An investigation of adherence to statin therapy in patients with rheumatoid arthritis

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Abstract

Background

Rheumatoid arthritis (RA) patients are more likely to experience a cardiovascular event (CVE) than the general population. This is a result of atherosclerotic disease augmented by systemic inflammation. HMG-CoA (3-hydroxy-3-methylglutarylcoenzyme A) reductase inhibitors (statins) lower the risk of CVEs; further, pleiotropic effects are of clinical relevance for RA disease activity. Many patients do not achieve ideal clinical outcomes because of poor medication adherence. This study sought to determine the rates and predictors of adherence in the TRACE-RA population.

Methods

Data collected from the Trial of Atorvastatin for the primary prevention of Cardiovascular Events in patients with Rheumatoid Arthritis (TRACE-RA) were used to meet these aims. Two thousand nine hundred and eighty six patients from 102 centres were randomised to receive either atorvastatin or placebo. Adherence was determined up to 3, 6 and 12 months using data on pill counts and self-reports. Rates and responses were dichotomised as adherent ($\geq$80% consumption or 'Most tablets consumed') and non-adherent (<80% consumption or 'Some/None tablets consumed'). Univariate logistic regression analysis and multivariate logistic regression analysis were performed to determine predictors of adherence for patients with complete data in both arms of TRACE-RA and for those solely in the atorvastatin arm. The multivariate models were adjusted for age and gender.

Results

Adherence to trial medication was 49.4%, 49.1% and 50.1% up to 3, 6 and 12 months respectively. No significant differences for the rates of adherence were observed between arms. Patients who consumed alcohol on a monthly or less basis (OR=0.65, 95%CI 0.42-0.97) were less likely to adhere to the allocated TRACE-RA intervention than patients who never consumed alcohol. Patients who reported 'extreme pain/ discomfort' were 67% more likely to adhere to the TRACE-RA intervention than those who reported no pain/ discomfort (OR=1.67, 95%CI 0.96-2.90). In the atorvastatin arm, patients with a high disease activity were more adherent towards statin therapy than patients in remission (OR=1.64, 95%CI 0.83-3.24).

Conclusion

Adherence to trial medication was sub-optimal in TRACE-RA. This research has importance for adherence in RA populations, predictors of adherence to statin therapy, and interventions such as counselling or adherence programmes. Underlying attitudes, motivations and beliefs of non-adherent patients require further examination.

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Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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List of abbreviations

ACE	Angiotensin converting enzyme
ACPA	Anti-citrullinated protein antibody
ACQUIP	Ambulatory Care Quality Improvement Project
bDMARD	Biological disease modifying anti-rheumatic drug
BMI	Body mass index
CABG	Coronary artery bypass graft
CARRE	Cardiovascular and rheumatoid arthritis study
CI	Confidence interval
CS-CS	Cross section cohort study
CMG	Cumulative multiple refill interval gap
COX	Cyclooxygenase
CRF	Case report form
CRP	C reactive protein
csDMARD	Conventional synthetic disease modifying anti-rheumatic drug
CVD	Cardiovascular disease
CVE	Cardiovascular event
DAS28	Disease activity score 28
DMA	Daily medication adherence
DMARD	Disease modifying anti-rheumatic drug

EQ-5D	Euroqol-5D questionnaire
FLS	Fibroblast-like synoviocyte
GRACE	Global Registry of Acute Coronary Events
HAQ	Health assessment questionnaire
HAQ-ADI	Health assessment questionnaire alternate disability index
HAQ-SDI	Health assessment questionnaire standard disability index
HDL	High-density lipoprotein
HBM	Health Belief Model
HLA	Human leukocyte antigen
ICD	International Classification of Diseases
IL	Interleukin
IQR	Inter-quartile range
JUPITER	Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
LDL	Low-density lipoprotein
LIPID	The Long term Intervention with Pravastatin in Ischaemic Disease (LIPID Trial)
LLD	Lipid lowering drug
MARS	Medication adherence rating scale
MEMS	Medication Event Monitoring System
MI	Myocardial infarction

mmHg	Millimeter of mercury
MMP	Matrix metalloproteinase
MPR	Medication possession ratio
MTX	Methotrexate
NK	Natural killer (cells)
ONS	Office for National Statistics
OR	Odds ratio
PCS	Prospective cohort study
PDC	Proportion of days covered
PP	Primary prevention
PR	Prevalence ratio
PTCA	Percutaneous transluminal coronary angioplasty
PTPN22	Protein tyrosine phosphatase non-receptor type 22
QE	Quasi experimental
RA	Rheumatoid arthritis
RCS	Retrospective cohort study
RCT	Randomised controlled trial
RhF	Rheumatoid factor
RR	Relative risk
SDD	Standardised mean daily dose
SP	Secondary prevention
TARA	Trial of Atorvastatin in Rheumatoid Arthritis

TC	Total cholesterol
TG	Triglyceride
TNFα	Tumour necrosis factor alpha
TRACE-RA	Trial of Atorvastatin for the primary prevention of Cardiovascular Events in Rheumatoid Arthritis
TRF	Traditional risk factor
VAS	Visual analogue scale

Chapter 1

This chapter is composed of introductions for rheumatoid arthritis, cardiovascular disease, statin therapy and medication adherence.

1 Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune disease that is characterised by inflammatory synovitis, autoantibody production, destruction of joints and subsequent disability. RA affects 0.8% of the UK adult population and is more prevalent in women (1). RA amounts to a serious economic burden on society. Estimates of the cost of RA work-related disability and RA associated to the UK economy range from £1.8 billion a year to £7.9 billion a year (2, 3). Systemic inflammation may lead to comorbidity and an increased risk of mortality. An increasing mortality gap over the past 4 decades between RA patients and the general US population has been observed (4). In particular, the cardiovascular mortality risk in RA patients is around 50% greater than that of the general population (5). The magnitude of the increased risk of cardiovascular mortality in RA patients has been likened to that of patients with diabetes mellitus type 2 (6, 7).

Cardiovascular disease (CVD) is the most common cause of death in the general population. Known risk factors for CVD (so called traditional risk factors [TRFs]) include smoking and dyslipidaemia. A high total cholesterol (TC): high density lipoprotein (HDL) ratio (atherogenic index) is associated with an increased risk of CVD in the general population. Statin therapy has been shown to reduce the TC:HDL ratio in the general population with an associated reduction in cardiovascular events (CVEs). The inflammation of RA is associated with a lowering of TC and even greater proportionate lowering of HDL leading to an adverse atherogenic index (8). However there has been no trial of the impact of statin therapy on CVEs in RA.

1.1 Rheumatoid arthritis

1.1.1 Epidemiology of rheumatoid arthritis

The incidence rate of a disease is defined as the number of new cases over a given span of time. The incidence of RA increases with age and is higher in women than men. RA incidence peaks between the ages of 65-74 (9). The prevalence of a disease can be defined as a cross-sectional representation of disease frequency in a given population. The prevalence of RA in the UK adult population is estimated at 1.1% in women and 0.4% in men(1). However, these figures vary between ethnicities and nationalities. For example, authors of one study observed a lower cumulative prevalence of RA in a black-Caribbean population of inner-Manchester when compared with the white population (0.3% vs 0.8% respectively) (10). These results are supported by estimates of prevalences in black rural African populations (11) and have been attributed, in part to genetic factors (12). In Native American communities, the prevalence of RA can be as high as 6.8%. In Chinese and Japanese populations, RA prevalence can be as low as 0.2%-0.3% of the general adult population (13).

The exact cause of RA is unknown; however many genetic and environmental factors have been identified that increase the risk of developing RA. Rheumatoid factor (RhF) is an autoantibody that, by binding to Fc regions of other antibodies, causes an autoimmune response. This occurs through the secretion of chemotactic factors that recruit macrophages thus encouraging inflammation (14). Anti-citrullinated protein antibody (ACPA) is another autoantibody associated with RA. ACPA can be present up to 14 years before clinical detection of RA and is associated with an increased risk of developing a more severe RA state (15, 16). The human leukocyte antigen (HLA) region of chromosome 6 is a susceptibility locus for

RhF or ACPA positive RA (17, 18). More recent genome wide association studies have identified over 100 risk loci associated with RA (19-22). Expression of amino acid motif QKRAA (shared epitope) of the HLA-DRB1 region is associated with an increased susceptibility to RA (23). It is suggested that the shared epitope may confer a pro-inflammatory outcome by inducing directed naïve T cell differentiation towards T_h17 cells (24). Outside of the HLA region, protein tyrosine phosphatase non-receptor type 22 (PTPN22) has been associated with RA. The PTPN22 gene regulates immunity at the innate level by controlling T cell receptor signalling (25). Certain single nucleotide polymorphisms at PTPN22 confer an increased risk for RA. Gene-gene interactions between HLA-DBR1 shared epitope and the A allele of PTPN22 have been associated with RA in ACPA positive patients. ACPA positivity has predicted a poorer prognosis for patients with RA (26).

Several environmental risk factors for RA have been identified through extensive research. Smoking is considered the strongest of these. One particular effect of smoking on the immune system is the activation of free radicals and subsequent impairment of antioxidant systems. This leads to an increase in oxidative stress (reviewed by Kalpakcioglu B and Senel K 2008) (see section 1.2.3) (27). Smoking is also associated with ACPA development and with RhF positivity (28, 29). The quantity of cigarettes smoked by an individual is associated with the risk of developing RA. Researchers of the Nurse's Health Study reported that the risk of RA increased with the number of pack-years of cigarette smoking when compared with those who have never smoked. Despite the reduced risk of RA following smoking cessation, the risk was still reported as elevated up to 20 years compared with non-smokers (30). Gene-environmental interactions have also been reported. Authors of the Swedish Epidemiologic Investigation of

Rheumatoid Arthritis study found that, for patients within one year of RA onset who did not carry the shared epitope, smokers had a 1.5-fold greater risk of developing ACPA than non-smokers. Smokers who carried two copies of the shared epitope had a 21 fold greater risk of developing ACPA compared with the non-smoking group who did not have the shared epitope (31). Another study reported that individuals who carried two copies of the shared epitope and smoked had an increased risk of RhF positive RA than non-smokers without a copy of the shared epitope (32). Other environmental factors may also associate with RA risk. Socioeconomic factors are also associated with an increased risk of developing RA. Individuals with a low level of education and individuals working in manual labour are at an increased risk of developing RA compared with patients who possess a university degree and those who do not work in manual labour (33). Alcohol consumption has been implicated in a number of diseases, however moderate consumption has been shown to protect against RA in an inverse dose dependent relationship (32, 34).

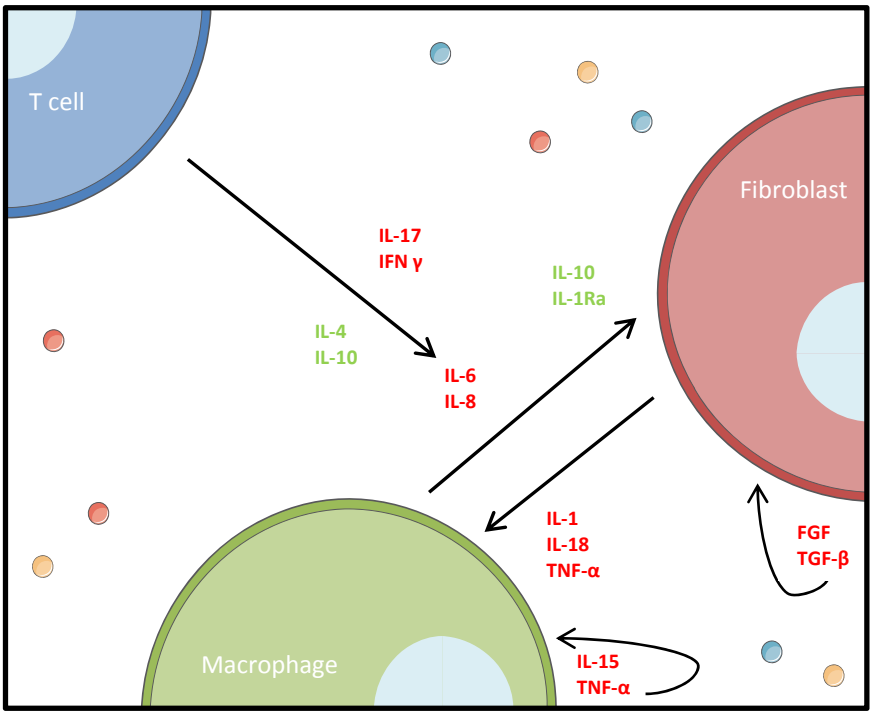
1.1.2 Mechanisms of Inflammation

The mechanisms of inflammation in RA are not completely understood; however the process of inflammation in the synovium of the joint is thought to mediate the destruction of cartilage and bone. The function of the synovial membrane is to provide lubrication, nutrients and fluid to the flexible joint. Here, inflammation is influenced by the recruitment of T cells which are activated in response to pro-inflammatory cytokine stimuli. Cytokines are small proteins that are important in the cell signalling process. They are secreted by a number of cells of the immune system. The self-regulation of pro and anti-inflammatory cytokines is of importance in maintaining homeostatic conditions. B cells are associated with the

pathogenesis of RA. Interest in the role of B cells has increased since the discovery that anti-CD20 monoclonal antibody therapy improves RA disease activity (35). T cells release cytokines that trigger B cell differentiation into plasma cells. These secrete autoantibodies including RhF and ACPA that also contribute towards the pathogenesis of RA (36).

Bone erosion is associated with more severe inflammation and a poorer outcome. The speed at which this occurs emphasises the need for faster diagnosis of RA (37). Cytokines interleukin (IL)-1, IL-6 and TNF-α have been associated with osteoclast differentiation. The enzymatic machinery of osteoclasts allows for the destruction of surrounding mineralised tissues, including mineralised cartilage, and these are subsequently replaced with inflammatory tissue (38). At RA onset, synovial fibroblast hyperplasia overlies an interstitial layer of proliferating CD4 $T_{(h)}$ cells, CD8 T cells, natural killer (NK) cells, NK T cells, B cells and plasma cells and is thought to be induced by IL-17a (39). A hypoxic environment is induced through articular damage and neo-antigens may mediate greater autoimmunity. Synovial hyperplasia cannot wholly be explained through the proliferation of fibroblast-like synoviocytes (FLSs). FLSs secrete matrix metalloproteinases (MMPs) that have the potential to degrade cartilage. Specifically, MMP14 is a frequently produced MMP that degrades type II collagen of which the cartilage is largely made (40). Macrophage and fibroblast cytokines are also abundant within the synovium of the joint and are secreted in a manner that encourages a positive feedback mechanism (see figure 1.1). In turn, this may moderate inflammation.

Figure 1. 1 Cytokine networks in rheumatoid arthritis



Source: Adapted from Firestein GS 2003 (14)

IL= Interleukin, IF= Interferon, TNF= Tumour necrosis factor, TGF= Transforming growth factor, FGF= Fibroblast growth factor, IL-1Ra= Interleukin-1 receptor antagonist. Cytokines highlighted in red mediate pro-inflammatory responses. Cytokines highlighted in green mediate anti-inflammatory responses.

1.2 Cardiovascular disease in patients with rheumatoid arthritis

CVD is a term to describe a number of diseases of the heart and vasculature such as coronary heart disease, stroke or unstable angina. It is the leading cause of mortality worldwide accounting for 31% of global deaths in 2012 (World Health Organization 'Fact Sheet'). The main causes of CVD-related mortality are CHD and stroke. In the general UK population, CVD accounted for 29% of deaths in men and 28% of deaths in women in 2014 (41). This amounts to a significant burden on the National Health Service. Between 2012 and 2013, health care spending on treating CVD amounted to £6.8 billion in England. Of this, £1.4 billion was spent on primary care (such

as GP services) and £4.4 billion was spent on secondary care (such as hospital admissions) (41). Mortality rates in RA patients are poor and are largely attributable to cardiovascular comorbidity (5, 42, 43). A study of 114342 women in the Nurses' Health Study found an increased risk of a myocardial infarction (MI) in RA patients compared with those without RA (relative risk= 2.0, 95%CI 1.23-3.29) (44). Important to the risk of a CVE is the development and risk of rupture of atherosclerotic plaque.

1.2.1 The development of atherosclerotic plaque

Atherosclerotic disease presents a risk for CVD. It is chronic and arises from the development of fatty deposits on the inner walls of arteries. Consequently, arterial walls harden and thicken and blood pressure increases. These deposits are composed of macrophages and debris and can cause scar tissue and plaque development. When a plaque breaks away, the patient is at risk of arterial blockage and a CVE such as stroke or an MI. Components of the endothelium of the artery wall are of importance in maintaining the surroundings for blood pressure regulation (45). The dysfunction of the endothelial layer can mediate the development of a fatty lesion that is facilitated by lipids and low-density lipoproteins (LDLs).

1.2.1.1 Low-density lipoproteins and oxidisation

LDLs are a major group of lipoprotein and a risk factor for CVD. As they are small, they can readily pass through the permeable endothelium allowing for a build-up of lipoproteins within the blood vessel wall (46). Here, LDLs are susceptible to oxidisation through exposure to circulating free radicals. Oxidised LDLs have a number of pro-atherogenic roles. They aid in the inititation of an inflammatory response in the wall of the artery and in the

recruitment of monocytes and macrophages via the presentation of leukocyte adhesion molecules (47). Further macrophages are recruited causing a vicious cycle of inflammation and further oxidation to LDLs (48). All of this is integral to 'foam cell' formation. Here, oxidised LDLs are consumed by macrophages in endocytosis. The accumulation of foam cells contributes to the generation of a fatty streak and subsequent plaque over time.

1.2.1.2 High-density lipoproteins

HDLs possess a role in reverse cholesterol transport whereby cholesterol is broken down into cholesterol esters and taken up by LDLs and converted into bile acid (49). They possess anti-inflammatory properties that are particularly important in protecting against atherosclerosis (50). Furthermore, HDLs encourage the synthesis of vasodilator nitric oxide, which in turn lowers blood pressure and prevents the accumulation of platelets within the vasculature. Further functions of HDLs include the ability to reduce the expression of vascular cell adhesion protein-1, encourage macrophage cholesterol efflux, and importantly, inhibit oxidisation of LDLs.

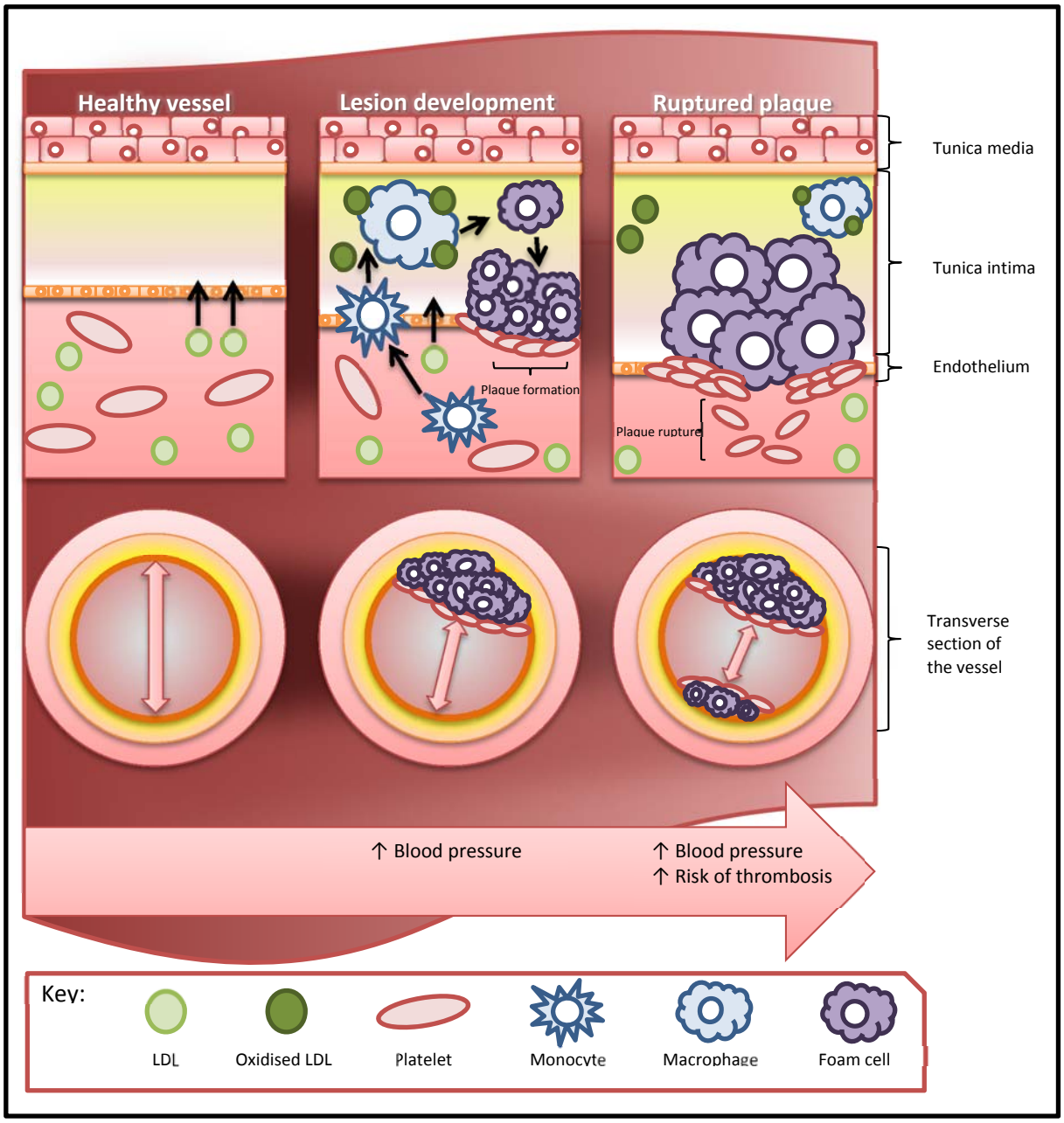
There is a growing body of evidence that suggests that HDLs lose many of their anti-atherogenic properties under inflammatory conditions; furthermore, levels of HDL can seriously fall. Plasma protein Serum Amyloid A, which is upregulated under inflammatory conditions, modifies the composition of HDL by binding to the lipoprotein and displacing apolipoprotein-1 (51), a major protein of HDL. Inflammation is also understood to mediate enzymes associated with the metabolism of

lipoproteins. On such enzyme is HL, which converts larger HDLs into smaller ones, thus increasing cholesterol uptake and helping in reverse cholesterol transport (52).

1.2.1.3 Systemic inflammation and atherosclerotic plaque

Cytokines such as TNFα, IL-1α, and IL-6 are released by macrophages and monocytes. These promote the proliferation and migration of endothelial cells and smooth muscle cells (53, 54). Further, IL-1α works to upregulate endothelin-1, a vasoconstrictor released from endothelial cells (55). In hypercholesteraemic conditions, the expression of adhesion molecules such as vascular cell adhesion protein-1 are increased. Such molecules function by binding cells of the immune system to the endothelium of the vessel, thus increasing stiffness. The pro-atherogenic effects of IL-1α are augmented by the upregulation of IL-1 receptor by platelet derived growth factor, thus creating an enhanced atherogenic environment (56). The accumulation of platelets within the blood vessel leads to the development of a plaque and causes the endothelial lining to thicken and subsequently harden (57). Platelet-derived growth factor is also released, enhancing the proliferation and migration of smooth muscle cells and supporting neointimal hyperplasia (58). Uneven areas of plaque wall are unstable and prone to rupture. Ruptured plaque can lead to the occlusion of the artery and ischaemia (see figure 1.2).

Figure 1. 2 The development of atherosclerosis



Source: Original

LDLs are oxidised by circulating free radicals. Oxidised LDLs encourage the recruitment of inflammatory cells that induce growth factor release. This accelerates inflammation. Acute phase reactants such as C reactive protein aid the endocytosis of LDLs and encourage foam cell formation. The accumulation of foam cells creates a fatty streak that accompanies a plaque. Subsequent rupture of a plaque can result in a CVE.

1.2.2 Cardiovascular disease in patients with rheumatoid arthritis

High levels of systemic inflammation in RA patients means that they are particularly prone to developing an atherosclerotic plaque. TNFα and IL-1α secreted by immune cells mediate inflammation within the vasculature and the proliferation and migration of endothelial and smooth muscle cells that ultimately lead to the build-up of an intermediate lesion and eventual plaque development (53, 54). Acute phase reactants such as C reactive protein (CRP) are observed in the preclinical state and may confer an increased vascular risk prior to RA diagnosis (59).

Rheumatoid cachexia is characterised by the wasting of skeletal muscle mass that may be replaced by fat and is caused by pro-inflammatory cytokines (60). Higher visceral fat has been linked with a greater risk of CVD, increased arterial stiffness (61) and an increased risk of MI in the general older adult population (62). The relative distribution of visceral and subcutaneous fat also contributes towards CVD development in RA patients (63).

It has been noted that higher atherogenic indices are observed in RA patients (64-66). While high levels of TC associate with a greater risk for CVEs in the general population (67), increasing the development of atherosclerosis through the deposit of more LDLs and thus a greater accumulation of foam cells, the inverse of this may be associated with an increased risk of CVEs in the RA population. This is likely a result of systemic inflammation. One study showed that systemic inflammation, as observed in RA, is associated with a reduced serum TC level and an increased atherosclerotic state (68). This can be the result of a relatively greater reduction of HDLs (that possess

anti-inflammatory properties) than other components of the lipid profile (69). The consequence is a higher TC:HDL ratio, or a higher atherogenic index, and a state of dyslipidaemia (66, 69). A number of studies have observed that an increase in lipid levels and a subsequent reduction in the atherogenic index in RA associates with a decrease in CVEs (68, 70). The collective outcome of an abnormal lipid profile and pro-inflammatory stimuli to the vasculature increases the risk of CVD comorbidity in RA patients.

1.2.3 Risk factors for the development of CVD

Smoking increases the risk of CVD by acting on a number of elements of the circulatory system. Stimulant nicotine drives the production of epinephrine which subsequently increases heart rate and blood pressure (71). Nicotine exposure also upregulates gene expression of von Willebrand factor and angiotensin-converting enzyme (ACE) (72). The upregulation of these proteins accelerates a hypertensive state by driving coagulation and vasoconstriction via the catalysis of angiotensin I to vasoconstrictor angiotensin II. Smoking has also been associated with an unfavourable lipid profile. Acrolein, found in cigarette smoke, causes the oxidative modification of apoE3-NT. This hinders the role of apoeE3 in the homeostasis of cholesterol in plasma (73). Heavier smokers have higher levels of TC, triglycerides and LDLs when compared with those who smoke less. A lipid profile that is lower in HDLs is also observed in heavier smokers compared with lesser smokers (74).

As described above, atherogenic dyslipidaemia is a risk factor associated with the development of CVD. It may be described as an abnormal quantity

of lipids and distribution of lipid types in the blood and is characterised by high levels of triglycerides and LDLs and frequently, low levels of HDLs. The atherogenic index has been identified as a prognostic marker for CVD (75). Lipid-lowering medication has been used to reduce levels of TC and together, the atherogenic index (76).

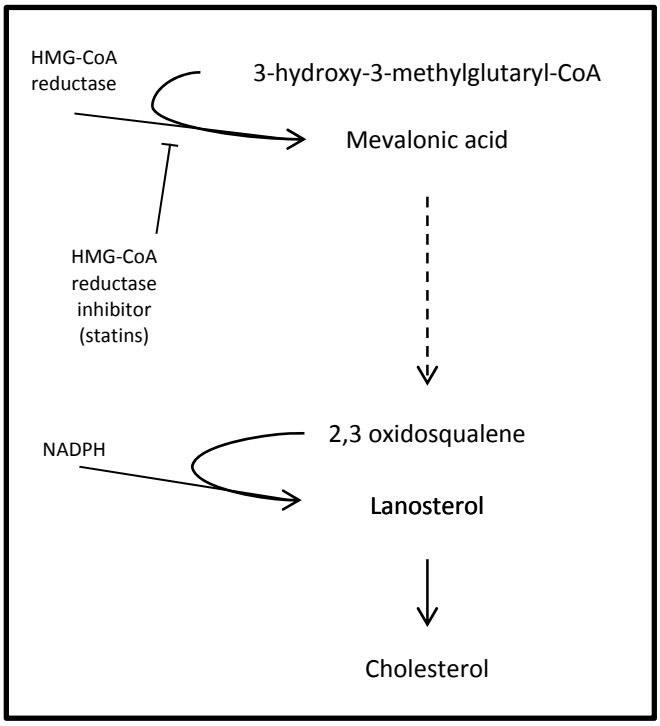
1.3 Statin therapy

Cholesterol synthesis is undertaken in the liver. Statins achieve cholesterol reduction by inhibiting the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase which is part of a 19 step process of the mevalonate pathway. The mevalonate pathway is important in the biosynthesis of sterols such as cholesterol. In turn, inhibition of HMG-CoA reductase prevents the catalysis of HMG-CoA and the production of mevalonic acid (see figure 1.3). Since lovastatin achieved Food and Drug Administration approval in 1987, numerous other types of statin have followed. It is widely acknowledged that statins reduce the risk of CVEs (77-81). A reduction of serum LDL by 1mmol/L was found to reduce CVE incidence by 20% in one meta-analysis of 26 randomised trials (169138 patients) (77). Another meta-analysis showed that patients on statins for the primary prevention of CVD were at a reduced risk of all-cause mortality and CVEs without an excess of adverse events (82).

Pro-inflammatory cytokines such as IL-6 mediate inflammation and so induce CRP synthesis. High CRP levels are a serological marker for vascular events and inflammation (83). The Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study reported the clinical benefits of statin therapy in healthy subjects with elevated CRP levels but without hyperlipidaemia. Patients receiving

rosuvastatin were 44% less likely to experience a CVE than the placebo group (84). It might therefore be supposed that RA patients with elevated CRP levels may benefit from statin therapy.

Figure 1. 3 An overview of the cholesterol synthesis pathway



Source: Adapted from a review by Charlton-Menys V and Durrington PN 2007 (85)

HMG-CoA= 3-hydroxy-3-methylglutaryl-coenzyme A, NADPH= Nicotinamide adenine dinucleotide phosphate. HMG-CoA reductase inhibitors prevent the catalysis of HMG-CoA to mevalonic acid.

Cross sectional analysis of baseline data from the Dutch Cardiovascular and Rheumatoid arthritis (CARRE) prospective cohort study of 353 RA patients found a direct relationship between CRP and the atherogenic index (86). This and further research (87) suggest that the TC:HDL ratio is relevant in the risk stratification of CVD in RA patients. Statin therapy to reduce levels of TC may improve the atherogenic indices of RA patients. The potential benefit of statin use in RA has been demonstrated in the proof-of-concept

TARA randomised controlled trial (RCT) (88). In TARA, the clinical effects of atorvastatin and placebo were compared in 116 RA patients. Clinical benefits of statin administration among 58 RA patients assigned to the atorvastatin group were reported compared with the placebo group. A notable reduction in systemic inflammation and IL-6 levels were observed and this was reflected in lower disease activity scores in the atorvastatin arm. In patients receiving atorvastatin, TC levels were reduced whereas HDL levels remained constant thus atorvastatin treatment resulted in a lower atherogenic index (88).

Statins possess a range of pleiotropic effects of clinical relevance in RA. Such effects may improve atherosclerotic plaque stability (89), inhibit vascular smooth muscle cell proliferation, reduce oxidative stress and reduce vasoconstriction(90-92). Like any drug, statins possess side effects. An increased risk of diabetes mellitus type 2 has been observed in otherwise healthy patients who were receiving rosuvastatin for the primary prevention of a CVE (84). More common side effects of statin therapy involve the muscles or the liver. Muscle pain is frequently cited as a side effect by patients (93). However, when compared with placebo in a population of 20,536 high-risk CVD individuals, a similar proportion of the simvastatin group (32.9%) and placebo group (33.2%) reported muscle aches (94). Supporting this, a systematic review of 39 studies found no significant difference between those reporting muscle pains in statin groups compared with placebo groups (95). There was also a distinct lack of evidence for whether statin use was associated with muscle pain in one group of 3058 patient with arthritis (96). This could be explained by a "masking"-effect that arthritis pain may have on any statin-related muscle pain. Events of myopathy (whereby muscle fibres fail and lead to muscle weakness) in patients receiving statin therapy are often reported between 1-5% in

randomised controlled trials (97). It is possible that this is an underestimation of the true prevalence of myopathy due to trial exclusion criteria and potential trial washout periods, as the reported prevalence of muscle pains in population-based studies is high.

Events of rhabdomyolosis, where muscle tissue is broken down further, are rarer than myopathy. Cerivastatin was notorious for causing fatal rhabdomyolosis in 52 users and was consequently withdrawn from the market in 2001 by its producer, Bayer (98). It is possible that such a prominent failure and poorly interpreted evidence have influenced the media's interpretation of statin studies. Indeed, a recent and comprehensive literature review of statin therapy published in The Lancet (99) that was directed at "clinicians, patients, and the public" emphasised the need of thoroughly understanding the strengths and limitations of the study designs in the vast literature on statins. Despite this, detailed interviews and online surveys targeting clinicians and patients showed a noticeable lack of confidence among both groups (100). Of the 729 surveyed GPs and cardiologists, 98% believed that the media coverage of statin therapy influenced patients who either questioned their advice or declined a prescription. Moreover, the media influence also impacted clinician confidence in prescribing statin therapy; more than one quarter of clinicians interviewed or who completed surveys stated that they "felt less confident" discussing statins with their patients. This lack of confidence also affected their prescribing practices, whereby one in five clinicians stated that they were "less confident" about prescribing statins due to the media's interpretations (100). It is clear that while statin users are at risk of a side effect such as myopathy, this risk may be over-exaggerated by the media.

Their only known interaction with an anti-rheumatic drug is with the immunosuppressant ciclosporin. Ciclosporin is metabolised via cytochrome P450 and so would increase the risk of myopathy with statin use (97, 101). Statins have other important interactions that need to be considered. Amiodarone, an antiarrhythmic medication for treating irregular heartbeats, is also metabolised by cytochrome P450 and increases the likelihood of an adverse reaction to statins (102). Other cytochrome P450 interactions are also salient. Warfarin, a common anticoagulant, is understood to interact with fluvastatin and simvastatin by competing for metabolism via the CYP2C9 mechanism (103). For statin therapy to be received optimally, so that adverse reactions are avoided and ideal clinical outcomes are achieved, a knowledge of potential statin-drug interactions is important for patient care.

1.4 Trial of Atorvastatin for the primary prevention of Cardiovascular Events in Rheumatoid Arthritis

The Trial of Atorvastatin for the primary prevention of Cardiovascular Events in Rheumatoid Arthritis (TRACE-RA) was a multi-centre, double blinded, randomised placebo-controlled trial and was established to determine whether atorvastatin was better than placebo for the primary prevention of fatal and non-fatal CVEs in patients with RA. Patients were included in TRACE-RA if they satisfied the 1987 ACR classification criteria for RA (104), were aged $\geq$50 years or had an RA disease duration of $\geq$10 years (see appendix table 1). Written informed consent was required of all patients. Patients were then randomised in a 1:1 ratio into either the atorvastatin arm (40mg atorvastatin taken once daily) or placebo arm (placebo tablet taken once daily). The primary endpoints were first major vascular events (defined as coronary events, presumed ischaemic stroke or transient ischaemic attack, any non-coronary revascularisation or any other

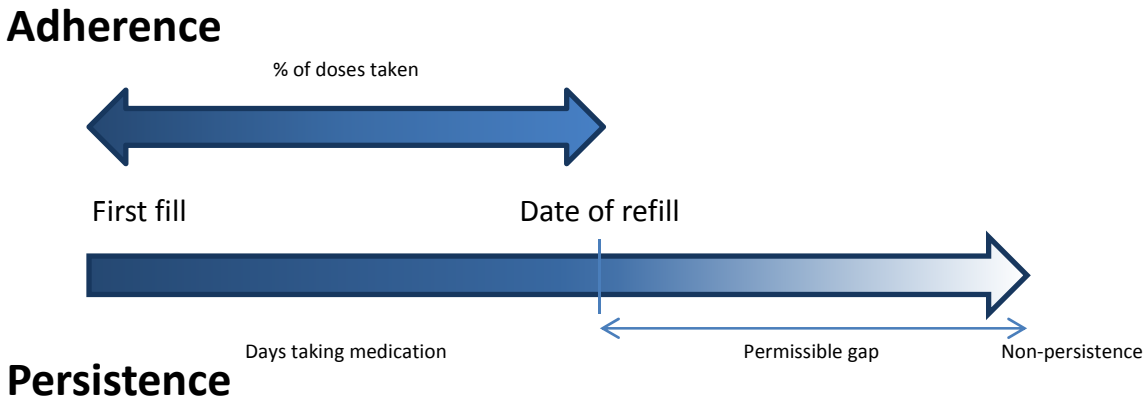
cardiovascular death excluding both confirmed cerebral haemorrhage [ICD I64-99, 10th International Classification of Diseases]) and non-coronary cardiac death (ICD I00-I15 and ICD I26-I52). Secondary endpoints for TRACE-RA included the separate components of the primary endpoint "first major vascular event" (as defined above), all-cause mortality, hospitalisations, functional outcome as determined by the health assessment questionnaire (HAQ) (105) and EuroQol-5D (EQ-5D) (see appendix figures 10 and 11) (106), changes in lipid levels across a random sample (over follow up) and statin safety related outcomes (see appendix table 2).

After randomisation, patients were issued with their first bottle of tablets which might contain a 3 month supply of atorvastatin or identical placebo. Prescriptions were issued every 3 months for the first 6 months and every 6 months thereafter. When patients were called to pick up their next prescription they returned their previous bottles of tablets to pharmacists for counting of the residual number of tablets. Records were filed within the 'Trial Medication Accountability Logs'. Patient ability to perform routine tasks such as turning taps on and off and opening jars were self-reported on a 4-point scale. The HAQ score was derived from patient responses to these questions. Mobility, self-care, activity, pain or discomfort, anxiety or depression and state of health were each self-reported on a 3-point scale using the EQ-5D. The EQ-5D visual analogue scale (VAS) was self-reported on a 100-point scale. The HAQ, EQ-5D, and lifestyle questionnaires (see appendix table 3) were completed at baseline. The HAQ and EQ-5D were also completed on an annual basis. Recruitment for TRACE-RA began in August 2007 and the trial was terminated in December 2012, following the recruitment of 2986 patients across 102 centres. Recruitment to the trial was stopped due to the low overall CVE rate (0.76% compared with the predicted 1.80% CVE rate) (107).

1.5 Adherence to medication

Patient outcomes are better if a treatment regimen is discussed with the healthcare provider, agreed and then followed by the patient. When treatment recommendations are not strictly followed, there may be serious implications for clinical outcomes and health economics. In the past, health care professionals have often taken a paternalistic approach to medication compliance. Indeed, the verb 'comply' has been defined as 'to accommodate oneself to the desires or wishes of…' (108). In the context of prescribed medication, this not only implies that the patient's behaviour in the consumption of medication is passive but that there is limited patient liberty and that therapy is enforced upon the patient. Because of this there has been a trend away from using the term 'compliance' towards 'adherence', particularly in recent years. The World Health Organisation defined adherence as 'the extent to which the patient follows medical instructions' (109). Despite differing from compliance, adherence maintains a paternalistic approach and the patient maintains passive behaviour. Another term frequently found in the literature is 'persistence'. This differs from compliance and adherence in that it is the duration of a regimen before discontinuation (see figure 1.4). The reasons for non-persistence may differ from those for non-compliance or non-adherence and can be attributed to different patient, physician and healthcare-related causes. Despite this, much of the literature accounts for non-persistence and non-adherence as one composite of 'overall adherence'. This oversimplifies the execution of medication consumption and no term is perfect. Providing treatment is well tolerated, to achieve the full clinical benefits of therapy, the patient must closely follow their prescribed regimen.

Figure 1. 4 A comparison of adherence and persistence



Source: Original

Adherence is defined as the extent to which a patient follows their prescribed regimen in accordance with their healthcare provider's instructions (109). Persistence is defined as the amount of time that a patient stays on therapy from initiation to discontinuation. A permissible gap is an arbitrary amount of time during which a patient does not return for a refill. If a patient exceeds this gap, they are considered non-persistent. The first fill is defined as the first date the patient receives their medication. Date of refill is defined as the date on which the patient receives another fill of the same medication.

In developed countries, it has been estimated that approximately 50% of patients who are prescribed treatment for a chronic disease do not follow their regimen (110, 111). Wastage of medicines in the UK is estimated to cost the National Health Service £300million annually (112). Because of this and the impact on clinical outcomes, there is an impetus to encourage patients to continue to take medication. This can be achieved, for example, through greater patient-physician communication, an improved awareness of poor adherence and a greater understanding of it. Throughout this piece of work, the term 'adherence' will be used in order to describe the quality of medication consumption.

1.6 Tests for determining adherence

There are numerous tests for determining adherence; however there is no gold standard and there is little accord over a favoured measure. Within the scope of this text, several have been selected according to their relevance to the literature review. Measures of adherence may be split into two general categories; direct and indirect measurements (reviewed by Farmer KC) (113). Direct measurements of adherence include the analysis of biological fluids such as serum, urine or synovial fluid. Biological fluid analysis provides objective evidence of drug metabolism or markers and is considered a more accurate and reliable gauge of adherence than many indirect measurements (114). Because of physiological differences in individuals, assays of biological fluids are not wholly reliable (113). Biological fluids may provide evidence that a drug had been taken. However, drugs with short half-lives may not be detected, depending on the timing of the sample relative to the dosing, and thus the patient may not appear adherent. Alternatively, a non-adherent individual may only consume their treatment prior to a scheduled biological fluid sample and thus would appear adherent. This has been termed the "white-coat effect" (115). Further, biological assays only capture a cross-sectional representation of adherence. These reasons and the fact that frequent direct measurements are impractical, costly and burdensome on the patient means that they are less commonly employed in studies as opposed to indirect measurements of adherence (reviewed by Vik SA and colleagues) (113, 116).

Indirect measurements of adherence encompass a range of methods that are generally practical and cheap to perform. Despite this, there can be no evidence to determine the actual consumption of medication. 'Pill counts' are an objective and quantifiable indirect measure of adherence. Patients are required to return their remaining medication for counting. Adherence is measured as the quantity of the drug that had been taken divided by the

quantity of the drug to be optimally taken (see below). Their low cost make them common in studies. However, pill counts may be manipulated by the patient. Despite the ease of measurement, pill counts are limited by 'medication dumping', or the event of the patient intentionally disposing of their tablets or medication to appear adherent (reviewed by Osterberg L and Blaschke T) (117).

$$\frac{\sum \text{tablets consumed}}{\sum \text{days in study period}}$$

Another indirect measurement of adherence is the Medication Event Monitoring System (MEMS®) (see figure 1.5, next page). MEMS is also considered objective, however it is not a perfect measure of adherence (118). MEMS is an electronic system that measures 'events' of the opening of the medication packet. For example, this may take the form of an electronic device attached to the lid of a bottle of tablets.

The advantage of the MEMS is that it provides a practical and non-invasive measure for accurately determining when treatment was taken. Despite this, awareness of being observed may influence patient behaviour and adherence in what is known as the 'Hawthorne effect' (119). As with all indirect measures of adherence, there is no evidence of the patient having actually taken the medication and electronic monitoring systems are expensive (117).

Figure 1. 5 Different variants of MEMS bottles

Examples of MEMS bottles. The bottle on the left is an example of an AdhereTech smart wireless pill bottle. Events of the bottle being opened are collected in real-time and are sent to a dashboard for analysis. The bottle features an alarm system and patients can receive automated reminders. The bottle on the right is an example of the eCap. Similar to the AdhereTech bottle, the eCap sends adherence data wirelessly. These data can be analysed using CertiScan software.

Cheaper than the MEMS are patient completed questionnaires. Questionnaires can be completed at visits to health care providers or they can be sent out to patients. They are less burdensome and more convenient when compared with direct measures. However, questionnaires can misrepresent patient adherence. This may be a result of 'social desirability bias', a systematic error when a patient may provide responses that overestimate their behaviour towards adherence in order to please the healthcare provider. Another example of a bias associated with questionnaires may be 'sampling bias'. This may occur when more adherent patients may be more willing to complete and return a questionnaire. Perhaps as a consequence of these forms of bias, self-reported adherence in the form of patient interviews or questionnaires have been shown to be less sensitive and less specific than pill counts (113). In one systematic review, patient overestimation of adherence in questionnaires and interviews when compared with objective indirect measurements of adherence was evident in

Table 1. 1 An overview of the tests for determining adherence

	Test	Description	Strengths	Limitations
Direct	Biological assay analysis	Analysis of bodily fluids such as serum or urine. This provides evidence of drug metabolism.	- Physiological evidence of medication consumption	- Not practical for use in large studies - "White-coat" effect(115)
	Direct observation	Patients are observed while taking their medication.	- Observation of actual consumption of medication	- Not practical for use in large studies - "White-coat" effect(115)
Indirect	Pill counts	The total number of pills consumed is divided by the total number of days in the study period.	- Objective and quantifiable	- Susceptible to medication dumping (117)
	MEMS	Device attached to the lid of a bottle of tablets. Each 'event' of the lid being opened is recorded as an event of medication consumption.	- Objective and quantifiable - Can determine patterns in adherence (117)	- "Hawthorne effect" (119) - No actual evidence of medication consumption
	Prescription refill data	Number of days of coverage by prescription is divided by the total number of days in the study period.	- Easy to calculate - Practical - Readily available data	- Cannot determine patterns of adherence - Does not measure actual medication consumption
	Questionnaires	Patients are provided a questionnaire to complete questions on their medication-taking behaviours.	- Cheap to perform - Practical	- Prone to biases associated with patient responses(120)
	Patient diaries	Patients are provided diaries to record events of medication-taking. The collection of qualitative data may provide additional insight.	- Additional insight with qualitative data	- Prone to biases associated with patient responses(120)
	"Chip on a pill"	Digestible chip attached to a pill. Tiny sensor relays data wirelessly to a mobile device.	- Objective and quantifiable - Can determine patterns of adherence - Quantifies actual medication consumption	- Old patients are less likely to possess a smart phone than young patients - Possible flaws or bugs with new technology

MEMS= Medication event monitoring system. Description, strengths and limitations for tests of medication adherence.

32 (87%) of 37 studies (120). Patient diaries are also an indirect measurement of adherence. Patients are required to record the event of medication consumption, usually in a paper diary. This has the advantage of limiting 'recall bias'. Despite the greater accuracy that can be produced, patient diaries have similar limitations that are found in other measures of adherence. The influence of the 'Hawthorne effect' may be observed in diary outcomes. Furthermore, without observation or a direct measure of adherence, there is no definitive proof that medication is consumed by patients.

1.7 Measures of adherence

Different rates of adherence can be used under different circumstances. The most frequently found in the literature are the medication possession ratio (MPR) and the proportion of days covered (PDC). The MPR divides the number of days' supply of medications by a given time period, for example the time period between prescriptions. In a review of 77 studies, MPR was most frequently defined as (121):

$$\frac{\sum \text{days supply of medications in study period}}{\sum \text{days in study period}}$$

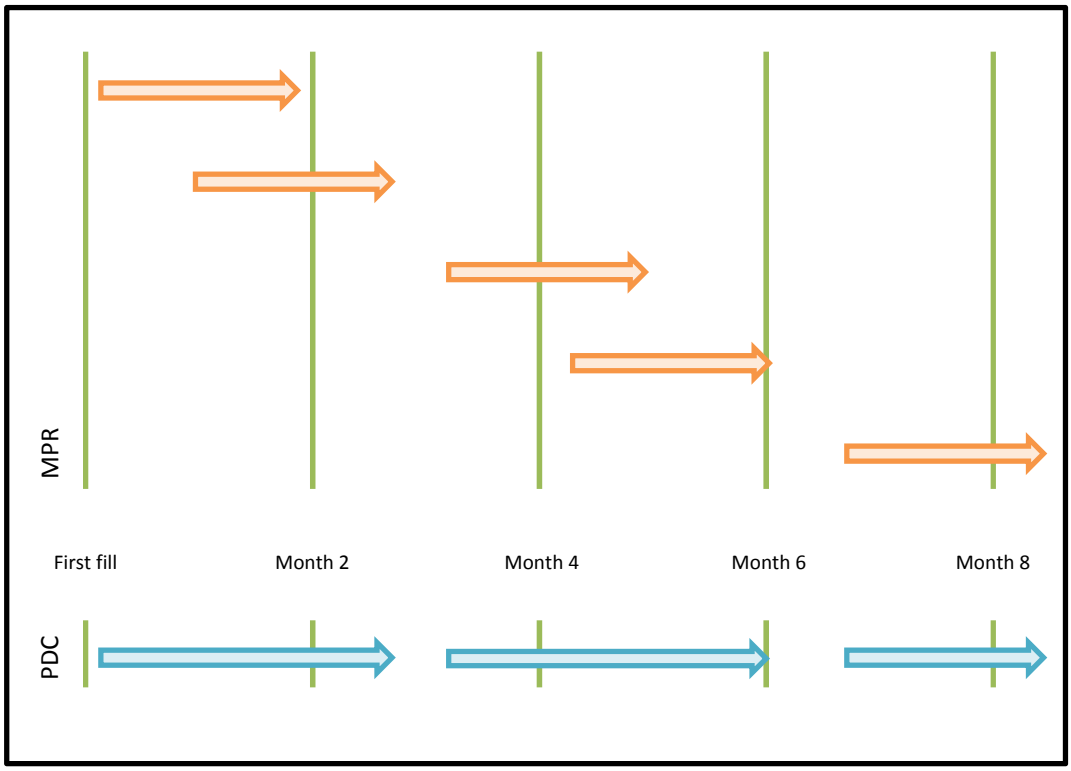
The numerator for the above expression is dependent on the day of refill for each patient (122). Like many rates of adherence, a threshold of $\geq$80% MPR has been used to define adherent behaviour. This threshold has the advantage of almost universal use and is also employed in the PDC rate of adherence. Despite this, there is little clinical relevance of the $\geq$80% threshold and patterns of poor adherence are not accounted for. Varying levels of

adherence to different drugs may have different clinical outcomes. For example, it may be more important to take a high proportion of medications for acute conditions than for chronic conditions. The simplicity of the MPR has meant that adherent behaviour is overstated as the measure is not as precise as that of other rates of adherence. An alternative measure of adherence to the MPR is the PDC. The PDC is the newer of these measures. The calculation is defined as the proportion of days that are covered by a prescription divided by the time course by which this was measured:

$$\frac{\sum \text{ days 'covered' in study period}}{\sum \text{ days in study period}}$$

As with the MPR, a score $\geq$80% indicates adherent behaviour. One study compared the differences between the two measures and found that the PDC presented a more conservative rate of adherence. When patients switched medications, the MPR overestimated adherence (123). The PDC is less influenced by a change in the time of measurement. Because the total number of days covered by prescription cannot exceed the time course, PDC rates are restricted at 100% and do not account for excess fills (ie patients request a repeat prescription early, see figure 1.6). For example, excess fills of drugs have been observed in a study of adherence to antipsychotic medication (124). An important limitation of both the PDC and the MPR is that neither account for non-persistence. For example, patients may cite forgetfulness or lack of convenience for poor adherence (125). Contrary to this, non-persistent patients most frequently cite a 'fear of side effects' and concerns about 'taking the medication' for the non-fulfilment of hyperlipidaemic medications (126).

Figure 1. 6 A comparison of the MPR and the PDC



Source: Original

A comparison of the MPR and PDC measures of adherence. The arrows represent medication coverage. The MPR (orange arrows) accounts for overlapping days of mediation coverage twice for each day of medication overlap. The PDC (blue arrows) does not account for overlapping days of medication coverage more than once.

1.8 Adherence in rheumatoid arthritis

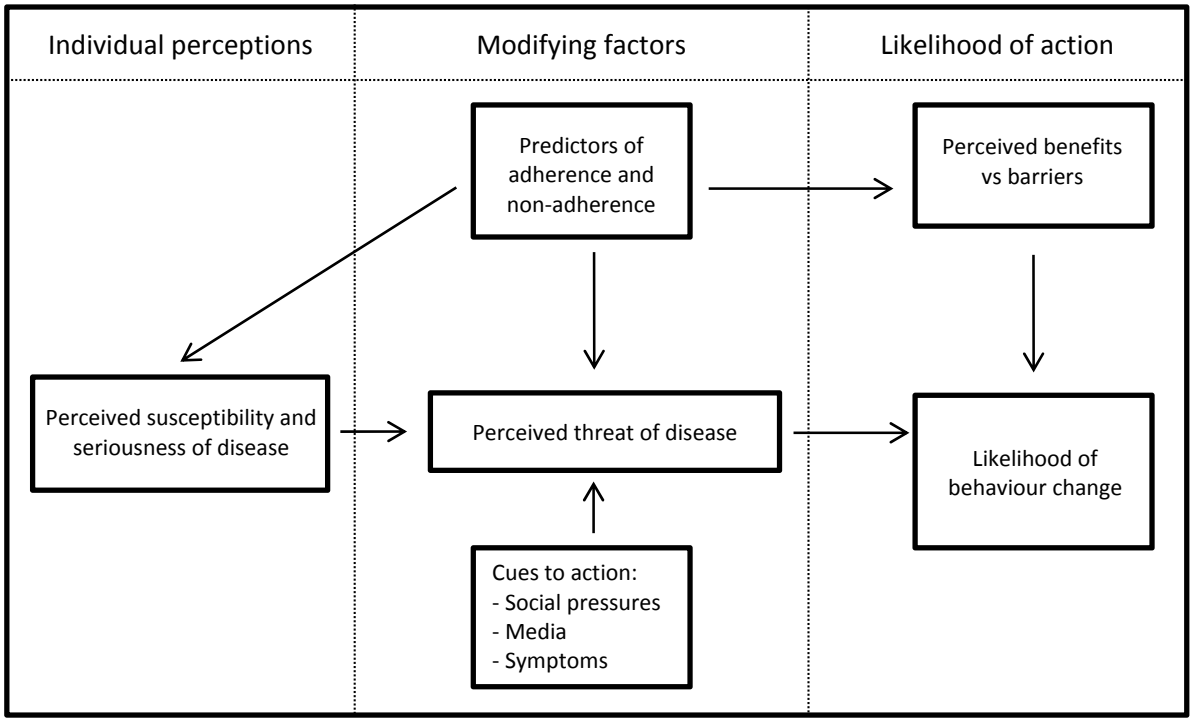
In RA, high levels of adherence are required from patients in order to gain the full therapeutic benefits of disease modifying anti-rheumatic drugs (DMARDs). Nevertheless, 2 separate studies found that adherence to DMARD therapy is poor and this is further compounded by the requirement for multiple medications (127, 128). A systematic review of 18 studies found that adherence for all treatments of RA ranged from 49.5-98.5% (reviewed

by Pasma A and colleagues) (129). Research on factors associated with adherence to treatment in RA patients is limited. A number of studies found that when compared with younger patients, older patients are more likely to be better adherers to DMARD therapy (130-132). Despite this, there is a lack of consensus among studies for sociodemographic factors as predictors of adherence.

There has been a focus on psychological factors as predictors of adherence to DMARD therapy in RA populations (133-135). The health belief model (HBM) has been used to explain the reasons for non-adherent behaviour. Patient perceptions of disease susceptibility and severity, and benefits and barriers to medication may influence their medication-taking behaviour (see figure 1.7). Indeed, beliefs of medications are more powerful predictors of adherence than sociodemographic and clinical characteristics (136). In a meta-analysis of 116 studies of adherence to medication in chronic illnesses, a positive relationship between adherence and a perception of disease severity was observed (meta-analysis by DiMatteo MR and colleagues) (137). Beliefs about RA therapy influence behaviours of adherence. Concern beliefs encompass the anxiety a patient may experience towards the consumption of medication and the harmful effects associated with medication consumption. On the other hand, necessity beliefs concern a patient's perceived need to take medication. Research has shown that weaker necessity beliefs and strong concern beliefs associate with poor DMARD adherence (128, 134). Beliefs may differ between ethnicities. A study by Kumar and colleagues demonstrated that concern beliefs towards DMARDs are high among patients of south Asian descent (138). This may explain why a non-white ethnicity has previously predicted poorer adherence to DMARD therapy in RA patients (139). Because strong beliefs influence patient

behaviour towards their medication regimen, van der Bemt and colleagues suggest patient-specific approaches to improving adherence (131).

Figure 1. 7 The health belief model



Source: Adapted from Rosenstock IM, 1966 (140)

The health belief model hypothesises that the likelihood of behavioural change is influenced by 3 patient perceptions: susceptibility and seriousness of disease, health concerns, and cost-benefits (141).

1.9 Adherence to statin therapy in the general population

Adherence to statin therapy is generally poor (142-144). The authors of one meta-analysis reported that adherence to statins in 771323 patients (12 studies) was 54%. Of the 12 studies, the MPR and PDC were the most frequently used measures of adherence (145). It has been shown that under the conditions of poor adherence, patients will receive around a 50% reduction in therapeutic gain (142) and a higher risk of CVEs when compared with adherent patients (146). NICE guidelines recommend that a

patient with ≥10% 10-year CV risk should receive statin therapy (147). A simulation study showed the clinical benefits of improving statin adherence. In the model where statin therapy was initiated upon reaching 20% 10-year CV risk, when adherence improved from 50% to 75%, twice as many CV related deaths were prevented when compared with a 15.5% 10 year-risk CV threshold (148). Ideal adherence has also been associated with a lower cost per life-year gained (142). To improve adherence to statin therapy, a greater understanding of the reasons, factors and beliefs associated with adherence are required.

1.10 Summary

"*Drugs don't work in patients who don't take them*" – C. Everett Koop, US Surgeon General.

RA patients are at an increased risk of a CVE. Important properties of statins such as cholesterol-reduction and anti-inflammatory effects could benefit such patients (88, 149, 150). However, non-adherers to statin therapy are more likely to suffer from a CVE or mortality than adherent patients (142, 146). "Predicting" those who are unlikely to adhere to their statin regimen is important for providing support to non-adherent patients in their treatment journey. The most recent literature reviews of predictors of statin adherence in the general population are more than 5 years old and since the publication of the more recent of these, further studies have identified new predictors of adherence. Pill count data and self-reported data collected in the TRACE-RA trial allows for the determination of rates of adherence to the allocated TRACE-RA intervention. Responses to patient lifestyle questionnaires and EQ-5D questions and clinical data mean that predictors to statin therapy can also be determined.

Chapter 2

This chapter is composed of the aims and objectives of this dissertation.

2 Aims and objectives

The above introduction to this dissertation has highlighted the need for further research on statin adherence and predictors of statin adherence. The aims and objectives of this dissertation are:

1) To review the literature on adherence to statin therapy in the general population
    a. To review the rates of adherence to statin therapy across studies that meet the inclusion criteria
    b. To review the predictors of statin therapy in the general population

2) To determine the rate of adherence to atorvastatin therapy in TRACE-RA up to 12 months
    a. To compare the rates of adherence to intervention in the atorvastatin arm and the placebo arm
    b. To identify predictors of adherence to statin therapy in the TRACE-RA study at 12 months

Chapter 3

This chapter is composed of a review of the literature of rates, measures and predictors of statin adherence in the general population.

3 A review of predictors of statin adherence in the general population

There have been 2 systematic reviews of the literature on predictors of statin adherence in the general population (151, 152). Since the publication of the more recent of these in 2011, there has been further research in this area. Both of these systematic reviews failed to include literature on the relationship of a variety of socioeconomic and lifestyle factors including education and employment status and statin adherence. Psychological wellbeing, behaviours and beliefs and self-rated health are associated with statin adherence and have not been reviewed.

3.1 Aims

The aim of this literature review was to identify and assess the available literature on predictors that are associated with adherence to statin therapy in the general population. This review will also seek to summarise literature on rates and measures of adherence.

3.2 Methods

An electronic literature search was performed across two databases: Medline and Embase. The search included all literature that met the inclusion criteria until 31/03/2015 (see table 3.1). The search terms used for the Medline and Embase databases are shown in table 3.2. A number of terms for 'statin' and 'adherence' were included in the search string due to a lack of consistency of a given term in the literature. Duplicate studies were removed from the combined total of publications that met the inclusion criteria and abstracts of

these were screened. Studies that did not include adherence specific to statin therapy, predictors of adherence to statin therapy or studies that were not written in English were removed. Literature reviews, notes, conference abstracts, editorials and letters were removed as these were not considered primary research. The entire manuscripts of each of the remaining publications were screened. They were considered irrelevant if they met the exclusion criteria for the abstract screening process. Studies that did not include statin adherence as the primary outcome and studies that assessed predictors of statin discontinuation were excluded.

Table 3. 1 Inclusion and exclusion criteria for the literature review

Inclusion criteria	Exclusion criteria
- Studies of an experimental or observational design - Studies in which the outcome measure was adherence to statin therapy in the general population - Studies that included predictors of adherence or non-adherence to statin therapy	- Case series and case reports - Studies that only analysed persistence of or discontinuation of statin therapy were excluded - Protocols, conference abstracts, systematic and literature reviews and meta-analyses were excluded - Studies not written in English - Animal studies

Publications that assessed predictors of adherence to statin therapy and that were of an experimental or observational design were included in this review. Case series and case reports, protocols, conference abstracts, literature reviews and meta-analyses were all excluded. Animal studies and studies that were not written in English were also excluded as were studies that solely assessed predictors of discontinuation.

Table 3. 2 Search string for the literature review

Number	Search term	MEDLINE	EMBASE
1	(atorvastatin OR cerivastatin OR fluvastatin OR lovastatin OR pravastatin OR simvastatin OR simvastatin OR lipitor OR baycol OR lescol OR mevacor OR altocor OR pravachol OR lipostat OR zocor OR mevinolin).mp.	20549	61711
2	(compactin OR fluindostatin OR rosuvastatin OR dalvastatin OR altocor OR pravachol OR lipostat OR zocor OR mevinolin).mp.	2780	16831
3	(medostatin OR mevinacor OR livalo OR pitava OR pitavastatin OR pravasin OR mevalotin OR gerosim OR lipex OR zenas OR crestor OR meglutol).mp.	775	3050
4	1 OR 2 OR 3	22517	67134
5	(randomized controlled trial OR controlled clinical trial OR randomized controlled trials OR double blind or single blind OR experimental).mp.	1529807	1720840
6	(((observational OR case control OR cohort OR cross sectional) NOT case report) OR case series).mp.	878899	1058430
7	5 OR 6	2356042	2715361
8	(adherence OR compliance OR medication refusal OR treatment refusal).ti,ab.	143927	219991
9	(concordance OR medication concordance OR treatment concordance).ti,ab.	27703	42164
10	(missed medication OR missed treatment OR resisted medication OR resisted treatment).ti,ab.	134	190
11	(discontinuation medicine OR discontinuation treatment OR persistence medication or persistence treatment).ti,ab.	55	120
12	(nonadherence OR noncompliance OR non adherence OR non compliance).ti,ab.	13230	22278
13	8 OR 9 OR 10 OR 11 OR 12	175017	266620
14	(Human$ NOT animal$).mp.	12858142	15645882
15	**4 AND 7 AND 13 AND 14**	206	482

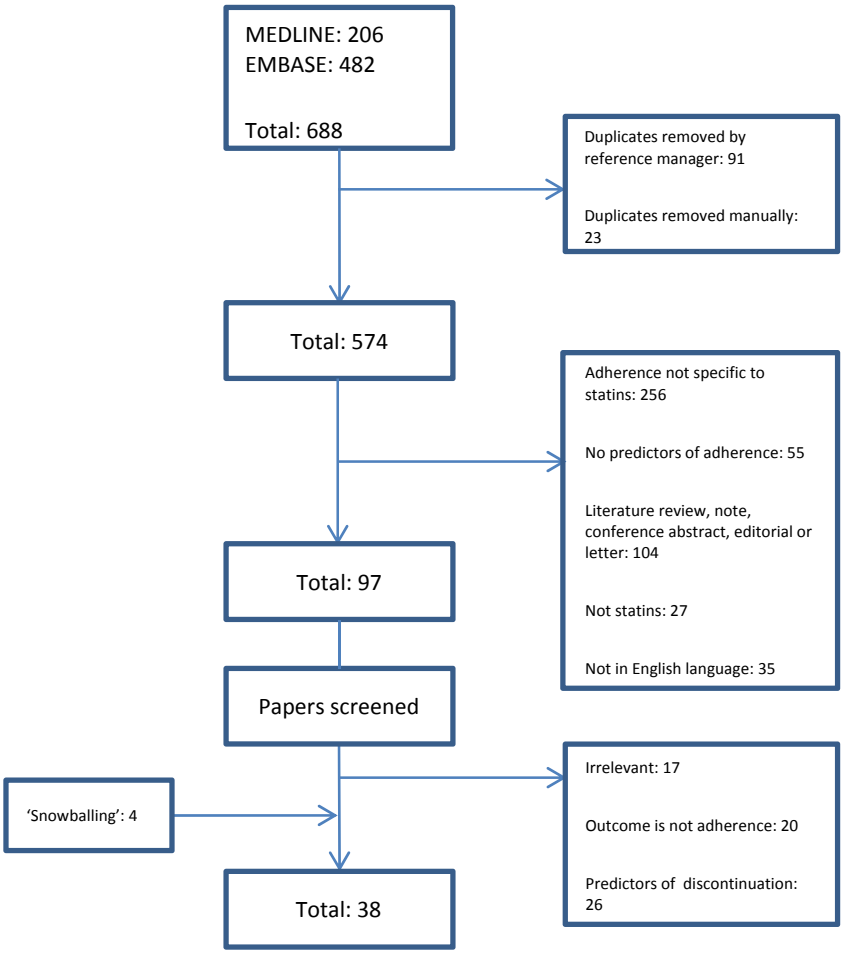
The above searches were performed using the OVID database. The search string for the literature review was co-ordinated with the inclusion and exclusion criteria so that relevant studies could be screened. Observational and experimental studies were included. A total of 688 publications were found using the above search criteria.

3.3 Results

3.3.1 Identification of papers for inclusion

A total of 688 abstracts were identified using the search criteria shown in table 3.2. One hundred and fourteen of these were removed as duplicates, either automatically by reference manager or manually. Of the remaining 574 abstracts, 97 met the criteria for the full manuscript to be screened. Of the 97 manuscripts that were screened, 34 met the inclusion criteria for the review (see figure 3.1). Four studies not identified in the literature search but were found in bibliographies were added in a process referred to as 'snowballing'. All studies included in this review can be found in table 3.3.

Figure 3. 1 PRISMA flow diagram of the literature screening process



A PRISMA flow diagram of the screening process for the literature review.

Table 3. 3 A list of the reviewed studies

Study	Design	Notes	Population (N=)	Groups	Measure of adherence	Adherence to statin therapy	Follow up
Aarnio EJ et al. (2014)	RCS	Pharmacy refills	Finnish (247051)		PDC ≥80%	54.6%	12 months
Lauffenburger JC et al. (2014)	RCS	Pharmacy refills, SP patients	US (85017)		PDC ≥80%	66%	12 months
Muntner P et al. (2014)	RCS	Pharmacy refills, SP	US (2695)	Fully adherent to antihypertensive	PDC ≥80%	67.1%	12 months
				Partially adherent to antihypertensive	PDC ≥80%	55.6%	12 months
				Non-adherent to antihypertensive	PDC ≥80%	46.8%	12 months
Ivers NM et al. (2013)	RCS		Canadian (16134)		PDC ≥80%	~60.0%	540 days
Wallach-Kildemoes H et al. (2013)	RCS	PP	Danish (76038)		PDC ≥80%	67.0%	12 months
Chan DC et al. (2010)	RCS	Prescription claims	US (14257)		PDC ≥80%	36.4%	12 months
Yang Y et al. (2009)	RCS	Prescription claims	US (1888682)		PDC ≥80%	46.4%	6 months
Choudhry NK et al. (2008)	RCS	SP	US (33646)		PDC ≥80%	38.6% (1995) 56.2% (2003)	96 months

PDC= Proportion of days covered, MPR= Medication possession ratio, DMA= Daily medication allowance, CMG= Cumulative medication refill gap, SDD= Standardised mean daily dose, RCS= Retrospective cohort study, PCS= Prospective cohort study, CS-CS= Cross section cohort study, RCT= Randomised controlled trial, QE= Quasi-experimental study, PP= Primary prevention patients, SP= Secondary prevention patients, ACQUIP= Ambulatory care quality improvement project, GRACE= Global registry of acute coronary events. The above studies are listed in order of measure of adherence, study design and year of publication.

Table 3. 3 A list of the reviewed studies

Study	Design	Notes	Population (N=)	Groups	Measure of adherence	Adherence to statin therapy	Follow up
Benner JS et al. (2005)	RCS		US (9510)		PDC ≥80%	51%	3 months
					PDC ≥80%	34%	12 months
					PDC ≥80%	28%	24 months
					PDC ≥80%	22%	36 months
Benner JS et al. (2004)	RCS		US (19422)		PDC ≥80%	51%	3 months
					PDC ≥80%	30%	12 months
					PDC ≥80%	27%	24 months
					PDC ≥80%	25%	36 months
Goswami NJ et al. (2013)	RCT	Prescription refills	US (208)	Adherence counselling	PDC ≥80% and MPR ≥80%	71.6% (PDC ≥80%) 76.8% (MPR ≥80%)	180 days
				No adherence counselling	PDC ≥80% and MPR ≥80%	71.7% (PDC ≥80%) 75.5% (MPR ≥80%)	180 days
Halava H et al. (2014)	RCS	Prescription refills	Finnish (9285)	Patients with CV comorbidities	PDC ≥80%	59.1%	12 months
				Patients without CV comorbidities	PDC ≥80%	50.9%	12 months
Chen SY et al. (2014)	RCS	Prescription claims	US (27553)	2010 tier reduction	PDC ≥80%	62.0%	6 months
				2011 tier reduction	PDC ≥80%	72.9%	6 months
				2010 non-tier reduction	PDC ≥80%	65.1%	6 months
				2011 non-tier reduction	PDC ≥80%	65.7%	6 months
Romanelli RJ and Segal JB et al. (2014)	RCS	Prescription claims	US (5156)		MPR ≥80%	73.0%	6 months

PDC= Proportion of days covered, MPR= Medication possession ratio, DMA= Daily medication allowance, CMG= Cumulative medication refill gap, SDD= Standardised mean daily dose, RCS= Retrospective cohort study, PCS= Prospective cohort study, CS-CS= Cross section cohort study, RCT= Randomised controlled trial, QE= Quasi-experimental study, PP= Primary prevention patients, SP= Secondary prevention patients, ACQUIP= Ambulatory care quality improvement project, GRACE= Global registry of acute coronary events. The above studies are listed in order of measure of adherence, study design and year of publication.

Table 3. 3 A list of the reviewed studies

Study	Design	Notes	Population (N=)	Groups	Measure of adherence	Adherence to statin therapy	Follow up
Calip GS et al. (2013)	RCS		US (1393)		MPR ≥80%	67.0% (one year prior to breast cancer diagnosis)	
Watanabe J et al. (2013)	RCS		US (4886)	Patients with 1-5 medications	MPR ≥80%	39.4%	12 months
				Patients with 6-10 medications	MPR ≥80%	48.0%	12 months
				Patients with 11-15 medications	MPR ≥80%	54.9%	12 months
				Patients with 16-20 medications	MPR ≥80%	59.6%	12 months
				Patients with over 20 medications	MPR ≥80%	66.1%	12 months
Daugherty JB et al. (2013)	RCS	Prescription claims	US (340350)	Generic statin users	MPR ≥80%	60.1%	12 months
				Non-coupon brand statin users	MPR ≥80%	53.8%	12 months
				Coupon brand statin users	MPR ≥80%	61.1%	12 months
PDC= Proportion of days covered, MPR= Medication possession ratio, DMA= Daily medication allowance, CMG= Cumulative medication refill gap, SDD= Standardised mean daily dose, RCS= Retrospective cohort study, PCS= Prospective cohort study, CS-CS= Cross section cohort study, RCT= Randomised controlled trial, QE= Quasi-experimental study, PP= Primary prevention patients, SP= Secondary prevention patients, ACQUIP= Ambulatory care quality improvement project, GRACE= Global registry of acute coronary events. The above studies are listed in order of measure of adherence, study design and year of publication.							

Table 3. 3 A list of the reviewed studies

Study	Design	Notes	Population (N=)	Groups	Measure of adherence	Adherence to statin therapy	Follow up
Kazerooni R et al. (2013)	RCS		US (4748)	Quintile 1 (lowest income), copay	MPR ≥80%	70%	12 months
				Quintile 1, no copay	MPR ≥80%	74%	12 months
				Quintile 2, copay	MPR ≥80%	70%	12 months
				Quintile 2, no copay	MPR ≥80%	77%	12 months
				Quintile 3, copay	MPR ≥80%	72%	12 months
				Quintile 3, no copay	MPR ≥80%	77%	12 months
				Quintile 4, copay	MPR ≥80%	73%	12 months
				Quintile 4, no copay	MPR ≥80%	74%	12 months
				Quintile 5 (highest income), copay	MPR ≥80%	72%	12 months
				Quintile 5, no copay	MPR ≥80%	74%	12 months
Jung K et al. (2012)	RCS		US (259465)	Medicare advantage prescription drug plans	MPR ≥80%	46.7% (unmatched) 47.0% (matched)	
				Standalone prescription drug plans	MPR ≥80%	46.9% (unmatched) 45.3% (matched)	

PDC= Proportion of days covered, MPR= Medication possession ratio, DMA= Daily medication allowance, CMG= Cumulative medication refill gap, SDD= Standardised mean daily dose, RCS= Retrospective cohort study, PCS= Prospective cohort study, CS-CS= Cross section cohort study, RCT= Randomised controlled trial, QE= Quasi-experimental study, PP= Primary prevention patients, SP= Secondary prevention patients, ACQUIP= Ambulatory care quality improvement project, GRACE= Global registry of acute coronary events. The above studies are listed in order of measure of adherence, study design and year of publication.

Table 3. 3 A list of the reviewed studies

Study	Design	Notes	Population (N=)	Groups	Measure of adherence	Adherence to statin therapy	Follow up
Barron TI et al. (2010)	RCS	Prescription refills	Ireland (79384)		MPR ≥80%	62.4%, single measure of compliance model (day 720)	900 days
					MPR ≥80%	50.7%, repeated measure of compliance model (day 360) 52.7%, repeated measure of compliance model (day 720)	900 days
					MPR ≥80%	52.3%, time to non-compliance model (day 360) 47.4%, time to non-compliance model (day 720)	900 days
					MPR ≥80%	77.7%, competing risks model (day 360) 75.3%, competing risks model (day 720)	900 days

PDC= Proportion of days covered, MPR= Medication possession ratio, DMA= Daily medication allowance, CMG= Cumulative medication refill gap, SDD= Standardised mean daily dose, RCS= Retrospective cohort study, PCS= Prospective cohort study, CS-CS= Cross section cohort study, RCT= Randomised controlled trial, QE= Quasi-experimental study, PP= Primary prevention patients, SP= Secondary prevention patients, ACQUIP= Ambulatory care quality improvement project, GRACE= Global registry of acute coronary events. The above studies are listed in order of measure of adherence, study design and year of publication.

Table 3. 3 A list of the reviewed studies

Study	Design	Notes	Population (N=)	Groups	Measure of adherence	Adherence to statin therapy	Follow up
Balu S et al. (2009)	RCS		US (8988)	Fixed dose niacin extended release and lovastatin	MPR ≥80%	34.2%	12 months
				Multi pill niacin extended release and simvastatin	MPR ≥80%	29.6%	12 months
				Multi pill niacin extended release and lovastatin	MPR ≥80%	25.9%	12 months
Ye X et al. (2007)	RCS	SP	US (5548)		MPR ≥80%	61.4%	12 months
Cooke CE et al. (2006)	RCS		US Indian (2095)		MPR ≥80%	60.5%	
Gibson TB et al. (2006)	RCS	Prescription claims	US (117366)	New users	MPR ≥80%	28.0%	18 months
				Existing users	MPR ≥80%	59.1%	18 months
Warren JR et al. (2013)	PCS		Australian (67307)	Concession card holders	MPR ≥80%	80.1%	24 months
				General beneficiaries	MPR ≥80%	56.7%	24 months
Sedjo RL and Cox ER et al. (2008)	QE		US (39888)	Branded simvastatin	MPR ≥80%	79.1%	270 days
				Non-branded simvastatin	MPR ≥80%	72.1%	270 days
PDC= Proportion of days covered, MPR= Medication possession ratio, DMA= Daily medication allowance, CMG= Cumulative medication refill gap, SDD= Standardised mean daily dose, RCS= Retrospective cohort study, PCS= Prospective cohort study, CS-CS= Cross section cohort study, RCT= Randomised controlled trial, QE= Quasi-experimental study, PP= Primary prevention patients, SP= Secondary prevention patients, ACQUIP= Ambulatory care quality improvement project, GRACE= Global registry of acute coronary events. The above studies are listed in order of measure of adherence, study design and year of publication.							

Table 3. 3 A list of the reviewed studies

Study	Design	Notes	Population (N=)	Groups	Measure of adherence	Adherence to statin therapy	Follow up
Natarajan N et al. (2007)	CS-CS	Self-reported, 31.5% SP, 68.5% PP	Canadian (284)		Adapted Morisky scale	63.4%	
Stilley CS et al. (2004)	RCT	MEMS	US (158)	Patients receiving 20mg lovastatin	≥80% statin consumption over 6 months	22.8%	
				Patients receiving placebo	≥80% statin consumption over 6 months		
Kopjar B et al. (2003)	RCS	Prescription refills, SP	US (8768)		≥80% statin consumption over 18 months	71.2%	18 months
Wei MY et al. (2013)	CS-CS	Internet survey	US (10138)			82.5%	1 month
Batal HA et al. (2007)	RCS	Prescription refills	US (3386)		RC ≥80%	47.5%	
Bruckert E et al. (1999)	RCT	Pill counts	French (3845)	Awareness group	≥90% as determined by practitioner	75.0%	3 months
				Non-awareness group	≥90% as determined by practitioner		
Bryson CL et al. (2008)	RCT	Prescription refills	US (35725)		Use of ACQUIP ≥80%	75.0% (teetotal after 90 days) 66.0% (teetotal after 1 year)	

PDC= Proportion of days covered, MPR= Medication possession ratio, DMA= Daily medication allowance, CMG= Cumulative medication refill gap, SDD= Standardised mean daily dose, RCS= Retrospective cohort study, PCS= Prospective cohort study, CS-CS= Cross section cohort study, RCT= Randomised controlled trial, QE= Quasi-experimental study, PP= Primary prevention patients, SP= Secondary prevention patients, ACQUIP= Ambulatory care quality improvement project, GRACE= Global registry of acute coronary events. The above studies are listed in order of measure of adherence, study design and year of publication.

Table 3. 3 A list of the reviewed studies

Study	Design	Notes	Population (N=)	Groups	Measure of adherence	Adherence to statin therapy	Follow up
Di Martino M et al. (2005)	PCS	32.65% PP patients, 35% SP patients	Italian (4764)		SDD ≥0.50	59.4%	
Eagle KA et al. (2004)	PCS	SP	Patients from 14 countries worldwide (GRACE) (13830)			87.4%	6 months
Ellis JJ et al. (2004)	RCS		US (4802)	Primary prevention	CMG >10%	43.6%	
				Primary prevention	CMG >20%	62.2%	
				Primary prevention	CMG >30%	72.0%	
				Secondary prevention	CMG >10%	44.0%	
				Secondary prevention	CMG >20%	61.2%	
				Secondary prevention	CMG >30%	73.3%	
Grant RW et al. (2004)	RCS	Prescription claims	US (5488)		DMA	82.1%	
Pedan A et al. (2007)	RCS	Prescription refills	US (6438)		Number of 30 day refills	4.75 refills	12 months

PDC= Proportion of days covered, MPR= Medication possession ratio, DMA= Daily medication allowance, CMG= Cumulative medication refill gap, SDD= Standardised mean daily dose, RCS= Retrospective cohort study, PCS= Prospective cohort study, CS-CS= Cross section cohort study, RCT= Randomised controlled trial, QE= Quasi-experimental study, PP= Primary prevention patients, SP= Secondary prevention patients, ACQUIP= Ambulatory care quality improvement project, GRACE= Global registry of acute coronary events. The above studies are listed in order of measure of adherence, study design and year of publication.

3.3.2 Adherence to statin therapy in the general population

Statin adherence ranged from 22.8% (measured using MEMS) to 87.4% (data collected across 104 hospitals in 14 countries and compiled in the Global Registry of Acute Coronary Events) in the reviewed studies (153, 154). Thirteen studies used the MPR and 12 studies used the PDC to determine adherence to statin therapy. One study compared the MPR and PDC measures of adherence (155). A lower rate of adherence for atorvastatin therapy was found when using the PDC compared with the MPR however this did not achieve statistical significance. An 80% threshold was applied in 30 of the 38 identified studies and in all studies that used the MPR and PDC to dichotomise patients as adherent or non-adherent. One study used pill counts to determine predictors of adherence to statin therapy (156). Twenty eight of the 38 reviewed studies were retrospective cohort studies. Only 4 of the 38 studies were randomised controlled trials (RCTs) in design. Sociodemographic, socioeconomic, treatment and medications, lifestyle, payment variables and psychological predictors all associated with statin adherence.

3.3.3 Demographic, lifestyle and socioeconomic predictors of adherence to statin therapy

Age

Twenty five out of 27 studies showed better adherence to statin therapy in patients of older age. The remaining 2 of 27 studies showed no significance for age as a predictor of adherence (153, 157). Whereas 6 studies showed that this increased association with adherence was maintained through all age groups past 65 years, other studies demonstrated that adherence plateaued and remained elevated with increased age (142, 158-160). For example, a retrospective cohort study by Wallach-Kildemoes et al of 76,038 Danish

patients receiving a statin for the primary prevention of CVD found that, compared with patients who were between 65-69 years of age, those below 65 years old were poorer adherers (161). Two studies found a 'threshold effect' within the age range of 55-64 (158, 159). In both studies, patients who were older than 64 were less adherent than those within the age range of 55-64; however their rate of adherence remained elevated against the reference groups of 18-34 years and 19-34 years respectively (158, 159). Consistency in the findings may be attributed to the fact that the authors used similar US managed care plan databases of south-eastern US patients. Self-reported data were collected by Natarajan and colleagues in a Canadian cross-sectional cohort study. A threshold effect was observed in patients over 65 years. These patients were better adherers than those who were between 40 and 54 years (65-74 years, OR=3.35, 95%CI 1.50-7.48, $\geq$ 75 years, OR=3.13, 95%CI 1.31-7.47) (160).

A retrospective cohort study of prescription claims data by Chan and colleagues found that 10 year increments in age were associated with better adherence (162). Chen et al performed a retrospective cohort study of pharmacy claims from a Medicare plan D sponsorship database and did not find a threshold in age after which adherence either plateaued or declined. Instead, an increase in odds for adherence was observed with an age above 74 years (75-84 years, OR=1.13, 95%CI 1.01-1.25, $\geq$85 years, OR=1.18, 95%CI 1.03-1.34) (163). It is clear that adherence to statin therapy improves in patients with increasing age to the age range of 55-69 years. However, further research may seek to determine how adherence differs in patients above the age of 69.

Gender

Eleven of the 17 papers that investigated the association between gender and statin adherence found significantly poorer adherence to statin therapy among women. The remaining 6 studies did not find a significant association between gender and statin adherence (153, 155, 157, 164-166). Adherence measures for 10 of the 11 studies came from refill data and prescription claims. Analysis of the Kaiser Permanente southern California database by Chan and colleagues found a lower odds for adherence in women when adjusted for age, RxRisk (comorbidity index) score and the number of patients with 90 days' supply of statins (OR=0.82, 95%CI 0.75-0.98) (162). Furthermore, in a retrospective cohort study of prescription refill data from the Denver Health Medical Centre there was a lower likelihood of adherence in women (RR= 0.92, 95%CI 0.86-0.98) (167).

Ethnicity

Eight of the 9 studies reported a significant relationship between ethnicity and statin adherence. Of these, African-American and black ethnicity were most frequently associated with poorer adherence. In a US managed care database of pharmacy claims of 4802 patients, analysis by Ellis and colleagues showed that, regardless of whether the threshold for adherence was at 10%, 20% or 30%, odds for African-American non-adherence were still greater compared with white ethnicities (168). Chan et al showed that patients who lived in neighbourhoods with a higher proportion of African-Americans had a poorer adherence to statin therapy (OR=0.88, 95%CI 0.85-0.91, per quartile increase) (162). Compared with white ethnicities, black and Hispanic ethnicities had poorer rates of statin adherence in both men and women (169). Seventy one US Veterans completed interviews and questionnaires over 6 months in a prospective cohort study by Mann et al.

The authors showed that when compared with non-Hispanic ethnicities, the odds for poor adherence among Hispanic patients was 3.9 (95%CI 1.0-15.2) (170).

Lifestyle factors (BMI, exercise, diet and smoking)

Four studies investigated BMI as a predictor for statin adherence. The largest of these studies included 67307 patients grouped as either Australian concession card holders or Australian general beneficiaries (165) . Concession card holders were defined as patients of concession status (patients who were 60 or above) who were given a lower per-prescription cost than both general beneficiaries and the general public. General beneficiaries were simply given a lower per-prescription cost than the general public. Data were analysed following data linkage. Three questionnaires were sent to each patient from 2005-2009 and data was collected on socioeconomic factors such as income, education and employment as well as lifestyle factors such as physical activity and smoking status. A greater likelihood of adherence was found in obese patients than those with a 'normal' weight (normal weight defined as BMI 20-24 kg/m^2, obesity defined as BMI$\geq$30 kg/m^2) (concession card holders, RR=1.02, 95%CI 1.01-1.04, general beneficiaries, RR=1.10, 95%CI 1.05-1.14); however these findings were not observed in 'overweight' patients when compared with patients of a 'normal weight' (overweight defined as BMI 25-30 kg/m^2) (165). One study stratified patients by cardiovascular comorbidity using linked survey response data with the Finnish prescription register in a retrospective cohort of 9285 participants (171). It was found that overweight and obese patients had better adherence to statin therapy (overweight patients, OR= 0.88, 95%CI 0.79-0.99, obese patients, OR=0.85, 95%CI 0.73-0.99 [odds for non-adherence]) (165, 171). Only 3 studies investigated physical

activity and association to statin adherence in patients. Neither Halava et al nor Warren et al found that physical activity was significantly associated with statin adherence (165, 171). However, another study found that patients on either a healthy diet, an exercise regime or both had significantly greater odds for better adherence when compared with patients who were not exercising and who were on a poor diet (patients who either exercise or have a healthy diet, OR= 3.18, 95%CI 1.41-6.76, patients who both exercise and have a healthy diet, OR= 3.14, 95%CI 1.46-6.78) (160).

Only four of the studies that were screened assessed smoking status as a predictor of adherence to statin therapy. All 4 studies found a significant relationship between smoking and adherence. Current smokers had suboptimal adherent behaviour in 3 of these studies (165, 172, 173). Halava et al reported that former smokers who did not have cardiovascular comorbidities were better adherers compared with those who had never smoked and who did not have cardiovascular comorbidities (OR=0.83 for non-adherence, 95%CI 0.74-0.93). The same authors also assessed groups of 3-4 unhealthy risk factors. These risk factors were defined as extreme drinking occasions (defined as the individual reporting having 'passed out' due to drinking alcohol in the 12 months prior to survey), regular and high alcohol consumption, obesity (defined as BMI$\geq$30 kg/m^2), current smoking and low physical activity. Patients who had 3-4 of these risk factors were poorer adherers than patients who did not have any of these (OR=1.65, 95%CI 1.16-2.34) (171).

Alcohol consumption

High and excessive alcohol consumption was a predictor for poor adherence in all 3 studies that investigated this association. For example, Halava and

colleagues reported a significant association between the number of extreme drinking occasions and poor adherence in patients with CV comorbidities (OR=1.48, 95%CI 1.11-1.97) (171). High alcohol consumption (as determined by more than 16 units of alcohol per week) in patients with comorbidities was also a predictor for poor adherence (OR=1.58, 95%CI 1.11-2.25). Similar associations were seen in individuals without CV comorbidities (171). A study of US Veterans examined whether self-reported alcohol consumption using the alcohol use disorders identification test – consumption (AUDIT-C) questionnaire was associated with adherence to a number of drugs. Statin adherence in veterans was reported as 66% (OR not given, 95%CI 64-68) in patients with an AUDIT-C score of 0 over 12 months. A greater score on the AUDIT-C questionnaire was associated with poorer statin adherence in patients. Veterans who had a score in the highest range (8-12) were poorest adherers compared with those who did not consume alcohol (OR not given, 95%CI 47-63) (174).

Education

There have been contrasting findings of the association between both length of education and achievement in education and patient adherence to statin therapy (see table 3.4). Warren and colleagues found poorer adherence in Australian concession card holders with a high school certificate(RR=0.99 95%CI 0.95-0.99), an apprenticeship(RR=0.97 95%CI 0.96-0.99), certificate or diploma (RR=0.97 95%CI 0.96-0.99) or a university degree (RR=0.94 95%CI 0.92-0.96) compared with those who did not have a school certificate (165). Wallach-Kildemoes et al showed poorer adherence with more years spent in education. Patients who had been in education for over 11 years were less likely to adhere to statin therapy than patients who had been in education

Table 3. 4 Education as a predictor of statin adherence in the general population

General factor	Study	Notes	Subpopulation (N=)	Analysis	Reference group	Results	
Education	Warren JR et al. (2013)	Self-reported education	Concession card holders (42492)	Poisson regression	No school certificate	School certificate, NS	
				Poisson regression	No school certificate	High school, RR=0.97 (95%CI 0.95-0.99)	↓ adherence
				Poisson regression	No school certificate	Trade apprenticeship, RR=0.97 (95%CI 0.96-0.99)	↓ adherence
				Poisson regression	No school certificate	Certificate/ diploma, RR=0.97 (95%CI 0.96-0.99)	↓ adherence
				Poisson regression	No school certificate	University or higher, RR=0.94 (95%CI 0.92-0.96)	↓ adherence
			General beneficiaries (16110)	Poisson regression	No school certificate	School certificate, NS	
				Poisson regression	No school certificate	High school, NS	
				Poisson regression	No school certificate	Trade apprenticeship, NS	
				Poisson regression	No school certificate	Certificate/ diploma, RR=0.92 (95%CI 0.87-0.96)	↓ adherence
				Poisson regression	No school certificate	University or higher, NS	

NS= Non-significant finding, RR= Relative risk, OR= Odds ratio, CI= Confidence interval, USAGE= Understanding Statin use in America and Gaps in Education. Studies that had NS findings did not predict a direction of adherence.

Table 3. 4 Education as a predictor of statin adherence in the general population

General factor	Study	Notes	Subpopulation (N=)	Analysis	Reference group	Results	
Education	Wallach-Kildemoes H et al. (2013)	Model 2, simultaneous analysis of education and income	Males, 40-64 years old (24886)	Multivariate logistic regression	7-10 years of education	11-12 years of education, NS	
						Over 12 years of education, OR=0.97 (95%CI 0.97-0.97)	↑ adherence
			Females, 40-64 years (26397)	Multivariate logistic regression	7-10 years of education	11-12 years of education, OR=1.11 (95%CI 1.11-1.12)	↓ adherence
						Over 12 years of education, OR=1.18 (95%CI 1.17-1.18)	↓ adherence
			Males, 65-84 years (8765)	Multivariate logistic regression	7-10 years of education	11-12 years of education, OR=1.01 (95%CI 1.01-1.01)	↓ adherence
						Over 12 years of education, OR=1.03 (95%CI 1.03-1.04)	↓ adherence
			Females, 65-84 years (15990)	Multivariate logistic regression	7-10 years of education	11-12 years of education, OR=1.03 (95%CI 1.02-1.03)	↓ adherence
						Over 12 years of education, OR=1.10 (95%CI 1.10-1.11)	↓ adherence

NS= Non-significant finding, RR= Relative risk, OR= Odds ratio, CI= Confidence interval, USAGE= Understanding Statin use in America and Gaps in Education. Studies that had NS findings did not predict a direction of adherence.

Table 3. 4 Education as a predictor of statin adherence in the general population

General factor	Study	Notes	Subpopulation (N=)	Analysis	Reference group	Results	
Education	Wei MY et al. (2013)	Self-reported statin adherence using the USAGE online survey		Multivariate logistic regression	College graduate	High school graduate or less, NS	
				Multivariate logistic regression	College graduate	Some college or associates degree, NS	
	Gibson TB et al. (2006)		New users (24113)	Multivariate logistic regression	No college degree	College degree, 95%CI 1.91-3.14	↑ adherence
			Existing users (93253)	Multivariate logistic regression	No college degree	College degree, 95%CI 1.12-1.49	↑ adherence

NS= Non-significant finding, RR= Relative risk, OR= Odds ratio, CI= Confidence interval, USAGE= Understanding Statin use in America and Gaps in Education. Studies that had NS findings did not predict a direction of adherence.

for between 7-10 years (161). These results contrast with analysis of 117336 patients of a US commercial claims database. Gibson et al showed that, compared with statin users who do not have a college degree, new and existing statin users with college degrees were more adherent to statin therapy (95%CI 1.91-3.14 and 95%CI 1.12-1.49 respectively) (175).

Income and employment

Five of 6 studies identified a significant association between increasing income and better adherence to statin therapy. Analysis of commercial claims and private health insurance databases showed better adherence to statin therapy in patients who were on a higher salary compared with the those in the lowest quintiles (164, 175). In both new and existing statin users, patients earning more than $25000 had better odds for adherence (175). A retrospective cohort study was performed by Grant and colleagues on US pharmacy claims data of 5488 patients. When comparing the lowest and highest income quartiles, Grant and colleagues reported higher adherence in patients in the highest quartile (79.2% vs 86.4%, lowest quartile vs highest quartile respectively) (164). Wallach-Kildemoes et al found greater odds of adherence in the highest income quintile when compared with the lowest income quintile after stratifying for both men and women between ages 40-64 years and 65-84 years (161). No significant relationship between income and adherence was found in a study by Warren and colleagues. However, a reduced likelihood of adherence to statin therapy in part-time and full-time working individuals when compared with unemployed patients was observed (165).

Language other than English at home and location

Only one study assessed language as a predictor of adherence. Warren et al reported that a language other than English spoken at home predicted significantly poorer adherence. Of Australian concession card holders and general beneficiaries, there was a respective 15% and 29% poorer adherence to statin therapy than patients who only spoke English (95%CI 0.83-0.87 and 0.67-0.76 respectively). The same study also found that more adherent patients resided in 'inner regional' and 'outer regional' areas of Australia as compared with patients who live in major cities (165). This had been adjudged by the accessibility and remoteness index for Australia plus (ARIA+); an index that uses road distance to service centres in order to determine remoteness .

Payment variables and health insurance

Screening identified 12 studies that found significant associations between payment for healthcare variables and adherence to statin therapy. Co-payment is a common policy of insurance groups that requires a financial contribution from the patient towards the cost of, for example, either prescriptions or hospital visits. All 12 of the studies showed an association between co-payments or out-of-pocket expenses and adherence. Eleven of these studies found that greater co-payment and expenses predicted poorer adherence to statin therapy. Compared with other low-middle income patients who did not co-pay, patients who co-payed were less adherent (176). Other studies showed that when co-pay rose in increments, patients who had to pay more were poorer adherers. Chan and colleagues reported that with $1 increments in co-pay per day, patients were less likely to adhere to their statin regimen (OR=0.54, 95%CI 0.48-0.60) (162). A retrospective

cohort study of data from 247051 patients of the Finnish prescription register was performed by Aarnio et al. Out-of-pocket expenses in Finnish patients showed a 20% poorer statin adherence per €0.10 increase in cost per statin tablet (OR=0.80, 95%CI 0.80-0.80) (142).

Of the 38 studies that reported significant predictors of statin adherence, 2 out of 3 studies found a significant relationship with the type of health insurance schemes. Findings by Warren and colleagues showed an increased likelihood of adherent behaviour to statins in patients with private health insurance compared with patients who did not have health insurance (165). A retrospective cohort study of 259465 US patients with Medicare part D sponsorship was performed by Jung K et al. Patients in the Medicare Advantage program (MA-PD) were found to be more adherent when compared with those on a stand-alone prescription drug plan (MPR=70.80% vs 69.44%, p=<0.001) (177). The third of the 3 studies did not find a significant relationship between a patient's level of health insurance and their rate of statin adherence (166).

3.3.4 Clinical predictors of adherence to statin therapy

Comorbidities and surgery

Sixteen out of 18 studies identified a significant association between a variety of clinical predictors and statin adherence. Such clinical factors that associated with adherence to statin included surgery, morbidities and comorbidities. Of these 16 studies, all 5 of the studies that investigated an association between hypertension and statin adherence found a significant result. However, there was conflict among these (see table 3.5). For example, compared with patients who did not have known hypertension, Benner and

colleagues found that patients with hypertension were more adherent to statin therapy (OR=1.13, 95%CI 1.07-1.19) (159). A further study found that hypertension associated with better adherence to statin therapy (161). However, a prospective cohort study of patients taking statins for the secondary prevention of acute coronary syndromes (ACS) showed that hypertension was associated with poorer adherence (OR=0.85, 95%CI 0.74-0.99) (157).

Statin adherence following surgery was assessed in 5 studies (see table 3.6). Coronary artery bypass grafts (CABG), percutaneous transluminal coronary angioplasty (PTCA) and general revascularisation following an MI event all significantly associated with adherence to statin therapy. Retrospective data obtained from computerised medical records and prescription claims in one study showed that patients who had undergone either PTCA or CABG were better adherers to statin therapy compared with those who had not undergone surgery(OR=1.48 95%CI 1.13-1.92) (158). However, compared with those who had not undergone surgery, CABG was associated with poorer adherence in a study by Choudhry and colleagues (OR=0.79, 95%CI 0.69-0.90). Furthermore angioplasty or stent insertion did not reach a level of statistical significance as a predictor of adherence compared with the same control group (157) . In existing statin users, Gibson et al found that PTCA predicted poor adherence whereas in new users it was shown to predict better adherence. The group did however find that CABG predicted better adherence in new statin users than those who had not had CABG surgery (175). Three studies found other comorbidities that associated with better adherence. These included stroke, severe dyslipidaemia, diabetes, chronic kidney disease, acute MI and ACS (142, 157, 175). Two of these

Table 3. 5 Clinical predictors of statin adherence in the general population

General factor	Study	Notes	Subpopulation (N=)	Analysis	Reference group	Results	
Atherosclerotic disease	Gibson TB et al. (2006)		New users (24113)	Multivariate logistic regression	No atherosclerosis	Atherosclerosis, 95%CI 1.08-1.36	↑ adherence
			Existing users (93253)	Multivariate logistic regression	No atherosclerosis	Atherosclerosis, 95%CI 1.10-1.18	↑ adherence
	Di Martino M et al. (2005)			Multivariate logistic regression	Atherosclerosis	No atherosclerosis, OR=2.35 (95%CI 1.58-3.50)	↓ adherence
Coronary heart disease	Aarnio EJ et al. (2014)	Nationwide register, CVD, previous CVEs and comorbidities		Multivariate logistic regression	No coronary heart disease	Previous coronary heart disease, OR=0.86 (95%CI 0.83-0.88)	↓ adherence
	Chan DC et al. (2010)	Patients who recently initiated statin therapy		Multivariate logistic regression	No coronary heart disease	Coronary heart disease, NS	
	Barron TI et al. (2010)			Multivariate logistic regression	No coronary heart disease	Single measure, coronary heart disease, OR=0.84 (95%CI 0.80-0.89)	↑ adherence
						Repeated measures, coronary heart disease, OR=0.79 (95%CI 0.77-0.82)	↑ adherence
	Gibson TB et al. (2006)		Existing users (93253)	Multivariate logistic regression	No chronic coronary heart disease	Chronic coronary heart disease, 95%CI 1.08-1.24	↑ adherence

NS= Non-significant finding, OR= Odds ratio, CI= Confidence interval, GP= General practitioner, CVD= Cardiovascular disease, CVE= Cardiovascular event, MPR= Medication possession ratio, PDC= Proportion of days covered. Studies that had NS findings did not predict a direction of adherence.

Table 3. 5 Clinical predictors of statin adherence in the general population

General factor	Study	Notes	Subpopulation (N=)	Analysis	Reference group	Results	
Hypertension	Wallach-Kildemoes H et al. (2013)	Model 2, simultaneous analysis of education and income	Males, 40-64 years old (24886)	Multivariate logistic regression	No hypertension	Hypertension, OR=0.70 (95%CI 0.70-0.71)	↑ adherence
			Females, 40-64 years (26397)	Multivariate logistic regression	No hypertension	Hypertension, OR=0.75 (95%CI 0.75-0.75)	↑ adherence
			Males, 65-84 years (8765)	Multivariate logistic regression	No hypertension	Hypertension, OR=0.68 (95%CI 0.68-0.68)	↑ adherence
			Females, 65-84 years (15990)	Multivariate logistic regression	No hypertension	Hypertension, OR=0.79 (95%CI 0.79-0.79)	↑ adherence
	Goswami NJ et al. (2013)	PDC definition of adherence		Multivariate logistic regression	No hypertension	Hypertension, OR=0.20 (95%CI 0.06-0.63)	↓ adherence
		MPR definition of adherence		Multivariate logistic regression	No hypertension	Hypertension, NS	
	Choudhry NK et al. (2008)			Multivariate logistic regression	No hypertension	Hypertension, OR=1.14 (95%CI 1.03-1.26)	↑ adherence
	Benner JS et al. (2004)			Multivariate generalised linear model	No hypertension	Hypertension, OR=1.13 (95%CI 1.07-1.19)	↑ adherence
	Eagle KA et al. (2004)			Multivariate logistic regression	No hypertension	Hypertension, OR=0.85 (95%CI 0.74-0.99)	↓ adherence

NS= Non-significant finding, OR= Odds ratio, CI= Confidence interval, GP= General practitioner, CVD= Cardiovascular disease, CVE= Cardiovascular event, MPR= Medication possession ratio, PDC= Proportion of days covered. Studies that had NS findings did not predict a direction of adherence.

Table 3. 6 Surgical predictors of statin adherence in the general population

General factor	Study	Notes	Subpopulation (N=)	Analysis	Reference group	Results	
Coronary artery bypass graft	Choudhry NK et al. (2008)			Multivariate logistic regression	No coronary artery bypass graft	Coronary artery bypass graft, OR=0.79 (95%CI 0.69-0.90)	↓ adherence
	Gibson TB et al. (2006)		New users (24113)	Multivariate logistic regression	No coronary artery bypass graft	Coronary artery bypass graft, NS	
			Existing users (93253)	Multivariate logistic regression	No coronary artery bypass graft	Coronary artery bypass graft, 95%CI 1.14-2.00	↑ adherence
Percutaneous transluminal coronary angioplasty	Choudhry NK et al. (2008)			Multivariate logistic regression	No angioplasty	Angioplasty, NS	
	Gibson TB et al. (2006)		New users (24113)	Multivariate logistic regression	No percutaneous transluminal coronary angioplasty	Percutaneous transluminal coronary angioplasty, 95%CI 1.14-2.01	↑ adherence
			Existing users (93253)	Multivariate logistic regression	No percutaneous transluminal coronary angioplasty	Percutaneous transluminal coronary angioplasty, 95%CI 0.79-0.99	↓ adherence
NS= Non-significant finding, OR= Odds ratio, CI= Confidence interval. Studies that had NS findings did not predict a direction of adherence.							

three studies found that chronic obstructive pulmonary disease and angina predicted poorer adherence (157, 175). Whereas Gibson et al and Barron et al reported better adherence to statin therapy in patients with CAD, Aarnio et al showed that previous CAD predicted poor adherence (142, 175, 178).

Medications

Fifteen out of 17 studies reported that the number of medications consumed, the type of statin prescribed, the supply of statin, the length of the delay in statin prescription and the dosage of statin therapy are associated with better adherence. Because statins have a good safety profile, they can be taken in conjunction with many other therapies. Five studies showed a significant relationship between the number of medications taken in conjunction with statin therapy. Interestingly, the studies produced contrasting findings. Natarajan and colleagues found that between 4-6 co-prescribed medications were associated with better statin adherence when compared with 0-3 co-prescribed medications (OR=2.69, 95%CI 1.37-5.29) (160). Findings of increased adherence with more medications were also shown by Watanabe and colleagues and by Grant et al (164, 179). In contrast, Aarnio and colleagues reported that extra medication associated with poorer adherence compared with those who did not receive extra medication (OR=0.98, 95%CI 0.98-0.99) (142). Poorer adherence to statin therapy was also found with an increased number of medications in both new and existing users (OR95%CI 0.97-0.99) (see table 3.7) (175).

When adherence was suboptimal to anti-hypertensives, statin therapy was also poorly adhered to (180). However when compared with patients who were not prescribed anti-hypertensives, patients prescribed anti-hypertensives were more adherent to statin therapy (86% vs 81%). Analysis

from the same study showed that when patients were dispensed a greater quantity of statins, they were better adherers to their regimen (164). Ellis and colleagues showed that a greater supply of statins is also significantly associated with adherence. Fewer than 65 days' supply of statins predicted poorer adherence when compared with a supply of 65 days or more (168). When adjusted for age, gender, medical history, statin type and payment variables, a delay in statin dispensing process within the range of 2-20 days associated with poorer adherence (OR=0.76, 95%CI 0.74-0.77). A delay in receiving statins over 48 days was associated with even poorer odds for optimal adherence compared with patients who did not endure a delay (OR=0.49, 95%CI 0.47-0.51) (142).

The prescribed class of statin predicted adherence in 2 studies. Both of these studies showed that atorvastatin and rosuvastatin were associated with better adherence than simvastatin. A retrospective cohort study that used patient data from the Irish Health Care Executive and Primary Care Reimbursement Services databases found that fluvastatin associated with poorer adherence when compared with patients on pravastatin (OR=1.19, 95%CI 1.02-1.30 for non-adherent behaviour) (178). However Aarnio and colleagues found that, compared with simvastatin users, fluvastatin users were more adherent (OR=1.17, 95%CI 1.14-1.21 for fully adherent behaviour) (142). Other predictors for good adherence to statin therapy included the prescription of nitrate-based anti-anginal therapies and anti-thrombotic use (142, 164). One study found that patients who switched brands multiple times or had their dose changed multiple times were less adherent to their statin regimen than those who stayed with the same brand at the same dose (168). Another retrospective cohort study found that when compared with patients on a low dose (defined as either 10mg simvastatin or less, 5mg rosuvastatin or less or 20mg pravastatin or less), patients on a high dose of statin were less adherent (181).

Table 3. 7 Medication as a predictor for adherence

General factor	Study	Notes	Subpopulation (N=)	Analysis	Reference group	Results	
Increased number of concurrent medications	Aarnio EJ et al. (2014)			Multivariate logistic regression	No extra medications	Number of extra medications (per medication), OR=0.98 (95%CI 0.98-0.99)	↓ adherence
	Watanabe J et al. (2013)	Association with adherence to new regimen of statins		Generalised linear regression	1-5 medications at baseline	6-10 medications at baseline, 0.04 MPR increase	↑ adherence
				Generalised linear regression	1-5 medications at baseline	11-15 medications at baseline, 0.07 MPR increase	↑ adherence
				Generalised linear regression	1-5 medications at baseline	16-20 medications at baseline, 0.10 MPR increase	↑ adherence
				Generalised linear regression	1-5 medications at baseline	Over 20 medications at baseline, 0.14 MPR increase	↑ adherence
	Chan DC et al. (2010)			Multivariate logistic regression	No additional medications	Additional medications, NS	
	Natarajan N et al. (2007)	Self-reported adherence		Multivariate logistic regression	0-3 medications	4-6 prescribed medications, OR=2.69 (95%CI 1.37-5.29)	↑ adherence
				Multivariate logistic regression	0-3 medications	>7 prescribed medications, NS	

NS= Non-significant finding, OR= Odds ratio, CI= Confidence interval, MPR= Medication possession ratio, DMA= Daily medication allowance. Studies that had NS findings did not predict a direction of adherence.

Table 3. 7 Medication as a predictor for adherence

General factor	Study	Notes	Subpopulation (N=)	Analysis	Reference group	Results	
Increased number of concurrent medications	Gibson TB et al. (2006)		New users (24113)	Multivariate logistic regression	No concurrent medications	Increased number of medications, 95%CI 0.97-0.99	↓ adherence
			Existing users (93253)	Multivariate logistic regression	No concurrent medications	Increased number of medications, 95%CI 0.987-0.992	↓ adherence
	Grant RW et al. (2004)			Univariate logistic regression	No concurrent medications	Increased number of medications. 1.3% DMA increase per additional medication	↑ adherence
Fluvastatin prescription	Aarnio EJ et al. (2014)			Multivariate logistic regression	Patients who were prescribed simvastatin	Patients who are prescribed fluvastatin, OR=1.17 (95%CI 1.14-1.21)	↑ adherence
	Barron TI et al. (2010)			Multivariate logistic regression	Patients who were prescribed pravastatin	Single measure model, patients who are prescribed fluvastatin, OR=1.15 (95%CI 1.02-1.30)	↓ adherence
						Repeated measure model, patients who are prescribed fluvastatin, OR=1.19 (95%CI 1.09-1.30)	↓ adherence

NS= Non-significant finding, OR= Odds ratio, CI= Confidence interval, MPR= Medication possession ratio, DMA= Daily medication allowance. Studies that had NS findings did not predict a direction of adherence.

Psychological and behavioural predictors

Five of the 6 studies that investigated psychological wellbeing demonstrated the predictive value of psychological and behavioural factors. Of these, depression was most frequently associated with poor adherence. An RCT of 158 patients between 24-60 years in America by Stilley et al used MEMS to measure patient adherence and found that over a 6 month period, 22.8% of patients were adherent (≥80%). The group found 4 psychological predictors for better adherence and 3 predictors for poorer statin adherence (154). Using the Hamilton depression score to assess depression, a negative coefficient towards adherent behaviour in patients with depression was reported (β coefficient=-0.24, p=<0.01) (154). Another study used a one-year identification period for patients with depression. Findings showed lower odds of adherent behaviour compared with patients who did not suffer from depression (OR=0.87, 95%CI 0.84-0.89) (142). Accounting for patient adherence over a 900 day period, Barron and colleagues reported better adherence in patients with depression in a sample of the 79384 population compared with those who did not have depression (OR=1.03, 95%CI 1.01-1.06). The single measure model that accounted for a cross sectional measure at day 720 contrasted with this (OR=0.95, 95%CI 0.91-0.98). The contrasting findings for each model may be attributed to discontinuation. The authors of the study reported an increased risk of non-persistence among patients with depression (HR=1.12, 95%CI 1.08-1.15) (178). This may leave more adherent patients who have not been diagnosed with depression in the repeated measures model.

High psychological stress also predicted poor adherence to statin therapy. Warren et al used the Kessler-10 10 item survey in order to assess psychological stress. Patients with moderate- very high distress were found

to be less likely to optimally adhere to statin therapy (MPR ≥80%) (165). Aarnio et al also reported that, compared with patients who did not have a mental disorder, patients with a mental disorder were better adherers (OR=1.26, 95%CI 1.20-1.32) (142).

3.4 Summary of results

Screening of the literature found 38 studies of predictors of statin adherence in the general population. The rate of adherence in these studies ranged from 22.8% to 87.4% (153, 154). The most frequently used measures of adherence were the MPR and the PDC. Only one study used pill counts to determine adherence to statin therapy.

A number of sociodemographic, socioeconomic and clinical factors associated with adherence to statin therapy. There was no consensus as to whether a greater number of years spent in education predicted statin adherence (see table 3.8) (161, 165, 175). Furthermore, there were conflicting findings among a number of studies for certain clinical factors such as hypertension. Further research needs to be conducted to elucidate whether an increased number of concurrent medications predicts statin adherence. Further research also needs to elucidate whether patients who have had surgery are more or less likely to adhere to statin therapy compared with those who have not had surgery. These issues are all pertinent to patient beliefs about their medication and are explored in further detail in Chapter 5 – Discussion.

Table 3. 8 A summary of findings from the above review

Predictor		Number of studies	Change in adherence
Adverse effects		2 (156, 166)	↓ adherence
Age	Increasing age	25 (142, 155, 157-162, 164-168, 170, 173, 175, 178, 181-187)	↑ adherence
Alcohol consumption	High or excessive consumption	3 (165, 174, 188)	↓ adherence
Beliefs	Poor self-rated health	1 (165)	↑ adherence
	Negative view of statin therapy	1 (170)	↓ adherence
BMI	Overweight	1 (171)	↑ adherence
	Obese	3 (165, 171, 173)	↑ adherence
Clinical factors	ACS	2 (142, 162)	↑ adherence
	Acute MI	2 (153, 158)	↑ adherence
	Angina	1 (175)	↓ adherence
	Atherosclerotic disease	2 (175, 189)	Conflicting findings
	CHD	3 (142, 175, 178)	Conflicting findings
	CKD	1 (157)	↑ adherence
	CVD	1 (165)	↑ adherence
	COPD	1 (157)	↓ adherence
	Diabetes	1 (178)	↑ adherence
	Dyslipidaemia	1 (187)	↑ adherence
	Dyslipidaemia (severe)	1 (142)	↑ adherence
	Hypertension	5 (153, 157, 158, 161, 173)	Conflicting findings
	Stroke	1 (142)	↑ adherence
Co-payment	Increased co-payment	11 (142, 158, 161, 162, 173, 175, 176, 181, 182, 185, 187, 190)	↓ adherence
Education	More years spent in education or a higher level of education	3 (161, 165, 175)	Conflicting findings

ACS= Acute coronary syndrome, CHD= Coronary heart disease, CKD= Chronic kidney disease, COPD= Chronic obstructive pulmonary disorder, MA-PD= Medicare advantage-prescription drug, PDP= Prescription drug plan, LLD= Lipid lowering drug, PT= Part time, FT= Full time. A summary of the findings for the above literature review.

Table 3.8 A summary of findings from the above review

Predictor		Number of studies	Change in adherence
Employment status	PT/ FT employed	1 (165)	↓ adherence
Ethnicity	Non-white	8 (157, 167-170, 173, 184, 186)	↓ adherence
Exercise and diet	Exercise or a healthy diet	1 (160)	↑ adherence
Gender	Female	11 (162, 167, 168, 175, 178, 181, 182, 185-187)	↓ adherence
Health insurance	Private health insurance	1 (165)	↑ adherence
	MA-PD vs PDP	1 (177)	↑ adherence
Health care setting	A greater number of inpatient days	1 (142)	↑ adherence
	Visit to the cardiologist within 15 months of study baseline	1 (173)	↓ adherence
	Increased volume of statin patients per physician	1 (181)	↓ adherence
	Increased volume of statin patients per pharmacy	1 (181)	↑ adherence
Income	A higher income	5 (159, 164-166, 175)	↑ adherence
Influence of cost	Large influence of cost of statin prescription	1 (166)	↑ adherence
Language spoken at home	Language other than English	1 (165)	↓ adherence
Lifestyle factors	Unhealthy lifestyle	1 (171)	↓ adherence
Location	"Remoteness"	1 (165)	↑ adherence
	Higher income neighbourhood (per quartile increase)	1 (162)	↑ adherence
	African American neighbourhood (per quartile increase)	1 (121)	↓ adherence

ACS= Acute coronary syndrome, CHD= Coronary heart disease, CKD= Chronic kidney disease, COPD= Chronic obstructive pulmonary disorder, MA-PD= Medicare advantage-prescription drug, PDP= Prescription drug plan, LLD= Lipid lowering drug, PT= Part time, FT= Full time. A summary of the findings for the above literature review.

Table 3.8 A summary of findings from the above review

Predictor		Number of studies	Change in adherence
Medications	A greater number of days' supply of statin pills	3 (167, 184, 191)	↑ adherence
	New statin users	1 (173)	↓ adherence
	A greater number of refills	1 (181)	↓ adherence
	Longer delay in prescription refill	1 (142)	↓ adherence
	Antithrombotic prescription	1 (142)	↑ adherence
	Aspirin prescription in the past 15 months	1 (173)	↓ adherence
	ACE-I prescription in the past 15 months	1 (173)	↓ adherence
	Poor adherence to an antihypertensive prescription	1 (180)	↓ adherence
	An increased number of concurrent medications	5 (142, 160, 164, 175, 179)	Conflicting findings
	Non-statin LLD prescription	1 (187)	↓ adherence
	Multi-pill therapy	1 (182)	↓ adherence
Out of pocket expenses	Increased out of pocket expenses	1 (142)	↓ adherence
Psychological health	Anxiety	1 (154)	↓ adherence
	Depression	4 (142, 154, 178, 187)	↓ adherence
	Moderate- very high distress	1 (165)	↓ adherence
	'Mental disorder'	1 (142)	↑ adherence
Relationship status	Married (or partner)	2 (165, 173)	↑ adherence
Smoking status	Current smoker	3 (165, 173, 189)	↓ adherence
	Former smoker	1 (171)	↑ adherence
	Unknown smoker	1 (173)	↑ adherence
ACS= Acute coronary syndrome, CHD= Coronary heart disease, CKD= Chronic kidney disease, COPD= Chronic obstructive pulmonary disorder, MA-PD= Medicare advantage-prescription drug, PDP= Prescription drug plan, LLD= Lipid lowering drug, PT= Part time, FT= Full time. A summary of the findings for the above literature review.			

Table 3.8 A summary of findings from the above review

Predictor		Number of studies	Change in adherence
Surgery	CABG	2 (157, 175)	Conflicting findings
	PTCA	1 (175)	Conflicting findings
	PTCA or CAGB	1 (158)	↑ adherence
	PTCA, CABG or CHD	1 (159)	↑ adherence
Type of statin	Lovastatin prescription	1 (142)	↓ adherence
	Pravastatin prescription	1 (142)	↑ adherence
	Fluvastatin prescription	2 (142, 178)	Conflicting findings
	Atorvastatin prescription	2 (142, 178)	↑ adherence
	Rosuvastatin prescription	2 (142, 178)	↑ adherence
	Simvastatin and ezetimibe prescription	1 (178)	↑ adherence
ACS= Acute coronary syndrome, CHD= Coronary heart disease, CKD= Chronic kidney disease, COPD= Chronic obstructive pulmonary disorder, MA-PD= Medicare advantage-prescription drug, PDP= Prescription drug plan, LLD= Lipid lowering drug, PT= Part time, FT= Full time. A summary of the findings for the above literature review.			

Chapter 4

This chapter is composed of the baseline characteristics, rates of adherence, and predictors of adherence in TRACE-RA.

4 Adherence to statin therapy in a randomised controlled trial of atorvastatin vs placebo in patients with rheumatoid arthritis

4.1 Introduction

Previous studies have demonstrated the benefits of statin therapy in RA patients; however, few studies have examined the statin-taking behaviours of RA patients. Indeed, in the literature search, only four papers were identified that concerned either statin initiation or discontinuation (192-195). These studies were performed in large administrative and pharmacy claims database whereby pill counts were not collected.

A theme of poor statin-taking behaviour and poor clinical outcomes was outlined in the existing literature of statins and RA patients. One study of 66107 Danish individuals who had a previous MI event in a nationwide register identified 877 RA patients (1.3% of the cohort). One hundred and sixty five (18.8%) of these were prescribed a statin for the secondary prevention of a CVE. Comparing RA patients to those without RA, statin initiation was 31% poorer in RA patients (OR=0.69, 95%CI 0.58-0.82) (194). The clinical implications for poor rates of initiation were shown in a recent study by Schoenfeld et al. A UK-based cohort of 2943 RA patients who initiated statin therapy were matched on a 1:1 basis with non-initiators. A lower likelihood of all-cause mortality in patients who initiated statin therapy was found compared with RA patients who did not initiate statin therapy (HR=0.79, 95%CI 0.68-0.91) (195).

Two studies of a cohort of 4102 statin-taking RA patients evaluated an association between discontinuation, CVEs and mortality. Discontinuation was defined as a period of ≥3 consecutive months of no statin consumption. The authors of the first study found that discontinuation was associated with an increased risk of MIs (HR=1.67, 95%CI 1.24-2.25) compared with persistent patients. For every additional month of discontinuation, RA patients were at a 2% increased risk of a MI than persistent patients (HR=1.02, 95%CI 1.01-1.03) (193). The follow up study to this confirmed the importance of persistence to statin therapy in an RA population. In the same population, 198 CVD-related deaths and 467 deaths overall were recorded. Discontinuation of statin therapy was associated with an increased risk of CV related mortality (HR=1.60, 95%CI 1.15-2.23) and all-cause mortality (HR=1.79, 95%CI 1.46-2.20) compared with patients who persisted with therapy (192).

Despite the above work of statin initiation and persistence in RA populations, no studies have assessed adherence for the primary prevention of CVEs in RA patients. Characteristics of RA may prevent ideal medication consumption. For example, severe disease activity may hinder the opening of tablet bottles and access to healthcare may be limited by poor mobility. Indeed, EQ-5D responses have predicted medication-taking behaviour in RA patients (196). Research of such characteristics could provide a novel insight into predictors of adherent and non-adherent behaviour to statin therapy in an RA population and could elucidate conflict in the literature.

4.2 Aims

The aims of this project were:

- To describe the baseline characteristics of the two arms of the TRACE-RA study
    - To compare the baseline characteristics of men and women in TRACE-RA
- To determine the rates of adherence to atorvastatin and placebo from 0-3, 0-6 and 0-12 months in patients recruited to TRACE-RA
- To identify baseline predictors of adherence to the allocated TRACE-RA intervention
    - To identify baseline predictors of adherence to atorvastatin

4.3 Patients and methodology

4.3.1 Definition of adherence

Adherence can be defined as the 'extent to which the patient follows medical instructions' (109). In TRACE-RA, adherence was defined using data collected on the number of tablets dispensed and the number of tablets returned (pill counts). Patients received 100 tablets for each of the first two 3 months of follow up, and 200 tablets thereafter for every 6 months of follow up. Used bottles of tablets were returned to hospital pharmacists where records of the number of remaining tablets were collected using patient specific 'Trial Medication Accountability Logs'. Remaining tablets were subsequently destroyed on site. Date of prescription refill, date of tablet return, the number of tablets dispensed and the number of tablets returned were recorded. Using the available data, it was possible to measure adherence in the TRACE-RA population using the expression (see next page):

$$\frac{\text{Total number of tablets consumed}}{\text{Total number of days in study period}}$$

The numerator in the above expression can be described as the number of pills that a patient consumed over the course of the study. This was calculated by subtracting the number of pills returned from the number of pills dispensed. The denominator for this expression is the number of days covered over the course of the study. For example, if a patient consumed 1400 tablets over 1750 days, their adherence would be calculated:

$$\frac{1400}{1750} \times 100 = 80\%$$

Following the implementation of the 5th version of the protocol (12/2010), adherence could be self-reported (see appendix table 6). Version 3 CRFs (also 12/2010) contained the following question; "since the last visit, approximately how many tablets have you taken per week? Most, some, none". Rates of adherence were dichotomised into adherent behaviour ($\geq$80% tablet consumption) and non-adherent behaviour (<80% tablet consumption) from 0-3 months, 0-6 months and 0-12 months. The $\geq$80% threshold is consistent with much of the reviewed literature (see table 3.3, section 3.3.1). Self-reported adherence was dichotomised into adherent (Most) and non-adherent (Some/None) behaviour after the completion of CRFs at 3, 6 and 12 months.

4.3.2 Patient selection and description of baseline characteristics

All patients who received their allocated TRACE-RA intervention were included in the description of baseline characteristics. Baseline characteristics for sociodemographic, socioeconomic, lifestyle and clinical characteristics were compared between genders. The rates of adherence for all the patients were compared between arms. More data were available for pill counts than for self-reported adherence therefore pill counts were used for subsequent analyses of predictors of adherence. Patients were considered to have complete data when they did not have missing data for any of the selected characteristics (see section 4.3.3). Baseline characteristics for patients with complete data were completed for all patients who had pill counts up to and including 12 months. These patients were included for analysis of baseline predictors of adherence. Separate analysis of predictors of adherence was also conducted for patients of the atorvastatin arm with complete pill counts up to and including 12 months.

4.3.3 Selection of potential predictors of adherence

Potential predictors of adherence were selected based on the above literature review (see section 3.3.1). Research conflicted over whether educational achievement, known hypertension, and an increasing number of concurrent medications were associated with statin adherence or non-adherence. These characteristics were included for analysis (see table 4.1, page 92). Further characteristics were selected for assessment as potential predictors of adherence. Both smoking status and occupation status were included in analysis of predictors of statin adherence to add to the limited findings that were reported in the literature. Smoking status was recorded as never, former or current using data collected on whether a patient had ever

smoked, the age a patient stopped smoking and whether a patient was a smoker at baseline. Synthesised results of the literature review of this dissertation (see section 3.3) showed one study that identified former smoking as a predictor of statin adherence in the general population and so smoking status (171). Further, only one study had assessed occupation status as a potential predictor of statin adherence. It was found that those in either full or part-time employment were poorer adherers than those who were unemployed (165). This research had not considered other potential employment situations. In this dissertation, patient occupation status was categorised as either full-time employed, part-time employed, unemployed, student, semi-retired or retired.

Frequency of alcohol consumption and exercise were self-reported as never, monthly or less, 2-4 times per month, 2-3 times a week and 4+ times a week. Previous research showed that HAQ scores and responses to EQ-5D questionnaires predict adherent behaviour to DMARD therapy in RA patients (196). These may be of importance for adherence to statin therapy and poor physical function, mobility or self-care may hinder medication consumption. Responses from both HAQ and EQ-5D were included in analysis of potential predictors of adherence to the allocated TRACE-RA intervention and atorvastatin. Clinical characteristics were collected at baseline medical examinations. Patient DAS28 score, a first degree relative with premature CVD, a family history of diabetes, and an increasing number of concurrent DMARDs were also assessed as potential predictors(see table 4.1). These characteristics may be associated with perceived severity of disease or susceptibility of a CVE and may contribute towards the growing body of evidence linking clinical factors, the health belief model and attitudes and likelihood of behaviour change (140).

Table 4. 1 Characteristics that were included for univariate analysis

Source of data	Baseline characteristic	Reason for selection
Patient registration	Age	Multivariate logistic regression models were adjusted for age and gender
	Gender	
Lifestyle questionnaire	Ethnicity	
	Smoking status	Only one study assessed former smoking as a potential predictor of statin adherence
	Exercise frequency	
	Frequency of alcohol consumption	
	Occupation status	Only one study assessed occupation status as a potential predictor of statin adherence
	Age leaving full-time education	Conflicting findings in the literature as a potential predictor of statin adherence
Medical examination or medical records	DAS28	Not previously been studied as potential predictors of adherence to statin therapy
	HAQ score	
	First degree relative with premature CVD	
	Family history of diabetes	
	Known hypertension	Conflicting findings in the literature as a potential predictor of statin adherence
	Number of concurrent DMARDs	Not previously been studied as a potential predictor of adherence to statin therapy
	Number of concurrent drugs	Conflicting findings in the literature as a potential predictor of statin adherence
EQ-5D questionnaire	Mobility	Responses have relevance for medication-taking behaviour in RA patients (196) and have not been studied as potential predictors of adherence to statin therapy
	Self-care	
	Usual activities	
	Pain/ discomfort	
	Anxiety/ depression	
	Health state compared with previous 12 months	
	EQ-5D VAS	

DAS28= Disease activity score, HAQ= Health assessment questionnaire, CVD= Cardiovascular disease, DMARDs= Disease modifying anti-rheumatic drugs, EQ-5D= EuroQol-5D, VAS= Visual analogue score.

4.3.4 Statistical methodology

All analyses were conducted using STATA 13.1 (StataCorp LP, College Station, Texas, USA). Continuous data were reported using the median value and interquartile range (IQR, 25th percentile to 75th percentile). Categorical data were reported as total numbers and percentages. Throughout this work, a p value less than 0.05 was considered statistically significant.

Descriptive analyses were performed between TRACE-RA arms and between genders of TRACE-RA. A Mann-Whitney rank-sum test was used to test whether the differences between groups were statistically significant for continuous data. The analysis of categorical data was performed using Pearson's χ^2 test. No tests for differences between baseline characteristics of TRACE-RA arms were conducted. This was justified by the fact that any resultant p values would be chance findings due to the randomisation process. Differences between arms for proportions of adherent patients were however determined using Pearson's χ^2 test. The atherogenic index for patients was calculated using the equation: "Atherogenic Index = TC/HDL". Analysis of adherence as determined by pill counts was performed as a complete case analysis. Patients with complete data for each of the selected characteristics (see section 4.3.3) were included for analysis of predictors of adherence. Potential baseline predictors were fit independently into a univariate logistic regression model. Analyses were performed separately, firstly for all patients of TRACE-RA and then for the atorvastatin arm. Characteristics with a p value less than 0.10 were entered into a forward selection multivariate logistic regression model that was adjusted for age and gender.

4.4 Results

4.4.1 Baseline characteristics

Of the 2986 TRACE-RA patients, 1492 were randomised into the atorvastatin arm and 1494 were randomised into the placebo arm. The median age of patients in the TRACE-RA population was 61.0 years (IQR 55.0-66.5 years). The median disease duration and number of years since onset of disease symptoms were 11 years (IQR 5-19 years) and 13 years (IQR 6-21 years) respectively. The population was largely white in self-reported ethnicity (95.0%) and was predominantly female (74.2%). The median BMI was 26.7 kg/m^2 (IQR 23.8-30.2 kg/m^2). One thousand one hundred patients (38.3%) were overweight (BMI 25-29.99 kg/m^2) and 748 (26.1%) patients were obese (BMI of $\geq$30 kg/m^2) (see table 4.2).

4.4.1.1 Baseline lifestyle characteristics

The majority of patients in TRACE-RA (83.6%) were not current smokers at baseline. There were more current smokers in the atorvastatin arm than the placebo arm (18.4% vs 14.5% respectively), whereas there were more former smokers in the placebo arm than the atorvastatin arm (44.6% vs 42.6% respectively) (see table 4.3). Overall, more patients (N=802, 28.3%) self-reported never exercising than reported exercising 4 or more times per week (N=553, 19.5%). Five hundred and thirty eight patients (18.9%) in TRACE-RA were self-reported 'never' drinkers. Almost half of patients (45.9%) were retired and only 22.4% of patients were in full-time employment at baseline. The median age before patients left full-time education was 16 (IQR 15-17 years) in each arm (see table 4.3).

Table 4. 2 Baseline sociodemographic and anthropometric characteristics of the two arms of TRACE-RA

Baseline characteristic	N=Number of patients with complete data (% of 2986)	All patients	N=Number of atorvastatin patients with complete data (% of 1492)	Atorvastatin arm	N=Number of placebo patients with complete data (% of 1494)	Placebo arm
Median age, years (IQR)*	2965 (99.3%)	61.0 (55.0-66.5)	1484 (99.4%)	60.9 (55.2-66.5)	1481 (99.1%)	61.1 (54.9-66.6)
Gender (n, %)*	2986 (100%)		1492 (100%)		1494 (100%)	
Women		2214 (74.2%)		1097 (73.5%)		1117 (74.8%)
Ethnicity (n, %) †	2836 (95.0%)		1410 (94.5%)		1426 (95.5%)	
White		2786 (98.2%)		1383 (98.1%)		1403 (98.4%)
Asian/ Mixed Asian		25 (0.9%)		10 (0.7%)		15 (1.1%)
Black/ Mixed Black		15 (0.5%)		10 (0.7%)		5 (0.4%)
Chinese/ Mixed Chinese		2 (0.1%)		1 (0.1%)		1 (0.1%)
Other ethnicity		8 (0.3%)		6 (0.4%)		2 (0.1%)
Median no of years of disease duration (IQR)*	2978 (99.7%)	11 (5-19)	1490 (99.9%)	11 (4-18)	1488 (99.6%)	11 (5-20)
Median no of years since onset of symptoms (IQR)*	2921 (97.8%)	13 (6-21)	1462 (97.9%)	13 (6-21)	1459 (97.7%)	13 (6-21)
Median BMI, kg/m^2 (IQR)	2869 (96.1%)	26.7 (23.9-30.1)	1442 (96.7%)	26.4 (23.8-30.2)	1427 (95.5%)	26.8 (24.0-30.1)
BMI (n, %)						
Underweight, <18.5		22 (0.8%)		13 (0.9%)		9 (0.6%)
Normal weight, 18.5-24.99		999 (34.8%)		512 (35.5%)		487 (34.1%)
Overweight, 25-29.99		1100 (38.3%)		538 (37.3%)		562 (39.4%)
Obese, ≥30		748 (26.1%)		379 (26.3%)		369 (25.9%)
Median waist, cm (IQR)*	2526 (84.6%)	91 (82-100)		91 (81-100)		91 (82-100)

N= Number of patients, IQR= Interquartile range, BMI= Body mass index, kg/m^2= Kilograms per square meter, cm= Centimetre. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Items marked with an * were recorded in TRACE-RA CRFs. Items marked with a † were recorded in TRACE-RA lifestyle questionnaires.

Table 4. 3 Baseline lifestyle characteristics of the two arms of TRACE-RA

Baseline characteristic	N=Number of patients with complete data (% of 2986)	All patients	N=Number of atorvastatin patients with complete data (% of 1492)	Atorvastatin arm	N=Number of placebo patients with complete data (% of 1494)	Placebo arm
Smoking (n, %) †	2838 (95.0%)		1411 (94.6%)		1427 (95.5%)	
Never		1134 (40.0%)		550 (39.0%)		584 (40.9%)
Former		1237 (43.6%)		601 (42.6%)		636 (44.6%)
Current		467 (16.5%)		260 (18.4%)		207 (14.5%)
Exercise (n, %) †	2831 (94.8%)		1408 (94.4%)		1423 (95.3%)	
Never		802 (28.3%)		407 (28.9%)		395 (27.8%)
Monthly or less		340 (12.0%)		171 (12.1%)		169 (11.9%)
2-4 times per month		450 (15.9%)		217 (15.4%)		233 (16.4%)
2-3 times per week		686 (24.2%)		343 (24.4%)		343 (24.1%)
≥4 times per week		553 (19.5%)		270 (19.2%)		283 (19.9%)
Frequency of alcohol consumption (n, %) †	2846 (95.3%)		1416 (94.9%)		1430 (95.8%)	
Never		538 (18.9%)		245 (17.3%)		293 (20.5%)
Monthly or less		760 (26.7%)		391 (27.6%)		369 (25.8%)
2-4 times per month		603 (21.2%)		312 (22.0%)		291 (20.4%)
2-3 times per week		640 (22.5%)		317 (22.4%)		323 (22.6%)
≥4 times per week		305 (10.7%)		151 (10.7%)		154 (10.8%)
Occupation (n, %) †	2833 (94.9%)		1411 (94.6%)		1422 (95.2%)	
Full-time employed		634 (22.4%)		315 (22.3%)		319 (22.4%)
Part-time employed		357 (12.6%)		165 (11.7%)		192 (13.5%)
Unemployed		397 (14.0%)		215 (15.2%)		182 (12.8%)
Student		64 (2.3%)		35 (2.5%)		29 (2.0%)
Semi-retired		82 (2.9%)		42 (3.0%)		40 (2.8%)
Retired		1299 (45.9%)		639 (45.3%)		660 (46.4%)
Median age leaving full-time education (IQR) †	2835 (94.9%)	16 (15-17)	1408 (94.4%)	16 (15-17)	1427 (95.5%)	16 (15-17)

N= Number of patients, IQR= Interquartile range. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Items marked with a † were recorded in TRACE-RA lifestyle questionnaires.

4.4.1.2 Baseline RA characteristics

One thousand two hundred and fifty nine TRACE-RA patients (43.0%) had a moderate (DAS28 score 3.2-5.1) disease activity whereas a smaller proportion of patients (16.6%) had a high (DAS28 score >5.1) disease activity at baseline. The median HAQ-SDI and HAQ-ADI scores for patients in TRACE-RA were 1.3 (IQR 0.4-1.8) 0.9 (IQR 0.3-1.5) respectively. The median EQ-5D VAS score for patients was 70 (IQR 51-84). The median EQ-5D VAS scores were 70 for each arm; however the distributions of scores differed. The IQR of EQ-5D VAS scores were from 50 to 82 and 54 to 85 for the 25th and 75th percentiles of the atorvastatin and placebo arms respectively. One thousand four hundred and nine (59.8%) of 2405 patients who provided a blood sample for RhF testing were RhF positive. Very few patients (11.3% of the study population) were tested for ACPA positivity. Of those tested, 258 (76.3%) were ACPA positive. The median CRP level in TRACE-RA was 5 mg/L (IQR 3-11 mg/L) and the median ESR value was 16mm/h (IQR 8-28mm/h) and were similar between arms (see table 4.4).

Table 4. 4 Baseline RA characteristics of the two arms of TRACE-RA

Baseline characteristic	N=Number of patients with complete data (% of 2986)	All patients	N=Number of atorvastatin patients with complete data (% of 1492)	Atorvastatin arm	N=Number of placebo patients with complete data (% of 1494)	Placebo arm
Median DAS28 (IQR)*	2926 (98.0%)	3.6 (2.5-4.6)	1459 (97.8%)	3.6 (2.6-4.7)	1467 (98.2%)	3.5 (2.5-4.6)
DAS28 (n, %)*						
Remission, <2.6		765 (26.1%)		368 (25.2%)		397 (27.1%)
Low activity, 2.61-3.19		416 (14.2%)		199 (13.6%)		217 (14.8%)
Moderate activity, 3.2-5.1		1259 (43.0%)		639 (43.8%)		620 (42.3%)
High activity, >5.1		486 (16.6%)		253 (17.3%)		233 (15.9%)
Median tender joint count (IQR)*	2962 (99.2%)	3 (1-8)	1477 (99.0%)	3 (1-8)	1485 (99.5%)	3 (0-8)
Median swollen joint count (IQR)*	2961 (99.2%)	2 (0-5)	1475 (98.9%)	2 (0-5)	1486 (99.6%)	2 (0-6)
Median total HAQ-SDI score (IQR) §	2939 (98.4%)	1.3 (0.4-1.8)	1469 (98.5%)	1.3 (0.4-1.9)	1470 (98.4%)	1.3 (0.4-1.9)
Median total HAQ-ADI score (IQR)§	2939 (98.4%)	0.9 (0.3-1.5)	1469 (98.5%)	1.0 (0.4-1.5)	1470 (98.4%)	0.9 (0.3-1.5)
Median EQ-5D VAS (IQR)§	2904 (97.2%)	70 (51-84)	1450 (97.2%)	70 (50-82)	1454 (97.3%)	70 (54-85)
Median early morning stiffness (IQR)	2529 (84.7%)	30 (5-60)	1269 (85.0%)	30 (5-60)	1260 (84.3%)	30 (5-60)
Median wellness score (IQR)*	2955 (99.0%)	30 (14-52)	1476 (99.0%)	31 (15-53)	1479 (99.0%)	30 (14-52)
Blood tests						
Rh factor positive (n, %)*	2405 (80.5%)	1439 (59.8%)	1207 (80.9%)	724 (60.0%)	1198 (80.2%)	715 (59.2%)
ACPA positive (n, %)*	338 (11.3%)	258 (76.3%)	167 (11.2%)	128 (76.6%)	171 (11.4%)	130 (76.0%)
Median CRP, mg/L (IQR)*	1550 (51.9%)	5 (3-11)	774 (51.9%)	5 (3-11)	776 (51.9%)	5 (3-11)
Median ESR, mm/hr (IQR)*	2169 (72.6%)	16 (8-28)	1076 (72.0%)	17 (8-29.5)	1093 (73.2%)	16 (8-27)

N= Number of patients, %=, IQR= Interquartile range, DAS28= Disease activity score 28, HAQ-SDI= Health assessment questionnaire standard disability index, HAQ-ADI= Health assessment questionnaire alternate disability index, EQ-5D VAS= EuroQol-5D Visual analogue score, Rh= Rheumatoid, ACPA= Anti-citrullinated protein antibody, CRP= C Reactive protein, ESR= Erythrocyte sedimentation rate, mg/L= Milligram per litre, mm/Hr= Millimetres per hour. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Items marked with an * were recorded in TRACE-RA CRFs. Items marked with a § were recorded in a document that included both HAQ and EQ-5D questionnaires.

4.4.1.3 Baseline CV risk factors

Data for non-fasting lipid concentrations were incomplete. Only 39% of patients in TRACE-RA had complete data for all lipid levels. Conversely, 44% of patients did not have data for any of the tested lipids. The remaining 17% of patients had available data for some but not all lipids. TRACE-RA patients had a median TC level of 5.4mmol/L (IQR 4.8-6.0mmol/L), median HDL levels of 1.5mmol/L (IQR 1.3-1.9), median LDL levels of 3.2mmol/L (IQR 2.7-3.8) and median triglyceride levels of 1.3mmol/L (IQR 0.9-1.8mmol/L) (see table 4.5). The median atherogenic index for TRACE-RA patients was 3.5 (IQR 2.9-4.3). Five hundred and forty six patients (18.3%) reported a first degree relative who suffered from premature CVD and 642 patients (21.5%) reported a family history of diabetes (see table 4.5).

Table 4. 5 Baseline CV characteristics of the two arms of TRACE-RA

Baseline characteristic	N=Number of patients with complete data (% of 2986)	All patients	N=Number of atorvastatin patients with complete data (% of 1492)	Atorvastatin arm	N=Number of placebo patients with complete data (% of 1494)	Placebo arm
Lipid concentrations*						
Median non-fasting TC, mmol/L (IQR)	1663 (55.7%)	5.4 (4.8-6.0)	836 (56.0%)	5.4 (4.8-6.1)	827 (55.4%)	5.4 (4.8-6.0)
Median non-fasting HDL, mmol/L (IQR)	1537 (51.5%)	1.5 (1.3-1.9)	777 (52.1%)	1.6 (1.3-1.9)	760 (50.9%)	1.5 (1.3-1.8)
Median non-fasting LDL, mmol/L (IQR)	1173 (39.3%)	3.2 (2.7-3.8)	595 (39.9%)	3.2 (2.7-3.8)	578 (38.7%)	3.2 (2.7-3.8)
Median non-fasting TG, mmol/L (IQR)	1375 (46.0%)	1.3 (0.9-1.8)	694 (46.5%)	1.3 (0.9-1.8)	681 (45.6%)	1.3 (0.9-1.8)
Median atherogenic index, TC/HDL (IQR)	1532 (51.3%)	3.5 (2.9-4.3)	773 (51.8%)	3.5 (2.9-4.3)	759 (50.8%)	3.5 (2.9-4.3)
First degree relative with premature CVD (n, %)*	2900 (97.1%)	546 (18.3%)	1452 (97.3%)	284 (19.6%)	1448 (96.9%)	262 (18.1%)
Family history of diabetes (n, %)*	2930 (98.1%)	642 (21.5%)	1463 (98.1%)	315 (21.5%)	1467 (98.2%)	327 (22.3%)
Hypertension (n, %)*	2942 (98.5%)	654 (22.2%)	1474 (98.8%)	321 (21.8%)	1468 (98.3%)	333 (22.7%)
Systolic blood pressure*						
Median reading 1, mmHg (IQR)	2927 (98.0%)	135 (122-144)	1434 (96.1%)	135 (122-147)	1431 (95.8%)	135 (122-147)
Median reading 2, mmHg (IQR)	2545 (85.2%)	134 (121-146)	1274 (85.4%)	134 (121-145)	1271 (85.1%)	133 (120-147)
Diastolic blood pressure*						
Median reading 1, mmHg (IQR)	2894 (96.9%)	80 (73-88)	1451 (97.3%)	80 (73-87)	1448 (96.9%)	80 (73-89)
Median reading 2, mmHg (IQR)	2641 (88.4%)	80 (72-86)	1325 (88.8%)	80 (72-85)	1316 (88.1%)	80 (72-86)

N= Number of patients, IQR= Interquartile range, TC= Total cholesterol, HDL= High-density lipoprotein, LDL= Low-density lipoprotein, TG= Triglyceride, CVD= Cardiovascular disease, mmol/L= Millimole per litre, mmHg= Millimetre of mercury. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Items marked with an * were recorded in TRACE-RA CRFs.

Six hundred and fifty four patients (22.2%) were known to have hypertension at baseline (see table 4.5). Two readings of blood pressures were taken from patients. The median systolic and diastolic blood pressures for TRACE-RA patients were 135 mmHg (IQR 122-144 mmHg) and 80 mmHg (IQR 73-88 mmHg) respectively (at the first reading). At the second reading, median systolic and diastolic blood pressures for patients were 134 mmHg (IQR 121-146 mmHg) and 80 mmHg (IQR 72-86 mmHg) respectively. In patients with known hypertension, the median systolic and diastolic blood pressures were 141mmHg (IQR 130-151 mmHg) and 82 mmHg (IQR 76-89 mmHg) respectively. Patients who did not have known hypertension had median systolic and diastolic blood pressures of 132mmHg (IQR 120-145 mmHg) and 80 mmHg (IQR 72-87 mmHg) respectively (see table 4.6).

Table 4. 6 Median baseline blood pressure readings stratified by 'known hypertension' at baseline

	Hypertension	No hypertension
Median systolic reading 1, mmHg (IQR)	141 (130-151)	132 (120-145)
Median diastolic reading 1, mmHg (IQR)	82 (76-89)	80 (72-87)
Median systolic reading 2, mmHg (IQR)	140 (129-151)	131 (120-143)
Median diastolic reading 2, mmHg (IQR)	81 (75-88)	80 (71-85)

mmHg= Millimetres of mercury, IQR= Interquartile range.

4.4.1.4 Baseline concurrent medications

Polypharmacy was common in the TRACE-RA population (median number of concurrent drugs was 6, IQR 4-8). Two thousand six hundred and forty three (90.9%) patients were receiving DMARD therapy at baseline. Of these patients, the median number of concurrent DMARDs was 1 (IQR 1-2). A high proportion of the TRACE-RA population (86.4%) was receiving a conventional synthetic disease modifying ant-rheumatic drug (csDMARD) at baseline. MTX was the most common concurrent DMARD in TRACE-RA. Around three-quarters of patients (73.6%) were receiving MTX at baseline. Only 18.2% of the study population was receiving a biological disease modifying anti-rheumatic drug (bDMARD) at baseline. A small proportion of patients (13.6%) were receiving csDMARD and bDMARD therapy at baseline (see table 4.7).

Table 4. 7 Baseline concurrent medications of each arm of TRACE-RA

Baseline characteristic	N=Number of patients with complete data (% of 2986)	All patients	N=Number of atorvastatin patients with complete data (% of 1492)	Atorvastatin arm	N=Number of placebo patients with complete data (% of 1494)	Placebo arm
Median number of concurrent drugs (IQR)	2909 (97.3%)	6 (4-8)	1455 (97.5%)	6 (4-8)	1454 (97.3%)	6 (4-8)
Median number of concurrent DMARDs (IQR)	2622 (87.8%)	1 (1-2)	1315 (88.1%)	1 (1-2)	1307 (87.5%)	1 (1-2)
DMARD therapy (n, %)*	2909 (97.3%)	2643 (90.9%)	1455 (97.5%)	1326 (91.1%)	1454 (97.3%)	1317 (90.6%)
csDMARDS (n, %)*	2909 (97.3%)	2512 (86.4%)	1455 (97.5%)	1266 (87.0%)	1454 (97.3%)	1246 (85.7%)
Methotrexate		2140 (73.6%)		1082 (74.4%)		1058 (72.8%)
Hydroxychloroquine		77 (2.7%)		43 (1.5%)		34 (1.2%)
Chloroquine		11 (0.4%)		3 (0.2%)		8 (0.5%)
Sulfasalazine		572 (19.7%)		304 (20.9%)		268 (18.4%)
Penicillamine		14 (0.1%)		10 (0.7%)		4 (0.3%)
Other		251 (8.6%)		115 (7.9%)		136 (9.4%)
bDMARDs (n, %)*	2909 (97.3%)	528 (18.2%)	1455 (97.5%)	260 (17.9%)	1454 (97.3%)	268(18.4%)
Rituximab		68 (2.3%)		31 (2.1%)		37 (2.5%)
Tociluzimab		0 (0.0%)		0 (0.0%)		0 (0.0%)
Adalimumab		108 (3.7%)		57 (3.9%)		51 (3.5%)
Etanercept		288 (9.9%)		138 (9.5%)		150 (10.3%)
Certolizmab pegol		3 (0.0%)		2 (0.0%)		1 (0.0%)
Other		61 (2.1%)		32 (2.2%)		29 (2.0%)
csDMARD and bDMARD therapy (n, %)*	2909 (97.3%)	397 (13.6%)	1455 (97.5%)	200 (13.7%)	1454 (97.3%)	197 (13.5%)

N= Number of patients, DMARD= Disease modifying antirheumatic drug, csDMARD= conventional synthetic disease modifying antirheumatic drug, bDMARD= Biological disease modifying antirheumatic drug. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Items marked with an * were recorded in TRACE-RA case report forms (CRFs). DMARDs are categorised according to the final CRF version (v3).

4.4.2 Baseline characteristics by gender

Baseline characteristics of patients were compared by gender. Seven hundred and seventy two male and 2214 female patients were recruited into TRACE-RA. Females were younger (median 60.8 years, IQR 54.9-66.2 years) than males (median 61.8 years, IQR 55.8-67.3 years, p=0.011) and also had longer disease durations (12 years, IQR 5-20 years) than males (10 years, IQR 4-17 years, p<0.001). Moreover, females had more years since the onset of RA disease symptoms (13 years, IQR 7-22) years compared with males (11 years, IQR 5-19 years, P<0.001). A higher proportion of females (29.3%) were categorised as obese (BMI of $\geq$30 kg/m^2) than male patients (25.1%, p<0.001). However, a greater proportion of men than women were either overweight or obese (BMI of $\geq$25 kg/m^2) (72.0% vs 65.8%) (see table 4.8).

Table 4. 8 Baseline characteristics of male and female patients of TRACE-RA

Baseline characteristic	N=Number of male patients with complete data (% of 772)	Male	N=Number of female patients with complete data (% of 2214)	Female	P value
Median age, years (IQR)*	770 (99.7%)	61.8 (55.8-67.3)	2195 (99.1%)	60.8 (54.9-66.2)	0.011[b]
Ethnicity (n, %) †	727 (94.2%)		2109 (95.3%)		
White		718 (98.8%)		2068 (98.1%)	0.374[a]
Asian/ Mixed Asian		6 (0.8%)		19 (0.9%)	
Black/ Mixed Black		1 (0.1%)		14 (0.7%)	
Chinese/ Mixed Chinese		1 (0.1%)		1 (0.0%)	
Other ethnicity		1 (0.1%)		7 (0.3%)	
Median no of years of disease duration (IQR)*	771 (99.9%)	10 (4-17)	2207 (99.7%)	12 (5-20)	<0.001[b]
Median no of years since onset of symptoms (IQR)*	750 (97.2%)	11 (5-19)	2171 (98.1%)	13 (7-22)	<0.001[b]
Median BMI, kg/m^2 (IQR)	753 (97.5%)	26.8 (24.5-29.7)	2116 (95.6%)	26.6 (23.7-30.4)	0.220[a]
BMI (n, %)					<0.001[b]
Underweight, <18.5		3 (0.4%)		32 (1.5%)	
Normal weight, 18.5-24.99		169 (22.4%)		632 (29.9%)	
Overweight, 25-29.99		353 (46.9%)		772 (36.5%)	
Obese, $\geq$30		189 (25.1%)		619 (29.3%)	
Median waist, cm (IQR)*	643 (83.3%)	97 (90-104)	1883 (85.0%)	88 (80-98)	<0.001[b]

N= Number of patients, IQR= Interquartile range, BMI= Body mass index, kg/m^2= Kilograms per square meter, cm= Centimetre. Pearson's χ^2 was used to compare the proportion of patients for each group. These items are marked with [a]. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Mann Whitney rank-sum tests were used to determine differences between means and are marked with [b]. Items marked with an * were recorded using in TRACE-RA CRFs. Items marked with a † were recorded in TRACE-RA lifestyle questionnaires.

4.4.2.1 Baseline lifestyle characteristics by gender

Differences between genders were observed for lifestyle characteristics. Female patients were less likely to be current smokers at baseline than male patients (14.4% vs 22.5% respectively, $p<0.001$). There were also a smaller proportion of female former smokers (41.4%) than male former smokers (50.1%). A greater proportion of females than males exercised four or more times per week (17.1% vs 26.5% respectively, $p<0.001$). Further, female patients (20.5% consumed alcohol 2-3 times per week, 9.3% consumed alcohol four or more times per week) consumed alcohol less frequently during the week than male patients(28.2% consumed alcohol 2-3 times per week, 14.7% consumed alcohol four or more times per week, $p<0.001$). Almost half of female patients (48.4%) were retired at baseline. This is noticeably greater than the proportion of male patients in retirement at baseline (38.5%). A lower proportion of female than male patients were in full time employment (18.8% vs 32.9% respectively, $p<0.001$). Both females and males had a median age of 16 years at the time of leaving full time education; however the distribution of these ages differed. At the 75th percentile, females left education at 17 years whereas male patients left education at 16 years (see table 4.9).

Table 4. 9 Baseline lifestyle characteristics of male and female patients of TRACE-RA

Baseline characteristic	N=Number of male patients with complete data (% of 772)	Male	N=Number of female patients with complete data (% of 2214)	Female	P value
Smoking (n, %) †	721 (93.4%)		2117 (95.6%)		
Never		198 (27.5%)		936 (44.2%)	<0.001[a]
Former		361 (50.1%)		876 (41.4%)	
Current		162 (22.5%)		305 (14.4%)	
Exercise (n, %) †	725 (93.9%)		2106 (95.1%)		
Never		191 (26.3%)		611 (29.0%)	<0.001[a]
Monthly or less		66 (9.1%)		274 (13.0%)	
2-4 times per month		103 (14.2%)		347 (16.5%)	
2-3 times per week		173 (23.9%)		513 (24.4%)	
≥4 times per week		192 (26.5%)		361 (17.1%)	
Frequency of alcohol consumption (n, %) †	727 (94.2%)		2119 (95.7%)		
Never		99 (13.6%)		439 (20.7%)	<0.001[a]
Monthly or less		156 (21.5%)		604 (28.5%)	
2-4 times per month		160 (22.0%)		443 (20.9%)	
2-3 times per week		205 (28.2%)		435 (20.5%)	
≥4 times per week		107 (14.7%)		198 (9.3%)	
Occupation (n, %) †	724 (93.8%)		2109 (95.3%)		
Full-time employed		238 (32.9%)		396 (18.8%)	<0.001[a]
Part-time employed		37 (5.1%)		320 (15.2%)	
Unemployed		111 (15.3%)		286 (13.6%)	
Student		23 (3.2%)		41 (1.9%)	
Semi-retired		36 (5.0%)		46 (2.2%)	
Retired		279 (38.5%)		1020 (48.4%)	
Median age leaving full-time education, years (IQR)	733 (94.9%)	16 (15-16)	2130 (96.2%)	16 (15-17)	<0.001[b]

N= Number of patients. Pearson's χ^2 was used to compare the proportion of patients for each group. These items are marked with [a]. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Mann Whitney rank-sum tests were used to determine differences between means and are marked with [b].

4.4.2.2 Baseline RA disease characteristics by gender

Differences were also observed between genders for RA disease characteristics. Overall, as well as having a longer disease duration than male patients, female patients had more severe disease. Female patients had a higher DAS28 score (3.7, IQR 2.7-4.8) compared with male patients (3.1, IQR 2.1-4.1, p<0.001). Furthermore, a lesser proportion of female patients (21.9%) were in remission (DAS28 <2.6) than male patients (38.5%). Moreover, more female than male patients (18.8% vs 10.2% respectively) had a high disease activity (DAS28 >5.1) at baseline. In keeping with this, women had a greater number of median tender and swollen joints (4 tender joints,

IQR 1-9, 3 swollen joints, IQR 0-6) than men (2 tender joints, IQR 0-6, 2 swollen joints, IQR 0-6).

Self-reported physical disability was higher in women than men. HAQ-SDI and HAQ-ADI scores were higher in females than males (HAQ-SDI= 1.4, IQR 0.6-1.9 vs 0.8, IQR 0.1-1.5 respectively, $p<0.001$) (HAQ-ADI= 1.0, IQR 0.4-1.6 vs 0.6, IQR 0-1.3 respectively, $p<0.001$). Female patients reported longer durations of early morning stiffness (median 30 minutes, IQR 10-60 minutes vs median 15 minutes, IQR 1.5-60 minutes respectively, $p<0.001$) and higher patient wellness (median 32, IQR 16-5) scores than males (median 25, IQR 10-50, $p<0.0013$, $p<0.001$). Of those tested for ACPA positivity, 192 females (76.2%) and 66 males (76.7%) were ACPA positive. The median CRP level was 5 mg/L (IQR 3-11 mg/L) for each gender. The median ESR value for female patients was 18mm/hr (IQR 9-30mm/hr). For male patients, the median ESR value was lower (11mm/hr, IQR 5-23mm/hr). This difference was statistically significant ($p<0.001$) (see table 4.10).

Table 4. 10 Baseline RA characteristics of male and female patients of TRACE-RA

Baseline characteristic	N=Number of male patients with complete data (% of 772)	Male	N=Number of female patients with complete data (% of 2214)	Female	P value
Median DAS28 (IQR)*	754 (97.7%)	3.1 (2.1-4.1)	2172 (98.1%)	3.7 (2.7-4.8)	<0.001 [b]
DAS28 (n, %)*					
Remission, <2.6		290 (38.5%)		475 (21.9%)	<0.001 [a]
Low activity, 2.61-3.19		105 (13.9%)		311 (14.3%)	
Moderate activity, 3.2-5.1		282 (46.9%)		977 (45.0%)	
High activity, >5.1		77 (10.2%)		409 (18.8%)	
Median tender joint count (IQR)*	766 (99.2%)	2 (0-6)	2166 (97.8%)	4 (1-9)	<0.001 [b]
Median swollen joint count (IQR)*	766 (99.2%)	2 (0-4)	2165 (97.8%)	3 (0-6)	<0.001 [b]
Median total HAQ-SDI score (IQR) §	759 (98.3%)	0.8 (0.1-1.5)	2180 (98.5%)	1.4 (0.6-1.9)	<0.001 [b]
Median total HAQ-ADI score (IQR)§	759 (98.3%)	0.6 (0-1.3)	2180 (98.5%)	1 (0.4-1.6)	<0.001 [b]
Median EQ-5D VAS (IQR)§	746 (96.6%)	75 (56-88)	2158 (97.5%)	70 (50-82)	<0.001 [b]
Median early morning stiffness (IQR)	644 (83.4%)	15 (1.5-60)	1885 (85.1%)	30 (10-60)	<0.001 [b]
Median wellness score (IQR)*	762 (98.7%)	25 (10-50)	2193 (99.1%)	32 (16-53)	<0.001 [b]
Blood tests					
Rh factor positive (n, %)*	614 (79.5%)	390 (63.5%)	1791 (80.9%)	1049 (58.6%)	0.031 [a]
ACPA positive (n, %)*	86 (11.1%)	66 (76.7%)	252 (11.4%)	192 (76.2%)	0.917 [a]
Median CRP, mg/L (IQR)*	420 (54.4%)	5 (3-11)	1130 (51.0%)	5 (3-11)	0.253 [b]
Median ESR, mm/hr (IQR)*	553 (71.6%)	11 (5-23)	1616 (73.0%)	18 (9-30)	<0.001 [b]

N= Number of patients, IQR= Interquartile range, DAS28= Disease activity score 28, HAQ-SDI= Health assessment questionnaire standard disability index, HAQ-ADI= Health assessment questionnaire alternate disability index, EQ-5D VAS= EuroQol-5D Visual analogue score, Rh= Rheumatoid, ACPA= Anti-citrullinated protein antibody, CRP= C Reactive protein, ESR= Erythrocyte sedimentation rate, mg/L= Milligram per litre, mm/Hr= Millimetres per hour. Pearson's χ^2 was used to compare the proportion of patients for each group. These items are marked with [a]. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Mann Whitney rank-sum tests were used to determine differences between means and are marked with [b]. Items marked with an * were recorded in TRACE-RA CRFs. Items marked with a § were recorded in a document that included both HAQ and EQ-5D questionnaires.

4.4.2.3 Baseline CV characteristics by gender

Noticeable differences were observed between genders for lipid profiles, self-reported risk factors and blood pressure readings. Female patients had higher median levels of TC (5.5mmol/L, IQR 4.9-6.1mmol/L) and LDLs (3.2, IQR 2.7-3.8mmol/L) than males (5.1mmol/L, IQR 4.5-5.7mmol/L and 3.1mmol/L, IQR 2.6-3.6mmol/L). Female patients also had higher median HDL levels (1.6mmol/L, IQR 1.4-1.9mmol/L) compared with males (1.3mmol/L, IQR 1.1-1.63mmol/L) and lower triglyceride levels (median 1.2

mmol/L, IQR 0.9-1.7mmol/L) than male patients (median 1.4mmol/L, IQR 1.0-2.0mmol/L). Finally, women had a lower median atherogenic index (3.4, IQR 2.8-4.1) than men (3.9, IQR 3.2-4.7) (see table 4.11).

Table 4. 11 Baseline CV characteristics of male and female patients of TRACE-RA

Baseline characteristic	N=Number of male patients with complete data (% of 772)	Male	N=Number of female patients with complete data (% of 2214)	Female	P value
Lipid concentrations*					
Median non-fasting TC, mmol/L (IQR)	432 (56.0%)	5.1 (4.5-5.7)	1231 (55.6%)	5.5 (4.9-6.1)	<0.001 [b]
Median non-fasting HDL, mmol/L (IQR)	392 (50.8%)	1.3 (1.1-1.6)	1145 (51.7%)	1.6 (1.4-1.9)	<0.001 [b]
Median non-fasting LDL, mmol/L (IQR)	297 (38.5%)	3.1 (2.6-3.6)	876 (39.6%)	3.2 (2.7-3.8)	0.003 [b]
Median non-fasting TG, mmol/L (IQR)	347 (44.9%)	1.4 (1.0-2.0)	1028 (46.4%)	1.2 (0.9-1.7)	0.001 [b]
Median atherogenic index, TG/HDL (IQR)	392 (50.8%)	3.9 (3.2-4.7)	1140 (51.5%)	3.4 (2.8-4.1)	<0.001 [b]
First degree relative with premature CVD (n, %)*	750 (97.2%)	91 (12.1%)	2150 (97.1%)	455 (21.2%)	<0.001 [a]
Family history of diabetes (n, %)*	759 (98.3%)	123 (16.2%)	2171 (98.1%)	519 (23.9%)	<0.001 [a]
Hypertension (n, %)*	753 (97.5%)	152 (20.2%)	2189 (98.9%)	502 (22.9%)	0.192 [a]
Systolic blood pressure*					
Median reading 1, mmHg (IQR)	735 (95.2%)	137 (125-149)	2130 (96.2%)	134 (121-146)	<0.001 [a]
Median reading 2, mmHg (IQR)	648 (83.9%)	135 (124-147)	1897 (85.7%)	132 (120-146)	0.004 [a]
Diastolic blood pressure*					
Median reading 1, mmHg (IQR)	745 (96.5%)	82 (76-90)	2154 (97.3%)	80 (72-86)	<0.001 [a]
Median reading 2, mmHg (IQR)	676 (87.6%)	81 (76-88)	1965 (88.8%)	79 (71-85)	<0.001 [a]

N= Number of patients, IQR= Interquartile range, TC= Total cholesterol, HDL= High-density lipoprotein, LDL= Low-density lipoprotein, TG= Triglyceride, CVD= Cardiovascular disease, mmol/L= Millimole per litre, mmHg= Millimetre of mercury. Pearson's χ^2 was used to compare the proportion of patients for each group. These items are marked with [a]. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Mann Whitney rank-sum tests were used to determine differences between means and are marked with [b]. Items marked with an * were recorded in TRACE-RA CRFs.

A higher proportion of female patients (21.2%) than male patients (12.1%) reported a first degree relative with premature CVD (p<0.001). Furthermore, female patients were more likely to report a family history of diabetes than male patients (23.9% vs 16.2% respectively, p<0.001). Female patients had lower blood pressure readings than male patients. The median systolic and diastolic blood pressures for women at the first reading were 134mmHg

(IQR 121-146mmHg) and 80mmHg (IQR 72-86mmHg) respectively. For men, these were 137mmHg (IQR 125-149mmHg) and 82mmHg (IQR 76-90mmHg). At the second reading, the median systolic and diastolic blood pressures for women were 132mmHg (IQR 120-146) and 79mmHg (IQR 71-85mmHg) respectively. In men, these values were 135mmHg (IQR 124-147mmHg) and 81mmHg (IQR 76-88mmHg) (see table 4.11).

4.4.2.4 Baseline concurrent medications by gender

The median number of concurrent medications for female patients (6, IQR 4-8) was higher than in male patients (5, IQR 4-7, $p<0.001$). No differences in median concurrent DMARDs were observed between genders after removing patients who did not receive a DMARD at baseline. However women were less likely to receive sulfasalazine than men (18.7% vs 22.4%, $p=0.030$) (see table 4.12).

Table 4. 12 Baseline concurrent medications of male and female patients of TRACE-RA

Baseline characteristic	N=Number of male patients with complete data (% of 772)	Male	N=Number of female patients with complete data (% of 2214)	Female	P value
Median number of concurrent drugs (IQR)	751 (97.3%)	5 (4-7)	2158 (97.5%)	6 (4-8)	<0.001 [b]
Median number of concurrent DMARDs (IQR)	673 (87.2%)	1 (1-2)	1949 (88.0%)	1 (1-2)	0.969 [b]
DMARD therapy (n, %)*	751 (97.3%)	685 (91.2%)	2158 (97.5%)	1958 (90.7%)	0.695 [a]
csDMARDS (n, %)*	751 (97.3%)	651 (86.7%)	2158 (97.5%)	1861 (86.2%)	0.758 [a]
Methotrexate		553 (73.6%)		1587 (73.5%)	0.960 [a]
Hydroxychloroquine		21 (2.8%)		56 (2.6%)	0.767 [a]
Chloroquine		4 (0.5%)		7 (0.3%)	0.423 [a]
Sulfasalazine		168 (22.4%)		404 (18.7%)	0.030 [a]
Penicillamine		5 (0.7%)		9 (0.4%)	0.396 [a]
Other		57 (7.6%)		194 (9.0%)	0.239 [a]
bDMARDs (n, %)*	751 (97.3%)	125 (16.6%)	2158 (97.5%)	403 (18.7%)	0.214 [a]
Rituximab		13 (1.7%)		55 (2.5%)	0.202 [a]
Tociluzimab		0		0	
Adalimumab		29 (3.9%)		79 (3.7%)	0.802 [a]
Etanercept		71 (9.5%)		217 (10.1%)	0.635 [a]
Certolizmab pegol		0		3 (0.1%)	0.307 [a]
Other		12 (1.6%)		49 (2.3%)	0.268 [a]
csDMARD and bDMARD therapy (n, %)*	751 (97.3%)	91 (12.1%)	2158 (97.5%)	306 (14.2%)	0.156 [a]

N= Number of patients, DMARD= Disease modifying antirheumatic drug, csDMARD= conventional synthetic disease modifying antirheumatic drug, bDMARD= Biological disease modifying antirheumatic drug. Pearson's χ^2 was used to compare the proportion of patients for each group. These items are marked with [a]. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Mann Whitney rank-sum tests were used to determine differences between means and are marked with [b]. Items marked with an * were recorded in TRACE-RA case report forms (CRFs). DMARDs are categorised according to the final CRF version (v3).

4.4.3 Rates of adherence in TRACE-RA

Adherence was defined in two ways. The first definition was having consumed ≥80% of prescribed medication based on pill counts of returned medication. One thousand five hundred and twenty one patients had missing data for the number of tablets consumed during the first 3 months and were removed from analysis of rates of adherence. These patients had missing data for either a dispense date, return date, or the count of tablets remaining. One hundred and eleven patients were excluded due to missing data for the dispense date or return dates of tablets. A further 82 patients were excluded from the analysis of pill counts at 6 months because of missing data between 3-6 months. Finally, 178 patients were removed from

analysis for pill counts at 12 months because of missing data between 6-12 months.

Adherence by pill counts was poor in each arm throughout 3, 6 and 12 months of follow up. Around one half of patients were adherent at 3 (49.4%), 6 (49.1%) and 12 (50.1%) months. The proportion of adherent patients in the atorvastatin arm was 50.0%, 50.0% and 50.9% up to 3, 6 and 12 months of follow up respectively. In the placebo arm, adherence was lower up to 3 (48.8%), 6 (48.2%) and 12 months (49.4%). No significant differences were observed between arms for adherence at 3, 6 and 12 months (see table 4.13).

Because CRF v3 was introduced late in patient recruitment, fewer patients (N=411) completed this after 3 months of follow up than at 12 months of follow up (N=743). Adherence was defined as a self-report of taking 'most tablets'. Four hundred patients out of 411 (97.6%) who completed CRF v3 at 3 months also completed the self-reported adherence question. Three hundred and ninety seven out of 439 (90.4%) and 711 patients out of 743 (95.7%) who completed CRF v3 at 6 and 12 months respectively provided data on the self-reported adherence question. Rates of adherence were higher using the self-reported adherence definition (85.3% at 3 months, 86.9% at 6 months and 79.2% at 12 months) than when using the 'pill count' definition. The proportion of patients who self-reported taking 'Most' tablets in the atorvastatin arm was 84.7%, 87.2% and 76.3% at 3, 6 and 12 months of follow up respectively. At 3, 6 and 12 months, self-reported adherence in the placebo arm was 85.9%,, 86.6% and 82.1% respectively. There were no statistically significant differences between the two treatment arms for self-reported adherence (see table 4.14).

Table 4. 13 Proportion of adherent patients in TRACE-RA (pill counts)

	N=Number of patients with complete data (% of 2986)	Number of adherent patients in TRACE-RA study (% of N)	Number of adherent patients in the atorvastatin arm (% of patients with a pill count)	Number of adherent patients in the placebo arm (% of patients with a pill count)	P value
Pill counts					
3 months	1353 (45.3%)	668 (49.4%)	328 (50.0%)	340 (48.8%)	0.654 [a]
6 months	1271 (42.6%)	624 (49.1%)	308 (50.0%)	316 (48.2%)	0.531 [a]
12 months	1093 (36.6%)	548 (50.1%)	272 (50.9%)	276 (49.4%)	0.606 [a]

N= Number of patients with available data. Adherence was determined using pill counts. Pearson's χ^2 was used to compare the proportion of patients between the atorvastatin arm and the placebo arm. These items are marked with [a].

Table 4. 14 Proportion of adherent patients in TRACE-RA (self-report)

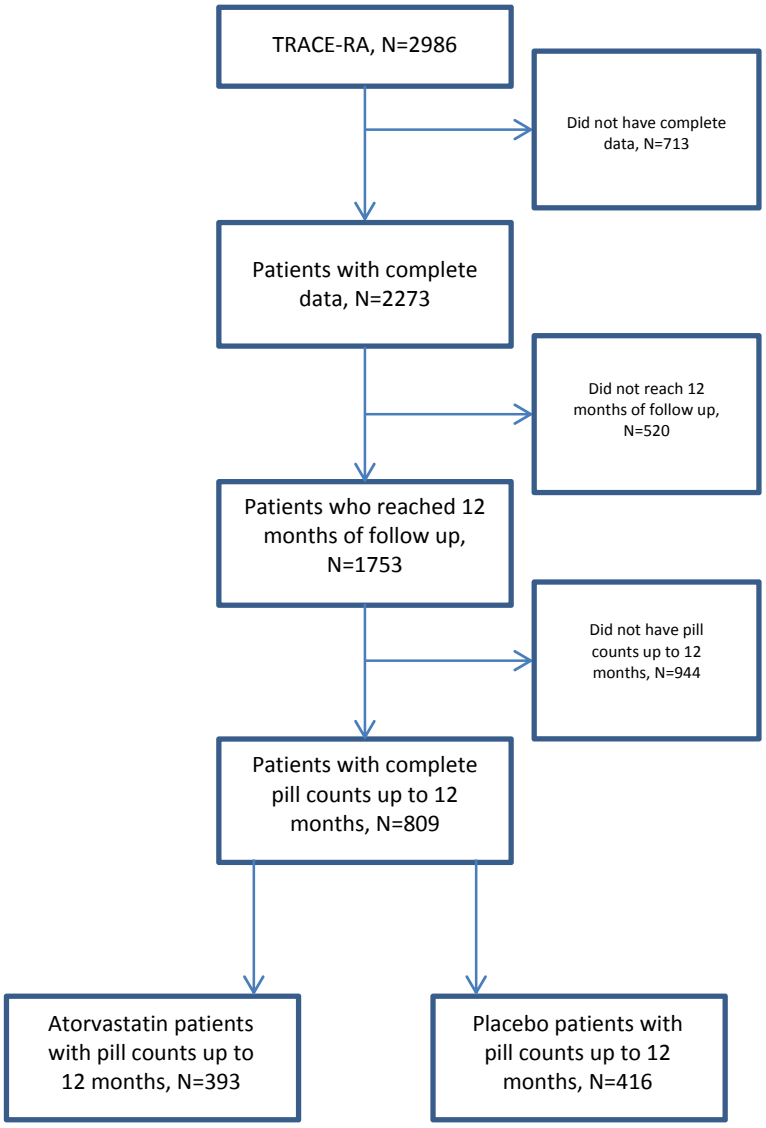
	N=Number of patients who completed CRF v3 forms	Number of patients who completed self-reported adherence question (% of N)	Number of adherent patients in the TRACE-RA study (% of patients who completed self-reported adherence question)	Number of adherent patients in the atorvastatin arm (% of patients who completed self-reported adherence question)	Number of adherent patients in the placebo arm (% of patients who completed self-reported adherence question)	P value
Self-reported adherence						
3 months	411	400 (97.6%)	341 (85.3%)	171 (84.7%)	170 (85.9%)	0.734 [a]
6 months	439	397 (90.4%)	345 (86.9%)	184 (87.2%)	161 (86.6%)	0.849 [a]
12 months	743	711 (95.7%)	563 (79.2%)	270 (76.3%)	293 (82.1%)	0.057 [a]

N= Number of patients who self-reported adherence. Pearson's χ^2 was used to compare the proportion of patients between the atorvastatin arm and the placebo arm. These items are marked with [a].

4.4.3.1 Baseline characteristics of TRACE-RA patients with complete data

Patients were considered to have complete data when they did not have missing data for any of the selected characteristics (see section 4.3.3). Complete data were available for 2273 patients. Of these patients with complete data, 1753 reached 12 months of follow up and of these patients, 809 had complete pill counts up to 12 months. Three hundred and ninety three of the 809 patients were receiving atorvastatin and 416 were receiving the placebo (see figure 4.1).

Figure 4. 1 A flow diagram of patients with complete data



N= Number of patients. A flow diagram of patients with complete data in TRACE-RA.

Patients with complete pill counts up to 12 months were generally representative of the whole TRACE-RA population. The 809 patients who had complete data for all selected characteristics were largely female (75.2%) and had a median age of 61.1 years (IQR 55.5-66.5 years). The majority (99.6%) of these patients were white. The remaining 0.4% were Asian/ Mixed Asian. No patients from a Black, Chinese or Other ethnicity had complete pill counts up to 12 months (see table 4.15).

Table 4. 15 Baseline sociodemographic and lifestyle characteristics of patients of TRACE-RA with complete data

Baseline characteristic	**TRACE-RA, n=2237**	**TRACE-RA patients who reached 12 months follow up, n=1753**	**TRACE-RA patients with pill counts up to 12 months, n=809**	**Atorvastatin patients with pill counts up to 12 months, n=393**
Median age, years (IQR)*	60.8 (55.5-66.2)	60.6 (55.0-65.9)	61.1 (55.5-66.5)	60.5 (55.4-66.4)
Gender (n, %)*				
Men	569 (25.4%)	446 (25.4%)	201 (24.9%)	86 (21.9%)
Women	1668 (74.6%)	1307 (75.6%)	608 (75.2%)	307 (78.1%)
Ethnicity (n, %) †				
White	2200 (98.4%)	1725 (98.4%)	806 (99.6%)	393 (100%)
Asian/ Mixed Asian	19 (0.9%)	16 (0.9%)	3 (0.4%)	0
Black/ Mixed Black	9 (0.4%)	6 (0.3%)	0	0
Chinese/ Mixed Chinese	2 (0.1%)	1 (0.1%)	0	0
Other ethnicity	7 (0.3%)	5 (0.3%)	0	0
Lifestyle				
Smoking (n, %) †				
Never	906 (40.5%)	725 (41.4%)	338 (41.8%)	151 (38.4%)
Former	975 (43.6%)	762 (43.5%)	365 (45.1%)	179 (45.6%)
Current	356 (15.9%)	266 (15.2%)	106 (13.1%)	63 (16.0%)
Exercise (n, %) †				
Never	601 (26.9%)	466 (26.6%)	226 (27.9%)	109 (27.7%)
Monthly or less	273 (12.2%)	226 (12.9%)	103 (12.7%)	53 (13.5%)
2-4 times per month	358 (16.0%)	282 (16.1%)	119 (14.7%)	61 (15.5%)
2-3 times per week	574 (25.7%)	442 (25.2%)	217 (26.8%)	99 (25.2%)
>4 times per week	431 (19.3%)	337 (19.2%)	144 (17.8%)	71 (18.1%)
Frequency of alcohol consumption (n, %) †				
Never	420 (18.8%)	322 (18.4%)	145 (17.9%)	68 (17.3%)
Monthly or less	592 (26.5%)	455 (26.0%)	206 (25.5%)	104 (26.5%)
2-4 times per month	477 (21.3%)	385 (22.0%)	180 (22.3%)	92 (23.4%)
2-3 times per week	497 (22.2%)	390 (22.3%)	180 (22.3%)	82 (20.9%)
>4 times per week	251 (11.2%)	201 (11.5%)	98 (12.1%)	47 (12.0%)
Occupation (n, %) †				
Full-time employed	530 (23.7%)	421 (24.0%)	164 (20.3%)	80 (20.4%)
Part-time employed	291 (13.0%)	232 (13.2%)	112 (13.8%)	52 (13.2%)
Unemployed	300 (13.0%)	245 (14.0%)	107 (13.2%)	61 (15.5%)
Student	45 (2.0%)	35 (2.0%)	14 (1.7%)	8 (2.0%)
Semi-retired	68 (3.0%)	50 (2.9%)	15 (1.9%)	6 (1.5%)
Retired	1003 (44.8%)	770 (43.9%)	397 (49.1%)	186 (47.3%)
Median age leaving full-time education (IQR) †	16 (15-17)	16 (15-17)	16 (15-17)	16 (15-17)

N= Number of patients, IQR= Interquartile range. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Items marked with a † were recorded in TRACE-RA lifestyle questionnaires.

No important differences were observed between groups for smoking status, exercise or frequency of alcohol consumption. A large proportion of TRACE-RA patients were in retirement at baseline. For patients who reached 12 months of follow up, the proportion of those in retirement was 43.9%. After excluding patients who did not have complete pill counts up to 12 months, almost half were retired (49.1%). Only 164 patients (20.3%) with complete pill counts up to 12 months were employed on a full-time basis at baseline. Including all other patients who reached 12 months of follow up, the proportion of those in full-time employment was 24.0% (see table 4.15).

The median DAS28 score for all patients with complete data was 3.6 (IQR 2.5-4.6). Around one quarter (26.8%) of TRACE-RA patients were categorised as being in remission (DAS28 <2.6) and 16.3% had a high disease activity (DAS28 >5.1). After excluding patients who did not have pill counts up to 12 months, 24.1% were in remission and 17.2% had a high disease activity. The median DAS28 score for these patients was 3.7 (IQR 2.7-4.7). Ninety patients (22.9%) in the atorvastatin arm were in remission and 18.1% had a high disease activity at baseline. The median DAS28 score for the patients with complete pill counts in the atorvastatin arm was 3.8 (2.7-4.8) (see table 4.16).

Table 4. 16 Baseline clinical characteristics of patients of TRACE-RA with complete data

Baseline characteristic	TRACE-RA, n=2237	TRACE-RA patients who reached 12 months follow up, n=1753	TRACE-RA patients with pill counts up to 12 months, n=809	Atorvastatin patients with pill counts up to 12 months, n=393
Clinical				
Median DAS28 (IQR)*	3.6 (2.5-4.6)	3.6 (2.6-4.6)	3.7 (2.7-4.7)	3.8 (2.7-4.8)
DAS28 (n, %)*				
Remission, <2.6	599 (26.8%)	454 (25.9%)	195 (24.1%)	90 (22.9%)
Low activity, 2.61-3.19	323 (14.4%)	259 (14.8%)	108 (13.4%)	43 (10.9%)
Moderate activity, 3.2-5.1	961 (43.0%)	755 (43.1%)	367 (45.4%)	189 (48.1%)
High activity, >5.1	354 (15.8%)	285 (16.3%)	139 (17.2%)	71 (18.1%)
Median HAQ score (IQR) §	1.1 (0.4-1.9)	1.1 (0.4-1.9)	1.3 (0.5-1.8)	1.3 (0.5-1.8)
First degree relative with premature CVD (n, %)*	422 (18.9%)	365 (20.8%)	160 (19.8%)	76 (19.3%)
Family history of diabetes (n, %)*	494 (22.1%)	427 (24.4%)	195 (24.1%)	94 (23.9%)
Hypertension (n, %)*	500 (22.4%)	403 (23.0%)	192 (23.7%)	102 (26.0%)
Median number of concurrent DMARDs (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)
Median number of concurrent drugs (IQR)	5 (3-7)	6 (4-8)	6 (4-8)	6 (4-8)

N= Number of patients, IQR= Interquartile range, DAS28= Disease activity score 28, HAQ= Health assessment questionnaire, CVD= Cardiovascular disease, DMARD= Disease modifying antirheumatic drug. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Items marked with an * were recorded in TRACE-RA CRFs. Items marked with a § were recorded in a document that included both HAQ and EQ-5D questionnaires.

Five hundred (22.4%) of the TRACE-RA population with complete data had known hypertension at baseline. After excluding patients who did not have pill counts up to 12 months of follow up, the proportion of patients with known hypertension was 23.7%. The proportion of patients was 26.0% in the atorvastatin arm (see table 4.16). The median number of concurrent drugs that patients who reached 12 months of follow up were receiving at baseline was 6 (IQR 4-8) (see table 4.16).

Responses to the EQ-5D questionnaire were also described. Over half (53.8%) of TRACE-RA patients who reached 12 months of follow up reported 'some problems' with usual activities at baseline in the EQ-5D questionnaire (see table 4.17).

Table 4. 17 Baseline EQ-5D responses of patients of TRACE-RA with complete data

Baseline characteristic	TRACE-RA, n=2237	TRACE-RA patients who reached 12 months follow up, n=1753	TRACE-RA patients with pill counts up to 12 months, n=809	Atorvastatin patients with pill counts up to 12 months, n=393
EQ-5D				
Mobility (n, %) §				
No problems	850 (38.0%)	667 (38.1%)	297 (36.7%)	135 (34.4%)
Some problems	1273 (56.9%)	1002 (57.2%)	476 (58.8%)	237 (60.3%)
Confined to bed	114 (5.1%)	84 (4.8%)	36 (4.5%)	21 (5.3%)
Self-care (n, %) §				
No problems	1288 (57.6%)	1004 (57.3%)	464 (57.4%)	215 (54.7%)
Some problems	887 (39.7%)	703 (40.1%)	327 (40.4%)	170 (43.3%)
Unable to wash or dress	62 (2.8%)	46 (2.6%)	18 (2.2%)	8 (2.0%)
Usual activities (n, %) §				
No problems	859 (38.4%)	673 (38.4%)	299 (37.0%)	132 (33.6%)
Some problems	1203 (53.8%)	955 (54.5%)	458 (56.6%)	234 (59.5%)
Unable to perform usual activities	175 (7.8%)	125 (7.1%)	52 (6.4%)	27 (6.9%)
Pain/Discomfort (n, %) §				
No pain/discomfort	313 (14.0%)	241 (13.8%)	106 (13.1%)	39 (10.0%)
Some pain/discomfort	1638 (73.2%)	1289 (73.5%)	604 (74.7%)	310 (78.9%)
Extreme pain/discomfort	286 (12.8%)	223 (12.7%)	99 (12.2%)	44 (11.2%)
Anxiety/Depression (n, %) §				
Not anxious/depressed	1551 (69.3%)	1222 (69.7%)	568 (70.2%)	273 (69.5%)
Moderately anxious/depressed	636 (28.4%)	493 (28.1%)	228 (28.2%)	116 (29.5%)
Extremely anxious/depressed	50 (2.2%)	38 (2.2%)	13 (1.6%)	4 (1.0%)
Current health state compared with previous 12 months (n, %) §				
Better	676 (30.2%)	536 (30.6%)	244 (30.2%)	121 (30.8%)
Much the same	1251 (55.9%)	968 (55.2%)	459 (56.7%)	219 (55.7%)
Worse	308 (13.8%)	249 (14.2%)	105 (13.0%)	52 (13.2%)
Median EQ-5D VAS (IQR)	70 (54-85)	72 (54-85)	74 (58-84)	70 (52-82)

N= Number of patients, IQR= Interquartile range, EQ-5D= Euroqol-5D, VAS= Visual Analogue Scale. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Items marked with a § were recorded in a document that included both HAQ and EQ-5D questionnaires.

After excluding those who did not have pill counts up to 12 months, this increased to 56.6%. The proportion of patients who reported 'some problems' with usual activities was 59.9% in the atorvastatin arm. A large proportion (74.7%) of patients with pill counts up to 12 months also had 'some pain or discomfort'. Fitting this, a smaller proportion (12.2%) reported 'extreme pain or discomfort' in the EQ-5D questionnaire (see table 4.17).

4.4.4 Univariate analysis of sociodemographic and lifestyle characteristics as predictors of adherence to the allocated treatment in TRACE-RA

No significant sociodemographic predictors of adherence to either statin or placebo in the TRACE-RA population were identified. Neither age nor ethnicity were significant predictors of adherence. Women were better adherers than men (OR=1.19, 95%CI 0.87-1.64) however this was not statistically significant (p=0.275) (see table 4.18).

Former smokers were less likely to adhere to the TRACE-RA intervention than 'never smokers' (OR=0.78, 95%CI 0.58-1.04, p=0.094). Current smokers also had poorer odds of adherence than 'never smokers' (OR=0.71, 95%CI 0.46-1.09), however this did not reach statistical significance (p=0.104). Patients who consumed alcohol on a 'monthly or less' basis were poorer adherers than patients who never consumed alcohol (OR=0.64, 95%CI 0.42-0.97). This reached statistical significance (p=0.037). Patients who consumed alcohol 2-4 times per month (OR=0.78, 95%CI 0.51-1.20, p=0.260) and patients who consumed alcohol 2-3 times per week (OR=0.80, 95%CI 0.52-1.24, p=0.324) were also less adherent than those who did not consume alcohol. Part-time employed and retired patients were more likely to adhere to their allocated treatment than full-time employed patients (OR=1.47, 95%CI 0.90-2.39, p=0.117, OR=1.33, 95%CI 0.92-1.91, p=0.123, respectively) (see table 4.18).

Table 4. 18 Univariate analysis of sociodemographic and lifestyle characteristics and allocated treatment adherence in TRACE-RA

Baseline characteristic	Patients who had a pill count at 12 months of follow up, n=809(% of n)	Odds ratio (95% Confidence interval)	P value
Age, years	61.1 (55.5-66.5)	1.00 (0.98-1.01)	0.732
Gender			
Men	201 (24.9%)	(ref)	
Women	608 (75.2%)	1.19 (0.87-1.64)	0.275
Ethnicity †			
White	806 (99.6%)	(ref)	
Asian/Asian mixed	3 (0.4%)	0.91 (0.13-6.49)	0.925
Black/Black mixed	0		
Chinese/Chinese mixed	0		
Other	0		
Lifestyle			
Smoking status †			
Never	338 (41.8%)	(ref)	
Former	365 (45.1%)	0.78 (0.58-1.04)	0.094
Current	106 (13.1%)	0.71 (0.46-1.09)	0.121
Exercise †			
Never	226 (27.9%)	(ref)	
Monthly or less	103 (12.7%)	0.90 (0.57-1.42)	0.653
2-4 times per month	119 (14.7%)	1.20 (0.77-186)	0.418
2-3 times a week	217 (26.8%)	1.09 (0.76-1.57)	0.642
4+ times a week	144 (17.8%)	0.95 (0.63-1.42)	0.797
Alcohol consumption †			
Never	145 (17.9%)	(ref)	
Monthly or less	206 (25.5%)	0.64 (0.42-0.97)	0.037
2-4 times per month	180 (22.3%)	0.78 (0.51-1.20)	0.260
2-3 times a week	180 (22.3%)	0.80 (0.52-1.24)	0.324
4+ times a week	98 (12.1%)	0.97 (0.58-1.63)	0.919
Occupation †			
Full-time employed	164 (20.3%)	(ref)	
Part-time employed	112 (13.8%)	1.47 (0.90-2.39)	0.117
Unemployed	107 (13.2%)	1.40 (0.86-2.29)	0.173
Student	14 (1.7%)	1.58 (0.52-4.76)	0.415
Semi-retired	15 (1.9%)	1.36 (0.47-3.91)	0.573
Retired	397 (49.1%)	1.33 (0.92-1.91)	0.123
Age leaving full-time education, years	16 (15-17)	1.01 (0.97-1.05)	0.726

N= Number of patients, IQR= Interquartile range, (ref)= Reference group. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Items marked with a † were recorded in TRACE-RA lifestyle questionnaires. Odds ratios were calculated using independent univariate logistic regression models.

4.4.4.1 Univariate analysis of clinical characteristics as predictors of adherence to the allocated treatment in TRACE-RA

No clinical baseline characteristics significantly predicted adherence in the univariate analysis. Patients with a high DAS28 score (DAS28 >5.1) were poorer adherers to the TRACE-RA intervention than patients in remission (DAS28 <2.6) (OR=1.33, 95%CI 0.87-2.05, p=0.192). For each additional

concurrent DMARD, patients were 16% less likely to adhere to their allocated treatment (OR=0.84, 95%CI 0.68-1.06, p=0.147)(see table 4.19).

Table 4. 19 Univariate analysis of clinical characteristics and allocated treatment adherence in TRACE-RA

Baseline characteristic	Patients who had a pill count at 12 months of follow up, n=809(% of n)	Odds ratio (95% Confidence interval)	P value
Clinical			
DAS28 *	3.7 (2.7-4.7)	1.05 (0.96-1.15)	0.268
DAS28 Category*			
Remission, <2.6	195 (24.1%)	(ref)	
Low activity, 2.61-3.19	108 (13.4%)	1.11 (0.70-1.76)	0.660
Moderate activity, 3.2-5.1	367 (45.4%)	1.02 (0.72-1.44)	0.900
High activity, >5.1	139 (17.2%)	1.33 (0.87-2.05)	0.192
HAQ score §	1.3 (0.5-1.8)	1.12 (0.94-1.33)	0.196
First degree relative with premature CVD *	160 (19.8%)	0.79 (0.90-1.78)	0.184
Family history of diabetes *	195 (24.1%)	1.11 (0.80-1.52)	0.538
Known hypertension *	192 (23.7%)	1.09 (0.83-1.43)	0.537
Number of concurrent DMARDs	1 (1-2)	0.84 (0.68-1.06)	0.147
Number of concurrent drugs	6 (4-8)	1.01 (0.77-1.44)	0.777

N= Number of patients, IQR= Interquartile range, DAS28= Disease activity score 28, HAQ= Health assessment questionnaire, CVD= Cardiovascular disease, DMARD= Disease modifying antirheumatic drug, (ref)= Reference group. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Items marked with an * were recorded in TRACE-RA CRFs. Items marked with a § were recorded in a document that included both HAQ and EQ-5D questionnaires. Odds ratios were calculated using independent univariate logistic regression models.

4.4.4.2 Univariate analysis of EQ-5D responses as predictors of adherence to the allocated treatment in TRACE-RA

There were no significant responses to the baseline EQ-5D questionnaires which predicted adherence to the treatment allocated to patients at baseline. Patients who self-reported 'some problems' with self-care were more likely to adhere to the TRACE-RA intervention than those who reported 'no problems' (OR=1.22, 95%CI 0.92-1.62, p=0.173). 'Extreme pain or discomfort' was also associated with better adherence to the TRACE-RA intervention. Patients who reported 'extreme pain or discomfort' were 61% (OR=1.61, 95%CI 0.93-2.76) more likely to adhere than those who reported no pain or

discomfort, however this was not a significant association (p=0.087). Finally, patients who reported moderate or depression were poorer adherers than those who reported no anxiety or depression at baseline (OR=0.78, 95%CI 0.57-1.06). This did not reach significance (p=0.117) (see table 4.20).

Table 4. 20 Univariate analysis of EQ-5D responses and allocated treatment adherence in TRACE-RA

Baseline characteristic	Patients who had a pill count at 12 months of follow up, n=809(% of n)	Odds ratio (95% Confidence interval)	P value
EQ-5D			
Mobility §			
No problems	297 (36.7%)	(ref)	
Some problems	476 (58.8%)	1.16 (0.86-1.54)	0.328
Confined to bed	36 (4.5%)	0.79 (0.40-1.59)	0.517
Self-care §			
No problems	464 (57.4%)	(ref)	
Some problems	327 (40.4%)	1.22 (0.92-1.62)	0.173
Unable to wash or dress	18 (2.2%)	0.49 (0.18-1.33)	0.162
Usual activities §			
No problems	299 (37.0%)	(ref)	
Some problems	458 (56.6%)	1.10 (0.82-1.48)	0.511
Unable to perform usual activities	52 (6.4%)	0.90 (0.50-1.61	0.713
Pain/Discomfort §			
No pain/discomfort	106 (13.1%)	(ref)	
Some pain/discomfort	604 (74.7%)	1.10 (0.73-1.66)	0.649
Extreme pain/discomfort	99 (12.2%)	1.61 (0.93-2.76)	0.087
Anxiety/Depression §			
Not anxious/depressed	568 (70.2%)	(ref)	
Moderately anxious/depressed	228 (28.2%)	0.78 (0.57-1.06)	0.117
Extremely anxious/depressed	13 (1.6%)	1.95 (0.59-6.42)	0.270
Current health state compared with previous 12 months §			
Better	244 (30.2%)	(ref)	
Much the same	459 (56.7%)	1.17 (0.86-1.60)	0.318
Worse	105 (13.0%)	1.34 (0.85-2.13)	0.204
EQ-5D VAS	74 (58-84)	1.00 (0.99-1.00)	0.438

N= Number of patients, IQR= Interquartile range, (ref)= Reference group. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Items marked with a § were recorded in a document that included both HAQ and EQ-5D questionnaires. Odds ratios were calculated using independent univariate logistic regression models.

4.4.5 Univariate analysis of sociodemographic and lifestyle characteristics as predictors of adherence in the atorvastatin arm

No baseline sociodemographic or lifestyle characteristics were predictors of atorvastatin adherence in the TRACE-RA population. Former smokers were

more likely to adhere than those who had never smoked (OR=1.08, 95%CI 0.70-1.67). Current smokers were 15% less likely to adhere to atorvastatin therapy (OR=0.85, 95%CI 0.47-1.53). Neither of these characteristics was statistically significant (p=0.720 and p= 0.591 respectively). Patients who exercised 2-3 times per week or 4 times per week had better odds for adherence to atorvastatin than those who never exercised (OR=1.28, 95%CI 0.74-2.21, p=0.378 and OR=1.27, 95%CI 0.69-2.23, p=0.432). Patients who were employed part-time were 36% (95%CI 0.67-2.76) more likely to adhere to statin therapy than patients who were in full-time employment (p=0.387). Finally, patients had poorer odds for adherence to statin therapy (OR=0.97, 95%CI 0.90-1.04) for each additional year of leaving full-time education (p=0.330) (see table 4.21).

Table 4. 21 Univariate analysis of sociodemographic and lifestyle characteristics and atorvastatin adherence in TRACE-RA

Baseline characteristic	Atorvastatin patients who had a pill count at 12 months of follow up, n=393(% of n)	Odds ratio (95% Confidence interval)	P value
Age, years	60.5 (55.4-66.4)	0.99 (0.97-1.02)	0.536
Gender			
Men	86 (21.9%)	(ref)	
Women	307 (78.1%)	0.98 (0.60-1.58)	0.930
Ethnicity †			
White	393 (100%)	(ref)	
Asian/Asian mixed	0		
Black/Black mixed	0		
Chinese/Chinese mixed	0		
Other	0		
Lifestyle			
Smoking status †			
Never	151 (38.4%)	(ref)	
Former	179 (45.6%)	1.08 (0.70-1.67)	0.720
Current	63 (16.0%)	0.85 (0.47-1.53)	0.591
Exercise †			
Never	109 (27.7%)	(ref)	
Monthly or less	53 (13.5%)	0.75 (0.39-1.45)	0.399
2-4 times per month	61 (15.5%)	0.95 (0.50-1.78)	0.873
2-3 times a week	99 (25.2%)	1.28 (0.74-2.21)	0.378
4+ times a week	71 (18.1%)	1.27 (0.69-2.23)	0.440
Alcohol consumption †			
Never	68 (17.3%)	(ref)	
Monthly or less	104 (26.5%)	0.85 (0.46-1.58)	0.622
2-4 times per month	92 (23.4%)	1.19 (0.64-2.23)	0.586
2-3 times a week	82 (20.9%)	1.21 (0.64-2.31)	0.552
4+ times a week	47 (12.0%)	1.35 (0.64-2.85)	0.432
Occupation †			
Full-time employed	80 (20.4%)	(ref)	
Part-time employed	52 (13.2%)	1.36 (0.67-2.76)	0.387
Unemployed	61 (15.5%)	1.17 (0.60-2.30)	0.630
Student	8 (2.0%)	1.67 (0.37-7.45)	0.504
Semi-retired	6 (1.5%)	2.00 (0.35-11.54)	0.438
Retired	186 (47.3%)	0.98 (0.58-1.65)	0.936
Age leaving full-time education, years	16 (15-17)	0.97 (0.90-1.04)	0.330

N= Number of patients, IQR= Interquartile range, (ref)= Reference group. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Items marked with a † were recorded in TRACE-RA lifestyle questionnaires. Odds ratios were calculated using independent univariate logistic regression models.

4.4.5.1 Univariate analysis of clinical characteristics as predictors of adherence in the atorvastatin arm

No clinical baseline characteristics were significantly associated with atorvastatin adherence. A high DAS28 score (DAS28 >5.1) was associated with better adherence to statin therapy than a DAS28 score less than 2.6 (remission) (OR= 1.70, 95%CI 0.91-3.19, p=0.096). Patients who reported a

family history of diabetes were more likely to adhere to statin therapy than those who did not have a family history (OR=1.34, 95%CI 0.84-2.14, p=0.219). For each additional concurrent DMARD, patients had poorer odds of adherence to statin therapy (OR=0.82, 95%CI 0.59-1.13, p=0.228) (see table 4.22).

Table 4. 22 Univariate analysis of clinical characteristics and atorvastatin adherence in TRACE-RA

Baseline characteristic	Atorvastatin patients who had a pill count at 12 months of follow up, n=393(% of n)	Odds ratio (95% Confidence interval)	P value
Clinical			
DAS28*	3.8 (2.7-4.8)	1.07 (0.93-1.23)	0.357
DAS28 Category*			
Remission, <2.6	90 (22.9%)	(ref)	
Low activity, 2.61-3.19	43 (10.9%)	1.00 (0.49-2.02)	1.000
Moderate activity, 3.2-5.1	189 (48.1%)	0.96 (0.58-1.58)	0.872
High activity, >5.1	71 (18.1%)	1.70 (0.91-3.19)	0.096
HAQ score §	1.3 (0.5-1.8)	1.02 (0.79-1.32)	0.864
First degree relative with premature CVD*	76 (19.3%)	0.91 (0.55-1.50)	0.711
Family history of diabetes*	94 (23.9%)	1.34 (0.84-2.14)	0.219
Known hypertension*	102 (26.0%)	1.03 (0.69-1.54)	0.872
Number of concurrent DMARDs	1 (1-2)	0.82 (0.59-1.13)	0.228
Number of concurrent drugs	6 (4-8)	1.00 (0.94-1.08)	0.928

N= Number of patients, IQR= Interquartile range, DAS28= Disease activity score 28, HAQ= Health assessment questionnaire, CVD= Cardiovascular disease, DMARD= Disease modifying antirheumatic drug, (ref)= Reference group. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Items marked with an * were recorded in TRACE-RA CRFs. Items marked with a § were recorded in a document that included both HAQ and EQ-5D questionnaires. Odds ratios were calculated using independent univariate logistic regression models.

4.4.5.2 Univariate analysis of EQ-5D as predictors of adherence in the atorvastatin arm

Being confined to bed was associated with poorer adherence to statin therapy (OR=0.57, 95%CI 0.22-1.47) however this was not statistically significant (p=0.245). Patients who had 'some problems' with self-care and patients who suffered from 'extreme pain or discomfort' were more likely to adhere to statin therapy (OR=1.25, 95%CI 0.84-1.88 and OR=2.04 95%CI 0.85-

4.92 respectively) than patients who did not have problems with self-care and patients who did not suffer pain or discomfort. Neither association was statistically significant (p=0.270 and p=0.112 respectively). Patients who reported 'moderate' anxiety or depression in the EQ-5D were 20% less likely to adhere to statin therapy (OR=0.80, 95%CI 0.52-1.23, p=0.304) (see table 4.23).

Table 4. 23 Univariate analysis of EQ-5D responses and atorvastatin adherence in TRACE-RA

Baseline characteristic	Atorvastatin patients who had a pill count at 12 months of follow up, n=393(% of n)	Odds ratio (95% Confidence interval)	P value
EQ-5D			
Mobility §			
No problems	135 (34.4%)	(ref)	
Some problems	237 (60.3%)	1.05 (0.69-1.61)	0.807
Confined to bed	21 (5.3%)	0.57 (0.22-1.47)	0.245
Self-care §			
No problems	215 (54.7%)	(ref)	
Some problems	170 (43.3%)	1.25 (0.84-1.88)	0.270
Unable to wash or dress	8 (2.0%)	0.14 (0.02-1.17)	0.070
Usual activities §			
No problems	132 (33.6%)	(ref)	
Some problems	234 (59.5%)	1.24 (0.81-1.91)	0.315
Unable to perform usual activities	27 (6.9%)	0.71 (0.31-1.64)	0.422
Pain/Discomfort §			
No pain/discomfort	39 (10.0%)	(ref)	
Some pain/discomfort	310 (78.9%)	1.10 (0.73-1.66)	0.649
Extreme pain/discomfort	44 (11.2%)	2.04 (0.85-4.92)	0.112
Anxiety/Depression §			
Not anxious/depressed	273 (69.5%)	(ref)	
Moderately anxious/depressed	116 (29.5%)	0.80 (0.52-1.23)	0.304
Extremely anxious/depressed	4 (1.0%)		
Current health state compared with previous 12 months §			
Better	121 (30.8%)	(ref)	
Much the same	219 (55.7%)	1.22 (0.78-1.91)	0.374
Worse	52 (13.2%)	1.36 (0.71-2.63)	0.345
EQ-5D VAS	70 (52-82)	1.00 (0.99-1.01)	0.657

N= Number of patients, IQR= Interquartile range, (ref)= Reference group. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Items marked with a § were recorded in a document that included both HAQ and EQ-5D questionnaires. Odds ratios were calculated using independent univariate logistic regression models.

4.4.6 Multivariate analysis of smoking status, frequency of alcohol consumption and pain as predictors of adherence to the allocated treatment in TRACE-RA

Characteristics that achieved a p value of less than 0.10 patients who had complete pill counts up to 12 months were included in a multivariate logistic regression model that was adjusted for age and gender. Of interest were smoking status, frequency of alcohol consumption, and EQ-5D responses for 'pain or discomfort'. Former smokers (OR=0.78, 95%CI 0.58-1.05, p=0.105) and current smokers (OR=0.73, 95%CI 0.47-1.13, p=0.157) were 22% and 27% less likely to adhere to their allocated treatment than never smokers. Patients who consumed alcohol on a 'monthly or less' also had poorer odds of adherence than those who never consumed alcohol (OR=0.64, 95%CI 0.42-0.97). This achieved statistical significance (p=0.036). Finally, patients who reported extreme pain or discomfort were 67% more likely to adhere to their allocated treatment than those who reported experiencing no pain or discomfort (OR=1.67, 95%CI 0.96-2.90, p=0.070) (see table 4.24).

Table 4. 24 Multivariate analysis of baseline characteristics and treatment allocation adherence in TRACE-RA

Baseline characteristic	Patients who had a pill count at 12 months of follow up, n=809(% of n)	Odds ratio (95% Confidence interval)	P value
Smoking status †			
Never	338 (41.8%)	(ref)	
Former	365 (45.1%)	0.78 (0.58-1.05)	0.105
Current	106 (13.1%)	0.73 (0.47-1.13)	0.157
Alcohol consumption †			
Never	145 (17.9%)	(ref)	
Monthly or less	206 (25.5%)	0.64 (0.42-0.97)	0.036
2-4 times per month	180 (22.3%)	0.81 (0.52-1.25)	0.345
2-3 times a week	180 (22.3%)	0.86 (0.56-1.33)	0.503
4+ times a week	98 (12.1%)	1.04 (0.61-1.75)	0.895
Pain/Discomfort §			
No pain/discomfort	39 (10.0%)	(ref)	
Some pain/discomfort	310 (78.9%)	1.10 (0.71-1.64)	0.713
Extreme pain/discomfort	44 (11.2%)	1.67 (0.96-2.90)	0.070

N= Number of patients, IQR= Interquartile range, (ref)= Reference group. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Items marked with a † were recorded in TRACE-RA lifestyle questionnaires. Items marked with a § were recorded in a document that included both HAQ and EQ-5D questionnaires. Odds ratios were calculated in a multivariate logistic regression model that was adjusted for age and gender.

4.4.7 Multivariate analysis of DAS28 and self-care as predictors of adherence to atorvastatin in TRACE-RA

DAS28 and EQ-5D responses were input into a multivariate model that was adjusted for age and gender. Neither characteristic was found to be statistically significant. Patients with a high (DAS28 >5.1) were more likely to adhere to statin therapy than those in remission (DAS28 <2.6) (OR=1.64, 95%CI 0.83-3.24, p=0.153). Patients who self-reported being 'unable to wash or dress' were poorer adherers than those who did not report problems with self-care (OR=0.28, 95%CI 0.06-1.40, p=0.121) (see table 4.25).

Table 4. 25 Multivariate analysis of baseline characteristics and atorvastatin adherence in TRACE-RA

Baseline characteristic	Atorvastatin patients who had a pill count at 12 months of follow up, n=393(% of n)	Odds ratio (95% Confidence interval)	P value
DAS28 Category*			
Remission, <2.6	90 (22.9%)	(ref)	
Low activity, 2.61-3.19	43 (10.9%)	0.98 (0.48-1.99)	0.952
Moderate activity, 3.2-5.1	189 (48.1%)	0.97 (0.57-1.64)	0.900
High activity, >5.1	71 (18.1%)	1.64 (0.83-3.24)	0.153
Self-care §			
No problems	215 (54.7%)	(ref)	
Some problems	170 (43.3%)	1.09 (0.71-1.66)	0.703
Unable to wash or dress	8 (2.0%)	0.28 (0.06-1.40)	0.121

N= Number of patients, IQR= Interquartile range, (ref)= Reference group. Continuous data are presented as median values (IQR, 25th percentile to 75th percentile). Items marked with an * were recorded in TRACE-RA CRFs. Items marked with a § were recorded in a document that included both HAQ and EQ-5D questionnaires. Odds ratios were calculated in a multivariate logistic regression model that was adjusted for age and gender.

4.5 Summary of results for the adherence in TRACE-RA study

Adherence by pill counts was sub-optimal in the atorvastatin and placebo arms up to 3 (49.4%), 6 (49.1%) and 12 (50.1%) months. By self-reports, the proportion of adherent patients was higher (85.3%, 86.9% and 79.2% at 3, 6 and 12 months respectively). No significant differences were observed between arms. Patients with complete pill counts up to 12 months and

complete data for the selected characteristics (see section 4.3.3) were included in univariate analysis. A number of non-significant associations were found. Of note were smoking status, frequency of alcohol consumption and EQ-5D responses for pain/discomfort for adherence to the allocated TRACE-RA intervention and DAS28 and EQ-5D responses for self-care for adherence to atorvastatin. These characteristics were included in two final models for adherence to the allocated TRACE-RA intervention and atorvastatin separately. After adjusting for age and gender in the final models, former smokers (OR=0.78, 95%CI 0.58-1.05) and patients who consumed alcohol on a monthly or less basis (OR=0.65, 95%CI 0.42-0.97) had poorer rates of adherence to the allocated trial medication compared with never smokers and patients who never consumed alcohol. Patients who reported 'extreme pain/ discomfort' were 67% more likely to adhere to the TRACE-RA intervention than those who reported no pain/ discomfort (OR=1.67, 95%CI 0.96-2.90). Moreover, patients with a high DAS28 score were more likely to adhere to atorvastatin than those in remission (OR=1.64, 95%CI 0.83-3.24). Finally, patients who were unable to wash or dress were poorer adherers than patients who reported no problems with self-care (OR=0.28, 95%CI 0.06-1.40).

Chapter 5

This chapter is composed of a discussion for this dissertation and strengths and limitations. This chapter is completed with a conclusion.

5 Discussion

This discussion chapter is divided into two components. The first of these is a discussion of findings from the literature review (see section 3). The content of this covers the rates, measures and predictors of adherence to statin therapy in the general population that were identified in the included manuscripts. The strengths and limitations of this review are presented and concluding remarks are made. The second component of this chapter is a discussion of results from the study of adherence in TRACE-RA. The baseline characteristics of patients recruited to the TRACE-RA study, adherence to the allocated intervention (whether it was atorvastatin or placebo) and associations between baseline characteristics and adherent behaviour are discussed. This is followed by a discussion of the strengths and limitations of the adherence in TRACE-RA study. Suggestions for future research are proposed and concluding comments of the entire dissertation are made.

5.1 Discussion of results of the literature review

Section 3 of this dissertation is the most comprehensive and recent review of the literature of predictors of statin adherence in the general population. Six hundred and eighty eight studies were identified. Of these, 38 studies met the inclusion criteria for this review. Twenty eight of the 38 were of US-only cohorts. No UK-only cohorts met the inclusion criteria. Rates of adherence ranged from 22.8% to 87.4% in the studies that were included (153, 154). The proportion of adherent subjects fell within the range of 40-60% in 16 studies. Such a wide range of rates of adherence can be attributed to several factors. Firstly, a lack of consistency among methodologies. A variety of study designs were used to assess predictors of statin adherence in the general

population. These designs determined the measures of adherence that were used. For example, data for MEMS or pill counts were not found in large health insurance or prescriptions claims databases included in this review. Authors of studies of these databases calculated adherence by the number of days patients were covered by their prescription. In all, 12 different measures of adherence were used in studies that were included in the review. How these correlate with one another is not known.

Secondly, cohorts and healthcare services differed between many studies. In patients from RCTs, adherence was generally higher than when adherence was measured from retrospective cohort studies. This could be a result of patient awareness of observation and may not have affected studies of health insurance or prescriptions claims databases. Healthcare systems of other countries may also impact patient adherence. For example, Aarnio et al found that, in a cohort of 247051 patients identified in the Finnish Prescription Register, statin adherence was 20% poorer for each additional €0.10 per tablet (OR=0.80, 95%CI 0.80-0.80) (142). However, these findings may not be transferable to populations of other healthcare systems, such as the American healthcare system, as Finnish patients have the opportunity to claim for reimbursements.

Finally, rates of adherence are dynamic and change over time. A study in 2004 by Benner et al confirmed this. After 3 months of follow-up, around 51% of patients were adherent. Adherence declined up to 36 months of follow up, where 22% of patients were adherent (159). While the authors excluded patients who either died or dis-enrolled in the cohort, patients who discontinued their regimen of statin therapy were included in all analyses. For these non-persistent patients, reasons for discontinuing medication may

have differed from those of non-adherent patients. For example, patients who experience a serious adverse event may be discontinued from treatment and each additional day of non-persistence would be considered a day of non-adherence. The reasons for a wide range of rates of adherence are varied. Differing study designs, measures of adherence, cohorts, and follow up lengths mean that study outcomes are difficult to generalise. Homogeneity among methodologies would make future outcomes more comparable.

It is important to understand the predictors of adherence so that interventions can be applied to those at risk of not following their regimen. In total, 69 statistically significant predictors of adherence to statin therapy were identified in this literature review. These can be broken down into 4 distinct categories: Sociodemographic, socioeconomic, lifestyle, and clinical. Three sociodemographic and 13 socioeconomic predictors of statin adherence or non-adherence were identified. Of note, contrasting results were reported for an association between educational achievement and statin adherence and non-adherence. High and excessive alcohol consumption and smoking predicted poor adherence compared with no alcohol consumption and no smoking respectively. Six further lifestyle predictors of statin adherence and non-adherence were identified. Forty five clinical predictors of adherence were identified. These included comorbidities, whether surgery had been performed, the type of statin received, and the dose of statin received. Of the clinical characteristics, it was not determined whether the number of concurrent medications predicted statin-taking behaviour in 6 studies. Further, among 5 studies that investigated hypertension as a predictor of adherence to statin therapy, no definitive conclusion was achieved.

5.1.1 Methods and measures of adherence

Twelve unique measures of adherence were identified in this review. Adherence was most frequently measured using the MPR (13 studies) or PDC (12 studies). This observation is not surprising given that many of the published studies used pharmacy claims and health insurance data from which the MPR and PDC can be readily calculated. This review found that rates of adherence were generally higher when using the MPR than the PDC. This corresponds with previous research. Retrospective analysis of 7069 subjects in the North Carolina Medicaid administrative claims database found the rates of adherence to be 69.5% and 60.7% using the MPR and PDC respectively ($p<0.001$) (123). This can be explained by the fact that the MPR accounts for overlapping days of medication coverage whereas the PDC does not, thus the PDC is more representative of the time covered by statin therapy. Nevertheless, the MPR remains frequently used. Indeed, since 2010, 8 studies of predictors of statin adherence used the MPR as a measure of days covered by statin therapy whereas 7 used the PDC.

Only one study used pill counts to measure adherence. This study, the 3845-patient CREOLE trial, was established to determine whether information notices were better than no notices for improving rates of fluvastatin adherence in hyperlipidaemic patients (156). The proportion of adherent patients in the trial (75.0%) was generally higher than in other studies where adherence was calculated using the MPR or PDC. This is interesting as the threshold for the categorisation of patients as adherent in CREOLE was >90% whereas for the studies that used the MPR or PDC, this was $\geq$80%. This lack of consistency between measures makes comparisons difficult. It is possible that the nature of the CREOLE trial meant that patients were aware of observation and as a result, were inclined to take their statin. This is

known as the 'Hawthorne effect' and would not have affected statin-taking behaviour in patients from pharmacy claims and health insurance databases from which the MPR or PDC could be calculated. As pill count data were infrequently available in pharmacy claims databases, no retrospective cohort studies identified in this review used this measure. An important limitation of the pill count method is the Hawthorne effect and this has to be considered when evaluating rates of adherence. Further RCTs or prospective cohort studies would provide an opportunity to compare differences between the number of pills consumed and the number of days covered by statin therapy. Understanding how these correlate has importance for comparing studies that use these measures.

All studies that were included in the literature review used indirect measures to determine rates of adherence to statin therapy. Because of this, there was no evidence of actual medication consumption in any of the studies. For example, the calculations for PDC or MPR only account for the number of days a patient is covered by prescription. In the case of pill counts, 'medication dumping' may take place (117). Direct measures such as biological fluid analysis provide evidence of medication consumption; however these are impractical in large scale studies. One RCT (The Long term Intervention with Pravastatin in Ischaemic Disease [LIPID trial]) of 9014 Australian and New Zealand patients found that LDL monitoring could determine adherence to 40mg pravastatin treatment. When adherence was determined by pill counts, 16% of non-adherent patients compared with 4% of adherent patients had an increase in LDL concentration (197). Where biological data such as blood samples have been collected, the use of direct measures should be considered as an alternative to regularly used indirect measures of adherence.

In 30 of the 38 studies, patients were categorised as adherent if they took statin therapy for ≥80% of the observation period. Poor adherers took statin therapy for <80% of the observation period in these studies. The arbitrary grounds for selecting this threshold has meant that it has been questioned (198-200). For example, higher than 80% MPR rates have been associated with lower LDL levels, furthermore, greater TC reductions have been observed at a 90% than 80% threshold (199). In a retrospective cohort study of 4691 new statin users, Watanabe and colleagues found a greater likelihood of achieving a 25% reduction in LDL and TC profiles among patients who were consuming 90% or more of their statins than patients consuming 80-89.9%. Subsequently, the authors proposed a 90% threshold for dichotomising patients using the MPR (200). However, this study did not consider thresholds that were patient specific. Contemporary research has sought to deviate from the empirical 'one-size-fits-all' approach to categorising patients. Lo-Cignaic et al conducted a retrospective cohort study of 33130 Medicaid patients with type 2 diabetes who were receiving statin therapy. The authors proposed several thresholds for categorisation of adherence or non-adherence based on patient risk of hospitalisation. Still, the proportion of non-adherent patients in this study may be overestimated as non-initiators were not removed (198). New studies are driving forward the design of new thresholds for dichotomising patients as adherent or non-adherent. However, the majority still use an 80% threshold; hence, well-designed prospective cohort studies or RCTs that examine the relationship between clinical outcomes and adherence are required.

Only one of the 38 manuscripts accounted for drug discontinuation when measuring adherence. Barron and colleagues performed a retrospective cohort study of 79384 patients receiving statin therapy in an Irish Health Care Executive, Primary Care Reimbursement Services database. Adherence from a single cross-sectional measure at day 720, repeated measures over 900 days, and competing risks model (patients who discontinued statin therapy were removed from subsequent analysis) differed (62.4% vs 52.7% vs 75.3% respectively at day 720). After removing patients who discontinued statin therapy from analysis, adherent patients were more prevalent (79.4% up to 12 months) (178) than had been found in previous studies (30-54.9% up to 12 months) (159, 163, 201). This is explained by considering patients who discontinued statin therapy as non-persistent as opposed to non-adherent (178). When non-adherent and non-persistent patients were grouped, rates of adherence (55.0% up to 12 months) were similar to those of other studies that accounted for non-persistent patients in analysis of adherence (177, 202). The remaining studies in the literature review (see section 3) reported a rate of adherence that assumed that no patients discontinued statin therapy. Presumably this was done to make calculating adherence simple. It is well understood that the reasons for discontinuation differ from those for non-adherence. Therefore, identifying patterns of medication consumption is important to ensure that interventions to enhance adherence are targeted at non-adherent patients rather than non-persistent patients (203-206). Future studies should consider removing non-persistent patients from analysis of non-adherence.

Limitations of current measures for determining rates of adherence have implications for accurately dichotomising patients as either adherent or non-adherent (178, 198-200). A summary of these limitations have been made and revisions have been proposed (see table 5.1).

Table 5. 1 Limitations of current measures of adherence and how these can be addressed

Limitations of current measures	How these can be revised	The effects of these revisions
Patterns of medication consumption are not accounted for	Account for discontinuation	Exclude non-persistent patients from analysis of adherence
	Use measures of adherence such as MEMS	Be able to detect patterns such as times of 'drug holidays'
Arbitrary 80% threshold	Use of clinical outcomes to establish a new threshold	Will establish a relationship between adherence and health outcomes

The above table is a summary of limitations of measures of adherence found in the literature review of this dissertation. Revisions have been suggested.

For researchers and healthcare professionals to better understand adherence, a commonality in methodology, excision and discourse is absolutely vital. The field, at present, has many good studies of large cohorts, but fails to convince because of the lack of a homogenous approach. This makes comparisons difficult and confusing. The way forward requires investigations to conform to agreed terms and understandings and thus through a common discourse, studies can build on a shared foundation.

5.1.2 Predictors of adherence to statin therapy in the general population

This literature review confirmed that there is a great body of evidence for sociodemographic factors as predictors of adherence to statin therapy in the general population. These include an increasing age, male gender and white ethnicity and these have been identified as predictors of statin adherence in 2 previous reviews (151, 152). Although 25 out of 27 studies that were identified in this literature review found that adherence to statin therapy was better with increasing age, there was no consensus as to whether this plateaued and remained elevated or whether adherence to statin therapy

continued to increase with age above 55-69 years(210;211). Eleven of 17 manuscripts identified that female patients were poorer adherers to statin therapy than male patients in the general population (162, 167, 168, 175, 178, 181, 182, 185-187). The remaining 6 studies did not identify gender as a significant predictor of adherence to statin therapy in the general population (153, 155, 157, 164-166). Patients of a non-white ethnicity were poorer adherers to statin therapy compared with white patients in 8 of 9 studies (157, 167-170, 173, 184, 186). This may be explained by poor access to healthcare and a low income in non-white demographics (207). Alternatively, patient thoughts and attitudes towards their statin regimen may affect their medication-taking behaviour in non-white ethnicities. Beliefs of poor efficacy may discourage patients from taking their medication. Such 'concern beliefs' have been observed in non-white patients. These patients were more likely to express such beliefs compared with white patients in a cohort of 200 patients of either white or Asian ethnicity (138).

Socioeconomic characteristics

Socioeconomic factors have been researched in previous studies of medication adherence to anti-hypertensives in the general population (208-210). The literature of statin adherence contained a great number of studies that examined socioeconomic factors as potential predictors. Indeed, co-payment for medication was the most frequently studied potential predictor of statin adherence. A strong relationship between increasing co-payment and a decreasing level of adherence to statin therapy was found in all 11 studies that examined this relationship. However, there was less conclusive evidence for some socioeconomic factors as predictors of adherence to statin therapy in the general population.

There was no agreement among studies as to whether there was an association between educational achievement and adherence or non-adherence to statin therapy (161, 165, 175). In these studies, similar proportions of patients who achieved university qualifications or enough years in education to have reached university were observed. Two of the studies identified educational level as a predictor of poor adherence. Wallach-Kildemoes and colleagues carried out a retrospective cohort study to investigate the relationship between adherence to statin therapy and socioeconomic position. Of the 76038 Danish patients, 45845 were categorised as having spent 10+ years in education. These patients had poorer rates of adherence than those who spent 7-9 years in education (161). Separately, Warren and co-authors carried out a retrospective cohort study of 42492 concession card holders (patients over 60 years of age or patients who claimed a low income health card) and 16110 general beneficiaries. Both groups qualified for the Australian Pharmaceutical Benefits Scheme; however concession card holders received a further reduction in per-prescription fees. A significant trend was observed for higher than lower qualifications and poor adherence in the concession card holders whereas in general beneficiaries, qualifications did not significantly predict adherence to statin therapy (165). It appears that the low-income concession card holders were poor adherers to statin therapy, particularly those with a university degree.

It is possible that in patients with high levels of education, negative beliefs towards statin therapy may be more prevalent than in patients with low levels of education. Highly educated patients may possess a greater understanding of the potential adverse events associated with treatment. Therefore, it is important to nurture necessity beliefs such as a positive attitude towards medication and a belief of the benefits of medication to

health. A study of 324 patients by Horne and Weinman published in 1999 compared rates of adherence among those with concern beliefs and those with necessity beliefs. The authors found poorer rates of adherence among patients with concern beliefs compared with patients who had strong necessity beliefs towards their medication (136). While the authors described the educational experience of the cohort, medication beliefs according to this were not determined. What was lacking in the literature of educational achievement and statin adherence was an understanding of the beliefs towards treatment among highly educated patients compared with lesser educated patients. This could confirm the reasons for poor adherence that have been observed in the literature.

Findings from Gibson and colleagues conflicted with those of Wallach-Kildemoes et al and Warren et al. Their study of the Medstat MarketScan US database included 24113 new and 93253 existing statin users. Around one quarter of these were college graduates who had better rates of adherence to statin therapy than those without college degrees (175). This cohort comprised of middle-high income statin users whereas in research by Warren and co-authors, where a high qualification predicted non-adherent behaviour, patients were typically on a low annual income. It is likely that a low income acts as a barrier to receiving statin therapy and is also influential towards a patient's statin-taking. The 4 studies that have examined educational achievement as a potential predictor of statin adherence have done so in large cohorts; however the characteristics of these poorly reflect the general population. Future cohorts should feature a range of patients across all strata of the income ladder.

Five out of 6 studies (see section 3) found a relationship between a higher income and increasing statin adherence (159, 164-166, 175). This corresponded with research of high neighbourhood wealth and higher rates of adherence to statin therapy in another study. In a cohort of 14257 US patients, the median neighbourhood income of non-adherent patients was lower than that of adherent patients ($56,300 vs $60,600) (162). Patients with a higher income compared with those who have a lower income may have greater access to healthcare and may be more likely to afford medication. In a Canadian cohort of 716 low-income patients, the most common reasons for non-adherence were a dislike of side effects (33.3% of patients), cost-related reasons (14.7% of patients) and a lack of access to a doctor (11.3% of patients) (211). The evidence in the literature clearly points to a high income being associated with better statin adherence than a low income, thus more needs to be done to provide low income patients with cheaper healthcare access.

Clinical and healthcare characteristics

A number of studies identified clinical predictors of adherence to statin therapy in the general population. The most frequently studied of these were depression (4 studies), hypertension (5 studies) and heart surgery (5 studies). Patients with depression were poorer adherers to statin therapy than patients without depression in 4 studies that were generally well-designed (142, 154, 178, 187). Of these studies, one RCT of 158 US patients used MEMS to measure patient adherence (154). Using this measure, authors could objectively determine medication-taking behaviour; however in larger studies, this may prove expensive. Another of these 4 studies accounted for statin discontinuation. In a cohort of 79364 patients receiving statin therapy, Barron and co-authors produced a number of non-adherence (HR=1.02, 95%CI 1.00-1.04) and non-persistence (HR=1.12, 95%CI 1.09-1.15) estimates

for patients suffering from depression (178). Findings from these 4 studies concur with findings in patients with depression across a range of studies of medication adherence for other chronic illnesses (92, 212, 213). The reasons for poor medication adherence among patients suffering from depression are likely to be multi-faceted. Concerns about medication, feelings of hopelessness and a lack of energy are all thought to contribute to non-adherent behaviour (reviewed by Grenard JL and colleagues) (214). While a number of strong studies exist of statin adherence in patients suffering from depression, the field is lacking in research of beliefs towards statin therapy among these patients. Thorough qualitative research may elucidate such beliefs.

Evidence for whether hypertension predicts adherence to statin therapy was not clear. Of the 5 studies that assessed known hypertension as a predictor of adherence, 2 concluded that hypertensive patients were poorer adherers than non-hypertensive patients (153, 155). A study by Eagle and co-authors of 13830 patients discharged from hospital for acute coronary syndromes found lower rates of statin adherence among hypertensive patients than non-hypertensive patients. However, the authors acknowledged that the predictive capability of their model was poor and this was confirmed by a low C statistic (153). An RCT (Goswami NJ et al 2013) of 208 patients found no difference between either an integrated intervention program (that consisted of nurse counselling, an adherence tip sheet, co-pay relief card and the opportunity to enrol in a 12 week cholesterol management program) or no program for improving adherence to statin therapy. The authors did however find lower rates of adherence in hypertensive patients compared with non-hypertensive patients. Given the controlled nature of this study and the small population size, findings are difficult to generalise (155). Contrasting findings for hypertensive patients were found in 3 larger

studies. Wallach-Kildemoes and colleagues found higher rates of adherence in hypertensive patients compared with non-hypertensive patients in their study of 76038 patients enrolled into Danish nationwide registers (161). Further studies of large cohorts of 33646 and 19422 US patients confirmed these findings (145, 159). These studies are more generalisable due to their size and inclusion of patients that reflect the general population than findings from studies by Goswami et al and Eagle et al. Explanations for an association between hypertension and adherence may vary. It could be that the patient's perceived risk of a CVE may act as a cue to adherent behaviour. In a cohort of US veterans, those who believed they were not at risk of an MI were less likely to adhere to statin therapy than patients who believed they were at an increased risk of an MI (OR for non-adherence=3.1, 95%CI 1.1-8.7) (170). It is likely that similar concerns of a risk of a CVE in hypertensive patients may encourage adherent behaviour. Again, what is lacking in the literature is qualitative research that may elucidate this.

There was no consensus among 6 studies as to whether adherence to statin therapy increased or decreased with additional concurrent medications. In the two studies that found that additional concurrent medication predicted poor adherence, patients were not given healthcare support. In a cohort of 24113 new and 93253 existing statin users of middle-high income, patients received few healthcare benefits and little co-pay support (175). Similarly, in a cohort of 247051 Finnish patients who purchased their medication, adherence to statin therapy was poorer with each additional concurrent medication (142). The authors used the PDC to measure adherence, a more representative gauge of days covered by statin therapy than the MPR. The study was well-designed however did not report on socioeconomic factors such as patient income or access to healthcare. This is of importance as these characteristics may influence whether patients would claim for

reimbursement following payment. Increased adherence to statin therapy was observed in patients receiving additional concurrent medication in 3 studies (160, 164, 179). In these studies, socioeconomic factors were considered and patients were offered financial support for their healthcare. Watanabe and colleagues used the MPR and found higher rates of adherence in patients receiving 6 or more medications compared with those receiving 1 to 5 medications in a retrospective cohort study of 4886 US veterans (179). In a Canadian cohort where almost 90% of patients had health insurance covering out-of-pocket expenses, patients receiving 4-6 other prescribed medications (other than statin therapy) were more likely to adhere to statin therapy than those receiving 0-3 other prescribed medications (160). Whether additional concurrent medications predict improved adherence to statin therapy is likely dependent on out-of-pocket expenses associated with healthcare access and medication costs. When patients were expected to pay for additional concurrent medications, adherence to statin therapy was poor, even when patients were reimbursed. How these findings translate to the UK healthcare system is not yet known.

Out-of-pocket expenses are a particular issue for adherence to statin therapy as statin prices are particularly responsive to market demand. In a cohort of 11,550,464 patients from a US MarketScan database, patients receiving statin therapy were more likely to change their medication-taking behaviour in response to price changes than patients receiving NSAID therapy (price elasticity of demand= -0.064 vs -0.015 respectively) (215). Accordingly, it is important that patients maintain necessity beliefs for their medication use so that rates of adherence to statin therapy are sustained despite changes in market pressures (216). Research of the effects of market prices on statin adherence is likely to differ between each healthcare provider because of differing medication expenses and cohorts of differing socioeconomic

compositions. Further studies across cohorts of other healthcare providers will make findings more generalisable.

A total of 6 statin types (lovastatin, pravastatin, atorvastatin, rosuvastatin, fluvastatin, and simvastatin) were assessed as potential predictors of adherence to statin therapy in the general population. Statin type predicted adherent behaviour in 2 manuscripts (142, 178). In a study of 247051 Finnish patients by Aarnio et al, those receiving atorvastatin and rosuvastatin were better adherers than those receiving simvastatin (OR=1.51, 95%CI 1.48-1.54 and OR=1.89, 95%CI 1.82-1.97 respectively) (142). Similar findings were observed by Barron et al in a cohort of 79364 Irish patients when atorvastatin and rosuvastatin were compared with pravastatin (178). Authors of both studies calculated adherence using differing approaches. Whereas Aarnio and co-authors used the PDC to measure the number of days covered by statin therapy, Barron and co-authors used the MPR for their calculation. However, non-persistent patients were removed from analysis of non-adherence in the latter measure. This makes analysis by Barron et al more generalisable to non-adherent patients with statin prescriptions than analysis by Aarnio et al. Higher rates of adherence among those receiving atorvastatin or rosuvastatin than those receiving simvastatin and pravastatin could be explained by prescription practices. Atorvastatin and rosuvastatin are prescribed at lower doses than simvastatin or pravastatin due to their stronger lipid lowering potential. This is supported by results from a nationwide retrospective cohort study of 6436 US patients across 586 pharmacies. Authors of this study found higher rates of adherence in patients receiving a low dose compared with a high dose of statin therapy (181). Patients receiving high doses of statin therapy compared with patients receiving low doses are at an increased risk of adverse events such as myopathy (217). However, how a high dose effects patient beliefs towards

their treatment and subsequent statin-taking behaviour is yet to be made clear.

Unlike real world data from healthcare systems where medication is charged for, trial interventions received in RCTs are not commonly charged for. The implications of this are twofold. Firstly, increasing out-of-pocket expenses have been shown to predict poorer rates of adherence. In one study by Aarnio and colleagues, this finding was observed in spite of the opportunity for patients to claim for reimbursements on these expenses (142). Secondly, market pressures associated with price elasticity of demand have been shown to affect medication-taking behaviour (215). It can also be suggested that these factors make comparing real world US studies of adherence with those of other healthcare systems challenging. For example, such findings would poorly translate to the UK healthcare system. Further studies of adherence using real world data in the UK healthcare system are necessary. For example, Scotlands Prescribing Information System would provide a unique opportunity to investigate this. Here, linkable data on all prescriptions issued by Scottish general practitioners and community pharmacists would allow for the first nationwide study of medication adherence.

Patient beliefs could be disassembled into categories found in the HBM (see table 5.2). Establishing how patient characteristics either influence or are influenced by their beliefs requires substantial research. Questionnaires or patient diaries may provide additional insight into medication-taking behaviour.

Table 5. 2 Patient perceptions and how these may help in understanding predictors of adherence to statin therapy

Individual perceptions	Modifying factors	Findings
Perceived susceptibility to disease	Sociodemographic factors	↑ **adherence: Increasing age** (142, 155, 157-162, 164-168, 170, 173, 175, 178, 181-187)
		↓ **adherence: Female gender** (162, 167, 168, 175, 178, 181, 182, 185-187)
	Clinical factors	↑ **adherence: Dyslipidaemia** (187), **dyslipidaemia (severe)** (142), **hypertension** (153, 157, 158, 161, 173)
Perceived severity of disease	History of CVD or a CVE	↑ **adherence: ACS** (142, 162), **acute MI** (153, 158), **atherosclerotic disease** (175, 189), **CHD** (142, 175, 178), **CVD** (165), **stroke** (142)
	Comorbidities	↑ **adherence: CKD** (157), **diabetes** (178)
		↓ **adherence: COPD** (157)
	Previous surgery	↑ **adherence: PTCA or CABG** (158, 159)
	Concurrent medications	↑ **adherence: Additional free/cheap concurrent medications** (160, 164, 179)
		↓ **adherence: Additional concurrent medications** (142, 175)
Perceived benefits/ necessity of statin therapy	View of statin therapy	↑ **adherence: Positive view** (170)
Perceived barriers	Co-payment	↓ **adherence: Increasing co-payment** (142, 158, 161, 162, 173, 175, 176, 181, 182, 185, 187, 190)
	Out-of-pocket expenses	↓ **adherence: Increasing out-of-pocket expenses** (142)
	Income	↓ **adherence: A lower than higher income** (159, 164-166, 175)
	Employment	↓ **adherence: Full-time employment compared with unemployed** (165)
	View of statin therapy	↓ **adherence: Strong possibility of adverse effects** (156, 166)
	Psychological health	↓ **adherence: Depression** (142, 154, 178, 187), **anxiety** (154), **moderate-very high distress** (165)

ACS= Acute coronary syndrome, CABG= Coronary artery bypass graft, CHD= Coronary heart disease, CKD= Chronic kidney disease, COPD= Chronic obstructive pulmonary disorder, CVD= Cardiovascular disease, MI= Myocardial infarction, PTCA= Percutaneous transluminal coronary angioplasty. A table of how patient perceptions found in the HBM may explain predictors of statin adherence that were identified in this literature review.

5.2 Strengths and limitations

Strengths and limitations of this literature review must be noted. While this is the most comprehensive review of predictors of statin adherence, many studies of rates and measures of adherence were excluded. This was because the literature search criteria were narrowed to only include studies that sought to identify potential predictors of adherence. Heterogeneity among studies means that the interpretation of synthesised results needs to be seen with caution. For example, it has been shown that associations between characteristics and adherence to statin therapy may significantly differ depending on the method of measurement (155).

This review only drew manuscripts from searches of two databases: Embase and Medline. The use of other search engines such as PsycInfo was not employed due to time constraints. However, future reviews may seek to use such search engines to include more manuscripts that may have assessed beliefs and psychological health as potential predictors. Finally, this review was susceptible to publication bias as studies of negative results and those that were not written in English were excluded. This may be of particular importance for characteristics that were not extensively studied as potential predictors. A funnel plot was not used to test for publication bias due to time constraints.

5.3 Conclusions from the literature review

In summary, limitations of contemporary measures of adherence that were identified in this dissertation have made it clear that revisiting this is important. At present, there are many large studies, however a lot of these

have calculated adherence using these measures. If the PDC is to be used rather than the MPR in future retrospective cohort studies of pharmacy claims and health insurance databases, patterns of adherence and a threshold for dichotomising patients that is also based on health outcomes must be considered. Going forward, homogeneity among study designs, measures of adherence, and terms and understandings will improve the generalisability of research on adherence.

This review of the literature has shone light on conflicting research on predictors of statin adherence in the general population. Socioeconomic factors and patient beliefs appear to have important roles for statin-taking behaviour. A plethora of papers that published material on the relationship between socioeconomic factors and statin adherence were identified. It was clear that co-payment and a high income are associated with better rates of adherence compared with a low income. What was less clear was how market pressures influenced statin-taking behaviour outside the US. Further, no studies investigated how these pressures effect patient beliefs towards taking their medication.

Out-of-pocket expenses were of particular importance for statin adherence in healthcare systems where prescriptions are charged for. This is because statin-taking behaviour is particularly responsive to price changes (215). Adherence was generally higher in cohorts where patients received financial support for their healthcare than in cohorts where healthcare was charged for.

Finally, no studies investigated how beliefs of patients with the reviewed characteristics influenced their medication-taking behaviour. These beliefs are multi-dimensional and adherence cannot simply be explained by the characteristics that are associated with such behaviour. Understanding perceived needs for medication and concerns about either a lack of efficacy or side effects is important in developing interventions that encourage adherent behaviour. A distinct lack of qualitative research identified in the literature of statin adherence in the general population suggests that more work is necessary to explain the reasons for non-adherence.

5.4 Discussion of results of statin adherence in an RA population

Of the 2986 TRACE-RA patients, 2237 (74.9% of patients) had complete data for the characteristics described in this study of predictors of adherence (see section 4.3.3). The characteristics of patients in the TRACE-RA trial were largely consistent with other RA populations (1). The majority of patients were female (74.2%) and were elderly (median age 61 years old). More female than male patients were retired at baseline (48.4% vs 38.5% respectively); an observation possibly explained by the fact that women retire at a younger age than men.

Differences between genders were observed for some clinical characteristics. Female patients in TRACE-RA were more likely to have poorer physical function (median HAQ score 1.4 vs 0.8) and higher disease activity (median DAS28 score 3.7 vs 3.1) than male patients. This is consistent with previous research (218-221). Worse DAS28 scores in women are thought to be explained by higher ESR levels (222), particularly at an older age, and poorer

self-reported scores for patient global health (223). Indeed, poorer self-reported scores in women compared with men may reflect health concerns (224). In TRACE-RA, women were more likely to report a first degree relative with premature CVD (21.2% of women vs 12.1% of men) or a familial history of diabetes (23.9% of women vs 16.2% of men). Such findings have been observed for other familial diseases. A cohort of 331 subjects was identified following data linkage of a Kaiser Permanente Medical Program and the Utah Population genealogy database. The authors found that female reporting for family history of cancer was more sensitive than male reporting (80% sensitivity for females vs 67% sensitivity for males) (225). This could be due to greater health concerns or a higher perceived threat of disease in female than male patients. A high proportion of TRACE-RA patients reported some problems with mobility (56.9%), usual activities (53.8%), and pain or discomfort (78.9%). These responses to the EQ-5D questionnaires were consistent with responses in other RA cohorts. For example, in one cohort of 156 RA patients, 52.1%, 54.3% and 80.6% reported any problems with mobility, usual activities, and pain or discomfort respectively (226).

Blood pressure readings also differed between genders in patients of TRACE-RA. Men had higher blood pressures than women (median systolic blood pressure reading 2, 135mmHg vs 132mmHg, median diastolic blood pressure reading 2, 81mmHg vs 79mmHg). These findings have previously been observed in a cohort of similarly aged patients to those of TRACE-RA (227) and are thought to be explained by differences in oestrogen and androgen levels between genders (228, 229). The proportion of patients at baseline with known hypertension in TRACE-RA (22.2%) was lower than that observed in the general population, which is around 30-45% (230).

Research contrasts as to whether there is a greater prevalence of hypertension in RA patients (231). There is evidence to suggest that hypertension is underdiagnosed in the RA population (232). Further, early findings from the UK biobank suggest a greater risk of hypertension in 5333 participants with RA than participants who did not have inflammatory arthritis (233).

Characteristics at baseline in TRACE-RA differ from those of another study of medication adherence in a UK RA population (196). While the TRACE-RA population were studied under controlled RCT conditions, Morgan et al recruited from the British Society for Rheumatology Biologics Register for RA, a pharmacovigilance register for bDMARD therapy in RA patients. The patients included in their study were younger than TRACE-RA (mean age= 55.9 years vs median age 61.0 years in TRACE-RA); however the cohort was composed of a similar proportion of female patients (78.1% vs 74.2% in TRACE-RA) and white patients (97.3% vs 98.2% in TRACE-RA). The older TRACE-RA population may be explained by the fact that, for patients to be recruited into the trial, they had to be above the age of 50 years or had to have had an RA disease duration of more than 10 years. The cohort recruited by Morgan et al had higher DAS28 scores than observed in TRACE-RA (mean DAS28= 6.4 vs median DAS28= 3.6 in TRACE-RA). This difference can be explained by the fact that this cohort was receiving biologic treatment. This is prescribed for patients with severe disease activities (DAS28 >5.1) and who do not respond to csDMARD therapy or combination therapy.

Other studies of adherence in RA cohorts outside of the UK also differ from the TRACE-RA population. Three studies that assessed csDMARD

adherence in RA populations had younger patients, however had similar proportions of female patients compared with TRACE-RA (139, 234, 235). One study of csDMARD adherence using MEMS by de Klerk et al had a similarly aged cohort (mean age= 60 years) to that of TRACE-RA. However, this cohort had a lower proportion of female patients compared with TRACE-RA (66% vs 74.2%) (133). Ethnicity also differed between TRACE-RA and RA cohorts found in the literature (135, 139, 235). For example, of 3859 patients receiving MTX therapy in a study by Grijalva and colleagues, 72.4% were white (235). Similarly, in a smaller cohort of 108 patients receiving MTX therapy, 83% were white (139). These observations can be explained by the fact that these cohorts were recruited from the US where a lower proportion of the general population are white.

5.4.1 Discussion of adherence in TRACE-RA

This was the first study of adherence to statin therapy for the primary prevention of CVEs in an RA population. Patients with missing data for any of the selected characteristics (see section 4.3.3) were excluded from analysis of potential predictors of adherence. These patients were however similarly matched with the remaining cohort. Of the 2237 patients with complete data, 809 had complete data for pill counts up to 12 months of follow up. Three hundred and ninety three of these were allocated atorvastatin at baseline and 416 were allocated placebo. Using pill counts, the proportion of adherent patients to statin therapy was 50.0% up to 3 months. This remained somewhat consistent up to 6 (50.0%) and 12 months (50.9%). These rates of adherence are similar to those of other cohorts of primary prevention patients. For example, in one cohort of US veterans, 45% of patients were adherent to statin therapy up to 6 months of follow up (170). Rannanheimo and colleagues performed a large retrospective cohort study of 97575

primary prevention patients and found that 53% of patients were adherent up to 12 months of follow up. Like the atorvastatin arm of the TRACE-RA population, these patients were new users of statin therapy (236). Despite similarities in rates of adherence between this study and TRACE-RA, differing measures of adherence were used. Rannanheimo et al calculated adherence in the Statistics Finland registers using the PDC. While this can be used to accurately determine the number of days covered by statin therapy, it is less objective than pill counts as the assumption is made that medication is optimally taken for each day of coverage. Moreover, the different conditions under which patients were taking statin therapy in TRACE-RA and the Statistics Finland registers may also influence measures for adherence. In TRACE-RA, patient awareness of the pill count process may have encouraged either medication consumption or medication dumping. This makes the generalisability of rates of adherence in TRACE-RA less valid. To investigate how comparable pill counts are with measures of adherence used in real-world data, further investigation is required.

There were no statistically significant differences for rates of adherence between the atorvastatin arm or placebo arm. A separate RCT by Kremer and co-authors of 263 RA patients receiving MTX compared the efficacy and safety of combination therapy with either leflunomide or placebo. Adherence in the trial was measured using the pill count method. No significant differences for rates of adherence were observed between those receiving leflunomide and those receiving placebo (98.5% for those receiving placebo vs 97.4% for those receiving leflunomide) (237). Such high rates of adherence in this particular trial can be explained by the fact that patients who discontinued their allocated trial intervention were removed from analysis (30 patients removed from the leflunomide arm and 33 from the

placebo arm). Similar rates of adherence between both arms for each trial may be explained by the double blinded nature of study. Alternatively, one cross-sectional study performed by Wei and colleagues of 10138 US patients showed that patients who experienced an adverse event were less likely to adhere to their statin treatment than those who had not (166). However in TRACE-RA, similar proportions of patients experienced similar adverse events in each arm (19.7% in the atorvastatin arm and 19.5% in the placebo arm) (107). Further, in research by Kremer et al, the incidence of adverse events in each arm was also similar (89.2% in the leflunomide arm vs 89.5% in the placebo arm) (237). What has been established in the literature of adherence to the placebo is the 'healthy adherer effect'. Under the healthy adherer effect, patients who adhere to an intervention, even if it is a placebo, have better clinical outcomes than those who do not. A meta-analysis of 8 studies involving 19633 participants receiving a placebo found that adherers were at a lower risk of mortality than poor adherers (OR=0.56, 95%CI 0.43-0.74) (238). It is possible that better lifestyle decisions associated with positive medication-taking behaviour may reduce the risk of mortality in adherers compared with non-adherers. The causal association between adherence and ideal clinical outcomes requires further investigation.

A higher proportion of patients were categorised as adherent to atorvastatin at 3 months (84.7%), 6 months (87.2%) and 12 months (76.3%) when adherence was self-reported than when determined by pill counts. High rates of adherence as determined by self-reports have been observed in previous research. In a cohort of 136 Czech primary prevention patients who completed Medication Adherence Rating Scale (MARS) questionnaires, 94.1% were deemed to have a high rate of adherence to statin therapy (239). The MARS questionnaire is a widely used self-report measure for

medication adherence. In RA patients, it can be used as an alternative to the compliance-questionnaire rheumatology and medication adherence scale. One study of medication adherence in 108 RA patients found that, although the 3 measures were moderately correlated, the MARS questionnaire was the most valid and reliable (240). Self-reported measures of adherence are however limited by biases. In a study of a Canadian cohort by Grymonpre and colleagues, more patients were categorised as adherent when they self-reported adherence than when their tablets returned were counted (95.8% vs 74.0% respectively) (241). The wording of questions and the timeframe of recollection may influence self-reported outcomes (reviewed in Farmer 1999 and Hawkshead and Krousel-Wood 2007) (113, 242). In TRACE-RA, the timeframe of recollection for patients varied depending on their last visit to clinic. For example, at 6 months of follow up, patients had a 3 month period to recall medication use whereas at 12 months of follow up, patients had a 6 month timeframe of recollection. Patients may more accurately recall medication-taking behaviour in shorter timeframes than in longer timeframes. This may explain why adherence was lower when self-reported at 12 months than when reported at 3 or 6 months. While self-reported measures of adherence are cheap, other methods should be considered to limit bias associated with patient recollection.

Because of the limitations associated with self-reported measures of adherence and the fact that more data were collected for patient pill counts, adherence in the study of potential predictors of adherence in TRACE-RA was determined by pill counts. Adherence to statin therapy has been measured using pill counts in other RCTs. Identified in the literature review of this dissertation was the CREOLE trial. This also used pill counts to determine rates of adherence. Patients of the CREOLE trial were more

adherent than those of TRACE-RA up to 3 months of follow up (75.0% vs 50.0% respectively). This was surprising given the high threshold at which patients were categorised as adherent (>90% pravastatin consumed) in CREOLE. Again, this may be explained by the Hawthorne effect. One study found differences in rates of antihypertensive medication adherence between a group of patients who were aware of adherence as the primary outcome (95.1% of patients were adherent) and those who were not aware (78.0% of patients were adherent) (243). The effects of observation on medication-taking behaviour may have been less of an issue in TRACE-RA as adherence was not the primary outcome of the trial. Another possible explanation for the higher rates of adherence in the CREOLE trial may be the inclusion of secondary prevention patients. Such patients have previously been shown to attain higher rates of adherence than primary prevention patients (171, 244, 245). Finally, right censoring in the CREOLE trial could account for higher rates of adherence than in TRACE-RA. Seven hundred and eighty seven (17%) of patients from CREOLE were removed from analysis of pill counts as blister packs were not returned upon study completion (156). In TRACE-RA, patients who did not return a bottle of tablets at the scheduled date of refill were not removed from analysis.

Differences in findings for adherence between CREOLE and TRACE-RA cannot simply be explained by any one of the above differences in trial designs, rather by a combination of them. The CREOLE trial is limited by biases such as right censoring and the Hawthorne effect, furthermore, the application of a 90% threshold for dichotomising adherent and non-adherent patients was not consistent with the literature. How findings from the TRACE-RA and CREOLE trials compare with findings from studies that used the PDC or MPR is an area of interest. No studies have determined

how adherence by pill counts and by PDC or MPR are correlated. Such research is necessary to understand how rates of adherence in controlled studies can be compared with those of much of the literature of retrospective cohort studies.

5.4.2 Discussion of predictors of adherence to the allocated TRACE-RA intervention

Potential predictors of adherence to the allocated TRACE-RA intervention and atorvastatin were explored in this study. This was done to investigate whether clinical characteristics associated with RA predicted adherence to the allocated intervention and to statin therapy under trial conditions.

Univariate analysis of the allocated TRACE-RA intervention and adherence

Selected characteristics for the remaining 809 patients with complete pill counts were input into independent univariate logistic regression models (see section 4.4). This was the first study to find an association between part-time employment and retirement and adherence in an RA population. Univariate analysis showed that retired patients (OR=1.33, 95%CI 0.92-1.91) and patients in part-time employment (OR=1.47, 95%CI 0.90-2.39) were better adherers to the allocated TRACE-RA intervention than those in full-time employment. This supports studies that found high rates of adherence in older than younger patients; however, neither finding achieved statistical significance. One cross-sectional study by Salt and Frazier of 108 RA patients did not find that employment or retirement were predictors of adherence to MTX. It is however possible that the study was underpowered as only 10 patients (8%) were deemed non-adherent (139). Results from this study of adherence in TRACE-RA contrast with findings from previous studies of employment and adherence to statin therapy. In one prospective cohort

study of 9265 Swedish primary prevention patients, retirement predicted non-adherence in both men (prevalence ratio [PR] for non-adherence=1.18, 95%CI 1.13-1.25) and women (PR=1.18, 95%CI 1.11-1.24) when compared with men and women who were still employed (188). In a cohort of 3468 Finnish patients receiving antihypertensive treatment, poor adherence was more prevalent in retired patients than in those who were employed (OR=2.40, 95%CI 1.37-4.20) (246). Disparities in findings between the study of adherence in TRACE-RA and other studies may be explained by the cost of prescriptions in these particular cohorts. Indeed, the loss of income associated with retirement could exacerbate this. In TRACE-RA, the allocated intervention that patients received was not charged for. Therefore, out-of-pocket expenses did not influence medication-taking behaviour in TRACE-RA patients. Because of this, findings for retired patients from TRACE-RA more accurately translate to retired patients in the UK healthcare setting compared with findings from the Swedish and Finnish cohorts. Retired patients and those in part-time employment may be better adherers due to better availability to collect their medication. Indeed, full-time employed patients may be more likely to forget their medication. Whether employment status predicts whether a patient 'intentionally' or 'unintentionally' non-adheres is open to further investigation.

Only one study has examined certain EQ-5D responses (health state in the last 12 months and VAS) as potential predictors of adherence in an RA population. The study by Morgan and colleagues did not find a significant association between either health state in the last 12 months or VAS with adherence to bDMARD therapy (196). However, other EQ-5D responses such as mobility, anxiety/depression or pain/discomfort may be of relevance in an RA population. Univariate analysis in the study of adherence in

TRACE-RA showed that patients who reported moderate anxiety or depression in the baseline EQ-5D questionnaires were poorer adherers to the allocated trial intervention than patients who did not report anxiety or depression (OR=0.78, 95%CI 0.57-1.06). While not statistically significant, this finding is in line with previous findings in RA patients with depression. Waimann and colleagues conducted a prospective cohort study of 107 RA patients receiving oral MTX. The authors used the MEMS to measure rates of adherence. Those who had a high score on the Center for Epidemiological Studies Depression Scale (Revised) were poorer adherers to MTX than patients who obtained lower scores (Pearson's correlation coefficient=-0.19, p=0.05) (135). Findings from this study and findings from research by Waimann et al are important as RA patients are at an increased risk of developing depression. One study of 3698 newly diagnosed RA patients matched with 7369 subjects without RA found that the RA group were 74% more likely to develop depression than the control group (247). Depression encompasses a range of concerns and negative beliefs (248). An insight into the medication beliefs of patients suffering from depression would provide opportunities for the development of interventions to promote medication adherence among sufferers of depression. Patient diaries may be one such measure of adherence that could provide an insight into patient beliefs. Components of the EQ-5D encompass general health statuses of patients that should be explored in large-scale studies for other chronic conditions where access to healthcare may be affected.

Multivariate analysis of the allocated TRACE-RA intervention and adherence

Characteristics that achieved a p value of 0.10 or less in univariate analysis of predictors of adherence were input into two final multivariate models that were adjusted for age and gender. Smoking status, frequency of alcohol

consumption and EQ-5D responses for pain or discomfort were included in the final model for adherence to the allocated intervention in TRACE-RA. Patient DAS28 scores and EQ-5D responses for self-care were fit into the final model for atorvastatin adherence.

Multivariate analysis showed a statistically non-significant association for poor adherence for current (OR=0.73, 95%CI 0.47-1.13) and former smokers (OR=0.78, 95%CI 0.58-1.05) compared with never smokers. In a study of 329 RA patients by Morgan and co-authors, smoking was not a significant predictor of adherence (196). However, in the general population, findings for current smokers and poorer rates of adherence compared with never smokers accords with the literature. For example, in a cohort of 42847 Australian concession card holders, Warren and colleagues found that smokers were 7% less likely to adhere to statin therapy than those who had never smoked (RR=0.93, 95%CI 0.90-0.95) (165). These findings have been replicated in other large retrospective cohorts (173, 189). For former smokers, findings from the adherence in TRACE-RA study contrast with research of statin adherence in the general population. In a cohort of 6458 primary prevention patients, Halava and colleagues reported better rates of adherence among those who were former smokers compared with those who never smoked (OR for non-adherence=0.83, 95%CI 0.74-0.93) (171). In this study by Halava and colleagues, healthy lifestyle alterations such as changes in diet or exercise following smoking cessation were potential explanations for high rates of medication adherence in former smokers. RA patients may have difficulties with daily activities and exercise. This may make access to healthcare difficult and could explain discrepancies between findings from this study and those general population cohorts. EQ-5D responses from patients of TRACE-RA support this. For example, more than

half of the TRACE-RA population who had a complete pill count up to 12 months reported 'some problems' (56.6%) with 'usual activities' or 'pain or discomfort' (74.7%) at baseline.

Findings from multivariate analysis showed that patients who consumed alcohol on a monthly or less basis were significantly poorer adherers to the trial intervention than those who never consumed alcohol (OR=0.64, 95%CI 0.42-0.97). Previous associations between the frequency of alcohol consumption and poor adherence have been reported in the general population but not in an RA population. In a cohort of 2827 Finnish secondary prevention patients from the general population, those who reported consuming high quantities of alcohol on a regular basis were poorer adherers compared with those who reported never drinking (OR for non-adherence=1.58, 95%CI 1.11-2.25) (171). Low-level use of alcohol (AUDIT-C score between 1-3) compared with no alcohol use (AUDIT-C score of 0) has been associated with lower rates of adherence (63% vs 66% respectively) in one study by Bryson and co-authors (174). This can be attributed to the possibility of unintentional non-adherence following drinking sessions. However, findings from this study may not reflect drinking or medication-taking habits of the general population due to their analysis being performed in a limited cohort of 4989 veterans. As with smoking, alcohol consumption is a lifestyle choice that has been shown to predict poor rates of adherence to statin therapy. Further research is necessary to establish how lifestyle changes affect medication-taking behaviour. This is of particular importance in the RA population where problems with mobility and pain/discomfort are prevalent.

5.4.3 Discussion of predictors of adherence to atorvastatin in TRACE-RA

Univariate analysis of atorvastatin and adherence

Findings from the univariate analysis showed that patients who self-reported extreme pain in were more likely to adhere to the allocated TRACE-RA intervention than those who did not (OR=1.67, 95%CI 0.96-2.90). Only one other study has assessed pain as a potential predictor of adherence in an RA population. In a recent study by Harnett and colleagues of 373 RA patients receiving bDMARD therapy, 45.6% were deemed to have filled their prescription early (and subsequently had more days of medication coverage than those who filled their prescriptions late). In accordance with results from the study of adherence in TRACE-RA, Harnett et al found that higher pain scores as determined by a 100mm VAS predicted earlier refills for prescriptions than lower pain scores (249). Pain is an important component in a patient's perceived severity of disease and may predict their perceived need for medication (136). Understanding how difficulties with usual activities or pain or discomfort effect access to healthcare may provide further insight as to why adherence is sub-optimal.

Multivariate analysis of atorvastatin and adherence

Multivariate analysis showed that patients with a high DAS28 (DAS28 >5.1) compared with those in remission (DAS28 <2.6) were more likely to adhere to atorvastatin (OR=1.64, 95%CI 0.83-3.24). This contrasts with findings from a US study by Waimann and co-authors of MTX adherence in 90 RA patients who had a recorded DAS28 score. Here, patients with a DAS28 of <2.6 were better adherers than those with a score ≥2.6 (β=0.31, 95%CI 0.14-0.49) (135). The small sample of 90 US patients were largely Hispanic in ethnicity (64%

of patients) and most patients (67% of patients) were earning less than <$20,000/year. This limits how these findings transfer to the UK population. The issue of patients not refilling prescriptions in this cohort may be a result of expenses associated with healthcare (211). Further, poor access to healthcare associated with a low income in this cohort may be worsened by poor functionality and mobility associated with RA. In TRACE-RA, tablets were free of charge for patients and so out-of-pocket expenses would not have affected adherence. This study has shown that a high DAS28 score and extreme pain compared with remission and no pain were associated with better adherence in RA patients. As both symptoms and the severity of disease change over time, it can be supposed that the perceived need for medication changes. Whether improvements in pain or DAS28 scores affect adherence to medication in the long term is subject to investigation.

5.5 Strengths and limitations

A number of important limitations of this dissertation need to be considered. Rates of adherence and analysis of potential predictors were determined using pill counts. For this, assumptions were made that no medication dumping had taken place. Biases associated with self-reported measures may explain the higher rates of self-reported adherence compared with pill counts (113, 250). Social desirability bias may have meant that patients reported higher rates of medication consumption in the CRF v3 forms. However, the primary endpoint of TRACE-RA was not adherence and so patients may have been influenced by this. For the lifestyle questionnaires, social desirability bias may have meant that healthy behaviour was over-reported. Finally, the issue of recall bias could have influenced patient responses to the CRF v3 question on adherence. It was possible that some patients provided a response reflective of adherence from the immediate

weeks prior to completing CRF v3 rather than the whole period since the last follow-up visit.

An important limitation of the pill counts methodology used in this study was in the handling of missing data. Missing data were due to patients not returning tablet bottles, no recorded dates of tablet dispensing or no recorded return dates for bottles of tablets. Because adherence was not the primary endpoint in this study, data input for pill counts may not have been prioritised at the hospital pharmacies. Complete case analysis of patients with complete data was performed (see section 4.3). Consequently, if there were missing data for any of the four variables that were used to calculate adherence, a rate could not be produced. In performing a complete case analysis, bias was also introduced as data were not missing completely at random. Further, complete case analysis reduced the number of patients (74.9% of all TRACE-RA patients had complete data for all selected characteristics) that could be included in logistic regression analysis. It is possible that there was a lack of statistical power for these analyses, potentially affecting the confidence intervals attained in this thesis. Given more time, imputation techniques such as multiple imputation could have been used to account for missing data. Alternatively, using the MPR or PDC measures would have included more patients in analyses as patients with missing pill counts would not have been included. However, it is easy to overstate the adherence outcomes using the MPR and a lack of time for performing either measure meant that adherence by pill counts was better suited for this thesis.

Finally, a limitation of the above definition for adherence was the application of an arbitrary threshold that was used to categorise patients.

The 80% threshold that was used in this study was selected to ensure consistency with the literature.

5.6 Importance and opportunities for future work

This is the first study to determine rates of adherence to statin therapy for the primary prevention of CVEs in an RA population. This study offers evidence that supports previously tested predictors of statin adherence. Further, this study provides a novel insight of EQ-5D responses as predictors of adherence to statin therapy. A literature review highlighted the need for homogeneity between studies for methodologies, measures and definitions of adherence. Moreover, limitations of current measures of adherence were brought to light. Recent research has attempted to address these limitations. However, further investigations of the threshold used to dichotomise patients as adherent or non-adherent will help develop an understanding of the relationship between adherence and health outcomes in future research. Current rates of adherence that were reported in the literature did not account for discontinuation of medication and so findings were not representative of adherent behaviour in these cohorts. Commonality among measures of adherence is important and further investigations of measures of adherence will strengthen the field.

The study of adherence in TRACE-RA found that adherence to the trial intervention was sub-optimal. Comparing these findings with other studies proved difficult due to a lack of understanding as to how pill counts correlate with measures of adherence found in the literature. Data for dispense and return dates of tablets in TRACE-RA allow for the calculation of the MPR or PDC, for which more data are available than for pill counts.

Neither was used in this dissertation because of time constraints. However, the use of these would provide a unique opportunity to examine the relationship between pill counts and the number of days covered by medication (as determined by either the PDC or MPR). Such research would make future comparisons more valid. Additionally, future research on the relationship between placebo adherence and health outcomes can be achieved in TRACE-RA. This would add to the growing literature on the healthy adherer effect where good adherence may be a surrogate marker for positive beliefs, motivations and healthy behaviour (238).

This study found that EQ-5D responses for pain and self-care were predictors of statin adherence. Larger studies of adherence than this study may be required to confirm the strength of these associations. Furthermore, how pain and an inability to self-care affect patient beliefs towards their medication or their access to healthcare requires further research. Indeed, what were noticeably lacking in the literature of statin adherence were investigations into the beliefs associated with medication-taking behaviour. Such research may provide a foundation for further investigations of interventions that can be appropriately targeted at those with high concern beliefs of statin use. Future study designs may seek to integrate questions of necessity and concern beliefs in questionnaires. Qualitative research with information from patient diaries, for example, may provide a deeper insight of motivations and beliefs towards treatment. Responses could also be used to determine how beliefs explain predictors of adherence to statin therapy (see table 5.3).

Table 5. 3 A table showing how the findings of this study fit with findings in the literature

Individual perceptions	Modifying factors	Findings
Perceived susceptibility to disease	Sociodemographic factors	↑ **adherence: Increasing age** (142, 155, 157-162, 164-168, 170, 173, 175, 178, 181-187)
		↓ **adherence: Female gender** (162, 167, 168, 175, 178, 181, 182, 185-187)
	Clinical factors	↑ **adherence: Dyslipidaemia** (187), **dyslipidaemia (severe)** (142), **hypertension** (153, 157, 158, 161, 173)
Perceived severity of disease	History of CVD or a CVE	↑ **adherence: ACS** (142, 162), **acute MI** (153, 158), **atherosclerotic disease** (175, 189), **CHD** (142, 175, 178), **CVD** (165), **stroke** (142)
	Comorbidities	↑ **adherence: CKD** (157), **diabetes** (178)
		↓ **adherence: COPD** (157)
	Previous surgery	↑ **adherence: PTCA or CABG** (158, 159)
	Concurrent medications	↑ **adherence: Additional free/cheap concurrent medications** (160, 164, 179)
		↓ **adherence: Additional concurrent medications** (142, 175)
	RA disease activity	↑ **adherence: High than low DAS28 score**
	Pain	↑ **adherence: Extreme pain or discomfort**
		↑ **adherence: Extreme pain or discomfort**
Perceived benefits/ necessity of statin therapy	View of statin therapy	↑ **adherence: Positive view** (170)
Perceived barriers	Co-payment	↓ **adherence: Increasing co-payment** (142, 158, 161, 162, 173, 175, 176, 181, 182, 185, 187, 190)
	Out-of-pocket expenses	↓ **adherence: Increasing out-of-pocket expenses** (142)
	Income	↓ **adherence: A lower than higher income** (159, 164-166, 175)
	Employment	↓ **adherence: Full-time employment compared with unemployed** (165)
		↓ **adherence: Full-time employment compared with part-time employment or retirement**
	View of statin therapy	↓ **adherence: Strong possibility of adverse effects** (156, 166)
	Psychological health	↓ **adherence: Depression** (142, 154, 178, 187), **anxiety** (154), **moderate-very high distress** (165)
		↓ **adherence: Moderately anxious/ depressed**
	Self-care	↓ **adherence: Unable to wash or dress**

ACS= Acute coronary syndrome, CABG= Coronary artery bypass graft, CHD= Coronary heart disease, CKD= Chronic kidney disease, COPD= Chronic obstructive pulmonary disorder, CVD= Cardiovascular disease, MI= Myocardial infarction, PTCA= Percutaneous transluminal coronary angioplasty. A table of how patient perceptions found in the HBM may explain predictors of statin adherence that were identified in this literature review. Findings that are highlighted in red are predictors of statin adherence that were identified in this study. Findings that are highlighted in green are predictors of adherence to the trial intervention that were identified in this study.

5.7 Conclusions from the adherence in TRACE-RA study

In conclusion, this dissertation has shown that around 50% of the TRACE-RA population were adherent to their allocated intervention over the first 12 months of treatment. The explanation for this sub-optimal rate involves attitudes to medicine, social habits and economic factors worthy of careful study. Treatment must not be seen as simply prescribing medication but as a process involving frequent monitoring. This can be achieved through patient-physician concordance and by empowering the patient so that effective methods of self-care are developed. Deeper studies focussing on the course of treatment rather than on the medication alone would be both interesting and informative.

Lifestyle characteristics such as smoking status, frequency of alcohol consumption and additional socioeconomic factors such as employment status both influence and predict adherence to the allocated TRACE-RA intervention; however only the frequency of alcohol consumption achieved statistical significance. It is a well-publicised fact that poor health is related to lifestyle choices. What is not so obvious is the motivational dimension underpinning such choices, probably falling into the socio-psychological field, and which must form part of a treatment regime if adherence is to improve.

EQ-5D responses such as extreme pain also associated with adherence in TRACE-RA, and again, neither was statistically significant. Pain management and perception are two vital aspects of adherence which must form an important facet of statin treatment regimes in RA patients. This may well benefit from a thorough investigation into the prescription of

combinations of medicines and treatment courses: a very complex area though essential to the success of treatment.

This research has implications for future work on adherence in RA populations, predictors of adherence to statin therapy, and targeting interventions such as counselling or adherence programmes towards those most at-risk of poor adherence. It highlights the necessity of viewing treatment as a package involving prescribing attitudes and practice, understanding the wider implications to a patient, and understanding patient motivations and beliefs. This study is just the beginning: it has pointed to the necessity for thorough revision of the measures of adherence, high-powered studies, and the need to better understand patients' beliefs about their medication.

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Appendices

Appendix Table 1 Inclusion and exclusion criteria for TRACE-RA

Inclusion	Exclusion
- Patients who satisfy 1987 ACR classification criteria for RA applied cumulatively - Age ≥50 years OR RA disease duration ≥10 years - Written informed consent	- Already taking a statin - Known CVD deemed to require statin therapy - Diabetes - Regular use of contra-indicated drugs - Primary muscle disease or CK >3 x upper limits of normal - Known familial hyperlipidaemia - Acute liver disease - Severe renal dysfunction (stage 3 or 4) or creatine >200 mmol/l or receiving renal replacement - Uncontrolled hypothyroidism - Hypersensitivity or intolerance to statins - Pregnant, breast feeding or of child bearing potential not using adequate contraception - Alcohol abuse - Participating in another Clinical Trial of Investigational Medicinal Product - Drinking more than 240ml of grapefruit juice per day - Any other serious illness that may compromise safety or trial compliance

ACR= American college of Rheumatology, RA= Rheumatoid Arthritis, CVD= Cardiovascular disease, CK= Creatinine kinase, mmol/L= Micromoles per litre, ml= Millilitres. Inclusion and exclusion criteria for TRACE-RA are shown above.

Appendix Table 2 Primary, secondary and tertiary endpoints of TRACE-RA

Primary endpoints	Secondary and tertiary endpoints
- First major fatal or non-fatal vascular event (coronary events, presumed ischaemic stroke or transient ischaemic attack, any non-coronary revascularisation or any other cardiovascular death excluding both confirmed cerebral haemorrhage and non-coronary cardiac death [ICD I64-99, 10th International Classification of Diseases]) - Non-coronary cardiac death (ICD I00-I15 and ICD I26-I52)	- Separate components of the primary endpoint "first major vascular event" (coronary events, presumed ischaemic stroke or transient ischaemic attack, any non-coronary revascularisation or any other cardiovascular death excluding both confirmed cerebral haemorrhage and non-coronary cardiac death [ICD I64-99, 10th International Classification of Diseases]) - All-cause mortality - Hospitalisations - Functional outcome as determined by the HAQ and EQ-5D - Changes in lipid levels across a random sample (over follow up) - Statin safety related outcomes (ie. Myopathy as defined by CK>10x upper limit

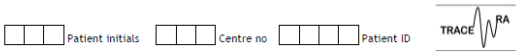
ICD= International Classification of Diseases, HAQ= Health assessment questionnaire, EQ-5D= EuroQol-5D questionnaire, CK= Creatinine kinase. Primary, secondary and tertiary endpoints are shown above.

Appendix Table 3 Components of the TRACE-RA lifestyle questionnaire

Number	Field
1	Date of birth
2	Gender
3	Ethnicity
4a	"Have you EVER smoked more than one cigarette a day?" Yes/No
4b	"If you EVER smoked, please could you state: - How many cigarettes per day - Age you started smoking - Age you stopped smoking"
4c	"Do you CURRENTLY smoke more than one cigarette a day?" Yes/No - If YES, how many cigarettes do you smoke per day?
5a	Frequency of alcohol consumption
5b	Average number of units consumed per week
6	Exercise
7	Education
8	Area of residence
9a	Occupation
9b	Amount of physical activity in a patient's "daily life"
10	Diet and food consumption

A synopsis of the content of the lifestyle questionnaire that was completed by participants at baseline. Lifestyle questionnaires were completed at baseline upon registration for TRACE-RA and at the end of trial.

Appendix Figure 1 Pages 1 and 2 of the lifestyle questionnaire



ARTHRITIS RESEARCH CAMPAIGN & BRITISH HEART FOUNDATION

TRACE RA CLINICAL TRIAL

Trial of Atorvastatin for the Primary Prevention
of Cardiovascular Events in Rheumatoid Arthritis

PATIENT LIFESTYLE QUESTIONNAIRE

This questionnaire is designed to help us understand whether certain aspects of lifestyle contribute to the development of heart disease in people with rheumatoid arthritis and if they affect response to treatment.

LIFESTYLE QUESTIONNAIRE (Page 1 of 3)

Today's date

1. Date of Birth

2. Sex — Male ☐ Female ☐

3. **Ethnic Group**
Please choose ONE section from A to E, and then tick the appropriate box to indicate your cultural background

A. WHITE
☐ British ☐ Irish ☐ Other → Please specify

B. MIXED
☐ Black Carribean /White ☐ Asian/ White ☐ Other → Please specify

C. ASIAN/ASIAN BRITISH
☐ Indian ☐ Bangladeshi ☐ Pakistani
☐ Other → Please specify

D. BLACK/BLACK BRITISH
☐ African ☐ Carribean ☐ Other → Please specify

E. CHINESE OR OTHER ETHNIC GROUP
☐ Chinese
☐ Other → Please specify

4. **Smoking**
a) Have you EVER smoked more than one cigarette a day? Yes ☐ No ☐
b) If you have EVER smoked, please could you state:
How many cigarettes you smoked per day
Age you started smoking
Age you stopped smoking
c) Do you CURRENTLY smoke more than one cigarette a day? Yes ☐ No ☐
If YES, how many cigarettes do you smoke per day?

5. **Alcohol**
a) Please tick ONE box to state how often you have a drink containing alcohol
☐ Never ☐ Monthly or less ☐ 2-4 times per month ☐ 2-3 times a week ☐ 4 or more times a week
b) Please state the number of units of alcohol you drink in an average week
NB One unit = half a pint of beer OR a glass of wine OR a single measure of spirits

CONTINUED OVERLEAF...
TRACE RA LIFE/1/2006

Appendix Figure 2 Pages 3 and 4 of the lifestyle questionnaire

Patient initials | Centre no | Patient ID

TRACE RA

LIFESTYLE QUESTIONNAIRE (Page 2 of 3)

6. EXERCISE
Please tick ONE box to state how often you exercise (for example, brisk walking, jogging, swimming, aerobics, or cycling for at least 20 minutes without stopping and sufficient enough to make you breathe more heavily and your heart beat faster) each week

- ☐ Never
- ☐ Monthly or less
- ☐ 2-4 times per month
- ☐ 2-3 times a week
- ☐ 4 or more times a week

7. EDUCATION
At what age did you leave full time education? ☐☐

8. AREA OF RESIDENCE
Please state the postcode of the area in the UK in which you permanently reside ☐☐☐☐ ☐☐☐☐

9. OCCUPATION/EMPLOYMENT
a) Please tick the ONE box which best describes what you are doing AT THE MOMENT

- ☐ Working for an employer full-time (more than 30 hours a week)
- ☐ Working for an employer part time (1 hour a week or more)
- ☐ Self-employed full-time (more than 30 hours a week)
- ☐ Self-employed part time (1 hour a week or more)
- ☐ Working full-time at home
- ☐ Unemployed but seeking work
- ☐ Not working due to long-term sickness or disability
- ☐ Student
- ☐ Semi-retired
- ☐ Retired

b) Please tick the ONE box which best describes the type and amount of physical activity involved in your daily life

- ☐ SEDENTARY occupation or lifestyle
  You spend MOST of your time sitting (such as in an office)
- ☐ STANDING occupation or lifestyle
  You spend MOST of your time walking or standing; however, the way you spend your time does not require intense physical effort (eg shop assistant, guard, hairdresser)
- ☐ PHYSICAL occupation or lifestyle
  This involves some physical effort, including handling of heavy objects and use of tools/instruments (eg nurse, plumber, cleaner, sports instructor, electrician, carpenter)
- ☐ HEAVY MANUAL occupation or lifestyle
  This involves very vigorous physical activity including handling of very heavy objects (eg docker, builder, bricklayer, construction worker)

CONTINUED OVERLEAF...

Patient initials | Centre no | Patient ID

TRACE RA

LIFESTYLE QUESTIONNAIRE (Page 3 of 3)

10. DIET AND FOOD CONSUMPTION
How often do you eat the following foods?

	NEVER	SELDOM	ONCE A WEEK	2-4 TIMES A WEEK	5-6 TIMES A WEEK	ONCE DAILY OR MORE	DON'T KNOW
FRESH FRUIT Eg apples, oranges, pears	☐	☐	☐	☐	☐	☐	☐
GREEN LEAFY VEGETABLES Eg cabbage, broccoli	☐	☐	☐	☐	☐	☐	☐
OTHER VEGETABLES Eg peas, carrots, beans, tomatoes	☐	☐	☐	☐	☐	☐	☐
FATTY FISH Eg herring, sprats, pilchards, mackerel	☐	☐	☐	☐	☐	☐	☐
OTHER FISH Eg cod, tuna, haddock	☐	☐	☐	☐	☐	☐	☐
CHICKEN	☐	☐	☐	☐	☐	☐	☐
MEAT Eg chops, roast, stews	☐	☐	☐	☐	☐	☐	☐
MEAT PRODUCTS Eg sausages, ham, beef burgers	☐	☐	☐	☐	☐	☐	☐
EGGS	☐	☐	☐	☐	☐	☐	☐
CHEESE	☐	☐	☐	☐	☐	☐	☐
WHOLEMEAL/BROWN BREAD	☐	☐	☐	☐	☐	☐	☐

THANK YOU FOR TAKING THE TIME TO COMPLETE THIS QUESTIONNAIRE

Please return it to:-

TRACE RA OFFICE
arc Epidemiology Unit
The University of Manchester
Stopford Building, Oxford Road
Manchester M13 9PT

Appendix Table 4 Differences between registration forms

	CRF version 1	CRF version 2 (07/2008)	CRF version 3 (12/2010)
Registration form	- No barcode for biobank	- Barcode for biobank	- Barcode for biobank
	- Date of consent for biobank/ TRACE-RA-DAS	- Date of consent for biobank/ TRACE-RA-DAS - Option for full use of cellular material or DNA only (biobank)	- No date of consent for biobank/ TRACE-RA DAS - Option for full use of cellular material or DNA only (biobank)

Appendix Table 5 Differences between baseline information forms

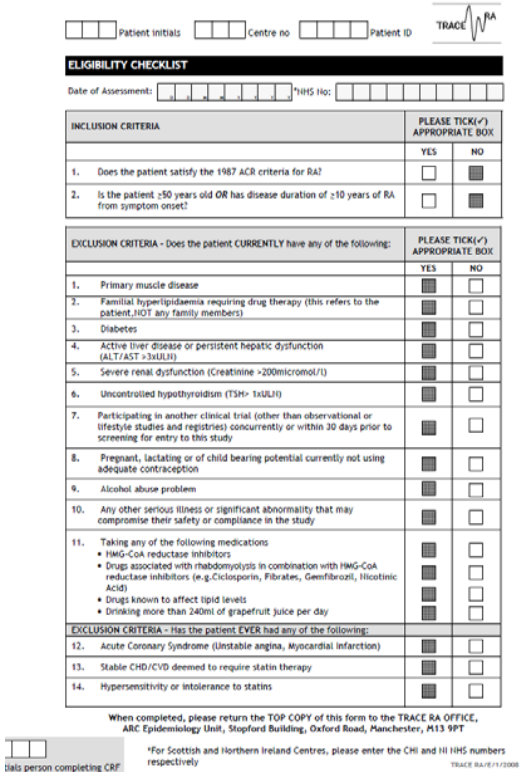
	CRF version 1	CRF version 2 (07/2008)	CRF version 3 (12/2010)
Baseline information form	- Questions on familial CVD, diabetes, adequate contraception and menopause	- Questions on familial CVD, diabetes, adequate contraception and menopause	- No questions on familial CVD, diabetes, adequate contraception and menopause
	- Hypertension? Yes/No/Don't know/N.A	- Hypertension? Yes/No/Don't know/N.A	- Hypertension? Yes/No/Unsure
	- Option for a pulse reading	- Option for a pulse reading	- No option for a pulse reading
	- Two readings for blood pressure	- Two readings for blood pressure	- One reading for blood pressure
	- Option for waist measurement	- Option for waist measurement	- No option for waist measurement
	- ECG assessment date	- ECG assessment date	- No ECG assessment date
	- Values for the components used to calculate the DAS28 are input in the baseline form	- Values for the components used to calculate the DAS28 are input in the baseline form	- Values for the components used to calculate the DAS28 are input in the DAS SCORE form
	- Early morning stiffness recorded	- Early morning stiffness recorded	- Early morning stiffness not recorded
	- Nodules recorded	- Nodules recorded	- Nodules not recorded
	- Values are taken for haemoglobin, platelets, total WBC, neutrophils, creatine kinase, AST, ALT and glucose	- Values are taken for haemoglobin, platelets, total WBC, neutrophils, creatine kinase, AST, ALT and glucose	- No values are taken for haemoglobin, platelets, total WBC, neutrophils, creatine kinase, AST, ALT and glucose
	- Value for RhF levels can be recorded	- Values for RhF and anti-CCP levels can be recorded	- Status for RhF positivity and a value for anti-CCP can be recorded
	- No date for lipid profile can be recorded	- Date for lipid profile can be recorded	- Dates for TC, LDL, HDL and triglycerides can be recorded

	- Open text box for concurrent medication, dose and frequency	- Open text box for concurrent medication, dose and frequency	- Yes/no/unsure for a set-list of sDMARDs, bDMARDs and other treatment
	- Patient VAS for pain and fatigue	- Patient VAS for pain and fatigue	- No patient VAS for pain and fatigue

Appendix Table 6 Differences between follow up forms

	CRF version 1	CRF version 2 (07/2008)	CRF version 3 (12/2010)
Follow up form	- No question on how the follow-up was being conducted - MI is considered as a cardiovascular outcome - Open text box to input adverse events, seriousness, severity, causality, expectedness and outcome - Open text box for concurrent medication, dose and frequency - No questions on statin adherence - Dichotomous yes/no for the completion of HAQ-DI and EQ-5D - Values are recorded for haemoglobin, platelets, total WBC and neutrophils - No question on how the next follow-up will be conducted - No reasons for statin discontinuation recorded	- No question on how the follow-up was being conducted - MI is considered as a cardiovascular outcome - Open text box to input adverse events, seriousness, severity, causality, expectedness and outcome - Open text box for concurrent medication, dose and frequency - No questions on statin adherence - Dichotomous yes/no for the completion of HAQ-DI and EQ-5D - Values are recorded for haemoglobin, platelets, total WBC and neutrophils - No question on how the next follow-up will be conducted - No reasons for statin discontinuation recorded	- Question on how the follow-up was being conducted - Stroke and MI are considered as cardiovascular outcomes - Dichotomous yes/no for a set-list of SAEs - Dichotomous yes/no(or unsure) for a set-list of sDMARDs, bDMARDs and other treatment - Question on statin adherence - No dichotomous yes/no for the completion of HAQ-DI and EQ-5D - Values are not recorded for haemoglobin, platelets, total WBC and neutrophils - Question on how the next follow-up will be conducted - Reasons for statin discontinuation recorded

Appendix Figure 3 Pages 1,2 and 3 of CRF v2



Patient initials | Centre no | Patient ID | TRACE RA

ELIGIBILITY CHECKLIST

Date of Assessment: | *NHS No:

INCLUSION CRITERIA	PLEASE TICK(✓) APPROPRIATE BOX	
	YES	NO
1. Does the patient satisfy the 1987 ACR criteria for RA?	☐	■
2. Is the patient ≥50 years old OR has disease duration of ≥10 years of RA from symptom onset?	☐	■

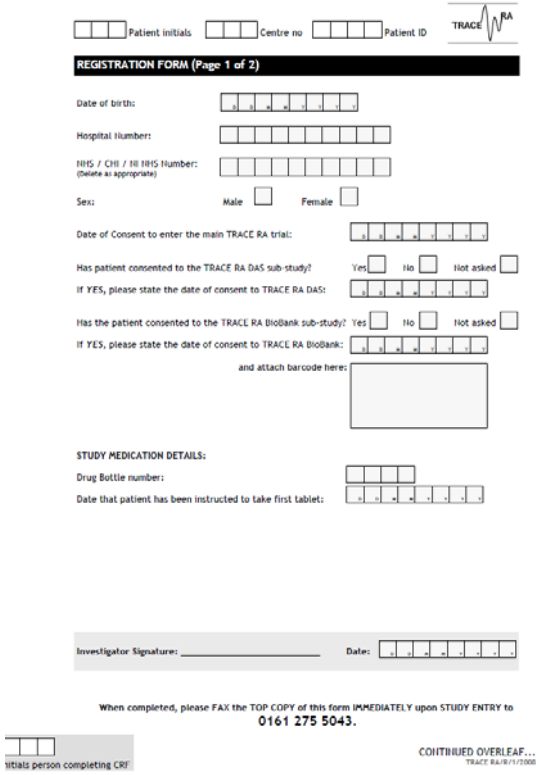
EXCLUSION CRITERIA - Does the patient CURRENTLY have any of the following:	PLEASE TICK(✓) APPROPRIATE BOX	
	YES	NO
1. Primary muscle disease	■	☐
2. Familial hyperlipidaemia requiring drug therapy (this refers to the patient,NOT any family members)	■	☐
3. Diabetes	■	☐
4. Active liver disease or persistent hepatic dysfunction (ALT/AST >3xULN)	■	☐
5. Severe renal dysfunction (Creatinine >200micromol/l)	■	☐
6. Uncontrolled hypothyroidism (TSH> 1xULH)	■	☐
7. Participating in another clinical trial (other than observational or lifestyle studies and registries) concurrently or within 30 days prior to screening for entry to this study	■	☐
8. Pregnant, lactating or of child bearing potential currently not using adequate contraception	■	☐
9. Alcohol abuse problem	■	☐
10. Any other serious illness or significant abnormality that may compromise their safety or compliance in the study	■	☐
11. Taking any of the following medications • HMG-CoA reductase inhibitors • Drugs associated with rhabdomyolysis in combination with HMG-CoA reductase inhibitors (e.g.Ciclosporin, Fibrates, Gemfibrozil, Nicotinic Acid) • Drugs known to affect lipid levels • Drinking more than 240ml of grapefruit juice per day	■ ■ ■ ■	☐ ☐ ☐ ☐
EXCLUSION CRITERIA - Has the patient EVER had any of the following:		
12. Acute Coronary Syndrome (Unstable angina, Myocardial infarction)	■	☐
13. Stable CHD/CVD deemed to require statin therapy	■	☐
14. Hypersensitivity or intolerance to statins	■	☐

When completed, please return the TOP COPY of this form to the TRACE RA OFFICE, ARC Epidemiology Unit, Stopford Building, Oxford Road, Manchester, M13 9PT

Initials person completing CRF

*For Scottish and Northern Ireland Centres, please enter the CHI and NI NHS numbers respectively

TRACE RA/F/1/2008



Patient initials | Centre no | Patient ID | TRACE RA

REGISTRATION FORM (Page 1 of 2)

Date of birth:

Hospital Number:

NHS / CHI / NI NHS Number: (Delete as appropriate)

Sex: Male ☐ Female ☐

Date of Consent to enter the main TRACE RA trial:

Has patient consented to the TRACE RA DAS sub-study? Yes ☐ No ☐ Not asked ☐

If YES, please state the date of consent to TRACE RA DAS:

Has the patient consented to the TRACE RA BioBank sub-study? Yes ☐ No ☐ Not asked ☐

If YES, please state the date of consent to TRACE RA BioBank:

and attach barcode here:

STUDY MEDICATION DETAILS:

Drug Bottle number:

Date that patient has been instructed to take first tablet:

Investigator Signature: _____ Date:

When completed, please FAX the TOP COPY of this form IMMEDIATELY upon STUDY ENTRY to 0161 275 5043.

Initials person completing CRF

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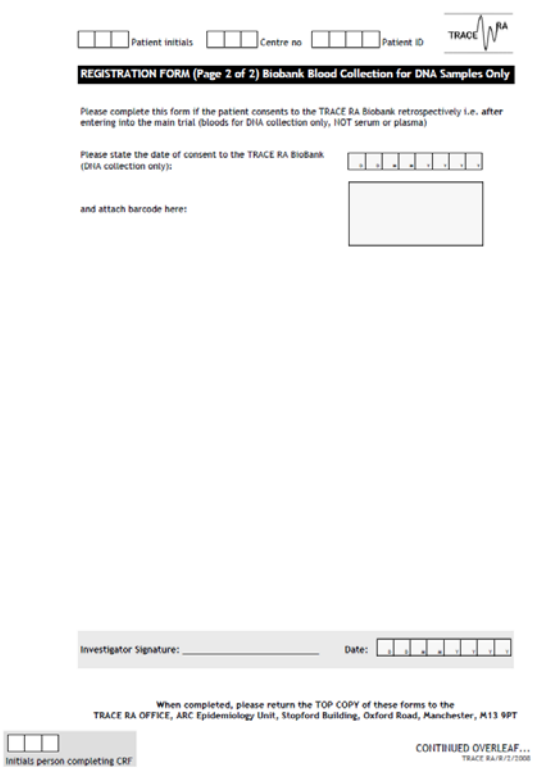
TRACE RA/R/1/2008



Patient initials | Centre no | Patient ID | TRACE RA

REGISTRATION FORM (Page 2 of 2) Biobank Blood Collection for DNA Samples Only

Please complete this form if the patient consents to the TRACE RA Biobank retrospectively i.e. after entering into the main trial (bloods for DNA collection only, NOT serum or plasma)

Please state the date of consent to the TRACE RA BioBank (DNA collection only):

and attach barcode here:

Investigator Signature: _____ Date:

When completed, please return the TOP COPY of these forms to the TRACE RA OFFICE, ARC Epidemiology Unit, Stopford Building, Oxford Road, Manchester, M13 9PT

Initials person completing CRF

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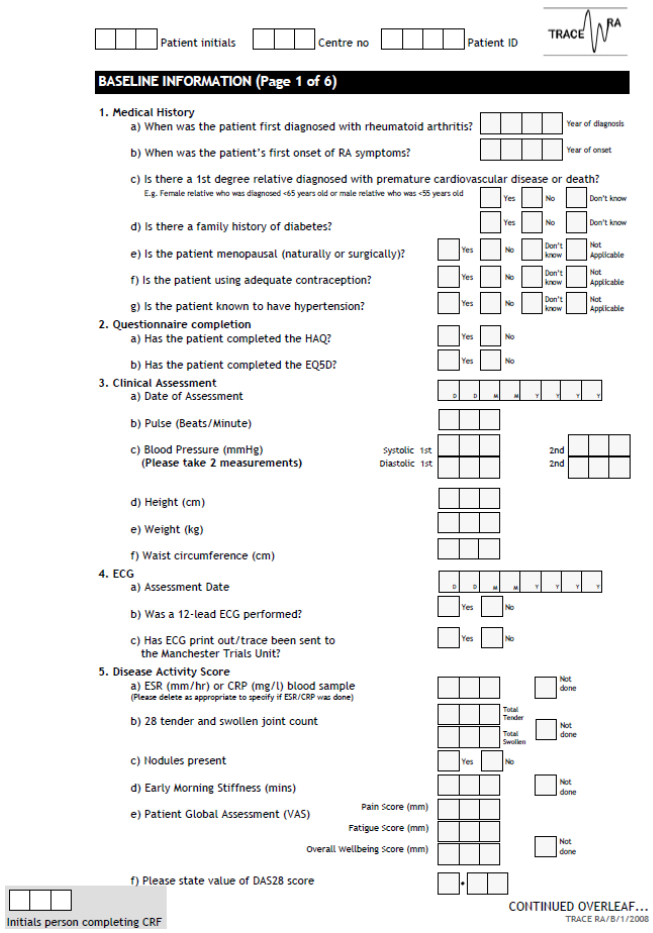
TRACE RA/R/2/2008

Appendix Figure 4 Pages 4 and 5 of CRF v2



Patient initials | Centre no | Patient ID | TRACE RA

BASELINE INFORMATION (Page 1 of 6)

1. Medical History

a) When was the patient first diagnosed with rheumatoid arthritis? Year of diagnosis

b) When was the patient's first onset of RA symptoms? Year of onset

c) Is there a 1st degree relative diagnosed with premature cardiovascular disease or death?
E.g. Female relative who was diagnosed <65 years old or male relative who was <55 years old — Yes / No / Don't know

d) Is there a family history of diabetes? — Yes / No / Don't know

e) Is the patient menopausal (naturally or surgically)? — Yes / No / Don't know / Not Applicable

f) Is the patient using adequate contraception? — Yes / No / Don't know / Not Applicable

g) Is the patient known to have hypertension? — Yes / No / Don't know / Not Applicable

2. Questionnaire completion

a) Has the patient completed the HAQ? — Yes / No

b) Has the patient completed the EQ5D? — Yes / No

3. Clinical Assessment

a) Date of Assessment — D D M M Y Y Y Y

b) Pulse (Beats/Minute)

c) Blood Pressure (mmHg) **(Please take 2 measurements)** — Systolic 1st / Diastolic 1st; 2nd / 2nd

d) Height (cm)

e) Weight (kg)

f) Waist circumference (cm)

4. ECG

a) Assessment Date — D D M M Y Y Y Y

b) Was a 12-lead ECG performed? — Yes / No

c) Has ECG print out/trace been sent to the Manchester Trials Unit? — Yes / No

5. Disease Activity Score

a) ESR (mm/hr) or CRP (mg/l) blood sample
(Please delete as appropriate to specify if ESR/CRP was done) — Not done

b) 28 tender and swollen joint count — Total Tender; Total Swollen; Not done

c) Nodules present — Yes / No

d) Early Morning Stiffness (mins) — Not done

e) Patient Global Assessment (VAS) — Pain Score (mm); Fatigue Score (mm); Overall Wellbeing Score (mm); Not done

f) Please state value of DAS28 score

Initials person completing CRF

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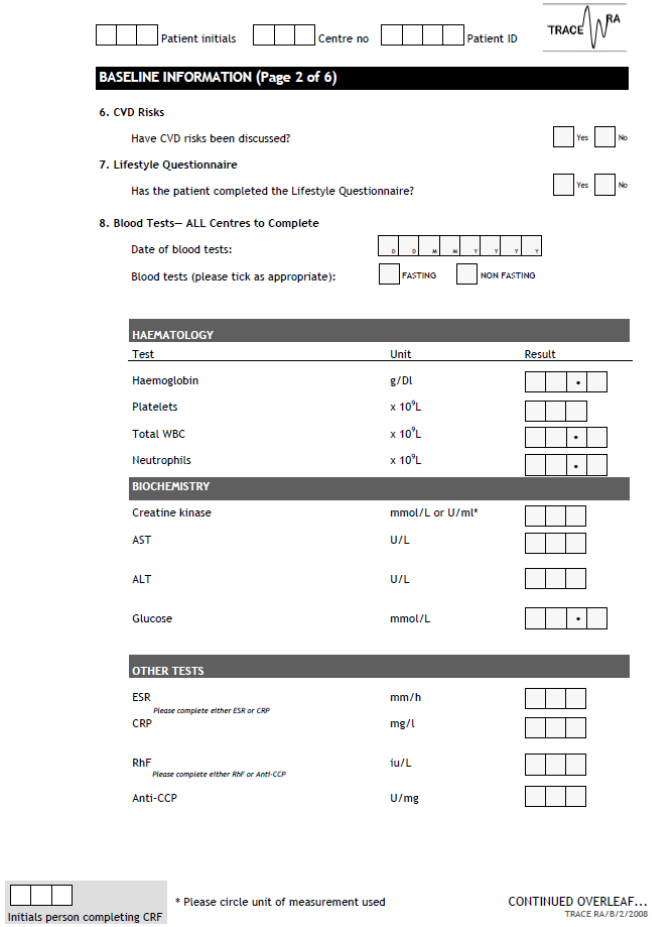
TRACE RA/B/1/2008



Patient initials | Centre no | Patient ID | TRACE RA

BASELINE INFORMATION (Page 2 of 6)

6. CVD Risks

Have CVD risks been discussed? — Yes / No

7. Lifestyle Questionnaire

Has the patient completed the Lifestyle Questionnaire? — Yes / No

8. Blood Tests– ALL Centres to Complete

Date of blood tests: D D M M Y Y Y Y

Blood tests (please tick as appropriate): FASTING / NON FASTING

HAEMATOLOGY		
Test	Unit	Result
Haemoglobin	g/Dl	.
Platelets	x 10^9L	
Total WBC	x 10^9L	.
Neutrophils	x 10^9L	.
BIOCHEMISTRY		
Creatine kinase	mmol/L or U/ml*	
AST	U/L	
ALT	U/L	
Glucose	mmol/L	.
OTHER TESTS		
ESR *Please complete either ESR or CRP*	mm/h	
CRP	mg/l	
RhF *Please complete either RhF or Anti-CCP*	iu/L	
Anti-CCP	U/mg	

Initials person completing CRF

* Please circle unit of measurement used

CONTINUED OVERLEAF...

TRACE RA/B/2/2008

Appendix Figure 5 Pages 6 and 7 of CRF v2

Patient initials | Centre no | Patient ID | TRACE RA

BASELINE INFORMATION (Page 3 of 6)

9. SUPPLEMENTARY BLOOD TESTS FOR CENTRES THAT ROUTINELY SCREEN FOR CARDIOVASCULAR RISK

LIPID PROFILE

Date of blood tests: D D M M Y Y Y Y

Blood tests (please tick as appropriate): ☐ FASTING ☐ NON-FASTING

Test	Unit	Result
Total Cholesterol	mmol/L	.
HDL	mmol/L	.
LDL	mmol/L	.
Triglycerides	mmol/L	.

Initials person completing CRF

CONTINUED OVERLEAF...

TRACE RA/B/3/2008

Patient initials | Centre no | Patient ID | TRACE RA

BASELINE INFORMATION: CONCOMITANT MEDICATION (Page 4 of 6)

DMARD Therapy, Oral Steroids and Steroid Injections

Medication (Generic Name)	Dose	Frequency	Treatment start date
			Start D D M M Y Y Y Y
			Start D D M M Y Y Y Y
			Start D D M M Y Y Y Y
			Start D D M M Y Y Y Y
			Start D D M M Y Y Y Y

NSAID Therapy (excluding low dose aspirin)

Medication (Generic Name)	Dose	Frequency	Treatment start date
			Start D D M M Y Y Y Y
			Start D D M M Y Y Y Y
			Start D D M M Y Y Y Y

Any other medication (including low dose aspirin)

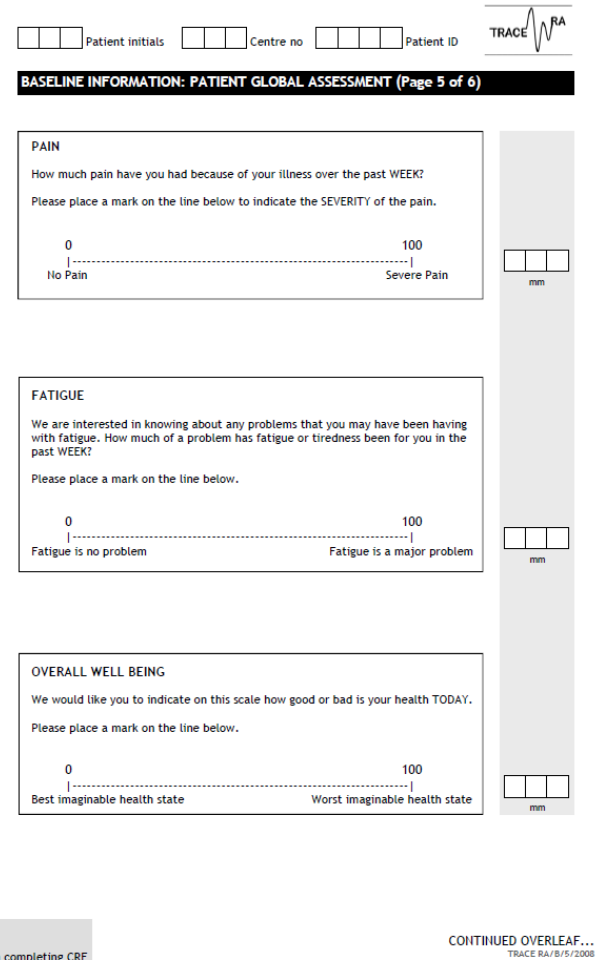
Medication (Generic Name)	Dose	Frequency	Medication (Generic Name)	Dose	Frequency

Initials person completing CRF

CONTINUED OVERLEAF...

TRACE RA/B/4/2008

Appendix Figure 6 Pages 8 and 9 of CRF v2



Patient initials | Centre no | Patient ID | TRACE RA

BASELINE INFORMATION: PATIENT GLOBAL ASSESSMENT (Page 5 of 6)

PAIN

How much pain have you had because of your illness over the past WEEK?

Please place a mark on the line below to indicate the SEVERITY of the pain.

0 — 100

No Pain — Severe Pain

mm

FATIGUE

We are interested in knowing about any problems that you may have been having with fatigue. How much of a problem has fatigue or tiredness been for you in the past WEEK?

Please place a mark on the line below.

0 — 100

Fatigue is no problem — Fatigue is a major problem

mm

OVERALL WELL BEING

We would like you to indicate on this scale how good or bad is your health TODAY.

Please place a mark on the line below.

0 — 100

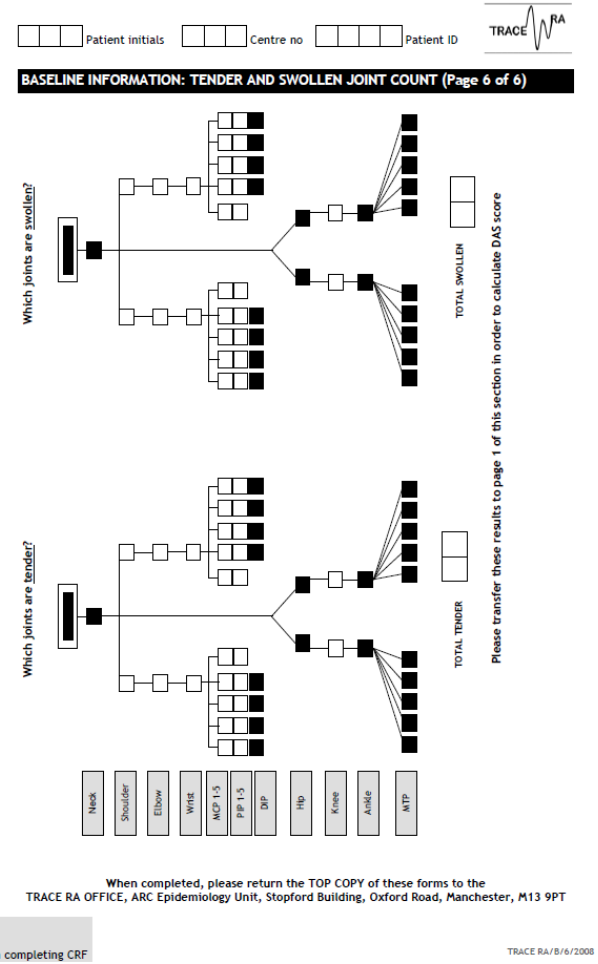
Best imaginable health state — Worst imaginable health state

mm

Initials person completing CRF

CONTINUED OVERLEAF...

TRACE RA/B/5/2008



Patient initials | Centre no | Patient ID | TRACE RA

BASELINE INFORMATION: TENDER AND SWOLLEN JOINT COUNT (Page 6 of 6)

Which joints are swollen?

TOTAL SWOLLEN

Which joints are tender?

TOTAL TENDER

Please transfer these results to page 1 of this section in order to calculate DAS score

Neck | Shoulder | Elbow | Wrist | MCP 1-5 | PIP 1-5 | DIP | Hip | Knee | Ankle | MTP

When completed, please return the TOP COPY of these forms to the TRACE RA OFFICE, ARC Epidemiology Unit, Stopford Building, Oxford Road, Manchester, M13 9PT

Initials person completing CRF

TRACE RA/B/6/2008

Appendix Figure 7 Pages 1 and 2 of CRF v3

Patient Initials ☐☐☐ Centre No ☐☐☐ Patient ID ☐☐☐☐ *Add ID when eligibility confirmed & consent given

TRACE RA

TRACE RA TRIAL: SCREENING FORM

Date of Assessment: D D M M Y Y Y Y NHS/CHI No: ☐☐☐☐☐☐☐☐☐☐

INCLUSION CRITERIA: BOTH must be YES to be eligible

Yes	No	
☐	☐	Does the patient satisfy the 1987 ACR (American College Rheumatology) criteria for RA?
☐	☐	Is the patient >50 years old OR if <50 years old has had RA for > 10 years?

If both 'YES' - proceed below

EXCLUSION CRITERIA: All MUST be NO to be eligible

Yes	No	
☐	☐	Already taking a statin
☐	☐	Known cardiovascular disease deemed to require statin therapy
☐	☐	Diabetes
☐	☐	Regular use of contra-indicated drugs (see back of form)
☐	☐	Primary muscle disease or CK>3xULN
☐	☐	Known familial hyperlipidaemia
☐	☐	Acute liver disease
☐	☐	Severe Renal dysfunction (Stage 3 or 4) or creatinine > 200 µmol/l or receiving renal replacement
☐	☐	Uncontrolled hypothyroidism
☐	☐	Hypersensitivity or intolerance to statins
☐	☐	Pregnant, breast feeding or of child bearing potential currently not using adequate contraception
☐	☐	Alcohol abuse
☐	☐	Participating in another Clinical Trial of Investigational Medicinal Product (CTIMP)
☐	☐	Any other serious illness that may compromise safety or trial compliance

If all above are 'NO' - please proceed below

Blood Results (within 6 weeks) - please round up to whole numbers

ALT (U/L) OR if ALT not available ☐☐☐ D D M M Y Y Y Y **Upper reference range for ALT** ☐☐☐

AST (U/L) ☐☐☐ D D M M Y Y Y Y **Upper reference range for AST** ☐☐☐

If ALT (or AST) ≤3 x ULN, patient is eligible.
Please take consent and proceed to registration & randomisation/baseline forms

Signature of Principal Investigator/Co-Investigator _____

Printed Name _____ **Date:** D D M M Y Y Y Y

ONCE COMPLETED, PLEASE MAKE A PHOTOCOPY & SEND ORIGINAL TO MANCHESTER CO-ORDINATING CENTRE
–RETAIN PHOTOCOPY AT SITE

TRACE RA/Scrn/3.0/2010

TRACE RA

DEFINITIONS

CONTRAINDICATED DRUGS (and brand names)

Patients already taking the following are NOT eligible for the trial

Statins:

- atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor), pitavastatin (Livalo), pravastatin (Lipostat), rosuvastatin (Crestor), simvastatin (Zocor)

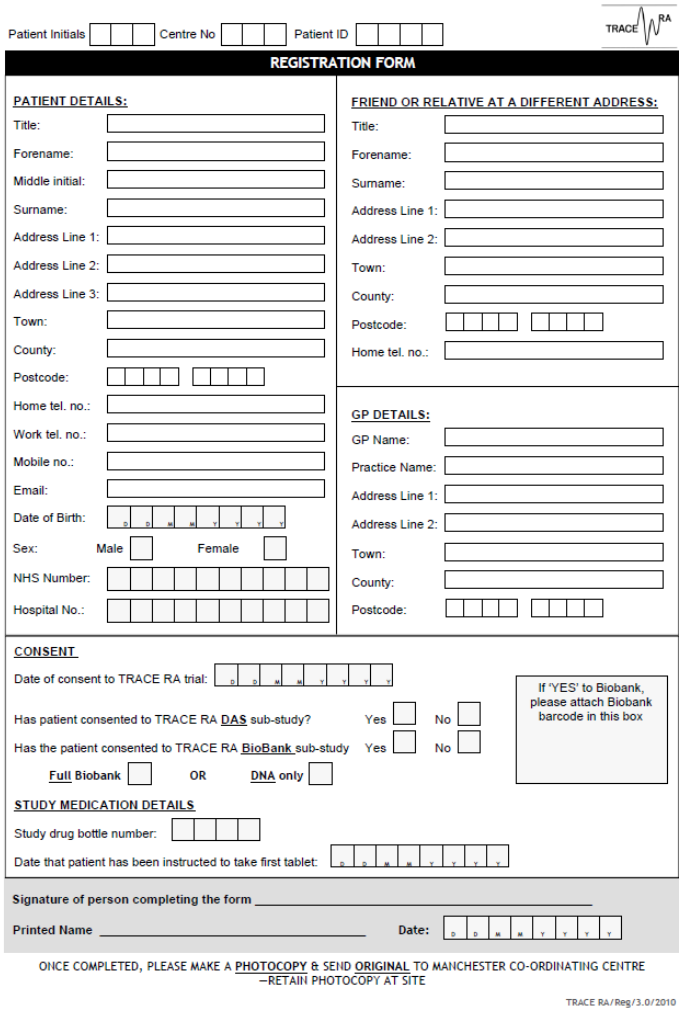
Other contraindicated drugs:

- i.e. amiodarone, azole anti-fungals (Fluconazole, Ketoconazole, Itraconazole), ciclosporin, fibrates, HIV protease inhibitors, macrolide antibiotics (erythromycin, telithromycin, clarithromycin), Niacin, verapamil

Drugs known to affect lipid levels:

- e.g. Colestipol, Ezetimibe
- **Drinking more than 240ml of grapefruit juice per day**

Appendix Figure 8 Pages 3 and 4 of CRF v3



Patient Initials | Centre No | Patient ID

TRACE RA

REGISTRATION FORM

PATIENT DETAILS:

Title:
Forename:
Middle initial:
Surname:
Address Line 1:
Address Line 2:
Address Line 3:
Town:
County:
Postcode:
Home tel. no.:
Work tel. no.:
Mobile no.:
Email:
Date of Birth: D D M M Y Y Y Y
Sex: Male Female
NHS Number:
Hospital No.:

FRIEND OR RELATIVE AT A DIFFERENT ADDRESS:

Title:
Forename:
Surname:
Address Line 1:
Address Line 2:
Town:
County:
Postcode:
Home tel. no.:

GP DETAILS:

GP Name:
Practice Name:
Address Line 1:
Address Line 2:
Town:
County:
Postcode:

CONSENT

Date of consent to TRACE RA trial: D D M M Y Y Y Y

Has patient consented to TRACE RA **DAS** sub-study? Yes No

Has the patient consented to TRACE RA **BioBank** sub-study Yes No

Full Biobank OR **DNA only**

If 'YES' to Biobank, please attach Biobank barcode in this box

STUDY MEDICATION DETAILS

Study drug bottle number:

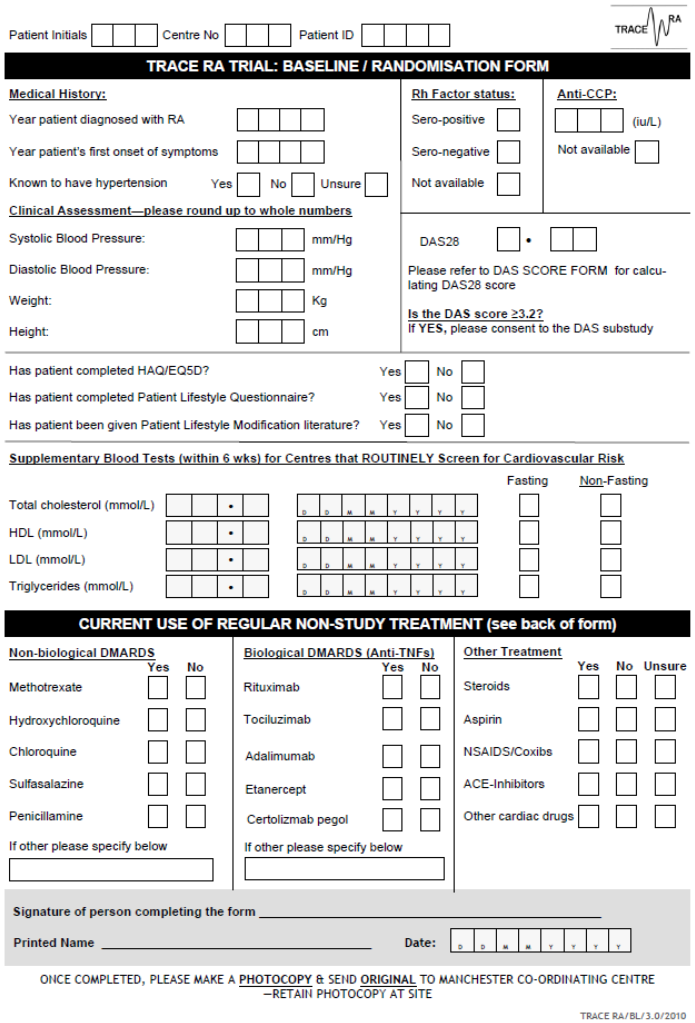
Date that patient has been instructed to take first tablet: D D M M Y Y Y Y

Signature of person completing the form _____

Printed Name _____ **Date:** D D M M Y Y Y Y

ONCE COMPLETED, PLEASE MAKE A **PHOTOCOPY** & SEND **ORIGINAL** TO MANCHESTER CO-ORDINATING CENTRE
–RETAIN PHOTOCOPY AT SITE

TRACE RA/Reg/3.0/2010



Patient Initials | Centre No | Patient ID

TRACE RA

TRACE RA TRIAL: BASELINE / RANDOMISATION FORM

Medical History:

Year patient diagnosed with RA
Year patient's first onset of symptoms
Known to have hypertension Yes No Unsure

Clinical Assessment—please round up to whole numbers

Systolic Blood Pressure: mm/Hg
Diastolic Blood Pressure: mm/Hg
Weight: Kg
Height: cm

Rh Factor status:

Sero-positive
Sero-negative
Not available

Anti-CCP:

(iu/L)
Not available

DAS28 .

Please refer to DAS SCORE FORM for calculating DAS28 score

Is the DAS score ≥3.2?
If YES, please consent to the DAS substudy

Has patient completed HAQ/EQ5D? Yes No
Has patient completed Patient Lifestyle Questionnaire? Yes No
Has patient been given Patient Lifestyle Modification literature? Yes No

Supplementary Blood Tests (within 6 wks) for Centres that ROUTINELY Screen for Cardiovascular Risk

		Fasting	Non-Fasting
Total cholesterol (mmol/L)	D D M M Y Y Y Y		
HDL (mmol/L)	D D M M Y Y Y Y		
LDL (mmol/L)	D D M M Y Y Y Y		
Triglycerides (mmol/L)	D D M M Y Y Y Y		

CURRENT USE OF REGULAR NON-STUDY TREATMENT (see back of form)

Non-biological DMARDS

	Yes	No
Methotrexate		
Hydroxychloroquine		
Chloroquine		
Sulfasalazine		
Penicillamine		

If other please specify below

Biological DMARDS (Anti-TNFs)

	Yes	No
Rituximab		
Tociluzimab		
Adalimumab		
Etanercept		
Certolizmab pegol		

If other please specify below

Other Treatment

	Yes	No	Unsure
Steroids			
Aspirin			
NSAIDS/Coxibs			
ACE-Inhibitors			
Other cardiac drugs			

Signature of person completing the form _____

Printed Name _____ **Date:** D D M M Y Y Y Y

ONCE COMPLETED, PLEASE MAKE A **PHOTOCOPY** & SEND **ORIGINAL** TO MANCHESTER CO-ORDINATING CENTRE
–RETAIN PHOTOCOPY AT SITE

TRACE RA/BL/3.0/2010

Appendix Figure 9 Pages 5 and 6 of CRF v3

TRACE RA

DEFINITIONS

CONTRAINDICATED DRUGS (and brand names)

Statins:

- Atorvastatin (Lipitor), Fluvastatin (Lescol), Lovastatin (Mevacor), Pitavastatin (Livalo), Pravastatin (Lipostat), Rosuvastatin (Crestor), Simvastatin (Zocor)

Other medicines:

- i.e. amiodarone, azole anti-fungals (fluconazole, ketoconazole, itraconazole), ciclosporin, fibrates, HIV protease inhibitors, macrolide antibiotics (erythromycin, telithromycin, clarithromycin), niacin, verapamil

Drugs known to affect lipid levels

- e.g. ezetimibe, colestipol
- **Drinking more than 240ml of grapefruit juice per day**

REGULAR NON-STUDY TREATMENT (and brand names)

Non-biological Disease Modifying Anti-Rheumatic Drugs (DMARDs):

- e.g. azathioprine (imuran), chloroquine, hydroxychloroquine, IM gold injections, leflunomide (arava), methotrexate, penicillamine, sulfasalazine (salazopyrin) etc

Biological DMARDs (Anti-TNFs)

- e.g. adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), infliximab (Remicade), rituximab (Mabthera), tocilizumab (RoActerma) etc

Steroids

- e.g. ACTH, hydrocortisone, prednisolone

NSAIDS (Non-steroidal anti-inflammatory drugs)

- e.g. diclenofac (Voltaren, Cataflam, Voltaren-XR), etodolac (Lodine, Etopan), flurbiprofen (Urbifen, Ansaid, Flurwood, Froben), ibuprofen (Brufen, Genpril, Nurofen, Advil, Motrin), indomethacin (Indocin, Indocid), meloxicam (Mobic), ketoprofen (Orudis, Oruvail), nabumetone (Relifex), naproxen (Aleve, Anaprox, Flanax, Naprelan), piroxicam (Feldene, Brexidol), sulindac (clinoril), etc

Coxibs

- e.g. Celecoxib (Celebrex), Etoricoxib (Arcoxia) etc

ACE Inhibitors

- e.g. lisinopril (Prinivil), perindopril (Coversyl, Aceon),Ramipril (Tritace) etc

Patient Initials ☐☐☐ Centre No ☐☐☐ Patient ID ☐☐☐☐

TRACE RA

BIOBANK BLOOD COLLECTION FOR DNA SAMPLES ONLY

Please complete this form if the patient consents to the TRACE RA Biobank RETROSPECTIVELY i.e. **AFTER** entering into the main trial (bloods for DNA collection only, NOT serum or plasma)

Please state the date of consent to the TRACE RA BioBank **(DNA collection only):** ☐☐☐☐☐☐☐☐ (D D M M Y Y Y Y)

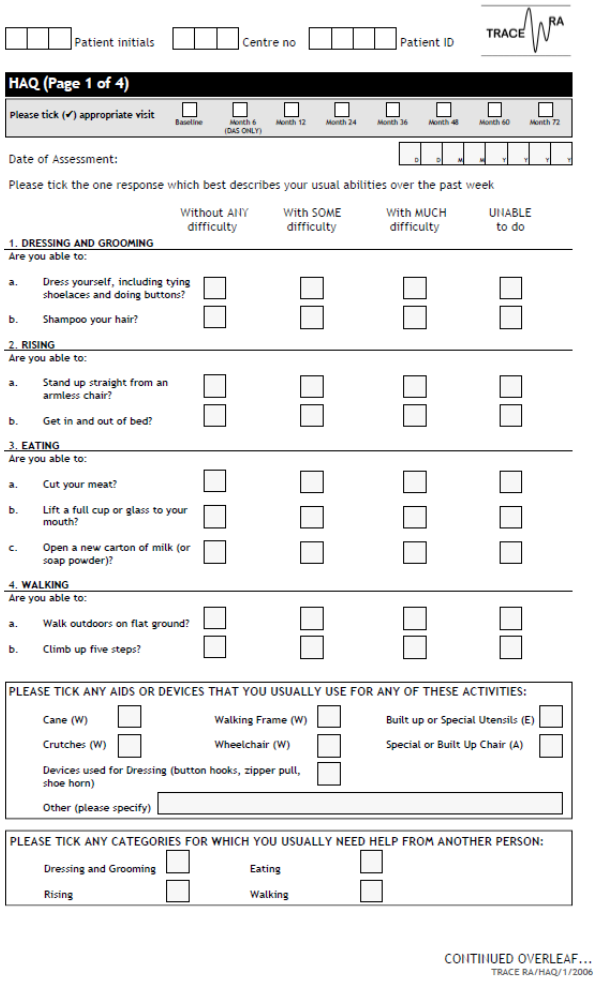
and attach Biobank barcode here:

Signature of person completing the form _____

Printed Name _____ **Date:** ☐☐☐☐☐☐☐☐ (D D M M Y Y Y Y)

ONCE COMPLETED, PLEASE MAKE A PHOTOCOPY & SEND ORIGINAL TO MANCHESTER CO-ORDINATING CENTRE
–RETAIN PHOTOCOPY AT SITE

Appendix Figure 10 The HAQ as distributed at baseline



Patient initials | Centre no | Patient ID | TRACE RA

HAQ (Page 1 of 4)

Please tick (✓) appropriate visit: Baseline | Month 6 (DAS ONLY) | Month 12 | Month 24 | Month 36 | Month 48 | Month 60 | Month 72

Date of Assessment: D D M M Y Y Y Y

Please tick the one response which best describes your usual abilities over the past week

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
1. DRESSING AND GROOMING Are you able to:				
a. Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
b. Shampoo your hair?	☐	☐	☐	☐
2. RISING Are you able to:				
a. Stand up straight from an armless chair?	☐	☐	☐	☐
b. Get in and out of bed?	☐	☐	☐	☐
3. EATING Are you able to:				
a. Cut your meat?	☐	☐	☐	☐
b. Lift a full cup or glass to your mouth?	☐	☐	☐	☐
c. Open a new carton of milk (or soap powder)?	☐	☐	☐	☐
4. WALKING Are you able to:				
a. Walk outdoors on flat ground?	☐	☐	☐	☐
b. Climb up five steps?	☐	☐	☐	☐

PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES:

Cane (W) ☐ | Walking Frame (W) ☐ | Built up or Special Utensils (E) ☐

Crutches (W) ☐ | Wheelchair (W) ☐ | Special or Built Up Chair (A) ☐

Devices used for Dressing (button hooks, zipper pull, shoe horn) ☐

Other (please specify) _____

PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON:

Dressing and Grooming ☐ | Eating ☐

Rising ☐ | Walking ☐

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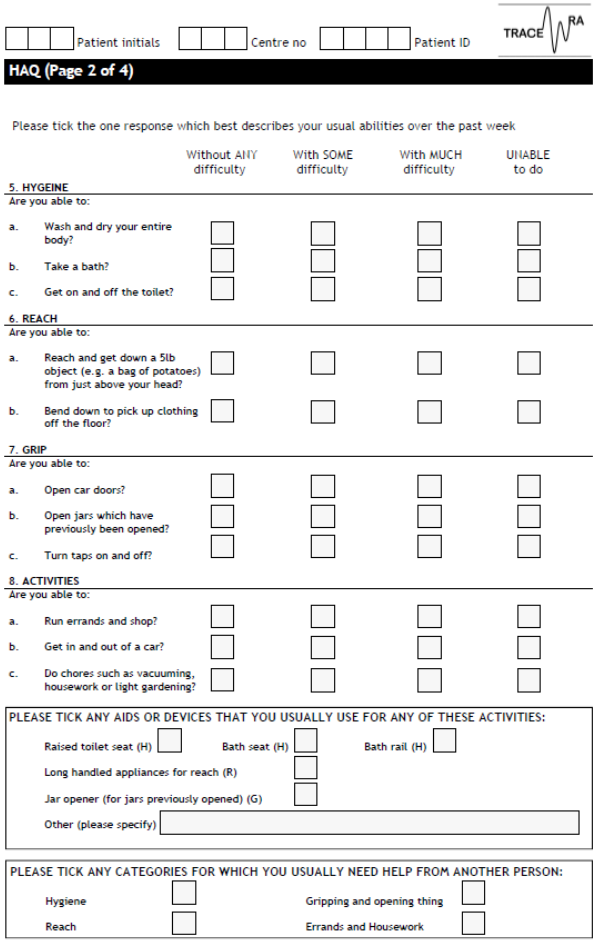
TRACE RA/HAQ/1/2006



Patient initials | Centre no | Patient ID | TRACE RA

HAQ (Page 2 of 4)

Please tick the one response which best describes your usual abilities over the past week

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
5. HYGEINE Are you able to:				
a. Wash and dry your entire body?	☐	☐	☐	☐
b. Take a bath?	☐	☐	☐	☐
c. Get on and off the toilet?	☐	☐	☐	☐
6. REACH Are you able to:				
a. Reach and get down a 5lb object (e.g. a bag of potatoes) from just above your head?	☐	☐	☐	☐
b. Bend down to pick up clothing off the floor?	☐	☐	☐	☐
7. GRIP Are you able to:				
a. Open car doors?	☐	☐	☐	☐
b. Open jars which have previously been opened?	☐	☐	☐	☐
c. Turn taps on and off?	☐	☐	☐	☐
8. ACTIVITIES Are you able to:				
a. Run errands and shop?	☐	☐	☐	☐
b. Get in and out of a car?	☐	☐	☐	☐
c. Do chores such as vacuuming, housework or light gardening?	☐	☐	☐	☐

PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES:

Raised toilet seat (H) ☐ | Bath seat (H) ☐ | Bath rail (H) ☐

Long handled appliances for reach (R) ☐

Jar opener (for jars previously opened) (G) ☐

Other (please specify) _____

PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON:

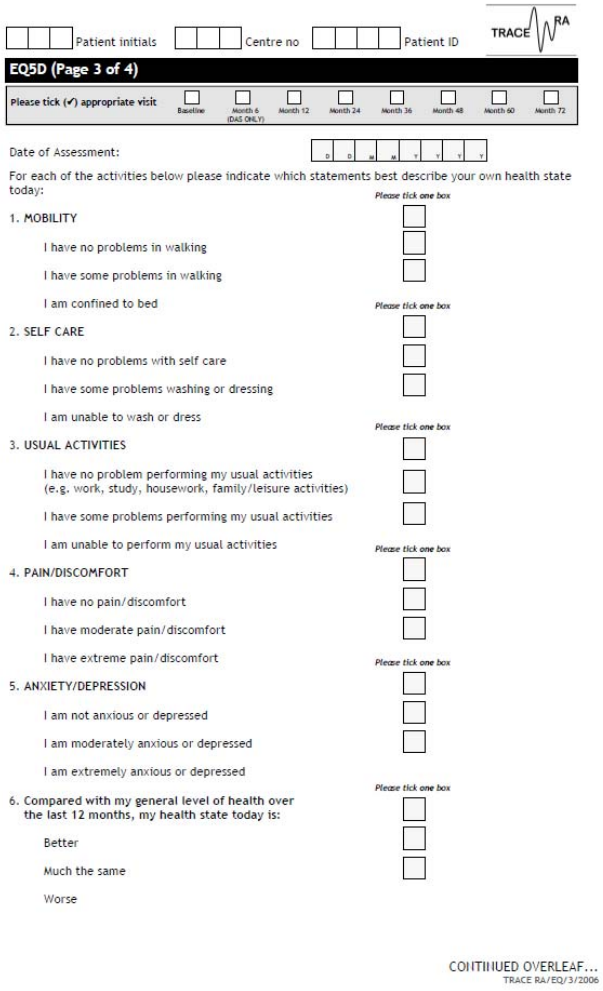
Hygiene ☐ | Gripping and opening thing ☐

Reach ☐ | Errands and Housework ☐

CONTINUED OVERLEAF...

TRACE RA/HAQ/2/2006

Appendix Figure 11 EQ-5D as distributed at baseline



Patient initials | Centre no | Patient ID | TRACE RA

EQ5D (Page 3 of 4)

Please tick (✓) appropriate visit: Baseline | Month 6 (DAS ONLY) | Month 12 | Month 24 | Month 36 | Month 48 | Month 60 | Month 72

Date of Assessment: D D M M Y Y Y Y

For each of the activities below please indicate which statements best describe your own health state today:

Please tick one box

1. MOBILITY
   - I have no problems in walking
   - I have some problems in walking
   - I am confined to bed

Please tick one box

2. SELF CARE
   - I have no problems with self care
   - I have some problems washing or dressing
   - I am unable to wash or dress

Please tick one box

3. USUAL ACTIVITIES
   - I have no problem performing my usual activities (e.g. work, study, housework, family/leisure activities)
   - I have some problems performing my usual activities
   - I am unable to perform my usual activities

Please tick one box

4. PAIN/DISCOMFORT
   - I have no pain/discomfort
   - I have moderate pain/discomfort
   - I have extreme pain/discomfort

Please tick one box

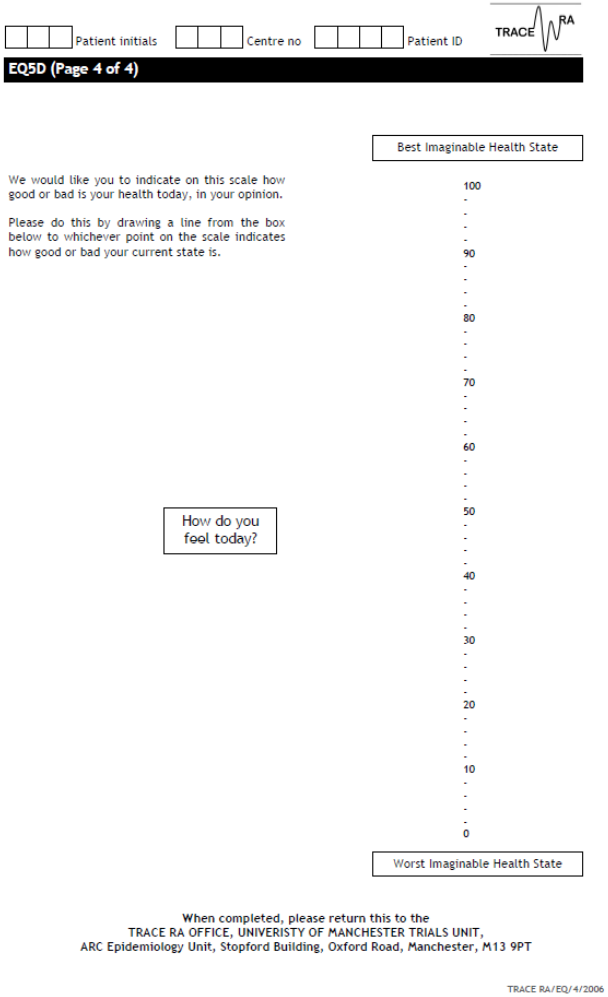
5. ANXIETY/DEPRESSION
   - I am not anxious or depressed
   - I am moderately anxious or depressed
   - I am extremely anxious or depressed

Please tick one box

6. Compared with my general level of health over the last 12 months, my health state today is:
   - Better
   - Much the same
   - Worse

CONTINUED OVERLEAF...

TRACE RA/EQ/3/2006



Patient initials | Centre no | Patient ID | TRACE RA

EQ5D (Page 4 of 4)

Best Imaginable Health State

We would like you to indicate on this scale how good or bad is your health today, in your opinion.

Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your current state is.

How do you feel today?

100 - 90 - 80 - 70 - 60 - 50 - 40 - 30 - 20 - 10 - 0

Worst Imaginable Health State

When completed, please return this to the
TRACE RA OFFICE, UNIVERISTY OF MANCHESTER TRIALS UNIT,
ARC Epidemiology Unit, Stopford Building, Oxford Road, Manchester, M13 9PT

TRACE RA/EQ/4/2006