CONCISE CLINICAL REVIEW

Is Disease Stability an Attainable Chronic Obstructive Pulmonary Disease Treatment Goal?

Dave Singh[1], MeiLan K. Han[2], Surya P. Bhatt[3], Marc Miravitlles[4], Chris Compton[5], Stefanie Kolterer[6], Tharishini Mohan[5], Suneal K. Sreedharan[5], Lee Tombs[7], and David M. G. Halpin[8]

[1]Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, University of Manchester, Manchester University NHS Foundation Trust, Manchester, United Kingdom; [2]University of Michigan, Ann Arbor, Michigan; [3]Division of Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham, Birmingham, Alabama; [4]Pneumology Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Barcelona Hospital Campus, CIBER de Enfermedades Respiratorias (CIBERS), Barcelona, Spain; [5]Global Medical Affairs, General Medicines, and [6]Specialty Medicines, GSK, London, United Kingdom; [7]Precise Approach Ltd., London, United Kingdom; and [8]University of Exeter Medical School, University of Exeter, Exeter, United Kingdom

ORCID IDs: 0000-0001-8918-7075 (D.S.); 0000-0002-9095-4419 (M.K.H.); 0000-0002-8418-4497 (S.P.B.); 0000-0002-9850-9520 (M.M.); 0009-0002-6798-4078 (T.M.); 0009-0004-0045-5838 (S.K.S.); 0000-0003-2009-4406 (D.M.G.H.).

Abstract

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by progressive airflow obstruction. Despite advancements in diagnosis and treatment, the disease burden remains high; although clinical trials have shown improvements in outcomes such as exacerbations, quality of life, and lung function, improvement may not be attainable for many patients. For patients who do experience improvement, it is challenging to set management goals given the progressive nature of COPD. We therefore propose disease stability as an appropriate and attainable treatment goal. Other disease areas have developed definitions of no disease activity or remission, which provide relevant information for defining and achieving stability for patients with COPD. Disease stability builds on related concepts already defined in COPD, such as clinical control and clinically important deterioration. Current components that could form part of a disease stability definition include exacerbations, health status (including quality of life and symptoms), and lung function. Considerations should be given to intervals over which stability is defined and assessed, appropriate thresholds, and defining a composite. Ensuring a holistic approach, objective measurements, and harmonious, clear communication between patients and physicians can further support establishing disease stability. Here we propose a preliminary definition of disease stability, informed by existing research in COPD. Further research will be needed to validate the framework for use in clinical and research settings. Exploring disease stability as a goal, however, is an opportunity to develop and validate an attainable treatment target to advance the standard of care for patients with COPD.

Keywords: COPD; disease management; treatment outcome

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition with a variable disease course, often characterized by persistent and progressive airflow limitation (1, 2). COPD causes irreversible, inflammation-driven, structural changes to the lungs (3), and each exacerbation negatively impacts the disease trajectory (4). Suboptimal treatment can also lead to rapid lung function decline and an increased risk of mortality (5).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report states COPD management should aim to

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Correspondence and requests for reprints should be addressed to Dave Singh, M.D., Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, University of Manchester, Manchester University NHS Foundation Trust, Manchester M23 9LT, UK. E-mail: dsingh@meu.org.uk.

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reduce current symptoms and reduce future risk of progression, exacerbations, and mortality (1). Although significant developments have been made in the diagnosis and treatment of COPD, the burden of disease is still significant, even in those already taking inhaled maintenance therapy (6, 7), and COPD fundamentally affects how patients manage their lives (8). There has been a paucity of effective disease-modifying therapies (DMTs) that significantly delay progression early in the disease (1, 9). However, recent clinical trials with biological treatments offer the hope of improved outcomes for selected subgroups (10, 11). Thus, treatment goals should balance the need for early diagnosis and manage the current burden faced by patients, while also aiming toward a future where highly effective DMTs might become available.

Multidisciplinary COPD management, encompassing pharmacological and nonpharmacological interventions, aims to improve health status and decrease future risk so that each individual may reach their "personal best." During follow-up, the concept of disease stability can be considered alongside the potential for improvement (Figure 1) and can be used to set long-term goals to prevent clinical worsening and minimize future risk. Stability of disease can be a treatment goal that is valuable to patients and a target for future DMTs.

Disease activity refers to reversible components of the disease (12, 13), and other chronic inflammatory diseases have developed management strategies designed to control disease activity. Untreated disease activity may cause irreversible pathology, resulting in greater disease severity. Ideally, the timing of therapeutic interventions should be as early as possible, before severe disease results in irreversible symptoms and/or disability. Targeting disease activity in COPD has been previously discussed (13, 14), and the concept of disease stability as a long-term goal is relevant when disease activity is low. Disease stability could be used as a treatment goal in clinical practice, regardless of disease stage, phenotype/etiotype, treatment/intervention, or comorbidities.

Here we consider the concept of disease stability in COPD and whether it is a valuable and achievable treatment target. We discuss the definition of stability in COPD, the use of disease stability as a treatment target in clinical practice and clinical trials, and future directions for this treatment target to help improve the standard of care for patients with COPD. Some *post hoc* analyses of clinical trial data examining disease stability in COPD have been previously reported in the form of abstracts presented at American Thoracic Society 2024 (15) and European Respiratory Society (ERS) 2024 (16, 17) conferences, as well as an abstract reporting the results of a patient advocacy advisory board presented at ERS 2024 (18) and a commentary summarizing a symposium at ERS 2024 (19).

Treatment Goals for Patients with COPD

COPD is currently described by GOLD as a disease characterized by persistent respiratory symptoms and airflow limitation (1). The progressive nature of the disease is also well acknowledged. Perhaps this has contributed to a lack of discussion regarding

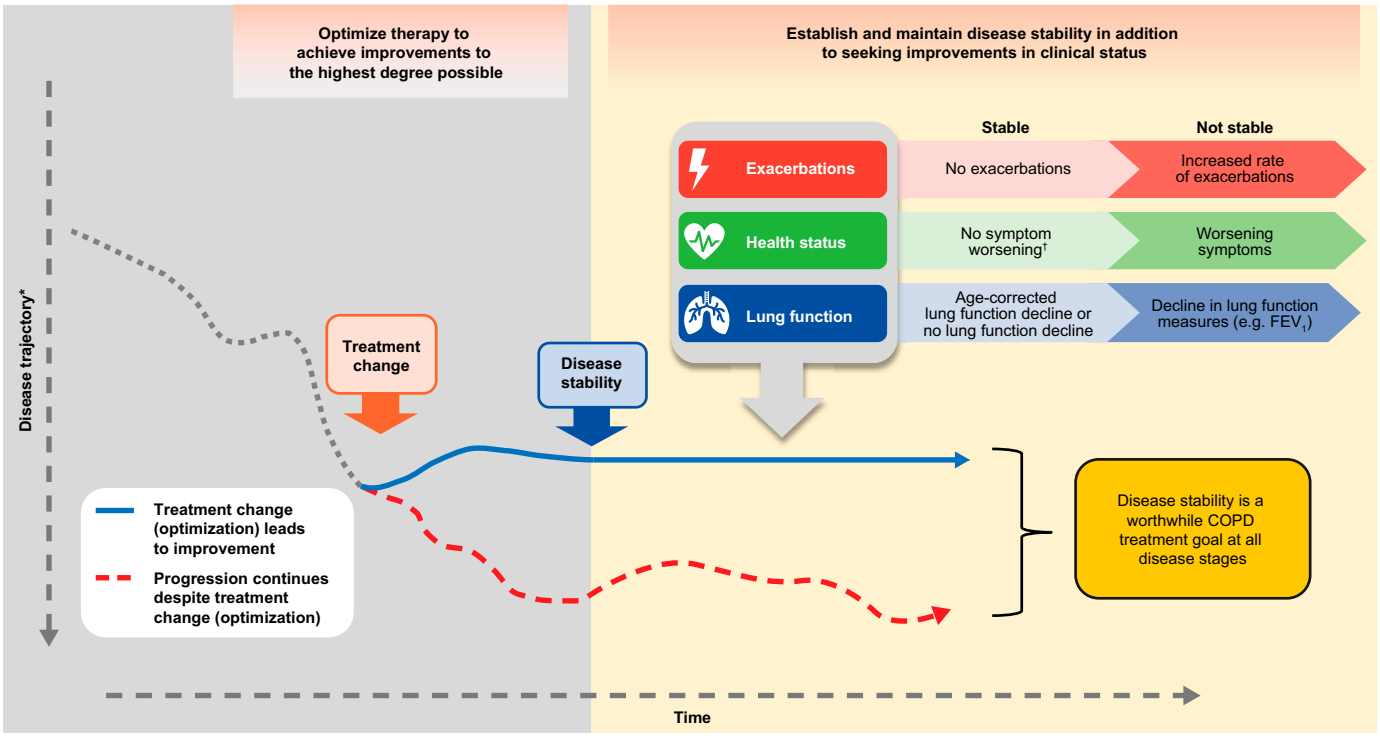

Figure 1. Disease stability across key clinical components in chronic obstructive pulmonary disease (COPD). Maintenance therapy includes inhaled mono, dual, or triple therapies, whereby escalation to dual, triple, or biologic therapy, respectively, may be considered based on symptom control and exacerbations, as well as de-escalation where appropriate (1). *Disease trajectory comprises worsening in exacerbation rate, health status, lung function, and other key components of disease activity in patients with COPD. †No symptom worsening or minimal worsening that is within day-to-day variation.

disease stability in COPD. Yet, at the same time, clinicians often describe patients as "stable." We now consider current treatment goals in COPD and in other chronic inflammatory diseases that are related to concepts of disease activity and stability.

Related Concepts in Other Chronic Inflammatory Diseases

Targeting disease activity is central to the management of rheumatoid arthritis (RA), with remission defined by the absence of disease activity plus low symptom burden (20–22). Different criteria for remission have been proposed, but all include disease activity evaluation by clinical assessment of joint tenderness and swelling plus C-reactive protein (CRP) to measure systemic inflammation. Earlier diagnosis and aggressive pharmacological treatment to target disease activity has improved clinical outcomes in RA, through the prevention or minimization of irreversible joint damage (23). Delayed or inadequate treatment may lead to permanent joint damage and disability (24), which cause chronic symptoms and hence reduce the possibility of remission. Although targeting remission in RA appears to be the ideal goal, the symptom burden may make this unachievable for some individuals (25, 26), and, consequently, aiming for low disease activity alone has also been recognized as a valuable target (22, 27).

In multiple sclerosis (MS), no evidence of disease activity (NEDA) has been developed as a goal of treatment, with NEDA-3 defined as no relapses, no disability progression, and no magnetic resonance imaging activity (i.e., no new or enlarging lesions) for 3–12 months (28, 29). The strategy focuses on preventing acute (flares) or chronic worsening, while accepting that a degree of symptoms and disability may be present but not progressing. In inflammatory bowel disease (IBD), remission is defined as a composite score comprising multiple measures of disease activity, including patient-reported outcomes and disease index scores (30), with endoscopic grading being increasingly used to assess response to therapy (30–32). These treatment goals have been shown to be achievable, with 35% of patients with MS achieving NEDA-3 (33), whereas rates of remission in IBD and RA have been reported from 18.5% to 71.0% and 21.5% to 23.5%, respectively, in patients on a variety of DMTs (34, 35).

Asthma provides an example of a respiratory disease in which treatment goals have evolved from achieving symptom control (36) toward targeting clinical remission, which is featured in the recent update of the Global Initiative for Asthma report (37). Remission in asthma has been defined as no systemic corticosteroid use, no exacerbations, symptom control, and stabilization or optimization of lung function (38–40). Spontaneous remission is well recognized in younger patients with asthma (41), whereas the use of biological treatments induces remission in severe asthma in 14.5–54.8% of patients, depending on the treatment and definition (42–45).

The definitions of low disease activity in these conditions reviewed encompass criteria including lack of flares or exacerbations (MS and asthma), a low level of inflammation (RA and IBD), and stable pathophysiology (MS and asthma). To achieve remission, it is also necessary to have a low burden of symptoms (Figure 2). For many individuals, because of irreversible pathophysiological changes, this may not be achievable; consequently, NEDA, and not remission, is the treatment target in MS, whereas there is debate concerning the clinical advantages of remission versus low disease activity in RA (25, 26, 46). For patients with COPD, targeting disease activity is also a logical treatment goal and could lead to time periods when exacerbations are absent and pathophysiology and symptoms are stabilized, similar to NEDA in MS. The definitions of disease activity and remission in other diseases have been applied to both clinical practice and research studies (20, 21, 47), and a stability definition in COPD, based on low disease activity, could have similarly wide use.

However, there are challenges to developing the concept of stability associated with low disease activity in COPD. In RA, the assessment of the joints plus a blood test (CRP) enables rapid and accessible evaluation of disease activity; equivalent clinical or biomarker tests are lacking in COPD, and, consequently, exacerbation history has been used. Furthermore, late diagnosis in COPD causing a high symptom burden due to the severity of lung pathology coupled with a lack of availability of DMTs to halt disease progression means that remission is currently an unrealistic concept. Stability over more narrow time frames, similar to the concept of NEDA in MS, may be more appropriate. Finally, lung function decline is a feature of aging, and stability in COPD must also be judged against this background.

Current Concepts in COPD

GOLD strategy report. The GOLD strategy report does not explicitly consider disease stability but does discuss some important related concepts (1). GOLD describes two key treatment goals: first, to address ongoing symptoms, improve exercise tolerance, and improve health status; second, to reduce future risk of exacerbations and disease progression. Initial evaluation includes assessing airflow obstruction, symptom severity, and exacerbation history. Follow-up involves cycles of review, assessment, and adjustment, with the dominant trait (dyspnea or exacerbations) guiding decisions on therapy escalation or de-escalation. The concept of disease stability, based on optimization and then stabilization of disease outcomes, aligns with GOLD recommendations (1).

Clinical control. Clinical control (CC) in COPD was first described in 2014 (48) and is assessed across two key domains: cross-sectional impact and longitudinal stability (49). A CC questionnaire has been developed that includes four key domains for impact (use of rescue medication, dyspnea, time spent walking per day, and sputum production) and two domains for stability (exacerbations in the last 3 months and changes in health perception since the last visit) (50). As an example, low impact for moderate COPD is defined as meeting at least three of the following: modified Medical Research Council dyspnea scale 0–2, rescue medication three or fewer times per week, $\geqslant$30 minutes time walked per day, and absent or white sputum (51). Patients fulfilling CC criteria demonstrate better quality of life (QoL) and lower risk of future exacerbations, hospitalizations, and mortality (51–54). Recently, the Spanish guidelines for the management of COPD recommended the use of CC as a treatment goal in ambulatory patients (50).

CC has been shown to be attainable in a population with mild-to-moderate disease, with 61.4% of patients having a modified Medical Research Council dyspnea score of 0–1 and approximately 60% of patients achieving CC, depending on the criteria (51). In patients with more severe disease (baseline mean post-bronchodilator FEV_1% predicted = 39%), this drops to approximately 30% (55).

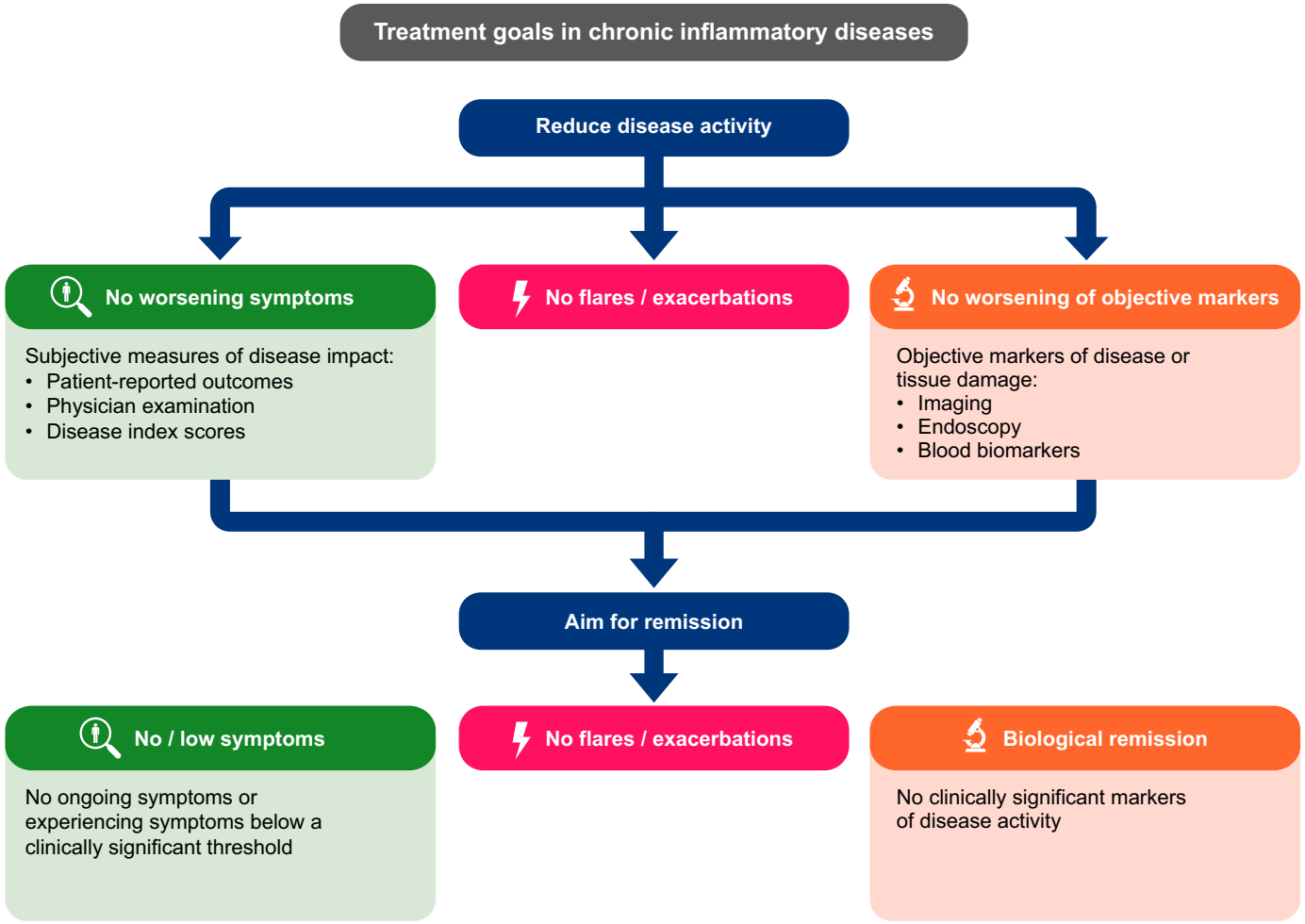

Figure 2. Development of related concepts to disease stability in other inflammatory diseases.

Treatment goals in clinical trials. Although it may not be achievable over the longer term (years), development of disease stability as a standardized outcome for clinical trials over the intermediate term (such as a 1-year time frame) could allow patients and physicians to better understand the efficacy of available and novel treatments. Endpoints in clinical trials often emphasize improvement in outcomes such as lung function and symptoms. However, the prevention of worsening is a parallel consideration that is relevant to clinical practice and could also be an endpoint of clinical trials. Time frames for clinical trials may also impact how disease stability is assessed; for example, measuring FEV_1 in clinical trials may require >3 years of follow-up to identify the average decline across the study groups (56); conversely, disease stability should be evaluated at the individual level.

The distinct, though closely related, concept of "stable COPD" defined as a lack of exacerbations (57), stable medication history (58), or stable symptoms (59), is a widely used criterion for clinical trial entry, across time periods 1–4 months (57–61). Although this concept is somewhat separate from the concept of disease stability as discussed here, it highlights the components that have been identified as important in evaluating disease status. Most large phase 3 trials analyzing the efficacy of inhaled (62–66) and biologic (NCT04133909; NCT04053634; NCT04456673) therapies in patients with COPD share key outcome measures that might be relevant to stability, including changes in exacerbation rates, lung function, symptoms, health status/QoL, and mortality; these trials have follow-up periods ranging from 1 to 5 years (63, 67, 68).

Clinically important deterioration. Clinically important deterioration (CID) is a composite endpoint developed to assess temporary or sustained disease worsening in clinical trials (69). One definition of CID is a composite of *1*) a decrease of ⩾100 ml from baseline in FEV_1 (70); *2*) any incidence of moderate or severe exacerbation; and *3*) ⩾4 units worsening in St. George's Respiratory Questionnaire (SGRQ) score (or COPD Assessment Test [CAT] score increase ⩾2) (71, 72); death has been included in other CID definitions. Patients who experience CID have poorer long-term outcomes up to between 12 and 36 months, including increased risk of exacerbation and mortality (73–75).

Disease stability as an evolution of existing treatment goals. Disease stability as a concept could further evolve the existing treatment goals as espoused by GOLD and the concepts of CC and CID. Implementation of disease stability as a treatment goal in daily clinical practice can

evolve COPD management toward a treat-to-target approach successfully implemented in other diseases (76), whereby treatment success is measured with specific and achievable goals. GOLD provides principles of management ("improvement" and "prevention") but does not specify treatment targets. The aim of achieving low disease activity, with associated stability, could be a treatment target. CC provides a definition of stability based on no exacerbations and no worsening of health status, but patients are also required to achieve a lower level of impact (symptoms), which may not be possible because of chronic, irreversible disease pathophysiology (due to previous disease activity) or comorbidities. In these individuals who cannot achieve all the criteria of CC, the concept of disease stability could still be highly relevant, allowing patients and physicians to focus on preventing further worsening. This may also help to foster a more positive outlook for patients, who often have low expectations of their disease trajectory (77) and are seeking stability and predictability of their disease (18).

CID has yet to be fully validated and has proven to be challenging to implement in clinical practice (71), particularly because of concerns about the equivalence of the components and whether the thresholds used are appropriate. Nevertheless, the documented prognostic relevance of a CID event highlights the relevance of prevention of COPD worsening.

Measuring Disease Stability in COPD

Although improvement in clinical status remains a key goal of management, disease stability is a parallel treatment goal associated with low disease activity resulting in no change or minimal worsening of key clinical components over a clinically relevant and pragmatic period (Figure 1). Achieving disease stability as a treatment goal is challenging, given the long-term disease progression in COPD. However, stability over more limited time frames compared with the natural history of the disease may be achievable; this was demonstrated in the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study, whereby a subset of patients showed either no decline or improvement in the annualized rate of change in FEV_1 over a 3-year period (78). Identifying which components to include should balance the need for a comprehensive evaluation while ensuring its practical utility in clinical settings. The most commonly used components to assess COPD outcomes that are relevant to disease activity include exacerbations, change in health status, and lung function (Table 1).

Exacerbations

COPD exacerbations are associated with worsening of symptoms, reduced exercise capacity, reduced lung function, reduced QoL, increased healthcare costs, and mortality (4). The frequency of these events can be modified by pharmacological interventions (10, 13, 63, 65), meaning that exacerbation susceptibility is a reversible component and hence related to disease activity. Exacerbations are important clinical events (79) that should be an integral component of a disease stability assessment.

Exacerbation rates in the community vary considerably, with some patients having none and others having multiple (80, 81), with mean annual rates around 0.4 (82). Rates vary from year to year even within individual patients (80, 82). There is evidence in frequent exacerbators, defined as two or more exacerbations per year, that this classification occurs approximately 30–45% of the time because of random occurrence of events within a given time frame (83) and thus may not always indicate a change in disease activity. In addition, reporting of exacerbations is often subjective, and patients often may not recognize an exacerbation, particularly mild ones, instead describing "good" and "bad" days (84). Therefore, a significant proportion of exacerbations are unreported (85).

Disease stability might aim for patients to experience no exacerbations in a year, given the prognostic significance of having even one exacerbation (86). For some frequent exacerbators, having no exacerbations may be unachievable with current therapies. However, large clinical studies in high-risk frequent exacerbators showed that, with treatment optimization, >50% of patients had no exacerbations during the 1-year study period (10, 63, 87). Therefore, stability of exacerbations may be possible when treatment is optimized, even in those with more high-risk disease.

Health Status

Measures of health status usually include items related to specific symptoms, such as cough and dyspnea, as well as physical activity and overall QoL. These can be affected by the variability of day-to-day symptoms and thus are influenced by the time considered by the measure; they can also be influenced by comorbidities and patient perception (88–91). Health status varies over time (92), and, in those who deteriorate, slowing the decline of health status is an important management goal.

Health status is most often measured using questionnaires, some of which have been designed for use in clinical settings and others for research studies. Both disease-specific (SGRQ, CAT, Clinical COPD Questionnaire [CCQ]) and generic measures (EuroQoL, Short-Form Health Survey) are available; however, disease-specific measures may be more sensitive to changes in clinical status after treatment and thus more appropriate (93, 94). The limited time clinicians have with patients, as well as the need to process the results, makes the use of tools such as the SGRQ impractical in clinical settings, but they remain valuable in research settings (95–97). In clinical practice, measures that are valid and reliable, responsive to changes in clinical status, applicable to a primary care population, practical and easy to administer, tested in practice, and available in multiple languages, include the CAT and CCQ (96).

Stability of health status in COPD in a clinical trial or in clinical practice could be defined as no clinically meaningful symptom worsening, or minimal worsening that is within day-to-day variation.

Lung Function

Lung function can vary widely day to day as well as on repeated measurements (88, 98), which complicates interpretation of spirometry over time (99). In addition, it may be complex to establish a clinically relevant threshold for change according to disease severity, and spirometry may be more readily available in clinical trial settings than in primary care. Monitoring of both the current level of lung function and the trend over time is crucial to assessing future risk, as evidence suggests that any decrease in lung function is associated with poorer clinical outcomes (Figure 3) (100). Establishing the rate of lung function decline through regular spirometry can identify patients with rapid lung function decline and increased risk of

Table 1. Considerations for Potential Components of Disease Stability

Component	Attributes	Considerations
Exacerbations	• Lead to worse outcomes in the short and long term • Rates vary widely between patients • Yearly variation may not always reflect disease worsening • Subjective and often goes unreported	• Elimination of exacerbations? OR • Reducing current exacerbation rate or severity?
Health status	• Symptoms, physical activity, and quality of life • Impacted by daily symptom variability, comorbidities, and patient perception • Disease-specific measures may detect clinically meaningful changes	• Most relevant measures (i.e., research vs. in the clinic)? • Frequency/number of measurements needed to identify decline?
Lung function	• COPD involves persistent loss of lung function • Used to diagnose COPD • Spirometry is objective and inexpensive • Any decrease in lung function leads to poorer outcomes • High day-to-day and between-measurement variability	• Differing thresholds of decline based on severity (airflow limitation) • Accounting for age-related decline • Frequency/number of measurements needed to identify decline? • Most relevant spirometric measurements

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

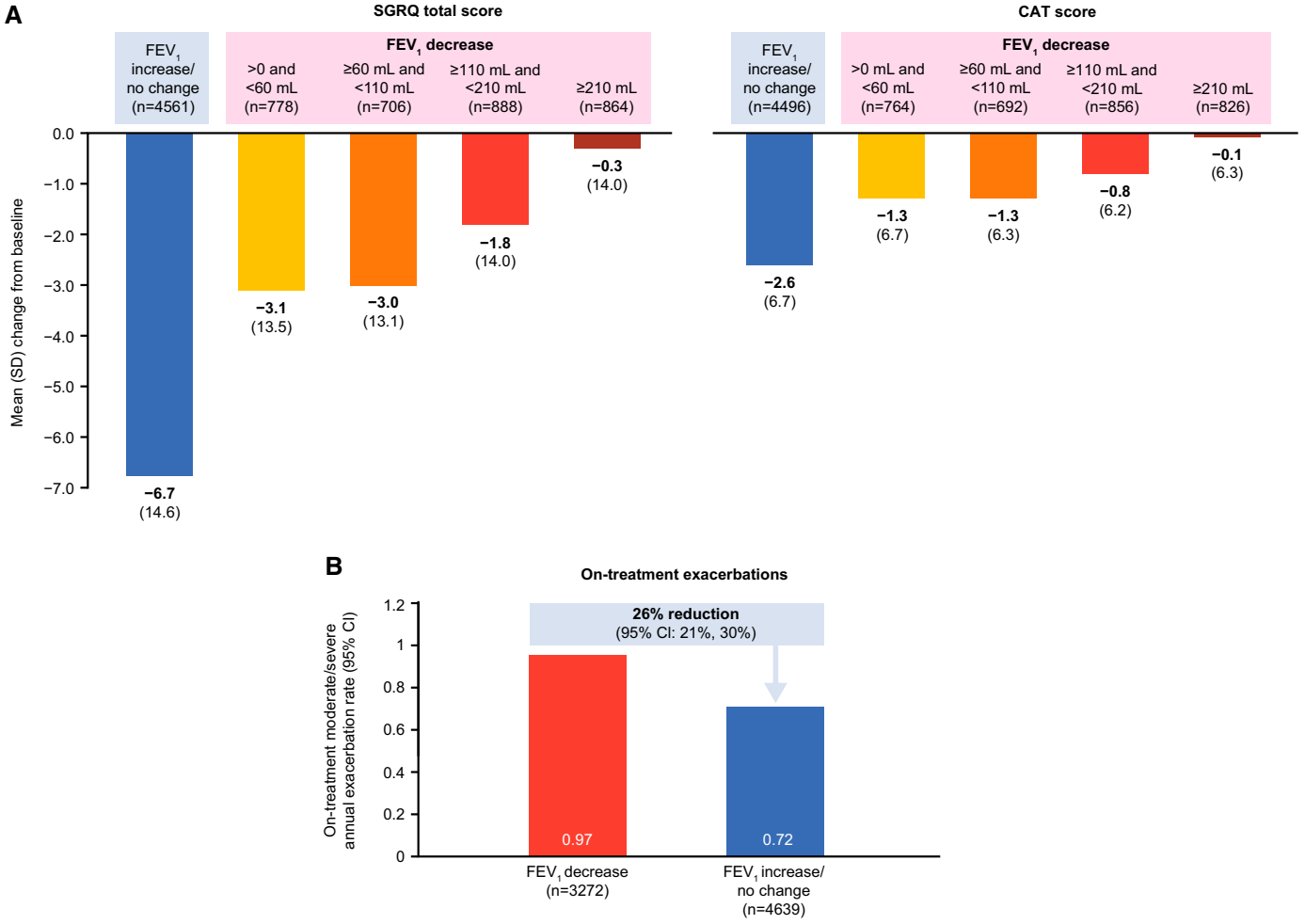

Figure 3. Effect of decline in FEV_1 versus no change/improvement on (*A*) heath status scores (SQRG and CAT) and (*B*) annual rate of moderate/severe exacerbations, at Week 52 (100). CAT = COPD Assessment Test; CI = confidence interval; COPD = chronic obstructive pulmonary disease; SGRQ = St. George's Respiratory Questionnaire. Recreated by permission from Reference 100.

mortality (101). Excessive loss of lung function over time is a general characteristic of COPD; however, although GOLD uses spirometry to diagnose COPD and guide treatment initiation, lung function is not featured as a treatment goal in follow-up algorithms (1). Nonetheless, spirometry offers an inexpensive and objective method to monitor disease status and response to treatment (1).

When considering "stability" of lung function, there are several questions to be answered. First, given that absolute measures of lung function decline slow with disease severity (2), are different thresholds required at different disease severities? Second, can a decline in lung function within the range of normal, age-related decline be considered "stable"? Third, how frequently should lung function be measured? Several years of follow-up are needed to reliably identify persistent decline (102). However, follow-up time frames must consider the constraints of both everyday practice and clinical trials.

Individual versus Composite Assessments

As already discussed, composite measures of disease activity and remission are commonly used in other diseases and can capture different and relevant components within complex diseases (30, 38, 39). Ideally, patients should achieve stability across all components proposed here (i.e., exacerbations, health status, and lung function). However, the heterogeneous reality of COPD is that some patients may achieve stability for some components but not others; for example, a patient may have a decrease in lung function but no worsening of symptoms and no exacerbations. As lung function decline is often gradual and continuous with both age and disease progression, this is likely to be the case for some patients (2). Changes in lung function may not always be reflected in the severity of symptoms (103). Similarly, although there is an association between FEV_1 and exacerbation risk on a population level, there is often a dissociation on an individual level (104). We propose that disease stability should be considered for each component individually and that combining these into a composite offers additional information that the individual has reached overall stability. In addition, some components used in clinical trials may not be feasible in the clinic because of availability of equipment or complexity of testing (96, 97, 105), and so a pragmatic approach with fewer components (e.g., health status and exacerbations) may be more practical in the clinic (47).

Minimal Clinically Important Differences

What are the most clinically meaningful thresholds for assessing disease stability? The minimal clinically important difference (MCID) for improvement in COPD has been defined for lung function and health status (106); for exacerbations, although there is no established MCID, prevention of future exacerbations is the ultimate goal (1). The MCID for FEV_1 has been defined as absolute changes from 100 to 140 ml or a 15% change from baseline (70, 98, 106). However, variability in lung function measurements may reach 150 ml, and the impact of any absolute change in FEV_1 may differ depending on baseline lung function (70, 98). For patient-reported outcomes, the MCID for CAT is $\geqslant$2 units in the total score (107) and $\geqslant$0.4 units for the CCQ (108). However, the usefulness of these thresholds may be limited at the extremes of scores; the maximum benefit achieved by responders may be limited by "ceiling effects," and, conversely, worsening in nonresponders may be limited by "floor effects" (107).

Whether a degree of improvement is equivalent to the same degree of worsening is not clear. Although small improvements may not translate to clinically relevant changes, the same cannot always be said for decline, as shown with lung function and exacerbations (86, 100). As MCIDs are population-based estimates, they should be used as a guide rather than a binary cutoff (106), because individual patient benefits may occur below the estimated MCID. In addition, certain thresholds may not be achievable in more severe disease, and thus a threshold that can apply across all severities should be considered. In addition, stricter thresholds may be used in clinical trials, whereas everyday clinical treatment goals may need to be more pragmatic.

Intervals

What is the ideal assessment interval for disease stability? Sufficiently frequent follow-up is needed to assess the true trend for stability or decline. Patients often do not recognize their disease has worsened until their symptoms have become severe or reached a "crisis point" (85, 109). More frequent outpatient visits may provide an earlier and objective assessment, improve outcomes (110), and align with patient preference for more regular visits with their doctor (111). Frequency of testing should be considered within the limits of healthcare resources, and telemedicine may play a role in meeting this demand (112).

For defining intervals, a similar approach to "tight control" in IBD may be implemented, whereby patients are evaluated across multiple criteria at specific intervals depending on whether their disease is active ($\sim$3–9 months) or in remission ($\sim$6–12 months) (113). For patients with COPD, a pragmatic interval may be every 6–12 months; however, as in IBD, this may vary based on whether a patient is currently stable or actively experiencing disease worsening. This approach may also require accounting for exacerbation frequency and severity, as recovery time may be prolonged in those with frequent exacerbations and after severe exacerbations.

Definition of Disease Stability

We propose a preliminary definition of disease stability, illustrated in Table 2, that should apply to all phenotypes, disease severities, and regardless of what intervention a patient is receiving; however, the extent to which all or some of the components of disease stability can be achieved will differ among individuals. Although the goal is for each individual patient to achieve and maintain their "personal best", disease stability offers an opportunity to evaluate this longitudinally. We propose the inclusion of exacerbations, health status, and lung function as key components of disease stability. Disease stability can be achieved in one, two, or all the key components proposed and may depend on the availability of spirometry or whether patients are being evaluated in the clinic or a research trial. In clinical practice, understanding which components are stable and which are unstable can direct personalized management plans. The timeline over which exacerbations are reported is crucial to prevent the false impression of stability because of short time frames. Therefore, we suggest a timeline of 6–12 months to evaluate stability, with each visit benchmarked against the previous 6–12 months. For health status, two measures have been suggested: the SGRQ is a complex instrument widely used in clinical trials, whereas the CAT is less complex and

Table 2. Preliminary Definition for Disease Stability

Components	Exacerbations: Frequency	Health Status: SGRQ or CAT	Lung Function: FEV_1
Thresholds*	No exacerbations	No worsening in SGRQ or CAT score; alternatively, no clinically significant worsening	No decrease; consideration of correction for age-related decline
Timeline	• 6–12 months, comprising one or multiple visits in that time • Benchmark current measurements against previous 6–12 months at each visit		
Individual vs. composite assessments	• Stability can be achieved in one or multiple components • Dependent on patient factors, availability of spirometry, and setting		
Context and setting	• Primary care or in-clinic and research settings • All disease severities, phenotypes/etiotypes, and interventions		
Other considerations	• "Clinically significant" worsening will require definition • Biomarkers may be implemented in future components once validated • An expert consensus on the definition of disease stability should be reached among key experts		

Definition of abbreviations: CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; SGRQ = St. George's Respiratory Questionnaire.
*Some patients may experience improvements with treatment optimization and other holistic interventions (e.g., smoking cessation, vaccination); this is also considered to be achieving disease stability.

commonly used in clinical practice. Although FEV_1 can be an important component of disease stability, spirometry may not always be available. In this case, symptom measures may provide indirect evidence of worsening lung function.

Regarding thresholds, the ideal scenario for a patient is that there is no worsening, or there is even improvement, in FEV_1 and health status. A practical consideration is how to evaluate small changes (worsenings) that may be within day-to-day variance and of no clinical significance. CID set strict thresholds to define this, but the validity of these thresholds was unclear (71). For FEV_1, the age-related decline in lung function should be considered (2), but this is more relevant over long-term compared with short-term assessments, for example, over 6 months. Minor worsenings of unclear significance could trigger a reassessment at a shorter interval (e.g., at 3 months), whereas the interpretation of such changes in clinical practice may be influenced by how many components are stable or unstable; for example, a small decrease in lung function is of less concern when exacerbations and health status have met the stability definition. This area requires further work to define the optimum approach in clinical practice and research studies.

The proposed definition has been informed by previous research in COPD and other chronic inflammatory diseases and is a conceptual approach that should be validated by high-quality evidence. Observational studies and *post hoc* analyses of large COPD trials may help to further refine disease stability and support an expert consensus.

Future Directions

Biomarkers and Future Therapies

Disease stability as a treatment goal and clinical trial endpoint should consider potential future developments, including better disease understanding, biomarker development, and effective DMTs.

In the future, the use of biomarkers may increase the probability of achieving disease stability through identifying patients who are more likely to respond to targeted pharmacological interventions. Assessing inflammatory biomarkers may be useful over the course of the disease to identify patients with high levels of inflammation. Inflammatory biomarkers may also have application according to clinical phenotype or molecular endotype. For example, up to 40% of patients with COPD exhibit type 2 inflammation, as evidenced by increased eosinophils (114). Blood eosinophil counts are associated with increased exacerbation risk (although this is confounded by inhaled corticosteroid use) and accelerated lung function decline (59, 115–117). Biological treatments, including anti–IL-5 and anti-alarmin treatments, reduce blood eosinophil counts (118, 119), and, consequently, this may be a suitable biomarker to measure in selected patients being considered for biological treatment. Similarly, higher levels of fractional exhaled nitric oxide are associated with increased exacerbation risk (120), and this might be a useful risk biomarker, particularly in ex-smokers (121). Such biomarkers may help to differentiate clinical stability, which has been the focus of our discussion so far, versus immunological stability.

Neutrophil–lymphocyte ratio is another candidate biomarker, as it has been associated with poorer outcomes, including exacerbations and mortality (59). Other mediators, such as IL-6 and CRP, have also been identified as potential biomarkers (115, 122–125). Cardiovascular biomarkers also hold promise for assessing disease stability, given COPD is often comorbid with cardiovascular disease (126), and cardiovascular markers such as troponins and fibrinogen have been associated with poorer prognosis (127, 128).

As understanding of the pathophysiology of COPD advances and more novel treatments, such as biologic therapies, are developed, there is the opportunity to incorporate biomarkers that evaluate disease activity into a stability assessment (10, 129). To validate biomarkers as a component of disease stability, future research should define robust thresholds and how they relate to disease worsening

measured by other clinical components of stability.

Imaging

Because computed tomography (CT) allows us to assess lung tissue and structure, it seems logical that it could be used to monitor disease stability in the future. Although CT is not required for a diagnosis of COPD, it is increasingly being used to help rule out other diagnoses, diagnose concomitant conditions such as bronchiectasis, aid with lung cancer screening, or support lung volume reduction procedures (1). Evidence suggests that the rate of lung function decline differs according to structural abnormalities, such as emphysema, bronchiectasis, and tuberculosis-destroyed lung, as shown using CT (130). Therefore, quantitative CT metrics could be considered to assess stability in COPD. The most widely available metric is lung density (percentage low attenuation area or "Percent emphysema") (131). As emphysema tends to progress slowly, it may be more useful to monitor with CT over the course of years versus over months (132). This metric is associated with less variability than spirometry but is dependent on the acquisition and may not be available or necessary in every patient with COPD (1, 131). Airway wall thickness and mucus plugging are additional measures that could also aid with disease stability monitoring (1). The focus of CT monitoring with regard to stability monitoring may therefore vary with the phenotypic characteristics determined by imaging studies, for example, emphysema or airway wall thickness or mucus plugging.

Conclusions

Given the continued burden of COPD worldwide, more attainable treatment goals should be sought to encourage better management and provide better outcomes for patients living with COPD. These goals should also be future-ready to adapt to the ever-evolving landscape of available therapies. This review has summarized some of the key considerations for development of a preliminary definition of disease stability as an achievable treatment goal for all patients with COPD, regardless of severity, phenotypes/etiotypes, and treatments. A holistic approach to COPD management can further support disease stability, including smoking cessation, reduction of exposure to risk factors, vaccination, pulmonary rehabilitation, and improved adherence (1, 133–136). In addition, harmonious goals and clear communication between patients and physicians are crucial in ensuring good clinical outcomes, good adherence, and improved overall well-being (137–139). Once empirically validated, these disease stability criteria may provide a clinical treatment goal and function as clinical trial endpoints. Future clinical trials and real-world studies should seek to validate and use disease stability as a treatment target to advance the standard of care for patients with COPD. ■

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