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Original article

The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review

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Abstract

Objectives. Patients with RA have an increased prevalence of cardiovascular disease (CVD). This is due to traditional risk factors and the effects of chronic inflammation. MTX is the first-choice DMARD in RA. We performed a systematic literature review to determine whether MTX affects the risk of CVD in patients with RA.

Methods. We searched Medline, Embase, Cochrane database, database of abstracts of reviews of effects, health technology assessment and Science Citation Index from 1980 to 2008. Conference proceedings (British Society of Rheumatology, ACR and EULAR) were searched from 2005 to 2008. Papers were included if they assessed the relationship between MTX use and CVD in patients with RA. Two reviewers independently assessed each title and abstract for relevance and quality.

Results. A total of 2420 abstracts were identified, of which 18 fulfilled the inclusion criteria. Two studies assessed the relationship between MTX use and CVD mortality, one demonstrated a significant reduction in CVD mortality and the second a trend towards reduction. Five studies considered all-cause CVD morbidity. Four demonstrated a significant reduction in CVD morbidity and the fifth a trend towards reduction. MTX use in the year prior to the development of RA decreased the risk of CVD for 3−4 years. Four studies considered myocardial infarction, one demonstrated a decreased risk and three a trend towards decreased risk with MTX use.

Conclusion. The current evidence suggests that MTX use is associated with a reduced risk of CVD events in patients with RA. This suggests that reducing the inflammation in RA using MTX not only improves disease-specific outcomes but may also reduce collateral damage such as atherosclerosis.

Key words: Rheumatoid arthritis, Methotrexate, Cardiovascular disease, Inflammation, Systematic literature review.

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Introduction

RA is a chronic inflammatory polyarthritis that often leads to joint destruction, deformity and loss of function [1, 2]. In addition, patients with RA have a reduced life expectancy [3, 4]. Early mortality is largely due to cardiovascular disease (CVD), which is the commonest cause of death in patients with RA [5, 6]. In a recent UK-based study, the standardized mortality ratio for CVD in RA was 1.49 (1.21, 1.77) [7]. In a large (*n* = 575) population-based study, the risk of RA patients developing chronic heart failure was approximately twice that of controls [8]. The increased prevalence of CVD is probably due to an increase in both the traditional risk factors for

atherosclerosis and the presence of chronic inflammation [9]. Active systemic inflammation has multiple effects which accelerate atherosclerosis. These include changes to the endothelium by ICs, CRP and cytokines. Induction of secondary dyslipidaemia, altered glucose metabolism and creation of a hypercoagulable state due to platelet activation and increased production of clotting factors also play a role [10]. The importance of inflammation in the development of atherosclerosis is supported by the association of cardiovascular death with elevated levels of CRP in patients with inflammatory polyarthritis [11]. In the general population, raised levels of highly sensitive CRP (HsCRP) predicts CVD events [12]. Given the importance of inflammation in the development of CVD, therapies aimed at reducing disease activity in RA may also have a positive impact on CVD risk by reducing the burden of systemic inflammation.

MTX has become the most frequently used DMARD in RA and the cornerstone in most DMARD and biologic combinations [13]. Its mechanisms of action are diverse and complex but in the doses used to treat RA its actions are likely to be anti-inflammatory. Several studies have suggested a beneficial effect of MTX on CVD risk. As part of the 2007–08 international 3E initiative (Experts, Evidence and Exchange) to develop consensus guidelines on the use of MTX in rheumatic disorders, we performed a systematic literature review to determine whether the use of MTX in patients with RA affects the likelihood of developing CVD, the frequency of traditional risk factors and the presence of atherosclerosis.

Methods

We searched for studies that investigated the relationship between the use of MTX in patients with RA and CVD outcomes. Studies were eligible for inclusion if they included adult patients, $\geqslant 18$ years with RA. Children were excluded as CVD and RA are relatively rare in this age group and the common condition of juvenile idiopathic arthritis is a distinct disease entity. To include the broadest range of studies, patients did not have to fulfil specific diagnostic criteria for RA, but this was considered when assessing the quality of studies. Studies could be included if they examined data on MTX use either orally, subcutaneously or intramuscularly within the normal dosing range (5–30 mg/week) for use in RA.

Our review was intended to inform clinicians when deciding on individual treatment plans and also to identify areas of lack of evidence and promote research agendas. The selected outcome measures were common clinical cardiovascular outcomes (e.g. ischaemic heart disease, cerebrovascular disease and peripheral vascular disease), established significant risk factors for CVD (e.g. hypertension and hypercholesterolaemia) or established methods for detecting subclinical or early atherosclerosis. Table 1 shows a complete list of the included outcomes.

Papers were included from 1980 onwards when the first studies demonstrating the efficacy of MTX in RA were published [14–17]. Studies could be experimental (clinical or other controlled studies) or observational. Case reports and case series were excluded. Only English language papers were included.

We searched Medline, Embase, Cochrane database, database of abstracts of reviews of effects, health technology assessment, Science Citation Index and clinical evidence from 1980 to 2008. The bibliographies of all included papers were manually searched and the first authors of each paper were contacted for information on any other relevant studies or unpublished work. Conference proceedings for the British Society of

Table 1 Outcomes measured

Clinical outcomes	Risk factors	Subclinical atherosclerosis
Death due to any CVD	Hypertension	Endothelial dysfunction
MI	Diabetes	Nitric oxide
Acute coronary syndrome	Type I diabetes	depletion/unfavourable vascular
Angina	Type II diabetes	nitric oxide profile
Ischaemic heart disease	Insulin-dependent diabetes	Vascular oxidative stress
Coronary artery disease	Tablet-controlled diabetes	Arterial IMT
Heart failure	Diet-controlled diabetes	Arterial calcification
Chronic heart failure	Insulin resistance	Coronary artery calcification
Ischaemic cardiomyopathy	Glucose intolerance	Arterial stiffness
Stroke	Smoking	Doppler ultrasound measuring
		atherosclerosis or atherosclerotic plaques
Cerebrovascular disease	Hypercholesterolaemia	
Transient ischaemic attack	Dyslipidaemia	
Peripheral vascular disease	Hypertriglyceridaemia	
Aortic aneurysm	Unfavourable lipid profile	
Abdominal aortic aneurysm	Obesity	
Thoracic aortic aneurysm	Morbid obesity	
	Raised/elevated BMI	
	Physical inactivity	
	Raised plasma homocysteine	

Rheumatology, ACR and EULAR were hand searched from 2005 to 2008 to identify unpublished studies.

We followed the methods recommended by the Centre for Reviews and Dissemination [18]. Two reviewers (S.L.W. and A.N.C.) independently assessed each title and abstract for potential relevance to the review. Full articles were retrieved if the title and abstract did not contain sufficient information and for papers fulfilling the inclusion criteria. Study quality was assessed using a tool based on 'STrenthening the Reporting of Observational studies in Epidemiology' (STROBE) for assessing the quality of observational studies and adapted from a tool used in a systematic literature review of infant growth and later obesity [19, 20]. Studies were assessed on their use of an appropriate source population, measurement methods of exposure and outcome, methods to deal with design-specific issues such as bias and lost to follow-up, use of analytical methods and use of statistics for primary analysis of effect. Study quality was numerically assessed with a checklist of these domains and summarized with an overall assessment of the risk of bias as low, medium or high. The confounding factors we considered important were age, disease characteristics (duration, severity, level of function, RF positivity), serological measures of systemic inflammation (ESR and CRP), other drug treatments (NSAIDs, COX-2 inhibitors, other DMARDs and biologics) and pre-existent CVD or risk factors for CVD. Consideration of these factors by the study authors was assessed when determining the study quality. In particular, as MTX treatment is often started in patients with a poorer prognosis (confounding by indication) studies were considered to have a lower risk of bias if they adjusted for disease characteristics such as disease severity, erosive state and level of function (see Tables 2–6 for individual studies of level of bias and confounding factors controlled for). Our approach to synthesis was mainly narrative but we explored the potential for meta-analysis according to standard procedures.

Results

A total of 2420 abstracts were identified. Eighteen articles fulfilled the inclusion criteria, all were observational studies (eight cohorts, six case–controls and four cross-sectional studies): 12 articles from the original search; 2 after correspondence with the first authors of included papers; and 4 unpublished studies identified from poster abstracts.

MTX and cardiovascular mortality in RA

Two cohort studies assessed the relationship between MTX and CVD mortality in patients with RA [21, 22] (Table 2). Both studies controlled for multiple confounding factors, including confounding by indication, i.e. patients with the severest disease are more likely to be prescribed MTX. One had a low risk of bias and the other a medium risk. The first, a large ($n = 1240$), high-quality study followed up patients for a mean of 6 years. Patients were recruited from a single US outpatient clinic and had a mean age of 57 years, 72% were females and 88% were RF positive. CVD death in patients ever treated with MTX compared with those never treated with MTX was reduced by 70% [hazards ratio (HR) 0.3 (0.2, 0.7)]. No dose-dependent relationship was demonstrated and no relationship was observed with the use of SSZ, penicillamine, HCQ and intramuscular gold. The risk of bias in this study was considered as low. Rigorous methods were used to adjust for the confounding effects of clinical indication for MTX treatment. The weighted Cox proportional hazards model that was used enabled study authors to take account of the fact that MTX therapy may improve patient disability, which is associated with increased CVD survival. Furthermore, the use of DMARDs with an efficacy similar to MTX was not associated with decreased CVD mortality in this study suggesting an MTX-specific effect. The second study, a large UK, unpublished cohort study (The Norfolk Arthritis Register; $n = 923$) followed patients with newly diagnosed inflammatory arthritis (2/3 of whom fulfilled the ACR criteria for RA) for 10–14 years. A non-significant trend towards a decreased CVD mortality was seen in patients ever treated with MTX, odds ratio (OR) 0.53 (0.25, 1.14). A significant decrease in overall mortality of 41% was seen in those treated with MTX. In this study, a marginal structural model to weigh time varying covariates was used to adjust for the potential effect of clinical indication for MTX use. The results of these large, well-conducted, cohort studies suggest that MTX is associated with a reduced risk of CVD death in patients with RA.

MTX and all-cause CVD morbidity in RA

The CVD morbidity outcomes considered were heterogeneous, but all studies included CVD, cerebrovascular disease and atherosclerosis. Five studies, three cohort, one case–control and one cross-sectional study, considered the risk of all-cause CVD morbidity and the use of MTX [23–27] (Table 3). One study (case–control) had a low risk of bias, two studies a medium risk of bias (one cohort and one cross-sectional) and two studies a high risk of bias (two cohorts) for our review. Four of the studies (including those with low and medium risk of bias) demonstrated a significant reduction in CVD morbidity in patients treated with MTX (89, 35, 17 and 15% reduction) [23, 24, 26, 27]. In the remaining study (unpublished), the direction of association, though not significant, was consistent with the findings of the other studies [25]. Three of the studies compared ever with never use of MTX [24–26]. One study measured years of exposure to MTX. Another study considered MTX use in the year prior to diagnosis of RA [International Classification of Diseases (ICD-9) criteria] [23, 27]. This large ($n = 16\,752$) US research database study demonstrated a 35% decreased risk of CVD events in patients treated with MTX in the year prior to the diagnosis of RA for up to 3.9 years of follow-up compared with non-users of MTX. The study with the lowest risk of bias recruited patients from outpatients in the Netherlands, and demonstrated a significantly decreased risk of CVD morbidity with use of MTX as

Table 2 Summary of studies of MTX use and CVD mortality

Study	Study type	No. of subjects	Exposure MTX use	CVD outcome	Method of adjusting for confounding factors and confounders adjusted for	Analysis and methods of adjusting for confounders	Size of effect	Conclusion (risk of bias)
Choi *et al.* [21]	Cohort study, mean follow-up 6 years	A total of 588 cases, 652 controls, mean age: 57 years, 72% females, 88% RF-positive	Ever or never use of MTX, mean dose: 13 mg/week, maximum dose: 25 mg	CVD mortality confirmed by review of medical records, death certificates and the National Death Index	Weighted Cox proportional hazards model Age, education, sex, smoking, RA duration, calendar year, tender joint count, patient's global assessment of disease status, ESR, HAQ, other DMARDs, prednisolone use. (The estimate did not change when further adjusted for annual income, insurance status, marital status, BMI, diabetes, hypertension, CVD drug use, aspirin, NSAIDs, other prednisolone exposure, grip strength, pain scale, depression white cell count and rheumatoid nodules.)	Mortality HR of MTX use compared with no MTX use (other or no DMARD)	Mortality HR for MTX use compared with no MTX use for cardiovascular mortality, 0.3 (0.2, 0.7).	MTX use significantly reduces the risk of CVD mortality (low)
Goodson (Unpublished) [22]	Cohort study, median follow-up: 10.7 years	A total of 923 with early inflammatory arthritis (2/3 fulfilled the ACR criteria for RA)	Ever or never use, 15.9% of the patients treated with MTX	CVD mortality confirmed by death notification and death certificates	Marginal structural model that appropriately accounts for time-varying measures of disease severity Age, gender, joint counts, RF, nodules, RA, NSAID, steroids, CRP, smoking, HAQ, number of comorbid medications used	Logistic regression to calculate OR for each interval of follow-up for MTX use	OR of CVD for MTX use compared with no MTX use 0.53 (0.25, 1.14)	MTX use is associated with a non-statistically significant trend towards a decreased risk of CVD mortality (medium)

The 95% CI values are given in parentheses.

Table 3 Summary of studies of MTX use and all-cause CVD morbidity

Study	Study type	No. of subjects	Exposure MTX use	CVD outcome	Method of adjusting for confounding factors and confounders adjusted for	Analysis	Size of effect	Conclusion (risk of bias)
Van Halm et al. [26]	Case–control	A total of 72 cases and 541 controls, mean age of cases: 67 years and mean age of controls: 67 years	Ever or never use of MTX monotherapy or in combination with SSZ and/or HCQ	Verified history of coronary artery disease, cerebral artery disease and peripheral vascular disease	Three logistic regression models were used (i) Age, gender, smoking ever, RA duration (ii) (i) + hypertension, diabetes, hypercholesterolaemia (iii) (i) + (ii) + RF and erosions on radiographs	ORs and 95% CIs of CVD for the various DMARD groups compared with the reference group of no DMARD treatment	OR: MTX monotherapy 0.11 (0.002, 0.56) MTX and SSZ 0.16 (0.6, 0.42) MTX, SSZ and HCQ 0.16 (0.06, 0.43)	MTX used as monotherapy or in combination with SSZ and HCQ reduces the risk of all CVD events (low)
Naranjo et al. [27]	Cross-sectional	A total of 4363 patients with RA (no prior history of CVD) from 15 countries, 78% females, 90% Caucasians, mean age: 57 years and mean disease duration: 11 years	Years of exposure to MTX	History of MI, angina, coronary disease, coronary bypass surgery and stroke were verified by a detailed record review and patient history	Each DMARD was analysed independently in Cox regression model, first unadjusted and then adjusted for confounders Age, gender, RF, extra-articular disease, hypertension, hyperlipidaemia, diabetes, smoking, obesity, DAS-28 and HAQ	Time of exposure to MTX was calculated in years. HR for CVD events by years of exposure to MTX	Adjusted HR for all CVD events 0.85 (0.81, 0.89) MI 0.82 (0.74, 0.91) Stroke 0.89 (0.82, 0.98) (i.e. 1 year of MTX treatment reduces CVD events by 15%, MI by 18% and stroke by 11%)	MTX use reduces the risk of all CVD events, MI and stroke (medium)
Hochberg et al. [23]	Cohort	A total of 16 752 cases with incident RA from an insurance database, mean age at diagnosis: 59.8 years, 72% females, mean follow-up: 3.9 years	MTX use in the year prior to fulfilment of ICD-9 criteria for RA (22.7% treated with MTX)	History of pericarditis, retinal vasculitis, other vasculitis, ischaemic heart disease, heart failure, cerebrovascular disease or atherosclerosis recorded by ICD-9 code	Cox proportional hazards model Gender, age, payer type, region, Charlston comorbidity index, chronic disease score, a baseline history of chronic obstructive airways disease or diabetes and a baseline use of MTX, other DMARDs, biologics, corticosteroids and NSAIDs	The HR for CVD events for use of MTX vs never use	Adjusted HR 0.65 (0.59, 0.72) (i.e. 35% reduction in risk of CVD if used in year prior to the diagnosis of RA)	MTX reduces the risk of all CVD events in patients with RA and in the year prior to the diagnosis of RA (medium)
Prodanowich et al. [24]	Cohort	A total of 6707 veterans with RA from a database, 10% females, mean age of cases with CVD: 69.4 years and without CVD 62.3 years	Ever vs never use of MTX, low-dose MTX defined as less than the median and high dose greater than the median (no actual doses given)	Coronary artery disease, cerebrovascular disease, peripheral vascular disease and atherosclerosis recorded by ICD-9 code	Multivariate logistic model Age, gender, comorbidities (including diabetes mellitus, hypertension and dyslipidaemia) and other medications (including folic acid, vitamin B6 and vitamin B12)	The OR for CVD for ever vs never use of MTX	OR 0.83 (0.71, 0.96), low-dose MTX 0.65 (0.52, 0.80), high-dose MTX 1.00 (0.83, 1.22)	Low-dose MTX reduces the risk of all CVD events (high)
Kremer [25]	Cohort	A total of 10 016 patients with RA from the CORRONA database, no demographics given, median follow-up 3 years	Ever vs never use of MTX	Coronary artery disease, MI, congestive heart failure and stroke; probably recorded by ICD-9 codes	MTX use was only assessed in unadjusted univariate analysis	CVD events rates and incident rate ratios (IRR) were analysed using mixed Poisson regression models	IRR for MTX vs no MTX 0.825 (P=0.2240)	MTX use makes no significant difference to the risk of all CVD events (high)

Table 4 Summary of studies of MTX use and MI and heart failure

Study	Study type	No. of subjects	Exposure to MTX use	CVD outcome	Confounding factors controlled for	Analysis	Size of effect	Conclusion (risk of bias)
Naranjo et al. [27]	Cross-sectional	A total of 4363 patients with RA from 15 countries: 78% females, 90% Caucasians, mean age: 57 years, mean disease duration: 11 years	Years of exposure to MTX	History of MI	Each DMARD was analysed independently in Cox regression model, first unadjusted and then adjusted for confounders. Age, gender, RF, extra-articular disease, hypertension, hyperlipidaemia, diabetes, smoking, obesity, DAS-28 and HAQ	Time of exposure to MTX was calculated in years. The HR for CVD events by years of exposure to MTX	Adjusted HR for MI 0.82 (0.74, 0.91)	MTX use reduces the risk of MI (medium)
Suissa et al. [29]	Case–control	A total of 558 cases and 5580 controls from an insurance database, mean age: 65 years and 55% females	Current use of MTX	Acute MI requiring hospitalization recorded by ICD-9 code	Conditional logistic regression. Age, NSAID, steroid use and comorbidity (IHD, heart failure, stroke, peripheral arterial disease, other CVDs, hypertension, diabetes mellitus, hypercholesterolaemia, respiratory disease and cancer)	The rate ratio (RR) of AMI in current MTX users compared with no current DMARD use	RR 0.81 (0.60, 1.08)	MTX use is associated with a non-statistically significant decrease in the risk of MI (medium)
Radovits et al. [28]	Case–control	A total of 41 cases and 181 controls, mean age of cases: 67.5 years, controls: 56 years, 51.2% cases male and 30.9% controls male	Total duration, cumulative dose and number of treatment courses of MTX	First episode of MI or unstable angina diagnosed by a cardiologist	None, MTX use was not the main focus of the study	Univariate logistic regression analysis with time-average disease activity as dependent variable	MTX use: cases 53.7%, controls 49.7% ($P = 0.389$) Cumulative MTX dose (mg): cases 2219.2, controls 1976.4 ($P = 0.489$). Duration (weeks): cases 167.9, controls 161.9 ($P = 0.551$)	MTX use is associated with no significant difference in the risk of MI (medium)
Edwards [30]	Case–control	A total of 33 210 cases and 103 089 controls from the general practice register database, mean age at diagnosis: 53.5 years, 72.2% females and median follow-up 7 years	Ever vs never use of MTX	First MI recorded by ICD-9 code	Results adjusted for age, gender, BMI, smoking, diabetes, hypertension, MI, renal failure, cardiac failure, cardiovascular drugs, DMARDs, prednisolone. Age, gender, BMI, hypertension, diabetes and smoking	The relationship of predictor variables to the incidence of MI was analysed using person-years analysis and Poisson regression and expressed as IRR	IRR for MTX vs no MTX = 0.67 ($P = 0.03$)	MTX use is associated with no significant difference in the risk of MI (medium)
Bernatsky et al. [31]	Case–control	A total of 520 cases and 5200 controls from an insurance database, mean age of cases: 67 years and controls: 65 years, 67% of cases were females and 75% of controls	Current use of MTX	First occurrence of congestive heart failure requiring hospitalization defined by ICD-9 code	Conditional logistic regression. Age, gender, duration of time in the cohort, comorbidity, NSAIDs, COX-2 inhibitors and other DMARDs	The RR of hospitalization for CHF with use of MTX	RR 0.8 (0.6, 1.0)	MTX use is associated with a significant decrease in the risk of CHF (medium)

Table 5 Summary of studies of MTX use and stroke

Study	Study type	No. of subjects	Exposure - MTX use	CVD outcome	Method of adjusting for confounding factors and confounders adjusted for	Analysis	Size of effect	Conclusion (risk of bias)
Naranjo et al. [27]	Cross-sectional	4363 patients with RA from 15 countries: 78% females, 90% Caucasians, mean age: 57 years, mean disease duration: 11 years	Years of exposure to MTX	History of MI	Each DMARD was analysed independently in Cox regression model, first unadjusted and then adjusted for confounders. Age, gender, RF, extra-articular disease, hypertension, hyperlipidaemia, diabetes, smoking, obesity, DAS-28 and HAQ	Time of exposure to MTX was calculated in years. The HR for CVD events by years of exposure to MTX	Adjusted HR for MI 0.82 (0.74, 0.91)	MTX use reduces the risk of stroke (medium)
Endean [32]	Case–control	33 191 cases with RA and 99 570 controls from GPRD	Ever vs never use of MTX	Stroke defined by ICD-9 code	Results adjusted for age, gender, BMI, smoking, diabetes, hypertension, MI, renal failure, cardiac failure, cardiovascular drugs, DMARDs, prednisolone	Person-year analysis and Poisson regression used to analyse the IRR of stroke in patients treated with MTX	IRR 1.31 (0.89, 1.93)	MTX use is associated with a non-statistically significant increase in the risk of stroke (medium)

monotherapy or in combination with SSZ and/or HCQ. Indicators of RA disease severity were included in regression analyses, and the association between DMARD use and CVD risk was apparent at all levels of RA severity. One study (high risk of bias) that recruited veterans with RA subdivided MTX use into low or high dose [24]. Low dose was defined as less than the median dose used by the cohort and high dose as greater than the median dose. No actual MTX doses were given in this study. Patients treated with low-dose MTX had a 35% reduced risk of CVD morbidity, whereas those treated with high-dose MTX had no alteration in risk. The reliability of these findings may, however, be limited by the lack of control for important disease-related confounding factors in the analysis and the demographics of the population—90% male. The consistency of the findings in these five studies suggests that MTX is associated with a significantly reduced incidence of all-cause CVD morbidity in patients with RA. This may occur very early in the disease course, with use as monotherapy or in combination with SSZ and HCQ and may be dependent on the dose of MTX used.

MTX, myocardial infarction and heart failure in RA

Four studies, one cross-sectional and three case–control, related MTX use to the risk of myocardial infarction (MI) [27–30] (Table 4). All the studies had a medium risk of bias for our review. One study defined the outcome as hospitalization with acute MI, a second an incidence of MI or unstable angina and the remaining studies as MI. One study (quantitative clinical assessment of patients with rheumatoid arthritis), a large multi-national study ($n = 4363$), demonstrated an 18% reduction in the risk of MI in patients treated for 1 year with MTX [27]. This study controlled for multiple confounders, including measures of disease severity and traditional CVD risk factors. However, there is a risk of selection bias in this study due to exclusion of patients with fatal CVD events. Ascertainment of outcomes relied on the reports of participating rheumatologists raising the possibility that reporting of an outcome data may have been incomplete. The other studies showed a non-statistically significant trend towards a reduction in the risk of MI with current or ever use of MTX [28–30]. One of these studies, aimed at determining the effect of disease activity on the risk of MI, was not powered to determine the effect of MTX on CVD risk [28]. One case–control study, with a medium risk of bias, considered MTX use and heart failure. Five hundred and twenty patients from the USA currently using MTX (mean age 67 years and 67% female) had a 20% reduction in the risk of hospitalization with congestive heart failure compared with non-current users of MTX [31]. However, as this study was based on an insurance claims database no adjustments could be made for disease severity and measures of inflammation. Taken together, these studies suggest that MTX use may be associated with a decreased risk of MI and congestive heart failure in RA.

Table 6 Summary of studies of MTX use and risk factors for CVD and atherosclerosis

Study	Study type	No. of subjects	Exposure to MTX use	CVD outcome	Confounding factors corrected for	Analysis	Size of effect	Conclusion (risk of bias)
Morgan et al. [57]	Cross-sectional	A total of 225 cases taking MTX and 175 controls not taking MTX, median age: 63.1 years, 73% females	Current use	Hypertension, mean of three readings taken on one occasion	None as MTX is not a significant univariate predictor of hypertension	Percentage of patients taking MTX in the hypertensive group was compared with the normotensive group	Of the hypertensive patients, 60.2% were using MTX and 54.6% of normotensive patients ($P = NS$)	MTX use is not associated with the risk of hypertension (high)
Park et al. [33]	Cohort study	A total of 39 cases treated with MTX and three controls with newly diagnosed RA, mean age: 43 years, mean disease duration of RA: 27 months, 90% females, 1 year follow-up	MTX used during the 1 year study	Change in serum lipid profile over 1 year of treatment	None	Analysis of covariance to compare disease responders and non-responders	No association between the use of MTX and change in lipid levels	MTX use is not associated with a change in lipid profile (high)
Georgiadis et al. [34]	Cohort study	A total of 58 cases with early RA > 1 year treated with MTX and prednisolone 7.5 mg/day, mean age: 53.6 years, 76% females, 1 year follow-up	One year of treatment with MTX, mean dose 15.5 mg/week	Change in serum lipid profile over 1 year of treatment	None	Correlation between variables examined using Pearson's correlation coefficient	Significant improvement in the total cholesterol to high density lipids ratio and low density lipids to high density lipids ratio after 1 year of treatment	MTX use may be associated with an improvement in lipid profile (high)
Dessein et al. [35]	Cohort study	A total of 10 cases treated with MTX and five controls, mean age of cases: 53 years, 86% females, mean disease duration: 7 years, mean age of controls: 49 years, 62% females, mean disease duration: 5 years	MTX used during the 3-month study	Change in serum lipid profile over 3 months of DMARD treatment and dietary intervention Change in insulin resistance	None	Simple linear regression	No change in lipid profile or insulin resistance in cases compared with controls	MTX use is not associated with a change in insulin resistance or insulin resistance (high)
Wallberg-Jonsson et al. [38]	Cross-sectional	A total of 39 cases with RA, mean age: 51.6 years, mean disease duration: 19–23 years	Ever vs never use of MTX	Atherosclerosis as measured by B-mode ultrasound. The common carotid and femoral arteries were investigated for IMT and the presence of atherosclerotic plaques	Age, tPA antigen, cholesterol, LDL-C, triglycerides and atherosclerotic plaques (univariate predictors)	Multiple regression model and a carefully designed multiplicative model	MTX decreased the IMT of the carotid artery by 17.6% which was nearly statistically significant. No association was seen with atherosclerotic plaques	MTX use is associated with a non-statistically significant reduction in the development of atherosclerosis (high)
Kumeda et al. [37]	Cross-sectional	A total of 138 cases with RA, 122 females, mean age: 55 years	Current use of MTX	Atherosclerosis, the IMT of the common carotid artery was measured by high-resolution ultrasound	None	Multiple regression analysis was performed to assess independent associations between common carotid artery IMT and various clinical factors	MTX use was not associated with common carotid artery IMT	MTX use is not associated with the development of atherosclerosis. (high)

MTX and stroke in RA

Two studies, one cross-sectional and one case–control, considered MTX and the risk of stroke [27, 32] (Table 5). Both studies had a medium risk of bias for our review. One large multi-national study demonstrated an 11% reduction in the risk of stroke with ever use of MTX [27]. In this study, the analysis was adjusted for features of RA [disease activity score (DAS)-28 and HAQ]. The second study, a large ($n = 33\,191$) unpublished study including patients with RA from a primary care database in the UK, demonstrated a trend towards an increased risk of stroke in ever users of MTX, although RA disease characteristics were not known, or controlled for in analysis. No firm conclusions can be drawn on the association of MTX and the risk of stroke in RA.

MTX and lipids in RA

Three studies, all cohort studies, considered MTX use and lipid profile (Table 6). All studies had a high risk of bias for our review [33–35]. One small study ($n = 42$) demonstrated no change in lipid profile in patients with newly diagnosed RA (mean disease duration 27 months) treated with MTX for 1 year [33]. In the second study in patients with newly diagnosed RA (<1 year), all patients were treated with MTX and prednisolone for 1 year [34]. After treatment there was a significant improvement in the lipid profile which correlated with changes in CRP and ESR. MTX was, however, not considered independent of improvements in inflammation and prednisolone use. The final, small study included 15 patients with RA [35]. Patients were treated with DMARDs, 10 with MTX, and some underwent dietary intervention for 3 months. No change in lipid profile was seen in patients treated with MTX despite a 76% reduction in CRP. The reliability of these findings is, however, likely to be limited as DMARD choice was based on previous response to DMARDs and a proportion of patients treated with MTX were also given dietary intervention. No firm conclusions can be drawn on the association of MTX and lipids in RA.

MTX and hypertension in RA

One cross-sectional study related MTX use to the risk of hypertension [36] (Table 5). This study had a medium risk of bias for our review. In this UK outpatient-based population ($n = 400$), there was no difference in the current use of MTX between RA hypertensive and normotensive patients. As MTX use was not a univariate predictor of hypertension no further analyses were carried out. There is insufficient evidence to draw any conclusions on the association of MTX and hypertension in RA.

MTX and insulin resistance in RA

One study, with a high risk of bias for our review, considered insulin resistance and MTX use (see above) [35] (Table 5). No change in insulin resistance was seen after 3 months treatment with DMARDs (including 10 individuals taking MTX) and dietary intervention. No firm conclusions can be drawn on the association of MTX and insulin resistance in RA.

MTX and atherosclerosis in RA

Two studies, both cohorts, related MTX use to the development of pre-clinical atherosclerosis [37, 38] (Table 5). Both studies had a high risk of bias for our review. Atherosclerosis, determined by measuring intima-media thickness (IMT), was determined by ultrasound in both studies. In the first study ($n = 138$), there was no difference between the carotid artery IMT in patients currently taking MTX ($n = 16$) and those not taking MTX ($n = 122$) [37]. In the second small study ($n = 39$) in patients with a long disease duration (19–23 years) treatment with MTX for at least 6 months decreased the carotid artery IMT by 17.6%, which was nearly statistically significant [38]. No firm conclusions can be drawn on the effect of MTX on atherosclerosis in RA.

Further analysis

We could not carry out a meta-analysis on the relationship between MTX use and CVD outcomes because of the heterogeneity in study design, participants, definition of MTX use and CVD outcomes in the studies.

Discussion

Our review suggests that the use of MTX in RA is associated with a decreased risk of clinical CVD morbidity and mortality. With the exception of one study, all the studies demonstrated either a significant reduction or trend towards a reduction in CVD events in patients treated with MTX [32]. The evidence is insufficient to draw conclusions on the association between MTX use and risk factors for CVD or pre-clinical atherosclerosis. Interestingly, the association between the reduction in CVD events and MTX use may occur very early in the disease course, potentially before the diagnosis of RA. This raises the exciting prospect that MTX use very early in the disease course may not only delay the onset of RA but may also reduce the risk of collateral damage such as atherosclerosis [39]. It is, therefore, possible that a window of opportunity exists early in the disease process not only for suppressing the disease activity but also for limiting the effect of inflammation on atherosclerosis. Atherosclerosis in itself is an inflammatory disease. It is unclear from the published literature whether the effects of MTX on reducing CVD are due to direct effects on atherosclerotic lesions or as a result of a reduction in rheumatoid-driven systemic inflammation.

Our findings are consistent with those of other studies that have demonstrated reduced mortality from acute MI in successive birth cohorts of RA patients during a period when the use of MTX increased substantially [40]. A decreased risk of all-cause mortality was also seen in patients with severe RA who responded to MTX treatment when compared with non-responders [41]. However, in one study the risk of all-cause mortality in patients with pre-existent CVD treated with MTX was significantly increased (relative risk of death 3.4, $P = 0.0054$) [42]. The description of this study was, however, limited as it was published as a letter, making it difficult to rule out a

chance finding and did not completely adjust for confounding by indication.

The mechanism by which MTX may reduce the risk of CVD in RA is likely to be complex. Multiple factors have been implicated in increasing the risk of CVD in RA. These include the effects of inflammation, an increase in traditional risk factors for CVD, drug therapies used in RA, hyperhomocystinaemia and the presence of RF.

Inflammation

Although the primary site of inflammation in RA is in the synovium, release of cytokines, including TNF and IL-6, produce chronically elevated cytokine levels [43]. This can induce changes in the vasculature that accelerate the process of atherosclerosis including endothelial dysfunction, secondary dyslipidaemia and activation of the coagulation cascade [10]. By reducing the disease activity and systemic inflammation, MTX would be expected to reduce the progression of atherosclerosis. However, in our review several studies showed reductions in CVD events after controlling for measures of systemic inflammation and disease activity, suggesting an additional benefit of MTX use. Indeed, in patients treated with TNF antagonists dramatic improvements in inflammation have not been mirrored by striking reductions in CVD events, such as MI [44]. This may suggest either that other factors, such as increases in traditional factors, may be equally important in contributing to the increased CVD risk or that inflammation in RA, despite being reduced by drug therapy, is not suppressed enough to prevent the progression of atherosclerosis. Indeed an elevated HsCRP is associated with an increased CVD risk in the general population [12]. In the healthy population without hyperlipidaemia, but a a raised HsCRP rosuvastatin significantly reduces the HsCRP and the risk of major CVD events [45]. HsCRP is not measured in routine clinical practice, and therefore cannot be controlled for in the studies included in our review.

It is also interesting to consider how different therapies used in the treatment of RA may have an effect on the different parts of the immune system, and therefore the different effects on CVD. MTX appears to reduce the disease activity in RA but has little or no effect on RF levels. RF has recently been associated with CVD in individuals with inflammatory arthritis (Norfolk arthritis register) and in the normal population [46, 47].

Traditional risk factors

Patients with RA have an increase in traditional risk factors for CVD. Treatment with MTX improves physical function and mobility, which may subsequently increase exercise levels leading to a reduced CVD risk [14–16]. Treatment with some DMARDs and biologics may improve the lipid profile and insulin resistance in patients with RA [48, 49]. One of our studies did demonstrate an improvement in lipid profile in patients with early RA after treatment with MTX and prednisolone [34]. However, this improvement could have resulted from decreases in inflammation rather than MTX use. Currently, there is not enough

evidence to determine the effect of MTX on traditional risk factors.

Drug therapies

Some studies in our review attempted to control for the use of other drug therapies. However, changes in other medications as a consequence of MTX use are difficult to capture. Some drugs used for RA are known to have an adverse impact on CVD or risk factors for CVD: non-naproxen NSAIDs and Coxibs are associated with an increased risk of CVD events and mortality [50]; glucocorticoids are associated with hypertension, dyslipidaemia and weight gain [51]; cyclosporin and LEF are associated with hypertension and TNF antagonists may increase the risk of heart failure [52–54]. Patients treated with MTX are often able to decrease their use of NSAIDs and glucocorticoids, producing a positive impact on their CVD risk. Thus, some of the benefits of MTX use on CVD risk may be through a reduction in other treatments that have an adverse effect on CVD risk.

Hyperhomocystinaemia

Hyperhomocystinaemia is associated with an increased risk of CVD, including mortality, stroke and heart failure, in the general population [55]. MTX inhibits the homocysteine–methionine pathway. Several studies have demonstrated increased levels of homocysteine in patients treated with low-dose MTX [56]. This can be reduced by the use of concomitant folic or folinic acid [57]. In the two studies that considered folic acid use as a confounding factor, no difference in the occurrence of CVD events was seen between users and non-users of folic acid [21, 24]. However, in a large cohort of patients with psoriasis treated with low-dose MTX users of folic acid had a reduced risk of CVD events compared with non-users, OR 0.56 (95% CI 0.39, 0.80) $P < 0.01$ [24].

Strengths and limitations

Our review used rigorous and standard methods: an extensive literature search was conducted; two reviewers independently assessed the relevance of abstracts for the review; grey literature was included in an attempt to overcome publishing bias; and authors of all included papers were contacted. The main limitation of our review is interpreting the evidence of observational studies. These are subject to significantly greater sources of bias than randomized controlled studies and can demonstrate association between MTX use and CVD events but not causality. The consistency of associations observed between MTX use and CVD events, however, suggests that the association is robust.

Potential sources of bias include any factors that are responsible for the initiation of MTX. Particularly important confounders include: confounding by indication, such that patients with severe RA, with the highest risk of CVD, are more likely to be treated with MTX; channelling bias, such that patients with a higher CVD risk were selectively treated, or not treated, with MTX; and bias caused by selective adherence to treatment. Whereas these

potential sources of bias cannot be completely overcome in observational studies, some of the studies attempted to control for them statistically which is reflected in our assessment of the level of bias. Confounding by indication would tend to underestimate any benefit of MTX on CVD risk and potentially strengthens the positive association demonstrated in our review. This is consistent with our finding that the studies with the lowest risk of bias, which attempted to control for confounding by indication, demonstrated the greatest reduction in CVD events with MTX use: a 70% reduction in CVD mortality and 89% reduction in all CVD events, respectively [21, 26]. A number of large-scale studies considered in this review were based on large health insurance databases that often lacked rich clinical information, thus increasing the risk of residual confounding. Nevertheless, the fact that the trends observed in these studies were consistent with those of the studies with more detailed clinical information suggests that their findings are robust. Channelling bias may have influenced the results of our review as physicians may avoid DMARD treatment in frailer patients such as those with pre-existent CVD or risk factors for CVD. Therefore, an association between reduced CVD events and MTX may be explained by a reduced comorbid CVD burden in patients prescribed MTX. Channelling bias cannot be entirely corrected for by statistical analysis; however, most of the studies in our review did attempt to minimize this by controlling the baseline levels of CVD (previous CVD events, cardiovascular drug use or risk factors for CVD). Finally, most of the studies used an intent-to-treat definition of MTX exposure irrespective of adherence to therapy (selective bias) and are therefore likely to demonstrate a conservative, or possible underestimate of the association between MTX use and the risk of CVD events.

Conclusions

The current evidence suggests that MTX use is associated with a reduced risk of CVD events in patients with RA. This may be important early in the disease course. The mechanism for this possible benefit cannot be fully determined from the current literature but is likely to be multi-factorial. As disease control continues to improve in RA, future studies need to address the impact of MTX and other DMARDs or biologics on CVD, which remains the leading cause of death and a significant comorbidity in these patients. It is unlikely that a randomized controlled trial designed to determine the impact of MTX on CVD should be conducted. However, all future studies assessing the efficacy of new or currently used DMARDs or biologics could collect data on CVD and risk factors for CVD. Furthermore, studies assessing the impact of MTX on pre-clinical atherosclerosis would also be helpful.

> **Rheumatology key message**
> - MTX reduces the likelihood of cardiovascular events in individuals with RA.

References

1   Scott DL, Shipley M, Dawson A, Edwards S, Symmons DP, Woolf AD. The clinical management of rheumatoid arthritis and osteoarthritis: strategies for improving clinical effectiveness. Br J Rheumatol 1998;37: 546–54.

2   McIntosh E. The cost of rheumatoid arthritis. Br J Rheumatol 1996;35:781–90.

3   Naz SM, Symmons DP. Mortality in established rheumatoid arthritis. Best Pract Res Clin Rheumatol 2007; 21:871–83.

4   Symmons DP, Jones MA, Scott DL, Prior P. Longterm mortality outcome in patients with rheumatoid arthritis: early presenters continue to do well. J Rheumatol 1998; 25:1072–7.

5   Prior P, Symmons DP, Scott DL, Brown R, Hawkins CF. Cause of death in rheumatoid arthritis. Br J Rheumatol 1984;23:92–9.

6   Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum 2005;52: 722–32.

7   Young A, Koduri G, Batley M *et al*. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. Rheumatology 2007;46:350–7.

8   Nicola PJ, Maradit-Kremers H, Roger VL *et al*. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum 2005;52:412–20.

9   Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how ''high-grade'' systemic inflammation accelerates

vascular risk in rheumatoid arthritis. Circulation 2003;108: 2957–63.

10 van Leuven SI, Franssen R, Kastelein JJ, Levi M, Stroes ES, Tak PP. Systemic inflammation as a risk factor for atherothrombosis. Rheumatology 2008;47:3–7.

11 Goodson NJ, Symmons DP, Scott DG, Bunn D, Lunt M, Silman AJ. Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: a ten-year follow up study of a primary care-based inception cohort. Arthritis Rheum 2005;52:2293–9.

12 Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? Circulation 2004;109:2818–25.

13 Edwards CJ, Arden NK, Fisher D *et al*. The changing use of disease-modifying anti-rheumatic drugs in individuals with rheumatoid arthritis from the United Kingdom General Practice Research Database. Rheumatology 2005;44: 1394–8.

14 Andersen PA, West SG, O'Dell JR, Via CS, Claypool RG, Kotzin BL. Weekly pulse methotrexate in rheumatoid arthritis. Clinical and immunologic effects in a randomized, double-blind study. Ann Intern Med 1985;103:489–96.

15 Weinblatt ME, Coblyn JS, Fox DA *et al*. Efficacy of low-dose methotrexate in rheumatoid arthritis. N Engl J Med 1985;312:818–22.

16 Williams HJ, Willkens RF, Samuelson CO Jr *et al*. Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis. A controlled clinical trial. Arthritis Rheum 1985;28:721–30.

17 Thompson RN, Watts C, Edelman J, Esdaile J, Russell AS. A controlled two-centre trial of parenteral methotrexate therapy for refractory rheumatoid arthritis. J Rheumatol 1984;11:760–3.

18 NHS Centre for Reviews and Dissemination. Undertaking systematic reviews of research: an effective CRD's guidance for those carrying out or commissioning reviews. Report No. 4. York: Centre for Reviews and Dissemination, 2001.

19 Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol 2007;36:666–76.

20 Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. Br Med J 2005;331: 929.

21 Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet 2002;359:1173–7.

22 Goodson NJ. The mortality association with DMARD use in early inflammatory polyarthritis [Abstract]. Rheumatology 2008;47:ii49.

23 Hochberg MC, Johnston SS, John AK. The incidence and prevalence of extra-articular and systemic manifestations in a cohort of newly-diagnosed patients with rheumatoid arthritis between 1999 and 2006. Curr Med Res Opin 2008;24:469–80.

24 Prodanovich S, Ma F, Taylor JR, Pezon C, Fasihi T, Kirsner RS. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. J Am Acad Dermatol 2005;52:262–7.

25 Kremer JM. An analysis of risk factors and effect of treatment on the development of cardiovascular disease in patients with rheumatoid arthritis [Abstract]. Ann Rheum Dis 2006;65(Suppl. II):307.

26 van Halm V, Nurmohamed MT, Twisk JW, Dijkmans BA, Voskuyl AE. Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study. Arthritis Res Ther 2006;8:R151.

27 Naranjo A, Sokka T, Descalzo MA *et al*. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. Arthritis Res Ther 2008;10:R30.

28 Radovits BJ, Popa-Diaconu DA, Popa C *et al*. Disease activity as a risk factor for myocardial infarction in rheumatoid arthritis. Ann Rheum Dis 2009;68:1271–6.

29 Suissa S, Bernatsky S, Hudson M. Antirheumatic drug use and the risk of acute myocardial infarction. Arthritis Rheum 2006;55:531–6.

30 Edwards CJ. Myocardial infarction in rheumatoid arthritis. The effects of DMARDs and prednisolone [Abstract]. Arthritis Rheum 2008;56(Suppl. 9):688.

31 Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of hospitalization for congestive heart failure in rheumatoid arthritis. Rheumatology 2005;44: 677–80.

32 Endean A. The risk of stroke in patients with rheumatoid arthritis compared to the general population [Abstract]. Arthritis Rheum 2007;56(Suppl. 9):S293.

33 Park YB, Choi HK, Kim MY *et al*. Effects of antirheumatic therapy on serum lipid levels in patients with rheumatoid arthritis: a prospective study. Am J Med 2002;113:188–93.

34 Georgiadis AN, Papavasiliou EC, Lourida ES *et al*. Atherogenic lipid profile is a feature characteristic of patients with early rheumatoid arthritis: effect of early treatment—a prospective, controlled study. Arthritis Res Ther 2006;8:R82.

35 Dessein PH, Joffe BI, Stanwix AE. Effects of disease modifying agents and dietary intervention on insulin resistance and dyslipidemia in inflammatory arthritis: a pilot study. Arthritis Res 2002;4:R12.

36 Panoulas VF, Metsios GS, Pace AV *et al*. Hypertension in rheumatoid arthritis. Rheumatology 2008;47:1286–98.

37 Kumeda Y, Inaba M, Goto H *et al*. Increased thickness of the arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. Arthritis Rheum 2002; 46:1489–97.

38 Wallberg-Jonsson S, Ohman M, Rantapaa-Dahlqvist S. Which factors are related to the presence of atherosclerosis in rheumatoid arthritis? Scand J Rheumatol 2004;33:373–9.

39 van DH, van AJ, Lard LR *et al*. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2007;56:1424–32.

40 Krishnan E, Lingala VB, Singh G. Declines in mortality from acute myocardial infarction in successive incidence and birth cohorts of patients with rheumatoid arthritis. Circulation 2004;110:1774–9.

41 Krause D, Schleusser B, Herborn G, Rau R. Response to methotrexate treatment is associated with reduced mortality in patients with severe rheumatoid arthritis. Arthritis Rheum 2000;43:14–21.

42 Landewe RB, van den Borne BE, Breedveld FC, Dijkmans BA. Methotrexate effects in patients with rheumatoid arthritis with cardiovascular comorbidity. Lancet 2000;355:1616–7.

43 Dhawan SS, Quyyumi AA. Rheumatoid arthritis and cardiovascular disease. Curr Atheroscler Rep 2008;10: 128–33.

44 Dixon WG, Watson KD, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2007;56:2905–12.

45 Ridker PM, Danielson E, Fonseca FA *et al*. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.

46 Edwards CJ, Syddall H, Goswami R *et al*. The autoantibody rheumatoid factor may be an independent risk factor for ischaemic heart disease in men. Heart 2007; 93:1263−7.

47 Goodson NJ, Farragher TM, Symmons DP. Rheumatoid factor, smoking, and disease severity: associations with mortality in rheumatoid arthritis. J Rheumatol 2008;35: 945–9.

48 Munro R, Morrison E, McDonald AG, Hunter JA, Madhok R, Capell HA. Effect of disease modifying agents on the lipid profiles of patients with rheumatoid arthritis. Ann Rheum Dis 1997;56:374–7.

49 Seriolo B, Paolino S, Ferrone C, Cutolo M. Impact of long-term anti-TNF-alpha treatment on insulin resistance in patients with rheumatoid arthritis. Clin Exp Rheumatol 2008;26:159–60.

50 McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. J Am Med Assoc 2006; 296:1633–44.

51 Maxwell SR, Moots RJ, Kendall MJ. Corticosteroids: do they damage the cardiovascular system? Postgrad Med J 1994;70:863–70.

52 Rozman B, Praprotnik S, Logar D *et al*. Leflunomide and hypertension. Ann Rheum Dis 2002;61:567–9.

53 Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med 2003;138: 807–11.

54 Kvien TK, Zeidler HK, Hannonen P *et al*. Long term efficacy and safety of cyclosporin versus parenteral gold in early rheumatoid arthritis: a three year study of radiographic progression, renal function, and arterial hypertension. Ann Rheum Dis 2002;61:511–16.

55 de Bree A, Verschuren WM, Kromhout D, Kluijtmans LA, Blom HJ. Homocysteine determinants and the evidence to what extent homocysteine determines the risk of coronary heart disease. Pharmacol Rev 2002;54:599–618.

56 van Ede AE, Laan RF, Blom HJ *et al*. Homocysteine and folate status in methotrexate-treated patients with rheumatoid arthritis. Rheumatology 2002;41:658–65.

57 Morgan SL, Baggott JE, Lee JY, Alarcon GS. Folic acid supplementation prevents deficient blood folate levels and hyperhomocysteinemia during longterm, low dose methotrexate therapy for rheumatoid arthritis: implications for cardiovascular disease prevention. J Rheumatol 1998; 25:441–6.