Review of Single Inhaler Triple Therapy (SITT) in Asthma

가톨릭대학교
최준영

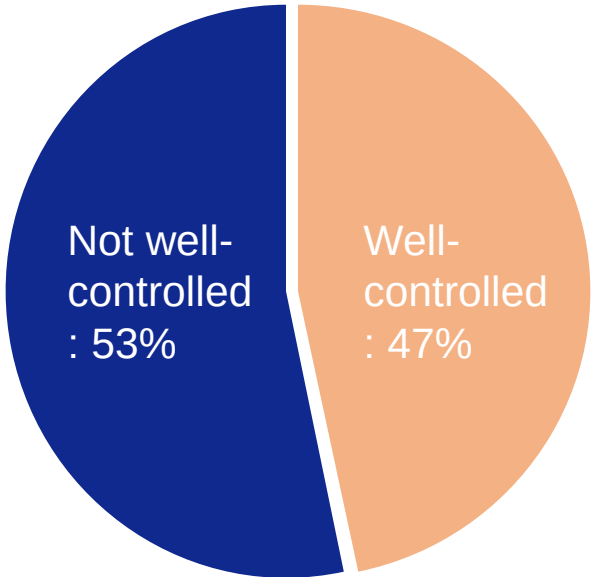
Unmet need in severe asthma

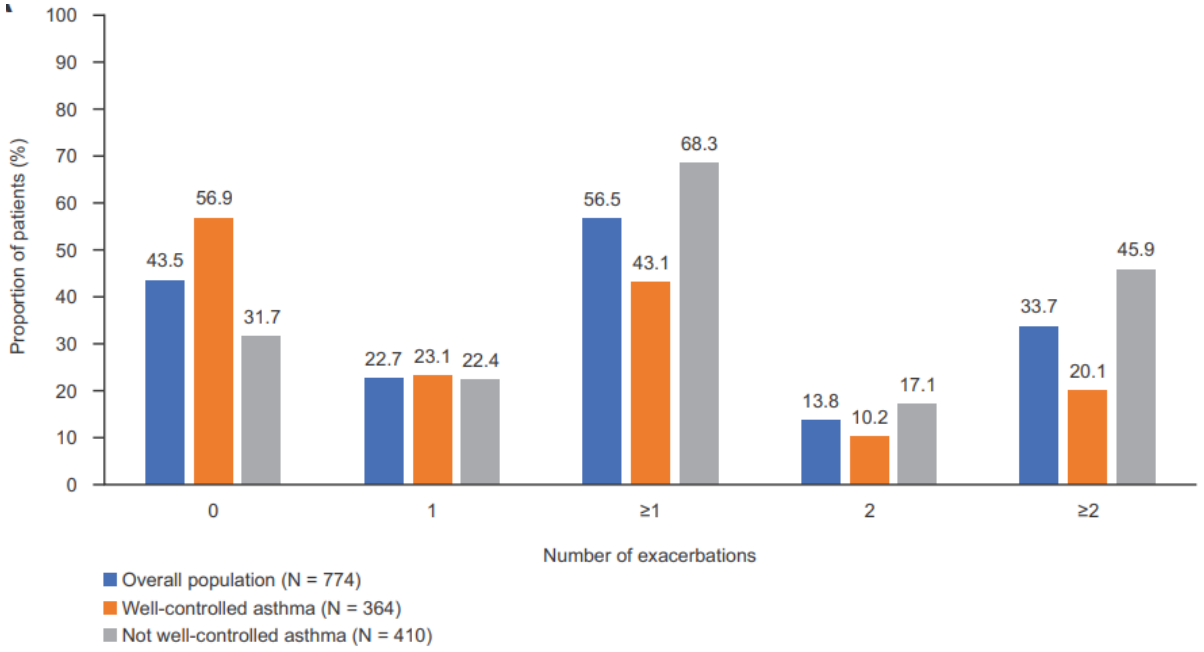
Real-world evidence

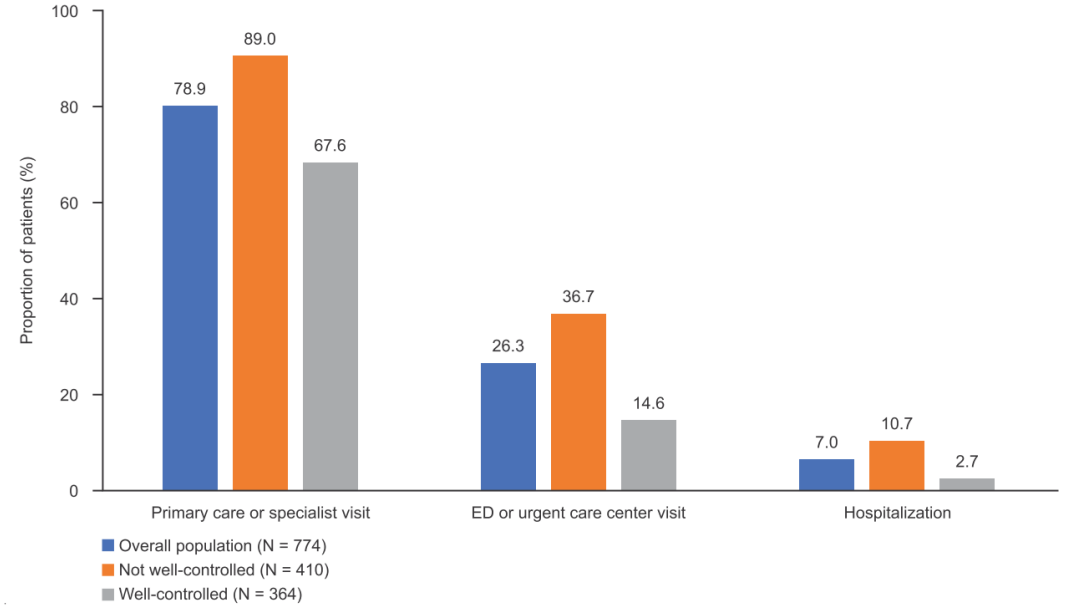
Patient views on asthma in respiratory specialist clinics in America

John Oppenheimer, MD [*]; David J. Slade, MD [†]; Beth A. Hahn, PhD [†]; Laurie Zografos, BS [‡]; Alicia Gilsenan, PhD [‡]; David Richardson, BS [‡]; David McSorley, MPH [‡]; Robson Lima, MD [†]; Nestor A. Molfino, MD [†]; Carlyne M. Averell, MS [†]

[*] *Department of Medicine, Rutgers New Jersey Medical School, Newark, New Jersey*
[†] *US Medical Affairs, GlaxoSmithKline plc, Research Triangle Park, North Carolina*
[‡] *Surveys and Observational Studies, RTI Health Solutions, Research Triangle Park, North Carolina*







Oppenheimer et al. Ann Allergy Asthma Immunol. 2021 Apr;126(4):385-393.

Triple therapy in asthma

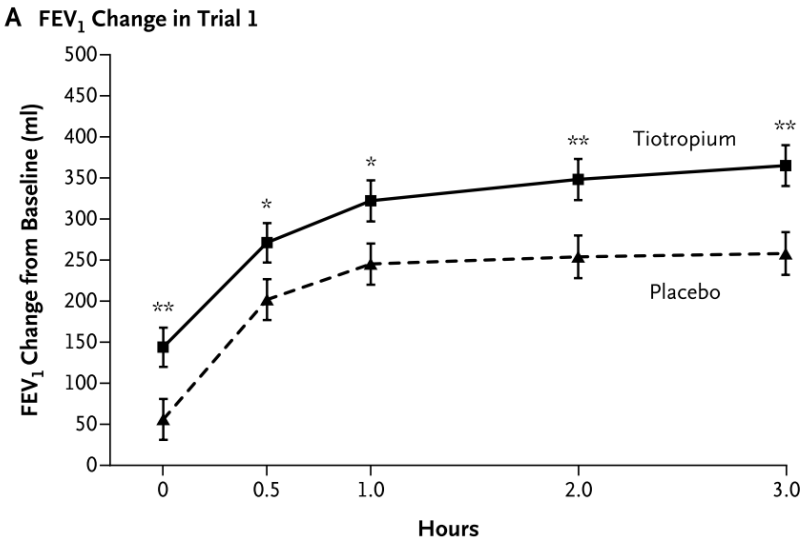
The NEW ENGLAND JOURNAL of MEDICINE

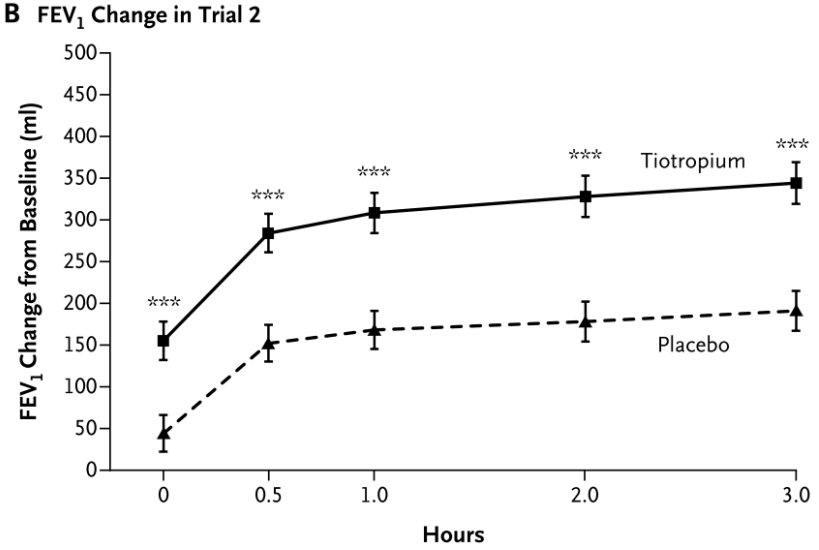
ORIGINAL ARTICLE

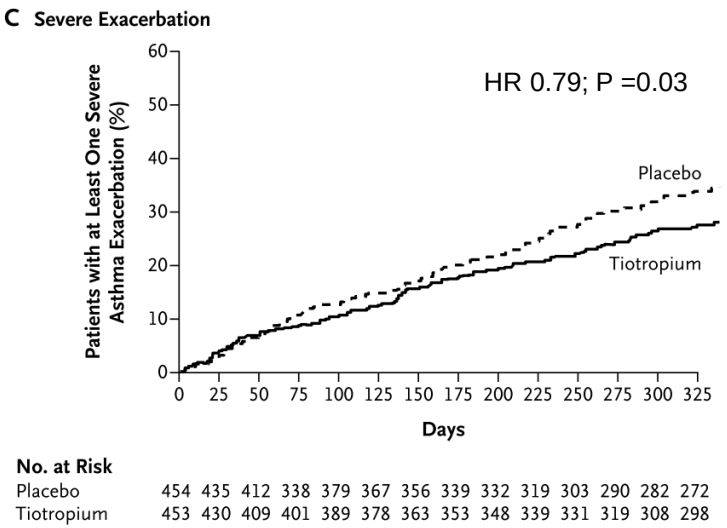
Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy

Huib A.M. Kerstjens, M.D., Michael Engel, M.D., Ronald Dahl, M.D., Pierluigi Paggiaro, M.D., Ekkehard Beck, M.D., Mark Vandewalker, M.D., Ralf Sigmund, Dipl.Math., Wolfgang Seibold, M.D., Petra Moroni-Zentgraf, M.D., and Eric D. Bateman, M.D.

- Two replicate, RCTs involving 912 patients
  - asthma patients who were receiving ICS/LABA
  - symptomatic
  - postBD FEV1 ≤80%
  - history of ≥1 severe exacerbation/yr
- Compared the effect on lung function and exacerbations of adding TIO or placebo, for 48 weeks.







Kerstjens et al. N Engl J Med. 2012 Sep 27;367(13):1198-207.

Studies	PFT	Design	Patients	Treatment period	Major findings
Fardon *et al.* [2007]	FEV_1: 51%	RCP. Half-dose of ICS+SM or half-dose of ICS +SM+TIO	18 nonsmoking severe asthmatics	4 weeks	Improvement in PEF and Raw in ICS+SM; improvement in PEF, Raw, FEV_1, FVC and eNO in ICS+SM+TIO; no difference in AQLQ
Magnussen *et al.* [2008]	FEV_1: 53%	RCP. Usual respiratory medications except for inhaled anticholinergics + TIO or placebo	472 patients with COPD and concomitant asthma	12 weeks	Increase in FEV_1, AUC, FVC, AUC from 0 to 6 h and in FEV_1 in TIO; reduction in rescue medication in TIO *versus* placebo
Park *et al.* [2009]	FEV_1: 58%	Open label. Add TIO to usual treatment 'ICS+LABA'	138 severe asthmatics	12 weeks	33.3% of patients responded to TIO. The presence of Arg16Gly in ADRB2 was associated with response to TIO
Peters *et al.* [2010]	FEV_1: 71.5%	Double-blind. Double ICS, ICS+SM or ICS+TIO	210 asthmatics	14 weeks	Improvement in PEF and FEV_1 in TIO *versus* double ICS. Improvement in FEV_1 in TIO *versus* SM; improvement in asthma control days and reduction in symptom score and ACQ in TIO and SM *versus* double ICS
Kerstjens *et al.* [2011]	FEV_1: 65%	RCP. ICS+LABA+ TIO 10/5 µg *versus* ICS+LABA+placebo	107 severe asthmatics	8 weeks	Improvement in FEV_1, FVC, PEF in both doses of TIO *versus* placebo; no differences in rescue medication, in symptom scores and in mini-AQLQ
Bateman *et al.* [2011]	FEV_1: 68% PEF: 358 l/min	RCP. ICS+ SM, TIO 5 µg or placebo	388 asthmatics with 'B16-Arg/Arg' genotype	16 weeks	TIO is as effective as SM in PEF improvement; difference 'non-statistically significant' in rescue medication, symptom scores, asthma-control days and mini-AQLQ
Kerstjens *et al.* [2012]	FEV_1: 62%	RCP. ICS+LABA+TIO 5 µg or placebo	912 severe asthmatics (24% exsmokers)	48 weeks	TIO improves FEV_1, reduces risk of exacerbation.

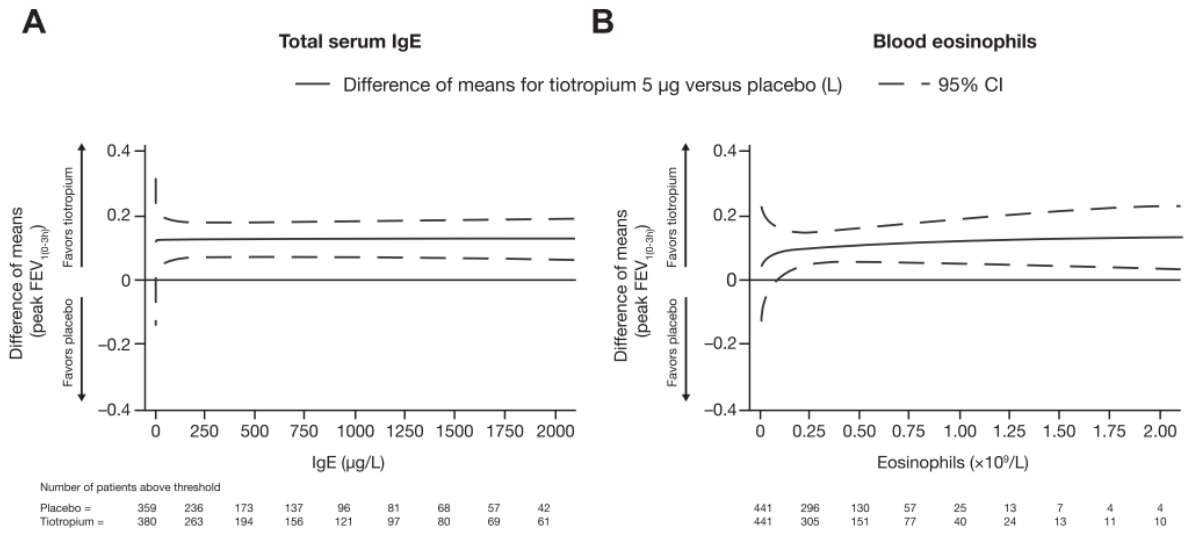
RPC, randomized placebo-controlled trial; SM, salmeterol; TIO, tiotropium; LABA, long-acting beta agonist; ICS, inhaled corticosteroid; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; AUC, area under curve; ADREB2, $beta_2$ adrenoceptor; ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; P/Y, packs/year; UNK, unknown; PFT, pulmonary function test.

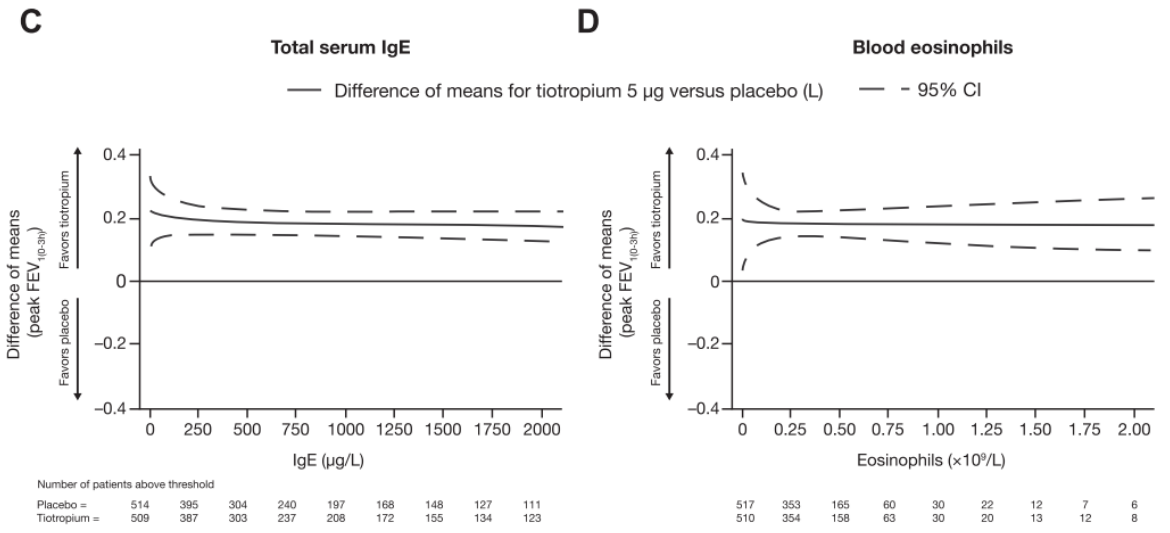
Alagha et al. Ther Adv Chronic Dis. 2014 Mar;5(2):85-98.

Original Article

Tiotropium Respimat Add-on Is Efficacious in Symptomatic Asthma, Independent of T2 Phenotype

Thomas B. Casale, MD[a], Eric D. Bateman, MD[b], Mark Vandewalker, MD[c], J. Christian Virchow, MD[d], Hendrik Schmidt, PhD[e], Michael Engel, MD[f], Petra Moroni-Zentgraf, MD[g], and Huib A.M. Kerstjens, MD[h] *Tampa, Fla; Cape Town, South Africa; Columbia, Mo; Rostock, Biberach an der Riss, and Ingelheim am Rhein, Germany; Sydney, NSW, Australia; and Groningen, The Netherlands*





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Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy

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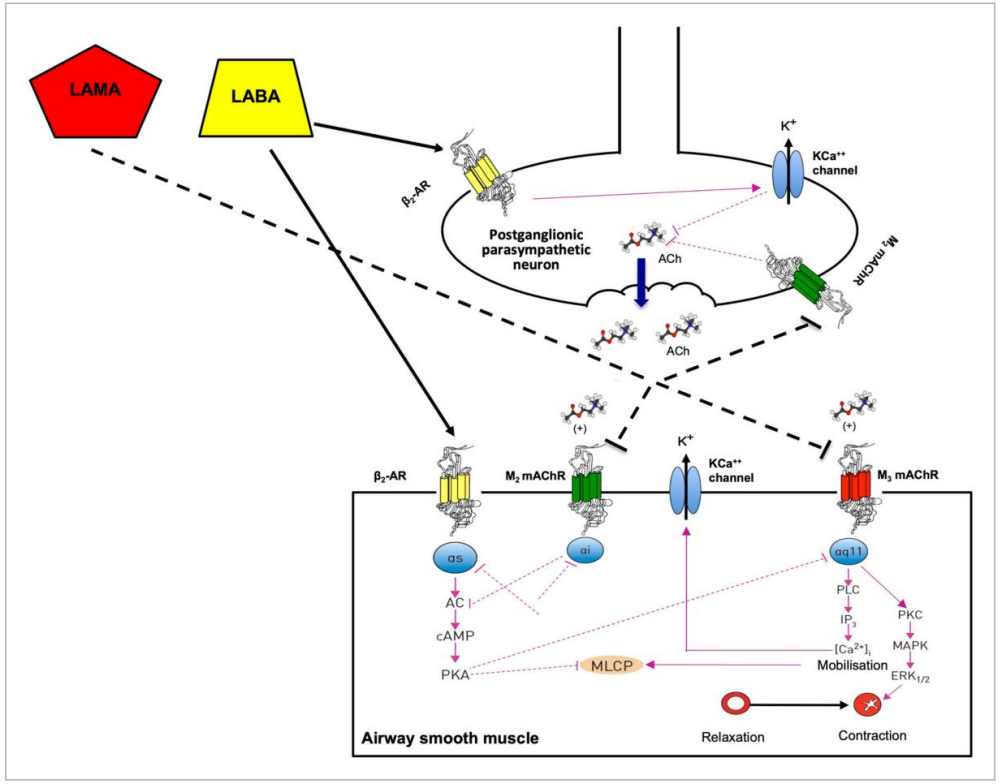
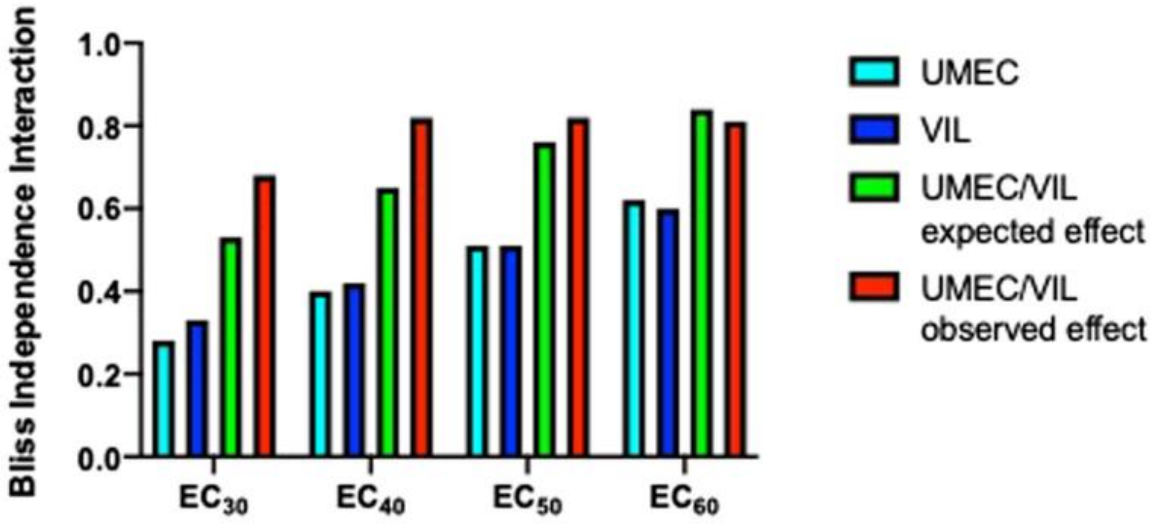
Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials

Huib A M Kerstjens, Thomas B Casale, Eugene R Bleecker, Eli O Meltzer, Emilio Pizzichini, Olaf Schmidt, Michael Engel, Loek Bour, Cynthia B Verkleij, Petra Moroni-Zentgraf, Eric D Bateman*

Casele et al. J Allergy Clin Immunol Pract. 2018 May-Jun;6(3):923-935.e9.

Synergetic effects of drugs





Cazzola et al. Br J Clin Pharmacol. 2022 Aug;88(8):3657-3673

MITT vs SITT

Factors affecting adherences

Medication

- Complex regimen
- Multiple inhalers
- Inhaler technique
- Efficacy/time to onset
- Side effects (and fear of)
- Cost

Unintentional

- Age-related factors
- Forgetfulness
- Misunderstood directions
- Comorbidities
- Health literacy

Intentional

- Perception of treatment/illness
- Denial/anger about disease
- Inappropriate expectations
- Dissatisfaction with HCPs
- Cultural/religious issues

George et al. Patient Prefer Adherence 13: 1325-1334.

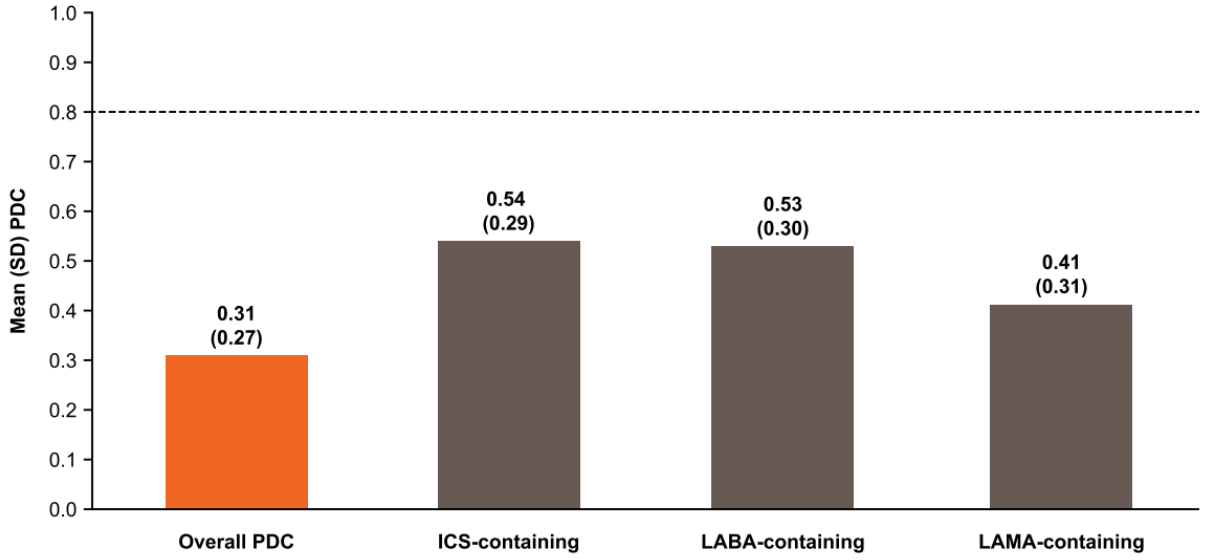
Original Article

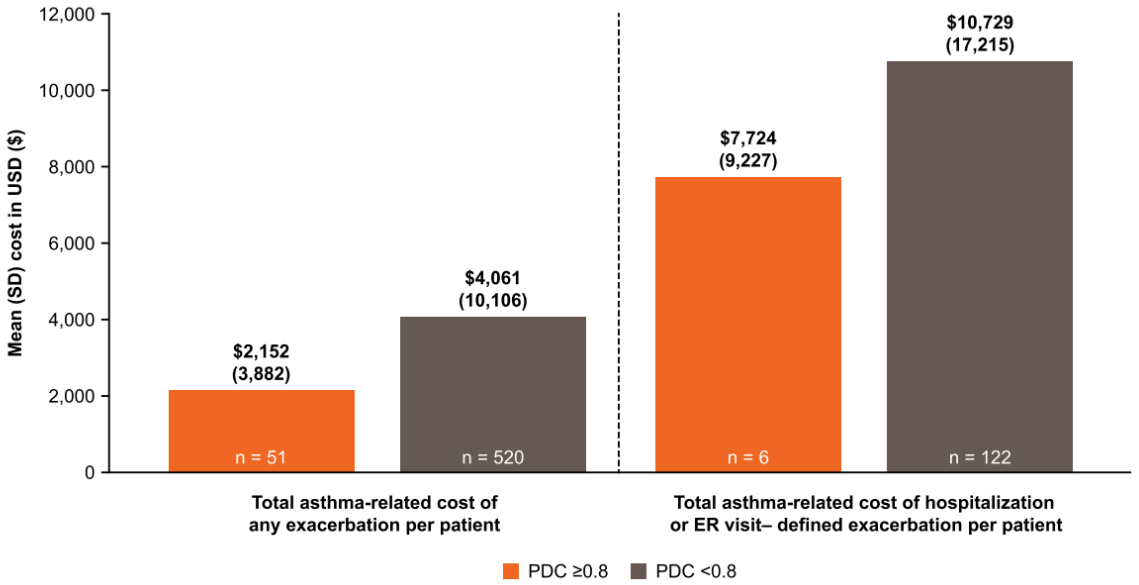
Treatment Patterns and Disease Burden Associated with Multiple-Inhaler Triple-Therapy Use in Asthma

John Oppenheimer, MD[a], Michael Bogart, PharmD[b], Lindsay G.S. Bengtson, PhD[c], John White, MSc[c], Kevin Sundquist, MSc[c], Robson Lima, MD[b], and Carlyne Averell, SM, MSc[b] *Newark, NJ; Research Triangle Park, NC; and Eden Prairie, Minn*

- Retrospective cohort study used medical and pharmacy claims
- Patients were diagnosed with asthma between 2013-2018, with evidence of MITT use
- Outcomes
  - Primary end point : Annual MITT prevalence
  - Secondary outcomes
    - Adherence : PDC (proportion of days covered)
    - MITT persistence
    - health care resource utilization
    - costs

Oppenheimer et al. J Allergy Clin Immunol Pract. 2022 Feb;10(2):485-494.e5.





Oppenheimer et al. J Allergy Clin Immunol Pract. 2022 Feb;10(2):485-494.e5.

Original Article

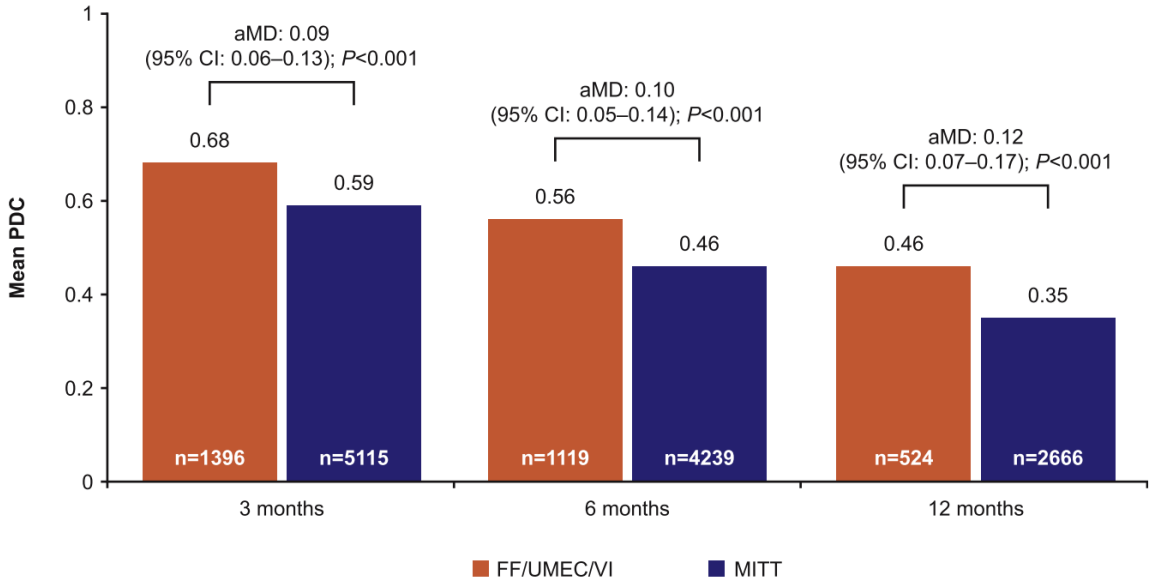
Adherence and Persistence to Single-Inhaler Versus Multiple-Inhaler Triple Therapy for Asthma Management

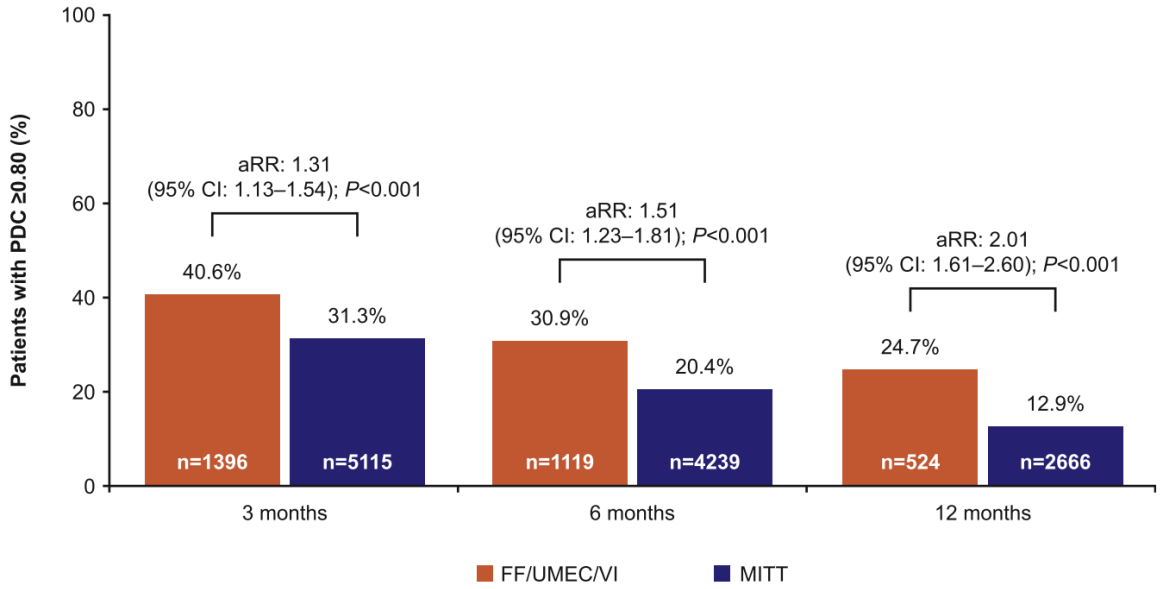
William W. Busse, MD[a], Carl B. Abbott, PharmD[b], Guillaume Germain, MSc[c], François Laliberté, MA[c], Sean D. MacKnight, MScPH[c], Young Jung, PhD[c], Mei Sheng Duh, MPH, ScD[d], and Carlyne M. Averell, SM, MS[b]

Madison, Wisc; Research Triangle Park, NC; Montréal, QC, Canada; and Boston, Mass

- Retrospective cohort study used IQVIA PharMetrics Plus data
  - medical and pharmacy claims data
  - approximately 40 million patients across all 50 US states,
  - an average length of health plan enrollment of 36 months
- Evaluate patients with asthma who initiated once-daily FF/UMEC/VI 1 or MITT
- Adherence was assessed using PDC
- Non-persistence was identified as a >45-day gap between fills.

Busse et al. J Allergy Clin Immunol Pract. 2022 Nov;10(11):2904-2913





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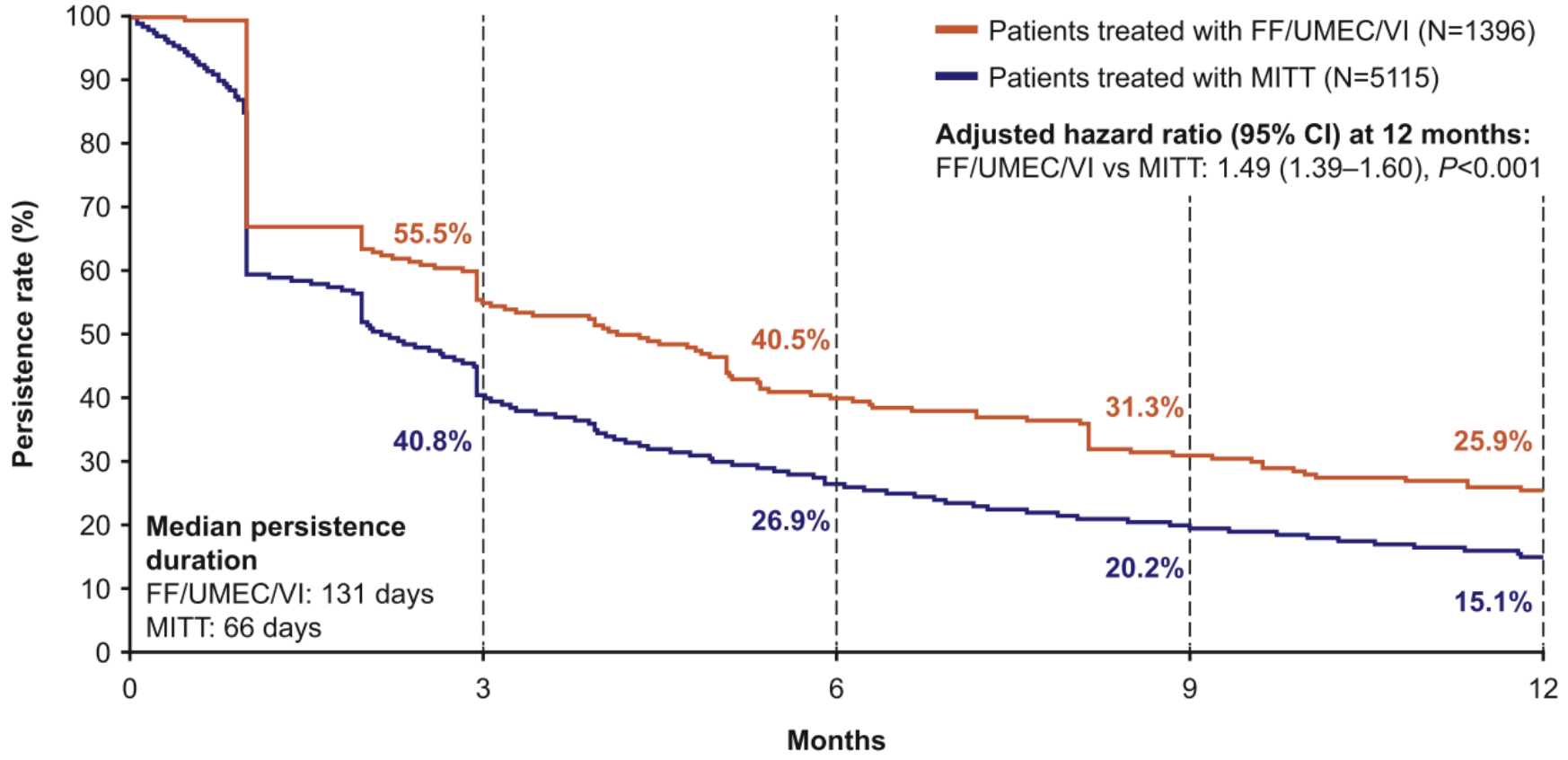

Number of patients at risk†

FF/UMEC/VI	1396	775	461	247	161
MITT	5115	2084	1092	637	350

Busse et al. J Allergy Clin Immunol Pract. 2022 Nov;10(11):2904-2913

ClinicoEconomics and Outcomes Research

Dovepress

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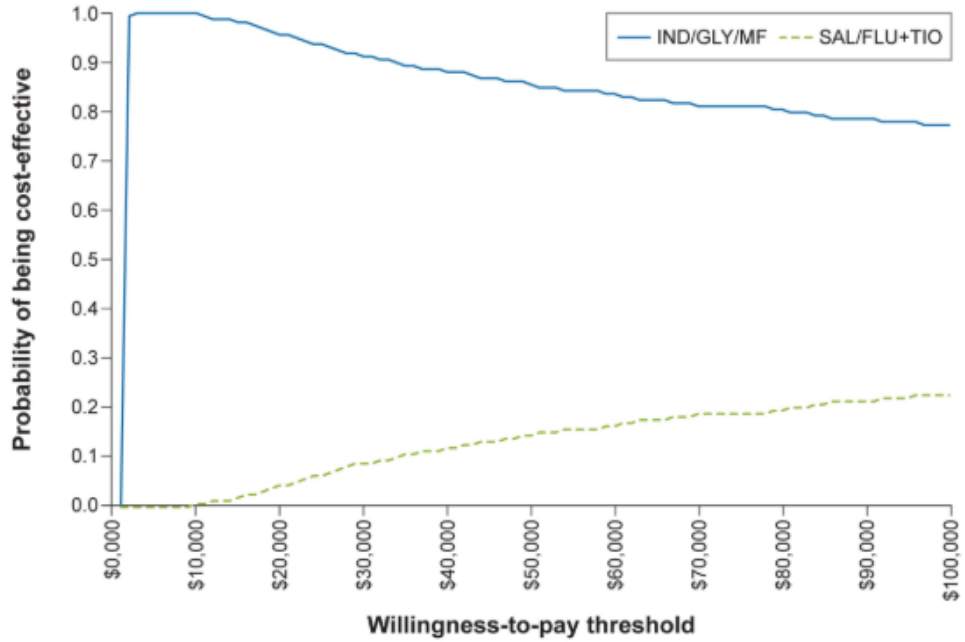
Open Access Full Text Article

ORIGINAL RESEARCH

Cost-Effectiveness of Once-Daily, Single-Inhaler Indacaterol Acetate/ Glycopyrronium Bromide/ Mometasone Furoate in Patients with Uncontrolled Moderate-to-Severe Asthma in Canada

Drug/Brand	Pack Size	Daily Dose	Cost Per Pack, CAD$	Annual Cost, CAD$	Source
IND/GLY/MF[a]	30	1	$102.82	$1,251.82	Ontario Drug Benefits formulary[44]
TIO[b]	60	2	$54.26	$660.62	
SAL/FLU[c]	60	2	$108.09	$1316.00	



Mtibaa et al. Clinicoecon Outcomes Res. 2021 Dec 3;13:957-967

Clinical trials of SITT

Clinical trials of SITT

TRIMARAN[1]

TRIGGER[1]

BDP/FF/GLY

IRIDIUM[2]

ARGON[3]

MF/IND/GLY

CAPTAIN[4]

FF/UMEC/VI

[1]Virchow et al. Lancet. 2019 Nov 9;394(10210):1737-1749. [2]Herstjens et al. Lancet Respir Med. 2020 Oct;8(10):1000-1012. [3]Gessner et al. Respir Med. 2020 Aug-Sep;170:106021. [4]Lee et al. Lancet Respir Med. 2021 Jan;9(1):69-84.

Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials

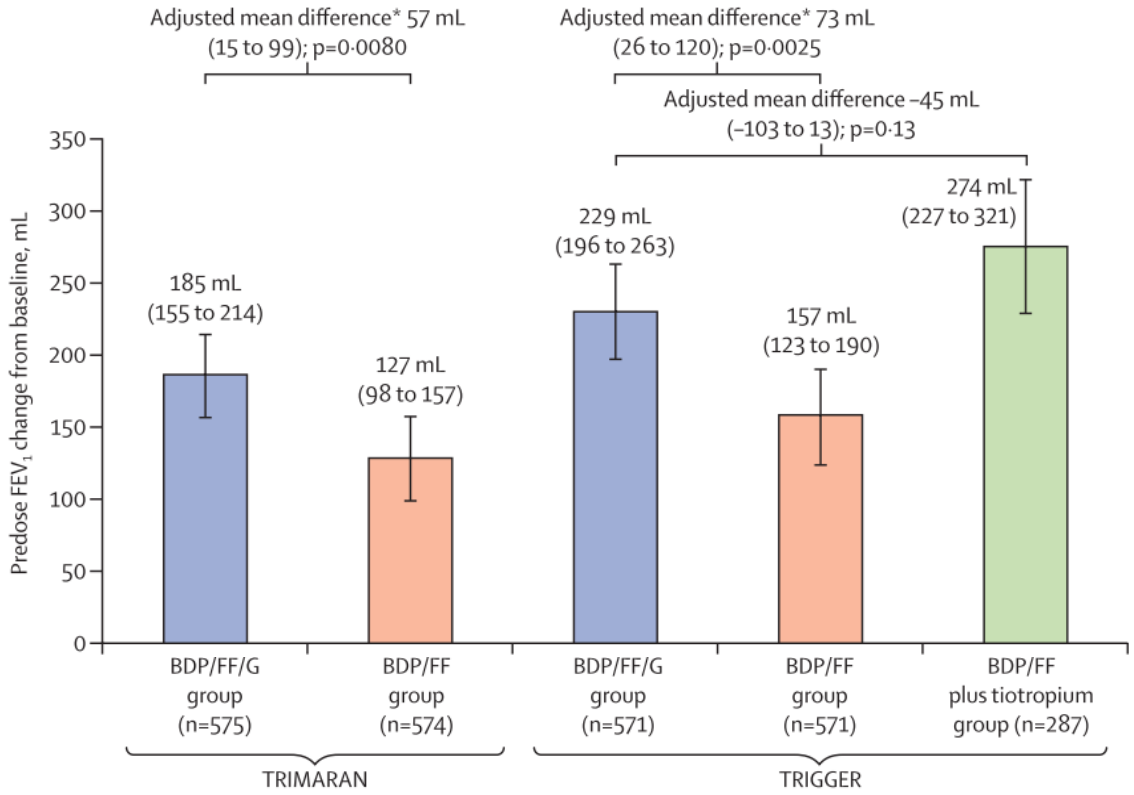
Johann Christian Virchow, Piotr Kuna, Pierluigi Paggiaro, Alberto Papi, Dave Singh, Sandrine Corre, Florence Zuccaro, Andrea Vele, Maxim Kots, George Georges, Stefano Petruzzelli, Giorgio Walter Canonica**

- Eligible patients
  - adults with uncontrolled asthma,
  - a history of ≥1 exacerbations in the previous year
  - previously treated with ICS/LABA
- TRIMARAN,
  - BDP/FF/G vs BDP/FF (medium dose ICS) (1:1)
- TRIGGER,
  - BDP/FF/G vs BDP/FF vs open-label BDP/FF plus TIO (high dose ICS) (2:2:1)
- Co-primary endpoints
  - pre-dose FEV1 at week 26
  - rate of moderate and severe exacerbations over 52 weeks.

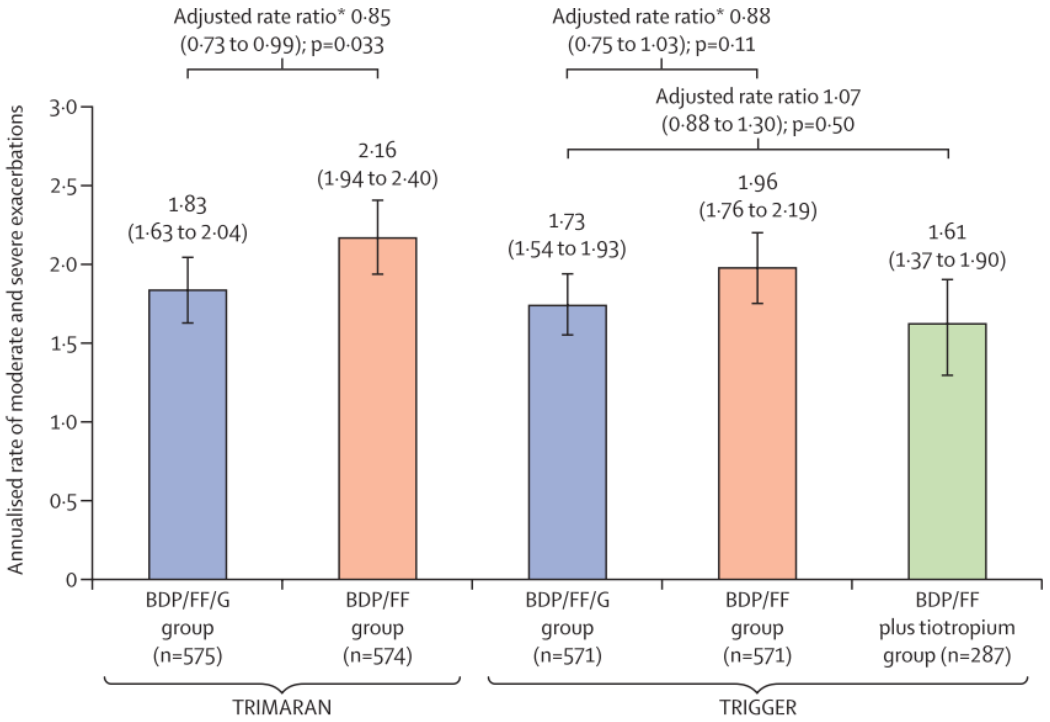
Virchow et al. Lancet. 2019 Nov 9;394(10210):1737-1749

Co-primary endpoints

Predose FEV1 at 26wks



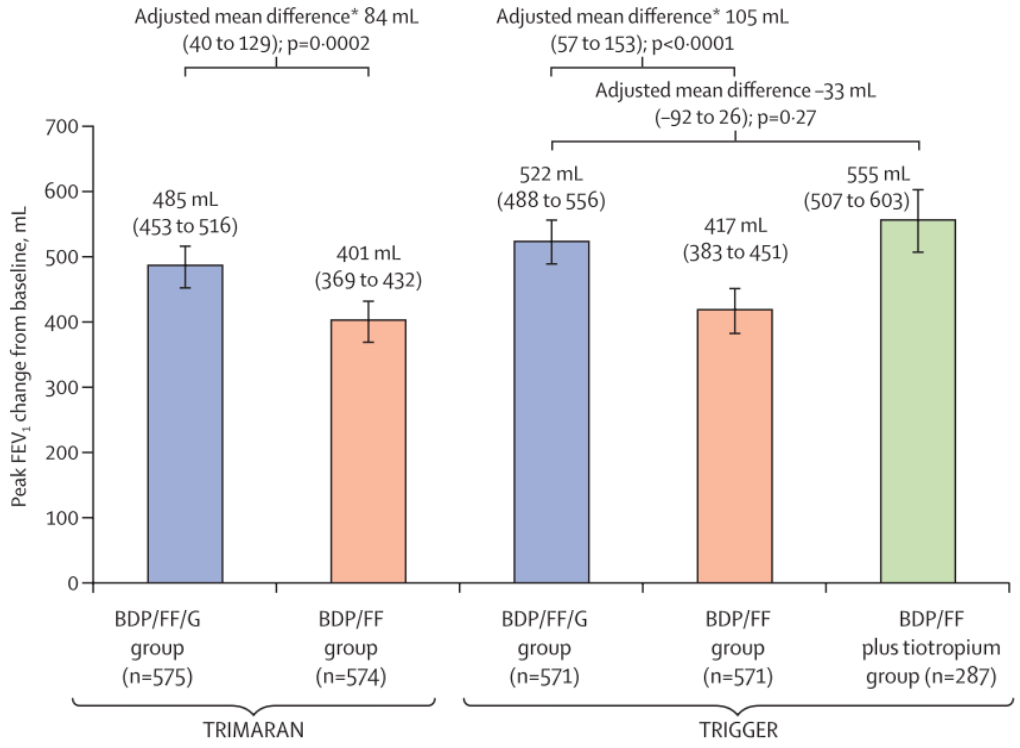
Rate of M-S exacerbation



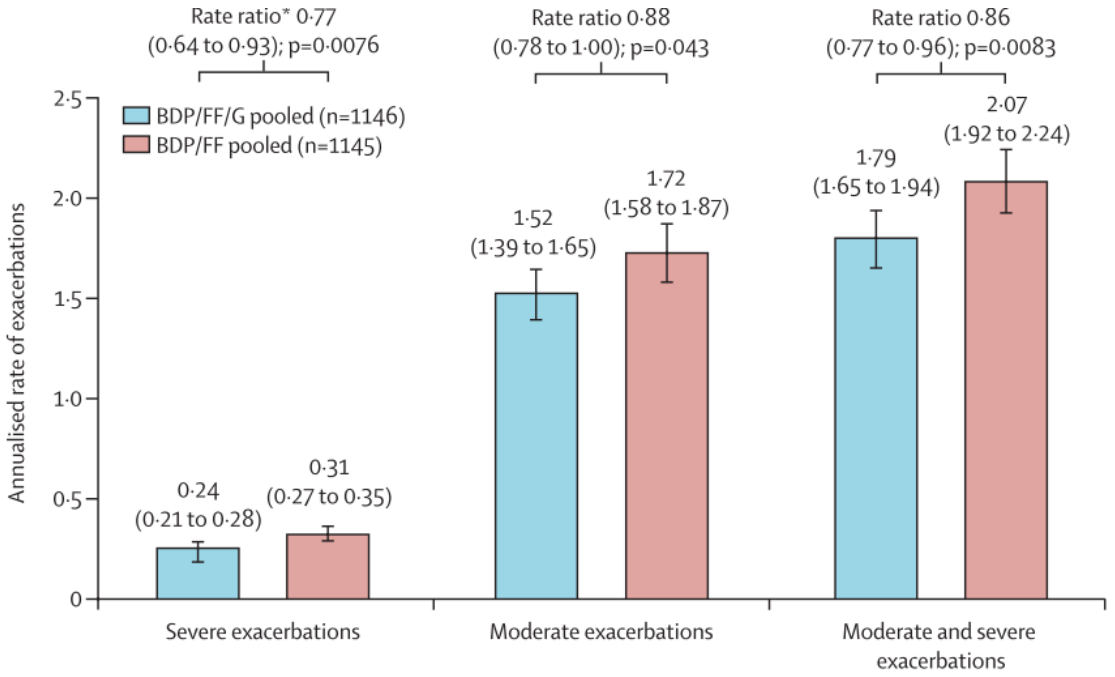
Virchow et al. Lancet. 2019 Nov 9;394(10210):1737-1749

Key secondary endpoints

Peak FEV1 change

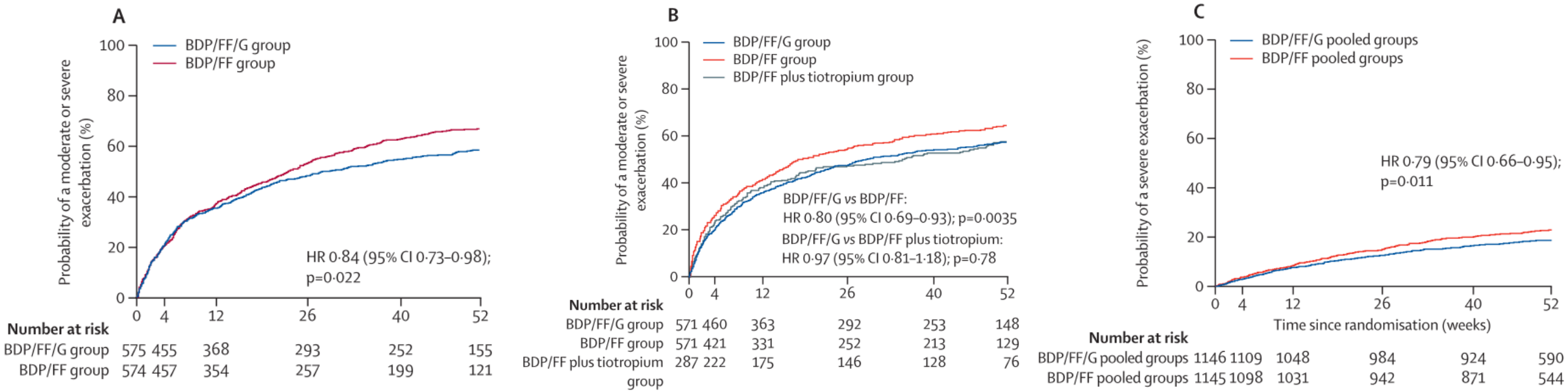


Annual exacerbation rate



Virchow et al. Lancet. 2019 Nov 9;394(10210):1737-1749

Time-to-exacerbation analysis



Virchow et al. Lancet. 2019 Nov 9;394(10210):1737-1749

Once-daily, single-inhaler mometasone–indacaterol–glycopyrronium versus mometasone–indacaterol or twice-daily fluticasone–salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study

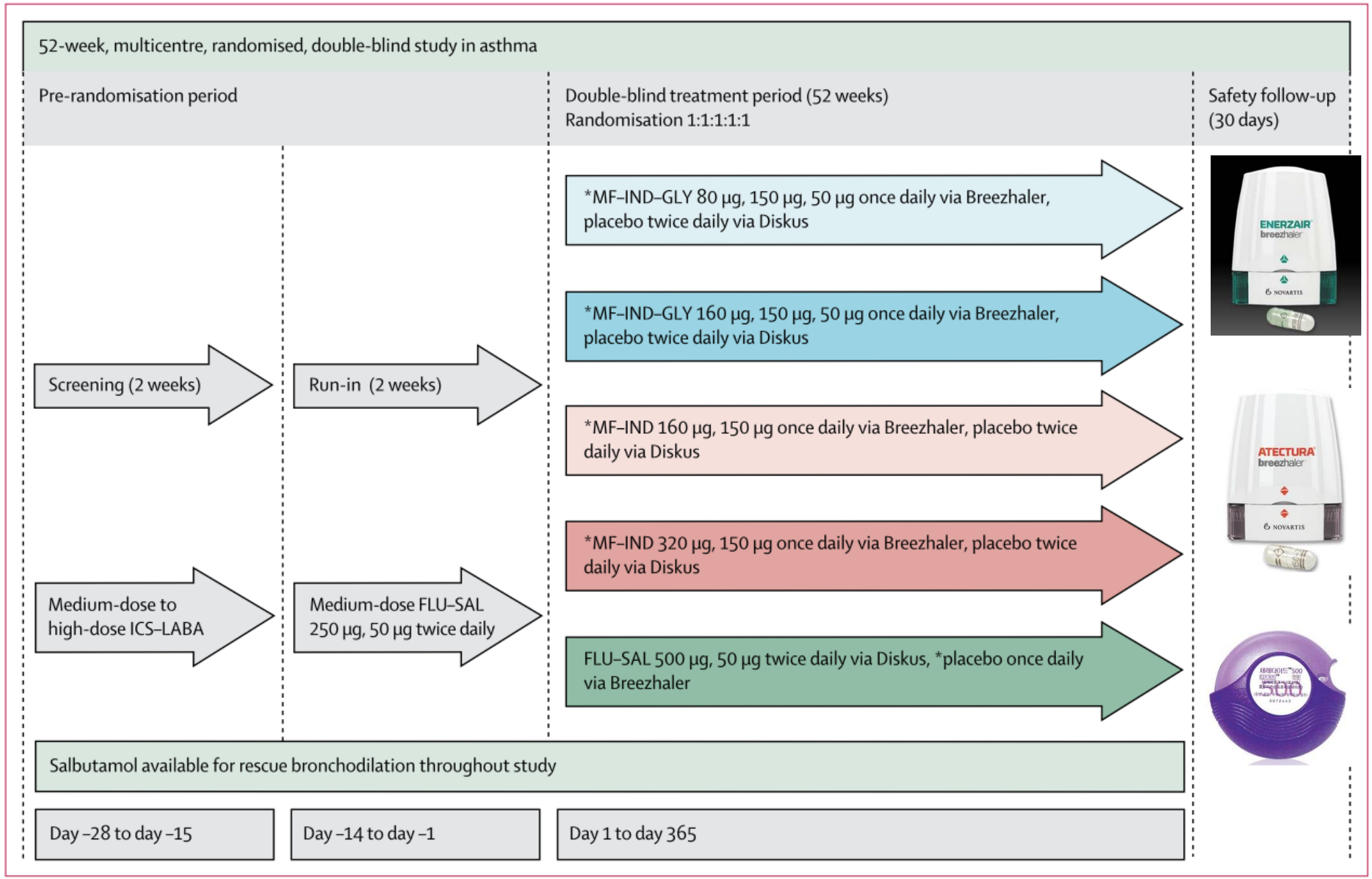
*Huib A M Kerstjens, Jorge Maspero, Kenneth R Chapman, Richard N van Zyl-Smit, Motoi Hosoe, Ana-Maria Tanase, Catherine Lavecchia, Abhijit Pethe, Xu Shu, Peter D'Andrea, on behalf of the IRIDIUM trial investigators**

- Eligible patients
  - asthma patients with aged 18-75
  - symptomatic despite treatment with medium-dose or high-dose ICS–LABA
  - ≥1 exacerbation in the previous year
  - FEV1< 80%

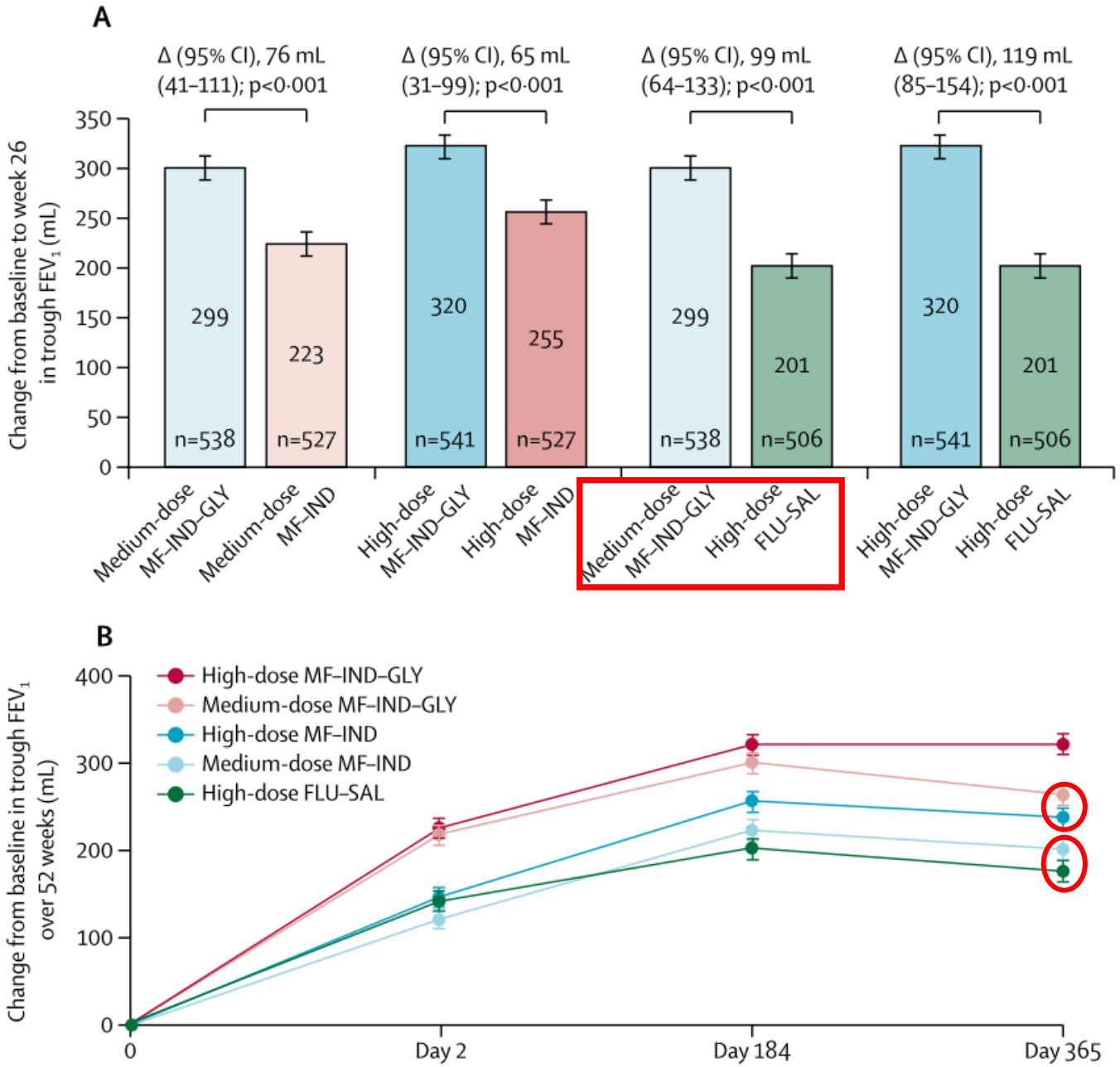
- MF–IND–GLY vs MF–IND vs high-dose FLU-SAL

- The primary outcome
  - change from baseline in trough FEV1 with MF–IND–GLY versus MF–IND at week 26

Kerstjens et al. Lancet Respir Med. 2020 Oct;8(10):1000-1012.



Kerstjens et al. Lancet Respir Med. 2020 Oct;8(10):1000-1012.



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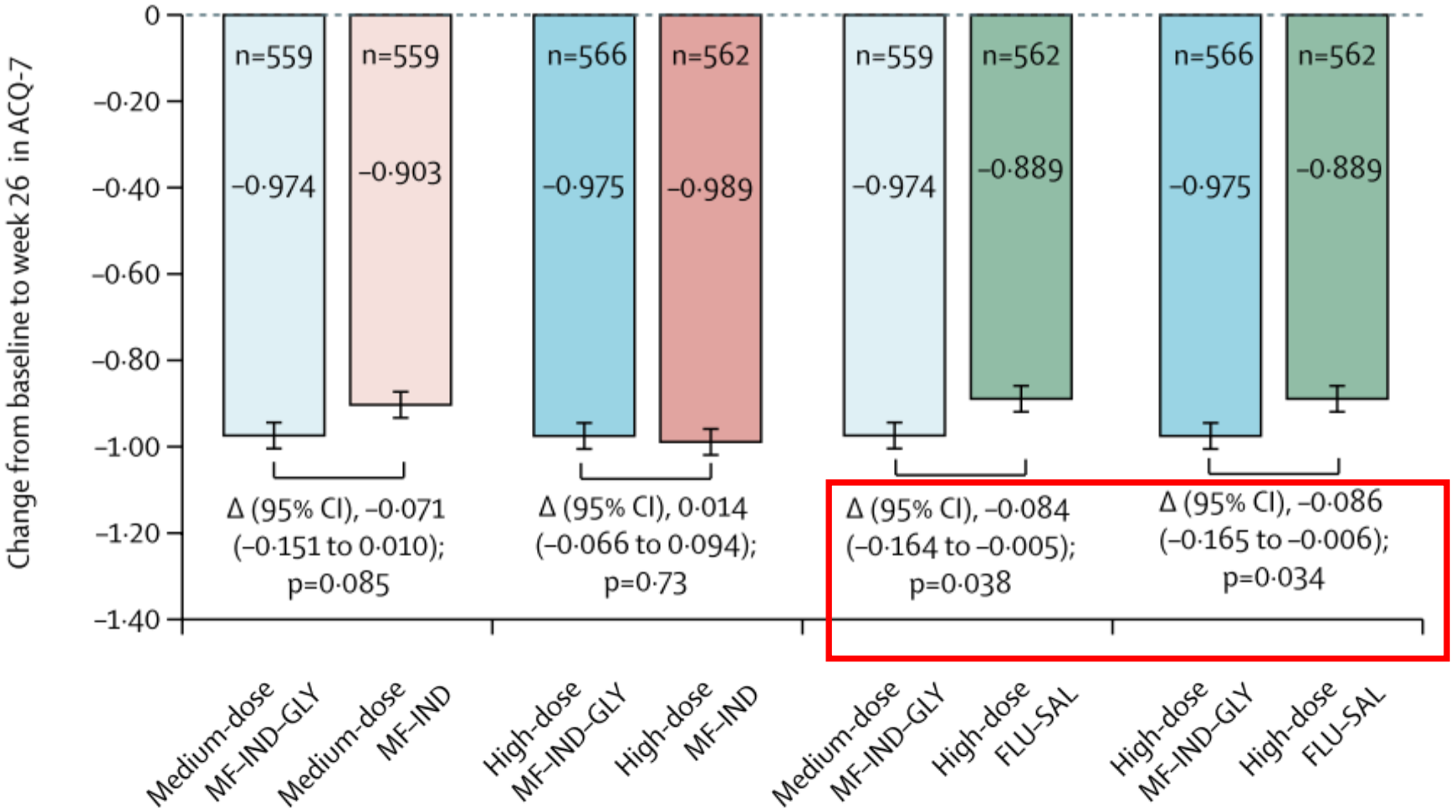

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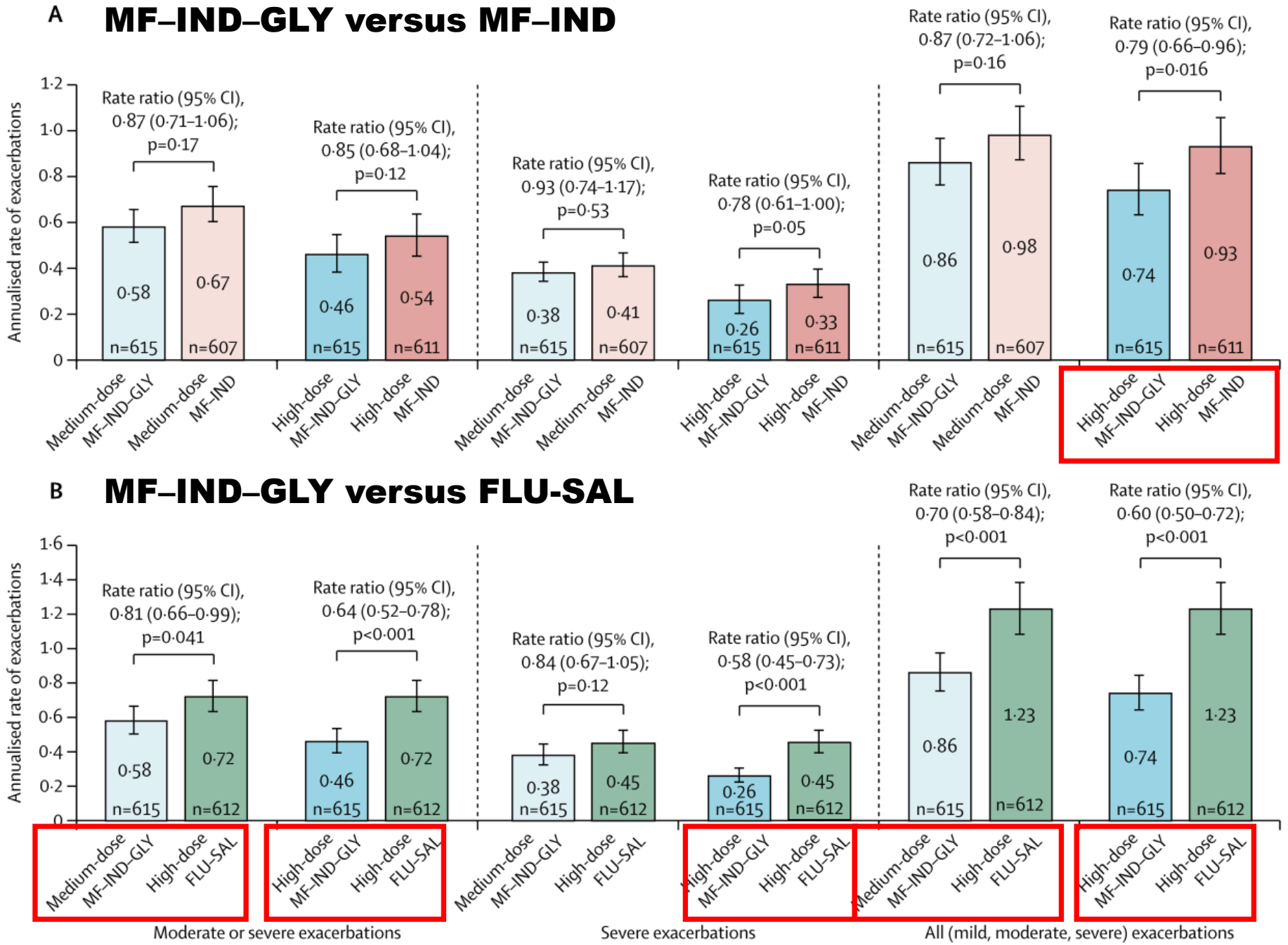
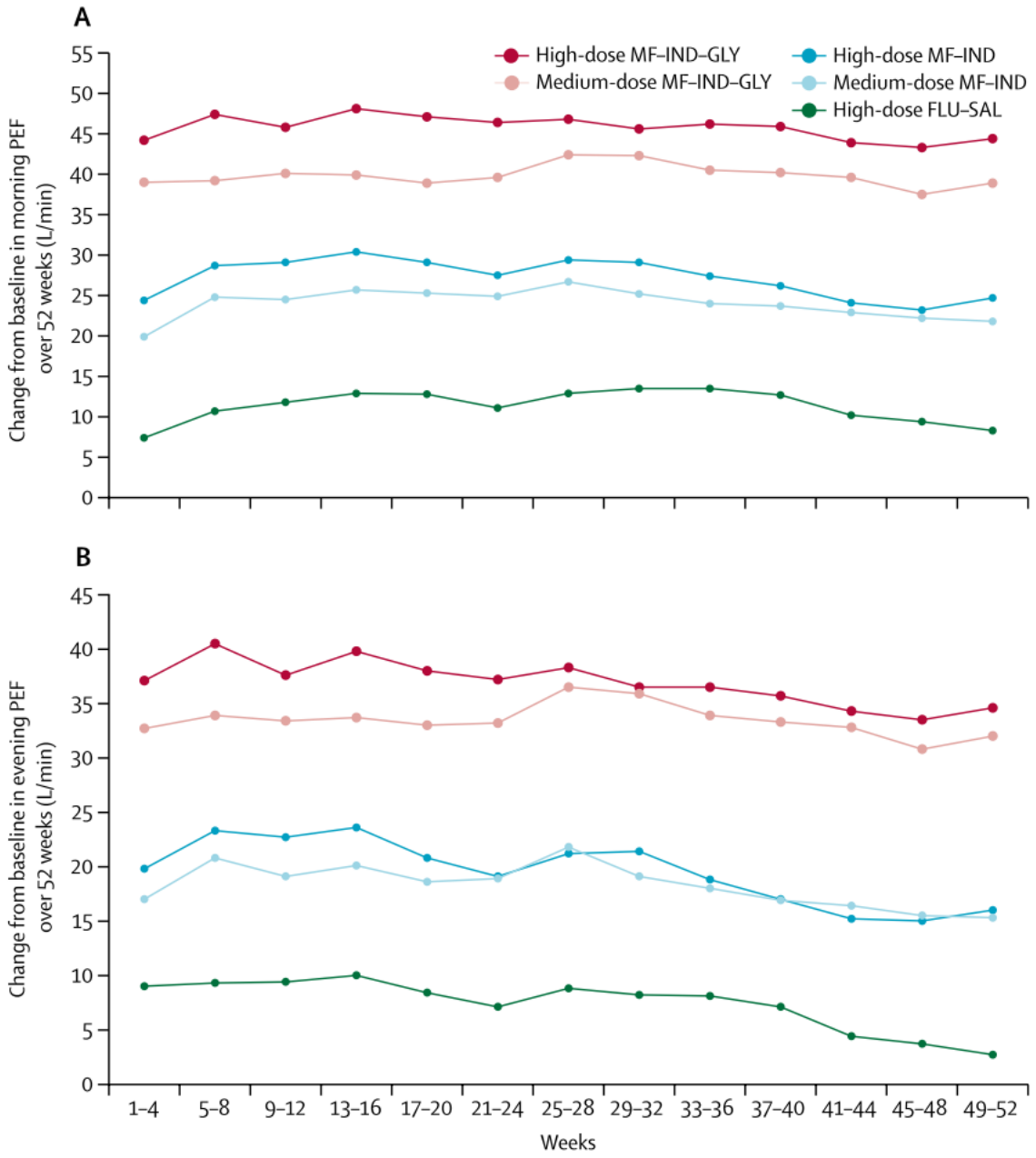

A
MF–IND–GLY versus MF–IND
Annualised rate of exacerbations
1·2
1·0
0·8
0·6
0·4
0·2
0
Rate ratio (95% CI), 0·87 (0·71–1·06); p=0·17
Rate ratio (95% CI), 0·85 (0·68–1·04); p=0·12
Rate ratio (95% CI), 0·93 (0·74–1·17); p=0·53
Rate ratio (95% CI), 0·78 (0·61–1·00); p=0·05
Rate ratio (95% CI), 0·87 (0·72–1·06); p=0·16
Rate ratio (95% CI), 0·79 (0·66–0·96); p=0·016
0·58 n=615
0·67 n=607
0·46 n=615
0·54 n=611
0·38 n=615
0·41 n=607
0·26 n=615
0·33 n=611
0·86 n=615
0·98 n=607
0·74 n=615
0·93 n=611
Medium-dose MF–IND–GLY
Medium-dose MF–IND
High-dose MF–IND–GLY
High-dose MF–IND
B
MF–IND–GLY versus FLU-SAL
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0
Rate ratio (95% CI), 0·81 (0·66–0·99); p=0·041
Rate ratio (95% CI), 0·64 (0·52–0·78); p<0·001
Rate ratio (95% CI), 0·84 (0·67–1·05); p=0·12
Rate ratio (95% CI), 0·58 (0·45–0·73); p<0·001
Rate ratio (95% CI), 0·70 (0·58–0·84); p<0·001
Rate ratio (95% CI), 0·60 (0·50–0·72); p<0·001
0·58 n=615
0·72 n=612
0·46 n=615
0·72 n=612
0·38 n=615
0·45 n=612
0·26 n=615
0·45 n=612
0·86 n=615
1·23 n=612
0·74 n=615
1·23 n=612
Medium-dose MF–IND–GLY
High-dose FLU-SAL
High-dose MF–IND–GLY
High-dose FLU-SAL
Moderate or severe exacerbations
Severe exacerbations
All (mild, moderate, severe) exacerbations



Kerstjens et al. Lancet Respir Med. 2020 Oct;8(10):1000-1012.

	Medium-dose MF–IND–GLY (n=617), exp=575·9 years	High-dose MF–IND–GLY (n=616), exp=583·8 years	Medium-dose MF–IND (n=608), exp=573·2 years	High-dose MF–IND (n=613), exp=578·9 years	High-dose FLU–SAL (n=618), exp=575·6 years
Patients with ≥1 adverse event	460 (174·2)	458 (163·3)	453 (163·8)	454 (169·0)	487 (193·9)
Asthma	248 (57·4)	247 (56·1)	268 (65·0)	256 (60·1)	309 (79·4)
Nasopharyngitis	77 (14·4)	64 (11·7)	64 (11·9)	73 (13·7)	83 (15·7)
Bronchitis	48 (8·8)	49 (8·8)	44 (8·0)	46 (8·3)	55 (10·0)
Upper respiratory tract infection	45 (8·2)	33 (5·9)	48 (8·8)	52 (9·4)	52 (9·5)
Headache	30 (5·4)	23 (4·0)	34 (6·1)	24 (4·3)	25 (4·4)
Viral upper respiratory tract infection	31 (5·5)	21 (3·7)	27 (4·8)	38 (6·8)	47 (8·6)
Respiratory tract infection viral	17 (3·0)	18 (3·1)	29 (5·2)	11 (1·9)	22 (3·9)
Upper respiratory tract infection bacterial	22 (3·9)	17 (2·9)	28 (5·0)	27 (4·8)	29 (5·2)
Patient with ≥1 adverse event suspected to be study drug-related	46 (8·4)	51 (9·2)	42 (7·6)	38 (6·9)	51 (9·3)
Patient with ≥1 serious adverse event	49 (8·8)	46 (8·2)	38 (6·8)	52 (9·3)	39 (7·0)
Asthma	15 (2·6)	9 (1·6)	8 (1·4)	12 (2·1)	9 (1·6)
Pneumonia	2 (0·3)	3 (0·5)	3 (0·5)	1 (0·2)	5 (0·9)
Lower respiratory tract infection	1 (0·2)	1 (0·2)	1 (0·2)	3 (0·5)	2 (0·3)
Cholelithiasis	0	3 (0·5)	1 (0·2)	0	1 (0·2)
Pulmonary embolism	0	1 (0·2)	0	3 (0·5)	0
Patient with ≥1 adverse event leading to permanent discontinuation of study drug	25 (4·3)	13 (2·2)	19 (3·3)	18 (3·1)	21 (3·7)
Asthma exacerbation	8 (1·4)	3 (0·5)	12 (2·1)	6 (1·0)	10 (1·7)
Death	1 (0·2)	2 (0·3)	0	4 (0·7)	0
Cancer	0	0	0	1 (0·2)	0
Cardiovascular	1 (0·2)	2 (0·3)	0	2 (0·3)	0
Accidental	0	0	0	1 (0·2)	0

Data are presented as n (IR). IR is reported per 100 patient-years (100 × number of patients with at least one event/time at risk for given adverse event in patient-years). Patients received medium-dose MF–IND–GLY (80 µg, 150 µg, 50 µg) once daily; or high-dose MF–IND–GLY (160 µg, 150 µg, 50 µg) once daily; or medium-dose MF–IND (160 µg, 150 µg) once daily; or high-dose MF–IND (320 µg, 150 µg) once daily; or high-dose FLU–SAL (500 µg, 50 µg) twice daily. exp=exposure in total number of patient-years. FLU–SAL=fluticasone–salmeterol. IR=incidence rate. MF–IND=mometasone–indacaterol. MF–IND–GLY=mometasone–indacaterol–glycopyrronium.

Table 2: **Adverse events, serious adverse events, and deaths in the safety set**

Kerstjens et al. Lancet Respir Med. 2020 Oct;8(10):1000-1012.

Contents lists available at ScienceDirect

Respiratory Medicine

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Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily *versus* salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomised, Phase IIIb, non-inferiority study (ARGON)

Christian Gessner [a,*], Oliver Kornmann [b], Jorge Maspero [c], Richard van Zyl-Smit [d], Matthias Krüll [e], Anna Salina [f], Pritam Gupta [g], Sebastien Bostel [f], Sebastian Fucile [h], Lorena Garcia Conde [f], Pascal Pfister [f]

- Eligible patients
  - aged ≥18 years
  - symptomatic despite treatment with ICS/LABA
- High or medium-dose IND/GLY/MF or high-dose SAL/FLU +Tio for 24 weeks.
- Primary objective
  - non-inferiority of AQLQ.
- Secondary endpoints: ACQ-7, lung function, SGRQ, exacerbations, and safety

Gessner et al. Respir Med. 2020 Aug-Sep;170:106021

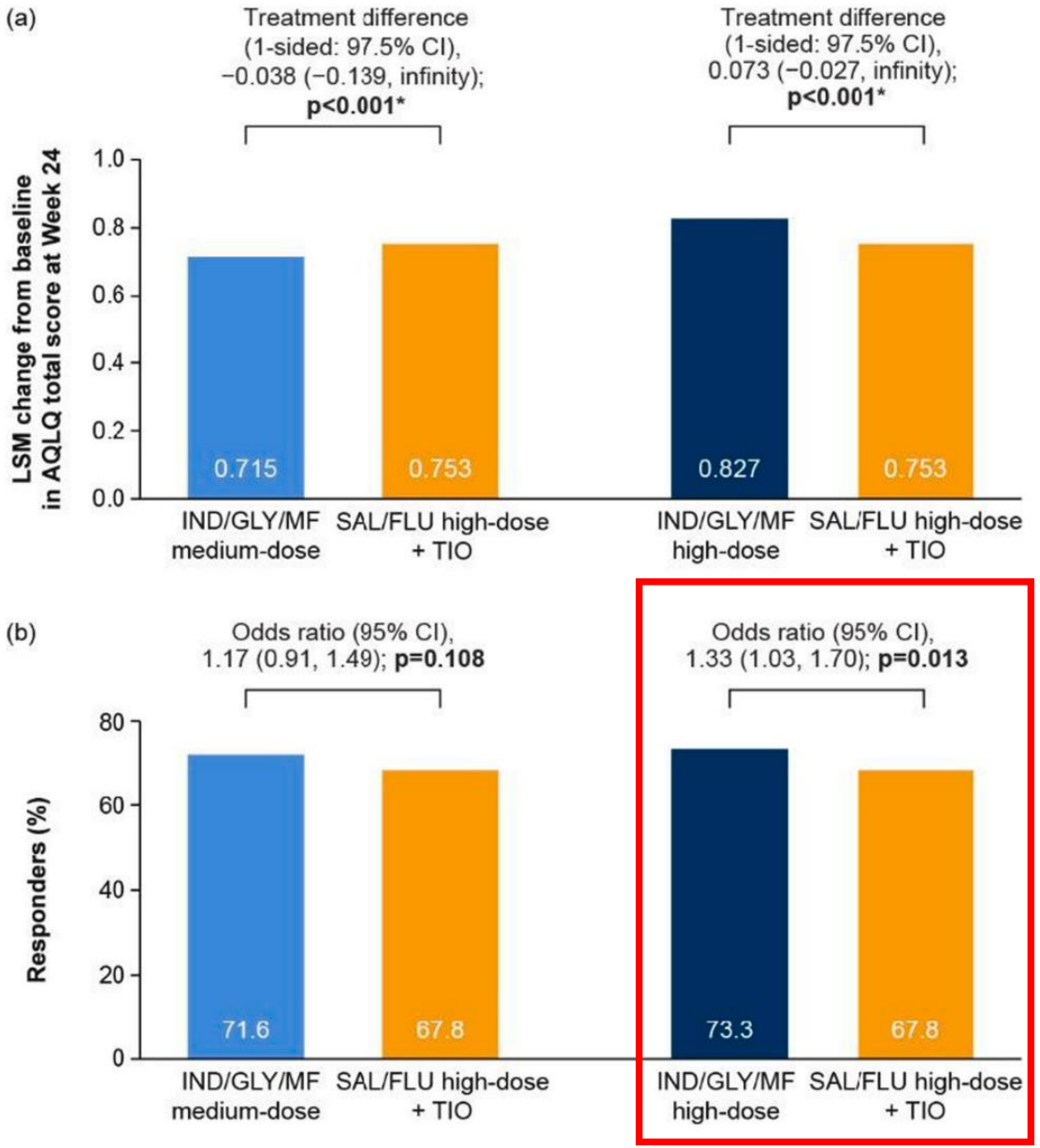
24-week, multicentre, randomised, partially-blinded, parallel-group, Phase III study in patients with uncontrolled asthma

Pre-randomisation period		Randomised treatment period (24 weeks)	Follow-up period
Screening period (1 week)	Run-in period (2 weeks): Open-label SAL/FLU 50/250 µg b.i.d. or 50/500 µg b.i.d.	IND/GLY/MF medium-dose (150/50/80 µg) o.d. via Breezhaler® IND/GLY/MF high-dose (150/50/160 µg) o.d. via Breezhaler® Open-label SAL/FLU high-dose (50/500 µg) b.i.d. via Accuhaler® + TIO 5 µg o.d. via Respimat®	
Day −21 to Day −14	Day −14 to Day −1	Day 1 to Day 169	7 days

Randomisation (1:1:1)

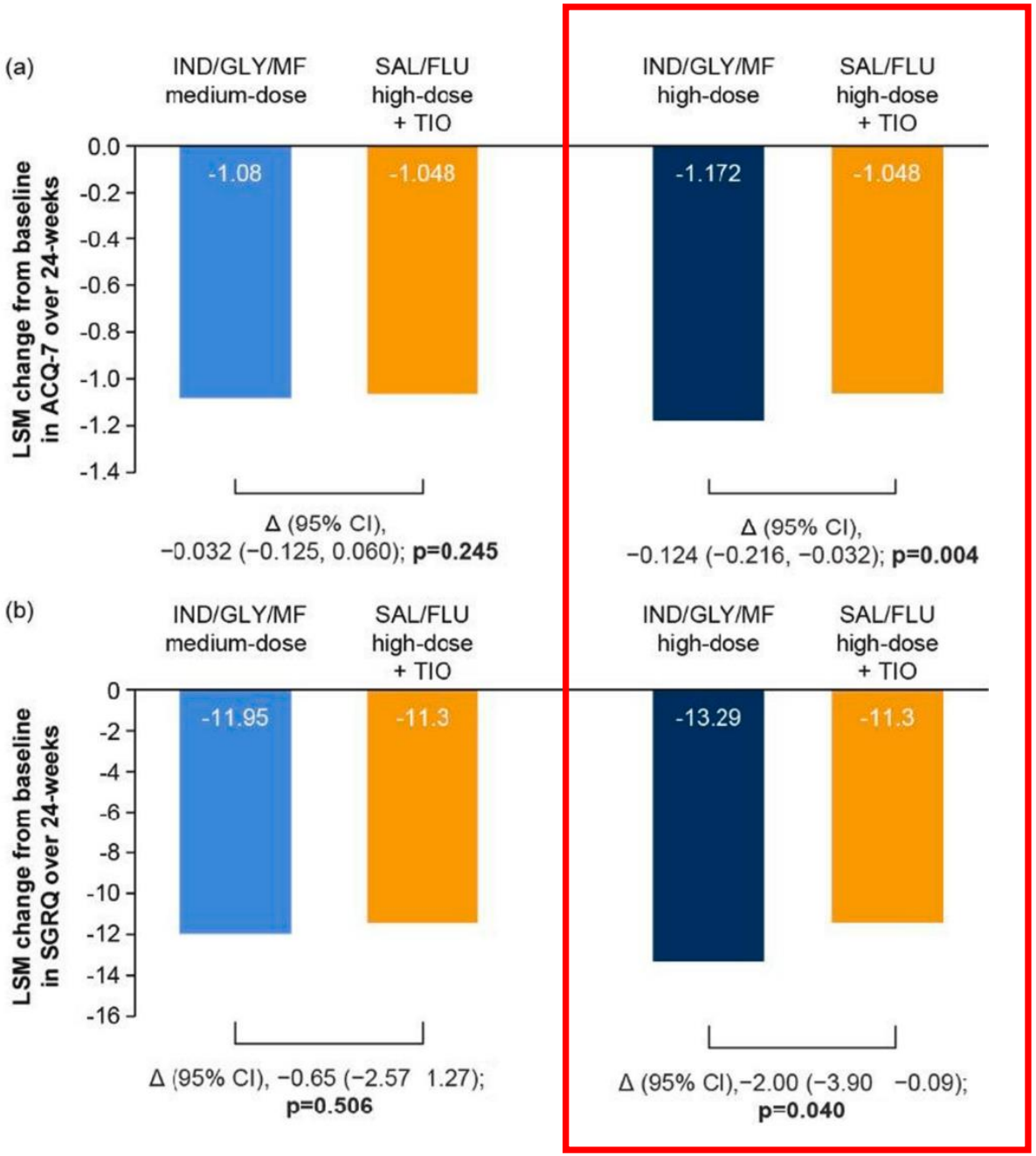
Rescue medication available

Gessner et al. Respir Med. 2020 Aug-Sep;170:106021

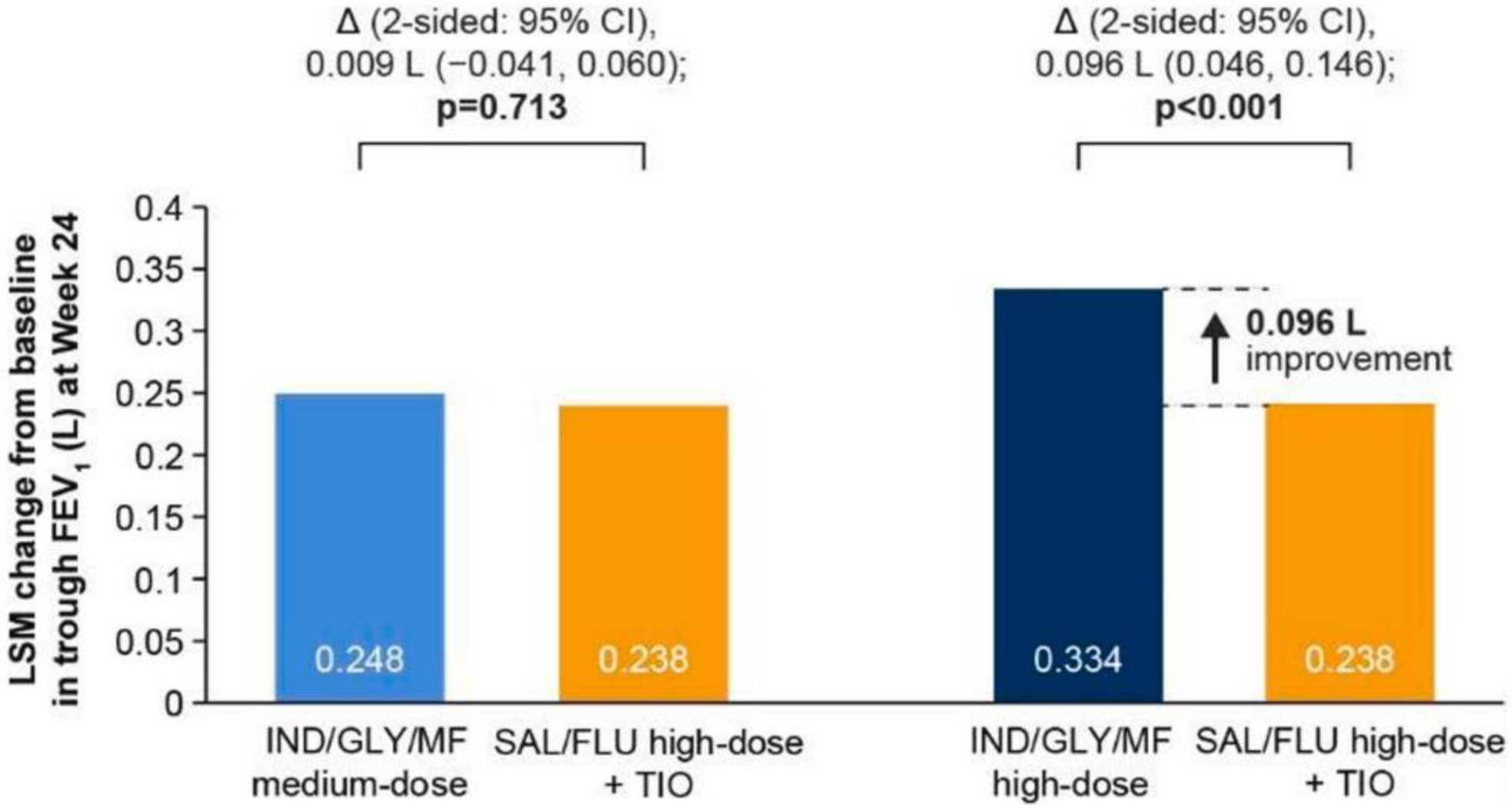


Non-inferior !

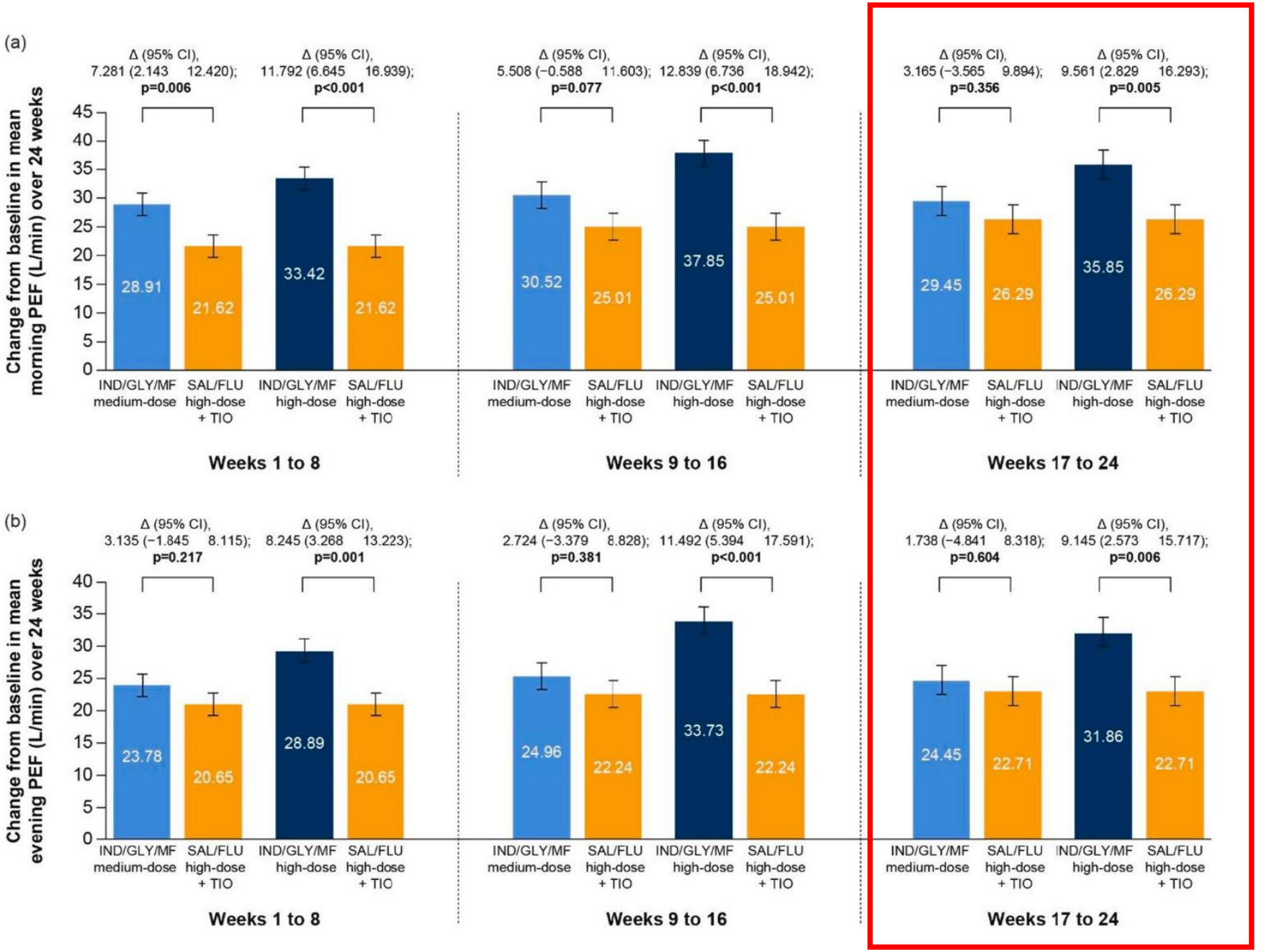
Gessner et al. Respir Med. 2020 Aug-Sep;170:106021



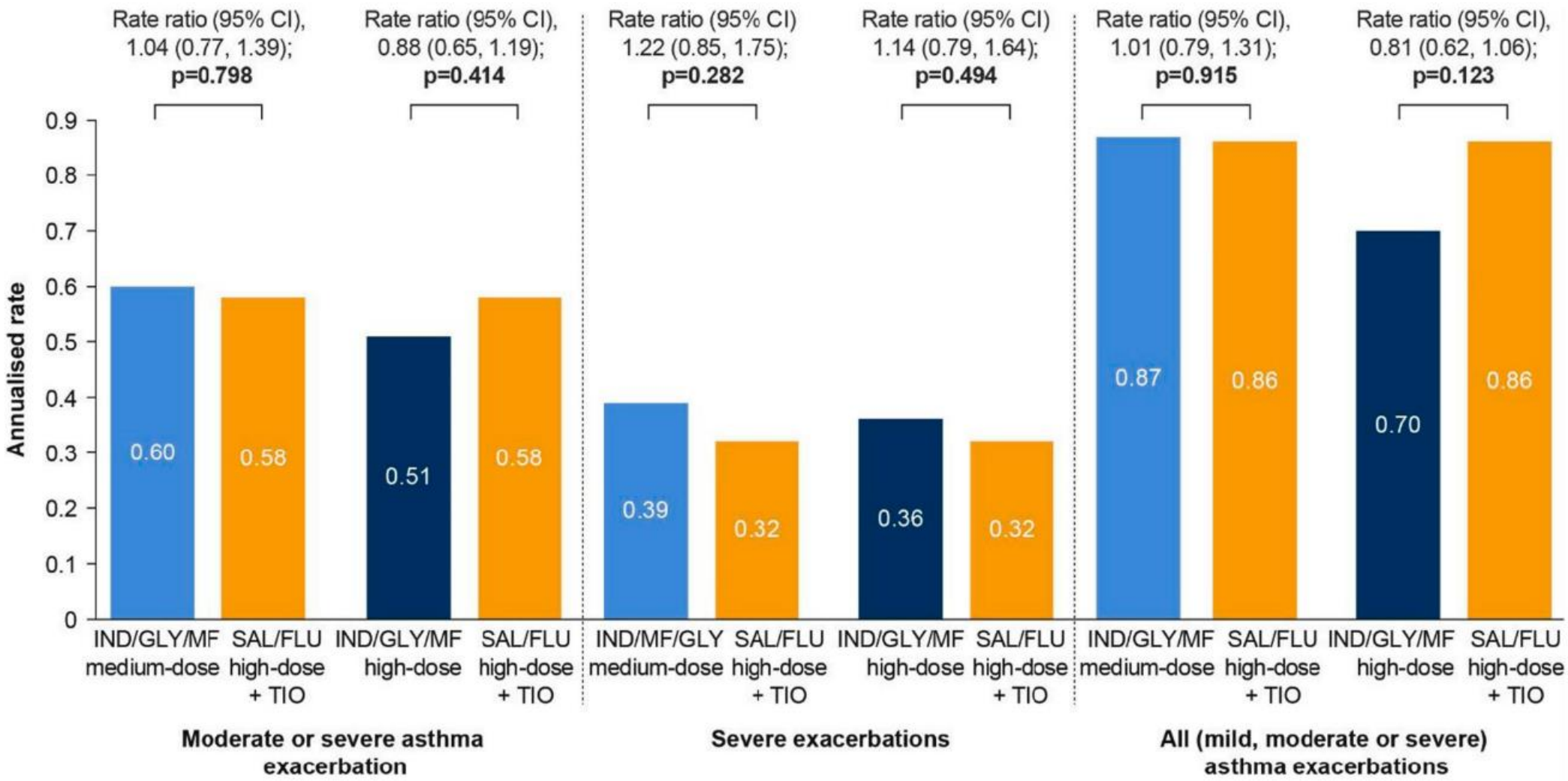
Gessner et al. Respir Med. 2020 Aug-Sep;170:106021



Gessner et al. Respir Med. 2020 Aug-Sep;170:106021



Gessner et al. Respir Med. 2020 Aug-Sep;170:106021



Gessner et al. Respir Med. 2020 Aug-Sep;170:106021

	IND/GLY/MF medium-dose o.d. (N = 474)	IND/GLY/MF high-dose o.d. (N = 476)	SAL/FLU high-dose b.i.d.+ TIO o.d. (N = 475)
Number of patients with ≥1 adverse event (AE)	252 (53.2)	249 (52.3)	245 (51.6)
AEs related to study drug	17 (3.6)	26 (5.5)	19 (4.0)
AEs leading to study drug discontinuation	5 (1.1)	3 (0.6)	3 (0.6)
Most frequently reported AEs (preferred term >2% in at least one treatment arm)			
Asthma (exacerbations)	129 (27.2)	115 (24.2)	126 (26.5)
Nasopharyngitis	34 (7.2)	34 (7.1)	43 (9.1)
Bronchitis	21 (4.4)	22 (4.6)	19 (4.0)
Pharyngitis	18 (3.8)	17 (3.6)	10 (2.1)
Upper respiratory tract infection	13 (2.7)	10 (2.1)	9 (1.9)
Headache	10 (2.1)	15 (3.2)	9 (1.9)
Respiratory tract infection viral	10 (2.1)	9 (1.9)	6 (1.3)
Viral upper respiratory tract infection	9 (1.9)	11 (2.3)	10 (2.1)
SAEs: Number of patients with ≥1 SAE	14 (3.0)	18 (3.8)	19 (4.0)
Most frequently reported SAEs			
Pneumonia	0	5 (1.1)	0
Asthma (severe exacerbation)	4 (0.8)	2 (0.4)	2 (0.4)
Serious cardiovascular events (Serious AEs of special interest)			
Atrioventricular block (second degree)	1 (0.2)	0	0
Myocardial infarction	0	0	1 (0.2)
Tachycardia	0	0	1 (0.2)
Carotid artery stenosis	0	0	1 (0.2)
Haemorrhagic stroke*	0	0	1 (0.2)
Deaths	0 (0.0)	0 (0.0)	1 (0.2)*
Cardiovascular	0	0	1 (0.2)
Fatal Stroke - Haemorrhagic	0	0	1 (0.2)*

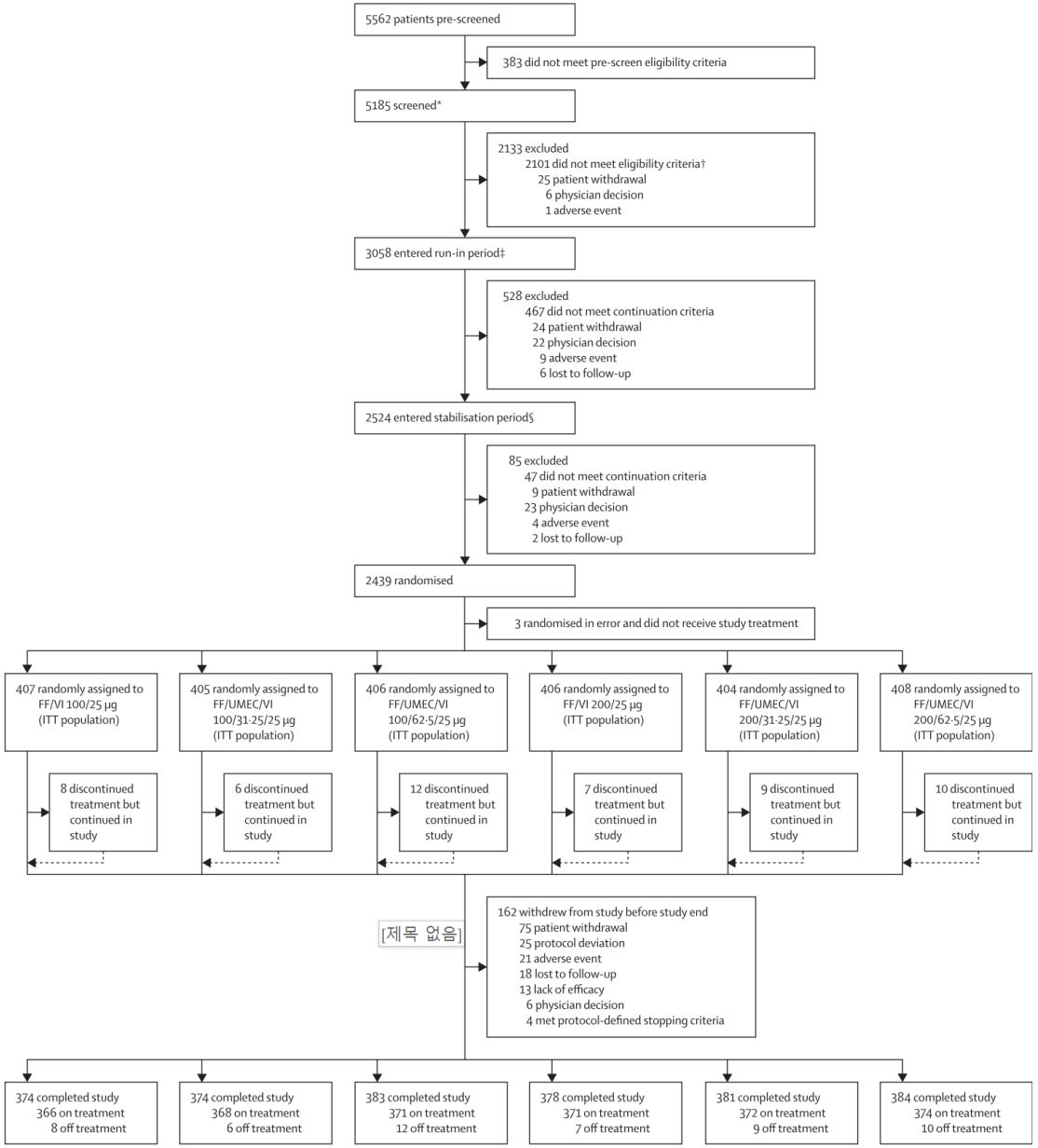
Gessner et al. Respir Med. 2020 Aug-Sep;170:106021

Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial

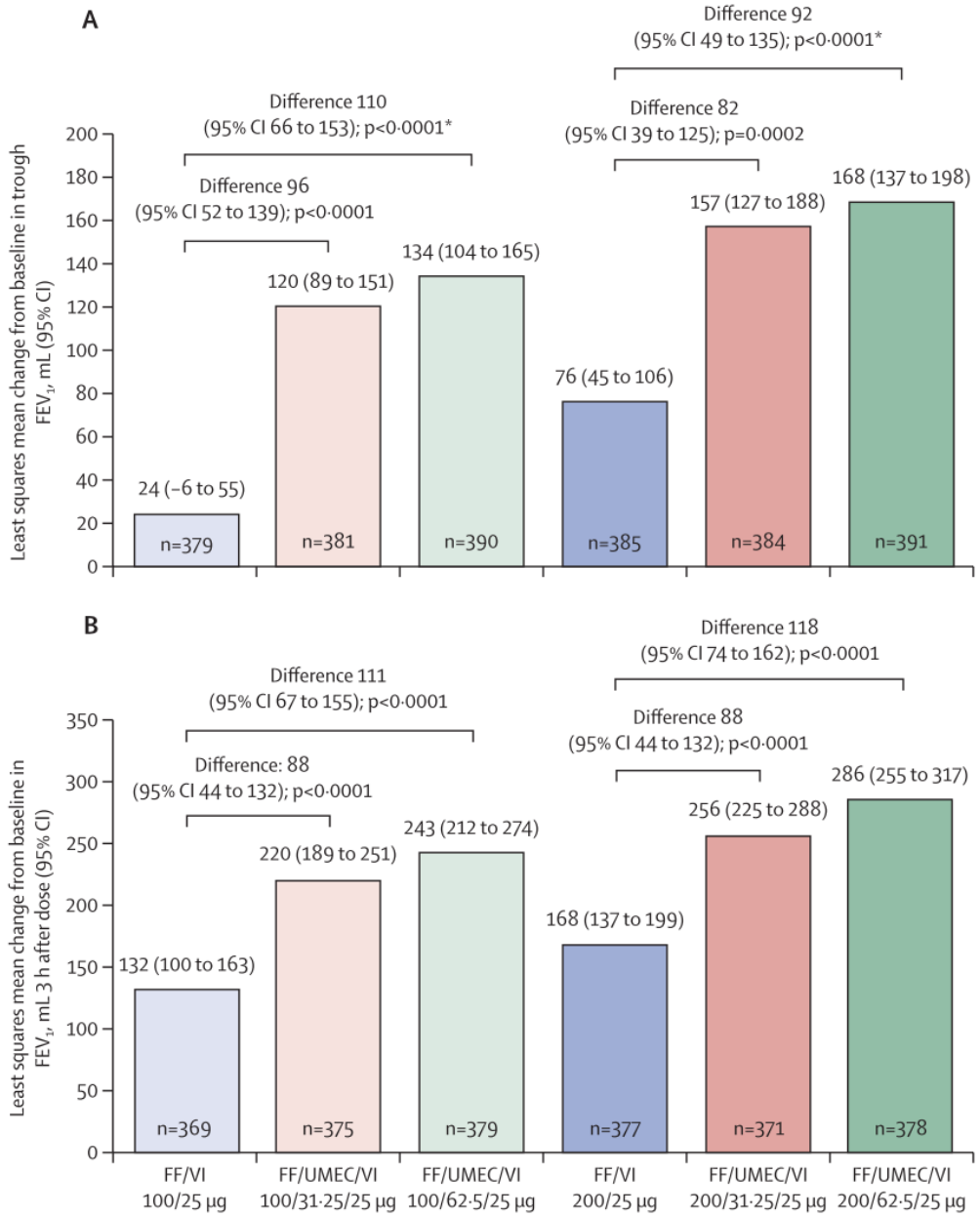
Laurie A Lee, Zelie Bailes, Neil Barnes, Louis-Philippe Boulet, Dawn Edwards, Andrew Fowler, Nicola A Hanania, Huib A M Kerstjens, Edward Kerwin, Robert Nathan, John Oppenheimer, Alberto Papi, Steven Pascoe, Guy Brusselle, Guy Peachey, Neal Sule, Maggie Tabberer, Ian D Pavord

- Eligible patients
  - aged ≥18 years
  - inadequately controlled asthma (ACQ-6 score of ≥1·5) despite ICS/LABA,
  - acute asthma symptoms in the previous year
  - preBD FEV1 30%-85% + BDR (+)
- FF/VI vs FF/UMEC/VI
- Endpoints
  - change from baseline in clinic trough FEV1 at at week 24
  - annualised moderate-severe asthma exacerbation rate
  - change from baseline in clinic FEV1 at 3 h post-dose, SGRQ, ACQ-7 at week 24.

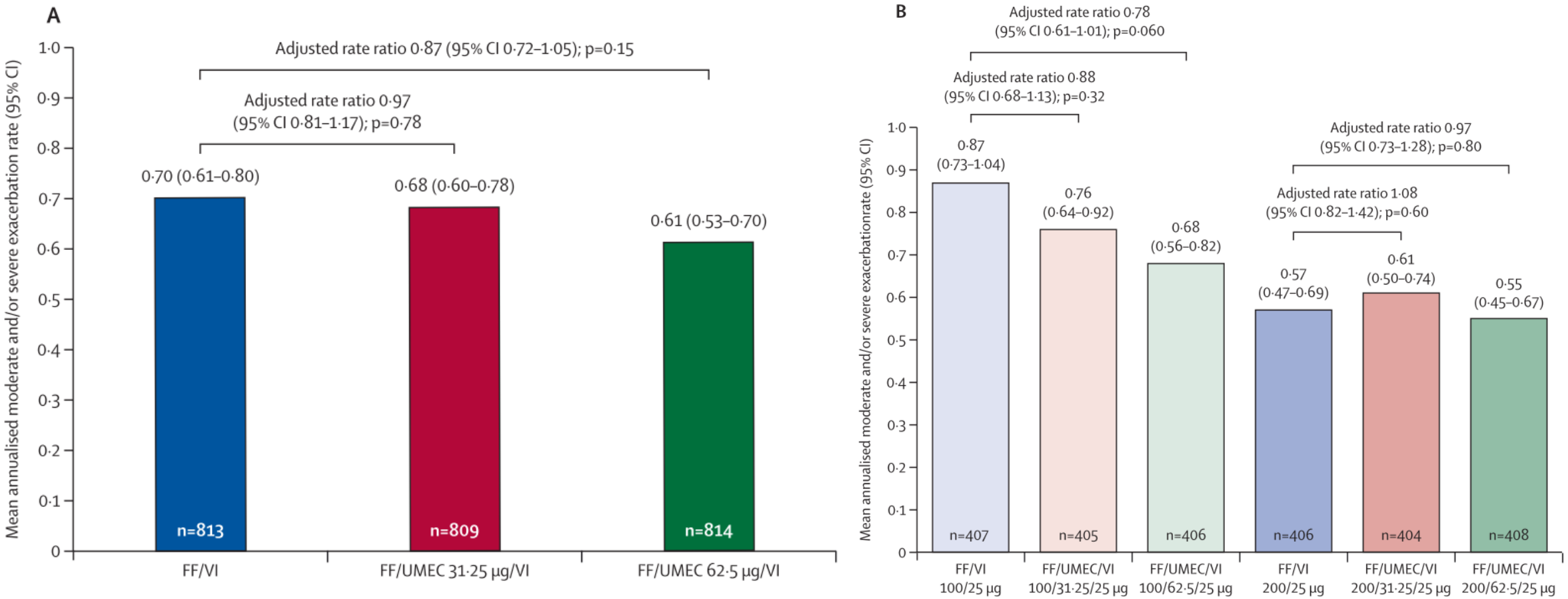
Lee et al. Lancet Respir Med. 2021 Jan;9(1):69-84



Lee et al. Lancet Respir Med. 2021 Jan;9(1):69-84



Lee et al. Lancet Respir Med. 2021 Jan;9(1):69-84



Lee et al. Lancet Respir Med. 2021 Jan;9(1):69-84

	FF/VI pooled groups (n=813)	FF/UMEC 31·25 µg/VI pooled groups (n=809)	FF/UMEC 62·5 µg/VI pooled groups (n=814)
ACQ-7 score			
Change from baseline			
Number of patients with analysable data at week 24	745	746	761
Least squares mean change from baseline (95% CI)	−0·68 (−0·73 to −0·63)	−0·73 (−0·78 to −0·69)	−0·77 (−0·81 to −0·72)
Treatment difference (95% CI; p value)	Ref	−0·06 (−0·12 to 0·01; 0·094)	−0·09 (−0·16 to −0·02; 0·0084)
Responders			
Responders,* n/N (%)	436/793 (55%)	464/795 (58%)	498/795 (63%)
Odds ratio (95% CI; p value)	Ref	1·15 (0·94 to 1·42; 0·18)	1·43 (1·16 to 1·76; 0·0009)

Lee et al. Lancet Respir Med. 2021 Jan;9(1):69-84

	FF/VI 100/25 µg (n=407)	FF/UMEC/VI 100/31·25/25 µg (n=405)	FF/UMEC/VI 100/62·5/25 µg (n=406)	FF/VI 200/25 µg (n=406)	FF/UMEC/VI 200/31·25/25 µg (n=404)	FF/UMEC/VI 200/62·5/25 µg (n=408)
Patients with ≥1 adverse event	258 (63%)	232 (57%)	239 (59%)	210 (52%)	233 (58%)	217 (53%)
Adverse events occurring in ≥3% of patients						
Nasopharyngitis	63 (15%)	56 (14%)	60 (15%)	53 (13%)	51 (13%)	51 (13%)
Headache	30 (7%)	31 (8%)	36 (9%)	23 (6%)	27 (7%)	19 (5%)
Upper respiratory tract infection	21 (5%)	24 (6%)	15 (4%)	13 (3%)	15 (4%)	19 (5%)
Bronchitis	14 (3%)	18 (4%)	15 (4%)	19 (5%)	17 (4%)	22 (5%)
Back pain	16 (4%)	12 (3%)	13 (3%)	6 (1%)	14 (3%)	9 (2%)
Respiratory tract infection viral	11 (3%)	17 (4%)	10 (2%)	7 (2%)	12 (3%)	9 (2%)
Influenza	13 (3%)	12 (3%)	15 (4%)	9 (2%)	8 (2%)	6 (1%)
Pharyngitis	8 (2%)	10 (2%)	9 (2%)	14 (3%)	11 (3%)	9 (2%)
Treatment-related adverse events	21 (5%)	16 (4%)	29 (7%)	17 (4%)	20 (5%)	19 (5%)
Serious adverse events	25 (6%)	18 (4%)	23 (6%)	21 (5%)	23 (6%)	21 (5%)
Major adverse cardiovascular event (broad focus)	5 (1%)	3 (<1%)	4 (<1%)	2 (<1%)	3 (<1%)	3 (<1%)
Adverse events leading to study treatment discontinuation	11 (3%)	5 (1%)	7 (2%)	5 (1%)	6 (1%)	3 (<1%)
Adverse events leading to death	0	2 (<1%)	0	1 (<1%)	0	0

Data are n (%). FF=fluticasone furoate. UMEC=umeclidinium. VI=vilanterol.

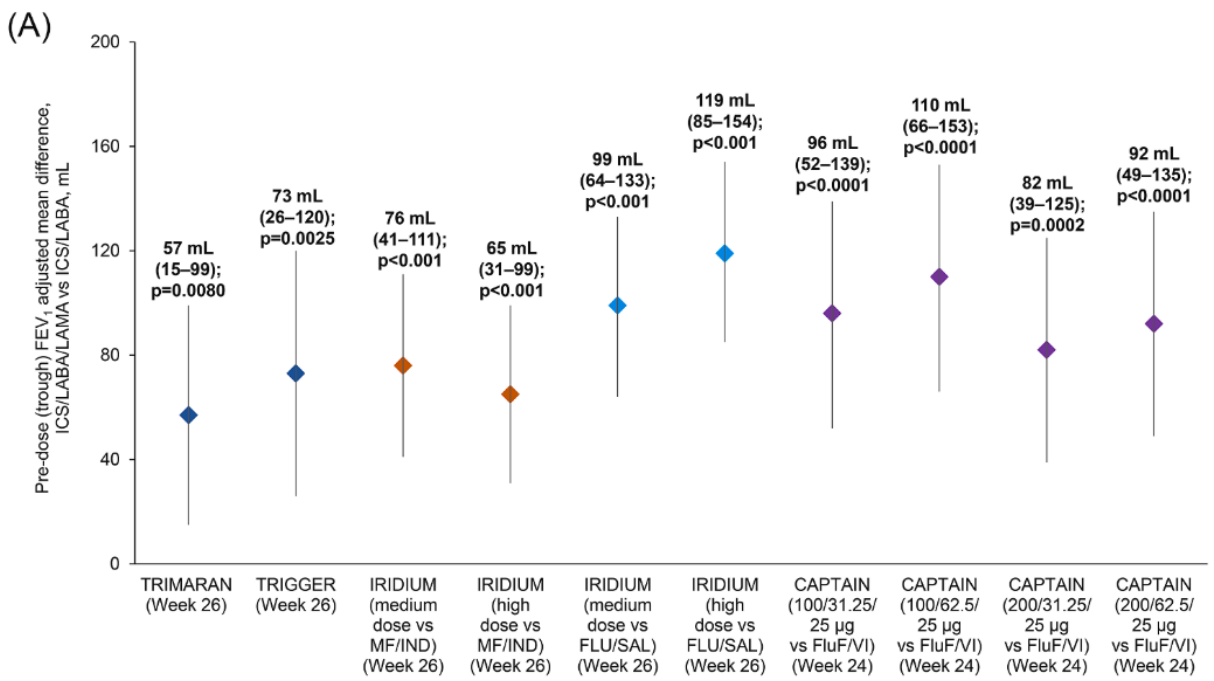
Table 3: **On-treatment adverse events in the intention-to-treat population**

Lee et al. Lancet Respir Med. 2021 Jan;9(1):69-84

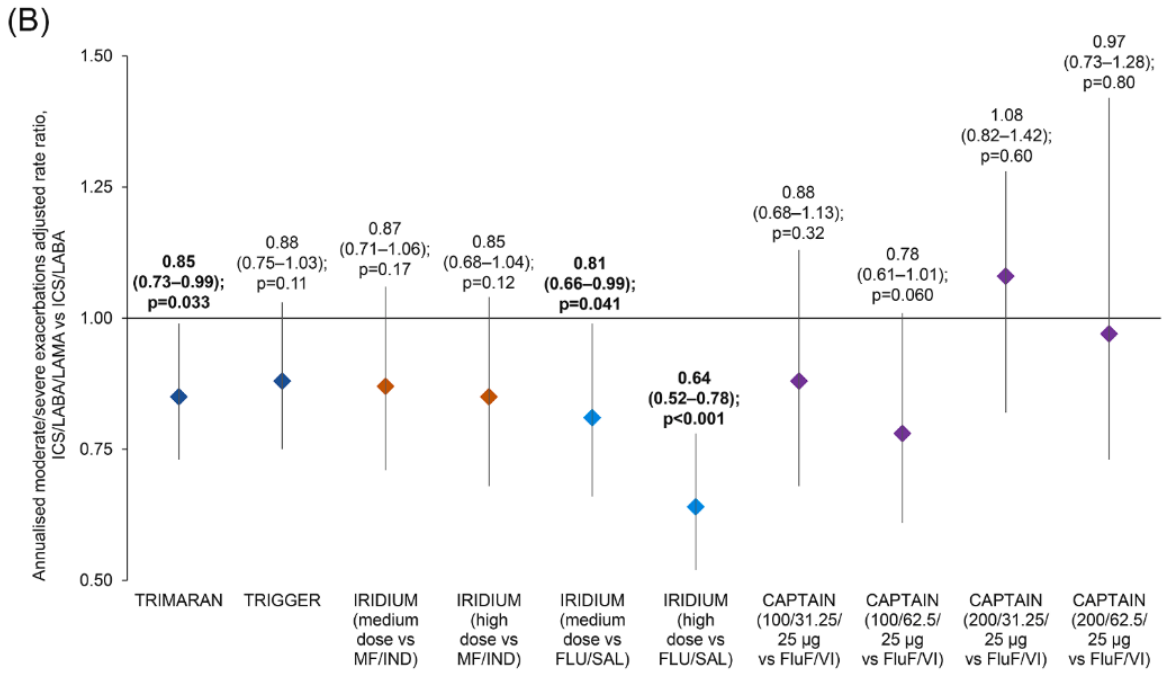
Study name	FEV1 improvement for SITT versus ICS/LABA	Reduction of moderate- severe exacerbation for SITT versus ICS/LABA
TRIMARAN ▪BDP/FF/GLY versus BDP/FF	57 mL (p = .0080) for medium dose	15% (RR 0.85, p = .033) for medium dose
TRIGGER ▪BDP/FF/GLY versus BDP/FF ▪BDP/FF/GLY versus BDP/FF+TIO	73 mL (p = .0025) for high dose – 45 mL (p = .13) for high dose	12% (RR 0.88, p = .11) for high dose 7% (RR 1·07, p = .50) for high dose
IRIDIUM ▪MF/IND/GLY versus MF/IND ▪MF/IND/GLY versus FP/SLM	• 76 mL (p < .001) for medium dose • 65 mL (p < .001) for high dose • 99 mL (p < .001) for medium dose • 119 mL (p < .001) for high dose	• 13% (RR 0.87, p = .17) for medium dose • 15% (RR 0.85, p = .12) for high dose • 19% (RR 0.81, p = .041) for medium dose • 36% (RR 0.64, p < .001) for high dose
ARGON ▪MF/IND/GLY versus FP/SLM+TIO	High- dose and medium- dose MF/IND/GLY were noninferior to high- dose FP/SLM+TIO for AQLQ (least square mean treatment difference: 0.073 and– 0.038, respectively; both p < .001). High- dose MF/IND/GLY improved trough FEV1 at Weeks 8 (Δ: 67 mL; p = .007), 16 (Δ: 66 mL; p = .007) and 24 (Δ: 96 mL; p < .001) versus high dose FP/SLM+TIO. Medium- dose MF/IND/GLY medium- dose versus high dose FP/SLM+TIO at Weeks 8 (Δ: 3 mL; p = .892), 16 (Δ: −2 mL; p = .945) and 24 (Δ: 9 mL; p = .713).	Medium- dose MF/IND/GLY versus FP/ SLM high dose+TIO • 4% increase (RR 1.04, p = .798) High- dose MF/IND/GLY versus FP/SLM high dose+TIO • 12% reduction (RR 0.88, p = .414)
CAPTAIN ▪F/UMEC/VI 100/62.5/25 versus F/VI 100/25 ▪F/UMEC/VI 200/62.5/25 versus F/VI 200/25	110 mL (66, 153; p < .001) for medium dose 92 mL (49, 135; p < .001) for high dose Adding UMEC 31.25 µg to F/VI produced similar improvements.	No statistically significant difference F/ UMEC 62.5 µg/VI versus F/VI (pooled analysis)

Virchow et al. Lancet. 2019 Nov 9;394(10210):1737-1749, Herstjens et al. Lancet Respir Med. 2020 Oct;8(10):1000-1012, Gessner et al. Respir Med. 2020 Aug-Sep;170:106021, Lee et al. Lancet Respir Med. 2021 Jan;9(1):69-84, Agusti et al. Allergy. 2022 Apr;77(4):1105-1113.

Pre-dose FEV1
ICS/LABA/LAMA vs ICS/LABA



Annualized M-S exacerbation aRR
ICS/LABA/LAMA vs ICS/LABA



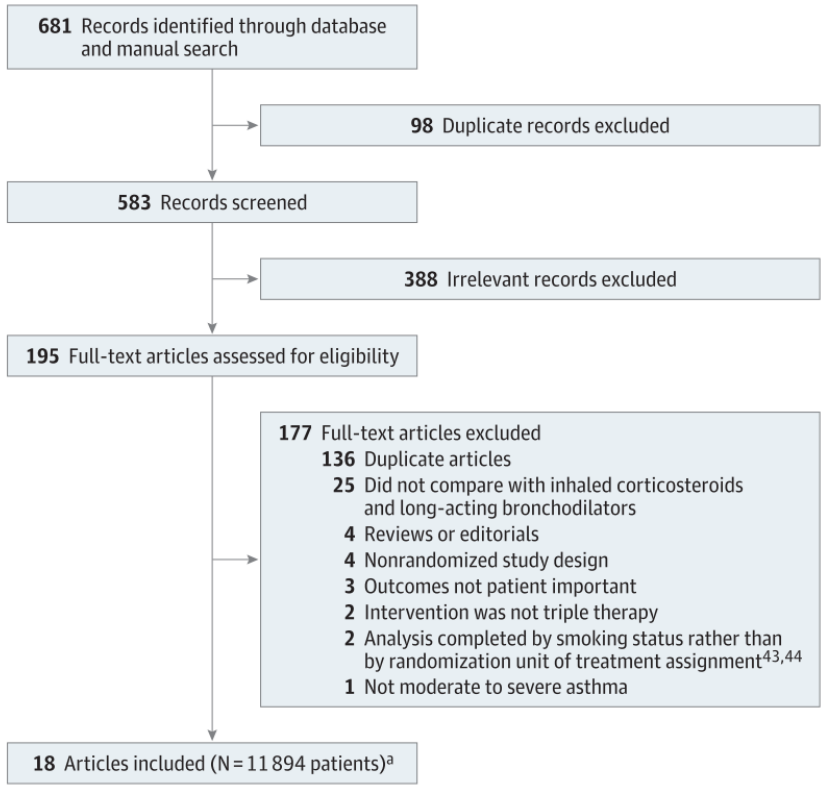
Papi et al. Eur J Intern Med. 2021 Mar;85:14-22

JAMA | Original Investigation

Triple vs Dual Inhaler Therapy and Asthma Outcomes in Moderate to Severe Asthma

A Systematic Review and Meta-analysis

Lisa H. Y. Kim, MD; Carol Saleh, MD; Anna Whalen-Browne, MD; Paul M. O'Byrne, MB; Derek K. Chu, MD, PhD



Kim et al. JAMA. 2021 Jun 22;325(24):2466-2479.

Exacerbations

A Incidence rate ratio of exacerbations

Source	Mean annualized exacerbation rate[a] Triple	Dual	Incidence rate ratio (95% CI)	Weight, %
Kerstjens et al,[46] 2012	0.53	0.66	0.80 (0.66-0.96)	21
Kerstjens et al,[55] 2020[b]	0.26	0.33	0.78 (0.61-1.00)	12
Kerstjens et al,[55] 2020[b]	0.38	0.41	0.93 (0.74-1.17)	14
Lee et al,[56] 2020[b]	0.38	0.41	1.04 (0.82-1.31)	14
Lee et al,[56] 2020[b]	0.39	0.38	0.92 (0.69-1.23)	9
Pearl Therapeutics,[57] 2017	0.44	0.55	0.79 (0.58-1.09)	8
Virchow et al,[45] 2019	0.27	0.35	0.77 (0.64-0.93)	22
Overall: $I^2 = 0\%$			0.85 (0.78-0.92)	100

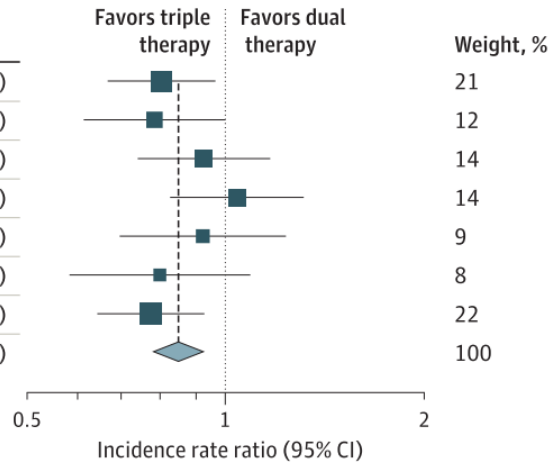
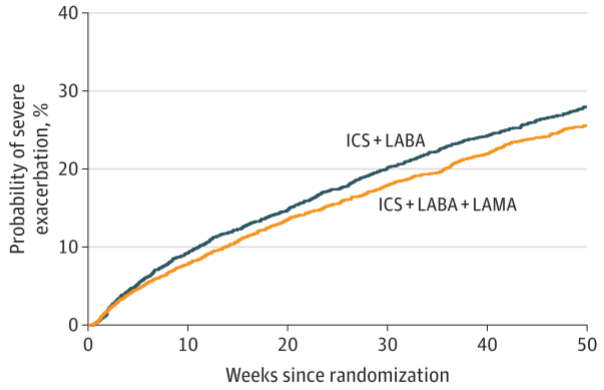


Figure 3. Kaplan-Meier Failure Curves of Time to First Severe Exacerbation in Patients Assigned to Triple vs Dual Asthma Inhaler Therapy



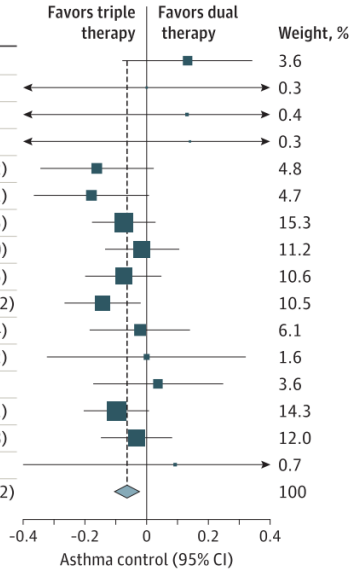
No. at risk						
ICS + LABA	4137	3650	3320	2922	2540	1760
ICS + LABA + LAMA	4159	3774	3396	2871	2332	1475
No. of studies	6	6	6	6	6	4

Kim et al. JAMA. 2021 Jun 22;325(24):2466-2479.

Asthma control & QOL

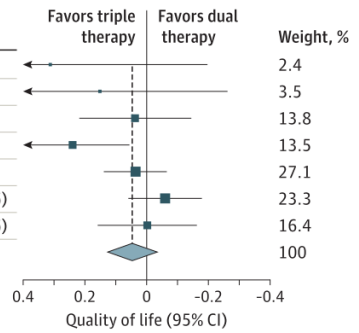
A Asthma control

Source	Scale[a]	Triple therapy No.	Triple therapy Mean (SD)	Dual therapy No.	Dual therapy Mean (SD)	Standardized mean difference (95% CI)	Weight, %
Hamelmann et al,[50] 2017	ACQ-7	256	-0.87 (0.82)	132	-0.97 (0.57)	0.13 (-0.08 to 0.34)	3.6
Ishiura et al,[52] 2019	ACT	17	0.40 (6.20)	17	0.40 (6.20)	0.00 (-0.67 to 0.67)	0.3
Ishiura et al,[53] 2020	ACQ-5	19	-0.40 (4.60)	19	-1.00 (4.60)	0.13 (-0.51 to 0.77)	0.4
Jabbal et al,[47] 2017	ACQ-7	14	-0.22 (0.44)	14	-0.28 (0.41)	0.14 (-0.60 to 0.88)	0.3
Kerstjens et al,[46] 2012[b]	ACQ-7	237	-0.71 (0.75)	222	-0.59 (0.75)	-0.16 (-0.34 to 0.02)	4.8
Kerstjens et al,[46] 2012[b]	ACQ-7	216	-0.57 (0.73)	232	-0.44 (0.74)	-0.18 (-0.36 to 0.01)	4.7
Kerstjens et al,[55] 2020[b]	ACQ-7	552	-1.09 (0.70)	1094	-1.05 (0.45)	-0.07 (-0.18 to 0.03)	15.3
Kerstjens et al,[55] 2020[b]	ACQ-7	537	-0.96 (0.67)	536	-0.96 (0.66)	-0.02 (-0.13 to 0.10)	11.2
Lee et al,[56] 2020[b]	ACQ-7	790	-0.77 (0.66)	374	-0.72 (0.66)	-0.08 (-0.20 to 0.05)	10.6
Lee et al,[56] 2020[b]	ACQ-7	784	-0.73 (0.67)	371	-0.64 (0.66)	-0.14 (-0.27 to -0.02)	10.5
Pearl Therapeutics,[57] 2017	ACQ-7	665	-0.86 (2.90)	187	-0.80 (0.77)	-0.02 (-0.18 to 0.14)	6.1
Singh et al,[59] 2014	ACQ-6	152	-0.19 (1.45)	49	-0.19 (0.55)	-0.00 (-0.32 to 0.32)	1.6
Szefler et al,[49] 2017	ACQ-7	262	-0.95 (0.73)	130	-0.97 (0.54)	0.04 (-0.17 to 0.25)	3.6
Virchow et al,[45] 2019[b]	ACQ-7	858	-0.82 (1.26)	571	-0.71 (0.73)	-0.10 (-0.20 to 0.01)	14.3
Virchow et al,[45] 2019[b]	ACQ-7	575	-0.74 (0.69)	574	-0.72 (0.70)	-0.03 (-0.15 to 0.08)	12.0
Wang et al,[60] 2015	ACT	30	-5.77 (7.87)	33	-6.38 (5.34)	0.09 (-0.40 to 0.59)	0.7
Overall: I^2=0%		5964		4555		-0.06 (-0.10 to -0.02)	100



B Quality of life

Source	Scale[a]	Triple therapy No.	Triple therapy Mean (SD)	Dual therapy No.	Dual therapy Mean (SD)	Standardized mean difference (95% CI)	Weight, %
Hoshino et al,[51] 2018	AQLQ	29	0.50 (1.00)	30	0.20 (0.90)	0.31 (-0.20 to 0.83)	2.4
Kerstjens et al,[48] 2011	Mini-AQLQ	67	0.21 (0.69)	33	0.11 (0.49)	0.15 (-0.26 to 0.57)	3.5
Kerstjens et al,[46] 2012[b]	AQLQ	237	0.55 (1.01)	222	0.51 (1.01)	0.04 (-0.15 to 0.22)	13.8
Kerstjens et al,[46] 2012[b]	AQLQ	216	0.48 (0.96)	232	0.24 (1.02)	0.24 (0.06 to 0.43)	13.5
Kerstjens et al,[55] 2020[b]	AQLQ	552	0.87 (0.82)	1093	0.83 (1.19)	0.04 (-0.07 to 0.14)	27.1
Kerstjens et al,[55] 2020[b]	AQLQ	535	0.76 (0.83)	536	0.81 (0.83)	-0.06 (-0.18 to 0.06)	23.3
Pearl Therapeutics,[57] 2017	AQLQ	667	0.95 (4.94)	188	0.96 (1.01)	-0.00 (-0.16 to 0.16)	16.4
Overall: I^2=32%		2303		2334		0.05 (-0.03 to 0.13)	100

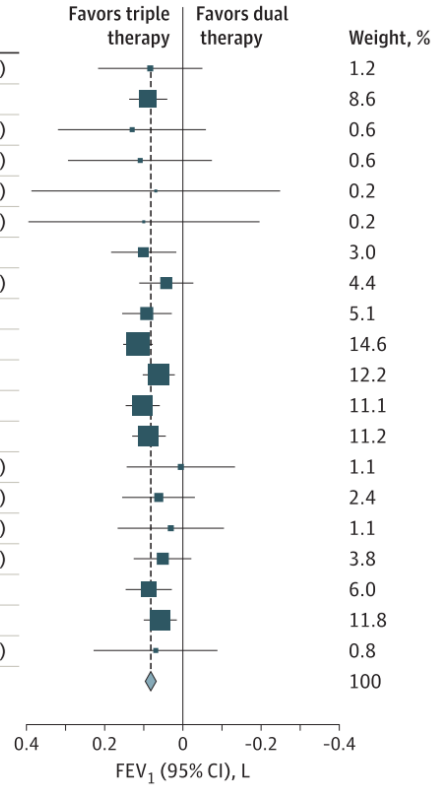


Kim et al. JAMA. 2021 Jun 22;325(24):2466-2479.

Lung function

Figure 5. Lung Function as Measured by FEV_1 in Randomized Trials of Triple vs Dual Therapy

Source	Triple therapy No.	Triple therapy FEV_1, mean (SD), L	Dual therapy No.	Dual therapy FEV_1, mean (SD), L	FEV_1, mean difference (95% CI), L	Weight, %
Hamelmann et al,[50] 2017	256	0.31 (0.78)	132	0.23 (0.55)	0.08 (-0.05 to 0.22)	1.2
Hoshino et al,[51] 2018	29	0.11 (0.08)	30	0.02 (0.11)	0.09 (0.04 to 0.14)	8.6
Ishiura et al,[52] 2019	17	0.20 (0.28)	17	0.07 (0.29)	0.13 (-0.06 to 0.32)	0.6
Ishiura et al,[53] 2020	19	0.10 (0.29)	19	-0.01 (0.29)	0.11 (-0.07 to 0.29)	0.6
Jabbal et al,[47] 2017	14	0.15 (0.43)	14	0.08 (0.43)	0.07 (-0.25 to 0.39)	0.2
Jabbal et al,[54] 2020	16	0.21 (0.43)	16	0.11 (0.42)	0.10 (-0.20 to 0.40)	0.2
Kerstjens et al,[48] 2011	67	0.15 (0.25)	33	0.05 (0.17)	0.10 (0.02 to 0.18)	3.0
Kerstjens et al,[46] 2012[a]	237	0.13 (0.39)	222	0.09 (0.37)	0.04 (-0.03 to 0.11)	4.4
Kerstjens et al,[46] 2012[a]	216	0.16 (0.34)	232	0.06 (0.35)	0.09 (0.03 to 0.16)	5.1
Kerstjens et al,[55] 2020[a]	614	0.45 (0.37)	1213	0.34 (0.42)	0.11 (0.08 to 0.15)	14.6
Kerstjens et al,[55] 2020[a]	614	0.39 (0.35)	602	0.33 (0.38)	0.06 (0.02 to 0.10)	12.2
Lee et al,[56] 2020[a]	803	0.13 (0.44)	400	0.02 (0.31)	0.10 (0.06 to 0.15)	11.1
Lee et al,[56] 2020[a]	804	0.16 (0.44)	403	0.08 (0.31)	0.09 (0.04 to 0.13)	11.2
Pearl Therapeutics,[57] 2017	702	0.13 (1.77)	193	0.13 (0.32)	0.01 (-0.13 to 0.14)	1.1
Ohta et al,[58] 2015	228	0.14 (0.41)	57	0.08 (0.29)	0.06 (-0.03 to 0.15)	2.4
Singh et al,[59] 2014	152	0.14 (0.70)	49	0.11 (0.28)	0.03 (-0.11 to 0.17)	1.1
Szefler et al,[49] 2017	263	0.19 (0.43)	130	0.14 (0.31)	0.05 (-0.02 to 0.13)	3.8
Virchow et al,[45] 2019[a]	826	0.24 (0.71)	547	0.16 (0.41)	0.09 (0.03 to 0.15)	6.0
Virchow et al,[45] 2019[a]	557	0.18 (0.36)	553	0.13 (0.36)	0.06 (0.02 to 0.10)	11.8
Zhang et al,[62] 2018	40	0.75 (0.44)	40	0.68 (0.26)	0.07 (-0.09 to 0.23)	0.8
Overall: $I^2 = 0\%$	6474		4902		0.08 (0.07 to 0.10)	100



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EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
P. ROGLIANI ET AL.

Triple therapy in uncontrolled asthma: a network meta-analysis of phase III studies

Paola Rogliani [1], Beatrice Ludovica Ritondo [1] and Luigino Calzetta [2]

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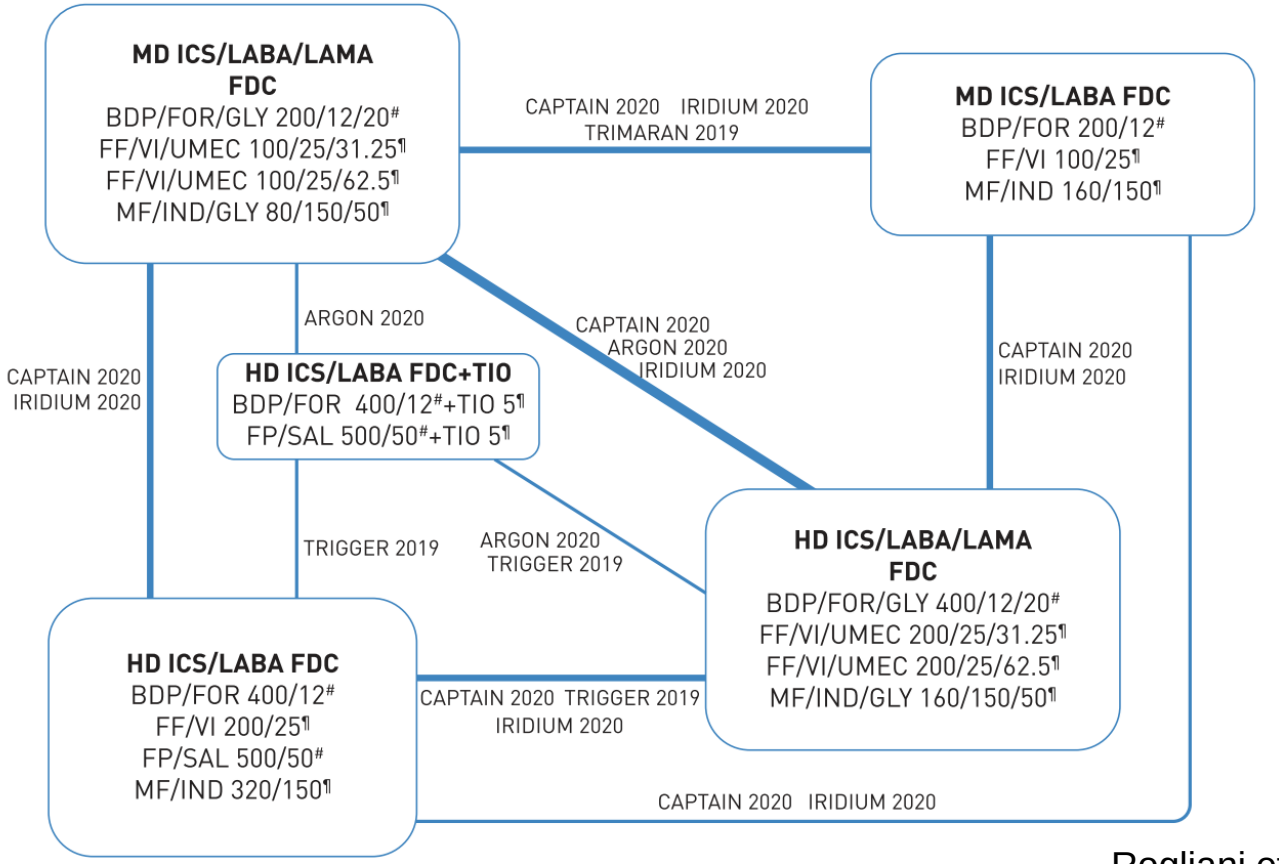
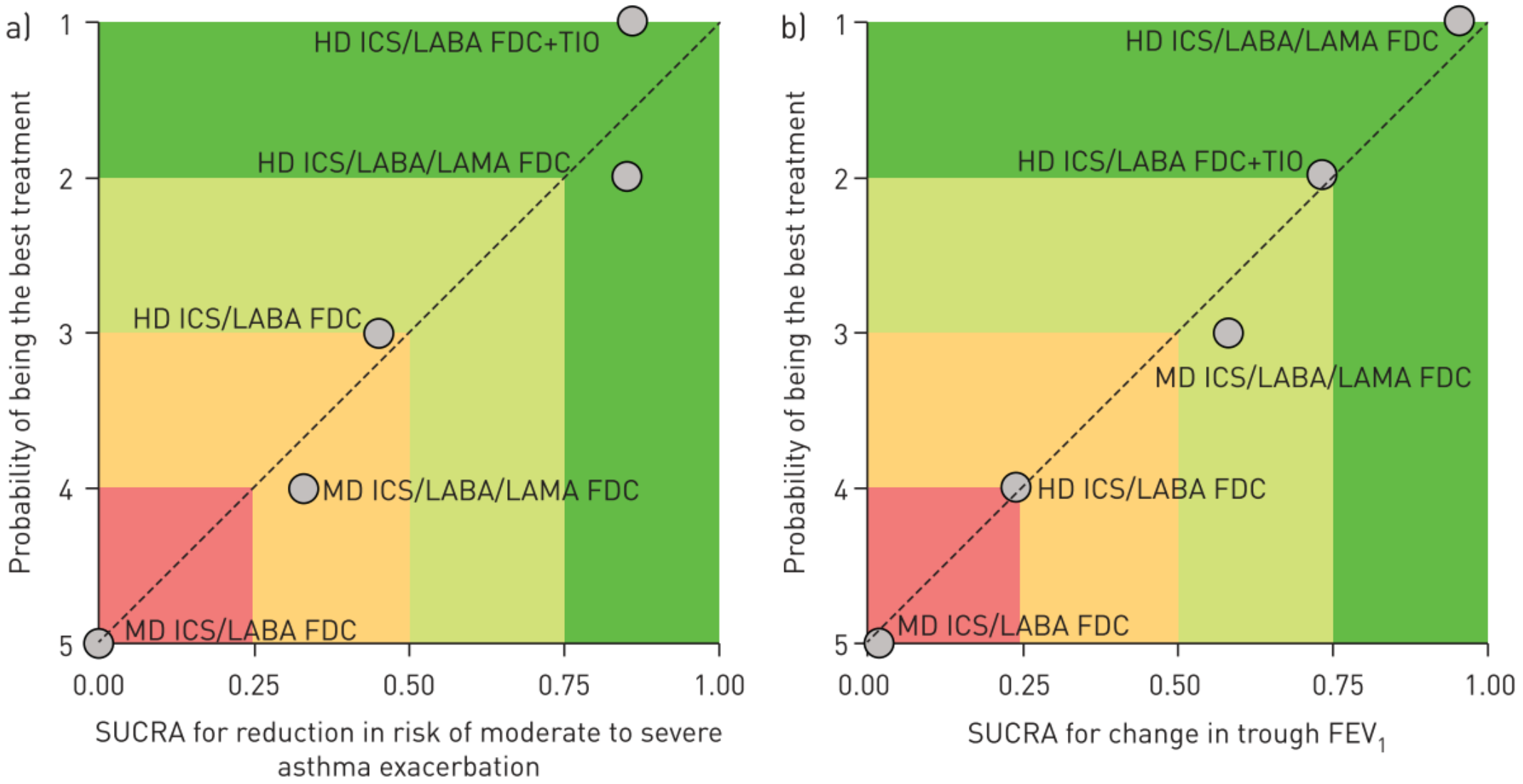


Rogliani et al. Eur Respir J. 2021 Sep 2;58(3):2004233.



Rogliani et al. Eur Respir J. 2021 Sep 2;58(3):2004233.

Which patients more likely to be benefit from Triple Thearpy?

Respiratory Medicine 117 (2016) 198–206

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Respiratory Medicine

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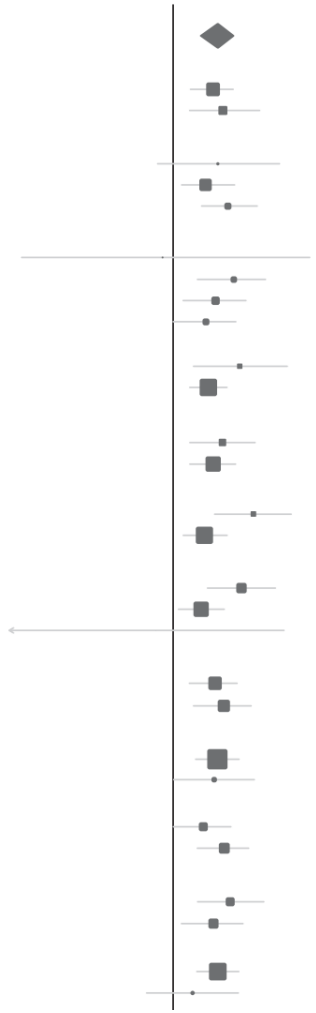
Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic status

Huib A.M. Kerstjens [a, *], Petra Moroni-Zentgraf [b], Donald P. Tashkin [c], Ronald Dahl [d], Pierluigi Paggiaro [e], Mark Vandewalker [f], Hendrik Schmidt [g], Michael Engel [b], Eric D. Bateman [h]

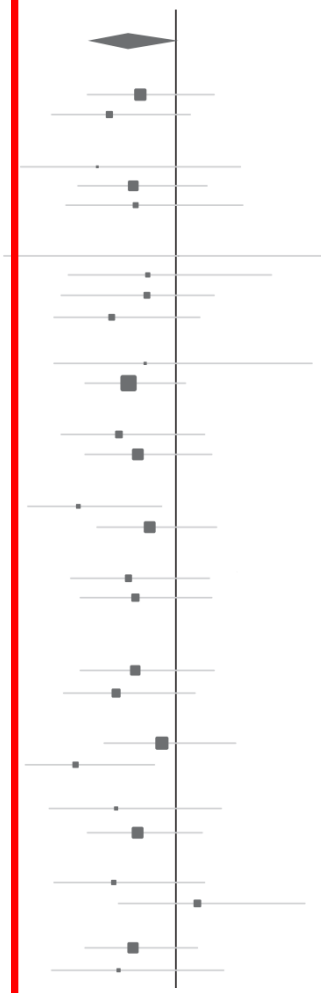
Kerstjens et al. Respir Med. 2016 Aug;117:198-206.

	Adjusted mean difference, mL (95% CI)	Patients: placebo/ tiotropium 5 µg	Interaction p value
Overall	**110 (63–158)**	**429/422**	
Gender			
Female	99 (48–151)	266/249	0.17
Male	130 (41–220)	163/173	
Age, years			
<40	115 (–37 to 267)	60/61	0.57
40–60	89 (24–155)	225/242	
>60	138 (75–201)	144/119	
Body mass index, kg/m^2			
<20	–18 (–378 to 343)	18/13	0.39
20–<25	154 (70–238)	127/119	
25–<30	108 (26–190)	160/154	
⩾30	81 (1–161)	124/136	
Disease duration, years			
5–<20	169 (52–285)	96/102	0.49
⩾20	90 (40–140)	333/320	
Age at asthma onset, years			
<18	126 (42–209)	143/135	0.30
⩾18	101 (43–159)	286/287	
Smoking status			
Ex-smoker	201 (104–299)	95/111	0.20
Never smoked	79 (25–134)	334/311	
FEV_1 % predicted at screening			
<60%	170 (86–254)	171/165	0.15
60–<80%	70 (14–127)	251/255	
⩾80%	–84 (–443 to 275)	7/2	
FEV_1 reversibility (⩾12% and ⩾200 mL)			
No	104 (44–165)	216/230	0.21
Yes	128 (55–200)	213/192	
LTRA use at baseline			
No	111 (57–165)	329/340	0.57
Yes	103 (2–203)	100/82	
Allergic status by clinician judgment			
No	76 (3–149)	166/169	0.21
Yes	130 (68–192)	263/253	
Serum IgE			
⩽430 µg/L	148 (73–224)	167/169	0.74
>430 µg/L	102 (27–176)	180/197	
Blood eosinophils			
⩽0.6×10^9/L	115 (63–167)	336/318	0.70
>0.6×10^9/L	58 (–64 to 180)	82/93	



Peak FEV1 at 24 weeks

	HR (95% CI)	Patients with event: placebo/ tiotropium 5 µg	Interaction p value
Overall	**0.80 (0.63–1.01)**	**149/122**	
Gender			
Female	0.85 (0.63–1.16)	93/78	0.49
Male	0.72 (0.48–1.06)	56/44	
Age, years			
<40	0.67 (0.35–1.27)	23/16	0.83
40–60	0.82 (0.59–1.13)	78/71	
>60	0.83 (0.54–1.28)	48/35	
Body mass index, kg/m^2			
<20	1.01 (0.28–3.63)	6/4	0.94
20–<25	0.88 (0.55–1.40)	39/33	
25–<30	0.77 (0.52–1.16)	53/42	
⩾30	0.73 (0.49–1.10)	51/43	
Disease duration, years			
5–<20	0.87 (0.49–1.57)	23/22	0.79
⩾20	0.80 (0.62–1.04)	126/100	
Age at asthma onset, years			
<18	0.76 (0.52–1.12)	62/45	0.59
⩾18	0.84 (0.62–1.15)	87/77	
Smoking status			
Ex-smoker	0.59 (0.38–0.94)	43/32	0.15
Never smoked	0.89 (0.67–1.17)	106/90	
FEV_1 % predicted at screening			
<60%	0.80 (0.56–1.14)	68/55	0.98
60–<80%	0.83 (0.60–1.15)	77/67	
⩾80%	0.00 (0.00–NC)	4/0	
FEV_1 reversibility (⩾12% and ⩾200 mL)			
No	0.83 (0.60–1.16)	75/70	0.66
Yes	0.75 (0.53–1.08)	74/52	
LTRA use at baseline			
No	0.94 (0.70–1.25)	94/92	0.08
Yes	0.58 (0.37–0.91)	55/30	
Allergic status by clinician judgment			
No	0.75 (0.47–1.19)	40/33	0.68
Yes	0.84 (0.63–1.11)	109/89	
Serum IgE			
⩽430 µg/L	0.74 (0.49–1.12)	52/41	0.17
>430 µg/L	1.09 (0.76–1.54)	58/68	
Blood eosinophils			
⩽0.6×10^9/L	0.82 (0.62–1.09)	104/85	0.75
>0.6×10^9/L	0.76 (0.48–1.20)	39/35	



Time-to-first severe exacerbation over 48 weeks

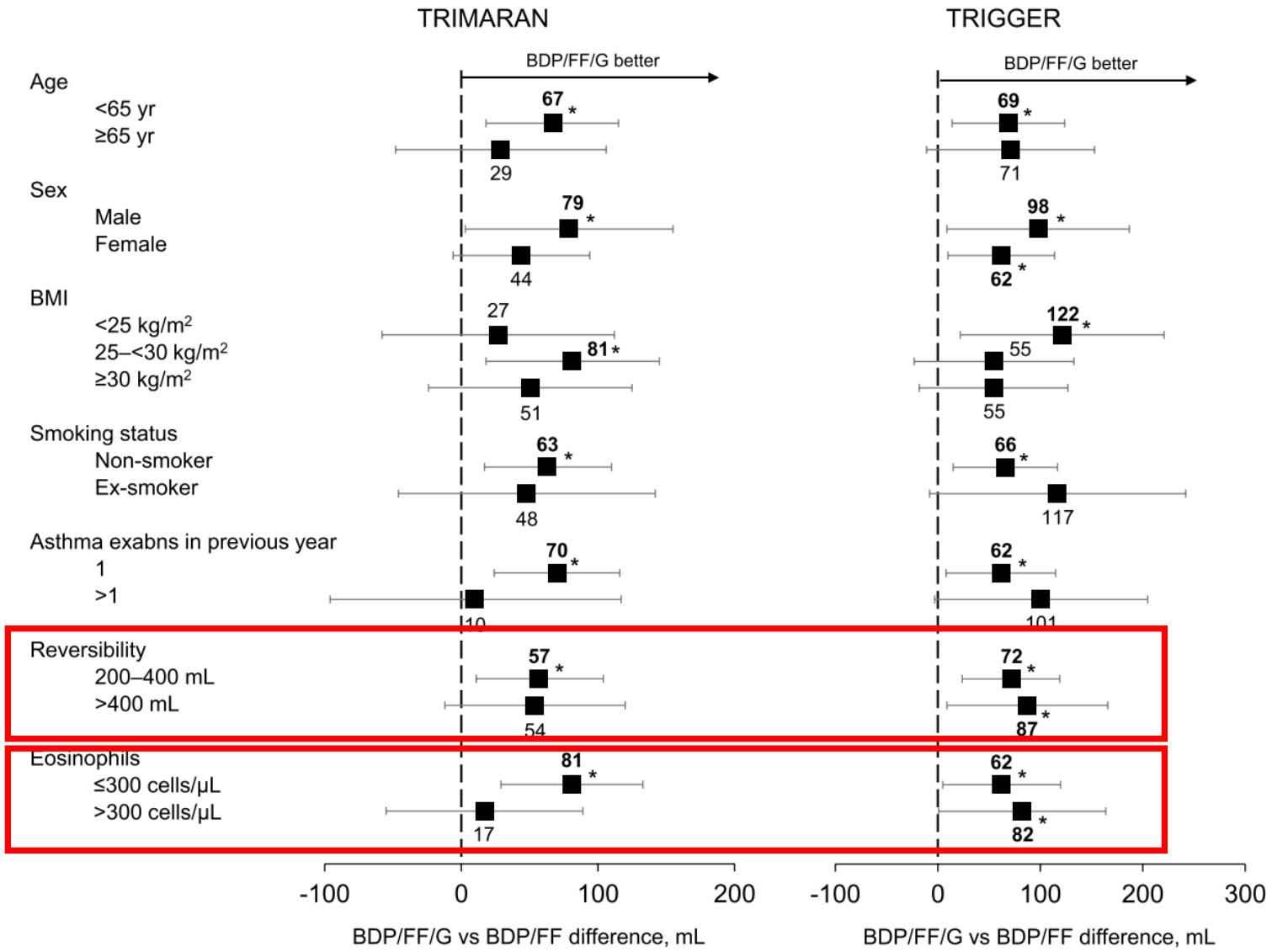
Singh et al. Respir Res (2020) 21:285
https://doi.org/10.1186/s12931-020-01558-y

Respiratory Research

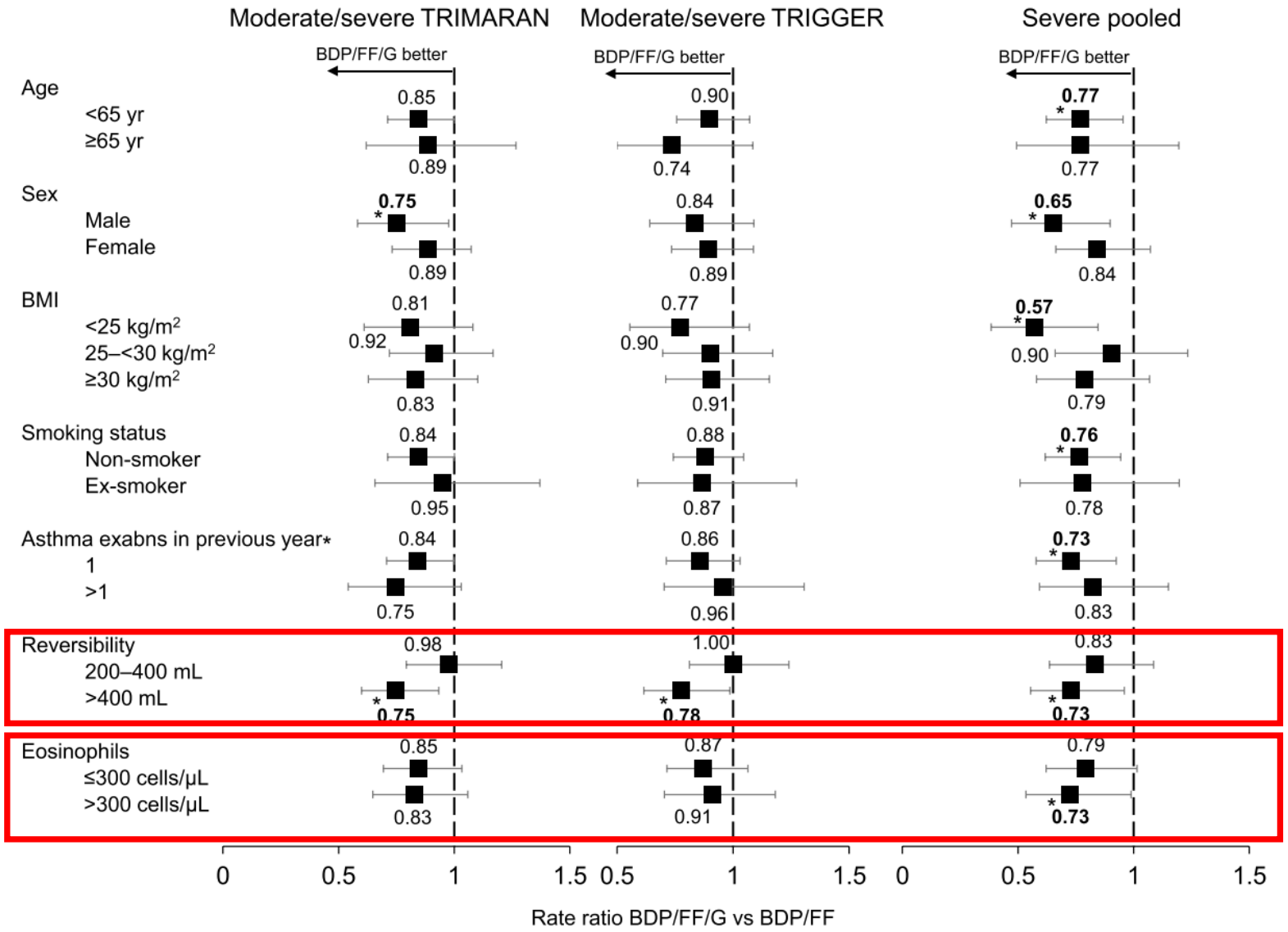
RESEARCH Open Access

Determinants of response to inhaled extrafine triple therapy in asthma: analyses of TRIMARAN and TRIGGER

Dave Singh[1*], Johann Christian Virchow[2], Giorgio Walter Canonica[3], Andrea Vele[4], Maxim Kots[4], George Georges[4] and Alberto Papi[5]



Singh et al. Respir Res. 2020 Oct 29;21(1):285



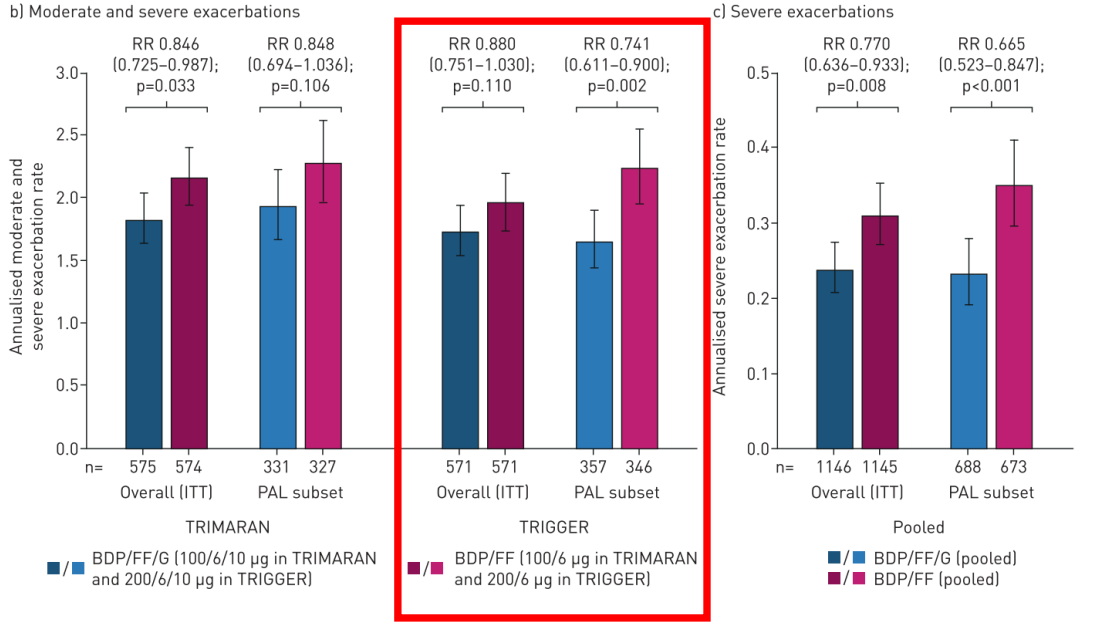
Singh et al. Respir Res. 2020 Oct 29;21(1):285

Extrafine triple therapy in patients with asthma and persistent airflow limitation

PAL :
Post-bronchodilator FEV1 ⩽80% +
FEV1/FVC ⩽0.7

a)

	TRIMARAN		TRIGGER	
	Overall (ITT) (n=1149)	PAL subset (n=658)	Overall (ITT) (n=1142)	PAL subset (n=703)
Pre-dose FEV_1 mL	57 (15–99); p=0.008	89 (38–140); p<0.001	73 (26–120); p=0.003	130 (79–181); p<0.001
Peak FEV_1 mL	84 (40–129); p<0.001	119 (64–175); p<0.001	105 (57–153); p<0.001	154 (100–208); p<0.001
PEF $L \cdot min^{-1}$	8.5 (3.6–13.3); p<0.001	11.3 (5.3–17.2); p<0.001	7.8 (3.0–12.6); p=0.001	14.6 (8.8–20.5); p<0.001



Singh et al. Eur Respir J. 2020 Sep 24;56(3):2000476

Summary

Summary

- Unmet needs in asthma care

  ; half of the patients are currently not well-controlled
- LAMA has shown additive effects on lung function, asthma control, symptom and exacerbation rates
- SITT > MITT : adherence, exacerbation, cost
- 5 key RCTs → SITT shown improvement in lung function, asthma control, symptoms and exacerbation rates
- Bronchodilator response (+), persistent airflow obstruction

  → may be indicators for more favorable outcome