Unmet needs in the management of cardiovascular risk in inflammatory joint diseases

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ABSTRACT

Introduction: Increased cardiovascular (CV) morbidity and mortality is observed in inflammatory joint diseases (IJDs) such as rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. However, the management of CV disease in these conditions is far from being well established.

Areas covered: This review summarizes the main epidemiologic, pathophysiologic, and clinical risk factors of CV disease associated with IJDs. Less common aspects on early diagnosis and risk stratification of the CV disease in these conditions are also discussed. In Europe, the most commonly used risk algorithm in patients with IJDs is the modified SCORE index based on the revised recommendations proposed by the EULAR task force in 2017.

Expert opinion: Early identification of IJD patients at high risk of CV disease is essential. It should include the use of complementary noninvasive imaging techniques. A multidisciplinary approach aimed to improve heart-healthy habits, including strict control of classic CV risk factors is crucial. Adequate management of the underlying IJD is also of main importance since the reduction of disease activity decreases the risk of CV events. Non-steroidal anti-inflammatory drugs may have a lesser harmful effect in IJD than in the general population, due to their anti-inflammatory effects along with other potential beneficial effects.

1. Introduction

The term inflammatory joint diseases (IJD) encompasses a group of chronic inflammatory diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA). IJD mainly affect the joints of the axial or peripheral skeleton and are associated with a wide spectrum of extra-articular manifestations that depend on the type of disease. They also share a set of common comorbidities, predominantly cardiovascular (CV), mood disorders (anxiety and depression), infection, cancer, bone loss, and liver, gastrointestinal and kidney alterations [1–4].

RA is a chronic systemic autoimmune and inflammatory disease which characteristically affects diarthrodial synovial joints leading to joint damage and physical disability [5]. AS is included in the group of spondyloarthritis (SpA) that also comprises forms of atypical AS without radiographic manifestations (non-Rx SpA), reactive arthritis, PsA and other arthropathies associated to inflammatory bowel disease. PsA is characterized by synovial and enthesal inflammation and psoriasis. The clinical presentation of joint disease in PsA is heterogeneous and can vary from peripheral arthritis to asymmetrical oligoarthritis or axial forms similar to AS.

Cardiovascular comorbidity is by far the most significant morbidity in these conditions, due to its frequency and impact on patient’s survival and quality of life. In fact, subclinical CV disease (CVD), CV events (CVE) and mortality are increased in IJD, as a consequence of a common process of endothelial damage and accelerated atherosclerosis [6–9]. The excess of CV morbidity observed in these patients [10,11] is the result of a combined effect of traditional CV risk factors (CVRFs), chronic inflammation and a genetic component that has more extensively been studied in RA [12–14]. Indeed, RA was considered the guide disease for this revision.

In this review we will focus on both well-known aspects of the CV disease in IJD, more specifically RA, AS and PsA, and those features that require further research as well as in the ‘unmet needs’ in this field nowadays.

2. Areas covered

2.1. Epidemiology of cardiovascular disease in IJD

The risk of atherosclerotic CVD in IJD, in particular in RA, AS and PsA is increased compared to the general population [9,11,12]. In a cross-sectional study conducted in Spain, the prevalence of CVD in a cohort of IJD was increased compared to a cohort of non-inflammatory subjects [15]. Mortality due to
CVD in IJD is also increased when compared to the general population [9].

More specifically, the risk of CVD in RA is comparable to that of type 2 diabetes mellitus (DM2), which translates into an increase in premature mortality due to CV events [10–12,16]. A meta-analysis made a few years ago showed that CV mortality in patients with RA was 50% higher than in the general population, with an increase in the coronary disease of 59% and an increase in cerebrovascular events of 52% [11]. Quite similar results were obtained in another study by the same authors: 68% of acute myocardial infarction (MI) and 41% of strokes [10], which were equivalent to those found in a population without RA but 10 to 15 years older.

CV morbidity and mortality are also increased in AS and PsA [9,12]. Several studies have shown an increase in the prevalence of coronary heart disease (CHD), stroke and peripheral arterial disease (PAD) in patients with AS and PsA with respect to the general population [9,12,17]. A meta-analysis confirmed an increase of MI (odds ratio [OR] 1.60; 95% CI: 1.32–1.93) and stroke (OR 1.50; 95% CI: 1.39–1.62) in patients with AS with respect to the general population [18]. PsA also seems to exhibit similar CV risk, although its estimates are more difficult to determine due to the bias related to the cutaneous involvement of the disease. In a cross-sectional study that compared non-fatal CV events in RA and PsA, the prevalence found was very similar in both entities: 10% in PsA vs. 12.4% in RA [19].

Finally, it is important to point out that the clinical manifestations of CVD in patients with IJD, particularly in relation to coronary events, are usually different from the general population. They frequently start with a silent ischemia, often attributed to mechanical pain of the thoracic wall, which frequently causes diagnostic delays of their heart disease and higher mortality [12].

2.2. Subclinical atherosclerosis in IJD

Subclinical CVD in patients with IJD can be detected years before the clinic appears, using different noninvasive methods [20–22]. Nowadays, there are several methods available for evaluating subclinical atherosclerosis in these patients (Table 1).

2.2.1. Assessment of endothelial dysfunction

Endothelial dysfunction and arterial stiffness are recognized as surrogate measurements of CVD [6,7]. Arterial stiffness can enhance CV risk by increasing atherogenesis or adverse hemodynamic effects. Arterial stiffness is most commonly assessed by aortic pulse wave velocity and augmentation index. Indeed, patients with IJD exhibit increased arterial stiffness [22]. Alternative measures of arterial stiffness include aortic distensibility, and the ankle-brachial elasticity index (ABI), measured using high-sensitivity brachial ultrasonography. Since these methods are laborious and not very sensitive, they are not commonly used in the routine clinical practice.

2.2.2. Carotid ultrasound

Ultrasound (US) is possibly the most simple and useful noninvasive surrogate marker of CVD from a practical point of view. Carotid US provides accurate and reproducible measurements of anatomical structures without harmful ionizing radiation. The two most commonly used measurements by US are the carotid artery intima-media wall thickness (cIMT) and the presence of atheroma plaques into the carotids. Both parameters have shown to be good predictors of CV events in patients with RA [23,24]. Several systematic literature search and meta-analysis have confirmed increased cIMT and greater presence of carotid plaques in patients with RA vs. controls [25,26].

Interestingly, US allows reclassifying the CV risk of IJD patients considered as intermediate or moderate CV risk through clinical scores in high or very high risk. In fact, an abnormally high incidence of carotid plaques was found in patients with RA that had been categorized as having moderate risk by application of the Systematic COronary Risk Evaluation (SCORE) scale [27,28]. Similar findings have also been observed in patients with AS and PsA without additional factors of CV risk [29–31]. As observed in RA, patients with AS and PsA also had higher cIMT than matched controls [31–33]. In AS, other abnormal carotid US, findings associated with subclinical atherosclerosis, such as higher frequency of plaques than matched controls [32], have also been reported.

Since carotid US is a simple, cheap and reproducible method, it is the most widely used method in the rheumatologic setting. In practical terms, patients with cIMT ≥ 0.9 mm are included in the category of high/very high CV risk [34,35]. More interestingly, the presence of carotid plaques reclassifies a patient into the category of very high CV risk, regardless of the information derived from applying CV risk charts. Moreover, carotid US is a good method to determine the progression of atherosclerotic disease in patients with IJD. In these patients, the CV risk increases proportionally with the number of plaques and it is greater when plaques are bilateral.

2.2.3. Computed tomography (CT)

CT can be used for evaluating the burden of coronary artery calcification (CAC) or for anatomical visualization of coronary arteries by CT coronary angiography (CTCA), being CAC score a good measure of premature atherosclerosis. Both, the American College of Cardiology (ACC) and the European...
Society of Cardiology (ESC) recommend the use of CAC score to monitor risk assessment when CV risk is unclear using traditional CVD risk algorithms [36,37]. CAC is also a good predictor of CVE in patients with RA and other autoimmune diseases. Indeed, it was found to be more sensitive than classic risk chart algorithms to identify high-CV risk RA patients [28].

### 2.2.4. Positron emission tomography

Positron emission tomography (PET) myocardial perfusion imaging detects uptake of positron-emitting radiotracers in the heart and perfusion of blood into the myocardium. PET has shown to predict CV mortality in patients with coronary artery disease [38], and it could potentially be applied to the CV risk stratification of high-risk patient groups such as those with IJD. Limitations of PET include its price, availability of tracers, use of ionizing radiation and limited assessment of cardiac structures [21].

### 2.2.5. Cardiovascular magnetic resonance

Cardiovascular magnetic resonance (CMR) provides detailed information on the structure and composition of myocardium allowing the detection of a wide variety of myocardial diseases. It is useful for the quantitative evaluation of left and right ventricular volumes, mass and function, cardiac tissue characterization and assessment of thoracic vessels [39]. It can be used for the CV evaluation of patients with IJD and autoimmune diseases [39]. The main limitations of CMR include price, its availability and general intrinsic contraindications to magnetic resonance [21,39]. Chronic myocardial ischemia can be assessed using myocardial perfusion at rest and during pharmacological vasodilator stress [40].

Table 1. Advantages and disadvantages of different noninvasive imaging techniques used in the diagnosis of cardiovascular disease in inflammatory joint diseases.

| Imaging technique                  | Advantages                                      | Disadvantages                                      | Experience in rheumatology |
|-----------------------------------|------------------------------------------------|---------------------------------------------------|----------------------------|
| Arterial stiffness assessment, ABI* | Cheap, innocuous No radiation exposure No contrast needed | Laborious Not very sensitive Inter-observer variability Not sufficiently validated | +                          |
| Carotid ultrasound                | Simple, cheap, rapid, innocuous & reproducible No contrast/venipuncture Large evidence supported No radiation exposure | Possible inter-observer variability Longitudinal studies are scarce | +++                       |
| Computed tomography (CT)          | Rapid Reproducible Evidence based on non-IJD patients | Reasonably expensive Less sensitive than US in IJD Dependent on radiologists Radiation exposure Contraindicated in allergic to contrast and in severe CKD | ++                        |
| Cardiac magnetic resonance        | Assessment of multiple measures of ACVD Reproducible Evaluation of additional heart/CV manifestations No radiation exposure | Expensive Limited evidence nowadays Gd contraindicated if severe CKD Contraindicated in subjects with some metal devices Claustrophobia | ++                        |
| Positron emission tomography      | Reproducible Evaluation of additional myocardium alterations | Expensive Radiation exposure Long scan times Not widely available | +                          |

*Arterial stiffness assessment includes aortic pulse wave velocity and augmentation index. Similar techniques are: aortic distensibility and ABI (ankle-brachial elasticity index).

ACS: acute coronary syndrome; ACVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; CV: cardiovascular; Gd: gadolinium; IJD: inflammatory joint diseases; (++/+++) = semi-quantitative evaluation in rheumatology.

Modified from Fent et al. [ref. 12].

Additionally, chronic inflammation causes an alteration in the lipid profile of patients with IJD. It leads to a reduction of serum total cholesterol (TC), LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C) levels. However, this quantitative reduction is associated with a paradoxical increase risk of atherogenesis since HDL-C loses its anti-atherogenic properties [50]. Furthermore, lipoprotein (a) (Lp(a)) is also an important promoter of atherogenesis. When oxidized, it can provoke an immune response similar to that of oxidized LDL, and increases in Lp(a) levels have been associated with inflammation [51]. Thus, Lp(a) is an independent risk factor for CVD that may be augmented in RA [51].

To determine if the reduction of the inflammatory burden without affecting lipid levels may reduce the risk of CVD, Ridker et al. performed a randomized, double-blind trial of canakinumab, a monoclonal antibody targeting interleukin-6

### 2.3. Inflammation and atherosclerosis

Inflammation plays an important role in the pathogenesis of atherosclerosis and CVD both in inflammatory rheumatic diseases [41–44] and in the general population [45]. In fact, it contributes to all stages of atherosclerosis, from plaque formation to plaque instability and eventual plaque rupture with its important consequences [43]. Abnormality of acute-phase reactants has been found to be associated with subclinical atherosclerosis and greater CV morbi-mortality in patients with RA [46]. Of note, C-reactive protein (CRP) level is an independent predictor of CV risk, particularly of MI, in the general population [47]. Notably, higher IL-6 levels are also associated with increased mortality in patients with acute coronary syndromes (ACS) and with increased risk of MI in healthy men [48,49].
in a large series of patients with previous myocardial infarction who had high-sensitivity C-reactive protein level ≥2 mg/L. Although this biologic agent did not reduce the lipid levels when compared with baseline results, at a median follow-up of 3.7 years, patients treated with canakinumab at a dose of 150 mg subcutaneously every 3 months had a significantly lower rate of recurrent CVE when compared with those receiving placebo [52]. Interestingly, this effect was independent of any lipid-level lowering. These findings highlight the pivotal effect of inflammation in the development of CVD in the general population. The results also suggest that the blockade of inflammatory pathways may reduce the risk of CVD in the general population. It may also more relevant in patients with IJD since these individuals have a chronic inflammation status.

A crucial aspect with major clinical relevance in patients with high inflammatory burden is the increased risk of vulnerability and rupture of atherosclerotic plaques [12,13]. In a postmortem study, 48% of plaques of patients with RA were classified as unstable by histologic criteria compared with 22% in non-RA controls. Additionally, inflammation in the coronary artery wall was more prominent in subjects with RA than controls [53]. In another study evaluating carotid plaque structure by carotid US comparing patients with RA and controls, active RA patients had lower gray-scale plaque values, a typical characteristic of vulnerability and rupture of plaques linked to atherothrombosis [13,54].

Adipokines are cytokines secreted by adipose tissue. In patients with IJD, there is a dysregulated secretion of these molecules due to adipose tissue dysfunction. In fact, it can contribute to the pathogenesis of atherosclerotic disease in this population. In patients with severe RA undergoing anti-TNF-therapy high-grade inflammation negative and independently correlated with circulating adiponectin concentrations whereas low adiponectin levels clustered with metabolic syndrome (MetS) features [55]. Adiponectin levels negatively correlated with triglycerides/HDL-C ratios, TC/HDL-C ratios and high fasting plasma glucose levels, independently of CRP levels and the body mass index (BMI) [55]. Furthermore, a strong association between laboratory markers of inflammation, particularly CRP and resistin levels was found in patients with severe RA undergoing anti-TNF therapy [56]. Also, a positive correlation between BMI and serum level of leptin was found in these patients.

As in RA, inflammation in SpA also plays a pivotal role in all phases of formation and development of atheroma plaques, intensifying the effects of conventional risk factors.

An important role of adipokine production in the inflammation and development of atherosclerosis has been found in SpA, particularly in PsA [57]. As previously discussed, an increase in the prevalence of MetS has been documented in patients with IJD [2], particularly in those with PsA [58,59].

In summary, inflammation has an important contribution to the development of CVD in patients with IJD. Using heart failure (HF) as an example, it has been calculated that classic CVRFs explains up to 80% of the risk of HF in non-RA subjects but only 40% of risk among RA patients, suggesting that mechanisms associated with inflammation are of major importance in these patients [60].

### 2.4. Traditional CV risk factors

Traditional CVRFs, such as smoking, DM, obesity, hypertension (HTN), and dyslipidemia, are independently associated with subclinical atherosclerosis, CVE and increased mortality in patients with IJD [12,61–63]. Smoking is known to be a risk factor for the development of RA, particularly in rheumatoid factor (RF) and anti-CCP positive RA patients. A recent meta-analysis showed an increased prevalence of cigarette smoking in patients with RA (OR 1.56, 95% CI 1.34, 1.80) [64]. Other studies also found a higher prevalence of current and past smokers among patients with RA compared to controls [11].

Although there are contradictory data in the literature, DM appears to be more common in RA patients than in controls. In this regard, insulin resistance (IR) and MetS are increased in patients with PsA and RA [58,59,65]. Interestingly, some anti-rheumatic medications such as some anti-tumor necrosis factor (TNF)-α monoclonal antibodies and anti-interleukin (IL)-6 tocilizumab exert a positive effect on IR in patients with RA and AS [66,67]. Likewise, hydroxychloroquine (HQC), and methotrexate (MTX) may also reduce the risk of DM in RA patients.

Obesity itself contributes to a low-grade inflammation status, as adipose tissue is a major organ producer of pro-inflammatory cytokines. A high BMI is associated with elevated CRP levels and increased risk of CVD in the general population [68]. Abnormal body fat composition in RA and PsA is also associated with higher CRP levels and more severe disease [69]. However, a severe and advanced disease in patients with RA is associated with sustained elevation of acute-phase reactants and weight loss, leading in extreme cases to a state of cachexia which also causes an increased risk CV.

HTN has frequently been found in patients with RA. Whereas some studies highlight HTN as an important risk factor for CVD in RA patients [61,62,70], others found similar prevalence of HTN in RA and in controls [71]. Nevertheless, HTN is frequently underdiagnosed in young people with IJD or undertreated in elderly patients [72]. In AS and PsA, HTN was found in 26% and 29.5% of patients, respectively [15].

The issue of lipids deserves a separate mention as independent CV risk factor in IJD. As already mentioned, and although the levels of total CT, LDL, and HDL-C decrease during active phases of the disease, the CV risk continues increasing [12,73]. Since in patients with active disease the decrease in the HDL-C fraction is more marked, it is advisable to assess the CT/HDLC ratio or ‘atherogenic index’ (AI) instead of CT. In this regard, the most adequate time to evaluate the lipid profile in patients with IJD is when the disease is in remission or with low activity since CT levels increase in the phases of inactivity or under the effects of treatment. Lipid abnormalities are also common in PsA with lower serum levels of HDL-C and higher serum levels of triglycerides [57,74]. Dyslipidemia is more prominent in PsA patients with active disease, suggesting a link between inflammation and the lipid profile [74,75]. Low total CT levels have also been reported in AS [76]. As with HTN, dyslipidemia is underdiagnosed and often undertreated in
patients with IJD, which can worsen the course and prognosis of this comorbidity [77,78].

Finally, it is important to remark that the effect of traditional CVRF on the vascular tree may be more harmful in patients with IJD than in the general population, because classic CV risk factors amplify the harmful effect that chronic inflammation produces on the wall of the arteries [12–14].

2.5. Genetics as a contributor to CV risk in IJD

Genetics, together with inflammation and traditional CVRF, constitutes the third basic component associated with an increased CV risk in patients with IJD (Figure 1). Family history of premature CVE in a first-degree relative – before 55 years in men and before 65 years in women – raises significantly the risk of CVD in inflammatory patients and in the general population [79].

There are a number of genetic studies on CVD in patients with IJD, particularly in patients with RA. Among them, the most interesting data regarding CVD risk are found in the genes of the human leukocyte antigen (HLA) region in patients with RA. HLA is also the main genetic factor implicated in inflammatory immune-mediated pathologies and it is associated with more diseases than any other region of the human genome [80].

Other genetic polymorphisms of genes implicated in different inflammatory and metabolic pathways, located inside and outside the HLA region, appear to increase the augmented risk of CVD in patients with RA [81–85].

2.6. Anxiety, depression, renal failure, and other emergent CV risk factors (Table 2)

Anxiety and depression are well-known factors associated with CV risk, although sparsely weighted in the current guidelines and CV risk scales. Recent meta-analyses proved that both depression and anxiety are independently associated with incident CVE rates [86,87]. Anxiety can increase CVD risk through decreased adherence to healthy behaviors as well as physiological mechanisms including autonomic dysfunction, inflammation, endothelial dysfunction and increased platelet aggregation [88]. The prevalence of depression and anxiety is increased in RA patients from high income countries [89,90]. They also predict long-term physical health outcomes and treatment response in RA [91]. In this line, the presence of negative feelings (anger, hostility, type D personality, etc.), especially when persistent, are associated with an increase in CVD and mortality [92]. On the other hand, low socioeconomic class individuals, lack of social support, stress at work and/or family life have a negative influence on patients with known CVD [93] (Table 2).

The link between periodontal disease and CVD in the general population is also well recognized. Although the cause–effect relationship is not well understood, there is a suspicion that periodontal bacteria may play a pathogenic role in CVD [94]. Chronic kidney disease (CKD) was associated with myocardial infarction and fatal coronary heart disease in black, but not in white Americans [95]. Even mildly reduced estimated glomerular filtration rate increases the risk of incident atherosclerotic CVD [96]. Moreover, RA enhances the incidence of CKD. In a cohort study of African RA patients, the estimated glomerular filtration rate (CKD-EPI eGFR) was lower than 90 ml/min/1.73m² in 49.1% of blacks and 30.6% of white participants, respectively [97]. Using receiver operator characteristic (ROC) curve analysis, the CKD-EPI eGFR predicted the presence of carotid artery plaque among black RA patients [97]. In fact, a CKD-EPI eGFR lower than 82 ml/min/1.73m² was associated with a 2.22-fold increased prevalence of carotid plaque in black African RA patients [97]. In consequence, in patients with IJD, periodic monitoring of microalbuminuria and proteinuria are recommended because they may help to quantify the organ damage degree secondary to vascular injury.

Figure 1. Overview showing the relationship between genetics, traditional cardiovascular risk factors, chronic inflammation, inactivity, and emergent cardiovascular risk factors in the pathogenesis of the cardiovascular disease in inflammatory joint diseases.

Footnotes: CV: cardiovascular; CVRFs: cardiovascular risk factors; NSAIDs: nonsteroidal anti-inflammatory drugs. Continuous lines indicate consistent or evidenced relationship; dashed lines indicate less recognized or consistent relationship. Modified from Castañeda et al. [Best Practice 2016; ref. 12].
Low levels of vitamin D have been found in several cohorts of patients with different IJD [98,99]. Several studies have demonstrated the beneficial effect of vitamin D in the control of HTN and CV risk and low levels of vitamin D have been associated with greater CV morbidity [100].

2.7. Effect of anti-rheumatic medication on CV disease risk

The use of non-steroidal anti-inflammatory drugs (NSAIDs), including coxibs, has been associated with an increased risk of CV mortality [101]. Nevertheless, a longitudinal cohort study of 17,320 patients with RA followed-up for 5-years average showed a modest increase of CV risk, smaller than that observed in the general population [102]. Whereas NSAIDs exposure was associated with a 22% risk increase in patients with RA, the risk following NSAIDs exposure was around 50% in non-RA patients [102]. A possible explanation for this finding might be related to the beneficial effect that NSAIDs confer on the mobility, which would counteract its direct harmful effect on the CV system. However, it seems prudent to minimize their use, especially in patients with a high CV risk and HTN associated.

We must take special attention to the combined use of NSAIDs and aspirin due to the increased risk of gastrointestinal complications. Besides, some NSAIDs appear to attenuate the antiplatelet effects of aspirin. However, coxibs do not seem to interact with the anti-platelet effects of aspirin. Thus, when a combination of NSAIDs and aspirin is necessary, celecoxib – a coxib with a relatively low CV toxicity – might be a reasonable alternative.

Glucocorticoids (GC) exhibit a complex effect on the vascular system. While short-term at low doses, GC do not appear to be harmful and even may be beneficial for the vasculature due to the reduction in inflammation and the improvement in patient mobility; high doses of GC, especially when maintained for long term, can promote atherosclerosis and increase CV risk.

In a study of 50,238 person-years in 8,384 RA patients, including 298 cases with MI, current use of GCs was associated with a 68% increased risk of MI in multivariable model. Current daily dose, cumulative duration and total cumulative dose of GC were all associated with a significant increased risk of MI [103]. By contrast, GC use was not associated with an increased risk of CVE in another study [104].

There is a general agreement on the fact that both synthetic DMARDS and biologic therapies aimed to reduce and control disease activity can attenuate atherosclerosis by reducing the systemic inflammatory burden. In fact, available data indicate that anti-TNF, MTX, and HCQ may reduce the CV risk [105,106]. The potential beneficial effect on CVD of other biological therapies is less known. Nonetheless, adequate control of disease activity would reduce the need for using NSAIDs and GC, which would eventually help reduce the incidence of new CVE in these patients.

2.8. Stratification of CV risk in patients with inflammatory joint diseases

In order to identify subjects at risk of developing CVE, it is critical to carry out an adequate stratification of the CV risk of patients with JD. This was classically performed by using scales or risk chart algorithms [21,79,107]. Currently, there are several scales available that are extrapolated from those designed for the general population. The best known are the SCORE, the Framingham, the Reynolds Index, and the QRISK2. In Europe, the most widely used and supported by the ESC is the SCORE, which calculates the risk of fatal coronary events at 10 years and stratifies the risk as low (<1%), moderate (≥1% and <5%), high (≥5% and <10%) and very high (≥10%) (Table 3). In addition, SCORE classifies patients as they come from countries with high or low CV risk. The QRISK2 is the scale most commonly used in the United Kingdom, while the Framingham Index (Framingham Risk Score or FRS) is the algorithm most commonly used in the USA and Canada. Unlike SCORE, it assesses the risk of fatal and non-fatal coronary events also at 10 years and classifies patients as having low (risk <10%), intermediate (≥10% and <20%) and high (≥20%) risk (Table 3).

Several pieces of evidence indicate that these algorithms underestimate (Framingham, Reynolds, and SCORE) or overestimate (QRISK2) the actual CV risk in patients with RA [21,107]. For this reason, a new scale, the expanded risk score for RA (ERS-RA), has been developed using data from the CORONA register [108]. This scale incorporates specific risk factors for RA. However, the ERS-RA has also a trend to reclassify patients below the actual CV risk value [21]. The application of these scales to other JD is not validated yet, so their usefulness in other diseases cannot be estimated.

The EULAR task force proposed a modified SCORE system as a mean of improving CV risk stratification [109]. It is obtained by using a multiplication factor of 1.5 applied to the calculated SCORE risk in patients with RA. The updated 2015/2016 EULAR recommendations indicate that this 1.5 multiplier factor must be applied to all patients with RA (other indexes such as QRISK2 multiply by 1.4) irrespective of other risk factors, and even then, we may fall short of the actual CV risk estimation of our patients with JD [110]. However, this CVD risk calculator has not been prospectively evaluated in patients with RA so that its validity has not yet proven [111].

For this reason, other recommendations such as the Dutch multidisciplinary guidelines for the management of CV risk
advise to increase systematically the age of the patient with RA by 10–15 years to calculate their CV risk more accurately [112]. Although the same could apply to AS and PsA, we do not have sufficient evidence today to extend the same correction factor to these two pathologies.

The use of noninvasive imaging techniques such as carotid US enables us to classify and stratify more accurately the CV risk of patients with IJD. This is especially true for intermediate risk patients. Thus, an increased cIMT>0.90 mm or the presence of unilateral or bilateral carotid atheroma plaques detected by US allowed reclassifying at high or very high risk up to 63% of patients with RA previously classified as moderate risk by indexes [27]. Recently, the same has been demonstrated in patients with AS [29]. In keeping with that, in a series of 226 patients with PsA, Eder et al. observed that 56.1% of the patients in the FRS-based low to intermediate risk groups had carotid plaques. Interestingly, 55.9% of the patients from the FRS-based intermediate risk category were reclassified into an US-based high-risk category, while 47.1% of the patients in the FRS-based low-risk category were reclassified into a higher US-based risk group [113].

Another scale of great clinical interest is the one proposed by the ACC/AHA for lipid-lowering treatment (LLT), in which three main risk categories are considered: low risk (<5%), intermediate risk (≥5 and <7.5%) and high risk (≥7.5% and/or age between 40 and 75 years plus DM and/or LDL-C > 4.9 mmol/L and/or established CVD) [114]. According to these guidelines, treatment is recommended for all high-risk patients, but not advised for low-risk patients, and it should be considered individually for intermediate-risk patients [79,114].

All the data mentioned have a direct impact on the treatment of patients with IJD. Strictly applying CV management recommendations will prevent CVE more appropriately and reduce mortality in these patients (Table 3).

2.9. Prevention and treatment of cardiovascular disease in IJD

Based on the aforementioned risk scales, particularly on the SCORE, the European League Against Rheumatism (EULAR) updated in 2016 the recommendations for CV risk management in patients with IJD. Although these recommendations are initially focused on RA, due to the increasing scientific evidence available, they can also be applied to other IJD [111].

Furthermore, the EULAR task force emphasizes the relevant role of the rheumatologists in this strategy. Indeed, rheumatologists should coordinate the overall treatment strategy of CV morbidity promoting healthy lifestyle habits, such as a cardioprotective diet, sodium restriction, regular physical exercise, adequate sun exposure, weight control, avoiding overweight and insisting on toxic habits cessation, especially smoking [111,115–118].

Interestingly, due to the negative effect of vitamin D deficiency on the CV system, an optimal intake of vitamin D and omega-3 acids (primarily from the diet) should be guaranteed. Besides other beneficial effects, omega-3 acids are likely to reduce CV risk and RA symptoms due to multiple functions, including an anti-inflammatory and NSAIDs sparing effect [119,120]. Moderate physical activity is advisable, preferably aerobic, at least 2.5–5 hours per week, ideally performing at least 30 min daily. Since many patients will have functional sequelae due to their underlying disease, special exercise programs directed by physiotherapists are suggested.

It is also important to keep in mind that intensive dental hygiene appears to reduce the CV risk in general population [121,122]. However, the effects of dental hygiene on CV morbidity in IJDs deserve further studies.

It is important to limit the use of potentially cardiotoxic medication, such as NSAIDs and GC [111,115]. Although NSAIDs may have a lesser harmful effect in IJD than in the general population, due to their potential anti-inflammatory effects along with other potential beneficial effects in these patients such as the improvement of mobility, they should be used at the lowest dose and for the shortest possible time [111,123,124]. Regarding GC, they should also be used with caution, at the lowest dose and for the shortest possible period of time, due to its harmful effect on the vascular system, especially at high and maintained doses [111,123]. Other medications such as leflunomide and cyclosporine A should be used with caution, especially in HTN patients with IJD [125].

Control of disease activity is a key objective as it has been associated with a reduction of CV mortality in patients with IJD. RA patients in remission have lower levels of inflammation

| Table 3. Cardiovascular disease risk categories and recommended lipid-lowering preventive treatment. |
| --- |
| **Lipid-lowering intervention (medication)** | **ACC/AHA** | **SCORE[^]** | **Framingham Risk Score (FRS)** |
| Treatment NO recommended | Risk < 5% | <1% and LDL-C < 130 mg/dL (3.4 mmol/L) ≥ 1% and LDL-C < 70 mg/dL (3 mmol/L) | Risk < 10% |
| Treatment considered | Risk 5 to 7.5% | High risk ≥ 5% to <10% and LDL-C ≥ 100 mg/dL (2.6 mmol/L) | Risk ≥ 10% to < 20% |
| Treatment recommended | Risk ≥ 7.5% and/or age 40–75 yrs + DM and/or LDL-C > 190 mg/dL (4.9 mmol/L) and/or diagnosed CVD | Risk ≥ 10% and LDL-C > 70 mg/dL (1.8 mmol/L) and/or diagnosed CVD | Risk ≥ 20% |

[^]: SCORE classifies patients differently as they come from countries with very-high, high, moderate or low CV risk. In IJD, in particular in patients with RA, modified SCORE is normally used, which is obtained by multiplying the result obtained by a correction factor of 1.5.

Overall, the THERAPEUTIC GOALS to start/continue a lowering lipid treatment in IJD patients by SCORE scale assessment are the following: Low risk: LDL always <130 mg/dL (3.4 mmol/L); Moderate risk: LDL <115 mg/dL (3 mmol/L); High risk: LDL <100 mg/dL (2.6 mmol/L); Very-High risk: LDL <70 mg/dL (1.8 mmol/L) or reduction LDL-C levels ≥ 50% vs. levels before therapy.

Modified from Semb et al. [ref. 79].
b biomarkers, lower blood pressure (BP) and better arterial compliance [126]. Among DMARDs, MTX use has been associated with reductions in CVD in several studies [127]. This evidence was stronger for the overall reduction in CV morbidity and mortality but weaker for stroke reduction [127].

TNF-α inhibitors may protect against CV events in patients with RA, as shown in a meta-analysis of 16 cohort studies, in which the risk reductions associated with TNF-α blockers use were 31% for any CV, 19% for MI and 15% for stroke [106]. The CORRONA registry, including 10,156 RA patients followed-up for a mean of 22.9 months, supported this beneficial role as the risk of CV (MI, stroke, and death) in the subgroup on TNF-α antagonists was lower than in the subgroup receiving MTX or other DMARDs [128]. Significant risk reductions were also found for nonfatal MI or stroke [128].

Regarding HTN, there are no specific recommendations different from those used in the general population. Currently, and according to the recommendations by the ESC, it is advisable to maintain systolic BP (SBP) figures <140 mm Hg and diastolic BP (DBP) <90 mm Hg, as in the general population [92,129]. According to the 2017 American HTN Guidelines [130], the use of antihypertensive agents for primary intervention is recommended in patients with SBP ≥130 mmHg or DBP ≥80 mmHg who have increased overall atherosclerotic CVD risk, whereas the cut points are SBP>140 mmHg or DBP>90 mmHg in patients without increased CV risk [130]. Therefore, tight control of BP is recommended in patients with IJD. In fact, BP values <130/80 mmHg should be desirable in these patients.

With respect to dyslipidemia, diet modification is the first step for its management. When this measure is unsatisfactory, lipid-lowering agents should be added. Among them, statins represent the first line of therapy [116,131]. Overall, statins induce a major decrease in CVE risk. According to a meta-analysis of 26 randomized controlled trials on statins, a reduction of 40 mg/dl in LDL-C levels is associated with a 20% decrease in CVE and a 10% decrease in mortality [132]. In secondary prevention, the LDL-C reduction with statins and MI recurrence rate were not different between patients with or without IJD [133].

According to the guidelines of the ESC, different risk categories and a series of target levels have been established [92]. In subjects with moderate CV risk (SCORE level ≥1 to <5%), they recommend achieving LDL-C < 115 mg/dL (3 mmol/L). In those at high CV risk (SCORE level ≥5 to <10%), an LDL-C goal <100 mg/dL (2.6 mmol/L) is recommended. Finally, in patients at very high CV risk (SCORE ≥10%), the recommended LDL target is <70 mg/dL (1.8 mmol/L) or a ≥50% reduction in LDL-C levels versus baseline levels when the therapeutic goal cannot be reached [92].

Nevertheless, these criteria have been much more stringent in the last ESC/EAS guidelines for the management of dyslipidemias of 2019 published online at the end of August this year [134]. These guidelines established the following therapeutic objectives: 1) An LDL-C reduction ≥ 50% from baseline and an LDL-C goal <1.4 mmol/L (<55 mg/dL) from baseline for secondary prevention and for primary prevention in patients at very high risk. 2) An LDL-C goal <1.0 mmol/L (<40 mg/dL) for patients with atherosclerotic CVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy. 3) An LDL-C reduction ≥ 50% from baseline and an LDL-C goal <1.8 mmol/L (<70 mg/dL) in patients at high risk. 4) An LDL-C goal <2.6 mmol/L (<100 mg/dL) in individuals at moderate risk, and an LDL-C goal < 3.0 mmol/L (<116 mg/dL) in individuals at low CV risk [134,135].

Despite their proved efficacy and remarkable safety, statins are not always sufficient to reach recommended LDL-C targets in individual patients. Based on findings in the general population, we recommend using ezetimibe in IJD patients when the LDL-C target is not reached despite maximally tolerated statin doses. Furthermore, in intolerant or refractory patients with high/very high CV risk, a proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitor should be added, although the experience with PCSK9 inhibitors in IJDs is still limited. This should be viewed in light of recently reported investigations including the ODYSSEY Outcomes trial [136].

IJD patients with moderate CV risk according to risk chart algorithms that are reclassified as having very high CV risk by a noninvasive technique (e.g., presence of plaques in the carotid US), LDL-C target could be similar to that for individuals with very high CV risk or SCORE ≥10% [137]. Regarding HDL-C, there is not enough scientific evidence for any figure to be considered as a therapeutic goal, although HDL-C < 40 mg/dL (<1.0 mmol/L) in men and <45mg/dL (<1.2 mmol/L) in women indicates high CV risk [92].

Due to the reduction of TC and cholesterol fraction levels detected during the phases of activity in patients with IJD, it is generally advised to measure lipid levels when the patient is in a stable/inactive phase. Likewise, according to the latest EULAR recommendations [111], it is advisable to evaluate CV risk in patients with IJD at least once every 5 years in low-risk patients (in the previous guideline, the control was advised to be done annually). In those with intermediate or high risk, it is advisable to do it more frequently, even on an annual basis, especially if there is evidence of progression of underlying disease or important changes in the treatment.

The recommendations for the use of low dose aspirin in IJD patients must follow those proposed for the general population. In this way, low dose aspirin has only been recommended in patients with established CVD [92,131].

Regarding vaccination, influenza epidemics are associated with an increased rate of CVE, and influenza vaccination in the general population appears to be a cost-effective CV prevention modality. This effect is probably greatest in high risk groups [138]. The European guidelines on CVD prevention in clinical practice recommended influenza vaccination in secondary CV prevention [139]. Similarly, the CV risk may also be reduced by pneumococcal vaccination [140]. Because IJD patients are at increased risk of infections due to immune dysregulation and immunosuppressive treatment, appropriate vaccination should be addressed, especially in high CV risk patients.

As it has been exposed in this section, most studies and recommendations discussed in this section are focused on RA. Although they cannot be generalized to other IJDs, it seems to be reasonable to think that some of them may be extrapolated to AS and PsA until we have specific data on every one of these entities.
2.10. Conclusions

Cardiovascular disease is a frequent cause of morbidity and mortality in IJDs. The increase of this comorbidity is determined by classic CV risk factors linked to the underlying disease and the persistence of inflammation in a host with a specific genetic component. The development of CVE can occur early in the course of disease or after years of subclinical disease. Since CVD is associated with high mortality, it is important to stratify the CV risk adequately to identify individuals at high risk of CVE before symptoms appear. More importantly, current recommendations for primary and secondary prevention of CVE should be strictly followed to prevent the occurrence of new events and reduce CV mortality.

3. Expert opinion

Cardiovascular disease is a common cause of morbidity and mortality in IJDs. The increase of this comorbidity is determined by traditional CVRF, genetic factors, and other factors dependent on the specific underlying disease. It should be noted that some of the traditional risk factors, such as HTN, dyslipidemia or diabetes can remain unnoticed for many years in these patients. There are also other less known emergent CVRF that are more difficult to evaluate. Clinical manifestations in these patients are often atypical and can be misdiagnosed, in the case of ACS, with musculoskeletal pain which often causes delayed diagnosis which may aggravate the prognosis and increase the mortality. Currently, some imaging techniques enable us to visualize the lesions anatomically and to establish a CV risk assessment early in the course of disease. Among them, carotid-US (cUS) is the simplest, cheapest, most reliable and reproducible available method at this moment. US has a high sensitivity and specificity, which may aggravate the prognosis and increase the mortality.

There are several scales to assess the CV risk for a specific patient. In Europe, the most commonly used risk algorithm is the modified SCORE according to the recommendations proposed by the EULAR task force [111], which enables us to classify patients as low, moderate, high or very high risk and apply different preventive measures according to the specific risk obtained. However, the calculation of risk through the application of these scales in some patients is far from reality, needing the help of complementary imaging techniques. In this way, it is possible to reclassify and stratify patients more appropriately. Thus, intermediate/moderate CV risk patients with increased cIMT or presence of carotid plaques on US should be considered as having high/very high risk and should be treated consequently. With respect to this, by using carotid US it has been possible to reclassify more than 50% of patients of intermediate or moderate risk as high or very high-risk patients [27].

Treatment of high CV risk patients must be multidisciplinary. However, we are aware of the lower adherence to cardioprotective therapy of these patients [72,77,78]. For this reason, it is important to remark that both physicians and patients should be concerned about the increased risk of CVE, sometimes fatal, in these population. An additional measure to be performed in the follow-up of these subjects is the periodical assessment of renal damage by quantifying microalbuminuria and proteinuria as the result of atherosclerotic organ damage.

Here, it is important to reinforce positively basic recommendations changing the patient’s lifestyle if necessary, advising healthy cardioprotective measures and frequent aerobic exercise adapted to every individual, avoiding toxic habits such as tobacco and alcohol. We must stimulate the patient to observe all the general recommendations and pharmacological measures established in the clinical guidelines with the final goal to reach the more suitable therapeutic objective individualized to every patient.

Table 4. Unmet needs in cardiovascular risk evaluation in inflammatory joint diseases.

| Main unmet needs in CV risk assessment |
|--------------------------------------|
| **1) Epidemiology of CVD in IJDs** |
| Evaluation of the incidence of CVD & CVE in early RA, as well as in early AS and PsA |
| Study of the prevalence of HF and PAD in patients with IJD, especially in AS and PsA |
| **2) Subclinical atherosclerosis** |
| Evaluation of the best method for early detection of subclinical atherosclerosis in IJDs |
| **3) Genetics** |
| Expand the knowledge of CVD genetics in patients with IJD, especially AS and PsA |
| **4) CV risk factors** |
| Potentiate campaigns for early detection of traditional CVRFs |
| Assess the real impact of mood disorders in CV risk scales in IJD patients |
| Study the possible relationship between periodontal disease and CVD in IJDs |
| **5) Anti-rheumatic medication and CVD** |
| Design longitudinal studies to identify the incidence of long-term CVE in patients with IJDs under biologics or small molecules and T2T control strategy |
| Evaluate CV safety in clinical trials testing new biologics and advanced therapies |
| **6) Stratification of CV risk in IJD patients** |
| Long-term validation of CV risk algorithms in RA patients |
| Establish specific CV risk scores for AS and PsA |
| **7) Imaging** |
| Design longitudinal studies to confirm the evolution of atheroma plaques and their impact on the reclassification of patients with IJDs |
| **8) Prevention and therapy of CVD** |
| Improve the adherence to CV therapy of patients with IJD and CVRFs |
| Potentiate the relationship with GPs to improve the attention to these patients |
| Reinforce the interaction between different disciplines to improve monitoring and follow-up of these patients |

AS: ankylosing spondylitis; CV: cardiovascular; CVD: cardiovascular disease; CVE: cardiovascular event; CVRF: cardiovascular risk factors; GP: general practitioners; HF: heart failure; IJD: inflammatory joint diseases; PAD: peripheral arterial disease; PsA: psoriatic arthritis; RA: rheumatoid arthritis; T2T: treat to target strategy.
Unfortunately, there are still many unmet needs in this field, as it is reflected in Table 4, but it is essential to take into account that early diagnosis and management of the subclinical atherosclerotic disease must be a key part in the context of the routine clinical practice in coming years incorporating to the management imaging techniques. Therefore, an overall CV risk assessment must be the ultimate goal to reduce the risk of CVD in patients with IJD.

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