

# Contents

<b>Foreword: Cardiovascular Comorbidities in Inflammatory Rheumatic Diseases</b>	<b>xiii</b>
Michael H. Weisman	
<b>Preface: Cardiovascular Comorbidities in Inflammatory Rheumatic Diseases</b>	<b>xv</b>
George A. Karpouzas and M. Elaine Husni	
<b>Time Trends of Cardiovascular Disease in the General Population and Inflammatory Arthritis</b>	<b>1</b>
Anna Södergren, Solbritt Rantapää-Dahlqvist, and Lotta Ljung	
Cardiovascular diseases (CVDs) are the leading causes of death in the world, but declining trends for cardiovascular (CV) mortality and morbidity have been observed during the last decades. Reports on secular trends regarding the excess CV mortality and morbidity in rheumatoid arthritis show diverging results. Data support that also patients with inflammatory arthritis have benefited from improved treatment and prevention for CVD, which can be observed, for example, in decreased case fatality after CV event. However, several recent studies indicate a remaining excess CV risk in patients with inflammatory arthritis.	
<b>Atherosclerotic Cardiovascular Risk Stratification in the Rheumatic Diseases: An Integrative, Multiparametric Approach</b>	<b>19</b>
Durga Prasanna Misra, Ellen M. Hauge, Cynthia S. Crowson, George D. Kitas, Sarah R. Ormseth, and George A. Karpouzas	
Cardiovascular disease (CVD) risk is increased in most inflammatory rheumatic diseases (IRDs), reiterating the role of inflammation in the initiation and progression of atherosclerosis. An inverse association of CVD risk with body weight and lipid levels has been described in IRDs. Coronary artery calcium scores, plaque burden and characteristics, and carotid plaques on ultrasound optimize CVD risk estimate in IRDs. Biomarkers of cardiac injury, autoantibodies, lipid biomarkers, and cytokines also improve risk assessment in IRDs. Machine learning and deep learning algorithms for phenotype and image analysis hold promise to improve CVD risk stratification in IRDs.	
<b>Myocardial Involvement in Systemic Autoimmune Rheumatic Diseases</b>	<b>45</b>
Alexia A. Zagouras and W.H. Wilson Tang	
Systemic autoimmune rheumatic diseases (SARDs) are defined by the potential to affect multiple organ systems, and cardiac involvement is a prevalent but often overlooked sequela. Myocardial involvement in SARDs is mediated by macrovascular disease, microvascular dysfunction, and myocarditis. Systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, eosinophilic granulomatosis with polyangiitis, and sarcoidosis are associated with the greatest risk of myocardial damage	

and heart failure, though myocardial involvement is also seen in other SARDs or their treatments. Management of myocardial involvement should be disease-specific. Further research is required to elucidate targetable mechanisms of myocardial involvement in SARDs.

### **Heart Failure in Rheumatic Disease: Secular Trends and Novel Insights**

67

Brian Bridal Løgstrup

There is a significant increase in risk of heart failure in several rheumatic diseases. Common cardiovascular risk factors and inflammatory processes, present in both rheumatic diseases and heart failure, are contributing to this increase. The opportunities for using immune-based strategies to fight development of heart failure in rheumatic diseases are evolving. The diversity of inflammation calls for a tailored characterization of inflammation, enabling differentiation of inflammation and subsequent introduction of precision medicine using target-specific strategies and immunomodulatory therapy. As the field of rheuma-cardiology is still evolving, clear recommendations cannot be given yet.

### **Cardiovascular Disease in Large Vessel Vasculitis: Risks, Controversies, and Management Strategies**

81

Alison H. Clifford

Takayasu's arteritis (TAK) and giant cell arteritis (GCA) are the 2 most common primary large vessel vasculitides (LVV). They share common vascular targets, clinical presentations, and histopathology, but target a strikingly different patient demographic. While GCA predominantly affects elderly people of northern European ancestry, TAK preferentially targets young women of Asian heritage. Cardiovascular diseases (CVD), including ischemic heart disease, cerebrovascular disease, aortic disease, and thromboses, are significantly increased in LVV. In this review, we will compare and contrast the issue of CVD in patients with TAK and GCA, with respect to prevalence, risk factors, and mechanisms of events to gain an understanding of the relative contributions of active vasculitis, vascular damage, and accelerated atherosclerosis. Controversies and possible mitigation strategies will be discussed.

### **Venous Thromboembolism in the Inflammatory Rheumatic Diseases**

97

Durga Prasanna Misra, Sakir Ahmed, Mohit Goyal, Aman Sharma, and Vikas Agarwal

Venous thromboembolism (VTE), which includes deep venous thrombosis and pulmonary embolism, is a cardiovascular event whose risk is increased in most inflammatory rheumatic diseases (IRDs). Mechanisms that increase VTE risk include antiphospholipid antibodies (APLs), particularly anticardiolipin antibodies, anti-beta2glycoprotein I antibodies and lupus anticoagulant present together, and inflammation-mediated endothelial injury. Patients with IRDs should receive long-term anticoagulation drugs when the risk of VTE recurrence is high. In the light of recent warnings from regulatory agencies regarding heightened VTE risk with Janus kinase inhibitors, these drugs should be initiated only after a careful assessment of VTE risk in those with IRDs.

**Lessons from Cardiac and Vascular Biopsies from Patients with and without Inflammatory Rheumatic Diseases** 129

Ivana Hollan

Feiring Heart Biopsy Study enables searching for potential pathogenetic mechanisms, therapeutic targets, and biomarkers through the assessment of clinical data and multiple blood and tissue samples from patients with and without inflammatory rheumatic diseases (IRDs), undergoing coronary artery bypass grafting. Some of our findings, for example, more inflammation (including the presence of immune cells and expression of proinflammatory cytokines) in vessels and the heart, and the presence of certain bacteria and autoantigens in vessels, could contribute to the increased risk of ischemia, aneurysms, and/or cardiac dysfunction in IRDs. Furthermore, some of the detected factors could be involved in the pathomechanisms of these conditions in general.

**Role of Lipoprotein Levels and Function in Atherosclerosis Associated with Autoimmune Rheumatic Diseases** 151

Nicoletta Ronda, Francesca Zimetti, Maria Pia Adorni, Marcella Palumbo, George A. Karpouzas, and Franco Bernini

Immune and inflammatory mediators in autoimmune rheumatic diseases induce modification in the activity of enzymes pivotal for lipid metabolism and promote a proatherogenic serum lipid profile. However, disturbances in low- and high-density lipoprotein composition and increased lipid oxidation also occur. Therefore, lipoprotein dysfunction causes intracellular cholesterol accumulation in macrophages, smooth muscle cells, and platelets. Overall, both plaque progression and acute cardiovascular events are promoted. Single rheumatic diseases may present a particular pattern of lipid disturbances so that standard methods to evaluate cardiovascular risk may not be accurate enough. In general, antirheumatic drugs positively affect lipid metabolism in these patients.

**Evidence for Biologic Drug Modifying Anti-Rheumatoid Drugs and Association with Cardiovascular Disease Risk Mitigation in Inflammatory Arthritis** 165

Brittany Weber and Katherine P. Liao

Systemic auto-immune inflammatory arthritides are associated with increased cardiovascular (CV) risk compared to those without these conditions, and is a leading cause of morbidity and mortality. Newer biologic drug modifying antirheumatoid drugs (bDMARD) and small molecules have transformed treatment paradigms enabling tighter control of disease activity and in some cases, remission. There is evidence to suggest that the majority of bDMARDs may also reduce cardiovascular risk, although prospective interventional data remain sparse. Additionally, recent results raise concern for treatments targeting specific pathways that may negatively affect cardiovascular risk. This review will cover key biologic pathways targeted in rheumatoid arthritis, psoriatic arthritis, and spondyloarthropathies.

**Recommendations for the Use of Nonsteroidal Anti-inflammatory Drugs and Cardiovascular Disease Risk: Decades Later, Any New Lessons Learned?** 179

Deeba Minhas, Anjali Nidhaan, and M. Elaine Husni

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most prescribed pharmacologic therapies worldwide due to their therapeutic

analgesic efficacy and relative tolerability. In the past several decades, various cardiovascular (CV) adverse events have emerged regarding both traditional NSAIDs (tNSAIDs) and cyclo-oxygenase 2 (COX-2) selective (coxibs). This review will provide an updated report on the CV risk profile of NSAIDs, focusing on several of the larger clinical trials, meta-analyses, and registry studies. We aim to provide rheumatologists with a framework for NSAID use in the context of rheumatologic chronic pain management. Recent findings: In patients with and without CV diseases, the use of NSAIDs, both tNSAIDs and coxibs, is associated with an increased risk of adverse CV events, myocardial infarction, heart failure, and cerebrovascular events. These CV risks have increased within weeks of coxib use and higher doses of tNSAIDs. The risk of adverse CV events is heterogenous across NSAIDs; naproxen and low-dose ibuprofen appear to have lower increased CV risk among NSAIDs. A variation in CV risk is associated with multiple factors, including NSAID class, COX-2 selectivity, treatment dose and duration, and baseline patient risk. Summary: Many important questions remain regarding the safety of NSAIDs and whether the culmination of research performed could inform us whether specific patient subtypes or NSAID class may have a more favorable profile. tNSAIDs such as naproxen and low-dose ibuprofen may have a lower CV risk profile, while coxibs have a more favorable GI risk profile. In general, any NSAID can be optimized if used at the lowest effective dose for the shortest amount of time, especially among individuals with increased CV risk.