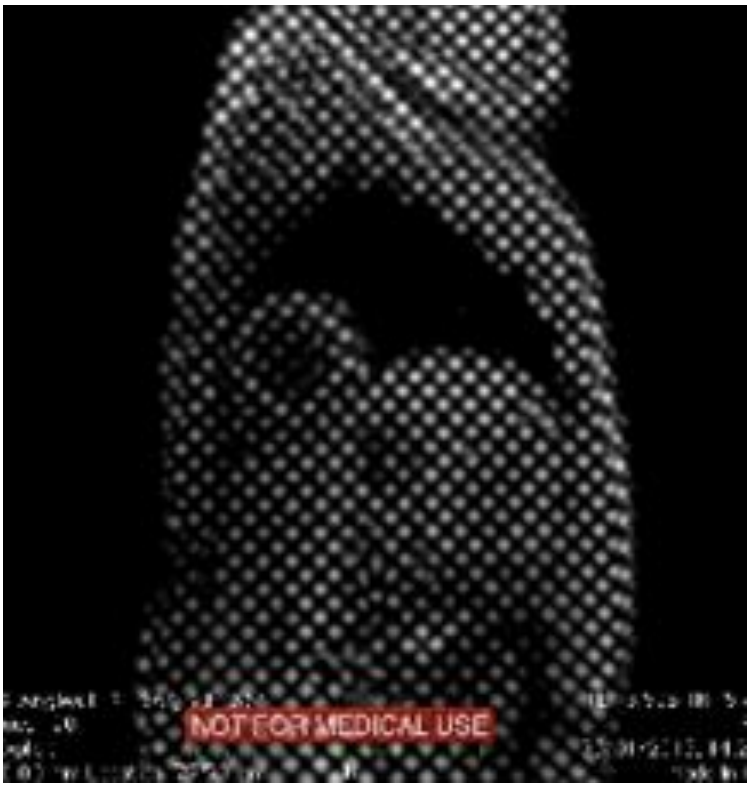
- Heart rate increase by ≥10%;
- Systolic blood pressure decrease of ≥10mmHg
- Symptoms attributed to adenosine administration.

If there is inadequate haemodynamic response then the dose will be increased to 170 and then to 210µg/kg/min for a further 2 minutes until haemodynamic response is achieved. The contrast injection will be performed using a dual-bolus technique, by intravenous route in the ante-cubital fossa, of 0.1mmol/kg of gadolinium-DTPA (gadopentetate dimeglumine; Magnevist, Bayer, Berlin, Germany) for the main bolus preceded by the same volume of a 10% dilute contrast agent dose for the pre-bolus, both administered at a rate of 4.0ml/s followed by a saline flush using a using a power injector (Spectris, Solaris, PA)[276].

4. Resting wall motion and LV function. Cine image stack covering the entire heart in the LV short axis plane at 1 slice per breath-hold in end-expiration and parallel to the mitral valve annulus[277, 278] (bSSFP, multiphase, 10-12 contiguous slices, spatial resolution 2.0x1.63x8mm³, 30 cardiac phases).

5. Tissue tagging for strain analysis and diastology, Figure 4-5. Spatial modulation of magnetization (SPAMM) pulse sequence (spatial resolution 1.51×1.57×10mm^3, tag separation 7 mm, ≥18 phases, typical TR/TE 5.8/3.5 ms, flip angle 10°).

Figure 4-5 - Example of a tissue-tagging image. Short-axis of the mid left ventricle.

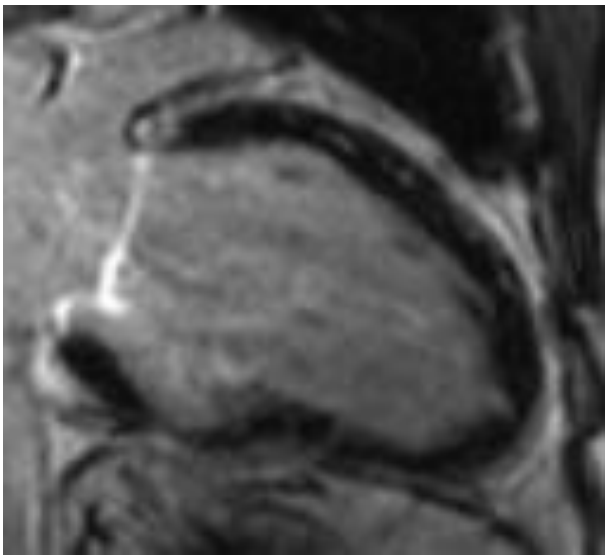


6. Aortic distensibility. Cine images of the ascending aorta (50 phases) at the level of the PA bifurcation and the descending aorta, transverse to the vessel according to Lee *et al*[219]. For aortic stiffness, blood pressure and heart rate are recorded immediately prior to the multi-phase SSFP cine image (24 phases).

7. Resting first-pass myocardial perfusion study. Pulse sequence, slice positioning, and injection characteristics identical to the stress perfusion scan as above in step (3).

8. Late gadolinium enhancement (LGE). Performed between 10-15 minutes after step (7). Inversion recovery-prepared T1-weighted gradient echo. The optimal inversion time to null signal from normal myocardium will be determined using a modified Look-Locker approach.[279] Typical parameters: TE 2.0 ms, TR 3.5 ms, flip angle 25^{o}, acquired spatial resolution $1.54x1.76x10mm^{3}$. Inversion time adjusted according to variable TI scout. Alternate heart beat acquisitions by navigator is an option for boor breath holders. Performed in 10-12 short axis slices with further slices acquired in the vertical and horizontal long axis orientations, or phase-swapped, if indicate based on LGE imaging obtained, wall-motion or perfusion defects.

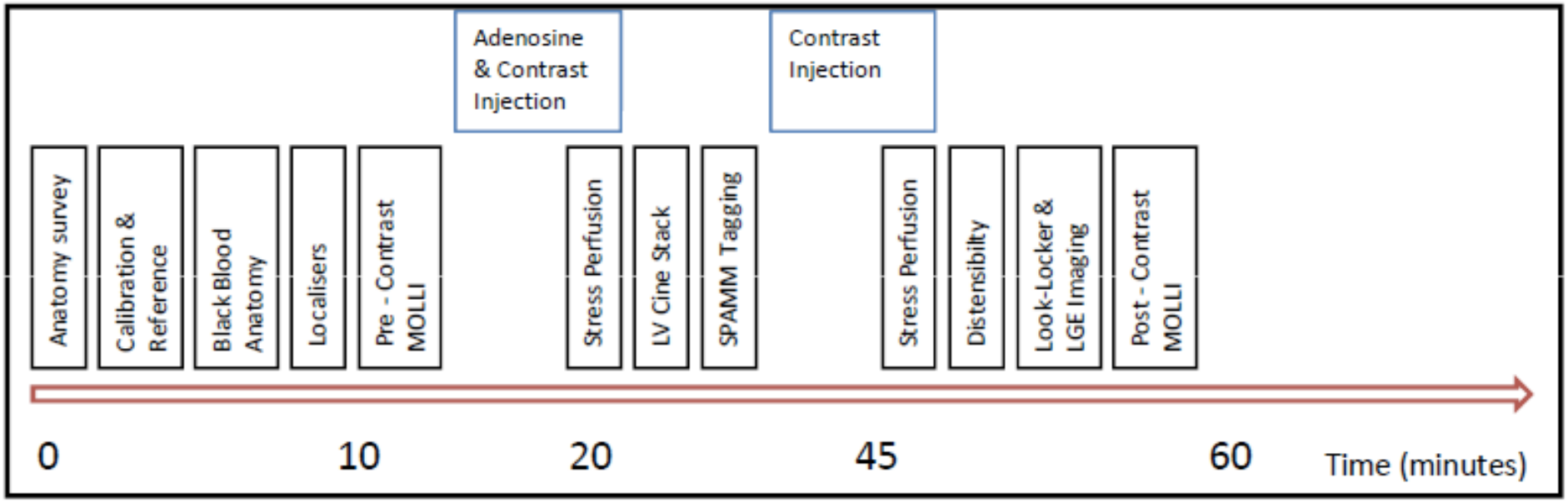
Figure 4-6 - A late-gadolinium enhancement image of the left ventricle in vertical long axis



9. Post contrast T1 mapping 15 minutes following last contrast injection at step (7). Acquisition and slice positioning as above in step (2).

T1 mapping, tissue tagging and perfusion imaging are performed in three identical short-axis positions. These will be determined using the '3-of-5' approach by acquiring the central 3 slices of 5 parallel short-axis slices spaced equally from mitral valve annulus to LV apical cap[280].

Figure 4-7 - Cardiovascular magnetic resonance protocol



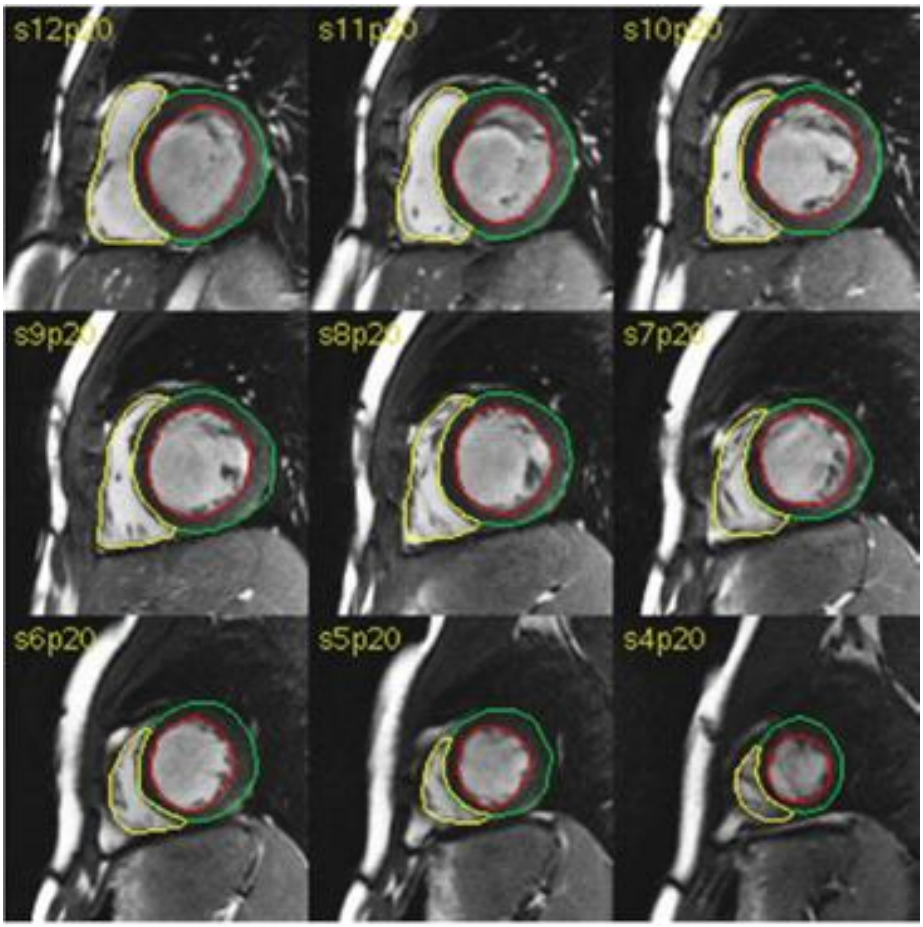
LGE, Late-gadolinium enhancement; LV, left ventricle; MOLLI, Modified Look-Locker Inversion; SPAMM, Spatial modulation of magnetization.

4.3.8 CMR image analysis and reporting

Image analysis is performed off-line, in a blinded fashion to patient characteristics and treatment arm, using commercially available software (cvi42 v4.1.3, Circle Cardiovascular Imaging Inc., Calgary, Canada and inTag v1.0, CREATIS lab, Lyon, France) according to international standards for reporting of CMR studies. [281]

LV volume and ejection fraction (EF) is calculated from the short axis cine-stack using standard criteria to delineate cardiac borders[281]. Regional wall motion in 17 cardiac segments is graded visually.

Figure 4-8 - Contouring of the ventricles for volumetric analysis



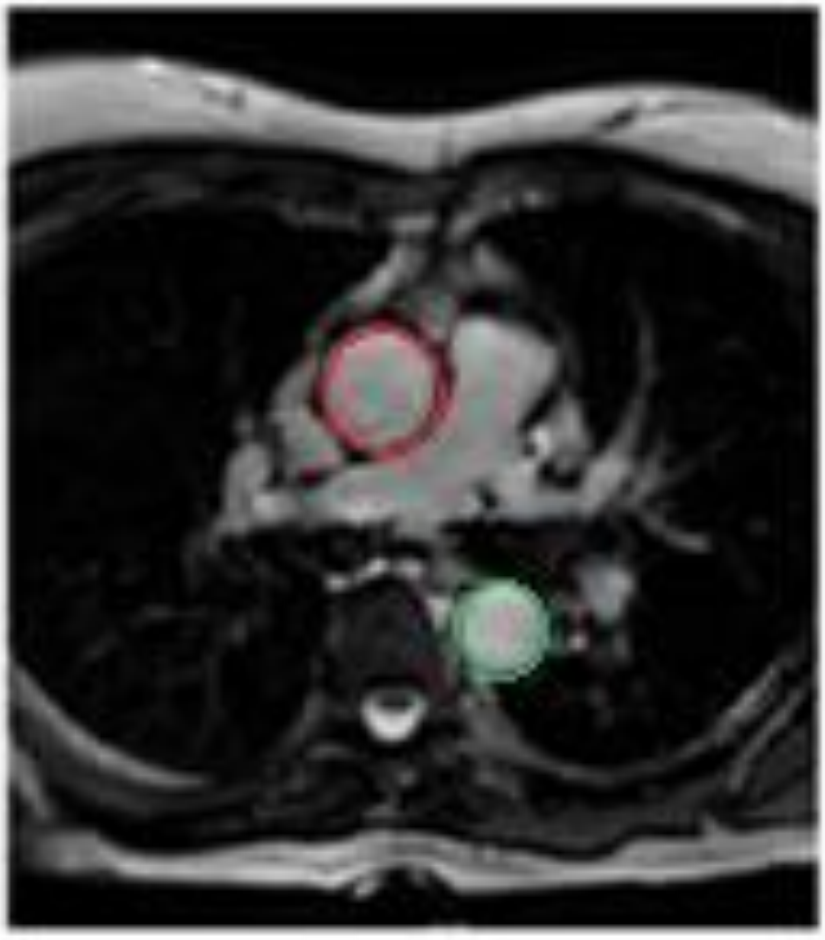
The yellow contours are of the right ventricle, the red contours are of the left ventricular endocardium and the green contours are of the left ventricular epicardium. All in end-diastole.

Aortic cross sectional measurements are made by manual planimetry of the endovascular-blood pool interface, at the times of maximal and minimal distension of the aorta,

Figure 4-9. Aortic distensibilty is calculated using non-invasive blood pressure measurements taken at the time of image acquisition using the standard formula below and listed in Table 4-2[282]:

$$Distensibility = \frac{Strain}{Pulse\ pressure\ (mmHg)} \times 1000$$

Figure 4-9 - Measurement of aortic cross sectional area



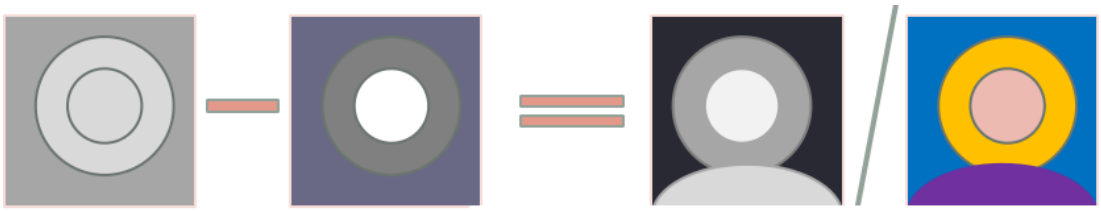
Cine image of the aortic cross sections. Red circle: ascending aorta. Green circle: descending aorta.

Table 4-2 - Definitions and formulas of Parameters used in the Assessment of Arterial Stiffness

Parameter	Definition	Formula
Aortic Compliance	The absolute change in vessel diameter (or area) for a given change in pressure	ΔD/ΔP
Aortic Distensibility	The absolute change in vessel diameter (or area) for a given change in pressure	ΔD/(ΔPxD)
Stiffness Index	The ratio of the natural logarithm of SBP/DBP to the relative change in diameter	ln(Ps/Pd)/[(Ds-Dd)/Dd)

D, diameter; P, pressure; s, systole; d, diastole. Adapted from Oliver, J.J. and D.J. Webb, Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. Arterioscler Thromb Vasc Biol, 2003. ***23****(4):p.554-66.*

Native and post-contrast myocardial T1 will be measured[283]. Care is taken to ensure a conservative region of interest and to avoid partial-volume effects from neighboring tissue or blood pool. Regions of interest are manually motion corrected as required. The reciprocal of T1 is calculated as R1. Extra-cellular volume (ECV) is calculated using the following equation[284]:

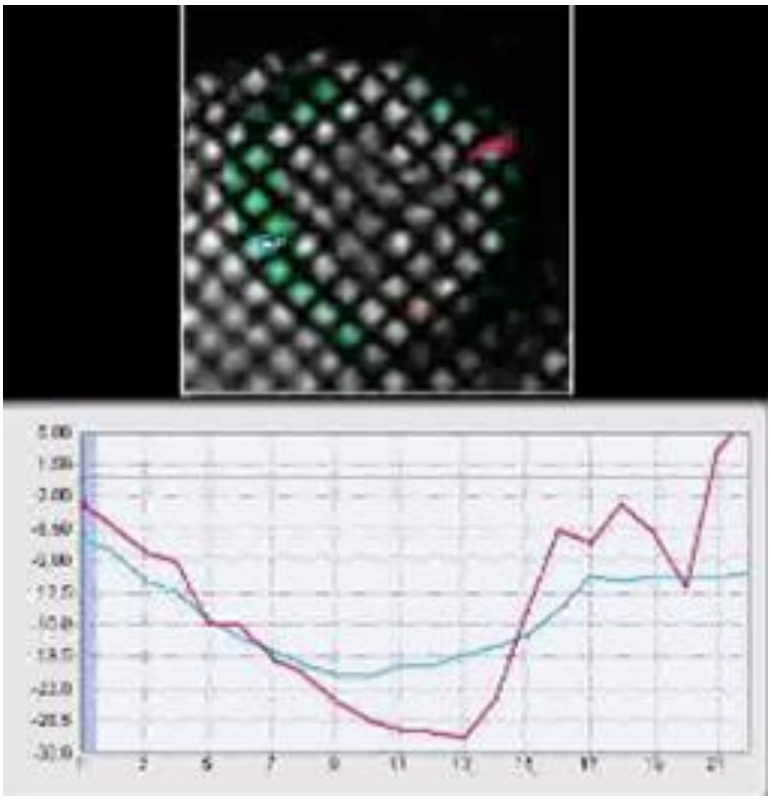


$$ECV = (1 - Hct)\frac{R1(myo\ pre) - R1(myo\ post)}{R1(blood\ pre) - R1(blood\ post)}$$

Strain analysis and LV torsion from the tagging series was derived using the open source software Osirix inTag (http://www.osrix-viewer.com) and using the tagged cine series, Figure 4-10. Endocardial and epicardial contours are drawn by a semi-automated process for each slice. Peak circumferential systolic strain and rotation will be calculated for the three short axis slices at the level of apex, mid-ventricle and base. LV twist is calculated by subtracting the basal rotation from the apical rotation. The method of determining torsion takes the radius and length of the heart into account, describing the torsion as the circumferential-longitudinal shear angle. This makes the measurement comparable between hearts of different sizes and is related to fiber orientation and processes in the myocardium[285, 286]. Basal and apical radius is calculated from measuring area by epicardial contours on cine imaging in diastole at the same slice location as the tagged images. Base to apex length is determined by subtracting the slice locations. The equation used to determine torsion is:

$$Torsion = \frac{Peak\ Twist\ x\ (Apical\ Radius + Basal\ radius)}{2\ x\ Apex\ to\ Base\ length}$$

Figure 4-10 - Strain analysis from tissue-tagged cine image



The red region of interest is strain the lateral wall of the left ventricle. The green region of interest is strain from the septal wall of the left ventricle. In this example, there is reduced strain in the septal wall.

Myocardial perfusion is assessed by visual comparison of stress and rest CMR perfusion scans (16 segments of the modified 16 segment AHA/ACC model)[287] with scores of 0 (normal), 1 (equivocal), 2 (non-transmural ischaemia <50%), 3 (non-transmural ischaemia ≥50%), 4 (transmural ischaemia).

LGE images are analysed visually by 2 experienced observers and any relevant patterns of enhancement are described based on a 17-segment model with scores of 0 (no hyperenhancement), 1 (1–25% mural thickness), 2 (26–50%), 3 (51–75%), or 4 (>75%) allocated to each segment.

4.3.9 Reproducibility

CMR measurements have been validated in previous reproducibility studies. In our hands, the inter- and intra-observer reproducibility for measurement of aortic distensibility by CMR is excellent. In a clinical study of 49 volunteers, the intra-observer mean difference for diastolic (minimum) aortic volume was 0.009±0.039ml and the mean difference for systolic (maximum) aortic volume was 0.0075ml±0.039ml (p=NS). The coefficient of variation (CoV) in the diastolic and systolic measurements were 1.4% and 1.1% with an intra-class correlation coefficient (ICC) of r=0.998 and r=0.998 respectively[288]. Analysis of tissue tagged CMR images shows an intra-observer CoV for circumferential strain of 4.3% and 1.2% for LV twist (n=12). Inter-study CoV of circumferential strain is 3.7% and 9.6% for LV twist. The ICC shows excellent intra-observer, inter-observer, and inter-study reproducibility of circumferential strain ranging from 0.95–0.98. The ICC suggested excellent intra-observer and inter-observer interstudy reproducibility (0.97 and 0.95, respectively) of LV twist and good inter-study reproducibility of LV twist (0.67)[230]. In this study, repeated measurements of 12 randomly selected scans, with blinding to the original measurements, have been performed for reproducibility analysis and reported on.

4.3.10 Safety and adverse events

CMR is a standard clinical imaging modality in every day clinical use and risks to the study participants are small. Adenosine stress agents carry a small risk of adverse effects including transient atrio-ventricular block and bronchospasm. CMR contrast agents carry a low risk of allergic reactions (~1:10,000). To avoid the development of nephrogenic systemic fibrosis relating to some CMR contrast agents, patients with renal failure and an eGFR of less than 30 ml/min/1.73m^2 will not be recruited. All serious adverse events that occur as a result of the CMR will be reported without formal statistical testing being undertaken.

4.3.11 Biomarkers

As part of exploratory objectives, there is analysis of biomarkers to CMR measurements of CVD. Specifically, the following are evaluated: RF, ACPA, CRP and ESR.

4.4 Discussion

Early diagnosis and immediate treatment of new onset, treatment-naive RA is crucial to ensure best possible treatment outcomes. Studies demonstrate TNFi agents confer additional structural benefit but in particular, may be able to modulate disease progression in a proportion of patients. It remains unclear whether use of MTX impedes this potential effect. The VEDERA study postulates that first-line TNFi therapy is qualitatively and quantitatively superior with better clinical, structural and immunological outcomes when compared with non-biological DMARDs. This bolt-on study provides a comprehensive CV evaluation of the VEDERA population assessing the prevalence and severity of CVD in a treatment-naive patient population of new-onset RA with comparison to clinical parameters, such as RA disease severity. The study evaluates whether effective RA disease control (remission) can improve CVD as assessed by CMR and importantly, whether achieving remission through first-line TNFi offers any additional benefit over initial synthetic DMARD-induced remission. The knowledge gained from these studies may contribute towards more effective use of targeted therapies for patients with RA and improve long-term health-economic benefits. This may be especially useful in people with RA and other risk factors for CVD.

5 Baseline analysis: Cardiovascular abnormalities exist in early rheumatoid arthritis

5.1 Abstract

5.1.0 Objectives

Mortality in RA is increased due to increased CVD. CMR can provide assessment of subclinical CVD but it is unknown if abnormalities exist in ERA. Our primary objective was to assess arterial stiffness, a surrogate marker for increased CVD risk, in ERA. Secondary objectives were to determine presence of CV abnormalities.

5.1.1 Methods

84 ERA patients without history of CVD underwent CMR at 3T. They had RA symptoms <1 year, had not received DMARDs and DAS28 ≥3.2. 30 healthy controls were prospectively age/sex matched to the first patients recruited.

5.1.2 Results

Aortic distensibility (AD) was reduced compared to controls (3.35±1.49 versus 4.70±1.95 $10^{-3}mmHg^{-1}$, p=0.003) after correction for age/sex and CV risk factors. Descending aortic diameter was increased in the ERA group (2.4 ±0.3cm versus 2.6 ±0.4cm, p=0.002). Cardiac structural change was evident with lower left ventricular mass/volume ratio (0.56±0.11 versus 0.6±0.10g/mL, p=0.007) and right ventricular volume (87±17 versus 82±17ml/m^2, p=0.036). ERA patients had increased myocardial extra-cellular volume fraction (27.4 ±3.5 versus 25.1 ±2.7%, p=0.001) and increased early diastolic strain rate (0.67 ± 0.03 versus 0.52 ± 0.15 $seconds^{-1}$, p=0.016). Aortic strain, compliance and stiffness index gave similar results. Higher CRP was associated with lower AD (13[29] versus 5[14]mg/L, p=0.027). Increasing CRP was associated with reduced peak systolic strain (r=0.250, p=0.038).

5.1.3 Conclusion

Abnormalities in vascular function, myocardial tissue composition and ventricular geometry/performance are present in ERA, inferring an increased risk of CVD at the earliest stages of the RA disease continuum.

5.2 Background

In established RA, various findings across multiple imaging modalities have supported concepts of microvascular pathology and accelerated atherosclerosis due to systemic inflammation[126, 128, 129, 144]. This may precede and contribute to the effects of coronary artery disease (CAD). The current knowledge gap in RA exists in knowing *when* CV risk increases and when CV abnormalities become identifiable. There have been no comprehensive, multi-parametric CMR studies of patients with ERA. This is becoming increasingly relevant given strategies of early use bDMARDs in attempt to interrupt progression along the RA disease continuum, and thereby the additional potential to impact on CV risk in ERA.

5.3 Methods

This study presents the baseline characteristics of ERA patients recruited to the CADERA trial, as described in chapter 4, and compares them to healthy non-RA controls. The methods are described in detail in chapter 4.

5.3.0 CMR details

Image analysis was performed off-line by BE and reproducibility studies were performed in a blinded fashion by BE/GF. Abnormal findings were further assessed by AKM and PS, with validation subsequently by SP/JPG. Scanning methods, parameters and formulae used are given in detail within chapter 4.

5.3.1 Statistical considerations

In addition to the statistical considerations described in chapters 3 and 4, AD was found to have a bimodal shaped distribution within the ERA group. Median AD was 3.21 10^{-3}mmHg^{-1} falling in the trough between these peaks on data exploration. AD was equally dichotomised to a <3.21 and a ≥3.21 10^{-3}mmHg^{-1} group for evaluation of differences between them.

5.4 Results

5.4.0 Demographics

93 ERA patients were invited and 84 ERA patients recruited. 9 were not scanned due to: claustrophobia (4); too large body habitus for scanner (2); needlephobia (1); scanner malfunction (2), with re-booking falling outside accepted trial timings. Figure 5-1 displays the recruitment flow chart. Demographics are presented in Table 5-1. The groups were well-matched for age and sex (p=0.65 and 0.70 respectively). No study participant had diabetes. Smoking was more prevalent in the ERA group (55% versus 30%, p=0.02) but other CV risk factors were similar. Rates of CV medication prescription overall and anti-hypertensives were similar, however there was increased primary prevention prescription in the healthy non-RA control group (anti-platelet and/or statin therapy) (2% versus 13%, p=0.04).

Figure 5-1 - Recruitment Flow Chart

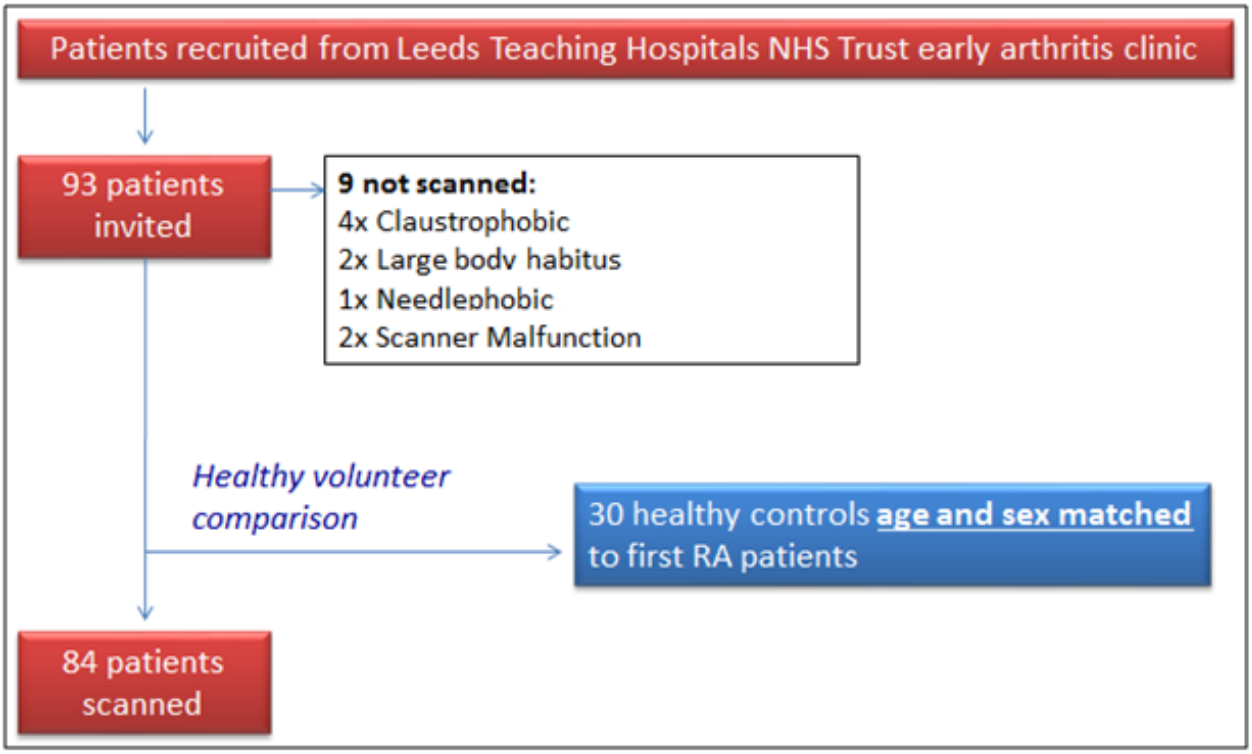


Table 5-1 - Demographic, clinical and RA disease characteristic data

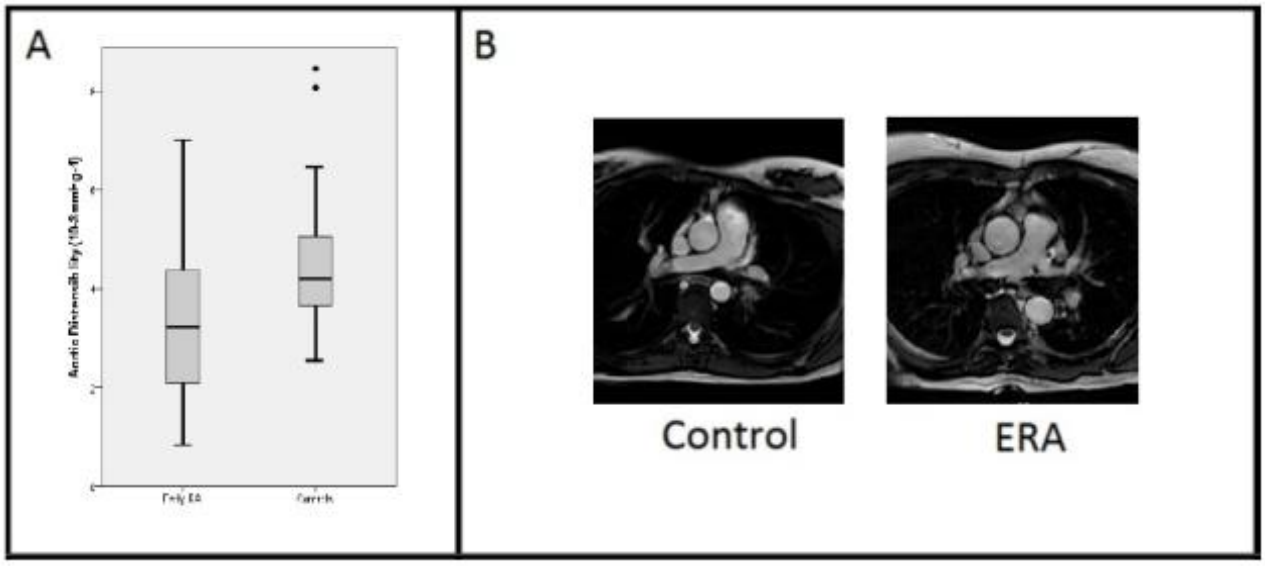
Characteristic	**Early RA N=84**	**Non-RA N=30**	**P Value**
Age, years	49 ± 13	50 ± 15	0.700
Female sex; n (%)	57 (68)	19 (63)	0.652
Weight, kg	73 ± 16	79 ± 17	0.062
Body mass index, kg/m^2	25.7 ± 4.5	27.1 ± 5.7	0.149
Current Smoker; n (%)	17 (20)	4 (13)	0.402
Ever smoked; n (%)	46 (55)	9 (30)	**0.020**
- Pack Years*	13 ± 13	6 ± 7	0.077
Hypertension; n (%)	7 (8)	3 (10)	0.721
Diabetes; n (%)	0 (0)	0 (0)	-
Family history of CVD; n (%)**	2 (2)	2 (7)	0.282
Hypercholesterolemia; n (%)	3 (4)	2 (7)	0.606
CV medication; n (%)	9 (11)	6 (20)	0.216
- Primary prevention; n (%)	2 (2)	4 (13)	**0.041**
- Anti-hypertensives; n (%)	9 (11)	3 (10)	1.000
DAS Score, median [IQR]	5.35 [1]	-	-
ESR, mm/hr, median [IQR]	30 [33]	-	-
CRP, mg/L, median [IQR]	8 [23]	-	-
RF; n (%)	61 (73)	-	-
ACPA; n (%)	72 (86)	-	-
Any seropositivity*; n (%)**	76 (91)	-	-

Data expressed as mean ± standard deviation unless otherwise stated. ACPA, anti-citrullinated peptide antibody; CRP, C-reactive protein; CV, cardiovascular; DAS Score, 3 variable 28 joint disease activity score using ESR; ESR, erythrocyte sedimentation rate; IQR, inter-quartile range; RA, rheumatoid arthritis; RF, rheumatoid factor; *Number of cigarettes per day x number of years smoked ÷ 20 = pack years; **defined as first degree relative with a history of CVD when 60 years old or younger if female, and 55 years old or younger if male; ***RF or ACPA positive.

5.4.1 Arterial stiffness in ERA versus non-RA controls

There was increased arterial stiffness in ERA with significantly lower AD (3.35 ±1.49 versus 4.70 ±1.95 10^{-3}mmHg^{-1}, p=0.003) after correction for age, sex and presence of CV risk factors (Figure 5-2, Figure 5-2 and Table 5-2**Error! Reference source not found.**). Aortic strain, arterial compliance and aortic stiffness index gave similar results. Descending thoracic aortic diameter was increased in the ERA group (2.4 ±0.3cm versus 2.6 ±0.4cm, p=0.002). On MVA, (Table 5-3), increased AD was associated with increasing age (r= -0.686, p<0.001) and male sex (r=0.424, p=0.007), presented in Figure 5-3. Despite associations with ESR and CRP on UVA, these did not continue to be significant in the regression model (Table 5-3 and Figure 5-3).

Figure 5-2 - Aortic distensibility between early RA patients and healthy non-RA controls



A; Box and whisker plot of AD between ERA and non-RA controls. B; Transverse images of increased ascending and descending aorta dimensions in ERA compared to RA.

Table 5-2 - Cardiovascular magnetic resonance imaging measurements in all study participants

CMR measurements	Early RA N=84	Non-RA N=30	Unadjusted P value	Adjusted for age, sex and CV risk factors*	
				P value	Mean difference (95% CI)
Aortic distensibility, 10^{-3}mmHg^{-1}	3.35 ± 1.49 N=83**	4.70 ± 1.95	**0.003**	**<0.001**	1.464 (0.966, 1.961)
Aortic strain, %	0.17 ± 0.07	0.25 ± 0.09	**<0.001**	**<0.001**	0.091 (0.069, 0.113)
Aortic compliance	12.0 ± 4.3	19.1 ± 7.1	**<0.001**	**<0.001**	7.128 (4.939, 9.317)
Aortic stiffness index, ß	4.1 ± 2.2	2.7 ± 0.84	**0.001**	**<0.001**	-1.482 (-2.184, -0.781)
LV end-diastolic volume indexed, ml/m^2	80 ± 13	80 ± 11	0.834	0.722	0.891 (-4.054, 5.837)
LV ejection fraction, %	61 ± 6	62 ± 5	0.308	0.460	0.836 (-1.400, 3.072)
LV mass indexed, g/m^2	44 ± 9	49 ± 8	**0.004**	**0.002**	5.134 (1.942, 8.326)
LV mass/volume ratio, g/ml	0.56 ± 0.11	0.62 ± 0.10	**0.004**	**0.007**	0.056 (0.016, 0.096)
RV end-diastolic volume indexed, ml/m^2	87 ± 17	92 ± 17	0.103	**0.036**	6.896 (0.471, 13.320)
RV ejection fraction, %	54 ± 5	54 ± 6	0.790	0.599	-0.609 (-2.902, 1.683)
Peak systolic strain	-0.23 ± 0.03	-0.23 ± 0.02	0.865	0.769	0.001 (-0.008, 0.011)
Peak systolic strain rate, seconds^{-1}	1.14 ± 0.15	1.15 ± 0.12	0.870	0.927	-0.003 (-0.066, 0.060)
Early diastolic strain rate, seconds^{-1}	0.67 ± 0.30	0.52 ± 0.15	**0.019**	**0.016**	-0.146 (-0.264, -0.028)
Late diastolic strain rate, seconds^{-1}	1.45 ± 0.34	1.50 ± 0.27	0.430	0.440	0.051 (-0.079, 0.180)
Peak twist, degrees	15.5 ± 4.0	15.9 ± 4.4	0.646	0.577	0.493 (-1.256, 2.242)
Torsion, degrees	13.8 ± 3.5	14.9 ± 4.5	0.151	0.151	1.117 (-0.415, 2.648)
Native T1, ms	1183 ± 41	1202 ± 35	**0.026**	**0.018**	20.391 (3.543, 37.239)
Extra-cellular volume fraction, %	27.4 ± 3.5	25.1 ± 2.7	**0.001**	**0.001**	-0.025 (-0.039, -0.011)
Presence of LGE; n (%)	8 (11) N=76	1 (3)	0.440	0.117	-0.097 (-0.220, 0.025)
Descending aortic diameter, cm	2.6 ± 0.4	2.4 ± 0.3	**0.002**	**0.002**	0.096 (0.036, 0.156)
Qualitative stress perfusion defect; n (%)	0 (0) N=71	0 (0)	-	-	-

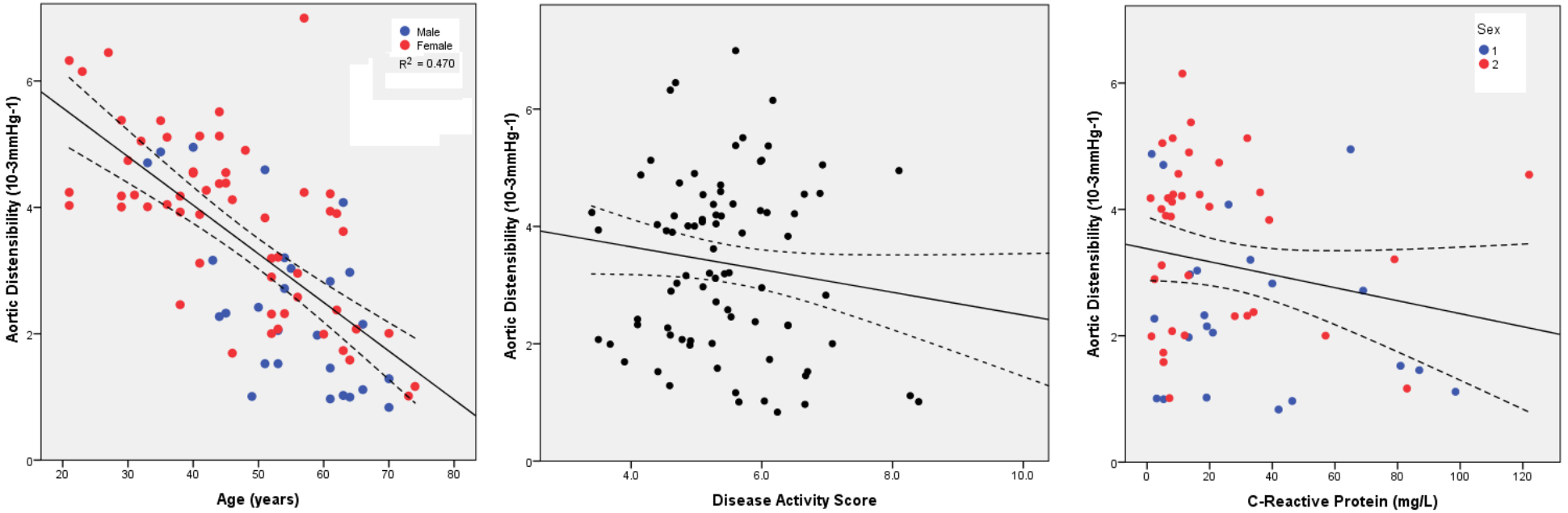
Data expressed as mean ± standard deviation unless otherwise stated. CV, cardiovascular; RA, rheumatoid arthritis; CV, cardiovascular; LGE. Late-gadolinium enhancement; LV, left ventricular. *CV risk factors defined as: hypertension (history of hypertension or anti-hypertensive agent), dyslipidaemia (history of dyslipidaemia or on lipid-lowering medication), ever smoked and family history of premature CVD. **One study was uninterpretable due to imaging artefact.

Table 5-3 - Univariate and multivariate analysis of variables with aortic distensibility

Characteristic	Aortic Distensibility				
	Univariate			Multivariate	
	Correlation Coefficient	Beta (95% CI)	P Value	Beta (95% CI)	P Value
Age	**-0.686**	**-0.077 (-0.095, -0.059)**	**<0.001**	**-0.066 (-0.086, -0.047)**	**<0.001**
Sex	**0.424**	**1.344 (0.709, 1.978)**	**<0.001**	**0.768 (0.212, 1.325)**	**0.007**
Current Smoker	0.052	0.190 (-0.623, 1.002)	0.644		
Hypertension	**-0.270**	**-1.548 (-2.769, -0.327)**	**0.014**	0.030 (-0.958, 1.019)	0.951
Family history of CVD*	-0.110	-1.070 (-3.197, 1.058)	0.320		
Hypercholesterolemia	-0.096	-0.767 (-2.517, 0.984)	0.386		
DAS Score	**-0.188**	**-0.194 (-0.418, 0.030)**	**0.089**	0.008 (-0.173, 0.189)	0.930
ESR	**-0.263**	**-0.014 (-0.025, -0.003)**	**0.016**	-0.004 (-0.016, 0.007)	0.472
CRP	**-0.255**	**-0.015 (-0.027, -0.002)**	**0.020**	0.001 (-0.012, 0.013)	0.912
RF	0.069	0.228 (-0.504, 0.960)	0.537		
ACPA	**0.188**	**0.792 (-0.125, 1.709)**	**0.089**	0.446 (-0.352, 1.244)	0.269
Any seropositivity**	0.104	0.522 (-0.584, 1.628)	0.350		

ACPA, anti-citrullinated peptide antibody; CRP, C-reactive protein; CVD, cardiovascular disease; DAS Score, 3 variable 28 joint disease activity score using ESR; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; *defined as first degree relative with a history of CVD when 60 years old or younger if female, and 55 years old or younger if male; **RF or ACPA positive.

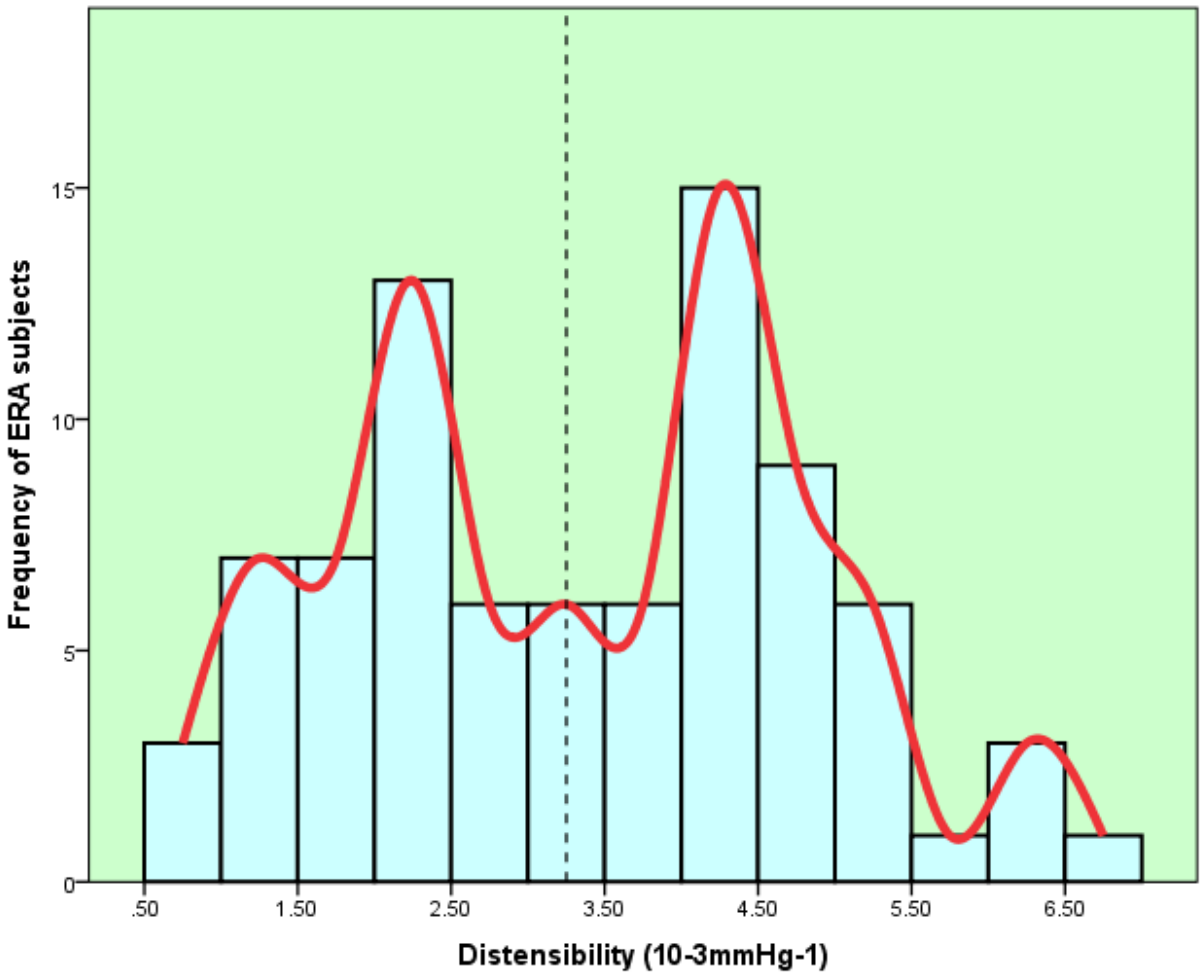
Figure 5-3 - Analysis of variables as compared with aortic distensibility in Early RA patients



5.4.2 Arterial stiffness versus RA disease activity markers and traditional CV risk factors

AD was found to have a bimodal shaped distribution (Figure 5-4). Median AD was 3.21 10^{-3}mmHg^{-1} falling in the trough between these peaks on data exploration. AD was equally dichotomised to a <3.21 and a ≥3.21 group. These data are shown in Table 5-4. Importantly, none of the demographic, clinical and RA disease characteristics had a bimodal distribution. Increased CRP was found in the lower AD group (median[IQR] 13[29] versus 5[14]mg/L, p=0.027) along with increasing age, male sex, hypertension and smoking. ERA patients with lower AD tended also to have an increased BMI.

Figure 5-4 - Histogram of aortic distensibility in all early RA patients



Line of best fit overlying the frequency histogram. The dashed central line represents the median aortic distensibility dichotomising the two peaks of the bimodal distribution.

Table 5-4 - Demographic, clinical and RA disease characteristic data between high and low AD groups within ERA

Characteristic	AD < 3.21 N=42	AD ≥ 3.21 N=41	P Value
Age, years	57 ± 9	41 ± 12	**<0.001**
Female sex; n (%)	20 (48)	36 (88)	**<0.001**
Weight, kg	77 ± 16	68 ± 14	**0.006**
Body mass index, kg/m^2	26.7 ± 4.4	24.6 ± 4.5	**0.038**
Current Smoker; n (%)	8 (19)	9 (22)	0.743
Ever smoked; n (%)	28 (67)	18 (44)	**0.037**
Pack Years*	13 ± 13	15 ± 14	0.847
Hypertension; n (%)	6 (14)	0 (0)	**0.026**
Family history of CVD; n (%)**	2 (5)	0 (0)	0.494
Hypercholesterolemia; n (%)	2 (5)	1 (3)	1.000
CV medication; n (%)	6 (14)	2 (5)	0.265
- Primary prevention; n (%)	2 (5)	0 (0)	0.494
- Anti-hypertensives; n (%)	6 (14)	2 (5)	0.265
DAS Score, median [IQR]	5.38 [1.60]	5.30 [1.28]	0.689
ESR, mm/hr, median [IQR]	31 [42]	28 [27]	0.353
CRP, mg/L, median [IQR]	13 [29]	5 [14]	**0.027**
RF; n (%)	28 (67)	32 (78)	0.247
ACPA; n (%)	33 (79)	38 (93)	0.068
Any seropositivity*; n (%)**	36 (86)	75 (90)	0.265

Data expressed as mean ± standard deviation unless otherwise stated. ACPA, anti-citrullinated peptide antibody; AD, aortic distensibility; CRP, C-reactive protein; CV, cardiovascular; DAS Score, 3 variable 28 joint disease activity score using ESR; ERA, early RA; ESR, erythrocyte sedimentation rate; IQR, inter-quartile range; RA, rheumatoid arthritis; RF, rheumatoid factor; *Number of cigarettes per day x number of years smoked ÷ 20 = pack years; **defined as first degree relative with a history of CVD when 60 years old or younger if female, and 55 years old or younger if male; ***RF or ACPA positive.

5.4.3 Arterial stiffness versus other CMR characteristics

On UVA analysis, a number of CV changes were present between the higher and lower AD groups. Lower AD had higher LV mass (47 ±10 versus 42 ±7g/m^2, p=0.023) and impaired peak systolic strain (-0.22 ±0.03 versus -0.24 ±0.02, p=0.011) and strain-rate. Diastolic strain rate was also lower in the low AD group. Once corrected to age, sex and CV risk factors only myocardial tissue composition differed with increased ECV associated with higher AD (Figure 5-5 and Table 5-5).

Figure 5-5 - Myocardial tissue composition between higher and lower AD groups

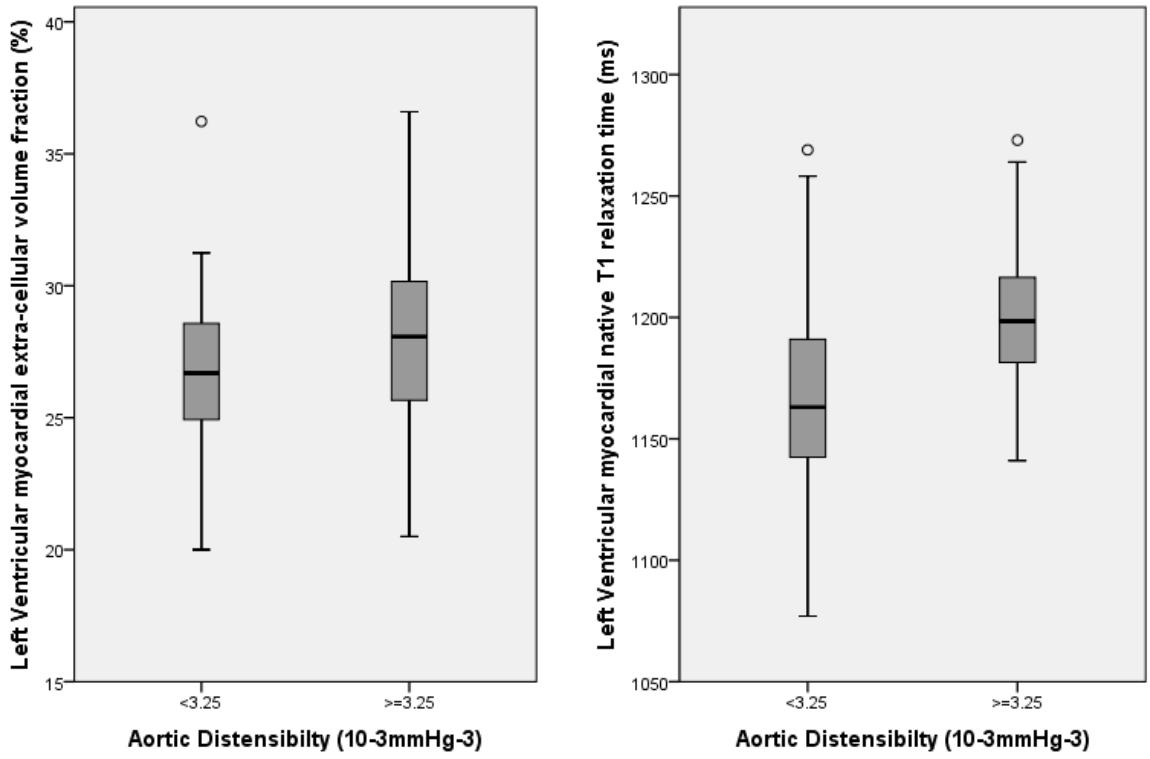


Table 5-5 - CMR measurements between high and low AD groups within ERA

CMR measurements	AD < 3.25 N=42	AD ≥ 3.25 N=41	Unadjusted P value	Adjusted for age, sex and CV risk factors	
				P value	Mean difference (95% CI)
LV end-diastolic volume indexed, ml/m^2	78 ± 12	83 ± 14	0.083	0.138	5.262 (-1.731, 12.256)
LV ejection fraction, %	60 ± 6	62 ± 5	0.098	0.343	1.517 (-1.649, 4.683)
LV mass indexed, g/m^2	47 ± 10	42 ± 7	**0.023**	0.791	-0.578 (-4.894, 3.739)
LV mass/volume ratio, g/ml	0.60 ± 0.11	0.50 ± 0.08	**<0.001**	0.154	-0.038 (-0.090, 0.014)
RV end-diastolic volume indexed, ml/m^2	84 ± 17	90 ± 15	0.103	0.181	5.769 (-2.743, 14.281)
RV ejection fraction, %	54 ± 5	54 ± 5	0.642	0.254	-1.724 (-4.708, 1.261)
Peak systolic strain	-0.22 ± 0.03	-0.24 ± 0.02	**0.011**	0.350	-0.007 (-0.021, 0.008)
Peak systolic strain rate, seconds^{-1}	1.11 ± 0.15	1.17 ± 0.14	**0.036**	0.404	0.039 (-0.053, 0.131)
Early diastolic strain rate, seconds^{-1}	0.61 ± 0.27	0.72 ± 0.32	0.091	0.724	0.033 (-0.153, 0.219)
Late diastolic strain rate, seconds^{-1}	1.36 ± 0.03	1.54 ± 0.38	**0.019**	0.704	-0.036 (-0.226, 0.153)
Peak twist, degrees	16.1 ± 3.9	14.9 ± 4.02	0.166	0.344	-1.134 (-3.509, 1.241)
Torsion, degrees	14.5 ± 3.6	13.1 ± 3.3	0.085	0.724	-0.344 (-2.276, 1.589)
Native T1, ms	1169 ± 46	1198 ± 28	**0.001**	**0.049**	**23.456 (0.075, 46.837)**
Extra-cellular volume fraction, %	26.6 ± 3.2	28.2 ± 3.7	**0.038**	**0.011**	**0.027 (0.006, 0.048)**
Presence of LGE; n (%) N=76	5 (12) N=41	3 (9) N=35	0.719	0.669	0.041 (-0.151, 0.233)

Data expressed as mean ± standard deviation unless otherwise stated. CV, cardiovascular; RA, rheumatoid arthritis; CV, cardiovascular; LGE. Late-gadolinium enhancement; LV, left ventricular. *CV risk factors defined as: hypertension (history of hypertension or anti-hypertensive agent), dyslipidaemia (history of dyslipidaemia or on lipid-lowering medication), ever smoked and family history of premature CVD. **One study was uninterpretable due to imaging artefact.

5.4.4 Cardiac structure and function in ERA

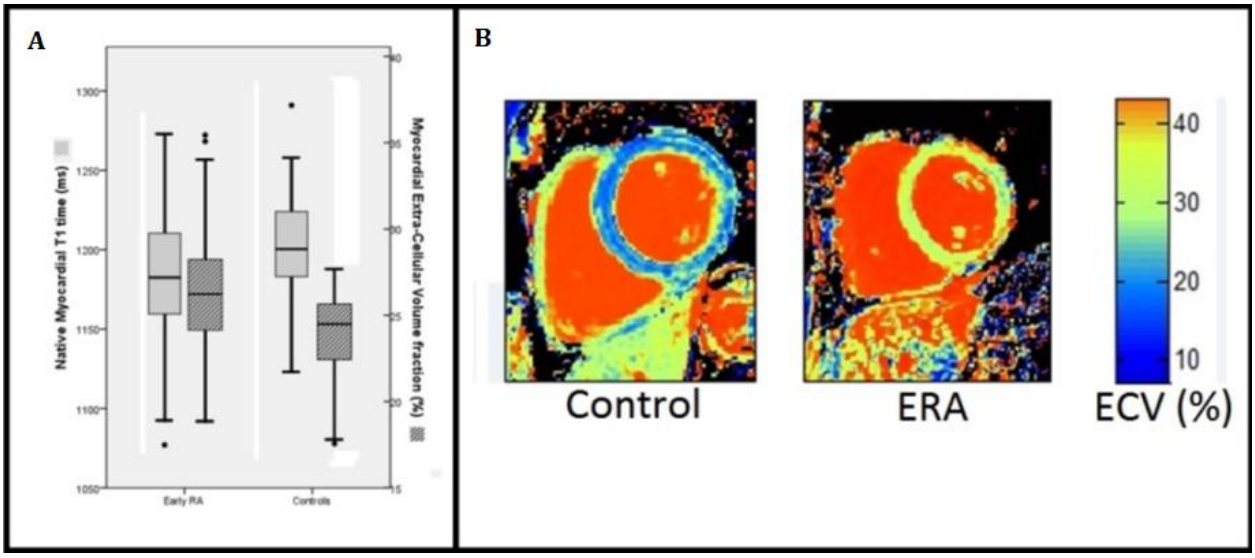
LV mass was significantly lower in the ERA group, in absolute values and when corrected to body surface area (BSA) (44 ±9 versus 49 ±8 g/m2, p=0.002). LV mass/volume ratio takes into account the LV end-diastolic volume (EDV) and the difference in LV mass was further shown with a lower LV mass/volume ratio (0.56 ±0.11 versus 0.62 ±0.10 g/mL, p=0.007). In the right ventricle (RV), the EDV, also indexed to BSA, showed a smaller cavity size in ERA (87 ± 17 versus 92 ± 17 ml, p=0.036) although remained within normal CMR nomograms.

Systolic performance, assessed by LV and RV ejection fraction, was not significantly different between ERA and controls (Table 5-2). LV peak systolic strain and strain-rate were also similar. Several measures of diastology were assessed and early diastolic strain rate showed a significant difference compared to controls (0.67 ±0.03 versus 0.52 ±0.15 seconds^{-1}, p=0.016).

71 of the 84 ERA patients underwent adenosine stress first-pass myocardial perfusion imaging to look for stress-induced hypoperfusion. All patients were offered to undergo this but 13 declined to have a symptom-inducing measurement performed. Qualitative visual analysis of all 101 participants who completed the imaging revealed no evidence of reversible ischaemia indicative of silent flow-limiting CAD.

Native myocardial T1 relaxation time and extra-cellular volume (ECV) fraction were both significantly different between ERA and controls (Table 5-2). There was increased ECV in ERA (27.4 ±3.5 versus 25.1 ±2.7%, p=0.001) with colour mapping showing a diffuse process (Figure 5-6). 8 patients did not have appropriate LGE imaging due to: scanner malfunction; image degradation; and patient wanting to cease test due to length of time. Hyperenhancement by LGE imaging was seen more in ERA than controls but not to significance (8 (11%) versus 1 (3%), p=0.117). The hyperenhancements seen were focal non-ischaemic patterns and distributed as follows; lateral wall 1 (13%), septum 1 (13%) and right-ventricular insertion points 6 (75%) (Figure 5-8).

Figure 5-6 - Myocardial tissue composition between early RA patients and non-RA controls



A; Box and whisker plot of Native T1 and extra-cellular volume (ECV) fraction between early RA and non-RA controls. B; Short-axis left-ventricular ECV maps at the mid-ventricle showing diffusely increased ECV in early RA compared to non-RA control.

Figure 5-7 - LV mass/volume ratio and RV dimension between Early RA and non-RA controls

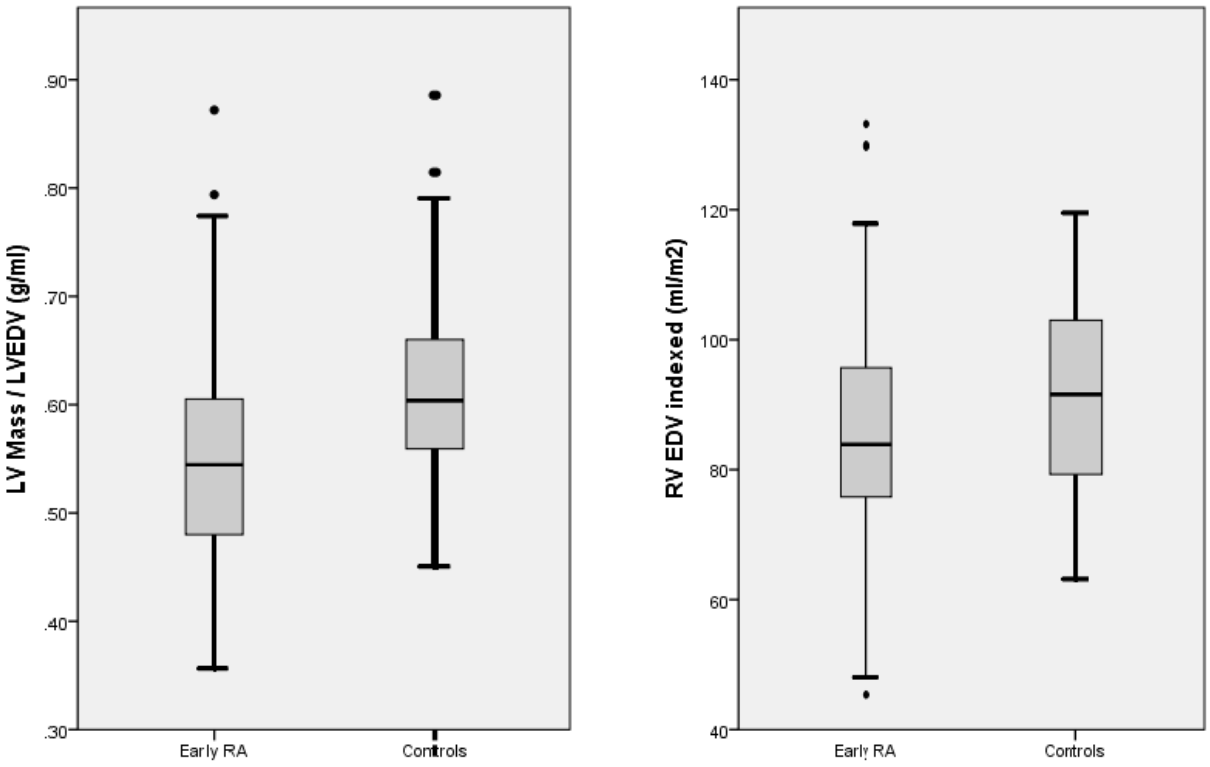
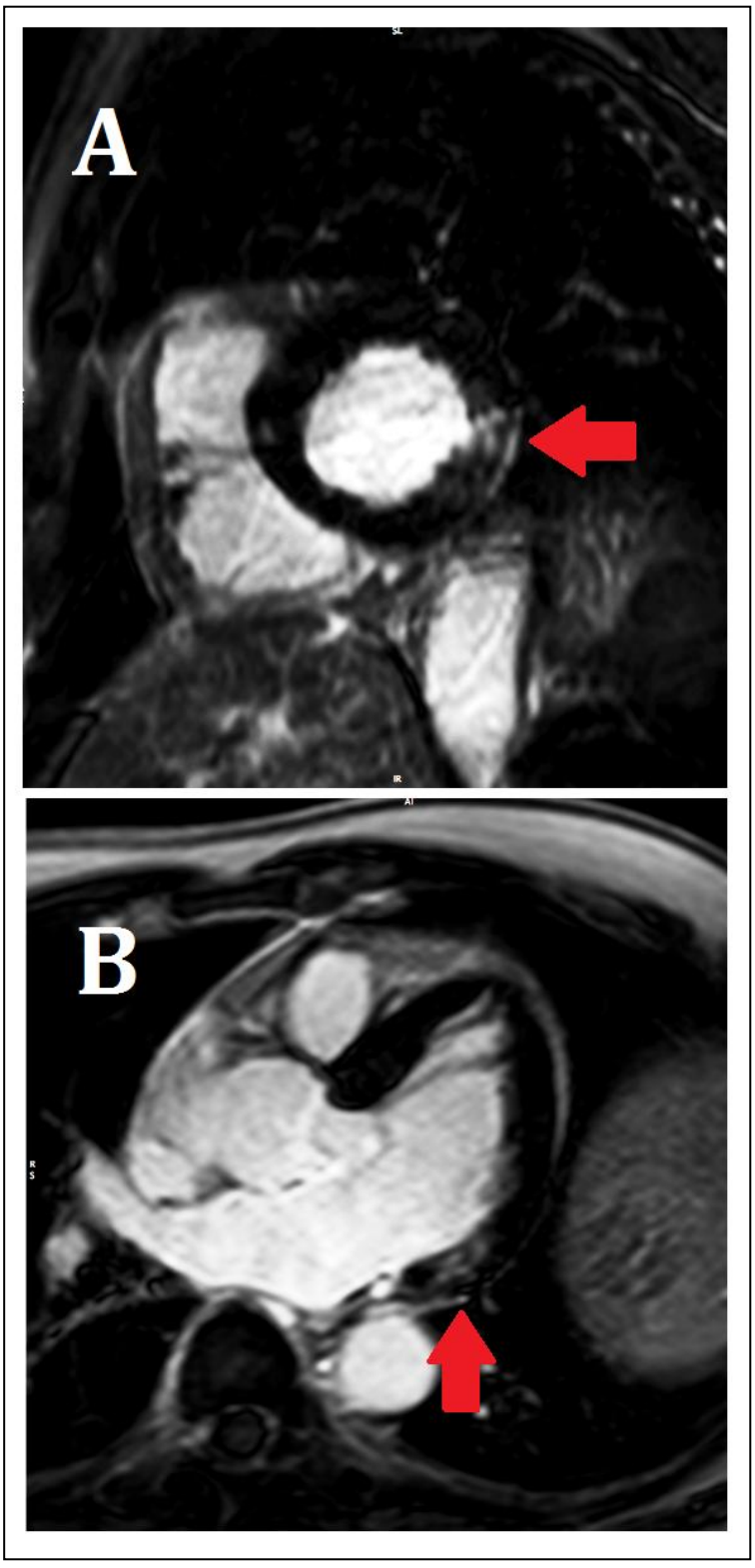


Figure 5-8 - Late-gadolinium enhancement in ERA patient



Panel A, Mid ventricular short axis LGE image; Panel B, 3-chamber LGE image.

Red arrows highlight patchy, intra-myocardial hyper-enhancement.

5.4.5 RA disease activity markers and traditional CV risk factors

T1, ECV, RVEDV indexed to BSA, LV Mass/LVEDV, Torsion and peak systolic strain were analysed in a MVA (Table 5-6, Table 5-7 and Table 5-8). These measurements were significantly different compared to control and/or previously described in established RA populations[64, 83, 84, 87]. The DAS score did not correlate with any CV abnormalities (Table 5-3, Table 5-4, Table 5-6, Table 5-7, Table 5-8 and Figure 5-11). RF and ACPA also did not correlate with any CV abnormalities; whether assessed within the whole ERA group or when seropositive only subjects were analysed. There was a trend, that didn't reach statistical significance, for increasing ESR and increased ECV (r=0.197, p=0.080) (Figure 5-9 and Table 5-6). Increasing CRP did correlate with reduced peak systolic strain (r=0.250, p=0.038, Figure 5-10).

Age was a powerful factor in multiple CV abnormalities (Figure 5-12, Table 5-3, Table 5-6, Table 5-7 and Table 5-8). Increasing age was associated with lower native T1 (r=-0.374, p=0.002), lower AD (r=-0.686, p<0.001), lower RVEDV-i (r=-0.314, p=0.003) and higher LVM/LVEDV (r=0.439, p=0.008). Traditional CV risk factors were associated with further CV abnormalities and were more powerful than RA disease activity markers after MVA (Table 5-3, Table 5-6, Table 5-7 and Table 5-8). Male sex correlated with lower AD (r=0.424, p=0.011) and higher LV mass (LVM/LVEDV, r= -0.412, p=0.007). Hypertension was associated with higher LVM/LVEDV (r=0.416, p=0.012) and increased LV torsion (r=0.317, p=0.005). Increased smoking pack years was also associated with increased LV torsion (r=0.327, p=0.012). These are shown as box-an-whisker plots and scatter plots in Figure 5-13.

Figure 5-9 - Scatter plot of erythrocyte sedimentation rate and myocardial extra-cellular volume

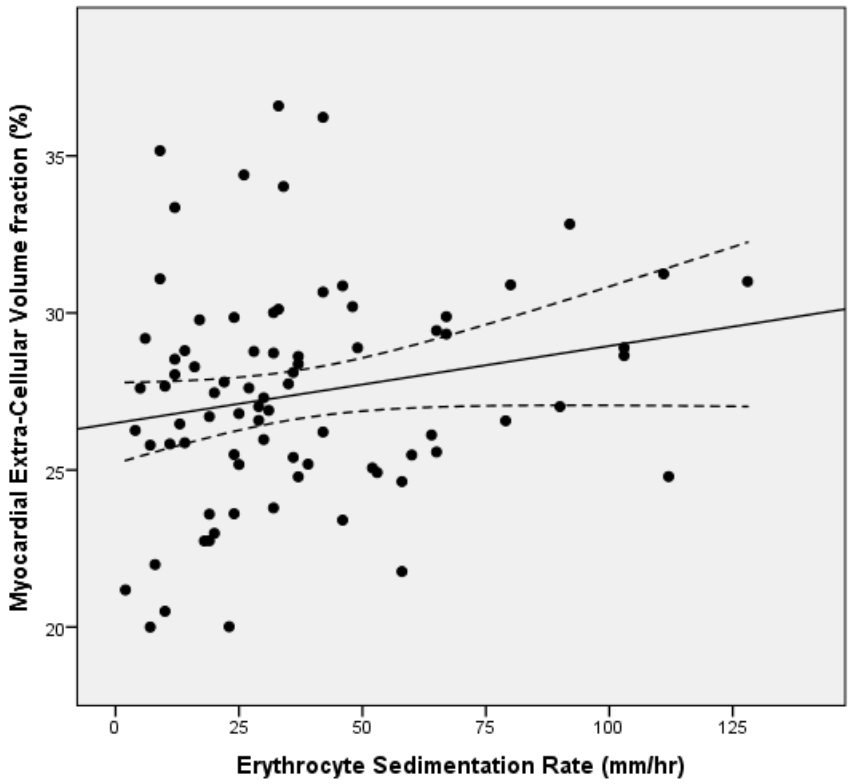


Figure 5-10 - Scatter plot of C-reactive protein and left ventricular systolic strain

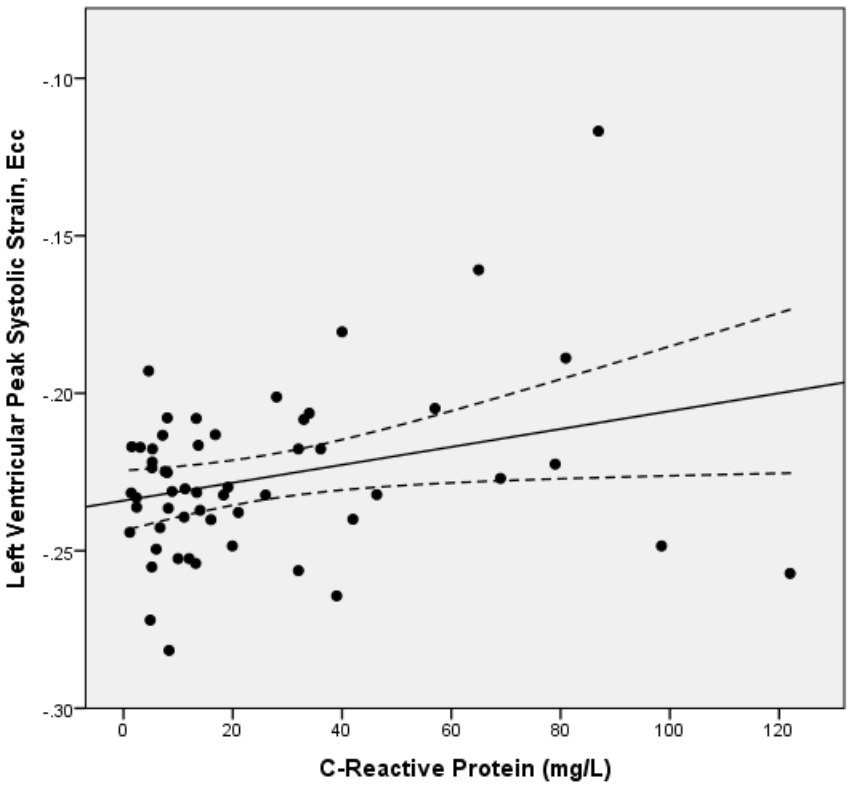


Figure 5-11 - Scatter plots of RA disease activity scores versus cardiac structural measurements

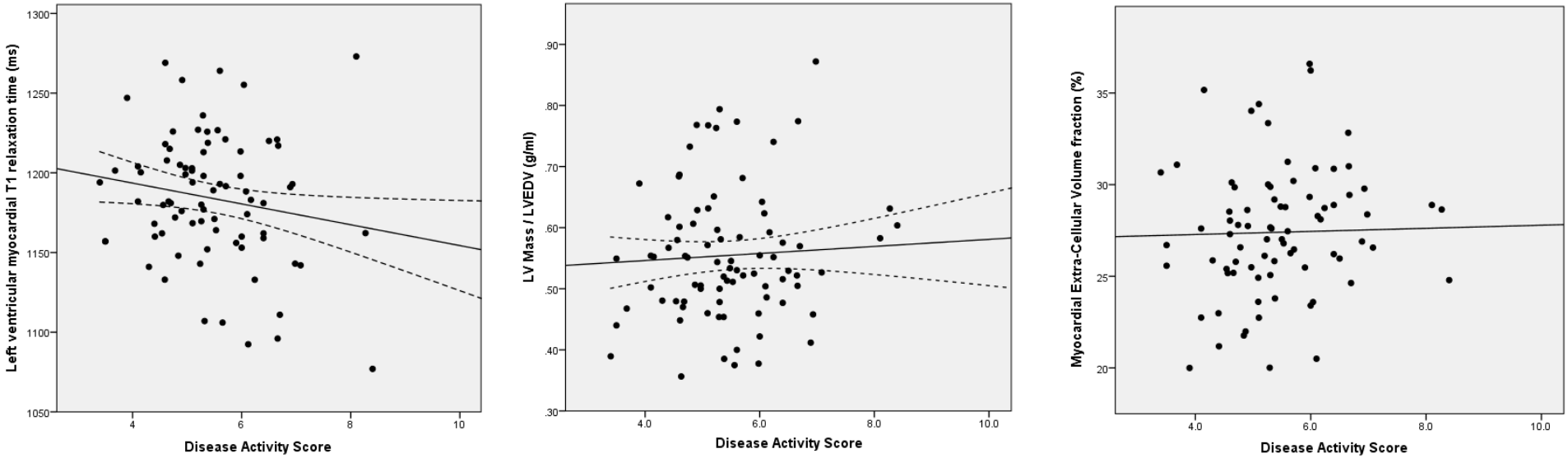


Figure 5-12 - Scatter plots of age versus cardiac structural measurements in early RA

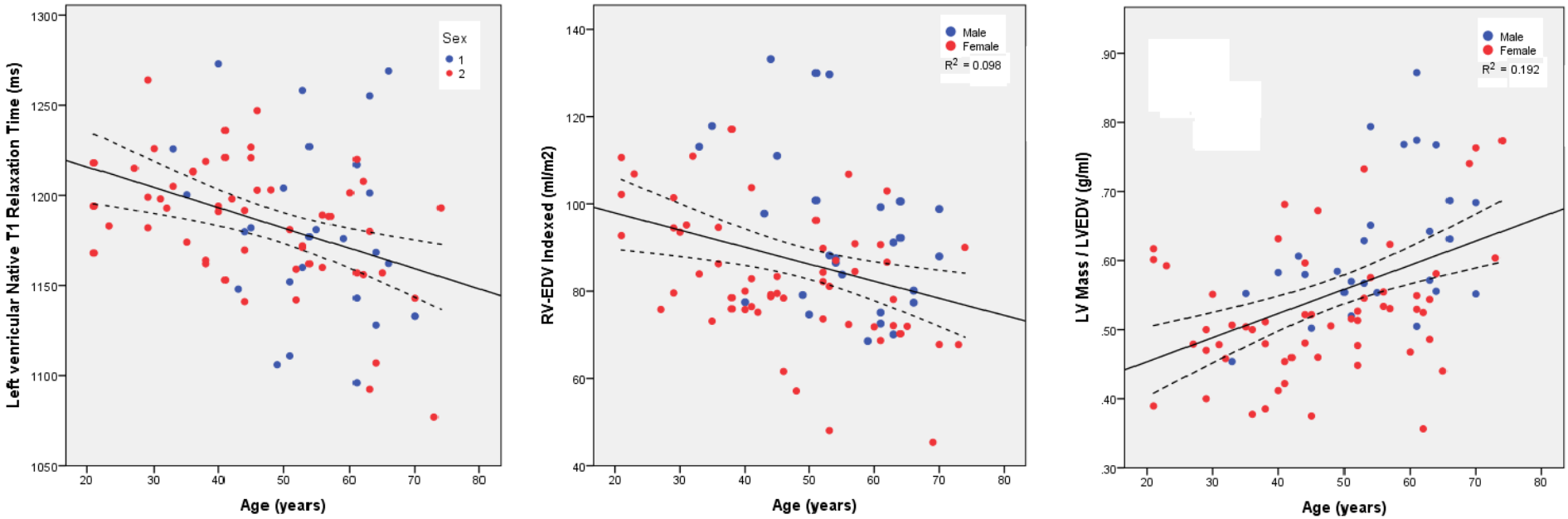


Figure 5-13 - Traditional cardiovascular risk factors versus cardiovascular structural measurements

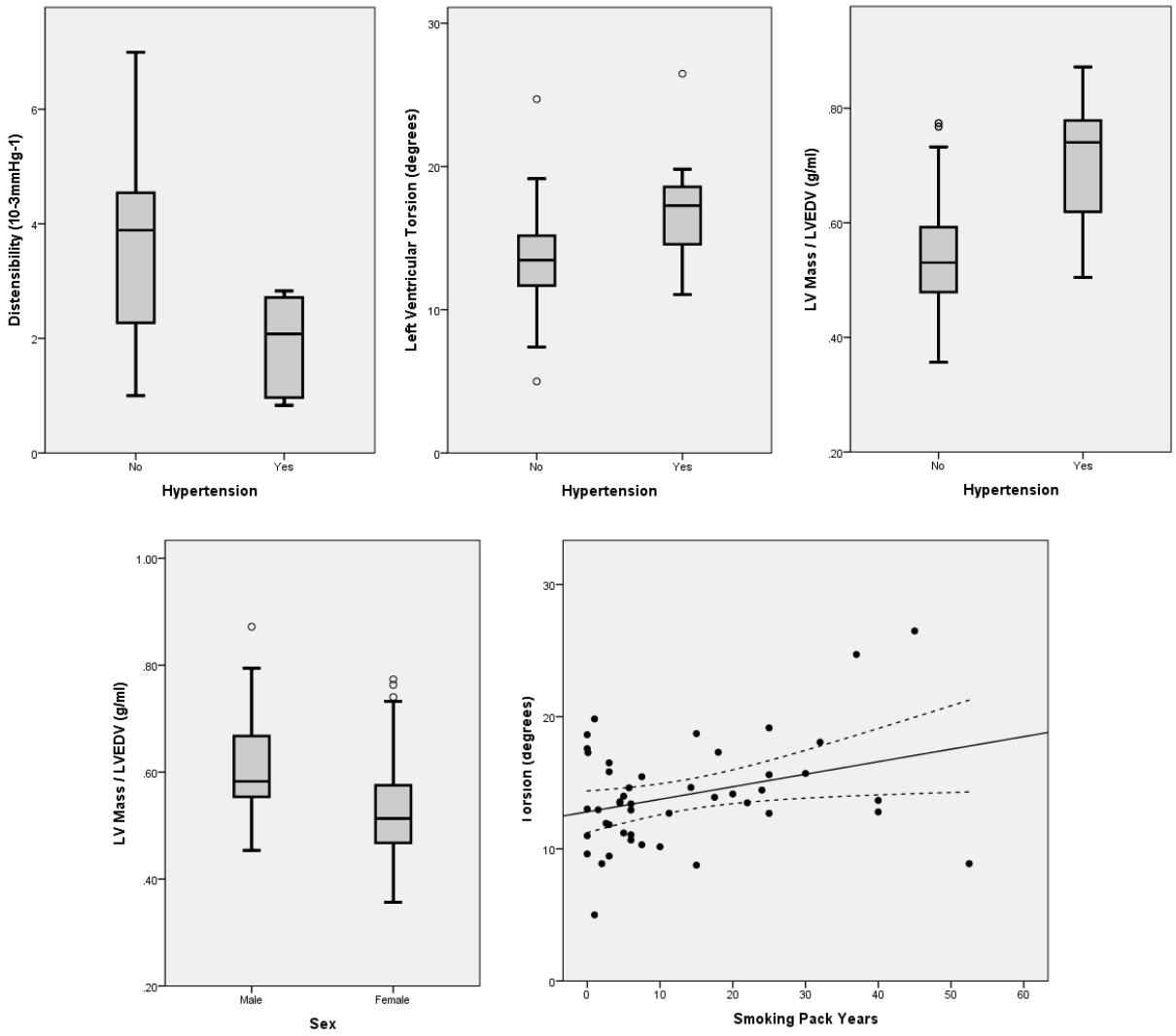


Table 5-6 - Univariate and multivariate analysis of variables with native T1 and ECV

Characteristic	T1					ECV		
	Univariate			Multivariate		Univariate		
	Correlation Coefficient	Beta (95% CI)	P Value	Beta (95% CI)	P Value	Correlation Coefficient	Beta	P Value
Age	**-0.374**	**-1.127 (-1.756, -0.497)**	**0.001**	**-1.017 (-1.659, -0.375)**	**0.002**	0.029	0.0000748 (- 0.001, 0.001)	0.800
Sex	0.055	4.675 (-14.581, 23.930)	0.630			0.153	0.011 (-0.005, 0.028)	0.174
Current Smoker	-0.069	-3.089 (-13.166, 6.988)	0.543			-0.081	0.002 (-0.019, 0.023)	0.834
Ever smoked	-0.047	-3.826 (-22.095, 14.442)	0.678			-0.065	-0.005 (-0.020, 0.011)	0.570
Pack Years	-0.214	-0.685 (-1.615, 0.244)	0.144			0.175	0.000 (0.000, 0.001)	0.233
Hypertension	-0.163	-25.106 (-59.260, 9.049)	0.147			0.041	0.005 (-0.024, 0.035)	0.718
Family history of CVD	-0.003	-0.878 (-59.284, 57.528)	0.976			-0.083	-0.019 (-0.069, 0.032)	0.465
Hypercholesterolemia	-0.133	-28.422 (-75.990, 19.146)	0.238			-0.141	-0.026 (-0.067, 0.015)	0.212
Any CV risk factor	-0.086	-7.098 (-25.552, 11.356)	0.446			-0.132	-0.009 (-0.025, 0.006)	0.242
DAS Score	**-0.236**	**-6.535 (-12.589, -0.481)**	**0.035**	-4.406 (-10.296, 1.484)	0.140	0.035	0.001 (-0.005, 0.006)	0.756
ESR	-0.170	-0.246 (-0.567, 0.075)	0.131			**0.197**	**0.000 (0.000, 0.001)**	**0.080**
CRP	-0.007	-0.011 (-0.359, 0.336)	0.948			0.152	0.000 (0.000, 0.000)	0.179
RF	0.119	10.593 (-9.413, 30.598)	0.295			-0.032	-0.002 (-0.020, 0.015)	0.780
ACPA	0.132	14.958 (-10.356, 40.272)	0.243			-0.104	-0.010 (-0.032, 0.012)	0.359
Any seropositivity	0.163	21.951 (-8.039, 51.942)	0.149			-0.110	-0.013 (-0.039, 0.013)	0.331

Table 5-7 - Univariate and multivariate analysis of variables with RVEDV-i and LVM/LVEDV

Characteristic	RVEDVi					LVM/LVEDV				
	Univariate			Multivariate		Univariate			Multivariate	
	Correlation Coefficient	**Beta (95% CI)**	**P Value**	**Beta (95% CI)**	**P Value**	**Correlation Coefficient**	**Beta (95% CI)**	**P Value**	**Beta (95% CI)**	**P Value**
Age	**-0.314**	**-0.391 (-0.651, -0.131)**	**0.004**	**-0.516 (-0.853, -0.178)**	**0.003**	**0.439**	**0.003 (0.002, 0.005)**	**<0.001**	**0.002 (0.001, 0.004)**	**0.008**
Sex	**-0.289**	**-10.258 (-17.736, -2.779)**	**0.008**	-8.114 (-16.772, 0.543)	0.066	**-0.412**	**-0.094 (-0.139, -0.048)**	**<0.001**	**-0.061 (-0.105, -0.017)**	**0.007**
Body surface area, m^2	**0.276**	**20.485 (4.842, 36.127)**	**0.011**	6.477 (-13.129, 26.083)	0.510	**0.197**	**0.093 (-0.009, 0.196)**	**0.072**	-0.019 (-0.124, 0.087)	0.727
Current Smoker	-0.058	-2.399 (-11.463, 6.665)	0.600			-0.084	-0.022 (-0.080, 0.036)	0.447		
Ever smoked	-0.063	-2.089 (-9.404, 5.225)	0.571			0.099	0.021 (-0.025, 0.068)	0.370		
Pack Years	**-0.267**	**-0.310 (-0.631, 0.012)**	**0.058**	-0.109 (-0.448, 0.230)	0.522	0.052	0.000 (-0.002, 0.003)	0.717		
Hypertension	-0.162	-9.757 (-22.780, 3.266)	0.140			**0.416**	**0.160 (0.083, 0.237)**	**<0.001**	**0.097 (0.022, 0.173)**	**0.012**
Family history of CVD	-0.013	-1.399 (-25.324, 22.525)	0.908			**0.199**	**0.138 (-0.012, 0.288)**	**0.070**	0.104 (-0.025, 0.234)	0.112
Hypercholesterolemia	-0.178	-15.961 (-35.302, 3.380)	0.104			0.131	0.075 (-0.050, 0.199)	0.236		
Any CV risk factor	-0.146	-4.959 (-12.348, 2.430)	0.186			**0.193**	**0.042 (-0.005, 0.089)**	**0.079**	0.012 (-0.035, 0.058)	0.624
DAS Score	-0.065	-7.49 (-3.287, 1.789)	0.559			0.078	0.006 (-0.010, 0.022)	0.481		
ESR	-0.176	-0.105 (-0.234, 0.024)	0.110			**0.229**	**0.001 (0.000, 0.002)**	**0.036**	0.0000441 (-0.001, 0.001)	0.977
CRP	-0.089	-0.057 (-0.198, 0.084)	0.422			**0.285**	**0.001 (0.000, 0.002)**	**0.009**	-0.046 (-0.106, 0.015)	0.196
RF	**-0.261**	**-9.724 (-17.620, -1.827)**	**0.016**	0.489 (-9.872, 10.850)	0.925	-0.163	-0.039 (-0.090, 0.013)	0.139		
ACPA	-0.057	-2.706 (-13.113, 7.701)	0.606			**-0.284**	**-0.086 (-0.150, -0.022)**	**0.009**	-0.038 (-0.097, 0.021)	0.205
Any seropositivity	-0.157	-8.855 (-21.128, 3.418)	0.155			-0.150	-0.054 (-0.133, 0.024)	0.174		

Table 5-8 - Univariate and multivariate analysis of variables with LV Torsion and peak systolic strain

Characteristic	Torsion					Peak Systolic Strain				
	Univariate			Multivariate		Univariate			Multivariate	
	Correlation Coefficient	**Beta (95% CI)**	**P Value**	**Beta (95% CI)**	**P Value**	**Correlation Coefficient**	**Beta (95% CI)**	**P Value**	**Beta (95% CI)**	**P Value**
Age	**0.342**	**0.091 (0.034, 0.147)**	**0.002**	0.080 (-0.023, 0.183)	0.126	0.170	0.000 (0.000, 0.001)	0.133		
Sex	0.081	0.599 (-1.077, 2.275)	0.479			**-0.386**	**-0.021 (-0.033, -0.010)**	**<0.001**	-0.011 (-0.027, 0.004)	0.155
Body surface area, m^2	-0.043	-0.676 (-4.234, 2.882)	0.706			**0.213**	**0.025 (-0.001, 0.051)**	**0.060**	-0.012 (-0.050, 0.025)	0.513
Current Smoker	-0.134	-1.158 (-3.106, 0.791)	0.240			0.036	0.002 (-0.012, 0.017)	0.750		
Ever smoked	0.086	0.599 (-0.977, 2.174)	0.451			0.037	0.002 (-0.010, 0.014)	0.745		
Pack Years	**0.327**	**0.095 (0.012, 0.178)**	**0.027**	**0.101 (0.024, 0.178)**	**0.012**	**-0.323**	**-0.001 (-0.001, 0.000)**	**0.029**	0.000 (-0.001, 0.000)	0.683
Hypertension	**0.317**	**3.887 (1.250, 6.523)**	**0.004**	**4.932 (1.536, 8.329)**	**0.005**	0.006	0.001 (-0.020, 0.021)	0.958		
Family history of CVD	-0.075	-1.657 (-6.673, 3.360)	0.513			**0.340**	**0.057 (0.021, 0.092)**	**0.002**	0.043 (-0.011, 0.140)	0.130
Hypercholesterolemia	-0.031	-0.559 (-4.691, 3.574)	0.789			**0.336**	**0.046 (0.017, 0.075)**	**0.002**	0.024 (-0.019, 0.067)	0.260
Any CV risk factor	0.059	0.419 (-1.181, 2.018)	0.604			0.138	0.007 (-0.005, 0.019)	0.226		
DAS Score	-0.010	-0.024 (-0.560, 0.512)	0.930			0.153	0.003 (-0.001, 0.007)	0.177		
ESR	-0.001	0.000 (-0.029, 0.029)	0.993			0.114	0.000 (0.000, 0.000)	0.315		
CRP	-0.064	-0.009 (-0.040, 0.022)	0.577			**0.250**	**0.000 (0.000, 0.000)**	**0.026**	**0.000 (0.000, 0.001)**	**0.038**
RF	-0.180	-1.401 (-3.135, 0.333)	0.112			-0.011	-0.001 (-0.014, 0.013)	0.926		
ACPA	**-0.261**	**-2.529 (-4.654, -0.403)**	**0.020**	-2.154 (-6.265, 1.956)	0.296	-0.074	-0.005 (-0.022, 0.011)	0.515		
Any seropositivity	-0.035	-0.401 (-3.019, 2.217)	0.761			-0.108	-0.009 (-0.029, 0.010)	0.345		

5.4.6 Reproducibility

Our Intra-observer and inter-study variability for AD, LV twist and strain are previously described[289]. 12 randomly selected studies, blinded to BE/GF, were selected for reproducibility of aortic and T1 measures. I wanted to repeat aortic reproducibility in my study given the fact it is the primary outcome. We have not published reproducibility of T1 measurements and so this was also assessed. There was excellent intra-observer variability. The intra-observer mean difference for diastolic aortic area was 0.033 ±0.101cm^2 and the mean difference for systolic aortic area was 0.037 ±0.124cm^2 (P=NS). The coefficient of variation (CoV) in the diastolic and systolic measurements were 1.7% and 1.9%, with an intra-class correlation coefficient (ICC) of r=0.999 and r=0.998, respectively. CoV for T1 measurement was also calculated. Native T1 CoV was 2.5% and post-contrast T1 CoV was 2.4%.

5.5 Discussion

5.5.0 Arterial stiffness

Increased inflammation has been measured in the carotid artery in ERA[290] using PET-CT and several studies have shown increased arterial stiffness in established, heterogeneous RA populations[24, 64, 256]. We have not previously known how soon the increased CV risk occurs in RA and when CV abnormalities become apparent and measureable. A 2015 systematic review showed increased arterial stiffness was present in early-stage disease but this was based on small numbers with various definitions of ERA; ranging from <1 year to 6 years[291]. We have shown that increased arterial stiffness, a surrogate marker for increased CV risk[23], is present at the earliest stages of RA. Increasing age and male sex were strongly associated with increased arterial stiffness. The bimodal distribution of AD was not expected and the dichotomised grouping of high and low AD found that the major CV risk factors of smoking, male sex, raised BMI and hypertension were associated with higher arterial stiffness. Increased biochemical evidence of inflammation, by measure of higher CRP, was found in lower AD group. The DAS score remained similar, without correlation in a wide range of CV changes, which suggests that the joint symptom severity of RA clinically is not important for the presence of CV abnormalities in ERA; but the presence of RA, traditional CV risk factors and serum inflammatory marker levels are.

5.5.1 Myocardial tissue composition

A focal and significant area of myocardial tissue change is required before appearance of LGE on CMR imaging. Several studies in established RA have shown an increase in LGE[267] and positively correlated its presence with CRP/ESR and disease activity[125] but not qualitative stress perfusion defects[84]. Although increased compared to controls, we did not find a significant difference in LGE. We would not expect to observe a significant amount of LGE in ERA, given that cellular insult may require chronicity prior to scarring, but it is interesting to see a trend. The expansion of ECV by T1 mapping infers a change in myocardial tissue composition. Fibrosis, inflammation and cardiac cell alteration/apoptosis may all increase ECV; with increased ECV linked to adverse CV outcomes[267]. However, the finding of lower native T1 in

ERA, albeit small, was unexpected. If the mechanism for ECV expansion is purely inflammation driven, then the higher myocardial water content would increase T1 relaxation. Tissue change to alter ECV may be by other undetermined mechanisms in ERA rather than just myocardial inflammation. These mechanisms are discussed in greater detail in the discussion section of chapter 6. As a new technique gaining ground in a variety of cardiac disease, only two previous studies have performed T1 mapping and ECV quantification in RA. Both studies are quite small in number. Ntusi *et al* in 2015 also found ECV expansion in established RA with median disease of 7 years and ongoing disease activity[87]. Interestingly, despite a heterogeneous RA population of N=39, it was found that DAS correlated well with ECV/T1 and subclinical cardiac performance markers. Greulich *et al* in 2017 studied 20 established RA patients with a range of therapies and disease activity and found higher native T1, ECV and T2 values but with no correlation to disease activity[292] in contrast to Ntusi *et al*. In this study, we found no correlation between DAS and tissue composition but only a subtle correlation to ESR. It may be that chronicity is required before these associations become apparent.

5.5.2 Cardiac structure & function

Established RA is associated with different LV structural change with recent CMR studies showing reduced LV mass, as well as LVEF[83]. We were surprised to see that LV structural change was already present in ERA. LV mass was lower compared to controls. Increasing mass was, unsurprisingly, associated with increasing age, history of hypertension and male sex. Recent smaller ERA studies have shown subclinical impairment of systolic[202] and diastolic dysfunction[265]. As expected in such early disease, and in keeping with these smaller studies in ERA, we did not find any overt reduction in systolic performance as assessed by LV and RV EF. Unlike these TTE studies, our CMR data did not find a reduction in subclinical systolic function parameters. Within the ERA group, increasing CRP was associated with reduced LV systolic strain, similarly to other CMR studies[87] in established RA. Diastolic dysfunction can also result in the clinical syndrome of heart failure and has been described in RA populations by TTE[141, 142]. Early diastolic strain rate was increased and may imply early relaxation change. Whereas, no traditional CV risk factors were associated LV strain, increased LV torsion was associated with smoking, hypertension and male sex. Traditional CV risk factors may therefore be

associated with subendocardial fibre/microvascular dysfunction in ERA when these patterns are analysed to LV torsion mechanics[229].

5.6 Limitations

Invasive coronary arteriography to exclude CAD was not performed or appropriate in asymptomatic patients and healthy controls. Stress perfusion imaging was carried out to exclude significant silent ischaemia. For the same reason of appropriateness and risk, myocardial biopsy was not performed to confirm increased ECV. ECV measured by CMR has been validated against histology in other disease processes[293]. Longitudinal tagging, pulse-wave velocity, atrial volumes, T2-imaging and feature-tracking were not assessed and so could not be compared to other CMR studies where they have been employed, as well as previous TTE studies where some measurements are methodically similar. This is because the scanning protocol to include measurements we have presented was already long in duration and recruitment in this well-defined population was paramount to increase uptake into the study and limit drop-out for follow-up CMR scans if patients had a negative experience. The analysis was not blinded to the presence or absence of RA; however analysis was blinded to treatment arm within the CADERA trial as a whole. Reproducibility was performed with randomly selected studies that were blinded to the observer and showed excellent CoV and ICC. We did not measure serum biomarkers of myocardial injury, including troponins and B-natriuretic peptides, in the ERA group or controls. Furthermore, previous medical history was taken from the patients' records rather than re-confirmation of diagnoses of hypercholesterolemia, diabetes and hypertension using serum tests and 24h ambulatory BP monitoring.

5.7 Conclusion

This is the first CMR study of treatment-naive ERA, and one of the largest CMR studies in RA to date. We demonstrate that arterial stiffness is present in ERA. Diffuse myocardial change, by measure of ECV and native T1, is present in ERA along with early changes in biventricular geometry. This highlights presence of CV abnormalities and infers increased CV risk at the earliest stages of the disease process. There are associations with RA activity markers; however traditional major risk factors continue to be more powerful. Further investigation will determine the natural history, including which effective therapies can modulate these abnormalities, and gives weight to further evaluating CV change in the pre-RA population.

6 Interim follow up analysis: Early aggressive control of Rheumatoid Arthritis reduces subclinical cardiovascular pathology at 1 year

6.1 Abstract

6.1.0 Introduction

The incidence of CVD in RA is increased compared to the general population. Immune dysregulation and systemic inflammation are thought to be associated with this increased risk. Early diagnosis with immediate treatment and tight control of RA forms a central treatment paradigm. It remains unclear however whether using TNFi to achieve remission confer additional beneficial effects over standard therapy, especially on the development of CVD. This chapter presents the interim follow up results and analysis of the CADERA randomised controlled trial.

6.1.1 Methods

The methods are described in chapter 4: CMR for the assessment of CV changes in patients with ERA and to measure the effect of early biological therapy. Patients included in this interim follow-up analysis had undertaken their 1 year follow up CMR before September 2015, marking the end time-point of my full-time supervision in the capacity as Clinical Research Fellow in CMR at the University of Leeds. Data analysis was undertaken once all the recruited CADERA patients had completed their 1 year CMR in November 2016.

6.1.2 Results

51 patients had successfully completed baseline and 1 year CMR studies by September 2015. Both treatment arms had similar baseline clinical characteristics and CMR measurements. There was improved aortic stiffness in both groups, to the point where they became similar to non-RA controls at 1 year follow up. Patients who had improved their AD the most began with higher baseline CRP and myocardial ECV. LV mass increased in both treatment arms but was more pronounced in the biological therapy group. LV mass/volume

ratio returned to being similar to controls with biological therapy whereas these changes were not as apparent in the MTX TTT regimen group.

6.1.3 Conclusion

CV abnormalities that are present in ERA can be modulated, improved and measured after 1 year of disease modifying therapy using a MTX TTT regimen or early biological therapy with etanercept. Early biological therapy with etanercept, over a MTX TTT regimen, appears to show greater cardiac reverse remodelling.

6.2 Methods

6.2.0 Recruitment for interim follow-up analysis

Patients included in this interim follow-up analysis were all ERA patients recruited into the CADERA trial until September 2015. I was a Clinical Research Fellow in CMR at the University of Leeds involved in the trial management until September 2015, then returning to a Cardiology clinical training programme after my allocated out of programme research time ended. Therefore, the interim follow-up analysis was of patients up to this time-point with the remaining analysis performed by the current trial team after final patient follow-up in November 2016. Un-blinding of patient treatment arm for this interim follow-up analysis did not occur until after all the CADERA patients had completed their 1 year follow up scan and had completed analysis, so as to not compromise or bias remaining data analysis.

6.2.1 CMR protocol and data analysis

This has been described in detail within Chapter 4. There were no CMR protocol changes throughout the study.

6.2.2 Statistical considerations

This has been described in detail within Chapter 3, 4 and 5. There were no changes in proposed statistical analysis. Within the follow up groups, further dichotomisation occurred in the final analysis to see if there were signals at baseline for patients that had improved their aortic stiffness versus those that didn't.

6.3 Results

6.3.0 Recruitment

At time of this interim analysis of the CADERA study, 51 patients had successfully completed baseline and 1 year follow up CMR studies between February 2012 and September 2015. Taking into account the revised statistical considerations and sample size alterations, for the primary outcome of aortic distensibility this interim analysis does surpass the minimum of 25 patients per group to maintain a 90% power at 5% significance level.

6.3.1 Demographics between treatment arms

Baseline demographic, clinical and RA disease characteristics are given in Table 6-1. There were 25 patients in the group 1 treatment arm (initial biological therapy with etanercept) and 26 patients in the group 2 treatment arm (MTX TTT regimen). Age, sex, BMI, BSA and RA disease characteristics were not significantly different between the 2 groups. CVD risk factors were also similar apart from previous history of smoking, where group 2 had a higher percentage of 'ever smoked' compared to group 1 (65% versus 28%, p=0.007). However, total smoking pack years and current smoking status was not statistically different. Overall, the randomisation of the RA patients into the 2 treatment arms has not resulted in vastly different groups with respect to clinical and demographic characteristics.

Table 6-1 - Baseline demographic, clinical and RA disease characteristic data

Characteristic	**All patients N=51**	**Group 1 Biological N=25**	**Group 2 MTX TTT N=26**	**P Value**
Age, years	49 ± 13	48 ± 12	49 ± 14	0.808
Female sex; n (%)	36 (71)	15 (60)	21 (81)	0.104
Body mass index, kg/m^2	25.7 ± 4.4	25.7 ± 4.5	25.7 ± 4.4	0.968
Body surface area, m^2	1.8 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	0.569
Current Smoker; n (%)	8 (16)	2 (8)	6 (23)	0.248
- Ever smoked; n (%)	24 (47)	7 (28)	17 (65)	**0.007**
- Pack Years*	14 ± 12	9 ± 6	16 ± 13	0.228
Hypertension; n (%)	3 (6)	1 (4)	2 (8)	1.000
Family history of CVD; n (%)**	3 (6)	1 (4)	2 (8)	1.000
Hypercholesterolemia; n (%)	3 (6)	1 (4)	2 (8)	1.000
DAS Score	5.8 ± 1.7	6.0 ± 2.1	5.6 ± 1.1	0.314
ESR, mm/hr	36 ± 28	34 ± 27	38 ± 29	0.609
CRP, mg/L	19 ± 29	21 ± 34	17 ± 23	0.612
RF; n (%)	38 (75)	16 (64)	22 (85)	0.091
ACPA; n (%)	43 (84)	19 (76)	24 (92)	0.140
Any seropositivity*; n (%)**	44 (86)	20 (80)	24 (92)	0.248

Data expressed as mean ± standard deviation unless otherwise stated. ACPA, anti-citrullinated peptide antibody; CRP, C-reactive protein; CV, cardiovascular; DAS Score, 3 variable 28 joint disease activity score using CRP; ESR, erythrocyte sedimentation rate; IQR, inter-quartile range; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; TTT, treat-to-target regimen. *Number of cigarettes per day x number of years smoked ÷ 20 = pack years; **defined as first degree relative with a history of CVD when 60 years old or younger if female, and 55 years old or younger if male; ***RF or ACPA positive.

6.3.2 Baseline CMR measurements between treatment arms

A baseline comparison was performed between the two treatment arms to see if there were any CV changes present between them at randomisation. The complete dataset is presented in Table 6-2. Importantly, the primary outcome measure of AD was similar between group 1 and group 2 (3.2 ±1.8 versus 3.2 ±1.5 10^{-3}mmHg^{-1}, p=0.943). Biventricular structure, function and geometry were not different and measures of tissue composition by T1, ECV and LGE were also not statistically different. Overall, the randomisation of the RA patients into the 2 treatment arms hasn't resulted in statistically different groups with respect to CMR characteristics and the primary outcome measure of AD.

Table 6-2 - Baseline CMR measurements between the two treatment arms

CMR measurements	**Group 1 Biological N=25**	**Group 2 MTX TTT N=26**	**P value**
LV end-diastolic volume, ml	150 ± 31	149 ± 36	0.909
LV end-diastolic volume indexed, ml/m^2	80 ± 13	81 ± 14	0.909
LV ejection fraction, %	60 ± 5	60 ± 6	0.722
LV mass, g	81 ± 20	79 ± 25	0.772
LV mass indexed, g/m^2	43 ± 9	42 ± 9	0.754
LV mass/volume ratio, g/ml	0.54 ± 0.09	0.53 ± 0.12	0.726
RV end-diastolic volume, ml	163 ± 43	157 ± 43	0.651
RV end-diastolic volume indexed, ml/m^2	87 ± 18	85 ± 16	0.709
RV ejection fraction, %	53 ± 5	55 ± 6	0.163
Peak systolic strain, apical LV	-0.25 ± 0.03	-0.25 ± 0.04	0.672
Peak systolic strain, mid LV	-0.23 ± 0.02	-0.22 ± 0.03	0.646
Peak systolic strain, basal LV	-0.21 ± 0.03	-0.21 ± 0.03	0.997
Peak systolic strain rate, seconds^{-1}	1.11 ± 0.20	1.15 ± 0.10	0.486
Early diastolic strain rate, seconds^{-1}	0.61 ± 0.25	0.58 ± 0.25	0.714
Late diastolic strain rate, seconds^{-1}	1.34 ± 0.33	1.46 ± 0.32	0.257
Torsion, degrees	13.5 ± 2.4	13.7 ± 3.2	0.881
Native T1, ms	1176 ± 41	1179 ± 48	0.864
Extra-cellular volume fraction, %	27.4 ± 4.3	27.7 ± 3.3	0.784
Presence of LGE; n (%)	2 (9)	3 (12)	1.000
Aortic strain, %	15.5 ± 7.2	15.9 ± 4.3	0.827
Aortic compliance	11.4 ± 5.0	11.6 ± 4.3	0.914
Aortic stiffness index, ß	4.6 ± 2.8	4.3 ± 2.4	0.754
Aortic distensibility, 10^{-3}mmHg^{-1}	3.2 ± 1.8	3.2 ± 1.5	0.943
Qualitative stress perfusion defect; n (%)	0 (0)	0 (0)	1.000

Data expressed as mean ± standard deviation unless otherwise stated. LGE. Late-gadolinium enhancement; LV, left ventricular; MTX, methotrexate; RV, right ventricular; TTT, treat-to-target regimen.

6.3.3 Follow up CMR measurements in all patients

6.3.3.1 Aortic stiffness

An analysis was performed to assess CMR changes in the entire patient group. All 51 patients' CMR measures were compared at baseline and 1 year follow up and the mean difference of CMR measurements were calculated. Table 6-3 shows these findings. The purpose of this analysis was to see, as a whole, what changes were apparent after strict RA disease therapy, whether by MTX TTT regimen or first-line biological therapy. Overall there was an increase in AD from baseline to follow up (3.2 ±1.6 to 4.4 ±2.8 10^{-3}mmHg^{-1}, mean difference +1.17 10^{-3}mmHg^{-1}, p=0.001). This is presented in Figure 6-1. Additional aortic measures of aortic strain and compliance also revealed statistically important improvements, with aortic stiffness index showing a trend for improvement without statistical significance (mean difference -0.68 ß, p=0.07).

6.3.3.2 LV structure and function

With respect to LV structure and geometry, LV volumes at follow up did not differ but there was a geometric change seen. LV Mass increased by a mean difference of 4g (p=0.005), which was also observed when indexed to BSA with a mean increase of 2g/m^2 (p=0.01). Given the static nature of the LVEDV, and indexed LVEDV, the LV mass/volume ratio also increased, as this is a division of mass and volume. This rose by a mean difference of 0.03 g/ml to 0.57 ±0.10 g/ml (p=0.027). On analysis of tissue composition, despite a reduction in ECV by 0.9% and fewer areas of LGE from 10% to 6% presence, these were not statistically significant. Native T1 relaxation time was almost identical at follow up, only rising by a mean of 3ms (p=0.792). LV function was assessed by ejection fraction and by subclinical measures of strain, strain-rate and torsion. LV ejection fraction, peak systolic strain and peak systolic strain rate at the mid LV did not differ at follow up. With respect to diastolic measures and mechanics, early diastolic strain rate fell from 0.61 ±0.24 to 0.50 ±0.14 seconds^{-1} (p=0.003) and there was a trend for reduction in LV torsion by a mean difference of -0.84 degrees (p=0.054) and increase in late diastolic strain rate by 0.1 seconds^{-1} (p=0.055).

6.3.3.3 RV structure and function

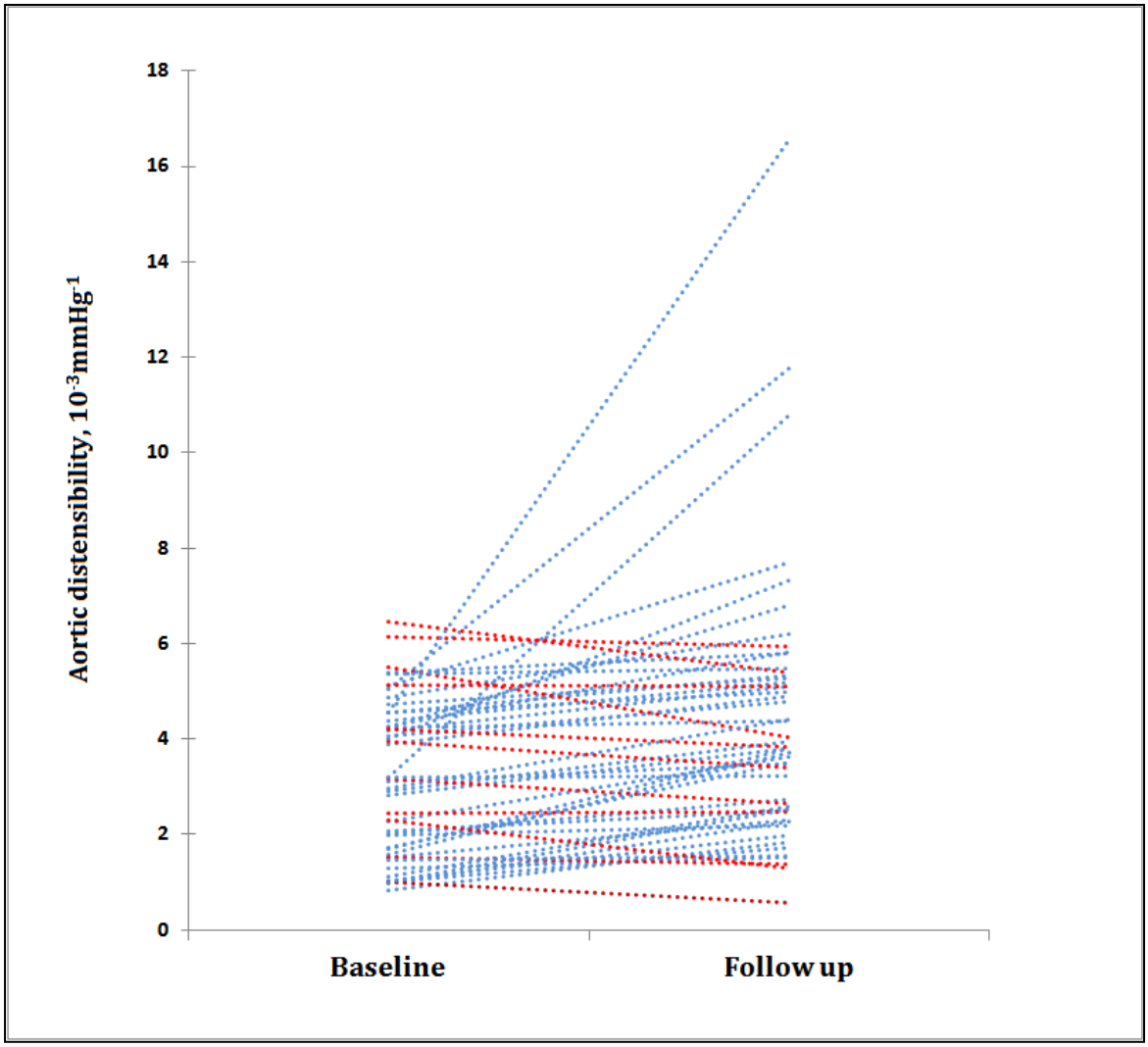
Volumetric analysis revealed similar RVEDV and indexed RVEDV from baseline to follow up, however, an increase in RVEF was observed. The RVEF increased by a mean difference of 1.8% to 56 ±5% (p=0.024).

Table 6-3 - Baseline and follow up CMR measurements in all ERA patients

CMR measurements	Baseline N=51	Follow up N=51	Mean difference	P value
LV end-diastolic volume, ml	149 ± 33	149 ± 33	-0.3	0.881
LV end-diastolic volume indexed, ml/m^2	81 ± 13	80 ± 13	-0.6	0.495
LV ejection fraction, %	60 ± 6	59 ± 6	-0.4	0.637
LV mass, g	80 ± 23	84 ± 24	4.2	**0.005**
LV mass indexed, g/m^2	43 ± 9	45 ± 10	2.0	**0.010**
LV mass/volume ratio, g/ml	0.54 ± 0.10	0.57 ± 0.10	0.027	**0.022**
RV end-diastolic volume, ml	160 ± 43	158 ± 39	-1.6	0.542
RV end-diastolic volume indexed, ml/m^2	86 ± 17	85 ± 14	-1.3	0.302
RV ejection fraction, %	54 ± 5	56 ± 5	1.8	**0.024**
Peak systolic strain, mid LV	-0.23 ± 0.02	-0.23 ± 0.02	-0.000	0.998
Peak systolic strain rate, seconds^{-1}	1.14 ± 0.14	1.15 ± 0.12	0.015	0.480
Early diastolic strain rate, seconds^{-1}	0.61 ± 0.24	0.50 ± 0.14	-0.107	**0.003**
Late diastolic strain rate, seconds^{-1}	1.40 ± 0.33	1.51 ± 0.35	0.103	0.055
Torsion, degrees	13.7 ± 2.7	12.9 ± 2.9	-0.838	0.054
Native T1, ms	1177 ± 44	1180 ± 69	2.7	0.792
Extra-cellular volume fraction, %	27.5 ± 3.8	26.6 ± 4.2	-0.91	0.220
Presence of LGE; n (%)	5 (10)	3 (6)	-	0.183
Aortic strain, %	15.7 ± 6.7	20.0 ± 9.2	5.3	**<0.001**
Aortic compliance	11.5 ± 4.6	15.5 ± 9.0	4.0	**0.001**
Aortic stiffness index, ß	4.5 ± 2.6	3.8 ± 3.2	-0.68	0.072
Aortic distensibility, 10^{-3}mmHg^{-1}	3.2 ± 1.6	4.4 ± 2.8	1.17	**0.001**

Data expressed as mean ± standard deviation unless otherwise stated. ERA, early rheumatoid arthritis; LGE, Late-gadolinium enhancement; LV, left ventricular; RV, right ventricular.

Figure 6-1 - Changes in aortic distensibility measured by CMR in all ERA patients.



N=51. Overall there was an increase in AD from baseline to follow up (3.2 ±1.6 to 4.4 ±2.8 $10^{-3}mmHg^{-1}$, mean difference +1.17 $10^{-3}mmHg^{-1}$, p=0.001). Blue lines represent ERA patients that had a higher AD at 1 year follow up and red lines represent ERA patients that had a lower AD at 1 year follow up.

6.3.4 Aortic stiffness changes between treatment groups

Table 6-3 has shown that as, an entire group, there has been an improvement in aortic stiffness by an increase in AD and other aortic measures. Table 6-5 presents CMR measurements at baseline and 1 year follow up in the different treatment arms and Figure 6-1 displays these data. Both groups have shown an improvement in aortic stiffness using the primary outcome measure of AD, as well as using aortic strain, compliance and stiffness index. Figure 6-2 and Figure 6-3 graphically displays the individual data points in both treatment groups. The absolute mean changes appear similar in both groups with respect to AD but the level of statistical significance appears greater in the MTX TTT regimen group 2 with a p value of 0.003 versus 0.033 (Figure 6-4). Mean differences of CMR measurements were analysed and compared between the treatment arms and are shown in Table 6-6. All aortic measures had greater changes in group 1, however none were statistically different to the mean changes observed in group 2.

Looking at the data points and spread within these figures reveal that the tighter standard deviation in group 2 accounts for the more statistically significant p value. There are 3 outlier patients with the highest AD after 1 year that can be clearly seen in Figure 6-1. The AD values were 16.6, 11.8 and 10.8 $10^{-3}mmHg^{-1}$. These patients with greatest increase in AD were re-analysed and found to be reproducible after further blinded measurement. Their baseline clinical characteristics are shown below in Table 6-5. They were all female. There does not seem to be any unifying clinical characteristic that was shared between them and nothing stood out that was particularly different when compared to the remaining ERA population.

The analysis was repeated excluding these outliers and there remained a significant increase in AD from baseline to follow up (3.2 ±1.6 to 3.8 ±1.7 $10^{-3}mmHg^{-1}$, $p<0.001$). The mean FU AD was predictably lower, at 3.8 versus 4.4 $10^{-3}mmHg^{-1}$ of the entire group.

In summary, both treatment groups had reduced aortic stiffness after 1 year and the magnitude of the mean difference was not statistically significant despite greater mean difference in group 1 in absolute values.

Table 6-4 - Clinical characteristics of outlier patients with high AD after 1 year follow up

Characteristic	Patient 1	Patient 2	Patient 3
Age, years	40	32	52
Body mass index, kg/m^2	23.7	18.6	40.3
Current Smoker	No	No	Yes
- Ever smoked	No	No	N/A
- Pack Years*	N/A	N/A	18
Hypertension; n (%)	No	No	No
Family history of CVD; n (%)**	No	No	No
Hypercholesterolemia; n (%)	No	No	No
DAS Score	5.1	6.9	5.4
ESR, mm/hr	26	17	15
CRP, mg/L	<5	5	<5
RF	Yes	No	Yes
ACPA	Yes	No	Yes

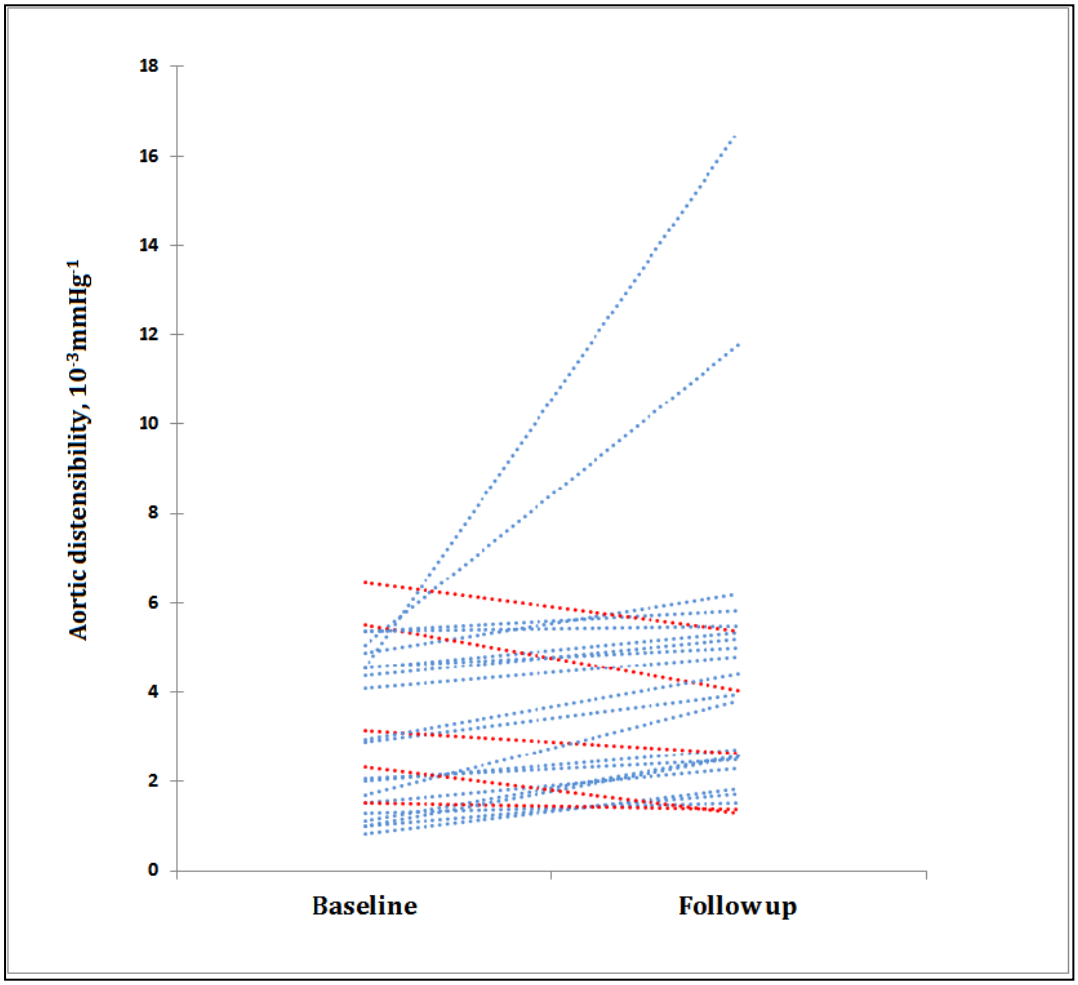
ACPA, anti-citrullinated peptide antibody; CRP, C-reactive protein; CV, cardiovascular; DAS Score, 3 variable 28 joint disease activity score using CRP; ESR, erythrocyte sedimentation rate; IQR, inter-quartile range; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; TTT, treat-to-target regimen. *Number of cigarettes per day x number of years smoked ÷ 20 = pack years; **defined as first degree relative with a history of CVD when 60 years old or younger if female, and 55 years old or younger if male.

Table 6-5 - Baseline and follow up CMR measurements in each treatment group

CMR measurements	Group 1 Biological Baseline N=25	Group 1 Biological Follow up	P Value	Group 2 MTX TTT Baseline N=26	Group 2 MTX TTT Follow up	P Value
LV end-diastolic volume, ml	150 ± 31	147 ± 31	0.340	149 ± 36	151 ± 35	0.138
LV end-diastolic volume indexed, ml/m^2	80 ± 13	78 ± 12	0.138	81 ± 14	82 ± 14	0.218
LV ejection fraction, %	60 ± 5	59 ± 6	0.240	60 ± 6	60 ± 6	0.640
LV mass, g	81 ± 20	85 ± 23	**0.036**	79 ± 25	84 ± 26	0.056
LV mass indexed, g/m^2	43 ± 9	45 ± 10	0.077	42 ± 9	45 ± 10	0.065
LV mass/volume ratio, g/ml	0.54 ± 0.09	0.58 ± 0.09	**0.025**	0.53 ± 0.12	0.55 ± 10	0.296
RV end-diastolic volume, ml	163 ± 43	161 ± 38	0.734	157 ± 43	156 ± 41	0.531
RV end-diastolic volume indexed, ml/m^2	87 ± 18	85 ± 15	0.519	85 ± 16	84 ± 14	0.391
RV ejection fraction, %	53 ± 5	55 ± 5	0.079	55 ± 6	56 ± 4	0.164
Peak systolic strain, mid LV	-0.23 ± 0.02	-0.22 ± 0.03	0.366	-0.22 ± 0.03	-0.23 ± 0.02	0.305
Peak systolic strain rate, seconds^{-1}	1.11 ± 0.20	1.17 ± 0.15	0.262	1.15 ± 0.10	1.15 ± 0.10	0.685
Early diastolic strain rate, seconds^{-1}	0.61 ± 0.25	0.50 ± 0.14	**0.007**	0.58 ± 0.25	0.50 ± 0.14	0.128
Late diastolic strain rate, seconds^{-1}	1.34 ± 0.33	1.51 ± 0.40	**0.044**	1.46 ± 0.32	1.50 ± 0.31	0.536
Torsion, degrees	13.5 ± 2.4	12.8 ± 3.0	0.125	13.7 ± 3.2	13.0 ± 2.9	0.259
Native T1, ms	1176 ± 41	1165 ± 74	0.431	1179 ± 48	1195 ± 67	0.272
Extra-cellular volume fraction, %	27.4 ± 4.3	27.0 ± 5.1	0.783	27.7 ± 3.3	26.2 ± 3.2	0.065
Presence of LGE; n (%)	2 (9)	1 (9)	0.162	3 (12)	2 (8)	0.574
Aortic strain, %	15.5 ± 7.2	20.4 ± 10.9	**0.005**	15.9 ± 4.3	19.6 ± 7.4	**<0.001**
Aortic compliance	11.4 ± 5.0	15.6 ± 10.6	**0.036**	11.6 ± 4.3	15.4 ± 7.4	**0.010**
Aortic stiffness index, ß	4.6 ± 2.8	3.6 ± 1.9	**0.027**	4.3 ± 2.4	3.9 ± 4.1	0.523
Aortic distensibility, 10^{-3}mmHg^{-1}	3.2 ± 1.8	4.4 ± 3.4	**0.033**	3.2 ± 1.5	4.4 ± 2.2	**0.003**

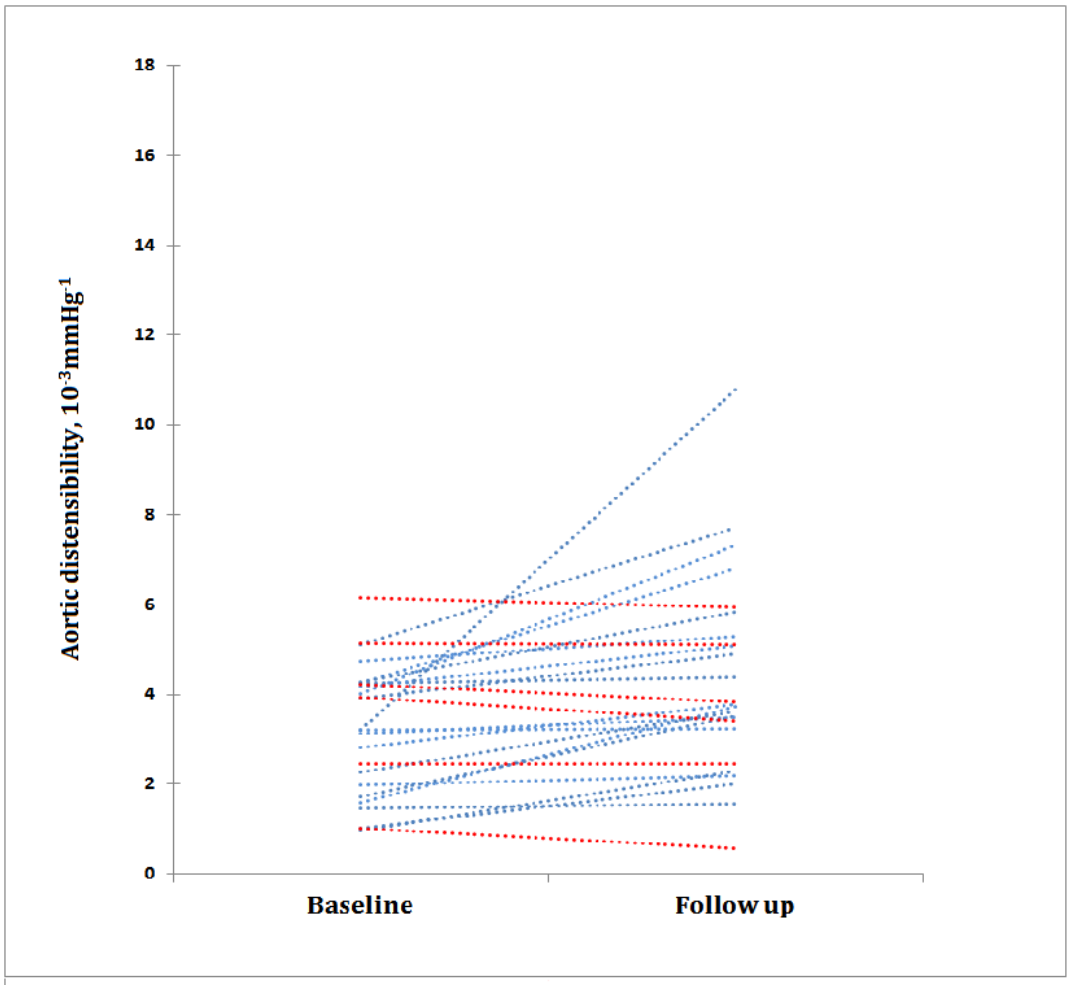
Data expressed as mean ± standard deviation unless otherwise stated. ERA, early rheumatoid arthritis; LGE, Late-gadolinium enhancement; LV, left ventricular; RV, right ventricular.

Figure 6-2 - Changes in aortic distensibility in early biological therapy group.



N=25. There was an increase in AD from baseline to follow up (3.2 ±1.8 to 4.4 ±3.4 10^{-3}mmHg^{-1}, p=0.033). Blue lines represent ERA patients that had a higher AD at 1 year follow up and red lines represent ERA patients that had a lower AD at 1 year follow up.

Figure 6-3 - Changes in aortic distensibility in methotrexate treat-to-target regimen group.



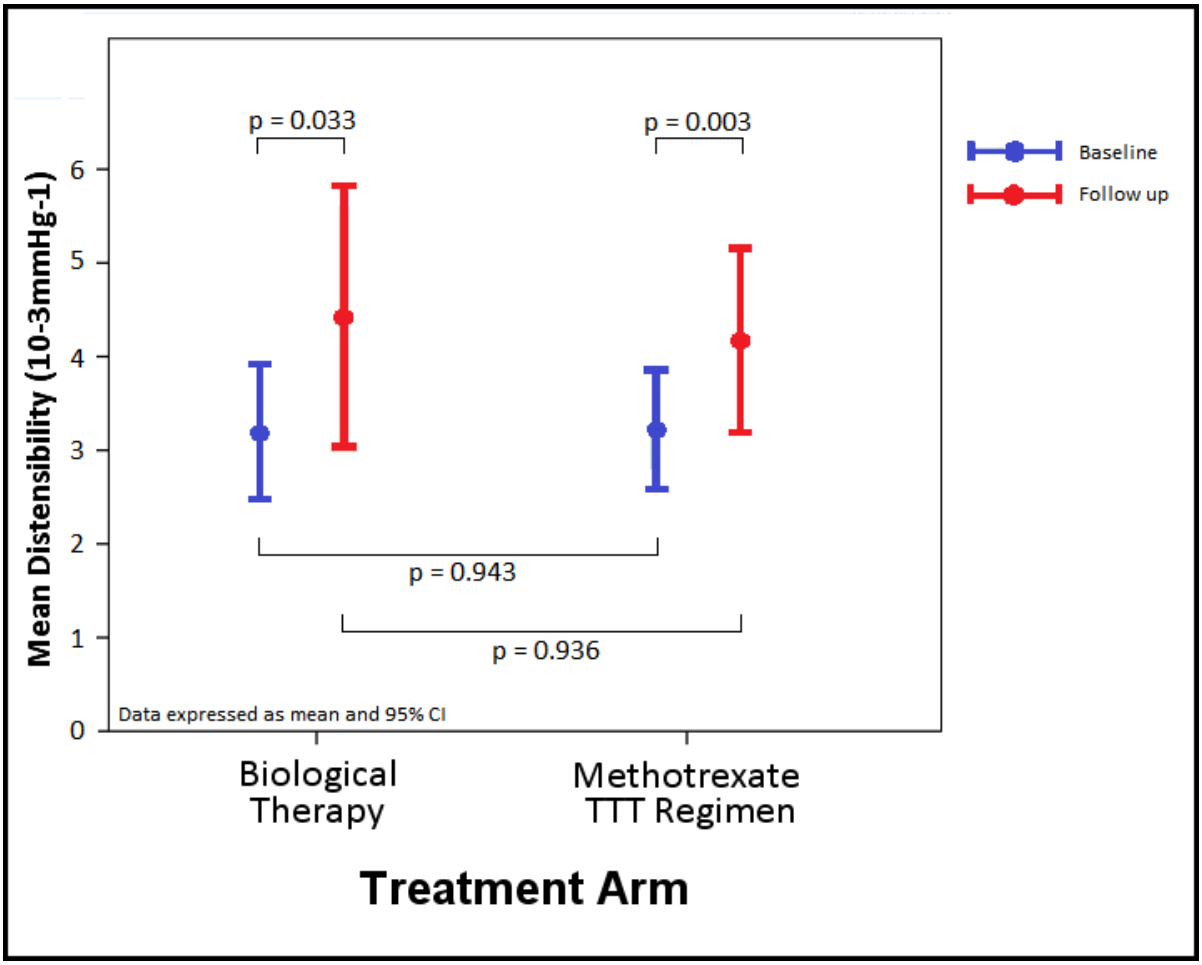
N=26. There was an increase in AD from baseline to follow up (3.2 ±1.5 to 4.4 ±2.2 10^{-3}mmHg^{-1}, p=0.003). Blue lines represent ERA patients that had a higher AD at 1 year follow up and red lines represent ERA patients that had a lower AD at 1 year follow up.

Table 6-6 - Comparison of mean difference in CMR measurement from baseline to follow up

CMR measurements	**Group 1** **N=25**	**Group 2** **N=26**	**P value**
Days between baseline and follow-up CMR	343 ± 30	352 ± 23	0.724
LV end-diastolic volume, ml	-3 ± 15	2 ± 8	0.123
LV end-diastolic volume indexed, ml/m^2	-2 ± 7	1 ± 4	0.056
LV ejection fraction, %	-1 ± 5	1 ± 5	0.248
LV mass, g	4 ± 9	4 ± 11	0.833
LV mass indexed, g/m^2	2 ± 5	2 ± 6	0.478
LV mass/volume ratio, g/ml	0.03 ± 0.07	0.02 ± 0.09	0.726
RV end-diastolic volume, ml	-2 ± 23	-2 ± 13	0.995
RV end-diastolic volume indexed, ml/m^2	-1 ± 11	-1 ± 7	0.958
RV ejection fraction, %	2 ± 5	2 ± 6	0.848
Peak systolic strain, mid LV	0.01 ± 0.03	-0.01 ± 0.03	0.171
Peak systolic strain rate, seconds^{-1}	0.04 ± 0.16	-0.01 ± 0.12	0.263
Early diastolic strain rate, seconds^{-1}	-0.13 ± 0.21	-0.08 ± 0.24	0.476
Late diastolic strain rate, seconds^{-1}	0.15 ± 0.35	0.05 ± 0.35	0.316
Torsion, degrees	-1.0 ± 2.9	-0.7 ± 2.8	0.773
Native T1, ms	-11 ± 41	17 ± 73	0.178
Extra-cellular volume fraction, %	-0.3 ± 6.1	-1.5 ± 3.7	0.451
Aortic strain, %	4.9 ± 8.0	3.7 ± 4.2	0.497
Aortic compliance	4.2 ± 9.4	3.8 ± 6.9	0.885
Aortic stiffness index, ß	-0.95 ± 2.02	-0.40 ± 3.11	0.460
Aortic distensibility, 10^{-3}mmHg^{-1}	1.2 ± 2.7	1.1 ± 1.7	0.865

Data expressed as mean ± standard deviation unless otherwise stated. LV, left ventricular; RV, right ventricular.

Figure 6-4 - Change in aortic distensibility from baseline to 1 year follow up

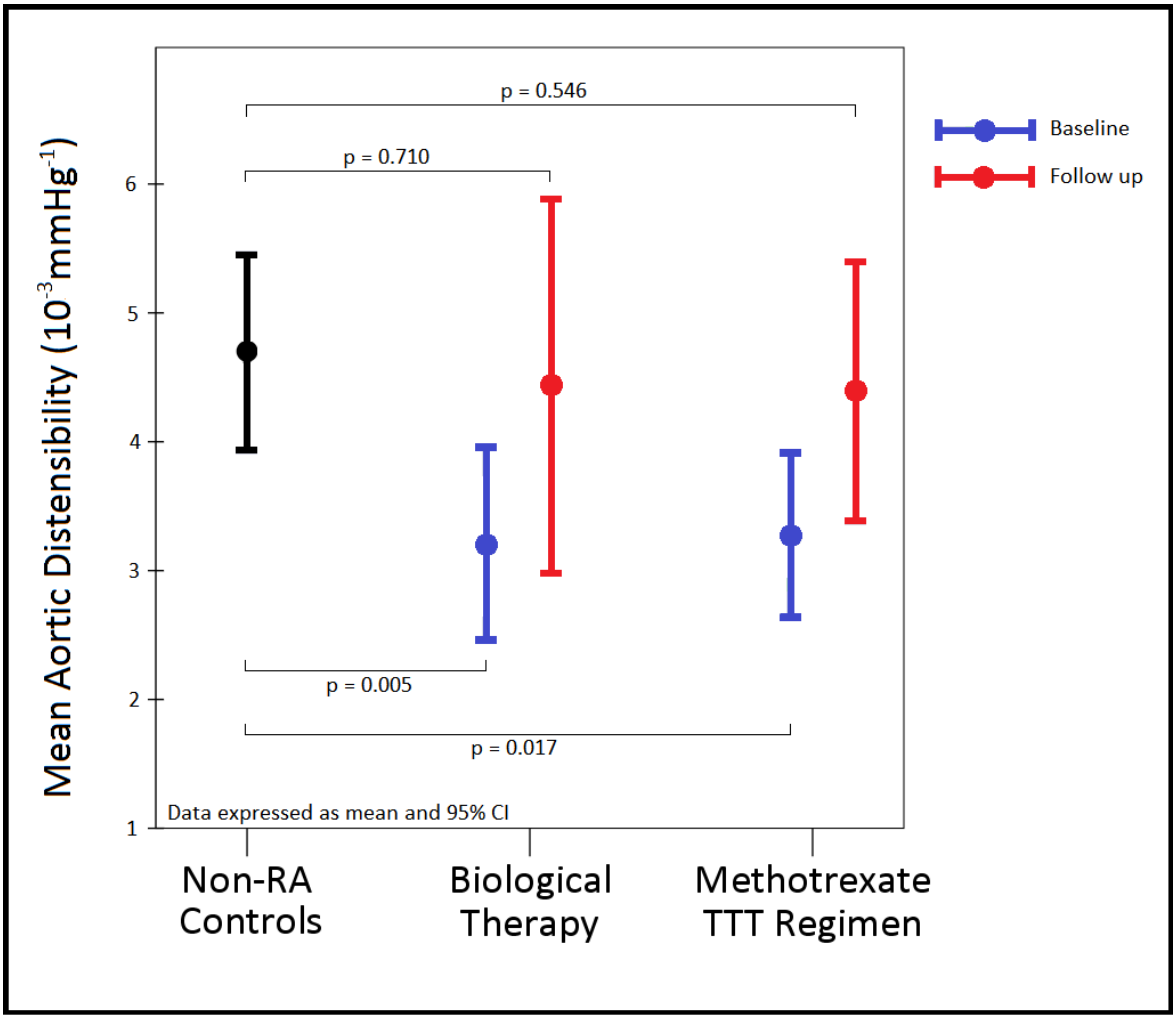


Biological therapy group: Increase in AD from baseline to follow up (3.2 ±1.5 to 4.4 ±2.2 10-3mmHg-1, p=0.003). Methotrexate TTT regimen group: An increase in AD from baseline to follow up (3.2 ±1.8 to 4.4 ±3.4 10-3mmHg-1, p=0.033).

6.3.5 Aortic stiffness changes between treatment groups and healthy controls

The 30 healthy controls described previous chapters were used to compare aortic stiffness in the follow up patients (Control group: mean AD = 4.70 ±1.95 10^{-3}mmHg^{-1}). This is shown in Figure 6-5. As expected and presented in chapter 5, both treatment groups had significantly lower AD compared to healthy controls. At 1 year follow up, both groups had improved aortic stiffness measured by AD. The higher AD in each follow up group was a slightly lower absolute value but not significantly different when compared to the healthy non-RA controls. After 1 year of either MTX TTT regimen or first-line biological therapy with etanercept, aortic stiffness improved to the level where is wasn't significantly different when compared to healthy non-RA controls. Biological therapy group: Control AD versus baseline and follow up = 4.7 versus 3.2 and 4.4 10^{-3}mmHg^{-1}, p=0.005 and p=0.710 respectively. Methotrexate TTT regimen group: Control AD versus baseline and follow up = 4.7 versus 3.2 and 4.4 10^{-3}mmHg^{-1}, p=0.017 and p=0.546 respectively.

Figure 6-5 - Change in aortic distensibility between treatment groups and non-RA controls



Control group: mean AD = 4.70 ±1.95 10-3mmHg-1. Biological therapy group: Control AD versus baseline and follow up = 4.7 versus 3.2 and 4.4 10-3mmHg-1, p=0.005 and p=0.710 respectively. Methotrexate TTT regimen group: Control AD versus baseline and follow up = 4.7 versus 3.2 and 4.4 10-3mmHg-1, p=0.017 and p=0.546 respectively.

6.3.6 Clinical characteristics between RA patients with increased and non-increased aortic stiffness at follow up

RA patients were divided into 2 groups characterised by if there was an increased AD value or decreased AD value at follow up. This was performed as an entire cohort, with both treatment arms included together. Table 6-7 presents these data. 40 RA patients had increased AD and 10 patients did not increase their AD. Of these, there was no significant difference if they were in treatment arm 1 or 2. Demographic measures and CVD risk factors did not differ between RA patients that had increased their AD versus ones that hadn't. Of the RA disease characteristics, DAS score was similar between increased AD and non-increased AD (5.8 ±1.8 versus 5.6 ±1.4, p=0.69) and there was no difference in seropositivity (35 (88%) versus 8 (80%), p=0.616). Of baseline inflammatory markers, CRP was found to be higher in the increasing AD group (22 ±31 versus 7 ±9 mg/L, p=0.010).

Table 6-7 - Baseline demographic, clinical and RA disease characteristic data between increased and non-increased AD groups

Characteristic	Increased AD N=40	Non-Increased AD N=10	P value
Biologic Treatment arm; n (%)	21 (53)	4 (40)	0.480
Age, years	49 ± 13	49 ± 14	0.958
Female sex; n (%)	27 (68)	8 (80)	0.702
Body mass index, kg/m^2	26.4 ± 4.6	23.7 ± 2.3	0.083
Body surface area, m^2	1.9 ± 0.2	1.7 ± 0.2	0.058
Current Smoker; n (%)	6 (15)	2 (20)	0.653
- Ever smoked; n (%)	19 (48)	4 (40)	0.736
- Pack Years*	12.3 ± 10	24 ± 16	0.076
Hypertension; n (%)	3 (8)	0 (0)	1.000
Family history of CVD; n (%)**	1 (3)	2 (20)	0.098
Hypercholesterolemia; n (%)	2 (5)	1 (10)	0.496
Any CV risk factor; n (%)	22 (55)	5 (50)	1.000
DAS Score	5.8 ± 1.8	5.6 ± 1.4	0.690
ESR, mm/hr	36 ± 28	35 ± 31	0.898
CRP, mg/L	22 ± 31	7 ± 9	**0.010**
RF; n (%)	31 (78)	6 (60)	0.420
ACPA; n (%)	34 (85)	8 (80)	0.653
Any seropositivity*; n (%)**	35 (88)	8 (80)	0.616

Data expressed as mean ± standard deviation unless otherwise stated. ACPA, anti-citrullinated peptide antibody; AD, aortic distensibility; CRP, C-reactive protein; CV, cardiovascular; DAS Score, 3 variable 28 joint disease activity score using CRP; ESR, erythrocyte sedimentation rate; IQR, inter-quartile range; RA, rheumatoid arthritis; RF, rheumatoid factor; *Number of cigarettes per day x number of years smoked ÷ 20 = pack years; **defined as first degree relative with a history of CVD when 60 years old or younger if female, and 55 years old or younger if male; ***RF or ACPA positive.

6.3.7 CMR characteristics between RA patients with increased and non-increased aortic stiffness at baseline

CMR characteristics at baseline and follow up were compared between the increased and non-increased AD groups in a similar method to comparison of clinical characteristics. These are displayed in Table 6-8 and Table 6-9. The time points between baseline and follow up CMR scans were not significantly differing to account for the CV changes seen on CMR, which were expected given the strict nature of the trial management. The only CMR measurement at baseline that was different was an higher myocardial ECV in the increased AD group (28.1 ±4.0% versus 25.4 ±2.2%, p=0.045). Of particular scrutiny, the baseline AD, and other aortic measures, between the 2 groups were not significantly different thus giving weight that the improvements seen were not small changes in patients with pre-existing abnormalities in aortic stiffness. At follow up, there were no additional changes in any CMR measurement that were not evident at baseline. Focussing on the ECV change seen at baseline, this fell in the increased AD group to 26.4 ±3.5% and rose in the non-increased AD group to 27.6 ±6.2% therefore making the p-value non-significant at p=0.403. Table 6-10 presents the mean differences between the two groups. In addition to ECV, myocardial native T1 relaxation time fell in the increased AD group and rose in the non-increased AD group (-10.4 ± 65.5 versus 52.5 ± 74.0 ms, p=0.012). Furthermore, and similarly to the data in Table 6-9 and Table 6-10, this shows that, apart from myocardial tissue composition, there were no statistical differences in cardiac CMR characteristics between the increased and non-increased AD groups.

6.3.8 Cardiac structural change between treatment groups

Table 6-5 and Table 6-6 display results of further CMR measurements at baseline and 1 year follow up for both treatment groups. We have already shown that as an entire cohort there are structural changes at 1 year (Table 6-3). But unlike aortic stiffness, where both groups showed significant change, the other CV CMR changes seem to be driven more by treatment arm 1, first-line biological therapy. In group 2, MTX TTT regimen, there were no significant differences between baseline and follow up with respect to biventricular volumes, mass and geometry (Table 6-5). In group 1, there was a significant increase in LV mass from 81g ±20 to

85g ±23 (p=0.036). There was a trend to an increase in LV mass in group 2 but not to statistical significance. The LV mass/volume ratio was higher at follow up in group 1 (0.54 ±0.1 versus 0.58 ±0.1 g/ml, p=0.025). With respect to tissue composition, in group 1 the native T1 relaxation time, ECV and presence of LGE were very similar at baseline and 1 year follow up. Surprisingly, despite the change in geometry being more powerful in group 1 it was the MTX TTT regimen group that showed a decrease in presence of LGE, reduction in ECV and increase in native T1 relaxation time. However, none of these changes were to any statistical significance.

6.3.9 Cardiac functional change between treatment groups

Table 6-5 and Table 6-6 display results of further CMR measurements at baseline and 1 year follow up for both treatment groups. We have already shown that as an entire cohort there are functional changes at 1 year (Table 6-3). In a similar fashion to the results of structural change, functional CV changes seem to be again driven more by treatment arm 1, first-line biological therapy. In group 2, MTX TTT regimen, there were no significant differences between baseline and follow up with respect to biventricular EF, LV strain, LV strain rates and LV torsion. The decreased early diastolic strain rate and increased late diastolic strain rate discussed above in the whole cohort is apparent only in treatment arm 1. The increased RVEF is not apparent in the individual treatment arms and is only significantly increased when taking all patients together.

Table 6-8 - Baseline CMR characteristics between increased and non-increased aortic distensibility

CMR measurements	Increased AD N=40	Non-Increased AD N=10	P value
Days between baseline and follow-up CMR	345 ± 26	362 ± 27	0.063
LV end-diastolic volume, ml	152 ± 33	140 ± 37	0.338
LV end-diastolic volume indexed, ml/m^2	81 ± 14	80 ± 12	0.951
LV ejection fraction, %	60 ± 6	60 ± 5	0.844
LV mass, g	81 ± 23	77 ± 23	0.609
LV mass indexed, g/m^2	43 ± 9	44 ± 8	0.706
LV mass/volume ratio, g/ml	0.54 ± 0.11	0.54 ± 0.05	0.851
RV end-diastolic volume, ml	162 ± 40	153 ± 53	0.581
RV end-diastolic volume indexed, ml/m^2	86 ± 16	87 ± 20	0.798
RV ejection fraction, %	53 ± 5	56 ± 6	0.101
Peak systolic strain, mid LV	-0.23 ± 0.03	-0.22 ± 0.02	0.816
Peak systolic strain rate, seconds^{-1}	1.13 ± 0.17	1.13 ± 0.11	0.983
Early diastolic strain rate, seconds^{-1}	0.61 ± 0.26	0.56 ± 0.18	0.601
Late diastolic strain rate, seconds^{-1}	1.37 ± 0.32	1.48 ± 0.37	0.348
Torsion, degrees	14.0 ± 2.6	12.1 ± 2.8	0.052
Native T1, ms	1182 ± 45	1160 ± 37	0.165
Extra-cellular volume fraction, %	28.1 ± 4.0	25.4 ± 2.2	**0.045**
Aortic strain, %	15.3 ± 6.7	17.3 ± 7.1	0.399
Aortic compliance	11.1 ± 4.4	13.1 ± 5.3	0.219
Aortic stiffness index, ß	4.6 ± 2.6	4.0 ± 2.5	0.584
Aortic distensibility, 10^{-3}mmHg^{-1}	3.1 ± 1.6	3.5 ± 1.7	0.485

Data expressed as mean ± standard deviation unless otherwise stated. LV, left ventricular; RV, right ventricular.

Table 6-9 - Follow up CMR characteristics between increased and non-increased AD

CMR measurements	Increased AD N=40	Non-Increased AD N=10	P value
LV end-diastolic volume, ml	152 ± 33	137 ± 28	0.206
LV end-diastolic volume indexed, ml/m^2	80 ± 14	78 ± 11	0.608
LV ejection fraction, %	59 ± 6	60 ± 5	0.823
LV mass, g	85 ± 25	79 ± 24	0.474
LV mass indexed, g/m^2	45 ± 10	45 ± 9	0.898
LV mass/volume ratio, g/ml	0.56 ± 0.10	0.57 ± 0.09	0.796
RV end-diastolic volume, ml	161 ± 38	146 ± 41	0.262
RV end-diastolic volume indexed, ml/m^2	85 ± 14	82 ± 16	0.574
RV ejection fraction, %	55 ± 5	57 ± 6	0.474
Peak systolic strain, mid LV	-0.22 ± 0.03	-0.22 ± 0.03	0.610
Peak systolic strain rate, seconds^{-1}	1.15 ± 0.14	1.14 ± 0.09	0.886
Early diastolic strain rate, seconds^{-1}	0.49 ± 0.13	0.51 ± 0.19	0.813
Late diastolic strain rate, seconds^{-1}	1.49 ± 0.38	1.49 ± 0.31	1.000
Torsion, degrees	12.9 ± 2.9	11.9 ± 2.8	0.338
Native T1, ms	1172 ± 70	1213 ± 60	0.096
Extra-cellular volume fraction, %	26.4 ± 3.5	27.6 ± 6.2	0.403
Aortic strain, %	21.0 ± 9.2	15.9 ± 8.4	0.118
Aortic compliance	16.8 ± 9.4	10.2 ± 4.6	**0.035**
Aortic stiffness index, ß	3.2 ± 1.6	6.0 ± 6.0	**0.011**
Aortic distensibility, 10^{-3}mmHg^{-1}	4.7 ± 3.0	3.1 ± 1.7	**0.031**

Data expressed as mean ± standard deviation unless otherwise stated. LV, left ventricular; RV, right ventricular.

Table 6-10 - Mean difference of CMR measurements from baseline to follow up between increased and non-increased AD groups

CMR measurements	Increased AD N=40	Non-Increased AD N=10	P value
LV end-diastolic volume, ml	0.4 ± 11.5	-2.9 ± 14.8	0.447
LV end-diastolic volume indexed, ml/m^2	-0.2 ± 5.5	-2.3 ± 7.9	0.336
LV ejection fraction, %	-0.4 ± 5.5	-0.3 ± 5.0	0.967
LV mass, g	4.6 ± 10.3	2.5 ± 7.9	0.559
LV mass indexed, g/m^2	2.3 ± 5.4	0.7 ± 4.7	0.390
LV mass/volume ratio, g/ml	0.03 ± 0.08	0.03 ± 0.09	0.943
RV end-diastolic volume, ml	0.1 ± 17.6	-7.3 ± 20.0	0.268
RV end-diastolic volume indexed, ml/m^2	-0.4 ± 8.3	-4.9 ± 10.5	0.158
RV ejection fraction, %	2.1 ± 5.2	0.3 ± 6.0	0.337
Peak systolic strain, mid LV	-0.001 ± 0.026	0.004 ± 0.029	0.537
Peak systolic strain rate, seconds^{-1}	0.02 ± 0.15	0.01 ± 0.12	0.899
Early diastolic strain rate, seconds^{-1}	-0.13 ± 0.24	-0.05 ± 0.17	0.362
Late diastolic strain rate, seconds^{-1}	0.13 ± 0.37	0.01 ± 0.23	0.331
Torsion, degrees	-1.0 ± 2.8	-0.2 ± 3.2	0.429
Native T1, ms	-10.4 ± 65.5	52.5 ± 74.0	**0.012**
Extra-cellular volume fraction, %	-1.7 ± 4.5	2.2 ± 6.1	**0.026**

Data expressed as mean ± standard deviation unless otherwise stated. LV, left ventricular; RV, right ventricular.

6.3.10 CMR characteristics compared to non-RA controls

The 30 healthy controls described previous chapters were used to compare other CMR characteristics in the follow up patients. As presented in chapter 5, a number of structural and functional changes were observed in ERA when compared to controls. Table 6-11 presents data of the follow up treatment arms to see, similarly to aortic stiffness described previously, whether changes returned to being similar to controls, stayed different or if new changes became apparent. The results table to refer to is Table 5-2.

6.3.10.1 LV mass and LV mass/volume ratio

With respect to LV mass, both treatment arms had an increase in absolute and indexed values that made the means not significantly different when compared to controls (LV mass indexed, 45 ± 10 and 45 ± 10 versus 49 ± 8 g/m^2, p=0.079 and p=0.095 respectively). LV mass/volume ratio, taking into account the LVEDV, showed that the biological therapy group had values at 1 year that were not different to controls whereas the MTX TTT regimen group continued to show significantly lower LV mass/volume ratio (0.55 ± 0.10 versus 0.62 ± 0.10 g/ml, p=0.011). Therefore, although both groups increased LV mass at follow up, only the biological group returned to a level that was not significant in geometry to controls.

6.3.10.2 Myocardial tissue composition

Despite some evidence above describing patients with increased AD having a falling ECV and rising native T1 relaxation time, there were no observable changes to baseline with respect to falling ECV as a whole and both treatment arms remained significantly different with higher ECV fractions compared to non-RA controls.

6.3.10.3 Cardiac function measures

In the previous chapter, only early diastolic strain rate was found to be higher in ERA when compared to controls. This measure fell in both treatment arms to values that were not significantly different compared to the controls at follow up. However, despite a non-significant fall in LV Torsion discussed above, and the fact it was similar at baseline to

controls, torsion was found to be lower in both treatment arms when compared to controls. For group 1 it was 12.8 ± 3.0 and for group 2 it was 13.0 ± 2.9 versus the control value of 14.9 ± 4.5 degrees (p=0.048 and p=0.028 respectively). The only new function measure that was different at follow up over the baseline data was that the biological treatment arm had a lower LVEF value by 1% making it different to controls whereas the MTX TTT regimen group remained at 60% mean LVEF.

Table 6-11 - Follow up CMR characteristics between treatment groups and healthy non-RA controls

CMR measurements	Group 1 Biological therapy N=25	Non-RA controls N=30	P Value	Group 2 MTX TTT Regimen N=26	Non-RA controls N=30	P Value
LV end-diastolic volume, ml	147 ± 31	154 ± 31	0.400	151 ± 35	154 ± 31	0.822
LV end-diastolic volume indexed, ml/m^2	78 ± 12	80 ± 11	0.596	82 ± 14	80 ± 11	0.643
LV ejection fraction, %	59 ± 6	62 ± 5	**0.037**	60 ± 6	62 ± 5	0.247
LV mass, g	85 ± 23	95 ± 19	0.088	84 ± 26	95 ± 19	0.077
LV mass indexed, g/m^2	45 ± 10	49 ± 8	0.079	45 ± 10	49 ± 8	0.095
LV mass/volume ratio, g/ml	0.58 ± 0.09	0.62 ± 0.10	0.116	0.55 ± 0.10	0.62 ± 0.10	**0.011**
RV end-diastolic volume, ml	161 ± 38	178 ± 42	0.117	156 ± 41	178 ± 42	**0.047**
RV end-diastolic volume indexed, ml/m^2	85 ± 15	92 ± 17	0.111	84 ± 14	92 ± 17	0.060
RV ejection fraction, %	55 ± 5	54 ± 6	0.536	56 ± 4	54 ± 6	**0.049**
Peak systolic strain, mid LV	-0.22 ± 0.03	-0.23 ± 0.02	0.492	-0.23 ± 0.02	-0.23 ± 0.02	0.912
Peak systolic strain rate, seconds^{-1}	1.17 ± 0.15	1.15 ± 0.12	0.604	1.15 ± 0.10	1.15 ± 0.12	0.367
Early diastolic strain rate, seconds^{-1}	0.50 ± 0.14	0.52 ± 0.15	0.924	0.50 ± 0.14	0.52 ± 0.15	0.985
Late diastolic strain rate, seconds^{-1}	1.51 ± 0.40	1.50 ± 0.27	0.981	1.50 ± 0.31	1.50 ± 0.27	0.918
Torsion, degrees	12.8 ± 3.0	14.9 ± 4.5	**0.048**	13.0 ± 2.9	14.9 ± 4.5	**0.028**
Native T1, ms	1165 ± 74	1202 ± 35	**0.031**	1195 ± 67	1202 ± 35	0.585
Extra-cellular volume fraction, %	27.0 ± 5.1	25.1 ± 2.7	**<0.001**	26.2 ± 3.2	25.1 ± 2.7	**<0.001**
Presence of LGE; n (%)	1 (4)	1 (3)	1.000	2 (8)	1 (3)	0.592
Aortic strain, %	20.4 ± 10.9	25.2 ± 8.5	0.076	19.6 ± 7.4	25.2 ± 8.5	**0.015**
Aortic compliance	15.6 ± 10.6	19.1 ± 7.1	0.152	15.4 ± 7.4	19.1 ± 7.1	0.058
Aortic stiffness index, ß	3.6 ± 1.9	2.7 ± 0.84	**0.036**	3.9 ± 4.1	2.7 ± 0.84	0.152
Aortic distensibility, 10^{-3}mmHg^{-1}	4.4 ± 3.4	4.70 ± 1.95	0.710	4.4 ± 2.2	4.70 ± 1.95	0.546

Data expressed as mean ± standard deviation unless otherwise stated. LGE, Late-gadolinium enhancement; LV, left ventricular; MTX, methotrexate; RA, rheumatoid arthritis; RV, right ventricular; TTT, treat-to-target regimen.

6.3.11 Summary

Both treatment arms had similar baseline clinical characteristics and CMR measurements. There was improved aortic stiffness in both groups, to the point where they became similar to non-RA controls at 1 year follow up. Patients who had improved their AD the most began with higher CRP baseline values and higher myocardial ECV values. LV mass and indexed LV mass increased in both treatment arms but was more pronounced in the biological therapy group. Both groups returned to levels that were not significantly different compared to controls. LV mass/volume ratio increased, where in group 1 it returned to being not different to controls whereas in group 2 it remained lower. EDSR increased and was mainly driven by changes in the biological group and LV torsion fell in both treatment arms and became statistically different when compared to controls.

6.4 Discussion

This chapter presented interim follow-up analysis of the CADERA trial, the first clinical trial in ERA using endpoints measured by CMR. Furthermore, this is one of the largest single CMR datasets in RA. Although these data are interim, and importantly without follow up clinical and biochemical parameters, the primary outcome of AD is powered and can be discussed with reasonable confidence.

6.4.0 Arterial stiffness

The interim analysis of this study, so far, supports that arterial stiffness is already present at diagnosis and that early biological therapy or conventional TTT MTX therapy can reduce arterial stiffness in treatment-naive ERA. The degree of reduction was to point of normalising, as compared to non-RA healthy controls. We have not demonstrated that one treatment regimen over another is more effective at reducing arterial stiffness.

Arterial stiffness is associated with an increased risk of CV events with a range of co-morbidities[23]. Aortic distensibility is a commonly utilised method to measure arterial stiffness due to the elastic vasculature hardening as atherosclerosis progresses[294]. In a general (non-RA) population, aortic distensibility predicts CV events [270] but there are few studies assessing it in RA. In patients with RA without traditional CV risk factors, aortic pulse wave velocity is higher than in controls[24] and correlates with age, mean arterial pressure and CRP. Increased inflammation has been measured in the carotid artery in ERA[290] using PET-CT and several studies have shown increased arterial stiffness in established, heterogeneous RA populations[24, 64, 256]. Given the fact it was not shown that either treatment arm was superior to one another in improving arterial stiffness, I assessed whether there were signals between ERA patients that had improved AD versus those that didn't. RA disease characteristics and demographics were similar but the ERA patients that appeared to improve their arterial stiffness the most began with higher baseline CRP values, which may imply that those with higher inflammatory activity have more to gain from strict disease-modifying therapy.

Mäki-Petäjä *et al*, in 2012, used ^{18}fluorodeoxyglucose-PET/CT imaging in 17 patients with established RA before and after 8 weeks of TNFi therapy[212]. They demonstrated that the RA patients had increased aortic uptake of the radiotracer, implying aortic inflammation, in comparison with 34 non-RA patients with stable CVD. There was also increased arterial stiffness by measure of pulse wave velocity. After 8 weeks of the TNFi therapy, there were improvements in tracer uptake that correlated with improved arterial stiffness. Haavisto *et al*, in 2016, showed the influence of triple DMARD therapy (non-biological) on carotid artery inflammation in drug-naive patients with recent onset of RA[213]. They recruited 15 non-diabetic ERA patients and, using (18)F-FDG-PET/CT, the target-to-background ratio decreased by 12.4% (P = 0.01) after 1 month of DMARD triple therapy. Carotid artery inflammation in drug-naive ERA patients could be efficiently reduced by 1-month DMARD triple therapy. A small prospective study in 2014 examining TNFi therapy in RA, evaluated ascending aorta distensibility measured by transthoracic echocardiography in 13 established RA patients. They found that TNFi treatment after 12 months significantly improved arterial stiffness[295].

Therefore, in line with previous studies investigating biological therapy or synthetic DMARD effects on vascular inflammation/stiffness in RA, these findings are consistent with improved aortic stiffness, by measure of lower AD, over 1 year from treatment naivety. We have not shown superiority of one regimen over another in altering aortic arterial stiffness with this interim data.

Synthetic DMARDs and TNFi therapy have some evidence in their effect on the risk of CVD and CV events. MTX use has been associated with a 21% lower risk of total CVD and 18% lower risk of MI in systematic reviews and meta-analysis[55]. Studies that controlled for underlying disease severity and medication use were associated with 36% and 27% lower CVD risk respectively compared with studies that did not[55]. A large prospective study of 3529 ETN treated patients and 2864 on conventional DMARDs found evidence of reduced CV events[65]. The CV benefit of TNFi treatment appeared to be strongest in RA patients over 65 years old in an observational study of 8656 new users of conventional DMARDs versus 11587 on TNFi, with the study showing an overall reduced risk of CV events in bDMARDs[69]. The data of MTX versus TNFi in reducing CV event rate is conflicting. A cohort

of nearly 2000 RA patients TNFi had a lower hazard ratio for new CVD diagnosis compared to MTX[296]. A further meta-analysis showed that TNFi and MTX were associated with comparable reductions in risk of CV events[297]. It should be noted, as concluded in a systematic review and meta-analysis of TNFi and CV events in RA by Barnabe *et al*, that there is heterogeneity amongst cohort studies and possible publication bias. There are wide confidence intervals in RCTs with CV outcome underpowered and assessed as secondary outcomes[298]. Although the mechanisms are unclear, the reduction in CV events and incident CVD diagnoses may be as a consequence of reduced inflammation rather than the specific actions of therapeutic agents.

6.4.1 Cardiac structure

Ventricular geometry was assessed between treatment groups and changes were apparent between them. We have demonstrated that ERA patients have altered LV remodelling with lower mass and mass/volume ratio consistent with previous CMR literature[83]. After 1 year, early biological therapy with ETN appears to have altered this ventricular geometry (increasing LV mass/volume ratio) whereas MTX TTT regimen remained different to controls and similar to baseline. This finding of changing LV geometry with immunotherapy has been demonstrated in a small pilot study by Kobayashi *et al*[253]. They found that tocilizumab treatment decreased left ventricular mass index, as measured by CMR, after one year of therapy. This conflicts with our data where we have seen an increase in LV mass/volume ratio after 1 year of therapy. The drug therapies, RA patient types and treatment regimens are different but the finding of higher LV mass at baseline compared to controls conflicts with this cohort - but also from the previous largest CMR study to date, of 75 RA patients, that demonstrated a reduced LV mass in RA compared to 225 matched controls[83]. This happens to be data from same group therefore this confliction is hard to reconcile. ETN has also been shown to be associated with a significant decrease in adverse left ventricle (LV) remodelling with medium-term treatment[67] supporting experimental studies that tumour necrosis factor alpha may induce adverse LV remodelling[68].

We found that myocardial ECV was increased in ERA but this did not reduce in either group after 1 year of therapy. Myocardial fibrosis is associated with adverse CV outcomes[267]. T1

mapping by CMR has previously demonstrated evidence of increased relaxation times in patients with established RA[87]. This may represent microvascular disease, whether as a result of ischaemic heart disease or inflammation from the RA disease process[299]. None of our ERA patients had regional areas of hypoperfusion on adenosine stress CMR imaging, however there was a weak correlation with rising ESR and ECV expansion. Late gadolinium enhancement imaging can measure focal myocardial tissue abnormalities, including focal fibrosis, but is limited in assessing diffuse changes. This is because the signal intensity between normal and fibrotic myocardium may not be a differentiator. T1 mapping, pre and post gadolinium contrast with haematocrit measurement, enables the calculation of extra-cellular myocardial volume with high spatial resolution. This direct parametric signal quantification for each voxel provides superior assessment of myocardium than conventional late enhancement techniques[300]. We found decreased pre-contrast T1 values and higher ECV values in ERA patients, indicating myocardial change at a cellular level. Myocardial fibrosis has been linked to lower myocardial strain[301] and we found a correlation with increasing CRP with reduced LV systolic strain, similarly to other CMR studies[87]. This data further adds to the literature the relationship between myocardial changes and impaired myocardial strain parameters.

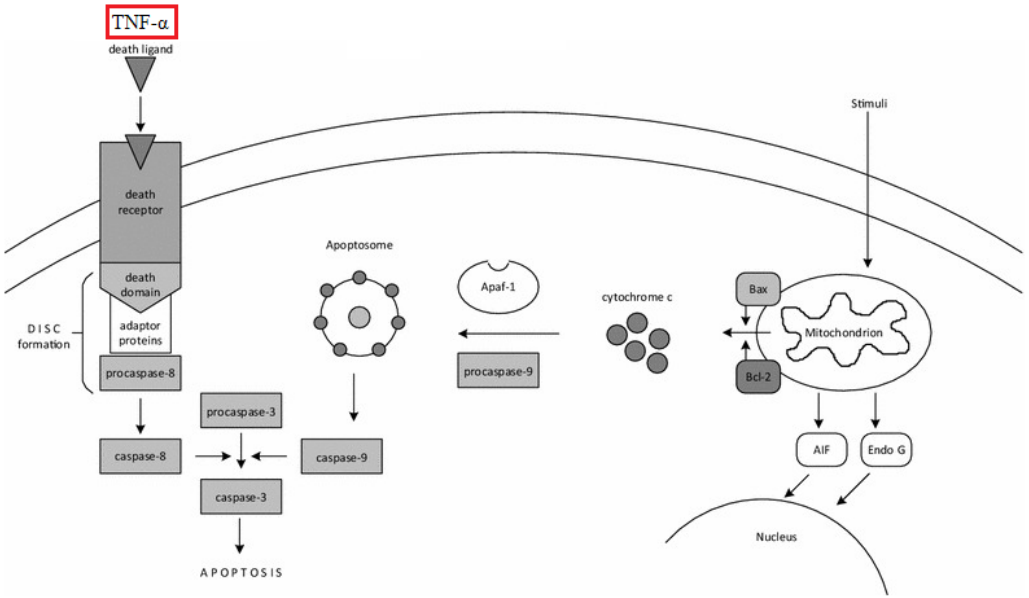
Fibrosis, inflammation and cardiac cell alteration/apoptosis may all increase ECV. Where our data differs from previous experiments in established RA is the finding of lower native T1 in ERA. Although this was a small change it was unexpected. If the mechanism for ECV expansion is purely inflammation driven, then the higher myocardial water content would increase T1 relaxation. Tissue change to alter ECV may be by other undetermined mechanisms in ERA rather than just myocardial inflammation. When the tissue composition is thought about critically, how can ECV expansion in RA be purely due to increase in water content from inflammation if there is a reduction of myocardial mass compared to controls? If ECV expansion was only due to myocardial inflammation, then it would reasonable to assume increased wall thickening and/or increased LV mass. This is not the case as described in these data as well as previous large CMR studies, RA is associated with lower LV mass in CMR studies. Another mechanism that could potentially reduce ventricular mass, lower T1 relaxation time and increase ECV fraction is by cellular apoptosis. Programmed cell death is a regulated process by signalling cascades and is important in normal physiological

processes[302]. Excessive apoptosis is implicated in many diseases, including RA[303]. It is also present in IHD[304] and correlates with LV remodelling[305]. Within the mechanisms of apoptosis, TNF acts as an apoptotic ligand binding to a 'death receptor' creating a death-inducing signalling complex[306] and creating an apoptotic cascade, Figure 6-6. In an in vitro rat study, TNF-α can induce apoptosis in cardiomyocytes[307] and high concentrations of TNF-α increase myocardial injury following ischaemia[308]. This mechanistic hypothesis may shed light on the results seen in this analysis. Both MTX and ETN did not change T1 and ECV after one year, which one would presume if myocardial composition was purely inflammation and oedema driven. However, ETN did alter LV mass/volume ratio and LV mass whilst MTX did not, which would imply a TNF-α specific role in change in cardiac structure.

A further mechanism that may explain lower of LV mass and LV mass/volume ratio, whilst increasing myocardial ECV is the process of physical deconditioning and/or RA cachexia. The heart can remodel quickly with respect to increasing or decreasing aerobic activity. For example, athletes who train and compete regularly develop changes in cardiac morphology and function, most notably an increase in LV mass [309]. This increase in LV mass occurs as early as 3-6 months after commencement of endurance training [310] and may be accompanied by an increase in LV end-diastolic volume (LVEDV) resulting in a typical phenotype of eccentric remodelling[311, 312]. Similar effects are seen when aerobic activity is ceased. It is therefore plausible that when an RA patient is untreated, in pain and has physical limitation due to joint disease and systemic illness, the general lack of activity may reduce the LV mass whilst myocardial ECV expansion occurs. The deconditioning may be more powerful with respect to overall LV mass than the small percentage rise in myocardial ECV with respect to changing the total volume of myocardium. With its association with reduced LV mass, leptin may have a role to play in ‘RA-cachexia’ (loss of body muscle mass with an increase in body fat mass)[313], distinct from physical deconditioning[314]. The Multi-Ethnic Study of Atherosclerosis CMR project reported higher levels of leptin associated with lower LV mass. This was independent of other charactersitics that included traditional CV risk factors, CRP and physical activity[315]. Leptin is higher in patients with RA and so adds another possible explanation for the change in LV mass. There is suggestion that RA cachexia is predominantly a TNF-α driven process, but studies have not shown

improvement following suppression of RA disease activity[313, 316]. There may be alternative pathological processes maintaining this state. A limitation of this work is that leptin was not studied and there were no objective measurements of physical activity, limitation or fitness. This is something that can be explored in future studies.

Figure 6-6 - Apoptotic signalling pathway



Schematic diagram of apoptotic signaling pathway. Apoptosis can be induced by the extrinsic or death receptor pathway and the intrinsic or mitochondrial pathway. The extrinsic pathway is initiated after an apoptotic ligand (e.g. FasL, TNF-α, TRAIL) binds to its death receptor. Subsequently, death-inducing signaling complex is formed resulting in caspase-8 activation. Caspase-8 activates effector caspases and triggers the terminal phase of the apoptotic cascade. The intrinsic pathway is initiated through wide range of none-receptor mediated stimuli (e.g. deprivation of growth factors, hypoxia, oxidative stress), resulting in changes of the mitochondrial membrane permeability. After its release from mitochondria, cytochrome c together with Apaf-1 and procaspases-9 forms an apoptosome, resulting in caspase-9 activation. Caspase-9 then activates effector caspases, such as caspase-3. AIF and EndoG are also released from mitochondria and translocate to cell nucleus where they cause DNA fragmentation, independently of caspase activation. Both extrinsic and intrinsic pathways converge on the same terminal pathway

Adapted from Teringova *et al*. Apoptosis in ischemic heart disease. J Transl Med. 2017 May 1;15(1):87[317]

6.4.2 Cardiac function

Ventricular function was assessed between treatment groups and some changes were apparent between them. Overall, there weren't overt changes in systolic performance by measure of ejection fraction and although rising CRP levels at baseline were correlated with worsening peak systolic strain, the values were not significantly different compared to controls at baseline, follow up or between treatment groups at one year. Recent smaller TTE ERA studies have shown subclinical impairment of diastolic dysfunction[265]. Subclinical diastolic parameters changed in the ETN group and not the MTX group in that early diastolic strain rate fell and late diastolic strain rate increased. Decreased LV torsion was apparent in both groups after 1 year and were lower than non-RA controls. The study was not powered to look at markers of ventricular function, with them being secondary outcomes, and these observations have to be therefore taken with these caveats in mind. Given the fact that we are assessing CV changes in ERA and these changes are subtle and sub-clinical, it is not surprising we are not seeing overt ventricular dysfunction as studies in asymptomatic, established RA without known CVD are only showing sub-clinical CV performance change without prevalent overt measures of dysfunction.

6.4.3 Limitations

Inherently, this is an interim follow-up analysis of trial data but seeing as the primary outcome measure of AD was surpassed there is some confidence at least in reporting these data. With further numbers of patients analysed between September 2015 and November 2016, there may be further data points that drive away existing weak statistical outcomes or indeed bring in current weaker trends that did not reach statistical significance. Furthermore, given the interim nature of this analysis, access to biochemical tests and clinical outcomes are not available to analyse and correlate with the CMR measurements. Secondary outcomes, that are already not powered, may be heavily influenced by the addition of remaining follow up patients. Adenosine stress perfusion is a highly efficient method detecting significant flow limiting coronary artery disease however I did not calculate myocardial perfusion reserve to analyse if there was any microvascular flow

disturbance. This was rather due to large amount of data to investigate and the Leeds CMR research group will continue this work in the future. Once the trial is analysed at completion, it would be of interest to analyse patients in the MTX TTT regimen group for amount of escalation to ETN and whether these patients differed in their CMR data compared to MTX alone and ETN alone. As per the previous limitations described in earlier chapters, invasive coronary arteriography to exclude CAD was not performed or appropriate in asymptomatic patients. For the same reason of appropriateness and risk, myocardial biopsy was not performed to confirm increased ECV. ECV measured by CMR has been validated against histology in other disease processes[293]. Longitudinal tagging, pulse-wave velocity, atrial volumes, T2-imaging and feature-tracking were not assessed and so could not be compared to other CMR studies where they have been employed, as well as previous TTE studies where some measurements are methodically similar. This is because the scanning protocol to include measurements we have presented was already long in duration and recruitment in this well-defined population was paramount to increase uptake into the study and limit drop-out for follow-up CMR scans if patients had a negative experience. The analysis was not blinded to the presence or absence of RA; however analysis was blinded to treatment arm within the study as a whole. Reproducibility was performed with randomly selected studies that were blinded to the observer and showed excellent CoV and ICC. Previous medical history was taken from the patients' records rather than re-confirmation of diagnoses of hypercholesterolemia, diabetes and hypertension using serum tests and 24h ambulatory BP monitoring.

6.5 Conclusion

Increased arterial stiffness, present in treatment-naive ERA can be modulated, improved and measured after 1 year of disease modifying therapy using a MTX TTT regimen or early biological therapy with ETN. Patients with baseline higher CRP appear to improve arterial stiffness the most. Early biological therapy with ETN, over a MTX TTT regimen, appears to show greater normalising of LV remodelling and subclinical diastolic performance parameters.

7 Dilation of the thoracic aorta and cardiovascular co-morbidity in patients with giant cell arteritis

7.1 Abstract

7.1.0 Objectives

In GCA, aortic inflammation is common but the prevalence of aortic structural damage in routine practice remains unclear. We sought to characterise thoracic aortic structural change in GCA using CMR.

7.1.1 Methods

Patients with GCA diagnosed at least 2 years beforehand, from two sites of UK GCA Consortium, underwent 3T CMR. Thoracic aortic dimensions were compared to published international nomograms. Controls without GCA were recruited for comparison.

7.1.2 Results

47 GCA patients (mean age 73) and 13 controls (mean age 65) were recruited. Based on nomograms, 31/47 (66%) of GCA patients (87% of females; 38% of males) had dilated thoracic aortas; all 31 had dilated descending aortas, of these, 9 also had dilated ascending aortas. Mean aortic diameter, adjusted for age, sex and CV risk factors, exceeded that of controls. 5/47 GCA patients had ascending aorta diameter approaching/exceeding surgical intervention thresholds. Where the descending aorta was dilated, loss of normal tapering was observed rather than saccular/fusiform aneurysm. Polymyalgic symptoms at onset were associated with greater aortic diameter. Aortic distensibility was lower in GCA than controls (1.2(±0.9) versus 3.7(±1.4) $x10^{-3}mmHg^{-1}$, $p<0.001$).

7.1.3 Conclusions

Dilatation of the thoracic aorta was common in GCA, with loss of tapering of the descending aorta. Polymyalgic symptoms may be a risk factor, but this requires replication. Patients with GCA had increased aortic stiffness than controls. Further longitudinal studies are required to establish the time-course of these changes.

7.2 Introduction

As with RA, GCA is another IMID distinguished by specific pathways of immune-dysregulation that lead to inflammation, organ damage and dysfunction[1]. GCA is the commonest primary systemic vasculitis affecting older people[4] and, like RA, is associated with an increased early mortality mainly due to CVD. There are inflammatory contributions in atherosclerosis from the formation of atherosclerotic plaques, the development, the reduction in their stability to the final conclusion of rupture and thrombosis. The additional CV mortality that GCA is associated with includes aortic syndromes[5].

Various guidelines and recommendations have been proposed for TAA screening and monitoring in GCA[43]. Current UK guidelines suggest a chest radiograph every 2 years[44] but this is insensitive compared to computed tomography or CMR of the aorta. It has been estimated that 5 to 10 GCA patients would need aortic imaging to detect a previously unknown TAA/TAD but this was based on small, heterogeneous datasets[40]. Furthermore this did not seem to fit with clinical experience: although thoracic contrast computed tomography (CT) is now performed for a multitude of indications, aortic aneurysm in patients with GCA seems to be rarely discovered incidentally. In large-scale routinely-collected clinical data the frequency of any aortic aneurysm diagnosis in patients with GCA was only 1%, compared with 0.7% of those without GCA[45]. Because of this, and bearing in mind the costs and burdens of sophisticated imaging tests used to screen for asymptomatic pathology, there is still no consensus amongst clinicians regarding the clinical utility of routine aortic imaging in patients with GCA.

In this study we tested the hypothesis that patients with GCA would have a higher prevalence of TAD, both when compared to controls without GCA, and when compared to population-derived CMR normal ranges. We also tested for association of TAD with putative risk factors for TAD in GCA. In exploratory analyses we also examined measures of CV structure and function assessed using CMR.

7.3 Methods

7.3.0 Enrolment criteria

Consecutive patients previously recruited from Leeds Teaching Hospitals NHS Trust and Harrogate and District NHS Foundation Trust sites to the UK GCA Consortium study were invited to participate in an aortic imaging study. The UK GCA Consortium study (approved York Research Ethics Committee, reference 05/Q1108/28) is an observational study recruiting patients with a firm clinical diagnosis of GCA from secondary care. Since temporal artery biopsy is an insensitive test, particularly in cases with predominant involvement of the aorta and its branches, inclusion was not limited to those with a positive temporal artery biopsy. At the time of this study temporal artery ultrasound was not routinely available at these two hospital sites. Recognising the uncertainty inherent in clinical diagnosis, all biopsy-positive patients were invited first, followed by biopsy-negative patients, until a pre-specified recruitment target of 50 was achieved. A target of 50 was chosen pragmatically rather than statistically determined. In attempt to match age as much as possible to the predictably older GCA cohort, the oldest healthy controls were used for comparison from existing studies already undertaken with the same CMR sequences from our department.

7.3.1 GCA Consortium project

As the patients have been approached from their enrolment into the GCA Consortium study, I now describe what the project involves and its rationale from the study protocol at the University of Leeds. This project was originally powered and directed towards immunogenetic characterisation of the FCGR locus within a UK Caucasian cohort. Preliminary data suggest that the FCGR locus may exert a strong effect on susceptibility and severity to GCA. Careful clinical characterisation of the cohort is required in order to identify potential co-morbidities (e.g. vascular disease), drugs (e.g. aspirin) and environmental triggers (e.g. smoking, recent infections) that may modify the immunogenetic contribution. Accounting for these gene-environment interactions will be essential to avoid imprecision and possible bias but again requires large numbers of patients. The immunogenetic studies will comprise both whole-genome and candidate-gene studies (initially investigating the MHC and FCGR loci and subsequently genes involved in other autoimmune, inflammatory and vascular disease

pathways). Clinical studies, of which this GCA aorta study is one, will focus on factors potentially relevant to autoimmunity, inflammation and vascular disease. Since temporal artery biopsy is the gold standard for diagnosis, temporal artery biopsy specimens, derived either retrospectively (from histopathology archives) or prospectively, will be examined to verify the diagnosis and to examine for disease subtypes (e.g. degree of inflammation and/or of intimal hyperplasia).

7.3.2 GCA Consortium eligibility criteria

Inclusion Criteria

- Willing to self-identify an ethnic group, such as Caucasian, Asian, Afro-Caribbean.
- Have a firm clinical diagnosis of GCA or PMR, or (for patients identified prospectively) GCA or PMR should be more likely than any alternative explanation for the patient's symptoms.
- Able and willing to give informed consent.
- Patients are 50 years of age or over, unless both biopsy-proven and a clinically classical case of GCA.

Exclusion Criteria

- Patient unwilling or unable to give fully informed consent.
- Pacemakers, surgical clips within the head, certain inner ear implants, neuro-electrical stimulators or metal fragments within the eye or head, eGFR <45mL/min/1.73m2

7.3.3 GCA Consortium recruitment details

Recruitment of the UK cohort of patients will include patients recruited prospectively (at or near diagnosis of GCA or PMR) and patients recruited retrospectively from medical records.

- Subjects were recruited by the Chief, Principal Investigator or designated Sub-Investigators.
- Patients were identified from the following sources (i) retrospectively from medical records and (ii) prospectively when patients initially present with suspected GCA and/or PMR.

7.3.4 Cardiovascular magnetic resonance protocol

7.3.4.1 Similarities as compared to RA CMR protocol

The methodologies and image acquisitions are the same as described in the RA chapters earlier in this thesis. The CMR study for the GCA cohort was performed on a dedicated 3T Philips Achieva system equipped with a 32-channel coil. Low resolution survey, reference scans and localisers determined the cardiac short axis, vertical long axis and horizontal long axis with cine imaging (balanced steady state free precession acquisition [bSSFP]). Left ventricle (LV) dimensions and function were obtained from cines covering the entire heart in the LV short axis[277, 278] (bSSFP, multiphase, contiguous slices, voxel size 1.2x1.2x10mm³, 50 cardiac phases).

Arterial stiffness was measured by aortic distensibility (AD). Cines were acquired to measure the diameter of the ascending aorta (AsAo) and descending aorta (DsAo) at the level of the main pulmonary artery (PA). For aortic area, cine images of the AsAo and DsAo at the level of the PA bifurcation were acquired transverse to the vessel[219]. Blood pressure (BP) was recorded immediately prior to image acquisition.

Tissue tagging for strain analysis and diastology were generated from the basal, mid and apical LV using the '3-of-5' approach[280] (spatial modulation of magnetization (SPAMM) pulse sequence, spatial resolution 1.51×1.57×10mm^3, tag separation 7 mm, ≥18 phases, typical TR/TE 5.8/3.5 ms, flip angle 10°).

7.3.4.2 Differences as compared to RA CMR protocol

Arterial stiffness was also measured by aortic pulse-wave velocity (PWV). Aortic PWV was assessed using identical geometry planning to the AD orientations with retrospectively gated, through-plane, phase-contrast velocity encoded images (breath-hold, single slice, 10mm thick, 50 phases, VENC 200cm/s). The addition of VENC imaging was not significant in time given the need for sagittal-oblique cine imaging of the thoracic aorta for a thorough dimension assessment. Additional arterial stiffness measures were implemented given the focussed nature of study of the thoracic aorta. Furthermore, we didn't want to have very low AD in focal regions of TAA/TAD whereas the total PWV of the thoracic aorta may not be as severe.

T1 mapping with gadolinium based contrast agents and adenosine-stress was not performed for this study. With the main focus being thoracic aortic assessment, it was not deemed ethical for cannulation, further blood sampling and further symptom inducing sequences for exploratory objectives. Given the more elderly cohort, fewer numbers and greater distance travelled to Leeds, recruitment for the primary outcome was of upmost importance. Therefore, a quicker protocol that was less invasive was more ideal.

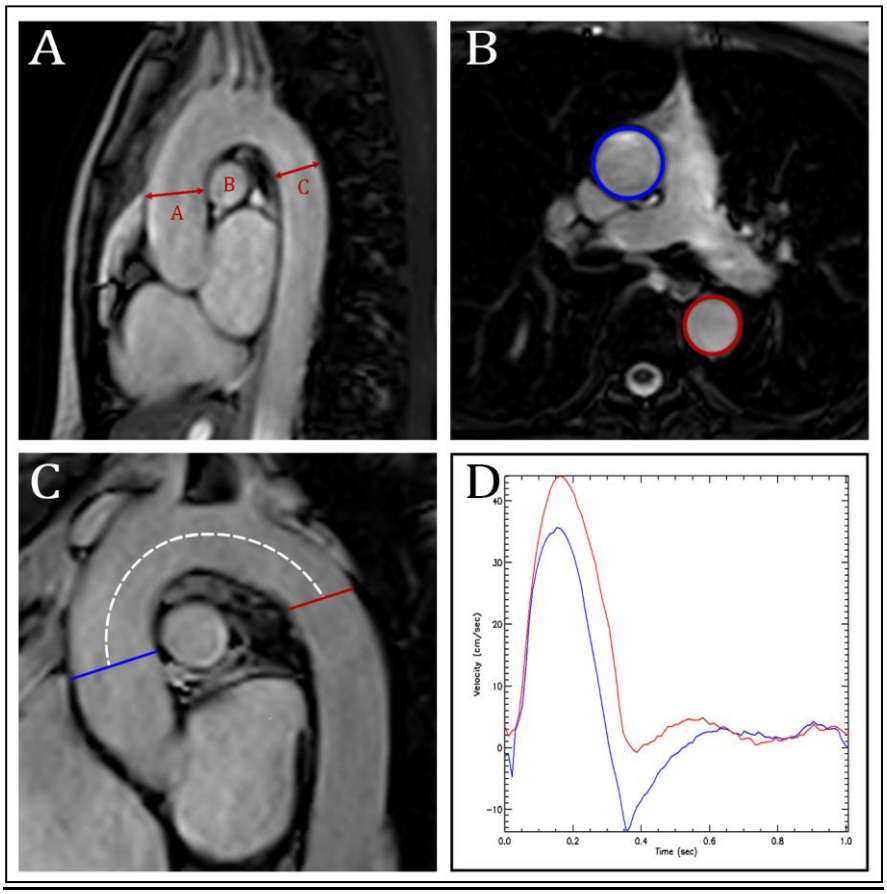
7.3.5 CMR data analysis

Image analysis of LV volumes, strain, torsion and AD was performed as per the RA studies described earlier in this thesis. The additional data analysis not in the earlier methods was that of PWV and thoracic aortic dimensions, described here forth.

The AsAo and DsAo luminal diameters were manually measured from luminal edge-to-edge using the sagittal oblique aortic acquisition Figure 7-1. The diameters were indexed to the patient's body surface area (BSA) and referenced to extrapolated existing regional aortic size CMR nomograms by sex and age[318]. Aortic sizes were determined to be dilated if they were greater than 2 standard deviations (SD) above the mean. European guidelines for aortic intervention were used to categorise if TAD/TAA were at surgical thresholds[319]. Aortic cross sectional measurements were made by manual planimetry of the endovascular-blood pool interface, at the times of maximal and minimal distension of the aorta (Figure 7-1).

Aortic PWV was calculated by dividing the distance separating the AsAo and DsAo and the transit time needed for the wave to cover this distance (Figure 7-1)[282, 320] ENREF 19. Analysis was performed using in-house software (PMI 0.4) based on IDL 6.4 (ITT Visual Information Systems, Boulder, CO, USA) (Figure 7-1)[321].

Figure 7-1 - Aortic image analysis methods by cardiovascular magnetic resonance



(A) Sagittal oblique cine image in diastole showing measurement points of the AsAo diameter (A) and proximal DsAo (C) at the level of the right PA (B). **(B)** AsAo (blue) and proximal DsAo (red) cross-sectional area measurements made by manual planimetry of the aortic endovascular-blood pool interface at minimal and maximal distension. Subsequent phase contrast cines are acquired with this planning. **(C)** Sagittal oblique cine image where the length of the aortic arch is manually measured. **(D)** Time-Velocity curve of AsAo (blue) and proximal DsAo (red) to calculate foot-foot delay. The curves are automatically adjusted to accommodate time delay.

7.3.6 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 20.0 (IBM Corp., Armonk, NY) except for linear regression which was performed in R (version 3.3.3). Continuous variables were expressed as mean ± SD. Categorical variables were expressed as N (%). Correlation was assessed with Pearson's correlation coefficient. Each aorta was classified as either non-dilated or TAD, as defined above. [318]. Differences between groups were assessed using Student's *t*-test for normally distributed data and the Mann-Whitney or Wilcoxon signed rank test on non-parametric data for independent groups and pairwise comparisons respectively. Chi-squared and Fisher's exact tests were used for comparing categorical data. According to convention, for the presentation of results a two-sided $p<0.05$ was considered statistically significant. Since aortic size increases with age and differs between sexs[322], adjustment was made for age, sex as well as presence of established CVD and CV risk factors. Linear regression was used to determine differences between GCA patients and controls when adjusted age, sex, and CVD/CV risk factors. CV risk factors were defined as hypertension (either history of hypertension or anti-hypertensive agent), dyslipidaemia (either history of dyslipidaemia or on lipid-lowering medication), diabetes, family history of CVD and ever smoked. CVD was defined as an established diagnosis of atherosclerotic vascular disease. Potential predictors of ascending (AsAo) and descending aortic (DsAo) diameter within the GCA patients (age, sex and prior diagnosis of atherosclerotic vascular disease) and features at onset of GCA ischaemic manifestations, acute-phase markers and polymyalgic features) were explored by linear regression in univariable analysis. These variables are defined in a previous publication[261]. Features at onset of GCA that were significant on univariable analysis were then adjusted for age, sex and prior diagnosis of atherosclerotic vascular disease) in multivariable linear regression and residuals were plotted to assess model fit.

7.4 Results

7.4.0 Demographics

53 GCA patients were invited and 47 completed the CMR protocol for assessment of thoracic aortic dimensions. 6 were not scanned due to: claustrophobia (3) and scanner malfunction (3). Comparison of characteristics of GCA patients versus controls revealed that the GCA group was slightly older and more likely to be ex-smokers (Table 7-1); there was no significant difference in other CV risk factors.

Table 7-1 - Demographics, cardiovascular risk factors and aortic measurements of Giant Cell Arteritis patients and healthy controls.

	GCA n = 47	**Controls n = 13**	**Unadjusted P value**	**Adjusted for age, sex, CVD and CV risk factors**	
				Difference of means (95% CI)	**P Value**
Age, years	73 ± 6	65 ± 5	**<0.001**	**-**	**-**
Female sex; n (%)	33 (70)	8 (62)	0.737	-	-
Body mass index, kg/m^2	26.1 ± 3.7	25.6 ± 3.7	0.662	-	-
Cardiovascular risk factors					
Hypertension, n (%)	11 (23)	2 (15)	0.713	-	-
Hyperlipidaemia, n (%)	12 (26)	2 (15)	0.713	-	-
Diabetes mellitus, n (%)	2 (4)	0 (0)	1.000	-	-
Current smoker, n (%)	7 (15)	1 (8)	0.671	-	-
- Ever smoked, n (%)	23 (50)	2 (15)	**0.026**	**-**	**-**
Any established vascular disease, n (%)	2 (4)	0 (0)	1.000	-	-
Aortic measurements					
Ascending aorta, mm	33 ± 6	30 ± 2	**0.043**	2.913 (-1.716, 7.543)	0.212
Ascending aorta indexed, mm/m^2	19 ± 5	16 ± 2	**0.019**	1.822 (-1.181, 4.825)	0.228
Aortic arch, mm	24 ± 3	22 ± 2	**0.006**	1.578 (-0.274, 3.430)	0.093
Descending aorta, mm	27 ± 3	21 ± 2	**<0.001**	**5.025 (2.935, 7.114)**	**<0.001**
Descending aorta indexed, mm/m^2	15 ± 2	11 ± 1	**<0.001**	**2.914 (1.638, 4.190)**	**<0.001**
Aortic distensibility, 10^{-3}mmHg^{-1}	1.2 ± 0.9 n = 46	3.7 ± 1.4	**<0.001**	**-2.302 (-3.146, -1.458)**	**<0.001**
Aortic Dilatation					
Dilated ascending aorta, n (%)	9 (19)	1 (8)	0.436	-	-
Dilated descending aorta, n (%)	31 (66)	0 (13)	**<0.001**	-	-
Any dilated aorta, n (%)	31 (66)	1 (8)	**<0.001**	-	-
Left ventricular measurements					
End-diastolic volume, ml	131 ± 26 n = 45	143 ± 31	0.179	-1.024 (-20.234, 18.185)	0.915

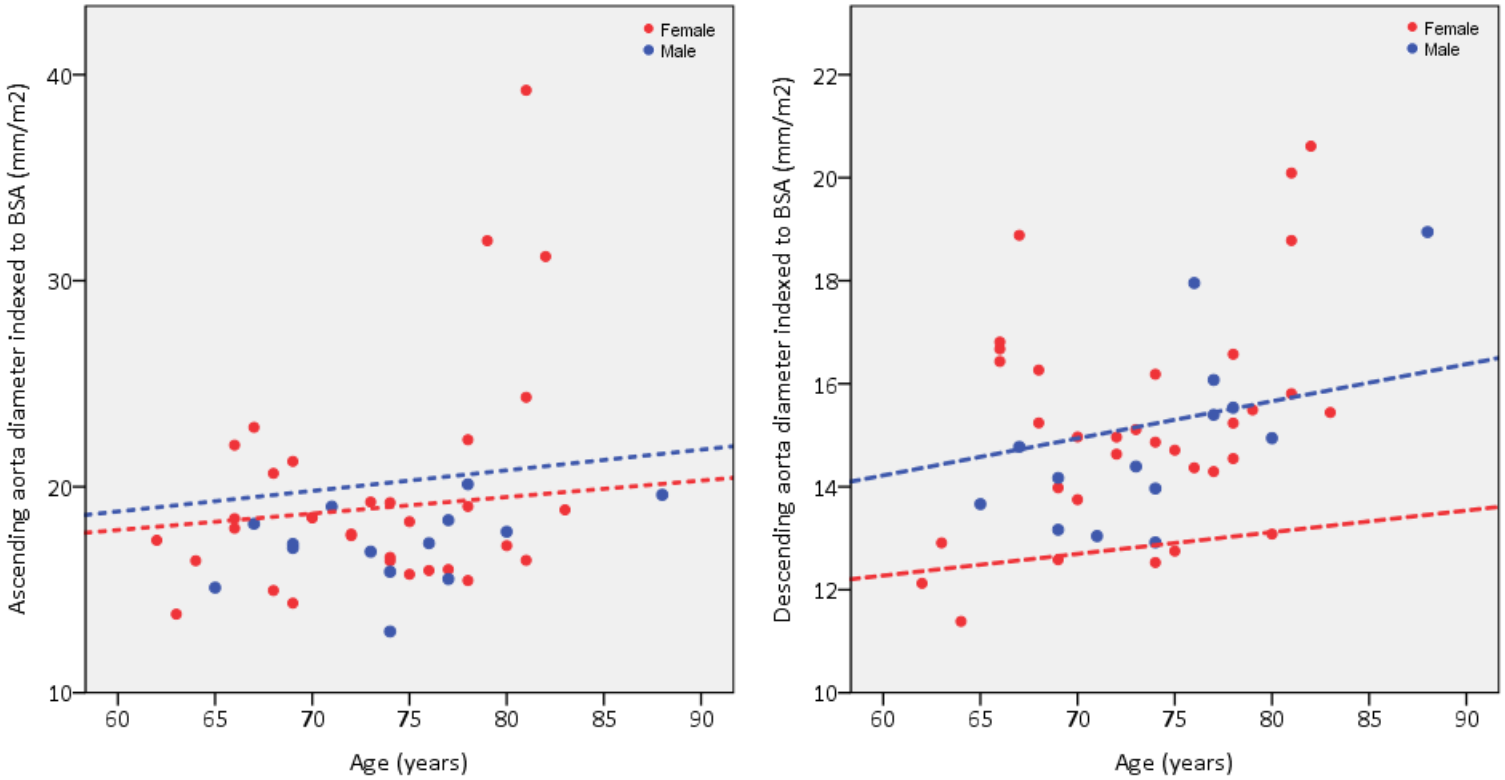
Ejection fraction, %	62 ± 6 n = 45	63 ± 5	0.821	-1.044 (-5.707, 3.619)	0.654
Mass, g	74 ± 15 n = 45	86 ± 22	**0.033**	-6.887 (-18.174, 4.399)	0.226
Mass/volume ratio, g/ml	0.58 ± 0.10 n = 45	0.61 ± 0.12	0.400	-0.042 (-0.129, 0.046)	0.347
Circumferential peak systolic strain	-0.20 ± 0.04 n = 40	-0.23 ± 0.03 n = 11	**0.024**	0.009 (-0.023, 0.042)	0.566
Torsion, degrees	16.4 ± 3.6 n = 40	13.9 ± 2.7 n = 11	**0.040**	2.583 (-0.251, 5.416)	0.073

Data expressed as mean ± standard deviation unless otherwise stated. CV, cardiovascular; CVD, cardiovascular disease.

7.4.1 Thoracic aortic dimensions compared to controls

The AsAo, aortic arch and DsAo diameters were all greater in patients with GCA than in controls, both in absolute values and when indexed to body surface area (BSA). After adjusting for age, sex and CVD, the DsAo diameter was significantly greater in GCA than in controls, both in absolute and indexed dimensions, with a mean difference of 5mm (95% CI: 3-7mm). Indexed AsAo and DsAo diameters were plotted against established CMR nomograms by age and sex to detect TAD. 9/47 of the GCA group had AsAo dilatation and 31/47 had DsAo dilatation (Figure 7-2). 1/13 of the healthy controls had a minor dilatation of the AsAo. Overall, TAD was commoner in the GCA group than in controls (31/47 versus 1/13, $p<0.001$).

Figure 7-2 - Indexed thoracic aorta dimensions of GCA patients plotted against CMR reference nomograms



CMR nomograms adapted from Davis et al[318]**. Red dashed lines represent 2-SD above mean for females and blue dashed lines represent 2-SD above the mean for males. Points above these lines for men (blue) and women (red) were considered to have thoracic aortic dilatation of the ascending aorta (left) or descending aorta (right).**

7.4.2 Thoracic aortic dilatation

Figure 7-3 gives an example of TAD in the DsAo showing a loss of the normal progressive reduction in aortic calibre [323]. Overall, 27/33 (82%) female GCA patients had evidence of TAD. Comparing the demographic and GCA disease characteristics between those GCA patients with and without TAD, only female sex was more common in the TAD group (Table 7-2). Figure 7-3 shows further examples of TAD in GCA patients.

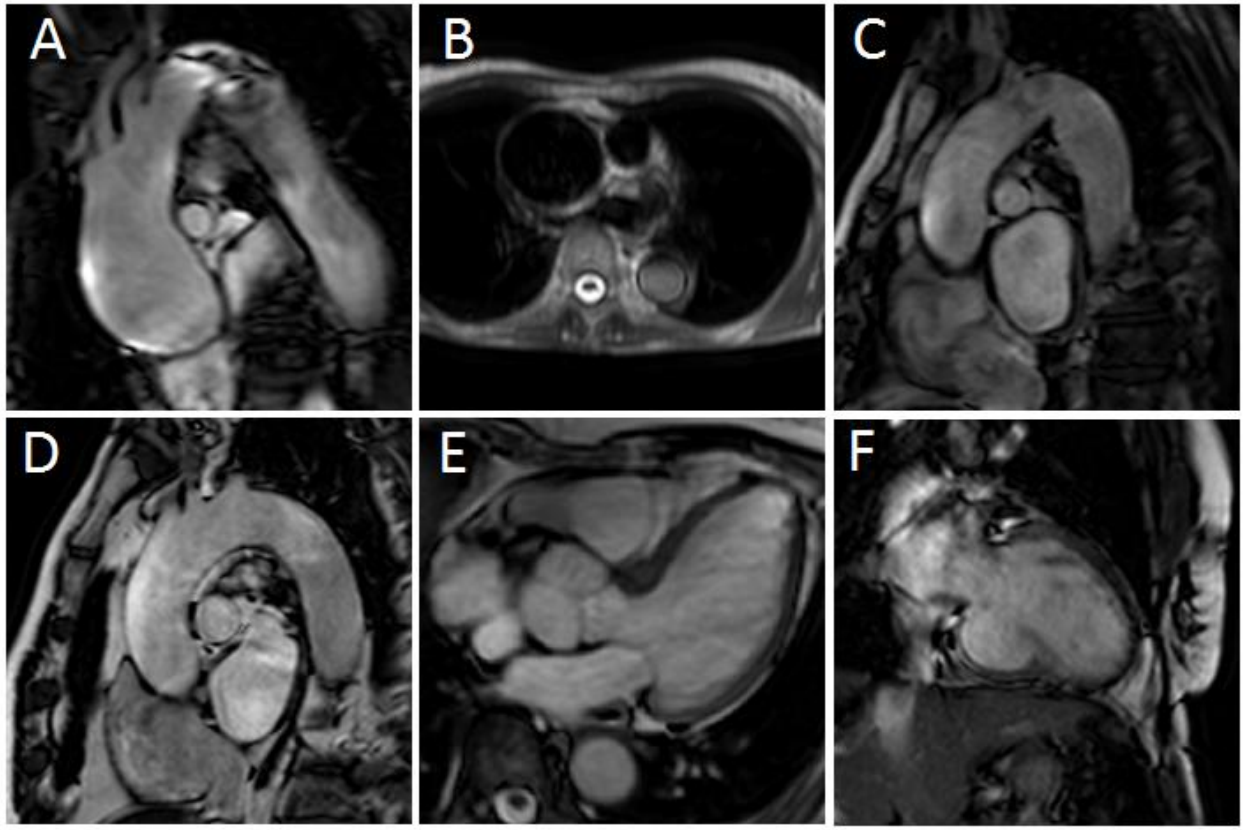
Table 7-2 - Comparison of characteristics of Giant Cell Arteritis patients with and without thoracic aortic dilatation

	All GCA patients **n = 47**	**Non-dilated thoracic aorta** **n = 16**	**Dilated thoracic aorta** **n = 31**	**P value**
Age, years	73 ± 6	72 ± 6	74 ± 6	0.257
Female sex; n (%)	33 (70)	6 (38)	27 (87)	**0.001**
Body mass index, kg/m^2	26.2 ± 4.2	26.4 ± 2.4	26.0 ± 4.3	0.677
Disease length, months	65 ± 37	64 ± 29	65 ± 41	0.897
Number of ACR criteria, median [IQR]	4 [1]	4 [2]	4 [2]	0.480
Headache, n (%)	44 (94)	13 (81)	31 (100)	**0.035**
Temporal artery abnormality, n (%)	33 (70)	13 (81)	20 (65)	0.321
Abnormal artery biopsy, n (%)	31 (74) n = 42	13 (93) n = 14	18 (64) n = 28	0.067
ESR > 50mm/hr, n (%)	35 (76) n = 46	13 (81) n = 16	22 (73) n = 30	0.549
C-reactive protein, mg/L	101 ± 78 n = 33	99 ± 43 n = 13	106 ± 30 n = 20	0.459
Platelets, 10^9/L	417 ± 129 n = 41	414 ± 124 n = 16	443 ± 147 n = 25	0.400
Plasma viscosity, mPa.s	2.0 ± 0.1 n = 41	2.0 ± 0.2 n = 13	2.0 ± 0.1 n = 28	0.871
History of PMR, n (%)	23 (50)	9 (56)	14 (47)	0.536
Symptoms of limb claudication, n (%)	8 (17)	3 (19)	5 (16)	0.821
Steroid sparing drugs, n (%)	7 (23) n = 30	4 (33) n = 12	3 (17) n = 18	0.392
Time taken to reach 7.5mg prednisolone, Weeks	10 ± 9 n = 20	8 ± 2 n = 6	11 ± 11 n = 14	0.484
Time taken to reach 5mg prednisolone, Weeks	18 ± 13 n = 22	17 ± 9 n = 7	18 ± 15 n = 15	0.847

Cardiovascular risk factors prior to GCA diagnosis				
Hypertension, n (%)	11 (23)	3 (19)	8 (26)	0.725
Hyperlipidaemia, n (%)	12 (26)	3 (19)	9 (29)	0.505
Diabetes mellitus, n (%)	2 (4)	0 (0)	2 (7)	0.545
Current smoker, n (%)	7 (15)	1 (6)	6 (20)	0.394
- Ever smoked, n (%)	23 (50)	5 (31)	18 (60)	0.120
Any established vascular disease, n (%)	2 (4)	0 (0)	2 (7)	0.536
Cardiovascular magnetic resonance measurements				
Ascending aorta distensibility, 10^{-3}mmHg^{-1}	0.9 ± 0.7 n = 46	0.7 ± 0.3	1.0 ± 0.8 n = 30	0.146
Descending aorta distensibility, 10^{-3}mmHg^{-1}	1.2 ± 0.9 n = 46	1.2 ± 0.8	1.2 ± 0.9 n = 30	0.787
Pulse-Wave Velocity, m/s	11.7 ± 6.0 n = 45	10.1 ± 4	12.6 ± 6.7 n = 29	0.177
LV end-diastolic volume, ml	131 ± 26 n = 45	138 ± 33 n =15	128 ± 22 n = 30	0.242
LV ejection fraction, %	62 ± 6 n = 45	63 ± 5 n = 15	62 ± 7 n = 30	0.447
LV mass, g	74 ± 15 n = 45	79 ± 20 n = 15	72 ± 11 n = 30	0.228
LV mass/volume ratio, g/ml	0.58 ± 0.10 n = 45	0.58 ± 0.11 n = 15	0.58 ± 0.10 n = 30	0.824
LV circumferential peak systolic strain	-0.20 ± 0.04 n = 40	-0.22 ± 0.04 n = 15	-0.21 ± 0.04 n = 25	0.623
LV torsion, degrees	16.4 ± 3.6 n = 40	15.9 ± 3.9 n = 15	16.6 ± 3.6 n = 24	0.553

Data expressed as mean ± standard deviation unless otherwise stated. ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; LV, left ventricular; PMR, polymyalgia rheumatica.

Figure 7-3 - Aortic and cardiac findings in study population



A, Dilated ascending aorta in sagittal-oblique cine imaging; B, Dilated ascending aorta in transverse view on black-blood imaging; C, Gothic arch shape seen in any aetiology of thoracic aorta dilation; D, Dilated descending aorta without normal tapering off of the aorta; E, Dilated aortic root on 3 chamber view; F, Incidental finding of inferior myocardial infarction with infero-basal aneurysm.

7.4.3 Arterial stiffness as assessed by CMR

AD was measured in GCA patients and controls, and aortic PWV was measured in GCA patients. The GCA group had significantly lower AD (1.2 versus 3.7 10^{-3}mmHg^{-1}, p<0.001) indicating greater arterial stiffness. Amongst those with GCA, there was no significant difference in either AD or PWV between those with and without TAD (Table 7-2).

7.4.4 GCA disease characteristics in thoracic aorta dilatation

No substantive difference in GCA disease characteristics was noted between those with and without TAD when it was categorised as dilated or non-dilated by means of international nomograms (Table 7-2).

Univariable analysis of predictors of AsAo and DsAo dimensions (Table 7-3) confirmed that aortic diameter was significantly associated with age at the time of the CMR scan, for both AsAo and DsAo. Neither age of onset of GCA, nor sex, was significantly associated with aortic diameter within the GCA patients. An established diagnosis of atherosclerotic vascular disease (cerebrovascular, peripheral vascular disease or CV disease) was significantly associated with DsAo but not AsAo dimensions. Regarding disease characteristics of GCA at presentation, neither presence of ischaemic manifestations nor laboratory measures of the acute-phase response (such as platelet count, CRP or ESR) was associated either with AsAo nor DsAo dimensions. However presence of “polymyalgic” symptoms at presentation was significantly associated with greater AsAo size. A prior diagnosis of PMR, treated with glucocorticoids, prior to GCA diagnosis was not associated with AsAo or DsAo size.

Following adjustment for age, sex and vascular disease in multivariable regression, polymyalgic symptoms at the original GCA presentation was still associated with an increased diameter of both AsAo and DsAo. For the influence of PMR on the ascending aorta diameter, the regression coefficient (95% CI) following adjustment for age, sex and vascular disease was 3.87 (1.28, 6.45), p=0.004; model adjusted R^2: 0.327. For the influence of PMR on the descending aorta diameter, the regression coefficient (95% CI) following adjustment for age, sex and vascular disease was 1.49 (0.27, 2.70), p=0.018; model adjusted R^2: 0.245.

Table 7-3 - Univariable analysis of ascending and descending aorta dimensions, indexed to body surface area, in patients with giant cell arteritis.

	Ascending aorta		Descending aorta	
Univariable modelling	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
Age at time of CMR scan, per year	0.29 (0.06, 0.51)	0.013	0.143 (0.045, 1.241)	0.005
Age at GCA diagnosis, per year	0.15 (-0.07, 0.36)	0.180	0.087 (-0.01, 0.18)	0.072
Male sex	-2.50 (-5.47, 0.49)	0.100	-0.36 (-1.74, 1.02)	0.598
Clinical diagnosis of vascular disease prior to GCA diagnosis	0.60 (-6.43, 7.63)	0.864	2.80 (-0.25, 5.85)	0.071
Ever smoked	-1.09 (-3.92, 1.75)	0.444	0.92 (-0.31, 2.14)	0.139
Presence of hypertension diagnosed prior to GCA	1.17 (-2.14, 4.48)	0.480	0.16 (-1.34, 1.66)	0.831
Presence of ischaemic manifestations of GCA	-0.34 (-3.37, 2.69)	0.822	0.77 (-0.61, 2.14)	0.267
CRP prior to glucocorticoid treatment of GCA, mg/L	36.92 (-17.36, 91.21) $x10^{-5}$	0.176	-9.92 (--34.4, 14.5) $x10^{-5}$	0.416
PMR symptoms at GCA presentation	3.26 (0.53, 5.98)	0.020	1.14 (-0.12, 2.40)	0.077
Previous diagnosis and treatment of PMR, before GCA onset	2.25 (0.53, 5.98)	0.196	0.96 (-0.66, 2.57)	0.237

CMR, CV magnetic resonance; CRP, c-reactive protein; GCA, giant cell arteritis; PMR, polymyalgia rheumatica.

7.4.5 Characteristics of GCA patients with clinically significant ascending aorta dilatation or aneurysm

Current European guidelines state that surgical intervention should be considered for patients with ascending TAD/TAA greater than 55mm diameter[319]. There are no specific guidelines for TAD/TAA associated with chronic IMID such as GCA. Amongst our 49 GCA patients, five had clinically relevant ascending TAD/TAA (Table 7-4). Three had concomitant AR, which has further clinical relevance in interventional decision making. All patients continued surveillance imaging. Patient 1, who had an AsAo diameter of 56mm with mild LV systolic dysfunction, did not undergo aortic intervention due to the concomitant discovery of other life-limiting co-morbidity (Figure 7-3, panel A).

Table 7-4 - Clinical characteristics of the five giant cell arteritis patients with dilated ascending aortas approaching/exceeding international surgical intervention thresholds.

	Patient 1	**Patient 2**	**Patient3**	**Patient 4**	**Patient 5**
Age and Sex	81F	81F	79F	71M	82F
Disease length, months	83	108	98	109	84
Time taken to reach 5mg prednisolone	19	2	n/a	15	44
Ascending aorta, mm	56	41	51	42	47
Aortic arch, mm	26	24	20	26	25
Descending aorta, mm	29	32	25	29	21
GCA disease characteristics	ACR Criteria 5 CRP 52 Active PMR	ACR Criteria 4 ESR 100	ACR Criteria 5 Active PMR	ACR Criteria 3 CRP 120 Limb claudication	ACR Criteria 4 Active PMR
Cardiovascular risk and disease	None	Ex Smoker	Hypertensive	Smoker	Hypertensive Smoker
Cardiac abnormalities	Mild LV dysfunction	Moderate aortic regurgitation	Moderate aortic regurgitation	None	Mild aortic regurgitation

ACR, American College of Rheumatology; CMR, cardiovascular magnetic resonance; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; PMR, polymyalgia rheumatica.

7.4.6 Cardiac structure and function in GCA patients

Further CMR cardiac measurements showed no substantive difference either in GCA versus controls (Table 7-1) or in those with TAD versus those without TAD (Table 7-2). 2/47 (4%) patients, without known previous history of IHD, were found to have evidence of prior myocardial infarction on CMR. A 78 year old female had evidence of inferior myocardial infarction with infero-basal LV aneurysm formation and moderate LV systolic dysfunction with LV ejection fraction (EF) of 43% (Figure 7-3). The other patient was a 79 year old female with an anterior myocardial infarction and LV EF of 44%. Neither had TAA/TAD.

7.5 Discussion

In this first characterisation of aortic structure and function using CMR in patients with GCA, we found TAD to be surprisingly common. 10% of our cohort had clinically relevant ascending TAA/TAD requiring referral into cardiology services for assessment. Rather than focal, fusiform or saccular aneurysm, the TAD found was characterised by loss of tapering of the descending aorta. This may perhaps explain why TAD is not more frequently commented on during routine imaging; this could help explain the relatively low absolute frequency of TAA in clinical practice[45] compared to studies imaging patients with GCA[40].

In a CT imaging study [41], Prieto-Gonzalez *et al* identified active thoracic aortitis in 65% of in newly-diagnosed GCA patients, with TAD already present in 15%. Our rate of TAD of 66%, after a mean of 65 months of disease, is similar to their initial large-vessel vasculitis (LVV) prevalence. Even after one year of therapy, they found persistent aortic wall thickening in 68%. In a follow-up study of 54 GCA patients with a median disease-length of 5.4 years[36], 22.2% were reported to have TAD/TAA. This may have been due to a higher threshold for their definition of TAA/TAD (>40mm or with evidence of focal TAA[36]), whereas our definition was indexed to BSA and compared to age/sex-matched established CMR nomograms, which is both more sensitive and more biologically relevant, given the known correlation of age with aortic dimensions in the general population. Aortic diameter increases linearly with age between the ages of 30 and 70 and we assumed that this linear increase continued for individuals over 70 years. Furthermore, in their cohort the initial screening test was a chest radiograph (CXR), and only those with abnormal CXR had CT imaging. Even in acute aortic syndrome the sensitivity of CXR is only 60%[324]. The proportion of patients categorised as approaching/exceeding thresholds for surgical intervention was similar in both studies.

As an additional check of the validity of our results we recruited healthy controls without GCA for comparison, which also allowed us to check our CMR measurements against published nomograms for ages 30-70 years. We then sought to determine factors associated with TAD in the GCA group. Whilst TAD was more common in older patients with GCA, the only GCA disease characteristic associated with TAD was polymyalgic symptoms at onset. One could speculate that shoulder and hip girdle symptoms prior to glucocorticoid treatment may reflect vasculitis

of the aorta and its branches, but this finding requires replication before firm conclusions can be made.

Much is unknown about the mechanism of TAD in GCA. Aortic dilatation might occur from direct inflammation-related damage to elastin; alternatively, dilatation might arise proximal or distal to a relatively stiff aortic segment[41]. In the general population, increased aortic stiffness caused by age-related loss of aortic elasticity is associated with increased CV risk. In diseases such as PMR and GCA, however, additional stiffening may relate to the inflammatory disease itself and be improved whilst on glucocorticoid therapy[42]. Diagnostic performance of LVV by cross-sectional imaging is well-described and can be performed with CT and CMR using wall thickness measurements with or without the of gadolinium-based contrast agents[214]. The lack of a gold standard creates problems in calculating sensitivity and specificity. Hybrid ^{18}F-FDG PET-CT may also be utilised if initial cross-sectional imaging is non-diagnostic[215], however, the utility for routine disease monitoring in GCA is not yet realised. Normal wall aortic thickness does not rule out active inflammation and, conversely, it may take time for increased wall thickness to respond to therapy and regress[216]. There is an emerging role for hybrid PET-CT/CMR and CMR with gadolinium-based contrast in indeterminate cases of relapse/response. Hybrid PET-CMR may aid management of GCA with reduced radiation exposure compared with PET-CT[217]. Contrast-enhanced CMR has been shown to be useful when evaluating the development of disease activity in primary LVV under biological therapies[325]. Pulse wave velocity is a biomarker for arterial stiffness, and can be clinically assessed by applanation tonometry. There is good intra- and inter-observer variability of CMR derived PWV compared to applanation tonometry and using freely available software tools[231]. We observed a striking association of two measures of aortic stiffness (aortic distensibility and pulse wave velocity) with GCA compared to healthy controls; this difference persisted following adjustment for age, sex, CVD and CV risk factors. However, neither of these measures was associated with presence or absence of TAD within the GCA group. We may speculate that aortic stiffness relates to the underlying disease process, with damage to the internal elastic lamina and collagen deposition, and that over time the haemodynamic effects of this might produce the changes in aortic shape that we observed in GCA; a loss of normal tapering of the DsAo, perhaps with later involvement of AsAo. As a second possibility, the aortic stiffening might reflect the atherogenic effects of long-term glucocorticoid treatment in our GCA patients. Thirdly, the stiffness in GCA might

occur due to residual confounding (for example, from a history of previous smoking, which was more common in GCA than controls) despite statistical adjustment for this. Longitudinal studies would be required to further explore these possibilities.

The question remains whether aortic imaging should be routinely carried out in unselected patients with GCA; we found that older patients appear more at risk, but older patients also have greater surgical risk, which should be considered before looking for TAD. The timing and frequency of imaging is also uncertain without further longitudinal studies to determine the natural history of these aortic structural changes. We estimate that a focussed CMR protocol looking at the thoracic aorta alone in GCA patients would take approximately 15mins of scanning time; this CMR protocol offers the opportunity to add further sequences to assess aortic valve function and cardiac structure and function which may be relevant to decisions about surgical intervention should TAA/TAD be found.

7.6 Conclusion

CMR offers a safe, sensitive and specific assessment of the heart and aorta in GCA, capable of identifying hidden pathology including TAD, AR and previously-unsuspected myocardial infarction. Rather than the classical fusiform or saccular aortic aneurysm, we observed a loss of tapering of the DsAo. This may explain why few cases of TAA/TAD are discovered incidentally on thoracic contrast CT studies conducted for other indications, as it is not something specifically looked with indexed measurements taken on routine thoracic imaging. Other than age, possibly female sex and polymyalgic symptoms, no clear clinical predictor of TAD within the GCA patients was identified. Future longitudinal studies may help to identify the time-course and prognosis of the aortic structural abnormalities described here.

8 Discussion

Immune-mediated inflammatory diseases are a group distinguished by specific pathways of immune-dysregulation that lead to inflammation, organ damage and dysfunction[1]. Cardiovascular disease (CVD) is the second largest cause of mortality in the UK, and an accelerated risk of CVD is observed in those with immune-mediated inflammatory diseases. Inflammation plays an important role in atherosclerosis. RA is a chronic inflammatory arthritis and one of the most common systemic autoimmune diseases affecting approximately 1% of the UK population[2]. It has been compared to the risk of other established CV risk factors such as type 2 diabetes mellitus [17]. It is accepted that CVD risk in RA is independent of, and incremental to, traditional CVD risk factors[18] with the likely predominant pathological process being immune dysregulation leading to systemic inflammation[19]. GCA is the commonest primary systemic vasculitis affecting older people[4]. In the elderly, GCA is even more common than rheumatoid arthritis. Most individuals with GCA also have a systemic inflammatory response. Classical descriptions focus on involvement of the superficial cranial arteries, but with modern imaging techniques it is increasingly recognised that aortic involvement is common and may lead to serious complications, such as aortic aneurysm[2]. Aortic involvement in GCA may manifest clinically as a syndrome of systemic inflammation without specific symptoms, or even be asymptomatic until aortic dissection or rupture supervenes with life-threatening consequences[35].

Patients with RA have a variety of clinical presentations with overlapping CV pathology that need to be recognised by first-line healthcare professionals, cardiology and rheumatology teams. The most notable presentation is the earlier and increased incidence of IHD and CCF. There is recent formal adoption of RA into the UK CVD risk calculators with QRISK®2 and the update of QRISK®3 in 2018. There is support that the use of contemporary medical and interventional therapy in cardiac disease is as valuable in patients with RA compared to those without but it is with intrigue and anticipation whether we learn that early use of conventional DMARDs and bDMARDs significantly alters the risk of developing premature CVD and altering CV mortality.

CMR provides accurate quantification of subclinical CV change in RA and GCA. The detection of subclinical change may have powerful diagnostic and prognostic potential that could integrate into clinical practice.

Transthoracic echocardiography remains the cornerstone of first-line cardiac imaging testing for a wide range of initial work-up and diagnostic questions. There is utilisation of carotid ultrasound in current guidelines for an attempt to assess intermediate risk patients, in a similar way that CT coronary calcium score has been used in the general, asymptomatic population. However, for symptomatic patients and accurate CV assessment, structural and functional non-invasive imaging should be utilised. It is recommended that future trials and studies adopt a multi-parametric CMR protocol with defined outcomes. This would help assess subclinical myocardial and vascular disease, allow lower patient numbers to be recruited given the excellent reproducibility and accuracy, and be able to assess multiple CV pathologies in one examination and relate them to future hard clinical endpoints and biochemical parameters.

The primary aim of this thesis was to characterise subclinical cardiovascular changes by CMR in patients with immune-mediated inflammatory disease, namely RA and GCA. The patient populations were refined in attempt to answer specific questions about CV change in their disease continuums. Namely:

1. The study of CV structural and functional change by CMR in patients with early RA (ERA) that have not begun any disease-modifying therapy, in attempt to see if already present at diagnosis or not.

2. The study of CV change, specifically of the thoracic aorta, in GCA patients with established disease. To contribute data surrounding prevalence of clinically important aortic dilatation and aid relevant screening assessment and monitoring.

Furthermore, with the assessment of CV change in ERA, the thesis has further assessed if disease-modifying RA therapy modulates CV changes seen at baseline CMR assessment. In this thesis I have used a variety of techniques from a multi-parametric CMR protocol to measure

and quantify a wide range of CV changes and the effects of disease modifying therapy. The main findings were:

8.1 Chapter 5 summary: assessing subclinical CV change in early RA

I. Arterial stiffness
   A. Lower AD is present in ERA when compared to controls
   B. Increasing age and male sex were strongly associated with AD
   C. A bimodal distribution of AD exists in ERA
   D. Smoking, male sex, raised BMI and hypertension associated with higher AD
   E. Higher CRP was associated with lower AD

II. Cardiac structure and function
   A. ERA patients had lower LVM and LV mass/volume ratio than controls
   B. Increasing CRP correlated with reducing LV strain
   C. EDSR was different in ERA than controls
   D. LV torsion was associated with smoking, hypertension and male sex

III. Myocardial tissue composition
   A. Increased ECV is present in ERA compared to controls
   B. A trend correlation of increasing ESR with ECV was seen
   C. Increased LGE in ERA compared to controls but not to significance

8.1.0 Chapter 5 synopsis

This is the first CMR study of treatment-naive ERA, and one of the largest CMR studies in RA to date. We have shown that increased arterial stiffness, a surrogate marker for increased CV risk[23], is present at the earliest stages of RA. Choosing the best outcome measure to determine CVD risk in RA remains to be determined. The outcome measure should ideally be a true surrogate endpoint[326], predicting future CVD, but few longitudinal trials are available and we extract from general population research. In my study, increasing age and male sex were strongly associated with increased arterial stiffness. The DAS score remained similar, without correlation in a wide range of CV changes, which suggests that the joint symptom severity of RA clinically is not important for the presence of CV abnormalities in ERA; but the

presence of RA, traditional CV risk factors and serum inflammatory marker levels are. Diffuse myocardial change, by measure of ECV and native T1, is present in ERA along with early changes in biventricular geometry. This highlights presence of CV abnormalities and infers increased CV risk at the earliest stages of the disease process. There are associations with RA activity markers; however traditional major risk factors continue to be more powerful. Although increased compared to controls, we did not find a significant difference in LGE. We would not expect to observe a significant amount of LGE in ERA, given that cellular insult may require chronicity prior to scarring, but it is interesting to see a trend. As expected in such early disease, and in keeping with these smaller studies in ERA, we did not find any overt reduction in systolic performance as assessed by LV and RV EF. Unlike these TTE studies, our CMR data did not find a reduction in subclinical systolic function parameters. Within the ERA group, increasing CRP was associated with reduced LV systolic strain, similarly to other CMR studies[87] in established RA. A non-atherosclerotic process may explain the increased risk of heart failure in those with RA unexplained by traditional CV risk factors[127]. Distinguishing between the pathologies may also help direct therapy in the management of CVD in RA.

8.2 Chapter 6 summary: effect of RA therapy on subclinical CV change

I. Arterial stiffness
   - A. AD normalised after 1 year therapy with MTX TTT regimen or first line ETN
   - B. Higher baseline CRP was associated with more improved AD
   - C. Higher baseline ECV was associated with more improved AD

II. Cardiac structure
   - A. First line ETN modulated LV mass/volume ratio whilst MTX TTT regimen did not
   - B. Myocardial ECV remained similar in both groups

III. Cardiac function
   - A. No changes in ejection fraction in either treatment group at 1 year
   - B. First line ETN affected diastology at 1 year but MTX TTT regimen did not
   - C. LV torsion decreased in both groups at 1 year

8.2.0 Chapter 6 synopsis

Increased arterial stiffness, present in treatment-naive ERA can be modulated, improved and measured after 1 year of disease modifying therapy using a MTX TTT regimen or early biological therapy with ETN. Patients with baseline higher CRP appear to improve arterial stiffness the most. We have not demonstrated that one treatment regimen over another is more effective at reducing arterial stiffness. Synthetic DMARDs and TNFi therapy have some evidence in their effect on the risk of CVD and CV events. MTX use has been associated with a 21% lower risk of total CVD and 18% lower risk of MI in systematic reviews and meta-analysis[55]. The CV benefit of TNFi treatment appeared to be strongest in RA patients over 65 years old in an observational study of 8656 new users of conventional DMARDs versus 11587 on TNFi, with the study showing an overall reduced risk of CV events in bDMARDs[69]. A further meta-analysis showed that TNFi and MTX were associated with comparable reductions in risk of CV events. Although the mechanisms are unclear, the reduction in CV events and incident CVD diagnoses may be as a consequence of reduced inflammation rather than the specific actions of therapeutic agents. In established RA, disease activity suppressed with any DMARD sub-type may reduce CV events and deaths[297, 327]. A recent study of therapy in ERA demonstrated no increase in CV mortality in 14,000 patients receiving consistent DMARD treatment between 1 and 7 years follow-up[328]. The modern approach of prompt management in ERA may be improving CV outcomes. In my findings, overall, there weren't overt changes in systolic performance by measure of ejection fraction and although rising CRP levels at baseline were correlated with worsening peak systolic strain, the values were not significantly different compared to controls at baseline, follow up or between treatment groups at one year. Given the fact that we are assessing CV changes in ERA and these changes are subtle and sub-clinical, it is not surprising we are not seeing overt ventricular dysfunction as studies in asymptomatic, established RA without known CVD are only showing sub-clinical CV performance change without prevalent overt measures of dysfunction.

8.3 Chapter 7 summary: aortic changes in established GCA

I. TAD is common in GCA

II. Lower AD and higher PWV is common in GCA

III. Significant dilatation, nearing surgical thresholds, is prevalent

IV. TAD was more common in females

V. PMR symptoms may be a risk factor in TAD

8.3.0 Chapter 7 synopsis

In this first characterisation of aortic structure and function using CMR in patients with GCA, we found TAD to be surprisingly common. 10% of our cohort had clinically relevant ascending TAA/TAD requiring referral into cardiology services for assessment. CMR offers a safe, sensitive and specific assessment of the heart and aorta in GCA, capable of identifying hidden pathology including TAD, AR and previously-unsuspected myocardial infarction. Rather than the classical fusiform or saccular aortic aneurysm, we observed a loss of tapering of the DsAo. Other than age, possibly female sex and polymyalgic symptoms, no clear clinical predictor of TAD within the GCA patients was identified.

8.4 Future work

A particular point of interest to me is the finding of CV changes in RA present at diagnosis. The RA disease continuum is not a discrete event and there may be a 'pre-RA' status phase where the pathological process has begun and perhaps even some measurable CV changes. The data gathered during these studies have already fed into pilot data and further projects at The University of Leeds into this pre-RA population. One method explored, in attempt to gain longitudinal data on this, is to collect biomarkers including RF and ACPA in primary care patients with joint symptoms that are yet to fulfil RA diagnostic criteria. These patients can be invited for CMR study and if they subsequently go on to be diagnosed with RA in the future, then a 'pre-RA' cohort can be analysed. These studies may shed light onto alternative processes other than direct inflammation or physical reconditioning to the CV changes observed in these ERA patients. Multiple CMR outcome measures and testing is observed in this thesis, as well as many CMR based IMID studies. The optimal outcome measure to assess for CVD risk in IMID remains to be determined. The data from these studies will continue to contribute to longitudinal studies at the University of Leeds, such as the IACON registry and will help determine which outcome measure (or combination of measures) is most predictive of CVD in IMID for use in future randomised control trials.

With its association with reduced LV mass, leptin may have a role to play in ‘RA-cachexia’ distinct from physical deconditioning. A limitation of this work is that leptin was not studied and there were no objective measurements of physical activity, limitation or fitness. This is something that may be explored in future studies of pre-RA, ERA and established RA to further describe the pathophysiological cardiac structural change seen in these patients.

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