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Normal FEV₁ without Reversibility in Asthma Trials: A Placebo Patient-Level Meta-Analysis

Simon Couillard^{1,2,3}, Samuel Mailhot-Larouche¹, Fleur L. Meulmeester², Guy Brusselle⁴, Philippe Lachapelle¹, Richard W. Beasley⁵, Jacob K. Sont⁶, Ewout W. Steyerberg⁶, Ian D. Pavord³, Njira Lugogo⁷, and the ORACLE2 Consortium

¹Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Sherbrooke, Québec, Canada; ²Department of Biomedical Data Sciences, Leiden University Medical Centre, Leiden, the Netherlands; ³Respiratory Medicine Unit and Oxford Respiratory National Institute for Health and Care Research Biomedical Research Council, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom; ⁴Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium; ⁵Medical Research Institute of New Zealand, Wellington, New Zealand; ⁶Julius Center, University Medical Center Utrecht, Utrecht, the Netherlands; and ⁷Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, Michigan

ORCID IDs: 0000-0002-4057-6886 (S.C.); 0000-0002-3028-2315 (S.M.-L.); 0000-0002-8910-9795 (F.L.M.); 0000-0001-7021-8505 (G.B.); 0000-0001-9290-1823 (P.L.); 0000-0003-0337-406X (R.W.B.); 0000-0002-5840-0651 (J.K.S.); 0000-0002-7787-0122 (E.W.S.); 0000-0002-4288-5973 (I.D.P.); 0000-0002-0235-7105 (N.L.).

To the Editor:

Randomized controlled trials (RCTs) in asthma typically exclude patients with normal spirometry and lack of bronchodilator reversibility. However, these and other inclusion criteria impede trial recruitment (screen failure rates are often >50%) (1), may be unnecessary if other high-risk criteria are met (2, 3), limit generalizability to real-world populations (>90% of such patients are ineligible for RCTs) (4), and potentially reduce treatment benefits by focusing on patients with evidence of damage (5, 6).

The risk of asthma attacks increases with a previous attack history, greater disease severity, and elevated type-2 biomarkers (blood eosinophils and fractional exhaled nitric oxide) (2, 7). Similarly, FEV₁ decline relates to such factors (3). Both asthma attacks and severe asthma may occur without persistent airflow limitation, and better baseline lung function increases the likelihood

of clinical remission with biologic therapy (5, 6). Moreover, bronchodilator reversibility is increasingly questioned both as a distinguishing feature of airway diseases and as a risk factor for asthma attacks (2, 8), especially given its lack of predictive value for treatment response (1, 9).

We aimed to assess the occurrence of clinically relevant asthma outcomes (attacks and FEV₁ decline) in the placebo arms of RCTs despite near-normal or normal spirometry, including lack of bronchodilator reversibility, at baseline.

Methods

We analyzed outcomes of placebo-treated patients with an FEV₁ ≥80% predicted and bronchodilator reversibility <12% (henceforth, “normal FEV₁ without reversibility”) in moderate-to-severe asthma from the ORACLE2 (Oxford Asthma Attack Risk Scale) meta-analysis (2, 10). The ORACLE2 patient-level meta-analysis included 6,513 control arm participants aged ≥12 years from 22 RCTs (PROSPERO#: CRD42021245337, protocol published and initial analysis reported) (2, 10). These trials examined fixed treatment effects on severe asthma attacks (≥3 d oral corticosteroids) over ≥6 months. Statistical analyses described were performed using R 4.4.2 (code on GitHub; <https://github.com/simoncouillard/ORACLE2-Screen-Failure-analysis/>). We analyzed 10 multiple imputed datasets (2), pooling results using Rubin’s rules. We first assessed the association of normal FEV₁ without reversibility compared with patients not meeting the definition (i.e., patients with FEV₁ <80% or reversibility ≥12%) with future asthma attacks using multivariable negative binomial regression, adjusting for sex, age, Global Initiative for Asthma treatment step (2), prior-year attack count, baseline lung function (% FEV₁, % FEV₁/FVC, % FEV₁ reversibility), symptom scores (5-item Asthma Control Questionnaire), type-2 biomarkers (log-transformed: blood eosinophils, fractional exhaled nitric oxide), and enrolling trial. Second, we analyzed prebronchodilator FEV₁ (liters) change from baseline to 52 weeks with placebo, adjusting for the same covariates.

Results

We identified 261 placebo-treated patients with normal FEV₁ without reversibility (215 attacks, 229 patient-years) from 12 trials contributing at least one such patient. Comparisons were made with the remaining 3,394 patients with moderate-to-severe asthma (3,343 attacks, 3,155 patient-years) from those same trials. Fifty-two-week prebronchodilator FEV₁ was available for 1,966 (54%) patients (Table 1).

Patients who had normal FEV₁ without reversibility had better lung function (FEV₁, FEV₁/FVC) and lower post-bronchodilator reversibility, were younger, and had lower blood eosinophil counts (Table 1). The proportion of patients with normal FEV₁ without reversibility ranged from 2% (QUEST [Evaluation of Dupilumab in Patients With Persistent Asthma]) to 66% (AZISAST [AZITHromycin in Severe ASThma] Study), significantly different between the two groups. However, the difference per trial varied by <15%, and regression models were adjusted for the participants’ enrolling trial.

Patients who had normal FEV₁ without reversibility trended toward a 23% (95% confidence interval [CI], −3% to 56%) higher attack risk than patients with low FEV₁ and/or high reversibility, although this was not statistically significant (Figure 1). Predicted

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Author Contributions: Study concept and design: S.C. and N.L. Data analysis: S.C., S.M.-L., and F.L.M. Interpretation of data: S.C., S.M.-L., F.L.M., G.B., P.L., R.W.B., J.K.S., E.W.S., I.D.P., and N.L. Investigators and/or study sponsors of the underlying trials contributed individual participant data: all authors and the ORACLE2 consortium (see reference 2). Drafting of the manuscript: S.C. Approved and reviewed the final manuscript: all authors. Guarantor of the study: S.C.

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Table 1. Baseline Characteristics and Trial Outcomes of Normal FEV₁ without Reversibility versus Other Moderate-to-Severe Asthma Randomized Controlled Trial Placebo-treated Patients

	FEV ₁ ≥ 80%, REV < 12% (n = 261)	Other Placebo Arm Patients (n = 3,394)	P Value
Age, mean (SD)	44 (16)	50 (13)	<0.001
Sex female, n (%)	179 (68.6)	2,209 (65.1)	ns
GINA Treatment step, n (%)			
Step 3	1 (0.4)	33 (1.0)	0.03
Step 4	96 (36.8)	1,502 (44.3)	
Step 5	164 (62.8)	1,859 (54.8)	
Severe asthma attacks in last year, mean (SD)	2.32 (1.08)	2.24 (1.56)	ns
FEV ₁ preBD baseline, % predicted, mean (SD)	88.82 (7.51)	59.43 (13.16)	<0.001
FEV ₁ reversibility baseline, %, mean (SD)	3.36 (7.10)	20.62 (19.28)	<0.001
FEV ₁ /FVC ratio, %, mean (SD)	75.94 (8.06)	63.26 (12.01)	<0.001
ACQ-5 baseline, mean (SD)	2.61 (1.04)	2.72 (0.90)	ns
F _{ENO} , ppb, median (IQR)	22 (11 to 33)	24 (9 to 39)	ns*
Blood eosinophils, ×10 ⁹ /L, median (IQR)	0.21 (0.08 to 0.33)	0.25 (0.10 to 0.40)	0.001*
Enrolling trial			
AZISAST	33 (12.6)	21 (0.6)	<0.001
BENRAP2B	36 (13.8)	175 (5.2)	
COSTA	2 (0.8)	143 (4.2)	
DREAM	1 (0.4)	154 (4.5)	
EXTRA	41 (15.7)	379 (11.2)	
LUSTER 1	19 (7.3)	279 (8.2)	
LUSTER 2	9 (3.4)	278 (8.2)	
NAVIGATOR	72 (27.6)	445 (13.1)	
PATHWAY	5 (1.9)	128 (3.8)	
QUEST	4 (1.5)	630 (18.6)	
STRATOS 1	18 (6.9)	370 (10.9)	
STRATOS 2	21 (8.0)	392 (11.5)	
In-trial severe asthma attacks, n	215	3,343	—
Total follow-up in patient-years, n	228.8	3,155.0	—
Unadjusted annualized asthma attack rate	0.94	1.06	—
Unadjusted ΔFEV ₁ preBD at 52 wk, L, mean (SD)	−0.10 (0.43)	0.14 (0.39)	<0.001
Missing ΔFEV ₁ data, n (%)	127 (49)	1,562 (46)	ns

Definition of abbreviations: ACQ5 = Asthma Control Questionnaire (5-item); BD = bronchodilator; F_{ENO} = fractional exhaled nitric oxide; GINA = Global Initiative for Asthma; ns = not significant ($P \geq 0.05$).

*P values for F_{ENO} and Eosinophils are *t* tests done on logged values.

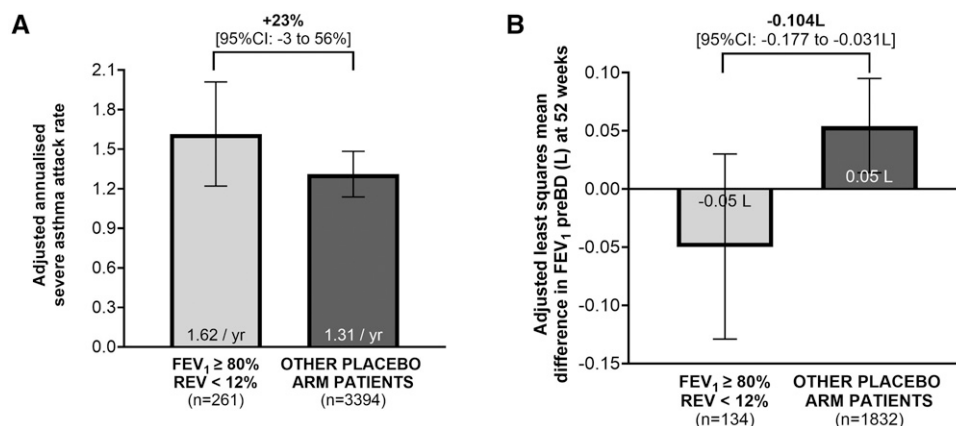


Figure 1. (A) Asthma attack rate and (B) 52-week FEV₁ change for placebo arm trial patients with normal FEV₁ without reversibility versus other placebo-treated trial participants with moderate-to-severe asthma. The multivariable models adjusted for age, sex, Global Initiative for Asthma treatment step, asthma attack history (number in previous year), FEV₁, FEV₁/FVC ratio, FEV₁ reversibility post-bronchodilator, blood eosinophils, fractional exhaled nitric oxide, and enrolled trial. CI = confidence interval; preBD = prebronchodilator; REV = reversibility.

annualized attack rates were 1.61 (1.22 to 2.01) in patients with normal FEV₁ without reversibility versus 1.31 (1.14 to 1.48) for other patients, respectively (Figure 1). The higher adjusted predicted rates compared with crude observed rates (Table 1) reflect adjustment for baseline differences between groups, standardizing both to the average risk profile of the study population and using the largest contributing trial (NAVIGATOR [Study to Evaluate Tezepelumab in Adults & Adolescents With Severe Uncontrolled Asthma]) as the reference. Similar to our previous report (2), blood eosinophil count, fractional exhaled nitric oxide, asthma attack history, disease severity, and symptoms (5-item Asthma Control Questionnaire score) were key predictors of asthma attacks in the multivariable model. Three sensitivity analyses yielded adjusted rate ratios of: 1) 0.96 (0.61 to 1.49) (excluding continuous baseline lung function adjustments), 2) 1.04 (0.67 to 1.62) (high-FEV₁ only, *n* = 356), and 3) 1.17 (0.77 to 1.80) (low-reversibility only, *n* = 1,333).

Patients with normal FEV₁ without reversibility showed significantly greater FEV₁ decline over 12 months (−0.050 [−0.129 to 0.030] vs. +0.054 [0.014 to 0.095] L; adjusted least squares mean difference, −0.104 [−0.177 to −0.031] L) (Figure 1).

Discussion

In this patient-level meta-analysis of RCT placebo arms for moderate-to-severe asthma, we found that patients with a baseline FEV₁ ≥80% without reversibility who otherwise met criteria for inclusion in the trial had a nonsignificant trend toward increased asthma attack risk and significantly greater lung function decline. Patients with normal FEV₁ without reversibility are typically excluded from trials (2, 4). Our findings do not support the view that these patients are low risk when compared with patients with classic obstructive patterns.

These findings challenge the dogma that airflow limitation and reversibility are necessary markers of definite and/or high-risk asthma for trial readout. Second, they suggest that current enrollment criteria excluding an asthma phenotype with preserved lung function but poor prognosis—potentially leaving out patients with traits that predict benefit from novel therapies, such as prior asthma attacks and other patient characteristics (2). Notably, the primary analysis, adjusting for baseline lung function, suggests only modest increased asthma attack risk. This concurs with our previous report (2) on greater asthma attack risk with lower reversibility.

There are several limitations to our study. First, we analyzed a relatively small subgroup of patients with near-normal spirometry based on FEV₁ and post-bronchodilator reversibility, not FEV₁/FVC, although we adjusted for the latter. In this group of 261 patients, 215 severe asthma attacks occurred, and 134 had 52-week FEV₁ data, providing sufficient power for multivariable modeling. These patients' normal FEV₁ without reversibility values represented either enrollment after rescreening or participation in trials with less stringent lung function parameters. Second, the increased risk estimates for FEV₁ decline in patients with normal FEV₁ without reversibility may be explained by regression to the mean, despite adjusting for baseline FEV₁. This aligns with higher attack risk despite similar history, further suggesting that patients with normal FEV₁ without reversibility may exhibit other high-risk features (e.g., raised type-2 biomarkers). Third, we acknowledge that, in many cases, these patients would have had at least one screening or randomization spirometry satisfying inclusion criteria. Nevertheless, the fact that the data extraction identified normal or near-normal spirometry values

within the prerandomization timeframe suggests that these patients were indeed “near screen failures.” Finally, our analysis was *post hoc* using placebo or control arms from a large patient-level meta-analysis, without intervention arm data, and not entirely representative of real-world asthma (10).

Our findings support broader inclusion in asthma trials to better represent the full spectrum of disease. A requirement for abnormal spirometry may miss high-risk patients who may derive more therapeutic benefits and in whom decline in FEV₁ is particularly likely to be seen. Integrating multiple risk factors may better identify suitable trial populations and improve generalizability to real-world settings. Crucially, restricting trial inclusion to patients who have experienced extensive damage from their underlying airway disease is unattractive for all those who are involved or benefit from RCTs: participants, investigators, real-world patients requesting therapeutic decisions based on relevant evidence, payers expecting optimal care before permanent morbidity occurs, and drug developers striving to achieve the best outcomes.

In conclusion, patients with moderate-to-severe asthma and normal FEV₁ without reversibility represent an understudied subgroup with measurable risk. Their exclusion from drug development clinical trials may leave important knowledge gaps regarding treatment efficacy across asthma populations. Future trials should consider broadening eligibility to assess emerging therapies before damage occurs, especially in those at greatest attack risk and on-treatment remission likelihood (6, 11). ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Correspondence and requests for reprints should be addressed to Simon Couillard, M.D., Centre Hospitalier Universitaire de Sherbrooke, 3001, 12^e Avenue Nord, pièce 2616, Sherbrooke, QC, J1H 5N4 Canada. Email: s.couillard@usherbrooke.ca.

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Premorbid Metabolic Syndrome Is Associated with the Hypoinflammatory Phenotype in Acute Respiratory Distress Syndrome and Sepsis

Avery M. Bogart^{1,4}, Sarah N. Obeidalla³, Rombout B. E. van Amstel⁵, Olaf Cremer^{5,6}, Lieuwe D. J. Bos⁵, Brian Bartek⁷, Pratik S. Sinha⁷, Carolyn S. Calfee^{8,9}, V. Eric Kerchberger^{2,3}, and Lorraine B. Ware^{1,3}; the MARS Consortium

¹Department of Pathology, Microbiology, and Immunology, ²Department of Biomedical Informatics, and ³Division of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee; ⁴Vanderbilt University School of Medicine, Nashville, Tennessee; ⁵Department of Intensive Care Medicine, Amsterdam University Medical Center, Locatie Amsterdam Medical Center, Amsterdam, the Netherlands; ⁶Department of Intensive Care, University Medical Center Utrecht, Utrecht, the Netherlands; ⁷Division of Clinical and Translational Research, Department of Anesthesia, Washington University in St Louis, St. Louis, Missouri; and ⁸Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, Department of Medicine and ⁹Department of Anesthesia, University of California, San Francisco, San Francisco, California

ORCID IDs: 0000-0002-3912-3177 (A.M.B.); 0000-0001-9296-8518 (R.B.E.v.A.); 0000-0002-0342-1965 (V.E.K.); 0000-0002-9429-4702 (L.B.W.).

To the Editor:

Sepsis and acute respiratory distress syndrome (ARDS) pose a substantial burden to public health (1). Recent work identified two phenotypes, hyper- and hypoinflammatory, in ARDS and sepsis

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(2, 3). Patients with the hyperinflammatory phenotype have greater illness severity and mortality, as well as differential responses to treatment (2–4). However, the mechanisms driving the separation between these phenotypes is unclear. Our study sought to provide insight into the heterogeneity of host responses in critical illness by defining if and how patient-specific factors associate with either phenotype. Preexisting medical conditions such as metabolic syndrome (MetS) could contribute to critical illness phenotypes by influencing the inflammatory response to infection. MetS is characterized by a chronic, low-grade inflammatory state, which could modify the immune response to an acute insult (5). A recent study of adults with coronavirus disease (COVID-19) found that MetS was associated with increased risks for ARDS, severe illness, and death (5). We also previously reported that chronic hyperglycemia, a feature of MetS, is associated with increased illness severity and the risk for ARDS in patients with sepsis (6). Given that critically ill patients with the hyperinflammatory phenotype similarly have worse clinical outcomes, we hypothesized that premorbid MetS would increase the risk for this phenotype among patients with ARDS or sepsis. Some of these results were previously reported in abstracts (7, 8).

Methods

We studied 3,142 patients with sepsis or ARDS from three prospective cohorts of critically ill adults: VALID (Validation of Acute Lung Injury biomarkers for Diagnosis; enrollment, 2007–2016; Nashville, TN), EARLI (Early Assessment of Renal and Lung Injury; enrollment, 2008–2019; San Francisco, CA), and MARS (Molecular Diagnosis and Risk Stratification of Sepsis; enrollment, 2011–2014; Amsterdam, The Netherlands). These cohorts represent large clinically and demographically diverse populations, are well phenotyped for ARDS and sepsis, and have a variety of ARDS risk factors. Data were missing at random. MetS was defined per the modified World Health Organization criteria (5). Because of the low prevalence of MetS in each cohort, the data were combined for analysis. Component MetS diagnoses (hypertension, diabetes, obesity, dyslipidemia) were collected from the electronic medical record at enrollment. In EARLI, diagnosis of dyslipidemia was not recorded; EARLI patients were defined as having MetS when the other three diagnoses were present. Phenotype assignment was derived by latent class analysis using the same clinical and biomarker data as previously (2–4). A probability cutoff of ≥ 0.5 was used to assign the hyperinflammatory phenotype (4). The association between MetS or its component diagnoses and phenotypes was analyzed in univariable and multivariable analyses controlling for age, sex, and Sequential Organ Failure Assessment score. These covariates were selected to account for differences in demographic characteristics and illness severity between the geographically distinct cohorts. A mixed-effects model with random intercepts was employed to assess the impact of study site on the relationship between MetS and phenotype.

Results

Among the 3,142 patients, 2,036 (64.80%) were classified as having hypoinflammatory disease and 1,106 (35.20%) were classified as having hyperinflammatory disease. Demographic and clinical data for each cohort are shown in Table 1. Unexpectedly, premorbid MetS was associated with the hypoinflammatory phenotype ($P = 0.01$; Figure 1A), and the proportion of patients classified as having hyperinflammatory disease decreased with each additional MetS