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Sex and Cardiovascular Involvement in Inflammatory Joint Diseases

Santos Castañeda[1,2] · **Carlos González-Juanatey**[3] · **Miguel A. González-Gay**[4]

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Abstract The term inflammatory joint disease (IJD) encompasses a group of chronic conditions with predominant joint involvement. They share an increased risk of cardiovascular (CV) complications. However, the implication of the sex in the risk of CV disease in IJD has not been specifically addressed. The aim of this work is to assess the influence of sex on the clinical expression of CV manifestations associated to IJD. With this objective, an update of the current knowledge of the sex influence on CV disease in patients with IJD was conducted. A PubMed database search of the most relevant literature on this topic was performed mainly based on studies published in English over the last 10 years. Although most studies on IJD were not specifically designed to address sex differences regarding CV complications, it seems that men with rheumatoid arthritis (RA) are at higher risk of pericarditis, ischemic heart disease, heart failure (HF) with reduced ejection fraction (EF), and CV mortality than women with RA. In contrast, HF with preserved EF and diastolic dysfunction is more frequent in women with RA. Men with ankylosing spondylitis present more frequently disorders of the conduction system and aortic valvulopathy than women. A limited number of studies addressed CV differences according to sex in psoriatic arthritis. Although there are some differences according to sex in the clinical expression of CV complications in patients with IJD, much research is still needed to better identify the implication of sex in the risk of CV disease in these patients.

Keywords Cardiovascular morbidity · Gender · Heart disease · Rheumatoid arthritis · Ankylosing spondylitis · Psoriatic arthritis

Introduction

The term "inflammatory joint diseases (IJD)" comprises a series of chronic inflammatory disorders that have a predominant involvement of the joint and related tissues. They are systemic diseases with frequent involvement of other organs besides the joints. Heart and blood vessel complications constitute an important source of morbidity in these patients [1, 2]. Therefore, higher awareness of the increased risk of cardiovascular (CV) complications in IJD is of critical importance for the management of these patients.

Rheumatoid arthritis (RA) is the prototype of IJD. It is a chronic inflammatory disease that primarily affects the joints but may also involve other organs including eyes, lung, kidney, heart and blood vessels. At present, ischemic heart disease (IHD) and congestive heart failure (CHF) secondary to coronary atherosclerosis represents the first cause of mortality in these patients [3].

✉ Santos Castañeda
scastas@gmail.com

✉ Miguel A. González-Gay
miguelaggay@hotmail.com

Carlos González-Juanatey
carlosjuanatey@secardiologia.es

[1] Rheumatology Division, Hospital de La Princesa, IIS-Princesa, c/ Diego de León 62, 28006 Madrid, Spain

[2] Universidad Autónoma de Madrid (UAM), Madrid, Spain

[3] Division of Cardiology, Hospital Lucus Augusti, c/ Dr. Ulises Romero 1, 27003 Lugo, Spain

[4] Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, IDIVAL, Rheumatology Division, Hospital Universitario Marqués de Valdecilla, University of Cantabria, Avda. de Valdecilla, s/n, 39008 Santander, Spain

Spondyloarthritis (SpA) represent a second great group of patients with IJD. They share a pattern of musculoskeletal and extra-skeletal involvement that includes ankylosing spondylitis (AS), inflammatory back pain, asymmetrical synovitis (e.g., psoriatic arthritis [PsA]), arthritis accompanying inflammatory bowel disease (Crohn's disease and ulcerative colitis), and reactive arthritis [4]. Recently, an association between premature atherosclerosis and the two most common types of SpA, AS, and PsA has been highlighted [2, 5]. Table 1 shows the main clinical features and CV risk factors of IJD.

Systemic lupus erythematosus (SLE) and other systemic autoimmune diseases, usually more frequent in women, are also associated with a number of cardiac and vascular complications [6–9]. However, the pathogenic mechanisms leading to an increase in CV morbidity and mortality in autoimmune diseases are somehow different and more complex than those of IJD. Because of that, in this review, we will focus exclusively on the study of the influence of gender in the development of CV complications observed in the most prevalent IJD: RA, AS, and PsA. For this purpose, an update of the current knowledge on sex influence and CV disease in patients with IJD was conducted. Due to this, a PubMed search of the most relevant literature was performed, in particular searching for those studies published in English since January 1, 2007 to April 30, 2017.

Cardiovascular Disease in IJD: Epidemiological Data

Standardized mortality ratios (SMR) in patients with IJDs are higher than in general population [1] (Table 1). In a study, the SMR in RA was increased in both men (1.9, 95% CI 1.9–2.0) and women (1.6, 95% CI 1.5–1.7) [10]. In contrast, Goodson et al. reported an increase of CV mortality rate in women with seropositive early arthritis (SMR 2.0, 95% CI 1.2–3.3), whereas such an increase did not reach statistical significance in men (SMR 1.3, 95% CI 0.8–2.2) [11].

IHD [2, 12–15] and CHF [16–18] are the main causes of the increased and often premature mortality among patients with IJD. CHF was found to be an independent risk factor for mortality in patients with RA, and it was responsible for 1 out of 8 deaths in these patients [18].

A meta-analysis of 24 observational studies demonstrated that CV mortality in RA was 50% higher than in the general population (meta-SMR of 1.50, 95% CI 1.39–1.61) [19], with a 59% increase of death due to IHD and a 52% increase of death from cerebrovascular accidents (CVA) [19]. Regarding mortality by sex, the results of this meta-analysis were quite similar in both men (meta-SMR 1.45, 95% CI 1.11–1.90) and women (meta-SMR 1.58, 95% CI 1.35–1.84) [19]. In another meta-analysis conducted by the same group, there was a 48% increased risk of incident CV disease (CVD) in patients with RA being the risk of MI and CVA increased by 68 and 41%, respectively, without major differences according to sex [20].

Table 1 Clinical features and cardiovascular risk of the main inflammatory joint diseases

	Rheumatoid arthritis	Ankylosing spondylitis	Psoriatic arthritis
Clinical features	Female/ male: 3/1 Onset in 4th–6th decades	Male/female: 3/1 Onset variable, usually <30 years	Slight predominance in men Onset variable, frequently 40–55 years
	Arthritis of ≥ 3 joints, usually symmetrical with involvement of hands and feet	Inflammatory back pain, inflammation of joints of the spine. Sacroiliitis	Asymmetrical arthritis of large and small joints; in hands: DIPs > PIPs Psoriasis in 85–90%
Laboratory	APR increased > 90% RF and ACPA (+) in 70–80%	APR increased in 50% HLA-B27 (+) in 70–90% RF and ACPA typically negative	APR increased > 50–60% RF and ACPA normally negative
Radiology	Bone erosions and typical deformities in hands/ft	Spinal ankylosis; syndesmophytes sacroiliitis (seen by MRI in early stages)	Erosions, periostitis in DIP joints of hands and feet, deformities in hands/feet
Traditional CVRF	Smoking; DM; HT; DL; overweight; usually underdiagnosed; physical activity ↓	Smoking; DM; HT; DL; physical activity ↓	Smoking; DM; HT; DL; frequent obesity; typical MetS features; physical activity ↓
CV risk & mortality	Twofold increased mortality rate (~DM2) (SMR 1.3–2.3) CV main cause death Sudden death ↑ (HR 2.36; 1.30, 4.27) CHF responsible 1/8 deaths	Increased mortality rate (SMR 1.6–1.9) CV main cause of death MI risk ↑ (OR 1.60; 1.32, 1.93)	Increased mortality rate (SMR 0.8–1.6) CV important cause of death MI risk ↑ (SPR 2.57; 1.73, 3.80)

ACPA anti-citrullinated cyclic peptide antibodies, *APR* acute phase reactants, *CHF* congestive heart failure, *CV* cardiovascular, *CVRF* cardiovascular risk factors, *DL* dyslipidemia, *DM* diabetes mellitus, *DM2* type 2 DM, *DIPs* distal interphalangeal joints, *HT* hypertension, *HR* hazard ratio, *MetS* metabolic syndrome, *MI* myocardial infarction, *MRI* magnetic resonance imaging, *OR* odds ratio, *PIPs* proximal interphalangeal joints, *RF* rheumatoid factor, *SMR* standardized mortality ratio, *SPR* standardized prevalence ratio. Modified from Agca et al. (Heart 2016; ref. 2)

Table 2 Spectrum of cardiovascular (CV) manifestations stratified by sex in inflammatory joint diseases

CV manifestations	Main findings	Gender predominance	References (most representatives)
Subclinical atherosclerosis	Increased common c-IMT; greater number of atheromatous plaques	Predominance in men	Ambrosino [24]
Atherosclerotic disease; CV events	↑ CV mortality rate	In RF+ RA women	Goodson [11]
	IHD in RA	↑ prevalence in men	Houri Levi [21]
	CV events in RA	↑ prevalence in men	Castañeda [22]
	MI incidence rate	↑ in men with RA	Zhang [23]
	Heart failure	RF+ RA women ↑	Nicola [16]
	Non-ischemic HF	↑ in men, early RF+ RA	Mantel [25]
		↑ in women with AS	
CVD (SpA)	IHD risk in SpA	↑ tendency in women	Essers [26]
	CVD in PsA		Horreau [27]
Structural heart disease	Pericarditis	Increased, especially in RF + RA middle-aged men	Hara [28]
	Myocarditis		Pappas [29]
	VHD in RA		Guedes [30]
	VHD in AS		Roldan [31]
		RF + RA ≈ in both genders	
		More frequent in men	
		More frequent in men in some series	
Left ventricular dysfunction	Heart failure	RF+ RA women ↑	Nicola [16]
	CHF in RA		Nicola [16]
	HFpEF in RA	More frequent in women	Hopper [32]
	HFrEF in RA		González [33]
	LVDD in AS	More frequent in women	Myasoedova [34]
	LVMD in SpA	More frequent in men	Heslinga [35]
			Chen [36]
		VF probably ↓ in women	
		VF probably ↓ in AS	
Arrhythmias and Conduction system disorders	Association of AF with CRP	Specially in men (general population)	Nyrnes [37]
	QTc prolongation		Panoulas [38]
	Conduction abnormalities		Forsblad [39]
			Gensler [40]
	Arrhythmias in PsA	Female gender, RA	Chiu [41]
		More frequent in men with AS	
		↑ in men, 20–40 yrs.	
	VTE incidence in RA	Similar in both genders	Holmqvist [42]
			Eriksson [43]
Venous thromboembolic disease	VTE prevalence	More frequent in men with AS and RA	

AF atrial fibrillation, *AS* ankylosing spondylitis, *CHF* congestive heart failure, *c-IMT* carotid intima-media thickness, *CRP* C-reactive protein, *CVD* cardiovascular disease, *HF* heart failure, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *IHD* ischemic heart disease, *LVDD* left ventricular diastolic dysfunction, *LVMD* left ventricular myocardial dysfunction, *MI* myocardial infarction, *PsA* psoriatic arthritis, *RF* rheumatoid factor, *SpA* spondyloarthritis, *VF* ventricular function, *VTE* venous thromboembolic disease

A case-control study that included 11,782 patients with RA and 57,973 age- and sex-frequency matched controls showed a higher prevalence of IHD in men [21]. Data from a recent cross-sectional study on Spanish subjects with IJD followed up at rheumatology outpatient clinics confirmed that the prevalence of CVD in IJD is increased when compared with a cohort of individuals without IJD [22]. In this study, the increase in the prevalence of CV events was mainly observed in men with RA [22]. Likewise, MI incidence rates in 44,418 eligible patients with RA were higher in men than in women in a retrospective cohort study on the association of inflammatory markers and serum lipids by Zhang et al. [23]. Table 2 shows the main heart complications and CV manifestations of IJD stratified by sex.

Besides having a higher likelihood of IHD, patients with RA are also at increased risk of developing HF [16, 18]. Retrospective cohort studies assessing the relative risk (RR) of HF in patients with RA have reported risk increases between 40 and 100% [16, 44, 45]. The augmented risk of HF was more pronounced in the subgroup of RA patients with rheumatoid factor (RF) positive than in those who were negative for RF [16]. HF tended to be increased in women compared with men (RR 1.9, 95% CI 1.4–2.5 vs. RR 1.3, 95% CI 0.9–2) [16]. With respect to the increase risk of developing HF in patients with RA [16, 18], women tend to suffer HF with preserved ejection fraction (EF), whereas EF is more frequently reduced in men [32–34] (Table 2).

Mantel et al. have recently demonstrated that HF occurring at the beginning of RA is mainly related to the activity of the disease, whereas the HF that appears throughout the evolution is more associated with IHD [25]. In their study, the stratification by sex did not disclose differences in the relative risk of HF, overall or ischemic HF, but there was an increased risk of non-ischemic HF among men with new-onset RA compared with women [25] (Table 2).

Remarkably, the presentation of cardiac symptoms in RA is often different from that observed in the general population. It is not uncommon to see RA patients with unrecognized coronary symptoms that are misdiagnosed as mechanical or atypical chest pain. Indeed, patients with RA often experience silent myocardial infarction (MI) with no symptoms before sudden cardiac death (SCD) [13]. Furthermore, SCD is almost twice as common in patients with RA as in the general population [13]. However, no difference between genders was found in this subject.

Regarding the most representative spondyloarthritis, AS and PsA, several studies have shown that IHD, CV events, peripheral arterial disease (PAD), and several CV risk factors (CVRF) are more common in patients with AS or PsA than in the general population [46, 47]. A meta-analysis of seven longitudinal studies revealed a significant increase in MI among AS patients when compared with the general population [48]. Data from the British Clinical Practice Research Datalink showed that patients with AS, especially women, had an increased age-adjusted risk of developing IHD. Nevertheless, after adjustment for non-steroidal anti-inflammatory drugs (NSAIDs) consumption, only a non-significant trend towards increased risk was found in women (HR 1.31, 95% CI 0.83–2.08) [26]. A retrospective cohort study using population-based administrative data from 8616 patients with AS reported and age- and sex-standardized prevalence ratio of 1.37 (95% CI 1.31–1.44) for IHD and 1.34 (95% CI 1.26–1.42) for HF, which was similar for individuals of both genders [47].

Estimation of the CV risk attributed to PsA is more difficult to determine due to the potential CV burden that skin disease itself confers to patients with PsA [49, 50]. One of the earliest prospective studies on CV morbidity in PsA showed significantly increased standardized prevalence ratios (SPRs) for MI (2.57, 95% CI 1.73–3.80), angina (1.97, 95% CI 1.24–3.12), and hypertension (1.90, 95% CI 1.59–2.27), whereas the SPR for CHF was not significantly increased. Factors associated with CVD in PsA included diabetes mellitus (DM), dyslipidemia, and high Psoriasis Area and Severity Index (PASI) score [51].

A meta-analysis and systematic literature review on morbidity and mortality in psoriasis and PsA also disclosed an increased risk of MI with odds ratio (OR) of 1.25 (95% CI 1.03–1.52) and 1.57 (95% CI 1.08–2.27) in psoriasis and PsA, respectively, in comparison with the general population [27]. The risk of MI was found to be higher in patients with severe psoriasis and in those with early onset of psoriasis. However, no differences between men and women were observed in this study [27]. In keeping with that, in one prospective study in patients with severe psoriasis, the CV mortality was very similar in men (SMR 1.65, 95% CI 1.09–2.4) to that observed in women (SMR 1.59, 95% CI 1.04–2.33) [52].

Finally, and as observed in RA, the increased risk of CVD in PsA occurs early in the course of the disease, since the onset of this inflammatory rheumatic disease. In this regard, a population-based cohort study that included mostly new diagnosed PsA patients the CVD risk was higher than the expected risk and it was underestimated when the Framingham CV risk scale was applied [53].

Traditional Cardiovascular Risk Factors in IJD

Traditional cardiovascular risk factors (CVRF), such as age, smoking, DM, obesity, exercise, hypertension, and dyslipidemia are independently associated with subclinical atherosclerosis, CV events, and increased risk of CV mortality in chronic IJD [54–56] (Fig. 1). Age is a major determinant for CVD risk. Indeed, the impact of aging on the CV risk in patients with RA may be even greater than that of the general population. A population-based inception cohort of patients with RA without CVD history demonstrated that the effect of age on CVD risk in seropositive RA was almost twice as high as that in the general population in men and even higher in women, with additional log (age) coefficients of 2.91 for women and 2.06 for men [57]. However, the impact of age on CVD risk in seronegative RA subjects and in patients younger than 50 years was similar to that seen in the general population [57].

Smoking is known to be a risk factor for the development of RA, particularly in RF and anti-citrullinated peptide antibodies (ACPA)-positive patients [58]. However, there are no differential data according to sex regarding the effect of smoking in IJDs.

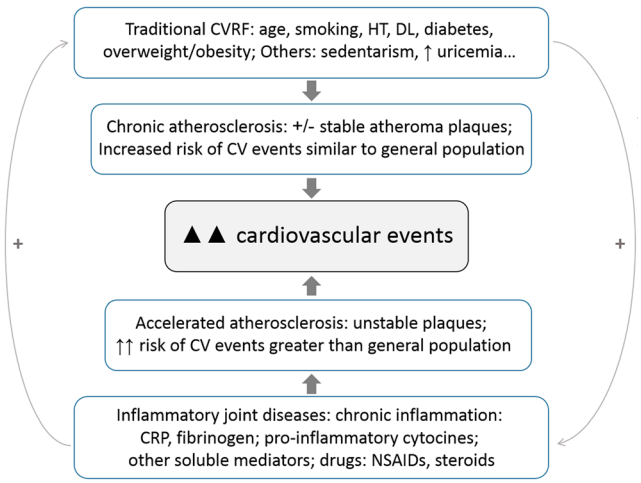

Fig. 1 Interplay between traditional CVRF, atherosclerosis, chronic inflammation, and CV events in inflammatory joint diseases. Footnote: *CV* cardiovascular, *CVRF* traditional cardiovascular risk factors, *CRP* C-reactive protein, *DL* dyslipidemia, *HT* hypertension, *NSAIDs* non-steroidal anti-inflammatory drugs; ↑/↑↑ (▲▲): levels of increase

In a recent meta-analysis of seven case-control studies (total 1230 patients with RA), the prevalence of DM was increased in cases of RA compared to controls (OR 1.74, 95% CI 1.22–2.50) [59]. Abdominal obesity, anti-hypertensive medication, disease activity, and use of glucocorticoids affect the glucose metabolism in RA. In this respect, insulin resistance (IR) and metabolic syndrome (MetS) features are more commonly observed in patients with PsA and RA [60, 61] and the homeostatic model assessment (HOMA)-IR index is also increased in RA subjects [62]. Regarding genders, a study using abdominal CT scans revealed that men with RA had more visceral fat compared to controls. Women with RA had more subcutaneous fat than controls with similar BMI and waist circumference [63].

Hypertension has frequently been found in patients with RA [64]. However, it remains unclear whether it is more common than in the general population. It is frequently underdiagnosed in young people with IJD or undertreated in elderly people with polymedication [64].

Regarding lipids, chronic inflammation causes characteristic alterations in the lipid profile of patients with IJD, with a reduction of serum levels of total and LDL-cholesterol and significantly, in the HDL-cholesterol fraction, increasing the atherogenic index secondarily [65]. Abnormality in the lipid profile can appear early in the course of disease, even 5 years before disease diagnosis, whereas there were no changes in the control group [66].

Lipid abnormalities are very common in PsA with lower serum levels of HDL-cholesterol and higher serum levels of triglycerides [46, 67]. Dyslipidemia is more prominent in PsA patients with active disease, suggesting a link between the degree of inflammation and the lipid profile [67, 68]. Low total cholesterol levels have also been reported in AS [69, 70]. In patients with AS and high CRP levels, HDL-cholesterol particles contain less apolipoprotein A1, the component responsible for the anti-inflammatory effects, and a higher proportion of serum amyloid A [70]. This alteration in the lipid profile is due to the presence of inflammation regardless of sex.

In line with the above, it is unclear whether there are differences between genders in terms of the classic CVRF in IJD. Nevertheless, the body fat distribution is different in healthy men and women. Therefore, we can assume that it also occurs in patients with IJD.

Chronic Inflammation and Subclinical Atherosclerosis

Chronic inflammation is the main non-classic CVRF in patients with IJD. With respect to this, levels of systemic inflammatory biomarkers, including C-reactive protein (CRP), fibrinogen, erythrocyte sedimentation rate (ESR), and diverse pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1, predict the development CVD in RA and they are related with the risk of subclinical atherosclerotic [71], CVD events, and CV mortality in these patients [72–74] (Fig. 1). Indeed, RA is a disease associated with accelerated atherogenesis [73]. This relationship may differ, depending on the degree and the duration of inflammation [75]. Systemic inflammation displays proatherogenic effects by induction of dyslipidemia, IR, hypercoagulation, endothelial dysfunction and oxidative stress, increasing atheromatous plaque vulnerability, and increased extent of coronary artery calcification (CAC) [68] (Fig. 1). Endothelial dysfunction has been linked to systemic inflammation and the development of early atherosclerosis since the first years of disease. Endothelial dysfunction with marked impairment of flow-mediated vasodilatation was also been observed in patients with RA [76], PsA, and AS [77, 78].

Recent studies in RA have also confirmed the influence of genetic factors in the increased risk of subclinical atherosclerosis and CVD in patients with RA [79].

Carotid ultrasound (US) studies have shown increased frequency of subclinical atherosclerosis in patients with RA, even in RA patients without traditional CVRF [80]. They have also unveiled the presence of augmented subclinical atherosclerosis in other IJD such as PsA [81] or AS [82].

An abnormally high frequency of carotid plaques was described in patients with RA included in the category of moderate (intermediate) risk when risk charts used for the stratification of the CV risk in the general population were applied to these patients [83, 84]. It was also the case for patients with AS [85]. Interestingly, in a meta-analysis of literature studies in patients with RA, Ambrosino et al. found an association between subclinical atherosclerosis and male gender, so that men had an increased common carotid intima media wall thickness and a greater number of atheromatous plaques compared to women [24] (Table 2).

In contrast to the general population, the risk of HF in RA depends not only on coronary artery disease (CAD) and traditional CVRF but also on the presence of systemic and/or cardiac inflammation [16]. Results from myocardial biopsies from the Feiring Heart Biopsy Study demonstrated a high occurrence of endothelial dysfunction and inflammation in cardiac microvessels, and inflammation in the cardiomyocytes of patients with CAD [86]. No differences according to gender were observed in this study.

Figure 2 shows an overview of the influence of sex on conventional atherosclerosis and that linked to autoimmunity and chronic inflammation and the pathophysiology of atherosclerotic plaque formation.

Structural Heart Disease in IJD

Pericarditis is the most common heart problem in RA. Postmortem incidence of pericarditis in patients with RA

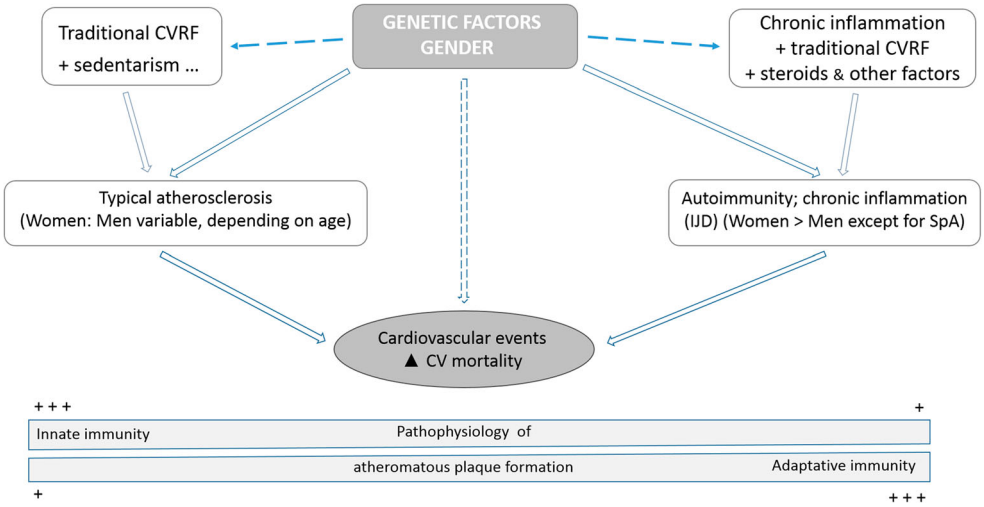

Fig. 2 Relationship between genetics, gender, inflammation, typical atherosclerosis, and autoimmunity in inflammatory joint diseases. Footnote: *CV* cardiovascular, *CVRF* traditional cardiovascular risk factors, *IJD* inflammatory joint diseases, *SpA* spondyloarthritis (in this review mainly ankylosing spondylitis and psoriatic arthritis); ▲: increase

ranges between 11 and 50% [87, 88]. Nevertheless, the actual number of individuals with RA who have pericarditis symptoms and clinical evidence of this complication is much smaller, being less than 5–10% [89, 90]. It typically occurs in RF-positive middle-aged patients with active disease, more frequently men. One-third of them may have rheumatoid nodules and other extra-articular features of RA [28]. The prognosis of rheumatoid pericarditis is generally good. Constrictive pericarditis with tamponade is an exceptional complication, and it constitutes an important diagnostic challenge.

Myocarditis in RA is less frequent than pericarditis, and it is generally associated with other extra-articular manifestations. It is also more frequent in RF-positive patients [29]. Regrettably, differences in the clinical presentation of myocarditis between men and women in RA have not been well established.

Valvular heart disease (VHD) is also a very prevalent complication in patients with IJD [91].

Transesophageal echocardiography studies have disclosed the presence of VHD in more than 20% of patients, with focal valve thickening in more than 40% and mitral regurgitation in up to 80% of patients with RA [12, 30, 92]. In some studies, the occurrence of VHD is associated with male gender and the presence of rheumatoid nodules, age, disease duration, and degree of inflammatory activity [30]. However, the association with sex has not been confirmed in other series [93].

VHD has also been observed in AS, PsA, and in other SpA. More specifically, VHD and conduction system disturbances are common manifestations in patients with AS, particularly in men. These complications usually occur in patients with long disease duration, and they are uncommon at the onset of the disease [31]. Clinically, VHD occurs in less than 20% of patients with AS. It may clinically manifest as a severe aortic or mitral regurgitation [92]. Atrio-ventricular blocks followed by sinus node dysfunction and bundle branch or fascicular blocks occur in around 20% of patients with AS, who are generally asymptomatic [39, 92].

The presence of valvular involvement was studied in 50 PsA patients (27 men/23 women) without clinically evident CV or traditional CVRF. The frequency of VHD in this series of PsA was compared with that found in 50 matched controls [94]. However, no significant differences in the presence of valvular disease between PsA patients (26%) and controls (20%) were found. This was also the case when the mean left end-diastolic and left end-systolic diameters and the mean left ventricular ejection fraction (LVEF) were compared [94]. In this study, it is important to remark that patients were actively treated and that no clinical differences between genders were found [94].

Left Ventricular Dysfunction in IJD

The main causes of left ventricular dysfunction (LVD) in the general population are hypertension, CAD, and aging. In general, hypertension leads to diastolic dysfunction (DD) by inducing interstitial fibrosis of the myocardium, modifying calcium homeostasis, and increasing local deposition of collagen [95, 96].

Left ventricular systolic dysfunction (LVSD) is characterized by a deficiency in the pump function of the left heart, and it is defined by a decrease in the LVEF below 50%, being severe when the ejection fraction (EF) is less than 30%. Unlike the previously mentioned, left ventricular diastolic dysfunction (LVDD) is characterized by an alteration in the filling of the left ventricle with an EF conserved. According to the European Society of Cardiology criteria of 2016, HF is comprised of three groups of patients based on clinical symptoms and signs and echocardiography findings: HF with reduced EF (LVEF <40% and increased NT-proBNP), HF with mid-range EF (LVEF 40–49% and increased NT-proBNP),

and HF with preserved EF (LVEF ≥ 50% and at least one additional criterion: left ventricular hypertrophy and/or left atrial enlargement or diastolic dysfunction) [97, 98].

LVDD was observed in RA patients without classic CVRF or clinical history of CVD [91]. The pathogenesis of LVDD in IJD is multifactorial, but inflammation seems to play a pivotal role [99–101]. LVDD is also quite common in the general population, with a prevalence between 28 and 65% [102, 103]. Furthermore, it is also an independent predictor of mortality and CHF [102–106]. HF with preserved EF accounts for 30–50% of all cases of HF, and its prognosis is almost as unfavorable as that of patients with HF with reduced EF (Table 2).

HF in IJD is more frequent in women and is often associated to concomitant diseases [107, 108]. Recent data from the Medicare & Medicaid Services demonstrated that 55% of patients coded as having HF had ≥5 chronic comorbidities [109]. Data from the ESC indicate that the majority of patients with chronic HF (74%) have at least one comorbidity, generally renal disease, anemia, or diabetes [110]. Accumulated evidence shows that the rate of CHF is higher in women with RA than in men, in contrast to the general population, where the incident CHF rate for women is lower [16, 111]. Moreover, HF in women with RA usually has the EF preserved whereas in men the EF is typically reduced [32] (Table 2).

Most studies reporting an increased prevalence rate of HF in RA (3.9–11.6%) are based on databases from clinically manifested CHF or HF patients requiring hospital admissions [16, 45, 112–114]. Nevertheless, echocardiography and cardiac MRI in patients with RA have detected a prevalence of LVDD ranging from 26 to 66% [91, 115]. These findings suggest that diastolic HF is probably underestimated in previous studies as well as in the daily practice.

A meta-analysis and systematic review disclosed that patients with RA are more likely to have echocardiographic parameters of LVDD, higher LV mass index, higher mean pulmonary artery systolic pressure (PASP), and larger left atrial sizes compared to controls [105]. In a series of long-standing RA without clinically apparent CVD, an estimated PASP≥30 mmHg was more commonly found in patients (53%) than in controls (13%) [91]. However, differences between men and women in most of these studies were not evaluated (Table 2).

Disturbances in ventricular function in SpA have been less commonly studied than in RA. In a recent meta-analysis and systematic literature review, the prevalence of LVDD ranged between 9 and 45% [35]. In contrast, in a cross-sectional study performed in 187 patients with AS, LVDD was infrequent, and only 12% of them had mild LVDD [116]. Nevertheless, in another study performed in 104 patients with axial SpA compared with age- and gender-matched healthy controls, patients with axial SpA demonstrated impaired LVSF, abnormal diastolic function, and accelerated atherosclerosis, as evaluated by advanced 2D speckle tracking strain analysis [36].

Regarding PsA, Shang et al. found that 4% of 94 patients had systolic dysfunction 38% LVDD, and 22% both systolic and DD when evaluated with conventional echocardiography and tissue Doppler imaging even in those patients without established CVD or traditional CVRF. Multivariate regression analysis showed that the age at the time of disease diagnosis greater than 40 years and hypertension, but not genders, were independent predictors of subclinical LV dysfunction [117]. In contrast, in another study carried out by the same authors, an increased frequency of ventricular and arterial stiffness was observed in patients with PsA, especially in women [118] (Table 2).

Arrhythmias and Conduction System Disorders

This is a frequent and often underreported complication in patients with IJD. The risk of conduction system disorders was found to be increased in patients with RA (HR 1.94, 95% CI 1.06–3.55), after multivariable-adjustment for age, sex, smoking status, BMI, and other risk factors [68, 119]. Therefore, an increased incidence of "malignant arrhythmias" may have an influence in augmented mortality observed in these patients.

The underlying mechanisms accounting for the increased risk of arrhythmias in IJDs are complex. Chronic systemic inflammation may promote an increased arrhythmogenicity either indirectly, by accelerating atherosclerosis and the development of structural disorders, or directly through functional non-structural anomalies of electrophysiological origin [120]. Indeed, the inflammatory burden seems to play a major role in arrhythmogenesis described in RA patients through muscle remodeling and functional abnormalities. Several studies indicate that inflammatory mediators may induce significant changes in cardiomyocyte electrophysiology as the result of specific effects exerted at a molecular level. In vitro and animal studies have demonstrated that TNF-α exerts a direct effect on cardiomyocytes by modulating specific ion channels involved in the electrophysiological properties of these cells and inducing re-entrant ventricular arrhythmias secondarily [121, 122]. Unfortunately, there are no data specifically assessing differences according to sex in RA.

A common arrhythmia that deserves special attention in patients with IJD is the atrial fibrillation (AF), which constitutes the most common arrhythmic disorder in aging people, and is associated with an increased risk of stroke [123]. As with other arrhythmias, inflammation plays a key role in the pathogenesis of AF [124]. Since RA and AF are associated with an increased risk of IHD, HF, and stroke, a link between RA and AF appears to be plausible.

In this regard, a Danish longitudinal nationwide register-based study on more than 4 million participants, including about 18,000 subjects affected with RA, revealed that the overall incidence of AF in RA patients was 40% higher than in the general population (adjusted incidence rate ratio (IRR) 1.41, 95% CI 1.31–1.51) [125]. Again, no specific data on sex differences was reported (Table 2).

Several epidemiological studies have confirmed the association between inflammation markers, including TNF-α, IL-6, IL-2, and CRP, and the risk of developing AF [126, 127]. In this way, a recent study found an independent association between CRP and AF risk in men, but not in women in a large general cohort [37] (Table 2).

Other important predictors of AF are related with the P-wave and QT interval in the electrocardiogram (ECG). P-wave dispersion (PWD) is an ECG marker of non-homogeneous propagation of sinus impulses into the atrial myocardium [128]. PWD was observed in RA patients in association with high CRP levels and disease duration [129, 130]. Moreover, corrected QT interval (QTc) prolongation associates also with CRP levels and predicts global mortality in patients with RA [38]. Variables independently associated with QTc prolongation included advanced age, female gender, and CRP [38].

Available data on this issue in AS are limited. Typically, cardiac involvement in AS consists of conduction system abnormalities and/or aortic valve insufficiency. Cardiac conduction abnormalities have been observed in up to one-third of patients with AS. Blocking of the AV conduction may be intermittent at first, but tends to progress later. Conduction abnormalities appear to be related to the presence of HLA-B27 and are much more frequent in men [39, 40]. In a study of 210 patients with AS, conduction disturbances were diagnosed in 10–33% [39]. They were mostly first-degree atrioventricular block and QRS prolongation. Conduction abnormalities were associated with age, male gender, and higher weight, but not with disease activity or with the degree of functional limitation [39]. Dik et al. disclosed associations between the PQ interval and age, disease duration, and BMI, as well as between the QRS duration and male gender, disease duration, and Bath Ankylosing Spondylitis Metrology Index (BASMI) in patients with AS [131].

It is probable that arrhythmias and cardiac conduction system disorders may also occur in patients with PsA in a similar way to that observed in other chronic IJD. However, available data are limited. In a nationwide population-based cohort study including 40,637 patients with psoriasis and 162,548 subjects without psoriasis matched by age, sex, history of CAD, hypertension, and DM, patients with psoriasis were at higher risk of developing arrhythmias, particularly those with PsA, independently of traditional CVRF [41]. Stratified by gender, arrhythmias were more frequent in men between 20 and 39 years. Paroxysmal supraventricular tachycardia was the most common type of arrhythmia in psoriasis patients [41]. Regarding the pathogenesis, inflammation may contribute to cardiomyocyte electrophysiology disorders leading to an increased risk of arrhythmias in these patients [41].

Venous Thromboembolic Disease in IJD

Chronic inflammatory diseases are associated with an increased risk of venous thromboembolic (VTE) disease. Atherothrombosis and VTE share common risk factors and pathophysiological characteristics of inflammation.

Chronic inflammation is associated with prothrombotic factors, endothelial dysfunction, and hypercoagulability status that favor the development of atherothrombosis and VTE in patients with RA and other inflammatory arthritis [132–134]. Recent studies indicate that patients with RA have a 1.5- to 6-fold increased risk of VTE, both pulmonary embolism (PE) and deep venous thrombosis (DVT), compared to non-RA subjects [42, 135–142]. Data files from Taiwan National Health Insurance Research Database that included approximately 30,000 patients with RA with 193,753 follow-up person-years showed that patients with RA have 3.36-fold and 2.07-fold increased risks of developing DVT and PE, respectively when compared with the general population [142]. Interestingly, a prospective population-based cohort study from Sweden disclosed that VTE increased with age, but the prevalence was largely similar regardless of sex and RF status in RA [42] (Table 2).

Information of VTE in SpA is scarce. Data from national and population-based registers have shown increased incidence rates of DVP and PE in AS compared with the general population (IRs per 1000 person-years of 3.3 (95% CI 2.4–4.2) vs. 2.1 (95% CI 1.7–2.4)), although lower than those found in RA (IR 7.7 (95% CI 6.8–8.6)) [43]. Interestingly, CV events in general and VTE disease in particular were more frequent in men than in women both in AS and RA [43] (Table 2).

Comorbidities and Heart Failure in IJD

The presence of other non-CV comorbidities in patients with IJD is very common. More importantly, the coexistence of CV complications with other comorbidities worsens the prognosis and health outcome, increasing the already high mortality risk of patients with RA and other IJDs. In addition, it is likely that patients with several comorbidities have a lower adherence to treatments, which is an additional factor of bad prognosis. These aspects are especially important in patients with RA and HF.

In general, when compared with men, women with HF are often older, smoke less, and have more preserved ejection

fraction (EF) and hypertensive HF than HF of ischemic etiology [32]. In fact, most of the current evidence suggests that overall prognosis and survival of patients with HF may be better in women, regardless of EF and age, with a higher global mortality in men [143–151]. This seems to be the case in the general population and also in patients with RA [32].

Several common comorbidities such as diabetes, anemia, iron deficiency, depression, and thyroid disturbances are more frequent in women than in men. Furthermore, all these comorbidities are more frequent in patients with IJD [152, 153]. However, chronic kidney disease (CKD), another adverse prognostic indicator in HF subjects, does not present a clear gender difference. In contrast, chronic obstructive pulmonary disease, another frequent comorbidity that affects negatively in HF prognosis, has a clear predominance in men [32].

Remarkably, it is interesting to underline that some comorbidities such as diabetes, anemia, iron deficiency, and obesity were more commonly observed in patients with HF with preserved EF (HFpEF) [154, 155], which is the most frequent clinical form of HF seen in women with RA.

Therefore, in the integral management of patients with IJD, it is very important to take into account comorbidities for improving their quality of life and survival of our patients [156–159].

Summary and Conclusions

CVD is common in patients with IJDs. Endothelial dysfunction and subclinical atherosclerosis leading to accelerated atherosclerosis are frequent in patients with these conditions [160]. In this setting, patients with IJD, particularly those with RA, are more frequently exposed to coronary syndrome, heart failure, and cerebrovascular disease.

Currently, there are controversial results on the influence of gender in the risk of CV morbidity and mortality in patients with RA and other IJD. RA is more common in women, whereas AS is more frequent in men. This different prevalence according to gender of the IJD makes difficult to reach strong conclusion on the actual influence of sex on the risk of CVD and heart complications in these chronic inflammatory rheumatic diseases. Further studies addressing this specific issue are still needed.

ACPA, anti-citrullinated peptide antibodies; ACS, acute coronary syndrome; AF, atrial fibrillation; Apo (a), apolipoprotein (a); APR, acute phase reactants; AS, ankylosing spondylitis; A-V, atrio-ventricular; BASMI, Bath Ankylosing Spondylitis Metrology Index; BMI, body mass index; CAC, coronary artery calcification; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; Coxibs, selective inhibitors of cyclooxigenase 2; CRP, C-reactive protein; CV, cardiovascular; CVA, cerebrovascular accidents; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; DD, diastolic dysfunction; DIPs, distal interphalangeal joints; DL, dyslipidemia; DM, diabetes mellitus; DVT, deep venous thrombosis; ECG, electrocardiogram; EF, ejection fraction; ESC, European Society of Cardiology; ESR, erythrocyte sedimentation rate; HDL, high density lipoproteins; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HOMA-IR, homeostatic model assessment of insulin resistance; HR (aHR), hazard ratio (adjusted HR); HT, hypertension; IHD, ischaemic heart disease; IJD, inflammatory joint diseases; IL, interleukin; IR, insulin resistance; IRR, incidence rate ratio; LDL, low density lipoproteins; Lp (a), lipoprotein (a); LV, left ventricular; LVD, left ventricular dysfunction; LVDD, left ventricular diastolic dysfunction; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MetS, metabolic syndrome; MI, myocardial infarction; NSAIDs, non-steroidal anti-inflammatory drugs; NT-proBNP, N-terminal-pro-brain natriuretic peptide; OR, odds ratio; PASI, Psoriasis Area and Severity Index; PASP, pulmonary artery systolic pressure; PE, pulmonary embolism; PIPs, proximal interphalangeal joints; PsA, psoriatic arthritis; PWD, P-wave dispersion; QRS, QRS space in the electrocardiogram; QTc, heart rate-corrected QT interval; QTD, QT interval dispersion; RA, rheumatoid arthritis; RF, rheumatoid factor; RR, relative risk; RRs, rate ratios; SCD, sudden cardiac death; SLE, systemic lupus erythematous; SMR, standardized mortality ratios; SpA, spondyloarthritis; SPR, standardized prevalence ratio; TNF-α, tumor necrosis factor-alpha; US, ultrasonography, echocardiography; VHD, valvular heart disease; VTE, venous thromboembolism

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they do not have conflict of interest in relation with this work.

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