Screening for cardiovascular disease in Rheumatoid Arthritis: a records-based investigation

Helen Laura Monk

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease affecting approximately 1% of the population. The life expectancy of those with RA is reduced, mainly due to an increased risk of cardiovascular disease (CVD). This thesis investigates whether this increased CVD risk is recognised and translated into screening for these patients in primary care.

First, a systematic literature review examined cardiovascular screening for patients with RA. Ten studies were identified. All included screening for serum lipids, six included blood pressure and three included blood glucose, smoking status and body mass index (BMI)/body weight. Variability in screening practice was identified between the included studies.

Second, 401 RA patients and 1198 age, gender and practice matched non-RA patients were identified from a primary care database (CiPCA). CiPCA was searched for evidence of screening for five traditional cardiovascular risk factors: blood pressure, body weight/BMI, smoking status, glucose levels and lipid status.

No difference in levels of screening for individual risk factors between RA and non-RA patients were identified, apart from smoking status, which was more likely to be recorded in RA patients, 62% versus 67% (percentage difference 5%: 95%CI 0.0%, 10.0%).

Screening for ≥1 cardiovascular risk factors was more common in RA patients, 88% versus 82% (5.8%: 1.4%, 9.2%). However, RA patients were not more likely to receive a standard CVD screen (screening of blood pressure, lipids and smoking status) (OR 0.95 (95% CI

0.70, 1.28)) or a comprehensive CVD screen (all five risk factors) (OR 0.84 (95% CI 0.61, 1.16)) when compared to non-RA patients.

These results suggest that the increased risk of CVD in RA has not been recognised and translated into screening in primary care. More emphasis needs to be focussed on identifying and aggressively treating CVD risk factors in this group.

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List of common abbreviations

ACR	American College of Rheumatology
ANTI-CCP	Anti-Cyclic Citrullinated Peptide
BP	Blood Pressure
BSR	British Society for Rheumatology
CHF	Congestive Heart Failure
COX	Cyclo-oxygenase
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
DMARD	Disease-Modifying Anti-Rheumatic Drug
DNA	Deoxyribonucleic Acid
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
GFR	Glomerular Filtration Rate
GP	General Practitioner
HR	Hazard Ratio
IHD	Ischaemic Heart Disease
IL	Interleukin
JBS	Joint British Societies
MCP	Metacarpophalangeal
MTP	Metatarsophalangeal
MI	Myocardial Infarction
NICE	National Institute for Health and Clinical Excellence

NSAID	Non-Steroidal Anti-Inflammatory Drug
NIDDM	Non-Insulin Dependent Diabetes Mellitus
OA	Osteoarthritis
OR	Odds Ratio
PIP	Proximal Inter-Phalangeal
PSA	Psoriatic Arthritis
QOF	Quality and Outworks Framework
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
RNA	Ribonucleic Acid
SIMDS	Scottish Index of Multiple Deprivation Score
SLE	Systemic Lupus Erythematosus
SMR	Standardized Mortality Ratio
TNF-α	Tumour Necrosis Factor alpha
WHO	World Health Organization

Chapter 1; Background

This thesis is concerned with the association between Rheumatoid Arthritis (RA) and Cardiovascular Disease (CVD) and the recognition of this association in primary care. This chapter summarizes the epidemiology, diagnosis and management of RA. In addition to this, CVD and the relationship between RA and CVD are considered. The aim of the thesis is to determine current practice with regards to cardiovascular screening in patients with RA and hence cardiovascular risk tools and the available guidance will also be reviewed.

1.1 Epidemiology

The prevalence of RA is estimated to be between 0.5 and 1.1% in Northern American and Northern European populations (Alamanosa Y & Drosos AA, 2005). Estimates from a sample derived from the United Kingdom, were of a prevalence of 1.16% in women and 0.44% in men (Symmons D, 2002). Women are affected three times more often than men, but this difference decreases in older age groups (Ahlmén M, 2010).

The annual incidence of RA varies between 20 and 50 cases per 100,000 inhabitants in Northern European and Northern American countries (Alamanosa Y & Drosos AA, 2005). Incidence and prevalence vary geographically and both are estimated to be lower in Southern European and developing countries, although fewer studies have been conducted in these populations (Alamanosa Y & Drosos AA, 2005).

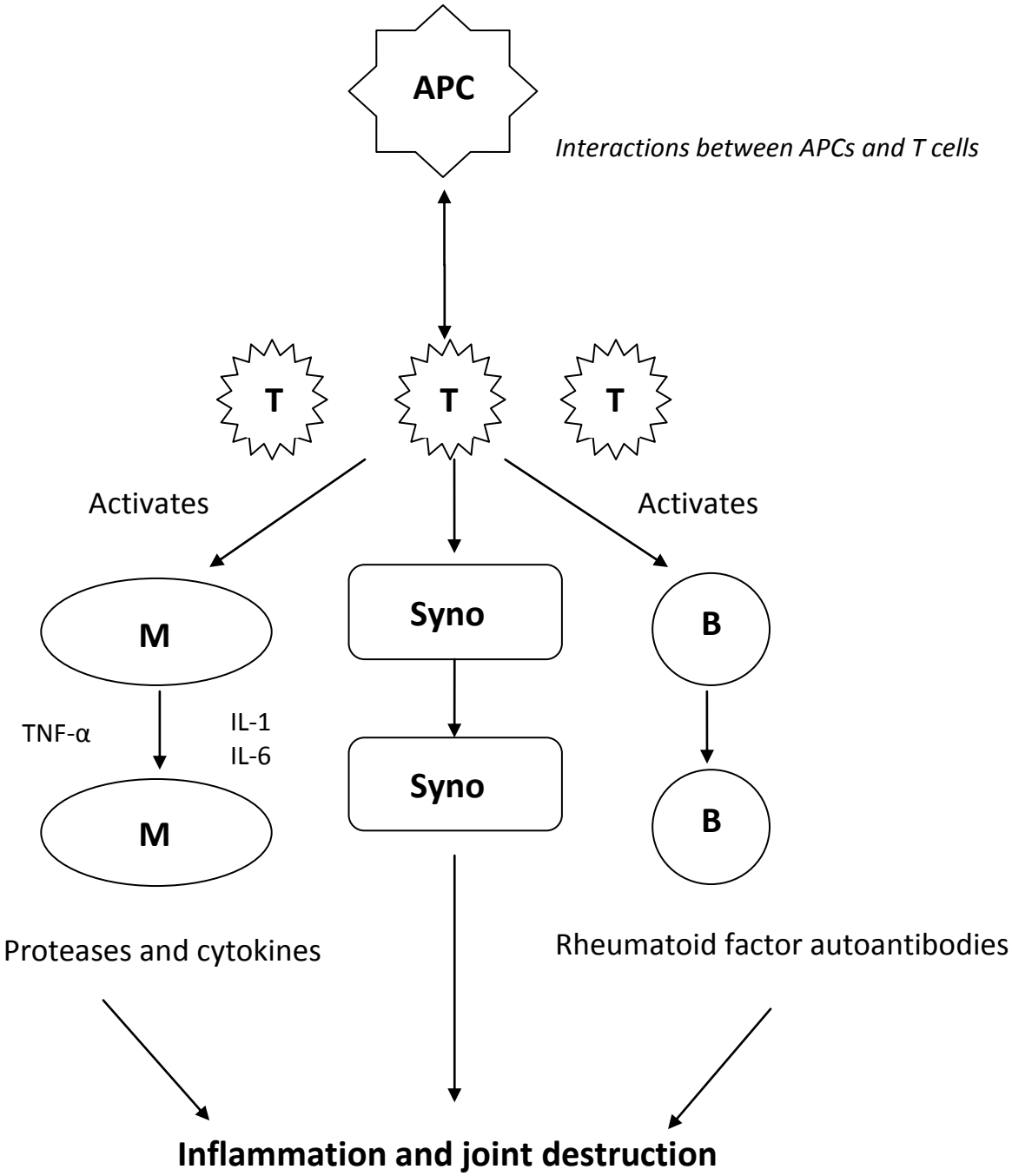
It has been suggested that there has been a decline in the incidence of RA in several populations (Doran MF et al, 2002). However, differences in case definition with different diagnostic criteria (from the 1958 New York classification criteria, to the 1987 revised American College of Rheumatology (ACR) criteria and now the ACR/European League Against Rheumatism (EULAR) 2010 criteria) means that despite a general consensus that the incidence has decreased, it is difficult to quantify this accurately.

1.2 Pathophysiology

RA is a chronic, systemic, autoimmune inflammatory disease, the pathophysiology of which is incompletely understood. It is thought to involve several inflammatory cascades leading to a common pathway in which synovial inflammation leads to damage to articular cartilage and bone (Scott DL et al, 2010).

One key inflammatory mechanism involves the overproduction of tumour necrosis factor alpha (TNF-α). This pathway drives synovial inflammation and joint destruction and results in the overproduction of many other cytokines such as interleukin-6 (IL-6), which also contribute to the state of persistent inflammation (Feldmann M et al, 1996). CD4 T cells, mononuclear phagocytes, fibroblasts and neutrophils also play major cellular roles in the pathophysiology of RA (Scott DL et al, 2010) (Figure 1.1).

Figure 1.1; Diagram to show the rheumatoid arthritis inflammatory cascade



Key
APC – Antigen - presenting cells, T – T cells, M – Macrophages, B – B cells, TNF-α – Tumour necrosis factor alpha, IL-1 - Interleukin 1, IL-6 - Interleukin 6, Syno – Synoviocytes.

Diagram adapted from the Rheumatology Nurses Society (2007)

B lymphocytes are responsible for the production of autoantibodies. Rheumatoid factor (RF) is the classic autoantibody described in RA (Scott DL et al, 2010). Other important autoantibodies include those directed against citrulllinated peptides (anti-CCP). Most, but not all anti-CCP positive patients are also positive for RF. Between 50% and 80% of those with RA are positive for RF, anti-CCP or both (Scott DL et al, 2010). Anti-CCP is generally regarded as being less sensitive but more specific than RF in RA diagnosis. Furthermore, both RF and anti-CCP are associated with articular erosions, suggesting their presence is a predictor of poor prognosis in RA (Lee DM & Schur PH, 2003 & van der Linden et al, 2009).

Inflammation and proliferation of synovium leads to destruction of various tissues, including cartilage, bone, tendons and ligaments. The primary sites affected by RA are synovial joints but many other organ systems can also be affected leading to extra-articular manifestations of the disease.

1.3 Aetiology

The cause of RA is unknown. Genetic, environmental and hormonal factors have all been suggested to play a role.

1.3.1 Genetics

Approximately 50% of the risk of developing RA is thought to be attributable to genetic factors. A polymorphism in the *PTPN22* gene has been associated with RA in several studies in Canada, Europe, and the USA (Wesoly J et al, 2005). However the risk associated with each genetic polymorphism is small and it is therefore unlikely that

individual poylmorphisms will be useful in diagnosing RA or in identifying healthy individuals at risk of RA (Goronzy JJ & Weyand CM, 2009). The only genetic region that has emerged in linkage and in genome-wide association studies in all ethnic groups is the major histocompatibility complex (MHC) region (Yamada R & Yamamoto K, 2007). However the strength of such association varies, depending on ethnic group.

Twin studies have demonstrated a four-fold greater concordance rate in monozygotic (15%) than in dizygotic (3.6%) twins (Silman AJ et al, 1993). The risk in siblings of those with RA compared to that of a 'normal' population has been estimated at between two and 17 times greater (Seldin MF et al, 1999).

1.3.2 Environmental factors

Smoking is the most researched environmental risk factor and accounts for a doubling of the risk of developing RA (Carlens C et al, 2010). Its effect is limited to patients with anti-CCP positive disease (Scott DL et al, 2010). A Swedish study found that such increased risk was only apparent after a long duration of smoking (≥20 years) and that the risk remained for several years following smoking cessation (Stolt P et al, 2003).

Other potential environmental risk factors include alcohol, coffee intake and lower socio-economic status, although evidence for these factors is weak (Liao KP et al, 2009).

1.3.3 Hormones

Sex hormones may play a role in the aetiology of RA, as suggested by the increased prevalence of disease in females. In addition, the symptoms of RA are often alleviated

during pregnancy, only to then recur in the postpartum period (Hazes JMW et al, 2011). There is also a reduced incidence of RA in women using the oral contraceptive pill (Brennan P et al, 1997).

1.4 Diagnosis

There is no single diagnostic test for RA. Therefore the standard and accepted way of defining RA is using classification criteria. Classification criteria enable the stratification of groups of individuals in order to standardize entry into clinical trials and studies. Historically, the diagnosis of RA has been based on the American College of Rheumatology (ACR) 1987 criteria. The ACR 1987 criteria attempt to discriminate between those with RA and other rheumatological diagnoses using seven criteria (Table 1.1). A person is said to have RA if they satisfy four of the seven criteria. The criteria are well accepted as providing a standard disease definition, but they have been criticised due to their inability to identify patients with early disease, and therefore those in need of early intervention.

In a meta-analysis by Banal et al, the pooled sensitivity and specificity of the ACR 1987 criteria were both reported at 77% (Banal F et al, 2009). '*Sensitivity is the proportion of true positives that are correctly identified by the test and specificity the proportion of true negatives correctly identified by the test*' (or criteria in this example) (Bland JM, 1994). When considering those with established disease, sensitivity and specificity were 79% and 90% respectively (Aletaha D et al, 2010).

Table 1.1; ACR 1987 criteria for the classification of rheumatoid arthritis	
Criterion	**Definition**
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, elbow, knee, ankle and metatarsophalangeal (MTP) joints.
3. Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP or PIP joint.
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician.
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects.
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

Scoring: For classification purposes, a patient is said to have rheumatoid arthritis if he/she has satisfied at least four of these seven criteria. Criteria one to four must have been present for at least 6 weeks (Arnett FC et al, 1988).

Early diagnosis and therapeutic intervention are now recognised as key to improving clinical outcomes and reducing joint damage and disability. Collaboration between the ACR and the EULAR resulted in new classification criteria – the 2010 RA classification criteria (Table 1.2). These criteria are designed to identify patients with a short history of inflammatory arthritis, affecting at least one peripheral joint, who may benefit from early intervention (Aletaha D et al, 2010).

Several studies have sought to compare the diagnostic accuracy of the 2010 ACR/EULAR criteria and the ACR 1987 criteria. Varache et al concluded that diagnostic accuracies of the ACR/EULAR score and ACR 1987 criteria were not significantly different (Varache S et al, 2011). Britsemmer et al found that both criteria achieved similar results but that the ACR/EULAR 2010 criteria were slightly more sensitive (Britsemmer K et al, 2011).

The key difference between the ACR 1987 criteria and the ACR/EULAR 2010 criteria is that the new criteria attempt to identify those with early disease and therefore prevent the chronic, erosive disease state exemplified in the 1987 ACR criteria (Banal F et al, 2009).

Table 1.2; The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis	
	Score
Target population: Patients who	
1) Have at least 1 joint with a definite clinical synovitis	
2) With the synovitis not better explained by another disease	
Classification criteria for RA (score-based algorithm: add score of categories A-D; a score of ≥6/10 is needed for classification of a patient having definite RA)	
A. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least one small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative rheumatoid factor (RF) and negative anti-citrullinated protein antibody (ACPA)	0
Low positive RF or low positive ACPA	2
High Positive RF or high positive ACPA	3
C. Acute –phase reactants (at least one test result is needed for classification)	
Normal C-reactive protein (CRP) and normal erythrocyte sedimentation rate (ESR)	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

Scoring: A score of ≥6 must be met for a classification of definitive RA (Aletaha D et al, 2010).

Note: Large joints refer to shoulders, elbows, hips, knees and ankles. Small joints refer to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints and wrists.

1.5 Management

Several guidelines exist to aid in the management of RA. These include those produced by the ACR, EULAR and the National Institute for Health and Clinical Excellence (NICE). Although produced by different bodies, the guidelines agree that management of rheumatoid arthritis requires a multi-disciplinary approach and that the ultimate aim of management is remission or a sustained low disease state.

1.5.1 Treatment of symptoms

Analgesics are the mainstay of symptomatic therapy. Historically non-steroidal anti-inflammatory drugs (NSAIDs) were the first line treatment for RA. It is generally accepted that NSAIDs work by inhibition of the enzyme cyclo-oxygenase (COX) of which there are two forms, COX-1 and COX-2 (Vane JR & Botting RM, 1999). Clinically, this reduces pain and stiffness. However, their popularity has decreased due to their inability to modify the long term course of disease and their many unfavourable side effects. These include renal impairment, increased risk of myocardial infarction (MI), cerebrovascular accident (CVA) and gastrointestinal effects such as dyspepsia and peptic ulcer disease (Brooks P, 1998). Simple analgesics such as paracetamol and codeine are now preferred and help to reduce reliance on NSAIDs (NICE, 2009).

1.5.2 Glucocorticoids

Glucocorticoids are effective at reducing synovitis in the short term and they have the ability to reduce joint damage in the long term. However, their long term use is limited by their unfavourable side effect profile including osteoporosis, impaired glucose tolerance and increased vulnerability to infection (Schacke H et al, 2002).

Despite this, glucocorticoids can be used successfully in two ways. First, they can be used as a short term therapy while waiting for other treatments, such as Disease Modifying Anti-Rheumatic Drugs (DMARDs) to become effective. Second, they can be administrated via the intra-articular and intramuscular route.

1.5.3 Disease-Modifying Anti-Rheumatic Drugs

DMARDs are a heterogeneous collection of drugs grouped together by their use. They are now recognised as the mainstay of treatment for RA, although their diverse mechanism of action is still incompletely understood. However, it is known that DMARDs reduce synovitis, pain, joint damage and acute inflammatory markers, thereby resulting in an improvement in function.

Methotrexate, a folic acid antagonist, is the most widely used DMARD. The precise mechanism of action of methotrexate in RA is unclear. It is thought that methotrexate prevents the synthesis of purine and pyrimidine, necessary for Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) synthesis (Wessels JAM et al, 2008). This results in inhibition of proliferation of lymphocytes, an integral component of the inflammatory process.

Sulphasalazine and leflunomide are also used extensively. Recently, combination DMARD therapy has been advocated, particularly in early or poor prognosis disease (NICE, 2009). Several combinations of DMARDs can be used. An example is methotrexate, sulphasalazine and hydroxychoroquine – often termed triple therapy (Scott DL et al, 2010).

DMARDs have many potential adverse effects. These include minor effects such as nausea and serious effects such as hepatotoxicity, blood dyscrasias and interstitial lung disease (Salliot C et al, 2009). To reduce the risk, adequate pre-treatment screening and subsequent monitoring of blood counts and liver function are necessary (Scott DL et al, 2010).

1.5.4 Biological agents

Following the recognition of TNF-α and IL-1 as crucial pro-inflammatory cytokines, medications have been developed to block these cytokines or to reduce their effect. The first licensed biological agents were TNF inhibitors (Alonso-Ruiz A, 2008). The TNF inhibitors bind TNF-α and therefore prevent it interacting with its receptors. Examples include etanercept, infliximab, and adalimumab.

Following TNF inhibitors several immunomodulators have been developed. These include anakinra (IL-1 receptor antagonist), abatacept (a selective costimulation modulator that inhibits T-cell activation) and tocilizumab (an IL-6 receptor inhibitor).

Biological agents are usually reserved for those patients whose disease is unresponsive to traditional DMARDs as they are expensive and there are numerous adverse events

associated with biological agent use. These include reactions and infection at the infusion or injection site and development of antibodies against the agents (Scott DL, 2010). There is also an increased risk of infections including tuberculosis with TNF inhibitor use and therefore screening is recommended.

There has been concern that biological agents may increase the risk of developing cancer and such risk has been studied by a meta-analysis of trials (Bongartz T et al, 2006). Lymphoma risk in particular has been investigated. An increased risk of lymphoma in severe rheumatoid arthritis is well documented and these are the patients most likely to receive biological agents. Therefore no evidence was found to support the idea that biological agents increase the risk of lymphoma above that of RA alone (Kaiser R, 2008).

1.5.5 Adjunctive treatment

Non-pharmacological therapy includes exercise, splints and orthotics, joint protection, foot care and psychological support. Patient education is also crucial. These strategies are best delivered by a multi-disciplinary team of physicians, nurses, physiotherapists, occupational therapists and podiatrists (Scott DL et al, 2010).

1.6 Complications of disease

The hallmark of RA is a symmetric polyarthritis affecting the hands and feet. However RA can also result in extra-articular disease and much other comorbidity.

1.6.1 Extra-articular features

RA is a systemic disease and thus has the ability to affect almost any organ system. Extra-articular features of the disease can be divided into general and organ specific. General features are often present early within the disease course, with organ specific manifestations generally affecting those with severe articular disease of a long duration (Kelly CA, 2002). General features include malaise, depression, lethargy, weight loss and occasionally fever (Kelly CA, 2002). These non-specific features are often seen in those with active RA.

Organ specific manifestations of extra-articular disease (Table 1.3) are less common and it is thought that their incidence is decreasing with the early aggressive treatment now advocated for RA (Kelly CA, 2002).

Several syndromes may also occur in conjunction with RA. The most common is Sjogren's syndrome which occurs in up to 40% of patients with RA. Clinical features include dryness and discomfort in the eyes, nose and mouth. Felty syndrome is less common (<1% of RA patients) and is characterised by a triad of severe RA, splenomegaly and neutropaenia (Kelly CA, 2002).

Table 1.3; Organ specific involvement in rheumatoid arthritis (Kelly CA, 2002)
Cardiac – Mitral regurgitation (5-10%) – Pericardial effusion (5-30%) – Constrictive pericarditis (<1%)
Connective tissue – Rheumatoid nodules (20%)
Cutaneous – Palmar erythema (20-30%) – Leg ulcers / Pyoderma gangrenosum (<1%)
Haematological – Normochromic normocytic anaemia (Anaemia of chronic disease) (30-50%) – Microcytic anaemia (10-20%) – Macrocytic anaemia (<1%) – Lymphadenopathy (20%)
Neurological – Cervical myelopathy (2-10%) – Carpal tunnel syndrome and other entrapment neuropathies (50%)
Ocular – Keratoconjunctivitis sicca (40%) – Episcleritis and scleritis (1-5%)
Pulmonary – Small airways obstruction (35-50%) – Pleural effusion (5%) – Interstitial lung disease (2-20%)
Vascular – Small/medium vessel vasculitis (<15%) – Digital vasculitis (5-10%) – Raynaud's phenomenon (10%)

% - Prevalence amongst RA patients.

1.6.2 Comorbidity

As previously described, a slightly elevated risk of lymphoma is found in patients with RA which does not appear to be related to anti TNF treatment. The prevalence of lung cancer is also increased, for example a study by Mellemkjaer et al reported a relative risk of 1.5 for developing lung cancer (95% CI 1.3, 1.7) probably due to higher baseline rates of smoking. (Mellemkjaer L et al, 1996). Risk of melanotic and non-melanotic skin cancers is also raised, as is the risk of infection (Mellemkjaer L et al, 1996). Despite this, the majority of morbidity and mortality associated with RA is a result of cardiovascular disease. This will be discussed further in Section 1.8.

1.7 Prognosis

The clinical course of RA is generally characterised by exacerbations and remissions. The life expectancy of those with RA is estimated to be between 5 to 10 years less than that of the general population (Kvien TK, 2004) and such excess mortality is reflected in standardized mortality ratios (SMR) ranging from 1.28-3.00 (Hall FC & Dalbeth N, 2005). Approximately 50% of patients with RA become work disabled within twenty years of diagnosis (Wolfe F & Hawley DJ, 1998). However it is hoped that aggressive treatment with DMARDs will result in better long term functional outcomes in the future (Fries JF et al, 1996).

1.8 Cardiovascular disease

1.8.1 Cardiovascular disease in the general population

CVD is the leading cause of death in the UK, accounting for over 191,000 deaths in 2008 (NICE, 2010 & BHF, 2010). Despite death rates falling, the UK still fairs less favourably in comparison to some Western European countries (BHF, 2010).

CVD is estimated to cost the UK economy £30 billion a year (BHF, 2010). It is therefore unsurprising that an increasing emphasis has been placed on preventive medicine in primary care.

1.8.2 The association between rheumatoid arthritis and cardiovascular disease

Life expectancy for those with RA is reduced when compared with that of the general population. Several studies report elevated standardized mortality ratios (SMR) for those with RA. In a study by Gabriel et al excess mortality was more pronounced amongst women than men, with SMRs of 1.41 and 1.08 respectively (Table 1.4). Much of this excess mortality is due to an increased occurrence of cardiovascular events amongst RA patients (Table 1.5).

Table 1.4; Summary of the relationship between rheumatoid arthritis and overall mortality						
First author	**Year**	**Study type**	**Population included**	**Follow up time (years)**	**Location**	**Main findings**
Escalante	2005	Cohort study	779 RA patients	7	USA	• Patients with a BMI of ≥30 had the lowest rates of mortality, 1.7 deaths per 100 person-years (95% CI, 1.1-2.5). • The highest mortality rates were noted in those with a BMI of <20, 15 deaths per 100 person-years (95% CI, 9.9-23.0).
Gabriel	2003	Cohort study	609 RA patients	14.2	USA	• Excess mortality was more pronounced amongst women than men, with SMRs of 1.41 and 1.08 respectively.
Gonzalez	2007	Cohort study	822 RA patients	11.7	USA	• Between 1965-2005 mortality rates for female and male RA patients were relatively constant at 2.4 and 2.5 per 100 person-years respectively. • However the expected mortality rate decreased over time for both sexes in the general population; from 1.0 to 0.2 per 100 person years in females and 1.2 to 0.3 per 100 person years in males.
Gonzalez	2008	Cohort study	603 RA patients	16	USA	• Mortality for RF positive RA patients was significantly higher than the mortality of the general population (SMR 1.81 (95% CI 1.60, 2.05). • For those with RF negative RA the SMR was 0.99, suggesting no difference in mortality between RF negative RA and the general population.
Goodson	2002	Cohort study	1,236 RA patients	9	UK	• RF positive patients had an increased rate of death from all causes (SMR in men 1.51, in women 1.41) with the majority of excess mortality attributable to CVD.
Nicola	2006	Cohort study	603 patients with RA and 603 controls	12.7 years for RA patients and 14.9 years for non-RA patients.	USA	• During follow up, 345 RA deaths occurred but only 222 deaths were expected. • There was a significantly higher incidence of congestive heart failure (CHF) in patients with RA compared to the non-RA subjects (37.1% versus 27.7%).

Note: BMI- Body Mass Index, CVD – Cardiovascular Disease, RA – Rheumatoid Arthritis, RF – Rheumatoid Factor, SMR – Standardized Mortality Ratio

Table 1.5; Summary of the relationship between rheumatoid arthritis and cardiovascular disease events						
First author	**Year**	**Study type**	**Population included**	**Follow up time (years)**	**Location**	**Main findings**
Holmqvist	2009	Case-control study	8,454 RA patients; 42,267 controls	11	Sweden	• No increase in IHD, MI or angina pectoris prior to the onset of symptoms of RA.
Holmqvist	2010	Cohort study	7,469 RA patients; 37,024 controls	Up to 11	Sweden	• 233 patients with RA and 701 controls developed a first MI during follow up. Increased risk of MI was apparent as early as 1 to 4 years from diagnosis.
Gonzalez	2008	Cohort study	603 RA patients	16	USA	• Male gender, smoking and a personal cardiac history had weaker associations with cardiovascular events among RA patients. • For other traditional cardiovascular risk factors such as hypertension and diabetes there was no difference in the risk imparted from the risk factors between RA and non-RA patients.
Maradit-Kremers	2005	Cohort study	603 RA patients	14.7 for RA patients, 16.8 for non-RA patients	USA	• RA patients were twice as likely to experience unrecognized MI's (hazard ratio [HR] 2.13, 95% CI 1.13–4.03) and sudden deaths (HR 1.94, 95% CI 1.06–3.55). • RA patients were less likely to undergo coronary artery bypass grafting (HR 0.36, 95% CI 0.16–0.80) compared with non-RA patients.
Solomon	2006	Cohort study	25,385 RA patients 252,976 controls	5	USA	• The rate of a cardiovascular event was 14.8 for patients with RA compared to 9.8 for non-RA patients per 1000 person years. • RA patients experienced an approximate doubling of risk for myocardial MI and CVA and a 30% increase in CVD death.

Note: CVA – Cerebrovascular Accident, CVD - Cardiovascular Disease, IHD – Ischaemic Heart Disease, MI - Myocardial Infarction, RA – Rheumatoid Arthritis

A meta-analysis by Meune et al (Table 1.6) found that CVD was the major cause of death among patients with RA, accounting for 40% of observed deaths in one study (Meune C et al, 2009). This is much higher than the proportion of deaths attributable to CVD in the general population (30% in males and 22% in females) and suggests a mortality factor relating to the underlying disease (Meune C et al, 2009).

The study also identified predictors of higher mortality, of which there were several: increased age at RA onset, male gender, raised inflammatory markers, the presence of autoantibodies, diminished function within the first year of RA onset and, as in the general population, low socio-economic status.

Table 1.6; Table to show the main characteristics of the 17 studies included in 'Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies' (Meune C et al, 2009)						
First author	**Publication year**	**Localization**	**Study period**	**No. of patients**	**Follow up time**	**Main Findings**
Monson	1976	USA	1930-1960	1035	Up to 1972	• Death among RA patients from CVD was more common than expected, suggesting a mortality factor related to the underlying disease.
Lewis	1980	UK	1966-76	311	11 years	• Higher than expected death rate in 45-64 age group, with many of these deaths attributable to neoplasia and CVD.
Allebeck	1982	Sweden	1971	1165	Up to 1978	• Mortality amongst patients with RA was 2.5 times greater than the general population. The highest excess mortality was observed in females.
Vanderbrouke	1984	The Netherlands	1954-57	209	25 years	• Median life expectancy was shortened by 7 years in males and 3 years in females.
Erhardt	1989	UK	1979	308	8 years	• Comparison with an age and sex matched population showed an increased incidence of deaths related to MI. The presence of auto-antibodies also predicted poor prognosis.
Reilly	1990	England	1957-63	100	25 years	• Persistently raised ESR and lower haemoglobin was associated with a poor outcome.
Wolfe	1994	USA and Canada	USA: 1965-90 Canada – 1966-74	3501	USA: 8.5 years Canada: 15.8 years	• 361 of the 898 deaths in RA (40%) were attributable to CVD, the expected number of deaths was 161 (a risk ratio of 2.24).
Wallberg-Jonsson	1997	Sweden	1979	606	15 years	• Male sex, increased age at disease onset and hypertension increased the risk of a cardiovascular event.

Table 1.6 Continued; Table to show the main characteristics of the 17 studies included in 'Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies' (Meune C et al, 2009)						
First author	**Publication year**	**Localization**	**Study period**	**No. of patients**	**Follow up time**	**Main findings**
Symmons	1998	England	1964-78	448	21.5 years	• The majority of excess deaths were attributable to CVD but those patients who presented with RA earlier tended to do better.
Sanchez-Martinez	2001	Spain	1989	182	9 years	• The standardized mortality rate was 1.85 for RA patients. • The causes of death were: CVD, 5 (21%); infections, 5 (21%); amyloidosis 4, (17%); malignant diseases 2 (8%).
Bjornadal	2002	Sweden	1964-94	46,917	489 048 person years	• CVD was the major cause of death. Mortality was increased by 80%.
Thomas	2003	Scotland	1981-2000	33,318	6.9 years	• An increased risk of death in all International Classification of Disease chapters except those relating to mental disorders (in RA patients).
Sihvonen	2004	Finland	1988	1042	11 years	• RA patients had increased mortality when compared with the general population. Over 40% of deaths in all groups were due to CVD.
Book	2005	Sweden	1978	152	12.4 years	• Significant predictors of mortality were use of corticosteroids, ESR, and the physician and patient global assessment of disease activity. • RF and use of DMARDs were not significant predictors.
Goodson	2005	England	1981-96	1,010	11.4 years	• Standardized admission rates for CVD were not raised for men and women (1.20 and 1.10 respectively).
Young	2007	England	1986-97	1,429	9.1 years	• Risk factors for increased mortality were low socio-economic status and diminished function within 1 year of RA onset.

There are many possible explanations for the association between CVD and RA. One is a shared risk factor profile, as obesity and cigarette smoking are risk factors for both conditions. However, traditional risk factors can only partially account for the increased risk of CVD in RA, hence suggesting that another mechanism in RA itself, or its treatment, may be responsible (Peters MJL et al, 2010).

A proposed mechanism is that chronic inflammation itself may promote atherogenesis. This is supported by evidence that patients with elevated inflammatory markers have a higher rate of cardiovascular events (Peters MJL et al, 2010 & Kremers MH et al, 2005). The primary site of inflammation is the synovium but the systemic release of cytokines such as TNF-α, IL-1β and IL-6 results in chronic elevation of cytokine levels (Rho YH et al, 2009). This can affect the function of the liver, adipose tissue and vascular endothelium resulting in proatherogenic changes, such as dyslipidaemia and endothelial dysfunction (Satar N et al, 2003).

Treatment of RA may also influence the risk of CVD. NSAIDs are often used for symptom relief but are associated with an increased risk of CVD (Brooks P, 1998). Glucocorticoids could influence CVD risk in two ways; they may exacerbate traditional risk factors such as hypertension, dyslipidaemia and impaired glucose tolerance, or alternatively they may reduce the risk of atherosclerosis by suppressing inflammation (Dessein PH et al, 2004 & Hallgren R and Berne C, 1983). Other anti-rheumatic treatments, such as tumour necrosis factor blockers and methotrexate have shown to be associated with a lower CVD risk, although methotrexate is controversial due to the risk of hyperhomocysteinaemia (Jacobsson LT et al, 2005). Hyperhomocysteinaemia has a toxic and procoagulant effect on the endothelium and therefore may be a risk factor for CVD (Clarke R et al, 1991).

A further treatment-related argument is that patients with RA are less likely than non-RA patients to receive the appropriate secondary prevention with anti-platelet drugs (Colgazier L et al, 2005). This may help to explain the higher mortality rate post MI: 30 day mortality rates in one study were 17.6% for RA patients versus 10.8% for non-RA patients (Van Doornum S et al, 2006).

1.8.3 Comparison with diabetes mellitus

Several studies have compared the risk of CVD in RA and type 2 diabetes mellitus (DM). Van Halm et al found the prevalence of CVD to be 12.4% in the type 2 DM group and 12.9% in the RA group (Van Halm VP et al, 2009). Similarly, Peters et al similarly found the magnitude of risk to be equal amongst those with RA and type 2 DM: compared with the non-diabetic population, non-diabetic patients with RA and those with type 2 DM had comparable hazard ratios (HR), 2.16 (95% CI 1.28–3.63, *P* = 0.004) and 2.04 (95% CI 1.12–3.67, *P* = 0.019), respectively (Peters MJ et al, 2009).

1.8.4 Cardiovascular disease screening

The World Health Organisation (WHO) defines primary prevention as the prevention of occurrence of disease (WHO, 1998). Asymptomatic patients at high risk of CVD need to be identified so that they can be offered lifestyle advice and drug treatment where appropriate.

Many guidelines recommend that the risk of CVD should be determined by combining risk factors to create a numerical estimate of risk (Hippisley-Cox J et al, 2007). There are a

variety of risk calculators available to do this in many formats, for example risk prediction charts and computer programs (reviewed in section 1.8.5).

NICE recommends that all adults aged between 40 and 74 who may be at risk of CVD should be identified so they can be offered primary prevention in primary care (NICE, 2010). This is supported by the Joint British Society (JBS) whose guidelines recommend that anyone over 40 without a history of CVD and not on medications for any CVD risk factors should be considered for an opportunistic CVD assessment. Those people with familial dyslipidaemias, DM, hypertension with end organ damage and established CVD do not need formal risk estimation as it is already known that they are at high risk and therefore they should be managed accordingly (JBS 2 guidelines, 2005).

A CVD risk assessment should include documentation of ethnicity and smoking status and measurement of weight, waist circumference, blood pressure, non-fasting lipids and a non-fasting glucose (JBS 2 guidelines, 2005). These risk factors can then be combined using a risk equation to calculate CVD risk.

1.8.5 Risk equations

Once cardiovascular risk factors have been assessed, they can be combined using a risk equation to estimate the total risk of developing CVD over the following 10 years. The endpoints of CVD are angina, MI and CVA. High risk is usually defined as an estimated risk of ≥20% over a ten year period (JBS 2 guidelines, 2005). If the risk is high then appropriate management strategies can be commenced. This may encompass taking medication, such as anti-hypertensive and lipid lowering therapy (if appropriate) and advice regarding

lifestyle modifications such as, smoking cessation and weight reduction. Several risk equations are available and these are described below.

1.8.5.a Framingham risk equation

The Framingham Risk Equation is based on the Framingham cohort study which was established in 1948 in Framingham, Massachusetts (USA). The aim of the study was to identify common factors that contribute to the development of CVD (Framingham Heart Study, 2011). From this study the Framingham Risk Equation was developed. The Framingham Risk Equation is the most commonly used method of estimating CVD risk in the UK (Ramsay SE et al, 2011).

The risk assessment has been adapted by the Joint British Societies and is based on five risk factors:

- Age
- Sex
- Smoking status
- Systolic blood pressure
- Ratio of total cholesterol to High Density Lipoprotein cholesterol (Table 1.7).

The calculation gives an estimated probability of developing CVD over the next 10 years. A CVD risk of ≥20% is defined as being high risk and requires intervention such as lifestyle modification and drug therapy (JBS 2 guidelines, 2005).

However there are many criticisms of the Framingham Score. First, the majority of the Framingham cohort was Caucasian and as such the model may need to be adapted for use in other populations. Second, the risk equations were developed when CVD was at its peak in America resulting in overestimation of risk in European populations where the incidence of CVD is lower. For example Framingham equations used in current risk scoring methods over-predicted the risk of mortality from coronary heart disease and all fatal and non-fatal coronary heart disease events by 47% and 57%, respectively, compared with observed events in a representative sample of British men (Brindle P et al, 2003). Finally, the Framingham equation does not include several key parameters such as social deprivation and family history of CVD, which may result in underestimates of risk in some high risk groups (Tunstall-Pedoe H & Woodward M, 2006).

1.8.5.b ASSIGN score

The ASSIGN score was developed in response to several studies in Scotland. One such study, by Tunstall-Pedoe and Woodward, described how using the Framingham equation may lead to underestimation of risk in high risk groups, such as those from socially deprived populations, thus exacerbating health inequalities (Tunstall-Pedoe H and Woodward M, 2006). Therefore it was decided to use a Scottish database (the Scottish Heart Health Extended Cohort) to develop a CVD risk score that accounted for social deprivation using the Scottish index of multiple deprivation score (SIMDS) (Table 1.7). Results have shown that ASSIGN performs marginally better than the Framingham score overall and by accounting for social deprivation and family history it demonstrates a sense of fairness to a high risk population (Woodward M et al, 2007).

1.8.5.c QRISK

QRISK was developed from the QRESEARCH database, a large electronic primary care database containing the records of over 10 million patients, about 7% of the UK population. (Hippisley-Cox J et al, 2007). The original QRISK score included the traditional CVD risk factors, age, sex, systolic blood pressure, smoking status and total serum cholesterol: high density lipoprotein ratio, as were included in the original Framingham equation.

The updated QRISK1 also included body mass index, family history of CVD, use of anti-hypertensive medication and the Townsend score (Collins GS and Altman DG, 2010). The Townsend score is a measure of social deprivation. It is calculated from four variables; unemployment as a percentage of those aged >16 years, household overcrowding, none car ownership and none home ownership (as a percentage of all households). The four variables are combined to give an overall score, the higher the score the more socially disadvantaged an area is deemed. Performance data has shown that QRISK1 is better than the Framingham equation and ASSIGN at predicting CVD in a UK population. Overall, in the general population, the Framingham algorithm over predicted risk of CVD in the UK population by 35%, ASSIGN by 36% and QRISK by 0.4% (Hippisley-Cox J et al, 2007).

QRISK1's successor, QRISK2, contains all the variables that were in QRISK1 with the additions of ethnicity and conditions associated with increased cardiovascular risk including type 2 DM, renal disease, treated hypertension, atrial fibrillation, and notably for this thesis, RA (Table 1.7). QRISK2 has been shown to marginally outperform QRISK1 (Collins GS and Altman DG, 2010).

The benefits of greater accuracy in CVD risk assessment are numerous. It ensures that those at greatest risk are identified and offered the chance to benefit from treatment, therefore preventing health disparity. Conversely, preventing over-estimation of risk is essential as it prevents excessive numbers of people receiving unnecessary treatment. The cost of such treatment in terms of resources and prescriptions would place immense financial burden on the NHS, as well as imposing potential side effects on patients.

1.8.5d Reynolds risk score

The Reynolds risk score was developed and validated in America, initially using 24,558 non-diabetic women who were followed for a 10 year period for the development of heart attack, stroke, angioplasty, coronary artery bypass surgery, or death related to heart disease (Ridker PM et al, 2007). The Reynolds Risk Score for men was similarly developed using data from 10,724 initially healthy non-diabetic American men. The Reynolds risk score may only be used on patients without DM and those >45 years. The variables included in this score are age, sex, blood pressure, lipids, smoking, family history and CRP. It is thought that inflammation may play an important role in the development of cardiovascular disease in patients with RA, yet inflammatory markers are not included in many risk equations. By including CRP, the Reynolds risk score may be a more accurate predictor of risk in patients with RA, although this has yet to be assessed (Crowson CS et al, 2012).

1.8.5.e The use of risk equations

The latest NICE guidance on cardiovascular risk assessment for the primary and secondary prevention of CVD, issued in 2010, does not recommend the use of any specific risk equation. However it suggests that results based on the Framingham Risk Equation may be an overestimate of risk in the UK general population (NICE, 2010).

It has been suggested that with the exception of age and sex, three modifiable risk factors; blood pressure, smoking and lipids account for up to 80% of cardiovascular risk in the general population. These three factors are included in all of the risk equations, summarised in Table 1.7 (Emberson JR et al, 2003).

Crowson et al (2012) investigated the use of the Framingham Risk Equation in an RA population and found that it substantially underestimated CVD risk in RA patients of both genders (women by 102% and men by 65%) (Crowson CS et al, 2012). The difference between observed and predicted CVD risk was greatest in patients positive for RF and those with persistently elevated ESR. Similarly the Reynolds risk score underestimated CVD risk in women with RA, despite it including CRP (Crowson CS et al, 2012).

Table 1.7; Summary of cardiovascular disease risk equations															
Tool	**Variables included**														
	Age	Gender	Smoking	BP	Lipids	Family history	Social deprivation	BMI	Ethnicity	DM	Renal disease	Treated hypertension	AF	RA	CRP
Framingham/ JBS	✓	✓	✓	✓	✓										
ASSIGN	✓	✓	✓	✓	✓	✓	✓			✓					
QRISK	✓	✓	✓	✓	✓										
QRISK 1	✓	✓	✓	✓	✓	✓	✓	✓				✓			
QRISK 2	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Reynolds	✓	✓	✓	✓	✓	✓									✓

Risk – The variables are combined to give an estimated probability of developing CVD over the next ten years. High risk is defined as ≥20%.

Note: BP – Blood pressure, BMI – Body mass index, CRP – C reactive protein, DM – Diabetes mellitus, AF – Atrial fibrillation and RA – Rheumatoid arthritis.

1.8.6 Managing cardiovascular disease in rheumatoid arthritis

Multiple studies have highlighted the association between RA and CVD, but how to manage this excess risk of CVD is less well understood. Current guidelines recommend interventions to reduce coronary heart disease risk in those with known CVD, DM and those with a 10 year risk of an event in excess of 20% (JBS guidelines, 2005). However, The British Society for Rheumatology (BSR) and the EULAR both suggest that RA should be regarded as a condition associated with a high risk of CVD and hence screening for cardiovascular comorbidity should occur regularly (Peters MJL et al, 2010 and Luqmani R et al, 2009) .

In order to screen patients according to traditional risk score models, EULAR suggests that if a patient meets two of the following three criteria, then a multiplication factor of 1.5 should be applied to their score:

1) Disease duration greater than 10 years

2) Rheumatoid Factor or anti-CCP positivity

3) The presence of extra-articular manifestations of RA (Peters MJL, 2010).

The BSR also recommends that each patient should have an annual review (Luqmani R et al, 2009). This would allow global assessment of the patient and would allow evaluation of comorbidity and complications. The concept of an annual review is not evidence-based. However it is widely used in rheumatology, is well received by many patients and has also been used successfully for patients with DM to screen for complications (Davies LM et al, 2007).

There is no specific evidence to suggest that modifying cardiovascular risk factors in patients with RA is beneficial. It was hoped that trials such as The Trial of Atorvastatin for the primary prevention of Cardiovascular Events in Rheumatoid Arthritis (TRACE RA) would provide evidence as to whether the use of statins was beneficial for patients with RA, either by reducing blood lipid levels or possibly by reducing inflammation. However, TRACE RA has currently stopped due to inadequate recruitment and any possible conclusions drawn from the study are awaited.

1.8.7 The view in primary care

BSR and EULAR both agree that those with RA need to be targeted for CVD prevention. In addition the BSR recommends specific interventions be provided by primary care physicians when managing patients with RA. These include lifestyle advice and the measurement of blood pressure, lipids, glucose, weight (and BMI) and waist circumference (Luqmani R et al, 2009).

However, uptake of these interventions depends on General Practitioners (GPs) being aware that RA is an independent risk factor for CVD. A questionnaire survey of GPs in the Worcestershire Primary Care Trust suggests this may not be the case. Only 32% of GPs identified RA as an independent risk factor for CVD and only 15% and 34%, assessed their patients for primary and secondary prevention of CVD respectively (Bell and Rowe, 2011). In addition to this, even when GPs did identify RA as a risk factor for CVD, only 40% stated that they would target these patients for intervention (Bell and Rowe, 2011). This

suggests that at present, the increased risk of CVD conferred by RA is under-recognised and under-assessed in primary care.

1.8.8 The Quality and Outworks Framework (QOF)

QOF was introduced in 2004 as part of the new General Medical Services contract. QOF is a voluntary incentive programme for General Practice surgeries in the UK, with an objective to resource and reward good medical practice. Practices are scored against a set of indicators. These indicators cover a wide range of clinical areas as well as assessing the patient experience, practice organization and the additional services that the practice should provide (NHS, 2011). NICE is responsible for reviewing whether indicators should remain part of QOF and for prioritising areas for new indicator development (NICE, 2011).

Five indicators relating to RA are currently being piloted for the 2013/14 QOF. The five proposed indicators are:

1. The practice can produce a register of all patients aged 16 years and over with RA.

2. The percentage of patients with RA in whom CRP or ESR has been recorded at least once in the preceding 15 months.

3. The percentage of patients with RA aged 30-84 years who have had a cardiovascular risk assessment using a CVD risk assessment tool adjusted for RA in the preceding 15 months.

4. The percentage of patients with RA who have had an assessment of fracture risk using a risk assessment tool adjusted for RA.

5. The percentage of patients with RA who have had a face to face annual review in the preceding 15 months.

The QOF advisory committee will consider the results of the piloting and feedback from consultation in June 2012, before recommending which indicators should form part of the 2013/14 QOF menu. The final menu of indicators will be published by NICE in August 2012.

If these indicators are introduced they could have a major impact on the quality of care for people with RA. Several studies have evaluated the impact of QOF for other chronic conditions such as asthma and DM and have found that incentivising care results in an improvement in apparent care quality. An example of this is a study considering DM care, conducted in Shropshire, UK (Tahrani AA et al, 2007). Quality indicators such as the recording of blood pressure, BMI and lipids were assessed. Improvements were seen in all clinical quality indicators between implementation of the General Medical Services contract in 2004 and March 2006. These changes were highly statistically significant (P<0.001) for all indicators (Tahrani AA et al, 2007). Therefore the evidence suggests that QOF can be successful in helping to improve screening practice in primary care.

1.9 Summary

This chapter has summarized the epidemiology, diagnosis and management of RA and has considered the relationship between RA and CVD. The next chapter will present a systematic search and review of the current literature in relation to the screening of

traditional cardiovascular risk factors in patients with RA, before Chapters 3 and 4 describe a primary research study in the Consultation in Primary Care Archive (CiPCA) database.

Chapter 2; Systematic literature review: Screening for cardiovascular disease in rheumatoid arthritis

This chapter describes the systematic search and review of the literature relating to the practice of screening for traditional cardiovascular risk factors in patients with RA. Traditional risk factors for the purpose of this review include blood pressure, serum lipids, blood glucose, renal function, body weight and smoking status.

2.1 Introduction

It is increasingly recognised that patients with RA have a reduced life expectancy when compared to the general population, with the majority of this excess mortality attributed to CVD (Kvien, 2004 & Wolfe, 1994). Traditional cardiovascular risk factors include smoking, hypertension, obesity, hypercholesterolemia diabetes and renal disease. Other, novel factors that may contribute to the CVD burden in RA patients include chronic inflammation (as evident by raised inflammatory markers) and factors related to the treatment of RA such as corticosteroid use (Peters MJL et al, 2010 & Dessein PH et al, 2004).

Although traditional CVD risk factors alone do not account for all of the excess CVD risk in RA, their importance must not be underestimated in helping to reduce the burden of risk, particularly while the contribution of novel risk factors is evaluated (Peters MJL et al, 2010). In addition, many of the traditional cardiovascular risk factors are potentially

modifiable (except for age and gender). Both the BSR and the EULAR recommend regular screening of traditional cardiovascular risk factors in those with RA (Luqmani et al, 2006 & Peters et al, 2010). Despite this, previous studies have documented suboptimal preventative care for patients with RA (Lacaille D et al, 2005 & MacLean CH et al, 2000). Therefore the objective of this chapter is to determine from the current literature, if screening for traditional cardiovascular risk factors is occurring in RA patients.

2.2 Risk factor selection

There are several known cardiovascular risk factors. NICE produces guidelines in relation to these risk factors; stating that as part of an assessment for the primary prevention of CVD the following factors should be considered (NICE, 2010);

1. Smoking status
2. Alcohol consumption
3. Blood pressure
4. Body mass index or another measure of obesity
5. Fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides
6. Fasting blood glucose
7. Renal function
8. Liver function (transaminases)
9. Thyroid-stimulating hormone (TSH) if dyslipidaemia is present

Six CVD risk factors were chosen to form part of this review. The risk factors are **blood pressure, glucose level, renal function, body weight, serum lipids** and **smoking status**. There are several reasons why these risk factors were chosen.

First, the chosen factors are all regarded as traditional cardiovascular risk factors and are also factors generally identified and managed within primary care (Mavaddat N & Mant J, 2010).

Second, with the exception of age and gender, a combination of three risk factors – smoking, raised blood pressure and raised cholesterol – are considered the major contributor to CVD risk, since these are estimated to account for 80% of all cases of premature coronary heart disease (Emberson JR et al, 2003). In addition these three risk factors are necessary when calculating CVD risk using the Framingham Risk tool. Two other risk factors, increased body weight and raised glucose levels, are used to calculate risk in other risk tools such as ASSIGN and QRISK and hence the rational for their inclusion. This is important as the aim of assessing a patient's cardiovascular risk factors is to enable quantification of the level of risk to the individual and therefore whether this risk requires further intervention. These risk tools are a guide and should enhance but not replace clinical decision making.

Renal function was also included as a risk factor because it is used when calculating QRisk 2 and also because of the wealth of studies that have reported an association between renal insufficiency and cardiovascular disease (Sarnak MJ et al, 2003; Foley RN et al, 2005; Hallan S et al, 2007). In one study proteinuria and reduced glomerular filtration rate (GFR) were found to be predictors of CVD, independent of many potential confounders such as hypertension and elevated serum cholesterol levels (Muntner et al, 2002).

2.3 Methodology

The aim of the review was to identify, appraise and synthesise all relevant literature relating to the screening of traditional cardiovascular risk factors in RA. Individual studies can reach conflicting conclusions, but by combining studies in a systematic review, using pre-defined and reproducible methods, more reliable conclusions can be drawn.

2.3.1 Protocol

Following advice from a research information manager, a systematic review protocol was developed detailing the inclusion and exclusion criteria for studies to be included in the review. This approach reduced bias by setting agreed standards before the search commenced. The protocol also contained details of the methods of analysis. By making such decisions in advance, the chance of ad hoc decision making and therefore bias was reduced. The completed protocol was reviewed by a research information manager.

2.3.2 Eligibility criteria

In order to be included within the review, titles and abstracts had to meet all of the following criteria;

1. **An RA patient cohort** – The papers must have reported results of a sample of patients with RA or at least some of the patients in the study must have had RA.
2. **Screening** – The papers must have considered screening for at least one of the risk factors identified as relevant within section 2.2.

Papers were excluded from the review if the titles and abstracts met one or more of the following criteria;

1. **Not available in English language -** No translation facilities were available.
2. **Not related to humans -** The purpose of the review is to determine screening practices for cardiovascular disease in patients with RA.
3. **Not related to any of the relevant screening factors (blood pressure, glucose level, renal function, body weight/BMI, lipid status and smoking status) -**There are many cardiovascular risk factors but only those specified in section 2.2 will be considered as screening for the purpose of the review**.**
4. **Study sample does not contain any RA patients -** This review is only concerned with screening practices in patients with RA.

2.3.3 Information sources

The following electronic databases were searched from inception to October 2011 using the NHS interface:

- **MEDLINE (Medical literature analysis and retrieval system online)** – This is the largest medical database and covers mainly English language journals from North America and Europe. It uses a system called MeSH (Medical Subject Heading) to index entries.

- **EMBASE (Excerpta Medical Database)** – This is the second largest database and covers journals mainly from Europe and Asia. This database uses an indexing system based on EMTREE terms.
- **CINAHL (Cumulative Index to Nursing and Allied Health Care)** – This database mainly covers journals from nursing and other allied health professions. It uses an indexing system of CINAHL headings.
- **BNI (British Nursing Index)** – This is a nursing and midwifery database covering the most popular English Language Nursing journals. It also has limited content from medical and allied health journals.

These databases were utilised to give the widest possible coverage of the clinical literature.

2.3.4 Search strategy

The search strategy was developed following discussion with a research information manager and a senior clinician. Synonyms for the terms rheumatoid arthritis, body weight, blood pressure, blood glucose, smoking, renal function and lipid were also included. MeSH terms and exploding of terms were utilised to acquire as many relevant papers as possible. The terms used varied slightly according to which database was used. When all appropriate terms had been found, each term and its synonyms were combined with the OR operator and then groups of terms were combined with the AND operator.

The search strategy was discussed with an experienced research assistant at the Research Institute to ensure no important synonyms had been omitted.

A list of the search terms and the full search strategies for each database (MEDLINE, EMBASE, CINAHL and BNI) are available in Appendices 1 and 2.

2.3.5 Study selection

All of the titles were screened by the lead reviewer (HM). Following this, the abstracts were screened by the lead reviewer and a second reviewer (SM). In the event of disagreement, a third reviewer (SH) was utilised to help decide if the abstracts should be taken forward to the full text stage. All potentially relevant full papers were read by the first and second reviewer and consensus gained on whether each paper was appropriate for inclusion within the review.

Following completion of the initial search, the reference lists of the full papers were screened by the lead reviewer and the papers citation checked utilising the 'Web of Science.' No journals were hand searched.

2.3.6 Quality assessment

All of the full papers included in the review were assessed against a quality appraisal tool by the lead reviewer and one of three second reviewers (SM, SH and CM). The tool used for appraising the papers was based upon the Quality in Prognostic Studies (QuiPS) tool.

One item was also taken from the Newcastle-Ottawa tool. The quality appraisal tool, along with a description of where the items originated can be seen in Table 2.1.

2.3.7 Data extraction

Following identification and quality appraisal, all of the full papers were re-read and the relevant information extracted and tabulated.

2.3.8 Data synthesis

Data synthesis was dependent on the papers identified. If possible the results of the studies were to be combined using meta-analysis. However, if meta-analysis was not possible due to heterogeneous results, narrative synthesis would be utilised.

Table 2.1; Quality appraisal – modified from Quality in Prognostic Studies (QuiPS)			
	Origin of item	**Review items**	**Comments**
Bias related to study participation	QuiPS	1. The RA population is adequately described for its key characteristics. Yes □ Partly □ No □ Unclear □	Demographics such as geographical location, mean age of group and gender.
	QuiPS	2. The sampling frame and recruitment are adequately described. Yes □ Partly □ No □ Unclear □	Methods to identify the sample, time period of recruitment and place of recruitment. If the whole population is not in study, is selection random?
	QuiPS	3. The inclusion and exclusion criteria are adequately described. Yes □ Partly □ No □ Unclear □	Do patients have to meet specific diagnostic criteria to be included such as the 2010 ACR/EULAR criteria? Are those with pre-existing comorbidity such as CVD or DM included?
Bias related to outcome measurement	QuiPS	4. A clear definition of the outcome of interest is provided. Yes □ Partly □ No □ Unclear	At least one of the following assessments is undertaken; blood pressure, lipid screen, body weight, smoking status, glucose screen and/or renal function.
	QuiPS	5. The outcome measure and method used is adequately valid and reliable to limit misclassification bias. Yes □ Partly □ No □ Unclear □	The units of measurement for all outcomes are the same.
	QuiPS	6. The method and setting of measurement is the same for all study participants. Yes □ Partly □ No □ Unclear □	Primary or secondary care.
	Newcastle/ Ottowa	7. The follow up was long enough to allow outcomes to occur. Yes □ Partly □ No □ Unclear □	Did the papers study people for ≥12 months to see if screening had occurred?
Bias related to Confounding	QuiPS	8. All important confounders are measured. Yes □ Partly □ No □ Unclear □	Have the results been adjusted for demographic variables such as age, gender, race, geographic location and household income if applicable?
Bias relating to Analysis	QuiPS	9. There is sufficient presentation of data to assess the adequacy of analysis. Yes □ Partly □ No □ Unclear □	
	QuiPS	10. There is no selective reporting of results. Yes □ Partly □ No □ Unclear □	Are the results in accordance with the method?

2.4 Results

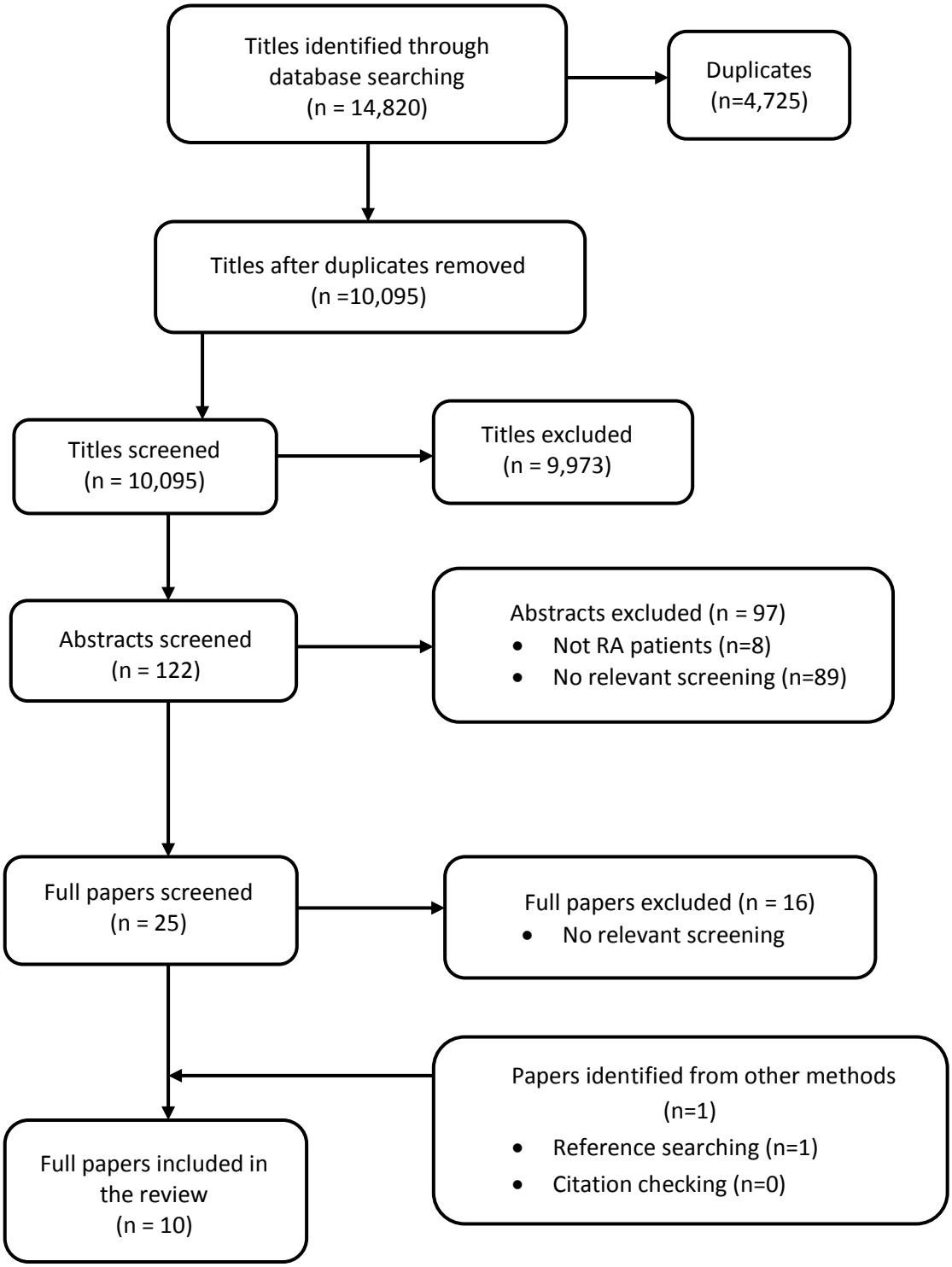
This section presents a description of the study selection and quality appraisal process, followed by results of the studies included within the review. General findings are presented first, followed by more specific results.

2.4.1 Study selection process

14,820 titles were identified, 4,725 of which were duplicates. Therefore 10,095 titles were screened by the lead reviewer (HM); the selection process can be seen in Figure 2.1. Following this 9,973 titles were excluded and 122 abstracts retrieved and reviewed. Consensus was reached without the need for a third reviewer on 119 out of the 122 abstracts, equating to an agreement level of 97.5%. Following discussion, 25 full papers were retrieved and screened by both the lead and second reviewer. Agreement was reached that nine of these full papers were suitable for inclusion within the review.

Following completion of the initial search, the reference lists of the nine full papers were screened in the same manner as described in section 2.3.5. One paper was found utilising this method (Figure 2.1). Following this all ten full papers were citation checked utilising the 'Web of Science'. Sixteen further abstracts were screened but none warranted retrieval of full papers for inclusion.

Figure 2.1; Article retrieval process



2.4.2 Utilising the quality appraisal tool

The ten publications were quality appraised, of which four were only available as conference abstracts and one of which was a letter. It was decided to include the abstracts and the letter due to the relatively small number of papers yielded from the search and to limit publication bias.

The lead reviewer and the other reviewers (SM, SH, CM) agreed on whether the papers met, partly met, did not meet or were unclear on 93% of the items using the quality appraisal tool. Points of disagreement were discussed and agreement regarding the quality of the paper obtained (Table 2.2).

Table 2.2; Agreed quality of papers											
Quality appraisal items											
First author	**Year**	**Participation**			**Outcome measurement**				**Confounders**	**Analysis**	
		1	2	3	4	5	6	7	8	9	10
Bailey*	2009	+	?	-	+	+	+	/	?	-	?
Bartels	2011	+	+	+	+	+	+	/	+	+	+
Bili	2011	+	+	+	+	+	+	+	?	+	+
Curtis	2010	+	+	+	+	+	+	+	+	+	+
Curtis*	2009	+	+	+	+	+	?	?	+	-	?
Hall*	2009	-	-	-	/	?	+	?	-	-	?
Keeling	2011	+	+	+	+	+	+	?	+	+	+
Kremers	2003	+	+	+	+	+	+	+	/	+	+
Litwic*	2010	+	+	/	/	/	?	+	+	+	?
Teir**	2008	-	+	-	+	+	+	?	?	-	+

* The paper is an abstract. ** The paper is a letter.

Note: Numbers in the header relate to the concepts described in Table 2.1.

Key	
+	Criteria met
/	Criteria partly met
-	Criteria unmet
?	Unclear

2.4.3 Data extraction

The 10 full papers were re-read and the relevant information extracted and tabulated (Tables 2.3 and 2.4).

Table 2.3 describes some of the demographics of the included papers, including first author, year of publication, location, study design, setting, follow up time period and the populations/samples involved (RA cohort and control group). Table 2.4 presents more specific information in relation to the participants and the specific cardiovascular risk factors for which they were screened.

Table 2.3; Study characteristics								
First author	**Year**	**Location**	**Study design**	**Setting**	**RA sample (n)**	**Control sample (n)**	**Caucasian (%)**	**Follow up (years)**
Bailey*	2009	UK	Retrospective cohort study	Secondary care	45	n/a	-	1
Bartels	2011	USA	Retrospective cohort study	Primary & secondary care	3,298	n/a	90%	3
Bili	2011	USA	Retrospective cohort study	Primary & secondary care	831	169,476 (general population)	97%	5
Curtis	2010	USA	Retrospective cohort study	Primary & secondary care	141,140	6,300 (PsA) 770,520 (OA)	90%	5
Curtis*	2009	USA	Retrospective cohort study	Primary &secondary care	30,586	107,534 (OA)	-	≥1.5
Hall*	2009	UK	Retrospective audit	Secondary care	135	n/a	-	-
Keeling	2011	Canada	Retrospective cohort study	Secondary care	440 with inflammatory arthritis (RA -433, PsA - 7)	64 (SLE)	-	-
Kremers	2003	USA	Retrospective cohort study	Secondary care	264	n/a	-	2 for blood pressure, 5 for serum lipids
Litwic*	2010	UK	Retrospective cohort study	Not clear	100	n/a	-	1
Teir**	2008	UK	Retrospective audit	Secondary care	100	65 (SLE)	-	1 for blood pressure, lipids and glucose. 5 for smoking status

Key
* The paper is an abstract **The paper is a letter - No data available
RA – Rheumatoid Arthritis, PsA -Psoriatic Arthritis, OA – Osteoarthritis, SLE – Systemic Lupus Erythematosus

Table 2.4; Patients with cardiovascular risk factors recorded (%)								
First author	**Mean age (years)**	**Female (%)**	**Lipid screen (%)**	**Blood pressure (%)**	**Smoking status (%)**	**Blood glucose (%)**	**BMI or body weight (%)**	**Renal function**
Bailey *	57.5	82.2	17.8	82.2	-	-	-	-
Bartels	-	83.4	45.1	-	-	-	-	-
Bili	63.0	72.0	86.0	-	-	-	-	-
Curtis	-	76.9	84.0	-	-	-	-	-
Curtis*	50.0	74.1	59.8	-	-	-	-	-
Hall*	-	-	25.0	65.0	75.0	65.0	15.0	-
Keeling	-	73.4	14.3	56.1	40.7	-	4.0	-
Kremers	64.4	74.6	88.0	95.0	-	-	-	-
Litwic*	61.5	70.0	72.0	100.0	-	71.0	100.0	-
Teir**	-	-	35.0	62.0	43.0	59.0	-	-

Key
* The paper is an abstract.
** The paper is a letter.

2.4.4 General findings

Ten papers were included in the review, of which four were conference abstracts and one was a letter. All of the papers included screening for serum lipids, six included blood pressure and three included blood glucose, smoking status and BMI or body weight. None of the papers included within the review considered screening of renal function.

All of the identified papers have been published relatively recently; the oldest study reported in 2003, and they all considered RA populations in developed countries (UK, USA and Canada). Five of the papers studied a secondary care sample, four studied a mixed primary and secondary care sample and in one study the sample was not described.

The RA cohorts varied considerably in size from a study of 45 patients to 141,140 patients. The follow up time was also variable, from one to five years.

The mean age of the participants ranged from 50 to 64 years, however this information was not available in five of the papers. As one would expect for an RA cohort, females predominated, accounting for between 70 and 82% of participants. Information regarding ethnicity was only available in three of the papers. In these papers the samples studied were largely Caucasian (90-97%).

2.4.5 Screening of cardiovascular risk factors

All 10 papers considered lipid screening but the results were variable, with screening rates varying from 14 to 88%. Six papers considered screening for hypertension with measurement of blood pressure occurring in between 62 and 100% of patients. Three papers considered smoking status as part of cardiovascular risk assessment. Rates of

recording of smoking status varied from 41 to 75%. Only three of the papers considered BMI or body weight with results which varied from only 4% of the cohort having a BMI or body weight record to 100% (Litwic AE & Ledingham JM, 2010). Finally, three papers considered screening for elevated glucose levels, with the assessment made in between 59 and 71% of participants.

None of the studies considered the screening of renal function and therefore renal function will not be considered further.

Several of the papers extended their work by comparing screening practice in different samples and by considering whether the setting of care influenced the likelihood of screening. One paper considered whether educating physicians impacted on practice and one considered what, if anything was done after a cardiovascular risk factor has been assessed. These results give context to cardiovascular screening in RA and are further described below.

2.4.6 Setting of care

Four papers (Bartels CM et al, 2011; Bili et al, 2011; Curtis JR et al, 2009; Curtis JR et al, 2010) compared screening in primary and secondary care populations, five considered secondary care only (Bailey KA & Kumar N, 2009; Hall FC et al, 2009; Keeling SO et al, 2011; Teir J et al, 2008; Kremers HM et al, 2003) and in the abstract by Litwic et al (Litwic AE & Ledingham JM, 2010) the population was not described.

Bartels et al (Bartels CM et al, 2011) investigated the association between lipid screening and visits to a primary care provider and a rheumatologist in the USA. They found that

only 45% of eligible patients received a serum lipid screen over a three year period but that any contact with primary care predicted a 26% greater chance of lipid screening than rheumatology care alone (26% [95% CI 21-32]).

Curtis et al (2010) et al also found similar results (Table 2.5). Shared rheumatology and primary care resulted in higher odds of screening than rheumatology care alone. However sole care from a primary care physician resulted in the highest odds of screening.

Table 2.5; Delivery of care (Curtis JR et al, 2010)

Physicians providing care	**Hyperlipidaemia testing OR (95% CI)**
Rheumatology but no primary care	1.00
Both rheumatology and primary care	1.28 (1.07, 1.53)
Primary care and no rheumatology	1.34 (1.12, 1.60)
No rheumatology or primary care	0.87 (0.66, 1.13)

A study by Bili et al took a different view and considered which physician had requested hyperlipidaemia testing in all those who had received it; 79% of lipid screening was ordered by a primary care provider (family medicine or internal medicine), 4% by a cardiologist, 2% by a rheumatologist and 15% by all other providers (Bili et al, 2011).

These results, in accordance with those by Bartels et al (2011) and Curtis et al (2010) suggest involvement of a primary care physician improves the likelihood of receiving CVD screening.

2.4.7 Influences on screening

Five of the papers compared their RA cohort with a control group. In one paper, (Bili A et al, 2011) this was a general population sample, while the other four studies used control

groups of patients with other musculoskeletal diseases, such as those with osteoarthritis, systemic lupus erythematosus and psoriatic arthritis. Two of the papers (Bili A et al, 2011; Curtis JR et al, 2009) considered whether comorbidity influenced screening and one (Bili A et al, 2011) considered whether those with more severe RA were more likely to be screened for cardiovascular risk factors.

2.4.7a Influence of other musculoskeletal disease

In the study by Bili et al (2011), patients with RA were more likely to be screened than the control (general) population for dyslipidaemia (86 vs. 75%) (Bili A et al, 2011). However in the remaining four studies that compared RA patients with cohorts of patients with other musculoskeletal diseases, those with RA were less likely to be screened than patients with other diagnoses.

Curtis et al (2009) found those with a diagnosis of RA were less likely to receive screening for hyperlipidaemia than those with OA (59.8% and 69% respectively. A further study by Curtis et al (2010) considered hyperlipidaemia screening in those with RA, Psoriatic Arthritis (PsA) and Osteoarthritis (OA) over a five year period and found that screening was very similar between the three groups (84%, 89% and 87% respectively).

Keeling et al (2011) compared screening in those with SLE and RA. Rates of screening were greater for dyslipidaemia but lower for the other three identified risk factors in RA patients (Table 2.6).

Table 2.6; Number (%) of SLE and Inflammatory Arthritis (IA) patients where traditional risk factors were recorded (Keeling SO et al, 2011)		
Cardiovascular risk factor	**No. (%) of SLE patients**	**No. (%) of IA patients**
Smoking	31 (48.4)	179 (40.7)
Dyslipidaemia	6 (9.4)	63 (14.3)
Systolic blood pressure	60 (93.8)	247 (56.1)
Obesity	5 (7.1)	18 (4)

A similar study by Teir et al (2008) found that screening for blood glucose, lipid screening, blood pressure and smoking status was more likely in patients with SLE compared to RA. In part, this may reflect greater recognition of the risk of cardiovascular disease in patients with SLE, since their risk of CVD is greater than those with RA (Santos MJ et al, 2010).

2.4.7b Influence of comorbidity

Bili et al (2011) found that those who received lipid testing had more traditional CVD risk factors such as DM and hypertension.

Curtis et al (2009) suggested that the lower rates of screening in RA compared to OA may have been due to lower rates of diagnosed DM (6.2% vs. 9.7%), obesity (2.2% vs. 4.1%) and hypertension (23.1% vs. 38.4%; $p < 0.0001$ all comparisons) in the RA group. However in this study, the mean age of the RA group was lower (50 vs. 56 years) and so comparison was not entirely fair.

2.4.7c Influence of disease severity

One paper considered screening in relation to RA severity (as inferred by RF or anti-CCP positivity, use of corticosteroids, methotrexate or TNF-α inhibitors). Corticosteroid or methotrexate use was associated with less screening in men and there was a trend towards less screening in anti-CCP positive women, although the numbers in this group were small (Bili A et al, 2011).

2.4.8 Education of physicians

Litwic & Ledingham (2010) investigated 100 consecutive patients at a rheumatology practice to determine if educating physicians affected screening practice. Letters sent to their GP's in the previous 12 months were analysed for information relating to the increased risk of CVD in patients with RA, the need for an annual screen of cardiovascular risk factors in patients with RA and the need to bear in mind this increased risk when setting thresholds at which intervention would be commenced (Litwic AE & Ledingham JM, 2010). This information was present in letters to GPs in 66 of the 100 patients studied. Of the 100 patients, a lipid screen was performed in 72%. For 60% of the 28 patients in whom a lipid screen had not been performed, their GP had been informed of the need for annual CVD screening and had been asked to check lipid status (Litwic AE & Ledingham JM, 2010).

2.4.9 Modifiable risk

Hall et al (2009) in their retrospective study of 135 secondary care RA patients investigated if screening led to a change in clinical practice. Each risk factor was rated on a four point scale: 0 – Not recorded, 1 – recorded, outside target range but no intervention, 2 – recorded, outside target range but appropriate intervention, 3 – recorded and within target range.

Table 2.7; Unmodified cardiovascular risk (Hall FC et al, 2009)

Risk factor	Level of intervention (0-3)	% of patients
Smoking	0	27
	1	13
	2	6
	3	54
Systolic BP	0	35
	1	13
	2	19
	3	34
Total cholesterol	0	65
	1	4
	2	14
	3	16

Screening was sub-optimal as evidenced by 27%, 35% and 65% of participants without a record of smoking status, systolic blood pressure or total cholesterol respectively (Table 2.7). Attempts to modify cardiovascular risk factors when outside of the target range were also poor, suggesting that even when screening was occurring, abnormal results did not lead to a change in management.

2.5 Discussion of review findings

According to the currently available literature, screening for five of the six identified cardiovascular risk factors is suboptimal. There is no published data regarding renal function screening in RA patients and therefore this has not been considered further. This is probably because many of the medications prescribed to people with RA (e.g. Methotrexate) require regular renal function monitoring as part of the safety requirements of this drug (Chakravarty K et al, 2008), regardless of its role in contributing to CVD.

None of the papers included are more than ten years old suggesting that the issue surrounding screening for CVD in RA has only been given attention relatively recently. In addition to this the follow up time was variable (1-5 years) which probably reflects the lack of guidance on CVD risk assessment in those with RA.

The following subsections will discuss factors that are related to cardiovascular screening in RA patients.

2.5.1 Primary versus secondary care

Primary care involvement consistently predicted a greater chance of lipid screening than rheumatology care alone. (Bartels CM et al, 2011 and Curtis JR et al, 2010). In addition, one study found that lone primary care increased the likelihood of screening when compared with shared care (OR, 1.34 (1.12, 1.6)) (Curtis et al, 2009).This suggests that primary care physicians take responsibility for screening when the care of the patient is solely their responsibility but that they are more likely to leave primary prevention to

rheumatologists when care is shared between the two specialties. These studies both consider populations in the USA and so it is fair to make such comparisons with regards to the responsibility of care.

It is important to consider the relationship between the setting of care and the likelihood of screening, as although care for patients with RA is often shared between primary care and rheumatologists, it is often unclear who is responsible for managing the associated CVD risk conferred by the presence of RA. This is further compounded by two factors. First, risk assessment and managing cardiovascular risk has long been considered the role of primary care physicians, particularly as such practice is already common place for those with other comorbidities such as DM. Therefore it may have been assumed that screening for cardiovascular risk factors in patients with RA is the responsibility of primary care physicians. Second, despite the association between RA and CVD being known for some time within the field of Rheumatology, the excess risk of CVD conferred by RA is under-recognized in primary care (Bell C & Rowe IF, 2011). Therefore this appears to have created a gap in care for those with RA, as evidenced by the suboptimal rates of screening identified in this review.

Primary care is likely to be the most appropriate setting for cardiovascular risk assessment in the UK, as GPs already have expertise in managing cardiovascular risk in other high risk groups. Implementation of QOF indicators and education would enable the success achieved in managing other high risk groups to be replicated in RA patients.

2.5.2 Influences on screening

There is a general trend of sub-optimal screening for those with RA and in particular screening is less likely to occur in RA patients compared to those with other musculoskeletal disease (Curtis et al, 2009; Curtis et al, 2010; Bili et al, 2011). Those with a diagnosis of OA were more likely to receive screening than RA patients, despite OA being a non-inflammatory arthritis and much less evidence of increased CVD risk in OA (Gabriel SE et al, 1999).

It also appears that in those patients who receive screening, other factors such as the presence of well-known cardiovascular risk factors such as DM and hypertension appear to be influential in prompting screening practice, rather than a diagnosis of RA itself. In addition severe disease state, as indicated by the presence of auto-antibodies and specific medications did not result in additional screening (although this was only considered in one study) (Bili et al, 2011).

2.5.3 Education of physicians

It is likely that the education of primary care physicians regarding the increased cardiovascular risk in RA is sub-optimal, evidenced by one study included in this review (Litwic AE & Ledingham JM , 2010). 72% of patients with RA were screened for hyperlipidaemia and while this is promising it still remains that over a quarter of RA patients would have had no assessment of lipid status, and this was in spite of the delivery of information regarding CVD risk to GPs.

In a study by Bell and Rowe (2010) only 20% of GPs had read a journal article about RA and cardiovascular risk and only 15% of GPs had received consultant communication about the need to assess cardiovascular risk in RA patients (Bell & Rowe, 2010). This suggests that despite a wealth of literature regarding the excess risk of cardiovascular disease and RA in the rheumatology literature, such information is not accessible to GPs. However, this study suggested GPs were receptive to information regarding this subject area. In a questionnaire survey, 84% of GPs felt a review article and 85% a presentation about RA and CVD risk would be beneficial to their clinical practice (Bell & Rowe, 2010). However, the effectiveness of such an educational intervention is not clear.

However, there are barriers to ensuring RA patients receive adequate risk reduction and these were discussed by both Teir and Hall. Teir cites time and information technology limitations as factors that can hinder CVD risk assessment (Teir J et al, 2008). Hall similarly found the main barriers to be time limitations and access to risk reduction software (Hall FC et al, 2009).

2.5.4 Modifiable risk

Risk assessment alone is not sufficient; if elevated risk is detected, then appropriate intervention is essential in order to improve outcomes. Hall et al assessed this and found that both the recording of risk factors and intervention was suboptimal (Hall FC et al, 2009).

This suggests that physicians need education on both risk assessment and modification. A possible explanation for disappointing recording of risk factors and intervention is that RA

is a complex multi-system disease that would undoubtedly consume a large amount of consultation time, leaving little time for discussion of risk assessment. In addition, it has been suggested that those with multiple chronic medical conditions are more likely to have some aspect of their disease/s neglected or undertreated (Bili A et al, 2011). This is particularly likely in instances when one medical condition can consume more attention of both the patient and clinician, as would be possible in RA.

It is also possible that patients may be reluctant to accept additional interventions or drug therapy (Kremers HM et al, 2003). This is particularly likely in a condition such as RA. Patients may be more willing to take medication for their RA which is painful than for hypertension which is asymptomatic. Therefore a patient may be unwilling to accept additional treatment for a condition which does not affect their everyday life. Similarly it may be that primary care physicians are reluctant to prescribe additional medication to a patient who may already be subject to polypharmacy. This is an unfortunate scenario, since patients with chronic diseases such as RA often have more contact with the health care system and each contact without consideration and modification of cardiovascular risk is a missed opportunity for implementation of preventive services.

2.6 Discussion of review methods

This section will consider the strengths and limitations of the review and any sources of potential bias that may be have been introduced through the study design.

2.6.1 Search strategy

The search strategy was formulated with the help of a health information manager and a senior clinician. This helped to ensure that no relevant terms were omitted. Performing the search on a range of databases and searching for terms as both free text and subject headings ('exploded' where available) helped to ensure a comprehensive list of titles was compiled. The combining of search terms using the 'AND' and 'OR' operators helped to ensure that as well as being sensitive, the search was also specific.

All of the potentially relevant titles were read only by the lead reviewer so there is a small possibility that a potentially relevant paper could have been missed due to human error. Following this, all potentially relevant abstracts and full papers were read by both the lead reviewer and a second reviewer, reducing the chance of such error at these stages of the process.

The reference lists of all relevant papers were checked. The papers were also citation checked. From this only one further paper was identified as relevant, which supports the strength of the initial search strategy.

A limitation of the search is that it was limited to English language papers only. This was necessary as no translation facilities were available, but it could mean that potentially relevant papers in a different language have been omitted.

A further limitation is that no attempt was made to search the 'grey literature' although some conference abstracts were identified. 'Grey literature' includes all sources of information that have not been formally published, such as dissertations, government information and reports.

This review, like all systematic reviews, is potentially at risk of publication bias. Publication bias arises as papers with significant results are more likely to be published than those with non-significant results. An attempt to counter this was made by including conference abstracts.

2.6.2 Quality appraisal

All of the full papers were subject to quality appraisal and a high level of agreement (93%) was obtained, which gives confidence to the strength of the quality appraisal process. As does the use of a specifically developed tool, adapted from published instruments.

The abstracts were generally judged to be of lesser quality, with considerably more of the items falling into the criteria not met, partly met or unclear when compared to the remaining six full papers, likely to be due to the limitation of space.

2.6.2a Participation

All of the full papers met all of the items in the participation section of the quality appraisal. The abstracts and the letter did not meet these quality criteria, with all having at least one item fulfilling the criteria not met/partly met, specifically the abstract by Hall (Hall FC et al, 2009) did not include any of the participation criteria. Nevertheless it was decided to include the abstract in the review as several relevant risk factors were considered.

2.6.2b Outcome measurement

The abstracts and letter also failed to include adequate detail on their sample, specifically in the abstract by Litwic et al, it was unclear whether their sample originated from primary or secondary care. In addition, two papers (Hall FC et al, 2009 & Keeling SO et al, 2011) failed to record how far back notes or databases were searched to look for evidence of screening practice. However, this is unlikely to have explained the results observed. Any possible effect of this on the review would be minimal as this would only be problematic if very short time frames were utilised, in which it would be inappropriate to expect clinicians to have organised all relevant screening.

2.6.2c Confounders

Five of the studies met the criteria for adjusting for confounders. One partly met, one did not meet and the remaining three articles were unclear. Confounders include variables such as age, race, and geographic location.

2.6.2d Analysis

All of the full papers met the criteria for analysis. In these studies there was sufficient presentation of data to assess the adequacy of analysis. However, this was not true of the abstracts, where, probably due to length restriction, all of the abstracts had at least one unclear or did not meet the criteria in one domain.

2.6.3 Data extraction

Data extraction was completed by the lead reviewer. This process may have been subject to human error as only one person was involved in the process. However the likelihood of this occurring was reduced by extracting all of the information twice and obtaining the same results each time.

2.6.4 Synthesis of results

Meta-analysis was not performed. Due to the heterogeneity in terms of screening for cardiovascular risk factors narrative synthesis was considered superior. However, limiting the synthesis to a narrative form has the potential to create bias. This may be particularly likely if one argument or area for discussion is discussed more often or given more prominence within the review. An attempt to prevent this has been made by considering each study in relation to the arguments posed where possible.

2.7 Conclusions

From the current literature it can be concluded that screening of patients with RA for CVD is suboptimal and variable. It can also be concluded that screening is less likely to occur in RA patients compared to those with other musculoskeletal disease, particularly SLE. Those that are screened are more likely to have comorbidities such as DM or hypertension but no association was found between disease severity and likelihood of screening. Finally, the setting of care was very influential, with involvement of a primary care physician having a positive effect on screening.

2.8 Justification for further study

Despite increased attention being focussed on cardiovascular disease prevention in RA, reflected in national (BSR) and international (EULAR) guidance, no studies looking solely at screening practice within a primary care population were found. The cross sectional study described in subsequent chapters will consider screening practice in a UK-based primary care population.

This chapter has helped to inform the objectives of the cross sectional study (presented in Chapters 3-6). For example, it has been demonstrated that considering renal function testing from a CVD screening perspective is inappropriate in this context. Therefore renal function will not be considered a risk factor for the original study. This review has also suggested that when a patient is screened, it is often the presence of comorbidity such as DM or hypertension that influences screening practice, rather than a diagnosis of RA itself. This will be examined in the study.

Finally, none of the papers in the review considered how often RA patients consulted in primary care. In the UK, the care of patients with RA is usually a shared responsibility between primary and secondary care physicians. Therefore it may be that RA patients consult less frequently in primary care and therefore have a reduced likelihood of receiving opportunistic CVD risk assessment. This will be explored in the cross sectional study.

Chapter 3 describes the aims and objectives of the cross sectional study in more detail, before Chapter 4 describes the methodology, Chapter 5 the results and Chapter 6 the implications.

Chapter 3; Study aim and objectives

Chapter 1 described the increased risk of CVD in those with RA and considered the available guidance. Chapter 2 comprehensively evaluated the current medical literature surrounding screening for cardiovascular risk factors in RA patients, and generated questions to be answered in the primary research study presented in this thesis. This chapter describes the aim and objectives of this original study.

3.1 Study aim

The overall aim of the study is to determine screening practice for traditional cardiovascular risk factors in patients with RA in a UK-based primary care population.

3.2 Study objectives

In order to meet this aim, specific objectives were formulated. These are to determine whether RA patients are more likely than their age, gender and practice matched counterparts to:

- be screened for individual cardiovascular risk factors
- be screened for any cardiovascular risk factors
- receive a standard screen (the recording of blood pressure, smoking and lipid status)

- receive a comprehensive screen (the recording of all five cardiovascular risk factors)
- receive screening compared to those with diagnosed comorbidity (diabetes, hyperlipidaemia and hypertension)
- consult in primary care

The next chapter describes how these objectives will be met.

Chapter 4; Methodology

The previous chapter described the aim and objectives of the study. This chapter will describe the study methodology. First, the databases utilised for the study - Consultations in Primary Care Archive (CiPCA), Investigations in Primary Care Archive (IiPCA) and Prescriptions in Primary Care Archive (PiPCA) - will be described. Second a description of how the data from the relevant databases was processed for use will be given. Finally, the statistical methods used for the study will be defined.

4.1 Databases

The data used in this study have been extracted from three interlinked regional primary care databases of frozen consultations housed at Keele University: the Consultations in Primary Care Archive (CiPCA), Investigations in Primary Care Archive (IiPCA) and Prescriptions in Primary Care Archive (PiPCA). These databases are often collectively referred to as CiPCA.

4.1.1 Consultations in Primary Care Archive (CiPCA) and Investigations in Primary Care Archive (IiPCA)

CiPCA is a database of frozen consultations from general practices in North Staffordshire, UK (Jordan K et al, 2007). Information recorded from the consultation includes the date, the Read Code and Read Term issued for the problem(s) addressed during the consultation. The location of the consultation (e.g. surgery, home visit) and the accompanying consultation text is also recorded. Doctors and nurses are requested to

assign every contact with at least one morbidity code. This could be a diagnostic code or a symptom code (Jordan K et al, 2007).

IiPCA is a similar database that provides a record of the investigations undertaken following the record of a problem in CiPCA. The code and terms used to describe the investigation are recorded in IiPCA. Examples of investigations include a glucose tolerance test and plasma lipid levels; investigations used to diagnose DM and hyperlipidaemia respectively. The documentation of screening spans CiPCA and IiPCA and therefore it was necessary to use both databases to gain an accurate understanding of screening practice. Patients are assigned a unique identifier so that their records can be linked over time and between different databases.

4.1.2 Prescriptions in Primary Care Archive (PiPCA)

PiPCA contains data relating to the prescription of medicines from the same General Practices in North Staffordshire.

Nine general practices contributed to the data used for this study, equating to 80,363 patients from the North Staffordshire area. Several practices were not included as they did not have complete data for the years 2000 to 2008.

4.1.3 Strengths and weaknesses of the CiPCA and IiPCA databases

The practices that generate the data included in these databases are part of the Keele GP Research Partnership and are therefore subject to regular cycles of training, assessment and feedback which helps to ensure the quality of the data is high (Jordan K et al, 2007).

Studies have demonstrated that CiPCA is a good local epidemiological resource (Jordan K et al, 2007). Local databases are useful for establishing local burden of disease and for demonstrating trends over time which can be useful for health planners and those commissioning services (Jordan K et al, 2006).

However, this local focus may limit generalisability. Their use is also weakened by general limitations that affect all electronic consultation databases. For example, not every problem discussed between a GP and patient may be coded and not everybody with morbidity will consult a General Practitioner. Such factors may result in underestimates of actual prevalence. However this is unlikely to influence the results of this study as the focus of interest is what happens to patients when they do consult.

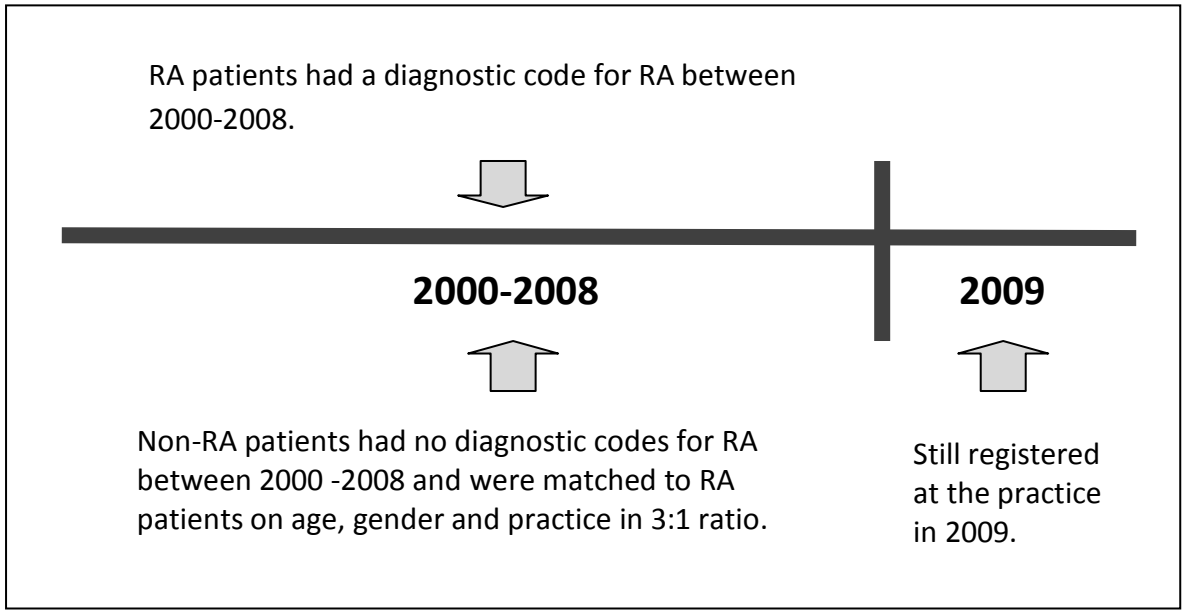
4.1.4 Strengths and weaknesses of the PiPCA database

The data quality of PiPCA is high as all medicines must be recorded on a computer before they can be prescribed. However the reason for the prescription is not recorded in this database and therefore it would be necessary to look at CiPCA for such information (i.e. the morbidity code). Even then, the reason for the prescription must be assumed, based on the date and problem title of the consultation.

4.2 Sample

All patients with a diagnostic Read Code for RA in the CiPCA database between 2000 and 2008 and still registered with the practice in 2009 were identified (Figure 4.1). Codes relating to RA were identified using the NHS Clinical Terminology Browser (Clinical Terminology Browser, 2010) and are presented in Appendix 3. These RA patients were matched to three age, gender and practice matched non-RA patients to allow for comparisons to be made. Non-RA patients had also consulted for something other than RA in the year in which the corresponding RA patient first consulted with RA. Several of the RA patients identified were elderly and there were inadequate non-RA patients in the database to allow for complete 3:1 matching. In this case, 2:1 or 1:1 matching was utilised.

Figure 4.1 Timeline of events



4.3 Codes

Diagnoses, screening tests and prescriptions are coded within CiPCA, IiPCA and PiPCA. Therefore it was necessary to identify relevant codes in order to identify the entries of interest. CiPCA and IiPCA use the Read code system (NHS, 2012), whilst PiPCA uses British National Formulary (BNF) codes (Joint Formulary Committee, 2009).

4.3.1 Risk factor screening identification

The records of RA and non-RA patients were searched to look for evidence of screening of five traditional cardiovascular risk factors (in 2009). The Read codes relating to these risk factors were identified by searching for terms related to blood pressure, body weight/BMI, glucose, smoking status and lipids. A participant was said to have been screened for a cardiovascular risk factor if they had a code reflecting an investigation or if they had been given a diagnosis relating to such a risk factor. For example, a participant was said to have been screened for hypertension if there was a record of blood pressure measurement or if there was a diagnosis of hypertension (as a diagnosis of hypertension could not be given without first assessing blood pressure). A list of Read codes is presented in Appendix 3.

In order to ensure that no codes had been missed, a system of checking was utilised. The read terms of remaining codes, utilised in the CiPCA and IiPCA datasets were searched to look for terms relating to the screening of interest. This helped to ensure that a comprehensive list of codes had been identified.

4.3.2 Comorbidity identification

The records of RA and non-RA patients were searched for codes relating to the diagnosis and investigation of DM, hypertension and hyperlipidaemia. If a participant had a diagnostic code for one of these comorbidities or had a test result that was diagnostic of such comorbidity then they were said to have the comorbidity. Comorbidity codes are presented in Appendix 4.

To enable the complete identification of comorbidity PiPCA was searched. The codes for entries in PiPCA were identified using the BNF (Joint Formulary Committee, 2009). If a participant had a code for an anti-hypertensive medication then they were said to have a diagnosis of hypertension. Similarly, a lipid lowering medication reflected a diagnosis of hyperlipidaemia and an anti-diabetic medication or insulin a diagnosis of DM. A list of prescription codes is presented in Appendix 4.

Therefore, a RA or non-RA patient was said to have a diagnosis of DM, hypertension or hyperlipidaemia if they had a diagnostic code, an investigation code (diagnosing the condition) or were prescribed medication (identified through PiPCA) relating to one of the aforementioned comorbidities. It is hoped that by using all three databases (CiPCA, IipCA and PiPCA), all comorbidity will be captured.

4.4 Defining screening outcomes

In order to assess the relative frequency of CVD screening in RA patients, it was necessary to define screening. This required thought about what was considered to be cardiovascular screening in practice.

The aim of cardiovascular screening is to allow quantification of risk, which along with clinical judgement, helps to guide thresholds for intervention, either by lifestyle advice or through therapeutic intervention. With this in mind, three outcomes were defined:

a) Any screening

b) Standard CVD screen

c) Comprehensive CVD screen

The rational for these outcomes and detailed definitions are given below.

4.4.1 Any screening

Any screening was defined as the screening of ≥1 of the five cardiovascular risk factors.

4.4.2 Standard cardiovascular disease screen

There is a wealth of literature suggesting that with the exception of age and sex, three modifiable risk factors - blood pressure, smoking and elevated lipid levels are responsible for up to 80% of CVD risk in the general population (Emberson JR et al, 2003). In addition, to allow quantification of risk, several risk factors are combined using risk equations (Chapter 1). Age, sex and the three modifiable risk factors; smoking status, blood pressure and the ratio of HDL: LDL cholesterol are necessary for the calculation of the Framingham Risk equation. Therefore if a patient was to have undergone a standard screen they could have their cardiovascular risk calculated using this equation.

Therefore as the three most important modifiable risk factors for CVD we defined these as a 'standard CVD screen'.

4.4.3 Comprehensive cardiovascular disease screen

A 'comprehensive CVD screen' was defined as the screening of all five identified cardiovascular risk factors (smoking status, blood pressure, body weight/BMI, glucose levels and lipid status).

These five cardiovascular risk factors are highlighted in both BSR and EULAR guidance and therefore these are ideally the risk factors that every RA patient should be screened for. Receipt of a comprehensive CVD screen could be thought to reflect a gold standard in CVD screening.

4.5 Statistical methods

Statistical analysis was completed using Stata version 12.1 (Stata Corp, 2011).

4.5.1 Descriptive statistics

Basic demographic information was compared between the RA and non-RA patients. The percentages of participants who had been screened for each of the five identified risk factors were compared. The number of risk factors that RA and non-RA patients had been screened for was also considered. The chi square test and t tests were used as

appropriate to determine whether any differences observed between RA and non-RA patients were statistically significant.

4.5.2 Logistic regression

Logistic regression is a type of regression analysis used to model a binary outcome variable. In this thesis logistic regression was used to assess the association between each of the screening outcomes and RA status. Adjustment was made for age, gender and comorbidity.

4.5.3 Comparison with diabetes mellitus

It is known that the risk of CVD is similar in RA and diabetes mellitus. To help understand the screening process in primary care, the odds of screening in those with RA but not diabetes mellitus and diabetes mellitus but not RA were compared to those with neither disease using logistic regression.

4.5.4 Primary care contact

To further understand the process of screening in primary care and how it relates to the diagnosis of RA, rates of primary care contacts (i.e. number of days with a contact with primary care in 2009) were compared between those with and without RA.

Results of the logistic regression analysis were presented as odds ratios (OR) with 95% confidence intervals. An OR of greater than one represented an increase in the odds of screening in all analyses.

4.6 Summary

In this chapter the three interlinked regional databases, CiPCA, IiPCA and PiPCA have been described, along with how the data from these databases has been processed for use. The statistical methods used in analysis have also been described. The next chapter will present the results of the study.

Chapter 5; Results of cross-sectional study

The previous chapter described the source of the study data and outlined the study design and analysis. This chapter will present the results of the study. First the characteristics of the sample obtained from CiPCA will be considered. Second, levels of screening for traditional cardiovascular risk factors in RA and non-RA patients will be compared, as will the effect of comorbidity on screening practice. Finally, the number of contacts that RA and non-RA patients receive in primary care will be compared.

5.1. Demographics of the study sample

The baseline characteristics of the RA and non-RA patients were compared and matching was successful for age, gender and practice (Table 5.1). As one would expect for a rheumatoid arthritis cohort, females predominated (66.1%) and the majority of participants fell within the older age groups, with a mean age of 58.7 (standard deviation 12.61) years. Patients originated from one of nine practices, with a greater proportion of patients drawn from practices I, K and M. This is likely to be due to these practices being three of the largest practices with 12574, 10441 and 9872 patients registered respectively. All RA patients had received a diagnostic read code for RA between 2000-2008, however, the proportion of patients drawn from each year was not evenly spread. This was probably because a large proportion of prevalent cases at the start of the time period were detected in the year 2000.

The prevalence of DM and hyperlipidaemia were very similar in RA and non-RA patients. However, the prevalence of hypertension was significantly greater amongst RA patients (52.1% vs. 45.7%).

The prevalence of the three comorbidities (DM, hyperlipidaemia and hypertension) is similar to that reported in the general population (Craig R & Hirani V, 2009).

Table 5.1; Comparison of RA and non-RA patients				
Characteristic		**RA (%)**	**Non-RA (%)**	***P-value***
Gender	Female	265 (66.1)	793 (66.2)	
	Male	136 (33.9)	405 (33.8)	
Age group (years)	≤35	4 (1.0)	13 (1.1)	
	36-50	61 (15.2)	170 (14.2)	
	51-65	142 (35.4)	433 (36.1)	
	66-74	104 (25.9)	327 (27.3)	
	75+	90 (22.4)	255 (21.3)	
Practice	C	35 (8.7)	105 (8.8)	
	D	40 (10.0)	120 (10.0)	
	E	50 (12.5)	149 (12.4)	
	G	16 (4.0)	48 (4.0)	
	H	38 (9.5)	114 (9.5)	
	I	63 (15.7)	188 (15.7)	
	K	64 (16.0)	192 (16.0)	
	L	36 (9.0)	106 (8.8)	
	M	59 (14.7)	176 (14.7)	
Year of 1st RA consultation or control year	2000	120 (29.9)	360 (30.1)	
	2001	47 (11.7)	139 (11.6)	
	2002	36 (9.0)	108 (9.0)	
	2003	33 (8.2)	97 (8.1)	
	2004	37 (9.2)	111 (9.3)	
	2005	40 (10.0)	119 (9.9)	
	2006	19 (4.7)	57 (4.8)	
	2007	35 (8.7)	105 (8.8)	
	2008	34 (8.5)	102 (8.5)	
Diabetes diagnosis		48 (11.9)	127 (10.6)	0.447
Hypertension diagnosis		209 (52.1)	547 (45.7)	**0.025**
Hyperlipidaemia diagnosis		134 (33.4)	398 (33.2)	0.943

5.2 Screening for individual cardiovascular risk factors

Table 5.2; RA and non-RA patients screened for each cardiovascular risk factor (n (%))				
Risk Factor		**RA**	**Non-RA**	***P-value***
Blood pressure	No	102 (25.44)	338 (28.21)	0.281
	Yes	299 (74.56)	860 (71.79)	
Body weight	No	182 (45.39)	566 (47.25)	0.518
	Yes	219 (54.61)	632 (52.75)	
Glucose level	No	213 (53.12)	633 (52.84)	0.923
	Yes	188 (46.88)	565 (47.16)	
Smoking status	No	132 (32.92)	460 (38.40)	**0.049**
	Yes	269 (67.08)	738 (61.60)	
Lipids	No	217 (54.11)	676 (56.43)	0.420
	Yes	184 (45.89)	522 (43.57)	
Total		401 (100.00)	1198 (100.00)	

Blood pressure was the most commonly recorded risk factor amongst both RA and non-RA patients (Table 5.2). Conversely, lipid levels were the risk factor least likely to be recorded amongst both groups. The rate of screening was similar between RA and non-RA patients for all risk factors except smoking status, which was significantly more likely to be recorded in patients with RA (67.1% vs. 61.6%).

5.3 Any cardiovascular disease screening

Individual risk factors do not allow quantification of risk and so Table 5.3 reports the number of risk factors screened for in each group.

Table 5.3: The number of cardiovascular risk factors screened for in RA and non-RA patients (n (%))

Number of risk factors	RA	Non-RA	Total
0	49 (12.22)	215 (17.95)	264 (16.51)
1	54 (13.47)	148 (12.35)	202 (12.63)
2	58 (14.46)	134 (11.19)	192 (12.01)
3	71 (17.71)	210 (17.53)	281 (17.57)
4	69 (17.21)	184 (15.36)	253 (15.82)
5	100 (24.94)	307 (25.63)	407 (25.45)
Total	401 (100.00)	1198 (100.00)	1599 (100.00)

Table 5.3 highlights that RA patients were more likely to have 'any CVD screening' (≥1 risk factors recorded). 88% of RA patients had screening for at least 1 risk factor compared to 82% of non-RA patients (percentage difference: 5.8% (95%CI 1.4%, 9.2%). This was due to an increased likelihood of smoking status being recorded in those with RA (Table 5.2).

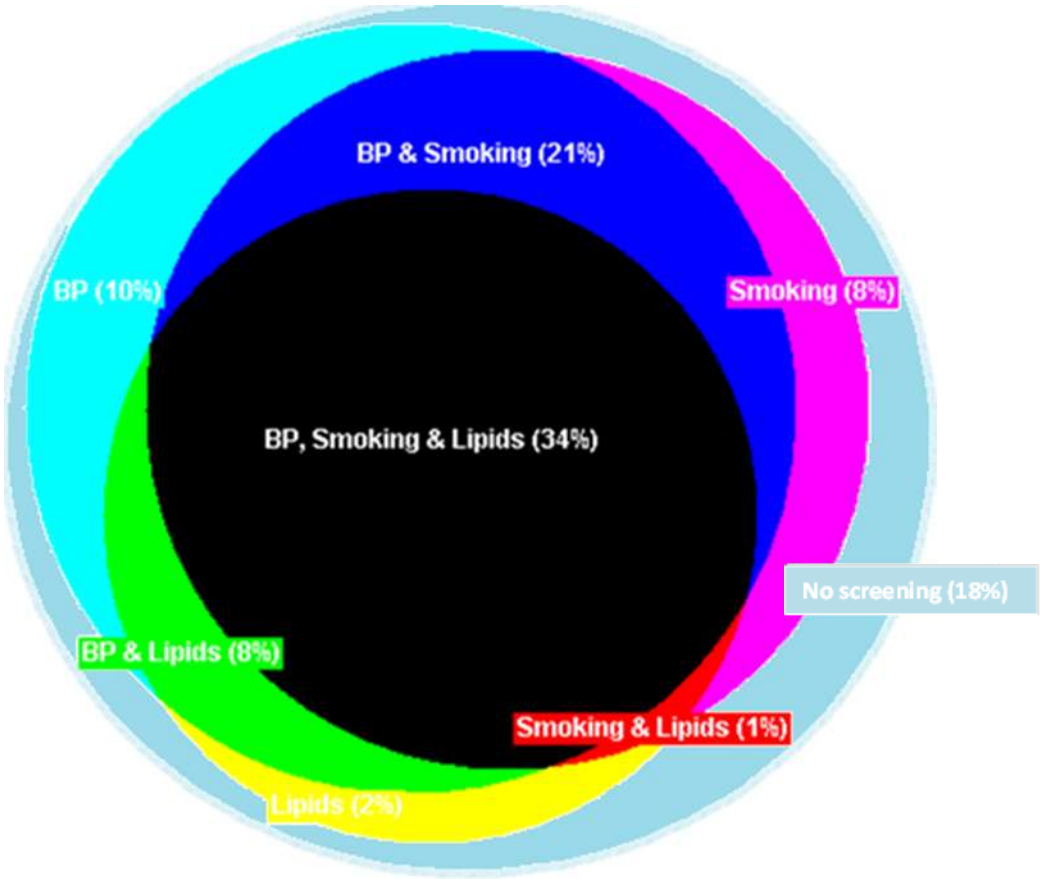
Table 5.4; Association between RA status and having ≥1 cardiovascular risk factors screened: Results from a logistic regression model			
	Odds Ratio (95% CI)		
	Unadjusted	**Age and gender adjusted**	**Age, gender and comorbidity adjusted**
RA	1.57 (1.13, 2.19)	1.59 (1.13, 2.23)	1.54 (1.07, 2.22)
10 years of age		1.55 (1.39, 1.73)	1.11 (0.99, 1.25)
Male Gender		0.79 (0.60, 1.05)	0.74 (0.55, 1.01)
Diabetes mellitus			10.65 (1.43, 79.39)
Hyperlipidaemia			6.85 (3.41, 13.79)
Hypertension			8.31 (5.03, 13.72)

RA patients had greater odds of being screened for ≥1 risk factors, or receiving 'any screening' than non-RA patients, even after adjustment for age, gender and comorbidity. However, the major influence on the likelihood of being screened for ≥1 cardiovascular risk factors was comorbidity; the presence of any one of the three identified comorbidities increased the odds of any screening.

5.4 Standard cardiovascular disease screen

As already defined (Chapter 4), a standard CVD screen is said to have occurred if an individual has a blood pressure check and their smoking and lipid status recorded. Approximately one third of patients met these criteria for a standard CVD screen (Figure 5.1).

Figure 5.1; Proportional Venn diagram to illustrate the number of participants who met the standard CVD screening outcome



Key
BP – Record of blood pressure measurement; **Smoking** – Record of smoking status; **Lipids** – Record of blood lipid measurement

Table 5.5; Logistic regression analysis to show the impact of RA, age, gender and comorbidity status on the likelihood of receiving a standard CVD screen			
	Odds Ratio (95% CI)		
	Unadjusted	**Age and gender adjusted**	**Age, gender and comorbidity adjusted**
RA	1.02 (0.80, 1.29)	1.01 (0.79, 1.30)	0.94 (0.70, 1.28)
10 years of age		1.47 (1.35, 1.60)	1.13 (1.01, 1.26)
Male Gender		1.47 (1.17, 1.83)	1.17 (0.89, 1.53)
Diabetes Mellitus			5.31 (3.14, 8.97)
Hyperlipidaemia			6.48 (4.92, 8.55)
Hypertension			2.19 (1.65, 2.91)

The odds of receiving a standard screen were similar in those with and without a diagnosis of RA (Table 5.5). This lack of association remained after adjustment for age, gender and comorbidity. However both increasing age and the presence of comorbidity resulted in an increase in the odds of receiving a standard screen.

5.5 Comprehensive cardiovascular disease screen

The proportion having a comprehensive CVD screen (documentation of all five risk factors) was low (RA 24.9% vs. Non-RA 25.6%) and similar in both groups.

Table 5.6; Association between RA status and comprehensive CVD screen: Results from a logistic regression model			
	Odds Ratio (95% CI)		
	Unadjusted	**Age and gender adjusted**	**Age, gender and comorbidity adjusted**
RA	0.96 (0.74, 1.25)	0.95 (0.73, 1.24)	0.84 (0.61, 1.16)
10 years of age		1.46 (1.32, 1.61)	1.13 (0.99, 1.29)
Male Gender		1.69 (1.33, 2.14)	1.36 (1.02, 1.82)
Diabetes mellitus			7.82 (5.10, 11.99)
Hyperlipidaemia			4.87 (3.63, 6.51)
Hypertension			2.33 (1.70, 3.20)

A diagnosis of RA did not result in increased odds of receiving a comprehensive CVD screen (Table 5.6). Such lack of association remained after adjusting for age, gender and comorbidity. Male gender and the presence of comorbidity did increase the odds of receiving a comprehensive CVD screen. DM was particularly influential, with nearly eight times the odds of receiving a comprehensive CVD screen in the presence of this condition.

5.6 A comparison with diabetes mellitus

Table 5.7; The influence of RA and diabetes mellitus on standard and comprehensive CVD screening				
	Odds Ratio (95% CI)			
	Standard CVD Screening		Comprehensive CVD Screening	
	Unadjusted	Age, gender and comorbidity adjusted	Unadjusted	Age, gender and comorbidity adjusted
No RA and no DM	1.00	1.00	1.00	1.00
RA and no DM	0.96 (0.74, 1.26)	0.91 (0.67, 1.25)	0.89 (0.65, 1.22)	0.82 (0.58, 1.17)
DM and no RA	12.15 (7.53, 19.61)	4.83 (2.82, 8.26)	16.31 (10.33, 25.76)	7.65 (4.61, 12.69)

Note: RA – Rheumatoid Arthritis, DM – Diabetes Mellitus

The odds of receiving a standard or comprehensive CVD screen are similar, regardless of the presence of RA (Table 5.7). However Table 5.7 highlights that a patient without RA but with a diagnosis of DM had nearly 12 times the odds of receiving a standard CVD screen and nearly 16 times the odds of receiving a comprehensive CVD screen. The association was reduced, but still present, after adjusting for age, gender and other comorbidity (hyperlipidaemia and hypertension).

5.7 Mean number of contacts

To determine if there was a difference in the consulting rate between RA and non-RA patients the mean number of contacts were determined and significance assessed using a t-test.

Table 5.8; Mean number of contacts in RA and non-RA patients			
		Mean (95% CI)	***P - value***
All Contacts	RA	20.41 (19.20,21.63)	<0.0001
	Non-RA	13.35 (12.74, 13.95)	
Non-RA Contacts	RA	19.08 (17.90, 20.26)	<0.0001
	Non-RA	13.34 (12.73, 13.95)	

Contact = Date with one or more recorded consultations.

RA patients had approximately 7 more contacts in 2009 than non-RA patients, suggesting a diagnosis of RA does not result in a decrease in primary care involvement of care. When all contacts relating to RA were removed for RA patients, there was still a significant difference in the mean number of contacts; RA patients had approximately 6 more contacts than non-RA patients.

5.8 Summary

RA patients are not more likely to be screened for traditional cardiovascular risk factors in primary care than non-RA patients, despite having more primary care contact.

RA patients are more likely to have a record of smoking status, reflected in RA patients having a greater likelihood of having ≥1 risk factors recorded. However, the preferential recording of smoking status is an isolated finding. RA patients are not more likely to receive a standard or comprehensive cardiovascular disease screen than age, gender and practice matched non-RA patients. This is in contrast to DM, which has a similar association with CVD and results in a significant increase in levels of screening.

These findings are discussed more fully in Chapter 6.

Chapter 6; Discussion

The previous chapter presented the results of the main study of the thesis. This chapter discusses these results and places the findings in the context of the existing literature.

6.1 Summary of results

A cohort of 401 RA patients were identified from a regional primary care database and compared to 1198 non-RA patients. This study found RA patients received similar rates of CVD screening as age, gender and practice matched non-RA patients. The only risk factor that was significantly more likely to be screened in those with RA compared to non-RA patients was smoking status (67.1% vs. 61.6%, p = 0.049). The increased likelihood of being screened for smoking status is reflected in patients with RA being more likely to be screened for at least one cardiovascular risk factor, or receive 'any CVD screening.'

The majority of both RA and non-RA patients were screened for ≥1 traditional cardiovascular risk factors (RA 88% vs. non-RA 82%, difference 5.8% (95% CI 1.4%, 9.2%)).

When CVD screening was defined as either a standard screen (the recording of blood pressure, lipids and smoking status) or a comprehensive screen (all 5 risk factors), RA patients were not more likely to receive either when compared to non-RA patients. Regardless of a diagnosis of RA, it appears that the presence of one of the three identified comorbidities was the major influence on screening practice.

The results of this study therefore suggest that either the association between RA and CVD has not been recognised or that the association is recognised but not being acted upon in primary care. These results are supported by the existing literature (Chapter 2).

There are several possible reasons why a diagnosis of RA is not prompting additional CVD screening. As suggested by Bell and Rowe (2011), it may be that the increased risk of cardiovascular disease associated with RA is not being recognised in primary care. Additionally, there may be confusion over whose responsibility it is to screen for CVD in those with RA. GPs are familiar with provision of primary prevention of CVD in the general population and for high risk patients, such as those with DM, but they may be reluctant to screen RA patients. It may be assumed that their care is the responsibility of the rheumatologist and that they feel they have inadequate time and/or expertise, particularly as RA is a complex medical condition which may consume a large part of the consultation.

6.2 What influences CVD screening?

It has already been stated that patients with RA are equally likely to be screened for traditional cardiovascular risk factors as non-RA patients. The exception to this was the screening of smoking status, which was more likely to be documented in RA patients. Smoking is a well-known environmental risk factor for the development of RA and it is also known that smoking is associated with a worse disease outcome (reviewed in section 1.3.2, Chapter 1). This association may prompt GPs to enquire about smoking status and hopefully promote smoking cessation in RA patients. Screening for smoking and subsequent promotion of smoking cessation could have a positive effect on

cardiovascular risk but it is unlikely that this alone represents recognition of the excess cardiovascular burden associated with RA.

Therefore the question remains what factors influence a physician's decision to screen in primary care?

6.2.1 Socio-demographics

In this study, age and gender influenced screening practice, with greater odds of receiving a standard screen with advancing age and of receiving a comprehensive CVD screen with male gender. Age and gender are well-known non-modifiable cardiovascular risk factors and it is therefore unsurprising that the presence of such factors influenced receipt of additional screening.

6.2.2 The presence of comorbidity

Participants with any one of the three identified comorbidities (DM, hyperlipidaemia and hypertension) had greater odds of having ≥1 risk factors screened, a standard screen or a comprehensive screen. A diagnosis of diabetes resulted in the highest odds of receiving the aforementioned types of screening; 10.65 (1.43, 79.39), 5.31 (3.14, 8.97) and 7.82 (5.10, 11.99) respectively. This supports previous literature suggesting screening is influenced by the presence of comorbidity (Curtis JR et al, 2009; Bili A et al, 2011) and suggests that there must already be effective identification and screening of patients with such comorbidities in primary care. An example of this is the QOF indicators that relate to

cardiovascular risk assessment in patients with DM and hypertension. The increased likelihood of receiving a standard and comprehensive screen in those with a diagnosis of DM and hypertension suggests that systems such as QOF are successful.

6.2.3 Primary care contact

It could be that RA patients are less likely to consult in primary care, due to their care often being a shared responsibility between primary and secondary care physicians. However this study found that RA patients had approximately 7 more contacts with primary care in 2009 than non-RA patients, suggesting that a diagnosis of RA does not result in a decrease in primary care involvement. Even when contacts relating to RA were removed in RA patients, RA patients still had approximately 6 more contacts in 2009 than non-RA patients.

The extent of comorbidity in RA is well documented in the literature and is discussed in this thesis (Chapter 1). RA has the potential to affect any organ system and the average established RA patient has two or more comorbid conditions (Michaud K & Wolfe F, 2007). Therefore it is likely that the RA sample in this study, like the RA population, had a higher prevalence of illness and was therefore more likely to consult in primary care. It may also be that patients with RA have a higher propensity to consult than non-RA patients

These results allow one to be sure that the reason RA patients did not receive additional screening was not because they were less frequent visitors to their general practice surgery. RA patients presented more often in primary care and therefore would have had at least as much chance as non-RA patients to receive opportunistic CVD risk assessment.

6.3 Diabetes and the role of incentivised care

The presence of DM was particularly influential in prompting CVD screening. It is known that risk of CVD in RA is increased to an extent at least comparable to that of DM (Van Halm VP et al, 2009; Peters MJL et al, 2009). However the results of this study suggest that despite the risk of CVD being similar in both conditions, screening practice is not: those with a diagnosis of DM had over five times the odds of receiving a standard screen and nearly eight times the odds of receiving a comprehensive screen, whilst the equivalent odds ratios for those with RA are 1.02 and 0.96.

It is necessary to consider why GPs are much more likely to screen those with DM, as this could provide answers to what needs to be done to increase screening in RA. DM is more prevalent than RA – overall 5.1% of adults in England have DM with increasing prevalence with age (15.7% of males and 10.7% of females >65 have DM) (Diabetes UK, 2010). This is compared to less than 1% of the adult population affected by RA. Therefore the average GP will have significantly more patients in their care with DM as opposed to patients with RA. Hence the management of such patients is more familiar to GPs, particularly as the majority of those with non-insulin dependent diabetes mellitus (NIDDM) are now managed exclusively in primary care. GPs are more likely to have a greater appreciation of

the risk of CVD associated with DM and are therefore more likely to identify and screen these patients.

The care of those with DM has also been optimised through QOF, with financial incentives for GPs who assess cardiovascular risk factors in those with a diagnosis of DM. This use of incentivised care may help to explain why screening practice is much better for those with DM when compared to patients with RA. New indicators relating to cardiovascular risk assessment are currently being piloted for those with RA (Chapter 1). If these risk factors are introduced in 2013/14 they may have a positive impact on CVD screening rates. Previous studies have found the introduction of financial incentives to be associated with apparent quality improvement for incentivised conditions. (Campbell S et al, 2007; Khunti K et al, 2007; Steel N et al, 2006).

Whilst incentivising care may not be the ideal solution to this problem, providing financial incentives is undoubtedly a powerful method to lead to changes in clinical practice. Highlighting a clinical area in this way may also have additional effects such as promotion of early diagnosis.

Nevertheless the use of financial incentives is not without criticism as it is likely that improvements in care quality are restricted only to incentivised conditions, with neglect of non-incentivised conditions. If the QOF indicators relating to RA are introduced, any potential benefit would probably be limited to RA. This is unfortunate, as there is an elevated risk of cardiovascular disease in other types of inflammatory arthritis such as psoriatic arthritis and ankylosing spondylitis (Peters MJ et al, 2004) yet it is unlikely that patients with these conditions will benefit.

6.4 An educational need

The sub-optimal rates of screening identified in the study suggest there is a lack of awareness in primary care regarding the excess risk of CVD in RA.

It must be remembered that recognition of cardiovascular risk alone is inadequate, as the aim of screening is to quantify risk and modify it if elevated. Due to the complexity of RA, modifying cardiovascular risk may require collaboration between primary and secondary care.

6.4.1 Education of patients

Education of the multi-disciplinary primary care team is crucial to improving cardiovascular risk assessment and modification in primary care. However, it must also be remembered that RA patients should be informed of their increased cardiovascular risk so that they can make informed choices regarding their care. This may also empower RA patients to make lifestyle changes and would ensure they are aware of the importance of complying with medication prescribed to address cardiovascular risk factors.

6.4.2 Difficulties in assessing cardiovascular risk

As already described, cardiovascular risk is assessed using a cardiovascular risk equation, however, the use of such a tool may be more complicated in RA. The proposed QOF indicator suggests that risk assessment should utilise a tool that is adjusted for RA. One risk assessment tool, QRISK2, does include a multiplier for RA, with an adjusted hazards ratio of 1.5 for women and 1.38 for men applicable to all RA patients (Hippisley-Cox J et

al, 2008). However, this conflicts with guidance produced by EULAR, which suggests that a multiplication factor of 1.5 should only be used if two out of the following three criteria are met: disease duration of greater than 10 years, extra-articular manifestations of RA and anti-CCP or RF positivity (Peters MJL, 2010). This highlights the need for clearer guidance to be given to GPs and practice nurses regarding which risk equation is most suitable for assessing cardiovascular risk in RA patients.

The approach to cardiovascular risk assessment also needs to be reviewed. It has already been discussed that RA patients are more likely to consult in primary care, yet despite this they did not receive additional or opportunistic screening. This suggests that cardiovascular risk assessment needs a targeted approach, with patients being invited to discuss CVD risk at the practice with a GP or practice nurse. This would ensure that CVD risk reduction is given the time necessary.

6.4.3 Difficulties in modifying cardiovascular risk

Difficulties in modifying cardiovascular risk, although not considered in this study, were identified as being important in the existing literature (Chapter 2). It is important to consider if there are difficulties for GPs above those normally encountered when modifying cardiovascular risk, as such difficulties could act as a barrier for risk modification in RA patients. It would be unfortunate to educate GPs on the cardiovascular burden in RA only for modification of risk to be too difficult to achieve within the constraints of primary care. This would not reduce the cardiovascular mortality and morbidity associated with RA, which is the desired outcome for patients.

It is accepted that modification of risk is more difficult in patients with RA compared to the general population due to the complexity of the disease itself and its pharmacological management. Several medications used to manage RA may interact with drugs used to address cardiovascular risk factors, for example, NSAIDs and angiotensin-converting enzyme (ACE) inhibitors. Other medications used in the treatment of RA such as corticosteroids may exacerbate established risk factors such as hypertension and make them more difficult to treat (Joint Formulary Committee, 2009).

Patients may be reluctant to accept additional medication, particularly if they are already taking several medications. It must also be remembered that drugs have side effects. For example, statins can result in muscular side effects such as pain and cramps. This may be unacceptable to the patient, particularly if already afflicted with joint pain and the systemic symptoms associated with RA.

In addition there is currently a lack of trial evidence to inform treatment choices for patients with RA and therefore GPs may be unsure which lipid-lowering or anti-hypertensive medicine to prescribe. The publication of trials such as Trial of Atorvavstatin in the primary prevention of Cardiovascular Endpoints in Rheumatoid Arthritis (TRACE RA 2010) may help to rectify this.

Such examples make it easy to understand why modification of risk may be difficult for GPs and indicate the need for clearer guidance, education of primary care physicians and effective collaboration between professionals responsible for delivering care to those with RA. This will help to ensure that the risk is not only assessed but also modified appropriately.

6.5 Study Strengths

The main strengths of the study including sample size, the matching process and comorbidity coding will be described below.

6.5.1 Sample size

401 patients with RA were identified in CiPCA. This is appropriate when considering the prevalence of the disease and the number of patients registered at the 9 practices (401 patients with RA were identified from a population of 80,363 patients, equating to a prevalence of 0.499%). Similar studies based in the UK report smaller sample sizes of between 45 and 135 RA patients (Bailey KA & Kumar N et al, 2009; Hall FC et al, 2009; Litwic AE & Ledingham JM, 2010; Teir J et al, 2008). Therefore 401 patients with RA and 1198 non-RA patients represented a relatively large sample for analysis.

6.5.2 Matching

Each of the 401 RA patients was matched to three age, gender and practice matched non-RA patients. This allowed comparisons to be made between RA and non-RA patients. However several of the RA patients were elderly and there were inadequate numbers of patients in the database to allow 3:1 matching of these patients. In this case, 2:1 or 1:1 matching was used. This is unlikely to affect the conclusions made but may have slightly reduced statistical power.

6.5.3 Quality morbidity coding

The data were extracted from CiPCA. As described in Chapter 4, the practices that contribute to CiPCA are part of the Keele GP Research Partnership and are therefore subject to regular cycles of training, assessment and feedback that help to ensure that the quality of the data utilised is high. This gives confidence that those patients identified as having a diagnosis of RA from the database really did have RA. This is important to consider as one can only expect GPs to offer additional screening to those who did have the disease.

6.6 Study limitations

This section presents the limitations of the study. The data source and the methods used to complete the study will be examined.

6.6.1 Study participants

RA participants were coded as having a diagnosis of RA between 2000 and 2008 and were still registered at their practice in 2009. Although RA is commonly thought of as a chronic progressive condition, it is possible that a minority of patients included in the study may have gone into drug free remission over time. A participant who no longer had evidence of inflammatory joint disease may no longer be a candidate for cardiovascular screening, although in this study design screening would still have been assessed for. This may have resulted in a few patients being expected to be screened, who from an RA perspective no longer required screening. Due to the minority of patients in whom drug free remission

would be likely to be achieved, this would have had a minimal impact on our results. In addition, it is unclear when or if cardiovascular risk returns to that of their age and gender non-RA equivalents in those patients who achieve drug free remission.

To try and limit the effect of this issue, further work to 'check' whether those patients identified as having RA in 2009 actually did have RA could have been attempted. One way this could have been done was to check whether those patients identified as having RA were prescribed medication relating to RA such as DMARDs. However this would have been very difficult as not all DMARDs are prescribed by primary care physicians and there was no access to secondary care prescriptions. In addition, many patients with RA are now treated with biologic monotherapy and this strategy would miss those patients. Therefore it would have been difficult to gain an accurate estimate of those patients receiving a prescription for a medication relating to RA.

6.6.2 Data

The data used in the study were from a one year period (2009). Therefore only screening in 2009 was identified. 2009 was chosen as it was the most recent year available with complete data. This is appropriate as guidance, such as that produced by the BSR suggests annual risk assessment and therefore patients with RA should have the five identified risk factors assessed on an annual basis. This is also in keeping with screening offered in other chronic diseases such as DM.

6.6.3 Data source

The data used in this study were extracted from the Consultations in Primary Care Archive (CiPCA) database. The major limitation is that it is a regional database and therefore has a very local focus. Clinical practice in Staffordshire is unlikely to be very different to that elsewhere in the UK. However Staffordshire is home to the Arthritis Research UK Primary Care Centre and so it may be suggested that primary care physicians in this area are a more informed group. Regardless of this claim, using a local database is unlikely to affect the generalisability of the results.

A further potential limitation of CiPCA is there is a chance that the data recorded within it does not reflect the complete consultation. This is because GPs are only required to code each consultation with one code, yet several problems (and therefore codes) could be discussed during the consultation. The effect of this should be minimal as the practices that contribute to CiPCA receive additional training regarding the coding of consultations.

6.6.4 Diagnostic and prescription codes

Diagnoses, screening tests and prescriptions were coded within the CiPCA, IiPCA and PiPCA databases. Searching for these codes was the sole responsibility of the lead author and therefore it is possible that a code could have been omitted due to human error. An attempt to counteract this was made by a system of checking; the read terms of entries were searched to identify any codes related to screening. Therefore it is unlikely that codes were missed. This is also supported by the existing literature, as although screening practice varied considerably, our results were in keeping with those described.

Prescription codes were used to help identify those with comorbidity. One can be fairly confident that if a patient is prescribed an anti-diabetic drug or insulin that they have a diagnosis of DM as these medications are specific to DM. Likewise if someone is prescribed a lipid lowering drug then this can only be because they have elevated lipid levels. However some of the medications used to reflect a diagnosis of hypertension such as Beta-adrenoceptor blocking drugs may be given to patients with diagnoses other than hypertension. This is because although Beta-adrenoceptor blocking drugs do act as anti-hypertensives they also have other uses - for example, patients with heart failure may be prescribed Beta-adrenoceptor blocking drugs. Therefore it may be that some of the patients identified as having a diagnosis of hypertension in this study did not, resulting in over-estimates of the prevalence for hypertension. Nevertheless, it is unlikely that this resulted in large over-estimates of hypertension as the prevalence of hypertension identified in the study (46-52%) was in keeping with that reported in the general population (Craig R & Hirani V, 2009).

6.6.5 Difficulties in defining screening outcomes

Three screening outcomes were defined: any screening, standard CVD screen and comprehensive CVD screen. This posed some difficulties as there is conflicting evidence regarding the relationship between some of the cardiovascular risk factors and CVD in RA. For example, in the general population it is well known that increased BMI is associated with increased mortality. Yet, for those with RA, in some studies BMI was found to be inversely associated with mortality, with the lowest mortality reported in those with a BMI >30 (Escalante A et al, 2005). In addition a study by del Rincon found those with RA

were significantly less likely to have hyperlipidaemia than the controls, but despite this were still four times more likely to suffer a cardiovascular event than age and sex matched controls (del Rincon I et al, 2001). This suggests that traditional risk factors do not account for all of the cardiovascular risk in RA, hence suggesting that novel risk factors such as chronic inflammation (evident by raised inflammatory markers) and treatment such as corticosteroid use may hold some responsibility.
Nevertheless it is important, particularly while the unknown contribution of novel risk factors is evaluated, that the cardiovascular health of those with RA is optimised by screening for traditional risk factors.

6.7 Clinical implications of the thesis

This thesis, in accordance with existing literature, has shown that despite the wealth of literature and national guidelines, current practice for cardiovascular screening of RA patients is suboptimal.

This thesis suggests that more needs to be done to educate primary care physicians, nurses and patients regarding the burden of cardiovascular risk associated with RA. It also suggests the need for more effective collaboration between primary and secondary care physicians. Although the proposed QOF indicators, if introduced, will most definitely help, they will do little to disentangle the complexity of risk modification in RA. Therefore clearer guidelines regarding calculating cardiovascular risk and thresholds for intervention will be necessary.

Qualitative work with GPs and patients to understand the barriers associated with risk assessment in primary care would be useful. As would the implementation and evaluation of a public health campaign to see if such a campaign could improve CVD screening rates.

6.8 Summary

This chapter has discussed the results of the study and has made comparisons with existing literature. This study found that patients with RA are not more likely to receive cardiovascular screening than age, gender and practice matched non-RA patients in primary care. The possible reasons for this have been explored. The next chapter presents the conclusions in relation to the initial aims and objectives of the thesis.

Chapter 7; Conclusions

The previous chapter discussed the results of the original study and made comparisons with existing literature. This chapter will present the final conclusions in relation to the thesis aim and objectives.

The aim of this thesis was to determine cardiovascular screening practice for patients with RA in the UK. To achieve this, a systematic search and review of the current literature was conducted, followed by a cross-sectional study.

The systematic literature review identified 10 studies relating to the screening of traditional cardiovascular risk factors in patients with RA. The systematic review found that cardiovascular screening for patients with RA was variable but sub-optimal. Patients with RA were less likely to receive screening than patients with other musculoskeletal disease such as psoriatic arthritis and SLE. However the presence of comorbidity such as DM and hyperlipidaemia increased the likelihood of receiving screening. Four of the studies included in the review were based in the UK but all were from secondary care, the RA cohorts utilised small (45-135 patients) and the results variable, hence the need for a larger, primary care-based study.

The cross-sectional study aimed to determine screening practice in the UK using a larger cohort of 401 RA patients and 1198 age, gender and practice matched non-RA patients. Specifically, the study aimed to determine if the presence of comorbidity influenced screening in primary care.

The study found no difference in screening between RA and non-RA patients, apart from smoking status, which was more likely to be recorded in RA patients. This was reflected in patients with RA being significantly more likely to have ≥1 risk factors recorded. However, RA patients were not more likely to receive a standard or comprehensive cardiovascular disease screen, despite more contact with primary care.

The study found that the presence of comorbidity significantly increased the odds of receiving any screening, standard screening and comprehensive CVD screening. This therefore suggests that the presence of comorbidity is a major driving force behind receiving CVD screening in primary care, possibly supported by incentives such as QOF.

This study has demonstrated that despite the association between RA and CVD being well recognised in the literature, such knowledge has not resulted in changes in clinical practice. Much more emphasis should be placed on screening and aggressively modifying traditional cardiovascular risk factors amongst patients with RA in primary care.

Chapter 8; Reflections

The previous chapter described the conclusions of the thesis. This chapter presents a personal reflection on completing the intercalated MPhil degree and the influence this year has had on my future career ambitions.

8.1 Challenges

Before embarking on this MPhil degree I had never been involved in research and I had limited experience of writing extended pieces of work. This year has been a steep learning curve, during which I have learnt many new skills.

I found writing the systematic review particularly difficult. As a medical student, I had only ever conducted a basic search on Medline. For the review I searched several databases which yielded over 10,000 titles. Completing the review also allowed me to appraise and ask questions of the literature. This has been quite a change from generally reading, accepting and trying to memorize medical textbooks! I think this is a very important skill, particularly as doctors are expected to practise evidence based medicine.

Data analysis also posed challenges. It was apparent that I needed to consider the rate of screening for each of the identified risk factors. However, taking the analysis further required more thought. I had to consider what constituted screening in primary care and how this related to screening in other chronic diseases such as diabetes mellitus, in order to give context to my own work.

The biggest challenge I have faced this year has probably been trying to structure something as long and complicated as a thesis. Writing something of this nature has prompted me to develop a clearer, more systematic way of reasoning thoughts and concepts. I have also tried to adapt my language to a more objective and scientific style. I have found this particularly difficult at times, but I have realised how important it is in order to produce a coherent piece of work and to allow the reader to follow a structured argument.

8.2 Highlights

This year has introduced me to academia. I have been fortunate to attend the internal and external seminar programme run within the Centre. This has enlightened me to the work taking place of researchers, both from at Keele and within the wider research community. I, along with the other postgraduate research students, was also able to present my work at the graduate symposium, held to showcase the work of the students based at the Primary Care and Health Sciences Research Institute. It was particularly interesting to hear about different methods and approaches other students were utilising in completing their projects.

The biggest highlight of this year was probably attending and presenting my work at the British Society for Rheumatology annual conference. This was a great experience, not only because it was the first time I had attended such an event, but also because it allowed me to appreciate the work of senior researchers.

8.3 The future

Completing this MPhil has been very rewarding. It has allowed me to become involved in scientific research and learn many new skills which I believe will be useful for my future career. I have learnt to work independently and be self-disciplined in managing my own time and workload. I have also realised the importance of senior researchers in helping those less experienced like myself and I have been grateful for the commitment of my supervisory team who have always supported my efforts. I hope to write up the CiPCA study as a paper in the near future.

I hope that this thesis will add to the existing body of work surrounding RA and CVD and that it will raise awareness of the need to screen RA patients in primary care. Hopefully this will lessen the burden of cardiovascular risk imposed on RA patients.

I am still undecided as to which medical specialty I would like to pursue, although I am now sure that I would like academia to form a large part of my future career.

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Appendix 1: Search terms and synonyms

Search terms and synonyms						
Rheumatoid arthritis	**Body mass index**	**Blood pressure**	**Blood glucose**	**Smoking**	**Renal function tests**	**Lipid screen**
rheumat* ADJ3 arthrit*	Body ADJ mass ADJ	blood ADJ pressure	blood ADJ glucose	Smoking	serum ADJ creatinine	cholesterol*
rheumat* ADJ3	index	hypertension	fasting ADJ glucose	SMOKING	urinalysis	dyslipid*
disease*	Bmi	HYPERTENSION	glucose ADJ		glomerular ADJ	hypercholesterol*
rheumat* ADJ3	body ADJ fat ADJ	BLOOD PRESSURE	tolerance ADJ test		filtration ADJ rate	hypertriglycerid*
condition*	distribution		BLOOD GLUCOSE		blood ADJ urea ADJ	lipid*
rheumat* ADJ3	(waist ADJ hip ADJ				nitrogen	hyperlipid*
nodule*	ratio				kidney ADJ function	CHOLESTEROL
caplan* ADJ syndrome	body ADJ weight				renal ADJ function	HYPERLIPIDEMIAS
caplan* ADJ disease	BODY MASS INDEX				proteinuria	HYPERCHOLESTER-
inflammatory ADJ	WAIST-HIP RATIO				PROTEINURIA	OLEMIA
arthritis	BODY FAT				KIDNEY FUNCTION	HYPERTRIGLYCER-
felty* ADJ syndrome	DISTRIBUTION				TESTS	IDEMIA
ARTHRITIS,	BODY WEIGHT				BLOOD UREA	
RHEUMATOID					NITROGEN	
					GLOMERULAR	
					FILTRATION RATE	
					URINALYSIS	

* - The term is truncated. ADJ – Refers to two or more words being adjacent to each other. Therefore 'inflammatory ADJ arthritis' means the words inflammatory and arthritis must be adjacent to each other. Terms in upper case are subject headings.

Appendix 2; Search strategies

This appendix contains the search strategies utilised to search the MEDLINE, EMBASE BNI and CINAHL databases.

MEDLINE

1. ((rheumat* ADJ3 (arthrit* OR disease* OR condition* OR nodule*))).ti,ab 85160
2. exp ARTHRITIS, RHEUMATOID 92398
3. (caplan* ADJ syndrome).ti,ab 106
4. (caplan* ADJ disease).ti,ab 2
5. (inflammatory ADJ arthritis).ti,ab 2297
6. (felty* ADJ syndrome).ti,ab 656
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6 122478
8. (bmi OR (body ADJ mass ADJ index)).ti,ab 96147
9. exp BODY MASS INDEX/ OR exp WAIST-HIP RATIO/ OR exp BODY FAT DISTRIBUTION/ 65126
10. (body ADJ fat ADJ distribution).ti,ab 1847
11. (waist ADJ hip ADJ ratio).ti,ab 2097
12. (body ADJ weight).ti,ab 127025
13. BODY WEIGHT/ 151088
14. BLOOD PRESSURE/ 223867
15. HYPERTENSION/ 179436
16. (blood ADJ pressure).ti,ab 195480
17. hypertension.ti,ab 243281
18. BLOOD GLUCOSE/ 116191
19. ((blood ADJ glucose) OR (fasting ADJ glucose) OR (glucose ADJ tolerance ADJ test)).ti,ab 53417
20. smoking.ti,ab 125842
21. SMOKING/ 106559

22. (serum ADJ creatinine).ti,ab 23561
23. KIDNEY FUNCTION TESTS/ OR BLOOD UREA NITROGEN/ OR GLOMERULAR FILTRATION RATE/ OR URINALYSIS/ 57958
24. urinalysis.ti,ab 5050
25. (glomerular ADJ filtration ADJ rate).ti,ab 21472
26. (blood ADJ urea ADJ nitrogen).ti,ab 5878
27. ((kidney ADJ function) OR (renal ADJ function)).ti,ab 59946
28. proteinuria.ti,ab 25451
29. exp PROTEINURIA/ 29765
30. CHOLESTEROL/ 98846
31. HYPERLIPIDEMIAS/ OR exp HYPERCHOLESTEROLEMIA/ OR HYPERTRIGLYCERIDEMIA/ 44442
32. DYSLIPIDEMIAS/ OR LIPIDS/ 85574
33. ((cholesterol* OR dyslipid* OR hypercholesterol* OR hypertriglycerid* OR lipid* OR hyperlipid*)).ti,ab 422978
34. 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 1584674
35. 7 AND 34 6094
36. 35 [Limit to: English Language] 4869

EMBASE

1. ((rheumat* ADJ3 (arthrit* OR disease* OR condition* OR nodule*))).ti,ab 98448
2. exp RHEUMATOID ARTHRITIS/ 116354
3. (caplan* ADJ syndrome).ti,ab 120
4. (caplan* ADJ disease).ti,ab 2
5. (inflammatory ADJ arthritis).ti,ab 2982
6. (felty* ADJ syndrome).ti,ab 635
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6 142779
8. (bmi OR (body ADJ mass ADJ index)).ti,ab 123326
9. exp BODY MASS INDEX/ 119506
10. exp BODY FAT DISTRIBUTION/ 2661
11. exp WAIST HIP RATIO/ 4065

12. (body ADJ fat ADJ distribution).ti,ab 2072
13. (waist ADJ hip ADJ ratio).ti,ab 2527
14. (body ADJ weight).ti,ab 138047
15. BODY WEIGHT/ 145947
16. BLOOD PRESSURE/ 165782
17. HYPERTENSION/ 303767
18. (blood ADJ pressure).ti,ab 223352
19. hypertension.ti,ab 288140
20. GLUCOSE BLOOD LEVEL/ 121760
21. ((blood ADJ glucose) OR (fasting ADJ glucose) OR (glucose ADJ tolerance ADJ test)).ti,ab 63563
22. smoking.ti,ab 142401
23. SMOKING/ 117567
24. (serum ADJ creatinine).ti,ab 27967
25. KIDNEY FUNCTION/ OR GLOMERULUS FILTRATION RATE/ 82133
26. urinalysis.ti,ab 6161
27. (blood ADJ urea ADJ nitrogen).ti,ab 6356
28. (glomerular ADJ filtration ADJ rate).ti,ab 23389
29. ((kidney ADJ function) OR (renal ADJ function)).ti,ab 68899
30. exp PROTEINURIA/ 49711
31. proteinuria.ti,ab 28546
32. CHOLESTEROL/ 121102
33. HYPERLIPIDEMIA/ OR HYPERCHOLESTEROLEMIA [+NT]/ OR HYPERTRIGLYCERIDEMIA/ 83341
34. DYSLIPIDEMIA/ 23683
35. LIPID/ 98223
36. ((cholesterol* OR dyslipid* OR hypercholesterol* OR hypertriglycerid* OR lipid* OR hyperlipid*)).ti,ab 46751
37. 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 1704796
38. 7 AND 37 10512
39. 38 [Limit to: English Language] 8971

BNI

1. ((rheumat* ADJ3 (arthrit* OR disease* OR condition* OR nodule*))).ti,ab 596
2. exp ARTHRITIS AND RHEUMATISM/ 823
3. (caplan* ADJ syndrome).ti,ab 0
4. (caplan* ADJ disease).ti,ab 0
5. (inflammatory ADJ arthritis).ti,ab 11
6. (felty* ADJ syndrome).ti,ab 0
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6 1044
8. (bmi OR (body ADJ mass ADJ index)).ti,ab 274
9. (body ADJ fat ADJ distribution).ti,ab 6
10. (waist ADJ hip ADJ ratio).ti,ab 5
11. (body ADJ weight).ti,ab 85
12. BLOOD PRESSURE/ 843
13. (blood ADJ pressure).ti,ab 854
14. hypertension.ti,ab 856
15. ((blood ADJ glucose) OR (fasting ADJ glucose) OR (glucose ADJ tolerance ADJ test)).ti,ab 364
16. smoking.ti,ab 2545
17. SMOKING/ 2419
18. (serum ADJ creatinine).ti,ab 6
19. urinalysis.ti,ab 39
20. (glomerular ADJ filtration ADJ rate).ti,ab 12
21. (blood ADJ urea ADJ nitrogen).ti,ab 6
22. ((kidney ADJ function) OR (renal ADJ function)).ti,ab 71
23. proteinuria.ti,ab 17
24. ((cholesterol* OR dyslipid* OR hypercholesterol* OR hypertriglycerid* OR lipid* OR hyperlipid*)).ti,ab 640
25. 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 5720
26. 7 AND 25 7

CINAHL

1. (rheumat* ADJ3 arthrit*).ti,ab 6422
2. (rheumat* ADJ3 disease*).ti,ab 1654
3. (rheumat* ADJ3 condition*).ti,ab 243
4. (rheumat* ADJ3 nodule*).ti,ab 49
5. exp ARTHRITIS, RHEUMATOID/ 9759
6. (caplan* ADJ syndrome).ti,ab 0
7. (caplan* ADJ disease).ti,ab 0
8. (inflammatory ADJ arthritis).ti,ab 507
9. (felty* ADJ syndrome).ti,ab 8
10. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 11949
11. (bmi OR (body ADJ mass ADJ index)).ti,ab 15682
12. BODY MASS INDEX/ OR WAIST-HIP RATIO/ 23457
13. (body ADJ fat ADJ distribution).ti,ab 258
14. (waist ADJ hip ADJ ratio).ti,ab 734
15. (body ADJ weight).ti,ab 7713
16. BODY WEIGHT/ 7244
17. BLOOD PRESSURE/ 12156
18. HYPERTENSION/ 19956
19. (blood ADJ pressure).ti,ab 18759
20. hypertension.ti,ab 20193
21. BLOOD GLUCOSE/ 9512
22. ((blood ADJ glucose) OR (fasting ADJ glucose) OR (glucose ADJ tolerance ADJ test)).ti,ab 7781
23. smoking.ti,ab 23130
24. SMOKING/ 22387
25. (serum ADJ creatinine).ti,ab 1564
26. KIDNEY FUNCTION TESTS/ OR BLOOD UREA NITROGEN/ OR GLOMERULAR FILTRATION RATE/ OR URINALYSIS/ 5861
27. urinalysis.ti,ab 552
28. (glomerular ADJ filtration ADJ rate).ti,ab 1498
29. (blood ADJ urea ADJ nitrogen).ti,ab 371
30. ((kidney ADJ function) OR (renal ADJ function)).ti,ab 3230

31. proteinuria.ti,ab 1303
32. exp PROTEINURIA/ 2128
33. CHOLESTEROL/ 5584
34. HYPERLIPIDEMIA/ OR HYPERCHOLESTEROLEMIA/ 7807
35. LIPIDS/ 4182
36. ((cholesterol* OR dyslipid* OR hypercholesterol* OR hypertriglycerid* OR lipid* OR hyperlipid*)).ti,ab 20801
37. 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 138463
38. 10 AND 37 691
39. 38 [Limit to: (Language English)] 689

Appendix 3; Codes for RA participants and Screening

This appendix contains the codes used to identify RA participants in CiPCA. It also contains codes relating to screening in the CiPCA and IiPCA databases. Codes were identified using the NHS clinical terminology browser.

RA participant identification

N040. Rheumatoid arthritis
N04X. Seropositive rheumatoid arthritis, unspecified
N042. Other rheumatoid arthropathy with visceral or systemic involvement
N047. Seropositive errosive rheumatoid arthritis
N04X. Seropositive rheumatoid arthritis, unspecified
N04z. Inflammatory polyarthropathy NOS

Blood pressure screening

```
gen blood_pressure = 1 if rc>="G2" & rc<"G3"
recode blood_pressure .=1 if rc>="246" & rc<"247"
recode blood_pressure .=1 if rc>="9OD" & rc<"9OE"
recode blood_pressure .=1 if rc>="R1y3" & rc<"R1y4"
recode blood_pressure .=1 if rc>="662L" & rc<"662M"
recode blood_pressure .=1 if rc>="8I3Y" & rc<"8I3Z"
recode blood_pressure .=1 if rc>="R1y2" & rc<"R1y3"
recode blood_pressure .=1 if rc>="ZV70B" & rc<"ZV70C"
recode blood_pressure .=1 if rc>="68B1" & rc<"68B2"
recode blood_pressure .=1 if rc>="ZV7B1" & rc<"ZV7B2"
recode blood_pressure .=1 if rc>="662V" & rc<"662W"
recode blood_pressure .=1 if rc>="9N03" & rc<"9N04"
recode blood_pressure .=1 if rc>="9OI" & rc<"9OJ"
recode blood_pressure .=1 if rc>="315B" & rc<"315C"
recode blood_pressure .=1 if rc>="6A2" & rc<"6A3"
recode blood_pressure .=1 if rc>="14A2" & rc<"14A3"
recode blood_pressure .=1 if rc>="G87" & rc<"G88"
recode blood_pressure .=1 if rc>="662P" & rc<"662Q"
recode blood_pressure .=1 if rc>="662c" & rc<"662d"
recode blood_pressure .=1 if rc>="662d" & rc<"662e"
recode blood_pressure .=1 if rc>="6N4L" & rc<"6N4M"
recode blood_pressure .=1 if rc>="6627" & rc<"6628"
```

```
recode blood_pressure .=1 if rc>="6628" & rc<"6629"
```

Body weight Screening

```
gen body_weight = 1 if rc>="22K" & rc<"22L"
recode body_weight .=1 if rc>="22A" & rc<"22B"
recode body_weight .=1 if rc>="6878" & rc<"6879"
recode body_weight .=1 if rc>="8IAH" & rc<"8IAI"
recode body_weight .=1 if rc>="22N7" & rc<"22N8"
recode body_weight .=1 if rc>="66C1" & rc<"66C2"
recode body_weight .=1 if rc>="66C2" & rc<"66C3"
recode body_weight .=1 if rc>="66CZ" & rc<"66D"
recode body_weight .=1 if rc>="66C9" & rc<"66C10"
recode body_weight .=1 if rc>="66CK" & rc<"66CL"
recode body_weight .=1 if rc>="66CJ" & rc<"66CK"
recode body_weight .=1 if rc>="9N4V" & rc<"9N4W"
recode body_weight .=1 if rc>="66C6" & rc<"66C7"
recode body_weight .=1 if rc>="66C7" & rc<"66C8"
recode body_weight .=1 if rc>="66CA" & rc<"66CB"
recode body_weight .=1 if rc>="66CG" & rc<"66CH"
recode body_weight .=1 if rc>="66CH" & rc<"66CI"
recode body_weight .=1 if rc>="C38z0" & rc<"C38z1"
recode body_weight .=1 if rc>="ZV778" & rc<"ZV779"
recode body_weight .=1 if rc>="C380" & rc<"C381"
recode body_weight .=1 if rc>="22A4" & rc<"22A5"
recode body_weight .=1 if rc>="22A6" & rc<"22A7"
recode body_weight .=1 if rc>="66CC" & rc<"66CD"
recode body_weight .=1 if rc>="R031" & rc<"R032"
recode body_weight .=1 if rc>="1D1A" & rc<"1D1B"
recode body_weight .=1 if rc>="R032" & rc<"R033"
recode body_weight .=1 if rc>="NQSU6" & rc<"NQSU7"
recode body_weight .=1 if rc>="1625" & rc<"1626"
recode body_weight .=1 if rc>="1624" & rc<"1625"
recode body_weight .=1 if rc>="66CB" & rc<"66CC"
recode body_weight .=1 if rc>="66CF" & rc<"66CG"
recode body_weight .=1 if rc>="13AC" & rc<"13AD"
recode body_weight .=1 if rc>="66C9" & rc<"66C10"
```

Glucose screening

```
gen glucose =1 if rc>="C10E" & rc<"C10F"
recode glucose .=1 if rc>="C10F" & rc<"C10G"
recode glucose .=1 if rc>="66An" & rc<"66Ao"
recode glucose .=1 if rc>="66Ao" & rc<"66Ap"
recode glucose .=1 if rc>="44V1" & rc<"44V2"
recode glucose .=1 if rc>="44V2" & rc<"44V3"
recode glucose .=1 if rc>="44V3" & rc<"44V4"
recode glucose .=1 if rc>="44V4" & rc<"44V5"
recode glucose .=1 if rc>="44V6" & rc<"44V7"
recode glucose .=1 if rc>="44VZ" & rc<"44W"
```

```
recode glucose .=1 if rc>="466" & rc<"467"
recode glucose .=1 if rc>="7P172" & rc<"7P173"
recode glucose .=1 if rc>="68K1" & rc<"68K2"
recode glucose .=1 if rc>="C11y2" & rc<"C11y3"
recode glucose .=1 if rc>="44TK" & rc<"44TL"
recode glucose .=1 if rc>="R10D0" & rc<"R10D1"
recode glucose .=1 if rc>="R10E" & rc<"R10F"
recode glucose .=1 if rc>="R10D" & rc<"R10E"
recode glucose .=1 if rc>="R1057" & rc<"R1058"
recode glucose .=1 if rc>="R102" & rc<"R103"
recode glucose .=1 if rc>="44U7" & rc<"44U8"
recode glucose .=1 if rc>="9m9" & rc<"9n"
recode glucose .=1 if rc>="46S4" & rc<"46S5"
recode glucose .=1 if rc>="4Q83" & rc<"4Q84"
recode glucose .=1 if rc>="46S" & rc<"46T"
recode glucose .=1 if rc>="44T" & rc<"44U"
recode glucose .=1 if rc>="68K1" & rc<"68K2"
recode glucose .=1 if rc>="44j" & rc<"44k"
recode glucose .=1 if rc>="4I39" & rc<"4I40"
recode glucose .=1 if rc>="C10F" & rc<"C10G"
recode glucose .=1 if rc>="66Ao" & rc<"66Ap"
recode glucose .=1 if rc>="1I0" & rc<"1I1"
recode glucose .=1 if rc>="C10E" & rc<"C10F"
recode glucose .=1 if rc>="66An" & rc<"66Ao"
recode glucose .=1 if rc>="6872" & rc<"6873"
recode glucose .=1 if rc>="46Z0" & rc<"46Z1"
recode glucose .=1 if rc>="90y" & rc<"90z"
recode glucose .=1 if rc>="ZV771" & rc<"ZV772"
recode glucose .=1 if rc>="4662" & rc<"4663"
recode glucose .=1 if rc>="4666" & rc<"4667"
recode glucose .=1 if rc>="4661" & rc<"4662"
recode glucose .=1 if rc>="4663" & rc<"4664"
recode glucose .=1 if rc>="44g1" & rc<"44g2"
recode glucose .=1 if rc>="44T2" & rc<"44T3"
recode glucose .=1 if rc>="466" & rc<"467"
```

Smoking screening

```
gen smoking= 1 if rc>="137k" & rc<"137l"
recode smoking .=1 if rc>="137R" & rc<"137S"
recode smoking .=1 if rc>="137P" & rc<"137Q"
recode smoking .=1 if rc>="137" & rc<"138"
recode smoking .=1 if rc>="137K" & rc<"137L"
recode smoking .=1 if rc>="137L" & rc<"137M"
recode smoking .=1 if rc>="137Q" & rc<"137R"
recode smoking .=1 if rc>="137S" & rc<"137T"
recode smoking .=1 if rc>="137j" & rc<"137k"
recode smoking .=1 if rc>="137X" & rc<"137Y"
recode smoking .=1 if rc>="13p4" & rc<"13p5"
```

```
recode smoking .=1 if rc>="137T" & rc<"137U"
recode smoking .=1 if rc>="8CAL" & rc<"8CAM"
recode smoking .=1 if rc>="745H" & rc<"745I"
recode smoking .=1 if rc>="13p" & rc<"13q"
recode smoking .=1 if rc>="8HTK" & rc<"8HTL"
recode smoking .=1 if rc>="8IAj" & rc<"8IAk"
recode smoking .=1 if rc>="67H1" & rc<"67H2"
recode smoking .=1 if rc>="137M" & rc<"137N"
recode smoking .=1 if rc>="137N" & rc<"137O"
recode smoking .=1 if rc>="137O" & rc<"137P"
recode smoking .=1 if rc>="137V" & rc<"137W"
recode smoking .=1 if rc>="137W" & rc<"137X"
recode smoking .=1 if rc>="137Y" & rc<"137Z"
recode smoking .=1 if rc>="137Z" & rc<"138"
recode smoking .=1 if rc>="137a" & rc<"137b"
recode smoking .=1 if rc>="137b" & rc<"137c"
recode smoking .=1 if rc>="137c" & rc<"137d"
recode smoking .=1 if rc>="137d" & rc<"137e"
recode smoking .=1 if rc>="137e" & rc<"137f"
recode smoking .=1 if rc>="137g" & rc<"137h"
recode smoking .=1 if rc>="137f" & rc<"137g"
recode smoking .=1 if rc>="137h" & rc<"137i"
recode smoking .=1 if rc>="137i" & rc<"137j"
recode smoking .=1 if rc>="137l" & rc<"137m"
recode smoking .=1 if rc>="137m" & rc<"137n"
recode smoking .=1 if rc>="9ko" & rc<"9kp"
recode smoking .=1 if rc>="9km" & rc<"9kn"
recode smoking .=1 if rc>="9kn" & rc<"9ko"
recode smoking .=1 if rc>="6791" & rc<"6792"
```

Cholesterol screening

```
gen cholesterol= 1 if rc>="44P" & rc<"44Q"
recode cholesterol .=1 if rc>="6879" & rc<"6880"
recode cholesterol .=1 if rc>="8I3w" & rc<"8I3x"
recode cholesterol .=1 if rc>="44PK" & rc<"44PL"
recode cholesterol .=1 if rc>="44d4" & rc<"44d5"
recode cholesterol .=1 if rc>="44d2" & rc<"44d3"
recode cholesterol .=1 if rc>="44P8" & rc<"44P9"
recode cholesterol .=1 if rc>="44d5" & rc<"44d6"
recode cholesterol .=1 if rc>="44d3" & rc<"44d4"
recode cholesterol .=1 if rc>="662a" & rc<"662b"
recode cholesterol .=1 if rc>="44O5" & rc<"44O6"
recode cholesterol .=1 if rc>="9N4K" & rc<"9N4L"
recode cholesterol .=1 if rc>="44O2" & rc<"44O3"
recode cholesterol .=1 if rc>="44O3" & rc<"44O4"
recode cholesterol .=1 if rc>="44O4" & rc<"44O5"
```

```
recode cholesterol .=1 if rc>="44O6" & rc<"44O7"
recode cholesterol .=1 if rc>="44OD" & rc<"44OE"
recode cholesterol .=1 if rc>="44OE" & rc<"44OF"
recode cholesterol .=1 if rc>="44PA" & rc<"44PB"
recode cholesterol .=1 if rc>="44IL" & rc<"44IM"
recode cholesterol .=1 if rc>="44IM" & rc<"44IN"
recode cholesterol .=1 if rc>="44P6" & rc<"44P7"
recode cholesterol .=1 if rc>="44IH" & rc<"44II"
recode cholesterol .=1 if rc>="44II" & rc<"44IJ"
recode cholesterol .=1 if rc>="44dB" & rc<"44dC"
recode cholesterol .=1 if rc>="44PE" & rc<"44PF"
recode cholesterol .=1 if rc>="44P5" & rc<"44P6"
recode cholesterol .=1 if rc>="44IF" & rc<"44IG"
recode cholesterol .=1 if rc>="44PF" & rc<"44PG"
recode cholesterol .=1 if rc>="44dA" & rc<"44dB"
recode cholesterol .=1 if rc>="44IG" & rc<"44IH"
recode cholesterol .=1 if rc>="44IG" & rc<"44IH"
recode cholesterol .=1 if rc>="44PG" & rc<"44PH"
recode cholesterol .=1 if rc>="44PC" & rc<"44PD"
recode cholesterol .=1 if rc>="44PB" & rc<"44PC"
recode cholesterol .=1 if rc>="44d2" & rc<"44d3"
recode cholesterol .=1 if rc>="44P8" & rc<"44P9"
recode cholesterol .=1 if rc>="13B3" & rc<"13B4"
recode cholesterol .=1 if rc>="ZV653" & rc<"ZV654"
recode cholesterol .=1 if rc>="44PD" & rc<"44PE"
recode cholesterol .=1 if rc>="44d4" & rc<"44d5"
recode cholesterol .=1 if rc>="C324" & rc<"C325"
recode cholesterol .=1 if rc>="C322" & rc<"C323"
recode cholesterol .=1 if rc>="C320" & rc<"C321"
recode cholesterol .=1 if rc>="44O" & rc<"44P"
recode cholesterol .=1 if rc>="44P" & rc<"44Q"
recode cholesterol .=1 if rc>="4405" & rc<"4406"
```

Appendix 4; Comorbidity Codes

This appendix presents the codes used to identify comorbidity. Codes relating to diagnoses and investigations relevant to each comorbidity are presented first, followed by prescription codes identified from the BNF.

Diabetes mellitus

```
gen diabetes= 1 if rc>="C10E" & rc<"C10F"
recode diabetes .=1 if rc>="C10F" & rc<"C10G"
recode diabetes .=1 if rc>="66An" & rc<"66Ao"
recode diabetes .=1 if rc>="66Ao" & rc<"66Ap"
recode diabetes .=1 if rc>="8B3I" & rc<"8B3J"
recode diabetes .=1 if rc>="44V3" & rc<"44V4"
```

BNF prescription codes

6.1.1 Insulins
6.1.2 Antidiabetic drugs

Hypertension

```
gen hypertension= 1 if rc>="G20" & rc <"G21"
recode hypertension .=1 if rc>="G2" & rc<"G3"
```

BNF prescription codes

2.5.1 (Vasodilator antihypertensive drugs)
2.5.2 (Centrally acting antihypertensive drugs)
2.5.3 (Adrenergic neurone blocking drugs)
2.5.4 (Alpha-adrenoceptor blocking drugs)
2.5.5 (Drugs affecting the renin-angiotensin system)
2.6.2 (Calcium-channel blockers)
2.2 (Diuretics)
2.4 (Beta-adrenoceptor blocking drugs)

Hyperlipidaemia

```
gen hyperlipidaemia= 1 if rc>="C324" & rc<"C325"
recode hyperlipidaemia .=1 if rc>="C322" & rc<"C323"
recode hyperlipidaemia .=1 if rc>="C3202" & rc<"C3203"
recode hyperlipidaemia .=1 if rc>="44P4" & rc<"44P5"
recode hyperlipidaemia .=1 if rc>="44P3" & rc<"44P4"
recode hyperlipidaemia .=1 if rc>="C32" & rc<"C33"
recode hyperlipidaemia .=1 if rc>="C328" & rc<"C329"
recode hyperlipidaemia .=1 if rc>="C3210" & rc<"C3211"
```

BNF prescription codes

2.12 (Lipid regulating drugs)