Joint Bone Spine 90 (2023) 105592

Contents lists available at ScienceDirect

Joint Bone Spine

journal homepage: www.elsevier.com

Recommendations and metaanalyses

Recommendations for assessing the risk of cardiovascular disease and venous thromboembolism before the initiation of targeted therapies for chronic inflammatory rheumatic diseases

Jérôme Avouac[a,*], Olivier Fogel[a,1], Sophie Hecquet[a,1], Claire Daien[b], Ismail Elalamy[c], Fabien Picard[d], Clément Prati[e], Jean Hugues Salmon[f], Marie-Elise Truchetet[g], Jérémie Sellam[h], Anna Molto[a], on behalf of the French Society of Rheumatology

[a] *Service de Rhumatologie, Hôpital Cochin, Centre – Université Paris Cité, Assistance publique–Hôpitaux de Paris (AP–HP), 75014 Paris, France*
[b] *Inserm U1046, CNRS UMR 9214, Montpellier University, CHU de Montpellier, Montpellier, France*
[c] *Department Hematology and Thrombosis Center, Medicine, Sorbonne University, Paris, France*
[d] *Service de Cardiologie, Hôpital Cochin, Centre – Université Paris Cité, AP–HP, 75014 Paris, France*
[e] *Service de Rhumatologie, Université de Franche-Comté, CHU de Besançon, boulevard Fleming, 25030 Besançon, France*
[f] *Department of Rheumatology, Reims University Hospital, University of Reims Champagne-Ardenne (URCA), 51100 Reims, France*
[g] *CNRS, UMR5164 ImmunoConcept, Department of Rheumatology, Bordeaux University Hospital, Bordeaux University, Raba Leon, place Amélie, 33076 Bordeaux cedex, France*
[h] *Paris Inserm UMRS 938, Department of Rheumatology, Centre de Recherche Saint-Antoine, Saint-Antoine Hospital, Sorbonne Université, AP–HP, Paris, France*

INFO ARTICLE

Historique de l'article :
Accepté le 27 avril 2023
Disponible sur Internet le 16 May 2023

Keywords :
Targeted therapies
JAK inhibitors
Chronic inflammatory rheumatic diseases
Cardiovascular disease
Venous thromboembolism
Recommendations

ABSTRACT

Background. – Patients with rheumatoid arthritis (RA) and other chronic inflammatory rheumatic disorders have increased risk of cardiovascular disease (CVD) and venous thromboembolism (VTE) compared with the general population. Moreover, recent data have raised concerns around a possible increased risk of major CV events (MACE) and VTE in patients treated with JAK inhibitors (JAKi). In October 2022, the PRAC has recommended measures to minimize the risk of serious side effects, including CV conditions and VTE, associated with all approved in chronic inflammatory diseases.
Objective. – To provide an adequate and feasible strategy to evaluate, at the individual level, the risk of CVD and VTE in patients with chronic inflammatory rheumatic diseases.
Methods. – A multidisciplinary steering committee comprised 11 members including rheumatologists, a cardiologist, a hematologist expert in thrombophilia and fellows. Systematic literature searches were performed and evidence was categorized according to standard guidelines. The evidence was discussed and summarized by the experts in the course of a consensus finding and voting process.
Results. – Three overarching principles were defined. First, there is a higher risk of MACE and VTE in patients with chronic inflammatory rheumatic diseases compared with the general population. Second, the rheumatologist has a central role in the evaluation of the risk of CVD and VTE in patient with chronic inflammatory rheumatic diseases. Third, the risk of MACE and VTE should be regularly assessed in patients with chronic inflammatory rheumatic diseases, particularly before initiating targeted therapies. Eleven recommendations were defined to prevent potentially life-threatening complications of CVD and VTE in patients with chronic inflammatory rheumatic diseases, providing practical assessment of CVD and VTE before considering the prescription of targeted therapies, and especially JAKi.
Conclusion. – These practical recommendations based on expert opinion and scientific evidence provide consensus for the prevention and the assessment of CVD and VTE.

* Corresponding author. Service de Rhumatologie, Hôpital Cochin, Université Paris Descartes, 27, rue du Faubourg Saint-Jacques, 75014 Paris, France.
Adresse e-mail : jerome.avouac@aphp.fr (J. Avouac).
[1] These authors have equally contributed.

https://doi.org/10.1016/j.jbspin.2023.105592

1. Introduction

Cardiovascular disease (CVD) and venous thromboembolism (VTE) risk in patients with rheumatoid arthritis (RA) and other chronic inflammatory rheumatic diseases, in particular axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA), is substantially elevated compared with the general population. For RA, the magnitude of the excess risk of CVD is comparable to that reported in patients with diabetes mellitus [1], and there is a 2-fold increase risk of VTE in RA compared to the general population [2]. Thus, a proactive and targeted CVD and VTE risk management is mandatory. The EULAR task force was convened to critically appraise existing evidence on CVD risk in patients with chronic inflammatory rheumatic diseases in 2009, leading to the formulation of 10 recommendations, which were updated in 2015/2016 [3]. However, these recommendations did not consider the risk of VTE and were elaborated prior to the launch of Janus Kinase inhibitors (JAKi), which have been added to the therapeutic arsenal for chronic inflammatory rheumatic disorders in 2017 in France. Currently, 4 JAKi are available in France in chronic inflammatory rheumatic diseases (tofacitinib, baricitinib, upadacitinib and filgotinib).

The ORAL Surveillance study has raised concerns about a possible increased risk of major cardiovascular events (MACE) and VTE in tofacitinib-treated patients in a specific population of RA patients with age > 50 years and at least one additional CV risk factor [4]. Moreover, early real-life data have also suggested a higher venous and arterial thromboembolic risk with baricitinib [5,6]. These data conducted to successive alerts from the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) between 2019 and 2022.

In 2019, the EMA's pharmacovigilance risk assessment committee (PRAC) has concluded that tofacitinib could increase the risk of VTE in patients who are already at high risk. As a result, the agency recommended that tofacitinib should be used with caution in all patients at high risk of VTE [7]. In 2021, the FDA released a document and warning on CVD and VTE risks of tofacitinib in comparison with TNF-inhibitors, based on the analyses of ORAL Surveillance [8]. The full data were then published in early 2022 [4].

In October 2022, the PRAC has recommended measures to minimize the risk of serious side effects associated with JAKi used to treat several chronic inflammatory disorders. These side effects include CV conditions, blood clots, cancer and serious infections. The committee recommended that these medications should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past and those at increased risk of cancer. The committee also recommended using JAKi with caution in patients with risk factors for VTE. The PRAC has also concluded that these safety findings apply to all approved uses of JAKi in chronic inflammatory diseases, including RA, axSpA and PsA. However, it is important to note that the PRAC has not modified the indications, the recommended dosages or the line of treatment of JAKi.

The PRAC conclusions urgently require an adequate and feasible strategy to evaluate, at the individual level, the risk of CVD and VTE in patients with chronic inflammatory rheumatic diseases before considering the use of JAKi. To this end, the aim of this Evidence-Based Guideline is to summarize available evidence and to provide practical recommendations agreed by consensus regarding the prevention and the assessment of CVD and VTE at the initiation of targeted therapies and especially JAKi.

2. Methods

The recommendations were conducted on behalf of the French Society of Rheumatology and followed the 2014 EULAR Standardized Operating Procedures (SOPs) [9].

Following approval by the French Society of Rheumatology, the convenor (JA) set up a steering committee which included a methodologist (AM), and two fellows (OF, SH) who conducted the systematic literature reviews (SLRs).

Subsequently, the remaining task force members were invited, making a total of 11 participants, including 9 rheumatologists, one cardiologist and one hematologist expert in thrombophilia.

The steering committee defined the research questions of the SLRs. Under the guidance of the methodologist, the two fellows performed two SLRs. The first focused on the risk of MACE upon all available JAKi (SH) in chronic inflammatory rheumatic diseases. The second addressed the prevalence and the risk factors associated with VTE, in and beyond the scope of all available JAKi, in chronic inflammatory rheumatic diseases (OF). These SLRs included studies published from 2011 until 2022 for MACE, without time limit for VTE and are published separately. The results of the SLRs were discussed with the steering committee first and the task force afterwards.

At the task force meeting in October 2022, the SLRs were first presented, and their findings discussed. In addition to the evidence from the SLRs, expert opinion was considered when formulating overarching principles and recommendations. Recommendations were edited according to the comments made, followed by a formal voting using anonymized polls. Consensus was reached if ≥ 75% of the members voted in favor of the recommendations in the first (or ≥ 67% and ≥ 50% in a second and third) round. Finally, each task force member anonymously indicated his or her level of agreement (LoA) through an online survey (numerical rating scale ranging from 0 = "do not agree at all" to 10 = "fully agree"). The mean of the LoA were presented. The draft of the manuscript was sent to all task force members for review. The final manuscript was approved by all authors and the French Society of Rheumatology executive board.

3. Results

The results of the SLRs will not be presented here in detail but are presented in respective parallel publications. However, if pertinent for the explanation of the results, parts of these data will be mentioned.

4. Overarching principles

The task force defined three overarching principles of CVD and VTE risk management in chronic inflammatory rheumatic diseases (Table 1).

4.1. The risk of CVD and VTE is higher in patients with chronic inflammatory rheumatic diseases compared with the general population, in particular in patients with RA

Increased CVD risk is now clearly acknowledged in RA with a risk of myocardial infarction (MI) in RA being found to be approximately 70% higher than in the general population [3]. Since the publication of the first EULAR recommendations in 2009 for CVD risk management in patients with RA, the evidence for an enhanced CVD risk has markedly increased [3,10]. It was reported in a large Danish cohort study that the risk of MI in RA patients is comparable to the risk of patients with diabetes [11]. New evidence strengthens

Table 1
Overarching principles and recommendations.

	Level of agreement (SD)
Overarching principles	
The risk of MACE and VTE is higher in patients with chronic inflammatory rheumatic diseases compared with the general population, in particular in patients with RA	
The rheumatologist has a central role in the evaluation of CVD and venous thromboembolic risks in patient with RA and other chronic inflammatory rheumatic diseases, with the use of validated tools	
The risk of MACE and VTE should be regularly assessed in patients with chronic inflammatory rheumatic diseases, particularly before initiating targeted therapies	
Recommendations	
1. Disease activity should be controlled optimally in order to lower the risk of MACE and VTE in patients with chronic inflammatory rheumatic disorders. Remission (or alternatively low disease activity) should be the therapeutic target	9.9 (0.3)
2. Smoking cessation should be encouraged to reduce the risk of MACE and VTE	10 (0)
3. NSAID and corticosteroid exposure should be minimized to reduce the risk of MACE and VTE	9.7 (0.5)
4. In the presence of ASCVD, the rheumatologist should ensure that a specialized follow-up is ongoing	10 (0)
5. A suitable therapeutic alternative to JAKi should be considered in patients with history of ASCVD or VTE	9.9 (0.3)
6. A suitable therapeutic alternative to JAKi should be considered in patients aged ≥ 65 years	9.1 (0.9)
7. A suitable therapeutic alternative to JAKi should be considered in patients at very high or high CVD risk or with major VTE risk factors	9.9 (0.3)
8. In the above situations, if no suitable treatment alternatives are available, the use of JAKi should be conditional on a collegial decision	8.5 (2.9)
9. In patients at very high and high CV risk, if no suitable treatment alternatives are available, the use of JAKi should also be conditional to approval from the referent cardiologist	9.6 (0.8)
10. In patients with previous VTE, if no suitable treatment alternatives are available, the use of JAKi should also be conditional on an expert advice	9.5 (0.8)
11. Thromboprophylaxis should be considered for patients at major risk of VTE in presence of transient risk factors	9.2 (1.2)

MACE: major cardiovascular event; VTE: venous thromboembolism; RA: rheumatoid arthritis; CVD: cardiovascular disease; NSAID: non-steroidal anti-inflammatory drug; ASCVD: atherosclerotic cardiovascular disease; JAKi: JAK inhibitors; SD: standard deviation.

the notion that the excess risk of CVD morbidity and mortality in RA patients is linked to both traditional and RA-related CVD risk factors including inflammation, extra-articular manifestations or anticitrullinated protein antibody positivity [12]. Compared with controls, patients with axSpA and PsA have an increased risk of vascular death and CVD events, influenced by greater prevalence of CVD risk factors as well as increased arterial stiffness [13].

Likewise, recent evidence has highlighted the increased risk of VTE in chronic inflammatory rheumatic diseases compared to healthy controls, and particularly in RA [14]. A recent meta-analysis of 10 observational studies has reported a risk of VTE in RA estimated by an odds ratio (OR) of 2.23 (95% confidence interval [CI] 1.79–2.77). The OR for deep vein thrombosis (DVT) and pulmonary embolism (PE) were 2.25 (95%CI 1.70–2.98) and 2.15 (95%CI 1.39–3.49), respectively [2]. Similar to the general population, the risk of VTE in RA is increased in several at risk situations including hospitalization, surgery, neoplasia (corresponding to 60% of provoked VTE) [15,16]. Several general (age, male sex, obesity, comorbidities) and disease-specific (disease activity, corticosteroids) VTE risk factors have been identified in RA patients [15,17–22]. The risk of VTE seems also significantly increased in axSpA compared to the general population, but with a less extent than in RA [18,23–26]. No increased risk of VTE has been reported in PsA [27–31]. Patients with chronic inflammatory rheumatic disorders do not seem to present an over-risk of inherited thrombophilia [32].

4.2. The rheumatologist has a central role in the evaluation of CVD and venous thromboembolic risks in patient with RA and other chronic inflammatory rheumatic diseases, with the use of validated tools

The task force therefore recommends that the treating rheumatologist has a central role in this evaluation, as stated in the EULAR recommendations. Indeed, several issues regarding CVD and VTE risk prevention plainly fall within the scope of practice of all rheumatologists. Achieving optimal disease control of rheumatic disease activity is an important treatment objective from a CVD/VTE standpoint and minimizing the use of corticosteroids and NSAIDs are some specific recommendations that rheumatologists could adopt to lower CV and VTE risk. The responsibility for CVD and VTE risk management should be defined locally given that different specialists may intervene to take over these complications. Moreover, CVD and VTE risk management may include healthcare professionals other than rheumatologists. In clinical practice, it is not always clear who is taking responsibility for CVD and VTE risk evaluation and management in patients with chronic inflammatory rheumatic disorders.

If the rheumatologist performs the risk assessment, he should use validated tools to provide the most reliable and accurate possible evaluation. Among the available tools, the 2021 recommendations from the European Society of Cardiology (ESC) have proposed the SCORE2 and the SCORE2-Older Persons (SCORE2-OP) risk scales to estimate 10-year fatal and nonfatal CVD risks (https://u-prevent.com/calculators) [33]. The SCORE2 is a new algorithm derived, calibrated and validated to predict the 10-year risk of a first CV event in European populations. It is an important advance in addressing some of the limitations of SCORE algorithm. It is an updated model based on individual international data from 13 million people with no initial CV history from more than 50 prospective cohort studies and national registries in European countries, in whom 60,000 incident CV events were recorded during the observation period (SCORE2 2021). This formidable effort was conducted in 3 steps:

- the model was derived from 677,684 participants from 45 cohorts without CV history recruited between 1990 and 2009;
- second, sex- and age-specific regional multipliers were determined for conversion of CV mortality rates to incidence rates involving nearly 10.8 million individuals with 731,265 CV events recorded during follow-up;
- finally, external validation of the risk models was performed using data from 1,133,181 individuals without a history of CV or diabetes in 25 prospective studies from 15 European countries.

SCORE2 has several improvements over the original SCORE model because it is based on more contemporary and representative data on CV events in Europe and also accounts for the impact

Table 2
Patient categories and CVD risk.

Patients at very high CVD risk			Patients at high CVD risk		
Patients with established ASCVD Patients with DM with established ASCVD and/or severe target organ damage[a] Severe chronic kidney disease[b]			Familial hypercholesterolemia[c] Patients with DM[d] without ASCVD and/or target organ damage Patients with moderate chronic kidney disease[e]		
Validated tools: SCORE2 and SCORE2-OP					
< 50 years	50–65 years	≥ 70 years	< 50 years	50–65 years	≥ 70 years
≥ 7.5%	≥ 10%	≥ 15%	2.5–7.5%	5– < 10%	7.5– < 15%

The identification of patients at high or very high CVD risk may be performed according to the validated tools SCORE2 or SCORE2-OP. In case validated tools cannot be applied, this risk stratification of CVD risk can be performed according to patient categories (atherosclerotic cardiovascular disease [ASCVD] – diabetes, familial hypercholesterolemia, chronic kidney disease); CVD: cardiovascular disease; ASCVD: atherosclerotic cardiovascular disease; DM: diabetes mellitus.

[a] eGFR < 45 mL/min/1.73 m^2 irrespective of albuminuria; eGFR 45–59 mL/min/1.73 m^2 and microalbuminuria (ACR 30–300 mg/g); proteinuria (ACR > 300 mg/g); presence of microvascular disease in at least 3 different sites (e.g., microalbuminuria plus retinopathy plus neuropathy).

[b] eGFR < 30 mL/min/1.73 m^2.

[c] Associated with markedly elevated cholesterol levels.

[d] Uncontrolled and/or long-standing diabetes mellitus (> 10 years).

[e] eGFR 30–44 mL/min/1.73 m^2.

of competing risks unrelated to CV events. The recalibration of SCORE2 to four European regions with different levels of CVD risk improves risk stratification. Most importantly, SCORE2 provides estimates for both fatal and nonfatal CV events, which is an improvement over calculators that predict only fatal events. Consideration of fatal events alone may underestimate the total burden of CV events, which in recent decades has shifted toward nonfatal events, particularly in younger subjects. To improve the accuracy of risk prediction in adults older than 70 years, the new SCORE2-OP model, was derived from the Cohort of Norway (CONOR) study with 28,503 participants from a low-risk region, recalibrated for 4 geographic regions, and validated in 338,615 persons from different regions (SCORE2-OP 2021). The main advantage of this model is that it considers sex-specific competing risk and interactions between age and risk factors. SCORE2-OP illustrates the broad distribution of 10-year CV risk in the elderly, emphasizing the need for accurate risk prediction to guide treatment decisions in this age group. The high and very high CVD risk categories based on SCORE2 and SCORE2-OP are provided in the Table 2. However, the suboptimal performance of risk scores used in general population when applied to patients with chronic inflammatory rheumatic disorders has to be recognized, leading to underestimation of CV risk in these populations. Thus, given the important gaps in knowledge still existing regarding the approach to CV risk stratification in clinical practice and the need of using disease-specific risk prediction models, there is clearly a need for new relevant and feasible methods to predict CV risk in RA. In the absence of validated tools, this risk stratification of CVD risk can be performed according to patient categories (atherosclerotic cardiovascular disease [ASCVD] – diabetes, familial hypercholesterolemia, chronic kidney disease) as presented in Table 2. This stratification ensures flexibility for CVD evaluation since it gives to the clinician the possibility to use the SCORE or to refer to patient categories.

Regarding the risk of VTE, different thrombosis risk assessment models (RAMs) have been developed for specific clinical scenarios [34], including the Caprini RAM for the use in patients undergoing surgery, the Padua prediction score, the IMPROVE risk score or the GENEVA risk score for non-surgical inpatients who are acutely ill [35–37]. Notably, most of these RAMs do not include chronic inflammatory rheumatic diseases as a risk factor. Unfortunately, there is no specific and validated screening tools for the assessment of the overall risk of VTE in patients with chronic inflammatory rheumatic diseases. Development of validated tools is imperative to enable correct assessment of the risk of thrombosis and to adequately implement tailored prophylactic measures in different clinical scenarios. In the absence of validated tools, the herein recommendations propose in Table 3 the list of risk factors to identify patients at risk of VTE.

Table 3
List of VTE risk factors in the setting of chronic inflammatory chronic diseases.

Major VTE risk factors	VTE risk factors
Age ≥ 65 years	Male sex
Previous VTE	Smoking
Obesity	Hormonal replacement therapy
Neoplasia	Oral contraceptives
Inherited thrombophilia	Antidepressants
	Sedentary lifestyle
	Pregnancy
	Chronic inflammatory rheumatic disorders
	RA disease activity

Transient VTE risk factors
Hospitalization
Travel > 4 hours
Recent surgery (≤ 1 months)
Immobilization > 7 days
High dose of corticosteroids
RA flare

VTE: venous thromboembolism; RA: rheumatoid arthritis.

4.3. The risk of MACE and VTE should be regularly assessed in patients with chronic inflammatory rheumatic diseases, particularly before initiating targeted therapies

CVD risk assessment is recommended for all patients with RA, axSpA or PsA at least once every 5 years, which is in line with the latest ESC guidelines [33], so that lifestyle advice and CVD preventive treatment can be initiated when indicated. Currently, there is no evidence that annual CVD risk assessment compared with 5-year risk assessment leads to a more significant reduction in CVD mortality or morbidity in patients with chronic inflammatory rheumatic diseases [3].

Risk factors for VTE, including in particular older age (≥ 65 years), history of VTE, obesity and ongoing malignancy (Table 3) should be assessed in all patients with chronic inflammatory rheumatic diseases. Several of these risk factors are transient (Table 3) and need a continuous re-evaluation especially when the clinically condition changes (such as flare, hospitalization, surgery discharge and so on). CVD and VTE risk evaluation should be reconsidered at the initiation of targeted therapies, which may modify the risk of CVD or VTE, so that clinicians can act accordingly [4,38–40].

5. Recommendations

The task force defined 11 recommendations of CVD and VTE risk management in chronic inflammatory rheumatic diseases. The list of the recommendations, including the level of agreement based on voting by the task force, is shown in Table 1. The recommendations follow a logical sequence and they are not listed in sequence of importance. All recommendations are discussed in detail below.

5.1. Disease activity should be controlled optimally in order to lower the risk of MACE and VTE in patients with chronic inflammatory rheumatic disorders. Remission (or alternatively low disease activity) should be the therapeutic target

The EULAR recommendations for CVD risk management have emphasized the importance of control of disease activity to lower CVD risk, and the association between higher cumulative inflammatory burden and increased risk of MACE in RA [3]. They have highlighted that reducing inflammation is crucial in RA for CVD risk management. Treatment should aim at reaching a target of sustained remission or, alternatively, low disease activity in every patient, as stated by the EULAR recommendations [41]. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), in particular methotrexate (MTX), as well as biological DMARDs (bDMARDs), such as the TNF inhibitors (TNFi), are often associated with a significant reduction in CVD risk in patients with RA [3]. A recent manuscript has reported that the addition of either a TNFi or triple therapy (MTX, sulfasalazine and hydroxychloroquine) resulted in important improvements in vascular inflammation [38]. Reduction of disease activity after treatment with tocilizumab or rituximab (RTX) showed a beneficial effect on surrogate markers of CVD [3]. The balance between JAKi-induced inflammation reduction and the risk of CVD is more difficult to apprehend because of the results of ORAL Surveillance. This was a large worldwide, multicenter, prospective, phase 3B/4, randomized, open-label, non-inferiority safety endpoint study, comparing the safety of tofacitinib (5 or 10 mg × 2/day) to TNF inhibitors (adalimumab in the US, etanercept in the rest of the world). Patients included had RA and inadequate response to MTX. At time of inclusion, patients were to be at least 50-years-old with at least one additional CV risk factor. A higher number of MACE were observed with tofacitinib compared to TNFα inhibitors (98/2911, 3.4% vs. 37/1451, 2.5%) and the non-inferiority of tofacitinib was not shown [4]. It is important to remind that:

- ORAL Surveillance included patients with RA having other risk factors that impact absolute risk of MACE, and this CVD-risk enriched population likely reflected a spectrum of CVD risk;
- tofacitinib was compared to TNFi which are associated with CVD reduction;
- the difference of MACE was formally observed in patients with ASCVD, and to a lesser extent in patients with only CV risk factors.

In addition, the potential effect on CVD of MTX, which was given in combination to tofacitinib or TNFi, was not evaluated.

For both axSpA and PsA, evidence for the association between inflammation and an enhanced CVD risk is less abundant compared with RA. In view of shared pathogenic mechanisms, it is plausible that decreasing the inflammatory burden in axSpA and PsA will also have favorable effects on the CVD risk in these patients. Therefore, control of disease activity, as is routinely recommended, is expected to lower CVD risk for both axSpA and PsA [42].

Disease activity has also been identified as a risk factor for VTE in patients with RA [19,20] (see OP1). Disease activity should be regarded as a modifiable risk factor for VTE in RA, and aggressive control of inflammation might reduce the risk of thrombosis in RA patients. TNFi may have the potential to reduce the risk of VTE by halting inflammation [43]. However, some RA therapies might have an intrinsic prothrombotic effect that could tilt the balance towards an increased risk of VTE. Indeed, corticosteroids and JAKi can be associated with an increased risk of VTE, especially in patients with risk factors of VTE [44,45]. No data are available yet regarding the beneficial effect of inflammation reduction for the risk of VTE in axSpA or PsA.

5.2. Smoking cessation should be encouraged to reduce the risk of MACE and VTE

Smoking is a known risk factor for arterial and venous events per se [29,46] and can also increase the risk of these events further through disease activity, given that smoking is associated with more aggressive disease in chronic inflammatory rheumatic disorders. Stopping smoking is potentially the most effective of all preventive measures, with substantial reductions in (repeat) MIs or death [47]. Lifetime gains in CVD-free years are substantial at all ages, and benefits would be obviously even more substantial if other complications from smoking were accounted for. Quitting must be encouraged in all smokers and patients should be directed towards the locally defined evidence-based smoking cessation programmes, even if they have failed previously. Moreover, passive smoking should be avoided as much as possible.

Other lifestyle interventions such as healthy diet, weight loss and regular exercise should be encouraged [48] There is accumulating data showing that exercise therapy has beneficial CVD effects in patients with chronic inflammatory rheumatic diseases [42,49,50]. The Mediterranean diet, characterized by a high consumption of fruit, vegetables, legumes and cereals, including olive oil or vegetable oil is the primary source of fat intake and containing less red meat and more fish compared with common Western diets, has been shown to be associated with a reduced incidence of major CVD events in the general population [51].

5.3. NSAID and corticosteroid exposure should be minimized to reduce the risk of MACE and VTE

NSAIDs and corticosteroids are commonly used for the treatment of chronic inflammatory rheumatic diseases and these agents effectively lower disease activity and inflammation. However, both treatment options have been associated with an increased risk of MACE and VTE [3,20]. The CV risk of corticosteroids is now well established in chronic inflammatory rheumatic disorders, especially RA. In a recent study from the National Databank for Rheumatic Disease in US (FORWARD), the use of corticosteroids was also independently associated with an increased risk factor for unprovoked VTE (adjusted hazard ratio, HR, 1.99, 95% CI 1.66–2.40) [20]. As these medications are often indispensable in tackling disease activity in patients with chronic inflammatory rheumatic disorders, their use should be evaluated on an individual patient level in accordance with treatment-specific recommendations.

5.4. In the presence of atherosclerotic cardiovascular disease, the rheumatologist should ensure that a specialized follow-up is ongoing

Multidimensional prevention is crucial for short- and long-term outcomes in patients with coronary artery disease (CAD), cerebrovascular disease or lower extremity artery disease (LEAD) considering the high risk of new CV event. According to the latest ESC guidelines, several therapeutic measures are strongly recommended in this population. This includes daily aspirin in patients with a previous myocardial infraction or revascularization, clopidogrel daily in addition to aspirin for 6 months following coronary

stenting in patients with chronic coronary syndromes, ACE inhibitors, beta-blockers among others in patients with left ventricular dysfunction and oral lipid lowering treatments [33]. Interventions for cerebrovascular diseases depend on the type of event, i.e., ischaemic or haemorrhagic. In patients with ischaemic stroke or transient ischaemic attack (TIA), prevention with antithrombotics is recommended. Use of an antiplatelet is recommended for patients with non-cardioembolic ischaemic stroke or TIA, and use of anticoagulants is recommended in patients with cardioembolic ischaemic stroke or TIA. Patients with lower extremity artery disease (LEAD) require lifestyle improvement, i.e., (smoking cessation, exercise and healthy diet) together with drug intervention, including platelet inhibitors [33]. Additionally, knowledge of local guidelines for management of hypertension, dyslipidemia and diabetes mellitus is needed to recognize thresholds and targets in order to tailor treatment in this specific high-risk population. These tasks may be beyond the scope of practice of the typical rheumatologist and a specialized follow-up is mandatory. Indeed, advances CV risk management using imaging and laboratory tests is required, as well as the optimization of lifestyle factors, hypertension and dyslipidemia and the investigation and management of cardiac-related symptoms. Thus, the rheumatologist should ensure that CVD risk assessment and management is being performed regularly, should record who is performing it (general practitioner, specialist) and should make sure that the patient is aware of the need for regular risk assessment, in coordination with primary care physicians.

5.5. A suitable therapeutic alternative to JAKi should be considered in patients with history of ASCVD or VTE

The part of the recommendation related to patients with ASCVD (i.e., history of coronary artery disease, cerebrovascular disease or peripheral artery disease) follows the statement form the PRAC, which indicated that JAKi should be used in patients with increased risk of major CV problems (such as heart attack or stroke) only if no suitable treatment alternatives are available [52]. Further, the PRAC has suggested that doses of JAKi should be reduced in some patient groups who may be at risk of cardiovascular problems. A recent post-hoc analysis of ORAL Surveillance showed an increased risk of MACE with tofacitinib 5 mg and 10 mg two times per day versus TNFi that was primarily observed in patients with a history of ASCVD at baseline. In patients without history of ASCVD but with CV risk factors, there did not appear to be a detectable difference in risk of MACE with tofacitinib 5 mg two times per day or the combined tofacitinib doses versus TNFi [39]. A large observational study that used US claims data to assess risk of CV outcomes (composite of hospitalization for MI or stroke) with tofacitinib versus TNFi in patients with RA (Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis; STAR-RA) was recently published [53]. Evidence for an increased risk of CV events with tofacitinib was not identified in this real-world cohort. However, STAR-RA also prespecified subgroup analyses of patients with or without previous ASCVD. These results were consistent with those of ORAL Surveillance; risk of CV events appeared to be increased with tofacitinib versus TNFi in patients with, but not in those without, pre-existing ASCVD (HR 1.27, 95% CI 0.95–1.70).

In the RA integrated report of baricitinib safety data, the incidence ratio of positively adjudicated MACE was 0.5/100 patients-year [54]. Patients in this analysis had a mean age at baseline of 53 years and 79% were female. No specific analysis has been performed in the subgroup of patients with ASCVD. However, of the 1780 patients (54.8% of the study population) with at least one CV risk factor, the IR of MACE was 0.70/100 patients-year and among those aged 50 years or older with at least one additional CV risk factor ($n = 1325$), the IR of MACE was 0.77/100 PYR. IRs for stroke, MI and CV death were 0.3/100 patients-year, 0.2/100 patients-year and 0.1/100 patients-year, respectively, in the all baricitinib data set [54]. In the Upadacitinib Clinical Trial Programs in RA, PsA, and axSpA, 4298 patients received ≥ 1 dose of upadacitinib 15 mg, 40–50% of patients had 2 or more CV risk factors, and the proportion of patients ≥ 65 years ranged from 6 to 23% [55]. Factors potentially associated with MACE occurrence in patients with RA receiving upadacitinib 15 mg included in particular age ≥ 65 years and ASCVD [55]. Taken together, these findings emphasize the importance of rheumatologists assessing medical history of ASCVD (Fig. 1), when considering tofacitinib or other JAKi as a treatment for patients with RA and other chronic inflammatory rheumatic diseases.

The PRAC also recommended using JAKi with caution in patients with risk factors for VTE, with possible dose reduction in this group of patients given the results of ORAL Surveillance suggesting a dose effect of tofacitinib for the risk of VTE, but without suggesting the use of a suitable alternative. Previous VTE is a major risk factor for the occurrence of new venous thromboembolic events [36,56]. In ORAL Surveillance and in the upadacitinib development program, across the treatment groups, VTE incidence ratios were higher in patients with vs. without a history of VTE [55,57]. Thus, the task force has considered that previous VTE is a foremost risk factor that justifies considering a suitable alternative to JAKi (Fig. 1).

5.6. A suitable therapeutic alternative to JAKi should be considered in patients aged ≥ 65 years

This recommendation follows the PRAC, who recommended that JAKi should be used in patients aged 65 years or above only if no suitable treatment alternatives are available [52] (Fig. 1). This statement is based on the results of ORAL Surveillance study, which showed that the increased risk of MACE and VTE with tofacitinib vs. TNFi was more pronounced in patients aged ≥ 65 years than in patients aged < 65 years [4,57]. Moreover, patients with a history of ASCVD were more likely to be ≥ 65 years [39]. These data were also observed in other JAKi. In the long-term baricitinib clinical trial dataset ($n = 3770$ patients, i.e.; 14,744 patient-years), the risk of MACE and VTE was more pronounced in patients ≥ 65 years or with risk factors (ASCVD, diabetes mellitus, hypertension, smoking, malignancy, low HDL, BMI > 30, severe mobility impairment (IR = 0.70 vs. 0.05 for MACE and 0.66 vs. 0.05 for VTE) [54]. The analysis of the safety profile of upadacitinib over 15,000 patient-years across the different indications has also revealed an increased incidence of MACE in RA and PsA patients ≥ 65 years (RA: 1.0 95% CI 0.6–1.7 vs. 0.3 95% CI 0.2–0.4; PsA: 0.4 95% CI 0.0–2.2 vs. 0.2 95% CI 0.1–0.6) [58]. Data from the phase 2, phase 3 and LTE trials of filgotinib revealed that the EAIRs of adjudicated MACE and VTE were higher in patients aged ≥ 65 years [59].

5.7. A suitable therapeutic alternative to JAKi should be considered in patients at very high or high CVD risk or with major VTE risk factors

In the population < 65 years and without ASCVD or previous VTE, major CVD and VTE risk factors should be actively assessed in patients with chronic inflammatory rheumatic diseases before a prescription of JAKi should be considered (Fig. 1).

The detection of major CV risk factors should lead to consider other therapeutic classes and a reduction of JAKi doses, as stated by the PRAC [52]. The task force has considered patients at very high or high CVD risk according to the last ESC guidelines as a population of major CV risk that should avoid JAKi in case of suitable therapeutic alternative [33]. This risk stratification of CVD risk can be performed according to patient categories (ASCVD, diabetes, familial hypercholesterolemia, chronic kidney disease) or according to the SCORE2/SCORE2-OP risk scores, as presented in Table 2

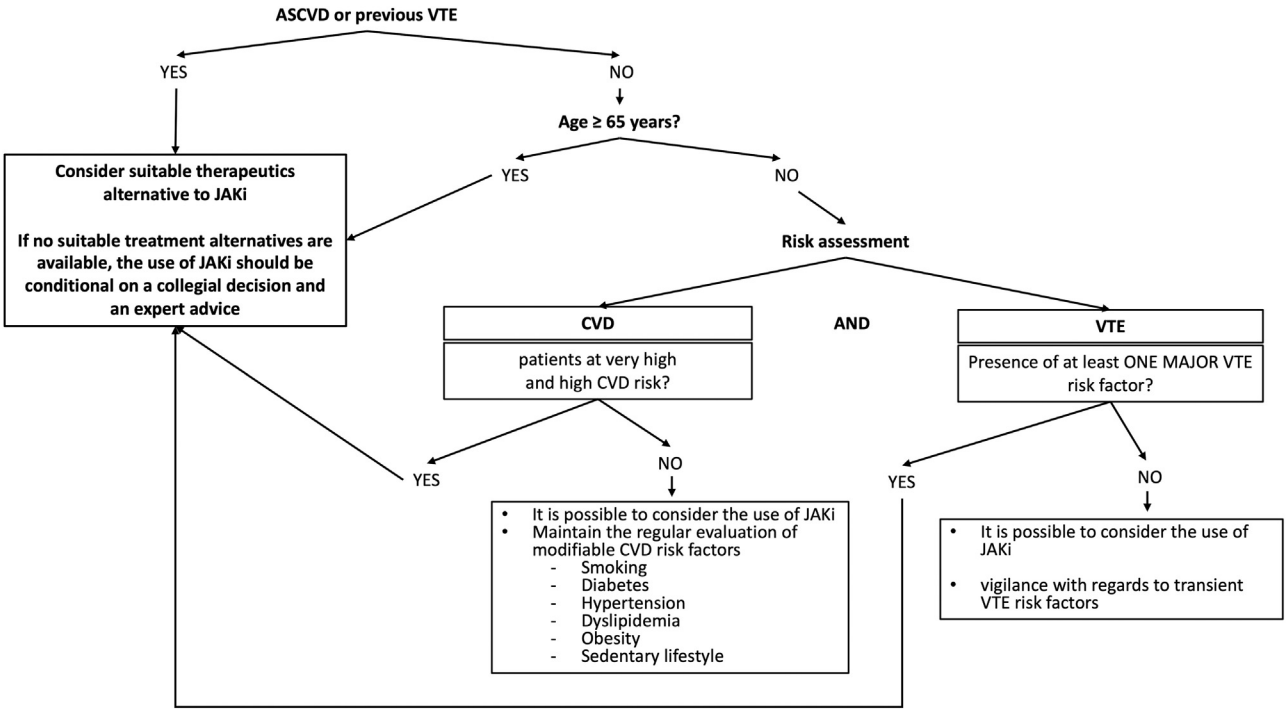

Fig. 1. Algorithm for assessing CVD and VTE risk before considering the prescription of a JAKi. ASCVD: atherosclerotic cardiovascular disease; CVD: cardiovascular disease; VTE: venous thromboembolism; JAKi: JAK inhibitors.

[33]. In addition to Oral Surveillance, the importance of CV risk factors in tofacitinib-treated patients has been highlighted by the STAR-RA study, which included a cohort that mirrored ORAL Surveillance inclusion and exclusion criteria (randomized controlled trial [RCT]-duplicate cohort). The primary outcome of the RCT-duplicate cohort aligned with the increased risk of MACE with tofacitinib versus TNFi observed in ORAL Surveillance (i.e., approximately 25% relative risk increase with tofacitinib 5 mg two times per day vs. TNFi) [4,53]. In the baricitinib, upadacitinib and filgotinib development programmes, the CVD-induced mortality and non-fatal MI occurred in patients at very high or high CVD risk [58,60–65].

The task force has also provided a definition of major VTE risk factors (Table 3). As previously stated above, age ≥ 65 years and previous VTE are recognized major VTE risk factors, which have been placed as priority risk factors in our risk assessment algorithm. Neoplasia and inherited thrombophilia are specific conditions that are usually known from patients and clinicians. Obesity is another major VTE risk factor that must be investigated prior to the use of JAKi. Obesity has been identified in the development programmes of the four JAKi in RA as a risk factor for VTE [57,62,66,67]. These data emphasize again the need of weight management in patients with inflammatory rheumatic diseases.

Other risk factors have been identified from the extensive literature review (Table 3), but do not represent, on their own, a contraindication to the use of JAKi. The combination of risk factors may increase the risk of VTE and should also be taken in consideration. Increased vigilance is also required with regard to transient VTE risk factors that are also listed in Table 3.

5.8. In the above situations, if no suitable treatment alternatives are available, the use of JAKi should be conditional on a collegial decision

This recommendation, based on expert opinion, was elaborated in order not to leave the rheumatologist alone to manage a difficult situation. A collegial decision among rheumatologists allows a synthesis of the different risk factors for each patient with a personalized approach. It also allows a discussion and synthesis of specialized opinions gathered from cardiologists, neurologist, vascular physician, hemostasis and/or thrombosis specialist in order to put the risk into perspective. It also allows a formal validation of the decision and the mention in the medical file of "the absence of suitable alternative to JAKi". The meaning of "no suitable alternative" has not been precisely defined but may correspond to the previous use of all other possible of authorized classes of targeted therapies.

Following this collegial decision, the task force feels that the rheumatologists will be more comfortable to have a concerted and thoughtful discussion with the patient for a shared decision-making. The group is fully aware of the constraints induced by this proposal. These procedures may evolve and be simplified in case of future reassuring data on JAKi.

5.9. In patients at very high and high CV risk, if no suitable treatment alternatives are available, the use of JAKi should also be conditional to approval of the referent cardiologist

To ensure the correct implementation of this recommendation, it will be important to clearly define the nature of the approval that will be sought from the cardiologist. Asking for confirmation of the use of a JAKi because of a complex cardiovascular situation may not result in productive advice since the cardiologist may not know the class of JAKi or be aware of the potential risks of CVD of this class. The approval must be directed towards the stability of the ASCVD and the potential risk of a new event that will preclude the use of a JAKi. Indeed, the prescription of a JAKi should be considered in a patient with the most stable CVD possible. To address this issue, the cardiologist may therefore proceed to advanced CV risk stratification using imaging and laboratory tests, optimize control of hypertension and dyslipidemia and investigate and manage possible cardiac-related symptoms. It would also be important to check the control of an associated diabetes mellitus [68].

If the cardiologist considers that the risk factors are controlled enough and that the prescription of a JAKi is validated following a collegial decision among rheumatologists, the nature and frequency of the cardiological follow-up will have to be specified, adapted and personalized.

5.10. In patients with previous VTE, if no suitable treatment alternatives are available, the use of JAKi should also be conditional on an expert advice

The risk of recurrent VTE is complex situation in which there is no clear recommendation. This risk is lowered by anticoagulation, with a large effect in the initial phase following the venous thromboembolic event, and with a smaller effect in terms of secondary prevention of recurrence when extended anticoagulation is performed [69]. On the other hand, extended anticoagulation is associated with an increased risk of major bleeding and thus leads to increased morbidity and mortality. Therefore, it is necessary to assess the risk of recurrence for VTE on an individual basis, and a recommendation for secondary prophylaxis should be specifically based on risk calculation of recurrence of VTE and bleeding, which falls beyond the scope of practice of all rheumatologists. Indeed, estimating the risk of recurrent VTE is complex and requires consideration of relevant risk factors for recurrent VTE, especially the presence of intrinsic risk factors that are known to promote recurrence. For this reason, the task force considered that the use of JAKi in patients with previous VTE should be conditioned to an expert opinion.

After an individualized assessment of the risk factors for VTE, a collegial decision among rheumatologists should be made to the feasibility of introducing an additional potential risk factor for VTE and, if it is considered as possible, whether the use of JAKi should be used at reduced dose and/or combined with thromboprophylaxis, the modalities of which should be determined. Many medical specialties are likely to manage VTE (internal medicine, vascular medicine, hematologist, pulmonologist. . .) and it is very important that the rheumatologist identifies a local referent for VTE within its health care structure.

5.11. Thromboprophylaxis should be considered for patients at major risk of VTE in presence of transient risk factors

In accordance with current guidelines on the presence of VTE during hospitalization, patients with chronic inflammatory rheumatic diseases should receive pharmacological thromboprophylaxis during the inpatient period, regardless of the cause of hospitalization [70]. In particular, RA patients hospitalized for a disease flare may be particularly at risk of VTE, especially if they receive high dose of corticosteroids (Table 2). An extended duration of thromboprophylaxis beyond hospital discharge is not routinely recommended in patients with chronic inflammatory rheumatic diseases. However, surgical and orthopaedic research have shown that the risk of VTE can remain elevated even after hospital discharge [71,72], and a subgroup of patients may benefit from an extended duration of VTE prophylaxis [73].

RA disease activity is a known risk factor for VTE [19,20]. Most RA flares occur in an ambulatory setting but given that the thresholds for hospitalization due to RA flares differ worldwide, the proportions of inpatients and outpatients with RA having a VTE event may vary. Given that the absolute risk of VTE remains low in outpatients with active RA, the use of thromboprophylaxis is not recommended in the absence of risk factors. On the other hand, outpatients with major VTE risk factors and at least a transient risk factor, including RA flare (Table 3), might be at particular risk of VTE and could benefit from thromboprophylaxis until the transient provoking factor disappears. There is a paucity of evidence regarding thromboprophylaxis in patients with RA, and this issue should be considered on a case-by-case basis. Guidelines recommend pharmacological over mechanical thromboprophylaxis, given that the former may be more effective in the prevention of PE and symptomatic VTE [70,74]. The preferred methods of prophylaxis are low molecular weight heparin (LMWH) or fondaparinux over unfractioned heparin (UFH) [70].

Table 4
Research agenda.

Are the MACE and VTE risks of JAKi as seen in the ORAL Surveillance study, different with JAK-1 or JAK-1/2-selective agents than with pan-JAKi?
What is the long-term risk of MACE and VTE of JAKi?
Do the risks of MACE and VTE observed in RA be extended to AxSpA and PsA?
Does the combination of JAKi plus methotrexate (MTX) decrease the risk of MACE and VTE?
Which mechanisms lead to MACE and VTE seen with JAKi?
How manage the risk of MACE and VTE in at risk patients with ongoing therapy with JAKi?
Does the dose reduction of JAKi have favorable effects for the risk of MACE and VTE?
What is the impact of the dose reduction of JAKi in patients with risk factors reaching low disease activity or remission to decrease the risk of MACE and VTE?
How manage ongoing JAKi in patients reaching the age of 65 years?
How manage ongoing JAKi in elderly patients (> 75 years) in long-term remission with baricitinib 2 mg/day?

6. Discussion

The ultimate goal of this consensus was to give multidisciplinary practical recommendations to prevent potentially life-threatening complications of MACE and VTE in patients with chronic inflammatory rheumatic diseases, following the communication of the PRAC. This consensus led to the development of a series of overarching principles and recommendations supported by available evidence regarding the background risk of MACE and VTE in patients with chronic inflammatory rheumatic diseases. Additionally, whenever appropriate consensus recommendations for the prevention of MACE and VTE were made (Table 1), as well as and the assessment of CVD and VTE at the initiation of targeted therapies, especially JAKi (Fig. 1). These recommendations may evolve according to new results obtained on JAKi in current practice, in particular with the help of registries, and thus, should be updated. Until now, most of publications that followed ORAL Surveillance did not firmly confirm the link between JAKi and MACE, whereas several concerns remain on the risk of VTE [44,53,75]. The acceptability of these recommendations should be further evaluated by rheumatologists and patients, as well as their future dissemination among the medical community and patients.

Treatment strategies of established MACE or VTE in patients with chronic inflammatory rheumatic diseases were beyond the scope of this consensus, and physicians should refer to available guidelines.

Further evidence is needed regarding the drug-related risk of MACE and VTE with JAKi. Several questions remain unsolved and would deserve dedicated studies. They are listed in the research agenda (Table 4). It will be important to determine which mechanisms lead to the MACE and VTE events seen with JAKi, and particularly tofacitinib and baricitinib in clinical practice. Then, real life data are mandatory to confirm whether these risks may be extended to JAK-1 more selective agents upadacitinib and filgotinib. It is important to consider that long-term follow-up data that will be obtained for upadacitinib and filgotinib will be influenced by the different recommendations and warnings, meaning that any risk reduction with these drugs might not be related to drugs themselves but to better management of JAKi.

The majority of available evidence was obtained in RA and how high is the CVD and VTE risk in patients with AS or PsA treated

with JAKi is not known. One important issue will be the management of at-risk patients with ongoing therapy with JAKi, as well as the potential value of JAKi dose reduction and the combination of JAKi with methotrexate to decrease the risk of MACE and VTE. In addition to real life studies specifically designed to address these important issues, the development of specific risk assessment tools for MACE and VTE in patients with chronic inflammatory rheumatic diseases are warranted, as they might influence management in some clinical scenarios.

Funding

None.

Disclosure of interest

JA: honoraria from Pfizer, Bristol Myers Squibb, UCB, Roche, Nordic, Novartis, Sanofi, Boehringer, Abbvie, Chugai, Galapagos, Biogen, Fresenius Kabi, Sandoz, AstraZeneca. Research grants: Pfizer, Bristol Myers Squibb, Fresenius Kabi, Novartis, Nordic Pharma, Galapagos.

OF: honoraria from Galapagos, Abbvie, MSD, Novartis, BMS, UCB. Research grants: Cellgene.

SH: honoraria from BMS.

CD: honoraria from Abbvie, Biogen, BMS, Fresenius-Kiabi, Galapagos, MSD, Novartis, Pfizer, Sandoz, UCB.

IE: honoraria from Afric-Phar, Amanys Pharma, Bayer Healthcare, Boehringer-Ingelheim, Bristol Myers Squibb, Galapagos, Gedeon Richter, Leo-Pharma, Pfizer, Recordati, Sanofi, Viatris.

FP: honoraria from Alliance BMS-Pfizer, Astra Zeneca, Bayer, BBraun, Biotronik, Boston Scientific, Sanofi and Servier.

CP: honoraria from Abbvie, Amgen, BMS, Fresenius, Galapagos, Janssen, Lilly, Novartis, Pfizer, Sandoz, UCB.

JHS: honoraria from AbbVie, BMS, Galapagos, Lilly, Janssen, MSD, Novartis, Pfizer, Roche, Sanofi, UCB, Viatris.

MET: honoraria from Pfizer, Galapagos, Roche, UCB, Lilly, MSD, Medac, Nordic, BMS, Roche, Abbvie, UCB, Lilly, BMS, SOBI, Werfen. Research grants from Pfizer, Galapagos.

JS: honoraria from Roche, Chugai, Pfizer, BMS, MSD, Abbvie, Sandoz, Hospira, Janssen, Novartis, Fresenius Kabi, Sanofi Genzyme, Galapagos, research grants from Roche, Pfizer, MSD, Schwa Medico, BMS.

AM: honoraria from Abbvie, Janssen, Lilly, Merck, BMS, Novartis, UCB.

Références

[1] van Halm VP, Peters MJ, Voskuyl AE, et al. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. Ann Rheum Dis 2009;68:1395–400.
[2] Hu LJ, Ji B, Fan HX. Venous thromboembolism risk in rheumatoid arthritis patients: a systematic review and updated meta-analysis. Eur Rev Med Pharmacol Sci 2021;25:7005–13.
[3] Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis 2017;76:17–28.
[4] Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med 2022;386:316–26.
[5] Montastruc F, Flumian C, Degboe Y, et al. Comparison of major cardiovascular and thromboembolic events in safety reports between rheumatoid arthritis patients treated with JAK inhibitors versus anti-TNF: results from VigiBase. Ann Rheum Dis 2022;81.
[6] Gouverneur A, Avouac J, Prati C, et al. JAK inhibitors and risk of major cardiovascular events or venous thromboembolism: a self-controlled case series study. Eur J Clin Pharmacol 2022;78:1981–90.
[7] https://www.ema.europa.eu/en/documents/press-release/ema-confirms-xeljanz-be-used-caution-patients-high-risk-blood-clots_en.pdf.
[8] https://www fda gov/drugs/drug- safety-and-availability/initial-safety-trial-results-find-increased-risk-serious-heart- related-problems-and-cancer-arthritis.
[9] van der Heijde D, Aletaha D, Carmona L, et al. 2014 update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. Ann Rheum Dis 2015;74:8–13.
[10] Avouac J, Amrouche F, Meune C, et al. Mortality profile of patients with rheumatoid arthritis in France and its change in 10 years. Semin Arthritis Rheum 2017;46:537–43.
[11] Lindhardsen J, Ahlehoff O, Gislason GH, et al. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. Ann Rheum Dis 2011;70:929–34.
[12] Solomon DH, Kremer J, Curtis JR, et al. Explaining the cardiovascular risk associated with rheumatoid arthritis: traditional risk factors versus markers of rheumatoid arthritis severity. Ann Rheum Dis 2010;69:1920–5.
[13] Brophy S, Cooksey R, Atkinson M, et al. No increased rate of acute myocardial infarction or stroke among patients with ankylosing spondylitis-a retrospective cohort study using routine data. Semin Arthritis Rheum 2012;4:140–5.
[14] Ketfi C, Boutigny A, Mohamedi N, et al. Risk of venous thromboembolism in rheumatoid arthritis. Joint Bone Spine 2021;88:105122.
[15] Kim SC, Schneeweiss S, Liu J, et al. Risk of venous thromboembolism in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2013;65:1600–7.
[16] Holmqvist ME, Neovius M, Eriksson J, et al. Risk of venous thromboembolism in patients with rheumatoid arthritis and association with disease duration and hospitalization. JAMA 2012;308:1350–6.
[17] Chung WS, Peng CL, Lin CL, et al. Rheumatoid arthritis increases the risk of deep vein thrombosis and pulmonary thromboembolism: a nationwide cohort study. Ann Rheum Dis 2014;73:1774–80.
[18] Li L, Lu N, Avina-Galindo AM, et al. The risk and trend of pulmonary embolism and deep vein thrombosis in rheumatoid arthritis: a general population-based study. Rheumatology (Oxford) 2021;60:188–95.
[19] Molander V, Bower H, Frisell T, et al. Risk of venous thromboembolism in rheumatoid arthritis, and its association with disease activity: a nationwide cohort study from Sweden. Ann Rheum Dis 2021;80:169–75.
[20] Ozen G, Pedro S, Schumacher R, et al. Risk factors for venous thromboembolism and atherosclerotic cardiovascular disease: do they differ in patients with rheumatoid arthritis? RMD Open 2021;7:e001618.
[21] Yoshimura M, Fujieda Y, Sugawara M, et al. Disease activity as a risk factor for venous thromboembolism in rheumatoid arthritis analysed using time-averaged DAS28CRP: a nested case-control study. Rheumatol Int 2022;42:1939–46.
[22] Choi HK, Rho YH, Zhu Y, et al. The risk of pulmonary embolism and deep vein thrombosis in rheumatoid arthritis: a UK population-based outpatient cohort study. Ann Rheum Dis 2013;72:1182–7.
[23] Eriksson JK, Jacobsson L, Bengtsson K, et al. Is ankylosing spondylitis a risk factor for cardiovascular disease, and how do these risks compare with those in rheumatoid arthritis? Ann Rheum Dis 2017;76:364–70.
[24] Ramagopalan SV, Wotton CJ, Handel AE, et al. Risk of venous thromboembolism in people admitted to hospital with selected immune-mediated diseases: record-linkage study. BMC Med 2011;9:1.
[25] Zoller B, Li X, Sundquist J, et al. Autoimmune diseases and venous thromboembolism: a review of the literature. Am J Cardiovasc Dis 2012;2:171–83.
[26] Avina-Zubieta JA, Chan J, De Vera M, et al. Risk of venous thromboembolism in ankylosing spondylitis: a general population-based study. Ann Rheum Dis 2019;78:480–5.
[27] Damian AC, Colaco K, Rohekar S, et al. The incidence and risk factors for venous thromboembolic events in patients with psoriasis and psoriatic arthritis. Semin Arthritis Rheum 2021;51:547–52.
[28] Gazitt T, Pesachov J, Lavi I, et al. The association between psoriatic arthritis and venous thromboembolism: a population-based cohort study. Arthritis Res Ther 2022;24:16.
[29] Galloway J, Barrett K, Irving P, et al. Risk of venous thromboembolism in immune-mediated inflammatory diseases: a UK matched cohort study. RMD Open 2020;6:e001392.
[30] Ogdie A, Grewal SK, Noe MH, et al. Risk of incident liver disease in patients with psoriasis, psoriatic arthritis, and rheumatoid arthritis: a population-based study. J Invest Dermatol 2018;138:760–7.
[31] Bengtsson K, Forsblad-d'Elia H, Lie E, et al. Are ankylosing spondylitis, psoriatic arthritis and undifferentiated spondyloarthritis associated with an increased risk of cardiovascular events? A prospective nationwide population-based cohort study. Arthritis Res Ther 2017;19:102.
[32] Regeczy N, Balogh I, Lakos G, et al. Hypercoagulability in various autoimmune diseases: no association with factor V Leiden mutation. Haematologia (Budap) 2000;30:35–9.
[33] Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227–337.
[34] Spyropoulos AC, McGinn T, Khorana AA. The use of weighted and scored risk assessment models for venous thromboembolism. Thromb Haemost 2012;108:1072–6.
[35] Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e227S–77S.
[36] Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost 2010;8:2450–7.
[37] Spyropoulos AC, Anderson Jr FA, FitzGerald G, et al. Predictive and associative models to identify hospitalized medical patients at risk for VTE. Chest 2011;140:706–14.

[38] Solomon DH, Giles JT, Liao KP, et al. Reducing cardiovascular risk with immunomodulators: a randomised active comparator trial among patients with rheumatoid arthritis. Ann Rheum Dis 2023;82:324–30.
[39] Charles-Schoeman C, Buch MH, Dougados M, et al. Risk of major adverse cardiovascular events with tofacitinib versus tumour necrosis factor inhibitors in patients with rheumatoid arthritis with or without a history of atherosclerotic cardiovascular disease: a post hoc analysis from ORAL Surveillance. Ann Rheum Dis 2023;82:119–29.
[40] Giles JT, Sattar N, Gabriel S, et al. Cardiovascular safety of tocilizumab versus etanercept in rheumatoid arthritis: a randomized controlled trial. Arthritis Rheumatol 2020;72:31–40.
[41] Smolen JS, Landewe RBM, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis 2023;82:3–18.
[42] Wendling D, Hecquet S, Fogel O, et al. 2022 French Society for Rheumatology (SFR) recommendations on the everyday management of patients with spondyloarthritis, including psoriatic arthritis. Joint Bone Spine 2022;89:105344.
[43] Schaefer M, Schneider M, Graessler A, et al. TNF inhibitors are associated with a reduced risk of venous thromboembolism compared to csDMARDs in RA patients. Ann Rheum Dis 2020 [OP0012].
[44] Molander V, Bower H, Frisell T, et al. Venous thromboembolism with JAK inhibitors and other immune-modulatory drugs: a Swedish comparative safety study among patients with rheumatoid arthritis. Ann Rheum Dis 2023;82:189–97.
[45] Dong Z, Ye X, Chen C, et al. Thromboembolic events in Janus kinase inhibitors: a pharmacovigilance study from 2012 to 2021 based on the Food and Drug Administration's Adverse Event Reporting System. Br J Clin Pharmacol 2022;88:4180–90.
[46] Mahmoodi BK, Cushman M, Anne Naess I, et al. Association of traditional cardiovascular risk factors with venous thromboembolism: an individual participant data meta-analysis of prospective studies. circulation 2017;135:7–16.
[47] Anthonisen NR, Skeans MA, Wise RA, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med 2005;142:233–9.
[48] Daien C, Czernichow S, Letarouilly JG, et al. Dietary recommendations of the French Society for Rheumatology for patients with chronic inflammatory rheumatic diseases. Joint Bone Spine 2022;89:105319.
[49] Metsios GS, Stavropoulos-Kalinoglou A, Veldhuijzen van Zanten JJ, et al. Individualised exercise improves endothelial function in patients with rheumatoid arthritis. Ann Rheum Dis 2014;73:748–51.
[50] Lemmey AB, Marcora SM, Chester K, et al. Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial. Arthritis Rheum 2009;61:1726–34.
[51] Estruch R, Ros E, Martinez-Gonzalez MA. Mediterranean diet for primary prevention of cardiovascular disease. N Engl J Med 2013;369:676–7.
[52] https://www.ema.europa.eu/en/news/ema-recommends-measures-minimise-risk-serious-side-effects-janus-kinase-inhibitors-chronic.
[53] Khosrow-Khavar F, Kim SC, Lee H, et al. Tofacitinib and risk of cardiovascular outcomes: results from the Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis (STAR-RA) study. Ann Rheum Dis 2022;81:798–804.
[54] Taylor PC, Takeuchi T, Burmester GR, et al. Safety of baricitinib for the treatment of rheumatoid arthritis over a median of 4.6 and up to 9.3 years of treatment: final results from long-term extension study and integrated database. Ann Rheum Dis 2022;81:335–43.
[55] Charles-Schoeman C, Choy EH, McInnes IB, et al. MACE and VTE across upadacitinib clinical trial programs in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis [abstract]. Arthritis Rheumatol 2022;74.
[56] Kanjee Z, Bauer KA, Breu AC, et al. Should you treat this acutely ill medical inpatient with venous thromboembolism chemoprophylaxis? Grand rounds discussion from Beth Israel Deaconess Medical Center. Ann Intern Med 2020;172:484–91.
[57] Charles-Schoeman C, Fleischmann R, Mysler E, et al. The risk of venous thromboembolic events in patients with RA aged ≥ 50 years with ≥ 1 cardiovascular risk factor: results from a phase 3b/4 randomized safety study of tofacitinib vs. tnf inhibitors [abstract]. Arthritis Rheum 2021;73.
[58] Burmester GR, Cohen SB, Winthrop KL, et al. Safety profile of upadacitinib over 15,000 patient-years across rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and atopic dermatitis. RMD Open 2023;9:e002735.
[59] Buch M, Burmester G, Mariette X, et al. Exploratory analysis of filgotinib safety data in patients with moderately to severely active RA and an increased risk of cardiovascular events: data from phase 2 and 3 clinical trials [abstract]. Arthritis Rheum 2022;74.
[60] Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med 2016;374:1243–52.
[61] Fleischmann R, Pangan AL, Song IH, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. Arthritis Rheumatol 2019;71:1788–800.
[62] Fleischmann R, Mysler E, Bessette L, et al. Long-term safety and efficacy of upadacitinib or adalimumab in patients with rheumatoid arthritis: results through 3 years from the SELECT-COMPARE study. RMD Open 2022;8:e002012.
[63] Smolen JS, Pangan AL, Emery P, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. Lancet 2019;393:2303–11.
[64] Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Lancet 2018;391:2513–24.
[65] Buch M, Combe B, Gomez-Puerta J, et al. Outcomes of filgotinib in patients with RA aged ≥ 65 years: a post hoc subgroup analysis of phase 2 and 3 clinical trials and ongoing long-term extensions [abstract]. Arthritis Rheum 2022;74.
[66] Mease P, Charles-Schoeman C, Cohen S, et al. Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data. Ann Rheum Dis 2020;79:1400–13.
[67] Fitton J, Melville AR, Emery P, et al. Real-world single centre use of JAK inhibitors across the rheumatoid arthritis pathway. Rheumatology (Oxford) 2021;60:4048–54.
[68] Avouac J, Elhai M, Forien M, et al. Influence of inflammatory and non-inflammatory rheumatic disorders on the clinical and biological profile of type-2 diabetes. Rheumatology (Oxford) 2021;60:3598–606.
[69] Fahrni J, Husmann M, Gretener SB, et al. Assessing the risk of recurrent venous thromboembolism–a practical approach. Vasc Health Risk Manag 2015;11:451–9.
[70] Schunemann HJ, Cushman M, Burnett AE, et al. Blood Adv 2018;2:3198–225.
[71] Felder S, Rasmussen MS, King R, et al. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. Cochrane Database Syst Rev 2019;8:CD004318.
[72] Forster R, Stewart M. Anticoagulants (extended duration) for prevention of venous thromboembolism following total hip or knee replacement or hip fracture repair. Cochrane Database Syst Rev 2016;3:CD004179.
[73] Vedovati MC, Becattini C, Rondelli F, et al. A randomized study on 1-week versus 4-week prophylaxis for venous thromboembolism after laparoscopic surgery for colorectal cancer. Ann Surg 2014;259:665–9.
[74] Fleming F, Gaertner W, Ternent CA, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guideline for the prevention of venous thromboembolic disease in colorectal surgery. Dis Colon Rectum 2018;61:14–20.
[75] Salinas CA, Louder A, Polinski J, et al. Evaluation of VTE, MACE, and serious infections among patients with RA treated with baricitinib compared to TNFi: a multi-database study of patients in routine care using disease registries and claims databases. Rheumatol Ther 2023;10:201–23.