Clinical Health Journal

VOLUME 21, MAY/JUNE, 2025

ISSN: 2636 - 7017

Treatment in the First Month After Hypertension Diagnosis Improves Blood Pressure Control

Inflammatory and clinical risk factors for asthma attacks (ORACLE2): a patient-level meta-analysis of control groups of 22 randomised trials

Women-specific reference ranges for serum TSH in Liguria: the impact of age and year of collection in a single-center cross-sectional study

The development of consensus recommendation to improve practice harmonization for Sickle Cell Disease through the National Alliance of Sickle Cell Centers

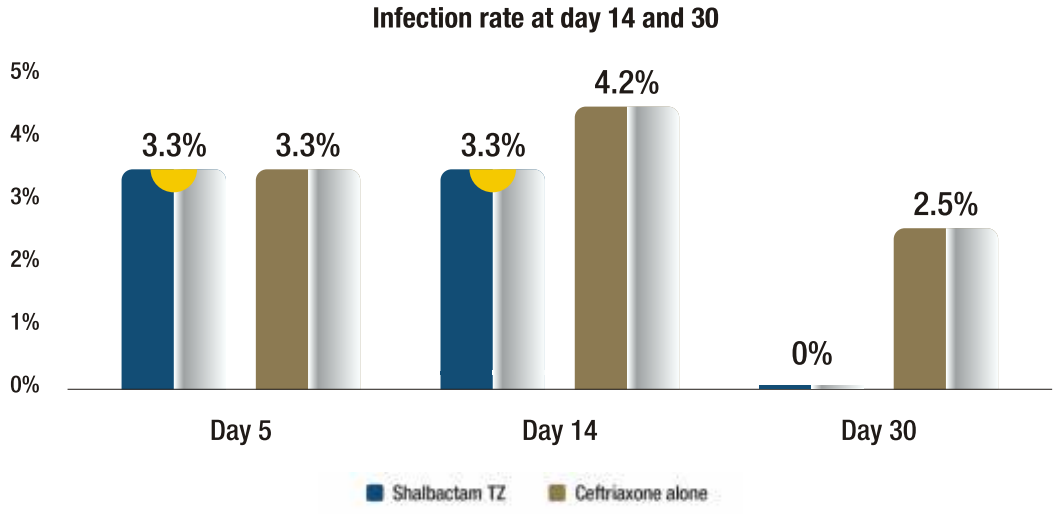
SHALBACTAM TZ

Ceftriaxone Sodium USP Equivalent to Ceftriaxone 1g + Tazobactam Sodium Equivalent to Tazobactam 125mg

The proven solution against the odds of bacterial resistance

In Surgical prophylaxis

Shalbactam TZ 0% infection rate vs 2.5% Ceftriaxone alone



Indications:

- Nosocomial Pneumonia
- Complicated Urinary Tract Infection
- Septicemia
- Catheter induced infections
- Contaminated and Clean Contaminated Surgical Prophylaxis

Dosage:

- Adults: 1.125 to 2.250 grams once daily (or equally divided doses, twice daily), not to exceed 4.5 grams/day
- Pediatric patients: 50 to 75 mg/kg, once daily (or equally divided doses, twice daily), not to exceed 2.250 grams/day
- For preoperative use: a single dose of 1.125 gm, ½ to 2 hours before surgery

1. J Clin Sci 2023;20:59-64;

Shalina
www.shalina.com

Shalina Healthcare Nigeria Limited
19 Fatai Atere Road, Matori, Mushin, Lagos State, Nigeria.
Contact No: +234 - 8107539929
nigeria@shalina.com

Shalina Healthcare DMCC
30th Floor, Almas Tower, Jumeirah Lakes Towers,
Dubai, U.A.E. P.O. Box 340575.
Tel.: +971 44309111, info@shalina.com

Uncontrolled Type 2 Diabetes

Rx NIDD

(Glibenclamide 5 mg)

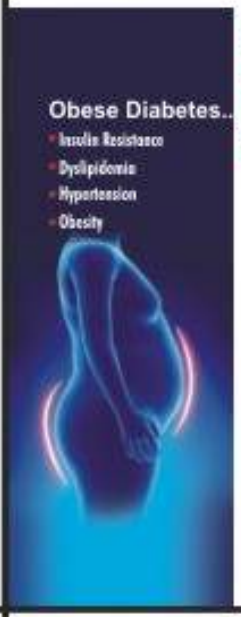
- Induces rapid insulin secretion
- Increases B cell sensitivity to glucose
- Can delay need for insulin
- Provides better patient compliance

The ideal Sulfonylurea for Glycemic control

Rx DIBINORM

Metformin 500 mg

First line choice for Obese DIABETICS



- Delays the progression of type 2 diabetes
- Effectively reduces plasma glucose level
- Reduces triglyceride and LDL-UKPDS
- Reduces diabetic complications and total mortality
- Offers enhanced compliance and safety profile

Metformin Beyond Diabetes

For comprehensive management of Type 2 Diabetes

Rx Glimefil

Glibenclamide 5mg + Metformin 500mg Tablets

Enhances insulin secretion and saves B-cell

- Standard therapy for precise blood sugar control
- Delays the progression of Type 2 Diabetes
- Ensures 24 hr. Glycemic control
- Once daily advantage

GLUCOSE ↑↑↑

Triggers Micro & Macro Vascular Complications

Rx GLYTROL

Gliclazide 80 mg

Excellent glycemic control

- Restores the First Phase Insulin secretion
- Increases B-cell sensitivity to glucose

Benefits beyond glycemic control

- Potent sulfonylurea with a low rate of secondary failure
- Better choice in long-term sulfonylurea therapy
- Prevents oxidative stress-induced B-cell damage

REFER TO THE PRODUCT INSERT FOR MORE INFORMATION

Manufactured by:
Unique Pharmaceuticals Limited
11, Fatai Atere Way, Matori, Mushin, Lagos.
Tel: 0809 742 1000 E-mail: mail@uniquepharm.com

...where only the best is good enough

E MAL®

NOW IN CERAMIC-PRINTED AMPOULES

Benefits

» Enhanced security
» No risk of label soiling
» Better visibility of content

In addition, a scratch panel is affixed, which conceals a code. The code is meant to be sent to 1393 at no cost to confirm product genuineness.

FIDSON
...We value life

CORPORATE HEAD OFFICE:
268, Ikorodu road, Obanikoro, Lagos,Nigeria.
Customer care line: 0807 700 8888.
Head Office: +234 (1) 3429102, 3429106
E-mail: info@fidson.com, www.fidson.com

FROST & SULLIVAN
2014 BEST PRACTICES AWARD
NIGERIAN PHARMACEUTICAL GROWTH EXCELLENCE LEADERSHIP AWARD

FIDSON

When the functional competence of the liver is at stake.

LIVOMYN®

Tablets/Syrup

Andrographis paniculata
(standardized at 5% andrographolide)

Viral Hepatitis

Alcohol Induced liver injury

Fatty Liver

Intra hepatic cholestasis of pregnancy

Drug Induced liver injury

Benefits:

- Improves liver functions
- Significantly suppresses HBV replication
- Protects, regulates and rejuvenates the liver
- Decreased hepato cellular injury and inflammation

Protects liver cell efficiency, correct liver cell insufficiency.

For More Enquiries
Customer Care Line: **0807 700 8888**

Ceflonac®-SP

Aceclofenac / Paracetamol / Serratiopeptidase Tablets

ACECLOFENAC

- Better safety profile than conventional NSAIDs due to it's preferential cox-2 blockade

SERRATIOPEPTIDASE

- Anti inflammatory, antiedemic and fibrinolytic activity
- Reduces swelling and improves microcirculation

PARACETAMOL

- Analgesic and antipyretic effect
- Rapidly and completely absorbed from the GI tract

Geneith PHARMACEUTICALS LIMITED
...offering quality healthcare

Integrity
Commitment
Innovation

Website: www.geneithpharm.com @geneithpharm +2348129008556

Rectal suppositories for aches, pains & feverish conditions.

Insert the Relief

Manufactured & Marketed by:

Daily-Need Industries Ltd

Quality | Integrity | Transparency

Email: info@dailyneedgroup.com | www.dailyneedgroup.com

FIDSON

Manage ENDOMETRIOSIS Naturally

- Management of chronic pelvic pain, dysmenorrhea, and dyspareunia
- Reduction of menstrual pain and cramps
- Improvement of fertility outcomes in endometriosis

wellnessnaturally.ng

ABOUT CLINICAL HEALTH JOURNAL

Clinical Health Journal aims at reaching your target audiences by promoting, sharing and distributing quality scientific and medical peer-reviewed contents source from credible and leading journals across the world thereby advancing scientific research benefits to the global scientific community.

With our multiple channels filtering strategy, we deliver authoritative and timely contents that are of immediate interest to the practicing physicians, drive quality traffic and meet publishers expectation. These include review articles, case reports, short communications, original scientific studies that have direct clinical significant and position papers on healthcare issues. The journal carry news on conferences, workshops and products. We cover extensively all areas of medicine. The journal publishes 6 issues per year.

ISSN
2636 - 7017
Frequency
Bi-monthly
Subject
All subjects in medicine
Readership
Medical doctors, Medical students, Pharmacists, Nurses and healthcare professionals

Volume in 2023
19
Published print since
August 2006
Online Full Text Availability
2023
Journal Type
Open Access
Journal Website
https://clinicalhealthjournal.com

Published By
Genmax Communications Nigeria Limited
(Clinical Health Journal)
No. 1 Bariyu Street, Isolo, Lagos, Nigeria.
clinicalhealthjournal1@gmail.com
bridget.clinicalhealthjournal@gmail.com

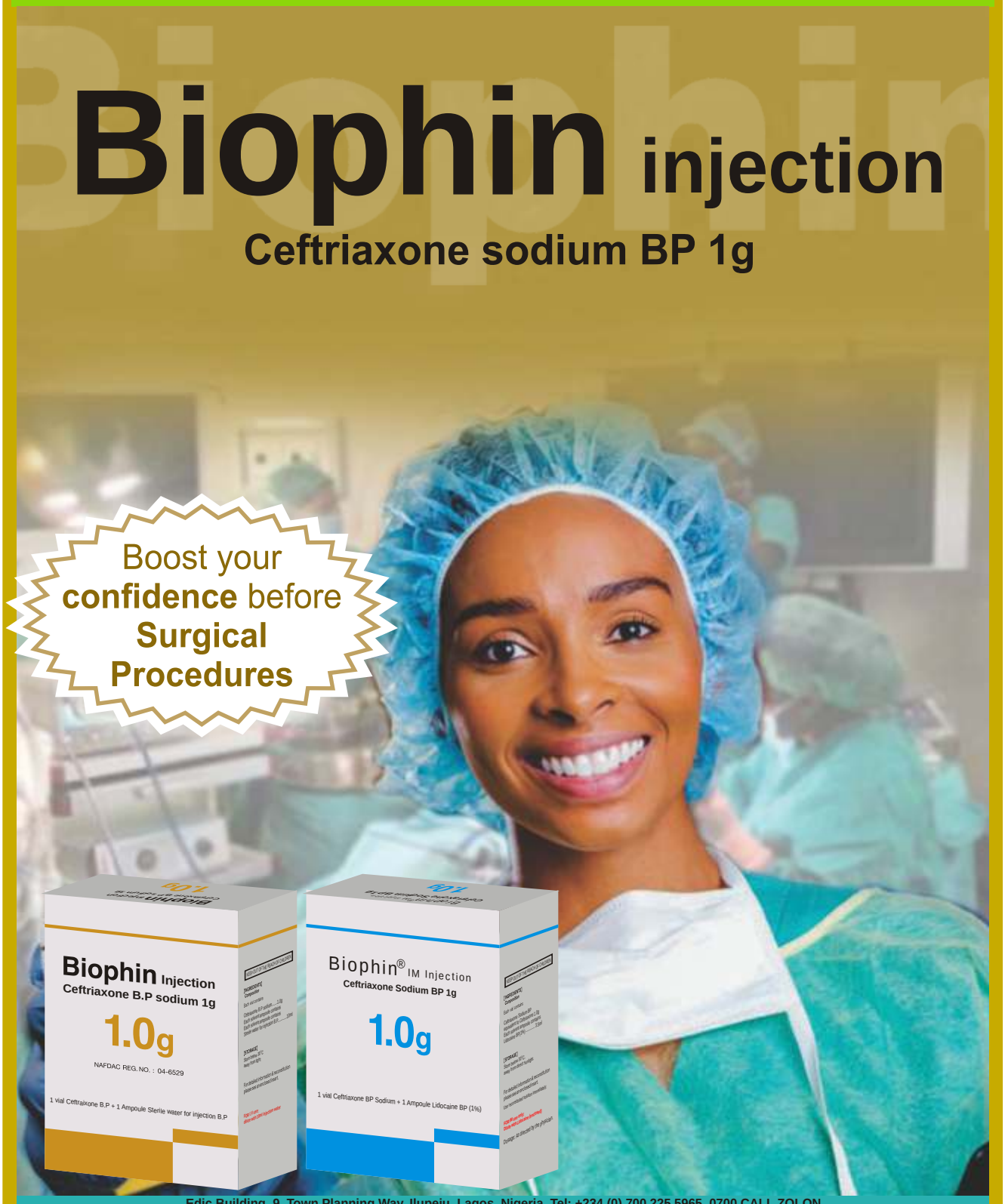
TABLE OF CONTENTS

zolon
Healthcare Limited
(A member of the Emzor Group)

INTELLIGENT zolon Healthcare Limited (A member of the Emzor Group) SOLUTIONS

Biophin injection

Ceftriaxone sodium BP 1g



Edic Building, 9, Town Planning Way, Ilupeju, Lagos, Nigeria. Tel: +234 (0) 700 225 5965, 0700 CALL ZOLON

Zolon Healthcare Limited Zolon Healthcare Limited Zolon Healthcare Limited Zolon Healthcare

www.zolonhealthcare.com

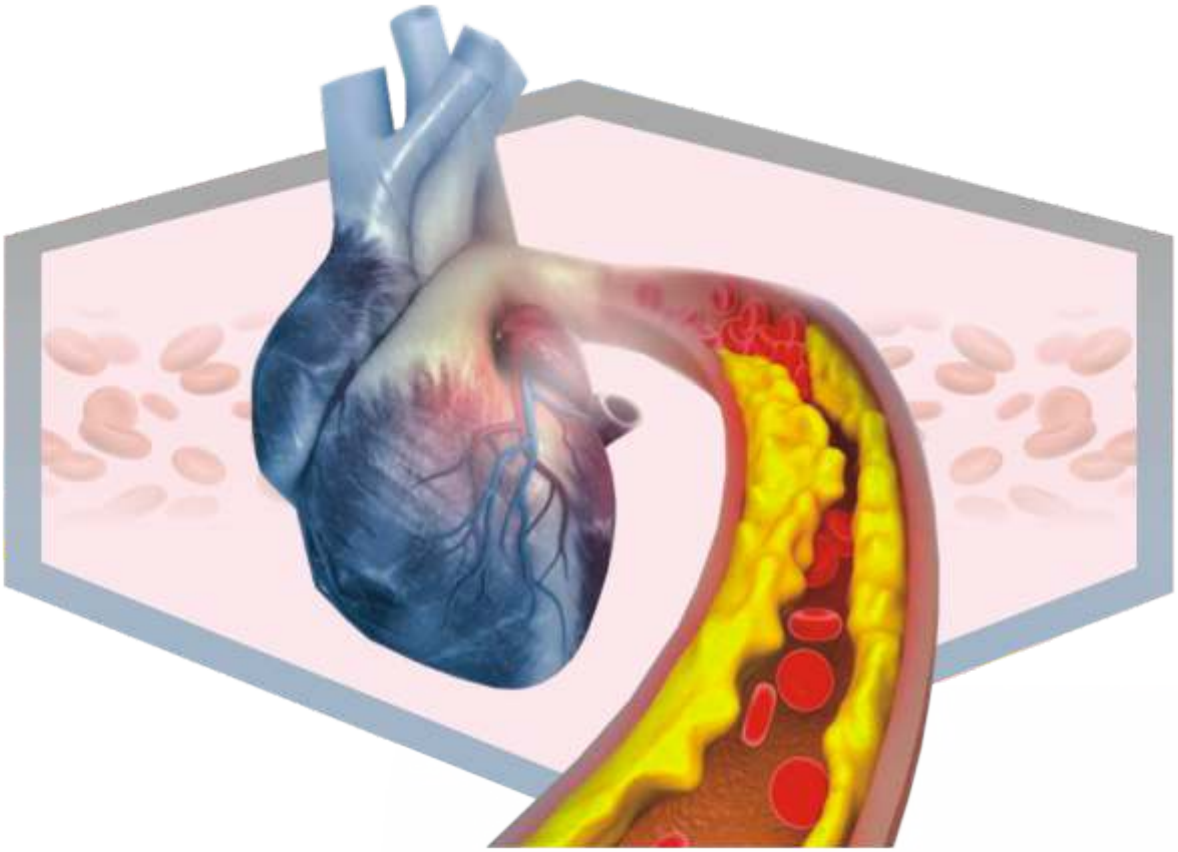
INTELLIGENT SOLUTIONS

zolon
Healthcare Limited
(A member of the Emzor Group)

INTELLIGENT zolon Healthcare Limited (A member of the Emzor Group) SOLUTIONS

ROSUDEX®

Rosuvastatin 10mg and 20mg Tablets



The Superior Statin in the Management of Dyslipidemia & CVD

"Among available statin, Rosuvastatin has been shown in both clinical trials and in routine clinical practice to produce significantly greater reduction in LDL-C compared with atorvastatin, fluvastatin, lovastatin, provastatin and simvastatin[1]

Proudly Nigerian

Manufactured in Nigeria

Edic Building, 9, Town Planning Way, Ilupeju, Lagos, Nigeria. Tel: +234 (0) 700 225 5965, 0700 CALL ZOLON

Zolon Healthcare Limited | Zolon Healthcare Limited | Zolon Healthcare Limited | Zolon Healthcare

www.zolonhealthcare.com

INTELLIGENT SOLUTIONS

Treatment in the First Month After Hypertension Diagnosis Improves Blood Pressure Control

Robert B. Barrett, Benjamin Riesser, Benjamin Martin, Neha Sachdev, Michael K. Rakotz, Susan E. Sutherland, and Brent M. Egan

Abstract

BACKGROUND:

Adults with hypertension have fewer cardiovascular events if controlled within the first 6 months of diagnosis, during which time they are excluded from many hypertension control metrics. We compared blood pressure (BP, mm Hg) control rates from 6 to 42 months in adults with hypertension who did or did not have antihypertensive treatment initiated (TI) with monotherapy during the first month after diagnosis, irrespective of subsequent changes in antihypertensive pharmacotherapy.

METHODS:

A retrospective cohort of 15 422 patients, mean age 56.0±14.8 years, from 5 health care organizations, was identified with previously undiagnosed and untreated hypertension. BP control (<140/ <90) and TI on visits with uncontrolled readings were assessed as a function of time since diagnosis, up to 42 months. Logistic regression models provided estimates of the odds of TI for initial BP, stratified by race, sex, and diagnosed diabetes. Cox proportional hazards regression estimated the hazard ratio of BP control over time.

RESULTS:

Patients with TI during the first month versus later time points had better BP control at 6 (57.7% versus 47.7%, P<0.001) through 30 months (66.8% versus 62.2%, P<0.001), with similar control rates thereafter.

CONCLUSIONS:

TI within the first month after diagnosis in contrast to later time points, leads to better BP control at 6 to 30 months, which is associated with better clinical outcomes and performance on standard hypertension control metrics. While better control is sustained for 30 months, treatment with monotherapy during the first month following diagnosis was insufficient to control hypertension in >30% of patients.

NOVELTY AND RELEVANCE

What Is New?

In adults with untreated and uncontrolled hypertension, starting monotherapy within the first month after diagnosis versus later time points provides better blood pressure control from 6 to 30 months after diagnosis.

What Is Relevant?

Despite better blood pressure control with prompt treatment initiation many remain uncontrolled suggesting subsequent treatment intensification is insufficient.

Confirming uncontrolled hypertension through repeated measurement during a medical encounter increases the probability of treatment initiation.

Clinical/Pathophysiological Implications?

Prompt initiation of antihypertensive therapy and timely intensification at subsequent visits are keys to better blood pressure control.

The benefits of antihypertensive pharmacotherapy accrue rapidly in primary care and clinical trials. When better blood pressure (BP, mm Hg) control is achieved during the first 3 to 6 months of treatment, fewer cardiovascular events occur during this time interval.[1–5] Standard hypertension control metrics typically exclude patients during the first 6 months following diagnosis, after which time they are included.[6] Thus, for both clinical outcomes and care quality metrics, controlling hypertension within the first 6 months after diagnosis is important.

Prompt initiation of antihypertensive pharmacotherapy is a key to realizing the time-sensitive benefits of BP reduction. Antihypertensive monotherapy is the norm for treatment initiation in clinical practice, despite evidence that monotherapy is insufficient to control hypertension in most patients. Furthermore, the 2017 American College of Cardiology/American Heart Association high BP guideline recommends treatment initiation with 2 different antihypertensive medications when BP is ≥ 20/≥ 10 mm Hg above target.[7]

Previous research indicates that not only are most adults with hypertension initiated on antihypertensive monotherapy, but also that most of them remain on monotherapy at 3 years.[8] Moreover, half of adults with uncontrolled hypertension were on monotherapy after 8 years.[9]

Given the evidence, our study was designed to determine if initiating treatment with antihypertensive monotherapy (TI) during the first month after the diagnosis of hypertension that was uncontrolled led to more prompt and better BP control over time than when TI did not occur in the first month. A secondary objective was to identify factors associated with the decision to initiate treatment during the first month following diagnosis of hypertension than later time points.

METHODS

Regulatory Considerations

This secondary analysis of a limited data set from the American Medical Association (AMA) Measure Accurately, Act Rapidly, Partner with Patients (MAP) Hypertension quality improvement program was reviewed by the institutional review board at the University of Illinois (Federal Wide Assurance 00000083), the institutional review board of record for the AMA, and determined not to meet the definition of human subjects research. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were used.[10] The Business Associate Agreements between the AMA and participating health care systems do not permit data sharing. The authors provided all critical data in the article.

The MAP Hypertension quality improvement program has been described.[11] Briefly stated, the program focuses on 4 key process measures for improving hypertensive population BP (mm Hg) control rates: measure accurately, assessed by documenting a confirmatory (repeat) measurement following an uncontrolled BP reading (systolic BP [SBP] ≥140 or diastolic BP [DBP] ≥90); Act rapidly, defined as therapeutic intensification for uncontrolled hypertension; and 2 partner with patients metrics defined as: (1) the percentage of patients having a ≥ 10 mm Hg reduction in SBP within 7 to 180 days after adding a new antihypertensive medication class, and (2) a follow-up BP measurement within 30 days of an outpatient visit where BP was uncontrolled. This study focused on the effects of TI within the first 30 days after diagnosis compared with later time periods on hypertension control.

Data Source

Patient data were obtained from the electronic medical record systems of 5 participating health care organizations or data warehouses containing electronic medical record data. These organizations located in the Southeast and Midwest, included 2 federally qualified health centers, a private, a county, and a university hospital-based health system. The data were then cleaned (eg, SBPs >300 or <80 were excluded), normalized for unit of measure (eg, height, weight), then ingested into a relational database using a custom common data model for harmonization between disparate systems. Analytical datasets were created in the form of limited data sets by removing individually identifiable data elements, both through masking and element exclusion. Dates of service were retained.

Inclusion Criteria

Patients were required to have a visit between January 2019 and January 2023 where essential hypertension (*International Classification of Disease, Tenth Revision, Clinical Modification* code I10) was first recorded in the electronic medical record and SBP ≥140 or DBP ≥90, and at least 1 visit at a participating program site before and after the diagnosis of hypertension. The requirement of at least 1 prior visit before receiving the diagnosis of hypertension was intended to increase the likelihood that the cohort was comprised of newly diagnosed patients. Follow-up visits for up to 42 months after the initial diagnosis were included.

Exclusion Criteria

Patients <18 or >85 years were excluded, which is consistent with the age range used in other quality metrics for controlling BP.[6] Patients with prescriptions for antihypertensive medications before the initial diagnosis of hypertension were also excluded.

Body mass index (kg/m^2) was calculated from height, measured intermittently, and weight, which was recorded on 85% of encounters.

BP values were obtained from primary care practice sites of participating institutions. If >1 BP value was recorded for an encounter, the minimum SBP and corresponding DBP were selected for analysis.

Hypertension was defined by an *International Classification of Disease, Tenth Revision, Clinical Modification* diagnostic code of I10. For this study, only patients with newly diagnosed and untreated hypertension were included. Untreated hypertension was defined as individuals with an initial visit BP of 140/90 mm Hg or greater with out previously prescribed antihypertensive medication.

Time since diagnosis was calculated as the number of months from the visit date of the first

observed hypertension diagnosis.

Hypertension control was defined by a medical encounter with SBP <140 and DBP <90. Visits were grouped into periods of 6 months, with BP control calculated as the percentage of encounters with BP <140/<90 for each patient.

TI was defined by a new prescription for an antihypertensive medication class in previously untreated patients with uncontrolled BP.

Treatment intensification, which includes TI, was defined as a new prescription for an antihypertensive medication class in a patient with uncontrolled hypertension, irrespective of whether the patient was treated or untreated.

Outpatient encounter was defined by data indicating that a patient received service from a clinician at a primary care program site, either in-person or virtually. Inpatient visits, canceled appointments, and visits where the context was clearly indicated as emergency, documentation only, or another nonclinical encounter were not included in the analytic data set.

Monotherapy was defined as treatment initiation with an antihypertensive medication of a single drug class.

Combination therapy was defined as coincident treatment with >2 antihypertensive medication classes.

Diabetes was identified from International Classification of Disease, Tenth Revision coding in the electronic health record system.

Data analysis was conducted using a combination of Mystructured query language (SQL) and Python libraries, including StatsModels (0.13.2), Lifelines (0.28.0), Numpy (1.21.5), and Pandas (1.4.4). Clinical and demographic characteristics of the patient cohort were summarized as the number and frequency for categorical data or mean and SD for continuous data. Comparisons of characteristics for patients with TI during the first month following diagnosis versus those without treatment in the first month were conducted using χ^2 statistics or pooled t tests. Patient characteristics were also examined at 3 time points, including 1 month, 24 months, and 42 months, to assess potential bias in loss to follow-up in the analysis cohort.

The primary analysis considered 2 outcomes of interest: (1) the incidence of TI during the first month since diagnosis versus later time points, and (2) BP control to <140/<90. Both outcomes were calculated as prevalence ratios for visits within 6-month intervals, with the first month following the diagnosis serving as the initial value. Multivariable models incorporated age, race, sex, diabetes, initial BP, and a confirmatory or repeat BP after an initial SBP $\geq$140 or DBP $\geq$90 as independent variables. Race was dichotomized as White or non-White by combining Black and other than White races. The relationship between each dependent variable and independent variable was examined as a function of time since diagnosis, comparing patients initiated on monotherapy to those remaining untreated during the first month following initial diagnosis of hypertension. Variables for each model were predetermined and potential effect modification was assessed by the inclusion of interaction terms in the model. When no significant effect modifications were detected, the interaction terms were omitted from the final model. Potential confounding effects were examined using stratified models to assess their influence.

Logistic regression models were used to compute the odds of TI for each 10 mm Hg increase in SBP and DBP, the presence of confirmatory BP measurements, and for each 5-year increment in patient age. Logistic regression models were constructed for the cohort and separately for patients with and without diabetes, for White and non-White race, and by sex. Models were not adjusted for body mass index, as this variable did not affect model outcomes. Cox proportional hazards regression was performed to estimate the rate of BP control over the 42-month study period (at both <140/<90 and <130/<80) for patients with TI in the first month compared with patients without TI in the first month. For all multivariable models, observations were limited to covariates with nonmissing data.

RESULTS

A patient cohort was selected from 5 health care organizations participating in the AMA MAP Hypertension quality improvement program to improve BP control (Figure 1). In this study, 15 422 eligible patients with 63 558 clinical encounters were followed for up to 42 months. Of these clinical encounters, 313 (0.5%) were without a documented race, and 10 850 (15%) without a body mass index. The median length of follow-up was 24 months overall, 18 months for patients with TI during the first month, and 24 months for those without TI in the first month.

Table 1 shows the demographic and clinical characteristics for all patients during the first month following hypertension diagnosis and stratified by treatment status in the first month. Non-White, female, younger ages, and those with higher BP values were more likely to have TI in the first month. Patients diagnosed with diabetes were less likely to have TI in the first month.

Table 2 captures demographic and clinical characteristics over the follow-up period. Those with longer

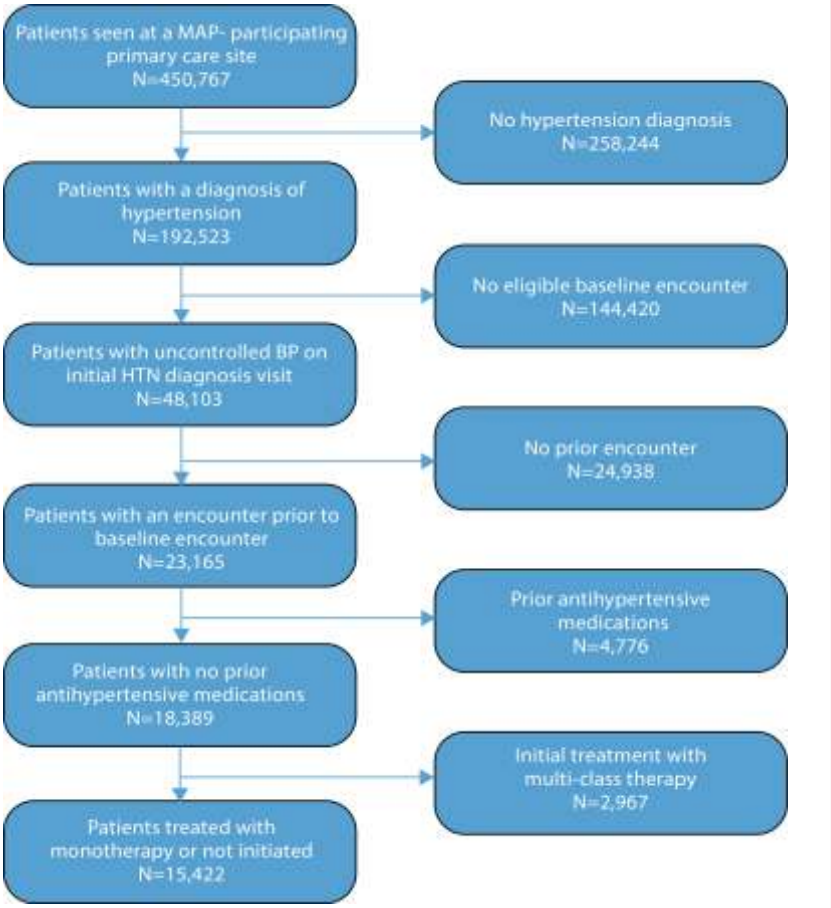


Figure 1. From a sample of 450 767 adults at Measure Accurately, Act Rapidly, Partner with Patients (MAP) primary care sites, 18 389 adults were identified with hypertension that was untreated. Among this group, the study sample of 15 422 adults were selected who were either initiated on monotherapy or remained untreated.

follow-up time were more likely to be female, older and have diabetes. Initial SBP and DBP values were similar across time points.

TI with monotherapy for uncontrolled hypertension was evaluated during the first month after diagnosis and at 6-month intervals thereafter (Figure 2). TI occurred in ≈44% of patients in the first month, 75% at 6 months, 82% at 1 year, and 90% at 2 years after diagnosis. The influence of TI with monotherapy during the first month after the diagnosis of hypertension versus later time points on BP control to <140/<90 at 6-month intervals is also shown in Figure 2. Patients with TI during the first month had a significantly higher control rate at 6 months time since diagnosis (57.4% versus 47.5%, P<0.001), which was maintained until 30 months (66.8% versus 62.0%, *P*<0.001). Further, patients treated in the first month had only a 1.9 mm Hg greater baseline mean SBP than their untreated counterparts, although the difference was statistically significant (154.4 versus 152.5 mm Hg, *P*<0.001).

The rate of treatment intensification for those who did and did not begin monotherapy in the first month is shown in Figure S1. For patients with TI during the first month, values from 6 through 42 months represent the rate of subsequent treatment intensification. For those who were not initiated on monotherapy in the first month, values from 6 through 42 months represent both TI and subsequent treatment intensification.

The likelihood of TI during the first month after the diagnosis of hypertension was 14% greater for each 10 mm Hg increment in SBP and 7% higher for each 10 mm Hg increment in DBP, adjusting for age, race, sex, and diabetes (Table 3). No significant interaction terms were found. The effect of SBP and DBP on TI was similar in groups by diabetes, race, and sex status. Confirming SBP ≥140 on repeated measurement(s) during the initial visit increased the likelihood of TI by ≈68%, with similar effects in groups defined by age, race, sex, and diabetes status. Each 5-year increment in age reduced the likelihood of TI by roughly 10%, with similar effects in groups defined by sex, race, and diabetes status.

BP control during the 42-month follow-up period was 19% more likely for patients with TI during the first month (hazard ratio [HR], 1.19 [95% CI, 1.13–1.25]) than patients untreated during the first month, which persisted after adjusting for age, race, sex, and initial SBP (HR, 1.21 [95% CI, 1.15– 1.27], Table 4). The benefit of TI in the first month after diagnosis of hypertension was also observed for the control threshold of <130/<80 mm Hg after multivariable adjustment (HR, 1.14 [95% CI, 1.07 –1.21]).

DISCUSSION

The principal finding of our study is that patients with untreated, uncontrolled hypertension who are initiated on monotherapy during the first month following the diagnosis of hypertension achieved better BP control at 6 months than patients who were not treated in the first month. Hypertension control within the first 6 months of treatment reduces the incidence of

Table 1. Clinical Characteristics of Adults With Hypertension Who Were Either Prescribed or Not Prescribed Antihypertensive Monotherapy Within 1 Month After the Diagnosis of Hypertension

Characteristics	1 mo TSD (All, n=15 422)	Treated first month (n=6885)	Untreated first month (n=8537)	*P* (treated vs untreated)
Race				<0.0001
White	7351 (47.7%)	3132 (45.5%)	4219 (49.9%)	
Non-White				
Black	6939 (45.0%)	3194 (46.4%)	3745 (43.9%)	
Other	1132 (7.3%)	504 (8.1%)	573 (6.7%)	
Ethnicity				<0.0001
Non-Hispanic	13 805 (89.5%)	6043 (87.8%)	7762 (90.9%)	
Hispanic	1522 (9.9%)	795 (11.5%)	727 (8.5%)	
Other	95 (0.6%)	47 (0.7%)	48 (0.6%)	
Sex				<0.0025
Male	6870 (44.5%)	3159 (45.9%)	3711 (43.5%)	
Female	8549 (55.4%)	3723 (54.1%)	4826 (56.5%)	
Age, y	56.0 (±14.8)	53.3 (±14.0)	58.2 (±15.0)	<0.0001
Baseline systolic BP, mm Hg	153.3 (±12.5)	154.4 (±12.5)	152.5 (±12.5)	<0.0001
Baseline diastolic BP, mm Hg	86.9 (±11.8)	88.5 (±11.5)	85.5 (±11.8)	<0.0001
Body mass index, kg/m^2	31.5 (±7.8)	31.5 (±7.8)	31.5 (±7.9)	1.000
Diabetes	3371 (21.9%)	1343 (19.5%)	2028 (23.8%)	<0.0001

Data are presented as number (n) and percent (%) or mean and SD. BP indicates blood pressure; and TSD, time since diagnosis. *Categories with n<5 were removed. Categories of Other represent values that were either noted as other, were not reported, or were present with low frequency.

cardiovascular events.[1–5] Moreover, superior control was maintained through 30 months in the group with TI in the first month than later time points.

Treatment with initial monotherapy was the focus, since most adults with hypertension are initiated on a single antihypertensive medication drug class.[8,12,13] While initial monotherapy predominates, initial combination therapy leads to better BP control[12–15] fewer cardiovascular events,[8,18] and is recommended in the treatment guidelines.[7,18]

In our study, the cumulative rate of TI increased as a function of time (Figure 2), whereas the rate of increase slowed over the course of 42 months (Figure 2). For patients initiated on monotherapy, subsequent treatment intensification is often required to attain BP control.[7,18,20–22] However, patients initiated on monotherapy in the first month did not achieve 70% or higher control rates to <140/<90. This finding is consistent with their low rates of subsequent therapeutic intensification for uncontrolled hypertension, which averaged ≈ 16% at 6 months, 14% at 12 months, and roughly 10% thereafter (Figure S1). Our findings coincide with other reports that treatment intensification occurs in <1 in 6 encounters when BP is uncontrolled and represents a key barrier to good BP control.[19–21]

Regression toward the mean is a phenomenon wherein a group of individuals selected for high or low values on biological variables, for example, BP, regress toward mean values over time.[22,23] This phenomenon may contribute to the decline of mean SBP in patients not treated during the first month after diagnosis, as well as in patients who were initially treated. The group treated during the first month after diagnosis experienced a greater decline in SBP than the untreated at 6 months (17.1 versus 12.4 mm Hg), providing evidence for the effectiveness of initial monotherapy in lowering BP and improving control. In multivariable analysis, patients with TI during the first month had a 21% greater likelihood of control to <140/<90 (HR, 1.21 [95% CI, [1.15–1.27]) across the 42-month study period, supporting the relationship between prompt treatment and time to BP control (Table 4). TI during the first month after diagnosis also improved control to <130/<80 (HR, 1.14 [95% CI, 1.07–1.21]).

The population mean SBP of ≈ 135 in this study is comparable to that in the SPRINT standard treatment group, where control rates to <140/<90 were ≈60%.[18] Evidence indicates that mean SBP <130 is required to control 80% or more of patients to <140/<90, which suggests that greater rates of antihypertensive treatment intensification are required to attain higher rates of control.[24,25] Estimates suggest that treatment intensification would need to occur on at least 5 of 8 visits with uncontrolled BP to improve control rates from 46% to 80% or higher.[19]

Our study highlights key variables associated with higher

Table 2. Clinical Characteristics of Adults With Initially Untreated, Uncontrolled Hypertension at 1, 24, and 42 Months Following the Diagnosis of Hypertension

Characteristics	1 mo TSD (n=15 422)	24 mo TSD (n=6300)	42 mo TSD (n=3907)
Race			
White	7351 (47.7%)	2985 (47.4%)	1771 (45.3%)
Non-White			
Black	6939 (45.0%)	2985 (47.4%)	1955 (50.0%)
Other	1132 (7.3%)	330 (5.2%)	181 (4.6%)
Ethnicity			
Non-Hispanic	13 805 (89.5%)	5876 (93.3%)	3683 (94.2%)
Hispanic	1522 (9.9%)	396 (6.3%)	208 (5.3%)
Other	95 (0.6%)	28 (0.4%)	16 (0.4%)
Sex			
Male	6870 (44.5%)	2517 (39.9%)	1480 (37.9%)
Female	8549 (55.4%)	3782 (60.0%)	2426 (62.1%)
Age, y	56.0 (±14.8)	58.1 (±14.5)	59.0 (±14.0)
Baseline systolic BP, mm Hg	153.3 (±12.5)	153.4 (±12.3)	152.8 (±12.2)
Baseline diastolic BP, mm Hg	86.9 (±11.8)	86.6 (±11.6)	86.1 (±11.6)
Body mass index, kg/m^2	31.5 (±7.8)	31.8 (±7.9)	31.9 (±7.9)
Diabetes	3371 (21.9%)	1800 (28.6%)	1233 (31.6%)

Data are presented as number (n) and percent (%) or mean±SD. BP indicates blood pressure; and TSD, time since diagnosis.
*Categories with n<5 were removed.

rates of TI. Higher SBP and DBP increased, while aging reduced the likelihood of TI. Of note, a repeat BP measurement confirming uncontrolled BP increased the likelihood of TI by over 60%, an effect which was similar across groups defined by diabetes, race, and sex (Table 3). Guidance to repeat the measurement of BP following an uncontrolled reading is an established feature of quality improvement programs, including Kaiser Permanente and AMA MAP Hypertension.[11,26] Confirmatory measurements partially address the concern of inaccurate and nonrepresentative BP values, which contribute to therapeutic inertia.[20]

Limitations of this study include reliance on electronic health record data, which are often incomplete and inconsistent, especially with interoperability challenges when integrating data from multiple heterogeneous health care organizations with differing information systems and documentation practices. When relying on real-world data systems, information potentially relevant to the scope of the study for patients receiving health care services at external locations is not available. Our database is dependent on the integrity of data extracted from electronic health record systems and data warehouses, with limited capabilities for validation against source documents. Further, numerous errors occur during BP measurement in usual care settings.[27] BP values are occasionally entered in a text field note, and our database includes only values in the vital signs fields. Information on prescribed medications is often incomplete or erroneous, depending on accurate and timely medication reconciliation, which includes medications prescribed by clinicians using different electronic health record systems.[28] Our study period included the COVID pandemic, during which in-person visits, typically including BP values, declined, and virtual visits, less often tracking relevant patient vitals, increased.[29] Further, while evaluating the risk of cardiovascular events as a function of the time to treatment initiation was of interest, the data to assess clinical outcomes was not reliably available.

Our study addressed some limitations through data cleaning and validation methods used by the MAP Hypertension program, which requires a higher standard of encounter, medication, and diagnostic documentation completeness. Patients included in the analysis were required to have an outpatient visit history within the organization before their initial hypertension diagnosis, reducing the likelihood of erroneous inclusion from incomplete history.

In summary, TI during the first month after the diagnosis of hypertension leads to better hypertension control for 30 months than delayed beyond the first month.

PERSPECTIVES

Adults with untreated and uncontrolled hypertension are more likely to achieve BP control to <140/<90 in the first 6 months after diagnosis when antihyper- tensive monotherapy is initiated during the first month of diagnosis than at later time points. Moreover, improved control was sustained

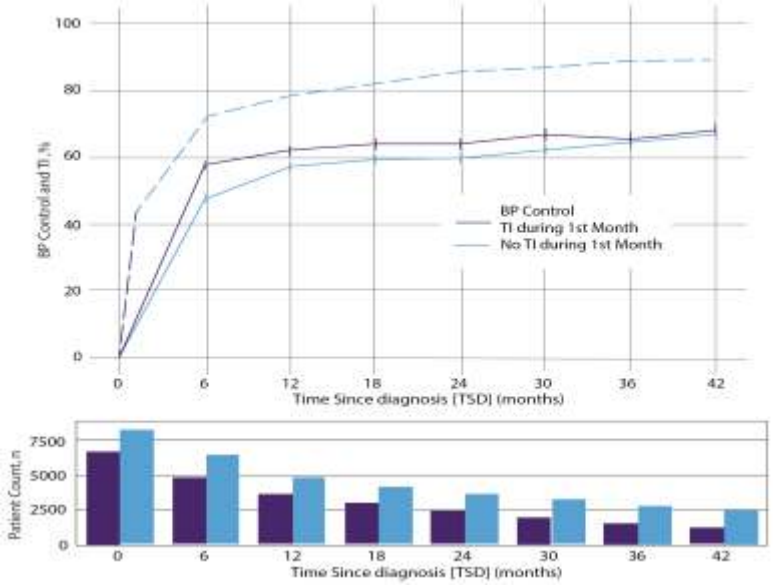


Figure 2. Top: The cumulative rate of treatment initiation (TI) over time is shown for all patients with distinction between those who had TI in the first month (dashed purple line) and those who did not have TI in the first month (dashed blue line) after the diagnosis of hypertension. Patients with TI during the first month (solid purple line) had higher blood pressure (BP) control rates from 6 up to 30 months after diagnosis of hypertension than those not initiated during the first month (solid blue line). Bottom: Count of patients by time period stratified by patients who were or were not initiated on antihypertensive therapy in the first month after the diagnosis of hypertension. TSD indicates time since diagnosis.

Table 3. Impact of Initial BP, Confirmatory Measurements, and Age on Odds Ratios (95% CI) for Therapeutic Initiation in Patients With Hypertension, Stratified by Clinical and Demographic Characteristics

Group	Initial SBP, 10 mm Hg	Initial DBP, 10 mm Hg	Confirmatory measurement	Age, 5 y
All patients (n=15 422)	1.14 (1.11–1.17)	1.07 (1.04–1.10)	1.68 (1.57–1.79)	0.90 (0.89–0.91)
Patients without diabetes (n=12 051)	1.14 (1.11–1.18)	1.06 (1.02–1.10)	1.64 (1.52–1.76)	0.91 (0.89–0.92)
Patients with diabetes (n=3371)	1.13 (1.07–1.20)	1.07 (1.00–1.15)	1.79 (1.54–2.08)	0.87 (0.85–0.90)
White patients (n=7351)	1.19 (1.14–1.24)	1.08 (1.03–1.14)	1.58 (1.43–1.75)	0.89 (0.87–0.91)
Non-White* patients (n=8071)	1.11 (1.07–1.15)	1.05 (1.01–1.10)	1.74 (1.53–1.91)	0.91 (0.90–0.93)
Male patients (n=6867)	1.16 (1.11–1.21)	1.09 (1.04–1.15)	1.63 (1.47–1.80)	0.92 (0.90–0.94)
Female patients (n=8555)	1.13 (1.09–1.18)	1.03 (0.99–1.08)	1.70 (1.55–1.86)	0.88 (0.87–0.90)

Data are shown as multivariable odds ratios and 95% CIs. Odds ratio for therapeutic initiation are provided according to differences in SBP, DBP, confirmatory measurement and age status. BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*
Non-White represents patients who had either a documented race of Black or other.

for 30 months following diagnosis in this initially treated group compared with the group that was not treated in the first month after diagnosis. While patients initiated on monotherapy during the first month following diagnosis of hypertension achieved higher control rates than individuals initiated at later time points, >30% remained uncontrolled at 3 years, indicating a need for more frequent treatment intensification. Confirming an uncontrolled BP during the visit was associated with a greater probability of treatment initiation. Importantly, hypertension control during the first 6 months after diagnosis provides greater cardiovascular protection than delayed control.

Acknowledgments

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the American Medical Association.

Affiliations

Robert B. Barrett - American Medical Association, Greenville, SC

Benjamin Riesser - American Medical Association, Greenville, SC

Benjamin Martin - Johns Hopkins University, School of Medicine, Baltimore

Neha Sachdev - American Medical Association, Chicago, IL

Michael K. Rakotz - American Medical Association, Chicago, IL

Susan E. Sutherland - American Medical Association, Greenville, SC

Brent M. Egan - American Medical Association, Greenville, SC

Table 4. Hazard Ratios (95% CI) for BP Control to <140/<90 Among Adults With Hypertension, Stratified by Clinical and Demographic Characteristics

Group	Initiated during first month	Initial SBP, 10 mmHg	Initial DBP, 10 mmHg	Age, 5 y
All patients (n=13 673)	1.21 (1.15–1.27)	0.87 (0.85–0.89)	0.94 (0.92–0.97)	0.98 (0.97–0.99)
Patients without diabetes (n=10 503)	1.22 (1.15–1.29)	0.88 (0.86–0.90)	0.95 (0.93–0.98)	0.98 (0.97–0.99)
Patients with diabetes (n=3170)	1.18 (1.06–1.31)	0.86 (0.82–0.89)	0.90 (0.86–0.95)	0.98 (0.96–1.00)
White patients (n=6557)	1.26 (1.17–1.35)	0.89 (0.86–0.92)	0.96 (0.93–0.99)	0.97 (0.96–0.98)
Non-White* patients (n=7116)	1.17 (1.09–1.25)	0.86 (0.83–0.88)	0.93 (0.90–0.96)	0.99 (0.98–1.01)
Male patients (n=5959)	1.18 (1.10–1.28)	0.86 (0.83–0.89)	0.93 (0.90–0.96)	1.00 (0.99–1.02)
Female patients (n=7714)	1.23 (1.16–1.32)	0.88 (0.85–0.90)	0.96 (0.93–0.99)	0.97 (0.96–0.98)

BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

* Non-White represents patients who had either a documented race of Black or other.

Footnote

Nonstandard Abbreviations and Acronyms

AMA	American Medical Association
BP	blood pressure
DBP	diastolic blood pressure
HR	hazard ratio
ICD10-CM	*International Classification of Disease, Tenth Revision, Clinical Modification*
MAP	Measure Accurately, Act Rapidly, Partner with Patients
SBP	systolic blood pressure
TI	treatment initiation

References

1. Martin-Ferna´ndez M, Vinyoles E, Real J, Soldevila N, Munoz MA, DelVal JL, Verdú JM, Domingo M, Mundet X. The prognostic value of blood pressure control delay in newly diagnosed hypertensive patients. J Hypertens. 2019; 36:426–431. doi: 10.10 97/HJH. 0000000000001896
2. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, et al; VALUE Trial Group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomized trial. Lancet. 2004;363:2022–2031. doi:10.1016/S0140-6736(04)16451-9
3. Laiteerapong N, John PM, Meltzer DO, Huang ES. Impact of delaying blood pressure control in patients with type 2 diabetes: results of a decision analysis. J Gen Intern Med.2011;27:640–646. doi: 10.1007/s11606-011-1951-y
4. Staessen JA, Thijs L, Fagard R, Celis H, Birkenhäger WH, Bulpitt CJ, de Leeuw PW, Fletcher AE, Forette F, Leonetti G, et al; Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Effects of immediate versus delayed antihypertensive therapy on out come in the Systolic Hypertension in Europe Trial. J Hypertens. 2004; 22:847–857. doi: 10.1097/0000 4872-2004 04000-00029
5. Miriampillai JE, Eskas PA, Heimark S, Kjeldsen SE, Narkewwicz K, Mancia G. A case for less intensive blood pressure control: it matters to achieve target blood pressure early and sustained below 140/90 mmHg. Prog Cardiov Dis. 2016; 59:209–218. doi:10.1016/j.pcad. 2016.09.002
6. Quality ID #236 (NQF 0018): Controlling high blood pressure. Dec 2021. https://qpp.cms.gov/docs/QPP_quality_measure_specifications/Claims-Registry-Measures/2022_Measure_236_MedicarePartBClaims.pdf.
7. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, DePalms SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. Hypertension. 2018;71:e13–e115.
8. Rea F, Corrao G, Merlino L, Mancia G. Initial antihypertensive treatment strategies and therapeutic inertia: evidence from a large population-based cohort. Hypertension. 2018; 72: 846–853. doi: 10.1161/HYPERTENSIONAHA.118.11308
9. De Backer T, Van Nieuwenhuyse B, De Bacquer D. Antihypertensive treatment in a general uncontrolled hypertensive population in Belgium and Luxembourg in primary care: therapeutic inertia and treatment simplification. The SIMPLIFY study. PLoS One. 2021; 16:e024 8471. doi: 10.1371/journal.pone. 0248471

10. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453–1457. doi: 10. 1016/S0140-6736(07)61602-X
11. Egan BM, Sutherland S, Rakotz M, Yang J, Hanlin RB, Davis R, Wozniak G. Improving hypertension control in primary care with the Measure accurately, Act rapidly and Partner with patients (MAP) Protocol: Results at 6 and 12 months. Hypertension. 2018;72:1320 –1327. doi: 10. 1161/HYPERTENSIONAHA. 118.11558
12. Smith SM, Winterstein AG, Gurka MJU, Walsh MG, Keshwani S, Libby AM, Hogan WR, Pepine CJ, Cooper-DeHoff RM. Initial antihypertensive regimens in newly treated patients: real world evidence from the OneFlorida+C Clinical Research Network. JAHA. 2022;11:e026652. doi: 10.1161 /JAHA.122.026652
13. Egan BM, Bandyopadhyay D, Shaftman SR, Wagner CS, Zhao Y, Yu-Isenberg KS. Initial mono- and combination therapy and blood pressure control in the first year. Hypertension. 2012; 59:1124–1131. doi: 10.1161/HYPERTENSIONAHA. 112.194167
14. Feldman RD, Zou GY, Vandervoort MK, Wong CJ, Nelson SA, Feagan BG. A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial. Hypertension. 2009; 53:646–653. doi: 10.1161 /HYPERTENSIONAHA. 108.123455
15. Chow CK, Atkins ER, Hillis GS, Nelson MR, Reid CM, Schlaich MP, Hay P, Rogers K, Billot L, Burke M, et al; QUARTET Investigators. Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial. Lancet. 2021;398:1043–1052. doi: 10.1016/S0140-6736(21)01922-X
16. Rodgers A, Salam A, Schutte AE, Cushman WC, de Silver HA, Di Tanna GL, Grobbee DE, Narkiewicz K, Ojji DB, Poulter NR, et al. Efficacy and safety of a novel low-dose triple single-pill combination of telmisartan, amlodipine and indapamide, compared with dual combinations for treatment of hypertension: a randomised, double-blind, active-controlled, international clinical trial. Lancet. 2024;404: 1536–1546. doi: 10.1016/S0140-6736(24)01744-6
17. Rea F, Corrao G, Merlino L, Mancia G. Early cardiovascular protection by initial two-drug fixed-dose combination treatment vs. monotherapy in hypertension. Eur Heart J. 2018;39:3654–366. doi: 10.1093/eurheartj/ehy420
18. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, Muiesan ML, Tsioufis K, Agabiti-Rosei E, Engi AEA, et al. 2023 ESH Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension. J Hypertension. 2023;41:1374– 2071. doi: 10.1097/ HJH.00000 00000003480
19. Bellows BK, Ruiz-Negrón N, Bibbins-Domingo K, King JB, Pletcher MJ, Moran AE, Fontil V. Clinic-based strategies to reach united states million hearts 2022 blood pressure control goals: a simulation study. Circ Cardiovasc Qual Outcomes. 2019; 12:e005 624.doi: 10.1161/ CIRCOUTCOMES .118.005624
20. Ali DH, Kiliç B, Hart HE, Bots ML, Biermans MCJ, Spiering W, Rutten FH, Hollander M. Therapeutic inertia in the management of hypertension in primary care. J Hypertens. 2021; 39:1238–1245. doi: 10.1097/ HJH.0000000000 002783
21. Okonofua EC, Simpson K, Jesri A, Rehman S, Durkalski V, Egan BM. Therapeutic inertia is an impediment to achieving Healthy People 2010 blood pressure control goals. Hypertension. 2006;47:1–7. doi:10. 1161/01. HYP.0000200702. 76436.4b
22. Linden A. Assessing regression to the mean effects in health care initiatives. BMC Med Res Methodol. 2013;13:119. doi: 10.1186/1471-2288-13-119
23. Wang N, Atkins ER, Salam A, Moore MN, Sharman JE, Rodgers A. Regression to the means in home blood pressure: analysis of the BP GUIDE study. J Clin Hypertension. 2020;22:1184–1191. doi:10. 1111/ jch.13933
24. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373: 2103–2116.
25. Egan BM, Li J, Wagner CS. Systolic blood pressure intervention trial (SPRINT) and target systolic blood pressure in future hypertension guidelines. Hypertension.2016;68: 318 –323. doi: 10.1161/HYPER-TENSIONAHA.116.07575
26. Jaffe MG, Young JD, Sidney S, Go AS. Improved blood pressure control associated with a large-scale hypertension program. JAMA. 2013;310:699–705. doi: 10.1001/ jama.2013.108769
27. Muntner P, Shimbo D, Carey RM, Charleston JB, Misra S, Myers MG, Ogedegbe G, Schwartz JE, Townsend RR, Urbina EM, et al. Measurement of blood pressure in humans: a scientific statement form the American Heart Association. Hypertension.2019; 73:e35–e66. doi: 10.1161/HYP.0000000000000087
28. Rangachari P, Dellsperger KC, Fallaw D, Davis I, Sumner M, Ray W, Fiedler S, Nguyen T, Rethemeyer RK. A mixed-method study of practitioners' perspective on issues related to EHR medication reconciliation at a health system. Qual Manage Health Care. 2019;28:84–95. doi: 10.1097 /QMH.0000000000000208
29. Alexander GC, Tajanlangit M, Heyward J, Mansour O, Qato DM, Stafford RS. Use and content of primary care office-based vs telemedicine care visits during the COVID-19 pandemic in the US. JAMA Netw Open. 2020;3:e2021476. doi: 10.1001 /jamanetworkopen.2020.21476

Therapeutic's

Diclomol®

Pain Buster

Caplets & Gel

Diclofenac Diethylamine 1.16% w/w

DICLOFENAC SODIUM (as enteric coated) 50mg

ACETAMINOPHEN 500mg

KNOCKS OUT

MUSCULAR & JOINT PAINS

Therapeutic Laboratories (N) Ltd.

372 Ikorodu Road, Maryland Ikeja.
Tel: 07013485520, 07013485527
therapeuticlabouratories@gmail.com

Therapeutic... Cares for your Health & Wellness

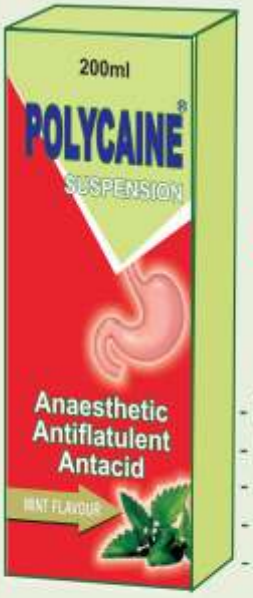
THE ONLY ANAESTHETIC ANTACID

POLYCAINE

Anaesthetic Antacid

With;

Oxethazaine & Simethicone

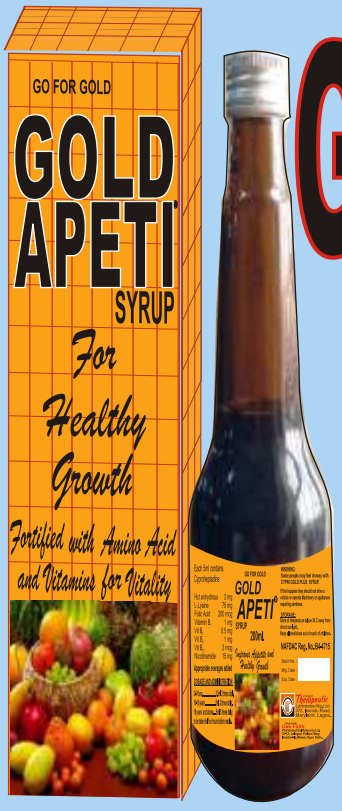


WORKS WHEN OTHER CONVENTIONAL ANTACIDS HAVE FAILED.

For Immediate Relief from;

- Ulcer pain and Pain due to hyperacidity
- Heartburn
- Gastric Acidity.
- Reflux Oessophagitis
- Flatulence & Dyspepsia

Therapeutic... Cares for your health



GOLD APETI®

SYRUP

For Improved Appetite & Healthy Growth

zolon
Healthcare Limited
(A member of the Emzor Group)

INTELLIGENT zolon Healthcare Limited (A member of the Emzor Group) SOLUTIONS

ZERO MALARIA

with **ZOMAL®**

Dihydroartemisinin 40mg + Piperaquine Phosphate 320mg

Curative Antimalarial

just **1 DOSE** per day for **3 DAYS**

If symptoms persist after 3 days, consult your Doctor

#LongerProtectionfromMalaria

Edic Building, 9, Town Planning Way, Ilupeju, Lagos, Nigeria. Tel: +234 (0) 700 225 5965, 0700 CALL ZOLON

Zolon Healthcare Limited | Zolon Healthcare Limited | Zolon Healthcare Limited | Zolon Healthcare

www.zolonhealthcare.com

INTELLIGENT SOLUTIONS

zolon Healthcare Limited
(A member of the Emzor Group)

INTELLIGENT zolon Healthcare Limited SOLUTIONS

ZOFIXIME®

Cefixime Tablets / Suspension USP

INDICATIONS

- Respiratory Tract Infections
- Otitis media
- ENT Infections
- Urinary tract Infections
- Bacterial Skin Infections
- Typhoid Fever (MDR)

Agent of choice over co-amoxiclav for empirical treatment of Community Acquired RTIs and Otitis media in Children

Sunderland R et al. (1994) Cefixime versus co-amoxiclav

WHO Recommended in Typhoid fever including Multi-Drug resistant strains

WHO Guidelines for the management of Typhoid Fever July 2011

Superior to ciprofloxacin in Community Acquired Pneumonia (CAP)

Annals of Ibadan Postgraduate Medicine Vol. 13 No. 2, December 2015

Effective in Gonococcal infections with no clinical resistance in Africa

South Africa J. Epilemial Infect page 103 2011: 26(3)

HDPE bottle provides good moisture barrier for better stability

Proudly Nigerian

Manufactured in Nigeria

Edic Building, 9, Town Planning Way, Ilupeju, Lagos, Nigeria. Tel: +234 (0) 700 225 5965, 0700 CALL ZOLON
Zolon Healthcare Limited Zolon Healthcare Limited Zolon Healthcare Limited Zolon Healthcare

Inflammatory and clinical risk factors for asthma attacks (ORACLE2): a patient-level meta-analysis of control groups of 22 randomised trials

Fleur L Meulmeester, MSc[a] · Samuel Mailhot-Larouche, MD[b] · Carlos Celis-Preciado, MD[b] · Samuel Lemaire-Paquette, MSc[c] · Sanjay Ramakrishnan, PhD[d] · Prof Michael E Wechsler, MD[e] · Prof Guy Brusselle, MD[f] · Prof Jonathan Corren, MD[g] · Jo Hardy, PhD[h] · Sarah E Diver, PhD[i] · Prof Christopher E Brightling, FMedSci[i] · Prof Mario Castro, MD[j] · Prof Nicola A Hanania, MD[k] · Prof David J Jackson, PhD[l] · Prof Neil Martin, MD[i,m] · Annette Laugerud, MD[m] · Emilio Santoro, PhD[n] · Chris Compton, MD[n] · Megan E Hardin, MD[o] · Cecile T J Holweg, PhD[p] · Allu Subhashini, MBBS[q] · Timothy S C Hinks, PhD[r] · Prof Richard W Beasley, DSc[s] · Jacob K Sont, PhD[a] · Prof Ewout W Steyerberg, PhD[a,t] · Prof Ian D Pavord, FMedSci[r] · Simon Couillard, MD[a,b,r]

Summary

Background

Clinical risk factors for severe asthma attacks have been identified, but their incremental prognostic values are unclear. Additionally, the incremental contribution of type 2 inflammation, a common, treatable process, is undetermined. We aimed to quantify the prognostic value of baseline characteristics and type 2 inflammatory biomarkers, specifically blood eosinophil count and fractional exhaled nitric oxide (FeNO), to predict asthma attacks.

Methods

In this systematic review and meta-analysis of randomised controlled trials (RCTs), Oxford Asthma Attack Risk Scale 2 (ORACLE2), we searched MEDLINE from Jan 1, 1993, to April 1, 2021, for trials investigating fixed treatment regimen effects on asthma attack rates for at least 6 months with baseline blood eosinophil count and FeNO. Eligible participants were aged 12 years or older with asthma (any severity) who had been randomly assigned to the control group of an RCT. Relevant trials were manually retrieved and reviewed by two independent reviewers (SC and IDP). Disagreements were discussed with five reviewers. Individual patient data (IPD) for meta-analysis were requested from study authors. We investigated the rate of severe asthma attacks (≥3 days of systemic corticosteroids) for at least 6 months and prognostic effects of baseline blood eosinophil count and FeNO in control group participants. Rate ratios (RRs) with 95% CIs were derived for annualised asthma attack rates from negative binomial models adjusted for key variables, including blood eosinophil count and FeNO, and interactions between these type 2 inflammatory biomarkers were explored. Certainty of evidence was assessed using GRADE. The heterogeneity of the included studies and potential for ecological bias were quantified by the concordance statistic (C-statistic). This study was registered with PROSPERO, CRD42021245337.

Findings

We identified 976 potentially eligible studies. After automated screening, we manually reviewed 219 full-text articles. Of these, 19 publications comprising 23 RCTs were eligible. 6513 participants (4140 [64%] female; 2370 [36%] male; three missing) spanning 22 RCTs were included for data analysis. 5972 (92%) of 6513 patients had moderate-to-severe asthma. 4615 asthma attacks occurred during 5482 person-years of follow-up (annualised rate 0·84 per person-year). Higher blood eosinophil count or FeNO was linked to higher asthma attack risk (per 10-fold increase, RR 1·48 [95% CI 1·30–1·68] for blood eosinophil count and 1·44 [1·26–1·65] for FeNO; high-certainty evidence). Other prognostic factors were attack history (yes vs no, RR 1·94 [1·61–2·32]); disease severity (severe vs moderate, RR 1·57 [1·22–2·03]); FEV1 percentage predicted (FEV1%; per 10% decrease, RR 1·11 [1·08–1·15]); and 5-item Asthma Control Questionnaire score (ACQ-5; per 0·5 increase, RR 1·10 [1·07–1·13]). High blood eosinophil

count and FeNO combined were associated with greater risk than either prognostic factor separately. Bronchodilator reversibility was associated with lower risk of severe asthma attacks (per 10% increase, RR 0·93 [0·90–0·96]), with the reduction observed primarily between 0% and 25%. Regarding heterogeneity of the included studies, the C-statistic ranged from 0·58 to 0·95, indicating major differences in patient and disease characteristics between studies. In the univariable meta-analysis per trial, we found substantial heterogeneity in associations between studies, with I2 statistics ranging from 0·56 to 0·97.

Interpretation

Blood eosinophil count, FeNO, asthma attack history, disease severity, low lung function (low FEV_1%), and symptoms (ACQ-5 score) are key predictors of asthma attacks. Conversely, we found that moderate bronchodilator reversibility was associated with reduced risk. These findings from high-quality multinational RCTs support incorporation of blood eosinophils and FeNO into clinical risk stratification for targeted risk reduction. More individualised clinical decision-making models should be explored.

Funding

National Institute of Health and Care Research Oxford Biomedical Research Centre; Association pulmonaire du Québec; Fonds de recherche du Québec—Santé; Québec Air-Intersectorialité-Respiratoire-Son network; Stichting Astma Bestrijding; Leiden University Fund; and Academy of Medical Sciences

Introduction

Asthma is a chronic disease affecting 400 million people worldwide and 10% of high-income country populations.[1] Due to morbidity, mortality, and health-care costs, asthma attacks are key outcomes that need to be predicted and prevented.[1,2]

Evidence supports risk assessment and treatment titration based on a history of a previous asthma attack and a list of clinical risk factors.[1] This framework is centred on symptoms (eg, night-time awakenings, activity limitations, and frequent reliever requirement) and evidence of damage (eg, lung function decline and previous attacks), which are identifiable only after they have happened. The limitations of this approach are that many of these prognostic factors, such as history of a previous asthma attack or sex assigned at birth, do not inform on modifiable pathways. Other factors, such as lung function and symptoms, are modifiable independently of an effect on asthma attacks. For example, long-acting bronchodilator monotherapy improves airflow and symptoms without reducing asthma attack risk.[3] Furthermore, lung function must decline to gain prognostic value, implying that the airways must be damaged to prompt more aggressive management. Identifying risk factors that inform on a causal and treatable biological pathway that underpins the adverse outcome of interest might be more useful than symptom management to improve outcomes.[4]

The past decade of research has revealed that type 2 inflammation is prevalent, measurable, treatable, and, in many cases, a cause of asthma attacks.[5–8] Type 2 inflammation is identifiable in the clinic by the use of two independent, complementary, and accessible biomarkers: the peripheral blood eosinophil count and fractional exhaled nitric oxide (FeNO).[5,9] Importantly, inflammation and the risk of attacks identified by these biomarkers are reduced with appropriate treatment,[7] be it low-dose inhaled corticosteroids in mild asthma,[10,11] a higher dose of inhaled corticosteroids in moderate asthma,[12,13] or biological agents targeting type 2 inflammatory pathways in moderate and severe asthma.[14–17] Blood eosinophils and FeNO have thus emerged as so-called treatable traits, crucial for redefining airway diseases.[5]

Research in context

Evidence before this study

Although risk factors for asthma attacks have been identified, there is limited understanding of the quantitative risk associated with these characteristics. We reviewed the 2023 findings of an annual, independent, international expert literature review that identified risk factors for asthma attacks. The list of 20 risk factors was based on 35 publications, none of which informed the multivariable prognostic relations across clinical profiles. We also reviewed 12 previously published clinical prediction models for asthma attacks and found none that included both blood eosinophil count and fractional exhaled nitric oxide (FeNO) as prognostic variables. Finally, we searched PubMed from Jan 1, 1993, to Feb 23, 2024, for clinical trials, systematic reviews, and meta-analyses assessing risk factors for asthma attacks. We used the search terms "asthma", "exacerbation", "risk", and "factors" with no language or time restrictions. This search yielded 192 results, including ten papers with multivariable analyses to predict asthma attacks. Only one publication included blood eosinophils and FeNO in their multivariable prediction model of asthma attacks. However, this analysis was a real-world randomised trial in adolescents in which background treatment fluctuated.

Added value of this study

We collaborated with academic, public, and pharmaceutical data providers to access high-quality individual patient data (IPD) from the control groups of 22 randomised controlled trials of asthma, for a total of 4615 attacks over 5482 person-years of follow-up. This first broad consortium in airway disease enabled us to perform a large IPD meta-analysis providing precise estimates of the prognostic value of type 2 inflammatory biomarkers and other characteristics while background therapy was controlled. Our multivariable analyses show that raised blood eosinophil count and FeNO are important, multiplicative, and prevalent predictors of asthma attacks, with synergistic prognostic effects (high-certainty evidence). The prognostic effects of blood eosinophil count and FeNO were incremental to other key risk factors, which our model adjusted for: asthma attack history, disease severity, lower lung function, and symptoms (high-certainty evidence). After adjusting for the presence of type 2 inflammation, we showed that moderate bronchodilator reversibility—traditionally considered the defining characteristic and diagnostic gold standard for asthma—was associated with reduced asthma attack risk (moderate-certainty evidence). These findings imply that clinical risk stratification in asthma should incorporate inflammatory phenotyping using blood eosinophil count and FeNO.

Implications of all the available evidence

This work quantifies the value of measurable inflammatory and clinical prognostic factors to identify patients at highest risk of asthma attacks. Unlike a predictor such as previous history of asthma attacks, tools such as the type 2 inflammatory biomarkers anticipate risk and provide opportunities to intervene preventively. In our large IPD meta-analysis, elevations in blood eosinophil count and FeNO were associated with an excess risk of asthma attacks. Considering the mechanistic, prognostic (ie, predicting adverse outcomes), and theragnostic (ie, predicting treatment responsiveness) values of type 2 inflammatory biomarkers, we speculate that individualised clinical decision making in asthma would be improved by a framework that includes these modifiable prognostic factors in clinical prediction models.

We previously proposed a proof-of-concept biomarker-stratified asthma attack scale, suggesting a novel framework for clinical decision making.[6,7] This conceptual prototype did not have a detailed and statistically robust assessment of multivariable prognostic relations and interactions. Importantly, previous studies have not yet shown the synergistic value of biomarkers in predicting asthma attacks, probably due to the correlation between the biomarkers and sample size constraints in previous analyses. In this individual patient data (IPD) meta-analysis, we aimed to quantify the prognostic value of baseline characteristics and type 2 inflammatory biomarkers, specifically blood eosinophil count and FeNO, to predict asthma attacks.

Methods

Search strategy and selection criteria

The study protocol was published and followed without deviation for this systematic review and meta-analysis.[18] We followed the PRISMA-IPD and REMARK checklists.[19,20] Eligible studies were randomised controlled trials (RCTs) published from Jan 1, 1993, to April 1, 2021, investigating fixed treatment regimen effects on asthma attack rates for 6 months or more, with baseline blood eosinophil count and FeNO. We searched MEDLINE using previously described terms (appendix p 4)18 with language restricted to English and French. Relevant trials were manually retrieved. Two reviewers (SC and IDP) independently reviewed retained publications to select trials for inclusion. Disagreements were discussed (SC, IDP, EWS, JKS, and FLM), with reasons for exclusion recorded. There were no specific trial exclusion criteria. Trial inclusion was unblinded. Authors of retained studies and trial sponsors were contacted and invited to contribute IPD and join the Oxford Asthma Attack Risk Scale 2 (ORACLE2) consortium. We contacted and received responses from all authors of included trials. Manual reference searching was performed for completed clinical trials that were in press at the time of the systematic review, which were identified through press releases.

We included IPD from patients aged 12 years or older diagnosed with asthma of any severity according to objective criteria who were randomly assigned to the control group of an RCT. The control group was the intervention corresponding to the lowest anti-inflammatory therapy intensity after randomisation (ie, randomly assigned to no inhaled corticosteroids, lowest-dose inhaled corticosteroids, or inhaled corticosteroids plus placebo). We excluded patients allocated to receive inhaled corticosteroids in the control group if they were not on inhaled corticosteroids before randomisation.[21] We also excluded patients missing data for both the baseline

blood eosinophil count and FeNO, asthma severity (Global Initiative for Asthma [GINA] treatment steps: 1 being very mild to 5 being severe asthma), follow-up duration, or number of severe asthma attacks during follow-up, or who did not consent to third-party data sharing.

Each study was analysed with the Cochrane Collaboration tool for assessing the risk of bias in randomised trials.[22] These judgments were made independently by two authors (CC-P and SC) based on the criteria for judging the risk of bias across five domains. Disagreements were resolved by discussion or consortium arbitration.

Data analysis

We requested anonymised IPD for 42 covariates (appendix pp 46–50). These data included demographics, GINA treatment step, baseline spirometry, severe asthma attack history, control group intervention, biomarkers, other GINA-defined risk factors at baseline,1 duration of follow-up under control therapy, and the outcome of interest (ie, the number of severe asthma attacks during follow-up). Severe asthma attacks were defined as acute asthma episodes requiring at least 3 days of systemic corticosteroids. Data were shared freely. The external data extraction programming code was requested and made available on GitHub whenever possible.

Extracted data were securely transferred to a digital storage solution provided by the University of Oxford. Under the terms of the data sharing agreements, access to the complete dataset was available to the primary authors and statisticians on the study protocol (FLM, EWS, IDP, and SC).

IPD were combined for the initial data analysis (IDA).[23] The IDA was conducted by two authors (FLM and SC) and comprised cleaning and screening of the extracted data, (graphical) description of the data distribution and missingness, and assessment of missingness. Detailed IDA steps are reported in the appendix (pp 4–7). Throughout the IDA process, discrepancies were resolved by consensus discussion, in direct collaboration with data providers. There were no duplicate data. In addition, R coding was supported by two independent statisticians. The heterogeneity of the included studies and potential for ecological bias were quantified by a membership concordance statistic (C-statistic). A high C-statistic reflects substantial differences between baseline characteristics of the patients in distinct studies. Outcome-specific heterogeneity across trials was quantified by I2 in univariable forest plots. All statistical analyses were performed with R version 4.4.1.3 The R code for data extraction and analysis is provided on Github.

The assessment of missingness and imputation methods are detailed in the appendix (pp 5–7). Briefly, the 42 covariates revealed patterns of systematically missing data within some trials (appendix pp 10–13). Missing values were estimated with multiple imputation by chained equations and the mice package in R, with results combined with Rubin's rules.[24] There were small discrepancies between some variable definitions across trials (appendix p 5). In some instances, more than 50% of observations were systematically missing in a variable, but key variables used in the analyses were not systematically missing (appendix p 13). Candidate predictors were sorted by standardisation and completeness. For example, blood eosinophil count, FeNO, IgE, age, BMI, sex, 5-item Asthma Control Questionnaire score (ACQ-5), spirometry, the number of severe asthma attacks in the previous 12 months, and treatment step had the most standard and complete reporting across trials (appendix p 73).

To assess the prognostic relationships between baseline characteristics and the risk of asthma attacks, we derived univariable and multivariable regression coefficients from negative binomial models for the annualised asthma attack rate using the R package MASS. To account for clustering of observations within studies, we specified enrolled trial as a factor in both the univariable (model one) and the main multivariable (model two) fixed-effects models. The univariable model assessed the variable of interest while accounting for log-transformed follow-up duration as an offset variable and enrolled trial as a factor. The main multivariable model further adjusted for covariates of asthma severity (treatment step 1–5), attack history of the previous year (any attack: yes or no), mean ACQ-5 symptom score, FEV1 percentage predicted (FEV1%) prebronchodilator, log-transformed blood eosinophil count, and log-transformed FeNO (both per 10-fold increase). These covariates were selected based on the conclusions of a previous systematic review of prediction models in asthma,[25] the expertise of the study statisticians and clinical experts, and the main study hypothesis that type 2 biomarkers are attractive predictors of risk that identify anti-inflammatory treatment opportunities while also being related to other prognostic factors.[5–7]

We quantified the incremental effects of each potential prognostic factor by clinically relevant changes in those variables (eg, typical treatment-associated changes in FeNO and blood eosinophil count, minimal clinically important

differences in ACQ-5 and FEV1%). Nagelkerke R2 was calculated for the multivariable model with the R package fmsb. Further univariable and multivariable rate ratios (RRs) and 95% CIs were derived for other prognostic factors with retrievable data, sequentially adding in then removing each factor in the main multivariable model.[1] A sensitivity analysis was conducted by repeating the univariable analyses per variable of interest for each trial separately. The trial-specific RRs (95% CIs) were subsequently pooled by person-years of follow-up to account for variations in trial characteristics. The relationship between a study's effect size and its precision was visualised for all analyses separately with funnel plots. Additionally, we performed two sensitivity analyses by excluding open-label trials and by excluding trials that we considered as having some risk of bias. We did not adjust for multiplicity since multiple prognostic factors were each considered relevant.[26] A spline curve was used to explore the prespecified [18] interaction analysis between biomarkers blood eosinophil count and FeNO with the annualised severe asthma attack rate (appendix pp 7–8). Finally, we explored the effect of FEV1 postbronchodilator reversibility on the annualised severe asthma attack rate with splines.

We assessed certainty of evidence using GRADE[27] for each prognostic factor. For assessments of the overall quality of evidence for each outcome that included pooled data from RCTs only, we downgraded the evidence from high quality by one for serious (or by two for very serious) study limitations (risk of bias), indirectness of evidence, serious inconsistency, or imprecision of effect estimates.

Ethical approval for individual studies was obtained from multiple local committees that were part of the underlying trials. We used anonymised data for secondary analysis and obtained additional ethical approval from the Oxford Tropical Research Ethics Committee. This systematic review and meta-analysis was registered with PROSPERO (CRD42021245337) and the protocol was previously published.[18]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We identified 976 reports in the literature review. After automated screening of titles and abstracts, we manually reviewed 219 full-text articles (appendix pp 52–66). Of these, 19 publications comprising 23 RCTs met our eligibility criteria (figure 1). Over 2·5 years, nine data sharing agreements were reached with three academic or public data providers and six pharmaceutical data providers to pool IPD from control groups centrally. An overview of the 23 identified RCTs is shown in table 1, with detailed study characteristics of the analysed trials provided in the appendix (pp 74–78). Data from one small RCT were no longer retrievable.[29] Of the 6841 control group patients for whom data were requested, 6513 participants spanning 22 RCTs were included for data analysis (figure 1). All trials except two had a low risk of bias (table 1; appendix p 14)[36] and there was no relevant overlap of participants. Of the 22 analysed trials, 20 were double-blind and two were open-label RCTs.

5972 (92%) of 6513 patients had moderate-to-severe asthma (treatment steps 3–5). The majority of participants had a history of severe attacks or poor asthma control, but 1280 (20%) of 6400 had not had an attack in the previous year and 929 (15%) of 6055 had at least partly controlled symptoms (ACQ-5 <1·5). Overall, 4615 attacks over 5482 person-years of follow-up occurred (annualised rate 0·84 per person-year), providing ample power for regression analyses and prediction modelling (table 2).[41] Extended variables and values disaggregated per trial are shown in the appendix (p 79–87).

In the main multivariable regression analyses, we observed that higher blood eosinophil count or FeNO values were each associated with higher risks of asthma attacks (per 10-fold increase, RR 1·48 [95% CI 1·30–1·68] for blood eosinophil count and 1·44 [1·26–1·65] for FeNO; high-certainty evidence). Other prognostic factors (high-certainty evidence) in the main multivariable model were attack history in the previous year (yes vs no, RR 1·94 [1·61–2·32]); disease severity (severe vs moderate, RR 1·57 [1·22–2·03]); FEV1% (per 10% decrease, RR 1·11 [1·08–1·15]); and ACQ-5 (per 0·5 increase, RR 1·10 [1·07–1·13]). The model had an explained variability of 23% (adjusted R2). The results of the univariable and multivariable regression models are shown in figure 2, with univariable outputs disaggregated per trial showing similar effect direction (appendix pp 15–35) and weighted-average effect size (appendix p 36). To assess biomarker prognostic differences further, risks at the 75th and 25th percentiles of the sample distribution were compared. A baseline blood eosinophil count of 0·42 × 109 cells per L versus 0·14 × 109 cells per L was associated with an adjusted RR of 1·16 (95% CI 1·12–1·21) and a baseline FeNO of 42 versus 14 parts per billion was associated with an adjusted RR of 1·11 (1·07–1·15; appendix p 37). RRs for 2-fold

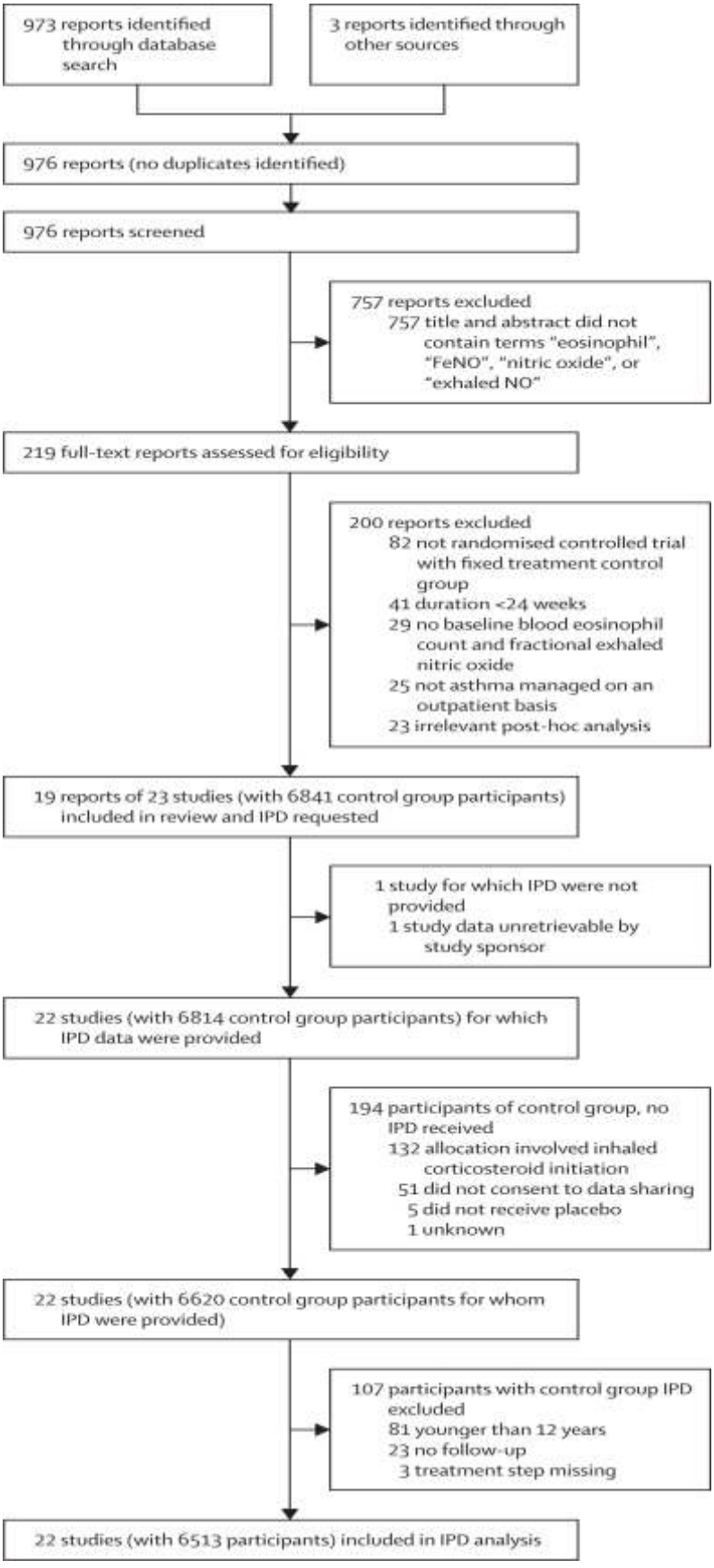


Figure 1 Study selection

changes in blood eosinophil count and FeNO values are shown in the appendix (p 37). The absolute rates are estimated with spline curves (figure 3 and appendix p 38).

Among other explored variables, we found that a higher risk of a severe asthma attack was predicted by female sex (RR 1·24 [95% CI 1·13–1·36]; high certainty), higher BMI (per kg/m^2, RR 1·01 [1·01–1·02]; high certainty), number of previous hospitalisations for asthma (per event, RR 1·23 [1·15–1·32]; moderate certainty, downgraded due to inconsistency in reporting), smoking status (ex-smoker vs non-smoker, RR 1·32 [1·18–1·47]; moderate certainty, downgraded due to selection bias), and greater pack-years (per pack-year, RR 1·04 [1·03–1·06]; moderate certainty, downgraded due to selection bias), allergic rhinitis (RR 1·12 [1·01–1·24]; moderate certainty, downgraded due to inconsistency in reporting), chronic rhinosinusitis with nasal polyposis (RR 1·16 [1·01–1·32]; moderate certainty, downgraded due to inconsistency in reporting), chronic rhinosinusitis without nasal polyposis (RR 1·20 [1·03–1·39]; moderate certainty, downgraded due to inconsistency in reporting), and lower FEV_1/FVC ratio (per 10% decrease, RR 1·14 [1·10–1·19]; high certainty). FEV_1 postbronchodilator reversibility was associated with a lower risk of severe asthma attacks (per 10% increase, RR 0·93 [0·90–0·96]; moderate certainty due to inconsistency in effect across trials). No prognostic effect was seen for higher age (high certainty), patient reported eczema (moderate certainty, downgraded due to inconsistency in reporting), patient-reported airborne allergen sensitisation (moderate certainty, downgraded due to inconsistency in reporting), inhaled corticosteroid adherence (low certainty, downgraded due to inconsistency in

	Control	Patients included from the control group	Duration of folllow-up, weeks	Overall bias assessment (concerns or comment)
AZISAST[28] (UZ Ghent)	Placebo tablets	54/54 (100%)	26	Low
Benralizumab phase 2a in South Korea and Japan[29] (AstraZeneca)	Placebo subcutaneous injections	0/27	52	Some concerns (data unretrievable by study sponsor)
Benralizumab phase 2b[30] (AstraZeneca)	Placebo subcutaneous injections	211/222 (95%)	52	Low
CAPTAIN[12] (GSK)	Fluticasone furoate 100 µg combinations (fluticasone furoate plus vilanterol, luticasone furoate plus vilanterol plus umeclidinium)	1218/1218 (100%)	24–52	Low
COSTA[31] (Genentech)	Placebo subcutaneous injections	145/145 (100%)	36	Low
DREAM[14] (GSK)	Placebo intravenous perfusions	155/158 (98%)	52	Low
Dupilumab phase 2b[32] (Sanofi-Regeneron)	Placebo subcutaneous injections (all volumes)	155/158 (98%)	24	Low
EXTRA[33] (Genentech)	Placebo subcutaneous injections (all schedules)	420/423 (99%)	48	Low
LAVOLTA I, LAVOLTA II[34] (Eli Lilly)	Placebo subcutaneous injections	726/726 (100%)	52	Low
LUSTER-1, LUSTER-2 [35] (Novartis)	Placebo tablets	585/585 (100%)	52	Low
LUTE, VERSE[36](Eli Lilly)	Placebo subcutaneous injections	116/116 (100%)	24	Some concerns (randomisation process and missing outcome data)
MILLY[37] (AstraZeneca)	Placebo subcutaneous injections	112/112 (100%)	24	Low
NAVIGATOR[16] (AstraZeneca)	Placebo subcutaneous injections	519/531 (98%)	52	Low (open label)
Novel START[10] (MRINZ)	Salbutamol 200 µg inhaled when required	218/223 (98%)	52	Low
PACT[38] (National Heart, Lung, and Blood Institute)	Montelukast 5 mg orally once a day plus placebo inhaled twice a day plus albuterol inhaled when required	16/95 (17%)	48	Low (many patients who were younger than 12 years excluded)
PATHWAY[39] (AstraZeneca)	Placebo subcutaneous injections	133/138 (96%)	52	Low
PRACTICAL[21] (MRINZ)	Budesonide 200 µg inhaled twice a day plus terbutaline 500 µg inhaled when required	307/448 (69%)	52	Low (open label; patients not on inhaled corticosteroid before randomisation excluded)
QUEST[15] (Sanofi-Regeneron)	Placebo subcutaneous injections (all volumes)	634/638 (99%)	52	Low
STRATOS 1, STRATOS 2[40] (AstraZeneca)	Placebo subcutaneous injections (all schedules)	801/828 (97%)	52	Low

Table 1

Summary of 19 reports of the 23 identified trials meeting inclusion criteria

Data are n/N (%). A more detailed summary is provided in the appendix (pp 63–67). MRINZ=Medical Research Institute of New Zealand

Table 2: Baseline characteristics of the control groups of 22 asthma randomised controlled trials

		Total (N=6513)
Demographics		
Age, years		50 (39–59), n=6510
Sex		
	Female	4140/6510 (64%)
	Male	2370/6510 (36%)
BMI, kg/m^2		27·0 (24·5–32·3), n=3774
History of smoking		1199/6396 (19%)
Ethnicity or race		
Asian		502/4781 (10%)
Black or African American		267/4781 (6%)
Other or multiple		187/4781 (4%)
White		3825/4781 (80%)
Region		
Asia		344/3909 (9%)
Europe		1475/3909 (38%)
North America		1244/3909 (32%)
Oceania		520/3909 (13%)
South Africa		88/3909 (2%)
South America		238/3909 (6%)
Patient-reported comorbidities		
Airborne allergen sensitisation		1721/2940 (59%)
Eczema		330/3184 (10%)
Allergic rhinitis		2501/5172 (48%)
Chronic rhinosinusitis without nasal polypsosis		439/4141 (11%)
Chronic rhinosinusitis with nasal polypsosis		598/4161 (14%)
Psychiatric disease		420/3300 (13%)
Baseline asthma medication		
Treatment step		
Step 1		226/6513 (3%)
Step 2		315/6513 (5%)
Step 3		859/6513 (13%)
Step 4		2555/6513 (39%)
Step 5		2558/6513 (39%)
On maintenance oral corticosteroids		261/5417 (5%)
Asthma symptoms and history		
Asthma Control Questionnaire-5 score		2·4 (1·8–3·0)
≥1·5		5126/6055 (85%)
<1·5		929/6055 (15%)
Severe exacerbation in past 12 months		
Yes		5120/6400 (80%)
No		1280/6400 (20%)
Previous intensive care unit admission or intubation		134/2545 (5%)
Lung function		
FEV$_1$ percentage predicted		63·9% (52·9–73·0), n=5948
FEV$_1$/FVC ratio		64·2% (56·0–72·3), n=5948
Percentage reversibility of FEV$_1$		17·0% (10·0–27·7), n=4654
Biomarkers		
Blood eosinophil count, ×10^9 cells per L		0·250 (0·140–0·420), n=6433
Fractional exhaled nitric oxide, parts per billion		23 (14–42), n=5981
Total IgE, ng/mL		171 (64–434), n=5889
Follow-up in trial		
Follow-up duration*, days		363 (251–365)
Total number of follow-up years in trial		5482
Total number of severe exacerbations in trial		4615
≥1 severe exacerbations		2268/6513 (35%)

Data are median (IQR), n, or n/N (%), unless otherwise specified. Full baseline characteristics are reported in the appendix (pp 68–76). The numbers of patients with available data are shown. FVC=forced vital capacity.

* Follow-up duration refers to the entire time participants were monitored under control group therapy.

reporting and over-representation of adherent patients), and serum IgE (high certainty).

When comparing the univariable and multivariable analyses, we observed that FEV$_1$ postbronchodilator reversibility (per 10% increase) had a stronger negative prognostic value, since the RR decreased from 0·98 (95% CI 0·95–1·01) in the univariable analysis to 0·93 (0·90–0·96) in the multivariable analysis.

Sensitivity analyses excluding open-label trials (Novel START [n=218] and PRACTICAL [n=307]) and excluding trials with some risk of bias (LUTE [n=66] and VERSE [n=50]) showed similar results (appendix pp 39–40). A post-hoc fully adjusted multivariable model (appendix p 41) showed similar prognostic effects to the main analysis.

We observed synergistic effects between blood eosinophil count and FeNO ($p_{interaction}$=0·045), as evidenced by the dissociating spline curves in figure 3A. High type 2 inflammatory burden was prevalent in the study population (figure 3B), an observation also found in the subset of RCTs not selecting patients according to biomarkers (appendix p 42). Synergy and high prevalence were also seen in categorical analyses, as the prespecified[18] combined elevation of a blood eosinophil count of 0·30 × 10^9 cells per L or higher and FeNO 50 parts per billion or higher was associated with nearly double the RR compared with a blood eosinophil count of less than 0·15 × 10^9 cells per L and a FeNO less than 25 parts per billion (RR 1·47 [95% CI 1·30–1·66] vs 0·76 [0·68–0·86]; appendix pp 88–89). However, FEV$_1$ postbronchodilator reversibility showed a non-linear relationship with future severe asthma attacks (figure 3C). Notably, the common 12% reversibility (figure 3D) was associated with some of the lowest adjusted attack rates, whereas risk

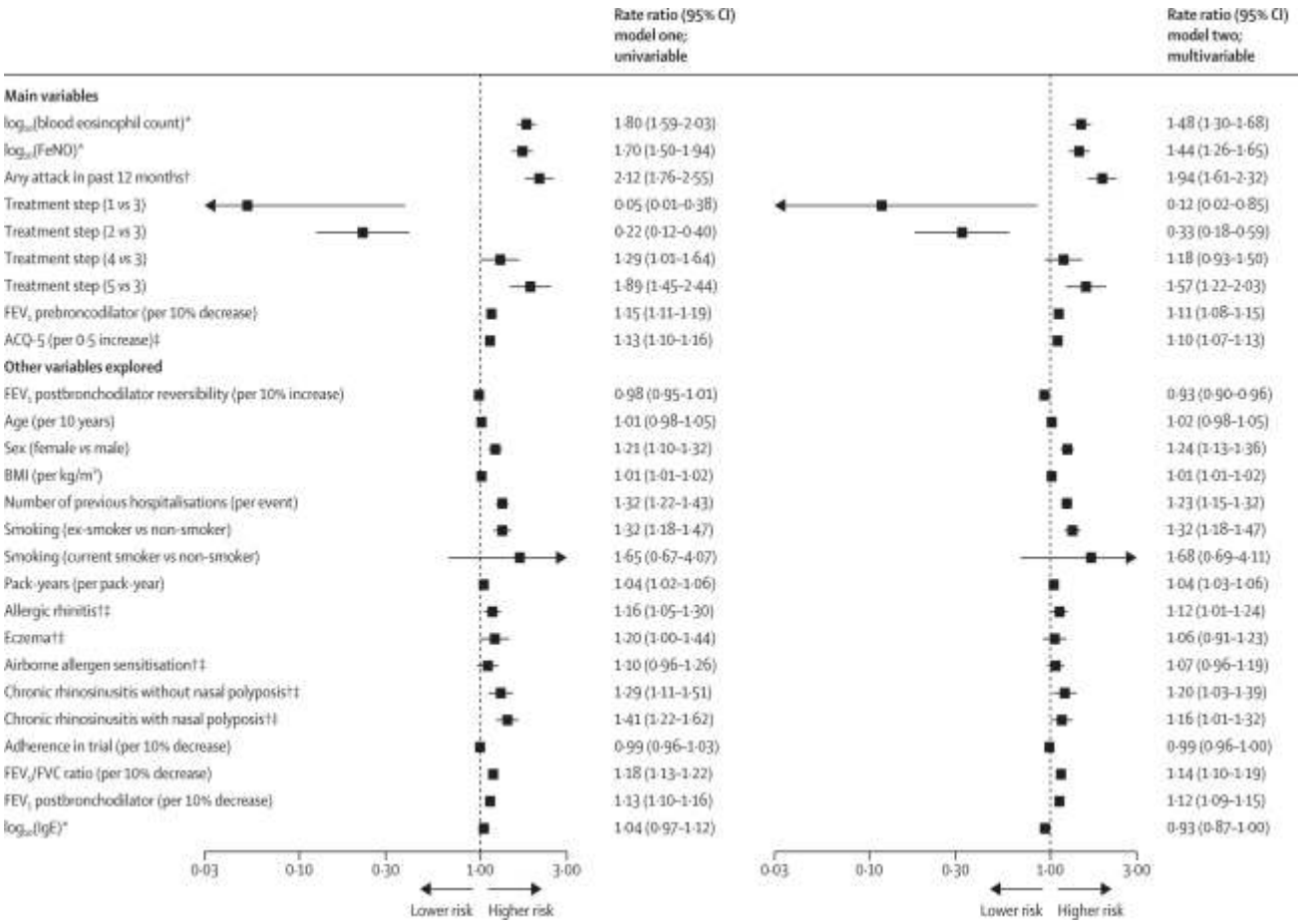


Figure 2 Forest plots of the associations between baseline characteristics and number of severe asthma attacks during follow-up

Rate ratios correspond to the univariable (model one) and multivariable (model two) models. Model one was adjusted for enrolled trial as a factor and follow-up duration as an offset variable. Model two was also adjusted for asthma attack in the past year (yes vs no), asthma severity (treatment step 1–5), FEV_1 prebronchodilator, ACQ-5 symptom score, blood eosinophil count, and FeNO. Asthma attacks were defined as acute asthma episodes requiring at least 3 days of s ystemic corticosteroids. ACQ-5=5-item Asthma Control Questionnaire. FeNO=fractional exhaled nitric oxide. FVC=forced vital capacity. *Per 10-fold increase. †Dichotomous variable (yes vs no). ‡Patient reported.

was higher with reversibility greater than 25%. A sensitivity analysis excluding the 11 RCTs that required postbronchodilator reversibility at baseline (removing 4269 [66%] of 6513 participants)[12,15,16,32,34,36,40] and evaluating the prognostic value by FEV_1% categories prebronchodilator and postbronchodilator, supported the overall negative prognostic effect of reversibility (appendix pp 43, 90). Reversibility was distributed similarly across asthma severities (appendix p 44).

The C-statistic for identification of a trial versus other trials ranged from 0·58 to 0·95 (appendix p 72), indicating major differences in patient and disease characteristics between studies. In the univariable meta-analysis per trial, we found substantial heterogeneity in associations between studies, with I2 statistics ranging from 0·56 to 0·97 (appendix p 15–35).

Discussion

In this large, IPD meta-analysis of control groups from RCTs across various clinical contexts, countries, and inclusion criteria, we showed that two biomarkers of type 2 airway inflammation—blood eosinophils and FeNO—provide valuable and synergistic incremental prognostic information regarding the risk of asthma attacks. The incremental relative risk associated with these biomarkers and key clinical prognostic factors implies that the absolute risk due to type 2 inflammation is greater in patients with additional clinical prognostic factors. Specifically, 10-fold increases in baseline blood eosinophil count and FeNO were each associated with a 1·4-fold higher risk of a severe asthma attack. Such substantial changes in these measurements reflect those that can occur with the initiation or discontinuation of an anti-inflammatory treatment.[14–16,30,42] These prognostic effects were greater than those associated

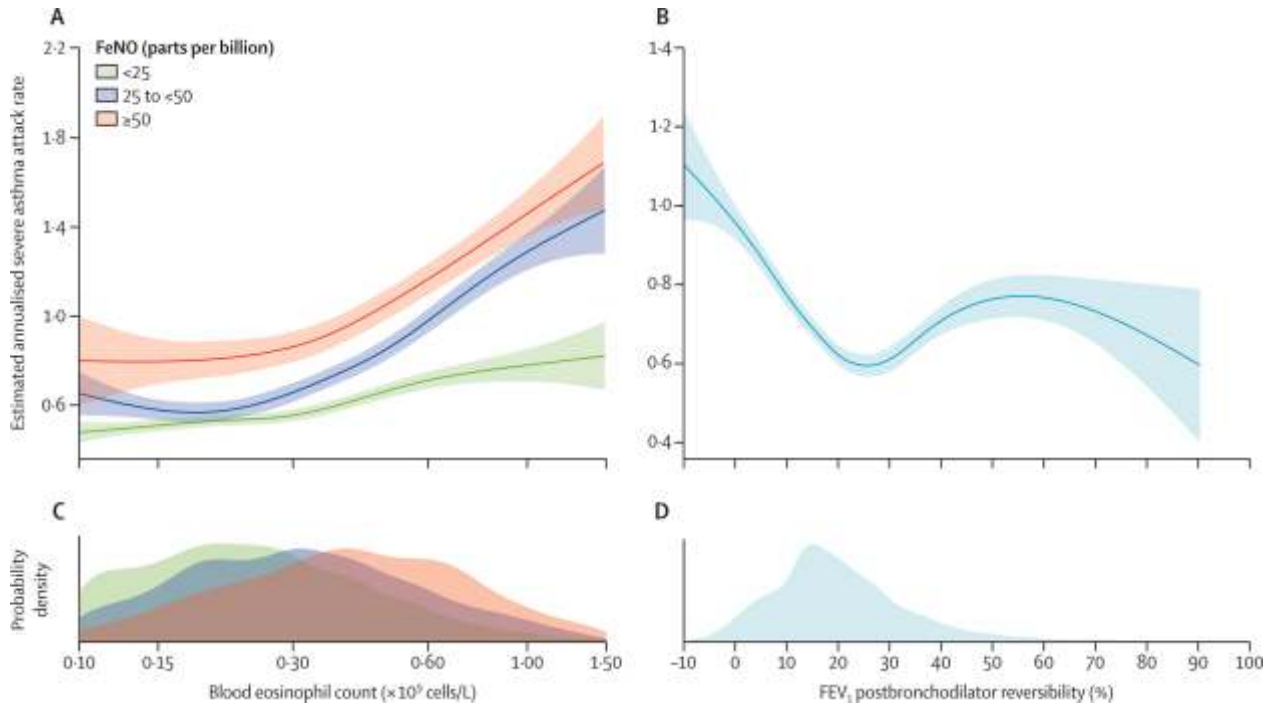


Figure 3 Relationships between baseline blood eosinophil count per FeNO group and FEV_1 postbronchodilator reversibility and the estimated annualised severe asthma attack rate, with density plots

(A) Spline plot of the relationship between blood eosinophil count ($\times 10^9$ cells per L) and the estimated annualised severe asthma attack rate,per group of baseline FeNO value. (B) Spline plot of the relationship between FEV_1 postbronchodilator reversibility (%) and the estimated annualised severe asthma attack rate. The y-axis has a different scaling in B than the scaling for the severe asthma attack rate in A. (C) Probability density of baseline blood eosinophil count observations per group of baseline FeNO value in the imputed datasets. (D) Probability density of baseline FEV_1 postbronchodilator reversibility observations in the imputed datasets. Density plots show the distribution of a continuous variable, with the area under the curve representing the likelihood of different values occurring. Higher peaks indicate more frequent values, with the total area representing all values. FeNO=fractional exhaled nitric oxide.

with minimal clinically important differences in baseline FEV_1 and ACQ-5. By contrast, after adjusting for type 2 biomarkers, moderate bronchodilator reversibility was associated with reduced risk of future asthma attacks.

The combination of blood eosinophils and FeNO might be more useful than either biomarker alone, since each reflects distinct components and compartments of the type 2 immune response in asthma. Blood eosinophil counts reflect circulating IL-5 and the systemic pool of available effector cells, whereas FeNO is an IL-13-mediated biomarker also reflecting type 2 cytokine, chemokine, and alarmin signalling in the airway compartment.[9] Accordingly, elevations of both of these biomarkers are likely to be associated with migration of eosinophils to the bronchi and the development of airway pathology associated with asthma attacks, including abnormal mucus production, airway wall thickening, and increased bronchial motor tone.[5,9,43] We previously found that patients with persistently elevated FeNO and blood eosinophil count had corticosteroid-resistant type 2 inflammation and refractory asthma despite adequate inhaled corticosteroid therapy.[42] Moreover, airway mucus plugging in people with asthma has been linked to eosinophilia and greater airflow obstruction.[43] Thus, raised type 2 biomarkers have substantial incremental utility to identify patients at risk. This finding is important as these measurements are known to identify patients who benefit most from anti-inflammatory therapies.[7,12–17]

Our analyses focused on type 2 biomarkers while adjusting for clinical prognostic factors that are generally acknowledged as important.[1] By quantifying the multivariable prognostic values for inflammatory and clinical covariates, we found that the strongest increases in risk were associated with asthma attack history and treatment step (reflecting increased therapeutic intensity of asthma). Although these two cardinal variables are robust to identify patients at risk, they do

not reveal targetable mechanisms on the individual level. Similarly, other identified prognostic factors, such as symptoms and impaired lung function, can be modified independently of an effect on asthma attacks. Our results support the incremental value of biomarkers to improve risk stratification. Notably, the combination of blood eosinophils and FeNO was not part of clinical prediction models identified in a systematic review published in 2018.[25] Surprisingly, bronchodilator reversibility, a common diagnostic tool and inclusion criterion for asthma trials, was associated with a reduced risk of asthma attacks. Overall, these findings have important implications for clinical practice as they highlight the shortcomings of relying on symptoms, lung function, and bronchodilator reversibility to identify patients at high risk and make individualised treatment decisions.[1,5,44] Acknowledging that asthma attack history and disease severity had the greatest prognostic effects, further analyses can focus on understanding the interactions between type 2 inflammation and other clinical predictors in the dataset.

A notable strength of this meta-analysis compared with other prognostic studies in airway disease is the collaboration of academic, public, and pharmaceutical data providers, allowing efficient use of high-quality RCT IPD. Our study of the control groups of RCTs contrasts with previous prognostic analyses involving blood eosinophils and FeNO that were conducted in real-world settings or clinical trials in which background treatment fluctuated.[45] The advantage of RCT data is that baseline prognostic factors and outcomes are assessed prospectively, with high confidence in diagnostic accuracy, treatment adherence, and stability. Further more, we adjusted our analyses for the heterogeneity observed between RCTs, improving the applicability of our findings across various clinical contexts, countries, and patient characteristics. In effect, the prognostic values we report in ORACLE2 are robust prospective estimates for a status quo scenario (ie, if treatment is unchanged following a clinical encounter).

We acknowledge that our study has limitations. First, our dataset comprised selected RCT populations that had lower asthma attacks rates than expected due to regression to the mean and a placebo response. Nonetheless, we believe RCTs are a key high-quality source of evidence for prognostic factors because their control groups provide long-term clinical observation under stable background treatment. Second, we identified discrepancies between definitions of some variables in the included RCTs. These discrepancies improve the generalisability of the results as the prognostic effects remained consistent despite variations in study definitions. In keeping with best practices,[23] we have disclosed our data dictionary, extraction code, and analytical code to ensure transparency and reproducibility of our study. Nevertheless, we acknowledge that patient-reported comorbidities, such as eczema, allergic rhinitis, airborne allergic sensitisation, and chronic rhinosinusitis with or without nasal polyposis, were unverified and inconsistently reported.[46] Accordingly, we downgraded the certainty of evidence for those characteristics' prognostic effects. Third, the IPD meta-analysis included studies published up to April 1, 2021, which were identified through MEDLINE only. We were constrained in our ability to expand or update the systematic review after protocol development due to contracting requirements and practicalities. Fourth, we were unable to conduct analyses on social determinants of health, such as race, ethnicity, or socioeconomic status, due to the absence of standardisation for race and ethnicity across trials and the absence of data for socioeconomic status.[1] Fifth, we quantified the risk attributable to type 2 inflammation using metrics adapted to the log-normal data distribution, and to maximise therapeutic relevance, we used 10-fold changes for the biomarkers to mirror the effects of initiation or discontinuation of an antiinflammatory treatment[14–16,30,42] and we estimated prognostic effects for absolute biomarker differences for pre-specified categories,[18] inter-quartile cutpoints,[41] and 2-fold changes. Finally, studies differed in patient profile and design. Although we included the full range of asthma severities, most patients had moderate-to-severe asthma, potentially due to the predefined exclusion of trials not measuring both blood eosinophils and FeNO. Notably, studies applied different control group formulations and schedules. Importantly, despite between-study differences in the selection of patients, intervention, and exact definitions of covariates, the prognostic effects were largely consistent across studies.

Our findings have substantial clinical implications. First, high-quality control group RCT IPD analyses show that inflammatory and clinical risk stratification should be combined to estimate risk on an individual basis. Second, our observation that blood eosinophil count and FeNO are synergistic prognostic factors in the context of the status quo scenario of RCT control groups (ie, no change in background therapy following assessment) has substantial implications for future risk prediction modelling.[18] Indeed, one approach to targeted risk reduction is to conjugate risk stratification with

mechanistic targeting (ie, to focus on prognostic factors that also predict benefits from specific preventive treatment).[47] This approach has been successful in cardiovascular disease,[4] in which the focus is on the effect of modifiable factors, such as blood pressure and cholesterol, on top of unmodifiable risk factors, such as age and sex. Just as meta-regression studies have shown that statin therapies target the modifiable risk of heart attacks in a biomarker-dependent way,48 the high asthma attack risk for people with type 2-high asthma in our dataset probably reflects the magnitude of the treatment opportunity. Specifically, we observed a higher annualised asthma attack rate for patients with high biomarkers than for those with low biomarkers, mirroring the previously reported treatment effect of higher-dose inhaled corticosteroids or biologics in biomarker-high asthma.[7] These findings support the development of a framework analogous to that used in cardiovascular medicine to predict and prevent asthma attacks on an individual basis.[47]

In conclusion, blood eosinophil count, FeNO, asthma attack history, disease severity, lower lung function, and symptoms (ACQ-5 score) are key predictors of asthma attacks when treatment is unchanged. Importantly, high blood eosinophils and high FeNO together are associated with a greater risk than either factor alone, each highlighting specific treatment opportunities.[12–17,49] Moderate FEV_1 postbronchodilator reversibility is associated with reduced risk of future asthma attacks. These findings underscore the importance of comprehensive risk stratification of people with asthma. Future prediction models using the ORACLE2 dataset could be centred on biomarkers for more individualised clinical decision making.

Contributors

FLM conducted data analyses and interpretation, verified the underlying data, and contributed to the first draft of the manuscript. SM-L, CC-P, SL-P, and SR contributed to data analysis. MEH, GB, JC, JH, SED, CEB, MC, NAH, DJJ, NM, AL, ES, CC, CTJH, AS, and MEW were primary investigators or employees of study sponsors of the underlying trials contributing IPD. TSCH contributed to data interpretation. RWB contributed to underlying trials, data interpretation, and study oversight. JKS and EWS contributed to data analysis, interpretation, and study oversight. IDP contributed to underlying trials, study preparation, data interpretation, and study oversight. SC set up the study, verified the underlying data, contributed to data collection, analysis, and interpretation, and is the guarantor of the study. FLM, EWS, IDP, and SC had access to the complete dataset. All authors read and approved the final draft of the manuscript and agreed to submit for publication.

Affiliations & Notes

a. Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, Netherlands
b. Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Sherbrooke, QC, Canada
c. Centre de recherche du CHUS, CIUSSS de l'Estrie—CHUS, Sherbrooke, QC, Canada
d. Institute for Respiratory Health, University of Western Australia, Perth, WA, Australia
e. National Jewish Health, Denver, CO, USA
f. Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium
g. UCLA, Los Angeles, CA, USA
h. North Bristol NHS Trust, Bristol, UK
i. Department of Respiratory Sciences, Institute for Lung Health, NIHR Respiratory BRC, University of Leicester, Leicester, UK
j. Pulmonary Critical Care & Sleep Medicine, University of Kansas, Kansas City, KS, USA
k. Baylor College of Medicine, Houston, TX, USA
l. Guy's Severe Asthma Centre, Guy's and St Thomas' Hospitals, London, UK
m. AstraZeneca, Cambridge, UK
n. GlaxoSmithKline, London, UK
o. Sanofi, Cambridge, MA, USA
p. Genentech, San Francisco, CA, USA
q. Novartis Healthcare Private, Hyderabad, India
r. Respiratory Medicine Unit and Oxford Respiratory NIHR BRC, Nuffield Department of Medicine, University of Oxford, Oxford, UK
s. Medical Research Institute of New Zealand, Wellington, New Zealand
t. Julius Center, University Medical Center Utrecht, Utrecht, Netherlands

Data sharing statement

Data underlying each trial are available according to the terms in the original trial publications. The aggregate dataset generated by this study might be shared if proposed use of the data has been approved by all original data providers. The external data extraction programming code was requested and made available on GitHub whenever possible (https://github.com/flmeulmeester/ORACLE2/).

Declaration of interests

Outside this work, CC-P has received speaker honoraria from AstraZeneca, GSK, and Sanofi-Regeneron; and consultancy fees from AstraZeneca, GSK, and Sanofi-Regeneron. SR has received salary support from the National Institute for Health and Care Research (NIHR) UK and the

Charlie's Foundation for Research. SR also declares speaker fees from GSK and AstraZeneca, and conference travel support from AstraZeneca. MEW has received consulting, advisory, or speaking honoraria from Allakos, Amgen, Areteia Therapeutics, Arrowhead Pharmaceutical, AstraZeneca, Avalo Therapeutics, Celldex, Connect Biopharma, Eli Lilly, Equillium, GSK, Incyte, Kinaset, Kymera, Merck, MyBiometry, Pharming, Phylaxis, Pulmatrix, Rapt Therapeutics, Recludix Pharma, Regeneron, Roche/Genentech, Sanofi/Genzyme, Sentien, Sound Biologics, Tetherex Pharmaceuticals, Uniquity Bio, Upstream Bio, Verona Pharma, and Zurabio. GB has received speaker honoraria from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Merck Sharp & Dohme, Novartis, and Sanofi-Regeneron; he is President of the Belgian Respiratory Society. JC has received grants or contracts from Regeneron, Sanofi, and Novartis. He also has received consulting fees from AstraZeneca, Amgen, Regeneron, and Sanofi and payment of honoraria from AstraZeneca, Amgen, Regeneron, and Sanofi. SED has received consultancy fees from AstraZeneca. CEB has received grants and consultancy fees from 4D Pharma, Areteia, AstrZeneca, Chiesi, Genentech, GSK, Mologic, Novartis, Regeneron Pharmaceuticals, Roche, and Sanofi. MC has received grants or contracts from American Lung Association, AstraZeneca, Gala Therapeutics, Genentech, GSK, National Institutes of Health, Nocion, Novartis, PCORI, Pulmatrix, Sanofi-Aventis, Shionogi, and Theravance Biopharma. He has also received consulting fees from Allakos, Amgen, Apogee, Apreo Health, Arrowhead Pharmaceuticals, Blueprint Medicines, Connect BioPharma, Evommune, Genentech, GSK, Jasper, Kinaset, Merck, Novartis, OM Pharma, Pfizer, Pioneering Medicines, Sanofi-Aventis, Teva, Third Rock Ventures, Upstream Bio, and Verona Pharmaceuticals; honoraria from Amgen, AstraZeneca, Med Learning Group, Regeneron Pharmaceuticals, and Sanofi; and stock options from Aer Therapeutics. NAH has received honoraria for serving as a consultant or advisor to GSK, AstraZeneca, Genentech, Sanofi, Regeneron, Verona, and Amgen; and research grant support from GSK, AstraZeneca, Genentech, Regeneron, and Sanofi. DJJ has received advisory board and speakers fees from AstraZeneca, Boehringer Ingelheim, Novartis, Teva, GSK, Sanofi-Regeneron, and Chiesi. NM is an employee and shareholder with AstraZeneca. AL is employed by AstraZeneca. ES is a former GSK employee and provided anonymised data from GSK studies CAPTAIN and DREAM; provided inputs into manuscript development; and holds GSK stock options. CC holds shares in GSK and is an employee of GSK. MEH is a Sanofi employee. CTJH is a former employee of Genentech. AS is a Novartis employee. TSCH was supported by a Wellcome Trust Fellowship (211050/Z/18/z); he reports grants from the Guardians of the Beit Fellowship, Pfizer, NIHR Oxford Biomedical Research Centre (BRC), University of Oxford, Kymab, Arcturis, and Asthma+Lung UK; and personal fees from AstraZeneca Pieris. RWB has received institutional research funding from AstraZeneca, Teva, Health Research Council, Cure Kidz, and Perpetual Guardian; personal fees from AstraZeneca, Avillion, and Teva; and is Chair of the Asthma Foundation of New Zealand adolescent and adult asthma guidelines, a reviewer for GINA, and a former member of the Global Initiative for Chronic Obstructive Lung Disease board. JKS has received non-restricted research grants from AstraZeneca, European Respiratory Society Severe Heterogeneous Asthma Research collaboration—Patient Centred Clinical Research Collaboration, Register of Adult Patients with Severe Asthma for Optimal Disease Management Foundation, and ZonMw. EWS has received consultancy fees from GSK. IDP has received honoraria for speaking at sponsored meetings from AstraZeneca, Circassia, AmgenNovartis, Chiesi, Sanofi-Regeneron, Menarini, and GSK; and payments for organising educational events from AstraZeneca, GSK, Sanofi-Regeneron, and Teva. He has received honoraria for attending advisory panels with Genentech, Sanofi-Regeneron, AstraZeneca, GSK, Novartis, Teva, Merck, Circassia, and Amgen. He has received sponsorship to attend international scientific meetings from GSK, AstraZeneca, Sanofi, and Regeneron. SC reports non-restricted research grants from NIHR Oxford BRC, the Quebec Respiratory Health Research Network, the Fondation Québécoise en Santé Respiratoire, AstraZeneca, Sanofi-Regeneron, and Circassia Niox group; speaker honoraria from AstraZeneca, GSK, Sanofi-Regeneron, and Valeo Pharma; consultancy fees from FirstThought, AstraZeneca, GSK, Sanofi-Regeneron, Access Biotech- nology, and Access Industries; and sponsorship to attend or speak at international scientific meetings by or for AstraZeneca and Sanofi-Regeneron. He is an advisory board member for and holds stock options in Biometry—a company that is developing an exhaled nitric oxide device (myBiometry). He advised the Institut national d'excellence en santé et services sociaux on an update of the asthma general practice information booklet for general practitioners. Within the submitted work, CC-P has received an education scholarship from the Université de Sherbrooke, and SC reports that he has received non-restricted research grants from the Québec Air-Intersectorialité-Respiratoire-Son network, the Academy of Medical Sciences, and the NIHR Oxford BRC, is the holder of the Association pulmonaire du Québec's Research Chair in Respiratory medicine, and is a clinical research scholar of the Fonds de recherche du Québec. All other authors declare no competing interests.

Acknowledgments

We thank Arianne Caron and Rachel Russel-Sharpe for administrative

support, Jack Howarth for legal expertise, Lars van der Burg and Edouard Bonneville for statistical expertise and support, André Carpentier, André Cantin, and Xavier Jamont (former Novartis employee) for feedback on the manuscript, and our patients for continued inspiration and motivation to advance knowledge in asthma. This work was supported by the NIHR Oxford BRC, Association pulmonaire du Québec, Fonds de recherche du Québec—Santé, Québec Air-Intersectorialité-Respiratoire-Son network, Stichting Astma Bestrijding, Leiden University Fund, and Academy of Medical Sciences. The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR, the Department of Health, or the other funders.

References

1. Global Initiative for Asthma Global strategy for asthma management and prevention https://gin asthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf
2. Couillard, S · Petousi, N · Smigiel, K · et al. Towards a predict and prevent approach in obstructive airways diseases J Allergy Clin Immunol Pract. 2023; 11:704-712
3. Lazarus, SC · Boushey, HA · Fahy, JV et al. Long-acting ß2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial
4. Conroy, RM · Pyörälä, K ·Fitzgerald, AP · et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project Eur Heart J. 2003; 24:987-1003
5. Pavord, ID · Beasley, R · Agusti, A · et al. After asthma: redefining airways diseases Lancet. 2018; 391:350-400
6. Couillard, S · Laugerud, A · Jabeen, M · et al. Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide Thorax. 2022; 77:199-202
7. Couillard, S · Do, WIH · Beasley, R · et al. Predicting the benefits of type-2 targeted anti-inflammatory treatment with the prototype Oxford Asthma Attack Risk Scale (ORACLE) ERJ Open Res. 2021; 8:1-5
8. Celis-Preciado, C · Leclerc, S · Duval, M · et al. Phenotyping the responses to systemic corticosteroids in the management of asthma attacks (PRISMA) Eur Respir J. 2025; published online Feb 13. https://doi.org/10.1183/13993003.02391-2024
9. Couillard, S· Shrimanker, R· Chaudhuri, R · et al. Fractional exhaled nitric oxide nonsuppression identifies corticosteroid-resistant type 2 signaling in severe asthma Am J Respir Crit Care Med. 2021;204: 731-734
10. Beasley, R · Holliday, M · Reddel, HK et al. Controlled trial of budesonide-formoterol as needed for mild asthma N Engl J Med. 2019; 380:2020-2030
11. Pavord, ID · Holliday, M · Reddel, HK et al. Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial Lancet Respir Med. 2020; 8:671-680
12. Lee, LA · Bailes, Z · Barnes, N · et al. 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 Lancet Respir Med. 2021; 9:69-84
13. Couillard, S · Pavord, ID Fluticasone furoate: CAPTAIN of fluticasones in type 2 inflammatory asthma Respirology. 2022; 27:184-186
14. Pavord, ID · Korn, S · Howarth, P · et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial Lancet. 2012; 380:651-659
15. Castro, M · Corren, J · Pavord, ID · et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma N Engl J Med. 2018; 378:2486-2496
16. Menzies-Gow, A· Corren, J · Bourdin, A · et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma N Engl J Med. 2021; 384:1800-1809
17. FitzGerald, JM· Bleecker, ER · Menzies-Gow, A· et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies Lancet Respir Med. 2018; 6:51-64
18. Couillard, S · Steyerberg, E · Beasley, R · et al. Blood eosinophils, fractional exhaled nitric oxide and the risk of asthma attacks in randomised controlled trials: protocol for a systemic review and control arm patient-level meta-analysis for clinical prediction modelling BMJ Open. 2022; 12, e058215
19. Stewart, LA · Clarke, M · Rovers, M · et al. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD Statement JAMA. 2015; 313: 1657-1665
20. Sauerbrei, W · Taube, SE· McShane, LM· et al. Reporting recommendations for tumor marker prognostic studies (REMARK): an abridged explanation and elaboration J Natl Cancer Inst. 2018; 110:803-811
21. Hardy, J · Baggott, C · Fingleton, J · et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial Lancet. 2019; 394:919-928
22. Higgins, J · Thomas, J · Chandler, J · et al. Cochrane handbook for systematic reviews of interventions (version 6.2). https://training.cochrane.org/handbook
23. Huebner, M · Vach, W · le Cessie, S · et al. Hidden analyses: a review of reporting practice and recommendations for more transparent reporting of initial data analyses BMC Med Res Methodol. 2020; 20:61
24. White, IR · Royston, P · Wood, AM Multiple imputation using chained equations: issues and guidance for practice Stat Med. 2011; 30:377-399
25. Loymans, RJB· Debray, TPA ·Honkoop,

PJ · et al. Exacerbations in adults with asthma: a systematic review and external validation of prediction models J Allergy Clin Immunol Pract. 2018; 6:1942-1952
26. Parker, RA· Weir, CJ Non-adjustment for multiple testing in multi-arm trials of distinct treatments: rationale and justification Clin Trials. 2020; 17:562-566
27. Langendam, MW · Akl, EA · Dahm, P · et al. Assessing and presenting summaries of evidence in Cochrane Reviews Syst Rev. 2013; 2:81
28. Brusselle, GG · Vanderstichele, C · Jordens, P · et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial Thorax. 2013; 68:322-329
29. Park, HS · Kim, MK · Imai, N · et al. A phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan Int Arch Allergy Immunol. 2016; 169:135-145
30. Castro, M · Wenzel, SE · Bleecker, ER · et al. Benralizumab, an anti-interleukin 5 receptor a monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study Lancet Respir Med. 2014; 2:879 -890
31. Harris, JM · Maciuca, R · Bradley, MS · et al. A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma Respir Res. 2016; 17:29
32. Wenzel, S · Castro, M · Corren, J · et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting ß2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial Lancet. 2016; 388:31-44
33. Hanania, NA · Wenzel, S · Rosén, K · et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study Am J Respir Crit Care Med. 2013; 187:804-811
34. Hanania, NA· Korenblat, P· Chapman, KR · et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials Lancet Respir Med. 2016; 4:781-796
35. Brightling, CE · Gaga, M · Inoue, H · et al. Effectiveness of fevipiprant in reducing exacerbations in patients with severe asthma (LUSTER-1 and LUSTER-2): two phase 3 randomised controlled trials Lancet Respir Med. 2021; 9:43-56
36. Hanania, NA · Noonan, M · Corren, J · et al. Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies Thorax. 2015; 70:748-756
37. Corren, J · Lemanske, Jr, RF · Hanania, NA · et al. Lebrikizumab treatment in adults with asthma N Engl J Med. 2011; 365:1088-1098
38. Sorkness, CA · Lemanske, Jr, RF· Mauger, DT · et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the pediatric asthma controller trial J Allergy Clin Immunol. 2007; 119:64-72
39. Corren, J · Parnes, JR · Wang, L · et al. Tezepelumab in adults with uncontrolled asthma N Engl J Med. 2017; 377:936-946
40. Panettieri, Jr, RA · Sjöbring, U · Péterffy, A · et al. Tralokinumab for severe, uncontrolled asthma (STRATOS 1 and STRATOS 2): two randomised, double-blind, placebo -controlled, phase 3 clinical trials Lancet Respir Med. 2018; 6:511-525
41. Steyerberg, EW Clinical prediction models. A practical approach to development, validation, and updating Springer, Cham, 2019
42. Couillard, S· Shrimanker, R· Lemaire-Paquette, S · et al. Longitudinal changes in sputum and blood inflammatory mediators during FeNO suppression testing Thorax. 2022; 77:933-938
43. Dunican, EM · Elicker, BM · Gierada, DS · et al. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction J Clin Invest. 2018; 128:997-1009
44. Beasley, R · Hughes, R · Agusti, A · et al. Prevalence, diagnostic utility and associated characteristics of bronchodilator responsiveness Am J Respir Crit Care Med. 2024; 209:390-401
45. Gruchalla, RS · Sampson, HA · Matsui, E · et al. Asthma morbidity among inner-city adolescents receiving guidelines-based therapy: role of predictors in the setting of high adherence J Allergy Clin Immunol. 2009; 124:213-221
46. Fokkens, WJ · Lund, VJ · Hopkins, C · et al. European position paper on rhinosinusitis and nasal polyps 2020 Rhinology. 2020; 58:1-464
47. Kent, DM · Steyerberg, E · van Klaveren, D Personalized evidence based medicine: predictive approaches to heterogeneous treatment effects BMJ. 2018; 363, k4245
48. Baigent, C · Blackwell, L · Emberson, J · et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials Lancet. 2010; 376:1670-1681
49. Couillard, S · Jackson, DJ · Pavord, ID· et al. Choosing the right biologic for the right patient with severe asthma Chest. 2025; 167:330-342

Credits: Meulmeester Fleur L, Mailhot-Larouche Samuel, Celis-Preciado Carlos, Lemaire-Paquette Samuel, Ramakrishnan Sanjay, Wechsler Michael E, Brusselle Guy, Corren Jonathan, Hardy Jo, Diver Sarah E, Brightling Christopher E, Castro Mario, Hanania Nicola A, Jackson David J, Martin Neil, Laugerud Annette, Santoro Emilio, Compton Chris, Hardin Megan E, Holweg Cecile T J, Subhashini Allu, Hinks Timothy S C, Beasley Richard W, Sont Jacob K, Steyerberg Ewout W, Pavord Ian D, Couillard Simon. Inflammatory and clinical risk factors for asthma attacks (ORACLE2): a patient-level meta-analysis of control groups of 22 randomised trials. The Lancet Respiratory Medicine, Elsevier, 2025; 2213-2600. https://doi. org/10. 1016/S2213-2600(25)00037-2

Women-specific reference ranges for serum TSH in Liguria: the impact of age and year of collection in a single-center cross-sectional study

[1]Massimo Giusti & [2]Marilena Sidoti

[1]Endocrine Unit, Centro Clinico Diagnostico Priamar, Via dei Partigiani 13R, Savona, 17100, Italy
Dipartimento di Medicina Interna, Università di Genova, Genoa, Italy

[2]Endocrine Unit, Centro Clinico Diagnostico Priamar, Via dei Partigiani 13R, Savona, 17100, Italy
Endocrine Unit, Azienda Sanitaria Locale 2 Savonese, Savona, Italy

Abstract

Background

TSH is the first-line test of thyroid function, and the normal TSH references provided by manufacturers are generally used in diagnoses. In the age of gender medicine, however, there is a need to refine normal TSH ranges.

Aim

The aim of this study was to construct a normal TSH range in women living in our district. The data were collected in a secondary-level centre located in Savona (Liguria, Italy).

Methods

From 2003 to 2022, 6227 medical records from women undergoing their first endocrinological examination were anonymously evaluated. After the application of exclusion criteria, statistical analysis was anonymously performed on a sample of 2597 medical records.

Results

The pooled median 2.5th and 97.5th percentiles of TSH provided by manufacturers were 0.20 mIU/l and 5.64 mIU/l, respectively. In the study population, median (2.5th - 97.5th percentiles) TSH was 1.70 mIU/l (0.37–6.95 mIU/l). TSH and patient age did not vary significantly over the years (2003–2022). A slight negative correlation was found between TSH and age (P = 0.05). On stratifying the sample into three age-groups (18–44 years, N = 1200; 45–64 years N = 934; ≥ 65 years, N = 463), TSH was 1.75 mIU/l (0.49–5.94 mIU/l), 1.70 mIU/l (0.30–6.89 mIU/l) and 1.64 mIU/l (0.30–7.69 mIU/l), respectively. When TSH was evaluated according to the age-related range instead of the pooled range reported by manufacturers, the number of women aged 18–44 years considered to have sub-clinical hyperthyroidism increased slightly (P = 0.02) and the number of women in the 45-64-year and ≥65-year age-groups considered to have sub-clinical hypothyroidism decreased significantly (*P* = 0.05 and *P* < 0.001).

Conclusions

This is the first study in Liguria aimed at establishing new age-specific reference values for TSH in women. Based on a large number of data, this new age-related range could be more extensively employed in order to improve diagnosis. The main result of implementing age-related normal TSH levels between the 2.5th and 97.5th percentiles seems to be both a slight increase in 18-44-year-old women and a significant reduction in > 45-year-old women in whom sub-clinical hyperthyroidism or hypothyroidism, respectively, should be promptly treated.

Introduction

Thyroid stimulating hormone (TSH) is the key indicator of thyroid function. Several factors can affect TSH in adults (heredity, ethnicity, iodine status, body weight, smoking status, concomitant diseases, drugs, autoimmunity, time of sampling, sex and age) [1]. Available assay methods and reference ranges influence TSH evaluation. The American Thyroid Association, in its centennial article, reports technical advances in laboratory thyroid tests in the last seven decades, with the third-generation TSH assay being available on most automated instrument platforms [2]. Moreover, despite improvements in functional sensitivity and the

use the same standard, TSH assays differ in their specificity, and the manufacturers' reference ranges are somewhat different [2]. In addition, inter-method differences, TSH isoforms or TSH antibodies and several sources of interference in assays can contribute to diagnostic errors[1,2].

Normal TSH ranges provided by manufacturers do not consider possible gender and age differences, except for the occasional specification of trimester-specific TSH ranges in pregnancy. Current guidelines on laboratory medicine recommend that each clinical analysis laboratory should establish its own reference intervals according to the characteristics of the local population. Reference limits can be obtained from strictly healthy individuals (direct method), with a minimum of 120 reference individuals being required in order to determine the reference interval of an analyte; this would represent approximately 95% of the values found in the given population [3]. In routine practice, however, the direct method is hard to apply in every laboratory[4,5]. The alternative approach is indirect. This method involves analyzing a large "healthy subpopulation", the hypothesis being that probably more than 80% of samples stored in laboratory information systems are negative for thyroid disease and include some pre-selected criteria [6,7]. Societies of laboratory medicine encourage this method in order to establish and verify TSH reference intervals [6]. The TSH range obtained from a sub-population study involving "non-diseased reference individuals" can be used by endocrinologists as a threshold, below or above which therapeutic action is recommended[7].

Establishing a normal reference TSH range is critical in diagnosing subclinical thyroid disorders accurately. However, there is currently no consensus regarding the optimal serum TSH level at which to initiate levothyroxine (L-T4) treatment in individuals diagnosed with subclinical hypothyroidism, particularly in the elderly [7,8]. On the other hand, the evidence of benefit of anti-thyroidal treatment in subclinical hyperthyroidism remains unclear [8,9].

Indirect reference intervals have recently been calculated on very large populations in north-eastern Italy[10,11,12]. The percentile normalization applied to TSH results obtained from 7 laboratories and 3 different immunoassays indicated similar TSH ranges in both males (0.40–4.62 mIU/l) and females (0.49–4.96 mIU/l) with a significant difference across age (e.g. lower 2.5th percentiles and higher 97.5th percentiles in subjects over 70 years of age) [11]. The authors emphasized the appropriateness of defining TSH reference intervals according to age, gender and ethnicity, but did not state whether refining the TSH range according to age and sex changed the rate of diagnoses of subclinical thyroid dysfunction in comparison with the normal laboratory range[10]. To our knowledge, no indirect methods have been used to define the normal TSH range in north-western Italy.

In the era of precision medicine, there seems to be a need to refine the normal range of TSH in real-world practice. The present study covers the last 20 years of TSH measurement with new-generation immunoassays in the district of Savona and neighboring districts in Liguria and southern Piedmont (north-western Italy). A large study population of women - constituting the vast majority of subjects undergoing endocrinological investigation was evaluated in order to determine local age-related normal TSH ranges (main outcome). A secondary objective was to reduce the over-diagnosis and over-treatment of sub-clinical thyroid dysfunction, which are expected to occur on a global scale.

Materials and methods

Subjects

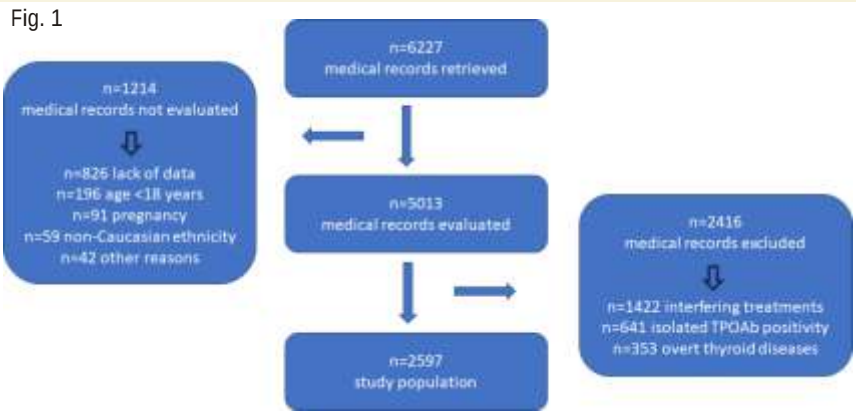
This cross-sectional retrospective single-center study was conducted at the Endocrine Unit of Priamar Clinical Diagnostic Center, a private secondary-level out-patient center located in the Savona district (Liguria, Italy). Endocrinological examination was mostly requested by general practitioners or other specialists, and sometimes directly by the patient. Examination was requested mainly for thyroid, metabolic and pituitary-gonadal or adrenal health problems, or endocrinological screening. All records collected from 2003 to 2022 were individually reviewed to ensure that the women met our inclusion criteria. We identified records of adult women who had undergone their first endocrinological examination. In this period of time, 6227 medical records were retrieved and anonymously evaluated. Initial exclusion criteria were: lack of baseline data (incomplete records), age < 18 years, pregnancy, non-Caucasian ethnicity and other reasons. Age, body mass index (BMI), thyroid stimulating hormone (TSH), thyroid peroxidase antibodies (TPOAb), pharmacological treatments and thyroid ultrasonography (US) findings were then collected. Figure 1 shows the flow diagram of medical records of patients undergoing their first endocrinological examination from 2003 to 2022. After preliminary evaluation, 19.5% (n = 1214) of records were excluded (Fig. 1). Other reasons for exclusion were: impossibility (n = 19) or refusal (n = 8) of physical examination, male-to-female transgender (n = 6), only

video consultation (n = 5), medical-legal reasons (n = 4). Subsequently, 2416 records were excluded owing to interfering treatments (58.9%; manly L-T4 administration), and TPOAb positivity with hypoechoic thyroid texture on US (26.5%) or the presence of overt thyroid diseases (14.6%; thyrotoxicosis n = 216, overt hypothyroidism n = 95, sub-acute thyroiditis n = 36, or post-partum thyroiditis n = 5). The final study sample comprised 2597 records of subjects undergoing their first endocrinological examination at the Priamar Center (Fig. 1; for details, see Supplementary material 1). The average age of the study population at the time of the first endocrinological examination was 47.0 ± 16.9 years (± SD; range 18–90 years).

Data collection

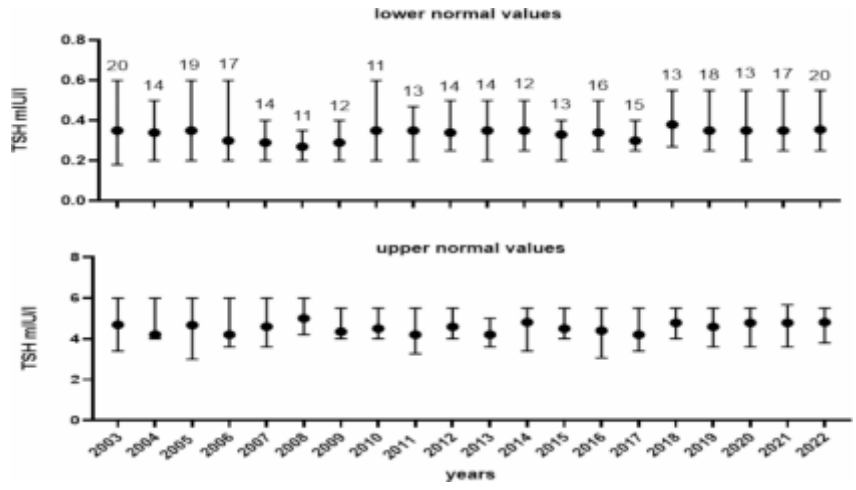
From the medical records, the following data were anonymously transferred to Excel files: chronological age (years), district of residence, reported reason for examination, pharmacological anamnesis, smoking habits (non-smoker, previous or current smoking), body weight and height for BMI evaluation, judgement of thyroid echotexture on on-site US examination, and thyroid data (f-T4, TSH, TPOAb) close to examination. One excel worksheet was filled in for each year from 2003 to 2022. Owing to the retrospective nature of the study, some clinical data were missing, but records were excluded from analysis only according to exclusion criteria; however, missing TPOAb data did not exclude records when thyroid US data were available. Data were retrieved from the database from June 2023 to March 2024. Data from the study population were subsequently divided arbitrarily into three age-groups: 18–44 years (n = 1200),

Fig. 1



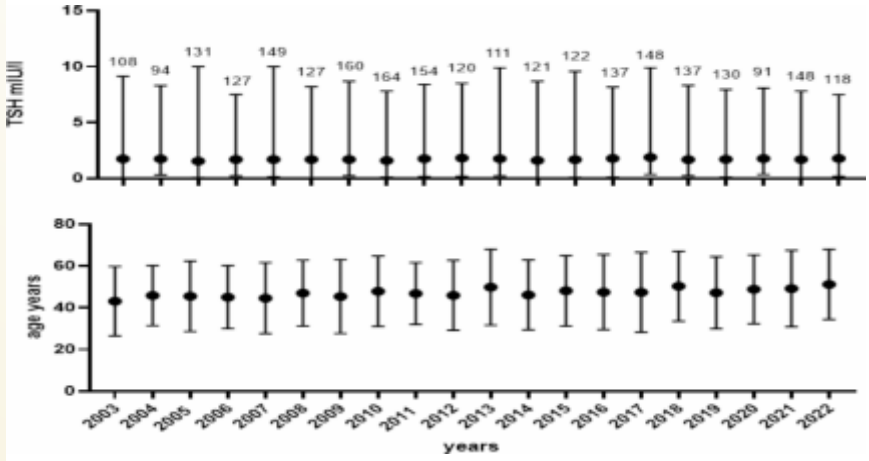
Flowchart of the study. Subjects with TPO-Ab isolated positivity and negative US finding were excluded because longitudinal evaluation was not the objective of the study and therefore evolution in sub-clinical autoimmune thyroid cannot be excluded

Fig. 2



Median, 2.5th percentile, and 97.5th percentile of lower normal and upper normal TSH ranges, as indicated by manufacturers. The numbers at the top indicate the laboratories involved each year

Fig. 3



Median, 2.5th percentile, and 97.5th percentile of TSH (upper panel) and age (lower panel) in the study population. The numbers at the top indicate the yearly numbers of women evaluated

45–64 years (n = 934) and ≥65 years (n = 463).

Objectives

The primary objective was to obtain a local TSH range from a large group of women in whom "healthy thyroid status" had been well defined during clinical and laboratory endocrinological examination. According to the experimental 2.5th and 97.5th percentiles of TSH, the secondary objective was to obtain the current local TSH range whereby subclinical thyroid dysfunctions were diagnosed. A further objective was to compare the percentage of subclinical thyroid dysfunction evaluated according to TSH obtained from our study population with those from the pooled (2003–2022) TSH ranges provided by manufacturers.

Methods

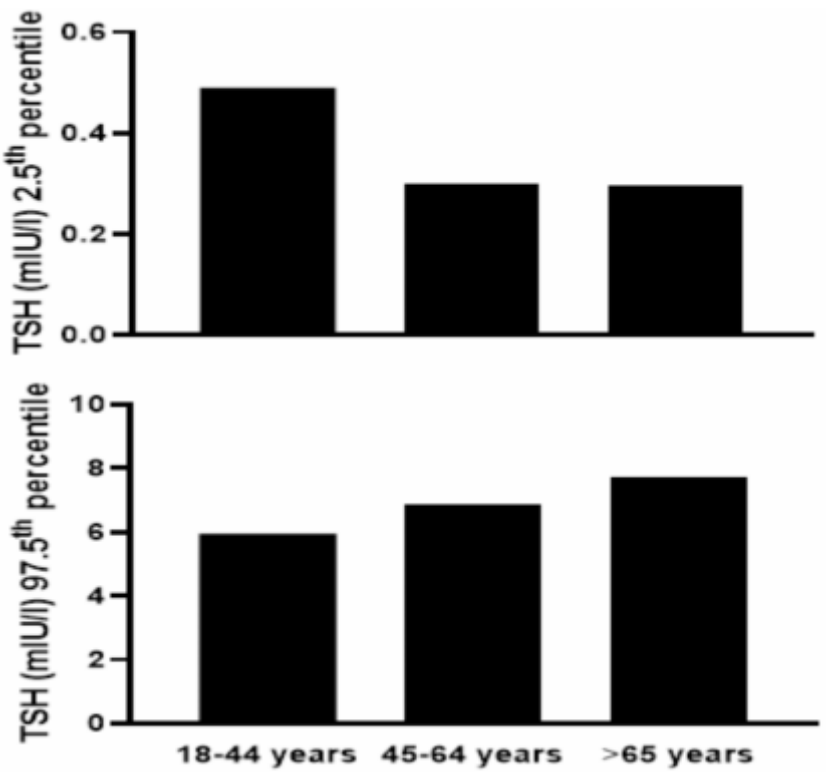
Body mass index (BMI) was calculated on the basis of the weight (kg) and height (m) reported in medical files, according to the following formula: kg/m^2. Smoking habits were investigated by applying a binary method (non-smoker = 0; former or current smoker = 1). All US examinations were performed by the same experienced endocrinologist (MG) using several machines (Esaote, General Electrics, Fukuda Denshi), all equipped with linear probes working at 7.5–15 MHz. Data on normal thyroid volume are available for women in our district [median 8.0 ml (IQR 6.7–9.8 ml; range 3.2–19.8 ml] [13]. Iodine status in the population of our districts has recently been deemed sufficient [14].

Assays

All diagnostic and laboratory tests were performed as part of routine (endocrinological) clinical care. Several commercial methods were used for f-T4 and TPOAb evaluations during the study period. Judgments of low/high f-T4 values, or negative/positive TPOAb values were assigned according to the normal range reported by the manufacturers. In the district of Savona, two public laboratories (Santa Corona Hospital, Pietra Ligure and Azienda Sanitaria Locale 5 Savonese) and six accredited private laboratories were available for TSH assays in the study period. In this period, our center also carried out endocrinological examinations on subjects living in the neighboring districts of Liguria (Imperia and Genoa districts) and in an area of South Piedmont, from which Savona is easier to reach. A few TSH data came from the University of Pisa in the adjacent region of Tuscany. Overall, TSH data were obtained from 14 public and 26 private centers (for details, see Supplementary material 2). In these laboratories, the TSH range in adults is often not broken down by age or sex. Since 1999, the third-generation TSH assay has been used in all centers. All TSH calibration curves were calibrated against World Health Organization International Reference Preparation standards (WHO IR 80/558, WHO IR 81/565).

Chemiluminescence microparticle immunoassay (CMIA), chemiluminescent immunoassay (CLIA), electrochemiluminescence immunoassay (ECLIA), and enzyme-linked fluorescent assay (ELFA) were the automated methods used for TSH assay. Manufacturers' TSH ranges were: CMIA: 0.35–4.5 mIU/l (ADVIA Centaur, Bayer), 0.45–5.3 mIU/l (Access TSH 3rd, Beckman Coulter Diagnostics); CLIA 0.20–3.30 miU/l (Liaison, DiaSorin), 0.30–3.74 mIU/l (Dimension VISTA, Simens), 0.35–4.94 mIU/l (Architect System, Abbot

Fig. 4



2.5th percentile (upper panel) and 97.5th percentile (lower panel) of TSH observed in the three age-groups of the study population

Diagnostics), 0.40-4.0 mIU/l (Imulite, DPC), 0.46–4.68 mIU/l (Vitros, Ortho Clinical Diagnostics), 0.55–4.78 mIU/l (LOCI, Simens Healthcare Diagnostics); ECLIA 0.27–4.7 mIU/l (Elecsys Cobas, Roche Diagnostics); ELFA 0.25-5.00 mIU/l (Vidas, BioMerieux). According to the manufacturers, the functional sensitivity of the TSH assays ranged from 0.004 to 0.07 mIU/l (median: 0.01 mIU/l).

Statistical analysis

Statistical analysis was performed on a sample of 2597 medical records (study population; Fig. 1). GraphPad 10 software (GraphPad, San Diego, CA, USA) was used. Data are reported as mean ± standard deviation (SD), median, IQR, range, and 2.5th - 97.5th percentiles. For statistical purposes, the functional sensitivity was set to 0.01 mIU/l, and TSH values below 0.01 mIU/l were reported as 0.01 mIU/l. Values ≤0.01 mIU/l or ≥10 mIU/l were generally excluded, as these are considered to be in the clinical hyperthyroid and hypothyroid range, respectively. The absence of normality in TSH levels was tested by means of the Kolmogorov-Smirnov test. To compare continuous data, the Kruskal-Wallis non-parametric analysis of variance was used. Percentages were compared by means of Fisher's exact test. Correlations were evaluated by means of Spearman test. Significance was set at $P \leq 0.05$.

Ethical approval

The study was approved by the Priamar Center's institutional board, and a waiver of informed consent was granted because the research involved no risk to patients. Before their examination at the Priamar Clinical Diagnostic Center, all patients had provided written informed consent to the management of data collected from their medical files and had agreed to their use for scientific purposes. Owing to the retrospective nature of collection of clinical and hormonal data, no further formal approval from the Liguria Ethics Committee was required. Data were managed anonymously. Data collection and subsequent analysis were performed in compliance with the Helsinki Declaration.

Results

In the study period (2003–2022) TSH was evaluated by means of various commercial assays. Normality of TSH was determined according to the ranges provided by the manufacturers. Figure 2 illustrates the yearly median and range of TSH obtained by pooling the available data from the manufacturers. On non-parametric analysis of variance, no significant differences were noted among lower ($P = 0.29$) or upper ($P = 0.78$) normal TSH values from 2003 to 2022 (Fig. 2). On pooling all normal values ($n = 296$) available from our laboratories between 2003 and 2022, the median lower normal limit of TSH was 0.35 mIU/l (IQR 0.27–0.40 mIU/l; range 0.18–0.60 mIU/) and the median upper normal limit of TSH was 4.50 mIU/l (IQR 4.00–5.00 mIU/l range 3.00–6.00 mIU/l). The 2.5th percentile of the TSH range was 0.20 mIU/l, while the 97.5th percentile of the TSH range was 5.64 mIU/l. If f-T4 values were normal, TSH values < 0.20 mIU/l and > 5.64 mIU/l were deemed diagnostic of sub-clinical hyperthyroidism and sub-clinical hypothyroidism, respectively.

The mean age of the whole population was 47.0 years (± 16.9 years; SD; age range 18–90 years). Figure 3 shows TSH levels and age in the 2597 records from 2003 to 2022. On analyse of variance, no significant differences among the years were observed in either TSH ($P = 0.38$) or age ($P = 0.06$) values. The yearly number of evaluable records ranged from 91 to 164 in the study period. Fewer than 100 evaluable records were retrieved in 2004, as the medical clinic in the Savona district moved its premises, and in 2020, owing to the COVID-19 pandemic. The median TSH was 1.70 mIU/l (IQR 1.20–1.75 mIU/l; range 0.02–15.62 mIU/l; 2.5th percentile 0.37 mIU/l, 97.5th percentile 6.95 mIU/l). No correlation was noted between TSH values and smoking status (n = 1552; Sr -0.02, $P = 0.90$) or BMI (n = 2579; Sr 0.03 $P = 0.19$), while a slightly significant negative correlation was found between TSH and age (n = 2579; Sr -0.04 $P = 0.05$).

The study population was stratified according to age: 1200 subjects were aged 18–44 years (mean [± SD] 31.7 ± 8.0 years), 934 were aged 45–64 years (mean [± SD] 54.2 ± 5.7 years) and 463 were aged ≥ 65 years (mean [± SD] 72.1 ± 5.5 years). The median TSH values were: 1.75 mIU/l (IQR 1.30-15.32 mIU/l; 2.5th percentile 0.49 mIU/l, 97.5th percentile 5.94 mIU/l) in the 18-44-year age-group; 1.70 mIU/l (IQR 1.11–2.80 mIU/l; 2.5th percentile 0.30 mIU/l, 97.5th percentile 6.89 mIU/l) in the 45-64-year age-group, and 1.64 mIU/l (IQR 0.97–2.96 mIU/l; 2.5th percentile 0.30 mIU/l, 97.5th percentile 7.69 mIU/l) in the ≥65-year age-group. No significant differences in TSH levels among the three age-groups emerged on analysis of variance ($P = 0.18$). Figure 4 shows the 2.5th and the 97.5th percentiles observed in the three age-groups. The 2.5th percentile of TSH decreased from the first to the second age-group, and then remained stable thereafter, while a progressively increasing trend in the 97.5th percentile of TSH was found across the age-groups (Fig. 4). Table 1 compares the number

and percentages of subjects with TSH values outside the 2.5th - 97.5th percentiles according to the manufacturers' ranges and data from our study group. In the 18-44-year age-group there were significantly more subjects (n = 27) with TSH < 2.5th percentile than that (n = 12) obtained from the manufacturers' data (P = 0.02). By contrast, significantly fewer subjects aged 45–64 years (n = 24) or aged ≥ 65 years (n = 12) had TSH > 95.5th percentile than the number (45–65 year group: n = 48, P = 0.005; >65 years group: n = 47, P < 0.0001) obtained from the manufacturers' data (Table 1).

Table 1 Number of subjects (% in brackets) with TSH outside the normal range (< 2.5th percentile or > 97.5th percentile) according to the present study (age-group 18–44 years n = 1200, age-group 45–64 years n = 934, ≥65 years n = 463) and according to manufacturer references. Significance values of present study vs. manufacturer references are: (a) P < 0.001, (b) P = 0.005, (c) P = 0.02, (d) P = 0.09, (e) P = 0.11, (f) P = 0.29

	Age-group	Subjects with TSH < 2.5th percentile	Subjects with TSH > 97.5th percentile
	18–44 years	*n* = 1200	
Manufacture's intervals		12 (1.0%)	42 (3.5%)
Study population intervals		27 (2.3%) c	28 (2.3%) e
	45–64 years	*n* = 934	
Manufacture's intervals		13 (1.4%%	48 (5.4%)
Study population intervals		20 (2.1%) f	24 (2.6%) b
	≥65 years	*n* = 463	
Manufacture's intervals		3 (0.6%)	47 (10.2%)
Study population intervals	10 (2.2%) d	12 (2.6) a	

Discussion

The diagnosis and management of thyroid dysfunction focus primarily on the measurement of TSH as the most sensitive and specific marker of thyroid status [7,9]. The population reference range for "normal" TSH is defined as containing 95% of a "normal" population - subjects who are believed to be free of conditions that could influence TSH levels, with 2.5% of subjects below (i.e. <2.5th percentile) and 2.5% of subjects above (i.e. >97.5th percentile) the range [1,15]. Reference ranges may be device-, laboratory- and population-specific. Moreover, several other factors (gender, age, BMI, smoking, autoimmunity, interfering substances) can influence TSH levels. Consequently, "normal" or "abnormal" TSH levels should be determined according to reference ranges from local populations and laboratories [4,8,10,11,15,16,17,18].

In order to establish reference ranges of TSH, several studies have utilized various direct [3,17,19] and indirect [5,10,20,21] methods in normal adult populations involving from hundreds to thousands of individuals. In real-world practice, however, laboratories generally apply the TSH reference ranges suggested by assay manufacturers, without considering possible gender and age differences.

In this study, women were arbitrary divided on the basis of the fact that middle age is generally defined as the time span from about 40–45 years to about 60 - 35 years and the elderly are defined as persons aged 65 years and older. We determined age-related TSH in a cohort of women whose clinical characteristics, hormonal data, US findings and therapies were known. All the women in our study population (n = 2,597) were adults (≥18 years) and Caucasian. About 70% were living in the Savona district. In the period 2003–2022, the median female (≥20 years) population of the Savona district was 126,500 individuals [22]. We therefore estimated that our study population involved about 1% of adult women living in the Savona district. Our median TSH was 1.70 mIU/l, with a percentile interval ranging from 0.37 mIU/l (2.5th percentile) to 6.95 mIU/l (97.5th percentile). These data are not strictly comparable with those obtained by means of a direct procedure in the Pordenone district (Friuli; north-eastern Italy) in "normal" volunteer women aged 20–65 years (i.e. no detectable autoantibodies, no history of thyroid dysfunction, non-palpable goiter, no interfering drugs), in whom the median TSH and 2.5th percentile were 1.66 mIU/l and 0.56 mIU/l, but the 97.5th percentile was set to 3.27 mIU/l [10]. This difference could be explained by the different upper age ranges in the study by Tozzoli et al. [10] (up to 65 years) and ours (≥65 years). On the other hand, in a sample of 8619 girls (> 12 years of age) and women without a history of thyroid disease, in the USA, the median TSH level was 1.50 mIU/l and the 97.5th percentile was 6.10 mIU/l [23]. In Sicily, a TSH reference range was determined by applying indirect methods to a large dataset (n = 22,602) stored in a laboratory from 2012 to 2018. Only a minority of data had been obtained from outpatients (12%), and information on possible interfering therapies, BMI, smoking status and thyroid morphology was lacking [4]. In women, the lower limit of the reference range (0.18 mIU/l) was similar to that provided by manufacturers (0.20 mIU/l), but the upper limit was calculated as

3.94 mIU/l, as opposed to the manufacturers' limit of 4.70 mIU/l [4]. In that study, median TSH values decreased with age, as noted in our population, with a slight negative correlation between age and TSH.

In one of our previous studies, a borderline status of iodine sufficiency (101 µg/l) was noted in a cohort of adult subjects living in our districts [14], and it may be supposed that the iodine status of the present study population was similar. Moreover, it has been reported that TSH may be higher in areas of both overt and partial iodine deficiency[24]. Indeed, in a study conducted in areas with excessive iodine intake, the 97.5th percentile of TSH in adult females (all ages) was set to 8.42 mIU/l [25]. While past or current smoking has been associated with lower TSH levels [26], the effect of smoking in our population of women can be considered marginal or absent. Regarding the relationship between BMI and TSH, there is no consensus in the literature, and both positive [27,28] and negative [29] correlations have been reported. In agreement with our data on women, Ivo et al. [28] found no significant correlation between BMI and TSH, even when a reference population of euthyroid subjects (normal TSH) was separately evaluated according to sex.

In our study, the 97.5th percentile of TSH increased by about 1.00 mIU/l per age-group, rising from 5.94 mIU/l to 7.69 mIU/l, while in other studies [4,10] it remained stable throughout life. Moreover, it is well known that the distribution curve of normal TSH is shifted to the right in the elderly [30], and several other studies have shown an increasing trend in the 97.5th percentile of TSH with age. In the Padoan et al. [12] study, women referred for TSH evaluation by general practitioners showed a slightly increasing TSH trend (from 4.96 mIU/l to 5.48 mIU/l) on passing from the ≤35-year group to the ≥ 70-year group. Other studies have reported an age-related increase in TSH, with the 97.5th percentile exceeding 7.0 mIU/l in individuals aged over 80 years [23,30,31]. Similar findings emerged from older data in Tuscany (Central Italy), with TSH measured by means of radio-immunoassay; in a small group of very elderly subjects (≥100 years), however, median TSH levels were lower than in subjects aged 20–64 years [32]. In a recent study by Luxia et al. [33], in which Han subjects with normal thyroid function were stratified into three age-groups (young: 18–44 years, middle-aged: 45–59 years, and elderly: >60 years), females, but not males, displayed a similar gradual increase in TSH, which peaked in middle age and subsequently declined.

Taylor et al. [30] reported an increase in hypothyroidism in the UK between 2005 and 2014 in subjects aged over 60 years, with a consequent increase in L-T4 initiation. On the other hand, in a recent investigation of the incidence and determinants of spontaneous TSH normalization in subjects > 65 years old with an initial TSH value between 4.60 and 19.99 mIU/l, van der Spoel et al. [34] observed that the hormone had spontaneously normalized after about 1 year in about 61% of subjects. After a further year, the same phenomenon was observed in 40% of subjects with abnormal TSH randomized to placebo [34]. Interestingly, female sex, negative TPOAb, less elevated TSH, higher initial f-T4 and TSH measurement in summer were independent determinants of normalization. The practical implication of this is that it may be advisable to wait at least one year before starting L-T4 treatment when TSH levels are above the manufacturer's range but below the population-derived age-related 97.5th percentile. Our study therefore suggests that, in the district of Savona and nearby areas, women with TSH levels above this percentile could be treated for sub-clinical hypothyroidism. However, according to the literature [34], the risk of unnecessary L-T4 treatment might require a longitudinal evaluation of TSH. In addition, we observed that, on redefining the upper limit of normal TSH, the incidence of sub-clinical hypo-thyroidism significantly decreased in subjects over 45 years of age when "study population" TSH ranges were adopted rather than laboratory-derived TSH ranges years, as observed in subjects > 65 years of age in other studies [8,35], an approach that prevents over-treatment.

Nevertheless, inappropriate anti-thyroidal treatment could be started in a supposed condition of sub-clinical hyperthyroidism when f-T4 is in the normal range but TSH is lower than the manufacturer's reference range. The decision to undertake a pharmacological approach must always be carefully considered, particularly in the elderly, in whom it is well known to engender a higher risk of all-cause mortality and cardiovascular morbidity and mortality [9]. Indeed, in a recent meta-analyses involving 134,346 participants with a median age of 59 years (range 18–106 years), f-T4 greater than the 85th percentile and TSH below the 20th percentile, 4.3% of whom were on thyroid medication at the baseline, the authors reported a higher risk of all-cause mortality and cardiovascular mortality [36].

In our study, the TSH value set at the 2.5th percentile was slightly lower in the 18-44-year age-group (0.49 mIU/l) than in the other two age-groups (0.30 mIU/l). A similar pattern has been reported in some [4,12,31,37], but not all, studies [8,38].

Differences among studies could stem from inhomogeneous division into subgroups, different sample sizes, iodine status and other reasons, including the assignment of subjects with pre-clinical thyroid nodular hyper-function to the category of "normal" elderly women. From our data, the suspicion of sub-clinical hyper-function seems slightly more frequent on applying the "study range" instead of the "manufacturer" range, especially in the group of women aged 18–44 years. This observation suggests that the lower limit of the reference TSH range may also need to be reassessed, as reported by Xu et al. [36].

The present study has several limitations. Firstly, the reference limits of laboratories vary greatly (see supplemental materials) and lumping these data together could hamper our findings; however, an ideal mixed model or stratification by assay was not possible. Secondly, age-related changes in the TSH range were not compared between females and males. In our experience, however, the demand for endocrinological examination in young and middle-aged males is reality quite low. Nevertheless, we hope to perform a similar cross-sectional study of a large data-set on males in the near future. Thirdly, our group of "normal healthy" women aged ≥65 years was smaller than the other two age-groups. However, our study population was larger than the minimum recommended limit in direct studies aimed at determining a normal range [3]. Moreover, a selection bias could have emerged from our cross-sectional study of subjects undergoing their first endocrinological investigation for several reasons, though strict exclusion criteria were applied. Indeed, it seems easier to identify a population free from clinical thyroid problems in data from national studies [4,10,12] employing "big data". In addition, on-site ultrasonography screening was routinely added, as in other studies [18,25,38]. Finally, the women who under went endocrinological examination at our centre might not be representative of the general population of our districts, owing to the expense of attending a private centre. However, the average income in our districts is not so low as to make socioeconomic status a real problem, and our study group represented about 1% of women living in the Savona district. Moreover, in the period 2003–2022, no age-related TSH range was available at public healthcare centers in Liguria. A further limitation from our study could the incompleteness of data on thyroid hormones on the first endocrinological examination.

Serum TSH reference ranges differ across laboratories [8,39]. In accordance with Razvi et al. [39], we sought to determine, in healthy women, a TSH range based more on clinical outcomes than on statistical techniques.

In conclusion, this is the first study in Liguria aimed at establishing new age- and gender-specific reference values for TSH. Based on a large number of women, this new age-related range could be more extensively employed in order to improve diagnoses. The main result of implementing age- and gender-related normal TSH levels between the 2.5th and 97.5th percentiles seems to be a slight increase in the number of 18-44-year-old women with sub-clinical hyperthyroidism and a very significant reduction in the hasty diagnosis of sub-clinical thyroid dysfunction in women aged 45–64 years and ≥65 years. Therapies for thyroid dysfunction must be started when TSH is outside age-related ranges, according to the patient's clinical condition and when this finding is confirmed some time later.

Data availability

No datasets were generated or analysed during the current study.

References

1. Razvi S. Thyroid-function reference ranges in the diagnosis of thyroid dysfunction in adults. Nat Rev Endocrinol. 2024;20(5):253–4. https://doi.org/10.1038/s41574-024-00972-2.
2. Spencer CA. Laboratory thyroid tests: a historical perspective. Thyroid. 2023;33(4):407–19. https://doi.org/10.1089/thy.2022.0397.
3. Clinical and Laboratory Standard Institute (CLSI). Defining, establishing, and verifying reference intervals in the clinical laboratory; approved guidelines. CLSI Socument EP28-A3c. 3rd ed.;28:pp1–59.Wayne PA.
4. Lo Sasso B, Vidali M, Scazzone C, Agnello L, Ciaccio M. Reference interval by the indirect approach of serum thyrotropin (TSH) in a Mediterranean adult population and the association with age and gender. Clin Chem Lab Med.2019; 57(10):1587–94. https://doi.org/10.1515/cclm-2018-0957.
5. Grossi E, Colombo R, Cavuto S, Franzini C. The REALAB project: a new method for the formulation of reference intervals based on current data. Clin Chem. 2005; 51(7):1232–40. https://doi.org/10.1373/clinchem.2005.047787
6. Katayev A, Balciza C, Seccombe DW. Establishing reference intervals for clinical laboratory test results: is there a better way? Am J Clin Pathol. 2010;133(2):180–6. https://doi.org/10.1309/AJCPN5BMTSF1CDYP.
7. Biondi B, Cappola AR. Subclinical hypothyroidism in older individuals. Lancet Diabetes Endocrinol. 2022; 10(2):129–41. https://doi.org/10.1016/S2213-8587(21)00285-0.
8. Yamada S, Horiguchi K, Akuzawa M, Sakamaki K, Yamada E, Ozawa A, et al. The impact of age- and sex-

specific reference ranges for serum thyrotropin and free thyroxine on the diagnosis of subclinical thyroid dysfunction: a multicenter study from Japan. Thyroid. 2023;33(4):428–39. https://doi.org/10.1089/thy.2022.0567.
9. Biondi B, Cooper DS, Subclinical Hyperthyroidism. N Engl J Med. 2018;378(25):2411–9. https://doi.org/10.1056/NEJMcp1709318.
10. Tozzoli R, D'Aurizio F, Metus P, Steffan A, Mazzon C, Bagnasco M. Reference intervals for thyrotropin in an area of Northern Italy: the Pordenone thyroid study (TRIPP). J Endocrinol Invest. 2018;41(8):985–94. https://doi.org/10.1007/s40618-018-0825-0.
11. Clerico A, Trenti T, Aloe R, Dittadi R, Rizzardi S, Migliardi M, et al. Italian section of the European Ligand Assay Society (ELAS). A multicenter study for the evaluation of the reference interval for TSH in Italy (ELAS TSH Italian Study). Clin Chem Lab Med. 2018;57(2):259–67. https://doi.org/10.1515/cclm-2018-0541.
12. Padoan A, Clerico A, Zaninotto M, Trenti T, Tozzoli R, Aloe R, et al. Percentile transformation and recalibration functions allow harmonization of thyroid-stimulating hormone (TSH) immunoassay results. Clin Chem Lab Med. 2020;58(10):1663–72. https://doi.org/10.1515/cclm-2019-1167.
13. Giusti M, Sidoti M. Normal thyroid volume in subjects evaluated in a primary ambulatory setting in Liguria. Minerva Endocrinol (Torino). 2023;48(1):19–26. https://doi.org/10.23736/S2724-6507.20.03312-X.
14. Conte L, Comina M, Monti E, Sidoti M, Vannozzi O, Di Ciolo L, et al. Urinary iodine concentration in a cohort of adult outpatients with thyroid diseases in Liguria 14 years after the law on salt iodization. Nutrients. 2019;12(1):11. https://doi.org/10.3390/nu12010011.
15. Razvi S, Bhana S, Mrabeti S. Challenges in interpreting thyroid stimulating hormone results in the diagnosis of thyroid dysfunction. J Thyroid Res. 2019;2019:4106816. https://doi.org/10.1155/2019/4106816.
16. Vadiveloo T, Donnan PT, Murphy MJ, Leese GP. Age- and gender-specific TSH reference intervals in people with no obvious thyroid disease in Tayside, Scotland: the thyroid epidemiology, audit, and Research Study (TEARS). J Clin Endocrinol Metab. 2013;98(3):1147–53. https://doi.org/10.1210/jc.2012-3191.
17. Cai J, Fang Y, Jing D, Xu S, Ming J, Gao B, et al. Reference intervals of thyroid hormones in a previously iodine-deficient but presently more than adequate area of Western China: a population-based survey. Endocr J. 2016;63(4):381–8. https://doi.org/10.1507/endocr
18. Gurgel MHC, Ponte CMM, Fontes R, Rocha ÍV, Batista LAA, Sousa TCS, et al. Establishment of reference interval for thyroid-stimulating hormone using electrochemiluminescence assay in a healthy adult population from Fortaleza, Brazil. Arch Endocrinol Metab. 2020;64(4):362–8. https://doi.org/10.20945/2359-3997000000264.
19. Hamilton TE, Davis S, Onstad L, Kopecky KJ. Thyrotropin levels in a population with no clinical, autoantibody, or ultrasonographic evidence of thyroid disease: implications for the diagnosis of subclinical hypothyroidism. J Clin Endocrinol Metab.2008;93(4):1224–30. https://doi.org/10.1210/jc.2006-2300.
20. Jones GRD, Haeckel R, Loh TP, Sikaris K, Streichert T, Katayev A, et al. IFCC Committee on Reference Intervals and decision limits. Indirect methods for reference interval determination - review and recommendations. Clin Chem Lab Med. 2018;57(1):20–9. https://doi.org/10.1515/cclm-2018-0073.
21. Giavarina D, Dorizzi RM, Soffiati G. Indirect methods for reference intervals based on current data. Clin Chem. 2006;52(2):335–7. https://doi.org/10.1373/clinchem.2005.062182.
22. Tuttitalia.itStatistiche.demografiche provincia di Savona 2002–2022. https://www.tuttitalia.it/liguria/provincia-di-savona/statistiche/popolazione
23. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002; 87(2):489–99. https://doi.org/10.1210/jcem.87.2.8182.
24. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol. 2015;3(4):286–95. https://doi.org/10.1016/S2213-8587(14)70225-6.
25. Kim M, Kim TY, Kim SH, Lee Y, Park SY, Kim HD, et al. Reference interval for thyrotropin in a ultrasonography screened Korean population. Korean J Intern Med. 2015;30(3):335–44. https://doi.org/10.3904/kjim.2015.30.3.335.
26. Asvold BO, Bjøro T, Nilsen TI, Vatten LJ. Tobacco smoking and thyroid function: a population-based study. Arch Intern Med. 2007;167(13):1428–32. https://doi.org/10.1001/archinte.167.13.1428.
27. Abdi H, Faam B, Gharibzadeh S, Mehran L, Tohidi M, Azizi F, et al. Determination of age and sex specific TSH and FT4 reference limits in overweight and obese individuals in an iodine-replete region: Tehran thyroid study (TTS). Endocr Res. 2021;46(1):37–43. https://doi.org/10.1080/07435800.2020.1854778.
28. Mele C, Mai S, Cena T, Pagano L, Scacchi M, Biondi B, et al. The pattern of TSH and fT4 levels across different BMI ranges in a large cohort of euthyroid patients with obesity. Front Endocrinol (Lausanne). 2022;13:1029376. https://doi.org/10.3389/fendo.2022.1029376.
29. Ivo CR, Duarte V, Veríssimo D, Silva J, Passos D, Lopes L, et al. Thyrotropin and body mass index, are they related? Horm Mol Biol Clin Investig. 2022;44(1):1–4. https://doi.org/10.1515/hmbci-2022-0002.
30. Taylor PN, Lansdown A, Witczak J,

Khan R, Rees A, Dayan CM, et al. Age-related variation in thyroid function - a narrative review highlighting important implications for research and clinical practice. Thyroid Res. 2023;16(1):7. https://doi.org/10.1186/s13044-023-00149-5.
31. Surks MI, Boucai L. Age- and race-based serum thyrotropin reference limits. J Clin Endocrinol Metab. 2010;95(2):496–502. https://doi.org/10.1210/jc.2009-1845.
32. Mariotti S, Barbesino G, Caturegli P, Bartalena L, Sansoni P, Fagnoni F, et al. A. Complex alteration of thyroid function in healthy centenarians. J Clin Endocrinol Metab. 1993;77(5):1130–4. https://doi.org/10.1210/jcem.77.5.8077303.
33. Luxia L, Jingfang L, Songbo F, Xulei T, Lihua M, Weiming S, et al. Correlation between serum TSH levels within normal range and serum lipid profile. Horm Metab Res. 2021;53(1):32–40. https://doi.org/10.1055/a-1191-7953.
34. van der Spoel E, van Vliet NA, Poortvliet RKE, Du Puy RS, den Elzen WPJ, Quinn TJ, et al. Incidence and determinants of spontaneous normalization of subclinical hypothyroidism in older adults. J Clin Endocrinol Metab. 2024;109(3):e1167–74. https://doi.org/10.1210/clinem/dgad623.
35. Yildiz Z, Dağdelen LK. Reference intervals for thyroid disorders calculated by indirect method and comparison with reference change values. Biochem Med (Zagreb). 2023;33(1):010704. https://doi.org/10.11613/BM.2023.010704.
36. Xu Y, Derakhshan A, Hysaj O, Wildisen L, Ittermann T, Pingitore A, Thyroid Studies Collaboration, et al. The optimal healthy ranges of thyroid function defined by the risk of cardiovascular disease and mortality: systematic review and individual participant data meta-analysis. Lancet Diabetes Endocrinol. 2023;11(10):743–54. https://doi.org/10.1016/S2213-8587(23)00227-9.
37. Adams R, Oh ES, Yasar S, Lyketsos CG, Mammen JS. Endogenous and exogenous thyrotoxicosis and risk of incident cognitive disorders in older adults. JAMA Intern Med. 2023;183(12):1324–31. https://doi.org/10.1001/jamainternmed.2023.5619.
38. Lu Y, Zhang WX, Li DH, Wei LH, Zhang YJ, Shi FN, et al. Thyroid hormone reference intervals among healthy individuals inIn Lanzhou, China. Endocrinol Metab (Seoul). 2023;38(3):347–56. https://doi.org/10.3803/EnM.2023.1638.
39. Razvi S, Jabbar A, Addison C, Vernazza J, Syed A, Soran H, et al. Variation in the reference range limits of thyroid function tests and association with the prevalence of levothyroxine treatment. Eur J Endocrinol. 2023;188(2):lvad016. https://doi.org/10.1093/ejendo/lvad016.

Acknowledgements

We thank Bernard Patrick for revising the language of the paper.

Funding

No funding was received.

Author information

Authors and Affiliations
Endocrine Unit, Centro Clinico Diagnostico Priamar, Via dei Partigiani 13R, Savona, 17100, Italy
Massimo Giusti & Marilena Sidoti

Dipartimento di Medicina Interna, Università di Genova, Genoa, Italy
Massimo Giusti

Endocrine Unit, Azienda Sanitaria Locale 2 Savonese, Savona, Italy
Marilena Sidoti

Contributions

M.G. and M.S. carried out this research. M.G. and M.S. were responsible for data collection. M.G. wrote the manuscript text. All authors reviwed and approved the final version of the manuscript.

Corresponding author

Correspondence to Massimo Giusti.

Ethics declarations

Ethical approval and consent to participate
All procedures were carried out in accordance with the ethical standards of the institution and with the 1975 Helsinki Declaration, as revised in 2008. Informed consent was obtained from all women.

Author Disclosure Statement

No competing financial interests exist.

Competing interests

The authors declare no competing interests.

Credit: Giusti, M., Sidoti, M. Women-specific reference ranges for serum TSH in Liguria: the impact of age and year of collection in a single-center cross-sectional study. Thyroid Res 18, 8 (2025). https://doi.org/10.1186/s13044-025-00225-y

The development of consensus recommendation to improve practice harmonization for Sickle Cell Disease through the National Alliance of Sickle Cell Centers

Julie Kanter, MD, Melissa Frei-Jones, MD, MSCI , Deepa Manwani, MD, Marsha Treadwell, PhD, Mohan Madisetti, Msc, Robin Miller, MD, Seethal A Jacob, MD, Sana Saif-Ur-Rehman, MD, Andrew Ross Wickman O'Brien, MD, Sophie Lanzkron, MD

Abstract

Introduction

SCD remains the most common inherited blood disorder. Due to a lack of strong evidence, the management of sickle cell is often anecdotal, local to individual centers, states, and countries. Even in areas of practice with high-level data to improve practice, implementation has not been consistent. The historical lack of an agreed-upon national registry has compounded this problem and resulted in a lack of comparative effectiveness data to identify areas of deficiency and improve practice. These barriers have resulted in centers developing local policies and procedures, often with limited communication with other centers, resulting in disparate and inconsistent care.

Objectives

To improve the situation, the National Alliance of Sickle Cell Centers (NASCC) was founded in 2020 and adopted a national registry, the Globin Research Network for Data and Discovery. To provide clear, practical, and measurable recommendations, the NASCC initiated a consensus procedure using a modified Delphi process to enhance the development of practice recommendations for SCD that include current guideline-based recommendations, use consensus where data are limited and identify areas where research is needed.

Methods

This manuscript explains the consensus process used, including the facilitation of the hybrid discussions and the categorization of practice-based recommendations as standard versus recommended.

Results

This paper describes the methods used to develop consensus recommendations to improve practice harmonization in SCD.

Conclusions

The recommendations resulting from this process will help us to provide consistent care to affected individuals, enhance the evidence base in SCD management and support quality improvement efforts.

Keywords: Sickle cell disease, Sickle Cell Centers, Delphi, recommendations, quality improvement

Lay Summary

SCD is a common inherited blood disorder both in the United States and globally. Managing this condition has often relied on local practices rather than strong evidence-based guide-lines, leading to inconsistencies in care across different centers and regions. To address these (and other) issues, the National Alliance of Sickle Cell Centers (NASCC) was established in 2020. One of its key initiatives is the use of a national registry called the Globin Research Network for Data and Discovery (GRNDaD) to collect detailed data that can identify gaps in care and facilitate improvements in SCD management. National Alliance of Sickle Cell Centers has also implemented a way to develop more recommendations for care using a consensus process, called a modified Delphi method. By harmonizing care practices across NASCC SCD centers and promoting the use of the GRNDaD registry, NASCC aims to enhance the quality and consistency of care for individuals with SCD. This collaborative approach is expected to bolster the evidence base for SCD management and support ongoing quality improvement efforts in the field.

BACKGROUND

SCD is the most common inherited blood disorder in the United States, disproportionately affecting people of African ancestry. Although systemic racism and socioeconomic inequities have adversely affected progress, the last 30 years have demonstrated significant improve-ment in outcomes, allowing far more individuals to grow into adulthood. A deeper under-standing of the pathophysiology of SCD, including the role of vascular endothelium in the disease process as well as the nature of hemoglobin S, has broadened the scope of clinical and academic research. Additionally, greater interest in drug development for SCD has led to more disease-focused treatment options. As new therapies become available, a system of care needs to be effectively developed with systems in place to monitor and understand their impact,

to ensure these therapies reach the people who need them, and to guide future avenues of research.

The lack of a strong evidence base for much of SCD care has led to significant variation in practice both within and across individual SCD centers, states, and countries. Even in areas of practice where high-level data exist to improve practice, recent SCD surveillance and implementation data have demonstrated that these evidence-based guidelines are not reaching clinical practice. This problem has been historically compounded by the lack of an agreed-upon national registry and has resulted in a lack of comparative effectiveness data to identify areas of deficiency and improve practice.

INTRODUCTION

To advance the practice of medicine for people with SCD, the National Alliance of Sickle Cell Centers (NASCC) was founded in 2020 and adopted the Globin Research Network for Data and Discovery (GRNDaD) as a national registry to ensure harmonized data collection. National Alliance of Sickle Cell Centers is a nonprofit organization formed to support SCD centers in delivering high-quality comprehensive care and employing the collaborative impact to improve health outcomes, quality of life, and survival in all patients with SCD.

Creating and sustaining more high-quality SCD centers will require the pooling of expertise, resources, perspectives, and community input. At its inception, NASCC identified board members, including physicians representing all regions of the United States, researchers, community members, affected individuals, and other stakeholders to establish a shared vision to enhance the quality of care for people with SCD by improving patient outcomes, reducing health disparities, and working in partnership while collecting data in the GRNDaD registry to better understand where care improvements are needed. Once established, NASCC needed to develop the collective impact framework necessary to measure outcomes for affected individuals. One aspect of this framework is an electronic data capture system (GRNDaD). The second requirement is for shared metrics that can be used to measure outcomes, including increased life expectancy, improved patient satisfaction, and decreased acute care utilization. Once these metrics are established, NASCC will employ data analytics to identify gaps in care and target interventions effectively.

While there have been efforts in the past to develop consensus recommendations for the treatment of SCD, including recommendations established by several SCD experts in collaboration with the National Heart Lung and Blood institute (NHLBI) in 2014 in the United States, these have not been updated to reflect the aging adult SCD population or to include novel treatment options.[1] The Sickle Cell Society in the United Kingdom developed the first edition of the "Standards for Clinical Care of Adults with Sickle Cell Disease in the UK" in 2008, which was revised in 2018 and has been instrumental in improving care for patients with SCD in the United Kingdom. Similar topic-specific standards of care have also been published by the British Society of Hematology (2015, 2018) and the National Institute for Health (2014).[1–3] In the United States, the American Society of Hematology (ASH) developed evidence-based guidelines in 2019-2021, which are organ-system-based, that is, cardiovascular, pulmonary, renal, and neurologic or therapy-focused, that is, blood transfusion, pain management, and stem cell transplant.[4–7] Comparatively, the ASH guidelines do not sufficiently address the holistic approach to care needed by people living with SCD and the UK guidelines are more specific for their patient population and system of care. Furthermore, neither of these guidelines has been implemented for quality assurance purposes and needs restructuring for long-term quality improvement activities. To truly improve care in SCD, a longitudinal clinical registry combined with practice harmonization and a plan for quality assurance and improvement activities is desperately needed. People with SCD require specialized and multidisciplinary care, including access to knowledgeable providers who are familiar with available treatment options to reduce both pain and organ complications, decreasing morbidity and mortality.

To formulate updated management recommendations that could be used to measure the delivery of quality care, NASCC opted to use a well-defined, accepted, consensus-based recommendation process using data-driven evidence where available, combined with a consensus-based approach amongst experts to enhance practice standardization and allow for quality assurance assessments. The initial smaller-scale projects using consensus included those undertaken to define the clinical standards needed to be recognized as an SCD center for children or adults. The definitions of "SCD centers" that resulted from these efforts allowed SCD centers to apply to NASCC to become a member-center recognized for delivering multidisciplinary SCD care.

Once NASCC was fully established and had over 20 member centers, a more defined consensus process was implemented to develop clinical standards of care. The goal of this manuscript is to detail the methodology used to develop the NASCC consensus practice recommendations. As per the Institute of Medicine's published standards for the production of clinical practice guidelines, this methodology is consistent and systematic; all resulting consensus statements are transparent and have specific notations where evidence is lacking.[8] These consensus recommendations are meant to be living documents that will be reviewed and rewritten as needed to ensure the recommendations are up to date and relevant to current treatments and findings in SCD. Finally, these documents are also meant as a call for action to the US Government and healthcare community to increase efforts to provide equitable services to all people living with SCD in the United States.

MATERIALS AND METHODS

This paper will present the method used by NASCC to develop clinical practice recommendations. It is important to note that the number of NASCC recognized centers has grown substantially since its inception (resulting in 114-NASCC NASCC-recognized full and associate member centers as of this article's submission). The consensus process is completed from January to December of each calendar year. Thus, each topic selected annually for the development of recommendations will have a different number of centers voting as the Alliance grows. However, the process for achieving consensus has remained unaltered despite the growth of the organization and the increased number of participating specialists. In addition, the Executive Board within NASCC reviews each set of recommendations to evaluate for relevant updates and changes that need to be made to ensure the data (and recommendations) remain current. If a specific change is needed, a vote will be reconvened across the centers to re-determine consensus for that item. In this way, the recommendations can remain as living documents.

Topic selection

The topics chosen each year are identified by the NASCC Executive Board with input from the participating recognized sickle cell centers. Topics must be deemed important and relevant to both patients and providers, as well as measurable for long-term evaluation and quality assessment. Each topic selected is also approved by the NASCC Board of Directors prior to the initiation of the process. The NASCC process does not focus on topics where a formal evidence-based review has already been conducted by others using Grading of Recommendations, Assessment, Development and Evaluations (GRADE)-like methodology.[9] The NASCC consensus recommendations may encompass components already included in other guidelines, such as age-specific screening recommendations, but are redefined and organized for SCD management to enhance clarity and readability. Further, in some cases, NASCC consensus processes can also be used to provide recommendations on how to optimally implement existing guidelines.

RAND/UCLA Modified Delphi Panel Methodology

The Delphi panel methodology systematically and quantitatively combines expert opinion and published literature (Figure 1). This method is consistent with established processes used for expert practice harmonization in health care decision making.[10,11] Delphi panels do not involve human subjects as defined by 45 CFR part 46, and therefore these procedures do not require institutional review board approval. There are 4 key characteristics required when using the original Delphi method: anonymity, iterative data collection, participant feedback, and statistical determination of group response. A classic Delphi process starts with a set of questions that are answered (anonymously) by experts in a series of rounds. The initial rounds are followed by a discussion in which participants can give feedback on the results of the previous round to explain their individual rationale. Panelists can revise their responses and offer a new vote in subsequent rounds. After each round, the items which have reached consensus are removed from the round, and the remaining items continue to be discussed/voted/revisited. This process can continue until either a predetermined percent consensus is reached or until the group completes a pre-arranged number of rounds. The RAND/UCLA (University of California, Los Angelos) Modified Delphi method is more specific and includes a comprehensive literature review prior to the initial voting, followed by only 2 rounds of ratings or voting on specific statements and a discussion in between rounds. At the end of the second round of voting, the group will have achieved consensus on each item or identified items as non-conclusive. This process removes the anonymity used in the original Delphi.

More recently, Rand et al developed a new tool that can be used with the modified Delphi process called the ExpertLens that combines their original Modified Delphi but expands the pool of stakeholders and allows for virtual engagement.[13] Specifically, ExpertLens is a tool (application) developed by the RAND corporation to enhance virtual engagement with more participants. It has 4 goals: to expand the pool of "expert" participants, to allow non-collocated participants to share their ideas and interact with each other anonymously through online discussion boards, to seamlessly integrate participants' votes (quantitative data) and comments (qualitative data); and to employ statistical analysis as a way to make decisions based on the input from diverse groups.[14–16] Importantly, the modified-Delphi process with the ExpertLens has been used in several previous methodological efforts and was also validated by articles published in the Journals of Clinical Epidemiology and Value in Health.[17–19] Importantly, these articles highlight the impact of the modified process on how study participants may change their responses after seeing their responses compared to others and having an opportunity for in-depth discussion.

The NASCC process uses the same modified-Delphi process but includes both virtual and in-person engagement with a larger group of experts as done using the ExpertLens. The actual ExpertLens tool is not used in this process, but the concepts developed by the RAND Corporation (virtual participation and expansion of the participant pool) are included. National Alliance of Sickle Cell Centers has 2 virtual voting rounds to allow for the inclusion of geographically distributed participants. In between these rounds, the participants gather for in-person/ hybrid discussion to review the initial voting results, review/ discuss and debate changes, and formulate the final items to be considered in the final voting round. National Alliance of Sickle Cell Centers asks each center to have 1 representative who will vote in the process to express their opinions on behalf of their SCD

center. Most often, the representative is the SCD center director. However, a center director may select someone else to serve in this capacity. The NASCC process remains iterative, asks participants to provide their judgments indepen- dently and encourages discussion before the solicitation of the final anonymous, independent votes.

Pre-consensus ratings survey

An initial survey is completed independently by each center to assess current practice patterns across all the recognized NASCC member centers (at that time) to identify areas of practice agreement and identify where there is significant variability. The length of the initial ratings survey depends on the topic undertaken.

Following this survey, NASCC member centers are asked to review the current literature available around the specific consensus topic. For the first consensus topics (age-based screening and prevention for children and adults with SCD), a thorough literature review was undertaken by Partnership for Health Analytic Research, LLC (PHAR). Partnership for Health Analytic Research, LLC was directed to conduct targeted literature searches to identify published information on routine screening and assessments for children and adults with SCD, established SCD guidelines, and previously published consensus recommendations or practice harmonization documents from any state in the United States and countries in Europe. Partnership for Health Analytic Research, LLC was used to assemble and condense the material for the screening and prevention topics due to the breadth of available material that included all age-related (ie, healthy person) screening in addition to SCD-specific screening and guidelines. Subsequent relevant literature reviews are assembled by the topic leaders or recommended by the local experts in the designated practice areas. In all cases, the designated literature is given to all NASCC members to review prior to the meeting.

The RAND/ULCA modified Delphi panel methodology. Source: Broder et al.[12]

Consensus ratings

For all consensus recommendations, NASCC adopted 2 grades of practical interventions:

Standards

Being that which providers must do to ensure safe and adequate care, or where omission could lead to poor clinical outcomes. These include key requirements of any service. Where possible, we have tried to ensure these are measurable.

Recommended

Being those that would be beneficial and that providers should try to follow, but for which there is less evidence or that are less certain to have a direct impact on clinical outcomes.

Hybrid meeting

After the literature review is completed, all NASCC member centers as of May 1 (in that year) are invited to attend a consensus meeting to discuss the designated consensus topics for that year. During this meeting, the results of the initial pre-meeting consensus are reviewed as a group and clarifying questions can be asked and discussed. The results of the pre-meeting surveys are presented to specifically call out areas of clear convergence and variation. After review, the center members are asked to self-select into workgroups. Each consensus topic has designated leaders who serve as moderators for this group discussion. Here, all members can discuss the logic behind their ratings, focusing on areas of difference. The goal is to specifically review the initial findings, discuss and debate areas of variation and divergence, and identify key statements to be included in the final recommendations. National Alliance of Sickle Cell Centers members can attend both in-person and via teleconference. During the live

discussion, NASCC members can also add new items to the recommendations that were not included in the initial survey that may develop during the conversation.

Hybrid meeting voting

During the hybrid meeting, a vote is taken on all items, including those that did reach initial consensus during the pre-meeting survey as well as those in which there was no agreement and the new items that were added during the discussion. Votes are taken on each item. Items that reached at least 70% agreement were considered agreed upon in this vote. If an item did not reach 70% agreement, it was identified as an area needing further study/ discussion.

Post-meeting assessments and community input

Following the live meeting, the working groups complete a summary of findings and develop the final list of statements based on the votes, including evidence and the level of data available. These statements are presented to a regionally diverse group of community-based organizations of SCD stakeholders for comments, additions, and recommendations. Community-stakeholder feedback is then included in the document prepared for the final vote.

Final vote

As noted, the initial vote is performed virtually and followed by a hybrid discussion on each point, which results in a final list of items to be voted on after undergoing community review. The final vote is also performed virtually. At the time of the final vote, each of the recognized NASCC centers can identify a single voting member for each consensus topic (1 vote/center). The lifespan or "whole life" NASCC centers who have separate pediatric and adult directors get 2 votes (one for each director). Importantly, any full NASCC center member can vote during the final vote even if they were not part of the initial pre-meeting survey or were not present at the annual hybrid meeting. The rationale for including all centers in the final vote is to be as inclusive as possible given the fluctuating number of NASCC centers. It is optimal that the final vote includes those representation from all current centers (which may have changed since the start of this process). Thus, the total number of voting centers may differ within a Delphi topic (from first to third vote) and between different topics as more centers joined the Alliance over time.

For each statement, the voting members rate the action (test, treatment, management change, etc) on a scale of 1-9, where 1 is highly inappropriate, risks outweigh the benefits, to 9 signifying highly appropriate, benefits outweigh the risks. Ratings of 1-3 are used when an action is considered by the voter to be inappropriate, and ratings of 7-9 are used for actions considered appropriate. The definition of consensus used by RAND/UCLA modified Delphi panels is variable. The consensus definition should be the percentage of agreement based on a predetermined cutoff. In previous studies by different groups, the percentage agreement varies from 50% to 97% and is usually arbitrary.[20] Importantly, the most common range required for consensus is 70%-80% because it reflects a substantial majority while remaining achievable in large, diverse expert panels. Higher percentages are more difficult when there are a large number of participants, as in this setting. Thus, the NASCC consensus here was pre-defined as being present when at least 70% of the response was in the same three-point range (1-3, 4-6, 7-9). Thus, for all recommendations and standards, at least 70% consensus is required for inclusion. For items that do not meet consensus, additional information is included in the document (areas of research needed, areas of controversy due to existing guidelines, or other points of inquiry). The modified Delphi process used for the development of the NASCC practice recommendations is shown in Figure 2.

RESULTS

As of January 2025, NASCC has convened to discuss over 12 different topics intended for NASCC consensus voting resulting in 5 sets of finalized recommendations including annual screening needed for infants <2 years of age with SCD, children 2-18 years of age and adults living with SCD as well as the requirements for documentation when patients transition from pediatric to adult care and the requirements needed to be a transformative therapy center (an SCD center optimized to perform allogeneic transplant and autologous gene therapy). In addition, there are several recommendations undergoing their final votes this year, including those for the treatment of uncomplicated pain crisis, optimal management and assessment for iron overload, the definition and training needed to be an SCD specialist, and the standards and recommendations for surveillance of neurocognitive functioning in SCD. The last recommendations will be finalized in the first quarter of 2025.

DISCUSSION

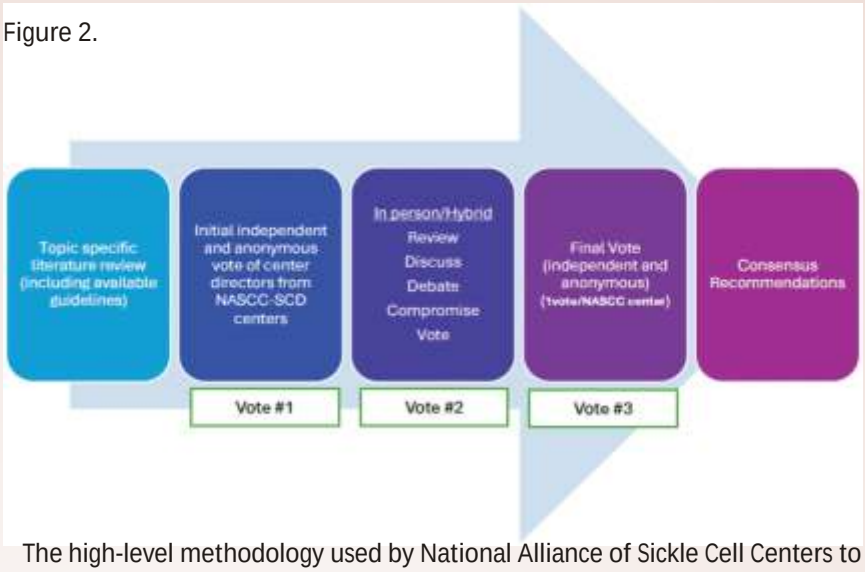
There are multiple areas of SCD management that remain under-studied, and clinical practice has relied on anecdotal experience. While practice guidelines exist in some spaces, they are often specific to a certain organ system or are limited in their ability to draw actionable conclusions due to the paucity of randomized controlled trials, lack of a clinical, longitudinal registry data, and lack of practice harmonization among experts on which to make evidence-based conclusions. The recommendations developed by the modified Delphi process will be living documents that are re-evaluated every 3 years (or sooner if new data arrives) and updated when change is needed. With improved harmonization of practice, ongoing clinical assessment and re-appraisal, NASCC can test the validity of these recommendations to make higher-grade evidence-based decisions in the future.

To be included as a voting member

of NASCC, you must be part of a recognized SCD center in the United States in order to ensure the recommendations can be undertaken as a means for practice harmonization. Notably, NASCC center directors (all of whom are recognized as SCD specialists) have different durations and types of experiences in the management of people with SCD, allowing for a highly heterogeneous but diverse group of members, adding to the richness of the discussion and deliberations.

The purpose of these recommendations is to help SCD centers foster practice harmonization in order to ensure people living with SCD receive consistent, high-level care, based on the most recent scientific discovery to guide practice decisions. Furthermore, by harmonizing practice, it allows for an improved ability to assess the outcomes of these practices for further decision making in the future. The target audience includes the SCD centers themselves as well as the primary care providers and other clinicians, nurses, and staff who provide emergency or continuity care to individuals with SCD. These recommendations address the care of individuals living with SCD throughout the lifespan with a goal of facilitating high-quality practice, encouraging the use of a common data collection tool (GRNDaD, the national registry used by NASCC), and improving cooperative thought and research within the SCD provider community.

Figure 2.



The high-level methodology used by National Alliance of Sickle Cell Centers to develop consensus-based recommendations.

CONCLUSION

The history of SCD both in the United States and worldwide has demonstrated a lack of commitment to clinical care and quality improve-ment by multiple governing bodies, resulting in a lack of available data, resources, and few high-quality clinical trials. These recommendations reflect the areas of agreement among NASCC member centers. There are noted limitations in data availability and several areas in which topics chosen for consensus will not have data but will require practice harmonization to ensure the safe and methodical delivery of novel therapies and treatments. Furthermore, as we now have a population of geriatric patients living with SCD, there are uncharted territories for which we need to studiously examine our practices and identify optimal treatments. The clinician-supported consensus statements developed through this validated method allow for faster dissemination of management recommendations compared to waiting on the results of a clinical study that has the potential to be underfunded (or never funded). We hope that these recommendations can aid in promoting research in SCD and further care improvement in a cooperative, data-driven environment with a focus on improving outcomes for all individuals living with SCD.

ACKNOWLEDGEMENTS

There is no funding for this work. National Alliance of Sickle Cell Centers (NASCC) is grateful to the pharmaceutical sponsorship obtained annually used to support the meeting space and NASCC administration used for the consensus conference. All consensus sessions are limited to SCD center members only and are closed to industry members. Special thanks to all the members of NASCC who took part in this initiative and for their commitment to providing excellent care to people living with SCD.

AUTHOR CONTRIBUTIONS

Julie Kanter (Conceptualization, Data curation, Methodology, Project administration, Writing—original draft, Writing—review & editing), Melissa Frei-Jones (Conceptualization, Data curation, Writing—review & editing), Deepa Manwani (Investigation, Methodology, Project administration, Writing—review & editing), Marsha Treadwell (Con-ceptualization, Writing—review & editing), Mohan Madisetti (Data curation, Formal analysis, Methodology, Project administration, Writing—review & editing), Robin Miller (Data curation, Writing—review & editing), Seethal A Jacob (Data curation, Writing—review & editing), Sana Saif-Ur-Rehman (Data curation, Writing—review & editing), Andrew Ross Wickman O'Brien (Data curation, Writing—review & editing), and Sophie Lanzkron (Conceptualization, Data curation, Methodology, Writing—original draft, Writing— review & editing)

FUNDING

None declared.

CONFLICTS OF INTEREST

J.K.: Consultant Beam, Novo Nordisk, Merck, Sanofi, Optum, Research:

HRSA, CDC, NIH. S.J.: Research NIH. D.M.: consultant Editas, Pfizer, Novartis. S.L.: Consultant: Beam, Novo Nordisk, Bluebird bio, Merck, Pfizer, Research: PCORI, HRSA. M.F., M.M., R.M., S.S.U.R., and A.R.W.O. have no conflict of interest. D.M., S.L., M.T., and J.K. serve on the Executive Board of the National Alliance of Sickle Cell Centers (uncompensated). S.L. is a member of the Editorial Board for the Journal of Sickle Cell Disease. Full peer review for this manuscript was handled by Journal of Sickle Cell Disease Associate Editor Betty Pace.

DATA AVAILABILITY

This paper reports on the methods used by the National Alliance of Sickle Cell Centers to achieve consensus using a blend of the Modified Delphi and Expert Lens techniques, including describing how the data are obtained to achieve practice harmonization. This manuscript does not include data.

REFERENCES

1 Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;312(10): 1033-1048. 10.1001/jama.2014. 10517

2 Howard J, Hart N, Roberts-Harewood M, et al. ; BCSH Committee. Guideline on the management of acute chest syndrome in sickle cell disease. Br J Haematol. 2015;169 (4):492-505. 10.1111/bjh.13348

3 Qureshi A, Kaya B, Pancham S, et al. ; British Society for Haematology. Guidelines for the use of hydroxy-carbamide in children and adults with sickle cell disease: a British Society for Haematology Guideline. Br J Haematol. 2018;181(4):460-475. 10.1111/bjh.15235

4 Liem RI, Lanzkron S, Coates TD, et al. American Society of Hematology 2019 guidelines for sickle cell disease: cardiopulmonary and kidney disease. Blood Adv. 2019;3 (23):3867-3897. 10.1182/blood-advances.2019000916

5 DeBaun MR, Jordan LC, King AA, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. Blood Adv. 2020;4(8):1554-1588.10.1182/bloodadvances.2019001142

6 Brandow AM, Carroll CP, Creary S, et al. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. Blood Adv. 2020;4(12):2656-2701. 10.1182/bloodadvances. 2020001851

7 Kanter J, Liem RI, Bernaudin F, et al. American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation. Blood Adv. 2021;5(18):3668-3689. 10.1182/bloodadvances.2021004394C

8 Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice G. In: Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E, eds. Clinical Practice Guidelines We Can Trust. National Academies Press (US). Copyright 2011 by the National Academy of Sciences. All rights reserved.; 2011.

9 Schunemann HJ, Mustafa R, Brozek J, et al. ; GRADE Working Group. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. J Clin Epidemiol. 2016;76:89-98. 10.1016/j.jclinepi.2016.01.032

10 Bojke L, Soares M, Claxton K, et al. Developing a reference protocol for structured expert elicitation in health-care decision-making: a mixed-methods study. Health Technol Assess. 2021; 25(37):1-124. 10.3310/hta25370

11 Bojke L, Soares MO, Claxton K, et al. Reference case methods for expert elicitation in health care decision making. Med Decis Making. 2022; 42(2):182-193. 10.1177/0272989X21 1028236

12 Broder MS, , Gibbs SN, , Yermilov I. An adaptation of the RAND/UCLA modified delphi panel method in the time of COVID-19. J Healthc Leadersh. 2022;14:63-70.

13 Dalal S, Khodyakov D, Srinivasan R, Straus S, Adams J. ExpertLens: a system for eliciting opinions from a large pool of non-collocated experts with diverse knowledge. Technol Forecast Soc Change. 2011;78(8): 1426-1444.10.1016/j.techfore.2011. 03.021.

14 Dalkey N, Helmer O. An experimental application of the DELPHI method to the use of experts. Manage Sci. 1963;9(3):458-467.

15 Khodyakov D, Grant S, Kroger J, Gadwah-Meaden C, Motala A, Larkin J. Disciplinary trends in the use of the Delphi method: a bibliometric analysis. PLoS One. 2023;18(8): e0289009. 10.1371/journal.pone. 0289009

16 Khodyakov, D. (2023, October 2). Generating evidence using the Delphi method. RAND Corporation. https://www.rand.org/pubs/commentary/2023/10/generating-evidence-using-the-delphi-method.html.

17 Khodyakov D, Chen C. Response changes in Delphi processes: why is it important to provide high-quality feedback to Delphi participants? J Clin Epidemiol. 2020;125:160-161. 10.1016/j.jclinepi.2020.04.029

18 Khodyakov D, Chen C. Nature and predictors of response changes in modified-Delphi panels. Value Health. 2020;23(12):1630-1638. 10.1016/j.jval.2020.08.2093

19 Scott TE, Costich M, Fiorino EK, Paradise Black N. Using a modified Delphi methodology to identify essential telemedicine skills for pediatric residents. Acad Pediatr. 2023;23(3): 511-517.10.1016/j.acap.2022.08.014

20 Nasa P, Jain R, Juneja D. Delphi methodology in healthcare research: how to decide its appropriateness. World J Methodol. 2021;11(4):116-129. 10.5662/wjm.v11.i4.116

Credit: Julie Kanter, Melissa Frei-Jones, Deepa Manwani, Marsha Treadwell, Mohan Madisetti, Robin Miller, Seethal A Jacob, Sana Saif-Ur-Rehman, Andrew Ross Wickman O'Brien, Sophie Lanzkron, The development of consensus recommendation to improve practice harmonization for Sickle Cell Disease through the National Alliance of Sickle Cell Centers, Journal of Sickle Cell Disease, Volume 2, Issue 1, 2025, yoaf011, https://doi.org/10.1093/jscdis/yoaf011

zolon
Healthcare Limited
(A member of the Emzor Group)

INTELLIGENT zolon Healthcare Limited (A member of the Emzor Group) SOLUTIONS

Rekmal® *Injection*

Artesunate 30mg/60mg/120mg Injection

...the difference in
SEVERE MALARIA

The **Benefit** of **3**

- **Efficacy**
- Safety
- Speed

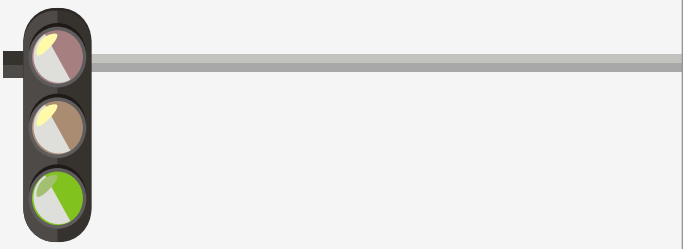
Edic Building, 9, Town Planning Way, Ilupeju, Lagos, Nigeria. Tel: +234 (0) 700 225 5965, 0700 CALL ZOLON
Zolon Healthcare Limited Zolon Healthcare Limited Zolon Healthcare Limited Zolon Healthcare

www.zolonhealthcare.com

INTELLIGENT SOLUTIONS

DE-DEON'S

SYRUP OF HAEMOGLOBIN
VITAMIN B12



Iron formulations are a means to an "end" - Hemoglobin.
De-Deon's Syrup of Hemoglobin, the "end" in itself.

Have you had your De-Deon's today?

YOU'RE GOOD TO GO...

Manufactured & Marketed by:

Daily-Need Industries Ltd

Quality | Integrity | Transparency

Email: info@dailyneedgroup.com | www.dailyneedgroup.com

MIPENEM®

Meropenem Injection
500mg & 1g

...more powerful
& smarter in
nosocomial infections

FIDSON
Fidson Healthcare Plc
...We value life

CORPORATE HEAD OFFICE:
268 Ikorodu Road, Obanikoro, P.O.Box 7210, Shomolu, Lagos. Nigeria.
Tel: +234-1-0700fidsonplc. Email: info@fidson.com, Website: www.fidson.com

Shalina MEDSPACE

Revolutionizing Medical Learning in Africa

Step into a new realm of medical learning with Shalina MedSpace

Access FREE Premium Medical Literature & Resources

Accessible anytime, anywhere on the go!

Ready to explore?

EXCITING PRIZES EVERYDAY

Register Now to Participate in

MedGenius Contest

Daily winners get exciting prizes worth

₦10,000 each

1. Scan the QR code or visit www.shalinamedspace.com to download & register on MedSpace.
2. Participate in the MedGenius Quiz accessible on the 'Featured Section' of the Homepage.

Watch MedSpace for announcements of 5 daily winners.