

Evidence-based Recommendations for the Management of Comorbidities in Rheumatoid Arthritis, Psoriasis, and Psoriatic Arthritis: Expert Opinion of the Canadian Dermatology-Rheumatology Comorbidity Initiative

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ABSTRACT. Objective. Comorbidities such as cardiovascular diseases (CVD), cancer, osteoporosis, and depression are often underrecognized in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or psoriasis (PsO). Recommendations may improve identification and treatment of comorbidities. The Canadian Dermatology-Rheumatology Comorbidity Initiative reviewed the literature to develop practical evidence-based recommendations for management of comorbidities in patients with RA, PsA, and PsO.

Methods. Eight main topics regarding comorbidities in RA, PsA, and PsO were developed. MEDLINE, EMBASE, and the Cochrane Library (1960–12/2012), together with abstracts from major rheumatology and dermatology congresses (2010–2012), were searched for relevant publications. Selected articles were analyzed and metaanalyses performed whenever possible. A meeting including rheumatologists, dermatologists, trainees/fellows, and invited experts was held to develop consensus-based recommendations using a Delphi process with prespecified cutoff agreement. Level of agreement was measured using a 10-point Likert scale (1 = no agreement, 10 = full agreement) and the potential effect of recommendations on daily clinical practice was considered. Grade of recommendation (ranging from A to D) was determined according to the Oxford Centre for Evidence-Based Medicine evidence levels.

Results. A total of 17,575 articles were identified, of which 407 were reviewed. Recommendations were synthesized into 19 final recommendations ranging mainly from grade C to D, and relating to a large spectrum of comorbidities observed in clinical practice: CVD, obesity, osteoporosis, depression, infections, and cancer. Level of agreement ranged from 80.9% to 95.8%.

Conclusion. These practical evidence-based recommendations can guide management of comorbidities in patients with RA, PsA, and PsO and optimize outcomes. (First Release July 15 2015; J Rheumatol 2015;42:1767–80; doi:10.3899/jrheum.141112)

Key Indexing Terms:

PSORIATIC ARTHRITIS RHEUMATOID ARTHRITIS COMORBIDITY PSORIASIS

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AbbVie sponsored a meeting on the management of comorbidities, held in Toronto, Ontario, Canada, on May 31 to June 1, 2013. This publication summarizes the results of the Canadian Dermatology-Rheumatology (DR) Co-morbidity Initiative systematic literature searches (MEDLINE, EMBASE, Cochrane Library, 2010–2012 American College of Rheumatology, European League Against Rheumatism, American Academy of Dermatology, European Academy of Dermatology and Venereology

abstracts) and consensus-based recommendations from that meeting. AbbVie provided funding to Pinnacle Marketing and Education Inc. to manage the Canadian DR Co-morbidity Initiative that led to this paper. AbbVie paid consultancy fees to BH, JP, LB, SK, RB, WG, JD, CL, and JK for their participation in the Canadian DR Co-morbidity Initiative. AbbVie paid Leading Edge for editorial support.

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Patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and psoriasis (PsO) are at increased risk of comorbidities such as cardiovascular diseases (CVD; likely related to accelerated atherosclerosis and systemic inflammation), osteoporosis, depression, infections, and cancer^{1,2}.

Comorbidities should be considered when managing patients with RA³, PsA, or PsO⁴, because these conditions contribute to increased early mortality, affect disease activity and response to treatments, and generate costs in these populations⁵. Further, medications used to manage the underlying inflammatory condition, including disease-modifying antirheumatic drugs (DMARD), tumor necrosis factor inhibitors (TNFi), corticosteroids (CS), and nonsteroidal antiinflammatory drugs (NSAID), may also increase or, conversely, decrease the likelihood of comorbidities.

The Canadian Dermatology-Rheumatology (DR) Comorbidity Initiative has combined scientific evidence with the clinical expertise of a panel of Canadian rheumatologists and dermatologists to develop detailed, evidence-based, practical recommendations for managing comorbidities in patients with RA, PsA, or PsO, in line with the 3E Initiative (Evidence, Expertise, Exchange) in rheumatology⁶. The target population for these recommendations is adults (aged > 18 yrs) with RA, PsA, or PsO, and the target users are rheumatologists, dermatologists, and other healthcare providers who treat patients with these conditions and who should be aware of specific comorbidity management.

MATERIALS AND METHODS

The Canadian DR Comorbidity Initiative group consisted of a steering committee, a bibliographic team, and an expert committee. The steering committee included 2 co-chairs [1 rheumatologist (BH) and 1 dermatologist (RB)], as well as 6 members [3 rheumatologists (LB, SK, and JP) and 3 dermatologists (JD, WG, and CL)]. The bibliographic team included 4 rheumatology trainees (CR, TS, AM, and SS) and 4 dermatology trainees (VR, CM, PF, and JK) who conducted the literature reviews. Eight Canadian rheumatologists and dermatologists from across Canada formed the expert committee (MK, DL, JT, ES, MB, PL, MG, and CH) that reviewed the evidence from the literature reviews and contributed to formulate practice recommendations.

The focus of the initiative was on comorbidities shared by RA and PsO/PsA. A comorbidity was defined as a condition that is associated with RA or PsO/PsA, but is not a systemic manifestation of the disease.

A Delphi voting process was used to select the comorbidities addressed

in this review. The 8 comorbidity topics that obtained the highest level of agreement in the Delphi vote (including CVD risk and outcomes, smoking, weight, malignancies, infections, osteoporosis, and depression) were then reformulated into searchable terms, according to the Population, Intervention, Comparison, Outcome method⁷. Each question could be subdivided into several parts to cover all facets of the topic, resulting in a total of 21 questions. A systematic literature review was performed for each question. Other comorbidities, such as chronic obstructive pulmonary disease/asthma, impaired renal function, and hypertension (HTN) were proposed, but did not get enough votes to be in the 8 selected topics.

A search of MEDLINE (by PubMed), Cochrane, and EMBASE databases from 1960 to December 2012, restricted to articles published in English, was carried out by the bibliographic team with the help of experienced librarians. The proceedings of relevant annual scientific meetings [American College of Rheumatology, European League Against Rheumatism (EULAR), American Academy of Dermatology, and European Academy of Dermatology and Venereology] from 2010 to 2012 were also searched. Additional references were identified by a hand search of reference lists from key articles. Titles, abstracts, and the full text of retrieved articles were screened according to predefined inclusion and exclusion criteria. Selected studies were reviewed for methodological quality assessment according to the levels of evidence of the Oxford Centre for Evidence-Based Medicine (www.cebm.net/?o=1025). Data extraction and synthesis were performed using a predefined data collection form. The evidence per question was summarized and random-effects metaanalyses performed when possible using RevMan (version 5.2) or Stata Software (version 12.0). Forest plots were constructed to summarize the adjusted relative risk (RR) estimates and their 95% CI. Q-tests (I²) were performed to measure heterogeneity across studies.

Summaries of the literature searches for the 8 main topics were presented to the Canadian expert committee. Nineteen recommendations were established using a Delphi voting process with prespecified cutoff agreement (75%). Committee members voted on their level of agreement using a scale of 1 to 10 (1 = no agreement, 10 = full agreement). If ≥ 75% of participants scored within the predetermined agreement range, then the recommendation was deemed to be agreed upon. If < 75% of participants scored within this range, the recommendation was debated and revised, and a second vote was taken (prespecified cutoff agreement of 66%). Each recommendation could be voted on a maximum of 3 times (prespecified cutoff agreement of 50%). Of note, all recommendations were agreed during the first round of voting. The grade of recommendation, ranging from A to D according to the levels of the related studies, was determined according to the Oxford Centre for Evidence-Based Medicine levels of evidence. The potential effect of each recommendation on practice was assessed using a Delphi vote with 3 statements: (1) "This recommendation will change my practice", (2) "This recommendation will not change my practice as it is already my practice", and (3) "This recommendation will not change my practice as I do not want to change my practice for this aspect."

This article presents the 19 recommendations while the details and results of the systematic literature review for each topic will be published separately.

RESULTS

The 8 research topics are listed in Table 1. A total of 17,575 articles were identified in the literature search, of which 407 were reviewed (Table 2). The 19 Canadian recommendations for the management of comorbidities in RA, PsA, and PsO are listed in Table 3, with the corresponding level of evidence and grade of recommendation. The effect on practice, as voted by the Canadian DR Comorbidity Initiative group (steering committee, bibliographic fellows, and expert committee), is reported in Table 4.

Recommendation 1. Individuals with RA, PsA, and PsO have

Table 1. Eight research questions relating to comorbidities in patients with RA, PsA, or PsO formulated by the Canadian Dermatology-Rheumatology Comorbidity Initiative.

Question	Description
1.	What are the risks of CVD in patients with RA, PsA, and PsO, including the effect of disease severity, disease duration, and comparison with traditional CV risk factors?
2.	Does the treatment of RA, PsA, and PsO with systemic agents have an effect on CV outcomes?
3.	Smoking: What is the prevalence of smoking in patients with RA, PsA, or PsO? What effect does smoking have on disease activity? What is the efficacy of smoking cessation strategies in terms of disease activity and response to treatment?
4.	Weight: Does weight/BMI relate to disease activity in RA, PsA, and PsO? What is the effect of treatment on weight? What is the effect of weight on response to treatment? What is the effect of weight management on disease activity?
5.	Other comorbidities: Are there any differences in malignancies and infections between patients with RA, PsA, and PsO? How common are malignancies and infections in these populations? What is the effect of treatment on malignancies and infections?
6.	Malignancies: Is there an increased risk of cancer recurrence or new cancers in patients with RA, PsA, or PsO with previous cancer treated with traditional DMARD or biologic DMARD?
7.	Osteoporosis: Is osteoporosis related to disease activity and biomarkers? What is the effect of treatment on osteoporosis?
8.	Depression: What is the prevalence of depression in patients with RA, PsA, or PsO? What are the risk factors for depression? What is the effect of treatment on depression?

RA: rheumatoid arthritis; PsA: psoriatic arthritis; PsO: psoriasis; CVD: cardiovascular diseases; CV: cardiovascular; BMI: body mass index; DMARD: disease-modifying antirheumatic drugs.

Table 2. Results of the systematic literature search for each of the 8 recommendation topics. Values are n.

Recommendations	References Identified by Systematic Literature Search	References Included in the Systematic Reviews
Risks of CV disease	3457	110
Effect of treatment on CV disease	2630	34
Smoking	1140	66
Weight	2108	88
Malignancies and infections	1993	47
Risk of cancer recurrence or new cancer linked to treatment	3428	6
Osteoporosis	2280	40
Depression	539	16
Total	17,575	407

CV: cardiovascular.

a greater risk of CVD than the general population. The diseases themselves and traditional risk factors contribute to this risk. The risk of myocardial infarction (MI) in RA is comparable to that in diabetes mellitus. This should be recognized by healthcare providers and patients (Grade of Recommendation: C).

Recommendation 2. Traditional modifiable risk factors should be screened for and managed appropriately to reduce the risk of CVD in RA, PsA, and PsO populations (Grade of Recommendation: D).

Based on our metaanalyses, patients with RA experience increased risk of all-cause early mortality (RR 1.59, 95% CI 1.47–1.71, 50 studies) and CV mortality (RR 1.58, 95% CI 1.47–1.70, 36 studies) compared with nonrheumatic populations, as well as elevated risk of overall CVD (RR 1.66, 95%

CI 1.51–1.82, 11 studies)⁸. Our metaanalyses showed that patients with PsO also have increased risk of CV mortality (RR 1.32, 95% CI 1.12–1.57, 7 studies), CVD (RR 1.29, 95% CI 1.11–1.50, 5 studies), and all other CV outcomes [including peripheral artery disease (PAD), cerebrovascular accident, MI, and ischemic heart disease], but not all-cause early mortality⁸. Based on our metaanalysis of 6 trials, patients with PsA also have higher risk of early all-cause mortality (RR 1.46, 95% CI 1.03–2.07) and CV mortality (RR 1.61, 95% CI 1.09–2.38) relative to the nonpsoriatic population⁸. No significant increase in risk of overall CVD was demonstrated for patients with PsA because of the paucity of data, although an increase in PAD and heart failure (HF) was found.

Using rheumatoid factor (RF) as a marker of increased disease severity, studies reported either an increased all-cause mortality rate^{9,10,11} or no difference in all-cause mortality rate¹² in RF-positive patients compared with RF-negative patients. No studies showed increased CV mortality in RF-positive patients, although some argued for an increased CV event (CVE) rate^{13,14}. Moreover, general trends toward increased rates of various CV and mortality outcomes were found in patients with RA with more severe disease (erosive joint disease, extraarticular features, increased active joints, and lower functional class)^{11,13,14,15,16,17,18} and in patients with PsO with more severe disease^{19,20,21}. No studies assessing the relationship between PsA severity and CV outcomes were found. In RA, PsA, and PsO, no clear association was reported between all-cause mortality, CV mortality, MI, or CVD and disease duration, which was inconsistently defined across studies.

After correcting for confounders, multiple studies also showed that RA^{22,23,24,25} and PsO^{26,27,28} are independent risk factors for various CV outcomes. One study²⁴ demonstrated

Table 3. Recommendations for the management of comorbidities in RA, PsA, and PsO from the Canadian Dermatology-Rheumatology Comorbidity Initiative. Listed according to the levels of evidence and grades of recommendations of the Oxford Centre for Evidence-Based Medicine (www.cebm.net/?o=1025).

Topic	#	Recommendation Description	Level of Evidence	Grade of Recommendation	Level of Agreement, %
Risks of CVD	1.	Individuals with RA, PsA, and PsO have a greater risk of CVD than the general population. The diseases themselves and traditional risk factors contribute to this risk. The risk of MI in RA is comparable to that in DM. This should be recognized by healthcare providers and patients.	2b, 3b (RA), 2b, 5 (PsA), 2b (PsO)	C	87.7
	2.	Traditional modifiable risk factors should be screened for and managed appropriately to reduce the risk of CVD in RA, PsA, and PsO populations.	5	D	95.8
Effect of treatment on CVD	3.	CS use should be minimized in RA, especially in patients with CV risk factors.	2b, 5	C	93.3
	4.	In patients with RA or PsA, especially those with additional CV risk factors, the risk and benefits of NSAID use should be weighed.	3b, 5	C	91.9
	5.	Healthcare providers and patients should be aware that MTX and/or TNFi use may decrease the risk of CVE in RA. Their use may help to reduce CS and NSAID use, especially in patients with CV risk factors.	2b, 5	C	84.6
	6.	Healthcare providers and patients should be aware that MTX and/or TNFi use may decrease the risk of CVD in PsA/PsO.	2b, 5	C	83.3
Smoking	7.	Statement: Current smoking is associated with an increased prevalence and/or incidence and possibly a negative effect on disease severity in RA, PsA, and PsO. Recommendation: Smoking status should be determined in all patients with RA, PsA, and PsO and smoking cessation should be encouraged.	2b, 5 5	C D	94.6
Weight	8.	Statement: PsO severity may be associated with increased BMI and obesity. Increased BMI may be associated with increased disease activity of RA and PsO. Recommendation: Healthcare providers should be aware that higher BMI is associated with a reduced treatment response in RA, PsA, and PsO. TNFi may be associated with a mild increase in weight in RA, PsA, and PsO, but the clinical relevance is unknown.	4, 5 (RA), 3b, 4, 5 (PsA), 2b, 5 (PsO)	C	82.2
	9.	Statement: The effects of dietary manipulations on disease activity in RA, PsA, and PsO are still uncertain. Recommendation: BMI should be determined in all patients with RA, PsA, and PsO.	5	D	80.9
	10.	Healthcare providers should encourage healthy BMI.	5	D	93.8
	11.	Patients and healthcare providers should be aware of increased risk of infection when initiating systemic therapies (biologics, DMARD, CS), especially in RA.	2b, 5	C (RA), D (PsA, PsO)	94.5
Malignancies and infections	12.	Risk of infection should be assessed (including relevant comorbidities) when initiating systemic therapy.	2b, 5	C (RA), D (PsA, PsO)	90.4
	13.	Prior to initiating systemic therapy, additional cancer screening beyond the nationally recommended guidelines for age and sex is not required. Individuals at increased risk for skin cancer may require closer monitoring.	2b, 5	C	89.2
	14.	In the absence of sufficient data on recurrent cancer, patients with a prior cancer or new cancer should be informed about a potential risk of new or recurrent cancers when treated for RA, PsA, or PsO with TNFi or some of the DMARD.	2b, 5	C	87.1
Risk of cancer recurrence or new cancer	15.	Individual disease-specific risk factors and markers for increased disease severity in RA, PsA, and PsO do not appear to be associated with increased bone loss. Usual profiling with standardized methods should be used to assess risk of osteoporosis and fracture.	4	D	86.3
	16.	Systemic CS have a negative effect on BMD. Usual CS-induced osteoporosis guidelines for prevention and treatment should be followed.	1b (RA), 5 (PsA, PsO)	A (RA), B (PsA, PsO)	92.5
Depression	17.	Healthcare providers should be aware of increased symptoms of depression in patients with RA, PsA, or PsO. Patients should be screened for these symptoms and managed appropriately.	2b, 5 (RA), 3b, 5 (PsA, PsO)	C	90
	18.	Healthcare providers treating RA, PsA, and PsO should be aware that symptoms of depression may affect disease activity measures and that disease symptoms may affect depression scores.	3b, 5 (RA), 5 (PsA, PsO)	D	92.2
	19.	Healthcare providers should be aware that disease control may reduce symptoms of depression in patients with RA, PsA, and PsO.	1b, 5 (PsO), 5 (RA, PsA)	B (PsO), D (RA, PsA)	90

RA: rheumatoid arthritis; PsA: psoriatic arthritis; PsO: psoriasis; CVD: cardiovascular diseases; MI: myocardial infarction; DM: diabetes mellitus; CS: corticosteroids; CV: cardiovascular; NSAID: nonsteroidal antiinflammatory drugs; MTX: methotrexate; TNFi: tumor necrosis factor inhibitors; CVE: cardiovascular events; BMI: body mass index; DMARD: disease-modifying antirheumatic drugs; BMD: bone mineral density.

Table 4. Effect of recommendation for comorbidity management on clinical practice, as voted by the Canadian Dermatology–Rheumatology Comorbidity Initiative group (steering committee, bibliographic fellows, and expert committee). Of note, recommendation 3 has no available data because of a technical failure of the voting system. Values are %.

Topic	Recommendation #	Description	The Recommendation Will Change my Practice	The Recommendation is Already My Practice	I Do Not Want to Change My Practice for This Aspect
Risks of CVD	1.	Individuals with RA, PsA, and PsO have a greater risk of CVD than the general population. The diseases themselves and traditional risk factors contribute to this risk. The risk of MI in RA is comparable to that in DM. This should be recognized by healthcare providers and patients.	36	55	9
	2.	Traditional modifiable risk factors should be screened for and managed appropriately to reduce the risk of CVD in RA, PsA, and PsO populations.	43	53	4
	3.	CS use should be minimized in RA, especially in patients with CV risk factors.	NA	NA	NA
Effect of treatment on CVD	4.	In patients with RA or PsA, especially those with additional CV risk factors, the risk and benefits of NSAID use should be weighed.	19	57	24
	5.	Healthcare providers and patients should be aware that MTX and/or TNFi use may decrease the risk of CVE in RA. Their use may help to reduce CS and NSAID use, especially in patients with CV risk factors.	50	25	25
	6.	Healthcare providers and patients should be aware that MTX and/or TNFi use may decrease the risk of CVD in PsA/PsO.	29	54	17
Smoking	7.	Smoking status should be determined in all patients with RA, PsA, and PsO and smoking cessation should be encouraged.	13	87	0
Weight	8.	Healthcare providers should be aware that higher BMI is associated with a reduced treatment response in RA, PsA, and PsO. TNFi may be associated with a mild increase in weight in RA, PsA, and PsO, but the clinical relevance is unknown.	32	64	4
	9.	BMI should be determined in all patients with RA, PsA, and PsO.	33	50	17
	10.	Healthcare providers should encourage healthy BMI.	22	74	4
Malignancies and infections	11.	Patients and healthcare providers should be aware of increased risk of infection when initiating systemic therapies (biologics, DMARD, CS), especially in RA.	12	88	0
	12.	Risk of infection should be assessed (including relevant comorbidities) when initiating systemic therapy.	17	83	0
	13.	Prior to initiating systemic therapy, additional cancer screening beyond the nationally recommended guidelines for age and sex is not required. Individuals at increased risk for skin cancer may require closer monitoring.	35	65	0
Risk of cancer recurrence or new cancer	14.	In the absence of sufficient data on recurrent cancer, patients with a prior cancer or new cancer should be informed about a potential risk of new or recurrent cancers when treated for RA, PsA, or PsO with TNFi or some of the DMARD.	35	65	0
Osteoporosis	15.	Individual disease-specific risk factors and markers for increased disease severity in RA, PsA, and PsO do not appear to be associated with increased bone loss. Usual profiling with standardized methods should be used to assess risk of osteoporosis and fracture.	17	61	22
	16.	Systemic CS have a negative effect on BMD. Usual CS-induced osteoporosis guidelines for prevention and treatment should be followed.	9	86	5
Depression	17.	Healthcare providers should be aware of increased symptoms of depression in patients with RA, PsA, or PsO. Patients should be screened for these symptoms and managed appropriately.	48	38	14
	18.	Healthcare providers treating RA, PsA, and PsO should be aware that symptoms of depression may affect disease activity measures and that disease symptoms may affect depression scores.	50	41	9
	19.	Healthcare providers should be aware that disease control may reduce symptoms of depression in patients with RA, PsA, and PsO.	55	35	10

RA: rheumatoid arthritis; PsA: psoriatic arthritis; PsO: psoriasis; CVD: cardiovascular diseases; MI: myocardial infarction; DM: diabetes mellitus; CS: corticosteroids; CV: cardiovascular; NSAID: nonsteroidal antiinflammatory drugs; MTX: methotrexate; TNFi: tumor necrosis factor inhibitors; CVE: cardiovascular events; BMI: body mass index; DMARD: disease-modifying antirheumatic drugs; BMD: bone mineral density; NA: not available.

that RA and diabetes mellitus pose a similar risk for MI. There were no data specifically for PsA.

The whole group agreed that randomized controlled trials are required to determine whether targeting traditional CV risk factors affects CV mortality and morbidity in patients with RA, PsA, or PsO, and that further research should define high-risk patients with CV and develop appropriate targets.

Recommendation 3. CS use should be minimized in RA, especially in patients with CV risk factors (Grade of Recommendation: C).

Recommendation 4. In patients with RA or PsA, especially those with additional CV risk factors, the risks and benefits of NSAID use should be weighed (Grade of Recommendation: C).

Few studies have evaluated the effect of CS or NSAID specifically on CVE in patients with RA (11 studies for CS and 8 studies for NSAID). Our metaanalyses showed that risk of all CVE was increased by use of both CS (RR 1.47, 95% CI 1.34–1.60) and NSAID (RR 1.18, 95% CI 1.01–1.38)²⁹. In RA, CS use increased the risk of all CV outcomes, including MI, HF, stroke, and major adverse cardiac events (MACE), while NSAID [including both cyclooxygenase (COX)-2 inhibitors and nonselective NSAID] increased stroke risk, but demonstrated no significant effect on MI, HF, or MACE. Use of COX-2 inhibitors significantly increased the risk of all CVE (RR 1.36, 95% CI 1.10–1.67) whereas nonselective NSAID did not (RR 1.08, 95% CI 0.94–1.24)²⁹. It is, however, noteworthy that some studies assessing the COX-2 inhibitor rofecoxib, which has already been withdrawn from the market, were included in the meta-analysis. Hence, we performed separate metaanalyses for rofecoxib and another COX-2 inhibitor, celecoxib²⁹. While rofecoxib increased the risk of all CVE (RR 1.58, 95% CI 1.24–2.00), celecoxib did not (RR 1.03, 95% CI 0.80–1.32). No specific studies on the CV effects of CS or NSAID in PsA or PsO were found. However, the whole group agreed that the present recommendation for patients with RA regarding NSAID should be extrapolated to patients with PsA with coexisting CV risk factors.

Recommendation 5. Healthcare providers and patients should be aware that methotrexate (MTX) and/or TNFi use may decrease the risk of CVE in RA. Their use may help to reduce CS and NSAID use, especially in patients with CV risk factors (Grade of Recommendation: C).

The risk of CVE was significantly decreased by use of TNFi (RR 0.70, 95% CI 0.54–0.90) or MTX (RR 0.72, 95% CI 0.57–0.91; metaanalysis of 16 and 8 studies, respectively)²⁹. TNFi specifically decreased the risk of MI (RR 0.59, 95% CI 0.36–0.97), stroke (RR 0.57, 95% CI 0.35–0.92), and MACE (RR 0.30, 95% CI 0.15–0.57), but had no significant effect on HF risk (RR 0.75, 95% CI 0.49–1.15). MTX specifically decreased the risk of MI (RR 0.81, 95% CI 0.68–0.96) and had a tendency to reduce HF (RR 0.80, 95% CI 0.60–1.00); however, no significant effect

on stroke (RR 0.78, 95% CI 0.40–1.50) or MACE (RR 0.38, 95% CI 0.05–2.84) was found, probably because of insufficient data.

Recommendation 6. Healthcare providers and patients should be aware that MTX and/or TNFi use may decrease risk of CVD in PsA/PsO (Grade of Recommendation: C).

Less evidence regarding the effect of therapy on CVE was found in PsA and PsO compared with RA. Our metaanalysis of 6 studies evaluated the pooled effect of any systemic therapy (including phototherapy) compared with topical treatment or the absence of systemic therapy on all CVE in PsA and PsO. This showed that systemic therapy significantly decreased the risk of all CVE in PsA and PsO (RR 0.75, 95% CI 0.63–0.91)²⁹. No stratification according to specific treatment or individual CV endpoint could be performed.

Recommendation 7. Smoking status should be determined in all patients with RA, PsA, and PsO (Grade of Recommendation C) and smoking cessation should be encouraged (Grade of Recommendation: D).

Our metaanalysis of 19 studies showed an RR for current smoking of 1.49 (95% CI 1.20–1.85) in patients with RA compared with patients without RA. Sensitivity analyses revealed that the RR for current smoking was maintained in patients with RA when evaluated in the following subgroups: men (RR 1.84, 95% CI 1.53–2.21), women (RR 1.21, 95% CI 1.02–1.64), patients with early RA (RR 1.35, 95% CI 1.25–1.45), patients with established RA (RR 1.36, 95% CI 1.22–1.52), current smokers (RR 1.43, 95% CI 1.34–1.53), and ex-smokers (RR 1.17, 95% CI 1.06–1.29). Interestingly, an increased prevalence of current smoking was found in RF-positive patients (RR 1.56, 95% CI 1.32–1.84), but not RF-negative patients, and anticitrullinated protein antibodies (ACPA)-positive patients (RR 1.64, 95% CI 1.45–1.84), but not ACPA-negative patients. Very limited and heterogeneous evidence suggested some association between smoking and greater disability in RA [as assessed by the Health Assessment Questionnaire (HAQ)]^{30,31}, but no significant association was found between smoking and other markers of disease activity, such as Disease Activity Score at 28 joints (DAS28), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or the Larsen score for radiographic joint damage. No study was found that evaluated the effect of smoking cessation on RA disease severity.

In PsO, our metaanalysis pooling data from 22 studies showed an RR for current smoking of 1.88 (95% CI 1.66–2.13) in patients with PsO compared with individuals without PsO. Various sensitivity analyses confirmed the increased prevalence of smoking in patients with PsO. Current smokers were found to have an RR of new-onset PsO of 1.94 (95% CI 1.64–2.28) compared with never smokers³². No clear association was found between PsO severity and smoking intensity, which was inconsistently defined across studies. While 8 studies suggested that increased PsO disease severity may be related to cigarette smoking^{33,34,35,36,37,38,39,40},

3 other studies did not^{41,42,43}. An RR of 3.12 (95% CI 2.07–4.69) for current smoking in new-onset PsA⁴⁴ and worse self-reported pain scores in smokers with PsA⁴⁵ were reported.

Therefore, the whole group agreed that current smoking is associated with RA, PsA, and PsO, and possibly has a negative effect on disease severity. Smoking is also associated with multiple well-established health issues, for which patients with RA, PsA, and PsO may already be at an increased risk. Thus, despite the absence of data on the effect of smoking cessation on RA, PsA, and PsO disease severity, smoking status should be determined in all patients with RA, PsA, and PsO, and smoking cessation encouraged.

Recommendation 8. Healthcare providers should be aware that higher body mass index (BMI) is associated with a reduced treatment response in RA, PsA, and PsO. TNFi may be associated with a mild increase in weight in RA, PsA, and PsO, but the clinical relevance is unknown (Grade of Recommendation: C).

Recommendation 9. BMI should be determined in all patients with RA, PsA, and PsO (Grade of Recommendation: D).

Recommendation 10. Healthcare providers should encourage healthy BMI (Grade of Recommendation: D).

No clear association between weight and disease activity or severity could be evidenced in RA. Conflicting heterogeneous studies provided mixed data that could not be pooled in a metaanalysis. Although BMI in the obese range was associated with more disease activity^{46,47}, some studies also found an association between higher BMI and lower mortality⁴⁸, lower rate of erosion changes⁴⁹, and less severe disease in ACPA-positive patients⁴⁹, and between decreased BMI or cachexia and increased early mortality^{50,51}, increased disability⁵², and increased joint space narrowing⁵³. Finally, 2 studies did not find any association between BMI and RA disease activity^{54,55}.

In PsO, disease severity may be associated with increased BMI or obesity^{43,56,57,58,59,60}. PsO was also reported to be associated with obesity or BMI > 25 kg/m², regardless of severity^{61,62,63}. In PsA, only 2 studies suggested that higher weight or BMI was associated with increased incidence of PsA^{57,64}, and no studies were found that assessed the relationship between PsA severity and BMI.

TNFi have been associated with weight gain in RA⁶⁵, PsA⁶⁶, and PsO^{67,68}. Obese patients with PsO^{69,70,71,72}, PsA^{73,74,75}, or RA^{76,77} may have a reduced response to treatment compared with nonobese patients, especially to biologic agents. Additionally, obese patients with PsO with a moderate-to-severe disease may increase their response to low-dose cyclosporine if a calorie-controlled diet is included in their treatment regimen⁷⁸, and bariatric surgery in obese patients with PsO was found to improve PsO in very small case series^{79,80}. The effects of dietary interventions on RA disease activity are uncertain⁸¹.

Recommendation 11. Patients and healthcare providers

should be aware of increased risk of infection when initiating systemic therapies (biologics, DMARD, CS), especially in RA (Grade of Recommendation C for RA, and Grade of Recommendation D for PsA and PsO).

Recommendation 12. Risk of infection should be assessed (including relevant comorbidities) when initiating systemic therapy (Grade of Recommendation C for RA, and Grade of Recommendation D for PsA and PsO).

Based on 7 studies, the average incidence rate of serious infections (defined as infections requiring hospitalization or treatment with intravenous antibiotics, without considering opportunistic infections) in subjects treated with TNFi was higher in RA [5/100 person-yrs (PY)] than in PsA (1.5/100 PY) or PsO (1/100 PY). Our metaanalysis solely included studies that reported incidence rates of serious infections. An increased risk of serious infections was found in subjects treated with systemic therapy, although there was stronger evidence in RA with 14 studies (RR 1.62, 95% CI 1.36–1.93) compared with 2 studies in PsO (RR 1.61, 95% CI 1.24–2.10)^{82,83} and 1 in PsA (RR 1.08, 95% CI 0.07–17.11)⁸⁴. TNFi initiation appeared to be associated with a higher risk of serious infections in RA (RR 1.68, 95% CI 1.40–2.01, based on 13 studies) than in PsA and PsO⁸⁵, possibly related to patient comorbidities and to the more frequent use of CS in RA^{82,86,87}. The interpretation of the PsO results is limited by the fact that the 2 included studies were not randomized. Therefore, the results may be related to differences in the populations exposed to treatment and those not exposed to treatment. The methodology of our metaanalysis in PsO was also different from a larger metaanalysis that did not find evidence of any increased risk of serious infections in patients with PsO treated with TNFi⁸⁸. Nevertheless, the experts agreed that while the evidence in patients with PsA and PsO treated with TNFi is unclear, this class of medication may increase the risk of serious infection. It was recommended that the risk of infection be assessed when initiating systemic therapy in the 3 diseases.

Recommendation 13. Prior to initiating systemic therapy, additional cancer screening beyond the nationally recommended guidelines for age and sex is not required. Individuals at increased risk for skin cancer may require closer monitoring (Grade of Recommendation: C).

Based on data from 8 studies, the average incidence rate of overall malignancies in subjects treated with TNFi was calculated at 1.8/100 PY for RA, 0.6/100 PY for PsA, and 1.7/100 PY for PsO. Our metaanalysis in subjects treated with systemic therapy found an overall RR of malignancy of 1.25 (95% CI 0.88–1.78) in RA and 1.12 (95% CI 0.88–1.42) in PsO. The RR of malignancy could not be estimated in PsA because of the lack of data. The initiation of TNFi was not associated with an increased incidence of overall malignancy in RA (RR 1.29, 95% CI 0.88–1.89) and could not be estimated in PsA or PsO because of insufficient data^{85,89,90}. Although site-specific malignancy analysis was not

performed, previous studies have shown that the risk of non-melanoma skin cancer and melanoma may be increased, particularly in RA. TNFi may contribute to this increased risk, but results are not consistent^{85,90,91,92}.

Recommendation 14. In the absence of sufficient data on recurrent cancer, patients with a prior cancer should be informed about a potential risk of new or recurrent cancer when treated for RA, PsA, or PsO with TNFi or some of the DMARD (Grade of Recommendation: C).

In RA, 2 cohort studies based on European registries [the Rheumatoid Arthritis Observation of Biologic Therapy cohort (RABBIT) and the British Society of Rheumatologists Biologics Registry (BSRBR)] assessing patients with RA with prior cancer^{89,93} and 1 cohort study of patients with cervical carcinoma *in situ*⁹⁴ compared the risk of recurrent or new cancers in patients with RA treated with TNFi versus patients with RA treated with conventional DMARD. In the RABBIT cohort of 122 patients with 124 prior cancers, 9 recurrent cancers occurring in 8 TNFi recipients were reported [incidence rate (IR) 45.5/1000 PY], compared with 5 recurrent cancers occurring in 5 DMARD recipients (IR 31.4/1000 PY)⁸⁹. In the BSRBR cohort of 177 patients with prior cancer treated with TNFi compared to 117 patients with prior cancer treated with conventional DMARD, 13 recurrent cancers in 11 TNFi recipients and 9 cancers in 9 DMARD recipients were reported, resulting in a crude IR of 25.3 and 38.3/1000 PY, respectively⁹³. The overall combined incidence rate ratio of recurrent malignancy was 0.87 (95% CI 0.45–1.70) for TNFi compared with conventional DMARD. From the cohort of 238 patients with RA with a history of cervical carcinoma *in situ*, no genital cancer was observed in the TNFi-treated group over a median of 5.2 years of followup compared with 2 incident genital cancers in the DMARD-treated group, during a median followup of 3.9 years⁹⁴. No studies were found that evaluated the risk of recurrent cancer in patients with PsA or PsO treated with TNFi compared with traditional DMARD.

Although current studies did not demonstrate an increased RR of recurrent or new cancer, the expert panel felt that patients treated with TNFi should be aware that they may have an increased risk of recurrent malignancy, this risk being difficult to quantify because of insufficient data from studies that included a very limited number of patients with prior cancer.

Recommendation 15. Individual disease-specific risk factors and markers for increased disease severity in RA, PsA, and PsO do not appear to be associated with increased bone loss. Usual profiling with standardized methods should be used to assess risk of osteoporosis and fracture (Grade of Recommendation: D).

No significant correlations were found between bone loss and disease duration, function as measured by HAQ, disease activity as measured by the DAS (RA, PsA), skin involvement as measured by the Psoriasis Area Severity

Index (PsA, PsO), joint erosions, ESR, CRP, RF (RA), ACPA (RA), and smoking status (RA). One cohort study in RA showed negative correlations between DAS and 5-year hand bone mineral density (BMD) in multivariate analysis⁹⁵. Univariate analysis also showed a correlation between 5-year BMD and HAQ, RF, and CRP; however, this association was not maintained in multivariate models. Experts recommended using standardized tools/risk profiling in assessing risk of osteoporosis in patients with RA, PsA, and PsO.

Recommendation 16. Systemic CS have a negative effect on BMD. Usual CS-induced osteoporosis guidelines for prevention and treatment should be followed (Grade of Recommendation A for RA, and Grade of Recommendation B for PsA and PsO).

In RA, our metaanalysis of randomized controlled trials that studied the effects of CS on bone loss showed an association between oral CS use and lumbar spine bone loss (mean difference in Δ BMD -0.3 , 95% CI $-0.55 - -0.04$)⁹⁶. Included studies used an average daily dose of prednisone or prednisolone ranging from 6 mg to 12 mg for a study period ranging from 20 weeks up to 2 years. Oral CS did not have any significant effect on hip bone loss in RA during the treatment period^{97,98,99,100,101,102}. A literature search did not yield any randomized controlled trials studying the effect of CS on bone loss in PsA or PsO. However, experts agreed that all patients who start taking systemic CS should be managed according to the usual CS-induced osteoporosis guidelines.

There is insufficient evidence to suggest a preferred route of CS administration to minimize bone loss. In 1 study, monthly administration of intramuscular CS was associated with lower hip BMD compared with placebo¹⁰³. Another study found that patients who received monthly pulses of intravenous methylprednisolone required lower cumulative doses of CS and had less bone loss compared with those who received daily oral methylprednisolone¹⁰⁴.

Recommendation 17. Healthcare providers should be aware of increased symptoms of depression in patients with RA, PsA, or PsO. Patients should be screened for these symptoms and managed appropriately (Grade of Recommendation: C).

Several studies have examined the prevalence of symptoms of depression in patients with RA, PsA, and PsO^{105,106,107,108,109,110,111} based on 1 or more depression rating scales that do not allow diagnosis of major depressive disorders, but can be suggestive of depression past a certain threshold. Because of the wide variability of the scales, data could not be pooled to perform a metaanalysis. In RA, a large retrospective cohort found that 15.2% of patients with RA had self-reported depression¹⁰⁵, a prevalence that is similar to patients with noninflammatory rheumatic diseases (14.5%), but less than patients with systemic lupus erythematosus (32.5%) or fibromyalgia (37.9%). A case-control study reported a prevalence of symptoms of depression of 30% in patients with RA¹⁰⁶. Two retrospective cohorts found

that all-cause mortality was higher in patients with both RA and depression compared with those with RA alone^{105,107}.

Regarding PsA, no studies were found that have compared the rate of symptoms of depression in patients with PsA to healthy controls. In a quasi-experimental study, the rate of symptoms of depression was higher in patients with both PsA and PsO compared with those with PsO alone¹⁰⁸. For PsO, 2 case-control studies found higher rates of symptoms of depression in patients with PsO compared with healthy controls^{109,110} and another study reported that 21% of patients experienced symptoms of depression using the Beck Depression Inventory scale, which was comparable to patients with prurigo nodularis¹¹¹.

Recommendation 18. Healthcare providers treating RA, PsA, and PsO should be aware that symptoms of depression may affect disease activity measures and that disease symptoms may affect depression scores (Grade of Recommendation D).

Some associations between RA disease activity and symptoms of depression severity were found^{106,112,113,114,115}. A British cross-sectional study found a weak positive correlation between depressive symptom score and visual analog scale (VAS) pain score and a moderate positive correlation with depressive symptoms score and both the HAQ and the number of affected joints¹¹². In 2 studies, depressed patients with RA were found to have higher DAS28 scores, ESR, and CRP than nondepressed patients with RA^{113,114}. A case-control study reported a moderate positive correlation between depressive symptoms and VAS pain scores¹⁰⁶. Moreover, in 1 RA trial, patients with clinical remission as assessed by DAS28 were less likely to have depression than nonremitters at Week 104, and reciprocally, more non-depressed patients achieved more clinical remission than those with depressive symptoms¹¹⁵.

Recommendation 19. Healthcare providers should be aware that disease control may reduce symptoms of depression in patients with RA, PsA, and PsO (Grade of Recommendation B for PsO, and Grade of Recommendation D for RA and PsA).

In addition to the study in which patients with RA with clinical remission were found less likely to have depression than those who had not achieved remission¹¹⁵, 3 randomized controlled trials explored the effects of biologics on symptoms of depression in PsO^{116,117,118,119}. Patients with PsO treated with antiinterleukin 12/23 agents reported fewer symptoms of depression at 24 weeks¹¹⁶, and those treated with adalimumab¹¹⁸ or etanercept (ETN)¹¹⁷ reported fewer symptoms of depression at 12 weeks. In an open-label trial, patients with PsO receiving ETN had reduced depression scores up to 96 weeks¹²⁰. The whole group agreed that future research should evaluate the role of therapy of RA, PsA, and PsO in the improvement of major depression in patients.

DISCUSSION

These 19 Canadian evidence-based recommendations

underline the crucial need for an integrated approach to diagnose, manage, and also prevent comorbidities in patients with RA, PsA, and PsO. Combining disease control and comorbidity management should become part of the daily practice in RA, PsA, and PsO to ensure optimal care and outcomes.

For this review, the panel of experts reached a consensus to select 8 common comorbid conditions prevalent in RA, PsO, and PsA. Other comorbidities, such as HTN, renal impairment, and pulmonary diseases were proposed, but were not retained based on the preset limit on the number of topics that could be included. Nonetheless, our working group recognizes the importance of screening and treating other comorbidities associated with RA, PsO, and PsA. The final recommendations were reached by consensus based on evidence graded according to the Oxford Centre for Evidence-Based Medicine method. Other recommended methods could have been preferably used, such as the Grading of Recommendations Assessment, Development, and Evaluation working group approach.

To date, the CVD issue has been addressed in recommendations, such as in the EULAR recommendations for RA¹²¹; however, extrapolation to patients with PsA and PsO is needed¹²². Most primary care physicians and cardiologists do not screen patients with PsO for CVD risk factors¹²³, although this has been recommended in guidelines published by the American Cardiology Association¹²⁴. Further, comorbidities are not limited to CVD burden and a more global approach is needed to include other important concerns, such as infection, malignancies, and psychiatric disorders in these patients.

Several national or professional society recommendations and guidelines for the management of RA, PsA, and PsO include screening and treatment, as well as the use of biologic agents^{125,126}. They have mostly focused on the screening of certain infectious diseases, such as tuberculosis and hepatitis B and C^{122,127}. Regarding prior malignancies, rituximab is the biologic recommended in patients with RA with previously treated solid malignancy, a nonmalignant skin cancer within the last 5 years, melanoma, or lymphoproliferative malignancy, despite the fact that little is known about the effects of biologic therapy in patients with a solid cancer within the past 5 years¹²⁷. However, besides these specific guidelines, the EULAR CVD recommendations, the Brazilian Society of Rheumatology recommendations for RA¹²⁸, and recommendations from a group of French dermatologists for PsO¹²⁹, no recommendations regarding the global management of comorbidities in RA, PsA, and PsO, or regarding the effect of comorbidities on the 3 diseases and the influence of RA, PsA, and PsO treatments on comorbidities have been published to date. The Brazilian recommendations underline the need for early diagnosis and management of comorbidities, including HTN, diabetes mellitus, atherosclerosis, and osteoporosis, based on multi-

disciplinary followup. They also recommend, among other measures, avoiding high doses of CS and/or NSAID in patients with RA who have HTN or diabetes mellitus. In PsO, the recommendations stress that the increased risk of CVD requires appropriate prevention. Nevertheless, to our knowledge, the present recommendations are the first evidence-based recommendations in the large field of comorbidities in the 3 conditions (RA, PsA, and PsO) developed with the expert opinion of both rheumatologists and dermatologists.

The rationale for the integrated management of comorbidities is based not only on an increased prevalence of comorbid conditions, but also on their potential effect on disease activity and response to treatment. In addition, RA, PsA, and PsO treatments may affect the prevalence and evolution of comorbidities. To support this point, MTX has been associated with a 70% reduction in mortality¹³⁰ and a reduced risk of CVD^{131,132} in patients with RA. TNFi may also be associated with a reduced risk of CVD in RA^{133,134}. Increased CVD, as well as depression symptom burden, resulted in recommending awareness and risk reduction of both traditional risk factors and disease-related factors when treating patients with RA, PsA, and PsO. The risk-to-benefit ratio of NSAID should be carefully considered in patients with CV risk factors, and CS use minimized. Smoking cessation and healthy BMI should be encouraged, not only for CV concerns, but also because current smoking and higher BMI may be associated with increased disease activity in RA and PsO, and higher BMI with a reduced response to treatment. Notably, while waist circumference is emerging as a better marker of atherosclerosis than BMI and has been associated with increased early mortality and CVD in the general population^{135,136}, very few data exist about the relationship between waist circumference and CVD, as well as disease activity and response to treatment in RA⁴⁷, PsA, or PsO. These associations should be further explored. Additionally, the global risk of infection, not limited to tuberculosis and hepatitis B and C, should be assessed when initiating systemic therapy. Standard guidelines for cancer screening in the general population and treatment and prevention of CS-induced osteoporosis should be considered.

One of the current issues is how to deal with comorbidities of RA, PsA, or PsO in clinical practice and what simple tools to use in such assessment. The practical modalities of how to screen and achieve integrated management of such comorbidities in patients with RA, PsA, and PsO requires systemizing and needs further specific recommendations. The frequency of monitoring should also be determined because several of these risks may change over time. Moreover, there is some confusion regarding certain issues, such as whether specific recommendations tailored to these populations, with specific targets and treatment thresholds, are required¹³⁷. Given the evidence supporting the present recommendations, tight disease control (including optimal DMARD and TNFi

use) combined with control of traditional CV risk factors may have a synergistic and complementary effect on CVD burden in RA, and perhaps also in PsA and PsO.

The challenges of managing such a critical health burden include the feasibility and cost of implementing recommendations in routine practice, not only for rheumatologists and dermatologists, but also for primary care physicians. The logistics of monitoring comorbidities should be taken into account to help healthcare providers integrate the management of comorbidities in their practice. A multidisciplinary care team model including physician assistants or nurse practitioners may become the new normal, with specifically defined roles for each team member. Adherence of patients to treatment recommendations should also be considered. Indeed, it can be speculated that greater understanding of the common pathways between comorbidities and RA, PsA, and PsO may improve patients' adherence to such a strategy, and in turn, increase the expected benefit.

We hope that these recommendations will be useful for all healthcare providers managing RA, PsA, and PsO, and may inform future recommendations for improving care of patients with RA, PsA, and PsO with comorbidities.

Because comorbidities in patients with RA, PsA, and PsO can be improved by specific preventive and therapeutic strategies, early detection and management are needed to reduce their effect. Nineteen practical evidence-based recommendations were developed, integrating literature reviews and expert opinion, with the aim of improving the management of the most frequent comorbidities encountered in RA, PsA, and PsO. A multidisciplinary and integrated approach should be encouraged to improve the patients' disease and comorbidity management. In the future, RA, PsA, and PsO management should become more patient-centered rather than joint- or skin-centered based on the coordinated effort of a network of rheumatologists, dermatologists, and other healthcare professionals.

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