Original Research Article

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An Italian Delphi Consensus on the Triple inhalation Therapy in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: The management of chronic obstructive pulmonary disease (COPD) lacks standardization due to the diverse clinical presentation, comorbidities, and limited acceptance of recommended approaches by physicians. To address this, a multicenter study was conducted among Italian respiratory physicians to assess consensus on COPD management and pharmacological treatment.

Methods: The study employed the Delphi process using the Estimate-Talk-Estimate method, involving a scientific board and expert panel. During a 6-month period, the scientific board conducted the first Delphi round and identified 11 broad areas of COPD management to be evaluated while the second Delphi round translated all 11 items into statements. The statements were subsequently presented to the expert panel for independent rating on a nine-point scale. Consensus was considered achieved if the median score was 7 or higher. Consistently high levels of consensus were observed in the first rating, allowing the scientific board to finalize the statements without requiring further rounds.

Results: Topics generating substantial discussion included the pre-COPD phase, patient-reported outcomes, direct escalation from a single bronchodilator to triple therapy, and the role of adverse events, particularly pneumonia, in guiding triple therapy prescriptions. Notably, these topics exhibited higher standard deviations, indicating greater variation in expert opinions.

Conclusions: The study emphasized the significance that Italian pulmonologists attribute to managing mortality, tailoring treatments, and addressing cardiovascular comorbidities in COPD patients. While unanimous consensus was not achieved for all statements, the results provide valuable insights to inform clinical decision-making among physicians and contribute to a better understanding of COPD management practices in Italy.

Key words: Chronic Obstructive Pulmonary Disease (COPD); Delphi process; triple combination therapy; long-acting beta2-agonist; long-acting muscarinic receptor antagonist, and inhaled corticosteroid

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Authors' contributions: All authors contributed equally to this manuscript. It was revised and edited by all authors, who also approved the final version.

Ethics approval and consent to participate: Ethical approval of his work was not required as no human or animal subjects were involved.

Availability of data and material: The data underlying this article are available in this article.

Conflict of interest: PS received personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Chiesi Farmaceutici Spa, Laboratori Guidotti Spa, Neopharmed Gentili spa, Novartis, Menarini Industrie Farmaceutiche Riunite Srl, ABC farmaceutici and Biotest Italia srl, outside the submitted work. CM received fees as a speaker in national and international congress from GSK, Novartis, Sanofi, AstraZeneca, Chiesi, Menarini, Boehringher, Berlin Chemie, Guidotti, Chesi, Zambon. AP reports grants from

Chiesi, AstraZeneca, GSK, BI, TEVA, Sanofi, and consulting fees, honoraria for lectures or advisory boards from Chiesi, AstraZeneca, GSK, Novartis, Sanofi, IQVIA, Avillon, Elpen Pharmaceuticals, Zambon, and Mundipharma. The other authors have no conflicts of interest to declare.

Funding: Writing and editorial assistance was provided by EDRA SpA (Milan, Italy) and supported by unconditioned grant from AstraZeneca.

Acknowledgement: The authors would like to thank all the participants in the panel of experts who provided a rating for each of the 11 statements.

Introduction

Chronic obstructive pulmonary disease (COPD) is a condition characterized by persistent and progressive airflow limitations along with respiratory symptoms, such as dyspnea, sputum production and cough [1]. It is associated with an abnormal inflammatory response of the lungs to harmful particles or gases [1] and with various risk factors, including cigarette smoking, respiratory infections, occupational exposures, air pollution, passive smoke and diet [1]. Globally, COPD is a significant cause of morbidity and mortality, resulting in a growing economic and social burden. According to the World Health Organization (WHO) report in 2021, COPD was responsible for 3.23 million deaths in 2019, making it the third leading cause of death globally [2].

The prevalence of COPD is projected to rise due to environmental factors and an aging population [3]. In Italy, COPD is responsible for a high proportion of respiratory disease-related deaths, accounting for 55% of such mortality [4-7].

Exacerbations are critical events in the course of COPD, having substantial short- and long-term impacts on patients and health care systems [1,8]. Frequent exacerbations are linked to reduced physical activity [9], poorer quality of life, increased mortality risk [10], and cardiovascular events [11,12]. Preventing exacerbations is a key objective in COPD management [13-15].

Early identification of the disease is a topic of discussion within the respiratory scientific community. As outlined in the current GOLD document, individuals of any age who exhibit respiratory symptoms and/or structural and/or functional abnormalities, but do not yet have airflow limitation (forced expiratory volume in the 1st second ([FEV_1]/ forced vital capacity [FVC] ≥ 0.7 post-bronchodilation) and have normal spirometry, are classified as pre-COPD patients [1]. These individuals are at an increased risk of developing airflow limitation in the future [1]. Currently, there is no established correlation between the timing of disease onset, the manifestation of symptoms, and the diagnosis of COPD. This is due to the fact that symptoms can indicate significant functional damage without providing a clear indication of when the disease initially started.

Triple therapy with inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β2-agonist (ICS/LAMA/LABA) is recommended for patients with significant symptoms and frequent exacerbations [1]. Based on the available evidence, triple therapy shows potential for offering clinical benefits and reducing mortality in patients with symptomatic COPD who are at risk of exacerbations even when they are already receiving LAMA/LABA therapy [1,16-23]. Recognizing the unanswered issues and lack of conclusive evidence in COPD management, an Italian expert panel conducted a consensus process, using a modified Delphi method. Their aim was to assess agreement among Italian pulmonologists regarding crucial steps in COPD management and decision-making process to guide clinical decisions in real-life conditions. The process involved a scientific board of six experts in the field and aimed to expand global discussions on early inhaled therapy approaches for eligible COPD patients.

This consensus document presents the procedures and results of the structured approach, providing insights from Italian respiratory physicians to increase

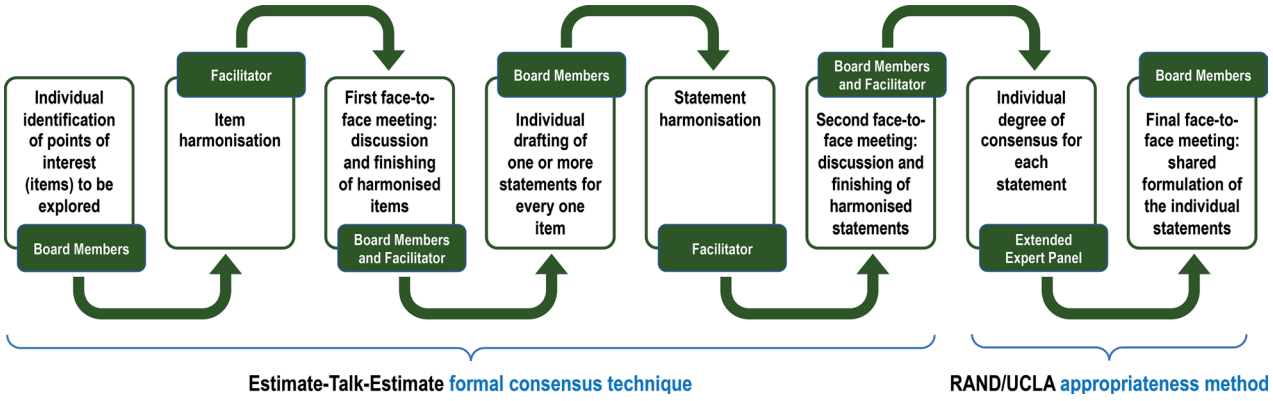

Figure 1. Workflow of the consensus process.

awareness and aid clinicians in making informed decisions, even in the early stages of the disease.

Methods

Figure 1 shows the workflow of the consensus process, which started using the Estimate-Talk-Estimate (ETE) method [24,25]. ETE (a formal means of reaching consensus that was developed to overcome some of the negative aspects of group dynamics) facilitates group decision making [26,27] by combining assembling of expert opinions on an anonymous basis during surveys with open exchange during workshops by a facilitator.

Identification of the statements

Firstly, five Italian experts in COPD management (SP, DF, MC, PG, PA, referred to as scientific board) were invited to individually identify points of interest (referred to as items) requiring further clarification or review. These were then harmonised and grouped by a senior clinical epidemiologist (GP) trained in developing group consensus (the facilitator) into 11 items that were proposed to the board members at a face-to-face meeting. The harmonised items were discussed to reach agreement between the facilitator's work and board members' opinions, after which the board members were invited to individually drew up one or more statements concerning each of agreed items. This led to the proposal of 11 statements, which were again subsequently harmonised by the facilitator. At a second face-to-face meeting, the board members and the facilitator reviewed and further discussed the harmonised statements until agreement was reached on their formulation.

Agreement rating of statements by the expert panel

The statements generated in this way were then presented via an on-line scoring platform to 104 experts chosen from specialized COPD management centers to represent the clinical practice in Italy for this field. The survey was conducted online through a secure survey website using a dedicated online platform (www.consensusdelphi-bpco.it). Experts expressed their degree of consensus by means of a RAND 9-point numerical rating scale ranging from 1 = totally disagree to 9 = totally agree, and consensus was reached that a statement had to be considered appropriate if the median score was ≥ 7 without disagreement, according to the RAND/UCLA Appropriateness Method User's Manual [28].

Collection and analysis of the results

After the completion of the individual and anonymous online survey, the scientific board thoroughly analyzed and discussed the gathered results and formulated comprehensive comments and indications regarding the optimal management of COPD patients in real-world clinical practice.

Results

Following the completion of the first Delphi round, the scientific board identified the following

broad areas of COPD management (referred to as items) that were deemed necessary to undergo evaluation within the context of Italian clinical practice (Table 1):

1. Identification and definition of the pre-COPD phase
2. Importance of patient-reported outcomes (PROs) in the management of COPD
3. Prevention of moderate to severe exacerbations
4. Reduction in the mortality rate as an efficacy outcome
5. Role of phenotypes and biomarkers in the definition of a therapeutic strategy
6. Role of the assessment of respiratory function in the management of COPD
7. Impact of comorbidities in the definition of the therapeutic strategy in COPD
8. Direct escalation from a single bronchodilator to triple therapy
9. Clinical and functional indices as drivers for first-line triple therapy
10. Possible occurrence of adverse events and their role as drivers in the prescription of triple therapy
11. Selection criteria for candidates for triple therapy

During the second Delphi round, the 11 items identified by the scientific board were translated into statements that were approved and then submitted to the experts for independent rating (Table 1).

A total of 73 out of 104 independent experts (70.2%) provided their rating on these statements expressing their agreement or disagreement. The names of the 73 experts who participated in the rating process can be found in the Appendix, listed alphabetically. The ratings provided by the experts were analyzed to determine the median rating and the percentages of experts who consented, were uncertain, or dissented for each statement, as presented in Table 1.

Consistently, the level of agreement among the experts was high, with median ratings ranging from 7 to 9 on the RAND nine-point scale. In the first round of voting, a median score of ≥ 7 was reached for all statements, indicating a consensus among the experts. As a result, no further rounds of rating were deemed necessary, and the scientific board proceeded to discuss and finalize the statements based on the obtained ratings.

Among the statements, numbers 1, 2, 8 and 10 were found to be the most controversial, as indicated by higher standards deviations ranging from 1.8 to 2.4. These statements generated more diverse opinions among the experts, reflecting greater variation in their individual ratings.

Discussion

The Italian experts involved in the field of COPD management reached a consensus on 11 statements, demonstrating their agreement as follows:

1. Identification and definition of the pre-COPD phase

Statement: All those situations characterized by the absence of $FEV_1/FVC < 0.7$ and highlighting a risk of developing COPD, such as cough and sputum persistence, increased residual volume, FEV_1 near to lowest normal limit, altered DL_{CO}, airways radiologic abnormalities, and emphysema in subjects exposed to cigarette smoke and/or other noxious inhaled agents, must be defined as pre-COPD.

The early identification of individuals who may eventually develop airflow obstruction consistent with a diagnosis of COPD can potentially allow for therapeutic interventions that can modify the course of the disease. In 2001, the GOLD (Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease) report introduced the concept of an "at risk" stage (GOLD stage 0) [29]. This stage was based on the presence of risk factors such as smoking and symptoms like chronic cough and sputum production, in the absence of spirometry abnormalities [29]. The pre-COPD population, defined by symptomatic individuals with structural or functional lung changes but without spirometric evidence of COPD, represents an at-risk group that shares many symptomatic and structural features with the established COPD population. However, they are distinct in terms of being predominantly female, older, having

Table 1. Statements approved by the scientific board and rated by the expert panel.

Item	Statement	Expert panel ranking
1. Identification and definition of the pre-COPD phase	All those situations characterized by the absence of $FEV_1/FVC < 0.7$ and highlighting a risk of developing COPD, such as cough and sputum persistence, increased residual volume, FEV_1 near to lowest normal limit, altered DLco, airways radiologic abnormalities, and emphysema; in subjects exposed to cigarette smoke and/or other noxious inhaled agents, have to be defined as pre-COPD	Median: 7 Consent: 68% Uncertain: 18% Dissent: 14%
2. Importance of patient-reported outcomes (PROs) in the management of COPD	Patient-reported outcomes (PROs) should be considered in the therapeutic management as well as the risk of exacerbation. The most commonly used questionnaires and scales are mMRC, CAT, TDI, and SGRQ	Median: 7 Consent: 70% Uncertain: 23% Dissent: 7%
3. Prevention of moderate to severe exacerbations	Available treatments (single or double bronchodilation, ICS/LABA, triple therapy and rehabilitation) are all able to reduce exacerbation risk after diagnosis	Median: 8 Consent: 87% Uncertain: 12% Dissent: 1%
4. Mortality rate reduction as efficacy outcome	Mortality is a mandatory outcome of therapy efficacy; as in other chronic diseases. Clinical trials and therapies should consider the reduction of mortality rate as a study endpoint	Median: 8 Consent: 83% Uncertain: 14% Dissent: 2%
5. Role of phenotypes and biomarkers in the definition of the therapeutical strategy	The presence of eosinophilia, identification of the emphysema as prevalent phenotype concomitant with the presence of bronchiectasis may or may not direct to the use of ICS as an add on to bronchodilator therapy	Median: 8 Consent: 86% Uncertain: 11% Dissent: 3%
6. Role of respiratory function in the management of COPD	Spirometry is required to make the diagnosis of COPD and it has also to be considered as a useful tool for disease management. Residual volume and DLco assessment can complement information provided by spirometry, and they are recommended after first COPD diagnosis. These second level respiratory functional assessments become mandatory when therapeutic goals are not reached	Median: 9 Consent: 93% Uncertain: 6% Dissent: 1%
7. Impact of comorbidities in the definition of the therapeutic strategy in COPD	The identification of comorbidities, due to their impact on symptoms, exacerbations, PROs, and mortality (particularly cardiovascular ones), is mandatory for a correct therapeutic management of COPD	Median: 8 Consent: 89% Uncertain: 10% Dissent: 1%
8. Direct escalation from single bronchodilator to triple therapy	In COPD management, direct escalation from single bronchodilator to triple therapy can be considered when therapeutic goals (exacerbations, PROs) are not reached	Median: 8 Consent: 74% Uncertain: 22% Dissent: 4%
9. Clinical and functional indices as drivers for a first-intention triple therapy	*Ab initio* triple therapy could be an option for patients recently discharged from hospital, or when dyspnea and exacerbations are both present in patients with reduced respiratory function	Median: 7 Consent: 69% Uncertain: 28% Dissent: 3%
10. Possible occurrence of adverse events and their role as drivers in the prescription of triple therapy	Controlled trials were not able to identify an increase of adverse events in patients on triple therapy compared with those on double therapy. Nevertheless, pneumonia risk and the type of therapy need to be evaluated before starting ICS therapy	Median: 7 Consent:68% Uncertain: 22% Dissent: 10%
11. Selection criteria for patients who are candidates for triple therapy	Failure to achieve therapeutic goals (presence of exacerbations in patients treated with double bronchodilators, persistence of respiratory symptoms after ICS/LABA) in patients adherent to therapy is an eligibility criterion for triple therapy	Median: 9 Consent:93% Uncertain: 6% Dissent: 11%

less smoking exposure, and fewer comorbidities. This highlights the importance of early identification and potential intervention in the pre-COPD stage to prevent progression to full-blown COPD [30].

Symptomatic individuals with "normal" spirometry results represent a heterogeneous group with various abnormalities, including cough, sputum production, dyspnea, exacerbation-like events, and radiographic features that may resemble the clinical and radiographic presentation of patients with spirometry-confirmed COPD. These individuals also experience a decreased health-related quality of life and are more likely to miss social and work activities.

The SPIROMICS study (Subpopulations and Intermediate Outcomes in COPD Study), a multicenter observational study of COPD aimed at guiding the development of future therapies for the disease [31], revealed that 42% of symptomatic smokers without spirometry-defined obstruction were prescribed bronchodilators, and 23% were prescribed inhaled corticosteroids, indicating that physicians recognized the need for treatment in these cases.

The category of GOLD stage 0 was eventually abandoned because not all individuals in this stage progressed to COPD [32]. However, reconsidering this decision, it may have been a missed opportunity. Many other therapeutic areas have embraced the concept of "predisease" (e.g., prediabetes, prehypertension, precancer, or preeclampsia) where not all patients will necessarily develop the disease, but identifying an at-risk population allows for stricter follow up and risk management.

A recent perspective by Martinez and colleagues [33] emphasized the urgency of identifying such individuals, particularly in the context of developing disease-modifying therapies. The COPD-Gene research group, in a recent publication, proposed combining symptoms, lung function, and computed tomography assessments to stage individuals with respect to their risk for developing COPD, suggesting a new disease classification scheme [34].

By going beyond the concept of GOLD stage 0, which solely identified at-risk individuals based on symptoms, we can identify a larger proportion of individuals who are likely to develop COPD. However, this statement sparked significant debate in our survey, with 68% of the panelists in agreement with it and 14% of the panelists who rated this statement with a score lower than 4, indicating their disagreement. They argued that the conditions proposed in the statement possibly qualify as overt COPD. These comments highlight the existence of a substantial grey area in the early identification of individuals who require close monitoring to initiate appropriate treatment promptly when their health condition worsens.

Slow Vital Capacity (SVC) can be different from FVC, and if FEV_1 is measured against FVC only, airway flow-limitation can be underestimated or missed. Brusasco et al. and Berton and Neder highlighted that SVC, which represents the total volume of air exhaled slowly, can often be greater than the FVC measured during a forced exhalation. This discrepancy can lead to an underestimation of airflow limitation if only the FEV_1/FVC ratio is used, thereby missing cases of mild to moderate obstruction [35,36].

Additionally, a thorough analysis of the flow-volume loop and assessment of flow limitation at lower pulmonary volumes is crucial. Pedersen and Butler emphasized that the shape and contour of the flow-volume loop can provide valuable insights into airway dynamics. Flow limitation at lower lung volumes can indicate small airway dysfunction, which may not be apparent in standard spirometric measurements. Recognizing these subtle abnormalities is essential for identifying individuals at risk for COPD who might benefit from early intervention. Integrating these comprehensive diagnostic approaches can significantly enhance the accuracy of COPD risk assessment and ensure timely and appropriate management [37].

2. *Importance of patient-reported outcomes in the management of COPD*

Statement: Patient-reported outcomes (PROs) should be considered in the therapeutic management as well as the risk of exacerbation. The most commonly used questionnaires and scales are modified Medical Research Council dyspnea scale (mMRC), COPD Assessment Test (CAT), Transition Dyspnea Index (TDI), and St George's Respiratory Questionnaire (SGRQ).

Patients with COPD experience impaired health-related quality of life (HRQoL) regardless of

disease severity [38,39]. Various key characteristics of COPD, such as chest symptoms, dyspnea, cough, sputum production, and exacerbations contribute to the negative impact on HRQoL. Other aspects like sleep disturbances, fatigue, emotional well-being, social functioning, and coping abilities can also be affected. PROs play a crucial role in assessing symptoms, their impact on daily activities, and treatment response [40,41]. In clinical trials, it is essential to incorporate PROs alongside clinical endpoints, to ensure a patient-centered approach in drug development.

In routine clinical practice, there is growing interest in this area, as evidenced by the 70% agreement with the formulation of this statement (7% disagreement). The presence of comorbidities (such as cardiovascular diseases, obesity, dumping syndrome, and obstructive sleep apnea syndrome) commonly observed in elderly patients with COPD can contribute to the subjective perception of HRQoL [42].

Some experts interviewed suggested that PRO data obtained from COPD patients without comorbidities which could potentially affect the overall assessment of HRQoL, are more reliable when collected using currently approved questionnaires. These considerations highlight the need for further research and literature focusing on the measurement of PROs in respiratory diseases. This would help address challenges associated with assessing these outcomes outside the context of clinical trials, which can be time consuming and subject to individual interpretation.

3. Prevention of moderate to severe exacerbations

Statement: Available treatments (single or double bronchodilation, ICS/LABA, triple therapy and rehabilitation) are all able to reduce exacerbation risk after diagnosis.

Preventing exacerbations is a crucial goal in the management of COPD [1] Prevention of exacerbations is based not only on bronchodilators (and antimicrobial therapy) [43] and rehabilitation but also on modification of risk factors, vaccinations and treatment of comorbid conditions [13,44,45]. The choice of medications within each class depends on achieving a favorable clinical response while considering factors such as adverse effects, availability, and cost. It is important to individualize treatment regimens because the relationship between symptom severity, airflow limitation, and exacerbation severity can vary among patients.

The expert panel achieved a significant consensus on this statement with only 1% disagreement (87% agreement). In the experts' comments, triple therapy was highlighted as a particularly effective approach in achieving the goal of preventing exacerbations. However, it is important to note that triple therapy is recommended as initial therapy in patients with ≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization and eosinophilia ≥ 300 cells/µl, while in other cases it should be considered as a follow up strategy [1]. Therefore, bronchodilators as single agents or in combination therapy, along with appropriate pulmonary rehabilitation programs, should always be considered as first-line treatments.

4. Reduction in the mortality rate as an efficacy outcome

Statement: Mortality is a mandatory outcome of therapy efficacy, as in other chronic diseases. Clinical trials and therapies should consider the reduction of mortality rate as a study endpoint.

COPD should be recognized as a systemic disease that significantly contributes to both all-cause and disease-related mortality [41]. It is associated with various cardiac and non-cardiac comorbidities that contribute to the risk of mortality. For instance, heart failure affects around 20-30% of COPD patients [46,47] and significantly increases the risk of mortality [48,49]. Additionally COPD-related pulmonary hypertension (PH) is a significant respiratory comorbidity with a prevalence of 39.2% in the COPD population [50] and it is associated with reduced survival, particularly in advanced stages of COPD [51].

Furthermore, it is important to note that the frequency and severity of exacerbations in COPD have a detrimental impact on mortality [52]: hospitalizations related to acute exacerbations have been identified as predictors of mortality rates, particularly in relation to cardiovascular disease (CVD) within the subsequent 90 days, with an escalated risk of mortality corresponding to an increase in the number of exacerbation events [53]. Moreover, an elevated number and greater

severity of exacerbations are associated with an augmented risk of future exacerbations, all-cause mortality and mortality specifically related to COPD [52,54].

However, measuring mortality as a primary outcome in COPD randomized controlled trials (RCTs) has been infrequent. Several factors may account for this, including improved COPD management leading to reduced mortality rates, variation in death rates based on baseline lung function (FEV_1), placebo controlled trials showing treatment effects more prominently, differing intervention timings and follow up durations, exclusion of severe cases in studies using licensed therapies and potential withdrawal of patients in less effective treatment arms in longer studies [55].

Nevertheless, there are a few exceptions where mortality was included as a primary outcome in COPD studies, such as the TORCH (Toward a Revolution in COPD Health) [56], TIOSPIR (Tiotropium Safety and Performance in Respimat) [57], SUMMIT [58] and the NETT [59] studies, two long-term oxygen therapy trials [60,61], and, more recently, the ETHOS trial and a secondary analysis of the IMPACT trials [21,22]. Notably, the IMPACT and ETHOS trials demonstrated a reduction in all-cause mortality rates among patients receiving triple therapy [21,22]. In particular, the risk of all-cause mortality with triple therapy relative to dual therapy was 0.72 (95% confidence interval (CI), 0.53–0.99, P = 0.042), equivalent to a number needed to treat (NNT) of 121, and 0.51 (95% CI, 0.33–0.80; P = 0.0035), equivalent to a NNT of 80 in the IMPACT and ETHOS trials, respectively [21,22].

A recent meta-analysis by Chen et al. [62] showed that inhaled therapy containing ICSs, especially triple therapy, reduced all-cause mortality, likely due to the anti-inflammatory effect that limits inflammation driven injury, small airway narrowing and lung parenchyma destruction. Interestingly, budesonide was associated with a lower risk of all-cause mortality compared to other corticosteroids [53], probably due to its decreased risk of pneumonia [63-65].

Overall, studies investigating the impact of pharmacotherapy on mortality in patients with more severe COPD have shown reduced mortality rates, improved lung function and decreased risk of exacerbations [57].

In terms of triple therapy administration, a real-world retrospective observational study comparing single-inhaler triple therapy (SITT) and multiple inhaler triple therapy (MITT) demonstrated a reduction of 12-month all-cause mortality rate in patients using SITT [66].

This finding is intriguing because utilization of SITT offers the advantage of simplifying intricate inhaler regimens [67] and enhancing adherence and persistence, as opposed to MITT [68,69].

The expert panel largely agreed (83% agreement, 2% disagreement) with the importance of considering patient heterogeneity and the high prevalence of comorbid conditions in COPD when designing studies. Ideally, study designs should stratify patients based on their disease stage and the presence of specific comorbidities. Additionally, the panelists agreed that mortality is a pivotal outcome to be considered in study designs, given that COPD patients are subject to exacerbations events and are affected by comorbidities, that both pose a risk of death.

5. *Role of phenotypes and biomarkers in the definition of the therapeutic strategy*

Statement: The presence of eosinophilia, identification of the emphysema as prevalent phenotype concomitant with the presence of bronchiectasis may or may not direct to the use of ICS as an add on to bronchodilator therapy.

Literature data indicate the clinical significance of biomarkers in evaluating patients with COPD [70]. The availability of a blood-based biomarker would be highly valuable in both clinical practice and the optimization of patient selection for clinical trials, given the convenience of blood sampling. The role of blood eosinophil levels in the clinical manifestation of COPD has been a topic of intense debate.

Since the 2019 GOLD release [71], eosinophilia has been proposed and maintained in subsequent versions as a factor influencing treatment choices in COPD, particularly in support of ICS-based regimens. Two meta-analyses conducted in 2021 suggested that a cut-off value of 300 cells/μL may indicate the use of ICS-containing therapies [22,70]. Conversely, patients with a blood eosinophil count < 100 cells/μL are less likely to benefit from ICS treatment [22,70]. Furthermore, the aforementioned meta-analysis by Chen et al. identified an eosinophil count ≥ 200/μL as a predictor

for the reduction of all-cause mortality in COPD patients treated with inhaled therapy containing ICSs [62]. Bafadhel et al. conducted a *post-hoc* analysis of data form the ETHOS trial and demonstrated clear evidence of treatment benefits with ICS-containing triple therapy in terms of symptoms, disease-related QoL and lung function for patients with EOS counts greater than 100/μL [72]. These findings are consistent with results from the KRONOS study, which observed a reduction in exacerbation rate and improvement in lung function in patients with EOS counts ≥ 100/ μL and ≥ 150/ μL, respectively, when treated with triple therapy compared to dual therapy [73].

Similarly, the IMPACT study showed superiority in treatment benefits with ICS-containing triple therapy over LABA-LAMA therapy for patients with an EOS count ≥ 100/μL. The degree of benefits generally increased with higher baseline EOS counts [72,73], with an EOS count of 300/μL identified as the threshold for the greatest likelihood of treatment benefits with ICS [1]. Therefore, blood eosinophil levels serve as important predictors of triple therapy efficacy and should be assessed in patients with COPD, considering that patients with EOS counts ≥ 100/μL can also benefit from ICS-containing triple therapy, in line with the GOLD guidelines [1].

Interestingly the study by Chen et al. identified additional predictors for the reduction in all-cause mortality with inhaled therapy containing ICSs, including a history of ≥ 2 previous moderate or severe exacerbations in the previous year, GOLD stages III or IV disease, treatment duration > 6 months, age younger than 65 years and BMI ≥ 25 kg/m^2 [62]. The emphysema-predominant phenotype, regardless of the severity of FEV_1 impairment, has been identified as a predictor of poor response to ICS/LABA therapies [74]. It has been reported that one-third of patients with a predominant emphysema may also have a significant component of overlapping chronic bronchitis and bronchiectasis, which is more commonly found in the lower lobes [75]. Given the association of bronchiectasis with bacterial colonization, caution should be exercised when administering ICS in such cases [1].

The expert panel reached a substantial consensus (86% agreement, 3% disagreement) regarding the potential to determine the inclusion of an ICS in the treatment approach based on the presence of eosinophilia and the identification of emphysema as the predominant phenotype accompanied by bronchiectasis.

6. *Role of the assessment of respiratory function in the management of COPD*

Statement: Spirometry is required to make the diagnosis of COPD and it has also to be considered as a useful tool for disease management. Residual volume and DL_{CO} assessment can complement information provided by spirometry, and they are recommended after first COPD diagnosis. These second level respiratory functional assessments become mandatory when therapeutic goals are not reached.

According to the GOLD document [1], persistent airflow obstruction is the cornerstone of COPD diagnosis. To confirm the diagnosis, parameters such as FEV_1, FVC, and FEV_1/FVC ratio obtained from spirometry are important predictors at the population-level, although they may not always accurately reflect the severity of COPD outcomes [70]. In particular, FEV_1 alone does not fully capture the impairment in the small airways, lung hyperinflation, and emphysema [70]. The abnormalities in the small airways play a crucial role in the pathogenesis of COPD and can precede the development of airflow obstruction and emphysema [76,77]. The severity of COPD in terms of airflow obstruction, quality of life, and prognosis directly relates to the degree of inflammation, narrowing, and thickening of the small airways [78].

Some studies have indicated that the diffusing capacity for carbon monoxide (DL_{CO}) may be an equally good or even better prognostic marker than FEV_1 in severe acute exacerbations of COPD [79,80]. DL_{CO} also provides an assessment of emphysema levels and reflects the patient's performance status [81,82]. These findings suggest that DL_{CO} could serve as a reliable predictor of early pulmonary dysfunction and prognosis. Classification based on DL_{CO} can be valuable in determining the treatment strategy for patients with severe COPD.

The expert panel reached a very high rate of agreement (93% agreement, 1% disagreement) on the role of spirometry for the initial diagnosis and the assessment

of residual volume and DL_{CO} to supplement the information, particularly when the therapeutic goals are not achieved.

7. *Impact of comorbidities in the definition of the therapeutic strategy in COPD*

Statements: The identification of comorbidities, due to their impact on symptoms, exacerbations, PROs, and mortality (particularly cardiovascular ones), is mandatory for a correct therapeutic management of COPD.

Comorbidity is common among patients with COPD and early identification of comorbidities is crucial for implementing comprehensive management strategies that improve outcomes and reduce the burden of the disease [83]. The presence of COPD along with other diseases increases the likelihood of hospital admissions [84,85], healthcare costs [86], and reduces quality of life and exercise tolerance [87]. Furthermore, comorbidity is associated with increased mortality [88]. Compared to the general population patients with COPD have a higher prevalence of comorbidities, with cardiovascular diseases, osteoporosis, hypertension, and gastroesophageal disease being among the most prevalent [46,89-97].

Cardiovascular diseases are particularly important comorbidities in predicting all-cause mortality in patients with COPD. Old age, smoking history, and increased systemic inflammation are common risk factors shared between COPD and cardiovascular diseases [98]. However, some studies have shown that patients with COPD have an increased susceptibility to cardiovascular diseases independent of these risk factors [99-101].

Processes associated with COPD, such as lung hyperinflation, hypoxemia and systemic inflammation contribute to the increased risk of CVD [102]. In particular the coexistence of heart failure and COPD further increases the risk for hospitalization and mortality in patients [103-105].

It is worth noting that concomitant chronic diseases are often misdiagnosed or undiagnosed, and therefore untreated, in patients with COPD.

This is especially true for individuals with preserved ratio impaired spirometry (PRISm) findings where the FEV_1 to FVC ratio is normal, but FEV_1 is reduced. Despite having an increased risk of hospitalization [106,107] and mortality [108], individuals with PRISm findings are often overlooked as a category. A recent study revealed that patients with COPD GOLD stage ≥ 2 and PRISm findings were twice as likely to develop CVD, compared to patients with normal spirometry values, independent of common risk factors and even in the absence of a documented history of previous CVD [109].

The expert panel largely agreed (89% agreement, 1% disagreement) on the importance of identifying comorbidities in COPD patients for an appropriate management of the disease.

8. *Direct escalation from single bronchodilator to triple therapy*

Statement: In COPD management, direct escalation from single bronchodilator to triple therapy can be considered when therapeutic goals (exacerbations, PROs) are not reached.

The clinical spectrum of COPD is diverse, and appropriate adjustments in therapy are necessary as the disease progresses. Since 2020, the GOLD recommendations have suggested treatment escalation or de-escalation based on the worsening or improvement of symptoms and the persistence of exacerbations. Specifically, the GOLD 2023 document recommends to take into account the possibility of escalating treatment to triple therapy in cases where patients experience exacerbations and dyspnea while on monotherapy with a long-acting bronchodilator and have an eosinophil blood count of ≥ 300 cells/μl [1,16]. Notably, de-escalations should be done under close medical supervision [1,71].

The panel agreed (74% agreement, 4% disagreement) with the step-by-step approach proposed in the GOLD recommendations for COPD management but acknowledges the existing gap in everyday clinical practice.

This is particularly evident in cases where the diagnosis is made late, with noticeable signs of functional decline and radiographic damage, as well as in individuals who experience rapid disease progression. In such cases, a more aggressive therapeutic approach may be beneficial for better symptom and exacerbation

management as well as for reducing mortality rates. As mentioned previously, the panelists once again emphasize the importance of conducting a thorough patient profile assessment to determine the predominant phenotype and the most appropriate therapy.

9. Clinical and functional indices as drivers for a first-intention triple therapy

Statement: Ab initio triple therapy could be an option for patients recently discharged from hospital, or when dyspnea and exacerbations are both present in patients with reduced respiratory function.

The role of triple therapy in COPD has been discussed in various reviews and editorials [19,110-114]. However, only a few of them address the issues associated with its use outside of strict indications or when triple therapy should not be considered even if recommended. The KRONOS study demonstrated the efficacy and tolerability of triple therapy, suggesting that it may be a more suitable treatment option than corresponding dual therapies for symptomatic patients with moderate to very severe COPD, regardless of their exacerbation history [73]. Two recent papers [115,116] based on data from COPD patients in the United States and Spain analyzed the clinical characteristics and factors associated with the initiation of triple therapy in newly diagnosed patients. Variables such as lower FEV_1, higher exacerbation frequency, male sex, increased age, smoking, concomitant asthma, previous ICS-containing regimen associated with initiation of triple therapy, previous pneumonia, and history of lung cancer, were found to be associated with the initiation of triple therapy. Vanfleteren et al. [117] suggested that triple therapy should be considered as the first choice rather than a step-up approach in at least two situations:

- in patients discharged from the hospital after an acute COPD exacerbation where the diagnosis of COPD was made as a consequence of that severe exacerbation. These patients often receive inhaled bronchodilators (mostly continuous short-acting β_2-agonists and short-acting muscarinic antagonists as nebulized therapy), systemic steroids, and antibiotics during their hospitalization and are at a high risk of re-hospitalization, particularly during the first month [52,118].
- in newly diagnosed patients with severe airway obstruction (FEV_1 <50%), who are symptomatic, have a history of frequent moderate (≥ 2) or severe exacerbations (resulting in ≥1 hospitalization) in the previous year, and exhibit peripheral eosinophilia (> 300 cells/μL). These patients are at a high risk of recurrent exacerbations and/or hospitalization [52,76,77,118-120].

A recently published retrospective study [121] has shown that the prompt initiation of single-inhaler fluticasone furoate/umeclidinium/vilanterol after a moderate to severe COPD exacerbation is associated with significant reductions in exacerbations and healthcare costs compared to delayed initiation.

Approximately two-thirds of the panellists (69% agreement, 3% disagreement) agreed to consider initial triple therapy among the options for patients recently discharged from hospital, or with concomitant dyspnea, exacerbations and reduced respiratory function.

10. Possible occurrence of adverse events and their role as drivers in the prescription of triple therapy

Statement: Controlled trials were not able to identify an increase of adverse events in patients on triple therapy compared with those on double therapy. Nevertheless, pneumonia risk and the type of therapy need to be evaluated before starting ICS therapy.

A recent systematic review and meta-analysis of randomized controlled trials [122] examined the safety outcomes of one-year of triple therapy, which includes LABAs, LAMAs, and ICSs, compared to dual therapies in patients with COPD. The findings indicated that there was no significant difference in the risk of adverse events, serious adverse events, cardiovascular events, and respiratory tract infections between the ICS/LABA/LAMA group and the dual-therapy groups [122]. However, the analysis revealed that the risk of pneumonia was higher in the ICS/LABA/LAMA group than in the LABA/LAMA group (risk ratio, 1.43; 95% confidence interval, 1.21–1.68; $P < 0.001$) [122]. As a result, the balance between the

potential benefits of reducing exacerbations and the increased risk of infective events should be carefully evaluated at an individual level in order to achieve the best personalized outcomes.

Approximately 10% of the panellists (68% agreement, 10% disagreement) showed disagreement with the need to carefully evaluate pneumonia risk and the choice of therapy before starting inhaled corticosteroids.

11. Selection criteria for candidates for triple therapy

Statement: Failure to achieve therapeutic goals (presence of exacerbations in patients treated with double bronchodilators, persistence of respiratory symptoms after ICS/LABA) in patients adherent to therapy is an eligibility criterion for triple therapy.

This statement further expands on point 9 by highlighting the recommended step-up approach from double to triple therapy in cases where exacerbations and symptoms persist during follow up, after ensuring therapy compliance and the continuation of healthy habits such as smoking cessation and an active lifestyle. It is important to note that this recommendation is applicable in the absence of comorbidities, particularly cardiovascular conditions, and is supported by the literature and international guidelines [1].

The expert panel largely agreed (93% agreement, 11% disagreement) on the appropriateness of escalating treatment to ICS-containing triple therapy when therapeutic goals are not achieved in patients adherent to dual therapy (i.e. presence of exacerbations in patients treated with double bronchodilators, persistence of respiratory symptoms after ICS/LABA).

Conclusions

The analysis of the current management of COPD patients in Italy has identified 11 items and corresponding statements. However, the evaluation of these statements by 73 physician experts in COPD management did not exceed 90% agreement, indicating the need for further work. The following areas were highlighted for future improvement:

- Increasing awareness in the Italian scientific community about the mortality risk associated with COPD, aiming for a consensus that surpasses 90% agreement;
- Emphasizing the importance of early diagnosis to prevent disease progression;
- Recognizing that early therapeutic intervention can lead to a better disease control and prevent exacerbations that may contribute to mortality over time;
- Strengthening the evidence base, particularly regarding the selection of biomarkers, pulmonary function indices, and characterization of phenotypes, to guide decision-making in selecting appropriate therapeutic approaches;
- Identify tools such as PROs and questionnaires that can be useful in managing COPD patients.

Moreover, there was unanimous agreement among the survey participants on the importance of implementing strategies that enhance patient profiling and enable tailored management approaches for individuals with COPD.

Abbreviations

CAT: COPD Assessment Test
COPD: chronic obstructive pulmonary disease
DLco: diffusion capacity in the lungs for carbon monoxide
FEV_1: forced expiratory volume in the 1st second
FVC: forced vital capacity
ICS: inhaled corticosteroids
LABA: long-acting β_2-receptor agonists
mMRC: modified Medical Research Council dyspnea scale
PRO: patient-reported outcome
SGRQ: St George's Respiratory Questionnaire
TDI: Transition Dyspnea Index.

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Received for publication: 30 November 2023 - Accepted for publication: 1 July 2024

Licensee Mattioli 1885, Italy
Multidisciplinary Respiratory Medicine 2024; 19: 949
doi: 10.5826/mrm.2024.949

APPENDIX

Expert Panel

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