Review

Cardiovascular morbidity and mortality in patients with rheumatoid arthritis: vascular alterations and possible clinical implications

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Summary

Mortality in patients with rheumatoid arthritis (RA) is higher than in the general population, which is due mainly to premature cardiovascular disease. Traditional cardiovascular risk factors cannot entirely explain the higher level of cardiovascular complications, and there is growing evidence that chronic inflammation is the main culprit. The aims of this review of the literature are to (i) summarize aspects of vascular alterations found in the cardiovascular system of RA patients and to relate them to the clinically relevant cardiovascular morbidity and mortality and (ii) evaluate what these abnormalities and complications might in the end imply for clinical management. A number of abnormalities in the cardiovascular system of RA patients have been identified, on the molecular level, in endothelial function, arterial stiffness, arterial morphology and, finally, in the clinical presentation of cardiovascular disease. Cardiovascular risk assessment should be part of the care of RA patients. While a great deal of data is published demonstrating abnormalities in the cardiovascular system of these patients, it is much less clear what specific interventions should be performed to reduce the incidence of cardiovascular complications. Cardiovascular care should be delivered in accordance with recommendations for the general population. Whether specific drugs (e.g. statins, aspirin) are of particular benefit in RA patients needs further investigation. Control of inflammation appears to be of benefit. Methotrexate and tumor necrosis factor-α blocking agents might reduce the number of cardiovascular events. Leflunomide, cyclosporine, non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors may worsen cardiovascular outcome. The role of glucocorticoids in active RA remains to be determined.

Introduction

Mortality in patients with rheumatoid arthritis (RA) is higher than in the general population. While deaths due to infections, lymphoproliferative disorders or gastrointestinal bleeding may be statistically more common in RA patients than in the general population, these are not the major causes of death from a clinical perspective. In recent years, it has become evident that the excess mortality is mainly due to
cardiovascular disease. This has raised the question of which factors might contribute to this excess mortality. A number of studies demonstrated that traditional cardiovascular risk factors, such as smoking, hypertension or diabetes, do not account for this difference. There is growing evidence that the—more or less persistent—high-grade inflammation present in RA is the main driver of the development of premature atherosclerosis and its complications. The aims of this review are to (i) summarize aspects of vascular alterations found in the cardiovascular system of RA patients and link them to the clinically relevant cardiovascular morbidity and mortality and (ii) evaluate the abnormalities and complications that might finally imply for clinical management.

The problem

Cardiovascular diseases are both more frequent and are found prematurely in patients who suffer from chronic inflammatory disease. The published evidence in this regard is strong for RA. There is also evidence for similar changes in the cardiovascular system of patients with systemic lupus erythematosus. In addition, there is limited evidence that this may also be true for other chronic inflammatory diseases such as ankylosing spondylitis or psoriatic arthritis. From a clinical perspective, the number of cardiovascular events in RA patients is of outstanding importance. In a meta-analysis, which included 24 observational studies with a total of 111,758 RA patients, 22,927 cardiovascular events were registered. There was a 50% increase of deaths due to cardiovascular disease. The incidence of deaths due to cardiovascular disease was 50% higher than in the general population, and mortality risks for ischemic heart disease and cerebrovascular accidents were higher by 59 and 52%, respectively. In another report, the mean standardized mortality ratio was found to be 1.7. This difference cannot be explained by traditional cardiovascular risk factors. It is most likely attributable to chronic inflammation. It is now well known that atherosclerosis is not simply a 'lipid storage disease', but that inflammation plays a major role in its initiation and progression. Acute coronary syndromes are not strictly related to the extent of plaques in the coronary arteries but are frequently caused by plaque rupture and superimposed thrombosis with occlusion of the affected vessel. Inflammation plays a central role in this process: accumulated inflammatory cells, released cytokines and collagen-breaking enzymes, an increased expression of adhesion molecules and activated T-cells are found in these vulnerable atherosclerotic plaques. Of particular interest is that these processes show similarities to the typical inflammatory state found in RA. All these changes cause alterations in the function and structure of the arterial vessels. This is finally reflected clinically in cardiovascular morbidity and mortality. In the following, these changes, which may be seen as an interactive progression, will be discussed.

The molecular level

Hypotheses exist that connect the inflammation found in RA to the accelerated atherosclerotic process: the synovitis, which appears at the joints, is associated with the release of a number of proinflammatory mediators. These cytokines not only lead to local inflammation and joint destruction, but also gain access to the vascular system. Thus, they circulate and potentially affect distant organs such as the liver, as well as adipose tissue or the endothelium. As a consequence, an unfavorable, 'proatherogenic' state may evolve.

One of the results of inflammation is insulin resistance. Anti-rheumatic treatment with corticosteroids and sulfasalazine seems to improve insulin resistance. Inflammation is further related to dyslipidemia. RA patients usually have low levels of total cholesterol (TC) and High-density lipoprotein cholesterol (HDL-C). In several studies, treatment of RA resulted in an increase in lipid levels. Interestingly, the atherogenic index TC/HDL-C did not increase. This is of relevance when interpreting lipid levels in RA patients. Low lipid levels may reflect active inflammation. The increase in lipid levels after treatment may in turn reflect better control of inflammation. The net effect may be reduced cardiovascular risk rather than an increased risk due to lipid levels. This interpretation of lipids is not unique to RA: in patients with end-stage kidney disease, for instance, the highest mortality is found in patients with low cholesterol levels. A number of markers of endothelial activation play an important role in RA. Endothelial adhesion molecules and chemokines are involved in the extravasation of inflammatory cells into the interstitial matrix. The level of adhesion molecules (such as intracellular adhesion molecules, which predict myocardial infarction) is higher in RA patients than in control patients. These processes are finally reflected in endothelial dysfunction, as described in the following section. In RA patients several prothrombotic factors such as fibrinogen, von Willebrand factor, tissue plasminogen activator antigen or D-dimer are elevated. This may also favor the development of atherothrombotic disease.
Endothelial dysfunction

Endothelial dysfunction precedes manifest atherosclerosis, and the endothelium of RA patients shows signs of dysfunction. It has been shown with the use of flow-mediated dilatation that endothelium-dependent dilatation is impaired in RA patients when compared with control patients. This is already present early in the course and improves with anti-inflammatory treatment. The impairment of the endothelium is also evident at the cellular level. Endothelial progenitor cells (EPCs) derived from the hematopoietic system participate in the development and maintenance of the endothelial cell layer and have a potentially reparative role, protecting against ischemia and atherosclerosis. The number of circulating EPCs was found to correlate inversely with the Framingham risk factor score and is also associated with vascular function as measured with flow-mediated brachial artery reactivity. It has been demonstrated that in RA patients there is a reduced number and an impaired function of EPCs, which is associated with endothelial dysfunction. In addition, this decrease in EPCs is correlated inversely with disease activity. Treatment with glucocorticoids (GCs) as well as with infliximab appears to reverse this depletion.

Alterations in vascular function

Several studies have demonstrated dysfunction of the vascular system in RA patients. Arterial stiffness is a predictor of cardiovascular disease and mortality. Pulse wave velocity is a marker of arterial stiffness: the higher the transit time of the pulse wave, the stiffer the vessels. Compared to controls, RA patients have a higher pulse wave velocity, thus reflecting increased arterial stiffness. In addition, the higher arterial stiffness in RA patients was found to be comparable to that in patients with traditional cardiovascular risk factors, such as smoking, hypertension or diabetes.

The augmentation index (Alx), a further marker of vascular dysfunction that is associated with cardiovascular risk, is a composite of arterial stiffness and pulse wave reflection. The foregoing pulse wave is reflected back in the periphery and increases the pulse pressure in the ascending aorta. This phenomenon also explains the increased pulse pressure in patients with stiff arterial vessels, which is usually found in an aging vascular system. Alx—as well as other functional hemodynamic markers—depends on the heart-beat rate. Therefore, Alx is usually given as Alx@75 (Alx corrected for 75 beats per minute). Pulse wave analysis demonstrated a higher Alx in RA patients than in controls. These changes are linked to an unfavorable energy requirement during systole of the contracting heart, as the ejection into a system of stiffer vessels is associated with a higher energy requirement and, as the consequence, an unfavorable supply/demand relationship of the myocardium. This may be especially important in the case of acute coronary compromise. Not only is vascular dysfunction to be found in the macrovascular system of RA patients, the microcirculation, too, is affected.

Large artery remodeling

The arterial system of RA patients exhibits signs of premature morphologic changes. Ultrasound studies have shown greater intima-media thickness of the carotid arteries in RA patients as compared with controls, this reflects large artery remodeling. Increased intima–media thickness is independently associated with cardiovascular morbidity and mortality. In addition, there is also evidence of a larger number of patients with carotid plaques when compared with controls. These morphologic changes are not only restricted to the carotid arteries, but studies have also demonstrated the involvement of the coronary arteries. Compared with controls, RA patients have increased coronary calcifications. Finally, there is also evidence that large artery remodeling is accelerated in longer standing RA. Whether rather new techniques as the use of contrast-enhanced ultrasound may be of benefit in the early detection of macroangiopathy in RA patients still needs to be investigated.

Cardiovascular morbidity and mortality

All these changes in the cardiovascular system are in line with increased cardiovascular morbidity and mortality in RA patients. The true extent of excess cardiovascular risk is not definitively established. However, RA may be a cardiovascular risk factor similar to diabetes. In a prospective study, the 3-year incidence rate of fatal and nonfatal cardiovascular events was 9.0% in RA patients and 4.3% in the general population. Compared with the non-diabetic population, non-diabetic patients with RA and those with type 2 diabetes had comparable hazard ratios, 2.16 [95% confidence interval (CI): 1.28–3.63, \( P=0.004 \)] and 2.04 (95% CI: 1.12–3.67, \( P=0.019 \)), respectively. It is very likely that the use of common risk calculators (e.g. Framingham, SCORE) will underestimate the cardiovascular risk in RA patients. Therefore, it was recommended that the use of risk score models should include a multiplication factor of 1.5 if RA patients...
meet two of the following three criteria: (i) disease duration of >10 years, (ii) positive for rheumatoid factor (RF) and/or anti-CCP antibodies and/or (iii) presence of certain extra-articular manifestations.64

It should be noted that the clinical presentation of cardiovascular disease in RA patients may differ in some respects from that in the general population. Douglas and co-workers found more recurrent cardiac events in RA patients (23/40, 57.5%) than in controls (12/40, 30%) (P = 0.013). While presentation with chest pain occurred in all controls, this was found only in 33/40 (82%) RA patients (P = 0.006). In addition, events were more often fatal (16/40, 40% deaths in RA vs. 6/40, 15% in controls; P = 0.012).65 This increased mortality after a cardiovascular event was also found in another study: the 30-day cardiovascular mortality after a first acute cardiovascular event was 17.6% in RA patients vs. 10.8% in non-RA patients.66 And Södergren and associates also found a higher overall case fatality compared with controls (hazard ratio 1.67, 95% CI: 1.02–2.71) as well as shorter survival time after a myocardial infarction.67 These findings are of interest, as similarities are shown to the increased cardiovascular risk in patients with type 2 diabetes.68 Going further, the rate of unrecognized ischemic events seems to be higher in RA patients. In one study, RA patients were twice as likely as controls to experience unrecognized myocardial infarctions (hazard ratio 2.13, 95% CI: 1.13–4.03) and sudden death (hazard ratio 1.94, 95% CI: 1.06–3.55). This was also true for the 2 years before the diagnosis of RA was established.69

**Conclusion**

A number of abnormalities in the cardiovascular system of RA patients are evident. These include those at the molecular level, in endothelial function, arterial stiffness, arterial morphology and, finally, the clinical presentation of cardiovascular disease. The existing evidence strongly supports the theory that chronic inflammation finally drives all of these processes. However, in assessing the given cardiovascular risk of an RA patient it is important to remember that not only inflammation is of relevance, but that traditional cardiovascular risk factors, such as smoking, hypertension, hypercholesterolemia or diabetes also affect RA patients. Figure 1 summarizes these factors. Given these facts, one might consider how interventions could reduce the increased cardiovascular risk of RA patients. If a risk calculator is used, a multiplier of 1.5 should be applied in certain patients, for example, those with a disease duration of >10 years.64 However, if the observations that the increased risk is not dependent on the disease duration of RA hold true,69 the question arises whether this threshold is perhaps an artificial construction.

**What to do?**

There is a great deal of information about how the cardiovascular system of RA patients dysfunctions. Thus, physicians caring for RA patients need to know how to manage the cardiovascular risk of these patients. From a theoretical viewpoint, a number of drugs could be of benefit in such a situation. However, prior to an intervention one should consider precisely the possible benefits and risks of the treatment. In today’s medicine, it is common that experiences that have been made in given situations are extrapolated to groups that appear to have similar characteristics. Therefore, reconsidering the given evidence makes sense. For RA patients there are two major strategies to tackle the cardiovascular risk: first, interventions that focus on the cardiovascular system, and second, interventions that focus on the inflammatory state.

**The cardiovascular focus**

**General recommendations**

There are recommendations that aim to reduce the cardiovascular risk of the general population.70 These include smoking cessation,71 actions to lower the lipids,72 a healthy diet,72,73 moderate...
exercise,74 weight control73 and blood pressure control.74 Even if most of these recommendations have never been formally tested in RA patients,75 one might agree that smoking cessation, a healthy diet or exercise will benefit the patients without adding any risk.

**Statins**

It is well recognized that statins are of benefit to patients with cardiovascular disease. The main effect of statins is the reduction of the LDL cholesterol level.76 However, ‘pleiotropic effects’ of the statins, besides lowering lipid levels, appear to contribute additional benefits beyond reducing cholesterol.77

In considering whether statins are beneficial to RA patients, it makes sense to first look at the lipid levels of these patients. In general, it appears that RA patients with active disease have lower lipid levels than those in remission. Effective treatment is associated with an increase in lipid levels. However, the atherogenic index (TC/HDL-C) is usually unchanged, as both TC and HDL-C increase.78 Thus the increase in the cholesterol level has to be interpreted carefully: it does not necessarily reflect an inverse development in the cardiovascular risk profile, but may just reflect better control of the inflammatory state.22 In fact this finding is not unique to RA. For example, also in patients with end-stage renal disease higher lipid levels are rather a positive prognostic factor.24

In the general population, the impact of statins on cardiovascular events differs depending on the investigated population. In secondary prevention, i.e. the prevention of further events in patients who already have overt atherosclerotic disease, several studies demonstrate a reduction of cardiovascular morbidity and mortality (e.g. 4S,78 CARE,79 LIPID80). Furthermore, a number of studies demonstrate the efficacy of statins in primary prevention, i.e. in patient groups that have increased cardiovascular risk but have not yet suffered a cardiovascular event (e.g. WOSCOPS,81 AFCAPS/TexCAPS,82 ASCOT-LLA83). However, the efficacy of statins in primary prevention—usually tested in patients with an increased risk for a cardiovascular event—is much lower than in secondary prevention. If statins are considered for RA patients, it is imperative to consider published evidence regarding statins especially in primary prevention: in a meta-analysis of statins the absolute risk reduction for major coronary events was found to be 1.66% in primary prevention and 2.4% in secondary prevention. When statins were used in primary prevention, there was no reduction in mortality from coronary heart disease or all causes after a mean follow-up of 4.1 years. Using the Framingham risk score, the numbers needed to treat were found to be 133 (low-risk group: <0.6% per year), 61 (intermediate-risk group: 0.6–2.0% per year) and 40 (high-risk group: >2.0% per year) to prevent one coronary heart disease event.84 A later meta-analysis found a statistically significant improved survival after a mean follow-up of 4.1 years, driven mainly by the inclusion of the JUPITER study.85 However, numbers needed to treat were not reported. The absolute overall treatment benefit observed was <1%, yielding a significant number of patients needing long-term treatment with statins to prevent one event.86

Statins have been tested in RA, but no trial was large enough to establish any benefit with regard to cardiovascular events. In the Trial of Atorvastatin in Rheumatoid Arthritis (TARA) study, 116 RA patients in a double-blind placebo-controlled trial were randomly allocated to either receive 40 mg atorvastatin or placebo over 6 months. The Disease Activity Score 28 improved significantly with atorvastatin (−0.5, 95% CI: −0.75 to −0.25) as did the swollen joint count (−2.69, 95% CI: −3.67 to −0.64). The level of C-reactive protein and the erythrocyte sedimentation rate declined by 50 and 28%, respectively. Adverse events were comparable in the atorvastatin and the placebo groups. In conclusion, atorvastatin leads to a statistically significant but clinically modest improvement in RA. The number of patients was too small to detect any cardiovascular benefit.87 In another study of the effect of statins in RA patients, the authors focused on the AIx, a surrogate of vascular dysfunction, which has been shown to improve under atorvastatin.88

If RA is considered as a disease with an increased cardiovascular risk, it is very likely that risk reduction in these patients is at best comparable to that in primary prevention in the general population. In our opinion, the given evidence does not support the administration of a statin to every RA patient. Experience in other areas demonstrates that, even if statins appear to be highly beneficial from a theoretical point of view in high-risk groups, reality can prove to be quite different.89 In addition, each drug may have side effects and due to their pleiotropic effects potential problems with the long-term use of statins have been discussed.90 It can be expected that the ongoing ambitious Trial of Atorvastatin in the primary prevention of Cardiovascular Endpoint in Rheumatoid Arthritis (TRACE RA), a trial that is scheduled to include >3800 participants will determine the place of statins in RA.91 On the contrary, it certainly makes sense to consider whether the patient would fulfill established criteria to receive a statin in any event. This is important, as in general
a large number of patients who should receive this treatment go unrecognized.

Toms and co-workers—using different risk calculators at standard calculation—identified 2–26% of RA patients without overt cardiovascular disease as high-risk patients who are eligible for statin treatment simply in accordance with the established general recommendations. The above proportions rise to 7–30% if a multiplier of 1.5 is applied for relevant patients. Of these patients, 58.1–94.8% did not receive treatment with statins. This underlines the importance of introducing general cardiovascular care in RA patients. Risk calculators such as the Framingham Risk Score (estimates 10-year risk of fatal or nonfatal cardiovascular event) in combination with the Adult Treatment Panel III from the National Cholesterol Education Program or the Systemic Coronary Risk Evaluation (SCORE) could help to identify patients who should receive lipid lowering therapy. The treatment goal depends on the individual cardiovascular risk and the risk model used for assessing the cardiovascular risk.

**Blood pressure**

Blood pressure control has been named as a treatment target in RA patients. Hypertension is common in RA patients and its control appears to be insufficient in a substantial proportion of patients. In addition, a number of drugs used to treat RA are associated with elevated blood pressure, as discussed below (e.g. NSAIDs, leflunomide, cyclosporine). However, there is little evidence that intensive blood pressure control beyond general recommendations is of specific benefit in RA patients. To date, there are no data that would suggest specific thresholds or medications for blood pressure control in RA patients. Therefore, recommendations for the general population should also be applied to RA patients. Recent evidence from diabetes cautions the physician against extrapolating from clinical wisdom. From a theoretical perspective, it would make sense to keep the blood pressure of patients with diabetes very low; however, reducing the blood pressure below a certain level does not add any benefit but is rather associated with more adverse events. Therefore, we need more data before specific recommendations for RA can be given. However, the large number of RA patients with target organ damage due to hypertension should underline the importance of blood pressure control in these patients simply in accordance with guidelines published for the general population. It still needs to be established whether ACE inhibitors or angiotensin receptor blockers, which are believed to exhibit anti-inflammatory action, should truly be the preferred drugs for blood pressure control in RA patients.

**Aspirin**

Anti-platelet therapy is recommended for patients with established cardiovascular disease. For patients with increased cardiovascular risk the benefit is lower. Therefore, possible risks, primarily bleeding from the gastrointestinal tract, might outweigh the possible benefits. The US Preventive Services Task Force offers a table that helps to determine whether the benefit or the risk is higher for a given patient with an established 1-year cardiovascular risk (Framingham Risk Score) and a given age. The European Society of Cardiology suggests giving aspirin to patients with a 1-year risk >10% as determined by SCORE. Again, a look at diabetes is of interest: a recent meta-analysis of the effectiveness of aspirin in diabetes did not find a clear benefit from aspirin in primary prevention of major cardiovascular events or mortality. Therefore, even if there are no data with regard to RA, it seems very unlikely that aspirin could provide a substantial benefit in RA patients without overt cardiovascular disease or in patients not at high risk. The combination of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) also needs to be considered. These drugs can interfere with the binding site of aspirin. This might reduce the efficacy of aspirin in preventing cardiovascular events and might be associated with an increased number of cardiovascular events. However, the clinical relevance has not been finally determined, as not all studies have found an increased risk for the aspirin–NSAID combination.

Summing up this section, even if there are some drugs that might be of potential benefit in reducing the cardiovascular risks of RA patients, premature optimism is not warranted. There are no data that support a general use of these drugs in RA. A statistically significant improvement in a particular setting, i.e. established cardiovascular disease, does not necessarily mean that a drug is also of benefit in another, e.g. RA. In addition, a statistically significant result might not necessarily mean that the result is also clinically relevant. We would argue that the number needed to treat would be much higher where there is increased cardiovascular risk in the absence of overt disease, e.g. in RA, than with established cardiovascular disease. This is supported by the fact that traditional cardiovascular risk factors appear to have a lower impact in RA patients than in
the general population. If this is true, then—from a theoretical perspective—treatment measures that focus on traditional cardiovascular risk factors are likely to be less effective in RA patients than in the general population. However, this consideration should not lead to neglecting these factors. Even if most traditional cardiovascular risk factors—with the exception of smoking and probably hypertension—in RA are comparable to those in the general population, they must not be considered irrelevant in RA. As traditional cardiovascular risk factors are often not well managed in RA patients, we would emphasize that the focus should not only be on disease activity but also on these risk factors. From the present point of view, it would be best to look for the presence of traditional cardiovascular risk factors such as hypertension, hypercholesterolemia, smoking, diabetes or overweight. Interventions should be based on general recommendations. If risk calculators are used to estimate the cardiovascular risk, it is recommended to multiply the result by 1.5 if two of the following three criteria are fulfilled: disease duration of >10 years, presence of RF or anti-CCP antibodies and/or presence of certain extra-articular manifestations.

The anti-inflammatory focus

Control of inflammation is a commonly mentioned goal when it comes to the reduction of cardiovascular risk in patients with RA. This is based on the experience that inflammation is associated with cardiovascular disease, as described in ‘The problem’ section, as well as on the fact that markers of inflammation, such as erythrocyte sedimentation rate and C-reactive protein predict cardiovascular death in RA patients. However, even if it is true that inflammation causes cardiovascular disease, this does not necessarily mean—even if it is very likely—that control of inflammation will prevent overt cardiovascular disease. This is, for instance, underlined by the fact that homocysteine is associated with cardiovascular risk. The reduction of homocystein, however, did not reduce the number of events. Therefore, it would be prudent to look at the evidence of how different drugs that are used to control inflammation in RA might influence cardiovascular morbidity and mortality.

Methotrexate

Methotrexate (MTX) is one of the cornerstones in the treatment of RA. MTX improves the clinical signs of disease activity and slows radiographic progression. A large study including 1240 RA patients investigated the impact of MTX on mortality. It was shown that, after adjustment for possible confounding factors, the hazard ratio for all-cause mortality among patients treated with MTX was 0.4 (95% CI: 0.2–0.8). In addition, the reduction in cardiovascular risk was statistically significant. This is of particular interest. MTX seems therefore to be able to reduce mortality rates in RA patients, and, while MTX may be associated with side effects, this impact on mortality would be an additional argument for using the drug in RA.

Tumor necrosis factor alpha blocking agents

Tumor necrosis factor (TNF-α) blocking agents are potent drugs used to reduce inflammation and radiographic progression in RA patients. Therefore, they might also be of benefit with regard to cardiovascular disease. TNF-α blocking agents may raise lipid levels while the atherogenic index TC/HDL-C, as mentioned earlier, remains stable. Whether TNF-α blocking agents improve or deteriorate arterial dysfunction, which is a surrogate for cardiovascular disease, is a matter of debate.

In a study from the British Society for Rheumatology Biologics Register, the rates of myocardial infarction were examined in 8670 RA patients treated with TNF-α blocking agents. The results were compared with the rate of myocardial infarction among 2170 patients with active RA treated with traditional disease-modifying antirheumatic drugs (DMARDs). Adjusting for baseline cardiovascular risk factors, there was no reduction in the rate of myocardial infarction in those patients who received TNF-α blocking agents [incidence rate ratio 1.44 (95% CI: 0.56–3.67)]. However, in the subgroup of patients who responded to therapy within 6 months compared with those who did not, the rates of myocardial infarction were 3.5 per 1000 patient-years for responders, as compared with 9.4 events per 1000 patient-years for non-responders, yielding a statistically significant lower adjusted incidence rate ratio of 0.36 (95% CI: 0.19–0.69) for responders.

In a retrospective Scandinavian study 983 patients with RA, 531 of whom received TNF-α blocking agents, were linked with national registers of inpatient care and cause of death. The authors defined a cardiovascular disease event as the first discharge from inpatient care for cardiovascular disease or death due to cardiovascular disease without such previous discharge during the study period. For those RA patients treated with TNF-α blocking agents the adjusted incidence rate of first cardiovascular event was 14.0/1000 person-years (95% CI: 5.7–22.4), compared with 35.4/1000 person-years (95% CI: 15.5–54.4) in those not treated. Controlling for disability, the age–sex adjusted rate
patients with Cushing’s syndrome. In addition, GCs are known to have cardiovascular side effects. This is supported by the increased mortality found in patients treated with TNF-α blocking agents. The opinion of these authors is that the risk of a cardiovascular event is lower in the patients treated with TNF-α blocking agents.

A US study investigated the impact of immunosuppressive medications on hospitalization for cardiovascular events (myocardial infarction or stroke) in 3501 RA patients covered by Medicare insurance. Patients receiving MTX monotherapy were the reference group. A total of 946 patients were hospitalized for a cardiovascular event. Biologic agents, mainly TNF-α blocking agents, showed neither protective nor deleterious effects [with biologics monotherapy, odds ratio (OR) 1.0, 95% CI: 0.5–1.9; with biologics-plus-MTX combination therapy OR 0.8, 95% CI: 0.3–2.0; and with biologics plus other immunosuppressive agents OR 1.2, 95% CI: 0.7–2.2]. Monotherapy with oral GCs was associated with increased risk for cardiovascular events (OR 1.5, 95% CI: 1.1–2.1). In addition, azathioprine, cyclosporine and leflunomide were associated with an increased risk for cardiovascular events (with both monotherapy and combination treatment, OR 1.8, 95% CI: 1.1–3.0).

In conclusion, these data support the assumption that TNF-α blocking agents are able to reduce the incidence of cardiovascular events, especially in those patients who respond clinically to therapy.

Other DMARDs

Only a paucity of data exists on the impact of DMARDs other than MTX on cardiovascular risk. As mentioned above, azathioprine, cyclosporine and leflunomide were found to be associated with increased cardiovascular events. Leflunomide as well as cyclosporine can cause hypertension, which may in part explain this finding. In addition, cyclosporine may cause calcineurin-inhibitor toxicity of the kidneys, which itself may lead to an unfavorable state with regard to cardiovascular risk. Antimalarial drugs can improve lipid profiles and have anticoagulatory effects. However, it may be questioned whether they actually reduce the cardiovascular risk. As long as there are no data on the impact of these antimalarials on cardiovascular events, no final recommendations can be made.

GCs

GCs are known to have cardiovascular side effects. This is supported by the increased mortality found in patients with Cushing’s syndrome. In addition, there are observational data that support this hypothesis. In a large study, 68,781 users of GCs were compared with 82,202 non-users. In the group of GCs users the incidence ratios for the rate of heart failure, myocardial infarction, a combination of stroke and transient ischemic attacks and all-cause mortality were 3.72, 3.25, 1.73 and 7.41, respectively. In a RA population GC exposure was associated with carotid plaque and arterial incompressibility, independent of cardiovascular risk factors and clinical manifestations of RA. In a retrospective study including 603 RA patients it was found that use of GCs was associated with increased vascular risk in patients who were RF positive, but not in those who were RF negative. In addition, the use of GCs in RA patients was associated with hypertension.

The problem in interpreting all these data is that it is difficult to distinguish whether the use of GCs or the underlying disease itself, which presents the indication for GCs treatment, is the main driver of the increased mortality. In general, a dosage of ~7.5 mg/day or more is believed to be associated with increased cardiovascular risk. However, it is difficult to estimate the true impact of GCs on cardiovascular risk in RA patients. On the one hand, GCs are associated with cardiovascular risk. On the other hand, GCs can reduce disease activity and inflammation, which appear to be the cause of premature atherosclerosis in RA and might therefore also have favorable effects on the cardiovascular system. As long as there are no data that could help to better interpret the impact of GCs, it is recommended to keep the doses of GCs as low as possible.

NSAIDs

NSAIDs as well as cyclo-oxygenase-2 (COX-2) inhibitors are commonly used in the treatment of RA. With the introduction of COX-2 inhibitors it became evident that, in comparison with placebo, there was an increased risk for cardiovascular events. In addition, NSAIDs and COX-2 inhibitors are associated with unfavorable side effects such as hypertension, congestive heart failure and impaired kidney function. Shortly after the increased risk from COX-2 inhibitors was discovered, it became clear that traditional NSAIDs, too, are associated with increased cardiovascular risk. This is best documented for commonly used drugs such as diclofenac and ibuprofen but may also be true for most other NSAIDs. In a large meta-analysis the use of a COX-2 inhibitor was associated with an approximately 2-fold increase in myocardial infarction. The increased number of vascular events was—when naproxen was excluded from the analysis—comparable to that of traditional NSAIDs. Of note is that the long-term use of
COX-2 inhibitors was estimated to be associated with at least three additional cardiovascular events per 1000 patients treated per year.\textsuperscript{143} There seem to be relevant differences between individual drugs, and side effects also appear to be at least in part dose dependent.\textsuperscript{143,144} In general, it is recommended to use the lowest possible dose of COX-2 inhibitors or NSAIDs and for as short a time as possible. If the decision is made that a NSAID should be used for treatment, a reasonable choice might be naproxen, as the cardiovascular risk for this drug seems to be lower than for others.\textsuperscript{143,144}

Summing up this section, it appears that control of disease might be parallel with improved cardiovascular outcome. Whether this is related to specific drugs or the control of disease in general needs further investigation. At present, the use of MTX and TNF-\(\alpha\) blocking agents appears to provide reduction of cardiovascular events, the latter probably only in those patients who respond clinically to treatment. To date we are still far from being able to definitely determine the final effect of all these drugs on improving cardiovascular outcome. This is especially true with regard to the number needed to treat. Drugs such as leflunomide, cyclosporine, NSAIDs and COX-2 inhibitors may worsen cardiovascular outcome. The specific role of treatment with (low-dose) GCs in active RA still needs to be determined.

**Conclusions**

RA is associated with increased cardiovascular morbidity and mortality, which cannot be explained by traditional cardiovascular risk factors. Dysfunctions in the cardiovascular system of RA patients are found on different levels, including the molecular level, in the endothelium, in arterial stiffness, the morphology of the vessels and finally in the presentation in case of a cardiovascular event. While the pathologic abnormalities in the cardiovascular system are well established, it is much less clear how to deal with this problem (Tables 1 and 2). Controlling disease activity is a reasonable goal, but its efficacy is yet to be proven conclusively. Whether drugs that are commonly used in established cardiovascular disease (e.g. statins) should

**Table 1** General approach for the cardiovascular care of RA patients

| Screening for (potentially modifiable) traditional cardiovascular risk factors |
| Smoking |
| Hypertension |
| Diabetes |
| Lipid levels |
| BMI |
| Inactivity |
| Evaluation of cardiovascular risk |
| Multiplier 1.5 in relevant patients (2 out of 3)\textsuperscript{64} |
| – Disease duration >10 years, |
| – RF or anti-CCP antibody positivity |
| – Presence of extra-articular manifestations |

Follow recommendation of cardiovascular care for general population\textsuperscript{70}

BMI: Body mass index

**Table 2** Drugs and their place in the cardiovascular care of RA patients

<table>
<thead>
<tr>
<th>Cardiovascular focus</th>
<th>Statins</th>
<th>Statistically significant, clinically modest anti-inflammatory activity.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Use should be based on general recommendations for cardiovascular care\textsuperscript{70,94}</td>
<td></td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>Use should be based on general recommendations.\textsuperscript{70,100}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whether ACE-inhibitors or angiotensin receptor blockers should truly be the preferred drugs still needs to be proven.</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>In patients without overt cardiovascular disease benefits and risks should be weighed.\textsuperscript{112}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>General recommendations may help to determine whether indicated.\textsuperscript{70} Consider interactions with NSAIDs.</td>
<td></td>
</tr>
<tr>
<td>DMARDs</td>
<td>MTX appears to be beneficial\textsuperscript{118}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leflunomide, azathioprine and cyclosporine are probably associated with unfavorable cardiovascular outcome\textsuperscript{126}</td>
<td></td>
</tr>
<tr>
<td>TNF-(\alpha) blocking agents</td>
<td>Are probably able to reduce the incidence of cardiovascular events, especially in those patients who clinically respond to therapy</td>
<td></td>
</tr>
<tr>
<td>GCs</td>
<td>Are associated with increased cardiovascular morbidity and mortality in the general population. Final place in RA needs to be established. Use lowest dose possible.\textsuperscript{64}</td>
<td></td>
</tr>
<tr>
<td>NSAIDs, COX-2 inhibitors</td>
<td>Are associated with increased cardiovascular risk. Naproxen may present the lowest risk and might therefore be preferred\textsuperscript{143,144}</td>
<td></td>
</tr>
</tbody>
</table>
generally be used in RA patients needs to be examined. Data answering this question are eagerly awaited. As general recommendations for cardiovascular care are often not fulfilled, looking for traditional cardiovascular risk factors in RA patients should be encouraged, so that intervention can be undertaken on the basis of established recommendations.

Conflict of interest: None declared.

References


29. Bergholm R, Leirisalo-Repo M, Vehkavaara S, Mäkimattila S, Taskinen MR, Yki-Järvinen H. Impaired responsiveness to...


