Abstract

Objectives. RA associates with significantly increased morbidity and mortality from cardiovascular disease (CVD). This may be due to complex interactions between traditional CVD risk factors, systemic rheumatoid inflammation and the vasculature. We reviewed the current literature to answer: (i) whether there is sufficient evidence that patients with RA have altered vascular function and morphology compared with normal controls; (ii) whether there is sufficient evidence to determine if such changes relate predominantly to systemic inflammation; and (iii) whether any changes of vascular function and morphology in RA can be modified with therapy.

Methods. The MEDLINE database was searched to identify publications from 1974 to 1 November 2010 pertaining to vascular function and morphology in RA. The total number of articles included in the present review was 93. This included 57 cross-sectional studies, 27 longitudinal studies without randomization and 9 longitudinal studies with randomization.

Results. Vascular function and morphology was impaired in RA relative to healthy controls. The majority of studies reported no associations between systemic inflammation and vascular function. Treatment with anti-inflammatory medication resulted in both transient and long-term improvements in the vasculature, but only a few studies reported associations between change in inflammation and change in vascular function and morphology.

Conclusion. The link between systemic inflammation and vascular function and morphology is not wholly supported by the available literature. Long-term studies examining specific predictors (including CVD risk factors) on the vasculature in RA are needed.

Key words: Rheumatoid arthritis, Endothelium, Cardiovascular disease, Systematic review, Endothelial function, Microvascular, Macrovascular, Atherosclerosis.
with chronic inflammation [15, 16]. On the basis of this, and the observation that elevated inflammatory molecules such as CRP, IL-6 and TNF-α are associated with an increased risk for CVD events in the general population [17–19], it has been speculated that RA disease-related inflammation might be contributing to accelerated atherosclerosis [20, 21]. Pro-inflammatory molecules may exert deleterious effects on the vascular endothelium, which may subsequently reduce the synthesis of nitric oxide (NO) and promote endothelial cell dysfunction (ECD) [22]. Pro-inflammatory molecules may also have metabolic effects on adipose tissue, skeletal muscle and the liver, which can contribute to the development of traditional CVD risk factors such as dyslipidaemia, insulin resistance and obesity [10, 23, 24]; these can also, in turn, contribute to ECD [25]. Adequate control of disease-related inflammation appears to lead to improvements in the CVD risk factor profile [26, 27] and reduce cardiac events [28, 29], both of which may possibly lower CVD mortality in RA. Non-invasive assessments of vascular function and morphology in patients with RA provide a means of disentangling these complex pathways and assess interventions that may reduce CVD risk and improve outcome in these patients.

Non-invasive assessments of the peripheral vasculature

Assessment of EC function in different vascular beds

The endothelium is the innermost layer of the blood vessels and forms an important part of the vasculature: it controls vascular function via the release of vasoactive factors, such as NO, prostacyclin (PGI₂) and ET-1, which affect vasomotion, inflammation and thrombosis [30]. Balanced production of these vasoactive factors is critical for maintaining an atheroprotective environment within the vessel. Endothelial cell (EC) exposure to injurious stimuli such as oxidative stress and/or inflammatory mediators, leads to disrupted production of vasoactive factors; the ensuing imbalance is a major contributor to ECD—an early indicator of atherosclerosis [31]. In recent years, a variety of non-invasive techniques have been used to assess vascular function and morphology as an easier and safer alternative to direct assessment of the coronary arteries [32]. These assessments are conducted in the peripheral circulation. Their use is supported by studies showing that peripheral vessel function correlates with the coronary circulation [33–35], associates with traditional CVD risk factors [25] and predicts future cardiovascular events in healthy older individuals [36], patients with CVD [37–40] or peripheral vascular disease [41].

NO is a vasoactive factor of particular importance. It is tonically released from EC and regulates the vasodilatory response to specific stimuli [30]. It also inhibits platelet aggregation and leukocyte adhesion to the vascular wall and prevents vascular smooth muscle cell (VSMC) proliferation [42]. Although other factors, such as prostacyclin, ET-1 and endothelium-derived hyperpolarizing factor, are involved in vascular homeostasis, their contribution appears to be greater when NO levels are reduced [43]. Therefore, techniques assessing peripheral vascular function are designed to primarily reflect endothelial release of NO and, as such, are considered good markers of EC function [31].

The principle underlying the assessment of NO bioavailability involves a stimulus that increases NO production from EC leading to subsequent vessel dilatation, which can then be quantified. ECs often display different structures and phenotypes depending on the vessel type [44] and have heterogeneous responses to stimulation in different vascular beds, and even in different sections of the same vascular bed [45–47]. Thus, different types of assessments are commonly used to measure endothelial function in different vascular beds. For example, the induction of increased blood flow (reactive hyperaemia) exerts shear stress on EC, activating specific receptors that cause an increase in NO bioavailability and consequent vasodilatation [48, 49]. Reduced vasodilatation following an increase in shear forces is representative of impaired NO bioavailability [50]. These phenomena can be carefully created by the widely used method of flow-mediated dilatation (FMD) in the large conduit vessels (macrovessels) [51]. FMD involves occluding the blood flow of conduit vessels for ~5 min to create reactive hyperaemia. The subsequent dilatation that is expressed as a percentage increase from the baseline diameter is mainly dependent on NO activity, with a low percentage indicating poor endothelial function [51]. In contrast, in the small resistance vessels (microvessels), NO activity is commonly examined via local administration of acetylcholine (ACh) that binds to muscarinic receptors on EC and stimulates NO release [52].

The release of NO from EC acts on VSMC to cause vasodilatation [53, 54]. However, impaired vasodilatation can be the result of either the endothelium not sending the signals to the VSMC or of the VSMC not being able to respond to the signal. Therefore, in order to distinguish between ED and smooth muscle dysfunction, endothelium-independent vasodilatation should also be characterized. In the macrovessels, this is most often achieved by the administration of the NO donor glyceryl trinitrate (GTN) that acts directly on VSMC to cause dilatation [55]. The assessment is typically carried out for 5 min, which is a sufficient time to capture the vessel’s peak dilatory capacity [56, 57]. In the microvessels, administration of sodium nitroprusside (SNP) is most regularly used as the NO donor due to its ability to activate smooth muscle cells to cause vasodilatation [58]. An overview of the most frequently reported assessments of EC and VSMC function is depicted in Fig. 1.

Assessment of vascular morphology

Assessing vascular morphology is critical for establishing the extent of atherosclerosis in the vessel. It is thought that morphological changes follow vascular dysfunction [59], but there is no evidence that these are two distinct processes. In contrast, there is evidence of an association between functional and morphological changes in the vessels of patients with early atherosclerosis [60].
The reduction in NO bioactivity appears to be a key event leading to a consequent imbalance of other vasoactive factors, particularly increased ET-1 levels [43]. ET-1 promotes inflammation and VSMC proliferation [42, 61]. ET-1 also has a strong vasoconstrictor effect, and it is highly likely that poor functional responses of vessels can be accounted for in part by ET-1 activity [62, 63]. This suggests that rather than functional and morphological changes occurring at distinct phases of atherosclerosis [64], they may be interrelated. A number of assessments can be conducted to measure vascular morphology at different stages of pre-clinical atherosclerosis.

Overlapping early functional and morphological changes in the vessel can be assessed by characterizing arterial wall stiffness using pulse wave velocity (PWV) and pulse wave analysis (PWA) [65]. During each contraction of the heart, pressure waveforms leave the aorta during systole and are reflected back to the heart by peripheral vessels during diastole. Arterial stiffness can be assessed by measuring the velocity of pressure waveforms (PWV), which leave the aorta, and/or by analysing the central aortic pressure waveforms for measures of arterial stiffness (PWA) [66]. Similar to FMD, arterial elasticity is affected by advancing age and increased CVD risk factor burden, both of which increase PWV and PWA [67]. Stiffening of the vascular wall can occur due to a reduction in NO production from ECs, loss of smooth muscle tone [68], as well as degeneration of elastin fibres and increased collagen deposition in the vascular wall [69]. Consequently, arterial stiffness is dependent on functional and morphological changes in the vasculature.

Measurement of the carotid intima–media thickness (cIMT) is a reliable indicator of more advanced, but still subclinical atherosclerosis [59, 70]. The assessment detects thickening of the medial layer of the vascular wall, which is a predictor of cardiac events in patients with early atherosclerosis [60] and for restenosis following percutaneous coronary intervention [40]. In addition, increased cIMT has been reported to relate to a number of classical CVD risk factors such as ageing, hypertension and dyslipidaemia [70]. Increases in cIMT represent a chain of events also resulting from a disruption in the balance of NO and ET-1, which, over time, allows increased production/expression of inflammatory cytokines, oxidative stress, adhesion molecules and thrombotic factors [71–73]. Increased cIMT has also been reported in hypertensive, obese adolescents [74]. A brief overview of the methods commonly used for assessing vascular morphology are depicted in Fig. 1.

Methods
Following an RA-specific evidence-based tool for searching the literature [75], the MEDLINE database was searched to identify publications from 1974 to 1 November 2010, in English, pertaining to vascular function and morphology and RA. The following limits were activated: humans, English language, clinical trial Phases I, II, III and IV, comparative study, controlled clinical trial, technical report and validation studies. The Medical Subject Heading (MeSH) term rheumatoid arthritis was employed in combination with endothelial function (181 articles),
endothelial dysfunction (56 articles), laser Doppler flowmetry (10 articles), laser Doppler imaging (7 articles), forearm blood flow (3 articles), venous occlusion plethysmography (1 article), flow mediated dilatation/dilation (7 articles), augmentation index (8 articles), PWA (9 articles), PWV (8 articles), cIMT (9 articles) and atherosclerosis (58 articles). The initial search identified 357 articles. The search was checked for duplicate articles that appeared under the different MeSH terms. Full articles were retrieved for assessment if the information in the abstract fulfilled both of the following criteria: (i) involving RA patients and (ii) examining any of the above-mentioned vascular assessments. Studies incorporating only participants with other types of inflammatory arthritis, degenerative arthritis or other inflammatory or CTDs as well as studies related to the vasculature of the joint were excluded. If the title and abstract did not provide sufficient information, the full-text manuscript was examined in order to evaluate if the article fitted the inclusion criteria. From the 337 articles that were initially identified, 68 matched the inclusion criteria and were thus included in the analysis.

The reference lists of all of the identified articles were further examined in order to identify publications that were relevant to microvascular or macrovascular endothelial function, arterial stiffness or cIMT in RA; 25 additional articles met the inclusion criteria and were included in the analysis. These additional articles along with those found from the initial searches brought the total number of articles in the present review to 93. These included 57 cross-sectional studies [13, 76–131], 27 longitudinal studies without using randomization [92, 95, 125, 128, 132–154] and 9 randomized controlled trials (RCTs) [131, 142, 155–161]. The assessments that were used in these studies to examine vascular function and morphology include venous occlusion plethysmography, laser Doppler imaging and flowmetry with iontophoresis, FMD, GTN-mediated dilatation, PWA, PWV, cIMT and nail-fold capillaroscopy. For more detail about these assessments see Fig. 1.

The quality of the RCTs was assessed using a previously described procedure [162]. For the cross-sectional and longitudinal studies, a quality index (QI) score was specifically developed. The criteria related to cross-sectional study design were choice of patient and control populations, matching of controls to patients, use of power calculations to determine sample size, inclusion/exclusion criteria, reporting medication regimen of patients and controls, adherence to published laboratory protocol guidelines (e.g. laboratory conditions, participant preparation/condition, reproducibility, blinding of assessor to test), statistical analysis (e.g. adjustment for group differences) and performing associations between vascular function and morphology and inflammation if such data were collected. For longitudinal studies the same criterion was used, but with the addition of the following categories: follow-up assessments conducted by the same assessor and statistical adjustment of factors that differ between populations and/or follow-up. A graded score was awarded depending on adherence to these criteria, ranging from 0 points (not mentioned at all) to 2 points (mentioned in detail). Given the variations in aims between the studies, there are variations in the highest potential total score. For example, adjustment for group differences is not appropriate when only RA patients are included in the study. Therefore, for easy comparison, the quality scores were converted into percentages (score achieved/highest potential score for study × 100). Two reviewers (A.S. and J.J.C.S.V.vZ.) assessed the QI score, and in case of a disagreement, the reviewers discussed the rationale for awarding the score until a consensus was reached.

Results

Cross-sectional studies

Microvascular function and morphology

In total, only five cross-sectional studies of highly variable quality (from 22 to 96%, average 64%) have assessed microvascular function in RA patients (for details, see supplementary table 1, available as supplementary data at Rheumatology Online) [76–79, 123]. Four studies included a comparison between RA patients and control participants (Table 1). These reveal subtle abnormalities in nail-fold capillary microscopy [78], attenuated response to endothelium-dependent and endothelium-independent microvascular stimuli assessed with venous occlusion plethysmography [76, 123] and increased hyperaemic vasodilatory response [79] in RA patients compared with healthy controls.

Microvascular function does not appear to be consistently associated with inflammatory markers (Table 2). For example, whereas CRP was associated with endothelium-dependent function but not endothelium-independent function in one study [77], the reverse has also been reported [76]. Endothelial function, expressed as the ratio between the dilation response to ACh and SNP, was associated with CRP in a mixed and small sample of RA patients and healthy control participants [123]. Finally, no association at all between endothelial function and measures of inflammation has also been reported [79]. Given the scarcity of available studies and the variety of methods applied, more research is needed to characterize microvascular function and its associations with inflammation in RA patients.

Macrovascular function

There are 13 cross-sectional studies that have assessed macrovascular function in patients with RA (see supplementary table 1, available as supplementary data at Rheumatology Online, for details) [79–85, 87, 88, 124–126]. The quality scores range from 32 to 96%, with an average of 64%. Eleven studies conducted a comparison of endothelial function between RA patients and control participants [79–85, 87, 88, 125, 126], eight of which showed attenuated endothelium-dependent macrovascular function in RA compared with controls (Table 1) [79, 81–85, 87, 88]. No differences between RA and control participants were
reported in endothelial-independent function in the three studies that explored this [80, 81, 85]. The decreased endothelium-dependent macrovascular function, assessed with FMD, appears to be already evident within 1 year of RA diagnosis [84], but does not appear to be further influenced by disease duration [80, 83].

Of the studies that assessed the relationship between measures of disease activity [i.e. CRP, ESR, 28-joint DAS (DAS-28)] and FMD, six studies (quality score ranging from 54 to 96%) did not find an association [80, 81, 85, 88, 125, 126]. The three studies that found associations between disease activity and FMD were mostly of good quality (32, 75 and 77%) [79, 83, 84], but there were some inconsistencies that are difficult to reconcile. For example, FMD was associated with CRP but not ESR in the same group of patients [79, 83]. A study comparing RA and diabetes mellitus yielded no difference in FMD, even though CRP was significantly higher in RA [88]. In separate analyses, the same authors also reported that the presence of RA and the presence of diabetes were both independent predictors of poor FMD; however, whereas

in diabetes this was due to classical CVD risk factors, this did not appear to be the case in RA [88]. Surprisingly, very few studies have examined the effects of classical CVD risk factors on macrovascular endothelial function in RA [83, 85, 86, 125], despite the fact that studies in the general population suggest that these may be major confounders. Associations were found with lipid levels in some [83, 86], but not all [85, 125], studies in RA. It is worth noting that endothelium-dependent macrovascular function in RA was lower than controls even when patients were matched for CVD risk or the comparison was statistically adjusted for CVD risk [85, 87, 88].

In summary, there is ample evidence that endothelium-dependent macrovascular function is compromised in RA compared with normal controls. The potential contribution of disease activity and classical CVD risk factors to this abnormality remains unclear, and due to the cross-sectional nature of these studies, no assumptions can be made as to the directionality of any associations found.

### Table 1
Summary table of cross-sectional studies on microvascular function, macrovascular function, arterial stiffness and intima-media thickness in patients with RA compared with control participants

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Microvascular function</th>
<th>Macrovascular function</th>
<th>Arterial stiffness</th>
<th>Intima-media thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA worse than control</td>
<td>3 (54; 22–73)</td>
<td>8 (60; 32–73)</td>
<td>13 (68; 36–96)</td>
<td>24 (64; 32–90)</td>
</tr>
<tr>
<td>RA not different from control</td>
<td>3 (76; 34–96)</td>
<td>3 (76; 34–96)</td>
<td>1 (44)</td>
<td>4 (62; 33–77)</td>
</tr>
<tr>
<td>RA better than control</td>
<td>1 (96)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are represented as the number of studies (average QI, %; range) for the QI as described in the Methods section.

### Table 2
Summary table of the number of studies on associations between measures of disease activity (ESR, CRP, DAS-28) with microvascular function, macrovascular function, arterial stiffness and intima-media thickness in patients with RA

<table>
<thead>
<tr>
<th>Study type</th>
<th>Microvascular function</th>
<th>Macrovascular function</th>
<th>Arterial stiffness</th>
<th>Intima-media thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional studies</td>
<td></td>
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</tr>
<tr>
<td>Association</td>
<td>2 (67; 61–73)</td>
<td>3 (61; 32–77)</td>
<td>5 (72; 55–100)</td>
<td>8 (66; 32–90)</td>
</tr>
<tr>
<td>No association</td>
<td>2 (82; 67–96)</td>
<td>6 (73; 54–96)</td>
<td>10 (72; 54–96)</td>
<td>24 (68; 33–89)</td>
</tr>
<tr>
<td>Not reported</td>
<td>1 (22)</td>
<td>4 (52; 36–67)</td>
<td>1 (36)</td>
<td>7 (42; 29–55)</td>
</tr>
<tr>
<td>Longitudinal studies*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Association</td>
<td>1 (69)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No association</td>
<td>1 (65)</td>
<td>3 (60; 55–67)</td>
<td>2 (64; 38–90)</td>
<td>1 (55)</td>
</tr>
<tr>
<td>Not reported</td>
<td>5 (53; 25–72)</td>
<td>10 (57; 23–88)</td>
<td>6 (62; 23–88)</td>
<td>4 (68; 58–77)</td>
</tr>
<tr>
<td>RCTs*</td>
<td></td>
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</tr>
<tr>
<td>Association</td>
<td></td>
<td></td>
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<tr>
<td>No association</td>
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<tr>
<td>Not reported</td>
<td></td>
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</tbody>
</table>

Values are represented as the number of studies (average QI, %; range); for cross-sectional and longitudinal studies, the QI is as described in the Methods section; for RCTs, published scoring criteria were used [162]. *Associations between change in disease activity and change in vascular function.
Arterial stiffness

Sixteen cross-sectional studies have assessed arterial stiffness in RA and are mostly of good quality (average 70%, ranging from 36 to 100%; see details in supplementary table 1, available as supplementary data at Rheumatology Online) [79, 80, 87–96, 126, 127, 130, 163]. Fourteen studies examined the difference in arterial stiffness between RA patients and a control group [79, 80, 87–94, 126, 127, 130, 163] (Table 1). The overwhelming majority of these studies have demonstrated increased arterial stiffness in RA compared with control participants [79, 80, 87–93, 96, 126, 127, 130, 163] (Table 1).

Similar to the functional assessments described above, no consistent association between arterial stiffness and markers of disease activity is apparent. The majority of studies (n = 10) reported no associations between arterial stiffness and disease activity (average QI = 72%) [79, 80, 88–90, 93, 126, 127, 130, 163], while five studies, reported such an association (average QI = 72%) [91, 92, 94–96].

cIMT

Most cross-sectional studies on vascular morphology in RA (39 studies) have assessed cIMT [13, 82, 84–88, 91, 97–122, 125, 129, 130, 164, 165] (for details see supplementary table 1, available as supplementary data at Rheumatology Online) (average quality 63%, ranging from 29 to 90%). Of the 30 studies that reported a comparison between RA and a control population, 24 studies found cIMT to be increased in RA patients compared with a control group [82, 84, 85, 87, 88, 97–100, 104, 106, 108–114, 118–120, 130, 164, 165] (Table 1). Unfortunately, even though most control participants are age and sex matched to RA patients, the comparison between RA and control participants has largely been done without correction for factors that could impact cIMT, such as global CVD risk or its individual components. This is surprising, given the fact that they are known to be associated with cIMT in the general population [166] and have been explored in RA. For example, global cardiovascular risk, using the Framingham Risk Score, was associated with higher cIMT [86] in RA. Similarly, the lipid profile (including total cholesterol, low- and high-density lipoproteins and triglycerides) was also related to cIMT, not only in univariate [85, 97, 107, 110, 125] but also in multivariate analyses [107, 111]. However, care should be taken when interpreting these results, as varying statistical analyses and multivariate models have been applied to assess the associations of individual risk factors in RA.

Increased cIMT is apparent even in patients with a recent diagnosis of RA [120, 131]. However, whether cIMT further increases with disease duration is not clear from the available data. Even though several studies provide evidence for greater cIMT with longer disease duration [13, 98, 99, 119, 130], others do not find such an association [100, 104, 108]. Caution should be exercised when interpreting these findings, as the impact of age on this association remains to be determined in the majority of cases. cIMT is known to increase with age in the general population [167], and is also the most consistent determinant of cIMT in RA, in both univariate and multivariate analyses [13, 97, 103, 106, 110, 111, 114, 121, 125, 164]. More studies specifically looking at the change over time are needed to clarify this.

As with the functional vascular assessments described above, cIMT does not appear to be consistently associated with contemporary markers of disease activity (Table 2). The majority of the studies do not find an association between cIMT and measures of disease activity [85, 86, 88, 91, 97, 98, 100, 102, 104, 106–108, 111, 112, 114–116, 119, 121, 122, 125, 129, 164, 165]. It is possible that classical CVD risk factors moderate the association between cIMT and inflammation in RA: ESR was found to associate with cIMT only in the presence of CVD risk factors in one study [13]. Direct comparison between the associations found in healthy participants and those found in RA patients might determine whether inflammation affects cIMT (and other vascular parameters) in RA patients in a different manner. This is likely, given that the presence of RA has been reported to independently predict cIMT [88, 98, 102, 106].

Summary of cross-sectional studies

Taken together, the cross-sectional studies reveal ample evidence for an attenuated vascular function in patients with RA. Even though a large number of studies have been conducted in this area, the quality of these studies with regard to study design, adherence to published protocols and appropriate statistical analyses varies widely (supplementary table 1, available as supplementary data at Rheumatology Online). Few studies conducted power analyses for the comparison between groups, and no data are available on appropriate power to examine factors associated with vascular function in RA. This has profound implications for the interpretation of the available data, and more research specifically and appropriately exploring the factors associated with vascular function in RA is needed.

Given that RA disease-related inflammation is widely assumed to contribute to the elevated CVD risk through its impact on the vasculature [20, 21], it is surprising to find that direct evidence for such an association is still lacking. In other populations, vascular function has been shown to be associated with inflammation [168], although it must be noted that the levels of inflammation that are generally seen in other populations are significantly lower than those seen in RA patients. Accordingly, it remains possible that low- to moderate-grade inflammation characteristic of these other populations, such as diabetic or cardiovascular patients, is a good predictor of endothelial function, whereas high-grade inflammation in RA is not predictive of vascular function or morphology.

It is also possible that it is long-standing, not current, inflammation that impacts the vasculature in RA patients [169]. A number of studies have explored disease activity longitudinally, but with varying methods of quantifying accumulated disease activity, and also varying results [83, 92, 97–99, 119]. Thus, even though RA has been
reported to be predictive of greater arterial stiffness [88], as well as IMT [102, 106], this does not seem to be due solely to disease-related inflammation. A comparison of RA and diabetes patients, for example, revealed similar vascular status despite higher levels of inflammation in the RA patients [88, 118]. As vascular impairments cannot be fully explained by current levels of inflammation, other factors must be contributing. Unfortunately, to our knowledge, little attention has been paid to other potential influences. There is, however, preliminary evidence of an interaction between inflammation and CVD risk factors affecting vascular function in RA [13]. A direct comparison between the association between vascular function and a range of potential determinants in different patient groups might help illuminate precisely which factors are particularly important in RA.

Longitudinal studies

Microvascular function

Six studies of low to medium quality (from 25 to 72%) examined the longitudinal effects of anti-inflammatory medications on endothelial function [132–136, 153]. With one exception [133], all reported improvements in endothelial-dependent function after follow-up (ranging from 2 days to 6 months) (supplementary table 2, available as supplementary data at Rheumatology Online). Endothelial-dependent function was even reported to be no longer significantly different from control participants following treatment [132, 135], whereas markers of inflammation were still increased relative to the control group [132]. All but one [153] study reported no changes in endothelial-independent function following treatment. Surprisingly, only a single study (of higher quality relative to most of the others) explored the associations between (changes in) inflammatory markers and endothelial function and revealed no such association [135]. However, caution should be exercised when interpreting these data. This pilot study included a small number of patients receiving a variety of anti-inflammatory medications and post-treatment assessments were not carried out at a set time point. In general, all of these studies are characterized by small sample sizes. Therefore, further research exploring the effects of anti-inflammatory medications on microvascular endothelial function is needed.

Macrovascular function

Fourteen studies examined the effects of anti-inflammatory medications (in particular anti-TNF-α) on macrovascular endothelial-dependent function [92, 120, 125, 137–147]. The average quality score is 58%, ranging from 23 to 88%. All [92, 120, 137–147] but one [125] study reported improvements in macrovascular endothelial function after treatment. Despite improvement in endothelial-dependent function being observed for as long as 18 months [145], there are also reports of transient improvement in endothelial-dependent function in response to anti-TNF-α [138, 139, 146]. The only study with no change in FMD involved patients with <12 months disease duration. These patients were followed for 18 months and the study did not explore the effects of a specific medication regime. It is also worth noting that FMD values at entry to the study were similar to those of healthy control participants [125]. Macrovascular endothelial-independent function remained largely unaltered following treatment; however, two studies reported an increase in endothelial-independent function following 2 weeks of treatment with rituximab [143] and 12 months of treatment with combination DMARD therapy [148] (supplementary table 2, available as supplementary data at Rheumatology Online). As can be seen in summary Table 2, it is striking that only four studies have reported associations between change in disease activity (either assessed with DAS-28, CRP or ESR) and endothelial function [120, 141, 145, 147], with equivocal results. Of these studies, only one found a significant association between changes in FMD and changes in disease activity [120]. Interestingly, this is the only study that used combination DMARD therapy as an intervention, with the others employing anti-TNF-α treatment [141, 145, 147]. However, care should be taken when interpreting the presence or absence of reported associations given the small sample sizes in these longitudinal studies. In addition, only two studies reported a priori power calculations on the basis of changes in vascular parameters over time [142, 144], while no power calculations were carried out for the associations between changes in disease activity and vascular function.

Arterial stiffness

Eight studies examined the longitudinal effects of anti-inflammatory medications on arterial stiffness, with an average QI of 62%, ranging from 23 to 90% (supplementary table 2, available as supplementary data at Rheumatology Online) [92, 128, 136, 142, 151–154]. The results of these studies are equivocal. Half of the studies found that a reduction in disease activity as a result of anti-rheumatic treatment was not accompanied by an improvement in brachial arterial stiffness [92, 136, 142, 151], even though an improvement was found in aortic arterial stiffness [92]. In contrast, anti-TNF-α treatment resulted in an improvement in arterial stiffness [95, 154], which was not seen in patients receiving MTX [95]. Atorvastatin was reported to induce a decrease in arterial stiffness in the absence of changes in disease activity [152]. Interestingly, there is also one study reporting an increase in arterial stiffness after 7 weeks of treatment with anti-TNF-α treatment [128]. Finally, the only two examinations of associations between changes in disease activity and arterial stiffness reported no significant association [128, 154] (Table 2).

cIMT

Only five published studies of moderate quality (average 65%, range 55–77%) have longitudinally examined cIMT [125, 145, 147, 149, 150]. Similar to arterial stiffness, the cIMT results in response to successful treatment are equivocal [145, 147, 150]; successful anti-TNF treatment induced an attenuation in cIMT compared with MTX treatment [150], but no change in response to anti-TNF
treatment has also been reported [145]. In addition, 16 weeks of rituximab treatment reduced IMT in three out of five patients [147]. A comparison with healthy control participants revealed that the change in IMT was greater in RA patients [125, 149]. The only study to explore the associations between changes in IMT and disease activity revealed no such association [147] (Table 2). As with the functional assessments, these studies all included small sample sizes, and no power calculations were conducted in order to determine the sample size for these analyses.

**Summary of longitudinal studies**

In sum, the longitudinal studies reveal that the vascular response to successful treatment is not clearly defined (supplementary table 2, available as supplementary data at *Rheumatology* Online), and there is no consistent evidence for an association between changes in vascular parameters and changes in disease activity. In addition, the incongruent findings between studies could be due to the patient’s clinical response to treatment. For example, classification of ‘responders’ or ‘non-responders’ according to European League Against Rheumatism (EULAR) response criteria [170] revealed that patients who responded to medication showed a trend for improved arterial stiffness compared with non-responders [95]. Indeed, analysis of the British Society of Rheumatology Biologics Register has revealed that patients who show a good clinical response after 6 months of anti-TNF-α treatment have a lower risk of myocardial infarction than non-responding patients [28]. Collectively, these findings suggest that the overall reduction in disease-related inflammation may be more important for improving endothelial function rather than any specific effect of medication. Unfortunately, most of the longitudinal studies assessing the effects of anti-inflammatory medications on endothelial function incorporated small sample sizes, making it difficult to perform such sub-analysis. It is clear that not all of the inflammatory markers were significantly reduced after treatment in some studies [137–139, 145]; therefore, further research that characterizes endothelial function according to clinical response using established guidelines (e.g. EULAR response criteria) in large cohorts will give sufficient power to conduct responder vs non-responder analysis.

The influence of changes in classical CVD risk factors on changes in vascular function or structure has not received much attention in the literature. Even though changes in lipid profiles have been explored in response to treatment, the results are equivocal. No reports are available on associations between changes in CVD risk factors and changes in vascular function or structure in RA. However, given the small sample sizes in the available studies, it remains possible that the studies are underpowered to analyse these associations.

**RCTs**

In comparison with longitudinal studies, RCTs on vascular function or morphology are even scarcer (supplementary table 3, available as supplementary data at *Rheumatology* Online) and, unfortunately, none of these studies have reported the associations between changes in vascular function and disease activity (Table 2). The following section details the studies according to the treatment group the patients were randomized to and also provides a quality score based on previously developed criteria [162].

**Anti-rheumatic medication**

In total, five studies examined the effects of anti-rheumatic medication on vascular function and morphology (Jadad score ranged from 1 to 3) [142, 155–157, 165] (supplementary table 3, available as supplementary data at *Rheumatology* Online). IL-1 receptor antagonist (anakinra) was associated with an acute improvement in FMD [142], whereas 2 weeks of selective or non-selective cyclooxygenase (COX) inhibitors did not change FMD or augmentation index (Alx) [156]; 56 weeks of anti-TNF decreased PWV but not Alx or IMT [157]. Following 5 years of either prednisolone or non-prednisolone treatment, there was no difference in IMT or FMD between the treatment and no-treatment arms of the trial [155]. However, due to the absence of baseline vascular assessments, this study does not provide information on changes in cIMT or FMD as a result of treatment with glucocorticoids. Finally, 18 months of treatment with anti-TNF or MTX did not change cIMT [165]. No changes were apparent in GTN-mediated dilatation following anti-inflammatory treatment in the two studies that examined this [142, 156].

**Cardiovascular medication**

Four studies (all with a Jadad score of 2) examined the effects of either statins or angiotensin-converting enzyme inhibitors over a period of 2–8 weeks [158–161] (supplementary table 3, available as supplementary data at *Rheumatology* Online). Overall these medications improved FMD and arterial stiffness [158–161], which is in line with studies in other populations [171, 172]. This emphasizes the potential importance of classical CVD risk factors in vascular function in RA, in particular the influence of lipid profiles. Statin treatment reliably shows an improvement in endothelium-dependent macrovascular function [158, 159, 161], which can occur in the absence of a reduction in disease activity [159]. However, more detailed and appropriately powered studies are needed to explore the complex interplay between lipid profiles, disease activity, and vascular function and morphology in more detail. There was no change in endothelial-independent function following treatment.

**Summary of RCTs**

The findings of the RCTs suggest that treatment with cardiovascular medications may have a greater beneficial effect on endothelial function than treatment with anti-inflammatory medications. However, given the paucity of RCTs with limited sample size and lack of power calculations, particularly in those studies testing anti-rheumatic medication, it is not possible to draw firm conclusions at this stage.
Conclusion

The studies presented in the present review provide clear evidence that vascular function and morphology are impaired in patients with RA. In addition, the relationship between systemic markers of inflammation and vascular function and morphology is not wholly supported by cross-sectional or longitudinal studies. This is accentuated by the inconsistent findings in vascular function or morphology following treatment with anti-rheumatic medication. There are very few studies that have examined the impact of CVD risk factors on the vasculature, and this warrants further investigation. In particular, longitudinal studies assessing the impact of interventions that reduce CVD risk (such as exercise) on the vasculature are needed.

To our knowledge, there are only two studies that have assessed accelerated atherosclerosis in RA. In both these studies, the increase in IMT was greater in RA patients compared with age- and sex-matched healthy controls [125, 149]. Unfortunately, with disease activity only assessed at baseline, a direct link between change in inflammation and IMT could not be explored. Longitudinal studies are necessary to explore the concept of accelerated atherosclerosis further. In order to determine how fluctuations in disease activity influence vascular changes over time, measurements must be made over a protracted period. The vascular assessments described in this review are generally considered to be associated with an increased risk for cardiovascular death. There is evidence for this in the general population [173], but only one study with a small sample has reported that high levels of IMT are predictive of hard cardiac end points in RA [174]. Therefore, in order to understand if and how vascular function is predictive for cardiovascular events, detailed longitudinal assessments are necessary. These assessments should include multiple vascular parameters as well as multiple potential determining factors. Once it is known what determines the impaired vascular function, interventions, either through medication and/or behavioural change, can be developed to improve vascular function as well as morphology in RA.

Rheumatology key messages

- Endothelial dysfunction is evident in patients with RA.
- The link between endothelial dysfunction and inflammation is not wholly supported by the available literature.
- Long-term studies examining specific predictors of endothelial dysfunction in RA are needed.

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Supplementary data

Supplementary data are available at Rheumatology Online.

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