An update on patient reported outcomes in type 2 inflammation airway disease

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Purpose of review
Patient reported outcome measures (PROMs) play an important role in assessing so-called *global airway disease* caused by type-2 inflammation, not only in terms of patients perspective on symptoms and treatment/side-effect, but they can also serve as a measure of disease control, and not least as an indicator of possible coexisting comorbidity otherwise unrecognized. The objective of this review was to investigate any newly developed PROMs for global airway disease and to give an overview of the most commonly used PROMs in the management of global airway disease.

Recent findings
The Standard Tests for Asthma, Allergic Rhinitis and Rhinosinusitis (STARR-15) is a recently developed PROM aimed to raise clinicians awareness of coexisting type-2 inflammation disease. Strengths of the STARR-15 is that is quick and symptom-centered, i.e. items are not specifically aimed at a disease the patients might not be aware they have. The STARR-15 has, however, not yet been validated, so details of responsiveness and reproducibility are yet to be determined.

Summary
PROMs are a quick and cheap way to assess patient perspectives in global airway disease, and can play an important role in unveiling otherwise overlooked co-existing double disease.

Keywords
global airways disease, Health-related quality of life, patient reported outcome measure, type 2 inflammation

INTRODUCTION

One of the biggest obstacles – and chief complaints of patients – in treating type 2 inflammation disease (T2ID) effectively is the lack of both coordination and sharing of information between medical specialties; a problem which begins with realizing the patient is affected in more than one organ system [1]. For the purpose of uncovering coexisting double-disease as well as assessing impact on health-related quality of life (HRQoL) of disease and treatment, patient reported outcome measures (PROMs) are playing an increasingly important role [2]. However, most PROMs are either disease-specific or generic, making assessment of comorbidity challenging since patients may need to complete both disease-specific tests and generic tests.

T2ID is gaining growing awareness as the underlying culprit in several diseases such as asthma, allergic rhinitis (AR) and chronic sinusitis with nasal polyposis (CRSwNP). The key drivers of type 2 inflammation are TH2- and type 2 innate lymphoid cell (ILC2)-secreted cytokines IL-4, IL-5 and IL-13 triggering eosinophilic inflammation, mucus production, tissue remodeling etc. The global prevalence of T2ID is rising, with up to 3%, 1–18%, and 10% affected by CRSwNP, asthma, and AD, respectively [3–5]

Patients with T2ID in one organ system often suffer from coexisting T2ID in another; studies have shown that comorbid asthma is present in up to 65% of CRSwNP patients and in nearly half of AD patients [6,7]. Furthermore, co-existing T2ID is known to worsen disease severity as well as increasing the risk

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Curr Opin Allergy Clin Immunol 2023, 23:1–8
DOI:10.1097/ACI.0000000000000873

KEY POINTS

- Type 2 inflammation is often the culprit in disease of both lower and upper airways.
- The realization of this connection has coined the term *global airway disease*.
- Upper- and lower-airway disease often co-exist without the patient or clinician knowing.
- Patient reported outcome measures (PROMs) are a useful way to raise clinicians awareness of otherwise overlooked global airways comorbidity.
- This study identified a new and promising PROM for global airways disease, the Standard Tests for Asthma, allergic Rhinitis and Rhinosinusitis, however, validation studies to asses responsiveness and reproducibility is needed.

of treatment failure, especially if ignored. On the other hand, studies suggest that treatment of lower airway disease improves upper airway symptom and vice versa [8]. In cases of severe disease, HRQoL is significantly impaired and treatment costs due to readmissions, surgery etc. are high [1].

Therefore, in the case of T2ID where concomitant comorbidities are often present, so-called *global airways* disease, there is a demand for PROMs that cover several organ systems at the same time.

The ideal global airways PROM could serve both to express patient perception of disease as well as a reliable diagnostic tool and measure of disease severity.

This study aims to give an update on type 2 inflammation-related PROMs. We will do so by first presenting the most commonly used PROMs, followed by a search aimed at identifying any recently published (i.e., within the past 18 months) PROMs focused on global airways disease.

COMMONLY USED PATIENT REPORTED OUTCOME MEASURES IN ASTHMA

PROMs focused on asthma symptoms is a useful tool when evaluating disease control. Disease control is the main goal in management and is the first step in patient care. Asthma control is a multidimensional concept, which cannot be captured by one single item. Some of the most frequently used questionnaires worldwide are the Asthma Control Questionnaire (ACQ) and the Asthma Control Test (ACT). Selection of which questionnaire to use, is dependent on the tradition in the clinic, as an overlap exists. Significant correlations have been found between ACT scores and ACQ scores ($r = -0.89$, $P < .001$).

Asthma Control Questionnaire

The ACQ is likely the most widely used standardized measure of asthma control in clinical trials and clinical settings. The original ACQ evaluation tool contains seven items assessed using seven-point Likert scales (ACQ-7), with levels of control from 0 (no impairment) to 6 (extreme impairment), using the past seven days as a recall period with all items equally weighted [9]. The original ACQ has also been reduced to the ACQ-6 and ACQ-5, in which the item concerning predicted FEV_1 percentage (FEV_1%) and the frequency of β_2-agonist use, respectively, has been eliminated. These simplified versions (ACQ-5 and ACQ-6) have been validated and each has been found to be satisfactory [10]. The higher scores indicating a greater degree of uncontrolled asthma. A mean score $\leq$0.75 is classified as 'well controlled', $\geq$1.5 as 'uncontrolled', and between these two cut-off points as 'somewhat controlled' [11]. When comparing different studies using ACQ-5 as the gold standard, examination of patients with well controlled asthma (score of $\leq$0.75) showed a negative predictive value (NPV) of 0.81, meaning that, if a patient achieves an ACQ-5 score of 0.75, there is only a 19% probability that his or her asthma is not well controlled [11,12]. Likewise, for patients with asthma that is not well controlled and who present a score of 1.50, a positive predictive value (PPV) of 0.84 has been found, meaning that, if a patient achieves a high ACQ-5 score of 1.50, there is only a 16% probability that his or her asthma is well controlled, despite the high score. The Minimal Clinically Important Difference (MCID) of the ACQ has been formally determined to be 0.5 by using anchor-based approaches in patients studied over time, with an standard deviation (SD) of 0.99 [12,13].

Asthma Control Test

The ACT has been developed by asthma experts as an easy-to-use test, both in clinical and research settings [14]. The ACT assesses the frequency of shortness of breath, night-time/early awakenings, rescue medication use, overall asthma control and loss of productivity. The ACT questionnaire is a five-item, patient-administered tool, including a five-point rating scale. In scoring the ACT survey, responses for each of the five items are summed to yield a total score ranging from five (poor asthma control) to 25 (complete asthma control). A score of $\geq$20 indicates 'well controlled' asthma, while a score $\leq$19 indicates asthma that is 'not well controlled'. There is a negative relationship between ACT points and the risk of asthma exacerbation, with the highest risk at an ACT of five, and the lowest at an ACT of 25, with almost no change between the 20–25 points. The ACT score provides patients and their

healthcare professionals with a useful measure for helping to determine the level of treatment required. The sensitivity of the ACT, with a cut-off of 19 points, was 71.3. The predictive value of a positive test (PPV) was 72.6 and of a negative test (PVN) was 69.3. The specificity was 70.8, and the area under the curve (AUC) was 0.710. The MCID was 3 with an SD of 4.42 [14,15].

COMMONLY USED PATIENT REPORTED OUTCOME MEASURES IN SINO-NASAL DISEASE

A variety of PROMs exist for sino-nasal disease and its impact on HRQoL. However, out of the available PROMs the SNOT-22 is the one best known.

Sino-nasal outcome test

The sino-nasal outcome test (SNOT-22) is the most commonly used PROM in CRS. It is recommended in EPOS2020 and broadly considered the most robust existing CRS-oriented PROM [2,3,16,17]. It contains 22 items related to sino-nasal and ear function, sleep quality, psychological impact, and productivity.

The SNOT-22 has its roots in the Rhinosinusitis Outcomes Measure-31 (RSOM-31), which was published in 1995 by Piccirillo *et al.* [18]. The RSOM-31 was developed in an attempt to assess the HRQoL of CRS patients in a holistic way by addressing seven domains including 'nasal symptoms', 'eye symptoms', 'ear symptoms', 'sleep', 'general symptoms', 'practical problems' and 'emotional consequences'. The RSOM-31 was later abbreviated to a 20-item questionnaire (the SNOT-20 [19]), which had 11 questions omitted, including the entire 'eye symptoms' domain. However, as this new abbreviated version did not include items regarding two cardinal symptoms; 'blocked nose' and 'decreased sense of smell/taste', these were included to produce the final version of the SNOT-22 validated by Hopkins *et al.* in 2009 in a UK multicenter study with over 9000 participants [20]. A 16-item version has also been developed, however less commonly used.

The 22 items are each scored on a Likert scale ranging from 0 ('No problem') to 5 ('Problem as bad as it can be'), thus producing a score ranging from 0 to 110. The recall period is two weeks. A score of up to 8 is normal, 8–20 is mild disease, 21–50 moderate, and >50 is severe [3]. Studies have shown a good correlation between the Visual Analog Scale (VAS) scores of >6 and severe CRS disease/SNOT22-scores >50. In the validation study, the SNOT-22 was validated in distinguishing patients with known CRS from healthy ones, identifying clinically relevant differences in patients with CRS, and correlating higher SNOT-22 scores with reduced HRQoL. The MCID was calculated at 8.9 points, meaning that a change of less than 9 points cannot be interpreted as relevant to the patient [20]. It has been suggested to set the MCID at 12 points in patients undergoing medical therapy [3]. Furthermore, factor domain analysis has revealed that the SNOT-22 can be further sub-divided into five domains (nasal symptoms, extranasal-rhinologic symptoms, ear-facial symptoms, sleep dysfunction and psychological dysfunction) [21].

Table 1 shows the most commonly used PROMs for assessing HRQoL in patients with global airway disease.

METHODS

This study included a literature review as stated below.

Literature search

The literature search was carried out in PubMed Medline in august 2022. The search was done in 'titles and abstracts' limited to articles published between 15th of February 2021 and 15 august 2022 in the English language, and focusing on humans, age >17 years.

The search strategy included a combination of the terms ['Global airway*' OR 'type 2 inflammation*' OR 'united airway*' OR 'CRSwNP'] AND ['patient reported outcome*' OR 'questionnaire*' OR 'test*'] AND ['Develop*' OR 'novel' OR 'new'], see Fig. 1.

Article selection

Two authors (C.P. and C.H.) completed title and abstract screening using an online tool (covidence.org). Articles that were not focused on newly developed T2ID HRQoL questionnaires or PROMs were excluded (Fig. 1). There were eight minor disagreements in article selection, which were discussed and resolved. This was followed by a round of full-text screening, resolving of minor conflicts and finally an agreement was made on the final included article.

RESULTS

Our search strategy yielded a total of 1029 articles (see Fig. 1). Only one article [40▪] fulfilled the inclusion criteria, namely a work by Backer *et al.* [40▪] describing the development of the Standard Tests for Asthma, Allergic Rhinitis and Rhinosinusitis (STARR-15).

Table 1. Some of the most commonly used PROMs in clinical trials and clinical practice when assessing type II inflammation/global airway disease

PROM	Description no. of items; domains; scoring	Score range	Time to complete (min)	Psychometric properties
General health assessment questionnaires				
EQ-5D [22–24]	15 items 5 domains; Mobility, self-care, Usual activity (i.e. impact of disease on usual social and occupational activities), pain/discomfort, anxiety/depression. Score of 1 equals best health (descriptive system). Furthermore, a VAS 0-100 to assess general health	0–1 0–100 (VAS)	<5	MCID for the descriptive system: CRS = 0.04 Asthma = 0.08 MCID for the VAS system CRS ≥8 Asthma = 12.3
SF-36 [25–28]	36 items 8 domains collected in Mental and physical composite score, pain etc. Scored on a VAS scale 0–100 generating a total score of 0–100with 100 indicating best health	0–100	5–10	MCID CRSwNP: ≥2 for physical composite score and ≥3 for mental composite score, ≥8 for each sub-domain. MCID asthma: 11 for PCS [range 10–12] and 7.5 for MCS [range 8.3–12.5] (based on expert panel decision using the Delphi method)
SF-12 [27,29]	Abbreviated version of the SF-36 containing 12 questions on 8 domains	0–100	<5	MCID not specified for CRS. Estimated at 10–12.5 for respiratory disease
VAS [30–32]	A horizontal line with word anchors in each end representing extreme feelings, typically generating a score of 0–100 mm.	0–100 (mm)	<1	-VAS in CRS: VAS ≥60 mm correlates with SNOT22 ≥50 meaning severe CRS -VAS in asthma: ≤15 mm = controlled, VAS >72 mm = uncontrolled -VAS in AR: ≥50–60 mm correlates with moderate-severe disease. In AR the MCID is 23 mm
Asthma-specific questionnaires				
ACQ [9–11]	7 items w. 1 week recall period scored on Likert scale 0–6 with 0 being totally controlled and 6 being severely uncontrolled 5 items for symptoms, 1 for medicine use, 1 objective (FEV_1) completed by health worker). Total score is mean of item scores.	0–6	2–4	MCID = 0.5 A score of 1.5 is defined as the cut-off for inadequately controlled asthma.
ACT [14,15,33]	5 items w. 4 week recall period scored on 1–5 Likert scale with 5 being complete asthma control.	5–25	2–4	MCID = 3 A score of <20 is defined as the cut-off for inadequately controlled asthma.
AQLQ [34,35]	32 items w. 2-week recall period scored 1–7 on Likert scale. 4 domains; symptom types, activity limitation, emotional function, environmental exposure. Score is calculated as mean of each item/domain, higher scores indicate better outcome.	1–7	5–10	MCID of ≥0.5 in overall score (a change in score ≥1 is moderate, while a change ≥2 is large)

Table 1 (*Continued*)

PROM	Description no. of items; domains; scoring	Score range	Time to complete (min)	Psychometric properties
CRS-specific questionnaires				
SNOT-22 [16,20,36]	22 items w. 2-week recall period. 5 domains; Rhinologic, extra-rhinologic, ear/face, psychological, sleep Higher scores indicate worse outcomes	0–110	5–10	MCID = 8.9 Subdomains validated specifically for CRSwNP A score of 0–8 is normal, 8–20 is mild disease, 21–50 moderate, and >50 is severe Able to differentiate CRS patients from healthy subjects.
SNOT-20 [19,37]	20 items w. 2-week recall period scored 0–5 on Likert scale. 5 domains; Rhinologic, ear, facial, functional, sleep Higher scores indicate worse outcomes	0–100	5	MCID = 16
RSOM-31 [18,27]	31 items w. 7 domains; nasal, eye, ear, sleep, emotional, functional, general Higher scores indicate worse outcomes	0–155	10–20	MCID > 30% change
Type 2 inflammation-disease questionnaires				
CARAT [32,38,39]	10 items w. 4-week recall period scored 0–3 on Likert scale. Higher scores indicate better outcomes 2 domains; Allergic rhinitis and Asthma	0–30	<3 min	MCID = 3.5 A score of >24 indicates good asthma- and AR control
STARR-15 [40▪]	15 items w. 12-week recall period. 3-point Likert scale (No problem to Severe problem) 3 domains; allergic rhinitis, CRS, asthma No sum-score is calculated	N/A	<5	Not yet clinically validated.

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; AR, allergic rhinitis; CARAT, Control of Allergic Rhinitis and Asthma Test; CRS, chronic rhinosinusitis; EQ-5D, EuroQoL 5 domain questionnaire; MCID, minimal clinically important difference; RSOM-31, Rhinosinusitis Outcome Measure 31 items; SF-12, Short Form 12 Health Survey; SF-36, Short form 36 Health Survey; SNOT-20, Sinonasal Outcome Test 20 items; SNOT-22, Sino-Nasal Outcome Test 22 items; STARR-15, Standard Tests for Asthma, allergic Rhinitis and Rhinosinusitis; VAS, Visual Analog Scale.

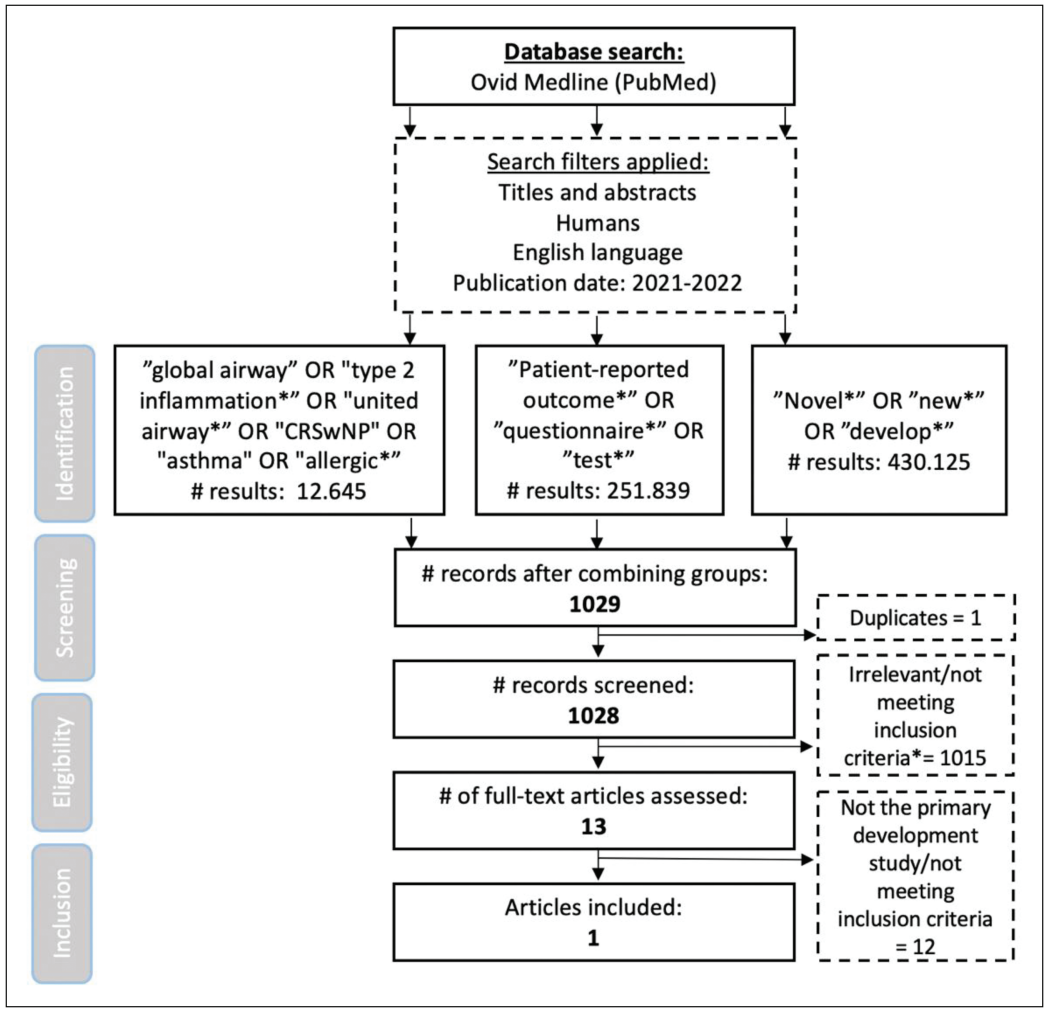

FIGURE 1. Flowchart of study identification and selection. *Inclusion criteria: article describing primary development of PROM assessing symptoms and/or quality of life in relation to type 2 inflammation disease, i.e. not solely CRS, asthma or allergic rhinitis. CRS, chronic sinusitis; PROM, Patient reported outcome measure.

Standard Tests for Asthma, Allergic Rhinitis and Rhinosinusitis [40▪]

The STARR-15 is a new 15-item PROM specifically developed as a screening tool for concurrent upper- and lower airway disease caused by type-2 inflammation. Developed in Denmark by Backer *et al.* [40▪], the STARR-15 aims to raise clinicians' awareness of airway double-disease.

The STARR-15 was developed via a combination of clinical experience and a data-driven approach. Firstly, 55 items were suggested based on clinical experience and with inspiration from other commonly used PROMS such as the SNOT-22 and ACQ. Pilot testing was performed in 11 patients with known global airway disease, leaving 44 items. These items were tested on 206 patients with confirmed disease in lower and/or upper airways, followed by a multistep item reduction phase leaving 18 items for further statistical analysis. Items showing floor-ceiling effects were excluded. Four items were removed due to not fitting in a meaningful category, whereas one item 'facial pain' was added, despite not being statistically significant, due to its clinical relevance. In the following phase the 15 items were tested for internal validity and their ability to differentiate between patients suffering from CRS, asthma and/or allergic rhinitis. The test subjects also completed the SNOT-22 and ACQ, and results were compared. Internal consistency was acceptable for all three factors; *asthma, CRS and allergic rhinitis*, with Cronbach's alpha values of 0.73, 0.76 and 0.63, respectively. Differentiation between the disease subgroups were not possible, possibly due to the nature of the disease with overlapping symptoms. Tests of reliability, responsiveness and MCID was not performed in this study.

Scoring and interpreting the Standard Tests for Asthma, Allergic Rhinitis and Rhinosinusitis

Subjects are asked to rate each item on a six-point Likert scale ranging from 'no problem' to 'problem as bad as it can be'. The recall period is 12 weeks. No sum-score is calculated.

Since a large overlap was found in responses from patients from the three disease groups, the authors do not expect the STARR-15 to hold great diagnostic potential. However, the overlapping symptoms support the concept of global airway disease, and the STARR-15 can prove to be a valuable screening tool to raise awareness of disease in other areas of the airways, and positive responses could warrant a systematic diagnostic evaluation to detect global airway disease.

The STARR-15 has not yet been clinically validated, and testing for reliability and responsiveness is yet to be performed. Severity scoring was not possible.

A strength of the STARR-15 is its briefness, the fact that it is a symptom-based test assessing respiratory complaints, without naming allergy, CRS or asthma, and that no score calculation is needed.

DISCUSSION

Our study was motivated by the need for collaboration between specialists treating airway disease. It is the opinion of the authors, that despite a well established knowledge of the marked association between CRS, allergies and asthma, there is still a lack of real-world integration of this knowledge. Therefore, there is a need for easy-to-use clinical tools to aid in assessing patients with concomitant airway disease – a challenge for which PROMs can be useful [3]. A recent meta-analysis pointed out the lack of items assessing common comorbidity associated with T2ID in the existing CRS-oriented PROMs [2]. The same is true for asthma and AR PROMs. The CARAT questionnaire includes both allergic rhinitis and asthma, however, does not cover CRS-oriented items. As this study shows, only one newly developed PROM is specifically intended to assess global airway disease and raise diagnostic awareness; the STARR-15. The STARR-15 has not yet been validated in real world patients, and has so far not been shown to be able to diagnose or rate severity of disease. However, it serves as a quick screening tool, helpful in raising diagnostic 'flags' of double disease.

A common point of criticism of disease-specific PROMs are the lack of some patient-centered items in regards to perception of treatment, for example medical therapy versus surgical in CRSwNP. Another important aspect is adherence to medication. The challenge of adherence in asthma is well described in several studies, but adherence in patients with CRS is an overlooked issue of great importance, since patients with diseases in global airways need to be 'double' adherent. Difficult-to-treat CRS could reflect an unmet need in effective management, one being better adherence to nasal steroid and saline irrigation [3,41].

This study highlights the need for the continued development and validity testing of global airway PROMs. The ideal PROM contains perspectives relevant to the patient, as well as serve as a reliable diagnostic tool and indicator of disease control/treatment effect for the clinician.

CONCLUSION

PROMs play an important role in assessing HRQoL in patients with global airway disease as they are a simple, cheap, quick and painless way to get an insight into the patient's perspective. Furthermore, they can aid clinicians in diagnosing comorbidity otherwise overlooked. This study describes a promising new tool. However, further research is needed to establish responsiveness and reproducibility of the STARR-15.

Acknowledgements

None.

The authors declare that this paper has not been published elsewhere in any form, has not been accepted for publication elsewhere, and is not under consideration for publication elsewhere.

Financial support and sponsorship

None.

Conflicts of interest

C.H., K.A., C.vB. and V.B. were part of the group who developed the STARR-15 mentioned in this study.

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