Comorbidity in rheumatoid arthritis

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Summary

Rheumatoid arthritis (RA) is a chronic inflammatory condition, which is associated with an increased risk of comorbidity from other diseases. RA disease severity is a major predictor of development of cardiovascular disease, serious infections and malignant lymphoma. This reflects the role of chronic inflammation in the underlying pathology. Recent surveys indicate that although clinical outcomes have improved in patients with RA, mainly owing to access to more efficient pharmacotherapy, comorbidity remains a major issue in many patients. Register-based observational studies are useful sources of information on the impact of comorbidity and the efficacy and safety of antirheumatic treatment in patients with coexisting diseases. As a part of strategies to improve further the management of patients with RA, multidisciplinary collaboration for prevention and early detection of comorbidities is of major importance.

Key words: rheumatoid arthritis; comorbidity; cardiovascular disease; malignancy; serious infections

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease, which is characterised by polyarthritis with progressive joint damage. The prevalence in the adult population is approximately 0.5–1.0% in most countries [1, 2], and the most common age at onset is between the fourth and sixth decade of life. About 70% of patients with RA are women, mainly the result of a higher incidence for women before the age of 60 years [3]. In recent years, there has been an improvement in clinical outcomes of RA [4, 5], and also a reduction over time in the need for orthopaedic surgery in patients with RA [6, 7]. This likely reflects more efficient pharmacological treatment, including more extensive use of disease-modifying antirheumatic drugs (DMARDs), and the initiation of biologic DMARDs in patients with severe disease.

RA is associated with increased mortality compared with the general population, mainly due to other coexisting diseases, such as cardiovascular disease (CVD) and infections. Although there has been major progress in the management of RA, the burden of comorbidity in these patients remains a major issue. The recent multinational, cross-sectional COMORA (Comorbidities in Rheumatoid Arthritis) study of patients with RA recruited from 17 countries demonstrated a high prevalence of comorbidities and their risk factors [8]. There was major variability among countries in the occurrence of different coexisting diseases, and in the compliance with recommendations for prevention and management of comorbidities [8].

Strategies to address this problem include early recognition and diagnosis of RA, optimal treatment to reduce inflammation, adequate screening and surveillance methods to detect comorbidities, and collaboration between different medical specialists in the prevention and management of comorbidity. The purpose of this paper is to review recent scientific findings on comorbidity in RA, with a focus on cardiovascular disease, serious infections and malignancy, and discuss important future action points.

Cardiovascular disease and rheumatoid arthritis

A major part of the excess mortality in patients with RA has been attributed to CVD [9]. Patients with RA are at increased risk of cardiovascular events overall, as well as death from CVD. The incidence of myocardial infarction has been found to be increased to a similar extent in men and women with RA [10]. By contrast, the risk of cerebrovascular events was not significantly increased in several population based studies [10, 11], although a meta-analysis demonstrated a modestly increased risk of cerebrovascular disease in patients with RA compared with the general population [9] (fig. 1).

The relative risk for experiencing a cardiovascular event has been shown to be in the range 1.5–2.0, compared with the general population [11–13]. The absolute risk has been estimated to be similar to that seen in non-RA subjects who are 5–10 years older [14, 15]. In a Swedish study based on the national Swedish Rheumatology Quality Register, the incidence of myocardial infarction was already increased within the first few years after diagnosis of RA [16]. Increased levels of biomarkers associated with endothelial dysfunction have been demonstrated in early RA [17], and there is evidence for rapid progression of atherosclerosis,

demonstrated as an increased carotid intima-media thickness 5 months after diagnosis [18].

Suggested explanations for the increased comorbidity from CVD include a direct impact of chronic inflammation on the vascular system [19] and secondary effects of physical inactivity [20]. Furthermore, drugs used in the management of RA, in particular nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, have been implicated [20].

Predictors of CVD in patients with RA include severe extra-articular manifestations, such as vasculitis and rheumatoid lung disease [21, 22] and persistently elevated markers of inflammation (e.g. erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) [21, 23]. In two recent large-scale studies of RA patients, even a modestly increased baseline CRP was associated with a doubled risk for CVD [24, 25].

Traditional risk factors, such as smoking [22] and hypertension [23], also contribute to the increased risk of CVD comorbidity in RA. Smoking is a risk factor for RA development [26, 27], and a history of current or previous smoking is therefore relatively common in patients with RA. Furthermore, smoking has been associated with extra-articular involvement [28] and a reduced response to treatment with several DMARDs [29], factors that would contribute to an increased risk of CVD comorbidity. By contrast, hyperlipidaemia, which is a risk factor for CVD in the general population [30], has not been consistently found to predict CVD development in patients with RA [25, 30]. This may be a result of particular patterns in patients with severe, uncontrolled disease, where inflammation contributes to low levels of total cholesterol and triglycerides [31]. This is most likely the explanation for the "lipid paradox" that has been described in some studies of patients with established RA, where low total cholesterol and triglyceride levels have been associated with increased risk of CVD events [32]. The long-term impact of lipid levels in patients with well-controlled disease may be quite different, and needs to be further studied. Interestingly, treatment with biologic DMARDs has been associated with an increase in lipid levels, although the atherogenic index (ratio of low-density lipoprotein cholesterol to high-density lipoprotein cholesterol) appears to be unchanged in most cases [33, 34]. Finally, high cholesterol levels have been demonstrated to predict the development of RA [35], in particular in women [36], suggesting that the preclinical phase could also contribute to atherogenesis and subsequent cardiovascular events.

Infections and rheumatoid arthritis

Patients with RA have an increased morbidity and mortality from infectious diseases [37]. This pattern was recognised long before the development of immunosuppressive drugs that inhibit the tumour necrosis factor (TNF) and other biologic DMARDs. In fact, the main risk factors for serious infections in older RA cohorts were markers of disease severity and the presence of other comorbidities [38]. Long-term use of glucocorticoids is also a major predictor of infections in patients with RA [38, 39]. These patterns are relevant also in the era of biologic DMARD treatment. A risk score for serious infections in patients with RA has been developed in the German Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) register [39]. It includes age, measures of disability, key comorbidities (renal failure and chronic lung disease), history of previous infections, history of previous treatment failure, and current treatment. Patients with a high risk score have a more than 30-fold increased risk of developing a serious infection [39]. Validation in a separate cohort demonstrated excellent agreement between observed and expected rates of serious infections [40].

The use of glucocorticoids is a major factor in the RABBIT-based risk score [39], which underlines the importance of tapering and discontinuing glucocorticoid use, in particular in patients with a history of severe infections. In early RA, the documented benefits of glucocorticoids must be weighed against the risks, in particular with long-term use. The European League Against Rheumatism (EULAR) recommendations for the management of RA state that low-dose glucocorticoids should be part of the initial treatment strategy in early RA for up to 6 months, but should be tapered as quickly as clinically feasible [41]. The recently updated American College of Rheumatology (ACR) guidelines, on the other hand, only include glucocorticoids as an addition in cases with active disease despite DMARD treatment, and recommend that the lowest possible dose should be used for the shortest possible duration [42]. Other guidelines, such as those from the Swedish Society of Rheumatology, recommend that low dose glucocorticoids should be used in early RA unless special circumstances speak against it, again emphasising the importance of individualised treatment and taking other factors, such as comorbidities, into account [43].
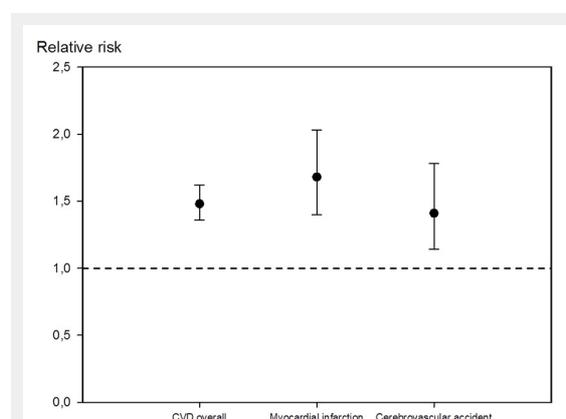
Malignancy and rheumatoid arthritis

An increased rate of lymphoma has been a consistent finding in studies of cancer and RA. In a large meta-analysis, the overall standardised incidence ratio for lymphoma was 2.1, with a greater risk of both Hodgkin's and non-Hodgkin's lymphoma in patients with RA compared with

Figure 1

Pooled relative risks with 95% confidence intervals of cardiovascular disease (CVD) events in patients with rheumatoid arthritis compared to the background population. Based on data from a meta-analysis of 41 490 patients in 14 observational studies (Avina-Zubieta et al. Ann Rheum Dis. 2012;71(9):1524–9 [9]).

the general population [44]. There appears to be a particularly strong association between RA and the diffuse large B-cell lymphoma [45], which has been reported to represent up to two-thirds of the non-Hodgkin's lymphomas in patients with RA, a considerably greater proportion than that observed in the general population [46, 47]. The risk of lymphoma appears to be higher in patients who have severe RA, in particular those with positive rheumatoid factor and those who have persistently high disease activity over time [47, 48]. Taken together, this is compatible with a role for chronic activation of B cells and T cells in the initiation of lymphoproliferative disorders in patients with RA. The risk of lymphoma is increased not only in RA, but also in other rheumatic diseases, such as systemic lupus erythematosus [49] and primary Sjögren's syndrome [50], and in several other autoimmune conditions (e.g., idiopathic thrombocytopenic purpura and sarcoidosis [46].

An increased risk of lung cancer has been reported in patients with RA [44]. This may be due to the well-established association between smoking and the development of RA [26, 27]. It is presently not known whether patients with RA have an elevated risk of lung cancer above the expected based on their smoking history.

The overall rate of cancer does not appear to be substantially elevated in patients with RA compared with the general population. Several studies of RA populations have reported a reduced incidence of colorectal cancer. This has been attributed to long standing treatment with NSAIDs in many patients [51]. A study of patients diagnosed with RA after 1995 did not find a significantly lower rate of colorectal cancer compared with the general population [52], possibly because of less extensive NSAID use in some patients who have responded to modern, early treatment with DMARDs.

Interestingly, reduced rates of other cancer types, including breast, ovary, endometrial and prostate cancer have been reported in some studies. This could be due to hormone-related exposures that predispose to RA development in middle-aged and older individuals, such as early menopause [53] and low testosterone levels in men [54].

Comorbidity and anti-rheumatic treatment

A key issue is whether the initiation of treatment with a DMARD puts the patient at increased risk of comorbidity. As stated above, RA disease severity is a risk factor for several comorbidities, introducing confounding or channelling bias as patients with severe RA are treated more intensively with DMARDs.

In the international QUEST-RA (Quantitative Monitoring of Patients with RA) study, longer use of biologic DMARDs and synthetic DMARDs such as methotrexate, leflunomide and sulfasalazine was associated with a decreased risk of CVD [55]. A recent meta-analysis of observational studies and randomised controlled trials also demonstrated reduced risks of CVD in patients treated with methotrexate or TNF inhibitors [56]. Furthermore, several studies have shown that patients with RA who are clinical responders to anti-TNF treatment have a lower risk of CVD than nonresponders [57, 58]. By contrast, the use of

NSAIDs was associated with increased risk of CVD comorbidity in RA, with a magnitude similar to that seen in the general population [56].

Treatment with TNF inhibitors and other biologic DMARDs has consistently been associated with an increased risk of serious infections in randomised clinical trials (RCTs) [59], as well as in short-term observational studies [60]. However, in long-term studies of patients with RA followed-up in registers, the excess risk appears to decline over time, [39, 61]. This has been shown to be due to both selection driven by treatment termination or loss to follow-up in patients at increased risk, and to a risk reduction through improvement in function and decreasing use of corticosteroids [39].

The most frequently used conventional synthetic (nonbiologic) DMARDs do not appear to be associated with an increased cancer rate overall in patients with RA, although specific types of lymphoma have been associated with azathioprine [48] and methotrexate [62]. Meta-analyses of RCTs [63] and observational studies [64] have not demonstrated a significantly increased risk of cancer overall in patients treated with TNF inhibitors. However, a recent survey of the Swedish biologics register reported a 50% increase in the risk of melanoma [65]. This increase appears to be driven by the immunosuppressive treatment, as patients with RA who had not received a biologic DMARD had a risk similar to the general population [65].

A crucial clinical question is whether patients with pre-existent malignancies should be exposed to biologic DMARD therapy. Patients with a history of cancer are excluded from most clinical trials, and, in clinical practice, physicians may be reluctant to treat such patients with TNF inhibitors and other biologic DMARDs, resulting in a channelling of treatment with these agents toward low-risk cohorts. Analyses from the German RABBIT register and the British biologics register detected no increased risk of recurrent malignancy in patients with pre-existing cancer treated with anti-TNF agents [66, 67]. However, event rates were low in these studies, further underlining the issue of channelling bias. In a recent survey of the Swedish biologics register, there was no increased risk of recurrence of breast cancer in patients with RA and a median time from breast cancer diagnosis until initiation of treatment with a TNF inhibitor of 9.4 years [68]. The generalisability of these findings to women with a very recent or a poor prognosis of breast cancer remains unknown.

Rituximab, a monoclonal anti-CD20 antibody, was originally developed as an anti-tumour drug for use against B-cell lymphoma. Based on this and on safety data indicating no increased risk of incident malignancies [69], rituximab has been suggested as a preferred biologic DMARD for patients with RA who have had a history of cancer [70]. There is considerably less experience with long-term treatment with other biologic DMARDs, such as abatacept or tocilizumab, but the published data have revealed no signals for increased malignancies [71, 72].

Future agenda

There is a limited evidence base for the management of patients with RA and comorbidity. The COMORA study

demonstrated a negative association between the presence of comorbidities and the use of biologic DMARDs, adjusted for potential confounders [73]. The avoidance of aggressive treatment in patients with comorbidities is most likely adequate in many cases as an example of an overarching "no-harm" principle, but it may also create a vicious circle where persistent disease activity in patients who are not extensively treated contributes to further RA-associated comorbidity. As comorbidities are listed as exclusion criteria in most RCTs, expanding knowledge on the safety and efficacy of biologic DMARDs in such patients can only come from observational studies in population-based registers. This is an important point on the agenda for future research on RA.
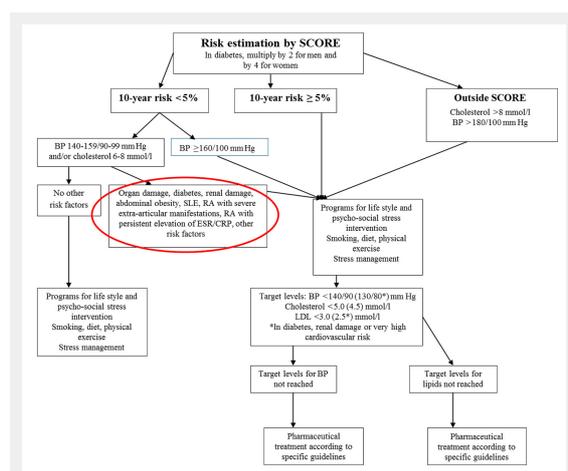
Recommendations for the risk assessment and prevention of CVD in patients with RA have been developed [74, 75]. These are based on decision algorithms such as the Framingham risk score [76] or the SCORE risk estimation system [77]. The increased risk of CVD in patients with RA is taken into account by either multiplying the estimated risk by 1.5 [74] or by classifying high-risk patients (e.g., those with severe extra-articular RA or persistent elevation of CRP/ESR) as having a risk corresponding to existing CVD-related organ damage, with a correspondingly lower threshold for intervention [75] (fig. 2). Ideally, risk assessment for CVD and other comorbidities should be based on data from observational studies of patients with RA, and the use of such algorithms in clinical decision making should be scientifically evaluated.

Further action is also necessary to reduce the burden of infections in patients with severe RA. Structured vaccination programmes are important in this context. Many, but not all, patients with RA who are treated with TNF inhibitors have a robust antibody response after vaccination with pneumococcal conjugate vaccine [78], and such a response has been shown to be associated with a reduced risk of serious infections in this patient population [78]. Current recommendations state that vaccination can be performed during the use of DMARDs and TNF blocking agents, but should ideally be initiated before starting B cell depleting biologic therapy, as this substantially reduces the antibody response [79]. Overall, the vaccination status should be assessed at the initial investigation of a patient with RA, but vaccination should ideally be administered during stable disease [79]. Based on this, a practical approach is to make a plan for vaccination at an early time-point, but await the achievement of stable low disease activity before administering, for example, pneumococcal vaccine. On the other hand, influenza vaccination, the timing of which is mainly determined by the availability of the current vaccine, is strongly recommended in patients with RA and other chronic rheumatic disorders [79], and should be given on an annual basis.

All efforts to prevent comorbidities in patients with RA, or to reduce the impact of existing comorbidities, require a multidisciplinary collaboration between rheumatologists and other medical specialities and other health professionals. Examples of key collaborative interventions are listed in table 1. In particular, general practitioners have an important role in the management of these complex patients. Patient education and access to patient support groups is of major importance for the success of interventions such as lifestyle modification. Finally, increasing awareness of the impact of comorbidity on the quality of life and prognosis in patients with RA and other chronic disorders in the medical community as well as in the society may contribute to improved outcomes in the future.

Figure 2

Recommended decision algorithm for interventions in the primary prevention of cardiovascular disease (CVD) in patients with rheumatoid arthritis and other inflammatory rheumatic disorders. This is based on estimation on the 10-year risk of death from CVD, using the SCORE system [77]. Reproduced, with permission, from: The Swedish Society of Rheumatology. Guidelines for cardiovascular primary prevention in patients with inflammatory rheumatic disease [75]. BP = blood pressure; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; LDL = low density lipoprotein; RA = rheumatoid arthritis; SCORE = Systematic COronary Risk Evaluation; SLE = systemic lupus erythematosus

Table 1: Examples of collaborative interventions to reduce the burden of comorbidity in patients with rheumatoid arthritis (RA).

Goal	Intervention
Reduce the risk of reactivation of latent tuberculosis	Structured screening programme with collaboration between rheumatologists and dedicated Infectious Diseases specialists
Prevent severe infections in patients with RA	Structured immunisation programme with collaboration between primary care and rheumatology
Life-style modification to prevent cardiovascular disease and other comorbidities	Rheumatology nurse clinic with structured life-style interventions Smoke cessation programmes Collaboration with physiotherapists to increase physical activity
Prevention of cardiovascular disease in high-risk individuals	Use of validated risk assessment tools and decision algorithms in collaboration with general practitioners, cardiologists, neurologists, etc.

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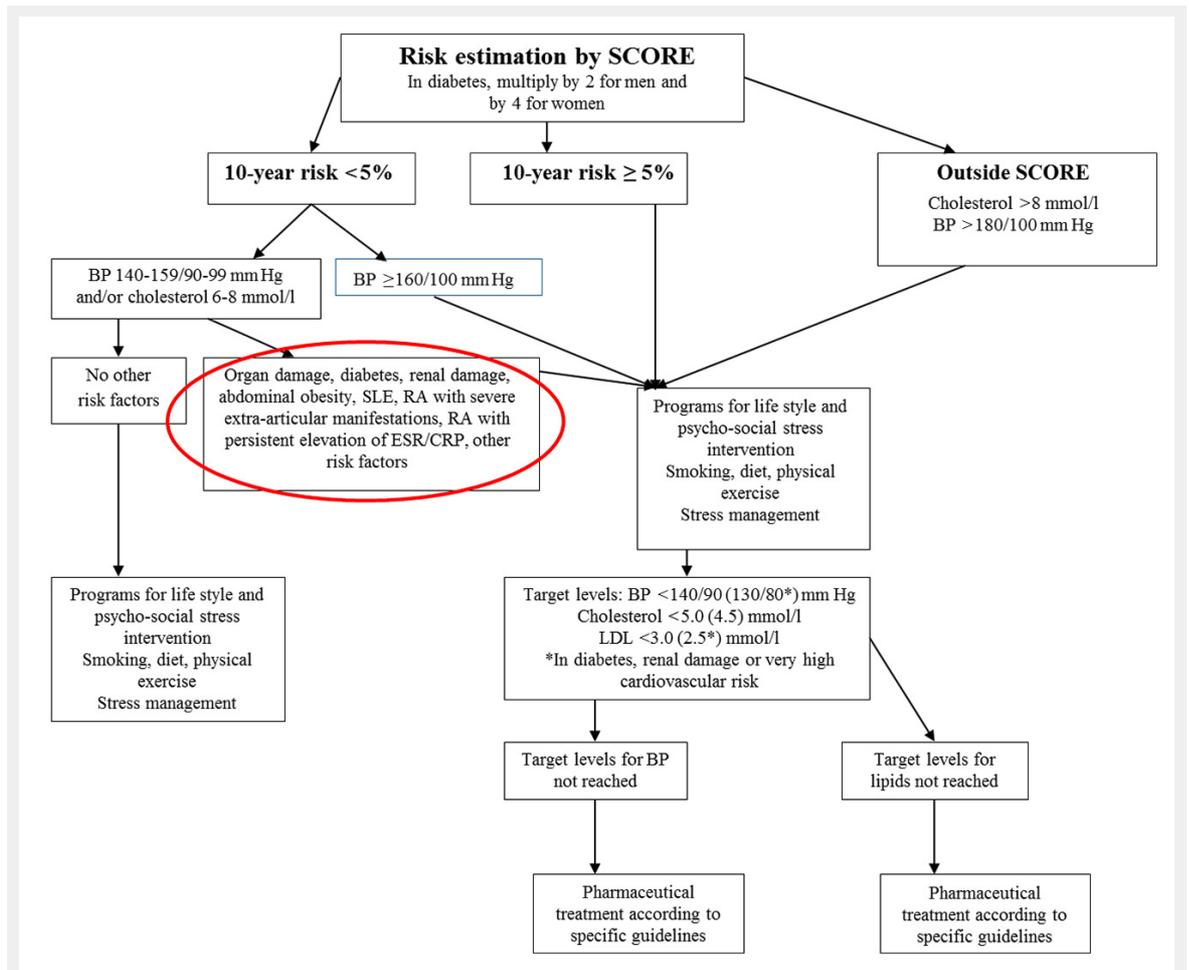
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Figures (large format)
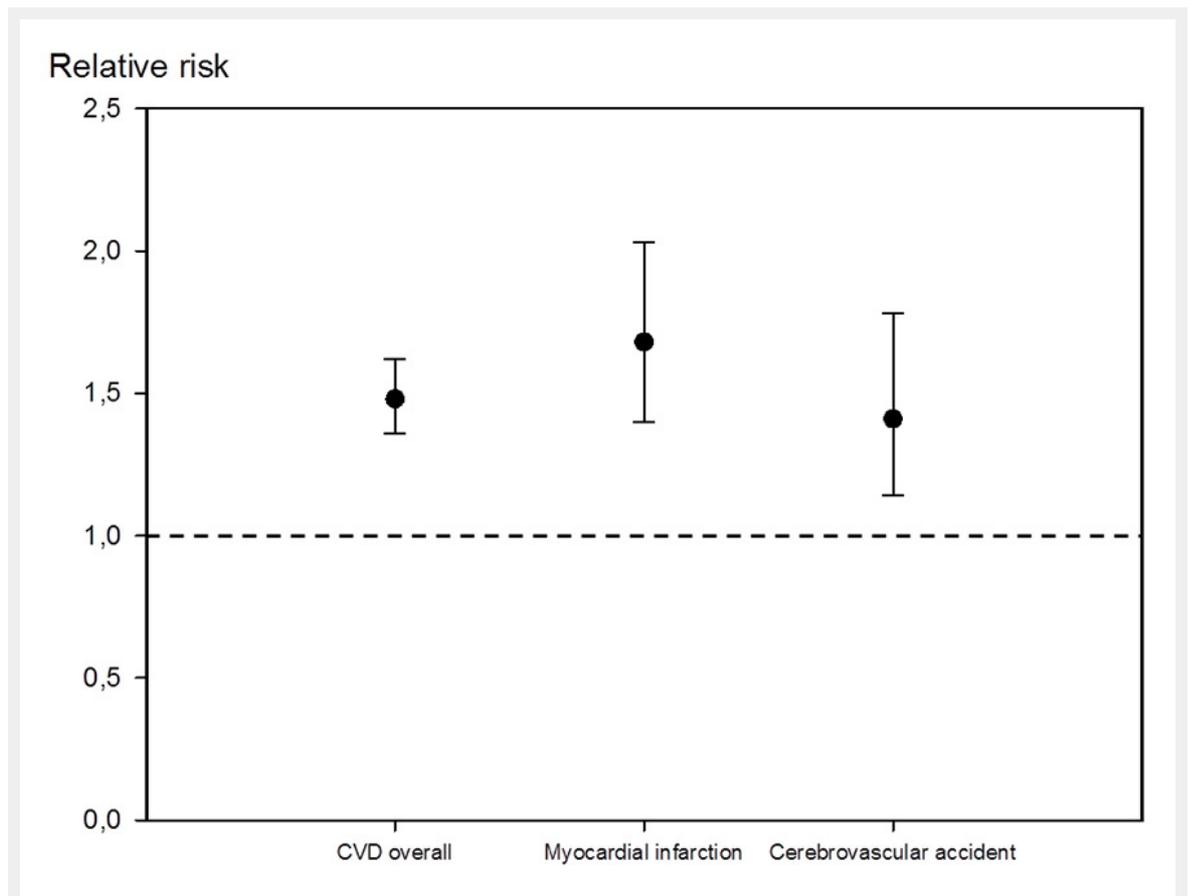
Figure 1

Pooled relative risks with 95% confidence intervals of cardiovascular disease (CVD) events in patients with rheumatoid arthritis compared to the background population. Based on data from a meta-analysis of 41 490 patients in 14 observational studies (Avina-Zubieta et al. Ann Rheum Dis. 2012;71(9):1524–9 [9]).

Figure 2

Recommended decision algorithm for interventions in the primary prevention of cardiovascular disease (CVD) in patients with rheumatoid arthritis and other inflammatory rheumatic disorders. This is based on estimation on the 10-year risk of death from CVD, using the SCORE system [77]. Reproduced, with permission, from: The Swedish Society of Rheumatology. Guidelines for cardiovascular primary prevention in patients with inflammatory rheumatic disease [75].

BP = blood pressure; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; LDL = low density lipoprotein; RA = rheumatoid arthritis; SCORE = Systematic COronary Risk Evaluation; SLE = systemic lupus erythematosus