REVIEW ARTICLE

Cardiovascular Comorbidity in Inflammatory Rheumatological Conditions

Jürgen Braun, Klaus Krüger, Bernhard Manger, Matthias Schneider, Christof Specker, Hans Joachim Trappe

SUMMARY

Background: Approximately 1.5 million adults in Germany suffer from an inflammatory rheumatological condition. The most common among these are rheumatoid arthritis and spondyloarthritis—above all axial spondyloarthritis, including ankylosing spondylitis (Bekhterev's disease) and psoriatic arthritis. These systemic inflammatory diseases often affect the heart as well.

Methods: This review is based on pertinent articles retrieved by a selective literature search, on current European guidelines, and on the authors' clinical experience.

Results: Rheumatic inflammation of cardiac structures can manifest itself as pericarditis, myocarditis, or endocarditis. The heart valves and the intracardiac conduction system can be affected as well, leading to AV block. Functional sequelae, e.g., congestive heart failure, can arise as a consequence of any inflammatory rheumatic disease. The long-term mortality of rheumatic diseases is elevated predominantly because of the increased risk for cardiovascular comorbidities. The cardiovascular risk profile should therefore be re-evaluated regularly (e.g., at 5-year intervals) in cooperation with the patient's primary care physician. The cardiovascular manifestations of rheumatic disease, such as pericarditis, myocarditis, and vasculitis, are treated initially with high-dose glucocorticoids and then over the long term with maintenance drugs such as methotrexate and azathioprine. Biological agents are sometimes used as well.

Conclusion: In patients with inflammatory rheumatic diseases, the elevated cardiovascular risk should be kept in mind and preventive measures should be initiated early. This subject should be further studied in controlled trials so that the treatment options for patients with cardiac involvement can be evaluated.

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In Germany, approximately 1.5 million adults suffer from inflammatory rheumatological conditions (e1). The prevalences of these diseases are listed in the *Table*. The frequency of direct cardiac involvement and/or cardiovascular comorbidities varies between these conditions. In the past, pericarditis, myocarditis, endocarditis, and valvular heart disease were common cardiac manifestations of rheumatic disorders. Due to the advances in the treatment of rheumatoid arthritis (RA) and conditions within the spondyloarthritis (SpA) group, the prevalence of clinically relevant direct cardiac involvement—minor changes can still be visualized with modern diagnostic imaging (1)—is declining (2).

In contrast, cardiovascular comorbidities—besides musculoskeletal conditions such as osteoarthritis and osteoporosis—continue to attract increasing attention; cardiovascular comorbidities are observed in 70 to 80% of patients with RA, axial spondyloarthritis (axSpA), psoriasis arthritis (PsA), or systemic lupus erythematoses (SLE) (e2). Among patients with these conditions, the prevalences of arterial hypertension and coronary artery disease (CAD) are in the ranges of 26 to 36% and 7 to 13%, respectively (3).

Today, cardiovascular comorbidities are among the leading causes of death in patients with inflammatory rheumatological conditions (4) and there is a direct relationship between the inflammatory activity associated with these diseases and cardiovascular morbidity and mortality. The cardiovascular risk can be reduced by adequate disease control (5). The risks of CAD and cerebrovascular events are higher among RA patients by almost 60% and 50%, respectively. Accordingly, the cardiovascular mortality rate is 45% higher in RA patients compared to the general population (1707 versus 775 per 100 000 patient years) (6).

Lastly, the drugs used to treat inflammatory rheumatological conditions play a role, too. The cardiovascular risk of RA patients is dose-dependently increased by the long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, but decreased by methotrexate and TNF inhibitors (7). A cardioprotective effect was also demonstrated for hydroxychloroquine in RA and SLE patients (e3, e4). In patients with gout, colchicine has a cardioprotective effect (8).

Rheumazentrum Ruhrgebiet, Herne: Prof. Dr. med. Braun

Rheumazentrum München, Munich: Prof. Dr. med. Krüger

Department of Medicine 3, Universitätsklinikum Erlangen: Prof. Dr. med. Manger

Department of Rheumatology, Hiller Research Center Rheumatology, University Hospital Düsseldorf: Prof. Dr. med. Schneider

Department of Rheumatology and Clinical Immunology, St. Josef Krankenhaus, Essen University Hospital: Prof. Dr. med. Specker

Department of Cardiology, Marien-Hospital Herne, University Hospitals of the Ruhr University of Bochum: Prof. Dr. med. Trappe

TABLE

Prevalence of rheumatic diseases in Germany (9)

	Prevalence (affected in Germany)	Incidence (incidence of new cases/year)
Inflammatory rheumatological conditions	2.1% approx. 1.5 million adults	
Rheumatoid arthritis	0.8% 550 000	0.04% 27 000
Total spondyloarthritis group	0.5–2%	
Axial spondyloarthritis, incl. ankylosing spondylitis	0.8% 550 000	20/100 000
Psoriatic arthritis	0.2% 140 000	
Total connective tissue disorders/vasculitis	0.3% 210 000	
– thereof systemic lupus erythematosus (SLE)*	0.04% 35 000	1–2/100 000 in Europe
Crystal arthropathies Gouty arthritis	3%	

* Health insurance data from the Federal State of North Rhine-Westphalia, Germany

Methods

The German Society of Rheumatology (DGRh, Deutsche Gesellschaft für Rheumatologie) issued clinical guidelines for the management of early RA (S3) and for the sequential pharmacotherapy of RA (S1) and axSpA (S3) (dgrh.de/qualitaetssicherung.html). For reasons of space, we have focused on the most important conditions.

We limited our selective literature search to the PubMed database, using as search terms the names of the diseases in conjunction with "heart" or "cardiac involvement". Only selected references are listed in this article. Due to the limited data available, evidence grades could not often be reported.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is the most common systemic inflammatory rheumatological condition with potential internal organ involvement. In patients with RA, signs of autoimmunity, such as rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPAs), but also antinuclear antibodies (ANAs), are observed. Organ involvement, for example interstitial lung disease and vasculitis, is more common in RF-positive and ACPA-positive patients (5, 10, e5). In RA, various cardiac structures may be affected (*Box 1*). Echocardiography frequently reveals a pericardial effusion without clinical significance (*Figure*) (1). Myocarditis or myocardial fibrosis are less common (11); cardiac amyloidosis is a rarity. Valvular changes, typically asymptomatic, are frequently reported. Patients with RA often suffer from impaired cardiac pump function and overt heart failure (12, 13). The cumulative incidence of heart failure among 80-year-old RA patients is at 36% almost twice as high as that among controls. While in controls "traditional" cardiovascular risk factors were responsible for the development of heart failure in the majority of cases (77%), this applied only to 54% of the RA patients (13). This difference may be explained by other RA-related risk factors such as myocarditis or heart valve defects.

BOX 1

Significant cardiac involvement in rheumatoid arthritis (1)

- Pericardial effusion (OR: 10.7; 95% CI: [5.0; 23.0])
- Nodules on cardiac valves (OR: 12.5 [2.8; 55.4])
- Tricuspid regurgitation (OR: 5.3 [2.4; 11.6])
- Aortic stenosis (OR: 5.2 [1.1; 24.1])
- Mitral regurgitation (OR: 3.4 [1.7; 6.7])
- Aortic regurgitation (OR: 1.7 [1.0; 2.7])
- Cardiac valve changes (OR: 4.3 [2.3; 8.0])
- Mitral valve thickening / calcification (OR: 5.0 [2.0; 12.7])
- Aortic valve thickening / calcification (OR: 4.4 [1.1; 17.4])
- Valvular thickening / calcification (OR: 4.8 [2.2; 10.5])
- Mitral valve prolapse (OR: 2.2 [1.2; 4.0])
- Atrial fibrillation (adjusted IRR: 1.41 [1.3; 1.5])
- Prolonged QT interval (cumulative incidence: 48%)

The odds ratios refer to the general population. IRR, Incidence Rate Ratio; OR, Odds Ratio; 95CI, 95% confidence interval

RA patients have a slightly increased risk of atrial fibrillation (prevalence 3 to 4%) which has no effect on mortality (14). QT interval prolongation, a possible predictor of cardiovascular mortality in RA, was more commonly observed among RA patients (48%) than among normal controls.

Spondyloarthritis

Spondyloarthritis (SpA) is a family of inflammatory rheumatological conditions, sharing clinical signs and symptoms as well as a genetic predisposition (15). These are further differentiated based on prevailing clinical features or according to subtypes. The most important subtype is ankylosing spondylitis (AS, formerly known as Bechterew's disease), now classed in the axial spondyloarthritis disease family. The other subtypes are characterized by psoriasis, inflammatory bowel disease or preceding infection (reactive arthritis). Psoriatic arthritis (PsA) usually affects peripheral joints.

Other organs typically involved include the eyes (anterior uveitis) and, more rarely, the heart. Typical features of cardiac involvement in patients with AS (Box 2) include aortic valve disease and cardiac arrhythmia (16). The increased mortality observed in patients with AS is primarily due to cardiovascular comorbidity. The standardized mortality rate was 1.63 in men and 1.38 in women; 40% of the deaths were caused by cardiovascular disease (17).

Pathoanatomical characteristics of AS include involvement of the ascending aorta, especially of the aortic root, but also of subaortic structures, such as the membranous part of the interventricular septum and the base of the anterior mitral cusp where inflammation may lead to mitral regurgitation (18). Cardiac conduction abnormalities are also frequently observed in patients with AS (19, 20). Aortitis—today rather uncommon—can be observed in combination with typical aortic regurgitation. Its prevalences range between 3 and 18%, subject to age and disease duration. Patients with AS frequently undergo aortic valve surgery (18).

Besides the focal destruction of histological structures in the tunica media, the characteristic histopathological features of aortitis include thickening of the intima and adventitia as well as vascular obliteration (21). In addition to the potential thickening of the aorta and aortic valve, the fibrotic changes may extend below the aortic valve to form a subaortic bump.

The prevalence of significant cardiac conduction abnormalities, especially of high-degree atrioventricular (AV) blocks with clinically relevant bradyarrhythmia, is increased among AS patients (5%); this complication is associated with HLA (human leukocyte antigen) B27. In almost all cases, the AV node, which is located above the HIS bundles, is involved. These patients usually require pacemaker treatment (19, 20). AV blocks may also occur in otherwise healthy HLA-B27-positive individuals, usually in combination with aortic regurgitation. HLA-B27 positivity is more common among patients with pacemakers than in the general population (19).

Figure: Echocardiography in a patient with pericardial effusion

In contrast, the prevalence of cardiac valve disease or conduction abnormalities is not increased among patients with PsA. Years ago, similar HLA-B27-associated aortic valve and AV node abnormalities were reported for patients with reactive arthritis (at that time referred to as Reiter's syndrome).

Today, the incidence and clinical relevance of acute rheumatic fever and even cardiac involvement in post-streptococcal reactive arthritis are regarded as being low (22).

There are only limited data available on the vascular, gastrointestinal or renal risks associated with NSAID treatment in patients aged <50 years with AS and PsA. However, an increase in risk is likely, especially among

BOX 2

Cardiac manifestations in ankylosing spondylitis (16)

- Aortitis
- Aortic bump (fibrotic structure at the anterior mitral cusp)
- Aortic regurgitation
 - Mitral regurgitation*
- Myocardial fibrosis
- Coronary artery disease
- Impaired left ventricular function und left-sided heart failure
- Cardiac conduction abnormalities (2nd degree and 3rd degree AV block)
 - Premature ventricular contractions*

* The two indented manifestations are less common and less characteristic.

older patients and patients with relevant risk factors (heart failure, renal failure, history of ulcers). Yet, the risk among patients receiving short-term NSAID treatment (23) or constantly high NSAID doses is not increased (24). Two independently conducted studies with AS patients (17, 25) showed that not the intake of high NSAID doses, but of low doses was associated with increased mortality. These results indicate that there may also be beneficial effects of NSAIDs that should be taken into account in the overall evaluation of the use of NSAIDs in patients with chronic inflammatory disease.

Connective tissue disorders

Manifestations of systemic lupus erythematosus, scleroderma (progressive systemic sclerosis [PSS]), idiopathic inflammatory myopathy (IIM), including dermatomyositis and polymyositis, and mixed connective-tissue disease (MCTD) are found on various structures of the heart, representing a key differential diagnosis for endocarditis, myocarditis and pericarditis. However, the diagnosis of connective tissue disorders relies more on non-cardiac manifestations, such as skin changes and arthritis, in addition to the detection of autoanti-

bodies (ANA, ENA, anti-dsDNA antibodies) which can be specific for some conditions.

Myocarditis occurs along with SLE and PSS in 10% and with IIM in 25% of cases (26). Regional wall motion abnormalities represent the first echocardiographic sign of myocarditis. The gold standard for the reliable diagnosis of myocarditis is endomyocardial biopsy. As a non-invasive technique, cardiac magnetic resonance imaging (cardiac MRI) can reveal signs of myocarditis (e.g. regional edema, late enhancement, wall motion abnormalities) at an early stage.

Cardiac involvement in PSS in the form of myocarditis and myocardial fibrosis with arrhythmia and potential right-sided heart failure in patients with pulmonary hypertension (scleroderma heart disease) is indicative of an unfavorable prognosis (27). Apart from routine cardiological investigations, right heart catheterization is indispensable for the quantitative assessment of pulmonary hypertension.

Pericarditis can occur with any connective tissue disorders; for example, it is found in 25 to 39% of SLE cases (e6, e7). Mitral valve involvement is typical of nonbacterial verrucous endocarditis (Libman–Sacks). In case of SLE-associated valvular

BOX 3

EULAR recommendations for the management of cardiovascular comorbidities (36)

- Disease activity should be controlled optimally in order to minimize CVD risk in all patients with RA, axSpA or PsA. IIb–III B
- CVD risk assessment is recommended for all patients with RA, axSpA or PsA at least once every 5 years and should be reconsidered following major changes in antirheumatic therapy. III–IV C
- This risk estimation should be performed according to national guidelines. The SCORE CVD risk prediction model (e24) should be used if no national guideline is available. III–IV C–D
- Total cholesterol and HDL cholesterol should be measured when disease activity in patients with RA, axSpA and PsA is low or when patients are in remission. Non-fasting lipid measurements can also be included in the risk assessment. III C
- When conventional models are used for CVD risk assessment, the resulting values should be adjusted in RA patients, for example by a 1.5 multiplication factor. III–IV C
- Screening for asymptomatic atherosclerotic plaques by methods such as carotid ultrasound may be considered as part of the CVD risk estimation in patients with RA. III–IV C–D
- Recommendations for lifestyle changes should be made available to all patients, emphasizing the benefits of a healthy diet, smoking cessation and regular exercise programs. III C
- CVD risk management should be carried out according to national guidelines in RA, axSpA or PsA. Antihypertensives and statins may be used for the same indications as in the general population. III–IV C–D
- Especially for patients with increased CVD risk or documented CVD, nonsteroidal anti-inflammatory drugs (NSAIDs) should be prescribed with caution, i.e. only after a careful risk/benefit assessment. IIa–III C
- For prolonged treatment, the glucocorticoid dosage should be kept to a minimum and a glucocorticoid taper should be attempted in case of remission or low disease activity. The reasons to continue glucocorticoid therapy should be regularly checked. III–IV C

The figures denote the level of evidence; the letters denote the strength of the recommendation.

axSpA, axial spondyloarthritis; CVD, cardiovascular disease; EULAR, European League Against Rheumatism; PsA, psoriatic arthritis; RA, rheumatoid arthritis

deposits, antiphospholipid antibody levels should be measured.

In pregnant patients, anti-SS-A/Ro autoantibodies are associated with an increased risk of congenital heart block. In rare cases (approx. 2%), this conduction system dysfunction of the fetal heart is irreversible.

Vasculitis

Vasculitis is characterized by cellular inflammation of the blood vessel wall which may cause ischemia and necrosis of down-stream tissues or organs as well as bleeding. Anti-neutrophil cytoplasmic antibodies (ANCA) are found in patients with granulomatosis with polyangiitis (GPA/Wegner), microscopic polyangiitis (MPA) and in some patients with eosinophilic granulomatosis with polyangiitis (EGPA/Churg–Strauss), while no autoantibodies are present in patients with giant-cell arteritis (GCA/Horton) and Takayasu arteritis (TA).

Altogether, direct cardiac manifestations of the various types of systemic vasculitis are at 5 to 25% comparatively rare (28, e8). Pericarditis, myocarditis, endomyocardial fibrosis, vasculitis-related coronary ischemia, valve regurgitation, and/or arrhythmia may also occur (28, e9).

Malignant hypertension is a characteristic feature of panarteritis nodosa (PAN), a condition frequently associated with hepatitis-B virus (HBV) infection. In patients with TA, typically younger adults, heart involvement (aortic regurgitation, aortic aneurysm, vasculitis-related ischemia, pump failure) occurs more frequently than in patients with GCA (e9).

Cardiac involvement in rare rheumatic diseases

The most common (20 to 30%) cardiac manifestation in adult Still's disease is pericarditis (e10) which is usually accompanied by fever and polyserositis.

In patients with Behçet's disease, cardiac manifestations are frequently observed (7–46%; e11), mainly in the form of pericarditis, including cases of constrictive pericarditis with hemorrhagic tamponade. Intracardiac thrombi, mostly in the right atrium, are the first manifestation of Behçet's disease in >50% of patients (e11). Coronary vasculitis as well as aortitis with aneurysmal dilation and aortic regurgitation may also occur—as is also observed for the rare relapsing polychondritis (e12). Aortic valve replacement is the most common cardiac surgery procedure undergone by patients with Behçet's disease (e13).

Secondary (AA) amyloidosis may, although rarely, develop in patients with longstanding and inadequately treated inflammatory rheumatological conditions (e14); in these cases, AA amyloid deposits can cause heart failure (e14).

Cardiovascular comorbidity

The risk of major cardiovascular events (all cause cardiovascular mortality, myocardial reinfarction, heart failure, re-revascularization due to ischemia) is

higher in RA than in other rheumatic diseases (29). CHD prevalence in RA is at 16.6% higher compared to controls (odds ratio 1.35); the incidence rate of cardiovascular events is 7.8 per 1000 RA patient-years (30). In 80% of RA patients, at least one modifiable traditional cardiovascular risk factor is present (31). Arterial hypertension is more common among RA patients (57%); this may also apply to type 2 diabetes, but here the increase is not so clear. Among RA patients, the prevalences of increased body mass index, LDL cholesterol levels and smoking are within the normal range (31).

The prevalences and incidences of cardiovascular events are elevated in patients with AS and PsA (25, 32). Patients with psoriasis more frequently suffer from metabolic syndrome (e15). The increased mortality among AS patients is primarily due to cardiovascular comorbidity and the increased prevalence of risk factors (33). AS patients more often undergo coronary bypass surgery (e16).

Likewise, arteriosclerotic processes are induced and accelerated in patients with connective tissue disorders. Myocardial infarction in a young person can be indicative of an underlying connective tissue disorder. Due to their increased life expectancy, arteriosclerotic vasculopathy now manifests more frequently in these patients. It is important to provide advice and treatment for traditional risk factors—even though in only about half of the cases they are causing the disease. In SLE patients, it is critical to diagnose CHD at an early stage. Electron-beam CT (EBCT) and multidetector CT (MDCT) can be used to detect increased coronary calcium deposits (34); cardiac MRI is regarded as the best non-invasive technology to demonstrate inflammatory changes (35).

Recommendations for the management of cardiovascular comorbidities have been issued by the European League Against Rheumatism (EULAR) (36, Box 3). These should be followed to facilitate early intervention. The use of high-dose statins appear to reduce the risk of developing rheumatoid arthritis (e17). In patients with RA, statins reduce mortality by 20% (e18).

Antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) are associated with the occurrence of necrotizing myopathy and the use of statins. However, this condition is rare and necrotizing myopathy also occurs in persons who never received such treatment (e19). The vast majority of patients treated with statins do neither develop anti-HMGCR antibodies nor signs and symptoms of myopathy (e20).

In some RA patients treated with the interleukin-6 receptor inhibitor tocilizumab, hypercholesterolemia occurred, but was not associated with an increased incidence of cardiovascular events; most likely because the anti-inflammatory effect of this drug outweighed the negative effect of increased cholesterol levels (e21).

Management and treatment of cardiovascular manifestations

In principle, whenever patients with certain rheumatic conditions, such as lupus erythematosus and polymyositis, present with increased disease activity, the cardiac manifestations of these diseases, such as pericarditis and myocarditis, should be taken into consideration and the corresponding diagnostic work-up should be initiated.

For some rheumatic diseases, such as scleroderma, routine follow-up echocardiography—for example, once per year—is recommended to enable the early detection of pulmonary arterial hypertension; the screening for this condition also relies on the heart failure marker NT-proBNP (e22). In long-term AS patients, echocardiography should be performed at 1- to 2-year intervals to facilitate early diagnosis of aortic-valve disease.

The initial treatment of direct inflammatory manifestations of rheumatological conditions, such as pericarditis, myocarditis and vasculitis, involves the use of high-dose glucocorticoids (37) and disease-modifying antirheumatic drugs, such as methotrexate (MTX) and azathioprine, among others. There are no controlled studies on cardiac involvement in rheumatic diseases available.

MTX is one of the few drugs with proven survival benefits in RA patients, primarily achieved by reducing cardiovascular mortality (38). In severe cases, biologicals, such as rituximab and tocilizumab, have been used successfully (39, 40). In adult Still's syndrome, interleukin-1 receptor antagonists were effective in treating myocarditis (e23).

Other manifestations and comorbidities are treated according to standard practice in cardiology.

KEY MESSAGES

- Besides direct cardiac involvement, such as pericarditis and myocarditis, inflammatory rheumatological conditions are associated with an increased risk of cardiovascular comorbidity, resulting in increased mortality.
- Good patient management extends beyond the consistent control of chronic inflammation and consequently disease activity to include traditional risk factors, such as arterial hypertension and hypercholesterolemia.
- Antihypertensives and statins should already be used, according to current guidelines and recommendations, for the primary prevention of cardiovascular disease.
- Especially in older patients with increased cardiac risk, NSAIDs should only be prescribed after careful consideration of the indication and assessment of risks and benefits.

Conflict of interest statement

Prof. Krüger has received lecture fees from Abbvie.

Prof. Manger has received consultancy fees from MSD and UCB and fees for a lecture or meeting preparation from Abbvie, MSD, Pfizer, and Roche.

Prof. Specker has received lecture fees from Roche.

Prof. Schneider has received reimbursement of meeting participation fees and travel expenses from MSD and Chugai.

Prof. Schneider and Prof. Braun received fees for a publication related to the topic.

Prof. Trappe declares that no conflict of interests exists.

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Corresponding author

Prof. Dr. med. Jürgen Braun
Rheumazentrum Ruhrgebiet
Claudiusstr. 45
44649 Herne, Germany
j.braun@rheumazentrum-ruhrgebiet.de

Supplementary material

For eReferences please refer to:
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Supplementary material to:

Cardiovascular Comorbidity in Inflammatory Rheumatological Conditions

by Jürgen Braun, Klaus Krüger, Bernhard Manger, Matthias Schneider, Christof Specker, and Hans Joachim Trappe

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