Cardiovascular risk and rheumatoid arthritis—the next step: differentiating true soluble biomarkers of cardiovascular risk from surrogate measures of inflammation

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Abstract

In the past decade, there has been a surge of interest in the examination of cardiovascular (CV) outcomes in RA, where it is widely accepted that there is an enhanced risk of CV disease (CVD). In recent years, a number of novel soluble biomarkers of CV risk have been examined in the general population to investigate whether any value is added to the routine measurement of traditional (Framingham) CV risk factors. We briefly review these novel markers and identify those markers that appear distinct to systemic inflammation, which may then be applicable to evaluation in patients with RA. We then investigate whether any of the soluble CV biomarkers provide additional information on the risk of developing subclinical CVD or cardiac events in an individual patient with RA, or whether they may only provide a surrogate measure of the systemic inflammatory load experienced by such patients.

Key words: Rheumatoid arthritis, Cardiovascular disease, Systemic inflammation, Soluble biomarkers.

Introduction

It is now well recognized that patients with RA have increased morbidity and mortality from premature cardiovascular (CV) disease (CVD). Up to 50% of this excess mortality is secondary to ischaemic heart disease (IHD) closely followed by cerebrovascular disease [1–3], with a 1.5-fold increase in the standardized mortality ratio due to CV events compared with the general population [4]. Of yet more concern, are data from the Rochester RA cohort, which suggest that the mortality gap between individuals with RA and the general population continues to widen, despite the dramatic advances made in the field of CV medicine since the 1960s [5]. It has been suggested that the enhanced risk of premature CVD in RA is equivalent to that seen in diabetes [6], occurs early in RA in some [7], but not all studies [8] and may even predate disease onset [9, 10].

All stages of the atherogenic process appear to be enhanced in RA, with evidence of endothelial dysfunction through to increased arterial stiffness, increased carotid intima-media thickness (IMT) and plaque formation, coronary artery calcification and finally clinical CV events [11–13]. However, it remains unclear whether the observed CV events arise through the same or different mechanisms from those in the general non-RA population. For example, patients with RA are significantly less likely to report anginal symptoms before the development of a CV event and their first CV manifestation is significantly more likely to be an acute myocardial infarction or sudden cardiac death [9]. Furthermore, a post-mortem series examining the coronary arteries of patients with RA compared with non-RA controls (matched for age, sex and CV history) concluded that there was less histological evidence of atherosclerosis, but greater evidence of inflammation and plaque instability in the coronary arteries of patients with RA compared with non-RA controls [14]. This lends support to the theory that the mechanisms responsible for CV events in RA may differ from those in the general population. Furthermore, traditional CV risk factors do not fully account for all of the enhanced morbidity and mortality seen in RA [9, 10, 15, 16], and the disease itself is now considered to be an independent risk factor for CVD.
Immune dysregulation and systemic inflammation are believed to be integral to the development of accelerated atherogenesis, in RA [12, 17, 18]. Indeed, there are many parallels between the pathological and immunological processes that occur in the synovium and the atherosomatous lesions in the vessel walls [13]. Correspondingly, RA severity markers such as autoantibody production (RF, anti-citrullinated peptide antibodies, aCL), markers of systemic inflammation (ESR, CRP, TNF, IL-6), number of inflamed joints, early functional decline and the presence of extra-articular features have all been reported to be strongly associated with adverse CV outcomes in RA [19–23].

The increasing acceptance by rheumatologists and the wider medical community that premature CVD causes a significant health burden to RA patients has led to the development of guidelines advising on how this increased CV risk should be identified and managed over and above the requirement for complete suppression of inflammation [24]. However, in view of the scarcity of long-term CV outcome data from RA cohorts, much of the guidance available has been extrapolated from CV studies performed in the general population. Many studies have reported on, and comprehensively reviewed, the now well-established traditional (Framingham) risk factors, including atherogenic lipid profiles, markers of haemostasis and thrombosis, and insulin resistance in RA that are frequently abnormal early in disease, strongly associated with systemic inflammation and potentially reversible with several therapeutic agents [10, 12]. More recently, a number of novel CV biomarkers have been studied and found to be associated with the future risk of CVD (the non-traditional CV risk factors) in the general population [25, 26]. However, it is not clear whether those CV biomarkers and/or surrogate end points that have been shown to add value when applied to the general population are directly transferable and/or applicable to RA, where the final hard end point of a CV event may arise through a different mechanism. Authors have postulated that, in addition to the enhanced risk of CVD that chronic systemic inflammation undoubtedly infers, there may be other disease-specific CV risk factors that are more prevalent in RA, such as lipid alterations, an increased incidence of sub-clinical hypothyroidism, insulin resistance or the metabolic syndrome (MetS) [27–31]. The latter is a complex cluster of metabolic abnormalities that include: abdominal obesity; hypertension; insulin resistance and glucose intolerance; an atherogenic lipid profile (increased low-density lipoprotein, triglycerides and reduced high-density lipoprotein); and pro-inflammatory and pro-thrombotic states [32–35]. While not an absolute risk indicator for CVD, it is well recognized that those with the syndrome have a 2-fold increased risk of developing CVD over the next 5–10 years compared with those without, and that the frequency of MetS continues to increase throughout the Western world [33].

The purpose of this review is to investigate whether any of the novel soluble markers of CV risk emerging from general population studies have the potential to predict the risk of future CVD in an individual RA patient, or alternatively, whether they may merely provide a surrogate measure of the systemic inflammatory load experienced by such patients (i.e. track with established markers of systemic inflammation).

What is a biomarker? What is a surrogate end point?

The terms biomarker and surrogate end point are utilized with increasing frequency in CV outcome studies. For the purposes of this review, we have conformed to the NIH Definition Working Group description of these entities. A biomarker is: ‘a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention’ [36]. Although often cheaper and easier to measure than a true end point (and information can be obtained at an earlier stage), biomarkers often fail as surrogate markers of a disease process because of a number of factors. For example, the surrogate does not cause the disease, the surrogate is only involved in one pathway in a multiple pathway disease, the surrogate is insensitive or not affected by the intervention’s effect or the surrogate measures an effect independent of the disease process [37].

A surrogate end point is ‘a biomarker intended to substitute for a clinical end point’. A surrogate end point should predict clinical benefit (or harm, or lack of benefit or harm) on the basis of epidemiological, therapeutic, pathophysiological or other scientific evidence [36]. All surrogate end points are biomarkers; however, not all biomarkers are useful surrogate end points. The Austin Bradford Hill guidelines (developed to help analyse association in determining causation) are helpful when deciding which biomarkers are good candidates for surrogate end points—whenever a biomarker conforms to these guidelines, it is more likely to be useful [38].

Numerous surrogate CV end points have been developed to detect subclinical atherosclerosis. Endothelial dysfunction and carotid IMT measured by high-resolution ultrasonography are widely used as surrogate CV end points in RA. Endothelial dysfunction represents a reversible aberrant arterial vasodilator response that occurs early in the disease process and is closely associated with markers of systemic inflammation [11]. Similarly, increased aortic and arterial wall stiffness, measured by pulse wave velocity, occurs early and can similarly be reversed with successful therapeutic suppression of inflammation [39, 40]. Chronic structural changes in the vessel wall can be directly visualized with an increased carotid IMT representing both lipid deposition and atheromatous plaque formation [41]. Coronary artery calcium detected by electron beam CT is an alternative screening modality and highly correlated with coronary artery plaque [42].

Soluble CV biomarkers—general population

The identification of novel CV biomarkers is growing rapidly due to developments in proteomic and molecular
techniques [43]. From studies investigating the pathophysiology of atherosclerosis [26, 44]; it is clear that a wide range of biological molecules are involved in all steps of atheroma formation, maturation, rupture and eventually clinical events. We focused on those CV biomarkers with some evidence to indicate that they were closely associated with a specific disease state or rate of disease progression [26].

Markers of systemic inflammation
It is now well established that systemic inflammation, albeit at a much lower level than that seen in RA, is an independent predictor of CV events. High-sensitivity (hs) assays for cytokines (TNF, IL-1 and IL-6) and inflammatory mediators are required, with hsCRP being the most reliable marker investigated to date [25, 32, 43, 45]. The level of circulating CRP is a prognostic marker of future CV events for men and women both with and without established CVD [46, 47]. It positively correlates with surrogate CVD end points, such as pulse wave velocity [48]. Of interest to the rheumatology community is the fact that the risk of future CV events in a general population is linear across a full range of CRP values, with those individuals with a CRP level >20 mg/l having the highest risk of future CV events [49].

Adipokines
In recent years, there has been an increased appreciation that adipose tissue should be viewed as an active endocrine organ. Adipo(cytok)okines, in particular adiponectin, are known to have anti-diabetic, insulin sensitizing, anti-inflammatory and vasculature protective properties [50]. Circulating adiponectin levels decrease with increasing adiposity (BMI) and visceral obesity, insulin resistance (MetS and Type 2 diabetes), atherogenic lipid profile, circulating inflammatory mediators (CRP, TNF, IL-6), risk of CVD and possibly coronary plaque vulnerability [51–53]. Paradoxically, adiponectin levels are also increased in chronic conditions with a clearly increased CV mortality, such as Type 1 diabetes (with or without nephropathy) [54], chronic heart failure [55], end-stage renal disease [56] and the inflammatory rheumatic diseases, RA and SLE, as outlined below. The synthesis and assembly of adiponectin is complex with different molecular weight isoforms and post-translational modifications that may in part explain the paradoxical and multi-faceted roles of adiponectin in vivo [57–59], which clearly warrant further investigation.

Furthermore, there is increasing awareness that some adipokines, such as adiponectin, leptin, visfatin and resistin may additionally play important roles in the regulation of inflammation and immune responses [60]. It has been proposed that leptin may provide an important link between obesity and CVD. In common with adiponectin it has diverse metabolic effects and CV actions that could modulate atherogenesis at many levels and serum levels appear to correlate with both coronary heart disease and chronic heart failure in addition to CV events such as myocardial infarction and stroke [61].

High leptin levels were associated with an increased risk of developing CVD, beyond that conferred by elevated CRP levels, in a study performed on 6251 participants from the Third National Health and Nutrition Examination Survey [62]. Leptin levels were also significantly higher in males who experienced a coronary event from The West of Scotland Coronary Prevention Study and were associated with an increased risk of a future coronary event in men with hypercholesterolaemia. Importantly, the predictive value of leptin remained after adjustment for BMI and traditional CV risk factors [63].

High plasma resistin, in parallel with high adiponectin levels, has also been shown to predict mortality in the year following myocardial infarction, which remained significant after adjustment for other risk factors [51]. However, much of the literature suggests a strong correlation with systemic inflammation that may limit its role as a biomarker and further studies are awaited [64]. The data currently available on visfatin in atherosclerosis and CVD is currently highly controversial and probably limited by discrepancies in some commercial assays [65].

Endothelial dysfunction
Endothelial dysfunction is a critical and early step in the development of atherosclerosis correlating closely with markers of systemic inflammation, particularly CRP and IL-6, MetS, insulin resistance and future CV events [35, 66]. Endothelial inflammation is believed to occur initially followed by endothelial activation, which results in monocyte chemotactic protein-1 (MCP-1) release and the up-regulation of adhesion molecule expression, which collectively play an important role in leucocyte adhesion and transmigration into the vessel wall [67, 68]. In addition to the role of MCP-1 in promoting plaque growth, the level of circulating MCP-1 is increased in acute CV events in the general population [67] and carotid IMT in chronic haemodialysis patients [69]. The level of circulating soluble intercellular adhesion molecule 1 (sICAM-1) is elevated in IHD and predicts future myocardial infarctions [70–72] and strokes [73], following adjustment for traditional risk factors. In patients with angiographically verified CVD the adhesion molecules sICAM-1, sE-selectin and soluble vascular cellular adhesion molecule 1 (sVCAM-1) were all associated with future fatal events, with sVCAM-1 in particular, adding to the predictive value of traditional risk factors [74]. However, similar associations with sVCAM-1 have not been observed in the general population [70, 75]. L-selectin is an adhesion molecule expressed on the majority of circulating leucocytes that appears to be shed following initiation of leucocyte rolling on the vessel wall [76]. Paradoxically, a low level of circulating sL-selectin is associated with all stages of CVD [77] and carotid plaque size [78], in the general population, with reduced cell surface expression that is also confirmed by flow cytometry [77].
Plaque destabilization/plaque rupture

There is considerable interest in the identification of biomarkers that detect unstable atherosclerotic plaques at an increased risk of rupture. These plaques become infiltrated with activated neutrophils and macrophages that release metal-independent myeloperoxidase (MPO) and lytic enzymes, such as MMPs, which digest collagen and produce thinning of the fibrous cap. Circulating MPO levels appear to provide some indication of plaque instability, but not ischaemia, although clinical utility is likely to be limited by the level of neutrophil and macrophage activation in a number of inflammatory and infectious diseases [79]. There is a large amount of data supporting the role of MMP9, also known as gelatinase B, in plaque instability [79]. Circulating levels of MMP9 are associated with future CV death in patients with both stable and unstable angina, which remained after correction for markers of systemic inflammation [80], and circulating MMP9 is also being investigated as a potential tool to assess remodelling following a myocardial infarction [79].

Many biologically active mediators are released during plaque rupture, including adhesion molecules, with soluble CD40 ligand (sCD40L) generating interest as a potential biomarker. Circulating sCD40L is largely produced by activated platelets. Both membrane-bound and sCD40L activate endothelial cells, monocytes, macrophages, B cells and T cells, which express the CD40 receptor and have dual pro-inflammatory and pro-thrombotic actions. Of direct relevance to plaque rupture, this leads to the activation of MMPs with disruption of the atherosclerotic plaque [81]. Induction of tissue factor expression on macrophages and endothelial cells leads to further platelet activation and sCD40L release, and also favours a local pro-coagulant and pro-thrombotic status by suppressing thrombomodulin expression [79, 82]. Elevated levels of sCD40L are associated with a high risk of future CV events [83–85], including in healthy women [86], and may provide additional information over established markers, such as troponin I or CRP [83]. However, in common with many biomarkers there is still a need for assay standardization and further evaluation in larger studies.

Cardiac overload/ventricular dysfunction

NT-pro brain natriuretic peptide (NT-proBNP) is a cardiac neurohormone that is expressed mainly in response to ventricular overload and hypoxia [87, 88]. The precise mechanism controlling NT-proBNP synthesis remains unclear, although it is thought to be related to myocyte stretch or increased ventricular wall tension [89]. The circulating level of NT-proBNP is an important clinical indicator of the severity of cardiac hypertrophy [90]. It is also a predictor of future cardiac events and mortality in patients with IHD and congestive cardiac failure, end-stage renal disease and diabetes [90–92]. NT-proBNP also appears to provide additional information and improve risk stratification for future CV events and CV mortality, when compared with traditional risk factors and inflammatory markers [93–95]. Of note, NT-proBNP appeared to be more strongly related to CV events than CRP [94].

Soluble CV biomarkers—RA population

It will become immediately apparent to the reader that there is a huge discrepancy between studies of CV risk biomarkers performed in the general population and those currently published in RA. A number of studies of soluble CV biomarkers in the general population contain tens of thousands of patients, a sample size beyond the scope of even the most enthusiastic clinical trialist within the field of rheumatology. Furthermore, most of the studies currently published in RA cohorts report on a single cross-sectional measurement, usually of a surrogate CV end point and frequently performed as part of a retrospective analysis of a study, where CV outcomes were not the prespecified primary or secondary end point. The most important molecules that are thought to be involved in the development of CVD in an RA population and the closely aligned MetS are shown in Fig. 1.

Markers of systemic inflammation

The utility of circulating cytokines and acute-phase proteins as biomarkers of CV events poses potential difficulties with clinical interpretation in RA. Even low disease activity states in RA are associated with significantly higher cytokine and CRP levels than those observed in the non-RA population at risk of CV events. However, the baseline level of CRP has been shown to predict CV mortality [96] and the relationship between CVD and CRP is almost linear in RA [20]. CRP may thus provide important prognostic information, by indicating poor disease control and high levels of systemic inflammation, rather than being a surrogate for the extent of vascular involvement in RA. Furthermore, there is increasing evidence that systemic inflammation and CRP in particular plays a major pathogenic role in atherogenesis by directly contributing to endothelial activation and dysfunction, insulin resistance, pro-thrombotic effects, dyslipidaemia, oxidative stress, alterations in circulating leucocyte subsets and up-regulation of MCP-1 [12, 97–99].

Adipokines

In RA, an elevated level of adiponectin has been observed in both serum and SF compared with healthy controls and OA patients [100, 101], which, in contrast to metabolic disorders, was positively correlated with markers of inflammation, such as CRP. High adiponectin concentrations may also be a normal counterpart of the local inflammatory process, which is supported by the observations that adiponectin levels: increase following MTX [100] and etanercept therapy [102]; are associated with an improvement in endothelial dysfunction, assessed by pulse wave velocity, following infliximab therapy [103]; and are negatively correlated with the number of leucocytes in the SF of RA patients [101]. The association with CVD and surrogate measures such as insulin resistance and carotid IMT in RA remain unconfirmed [104]. There have been no studies investigating the different adiponectin isoforms in RA to date, which will be required to fully understand this pathway.
Data on more recently discovered adipokines have started to emerge. Increased circulating levels of leptin and visfatin have been observed in RA, with the raised leptin level correlating with the presence of insulin resistance after adjustment for traditional risk factors, but not coronary artery calcification [105]. In one small study, circulating leptin levels were associated with obesity in RA, but did not reduce following infliximab therapy [106], indicating disassociation with systemic inflammation that may be clinically useful in the context of RA. The elevation in visfatin level was associated with increased levels of radiographic damage [105], but not insulin resistance [105] or MetS [107], following correction for other risk factors.

**Endothelial dysfunction**

The endothelial dysfunction observed even in the earliest stages of RA is likely to be multi-factorial, as outlined above. In early and established RA there is a weak to moderate correlation of endothelial dysfunction with RA disease activity measures, such as CRP, ESR and the DAS [108, 109]. Circulating levels of MCP-1 and adhesion molecules such as sICAM-1, sVCAM-1, sE-selectin and endothelial leucocyte adhesion molecule (ELAM-1) are elevated in RA subjects compared with healthy controls [110, 111], alongside increases in von Willebrand factor (VWF) and tPA and PAI-1, which are haemostatic factors also believed to reflect endothelial dysfunction [8, 111, 112]. Furthermore, sVCAM-1 and sL-selectin are associated with endothelial dysfunction [8, 113], and MCP-1, sICAM-1, sVCAM-1, sE-selectin, VWF, PAI-1 are associated with atherosclerosis/IMT in RA [8, 111]. In a prospective study in early RA, L-selectin was the endothelial biomarker that was most strongly associated with endothelial dysfunction measured by endothelial-dependent flow-mediated dilatation after correction for systemic inflammation [8]. L-selectin is down-regulated with chronic inflammation and an inverse correlation with endothelial dysfunction was observed in early RA.

Circulating levels of many adhesion molecules do appear to be associated with systemic inflammation, particularly IL-6, and dyslipidaemia in RA [108, 111]. There are some early indications that they may be associated with atheroma detected by carotid IMT after controlling for traditional CV risk factors [111, 114], with a fall in sICAM-1 also being observed following SSZ therapy [109]. However, in a recent prospective study in early RA, sICAM-1 and sVCAM-1 were elevated compared with healthy controls,
but they were not associated with endothelial dysfunction or IMT after correction for systemic inflammation.

MCP-1 also looks particularly interesting as a CV biomarker in RA. Elevated levels have been observed before the diagnosis of RA in autoantibody-positive patients, perhaps suggesting very early endothelial activation [110]. After adjustment for inflammation and traditional risk factors, MCP-1 and VWF were the two endothelial biomarkers that were most strongly correlated with carotid IMT in early RA [8]. Other pro-thrombotic haemostatic factors, such as tPA and PAI-1, were also increased early in disease, but were closely associated with systemic inflammation, as previously observed in diabetes mellitus, and did not offer additional prognostic value [8].

Plaque destabilization/plaque rupture

Many of the biomarkers associated with plaque destabilization and rupture in the general population are produced by activated neutrophils, macrophages and platelets and consequently, and in common with systemic inflammation, may have limited additional utility in predicting CV events in RA. Both MPO and MMP3 are elevated in RA, but are not associated with coronary artery calcification [45] after adjustment for inflammation. Likewise, sCD40L expression is significantly increased in the RA population [115, 116], but does not appear to correlate with evidence of CV dysfunction [116] or subclinical atherosclerosis assessed by IMT [115]. It is important to note that many of these studies were cross-sectional and included fewer than 100 participants and so further studies of these biomarkers are warranted, in RA.

Cardiac overload/ventricular dysfunction

NT-proBNP levels are elevated in up to 30% of patients with RA compared with healthy controls [117–119], including patients without clinically overt heart failure or CVD [120]. Although the level of circulating NT-proBNP is associated with markers of systemic inflammation, particularly CRP, IL-6 and TNF, the difference between the RA and control group remained highly significant after adjustment for age, renal function and systemic inflammation (CRP and ESR) [119, 121]. In RA, NT-proBNP levels fall following therapeutic TNF blockade [117] and are associated with incremental prediction of mortality [122] and also with systolic and diastolic volumes and left ventricular mass as measured by Doppler echocardiography [119].

Conclusions

Assessing the utility of soluble biomarkers of CV risk in RA is limited by the time taken to develop CVD following the development of RA and the relative scarcity of clinical CV events in a single RA cohort. In the general population, a combination of three soluble biomarkers, CRP, NT-proBNP and sensitive Troponin I, substantially improved estimation of 10-year risk for CV events in both men and women from middle-aged European populations [95] and comparable results were also observed for CRP and NT-proBNP in a different study, which did not examine Troponin I [123]. It is noteworthy that each of these biomarkers represents a different stage in the atherosclerotic pathway and it is likely that more multi-marker combinations will emerge in the forthcoming years. Further proof of the acceptance of CRP as a validated CV risk factor is its recent inclusion in a CV risk factor calculator, the Reynolds Risk Score [124]. Importantly, and unlike cytokines, each of the biomarkers outlined above is relatively stable in stored samples and thus amenable to evaluation in routine clinical biochemistry laboratories. MetS and insulin resistance, leptin [61–63], MCP-1 [67], sICAM-1 [70–73], sVCAM-1 [74], sL-selectin [77], MMP9 [80], sCD40L [83–86] and NT-proBNP [91–95, 125, 126] all show some utility as markers of CV events over and above traditional risk factors and/or systemic inflammation. Likewise, these biomarkers are associated with surrogate measures of subclinical atherosclerosis in the general population [80].

Despite the difficulties in interpreting the utility of CRP as a marker of CV risk in RA, the baseline level of CRP was a predictor of future death from CVD in a study of 506 RA patients followed up over a 10-year period [20]. Few other biomarkers have been evaluated against the gold standard of CV events, in RA, with most studies understandably focusing on surrogate measures of atherosclerosis. MetS, insulin resistance and NT-proBNP are markers of CV events or mortality in RA [122], with leptin independently predicting the MetS/insulin resistance [105]. In common with the general population, the adhesion molecules sVCAM-1 and in particular sL-selectin were markers of endothelial dysfunction [8, 113] and MCP-1, sICAM-1, sVCAM-1, sE-selectin, VWF, PAI-1 were markers of atherosclerosis defined by carotid IMI or coronary artery calcification [8, 111], with MCP-1 and VWF performing best in a prospective study in early RA [8]. Many of these findings need replication in additional cohorts with evaluation of whether the earliest stages of atherosclerosis are reversible by current therapies.

The purpose of this review was to focus on soluble CV biomarkers; however, a variety of imaging technologies can now also identify CV abnormalities with a high degree of sensitivity and specificity. Although showing promise, their utility will always be limited by the level of expertise required, their often significant cost, lack of widespread availability and in some cases the significant radiation dose required. Soluble biomarkers may lack the sensitivity of more sophisticated imaging methods, but have the advantages of widespread availability, ease of collection and storage and generally lower associated costs.

It is also clear that there is a need to expand our knowledge of the effects that biological therapies have on future CV risk in RA. There are a number of studies that have shown that TNF blockade has a transient beneficial effect on CV function [40, 127]. However, it is not yet known whether these agents have a sustained beneficial effect on the vasculature. Of even greater interest is whether, if given early in the disease course, biological therapy can remove the enhanced risk of CVD seen in RA entirely (analogous to the window of opportunity concept which
states that early aggressive intervention in inflammatory arthritis may lead to interruption of progression along the disease continuum). In future, we would hope that large, simple studies are performed that examine the CV effects of biological agents, with both short and also more importantly longer term CV outcomes featuring as the main end points of such studies.

The vast majority of studies investigating CV risk in RA, to date, have used surrogate CV end points rather than clinical CV events. An exception to this rule is the Trial of Atorvastatin for the primary prevention of Cardiovascular Events in patients with Rheumatoid Arthritis study, a randomized, controlled trial of atorvastatin for the primary prevention of CV events in RA. This study is currently active and has now recruited over 2400 patients. The investigators, led by Professor George Kitas of the Dudley Group of Hospitals, UK, are to be congratulated in their efforts to perform this ambitious and well-designed study, which is due to report in 2014. However, it is unlikely that such large-scale studies will be performed to assess CV outcomes in RA with any frequency, due to the large number of subjects and lengthy follow-up period that would be required to capture an adequate number of CV events. There is, therefore, a real need in the future to ensure robust collection of longitudinal CV data when performing RA registry studies. We would hope that in future an increasingly collaborative approach to examining CV outcomes in RA will develop both nationally and internationally. By taking a collaborative approach and ensuring that prospective studies are adequately powered with a robust study design the rheumatology world could make significant advances in its quest for further knowledge of the enhanced risk of CVD in RA.

Rheumatology key messages

- RA is a risk factor for CVD.
- Traditional risk factors and inflammation predict CVD in RA and should be aggressively managed.
- Long-term CV outcomes should be prospectively examined in future studies.

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References


40 Maki-Petaja KM, Hall FC, Booth AD et al. Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor-alpha therapy. Circulation 2006;114:1185–92.


46 Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham risk scores. Circulation 2004;109:1955–9.


49 Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham risk scores. Circulation 2004;109:1955–9.


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