UNIVERSITY ABOUBEKR BELKAID

LABORATORY OF RESEARCH ON DIABETES
مخبر بحث سكري
« LAREDIAB »
Code ATRSS/DGRST N° W0417700
FACULTY OF MEDICINE BENAOUDA BENZERDJEB
https://larediab.univ-tlemcen.dz
Mobile : 0770 218 100/ E-mail:ali.lounici@univ-tlemcen.dz

AMIWIT

ACADEMIC HOSPITAL TIDJANI DAMERDJI

EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS – 2022 UPDATE

Dr Sendani doha_Pr A.Lounici
Le 09/12/2022

- La prise en charge de la polyarthrite rhumatoïde (PR) évolue d'année en année, raison pour laquelle l'EULAR estime que les recommandations de prise en charge doivent être actualisées tous les 3-4 ans en se basant évidemment sur les dernières données et sur l'évolution des niveaux de preuve

- C'est Jozef Smolen (Vienne) qui a présenté l'actualisation 2022 de ces recommandations en les comparant à celles de 2019

eular

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs	2010 3 overarching principles 15 recommendations
EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update	2013 3 overarching principles 14 recommendations
EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update Recommendation	2016 4 overarching principles 12 recommendations
EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update	2019 5 overarching principles 12 recommendations

Que disent les recommandation EULAR 2022 ?

Il a été jugé opportun d'évaluer à nouveau :

1/ quels nouveaux médicaments ont été approuvés ou ont réussis l'essai de phase 3 ?

2/ quelles nouvelles informations ont émergées des essais ou des patients ?

3/ Des problèmes d'innocuité sont ils apparus lors d'essais cliniques ou des registres?

4/ Existent- il de meilleures preuves aujourd'hui pour les recommandations qui n'étaient basées que sur un faible niveau de preuves en 2019?

5/ Une des recommandation a-t-elle été contre dite depuis 2019?

les principes généraux :

Overarching principles 2019 = 2022	
A.	Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.
B.	Treatment decisions are based on disease activity and other patient factors, such as progression of structural damage, comorbidities and safety issues.
C.	Rheumatologists are the specialists who should primarily care for RA patients.
D.	Patients require access to multiple drugs with different modes of action to address the heterogeneity of RA; they may require multiple successive therapies throughout life.
E.	RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist.

LoA: 9.4 – 9.9

LoA: 9.7 – 10.0

LES RECOMMANDATIONS:

Les experts n'ont pas touché aux 5 premières recommandations:

1. DMARD doit être commencé dès que le diagnostic est posé.
2. Atteindre un objectif de rémission soutenue ou de faible activité chez tous les patients.
3. la surveillance fréquente lorsque la maladie est active (tous les 1 à 3 mois); si pas d'amélioration 3 mois maximum **ou** si l'objectif non atteint après 6 mois, le traitement doit être ajusté.
4. **le méthotrexate (MTX)** doit faire partie de la 1ère ligne de traitement.
5. Si contre-indication au MTX (ou une intolérance précoce), léflunomide ou sulfasalazine doivent être envisagés en 1ère ligne.

Final Set of Recommendations -2022 Update

eular

Recommendations 1-5 – 2019 = 2022	
1.	Therapy with DMARDs should be started as soon as the diagnosis of RA is made. (A)
2.	Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient. (A)
3.	Monitoring should be frequent in active disease (every 1-3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted. (B)
4.	MTX should be part of the first treatment strategy. (A)
5.	In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy. (A)

LoA: 9.0 – 9.8

LoA: 9.1 – 9.9

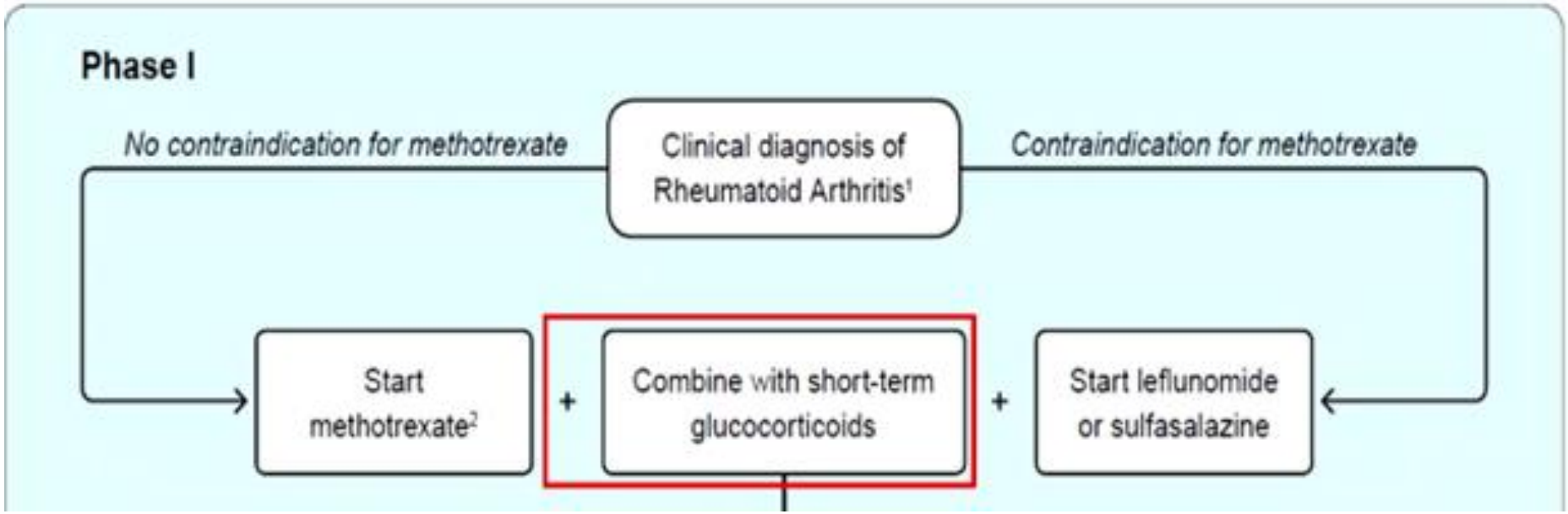
Première thématique remise en question

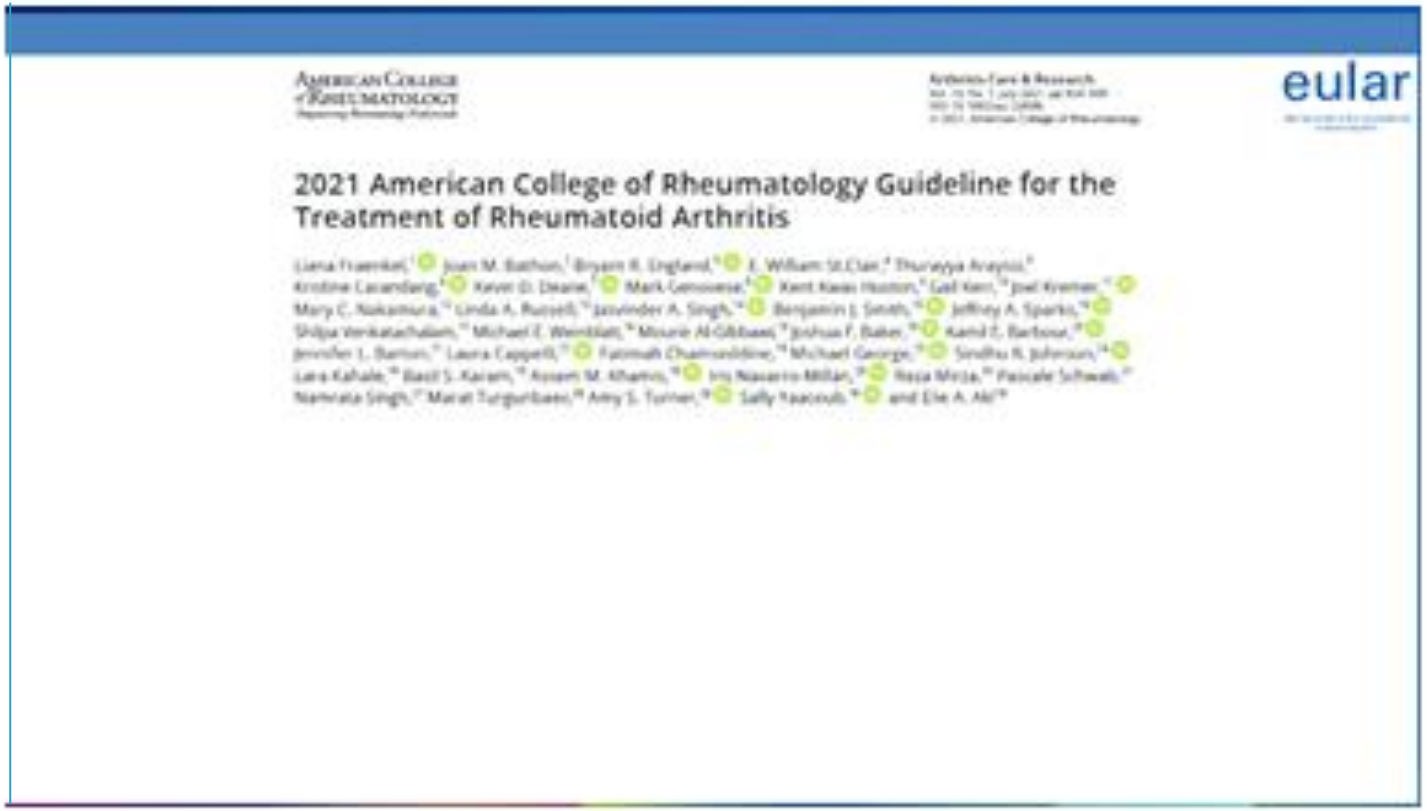
Final Set of Recommendations -2022 Update

eular

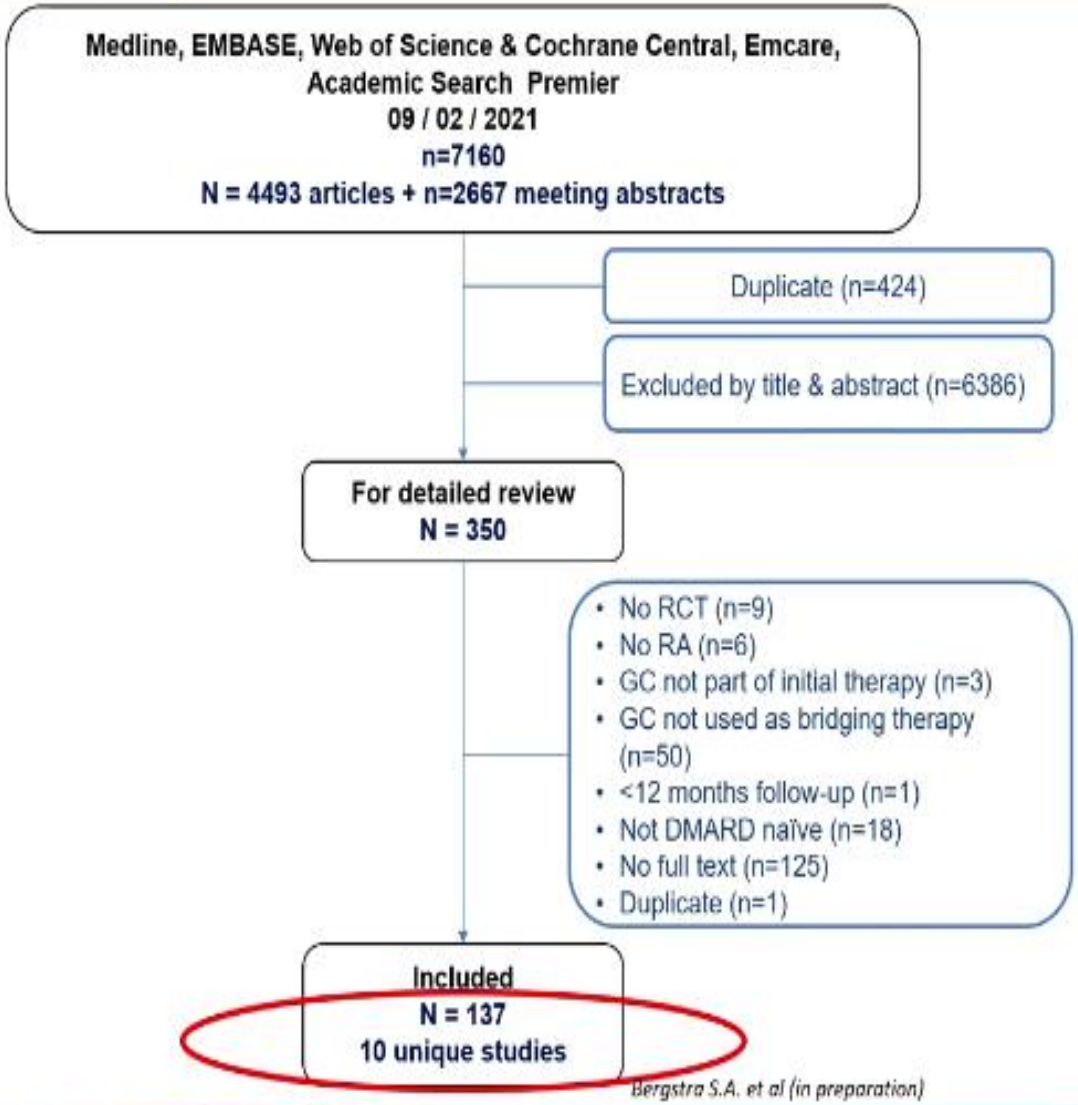
Recommendation 6 – 2019	
6.	Short term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible. (A)

1/ corticothérapie




American College of Rheumatology
Arthritis Care & Research
eular
2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

GLUCOCORTICOID PERSISTENCE



Bergstra S.A. et al (in preparation)

eular

GC use and risk of **cardiovascular disease**

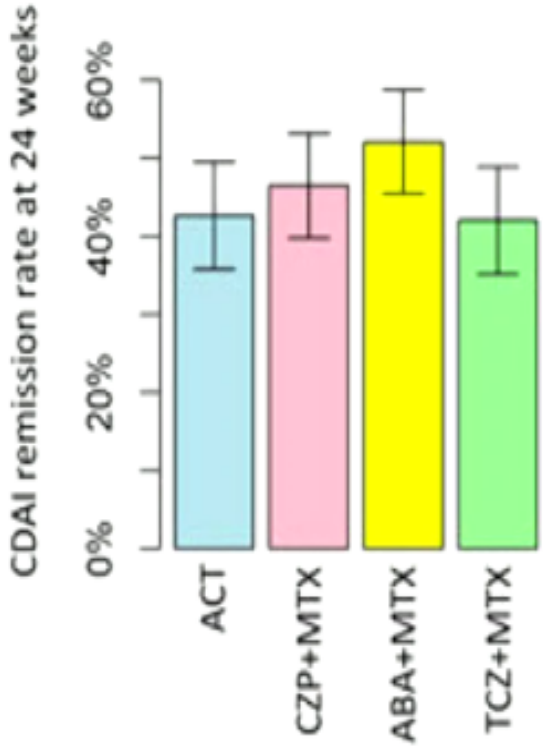
Study ID	Registry	Follow-up	Comparison groups	aHR
Van Stijl 2014 PLoS One *adjusted for baseline HAQ & DAS28	CARRÉ cohort	10 y	No GC use Ever GC use Duration of GC use ≤5 y >5 y Cumulative GC dose ≤1000 mg >1000 mg	Ref 0.89 (0.26; 3.09) 0.71 (0.15; 3.27) 1.48 (0.21; 10.45) 0.42 (0.05; 3.30) 1.80 (0.37; 8.74)

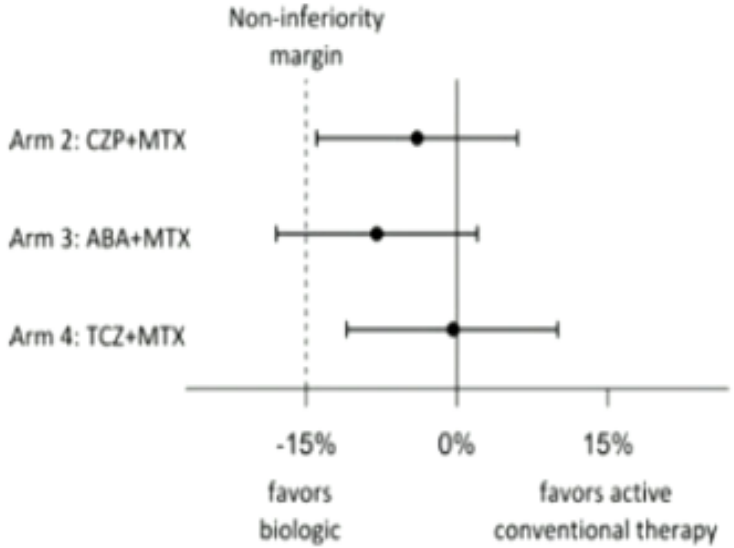
Study ID	Registry	Follow-up	Comparison groups	aHR
Ocon 2021 Ann Rheum Dis *adjusted for baseline HAQ & CDAI	CorEvitas (formerly Corrona)	Max. 16 y	Cumul. Dose prec. 1 y: 1 – 500 mg 501 – 1100 mg 1101 – 2100 mg >2100 mg	0.93 (0.60; 1.45) 1.19 (0.83; 1.70) **1.47 (1.06; 2.03)** **1.74 (1.25; 2.43)**

Bergstra S.A. et al (in preparation)

EFFICACY

More Evidence: MTX+GC is Non-Inferior to MTX+bDMARDs





Hetland et al, BMJ 2020; 2020 Dec 2;371:m4328

Final Set of Recommendations -2022 Update

eular

Recommendation 6 – 2019	
6.	Short term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible. (A)

LoA: 8.9 ± 1.3

Recommendation 6– 2022	
6.	Short term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered and discontinued as rapidly as clinically feasible. (A)

LoA: 9.3 ± 1.2

la recommandation n° 6 demande d'envisager **un GC à court terme** à l'initiation ou au changement de DMARD conventionnel quel que soit son dosage et son mode d'administration, **à condition de le titrer vers le bas et de l'arrêter (notion ajoutée par les experts) aussi rapidement que cliniquement faisable**

Final Set of Recommendations -2019 Update

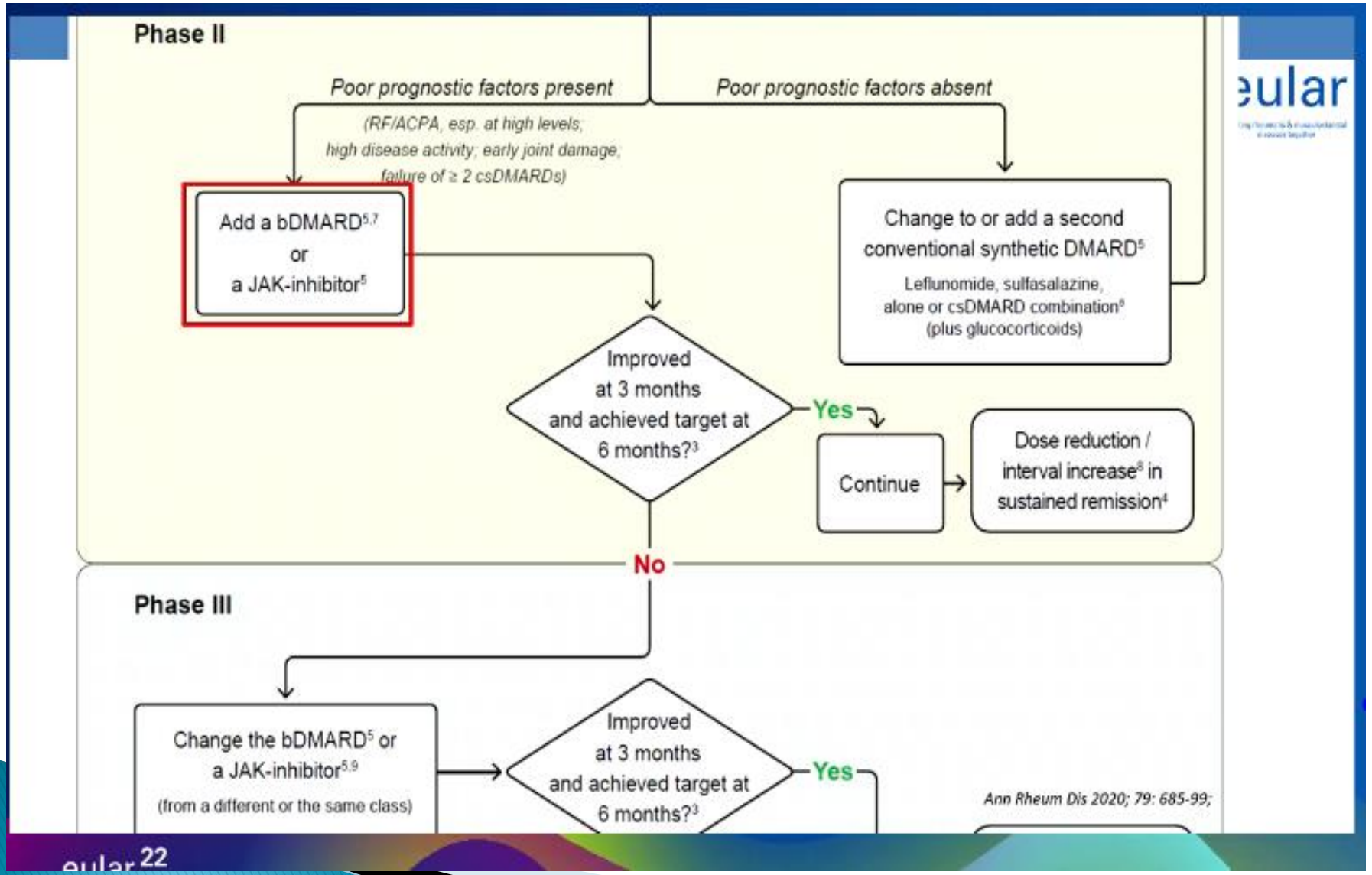
eular

Recommendation 7 – 2019 = 2022	
7.	If the treatment target is not achieved with the first csDMARD strategy, in the **absence of poor prognostic factors**, other csDMARDs should be considered. **(D)**

LoA: 8.4 ± 1.6 **LoA: 8.6 ± 1.4**

- si l'objectif de traitement n'est pas atteint avec la première stratégie par DMARD conventionnel, en l'absence de facteurs de mauvais pronostic, d'autres DMARD doivent être envisagés. **Cette recommandation inchangée conserve un très haut taux d'approbation de la part des experts**

Deuxième thématique remise en question



eular

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

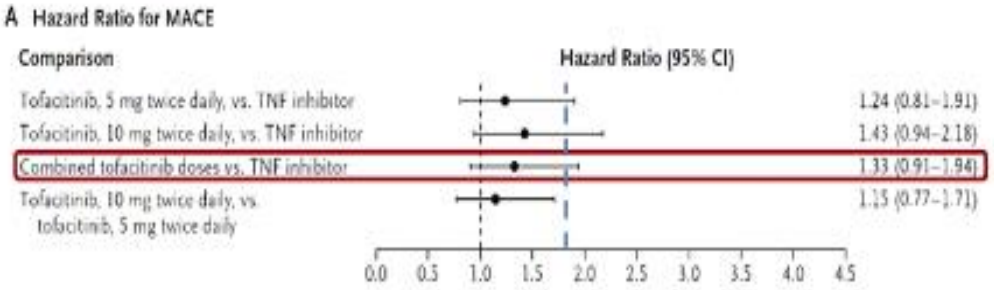
Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

Steven R. Ytterberg, M.D., Deepak L. Bhatt, M.D., M.P.H., Ted R. Mikuls, M.D., M.S.P.H., Gary G. Koch, Ph.D., Roy Fleischmann, M.D., Jose L. Rivas, M.D., Rebecca Germino, Ph.D., Sujatha Menon, Ph.D., Yanhui Sun, Ph.D., Cunshan Wang, Ph.D., Andrea B. Shapiro, M.D., Keith S. Kanik, M.D., and Carol A. Connell, R.N., Ph.D., for the ORAL Surveillance Investigators*

Ytterberg SR et al. NEJM 2022; 386: 316-326

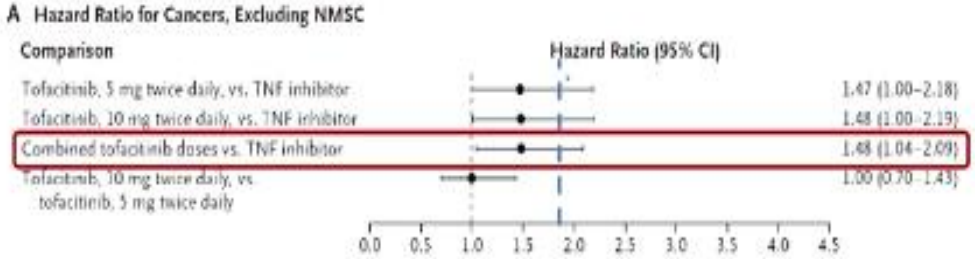
MACE ORAL Surveillance

Non-inferiority was not demonstrated for the coprimary endpoint: upper limit of the 95%CI > 1.8



Malignancies ORAL Surveillance

Non-inferiority was not demonstrated for the coprimary endpoint: upper limit of the 95%CI > 1.8



Ytterberg SR et al. NEJM 2022; 386: 316-326

Final Set of Recommendations -2022 Update

eular

Recommendations 6-8 – 2019	
8.	If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, a bDMARD or a tsDMARD should be added. (A)

LoA: 9.3 ± 1.0

Recommendations 6-8 – 2016	
8.	If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, a bDMARD ~~or a tsDMARD~~ should be added (A); JAK-inhibitors may be considered, but pertinent risk factors* must be taken into account. (A, B)
	** The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAK-inhibitor: Age over 65 years, history of current or past smoking, other cardiovascular risk factors, other risk factors for malignancy, risk factors for thromboembolic events*

LoA: 9.1 ± 1.1

Si l’objectif non atteint avec les DMARD conventionnel et en présence de facteurs de mauvais pronostic, un DMARD biologique doit être ajouté.

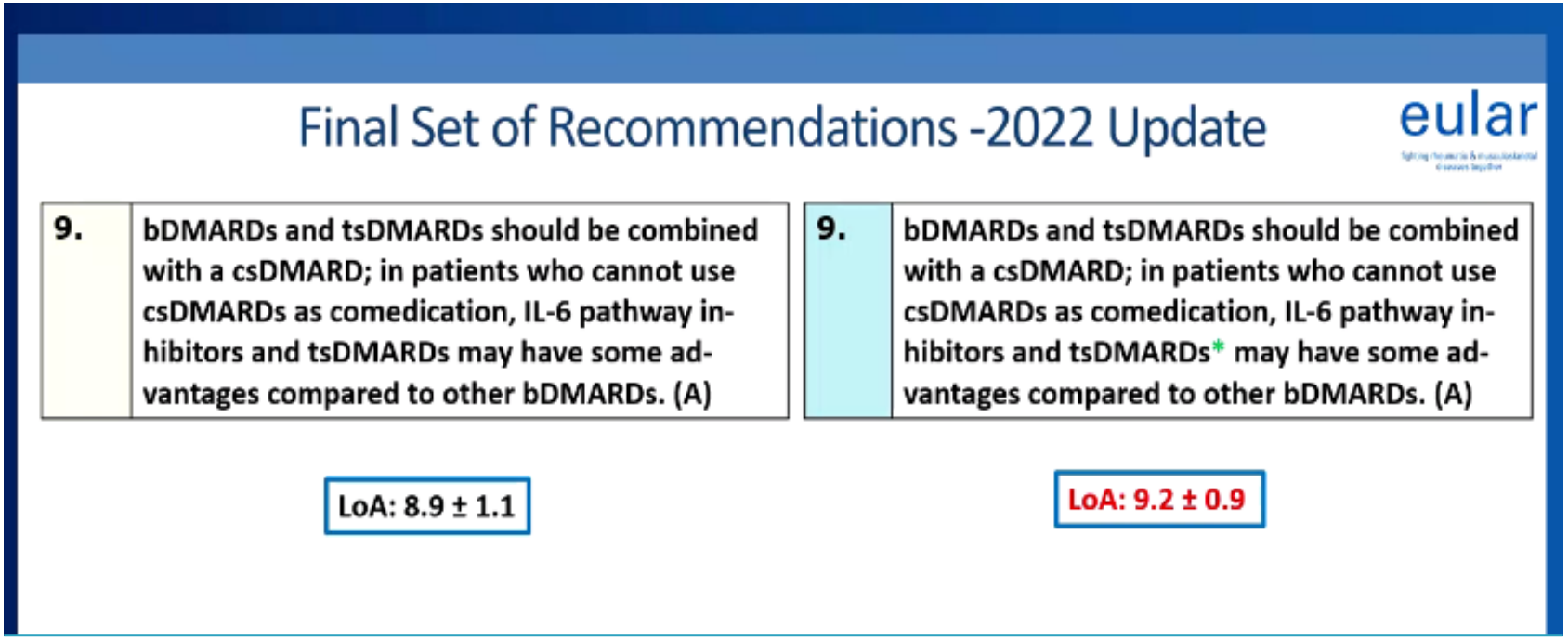
Nouveauté: les inhibiteurs JAK peuvent être envisagés à condition de tenir compte des facteurs de risque:

1/un âge > 65 ans

2/un tabagisme récent ou passé

3/les facteurs de risque cardiovasculaire classiques, y compris pour le risque thromboembolique

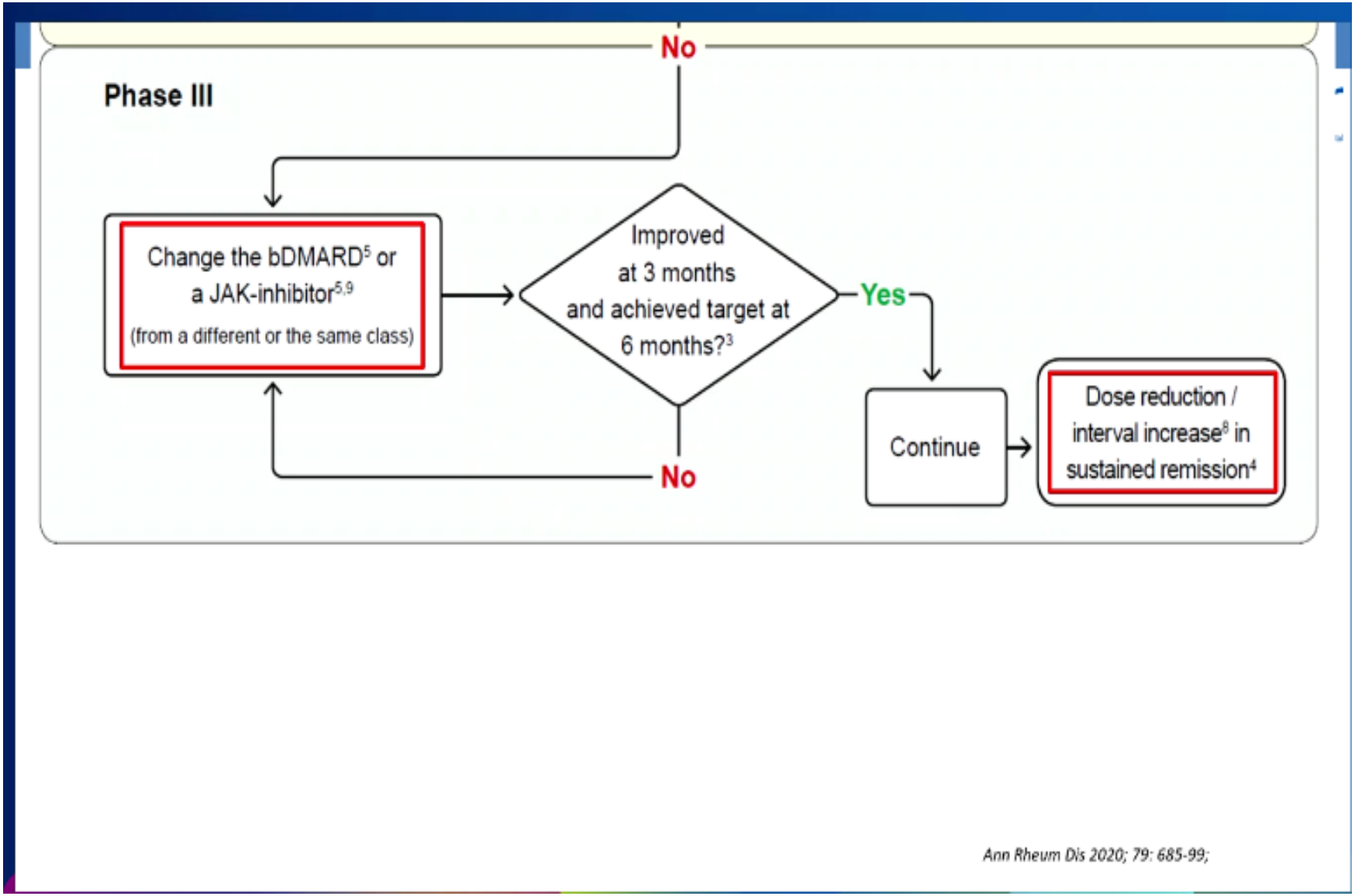
4/les facteurs de risque oncologiques classiques



les DMARD biologiques et les DMARD ciblés synthétiques doivent être associés à un DMARD conventionnel

Chez les patients qui ne peuvent pas utiliser un DMARD conventionnel en Co médication,

les inhibiteurs de la voie IL-6 et les DMARD ciblés peuvent présenter certains avantages par rapport aux autres DMARD biologiques. **Cette recommandation est inchangée**



Ann Rheum Dis 2020; 79: 685-99;

Final Set of Recommendations -2022 Update

eular

10.	**If a bDMARD or tsDMARD has failed, treatment with another bDMARD or a tsDMARD should be considered; if one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor. (A)**

LoA: 8.9 ± 1.2

10.	**If a bDMARD or tsDMARD has failed, treatment with another bDMARD or a tsDMARD* should be considered; if one TNF- or IL-6 receptor inhibitor therapy has failed, patients may receive *an agent with another mode of action or* a second TNF-/IL-6R inhibitor. (A)**

LoA: 9.3 ± 0.8

Si un DMARD biologique ou un DMARD ciblé n'a pas agi, un traitement par un autre DMARD biologique ou un DMARD ciblé doit être envisagé

Si un traitement par un anti-TNF **ou un anti-IL-6 (rajouté)** a échoué, les patients peuvent recevoir un agent avec un autre mode d'action ou un second anti-TNF **ou anti-IL-6 (rajouté)**;

Final Set of Recommendations -2022 Update

eular

11.	If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs or tsDMARD, especially if this treatment is combined with a csDMARD.(A)
12.	If a patient is in persistent remission, tapering the csDMARD could be considered. (B)

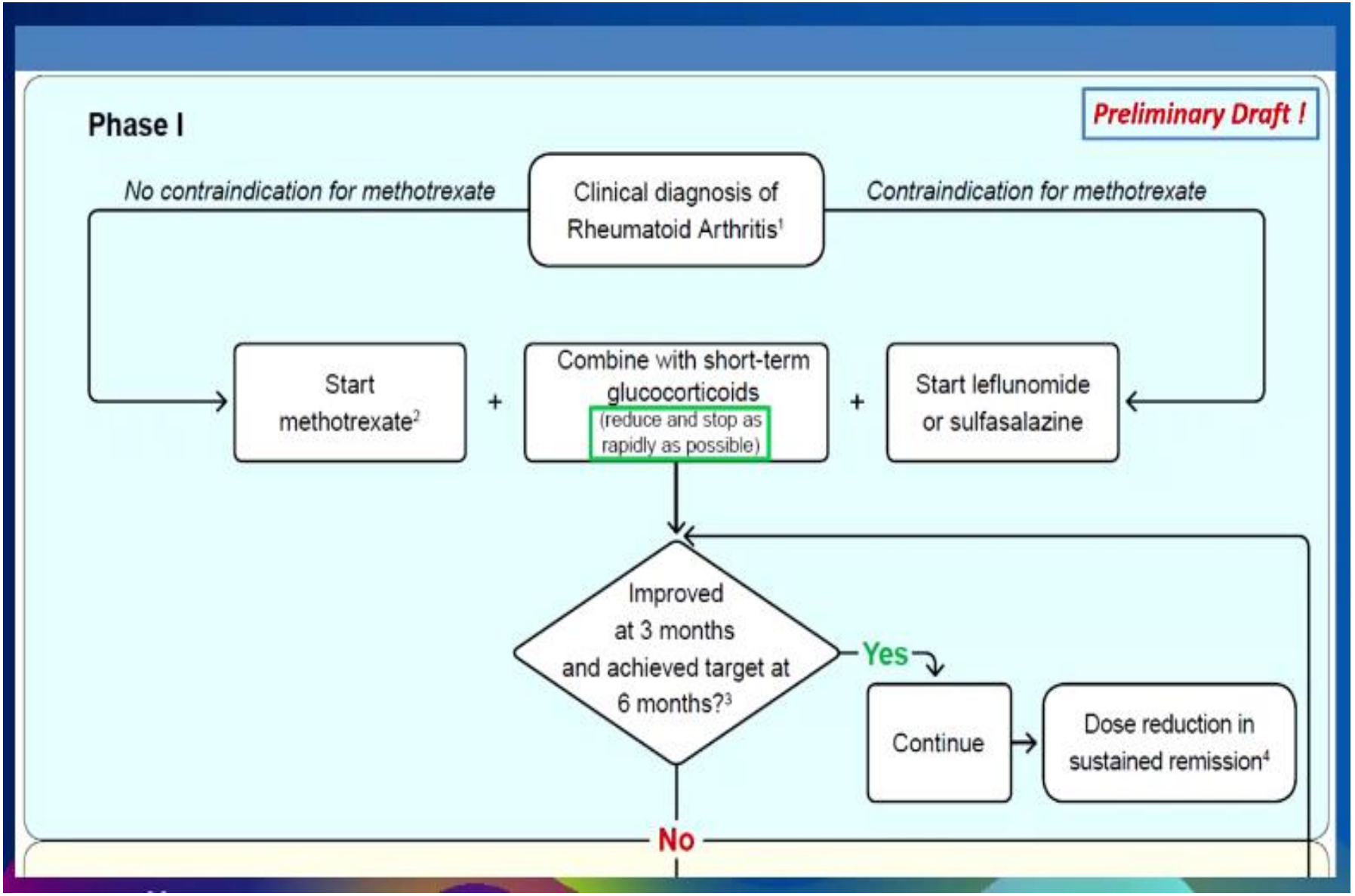
LoA: 9.2 ± 1.0

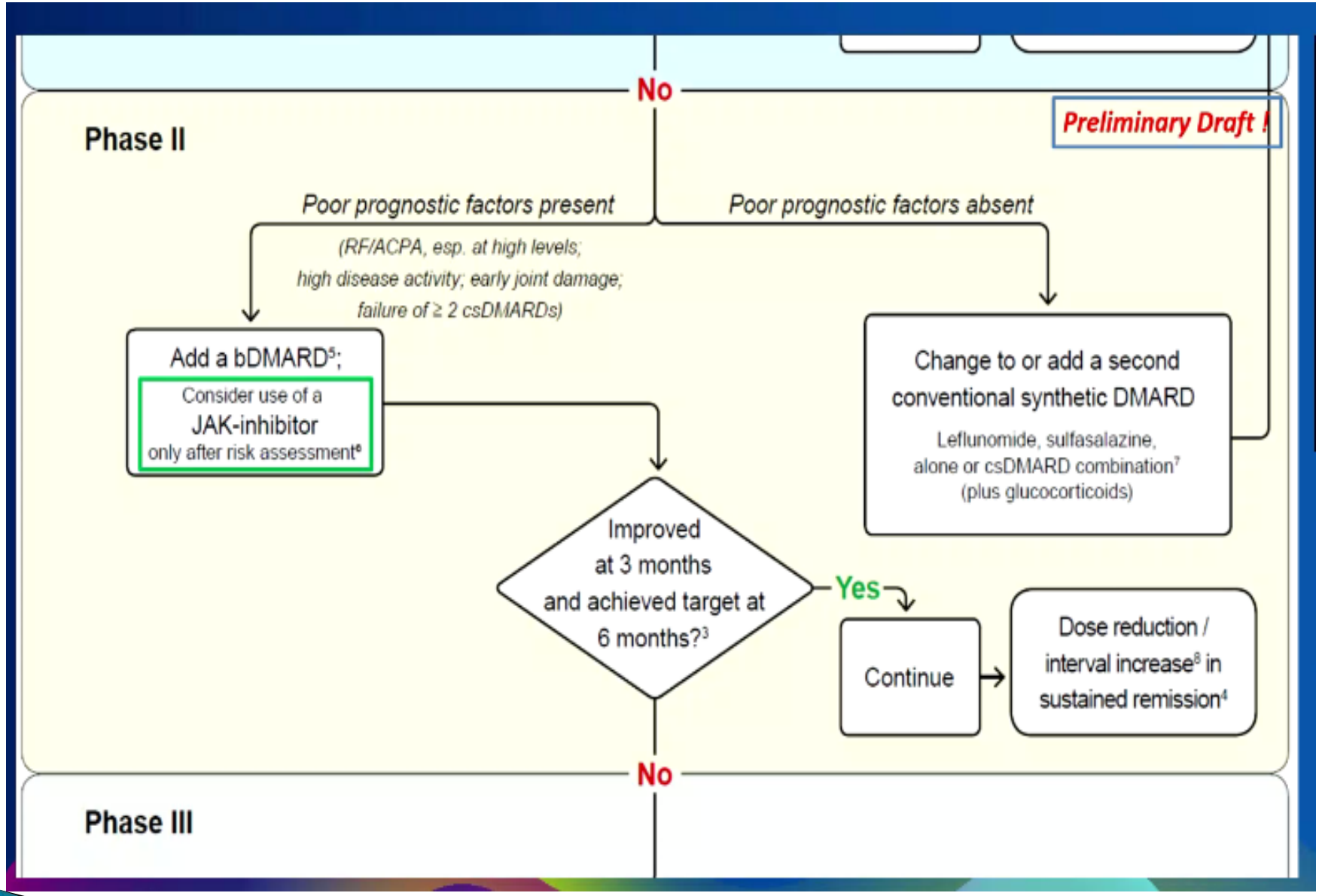
LoA: 9.0 ± 1.1

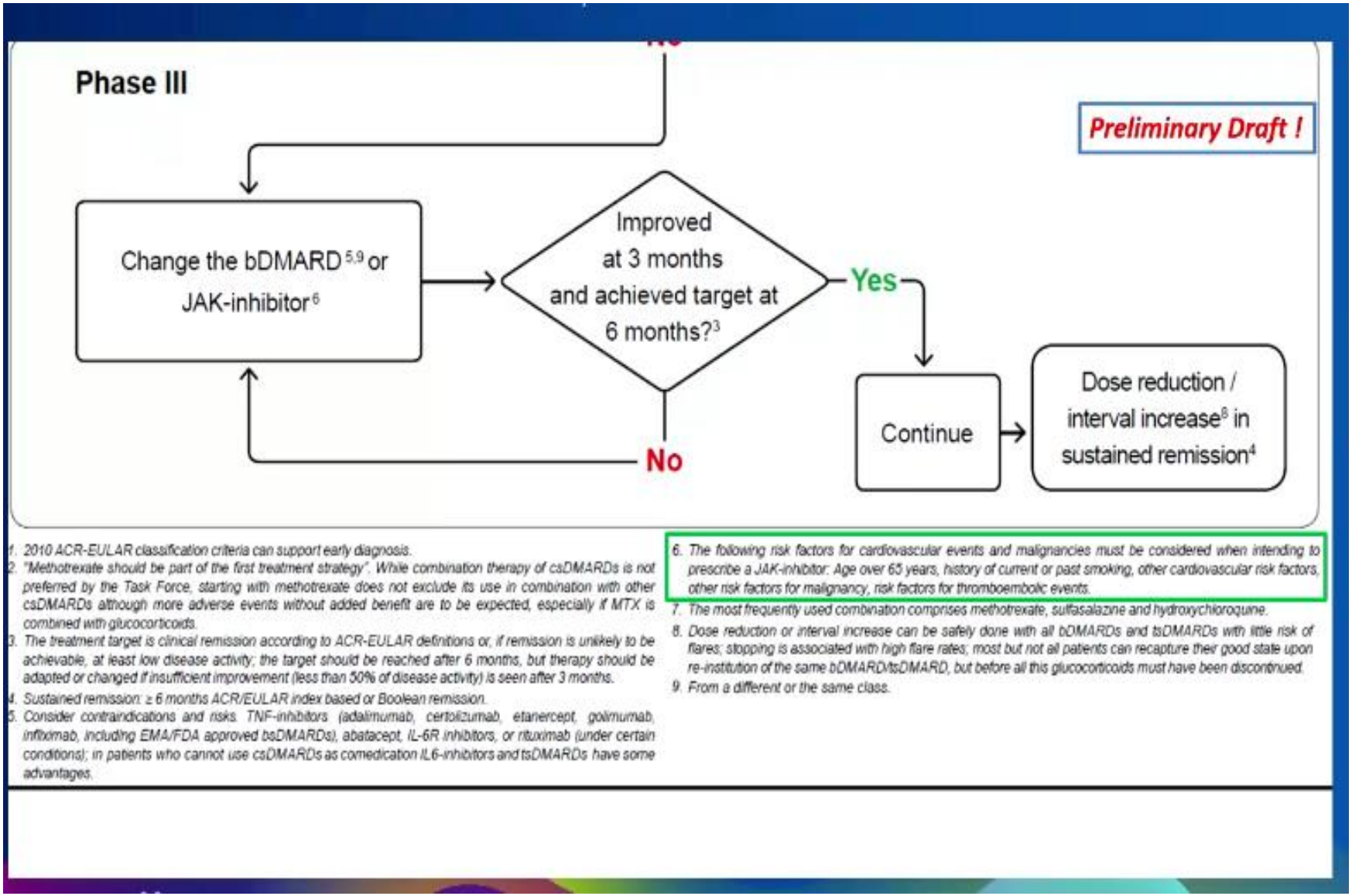
11.	After glucocorticoids have been discontinued and a patient is in sustained remission, dose reduction of DMARDs (bDMARDs/tsDMARDs and/or csDMARDs) may be considered. (A)

LoA: 9.3 ± 1.1

- si un patient est en rémission persistante et après arrêt des GC, on peut envisager de réduire les DMARD (biologiques, ciblés et/ou conventionnels).
- **Les experts ont supprimé la notion «surtout s'ils ont été combinés à un DMARD conventionnel»**


Phase I
Preliminary Draft !
No contraindication for methotrexate
Clinical diagnosis of Rheumatoid Arthritis[1]
Contraindication for methotrexate
Start methotrexate[2]
+
Combine with short-term glucocorticoids
(reduce and stop as rapidly as possible)
+
Start leflunomide or sulfasalazine
Improved at 3 months and achieved target at 6 months?[3]
Yes
Continue
Dose reduction in sustained remission[4]
No


No
Preliminary Draft !
Phase II
Poor prognostic factors present
(RF/ACPA, esp. at high levels;
high disease activity; early joint damage;
failure of ≥ 2 csDMARDs)
Poor prognostic factors absent
Add a bDMARD[5];
Consider use of a
JAK-inhibitor
only after risk assessment[6]
Change to or add a second
conventional synthetic DMARD
Leflunomide, sulfasalazine,
alone or csDMARD combination[7]
(plus glucocorticoids)
Improved
at 3 months
and achieved target at
6 months?[3]
Yes
Continue
Dose reduction /
interval increase[8] in
sustained remission[4]
No
Phase III



1. *2010 ACR-EULAR classification criteria can support early diagnosis.*
2. *"Methotrexate should be part of the first treatment strategy". While combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs although more adverse events without added benefit are to be expected, especially if MTX is combined with glucocorticoids.*
3. *The treatment target is clinical remission according to ACR-EULAR definitions or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if insufficient improvement (less than 50% of disease activity) is seen after 3 months.*
4. *Sustained remission: ≥ 6 months ACR/EULAR index based or Boolean remission.*
5. *Consider contraindications and risks. TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6R inhibitors, or rituximab (under certain conditions); in patients who cannot use csDMARDs as comedication IL6-inhibitors and tsDMARDs have some advantages.*
6. *The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAK-inhibitor: Age over 65 years, history of current or past smoking, other cardiovascular risk factors, other risk factors for malignancy, risk factors for thromboembolic events.*
7. *The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine.*
8. *Dose reduction or interval increase can be safely done with all bDMARDs and tsDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD/tsDMARD, but before all this glucocorticoids must have been discontinued.*
9. *From a different or the same class.*

Conclusion

- Les 5 principes généraux restent inchangés
- 6 des 12 recommandations st inchangées
  (2022:seulement 11 recommandations)
- L'association MTX + GC est recommandée avec plus de force

Conclusion

- La nécessité d'une réduction et d'un arrêt rapide de la corticothérapie est plus clairement souligné.
- Par ailleurs, les inhibiteurs JAK ne sont recommandés qu'en l'absence de facteurs de risque.
- Enfin, la réduction de dose des DMARD, qu'ils soient biologiques/ synthétiques ciblés ou conventionnels, est de plus en plus d'actualité, mais toujours après avoir obtenu l'arrêt des GC.