REMISSION
OR
SUPER RESPONDER
SPECIAL TWO PART SERIES

Remission or ‘super responders’ in severe asthma: same or different?

MAT-AU-2301789 | Date of preparation August 2023| Sanofi Australia (Macquarie Park, NSW)

RESPIRATORY ADVENT ADVANCES IN TYPE 2 INFLAMMATORY DISEASES

PANEL FOR TONIGHT'S MEETING

Prof Peter Wark (Chair)
Respiratory
Director of Cystic Fibrosis Service
Professor of Medicine
Monash University
AIRMED, Alfred Health

A/Prof Emily Stone
Oncology/Respiratory
Respiratory physician and clinician-researcher at St Vincent's Hospital Sydney and the University of NSW

Dr Michelle Tellus
Rheumatology
Consultant Rheumatologist
Private Practice
Melbourne

Prof Connie Katelaris
Immunology
Head of Unit, Immunology & Allergy
Campbelltown Hospital and
Professor of Immunology & Allergy,
Western Sydney University

ADVENT
TYPE 2 INFLAMMATORY DISEASES

REMISSION
OR
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SPECIAL TWO PART SERIES

Asthma definitions of remission

Prof. Peter Wark

Alfred Health

Monash University, Melbourne AUSTRALIA

RESPIRATORY ADVENT ADVANCES IN TYPE 2 INFLAMMATORY DISEASES

CHAIR

Prof Peter Wark

Director of Cystic Fibrosis Service, AIRMed, Alfred Health & Professor of Medicine, Monash University

Professor Peter Wark is the newly appointed Director of Cystic Fibrosis at AIRMed (Allergy, Immunology & Respiratory) at Alfred Health, Melbourne, and Professor of Medicine at Monash University. His research interests are airway inflammation in the context of chronic airways disease, innate immunity, and the role of infection in chronic airways disease. His group has developed expertise in identifying respiratory viruses in airway secretions and developing an in-vitro cell culture model of the airway epithelium that we use to model the effect of infection and inflammation. His research focuses upon factors that increase susceptibility to virus infection in asthma, COPD, cystic fibrosis (CF) and bronchiectasis. Characterising airway inflammation and innate immune responses in chronic airways disease and applying this to clinical care, as well as the development of precise individualised management strategies.

Disclosures

Requested to speak and will receive an honorarium at this Sanofi sponsored symposium

Employee NSW Health

Spoken or organised meetings sponsored by: Astra Zeneca, GSK, Boehringer Ingelheim, Mundipharma, Menarini, Novartis, CSL, Chiesi, Sanofi, Vertex.

Advisory boards; Astra Zeneca, Boehringer, Novartis, Sanofi, Vertex. PBAC Australia.

Outline

1. Defining the concepts of remission and disease modification.
2. What is asthma, what are the targets and what should be measured?
3. Achieving clinical remission, what does this look like?
4. Achieving disease modification. What might this look like? Is a cure possible? A framework for remission.

Defining concepts of clinical remission and disease modification

Clinical remission[1]

The state of no disease activity in patients on or off treatment

Disease modification[2]

A process that can affect the underlying pathophysiology of the disease, prevent structural or clinical progression, or cause a sustained reduction in disease activity beyond the temporal effects of other interventions

Cure[1]

Absence of symptoms and reversal to the normal pathological state of the airways, off treatment

1. Thomas D et al. Eur Respir J. 2022; 3; 60:2102583 **2.** Busse WW et al. Eur Respir Rev. 2022; 31:210183.

What is asthma?

GINA 2023[1]

Asthma is a heterogenous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough, that vary over time and in intensity, together with variable expiratory airflow limitation.

Lancet commission[2]

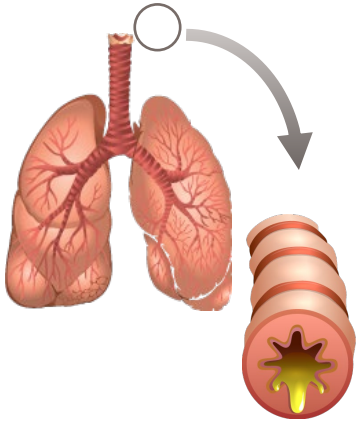
"asthma" was no more a diagnosis than is "arthritis" or "anaemia." It is an umbrella term that should be used to describe a constellation of clinical symptoms, namely wheeze, breathlessness, chest tightness and cough, and should be followed by the question "what sort of asthma is this?"

1. GINA 2023; Available at: https://ginasthma.org/wp-content/uploads/2023/07/GINA-2023-Full-report-23_07_06-WMS.pdf Accessed 7th August, 2023. **2.** Pavord, I.D., et al., Lancet 2018; 391: 350–400.

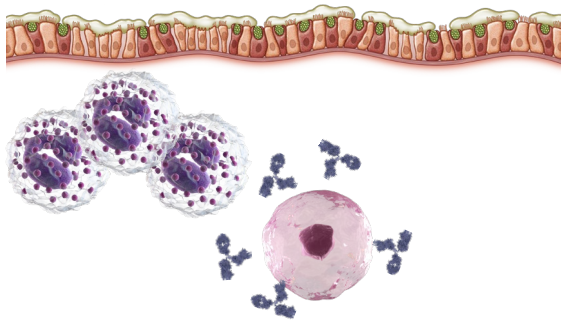
What is asthma? What are the goals of treatment?

Long term outcomes
Exacerbations
Loss of lung function
Mortality

Clinical symptoms
- Wheeze
- Cough
- Breathlessness



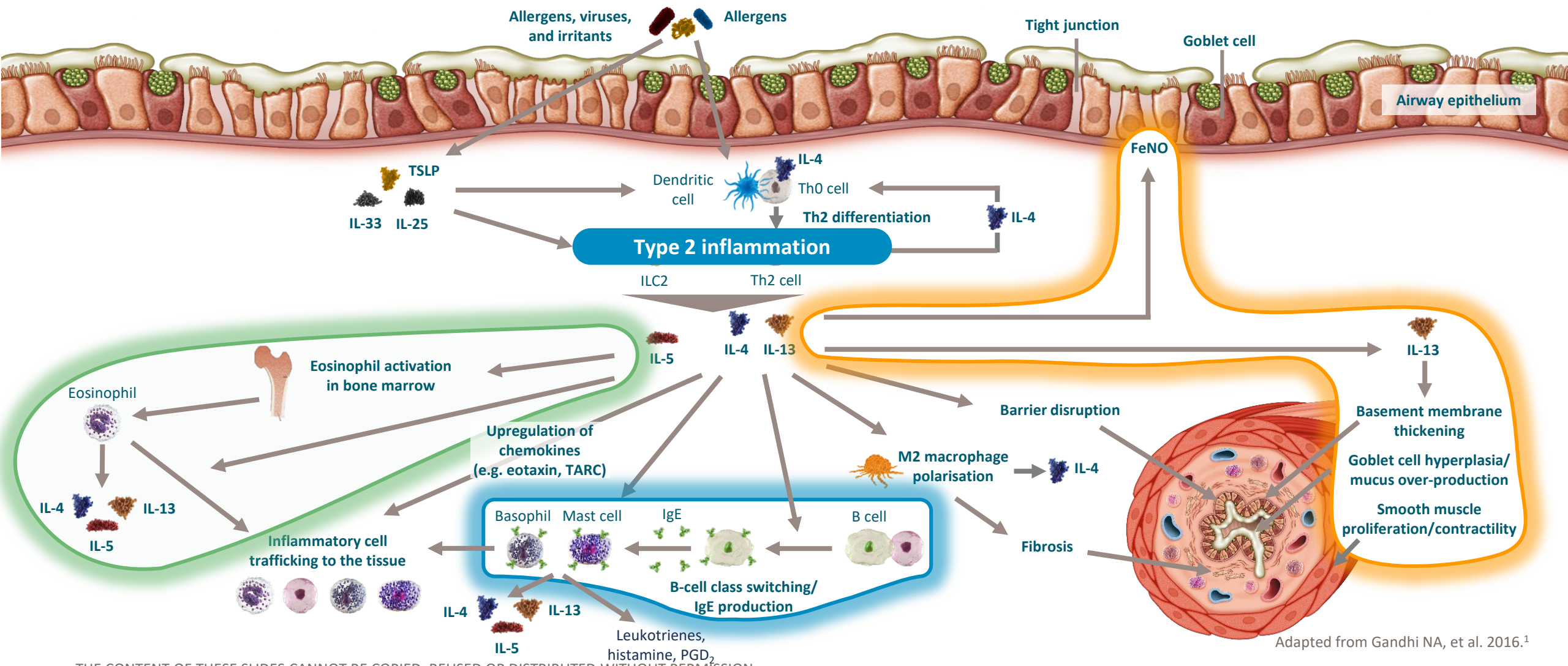
Airway obstruction
- Variable airflow obstructions
- Fixed airflow obstruction
- Airway wall remodelling



Airway inflammation
- Eosinophilic
- Allergic
- Non-type 2

Adapted from Shaw DE, et al. Lancet Respir Med. 2021;9:786–794.

Type 2 airway inflammation in asthma[1–4]

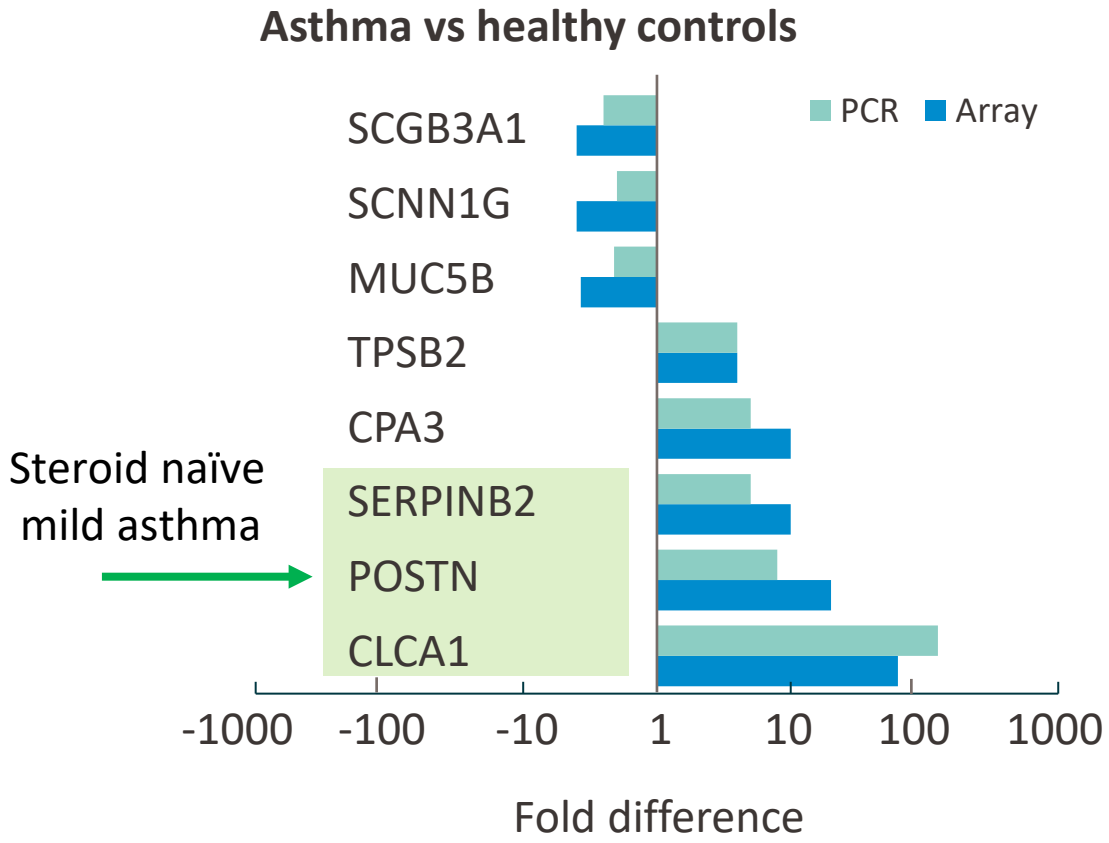


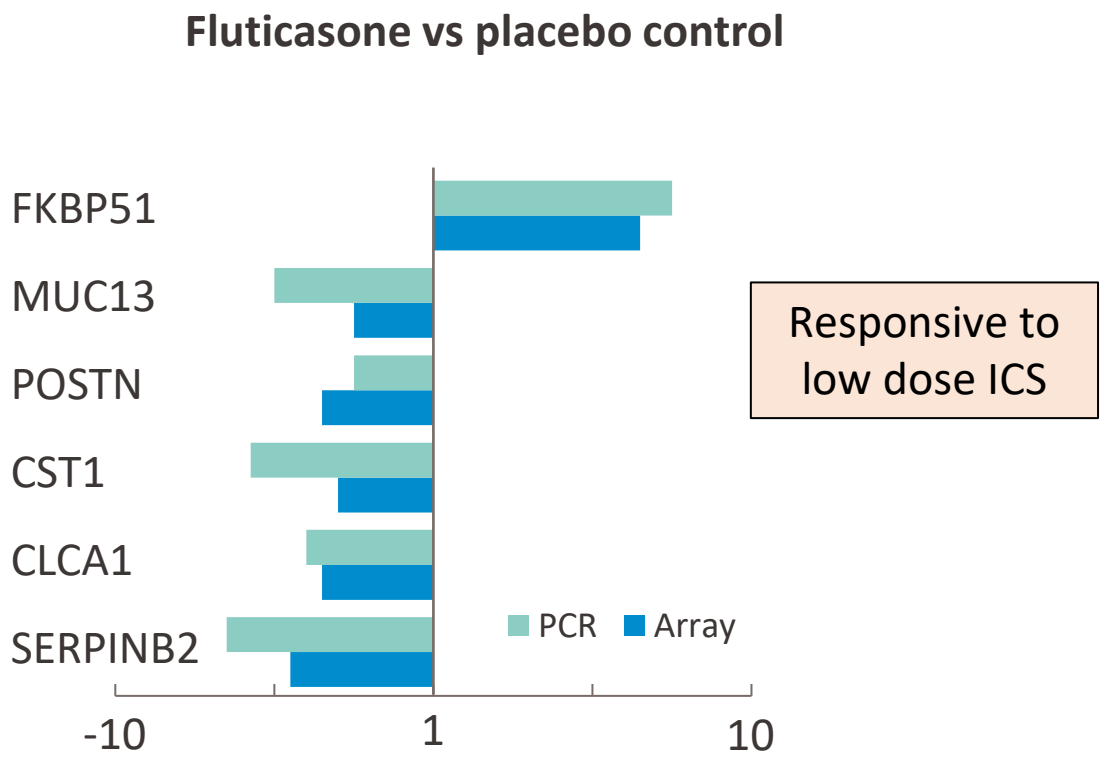
Adapted from Gandhi NA, et al. 2016.[1]

Ig, Immunoglobulin; **IL**, Interleukin; **ILC2**, type 2 innate lymphoid cell; **FeNO**, fractional exhaled nitric oxide; **PDG_2**; prostaglandin D2; **TARC**, thymus and activation-regulated chemokine; **Th**, T helper; **TSLP**, thymic stromal lymphopoietin

1. Gandhi NA, et al. Nat Rev Drug Discov. 2016;15:35–50. **2.** Fahy JV. Nat Rev Immunol. 2015;15:57–65. **3.** Nonaka M, et al. Int Arch Allergy Immunol. 2010;152:327–341. **4.** GINA. Global strategy for asthma management and prevention. 2023. Available at https://ginasthma.org/wp-content/uploads/2023/07/GINA-2023-Full-report-23_07_06-WMS.pdf Accessed August 2023.

Genome-wide profiling epithelial cells demonstrates an IL-13 induced T2 inflammation and response to corticosteroids?





PCR, polymerase chain reaction; **ICS,** inhaled corticosteroid; **POSTN,** periostin; **CLCA1**; calcium-activated chloride channel regulator; **CPA3**, carboxypeptidase A3; **TPSB2,** tryptase β; **MUC5B,** mucin 5B; **MUC13**, mucin 13; **SERPINB2**, Serine peptidase inhibitor B2; **SCNN1G**, Na^+ channel, nonvoltage-gated 1G; **SCGB3A1**, secretoglobulin 3A1; **FKBP51**, FK506-binding protein 51; **CST1,** epithelial cystatin SN.

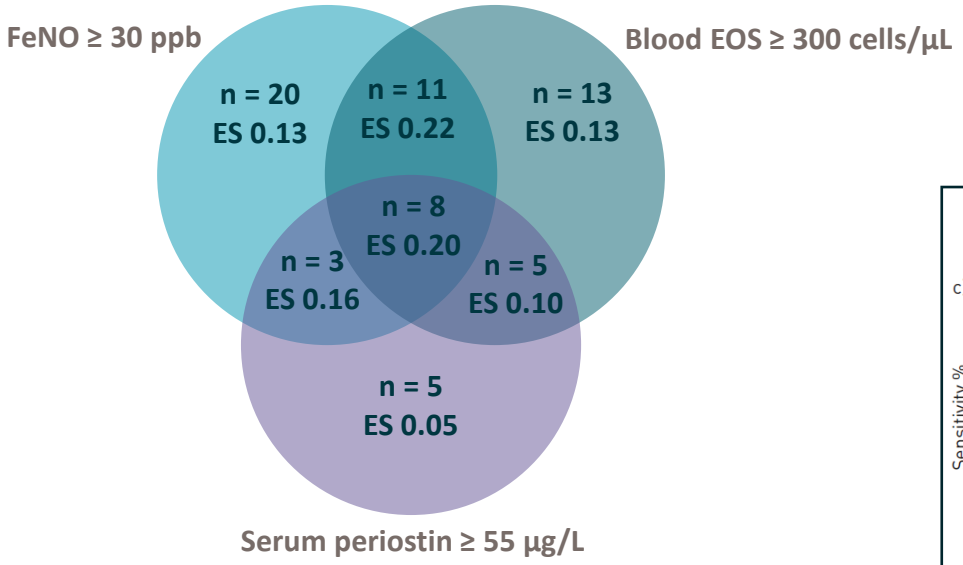
Adapted from Woodruff PG, et al. Proc Natl Acad Sci U S A. 2007;104(40):15858-15863.

Measuring type 2 high inflammation with biomarkers

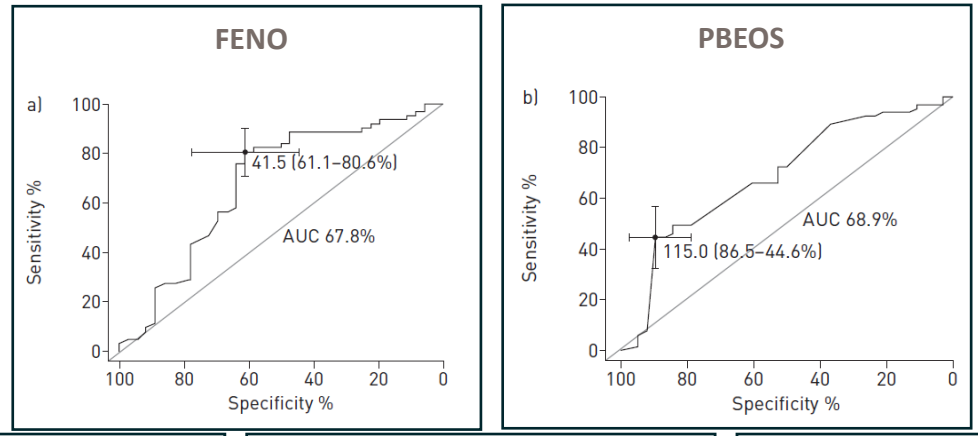
Transcriptome profile of airway epithelial cells exposed to T2GM (U-BIOPRED)

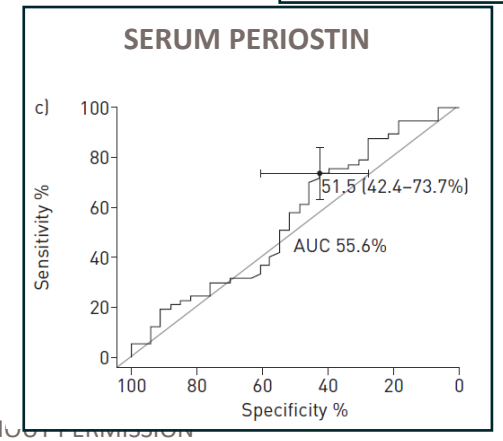
Correlated T2GM high

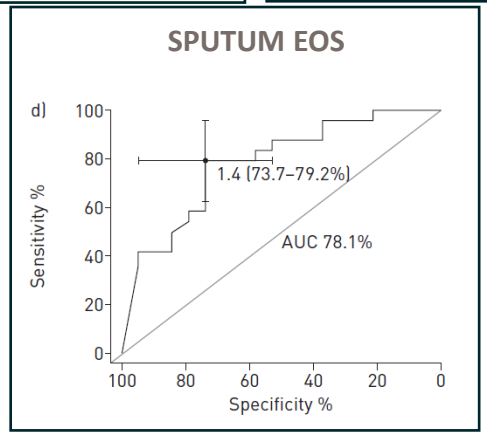
- Sputum eosinophilia correlated best
- FeNO (≥ 30 ppb)
- Blood EOS (≥ 300 cells/µL) moderate prediction

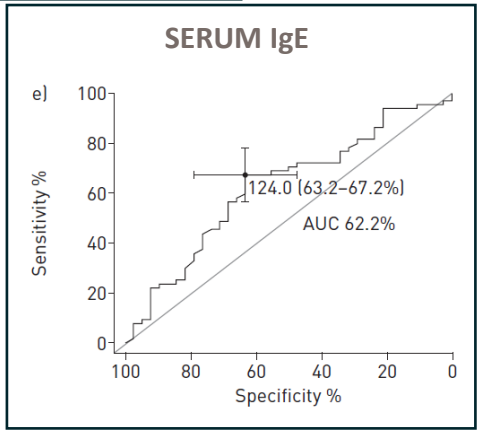


Receiver operating characteristic (ROC) curves







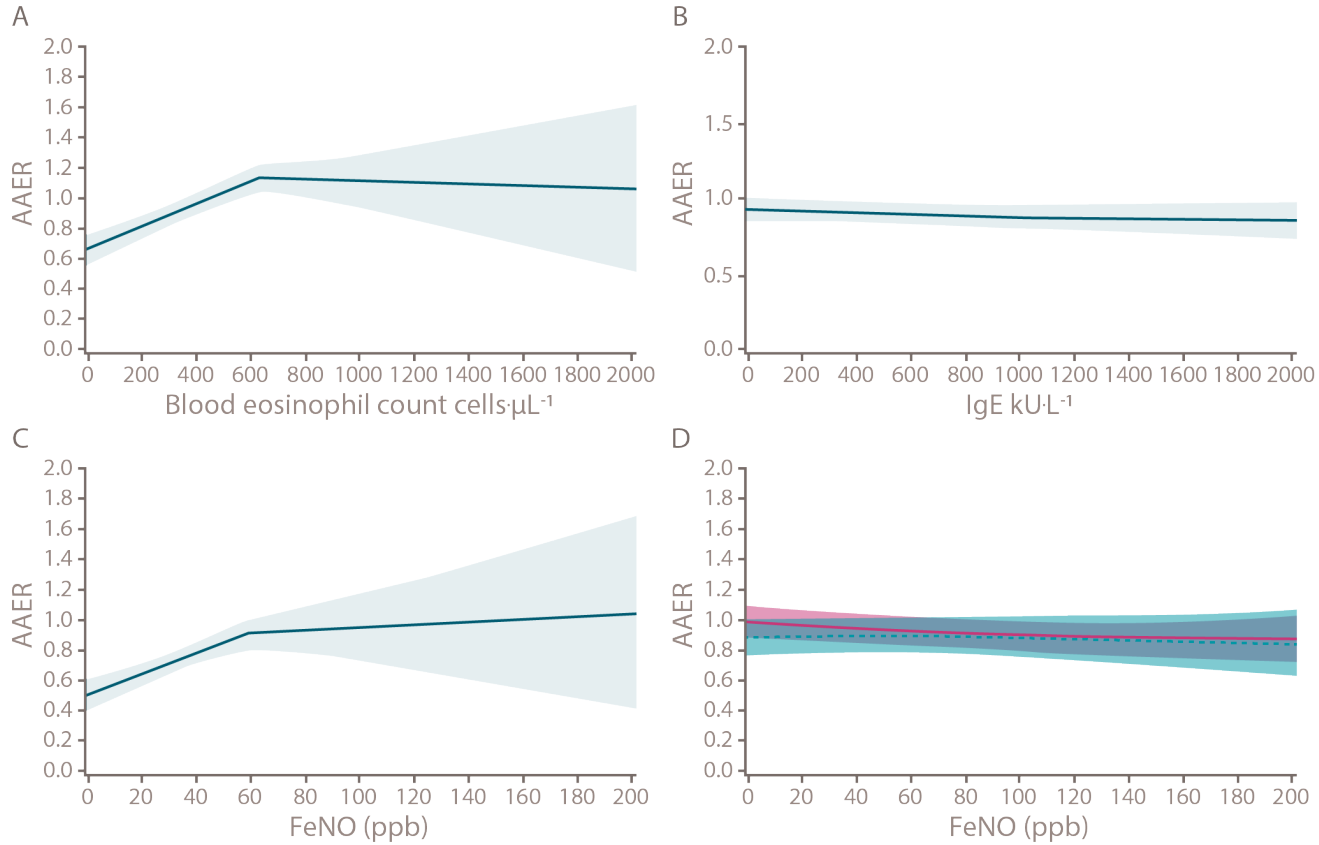


AUC, area under the curve**; EOS**, eosinophils; **ES**, enrichment score; **FeNO**, fractional exhaled nitric oxide; **IgE**, immunoglobulin E; **PBEOS**, peripheral blood eosinophils; **ppb**, parts per billion; **T2GM**, type 2 gene mean; **U-BIOPRED**, Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes

Pavlidis S, et al. Eur Respir J. 2019;53:1800938.

Refractory T2 airway inflammation predicts risk of exacerbation

Seven Phase 2/3 RCTs of moderate-to-severe asthma, all had medium–high ICS+LABA, assessed annual exacerbations, 48 - 56 weeks



Images adapted from Kraft, *et al.* 2021[1]

AAERs by eosinophil and FeNO subgroups

FeNO (ppb) \ Eosinophils cells·µL⁻¹	<150	≥150-<300	≥300
<20	0.58 (65/211, 30.8%)		
≥20 - <50	0.58 (157/467, 33.6%)		
≥50	0.83 (125/312, 40.1%)		1.00 (45/108, 41.7%)

ICS, inhaled corticosteroid; **LABA**: long-acting β_2-agonist; **RCT**, randomised controlled trial; **ppb**, parts per billion; **CI**, confidence interval; **IgE**, Immunoglobulin E; **FeNO**, fractional exhaled nitric oxide; **AAER**, annual asthma exacerbation rate.

1. Kraft M, et al. Eur Respir J. 2021;58(6).

Refractory T2 airway inflammation predicts risk of exacerbation

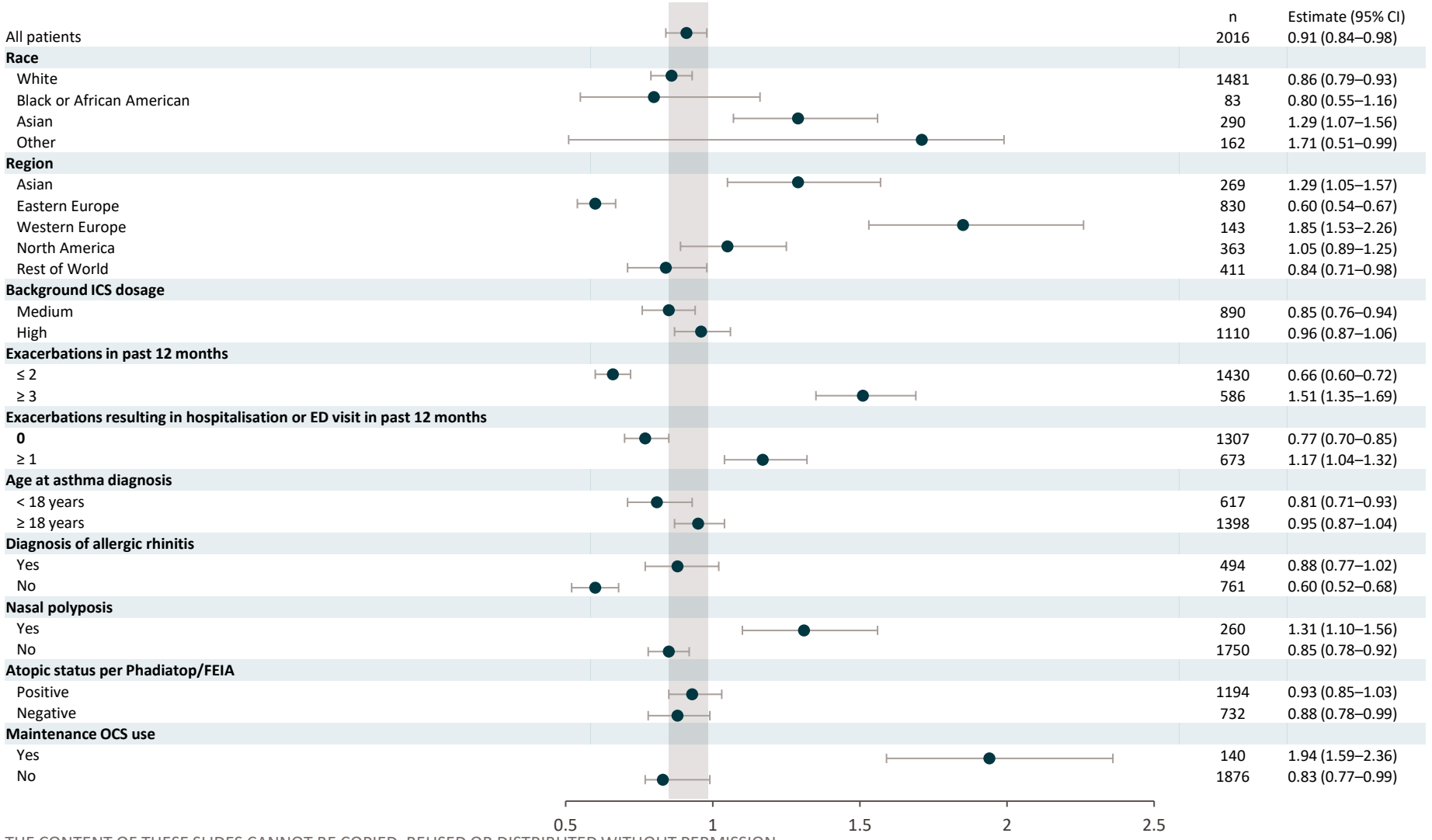


Image adapted from Kraft, *et al.* 2021[1]

Annualised asthma exacerbation rates in the placebo group by demographics and baseline clinical characteristics. Shading indicates the 95% confidence interval range for the AAER overall for patients in the placebo group.

ICS, inhaled corticosteroid; **ED**, emergency department; **FEIA**, fluorescence enzyme immunoassay; **OCS,** oral corticosteroid

1. Kraft M, et al. Eur Respir J. 2021;58(6).

ADVENT
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Remission in Lung Oncology

Emily Stone

St Vincent's Hospital Sydney,
School of Clinical Medicine, UNSW Sydney

RESPIRATORY ADVENT ADVANCES IN TYPE 2 INFLAMMATORY DISEASES

SPEAKER

A/Prof Emily Stone

Respiratory physician and clinician-researcher at St Vincent‘s Hospital Sydney and UNSW

Associate Professor Emily Stone is a respiratory physician and clinician-researcher at St Vincent’s Hospital Sydney and the University of NSW. Her research interests include lung cancer screening, tobacco control and the impact of multidisciplinary team care. She has served as past Chair of the IASLC Tobacco Control Committee and TSANZ Tobacco Control SIG. She is the current Deputy Chair of the Thoracic Oncology Group of Australasia and the recently appointed Editor-in-Chief of the *Journal of Thoracic Oncology Clinical and Research Reports*. She is committed to equity of access in lung cancer screening, integration of smoking cessation into lung cancer screening programs and to universally available, high-quality multidisciplinary lung cancer care.

Disclosures

2020-2022

- Speaker honoraria Astra Zeneca, MSD
- Advisory Board BMS

EUROPEAN RESPIRATORY JOURNAL

Asthma remission: what is it and how can it be achieved?

Dennis Thomas, Vanessa M. McDonald, Ian D. Pavord, Peter G. Gibson

*Disclaimer: macrolide antibiotics are not registered for the management of severe asthma in Australia.

Thomas D, et al. Eur Respir J. 2022;60(5).

Remission in asthma

Asthma Remission

What is asthma remission?

A high level of disease control – the absence of signs and symptoms of asthma for ≥12 months

Types of asthma remission

Types	Either on or off treatment:
Clinical remission	• No symptoms • No attacks • Optimisation of lung function
Complete remission	• Clinical remission plus normalisation of underlying pathology

Prevalence

Spontaneous remission in adult asthma patients **2–52%**

Potential treatments to induce remission

Biologics

- Highly effective in eosinophilic asthma

Macrolides

- Treat eosinophilic and non-eosinophilic asthma

Treatable traits approach

- Many underlying treatable traits contribute to the multifaceted aetiology of asthma
  - Identifying and treating all underlying traits may improve asthma outcomes

Early intervention

- People accumulate health and psychological issues over time, including iatrogenic issues
- Timely targeted intervention might halt asthma progression

*Disclaimer: macrolide antibiotics are not registered for the management of severe asthma in Australia.

Image from Thomas D, et al. Eur Respir J. 2022;60(5). Originally developed as part of the Centre of Excellence in Treatable Traits (https://treatabletraits.org.au).

Cancer Australia Glossary

REMISSION

Period of time when the symptoms of the cancer reduce or disappear.
A partial remission is when there has been a significant improvement in the cancer.
A complete remission is when there is no evidence of active disease.
This does not necessarily mean that the cancer is cured.

Australian Government. Cancer Australia. Glossary. Available at https://www.canceraustralia.gov.au/resources/glossary#R . Accessed August 2023.

WHAT IS REMISSION IN CANCER?

The term “remission” means that cancer treatment reduced or eliminated the symptoms and signs of cancer.
Remission may last for months, years or the rest of your life.
Remission may not mean you’re free of cancer (cured), but it’s an important turning point for you and your cancer care team.

The Cleveland Clinic. Remission in Cancer. Available at https://my.clevelandclinic.org/health/articles/24673-cancer-remission Accessed August 2023

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Remission in rheumatology: concept of treat to target

Dr. Michelle Tellus

Rheumatologist

St. Vincent's Private Hospital, Melbourne

RESPIRATORY ADVENT ADVANCES IN TYPE 2 INFLAMMATORY DISEASES

SPEAKER

Dr Michelle Tellus

Consultant Rheumatologist, Private Practice, Melbourne

Dr Michelle Tellus' interests lie within inflammatory diseases of the joints and muscles and in the field of osteoporosis. Dr Tellus has worked at the Royal Melbourne Hospital, Bone and Mineral Unit of the Royal Children's Hospital as a Research and in the field of Juvenile Chronic Arthritis and at the Essendon Hospital Bone and Metabolic Unit Outpatients Team.

Disclosures

No disclosures.

TREATMENT STRATEGIES AND RECOMMENDATIONS

Treat-to-target (T2T)

Recommendations of an international task force

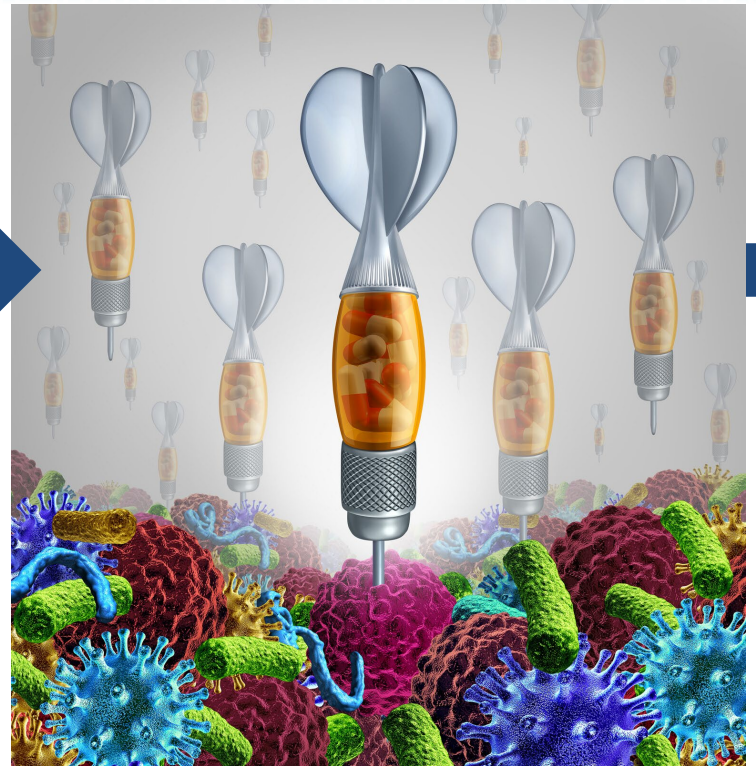
Treatment strategies and recommendations: overview

The treatment target is remission or a state of at least low disease activity, which should be attained within 6 months

First-line therapy

Methotrexate should be prescribed at an optimal dose of 25 mg weekly and in combination with glucocorticoids

40% to 50% of patients reach remission or at least low disease activity with this regimen



Second-line therapy

If first-line treatment fails, sequential application of targeted therapies, such as bDMARDs or JAK inhibitors in combination with MTX should be prescribed

75% of these patients reach the treatment target over time

bDMARD; biological disease-modifying antirheumatic drug; **JAK**, Janus-kinase; **MTX**, methotrexate

Image: Stock image

Aletaha D, et al. JAMA. 2018;320(13):1360-1372.

TREATMENT STRATEGIES AND RECOMMENDATIONS

EULAR recommendations for the management of rheumatoid arthritis

2022 update

EULAR recommendations: overarching principles


EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 up

1. Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist
2. Treatment decisions are based on disease activity, safety issues and other patient factors, such as comorbidities and progression of structural damage
3. Rheumatologists are the specialists who should primarily care for patients with RA
4. 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
5. RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist

RA, rheumatoid arthritis; **EULAR,** European Alliance of Associations for Rheumatology

As in previous versions of these recommendations, the task force continued to use overarching principles for information on the general aspects of the management of RA .

Smolen JS, et al. Ann Rheum Dis. 2023;82(1):3-18.

EULAR recommendations: initial therapy

1. Therapy with DMARDs should be started as soon as the diagnosis of RA is made
2. Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient
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
4. MTX should be part of the first treatment strategy
5. In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy
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[†]

Recommendations 1–5 remain unchanged.

[†] Small change implemented: Recommendation 6 now explicitly and unequivocally advocates not only a rapid tapering regimen but also timely discontinuation.

DMARD, disease-modifying antirheumatic drug, **csDMARD,** conventional synthetic disease-modifying antirheumatic drug; **RA,** rheumatoid arthritis; **MTX**, methotrexate; **EULAR,** European Alliance of Associations for Rheumatology

Smolen JS, et al. Ann Rheum Dis. 2023;82(1):3-18.

EULAR recommendations: treatment failures

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
8. If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, a bDMARD should be added; JAK-inhibitors may be considered, but pertinent risk factors* must be taken into account#
9. bDMARDs and tsDMARDs* should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs* may have some advantages compared with other bDMARDs
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

*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 (such as diabetes, obesity, hypertension), other risk factors for malignancy (current or previous history of malignancy other than successfully treated non-melanoma skin cancer), risk factors for thromboembolic events (history of myocardial infarction or heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients taking combined hormonal contraceptives or hormone replacement therapy, undergoing major surgery or immobile). Recommendations 7 and 9 remain unchanged.

Most extensive change implemented: Following new safety issues emanating from the ORAL-Surveillance trial, recommendation 8 now places JAK Inhibitors at the same level as bDMARDs, but only in patients in whom risk factors for cardiovascular or malignant diseases have been considered specifically.† Small change implemented: IL-6R Inhibition has now been tested after insufficient response to another IL-6R blocker, leading to including IL-6R blockade in addition to TNF-inhibition in patients in whom a previous bDMARD with the same mechanism of action has failed.

csDMARD, conventional synthetic disease-modifying antirheumatic drug; **bDMARD**, biological disease-modifying antirheumatic drug; **tsDMARD**, targeted synthetic disease-modifying antirheumatic drug; **IL-6**, interleukin 6; **IL-6R**, interleukin-6 receptor; **TNF**, tumour necrosis factor

Smolen JS, et al. Ann Rheum Dis. 2023;82(1):3-18.

EULAR recommendations: remission

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


Stock image

Recommendations 11 and 12 from 2019 were brought together as recommendation 11

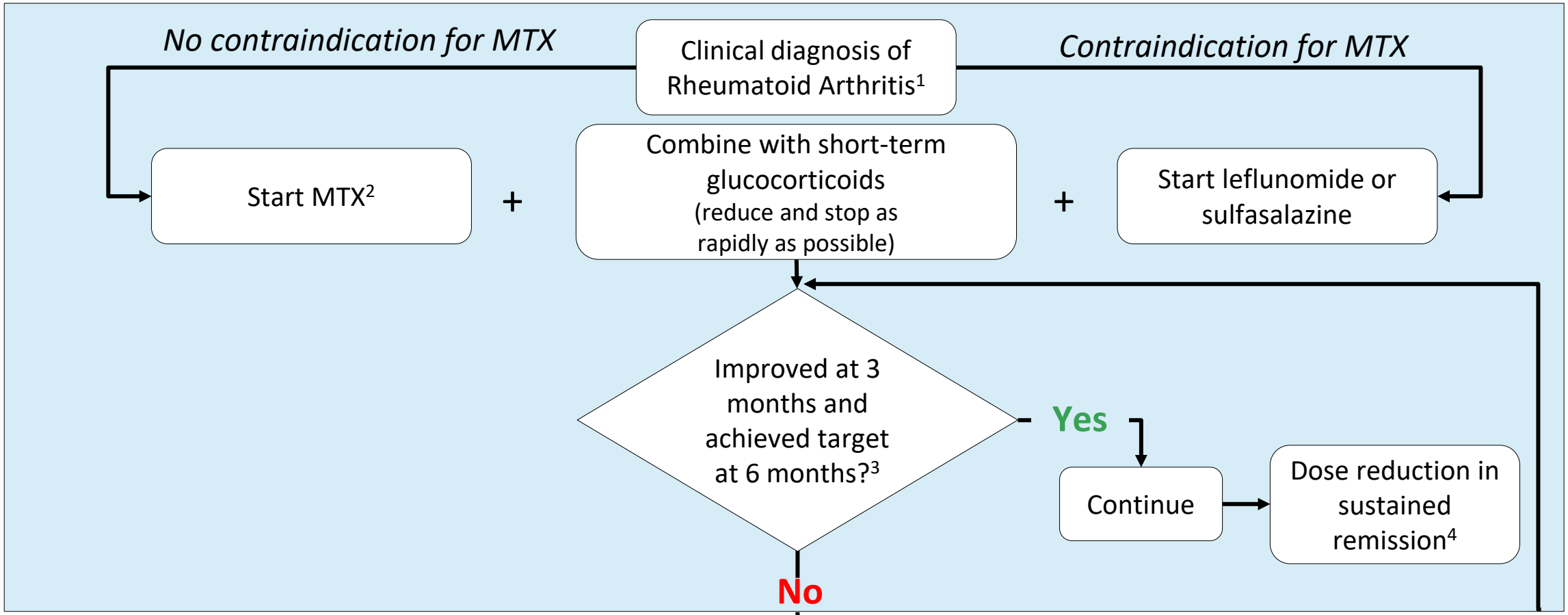
*The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAK-inhibitor: Age over 65 years, history of current or past smoking, other cardiovascular risk factors (such as diabetes, obesity, hypertension), other risk factors for malignancy (current or previous history of malignancy other than successfully treated non-melanoma skin cancer), risk factors for thromboembolic events (history of myocardial infarction or heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients taking combined hormonal contraceptives or hormone replacement therapy, undergoing major surgery or immobile).

DMARD, disease-modifying antirheumatic drug; **csDMARD,** conventional synthetic disease-modifying antirheumatic drug; **bDMARD**, biological disease-modifying antirheumatic drug; **tsDMARD,** targeted synthetic disease-modifying antirheumatic drug

Smolen JS, et al. Ann Rheum Dis. 2023;82(1):3-18.

Recommendations: Phase I

These recommendations can be applied for any patient at any point in time

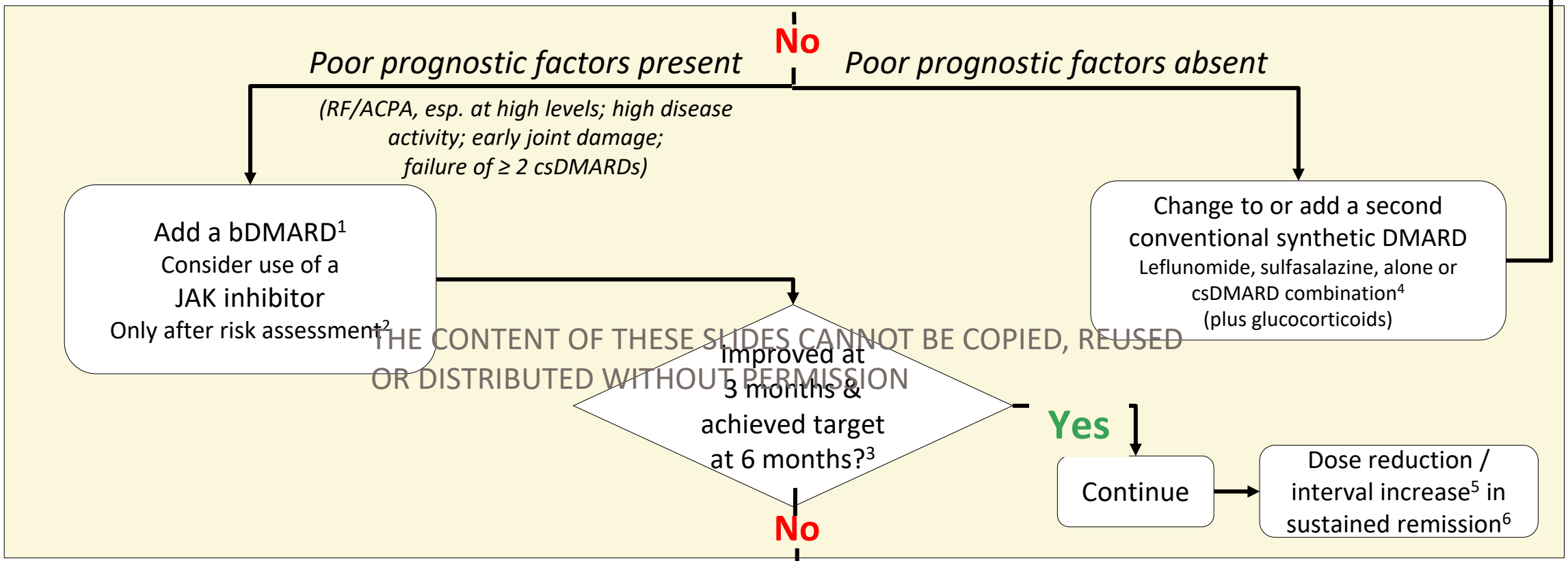


1. 2010 ACR-EULAR classification criteria can support early diagnosis.
2. "MTX should be part of the first treatment strategy". While combination therapy of csDMARDs is not preferred by the Task Force, starting with MTX does not exclude its use in combination with other csDMARDs although more adverse 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; target should be reached after 6 months, but therapy should be adapted or changed if insufficient improvements (less than 50% of disease activity) is seen after 3 months.
4. Sustained remission: ≥ 6 months ACR/EULAR index based or Boolean remission.

csDMARD, conventional synthetic disease-modifying antirheumatic drug; **MTX**, methotrexate; **ACR**, American College of Rheumatology; **EULAR,** European Alliance of Associations for Rheumatology
Smolen JS, et al. Ann Rheum Dis. 2023;82(1):3-18.

Recommendations: Phase II

For insufficient responders to MTX and/or another csDMARD



1. 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 comedications IL-6 inhibitors and tsDMARDs have some advantages.

2. The following risk factors for CV events and malignancies must be considered when intending to prescribe a JAK-inhibitor: Age over 65 years, history of current or past smoking, other CV risk factors (such as diabetes, obesity, hypertension), other risk factors for malignancy (current or previous history of malignancy other than successfully treated NMSC, risk factors for thrombotic events (history of MI or heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients taking combine hormonal oral contraceptive or hormone replacement therapy, undergoing major surgery or immobile).

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; target should be reached after 6 months, but therapy should be adapted or changed if insufficient improvements (less than 50% of disease activity) is seen after 3 months.

4. The most frequently used combination comprises MTX, sulfasalazine and hydroxychloroquine.

5. Dose reduction or interval increase can be safely done will 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 institution of the same bDMARDs/tsDMARDs, but before all this glucocorticoids must have been discontinued.

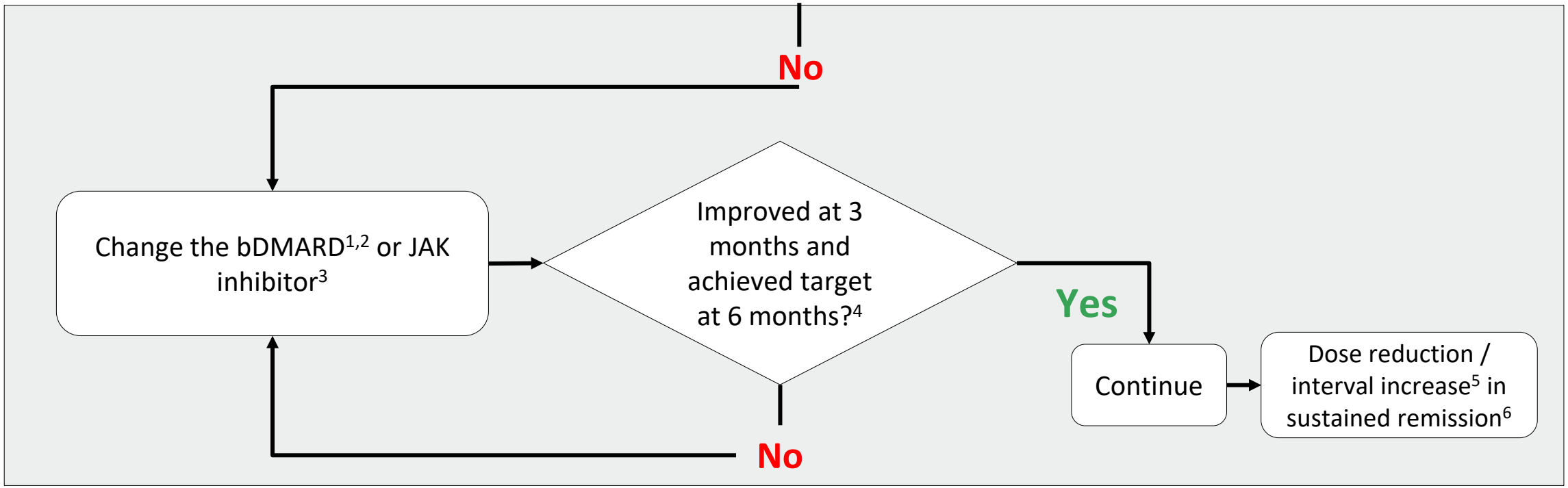
6. Sustained remission: ≥ 6 months ACR/EULAR index based or Boolean remission.

RF, rheumatoid factor; **ACPA**, anti-citrullinated protein antibodies; **csDMARD**; conventional synthetic disease-modifying antirheumatic drug; **bDMARD**, biological disease-modifying antirheumatic drug; **tsDMARD,** targeted synthetic disease-modifying antirheumatic drug; **IL-6**, interleukin 6; **IL-6R**, interleukin-6 receptor; **TNF**, tumour necrosis factor; **JAK**, Janus-kinase; **EMA**, European Medicines Agency; **FDA,** Food and Drug Administration; **ACR**, American College of Rheumatology; **EULAR**; European Alliance of Associations for Rheumatology; **NMSC**, non-melanoma skin cancer, **CV**; cardiovascular; **MI,** myocardial ischaemia

Smolen JS, et al. Ann Rheum Dis. 2023;82(1):3-18. THE CONTENT OF THESE SLIDES CANNOT BE COPIED, REUSED OR DISTRIBUTED WITHOUT PERMISSION

Recommendations: Phase III

For insufficient responders to a bDMARD or JAK inhibitor



1. 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 comedications IL-6 inhibitors and tsDMARDs have some advantages.
2. From a different or the same class.
3. The following risk factors for CV events and malignancies must be considered when intending to prescribe a JAK-inhibitor: Age over 65 years, history of current or past smoking, other CV risk factors (such as diabetes, obesity, hypertension), other risk factors for malignancy (current or previous history of malignancy other than successfully treated NMSC, risk factors for thrombotic events (history of MI or heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients taking combine hormonal oral contraceptive or hormone replacement therapy, undergoing major surgery or immobile).
4. The treatment target is clinical remission according to ACR-EULAR definitions or, if remission is unlikely to be achievable, at least low disease activity; target should be reached after 6 months, but therapy should be adapted or changed if insufficient improvements (less than 50% of disease activity) is seen after 3 months.
5. Dose reduction or interval increase can be safely done will 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 institution of the same bDMARDs/tsDMARDs, but before all this glucocorticoids must have been discontinued.
6. Sustained remission: ≥ 6 months ACR/EULAR index based or Boolean remission.

RF, rheumatoid factor; **ACPA**, anti-citrullinated protein antibodies; **csDMARD**, conventional synthetic disease-modifying antirheumatic drug; **bDMARD**, biological disease-modifying antirheumatic drug; **tsDMARD,** targeted synthetic disease-modifying antirheumatic drug; **IL-6**, interleukin 6; **IL-6R**, interleukin-6 receptor; **TNF**, tumour necrosis factor; **JAK**, Janus-kinase; **EMA**, European Medicines Agency; **FDA,** Food and Drug Administration; **ACR**, American College of Rheumatology; **EULAR**, European Alliance of Associations for Rheumatology; **NMSC**, non-melanoma skin cancer, **CV**, cardiovascular; **MI,** myocardial ischaemia

Smolen JS, et al. Ann Rheum Dis. 2023;82(1):3-18.

ADVENT
TYPE 2 INFLAMMATORY DISEASES

REMISSION
OR
SUPER RESPONDER

SPECIAL TWO PART SERIES

Pros and cons of remission vs super responder

Panel debate facilitated by Peter Wark

PANEL DISCUSSION

Prof Peter Wark (Chair)
Respiratory
Director of Cystic Fibrosis Service
Professor of Medicine
Monash University
AIRMED, Alfred Health

A/Prof Emily Stone
Oncology/Respiratory
Respiratory physician and clinician-researcher at St Vincent's Hospital Sydney and the University of NSW

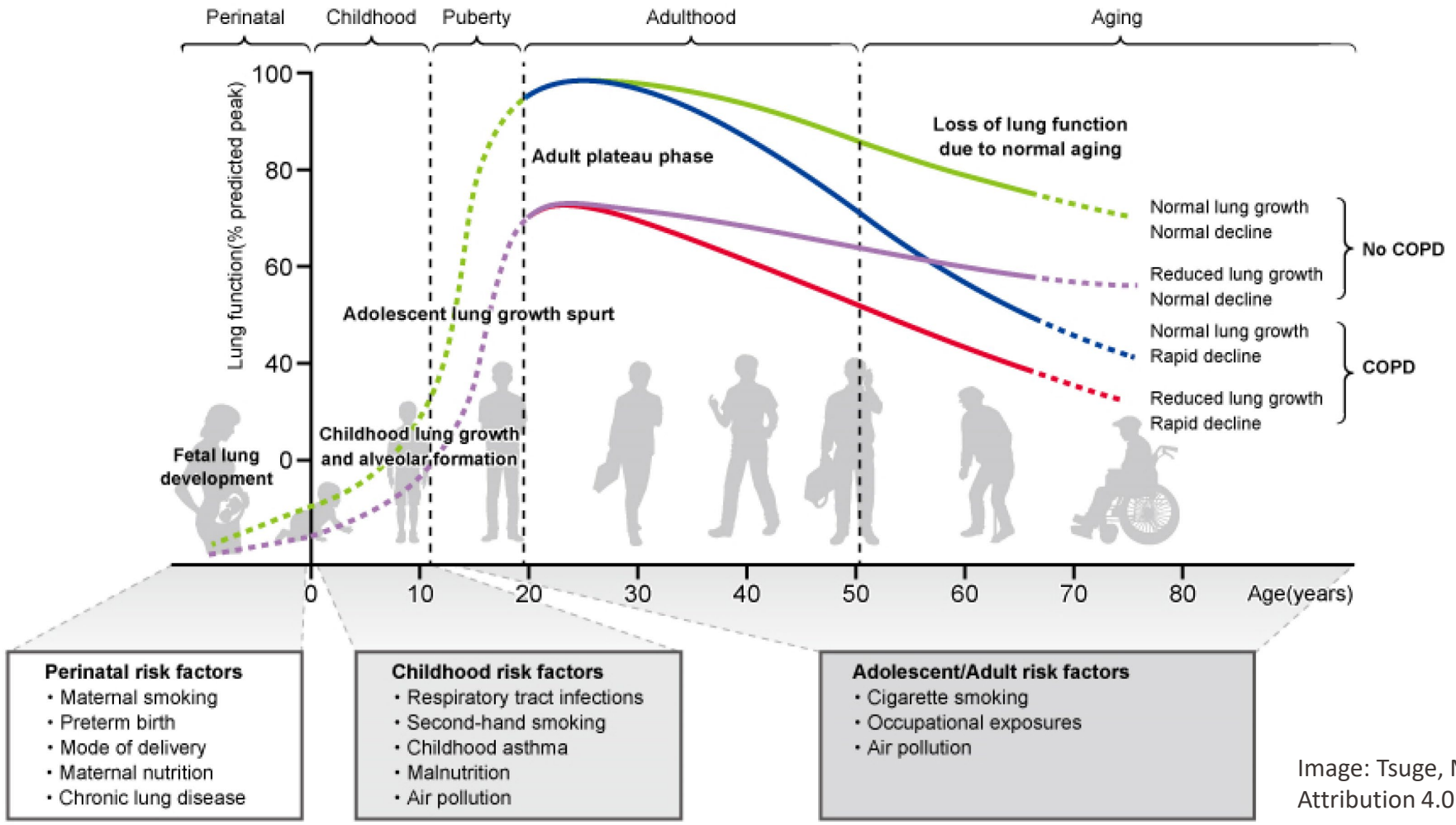
Dr Michelle Tellus
Rheumatology
Consultant Rheumatologist
Private Practice
Melbourne

Prof Connie Katelaris
Immunology
Head of Unit, Immunology & Allergy
Campbelltown Hospital and
Professor of Immunology & Allergy,
Western Sydney University

Variable airflow limitation a clinical phenotype that predicts outcome

RESPIRATORY ADVENT ADVANCES IN TYPE 2 INFLAMMATORY DISEASES

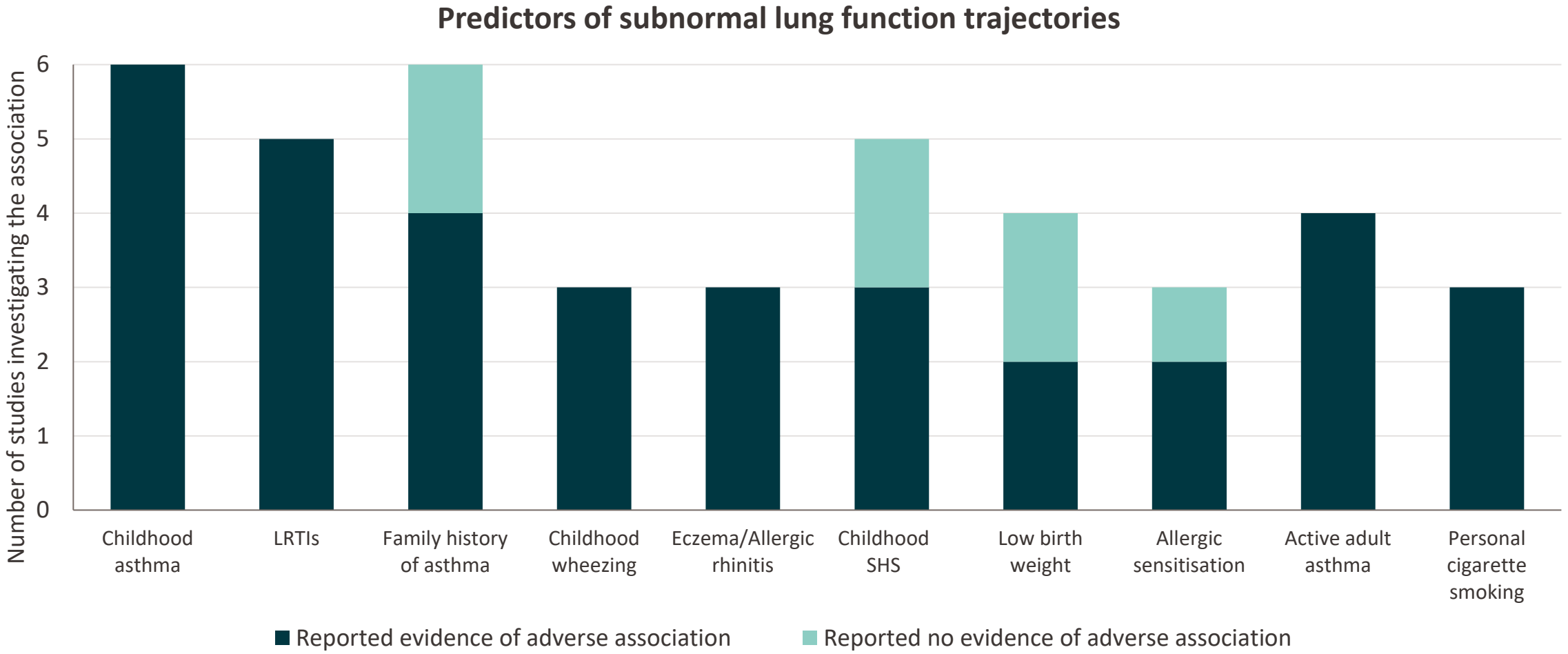
Failure to attain lung growth and loss of lung function



COPD, chronic obstructive pulmonary disease; **LRTI,** lower respiratory tract infection

Adapted from Tsuge, M., et al., Children. 2022. 9(8):1253.

Failure to attain lung growth and loss of lung function

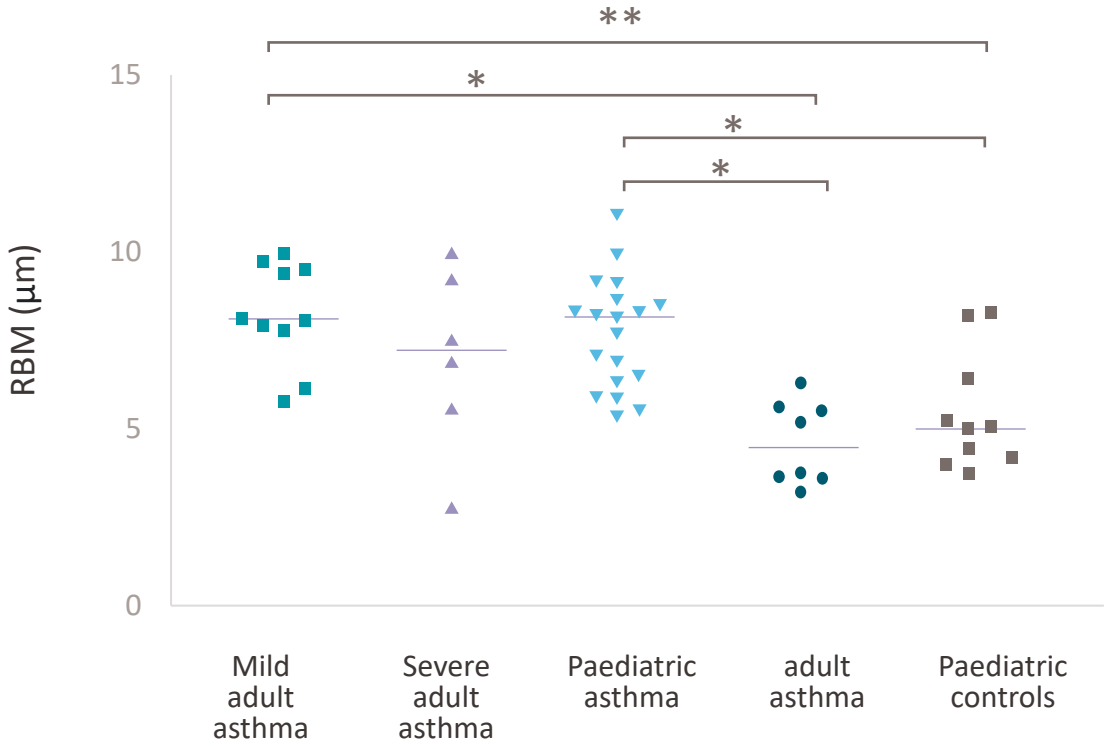


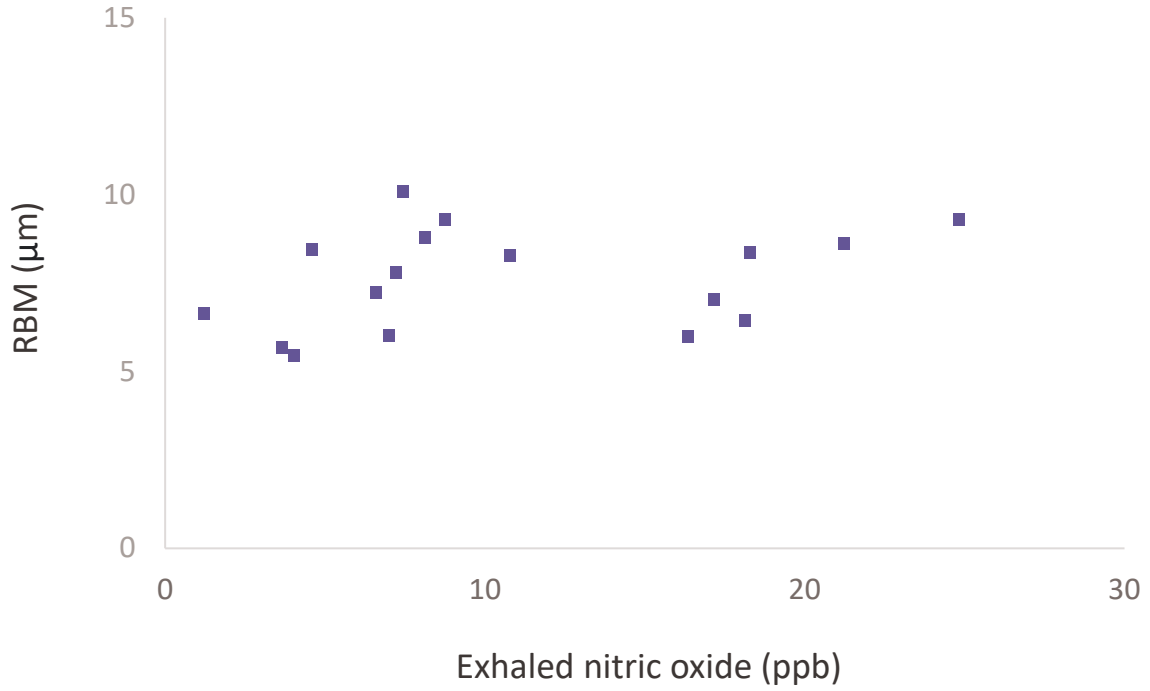
COPD, chronic obstructive pulmonary disease; **LRTI,** lower respiratory tract infection; **SHS**, second hand smoke

Adapted from Okyere DO, et al. Respirology. 2021;26(10):938-59.

Remodelling of the reticular basement membrane

Thickening of the RBM is present in children with difficult asthma,
similar extent as adults, independent of severity duration or airway inflammation



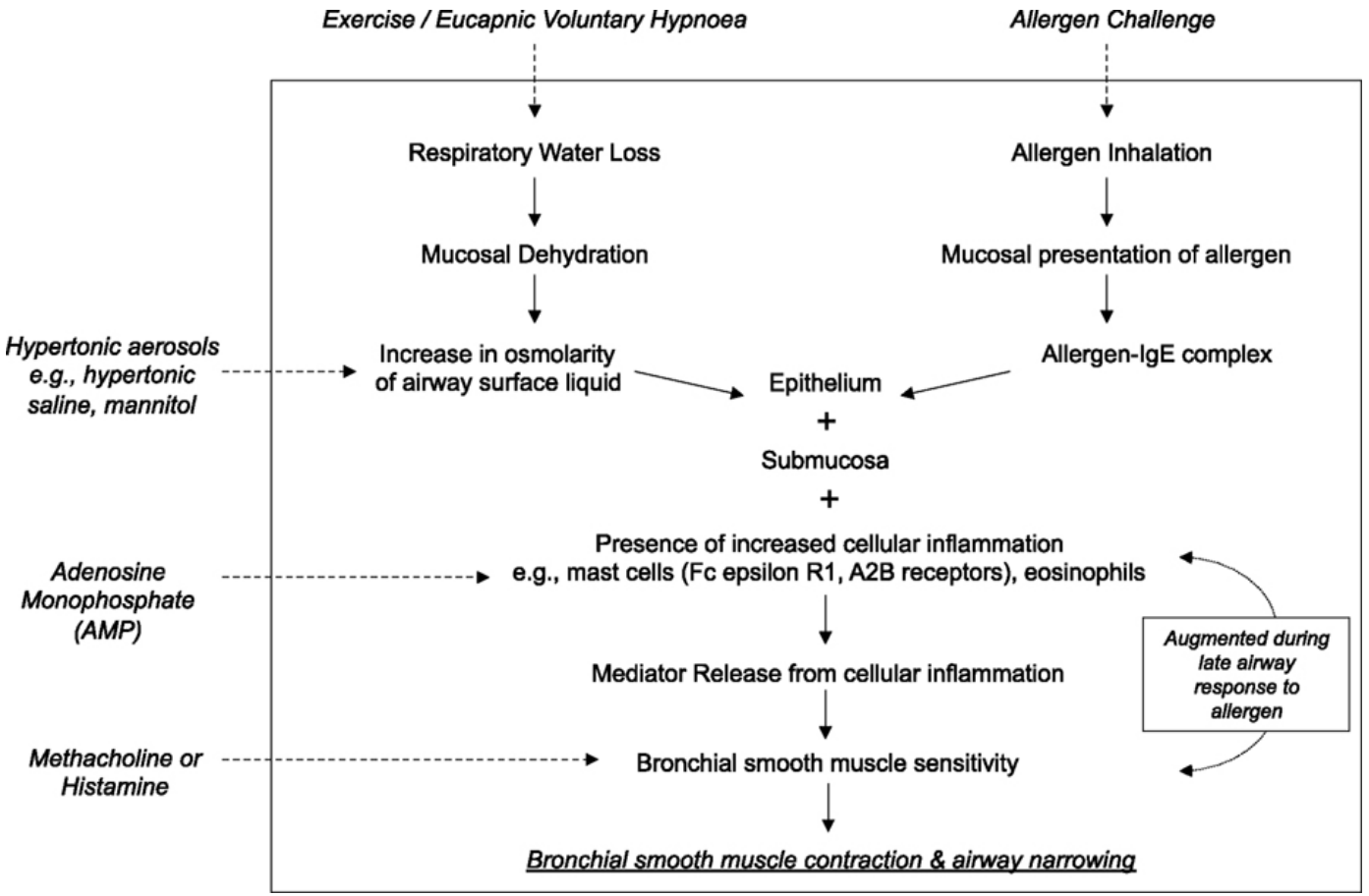


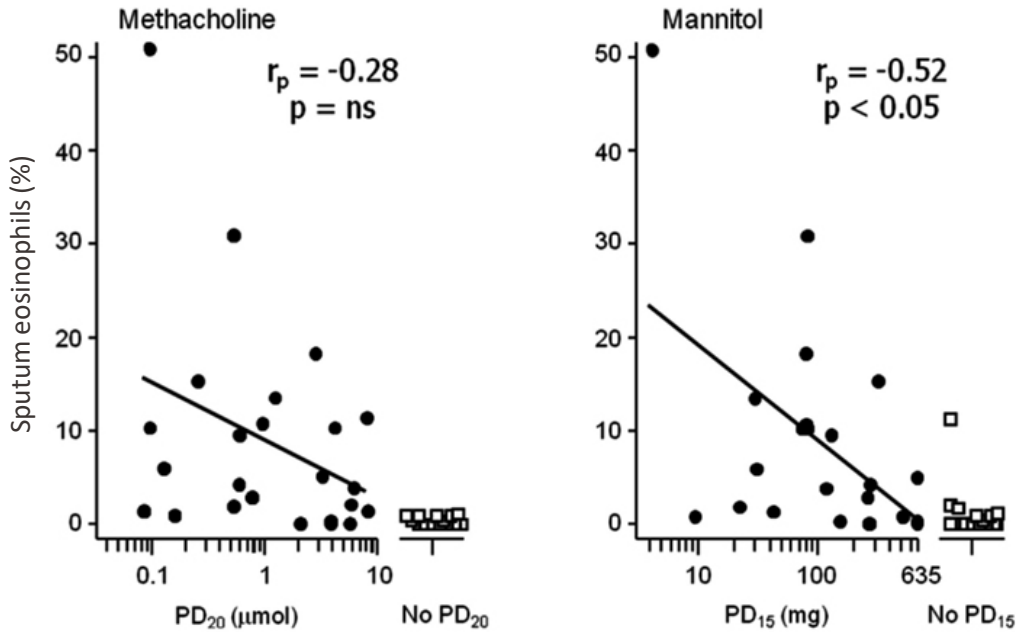
RBM, reticular basement membrane; **ppb,** parts per billion

*p<0.01; **p<0.05

Adapted from Payne DNR, et al. Am J Respir Crit Care Med. 2003;167(1):78-82.

The relationship between airway hyperresponsiveness and airway inflammation is imperfect

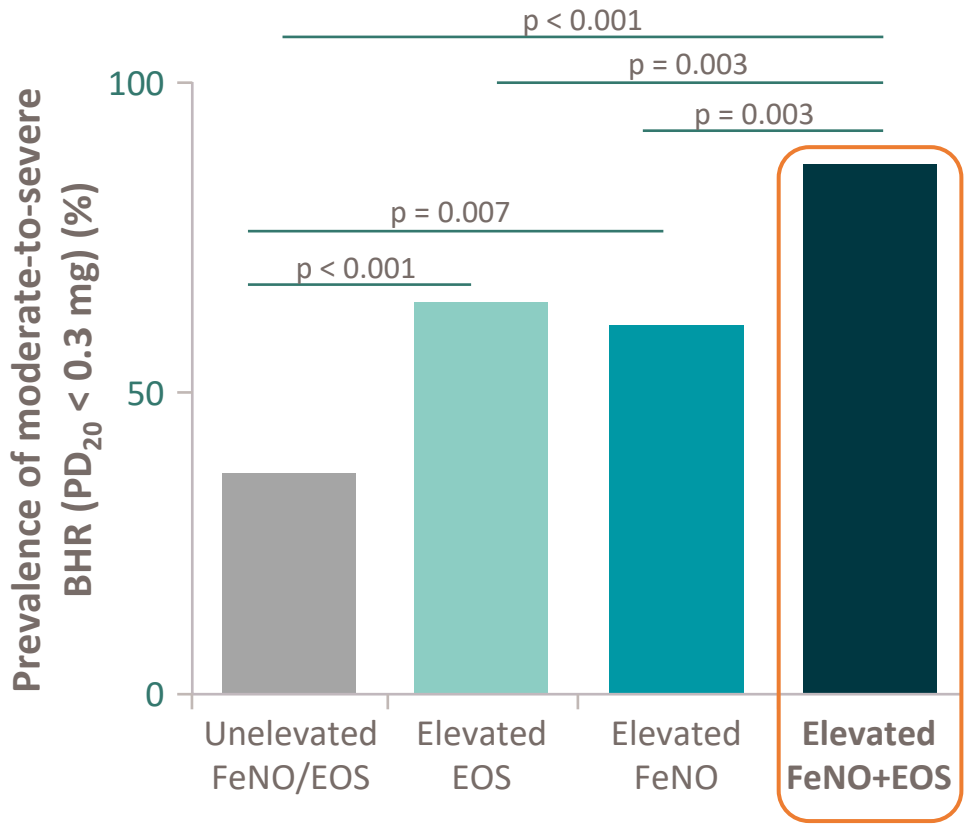




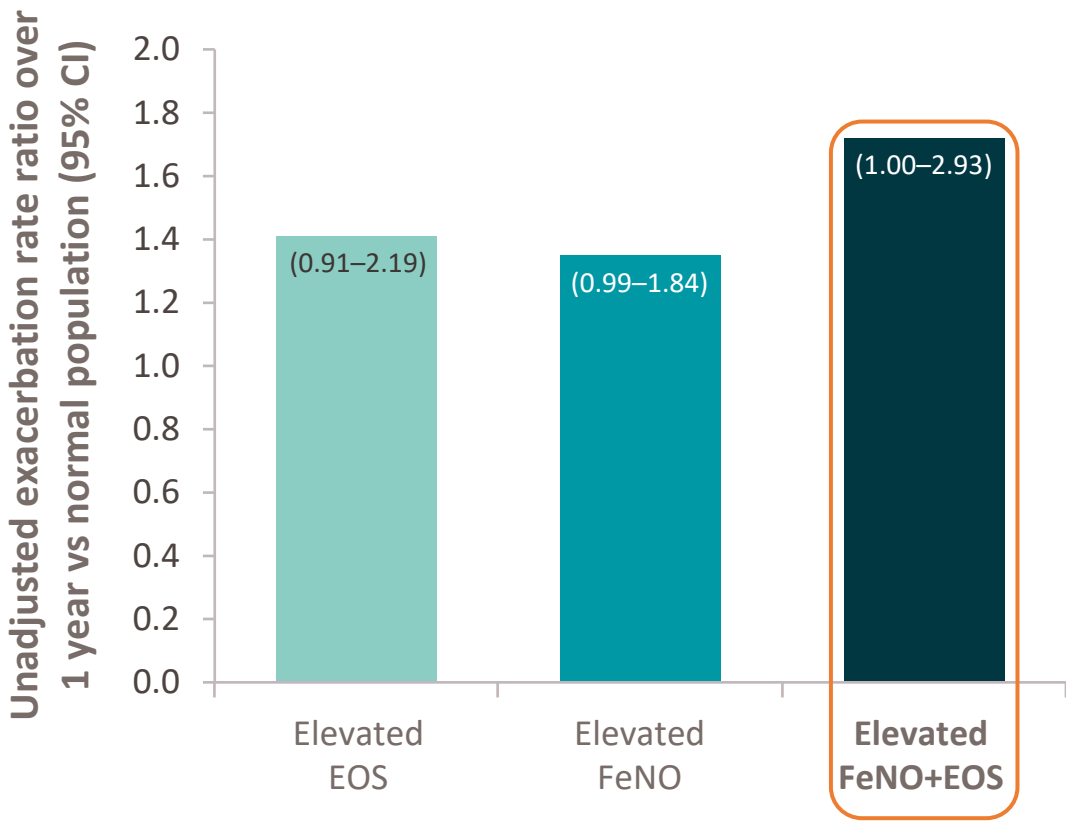
IgE, Immunoglobulin E; **AMP**, adenosine monophosphate; **PD_{20}**, provocation dose of methacholine causing a 20% decline in FEV_1; **PD_{15}**, provocation dose of mannitol causing a 15% decline in FEV_1

Refractory type 2 high disease (FeNO > 20 ppb and blood EOS ≥ 0.3 × 10^9/L) is associated with greater asthma disease burden

Increased bronchial hyperresponsiveness (n = 406)[1]



Greater severe exacerbation rates[a] vs normal controls (n = 610)[2]

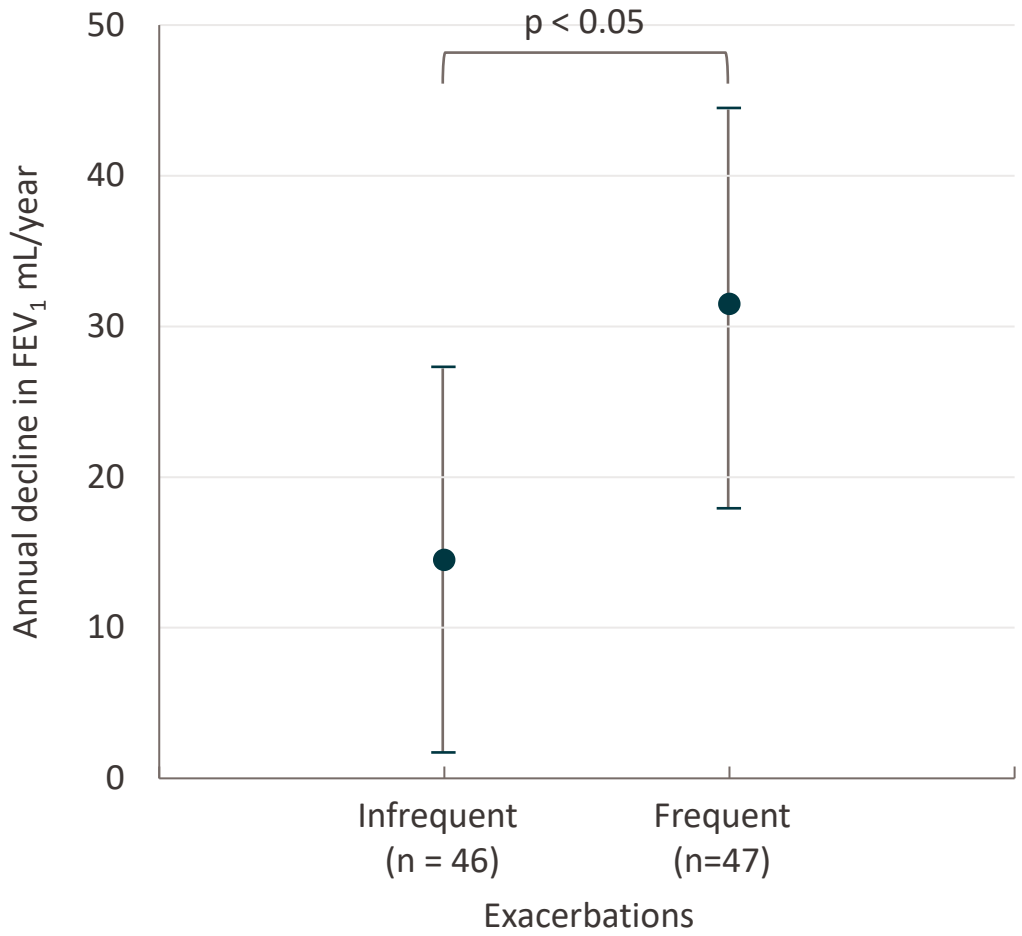


[a]Exacerbation: the occurrence of (1) respiratory-related hospitalisation (inpatient admission) AND/OR (2) emergency department attendance AND/OR (3) an acute course of OCS.

BHR, bronchial hyperresponsiveness; **CI,** confidence interval; **EOS**, eosinophils; **FeNO**, fractional exhaled nitric oxide; **OCS**, oral corticosteroids; **ppb**, parts per billion

1. Malinovschi A, et al. J Allergy Clin Immunol. 2016;138:1301–1308. e2. **2.** Rastogi S, et al. Thorax. 2017;72:A198.

One or more severe asthma exacerbations predict loss of lung function over 11 years (similar to COPD frequent exacerbators)



The analysis was adjusted for sex, height, the first available FEV_1 after age 25 years and the use of oral corticosteroids. The error bars represent 95% confidence intervals.

FEV_1, forced expiratory volume in 1 second; **COPD**, chronic obstructive pulmonary disease

Adapted from Bai TR, et al. Eur Respir J. 2007;30(3):452-6.

Achieving clinical remission - what does this look like?

Inhaled corticosteroids modify asthma disease

ICS reduce AHR

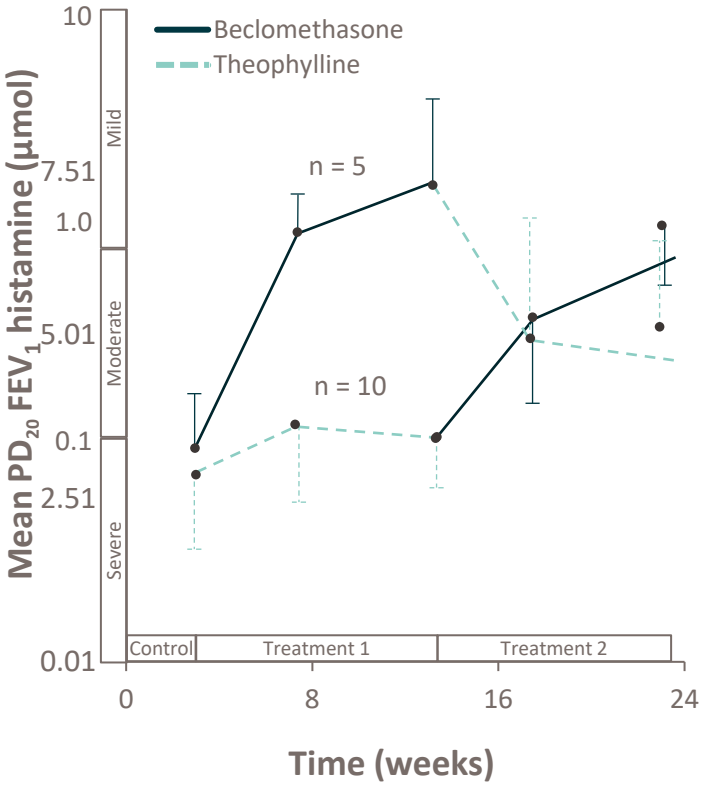


Figure adapted from Dutoit JI, et al. 1987.[1]

ICS improve PEF and AHR

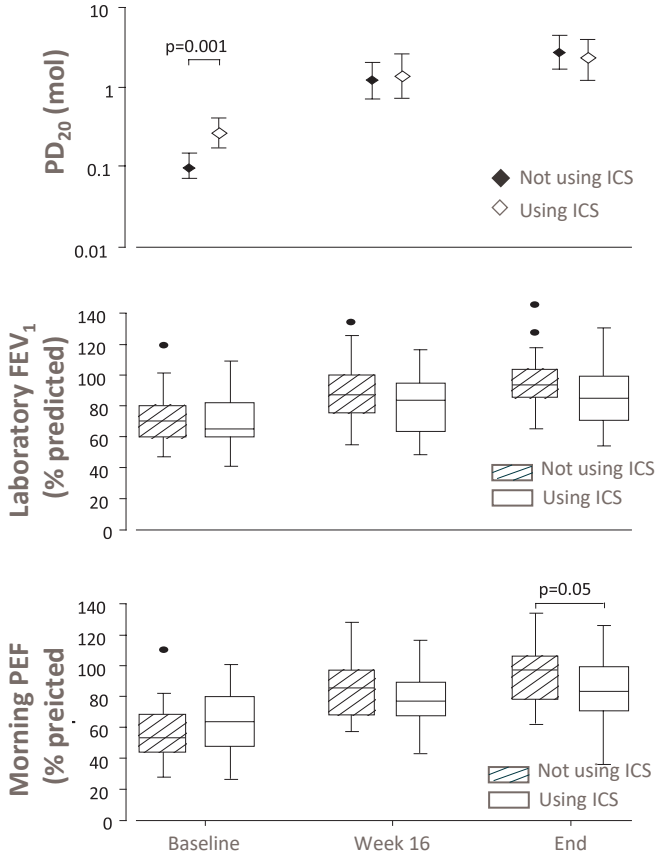
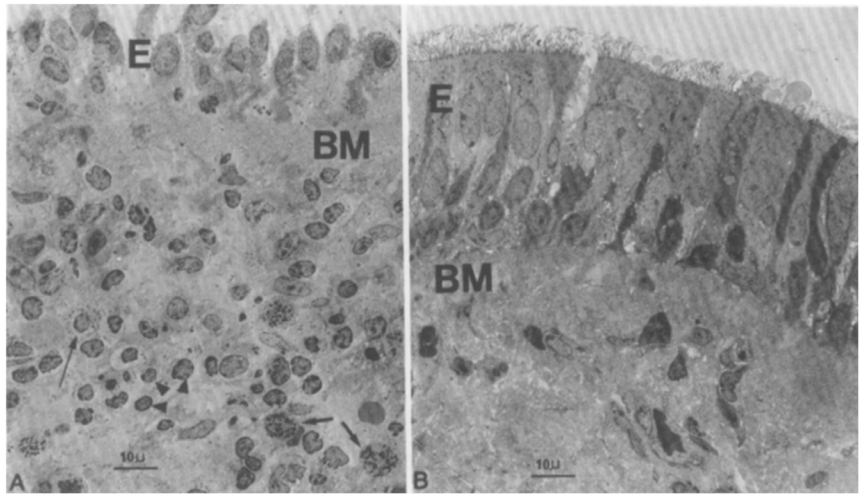


Figure adapted from Reddel HK, et al. 2000.[2]

ICS reduce airway inflammation



Terbutaline alone

Budesonide

Figure from Laitinen LA, et al. 1992.[3]

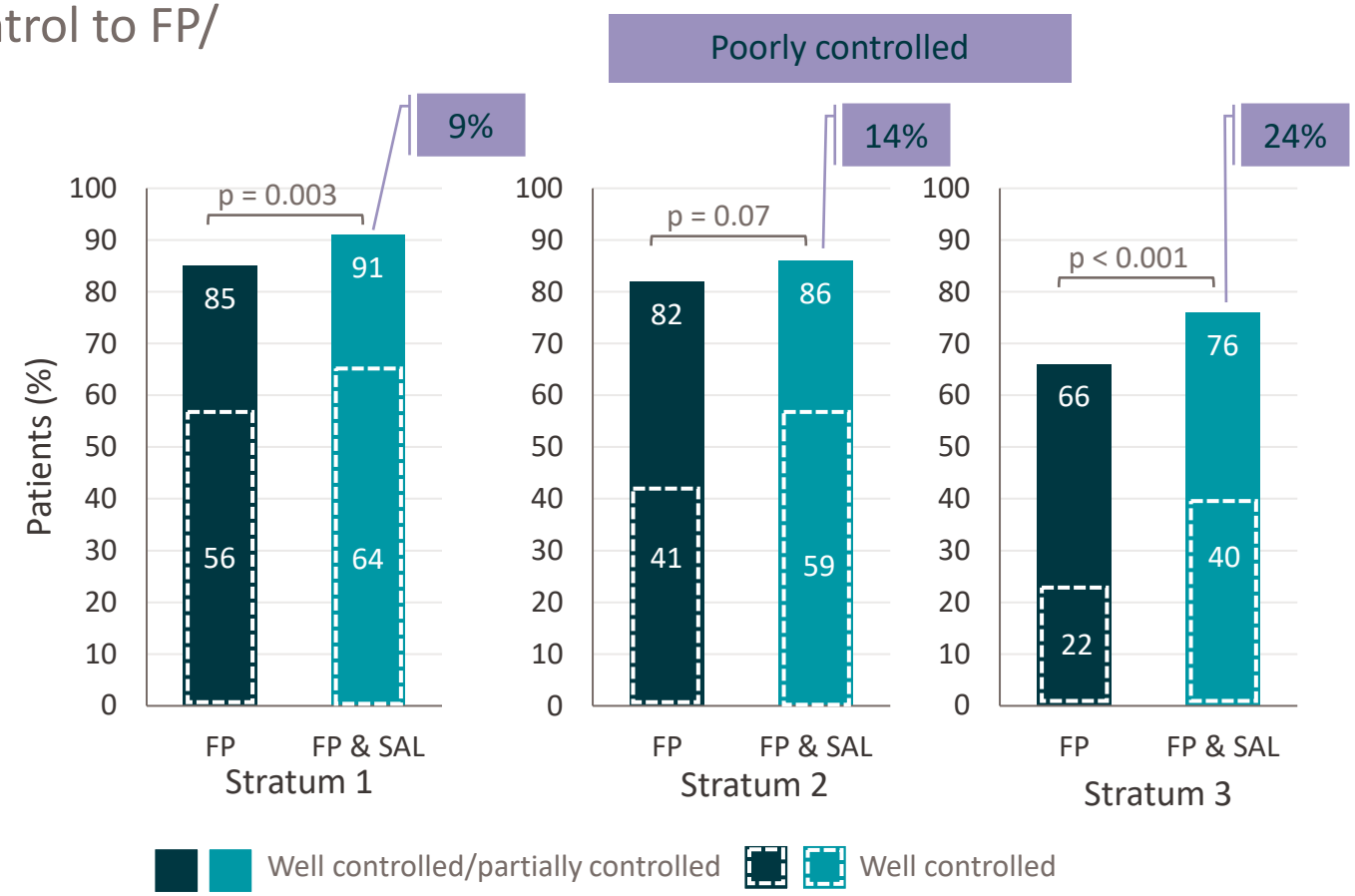
AHR, airway hyperresponsiveness; **BM,** basement membrane; **E,** airway epithelium; **FEV_1**, forced expiratory volume in 1 second; **ICS,** inhaled corticosteroids; **PEF**, peak expiratory flow; **PD_{20}**, provocation dose of histamine causing a 20% decline in FEV_1

1. Dutoit JI, et al. Am Rev Respir Dis. 1987;136:1174–1178. **2.** Reddel HK, et al. Eur Respir J. 2000;16:226–235. **3.** Laitinen LA, et al. J Allergy Clin Immunol. 1992;90:32–42.

Gaining Optimum Asthma Control (GOAL)

- 3416 (1-ICS naïve, 2-low dose ICS, 3-medium dose ICS) randomised to high dose ICS (FP) or FP/SAL.
- Treatment stepped up to achieve total control to FP/SAL 500/50 BD.

	Well controlled	Partially controlled
Criteria	Pass all	Pass 2–3
Day symptoms	≤ 2 days/wk	≤ 2 days/wk
SABA use	≤ 2 occasions/wk	≤ 2 occasions/wk
Night waking	None	None
Activity limitation	None	None
Exacerbations	None	None

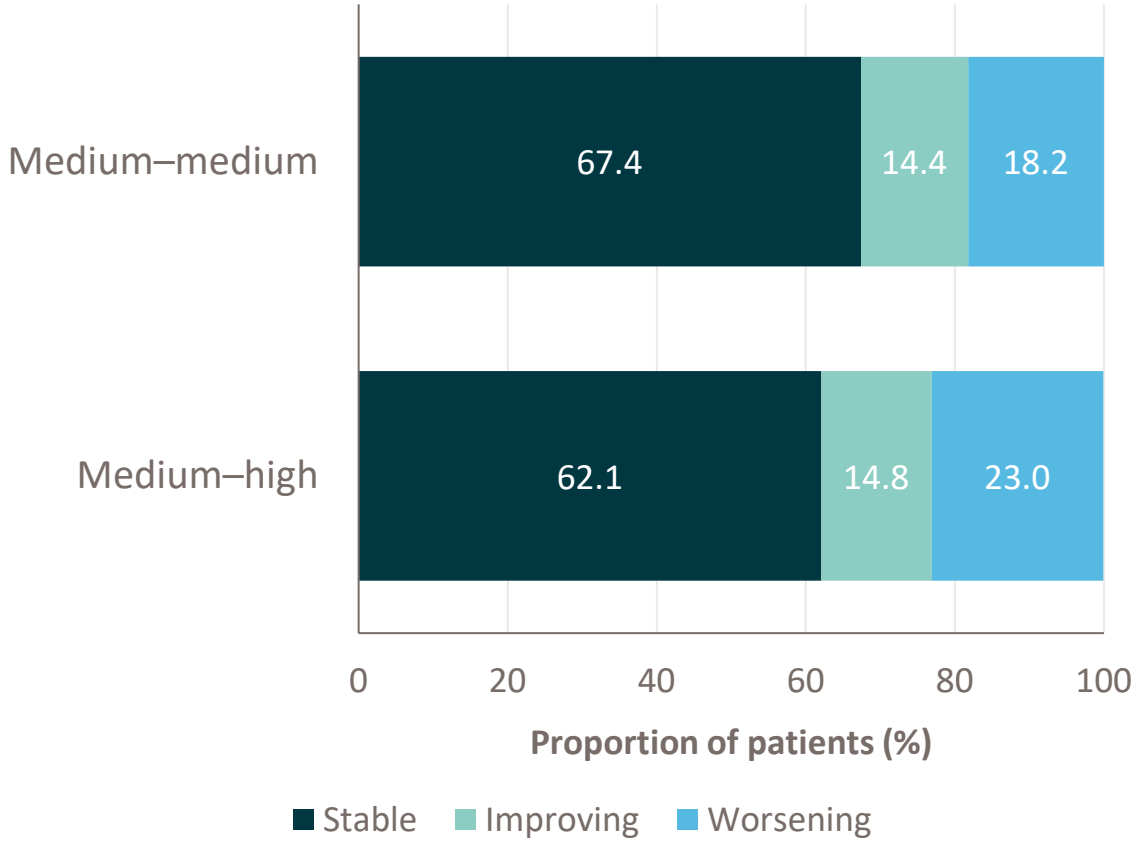


SABA, short-acting β_2-agonist; **WC**, well controlled; **PC**, partly controlled; **ICS**, inhaled corticosteroid; **FP**, fluticasone propionate; **SAL**, salmeterol; **BD**, twice daily**, wk,** Week

Bateman ED, et al. Ann Allergy Asthma Immunol. 2019;123(1):57-63.e2.

Stepping up from medium- to high-dose ICS does NOT prevent exacerbations

- UK database study > 13 years followed for a mean 2 years
- Stepped up medium- to high-dose ICSs (n = 6879) had a higher risk of exacerbations (hazard ratio, 1.17; 95% CI, 1.12-1.22)
- High ICS adherence (≥ 80%) was associated with increased OCS use, add-on therapies and asthma-related healthcare visits (adult-onset asthma)
- A step-up to high-dose ICSs was also associated with a higher number of asthma exacerbations and antibiotics courses



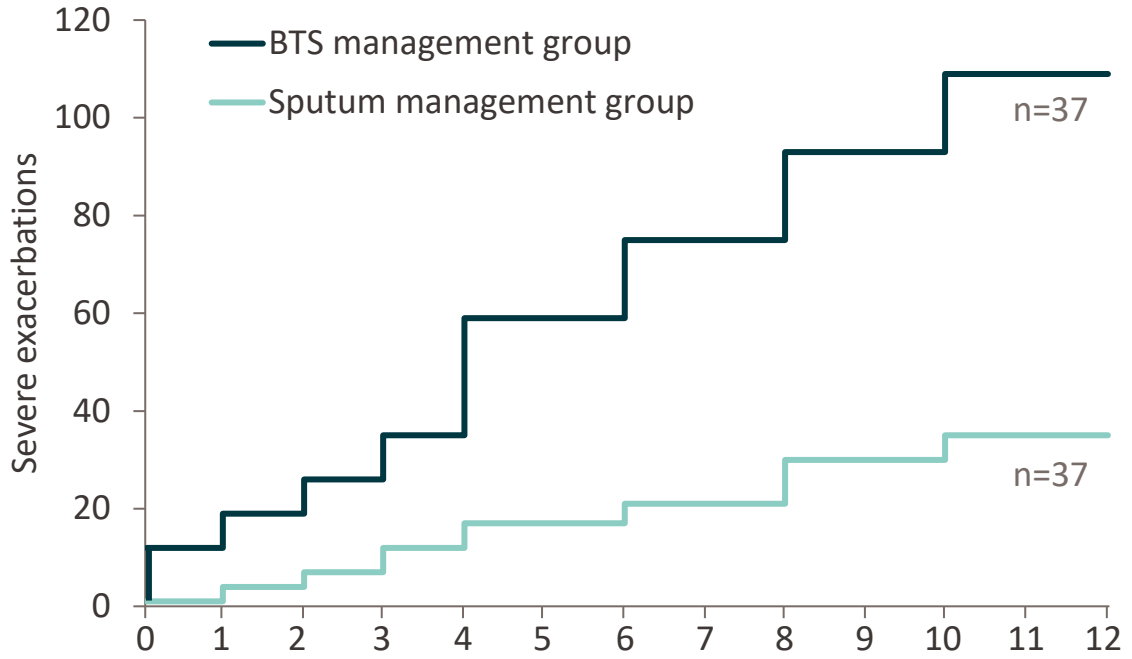
Adapted from Pavord ID, et al. 2023.

CI, confidence interval; ICS, inhaled corticosteroids; OCS, oral corticosteroids; UK, United Kingdom

Pavord ID, et al. J Allergy Clin Immunol Pract. 2023;11:532–543.

Suppression of sputum eosinophils reduces exacerbation risk

- 74 asthmatics, therapy adjusted
- Symptom-adjusted BTS asthma guidelines
- Sputum eosinophils-adjusted treatment
- Fewer severe exacerbations, 35 vs 109 (p=0.01)
- Fewer admissions to hospital, 1 vs 6 (p=0.047)



Number of exacerbations									
BTS group	0	12	19	26	35	59	75	93	109
Sputum group	0	1	4	7	12	17	21	30	35

Adapted from Green RH, et al. Lancet. 2002

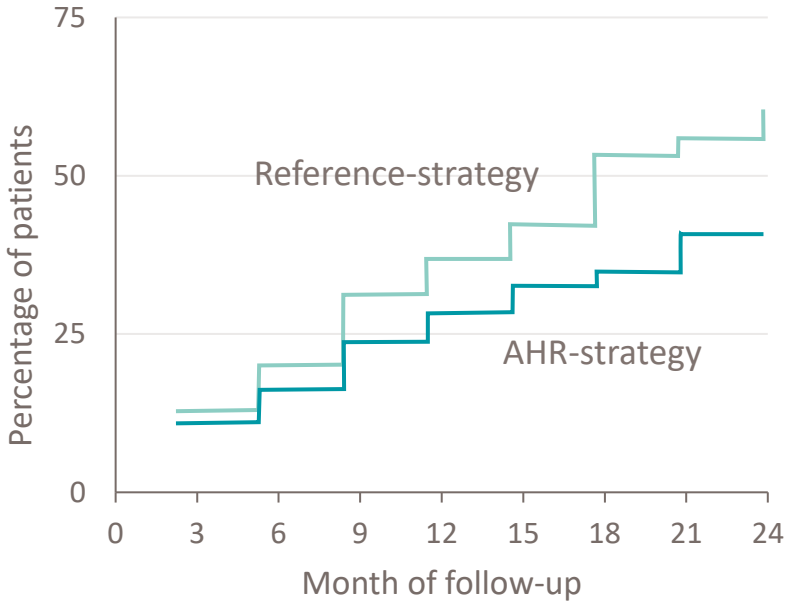
BTS, British Thoracic Society

Green RH, et al. Lancet. 2002;360(9347):1715-21.

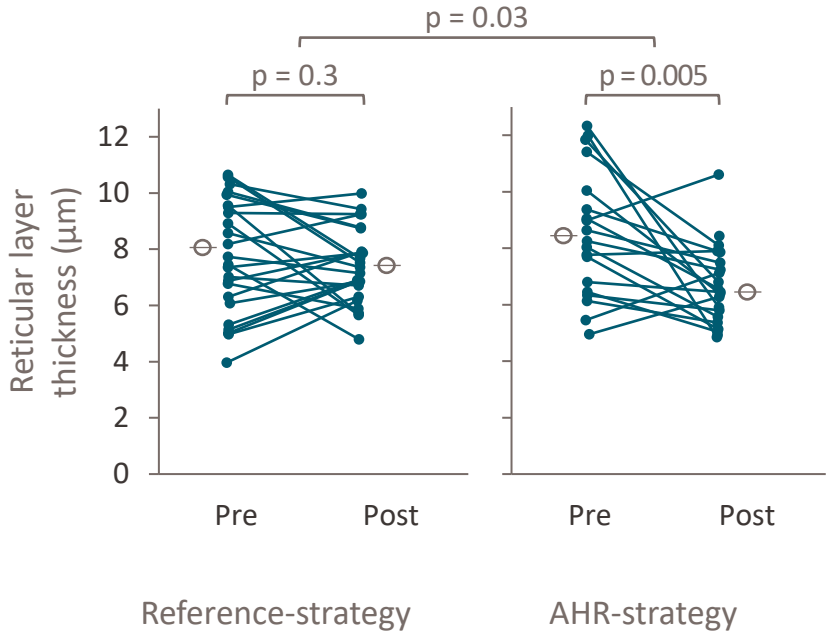
Targeting AHR improves remodelling and clinical outcomes

- 75 patients with mild-to-moderate asthma, followed for 2 years
- ICS adjusted to control methacholine AHR

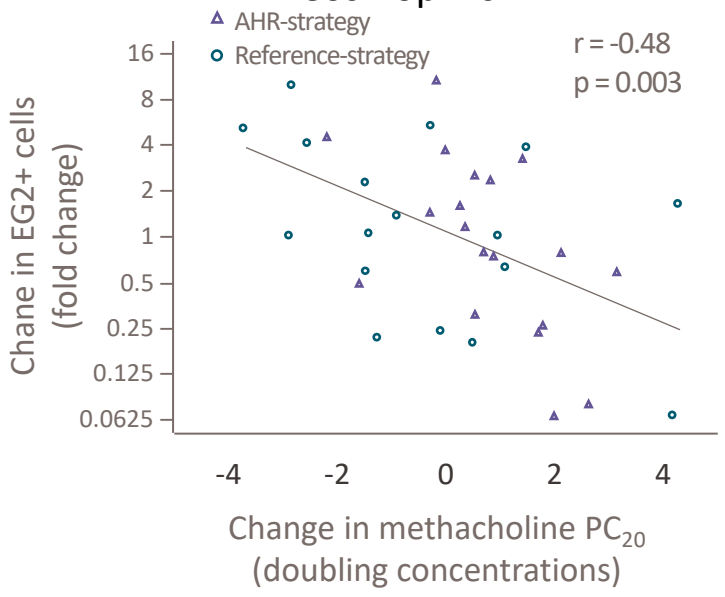
Exacerbations (symptom control)



Improved remodeling



ICS suppressed AHR and mucosal eosinophils



AHR, airway hyperresponsiveness; **ICS**, inhaled corticosteroids

Sont JK et al AJRCCM 1999;159(4):1043-51.

Biologic agents for severe type 2 high asthma

	Omalizumab[1-4]	Mepolizumab[5,6]	Benralizumab[7,8]	Dupilumab[9,10]
Blood EOS > 150 mm^3	Responder	Needed	Needed	Needed or FeNO
FeNO > 20 ppb on ICS	Responder	N/A	N/A	Needed or EOS
IgE sensitised	Needed	N/A	N/A	N/A
Age	12 years and above	12 years and above	12 years and above	12 years and above
Results				
Fall in ACQ-5	1.8[3]	0.44-0.52	0.55	0.19*-0.47
Exacerbations (% reduction)	25-53%	32-53%	49-70%	48-59%
FEV$_1$ diff placebo	94 mL	98–100 mL	159 mL	130–220 mL
Reduced OCS at least by 25%	28% (only phase 4)[3]	64%	78%	80%

Disclaimer: as head-to-head studies have not yet been conducted, these results should be interpreted with caution

*at 24 weeks

EOS, eosinophils; **ACQ-5**, asthma control questionnaire – 5; **ppb**, parts per billion; **FEV$_1$**, forced expiratory volume in 1 second; **IgE**, Immunoglobulin E; **FeNO**, fractional exhaled nitric oxide; **OCS**, oral corticosteroids; **T2**, type 2

1. Humbert M, et al. Allergy. 2005;60(3):309-16. **2**. Hanania NA, et al. Ann Intern Med. 2011;154(9):573-82. **3**. Hanania NA, et al. Am J Respir Crit Care Med. 2013;187(8):804-11. **4**. Gibson PG, et al. Int Med J. 2016;46(9):1054-62. **5**. Ortega HG, et al. N Engl J Med. 2014;371(13):1198-207. **6**. Bel EH, et al. N Engl J Med. 2014;371(13):1189-97. **7**. Bleecker ER, et al. Lancet. 2016;388(10056):2115-27. **8**. Nair P, et al. N Engl J Med. 2017;376(25):2448-58. **9**. Castro M, et al. N Engl J Med. 2018;378(26):2486-96. **10**. Rabe KF, et al. N Engl J Med. 2018;378(26):2475-85.

Achieving clinical remission. Achieving biological remission or disease modification?

RESPIRATORY ADVENT ADVANCES IN TYPE 2 INFLAMMATORY DISEASES

Spontaneous remission?*

- Melbourne cohort, at age 21 years 60% with mild intermittent wheeze at 14 years were symptom free, 25% with frequent asthma, 5% with persistent wheeze[1]
- Dutch cohort, asthma < 12 months, spontaneous remission 27/170, more likely in those with mild symptoms, absence of nasal polyposis and less AHR[2]
- Danish cohort followed for 30 years, complete remission (FeNO < 50 ppb and no AHR off treatment) occurred in 19/125. Longer duration symptoms less likely to undergo remission[3]

Disclaimer: as head-to-head studies have not yet been conducted, these results should be interpreted with caution

AHR, airway hyperresponsiveness; **FeNO**, fractional exhaled nitric oxide; **ppb**, parts per billion

1. Phelan PD, et al. J Allergy Clin Immunol. 2002;109(2):189-94. **2**. Westerhof GA, et al. J Allergy Clin Immunol. 2018;141(1):104-9.e3. **3**. Tupper OD, et al. J Allergy Clin Immunol Pract. 2021;9(4):1595-603.e5.

Current PBS criteria for success is not clinical remission

- A reduction in ACQ-5 of 0.5 from baseline
- Maintenance OCS reduced by 25% with no deterioration in ACQ-5 > 0.5

ACQ-5, asthma control questionnaire – 5; **OCS**, oral corticosteroids, **PBS**, pharmaceutical benefits scheme

Theoretical framework for clinical remission in severe asthma[1]

- Currently there is **no consensus definition** on remission in severe asthma that is broadly supported by respiratory societies and recognised by guidelines[1]
- A theoretical framework, recently proposed, provides a **basis** for a definition that will evolve over time in a data-driven way[1]

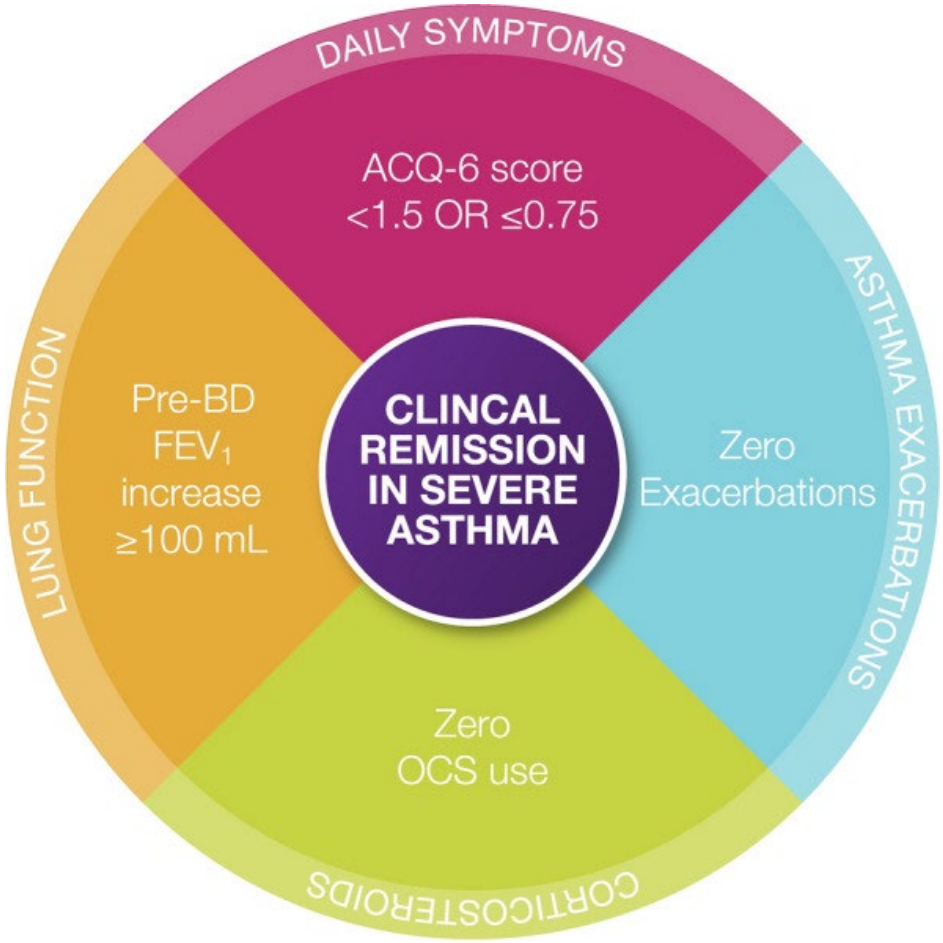


Image from Menzies-Gow et al. 2022.
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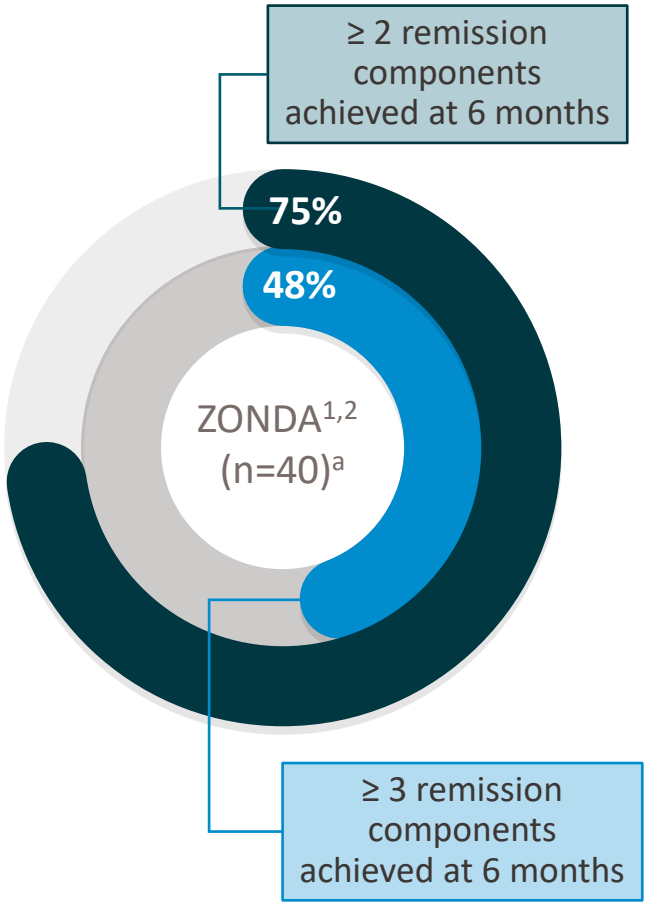
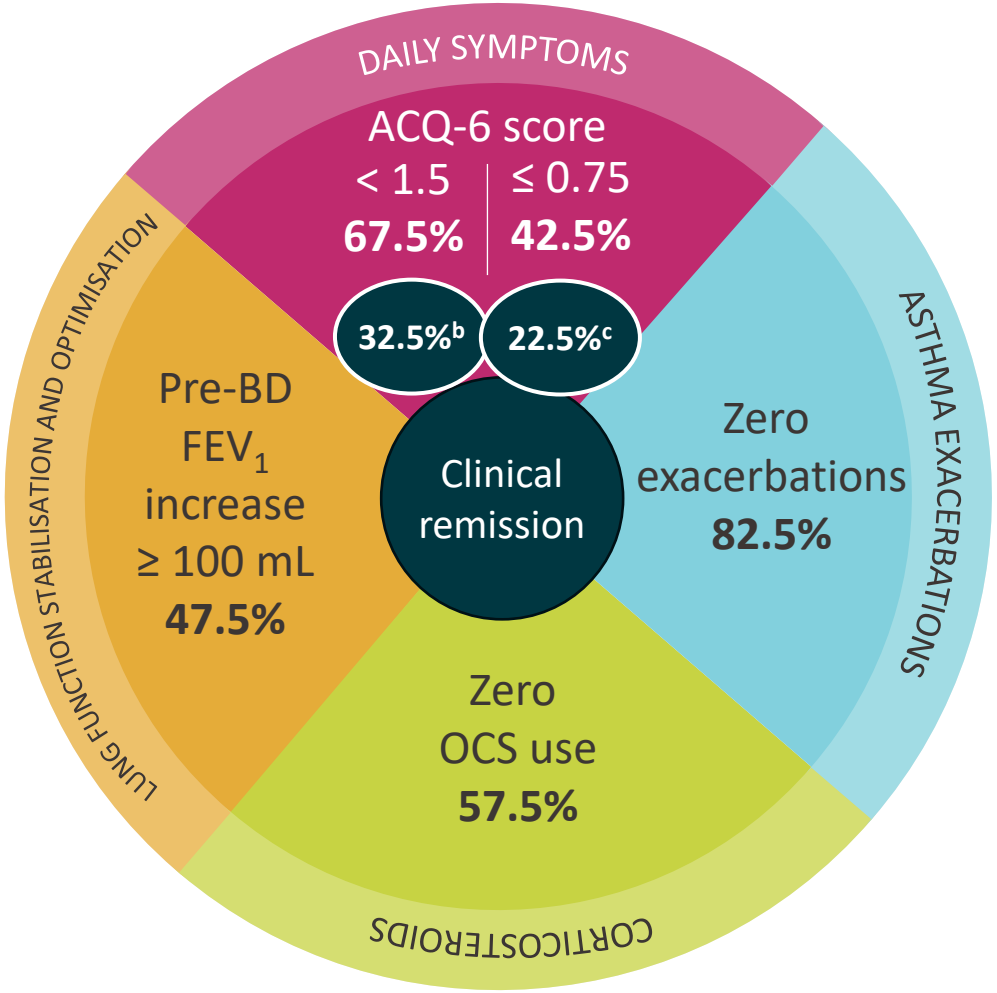
ACQ-5, asthma control questionnaire – 5; **FEV_1**, forced expiratory volume in 1 second; **OCS**, oral corticosteroids; **pre-BD**, pre-bronchodilator

1. Menzies-Gow A, et al. J Allergy Clin Immunol. 2020;145(3):757-765; **2**. Menzies-Gow A, et al. Adv Ther. 2022;39(5):2065-84.

Clinical remission, an example the ZONDA trial with benralizumab





Placebo results

- ACQ- 6 < 1.5: 37.5%
- ACQ-6 ≤0.75: 15%
- Zero exacerbations: 47.5%
- Pre-BD FEV_1 increase ≥ 100 mL: 52.5%
- Zero OCS use: 20%
- ≥ 2 RC achieved: 35%
- ≥ 3 RC achieved : 20%

[a]A post-hoc analysis of 40 patients from the ZONDA trial, patients had severe uncontrolled asthma at baseline and received benralizumab 30 mg Q8W. [b]No OCS, no exacerbation, ACQ-6 < 1.5, Pre-BD FEV_1 increase ≥ 100 mL. [c]Clinical remission, No OCS, no exacerbation, ACQ-6 ≤ 0.75, Pre-BD FEV_1 increase ≥ 100 mL.

ACQ-5, asthma control questionnaire – 5; **FEV_1**, forced expiratory volume in 1 second; **OCS**, oral corticosteroids; **pre-BD**, pre-bronchodilator; **RC,** remission component, Q8W, once every eight weeks.

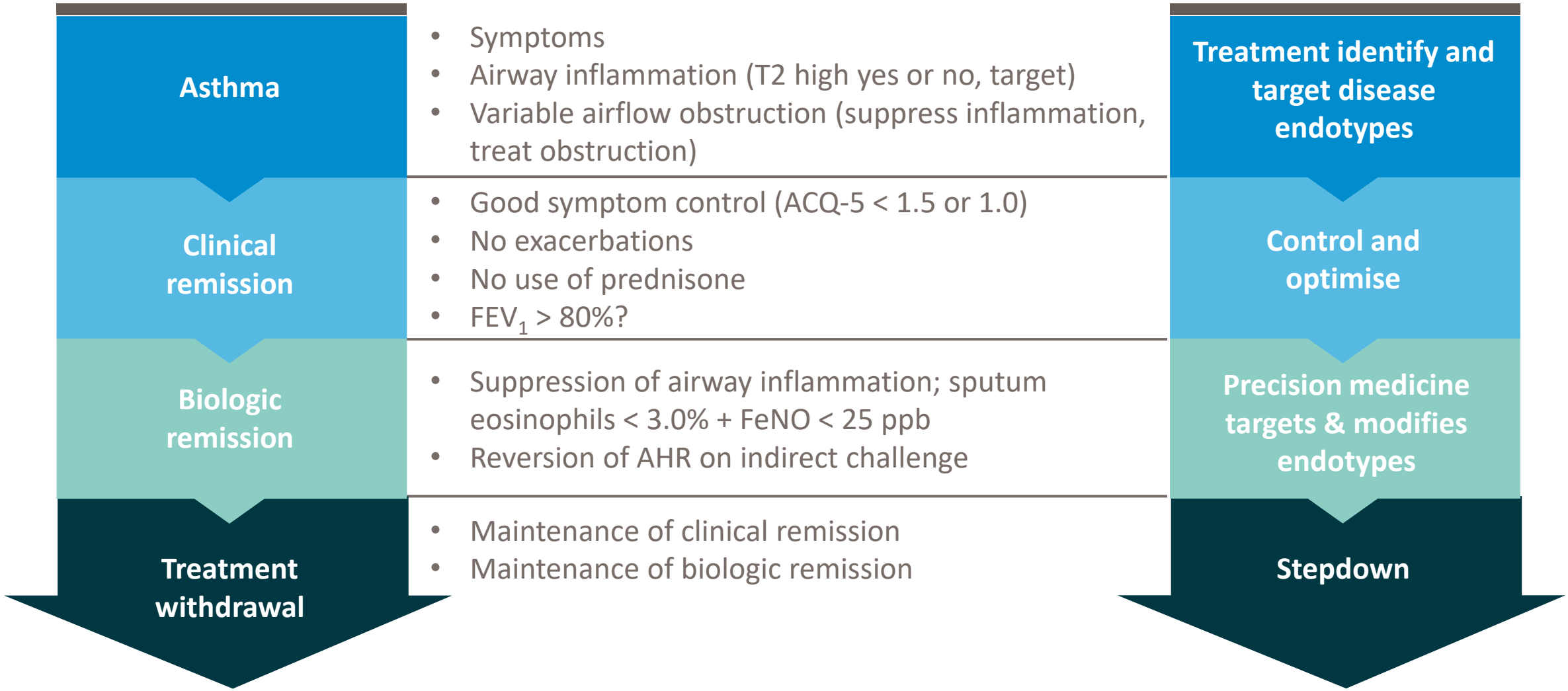
1.Nair P et al. N Engl J Med. 2017;376:2448-2458; 2. Menzies-Gow A, et al. Adv Ther. 2022;39(5):2065-84.

Dupilumab treatment leads to clinical asthma remission in patients with uncontrolled moderate-to-severe asthma with type 2 inflammation

- Post hoc analysis of LIBERTY ASTHMA QUEST (NCT02414854)
- Clinical asthma remission, at 52 weeks.
  - no exacerbations
  - 5-item Asthma Control Questionnaire [ACQ-5] total score < 1.5
  - post-bronchodilator $FEV_1 \geq 80\%$
- Dupilumab compared to ICS/LABA (=placebo)
  - Exacerbation free 73% (compared 46%)
  - Exacerbation free + ACQ-5 < 1.5 43% (compared to 22%)
  - Exacerbation free + ACQ-5 < 1.5 + FEV_1 > 80%, 20% (compared to 9%)

BD, twice daily; **ACQ-5**, asthma control questionnaire – 5; **ppb**, parts per billion; **PRN**, as needed; **FEV_1**, forced expiratory volume in 1 second; **FER**, forced expiratory ratio; **IgE**, Immunoglobulin E; **FeNO**, fractional exhaled nitric oxide; **LABA**: long-acting β_2–agonist; **ICS**, inhaled corticosteroid

Pavord I, et al. J Allergy Clin Immunol. 2021;147(2):AB4.



Schematic from P. Wark

ACQ-5, asthma control questionnaire – 5; **ppb**, parts per billion; AHR, airway hyperresponsiveness; **FEV_1**, forced expiratory volume in 1 second; **FeNO**, fractional exhaled nitric oxide

REMISSION
OR
SUPER RESPONDER

SPECIAL TWO PART SERIES

Resources

RESPIRATORY
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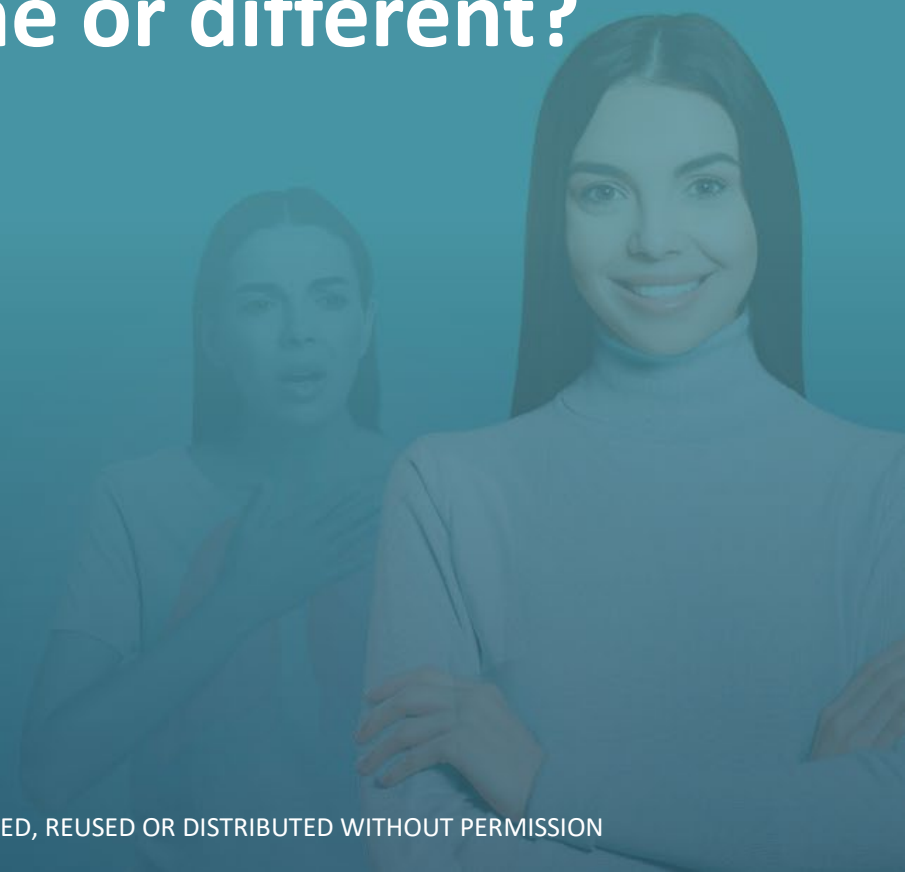
ADVANCES IN
TYPE 2 INFLAMMATORY DISEASES

Download the PDF of the full reference list

Remission or ‘super responders’ in severe asthma: same or different?

Full reference list



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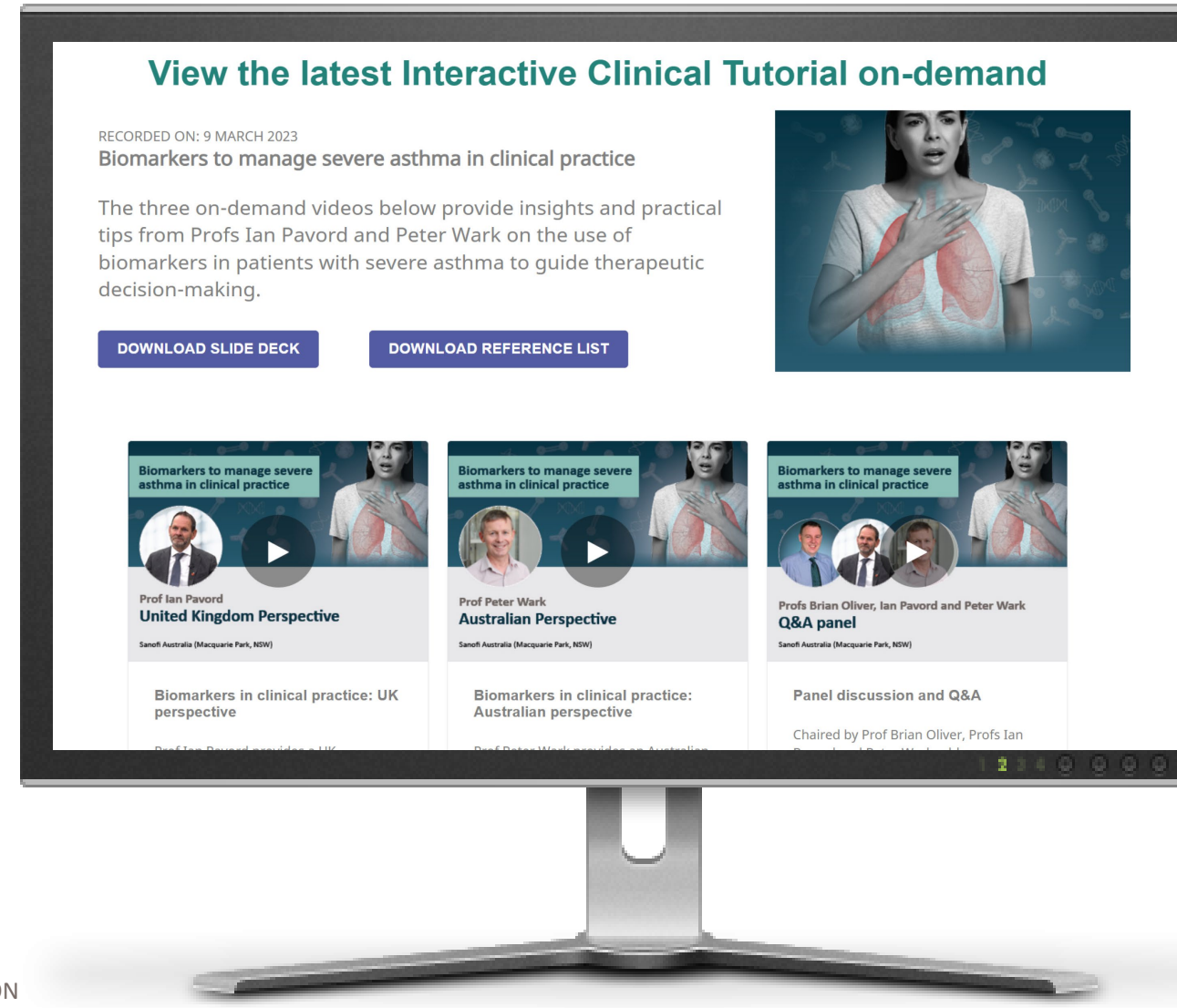

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Prescribing Information

PBS Information: Refer to PBS schedule for full authority information. Authority required for patients aged ≥12 years with chronic severe atopic dermatitis and uncontrolled severe asthma. This product is not listed on the PBS for infants aged 6 months to 5 years severe atopic dermatitis, children 6 to 11 years of age with severe atopic dermatitis or moderate to severe asthma, or for patients with uncontrolled chronic rhinosinusitis with nasal polyps.

Dupilumab PBS Information: Refer to PBS schedule for full authority information. Authority required for patients aged ≥12 years with chronic severe atopic dermatitis and uncontrolled severe asthma. This product is not listed on the PBS for children 6 to 11 years of age with severe atopic dermatitis or moderate to severe asthma, or for patients with uncontrolled chronic rhinosinusitis with nasal polyps.

Please review full Product Information before prescribing. Full Product Information is available from sanofi-aventis australia pty ltd at http://www.guildlink.com.au/gc/ws/sw/pi.cfm?product=swpdupix or by contacting 1800 818 806 or by scanning the QR code below.

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems

Date of preparation | August 2023 | MAT-AU-2301787

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