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Consensus recommendations on managing the selected comorbidities including cardiovascular disease, osteoporosis, and interstitial lung disease in rheumatoid arthritis

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Abstract

Background: Rheumatoid arthritis (RA)-related comorbidities, including cardiovascular disease (CVD), osteoporosis (OP), and interstitial lung disease (ILD), are sub-optimally managed. RA-related comorbidities affect disease control and lead to impairment in quality of life. We aimed to develop consensus recommendations for managing RA-related comorbidities.

Methods: The consensus statements were formulated based on emerging evidence during a face-to-face meeting of Taiwan rheumatology experts and modified through three-round Delphi exercises. The quality of evidence and strength of recommendation of each statement were graded after a literature review, followed by voting for agreement. Through a review of English-language literature, we focused on the existing evidence of management of RA-related comorbidities.

Results: Based on experts' consensus, eleven recommendations were developed. CVD risk should be assessed in patients at RA diagnosis, once every 5 years, and at changes in DMARDs therapy. Considering the detrimental effects of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids on CVD risks, we recommend using the lowest possible dose of corticosteroids and prescribing NSAIDs cautiously. The OP/fragility fracture risk assessment includes dual-energy X-ray absorptiometry and fracture risk assessment (FRAX) in RA. The FRAX-based approach with intervention threshold is a useful strategy for managing OP. RA-ILD assessment includes risk factors, pulmonary function tests, HRCT imaging and a multidisciplinary decision approach to determine RA-ILD severity. A treat-to-target strategy would limit RA-related comorbidities.

Conclusions: These consensus statements emphasize that adequate control of disease activity and the risk factors are needed for managing RA-related comorbidities, and may provide useful recommendations for rheumatologists on managing RA-related comorbidities.

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Abbreviations: ACPA = anti-citrullinated peptide antibody, BMD = bone mineral densities, CVD = cardiovascular disease, DMARDs = disease-modifying anti-rheumatic drugs, EULAR = European League Against Rheumatism, FRAX = fracture risk assessment, HRCT = high-resolution computerized tomography, ILD = interstitial lung disease, MDD = multidisciplinary decision, NSAIDs = nonsteroidal anti-inflammatory drugs, OP = osteoporosis, PFTs = pulmonary function tests, RA = rheumatoid arthritis, RF = rheumatoid factor.

Keywords: comorbidities, consensus, evidence-based, recommendations, rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease that leads to chronic synovitis, joint destruction, and poor life quality.[1,2] Although biologic disease-modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) therapies are effective and well-tolerated, comorbidities remain a challenge for RA patients. It has been estimated that up to 80% of RA patients have one or more comorbidities[3,4] resulting in shortening of life span.[5–7] The presence of comorbidities may also affect disease activity, become a barrier to optimal disease control, and lead to impairment in health-related quality of life (HRQoL).[8–11] However, RA-related comorbidities such as cardiovascular disease (CVD), osteoporosis (OP), and interstitial lung disease (ILD) are sub-optimally screened or managed.[12]

Atherosclerosis, a chronic inflammatory process, is associated with elevated risk of cardiovascular events.[13] Therefore, RA is commonly complicated by accelerated atherosclerosis and increased CVD risk.[14,15] The results of COMORA-trial reveal that CVD is the third most common diagnosed comorbidity in RA.[4] In addition, CVD is the leading cause of death in Taiwan general population.[16] Epidemiological studies have also disclosed an increased mortality due to CV events in RA patients.[5–7] These observations suggest the screening, management and preventive strategies for CVD are important in RA patients.

OP or bone fragility is the result of a complex interaction of traditional risk factors and systemic inflammation in RA. OP is recognized as a major source of morbidity in RA, and up to one-third of women with RA experience 1 episode of fracture during 5-year follow-up period.[17] Increased risks of OP or osteoporotic fractures have been reported in RA patients compared with healthy controls.[18,19] Schett et al. revealed decreased bone mineral densities (BMD) in patients with various states of chronic inflammation including rheumatic diseases.[20] Although OP and osteoporotic fracture are important causes of morbidity in RA patients,[4,21] the management of this comorbidity is suboptimal.

There are various pulmonary manifestations of RA, including ILD, pleural inflammation, and abnormalities of airways and pulmonary vasculature.[22] It is currently estimated that approximately 30% of patients with RA have subclinical ILD as shown by high-resolution computerized tomography (HRCT) scans.[23] Clinically significant RA-ILD has been noted in nearly 10% of RA population and is associated with shortened survival.[24,25] Chang et al reveal that patients with RA-associated ILD are older and have higher smoking rates, higher levels of rheumatoid factor (RF) or anti-citrullinated peptide antibody (ACPA), and higher values of erythrocyte sedimentation rate (ESR) compared with those without ILD.[26]

Despite the establishment of several guidelines for the management of RA-related comorbidities from European countries, Canada, and the United States,[27–32] the prevalence of RA-related comorbidities showed wide variations among different countries.[4,33] Based on the emergence of new evidence from the reported literature, an update of the recommendations on managing RA-related comorbidities is necessary.

2. Methods

2.1. The development of consensus statements

We used a multistep approach with Delphi methodology to develop the recommendations as previously described.[27–29] A special group on RA-related comorbidities is composed of 15 hospital-based rheumatologists from various regions in Taiwan. Another panel of rheumatology experts participated in the development of the present recommendations.

First, 34 experts of rheumatology selected the 3 top comorbidities in RA by using anonymous voting in July 2019. Subsequently, 11 questions for the 3 selected comorbidities including RA-related CVD, OP/ fragility fracture, and ILD were proposed using a Delphi prioritization procedure in a face-to-face meeting in December 2019. For the grading of the evidence and establishment of the strength of recommendations, the literature review regarding atherosclerosis, CVD risk score, CVD mortality, OP, fragility fracture, fracture risk assessment tool (FRAX), lung manifestations, ILD, pulmonary function tests (PFTs), HRCT, inflammation, epidemiology, risk factors, prevention, management, and the use of medications including csDMARDs, bDMARDs, or tsDMARDs. We searched the MEDLINE database using the PubMed interface and reviewed literature from 1981 to 2020.

The evidence from the literature review was presented during 2 workshops. The evidence was reported for each question and the grading of evidence in each statement was specified. Two rounds of Delphi exercises were conducted on the statements, followed by online voting for agreement. Statements with an agreement of less than 80% were evaluated again on the reasons for inconsistency. Modifications of the wordings were made and the statements were voted on again until a consensus was reached.

Ethical approval was waived because this was consensus statements based on the existed evidence.

2.2. Grading of evidence and strength of recommendation

The strength of the recommendation and the quality of evidence were evaluated based on the Grades of Recommendations Assessment, Development and Evaluation (GRADE) system (Table 1).[34] Four key elements of the evidence are evaluated: study design, study quality, consistency, and directness. Generally, randomized control trials (RCTs) with blinding and allocation concealment are considered as the highest quality source of evidence. The level of evidence would be decreased if

Table 1

Grading system used to rate the strength of the recommendations and quality of supporting evidence*.

Grade	Level	Meaning
Strength of recommendation		
A	Strong	Most well-informed participants would want the recommended course of action, and none or only a small proportion would not. Factors influencing the strength of recommendations include the quality of evidence, the presumed patient-important outcomes and an associated cost.
B	Weak	The majority of well-informed participants would want the recommended course of action, but a substantial minority would not. Variability in preferences, greater uncertainty, higher cost or resources consumption would lead to a weaker recommendation.
Quality of evidence		
A	High	Meta-analysis or randomized trials without important limitations or double-upgraded observational studies. Further research is very unlikely to change confidence in the estimate of effect. It is very confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	Downgraded randomized trials; upgraded observational studies. Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate. It is moderately confident in the effect estimate, the true effect is likely to be close to the estimate of the effect.
C	Low	Double-downgraded randomized trials; observational studies. The confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
D	Very low	Triple-downgraded randomized trials; downgraded observational studies; case series/case reports. Further research is very likely to have a critical impact on the confidence in the estimate of effect and is likely to change the estimate. Any estimate of the effect is uncertain.

* Based on the Grades of Recommendations Assessment, Development (GRADE) system[34].

important inconsistency, sparse data, and/or high probability of reporting bias occurs.

3. Results

A total of 11 recommendations on managing RA-related comorbidities were developed. Table 2 summarizes the statements with the levels of evidence, strength of the recommendations, and extent of agreement among experts.

Recommendation 1. The assessment of CVD risk is recommended in adult patients at the diagnosis of RA, at least once every 5 years, and at the time of major changes in DMARDs therapy (level of agreement 100%, level of evidence C, grade of recommendation A).

RA is complicated by accelerated atherosclerosis and an increased CVD risk.[14,15] A nationwide cohort study also reveals that RA is associated with the same risk of myocardial infarction (MI) as diabetes mellitus (DM).[35] Moreover, RA-related inflammation is implicated in the development of accelerated atherosclerosis, leading to increased CVD risk.[36] Therefore, the magnitude and chronicity of inflammation strongly correlated with the emergence of premature atherosclerosis in RA.[36–38] These findings resonate with the recently published treatment guidelines from the European League Against Rheumatism

Table 2

Consensus recommendations on the management of selected comorbidities in rheumatoid arthritis (RA) in Taiwan.

Recommendations	SoR	QoE	Agreement (%)
1. The assessment of CVD risk is recommended in adult patients at the diagnosis of RA, at least once every 5 years, and at the time of major changes in DMARDs therapy.	A	C	100
2. CVD risk assessment using QRISK2 is recommended for RA patients.	B	D	93.3
3. The management for RA patients with hypertension or dyslipidemia should be carried out according to national guidelines as for diabetes mellitus patients.	A	C	100
4. Adequate control of RA activity is recommended for all patients; if in low disease activity, use the lowest possible dose of corticosteroids and prescribe NSAIDs with caution.	A	B	100
5. Osteoporosis (OP)/fragility fracture risk assessment is recommended for RA patients, including clinical risk factors, DXA, FRAX and falls risk, at least once every 3 years.	A	C	100
6. A FRAX-based approach with intervention thresholds may be a useful strategy for the treatment of OP and glucocorticoids-induced OP.	A	D	93.3
7. Optimal management of RA patients with OP includes “treat to target” strategy for disease control and anti-osteoporotic medications.	A	C	100
8. ILD risk should be assessed, including risk factors, HRCT and PFTs in RA patients with persistent cough, unexplained dyspnea and/or abnormal CXR.	A	D	100
9. Assessment of pattern/extent of ILD using multidisciplinary decision (MDD) among rheumatologists, radiologists, and pulmonologists is recommended for RA-ILD patients.	A	C	100
10. The use of MTX or leflunomide should be avoided in RA patients with moderate/severe ILD. Rituximab or abatacept may be the first-line biologic in RA-ILD patients with limited evidence.	B	D	86.7
11. Treatment of moderate/severe RA-ILD should be individualized based on HRCT pattern/extent. Corticosteroids are the mainstay of management, and mycophenolate or cyclophosphamide may be effective but adverse effects should be monitored.	A	D	93.3

CVD = cardiovascular disease, DMARDs = disease-modifying anti-rheumatic drugs, DXA = dual-energy X-ray absorptiometry, FRAX = fracture risk assessment, HRCT = high-resolution computerized tomography, ILD = interstitial lung disease, NIDDM = non-insulin dependent diabetic mellitus, NSAIDs = nonsteroidal anti-inflammatory drugs, PFTs = pulmonary function tests, QoE = quality of evidence, SoR = strength of the recommendation.

(EULAR), which emphasize the importance of management of both traditional CVD risk factors and RA-related inflammation.[30] Given that CVD-related morbidity and mortality are increased in RA,[5–7,39] the assessment of CVD risk was recommended in several guidelines.[40–43] In addition, the used DMARDs may potentially affect CVD risk in RA.[44–49] Therefore, the assessment of CVD risk is recommended in adult patients at the diagnosis of RA, at least once every 5 years, and at the time of major changes in DMARDs therapy as the EULAR 2016 CVD guidelines for RA.[30] However, patients with a high CVD risk or pre-existing CVD should have an annual assessment for this comorbidity.

Recommendation 2. CVD risk assessment using QRISK2 is recommended for RA patients (level of agreement 93.3%, level of evidence D, grade of recommendation B).

High CVD prevalence in RA patients can be explained by both conventional CV risk factors and systemic inflammation in this disease.[50–52] A recent meta-analysis of traditional CVD risk factors in RA patients indicated an important role of low levels of high-density lipoprotein cholesterol (HDL-C) and increased frequency of DM.[53] Therefore, traditional risk factors including hypertension, dyslipidemia, DM, and smoking should be evaluated as in the general population.[54,55]

Given that RA-related inflammation contributes to CVD risk, the assessment scores for the general population such as the Framingham score are not accurate in RA patients.[55] The EULAR recommended a 1.5 multiplier for RA patients with at least 2 of the following conditions: a disease duration≥10 years, positivity for rheumatoid factor and/or ACPA, and presence of extra-articular manifestations.[30] The QRISK-2 score includes RA as a risk factor of CVD.[56] Although Crowson et al demonstrate that RA-specific CVD risk scores are not superior to general risk scores[57] and only 2 guidelines recommended the use of CVD risk score,[41,43] we proposed QRISK-2 score as an estimated calculator of global 10-year CVD risk in RA patients in Taiwan.

Recommendation 3. The management for RA patients with hypertension or dyslipidemia should be carried out according to national guidelines as for diabetes mellitus patients (level of agreement 100%, level of evidence C, grade of recommendation A).

The results of the COMORA-trial and other studies demonstrate that the risk factors of CVD such as hypertension and dyslipidemia are not optimally monitored and managed in 30% to 50% of RA patients.[4,58,59] Although CV interventional trials have not been done specially for RA population, 2 guidelines recommended the management of traditional CVD risk factors should be carried out according to "national guidelines" and that statins are the preferred therapeutic agent for dyslipidemia.[40,43] De Vera et al also revealed an effectiveness of statins on reducing AMI risk in RA patients.[60] Given RA is associated with the same risk of MI as DM,[35] the management for RA patients with hypertension or dyslipidemia should be carried out according to national guidelines as for DM patients.

Recommendation 4. Adequate control of RA activity is recommended for all patients; if in low disease activity, use the lowest possible dose of corticosteroids and prescribe NSAIDs with caution (level of agreement 100%, level of evidence B, grade of recommendation A).

Given that all RA guidelines recommend a treat-to-target approach as a means of improving RA outcomes, the EULAR guidelines[30,61] also suggest that adequate control of disease activity should reduce CVD risk. Moreover, RA guidelines proposed the potential of csDMARDs or bDMARDs to reduce CVD risk.[40,41,44] Recent observational studies also reveal a beneficial effect of bDMARDs on CV outcome in RA patients.[45–49] Based on these observations, we recommend a tight control of disease activity in RA patients, particularly in those with CVD risk.

Accumulating evidence indicates that corticosteroids are associated with hypertension and dyslipidemia[62] and nonsteroidal anti-inflammatory drugs (NSAIDs) may have an adverse impact on CV outcomes.[63] A serial study revealed that corticosteroids and NSAIDs are risk factors for CVD.[45,46,62] The British Society of Rheumatology guidelines outlined that corticosteroid may worsen the CVD risk,[41] and the EULAR guidelines recommend the use of the lowest dose of corticosteroids.[43] Therefore, the use of the lowest possible dose of corticosteroids and the prescription of NSAIDs with caution are recommended.

Recommendation 5. Osteoporosis (OP)/fragility fracture risk assessment is recommended for RA patients, including clinical risk factors, DXA, FRAX, and falls risk, at least once every 3 years (level of agreement 100%, level of evidence C, grade of recommendation A).

OP or bone fragility is the result of a complex interaction of traditional risk factors, systemic inflammation, circulating autoantibodies, inflammation, and reduced bone formation resulting from glucocorticoid use.[64–68] Several studies reveal a higher OP prevalence in RA patients compared with general population,[64,69,70] and the incidence of OP in RA patients is double that of the general population.[71] Moreover, their incidence rate of fractures is 1.5 times higher than that for the general population.[72] Joo et al also estimated OP prevalence in 134 Korean RA patients to be 13.4%.[73]

The WHO criteria, using BMD measured by dual-energy X-ray absorptiometry (DXA), are the most widely used for diagnosing OP.[74] Clinical risk factors are important predictors of the probability of fragility fractures independent of BMD.[75,76] The fracture risk assessment tool (FRAX) is a widely used risk algorithm developed in 2008 in UK that is used to predict the 10-year risk of hip and major osteoporotic fractures with/without femur neck BMD measurement.[77,78] Given increased risk of OP/fragility fracture in RA patients, assessment of OP/osteoporotic fracture is recommended for RA patients, at least once every 3 years. This assessment in RA patients should also include the effects of disease activity and bone-influencing medications such as glucocorticoids.

Recommendation 6. A FRAX-based approach with intervention thresholds may be a useful strategy for the treatment of OP and glucocorticoids-induced OP (level of agreement 93.3%, level of evidence D, grade of recommendation A).

OP-related fragility fracture is an important complication in RA patients, with a doubling of occurrences of both hip and vertebral fractures compared to age and gender-matched controls.[79] Given that clinical risk factors for fragility fractures are numerous, the FRAX is a valuable instrument to quantify the 10-year probability for both hip and major fractures.[77,78] Moreover, shared decision-making using FRAX scores can also improve drug adherence, which is important in the management of osteoporosis and prevention of fragility fracture.[80] In addition, a FRAX-based approach with intervention thresholds will provide further categorization into low, high, and very high risk of fragility fractures, and direct appropriate therapeutic

strategy.[81] For those with low fracture risk, adjustment of lifestyle and supplementation of calcium/vitamin D are recommended. For those with high fracture risk, therapy with antiresorptive agents is recommended. For those with very high fracture risk, we would consider anabolic agents followed by anti-resorptive agents.[81]

As previously described, the use of glucocorticoids is one of the risk factors for bone loss (GIOP) and fragility fractures.[82–84] Therefore, the measurement of FRAX score should be adjusted according to the dose of glucocorticoids.[84] RA patients with OP have been included in GIOP trials, in which a strong reduction in vertebral fractures was shown in bisphosphonates-treated GIOP patients.[85] An GIOP study in which most of the participants were RA patients revealed that teriparatide, not only significantly more increases in BMD levels but also in significant vertebral fracture reduction than alendronate.[86,87] A FRAX-based approach with intervention thresholds can also apply in the risk categorization and therapeutic strategy in GIOP patients.

Recommendation 7. Optimal management of RA patients with OP includes "treat to target" strategy for disease control and anti-osteoporotic medications. (Level of agreement 100%, level of evidence C, grade of recommendation A).

Although the association of RA activity, reflected by DAS28 score, with osteoporotic fractures is still inconclusive,[88] previous cross-sectional studies revealed that DAS28 was an independent risk factor for vertebral fracture.[89–91] Therefore, adequate control of RA activity with DMARDs is of major importance to reduce the risk of OP/fragility fracture.[92] Given that the main goal of osteoporosis treatment is to prevent fractures by increasing bone strength, several anti-osteoporotic drugs such as anti-resorptive or anabolic agents could be used to achieve this goal.[92,93] Therefore, optimal management of RA patients with osteoporosis includes "treat to target" strategies for RA activity and anti-osteoporotic medications.

Recommendation 8. ILD risk should be assessed, including risk factors, HRCT, and PFTs in RA patients with persistent cough, unexplained dyspnea and/or abnormal CXR (level of agreement 100%, level of evidence D, grade of recommendation A).

ILD remains a significant source of morbidity and mortality,[24,25] and becomes a leading cause of mortality in RA patients.[94] Although the exact pathogenesis in RA-ILD remains unclear,[95,96] previous studies revealed that smoking, male sex, older age, high titers of RF or ACPA, disease duration, and positivity of HLA-DR4 were risk factors for RA-ILD.[97–103] The circulating biomarkers could aid in the identification of RA-ILD risk and the prediction of disease outcomes,[96,104] but they are not fully explored. Based on HRCT, RA-ILD imaging patterns could be mainly as either usual interstitial pneumonia (UIP) with honeycombing, or nonspecific interstitial pneumonia (NSIP) distinguished by presentation of ground glass opacities.[105,106] The PFTs are a sensitive but relatively nonspecific measure of RA-ILD. The forced vital capacity (FVC) and diffusion capacity of carbon monoxide (DL_{CO}) are useful PFTs parameters in the screening and monitoring the progression of RA-ILD. As in the summarization of the international recommendations for the management of ILD,[107] assessment of ILD includes clinical risk factors, PFTs, and HRCT in RA patients with persistent cough, unexplained dyspnea, and/or abnormal CXR images. For RA-ILD patients, periodical monitoring of PFTs should be performed, and a 6- to 12-month decline in FVC of at least 10% or a decline in DL_{CO} of at least 15% may be associated with increased progression of ILD.[108]

Recommendation 9. Assessment of pattern/extent of ILD using multidisciplinary decision (MDD) among rheumatologists, radiologists, and pulmonologists is recommended for RA-ILD patients (level of agreement 100%, level of evidence C, grade of recommendation A).

The findings on HRCT images are variable in RA-ILD, including UIP, NSIP, organizing pneumonia, diffuse alveolar damage, desquamative interstitial pneumonia (DIP), lymphoid interstitial pneumonia (LIP), or "unclassified" subgroups.[105,106,109] In clinical practice, the evaluation of disease severity of RA-ILD is a multidisciplinary decision (MDD) process considering clinical manifestations, patterns and extent of HRCT involvement, and PFT results. Given a close association of patterns and extent of HRCT involvement with disease outcome,[110–113] the MDD approach is recommended to determine the severity of RA-ILD.

Recommendation 10. The use of MTX or leflunomide should be avoided in RA patients with moderate/severe ILD. Rituximab or abatacept may be the first-line biologic in RA-ILD patients with limited evidence (level of agreement 86.7%, level of evidence D, grade of recommendation B).

As an anchor drug, methotrexate (MTX) is recommended as the first choice of csDMARD for the treatment of RA.[114] Since 1983, acute MTX-induced pneumonitis has also been reported after low-dose therapy for RA.[115] A meta-analysis by Conway and colleagues reveal an increased risk of MTX-associated pneumonitis.[116] However, a recent systematic literature review supports the finding that MTX does not cause fILD in humans.[117] Leflunomide (LEF), an inhibitor of de novo pyrimidine synthesis, effectively reduces progression of RA. Similar to MTX, LEF has been reported to have associations with potentially fatal pneumonitis and ILD.[118,119] With regards to ILD, approximately 1% of patients treated with LEF develop new or worsening ILD[120] and RA patients treated with LEF have a twofold increase in risk of ILD.[121] Therefore, it may be prudent to avoid first-line use of MTX or LEF in RA patients with pre-existing moderate to severe ILD.

Although tumor necrosis factor-α inhibitors (TNFi) were effective on managing RA, new-onset or exacerbation of existing ILD has been reported following the use of TNFi.[122–125] In contrast, other studies argue against any association between anti-TNF and ILD in RA.[126,127] Therefore, current data are insufficient to draw firm conclusions.[111,128,129]

The finding of follicular B-cell hyperplasia and interstitial plasma cell infiltrates in RA-ILD patients suggested the use of rituximab (RTX) for this indication.[130] Two small observational studies assessing the safety of RTX in patients with RA with concomitant ILD.[131,132] Previous studies also showed some success of RTX as a rescue therapy for severe RA-ILD.[133] In a large observational study of rituximab-treated patients, most RA-ILD patients (n = 56) remained stable or even improved PFTs after therapy.[134] Another multivariate analysis of 68 patients with RA-ILD, RTX treatment resulted in a lower risk of pulmonary function impairment compared with non-rituximab therapy.[135] A recent systemic literature review suggests that RTX is a relevant therapeutic option for rheumatic disease-related ILD despite the existing uncertainties.[136] Abatacept has been proposed as an alternative therapy for RA-ILD.[129,137] In a safety observational study of abatacept-treated patients, FVC and DL_{CO} remained stable or improved in 86.1% and 91.7% of patients respectively.[138] A recent systemic literature review suggests that ABA may be a plausible alternative to treat RA

patients with ILD.[139] In addition, abatacept has not been shown to have any noninfectious pulmonary toxicity.[138,140] However, current data are insufficient to draw firm conclusions.[111,141,142]

Recommendation 11. Treatment of moderate/severe RA-ILD should be individualized based on HRCT pattern/extent. Corticosteroids are the mainstay of management, and mycophenolate or cyclophosphamide may be effective but adverse effects should be monitored (level of agreement 93.3%, level of evidence D, and grade of recommendation A).

Currently, there is no contemporary consensus for the treatment of RA-ILD.[128,142] Given a heterogeneity of HRCT imaging of RA-ILD with different therapeutic response and prognosis, it is prudent to individualize the treatment strategies based on pattern and extent of HRCT involve-

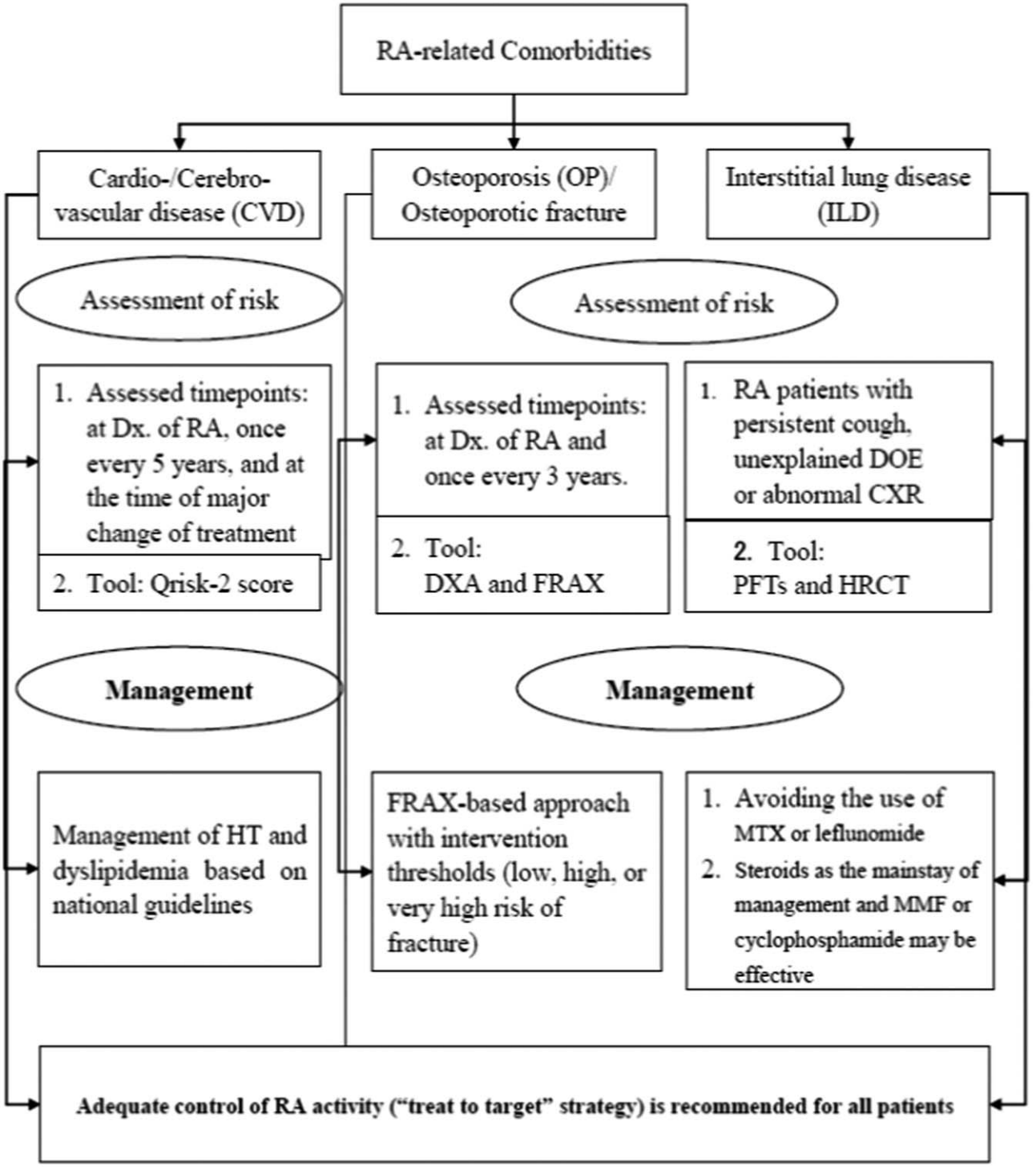

Figure 1. Algorithm summarizing the recommendations for the management of selected comorbidities in rheumatoid arthritis (RA).

ment.[128,129,142,143] With cigarette smoking implicated in the pathogenesis of both RA-ILD and persisted synovitis, smoking cessation should be a priority. Corticosteroids are the mainstay of management, and patients with cellular NSIP or organizing pneumonia may be managed with aggressive corticosteroid therapy initially, with gradual tapering based on therapeutic response.[142,144] Cyclophosphamide, an immunosuppressive drug commonly used to treat connective tissue disease (CTD)-ILD patients,[145] may be useful in extensive or rapidly progressive ILD with high inflammatory activity.[142,144,146] However, there is a lack of evidence from controlled studies regarding their efficacy in RA-ILD. Given the UIP pattern of pulmonary fibrosis is encountered in patients with RA-ILD, antifibrotic agents may be considered.[147,148]

A meta-analysis of mycophenolate mofetil (MMF) in scleroderma-ILD revealed that it had potential for preventing further FVC decline.[149] The studies in a mixed CTD cohort with a small number of RA-ILD patients revealed that MMF could achieve symptomatic improvement and stabilization in PFTs and HRCT imaging.[150] Therefore, MMF with relatively low toxicity may be as a first line agent over cyclophosphamide or a maintenance therapy after cyclophosphamide therapy.[142,151,152] However, there are no controlled studies directly comparing cyclophosphamide and MMF in RA-ILD.

Given a high prevalence of *Pneumocystis jirovecii* colonization with increased risk of pulmonary infection in ILD patients,[153] the benefit of prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) is well-documented in immunocompromised patients. However, the role of PJP prophylaxis in RA-ILD patients remains controversial.[154]

4. Discussion

The present consensus recommendations fulfill the crucial need for a holistic care strategy to manage and prevent 3 important comorbidities: CVD, OP/fragility fracture, and ILD in RA, as summarized in Figure 1. Given that tight control of RA activity could reduce the severity, even the probability of RA-associated comorbidities, the treat-to-target strategy is strongly recommended for this issue. Therefore, the treatment target of RA should be sustained remission or low disease activity when remission cannot be reached.

The CVD issue, the first selected comorbidity, has been addressed in several recommendations.[27–31] In order to implement a preventive strategy, CVD risk stratification is the first step to determine the overall CVD risk. However, the CVD risk scores used for RA are not conclusive. Given that high CVD burden is caused by both traditional CVD risk factors and RA-related inflammation, the QRISK-2 score including RA as a risk factor[56] is recommended in our experts' consensus. Based on the equal risk of MI between RA patients and DM,[35] we recommend that the management of hypertension and dyslipidemia should be carried out according to national guidelines for DM patients. Adequate control of RA disease activity and traditional CVD risk factors through a multidisciplinary approach is needed.

Although increased risks of OP/fragility fractures have been reported in RA patients compared with healthy controls, assessment, and management are suboptimal. Therefore, assessment of OP/osteoporotic fracture risks including clinical risk factors, bone-influencing medications, and 10-year risk of fracture by using FRAX is recommended in RA patients, at least once every 3 years. In order to have a personalized therapy, it would be better to manage RA-associated OP or GIOP according to the FRAX-based approach with intervention thresholds. The optimal management of RA patients with osteoporosis includes a "treat to target" strategy for disease activity and anti-osteoporotic medications. Considering the potential detrimental effects of corticosteroids on the risks of CVD and OP/fragility fracture in RA, we recommend using the lowest possible dose of corticosteroids if RA in low disease activity.

ILD is the leading cause of mortality in this disease.[96] Given the close association of patterns and extent of HRCT involvement with disease outcome,[113–116] the MDD approach is recommended to determine RA-ILD severity.[143,146] Considering a potential risk of interstitial pneumonitis in RA patients receiving MTX or leflunomide, it may be prudent to avoid using both drugs in those with moderate-severe pre-existing ILD. Although there are conflicting results regarding an association between TNF inhibitors and ILD, we recommended using TNF inhibitors with caution. For RA-ILD patients with an active status, rituximab or abatacept may be considered as the first-line biologic, but the evidence is limited.[138,140,142,146] Although there is no contemporary consensus for managing RA-ILD, mycophenolate or cyclophosphamide may be effective in RA-ILD,[146] but potential adverse effects should be monitored.

Despite the strengths of our recommendations presented here, there are 2 limitations in our study. First, the comorbidities were selected by the core group of Taiwan College Rheumatology and were not all-inclusive; some important comorbidities such as hypertension, malignancies, infection, and depression were not included. However, our working group recognizes the importance of management of hypertension in these recommendations. Second, we did not include the representative patients, nurses, and other healthcare professionals to participate in the discussion of our recommendations.

5. Conclusion

Although several guidelines on managing RA-associated comorbidities are currently available, a set of recommendations including ILD is limited. We hope these recommendations can serve as a guide for rheumatologists and general practitioners who are involved in the management of RA-related comorbidities. Regular update of these recommendations will be needed based on the emergence of new evidence from the reported literature.

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