Real World Studies in Pulmonary Medicine: More Insight Beyond Randomized Controlled Trials?

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Disclosure

Reynold A. Panettieri, MD

- **Consultant/Speaker: AstraZeneca, MedImmune, RIFM, Equillium, Theravance, Avillion, Boehringer-Ingelheim, Sanofi, Genentech**
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Learning Objectives

- Define real world studies.
- Compare and contrast the benefits of real world studies and randomized control studies.
- Identify a pragmatic study in asthma.
- Summarize and clarify the value of real world studies.

Real World Studies: Confusion or Solution

Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) Tool

Thorpe KE et al J Clin Epidemiol 2009;62(5):464-475

PRECIS-2, Loudon, K et al BMJ2015;350:h2147

1. Costa D et al J Allergy Clin Immunol 2011:127:920.
2. Pawson R J Eval Clin Pract 2019;1.

Trial elements, illustrating the extremes of the explanatory: pragmatic continuum

	Explanatory (or Efficacy Trial)	Pragmatic (or Effectiveness or Management) Trial
The question	Can this Rx work under ideal circumstances?	Does this Rx benefit under usual circumstances?
1. Participant eligibility	Strict: Restricted to high risk, highly responsive, highly compliant.	Free: Everyone with the condition of interest.
2. Experimental intervention	Inflexible, with strict instructions for every element. Both participants and practitioners are usually blind. Cross-overs are prohibited.	Highly flexible, as it would be used in routine health care. Nobody is blind. Cross-overs are permitted.
3. Comparison intervention	Inflexible, with strict instructions (often employs a placebo). Both participants and practitioners are usually blind. Cross-overs are prohibited.	Usual care for this condition in this setting. Nobody is blind. Cross-overs are permitted.

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Trial elements, illustrating the extremes of the explanatory: pragmatic continuum (cont)

4. Practitioner expertise	Only practitioners and settings with previously documented high expertise.	Full range of practitioners and settings in which a successful intervention would be applied.
5. Participant compliance with interventions	Closely monitored and may be a prerequisite for study entry. Both prophylactic strategies (to maintain) and "rescue" strategies (to regain) high compliance are used.	Unobtrusive (or no) measurement of compliance. No special strategies to maintain or improve compliance.
6. Practitioner adherence to protocols	Close monitoring into how well clinicians and centers are adhering to the trial protocol and "manual of procedures," triggering vigorous interventions whenever deficient.	Unobtrusive (or no) measurement of practitioner adherence. No special strategies to maintain or improve their adherence.

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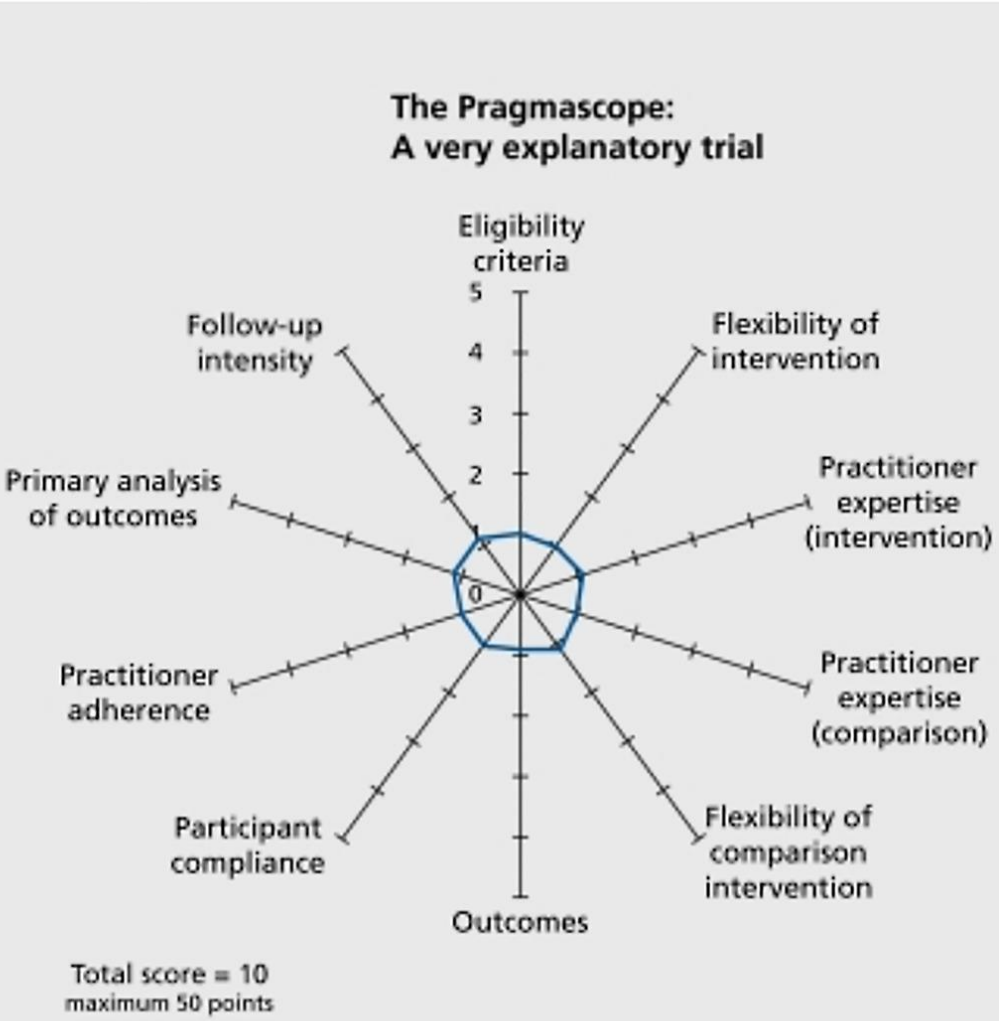
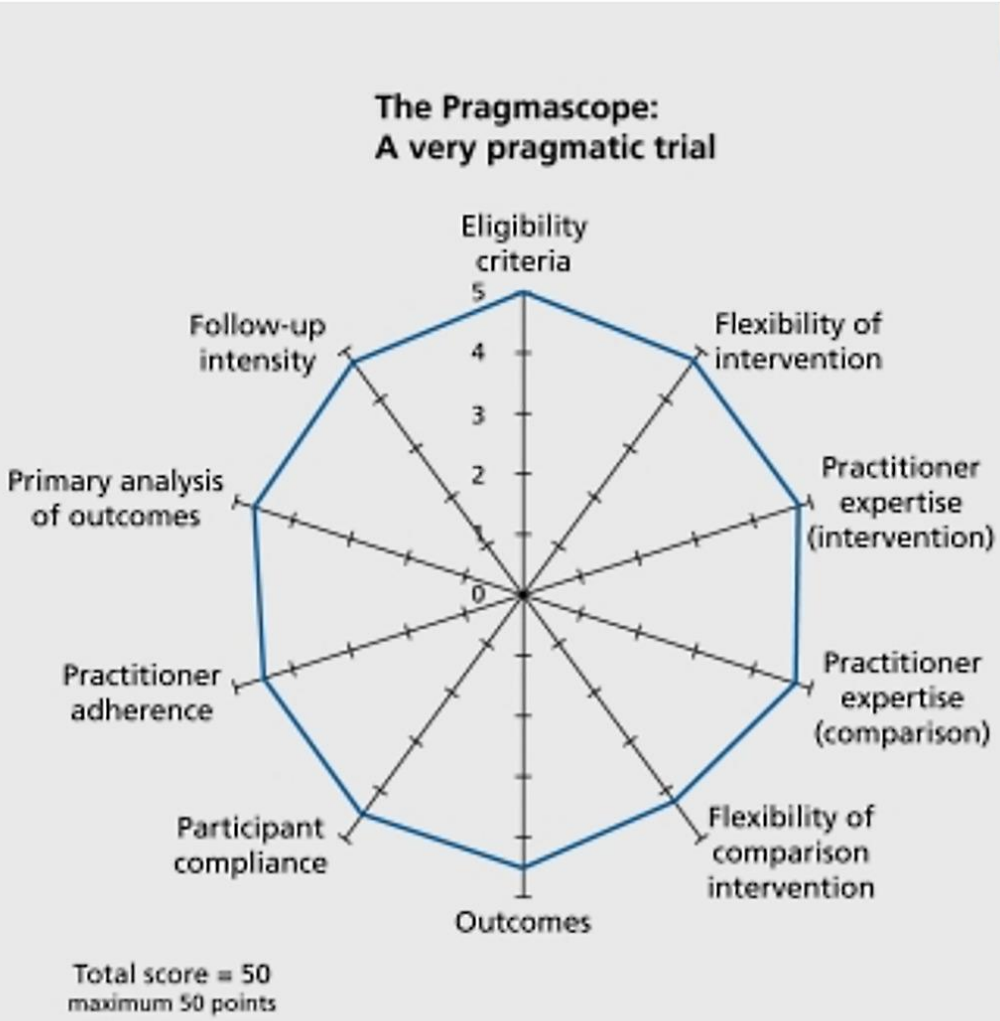
Trial elements, illustrating the extremes of the explanatory: pragmatic continuum (cont)

7. Follow-up intensity	Frequent, highly intense, with extensive data collection.	Usual intensity for this condition and setting, or restricted to administrative data bases on mortality and utilization.
8. Primary outcome	A restricted set of events, composite outcomes, or surrogate outcomes, often determined by blinded experts and adjudicators.	A broad set of events of importance to participants, determined in the routine course of health care.
9. Primary analysis	Might try to justify excluding non-compliers or non-responders.	Never deviates from “intention-to-treat” analysis of all participants who entered the trial.

Pawson R J Eval Clin Pract 2019;1.

The “pragmatic trial”: An essentially contested concept?





Pawson R J Eval Clin Pract 2019;1.

Real World Studies and Asthma

- An unmet met: enhance our understanding of severe asthma with contemporary data from large, real-world, longitudinal, observational studies.

- Global randomized controlled trials (RCTs) are the gold standard for establishing treatment safety and efficacy, but RCTs in severe asthma do not represent the overall patient population due to study inclusion/exclusion criteria and limited country-specific samples.

- Can address comparative efficacy without head-to-head studies.

- Typically diminish the no treatment group (nocebo)

Brown T, Jones T, Gove K, Barber C, Elliott S, Chauhan A, et al. Randomised controlled trials in severe asthma: selection by phenotype or stereotype. Eur Respir J 2018; 52.

Siddiqui S, Denlinger LC, Fowler SJ, Akuthota P, Shaw DE, Heaney LG, et al. Unmet needs in severe asthma subtyping and precision medicine trials. Bridging clinical and patient perspectives. Am J Respir Crit Care Med 2019; 199:823-9.

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- Help inform US standard of care for treatment of severe asthma
- A real-world prospective observational study of US severe uncontrolled asthma
- High-quality data describing specialist-confirmed, biologic-eligible population from diverse US sites
- Aligned with International Severe Asthma Registry (ISAR)

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Study Objective

- To describe patient characteristics, treatment patterns, and health outcomes among a large, geographically diverse cohort of US adults with severe asthma who are not controlled on high-dose ICS with additional controllers and/or require systemic corticosteroid or monoclonal antibody therapy
  - Goal is to help inform US standard of care for severe uncontrolled asthma
  - Better understand disease burden and treatment gaps
  - Potential to examine comparative safety/effectiveness of treatment regimens

- Designed to integrate with the International Severe Asthma Registry (ISAR), which is being conducted in multiple countries by an academic collaboration

the CHRONICLE study

Study Design

- Real-world longitudinal prospective study
- Non-interventional design
  - Enrollment not dependent on specific medicinal product
  - No required treatment, testing, or imaging
- Sites to approach all eligible patients, providing de-identified information on all
- Data collection for those enrolled
  - Longitudinal collection of information from routine care, as contained in medical records (from specialist and PCP)
  - Patient-reported outcomes every 1 to 6 months for asthma control, quality of life, work productivity, treatment and disease assessment
  - No specified visits

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Study Design

- Study population (target N = 4000):
  - Goal is to follow patients for at least 3-5+ years

- Approximately 125 US sites
  - Academic and community-based specialists (allergists and pulmonologists)
  - Geographically diverse sample

- Three outcome categories:
  - Patient characteristics: demographics, asthma history, comorbidities
  - Treatment patterns: medications, reasons for changes, adherence
  - Health outcomes: asthma control, healthcare utilization, major medical events, mortality

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Inclusion Criteria

1. Individuals with a diagnosis of severe asthma for at least 12 months prior to enrollment and confirmed by the Investigator not to be due to alternative diagnoses.

2. Currently receiving care from specialist physicians (e.g., pulmonologists and/or allergists) at the Investigator's or sub-investigator's site.

3. 18 years of age and older.

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Inclusion Criteria

4. Meeting at least one of the following three criteria (a, b, or c):

    a. Uncontrolled on asthma treatment consistent with GINA Step 4 or 5, receiving high-dose ICS with additional controllers

    b. Current use of a Food and Drug Administration (FDA)-approved monoclonal antibody agent for treatment of severe asthma (use is not primarily for an alternative condition).

    c. Use of systemic corticosteroids or other systemic immunosuppressants (any dose level) for approximately 50% or more of the prior 12 months for treatment of severe asthma (use is not primarily for an alternative condition).

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Inclusion Criterion 4a: Clarifications

- Uncontrolled is defined by meeting at least one of the following (per ATS/ERS):
  - Poor symptom control: Asthma Control Questionnaire consistently >1.5, ACT <20 (or "not well controlled" by NAEPP/GINA guidelines)
  - Frequent severe exacerbations: two or more bursts of systemic corticosteroids (>3 days each) in the previous 12 months.
  - Serious exacerbations: at least one hospitalization, intensive care unit stay or mechanical ventilation in the previous 12 months.
  - Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal).

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Exclusion Criteria

1. Not willing and able to sign written informed consent. Consent can be obtained from having a responsible, legally authorized representative acting on patient's behalf.

2. Not fluent in English or Spanish.

3. Unable to complete study follow-up or web-based patient reported outcomes (PROs).
   - If the patient does not have email or web access, minimal assistance from others to access the web-based PRO is permitted (i.e. receiving the email and/or assisting patient in navigating to the web page); PROs must be completed by the patient.

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Exclusion Criteria

4. Received an investigational therapy for asthma, allergy, atopic disease, or eosinophilic disease as part of a clinical trial during the 6 months prior to enrollment.

   NOTE: Once enrolled in the CHRONICLE Study, patients can enroll in trials of investigational therapies (as well as other non-interventional studies) as long as they continue to complete study follow-up.

   If a patient enrolls in a trial of an investigational therapy, the identity (National Clinical Trial [NCT] number) of the study and dates of the first and last investigational therapy administrations will be collected.

   If a patient receives blinded therapy in a trial, the Investigator will request the identity of that therapy at trial conclusion so that treatment information collected for the current study may be updated accordingly.

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General Schedule of Data Collection

- Investigator
  - Baseline and every 6 months based on medical records (specialist and PCP)
  - Electronic data capture system
- Patient Surveys
  - Web-based capture with email outreach/reminders
  - Baseline, every month, every 3 months, every 6 months depending upon the survey
  - Longer surveys (e.g. SGRQ) less frequent to reduce burden

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Study Measures

- Patient and provider characteristics:
  - Healthcare provider's specialty, setting, practice size, and other characteristics
  - Patient demographics
  - Smoking history and significant occupational exposures
  - Environmental exposures including allergen exposure
  - Physical examination
- Asthma history and evaluation:
  - Age at diagnosis and timing of first asthma care from a specialist
  - Dates/duration of first use of high-dose ICS/LABA, chronic systemic corticosteroids or systemic immunosuppressant use, and/or monoclonal antibody therapy
  - Specialist confirmation that severe asthma symptoms are NOT due to alternative diagnosis
  - Disease severity and treatment effectiveness
  - Clinical and laboratory test results and imaging collected as part of routine care

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Study Measures: Available routine test results

- CBC with differential
- Total IgE
- Skin prick test results
- Allergen-specific IgE blood test results
- FeNO
- Vitamin D
- PFTs
- Simple spirometry
- PEF
- Methacholine/Histamine challenge
- BAL and sputum testing results
- Chest X-rays
- Chest CT scans
- Bone densitometry

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Study Measures

- General medical history prior to and following enrollment
  - Relevant comorbidities
  - Relevant surgical procedures
  - Pulmonary toilet therapies and rehabilitation participation
  - Pneumococcal and influenza vaccine history
  - Special Medical Events of Interest: anaphylaxis, malignancies, serious infections
  - Complications of systemic corticosteroid therapy
  - Mortality information

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Study Measures

- Asthma treatment prior to and following enrollment
  - All FDA-approved and/or standard of care treatments for asthma
  - Investigator evaluation of treatment effectiveness
  - Adherence based on provider impression and pharmacy claims data
- Comprehensive adverse drug reactions NOT required to be collected for this non-interventional study
- Asthma control and healthcare utilization prior to and following enrollment
  - Visits, ER visits, admissions, exacerbations, and mechanical ventilation
- Patient-reported asthma control and QoL at and following enrollment
  - Not collected during healthcare visits (avoid healthcare provider bias)
  - Patients report through web-based tool

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Characteristics of Eligible and Enrolled Patients[a]

	All enrolled (N=659)	All eligible (N=1,168)
Age at enrollment, y		
Mean (SD)	54 (14)	54 (15)
Median (range)	55 (18–89)	56 (13–90)
Age at asthma diagnosis, y		
Mean (SD)	28 (21)	28 (21)
Median (range)	26 (0–80)	26 (0–82)
Female sex	67%	68%
Specialist currently providing care		
Allergist	48%	
Pulmonologist	41%	NA
Both allergist and pulmonologist	11%	
Insurance status		
Commercial: no PCP referral required	48%	47%
Commercial: PCP referral required	16%	13%
Medicare	23%	23%
Medicaid	8%	11%
Other	4%	4%
Uninsured	1%	2%
Asthma treatment category at enrollment		
HD ICS and additional controllers, no biologics or long-term SCS	18%[b]	36%[b]
Biologics,[c] no long-term SCS	69%	53%
Biologics,[c] long-term SCS	9%	7%
Long-term SCS, no biologics	3%	4%
Exacerbations[d,e] in the 12 months prior to enrollment		
≥1 exacerbation	63%	61%
Mean number, overall	2.1	1.8
Mean number, among those with any exacerbation	3.2	3.1
≥1 serious exacerbation that resulted in hospitalization	12%	NA

SD, standard deviation; NA, not available (not collected for nonenrolled eligible patients); PCP, primary care provider; HD ICS, high-dose inhaled corticosteroids; SCS, systemic corticosteroids; IgE, immunoglobulin E; IL-5, interleukin-5; IL-5Rα, interleukin-5 receptor α.

[a]Table based on nonmissing data; missing data were limited per field except for age at asthma diagnosis (missing for 67 eligible, nonenrolled patients). Fields marked NA represent data that were not collected for nonenrolled eligible patients. Percentages may not total 100% due to rounding.

[b]Per protocol, there was systematic undersampling of this population; sites approached every third patient in this category due to anticipated higher prevalence.

[c]Anti-IgE was reported in 67% of biologic recipients; anti–IL-5/anti–IL-5Rα was reported in 46%.

[d]Ten or more exacerbations counted as 10 for calculation of mean.

[e]An exacerbation was defined as a worsening of asthma that required SCS for ≥3 days (or a single depo-injectable dose), an urgent care or emergency room visit requiring SCS due to asthma, or an inpatient hospitalization.

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Baseline Demographic Characteristics of PRB and PNRB

	PRB (N=609)	PNRB (N=187)
Age at enrollment, years		
Mean (SD)	54 (14)	54 (15)
Median (range)	55 (18–87)	56 (18–89)
Age at asthma diagnosis, years		
Mean (SD)	28 (21)	28 (21)
Median (range)	25 (0–80)	28 (0–78)
Female	65%	73%
BMI, kg/m²		
Mean (SD)	33 (8)	34 (9)
Median (range)	31 (17–63)	32 (16–70)
Race/ethnicity		
Non-Hispanic white	73%	72%
Non-Hispanic black	15%	17%
Hispanic	8%	6%
Asian	2%	2%
Other	2%	3%
Residential area		
Rural	22%	23%
Suburban	50%	52%
Urban	28%	25%
Employment status[a]		
Employed full time	47%	37%
Employed part time	6%	8%
Self-employed	3%	4%
Unemployed	5%	7%
Homemaker	4%	4%
Full-time student	2%	1%
Disabled, due to asthma	8%	8%
Disabled, not due to asthma	4%	8%
Retired	22%	24%

BMI, body mass index; PNRB, patients not receiving biologic therapy; PRB, patients receiving biologic therapy; SD, standard deviation.
[a]Percentages may not total 100% due to rounding.

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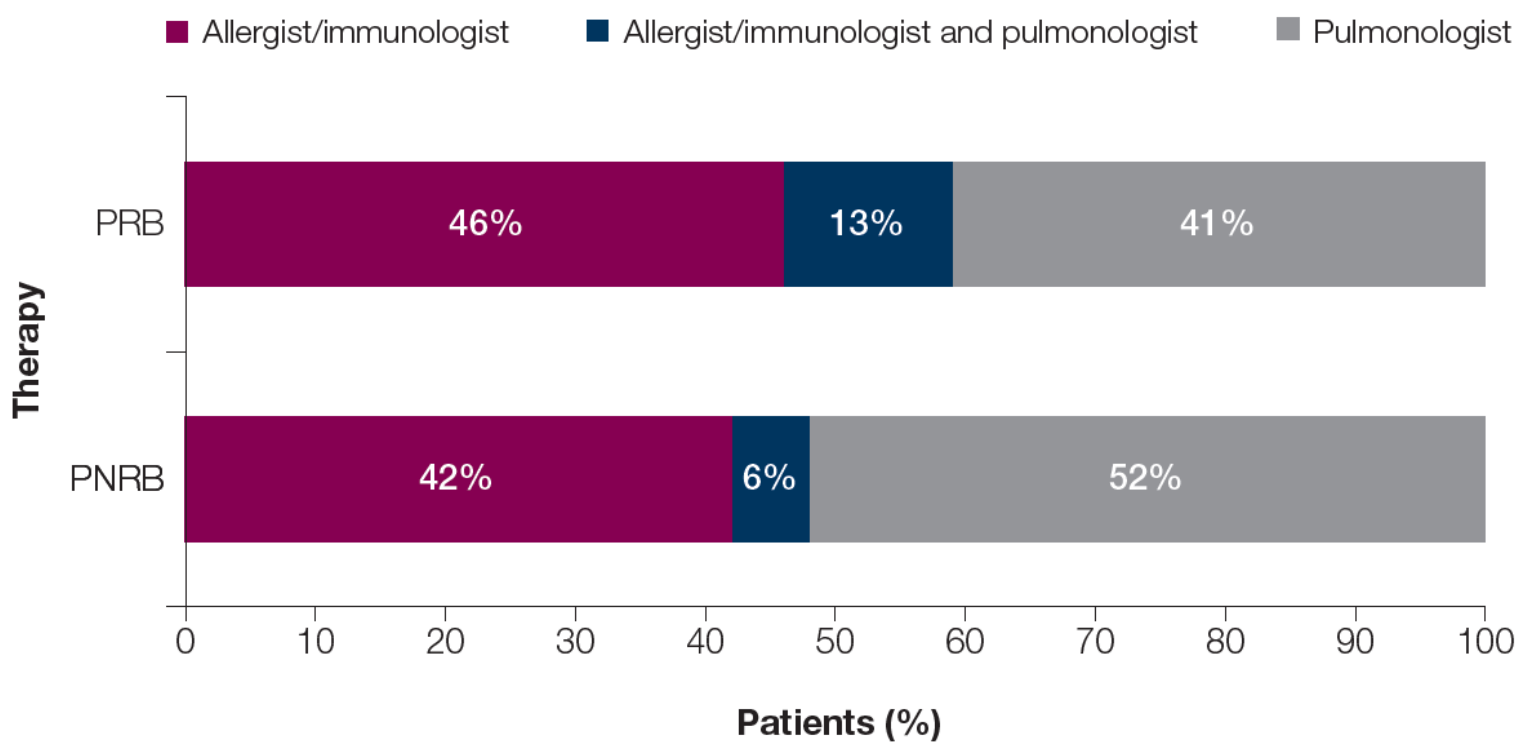
Subspecialist care.



PNRB, patients not receiving biologic therapy; PRB, patients receiving biologic therapy.

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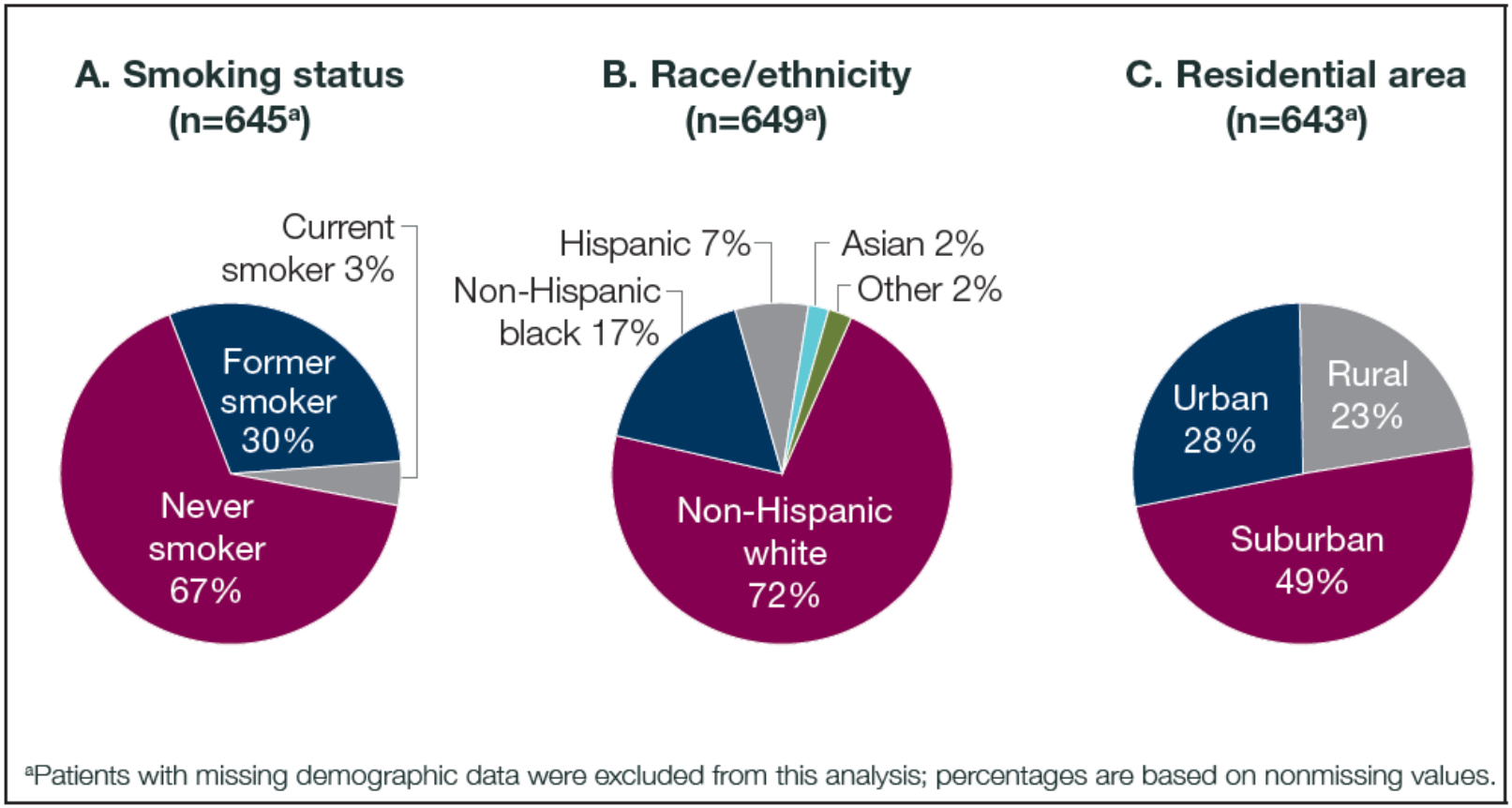
Distribution of enrolled patients by (A) smoking status (n=645[a]), (B) race/ethnicity (n=649[a]), and (C) residential area (n=643[a]).



[a]Patients with missing demographic data were excluded from this analysis; percentages are based on nonmissing values.

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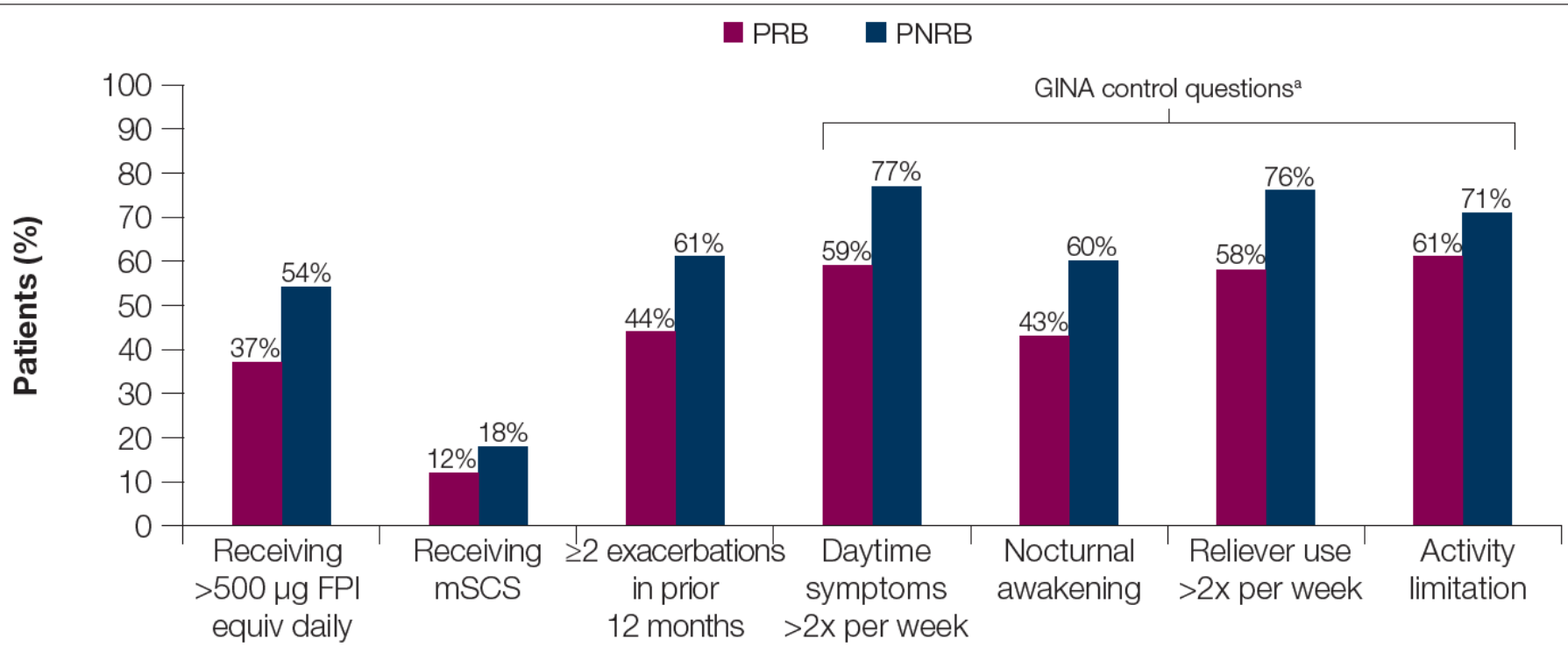
Concomitant medications and asthma burden.



Equiv, equivalent; FPI, fluticasone propionate; GINA, Global Initiative for Asthma; mSCS, maintenance systemic corticosteroids; PNRB, patients not receiving biologic therapy; PRB, patients receiving biologic therapy.

[a]For the GINA control questions regarding asthma symptoms, sites described symptoms as of the patient's most recent visit. Additionally, 7–17% of patients had "unknown" as a reported value. Those patients were excluded from the reported proportions.

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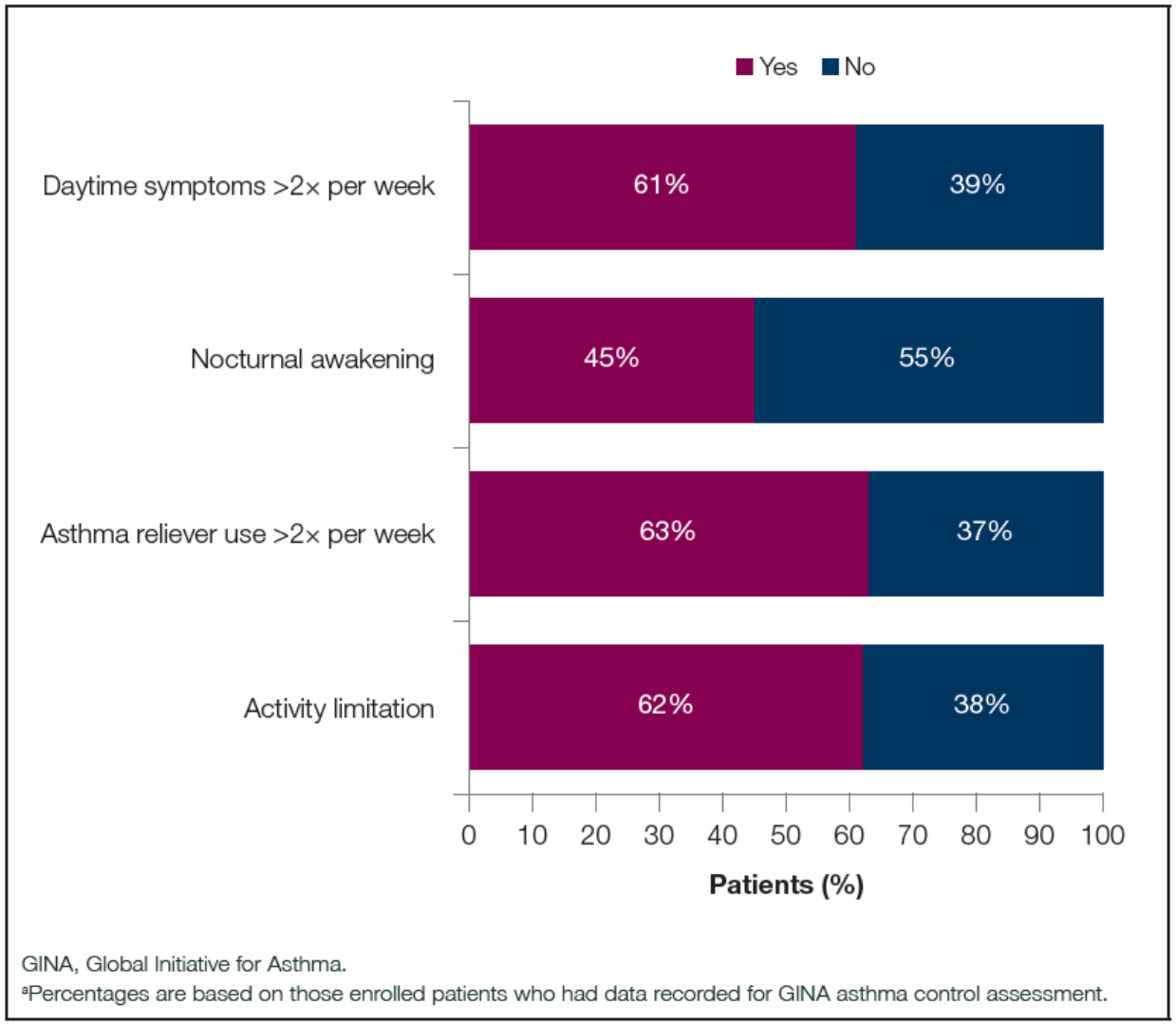
GINA asthma control assessment at enrollment (N=545).[a]



GINA, Global Initiative for Asthma.

[a]Percentages are based on those enrolled patients who had data recorded for GINA asthma control assessment.

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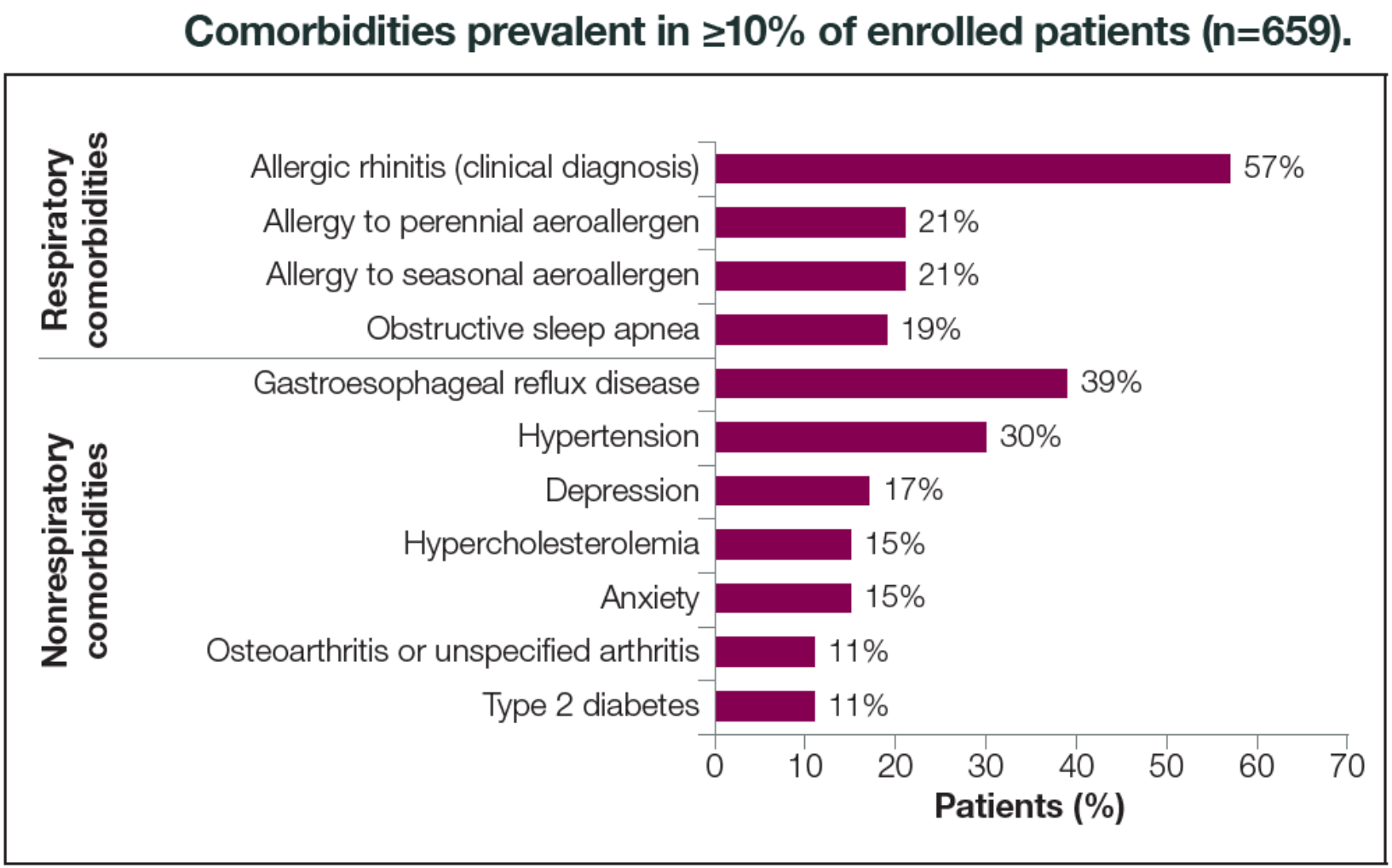

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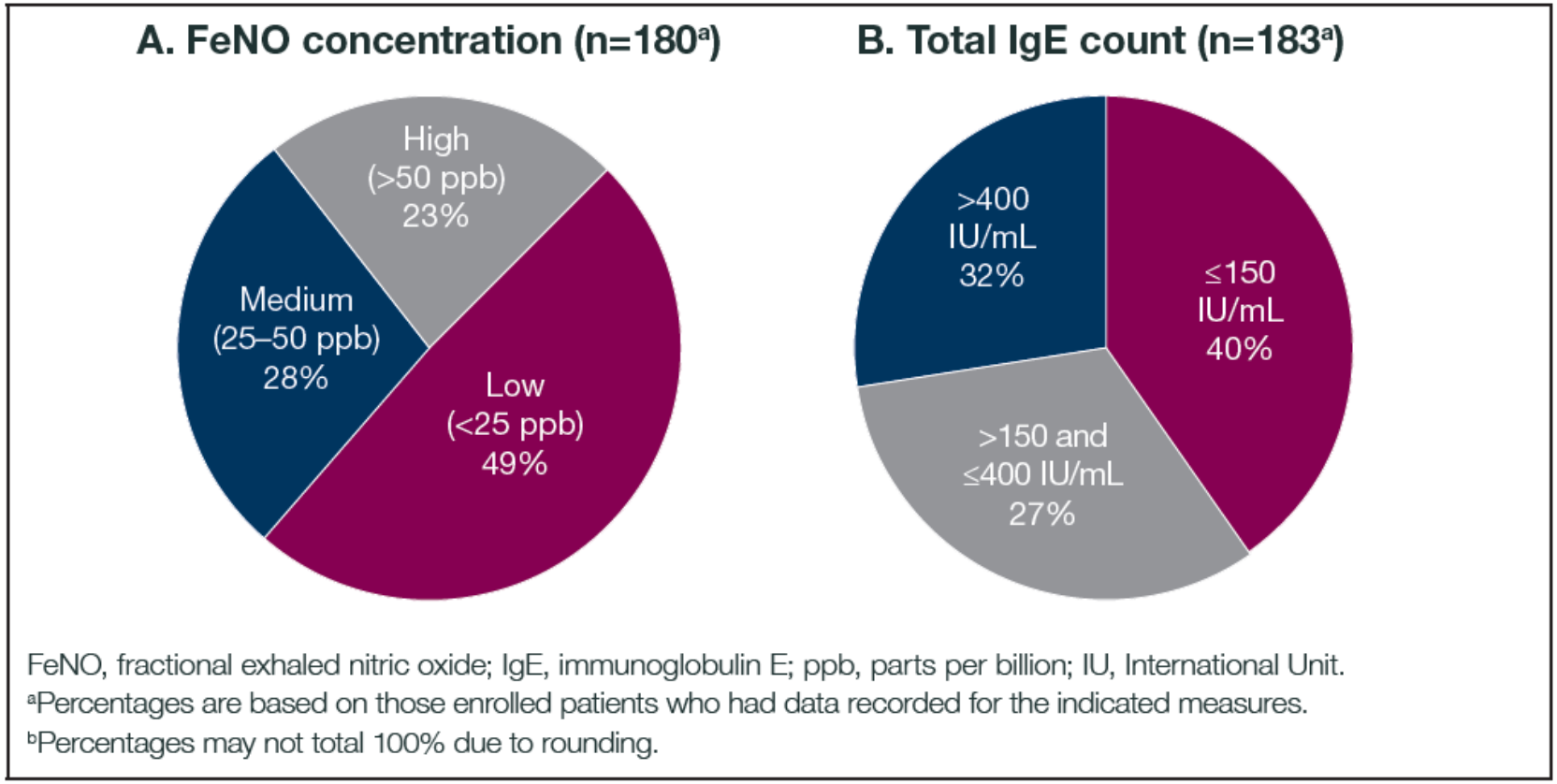
Baseline laboratory results for enrolled patients: (A) FeNO concentration (n=180[a]) and (B) total IgE count (n=183[a]).[b]



FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; ppb, parts per billion; IU, International Unit.
[a]Percentages are based on those enrolled patients who had data recorded for the indicated measures.
[b]Percentages may not total 100% due to rounding.

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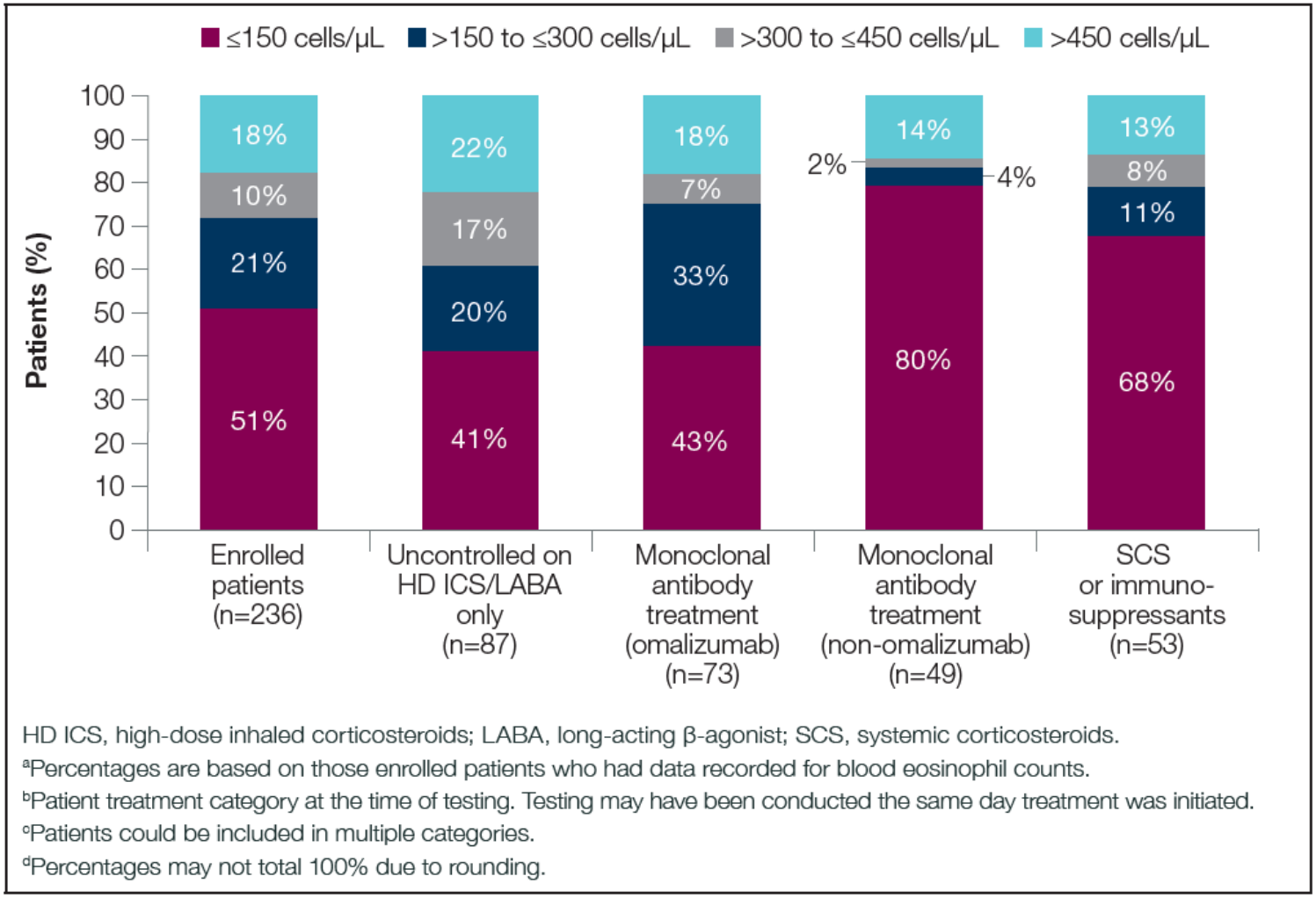
Most recent blood eosinophil counts for enrolled patients by treatment category.[a,b,c,d]



HD ICS, high-dose inhaled corticosteroids; LABA, long-acting β-agonist; SCS, systemic corticosteroids.

[a]Percentages are based on those enrolled patients who had data recorded for blood eosinophil counts.

[b]Patient treatment category at the time of testing. Testing may have been conducted the same day treatment was initiated.

[c]Patients could be included in multiple categories.

[d]Percentages may not total 100% due to rounding.

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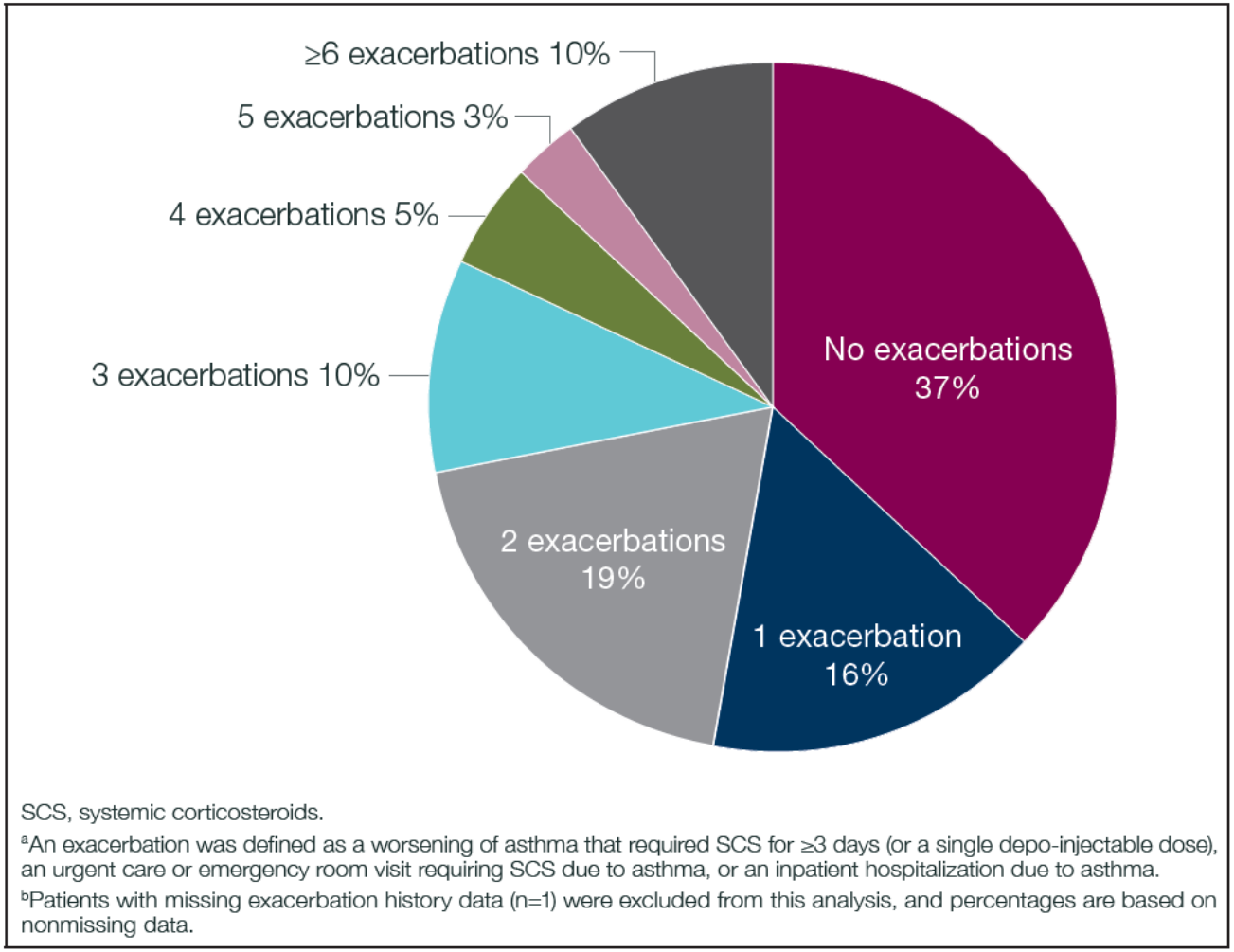
Exacerbation[a] history in the 12 months prior to enrollment among enrolled patients (n=658[b]).



SCS, systemic corticosteroids.

[a]An exacerbation was defined as a worsening of asthma that required SCS for ≥3 days (or a single depo-injectable dose), an urgent care or emergency room visit requiring SCS due to asthma, or an inpatient hospitalization due to asthma.

[b]Patients with missing exacerbation history data (n=1) were excluded from this analysis, and percentages are based on nonmissing data.

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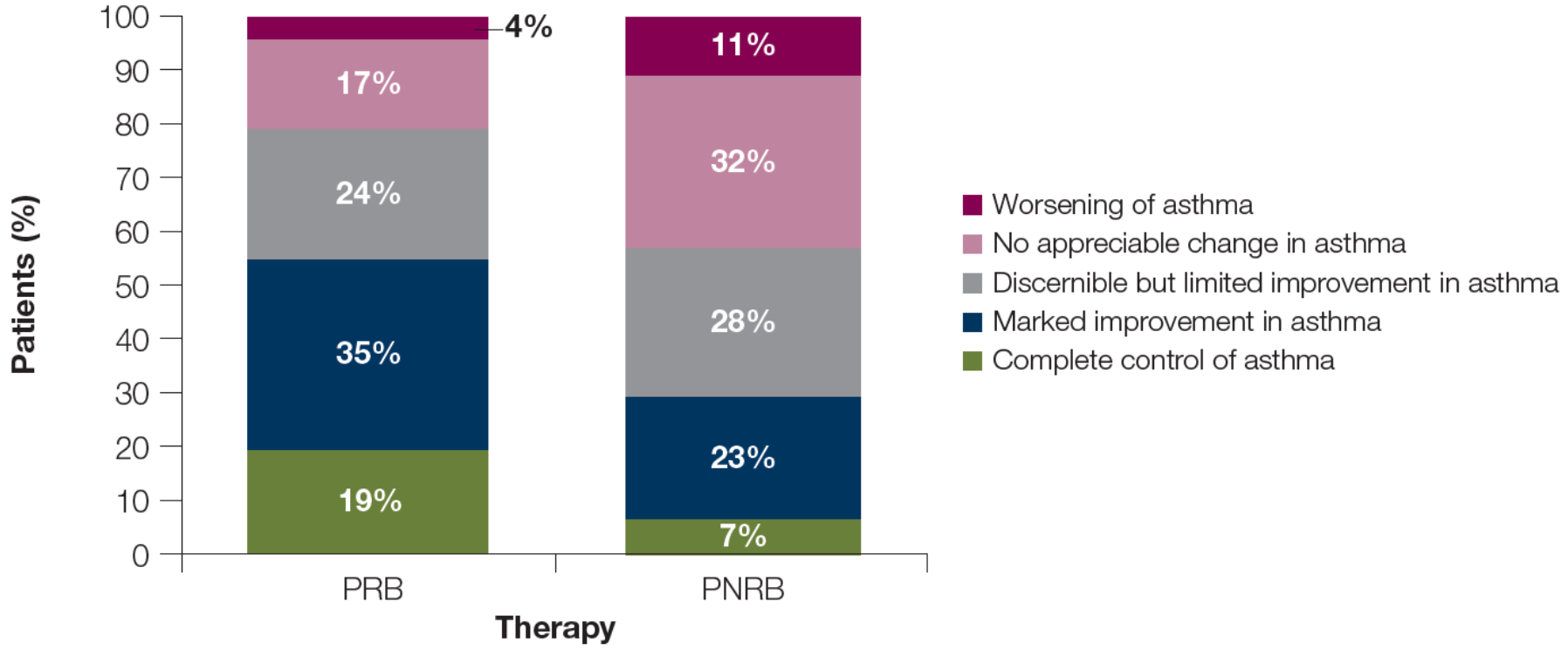
Specialist global evaluation of treatment effectiveness at enrollment.[a,b]



PNRB, patients not receiving biologic therapy; PRB, patients receiving biologic therapy.

[a]Percentages may not total 100% due to rounding.

[b]Figure results are based on data from the enrollment visit and reflect an assessment of the treatment the patient was on at enrollment.

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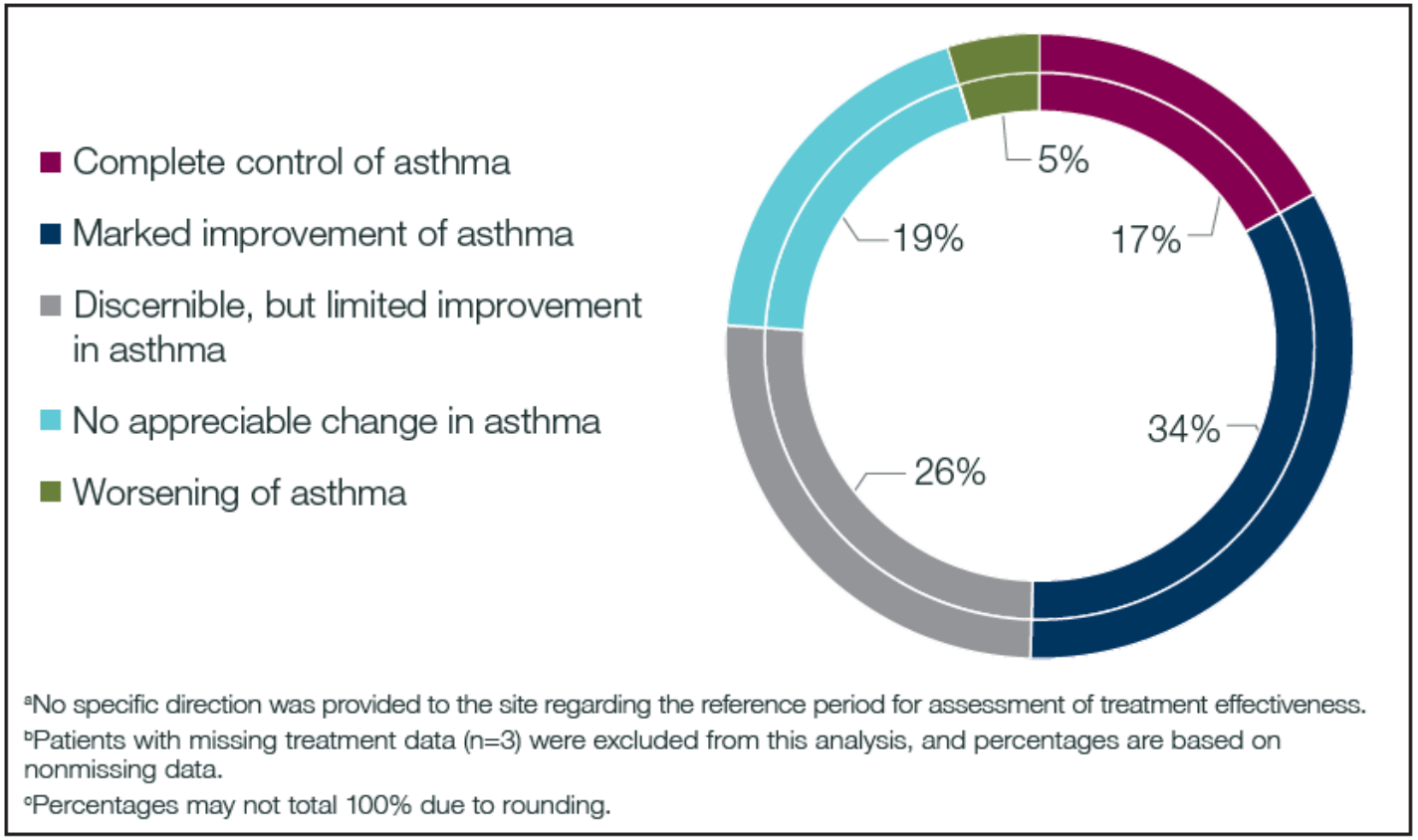
Physician evaluation of current treatment effectiveness at enrollment, measured by global evaluation of treatment effectiveness[a] (n=656[b]).[c]



[a]No specific direction was provided to the site regarding the reference period for assessment of treatment effectiveness.
[b]Patients with missing treatment data (n=3) were excluded from this analysis, and percentages are based on nonmissing data.
[c]Percentages may not total 100% due to rounding.

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Summary

- Real World studies offer advantages over RCTs.
- Comparative efficacy can be explored.
- Adherence and placebo concerns can be addressed.
- Approaches exist to improve scientific rigor or pragmatic studies.
- Impact on policy and practice guidelines can be expedited through Real World studies


Questions?