TITLE: Normal FEV_1 Without Reversibility in Asthma Trials – a Placebo Patient-Level Meta-Analysis

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- Investigators and/or study sponsors of the underlying trials contributed individual participant data; all authors + ORACLE2 consortium (see appendix)
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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 exhaled nitric oxide (FeNO)).(2, 7) Similarly, forced expiratory volume in 1st second (FEV_1) 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 FEV_1 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 $FEV_1 \geq 80\%$ predicted and bronchodilator reversibility < 12% (henceforth 'normal FEV_1 without reversibility') in moderate-to-severe asthma from the OxfoRd Asthma attaCk risk scaLE meta-analysis (ORACLE2).(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 days oral corticosteroids) over ≥6 months. Statistical analyses described were performed using R 4.4.2 (code on GitHub). We analyzed 10 multiple imputed datasets (2), pooling results using Rubin's rules. We first assessed the association of normal FEV_1 without reversibility compared to patients not meeting the definition (i.e. patients with FEV_1 <80% or reversibility ≥12%) with future asthma attacks using multivariable negative binomial regression, adjusting for sex, age, Global Initiative for Asthma (GINA) treatment step (2), prior-year attack count, baseline lung function (%$FEV_{1\%}$, %FEV_1/FVC, % FEV_1 reversibility), symptom scores (ACQ-5), type-2 biomarkers (log-transformed: blood eosinophils, exhaled nitric oxide), and enrolling trial. Secondly, we analyzed prebronchodilator FEV_1 (litres) change from baseline to 52 weeks with placebo, adjusting for the same covariates.

Results

We identified 261 placebo-treated patients with normal FEV_1 without reversibility (215 attacks, 229 patient·years) from 12 trials contributing at least one such patient. Comparisons were made with the remaining 3394 moderate-to-severe asthmatics (3343 attacks, 3155 patient·years) from those same trials. Fifty-two-week prebronchodilator FEV_1 was available for 1966 (54%) patients (Table).

Normal FEV_1 without reversibility patients had better lung function (FEV_1, FEV_1/forced vital capacity (FVC)), lower postbronchodilator reversibility, were younger, and had lower blood eosinophil counts (Table). The proportion of patients with normal FEV_1 without reversibility ranged from 2% (QUEST) to 66% (AZISAST), significantly different between the two groups. However, the difference per trial varied by less than 15%, and regression models were adjusted for the participants' enrolling trial.

Normal FEV_1 without reversibility patients trended towards a 23% (95% confidence intervals (CI): -3% to 56%) higher attack risk compared with patients with low FEV_1 and/or high reversibility, although not statistically significant (Figure). Predicted annualized attack rates were 1.61 [1.22 to 2.01] in patients

with normal FEV_1 without reversibility *versus* 1.31 [1.14 to 1.48] for other patients, respectively (Figure). The higher adjusted predicted rates compared to crude observed rates (Table) 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) as the reference. Similar to our previous report (2), blood eosinophil count, FeNO, asthma attack history, disease severity, and symptoms (ACQ-5 score) were key predictors of asthma attacks in the multivariable model. Three sensitivity analyses yielded aRRs of: i) 0.96 [0.61 to 1.49] (excluding continuous baseline lung function adjustments); ii) 1.04 [0.67 to 1.62] (high-FEV_1-only, n=356); iii) 1.17 [0.77 to 1.80] (low-reversibility-only, n=1333).

Normal FEV_1 without reversibility patients showed significantly greater FEV_1 decline over 12 months (-0.050 [-0.129 to 0.030] *versus* +0.054 [0.014 to 0.095]L; adjusted least squares mean difference: -0.104 [-0.177 to -0.031]L)(Figure).

Discussion

In this patient-level meta-analysis of RCT placebo arms for moderate-to-severe asthma, we found that patients with a baseline FEV_1 ≥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 FEV_1 without reversibility <are typically excluded from trials,(2, 4) Our findings do not support the view that these patients are low-risk when compared to 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 enrolment criteria exclude an asthma phenotype with preserved lung function but poor prognosis—potentially excluding 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 concords 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 FEV_1 and postbronchodilator reversibility, not FEV_1/FVC – although we adjusted for the latter. In this group of 261 patients, 215 severe asthma attacks occurred and 134 had 52-week FEV_1 data, providing sufficient power for multivariable modeling. These patients' normal FEV_1 without reversibility values represented either enrolment following re-screening or participation in trials with less stringent lung function parameters. Second, the increased risk estimates for FEV_1 decline in normal FEV_1 without reversibility patients may be explained by regression to the mean, despite adjusting for baseline FEV_1. This aligns with higher attack risk despite similar history, further suggesting that normal FEV_1 without reversibility patients 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 pre-randomization 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 FEV_1 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 that 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.

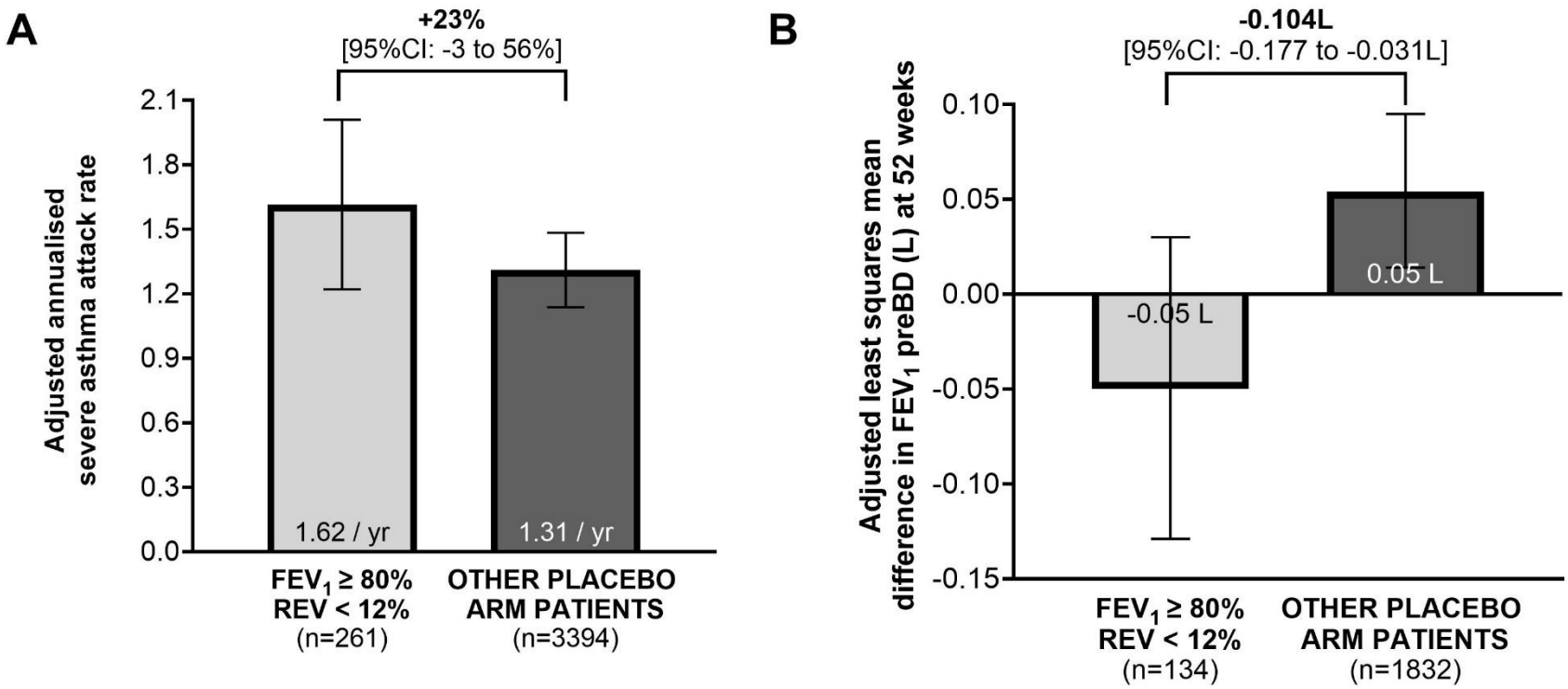
In conclusion, patients with moderate-to-severe asthma and normal FEV_1 without reversibility represent an understudied subgroup with measurable risk. Their exclusion from drug development clinical trials may leave important knowledge gaps regarding treatment efficacy across asthma populations. Future 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)

TABLE. Baseline characteristics and trial outcomes of normal FEV_1 without reversibility vs other moderate-to-severe asthma RCT placebo-treated patients

		FEV1 ≥ 80% REV < 12% (n=261)	Other Placebo Arm Patients (n=3394)	p
Age (mean (SD))		44 (16)	50 (13)	<0.001
Sex female, (n (%))		179 (68.6)	2209 (65.1)	ns
GINA Treatment step, (n (%))	Step 3	1 (0.4)	33 (1.0)	
	Step 4	96 (36.8)	1502 (44.3)	0.03
	Step 5	164 (62.8)	1859 (54.8)	
Severe asthma attacks in last year (mean (SD))		2.32 (1.08)	2.24 (1.56)	ns
FEV_1 preBD baseline, % predict (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
FeNO, ppb (median [IQR])		22 [11-33]	24 [9-39]	ns*
Blood eosinophils, $\times 10^9$/L (median [IQR])		0.21 [0.08-0.33]	0.25 [0.10-0.40]	0.001*
Enrolling trial	AZISAST	33 (12.6)	21 (0.6)	
	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)	<0.001
	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	3343	-
Total follow-up in patient-years (n)		228.8	3155.0	-
Unadjusted annualized asthma attack rate		0.94	1.06	-
Unadjusted ΔFEV_1 preBD at 52 w, L (mean (SD))		-0.10 (0.43)	0.14 (0.39)	<0.001
Missing ΔFEV_1 data, n (%)		127 (49%)	1562 (46%)	ns

*p values for FeNO and Eosinophils are t-tests done on logged values. ACQ5, asthma control questionnaire (5-item); BD, bronchodilator; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume 1st second; FVC, forced vital capacity; GINA, Global INitiative for Asthma; ns, not significant (p≥0.05)

151 **FIGURE**



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153 **FIGURE. Asthma attack rate (A) and 52-week FEV_1 change (B) for placebo arm trial patients with normal FEV1 without reversibility**
154 ***vs* other moderate-to-severe asthma placebo-treated trial participants.** The multivariable models adjusted for age, sex, GINA treatment
155 step, asthma attack history (number in previous year), FEV_1, FEV_1/FVC ratio, FEV_1 reversibility postbronchodilator, blood eosinophils,
156 exhaled nitric oxide, and enrolled trial. aRR, adjusted rate ratio; CI, confidence intervals; FEV_1, forced expiratory volume 1st second; FVC,
157 forced vital capacity; GINA, Global INitiative for Asthma, RCT, randomized control trial; Rev, reversibility.

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