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EXPERT OPINION

A Delphi Consensus Project to Capture Greek Experts' Opinion on the Position of Triple Therapies in COPD: Why, When and to Whom

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Background: In recent years, COPD treatment has become more personalized considering specific patient's characteristics.

Aim and Methods: We have performed a DELPHI consensus project to assess the level of consensus among Greek experts on the use of triple therapy in COPD as an initial and follow-up treatment. A three-round Delphi online survey was developed. The questionnaire was developed by a 6-member steering committee, included 54 statements, and divided into 3 domains: (A) triple therapy as initial treatment (divided into subdomains examining the impact of exacerbations based on lung function, bronchodilation reversibility and/or blood eosinophil count, smoking, symptoms, and comorbidities), (B) escalation to triple therapy from dual bronchodilation and (C) de-escalation from triple therapy to dual bronchodilation. The survey was funded by AstraZeneca and was hosted and analysed by an independent external company.

Results: Consensus was reached in 84.8%, 63% and 80% of statements for domains A, B and C, respectively. Experts agreed that initial treatment with triple therapy is a reasonable option for specific patients, while escalation from dual bronchodilation to triple therapy could be considered, besides frequent exacerbators, also in patients with a history of one moderate exacerbation, mainly in the presence of marked bronchodilator reversibility or high blood eosinophil count. Finally, there was a consensus that de-escalation from triple therapy to dual bronchodilation was inappropriate in patients who had experienced one moderate exacerbation in the previous year.

Conclusion: Although consensus was generated in several statements, panelists failed to reach consensus in many aspects of the use of triple therapy, identifying areas for further research.

Keywords: COPD, inhaled corticosteroids, exacerbations, dual bronchodilation, triple therapy

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is one of the leading causes of morbidity and mortality worldwide and is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities, resulting in persistent, often progressive airflow obstruction.[1] In the latest years, the Global Initiative for Obstructive Lung Diseases (GOLD) proposes a personalized approach for the treatment of COPD, considering specific patient's characteristics for the choice of both initial treatment strategy and for treatment alterations according to the patient's response, while the management of COPD follows a circle of continuous evaluation and treatment adjustment to achieve the best possible symptom improvement and to eliminate exacerbations.[1] Thus, an escalation and de-escalation of treatment can be performed by the treating physician, according to the patient's characteristics and response.

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The basis for the treatment of COPD patients is the administration of bronchodilators. Long-acting bronchodilators are preferred, while dual bronchodilation [ie the combination of a long acting beta agonist (LABA) with a long acting muscarinic antagonist (LAMA)] is suggested in more symptomatic patients due to its greater efficacy in the symptom improvement and on health-related quality of life (HRQoL) compared to single bronchodilation therapy.[2] Recent studies have shown that triple therapy (ie, dual bronchodilation plus inhaled corticosteroid) is more effective in both symptom improvement and exacerbation reduction compared to dual bronchodilation,[3,4] especially in patients who are more symptomatic and/or have a history of exacerbations. However, since inhaled corticosteroids (ICS) use is related to several adverse events (even though there are no major safety concerns about their use), the GOLD recommendations suggest adding ICS in the therapeutic regiment only in patients who experience frequent exacerbations and have elevated blood eosinophils, based on evidence that these patients benefit more from the addition of inhaled corticosteroids.[5] Although this personalized approach for the selection of COPD therapy is evidence-based and takes into account-specific disease features, the treating physicians recognize several other characteristics of COPD patients (such as moderate exacerbations, bronchodilation reversibility and comorbidities and smoking habit), which are not included in the recommendations, but often lead to consideration for or against the use of ICS.

The objective of this Delphi consensus study was to assess the level of consensus (agreement or disagreement) among respiratory experts with great experience on COPD on the use of triple therapy for both initial treatment and follow-up according to specific patient characteristics such as frequency and severity of exacerbations, bronchodilator reversibility, smoking status, the presence of comorbidities and/or blood eosinophil count.

Materials and Methods

This project aimed to generate a national consensus based on experts' opinions on the position of triple therapies in COPD, using the Delphi technique. This is a widely used and accepted systematic and structured framework of group decision-making using the collective opinion of panelists through online surveys, enabling the generation of insights on controversial or complex topics while mitigating the inherent challenges of face-to-face consensus methods, such as biases of influence or non-confidential interaction.[6] Although there is no restriction on the number of rounds, Delphi studies are typically conducted for 2 or 3 rounds.[7] Between rounds, responses are analyzed, summarized, and communicated back to the panelists through a process of anonymized controlled feedback which reduces the effect of "noise" while allowing participants to reflect on their response and compare it with the overall direction of the collective group.[8]

For this project, a three-round Delphi online survey was developed by the Project Initiator Group which comprised of six nationally recognized experts in COPD (AIP, KK, SL, NT, TV and GH). The survey was run, hosted, and analysed by an independent external vendor, [OPTIMAPHARM Greece, the Greek affiliate of OPTIMAPHARM, a globally operating full-service CRO (https://optimapharm.eu/corporate-information/)] ensuring confidentiality and anonymity of the information provided by the expert panel. The project flow is presented in Figure 1. The full protocol of this Delphi consensus project is presented as Appendix 2. The study was funded by AstraZeneca. AstraZeneca had no involvement or intervention on the content in any stage of the implementation of Delphi consensus, except that received the final results of Delphi consensus and in the context of notification of the upcoming publication by the authors, gave approval for the publication of the manuscript.

Study Participants

Formation of the Steering Committee (SC)

The Project Initiator Group also acted as the SC of this project (Appendix 1). The SC was actively involved in all aspects of the project, including literature review (performed for the needs of the project) to identify the topics to be addressed, agreement on the domains and statements to be rated, protocol and questionnaire preparation, definition of panellist selection criteria and panellist invitation, formation of consensus decision rules, selection and appointment of the independent external provider, and review/approval of the project report. The SC also convened meetings following each round of the process; these meetings were essential for reviewing and discussing the results, providing expert input, and directing potential revisions for subsequent rounds, as well as shaping the final set of statements. The entire process

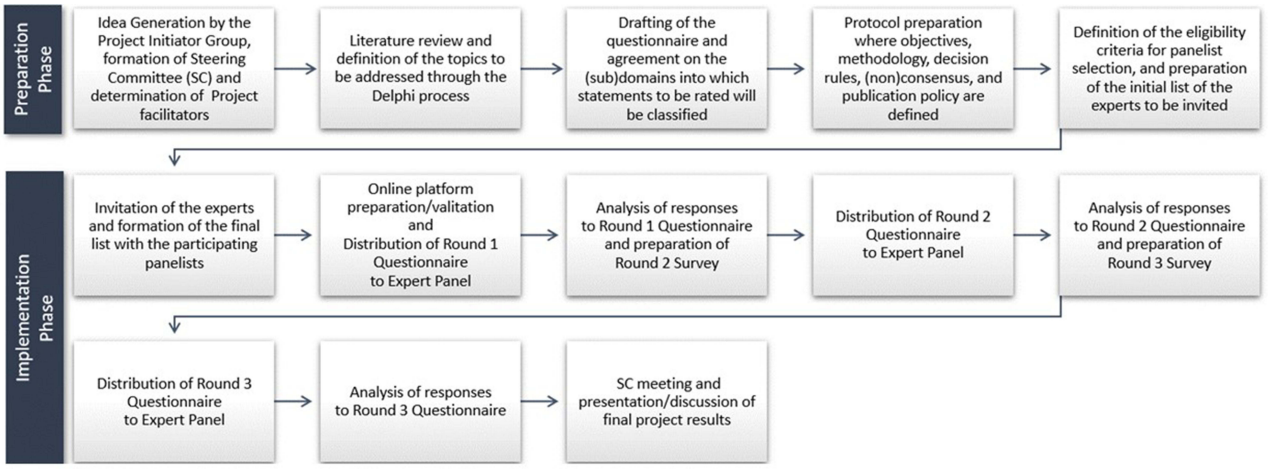

Figure 1 Delphi project flow.

was moderated by two SC members, who served as project facilitators and undertook the overall coordination of all project phases.

Considering the fact that all SC members had voting rights, rendering complete anonymity infeasible, a modified Delphi method was followed implementing partial and quasi-anonymity throughout the process.[9] In this way, SC members were aware of the identity of all expert panel members, but the opinions of the individual participants remained anonymous. Furthermore, the expert panel (excluding the SC members) was only aware of the identity of the SC members but not of the other panellists.

Formation of the Expert Panel

Agreement on the optimal panel size for Delphi studies is currently lacking,[10,11] since it does not depend on statistical power but on the problem being investigated, with representativeness being assessed based on the qualitative characteristics of the panel.[12] Selection of the sample size also depends on the degree of panel homogeneity, with a sample of 15–30 being suggested for homogenous samples from the same discipline.[13,14] In view of the aforementioned and considering the homogeneity of the target sample, the panel size comprised 27 experts, aiming to complete the process with at least 21 experts, assuming a maximum dropout rate of 20% over all rounds in line with previous Delphi studies.[15–18]

Eligible panel members were respiratory medicine specialists, selected by the SC in a non-random manner with the criterion of having impact on decision-making in respiratory care, professional recognition for their experience and scientific opinion, and special interest in the field of COPD. More specifically, selected panel members were chosen to use prespecified criteria which included medical experience more than 10 years, special interest in COPD including peer review publications in the field and active participation in workshops and seminars on several topics of COPD management. Thus, before beginning to answer the first round of the survey, the experts were requested to answer a series of questions about their area of focus (patient care, research, both patient care and research), years of professional practice in respiratory care focusing on COPD, work setting, and location of practice. Any conflict of interest with the present project including, among others, current or forthcoming employment in the pharmaceutical industry, or ownership in a pharmaceutical company served as exclusion criterion. All experts were requested to answer a series of questions about their area of focus, years of practice in respiratory care focusing on COPD, work setting, and location of practice; in addition, key demographic information was collected.

Questionnaire and Analysis Methodology

Based on the evidence generated by the targeted literature review, a final questionnaire was formed by the SC which included 54 statements, divided into the following 3 key domains (Figure 2):

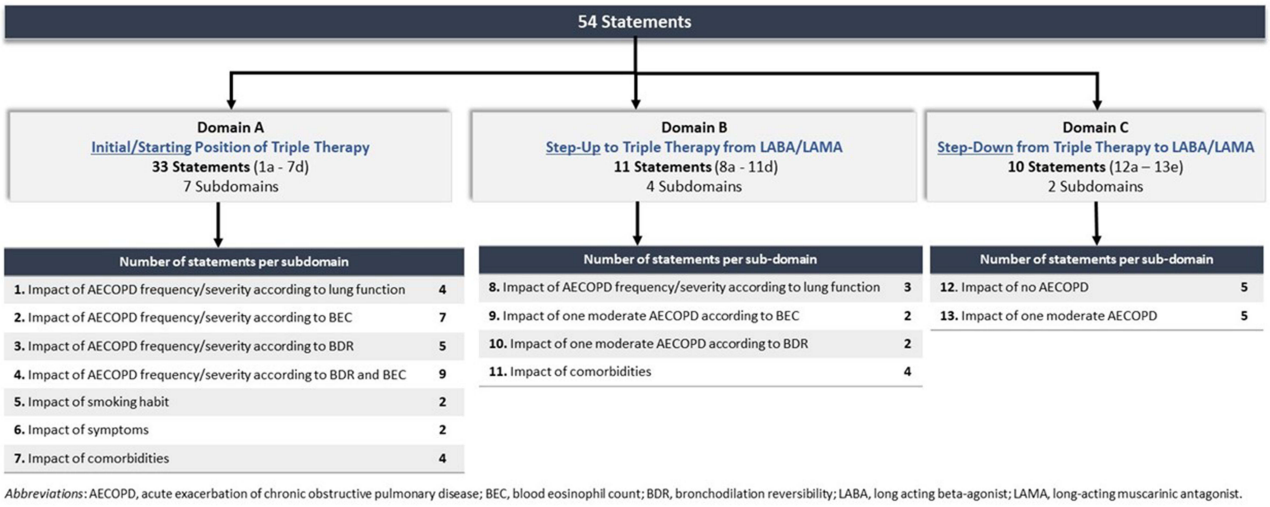

Figure 2 Survey domains and subdomains.

a) Triple therapy initial/starting position: comprising 33 statements further classified into 7 subdomains, examining the impact of exacerbation frequency/severity [according to lung function, blood eosinophil count (BEC) and bronchodilation reversibility (BDR)], smoking habit, symptoms, and comorbidities, on the decision-making to start triple combination therapy in previously undiagnosed untreated COPD patients (ie, without prior COPD diagnosis and therapy for COPD).
b) Escalation to triple therapy from LABA/LAMA: comprising 11 statements further classified into 4 subdomains, examining the impact of exacerbation frequency/severity (according to lung function, BEC and BDR) and comorbidities on the decision-making to escalate to triple combination therapy in COPD patients under treatment with a LABA/LAMA.
c) De-escalation from triple therapy to LABA/LAMA: comprising 10 statements further classified into 2 sub-domains, examining the impact of exacerbation frequency/severity on the decision-making to de-escalate from ICS/LABA/LAMA combination to LABA/LAMA.

All described scenarios pertained to a patient with definite diagnosis of COPD without any evidence of asthma or any other kind of concomitant respiratory disease.

A nine-point Likert-type ordinal scale (with anchors: 1=strongly disagree; 5=undecided; 9=strongly agree) was used for the rating of all questions, according to the format proposed in the RAND/UCLA Appropriateness Method User's Manual,[19] and as it is the most frequently employed in Delphi studies.[20–22]

The RAND/UCLA appropriateness method was also used to analyze the responses from each round.[23] Based on this methodology, the following metrics were calculated for each statement: median score, inter-percentile range (IPR), IPR adjusted for symmetry (IPRAS), and Disagreement Index (DI) (IPR/IPRAS). The DI was calculated using the equations shown in Supplementary Figure 3.

The median score was used to determine the level of appropriateness for a given statement (ie, appropriate or inappropriate therapeutic option), while the DI defined the presence or lack of consensus for this item. Specifically, "*consensus*" was considered when DI ≤1 (ie, IPR ≤ IPRAS, indicating no extreme score dispersion; with lower DI, denoting higher level of agreement), while "*lack of consensus*" was established when DI >1 (ie, IPR > IPRAS, indicating extreme variation across ratings).

Considering the above, a therapeutic option was considered "Appropriate" when the panel median was 7–9 without disagreement (DI ≤ 1), "Uncertain" when the panel median was 4–6 or any median with disagreement (DI > 1), and "Inappropriate" when the panel median was 1–3 without disagreement (DI ≤ 1).

The statements not reaching consensus as well as those with "uncertain" rating in the first round (R1) were fed back in the second (R2) and third round (R3) to allow the panelists to possibly amend their answers based on the other participants' opinions. During each survey round, weekly reminder emails were sent to the panellists aiming to ensure the highest possible response rate.

Survey responses were collected online utilising an encrypted internet server, with no hard copies involved. The web-based survey system was designed, validated, hosted, and processed by the external vendor, adhering to all applicable data protection regulations and requirements regarding electronic records and database validation. Statistical analysis was also performed by the external vendor using SAS® v.9.4 (SAS Institute Inc., Cary, NC, USA).

No formal ethics approval was required. Survey responses were collated anonymously using an identifying number known only to the participant and the independent web-based system administrator and data processor.

Results

The expert panel (including the SC members) comprised 27 respiratory medicine specialists (66.7% males, 88.9% <60 years old) with a balanced representation in terms of healthcare sector (55.6% practicing at public academic institutions) and location of practice (48.1% practicing in institutions located in Attica). Most participants (92.6%) had >10 years of practice in respiratory care focusing on COPD, with the area of focus being both patient care and research for most of them (81.5%). Panelist characteristics are provided in Table 1 in the online supplementary material.

The project was executed in 3 successive rounds, between 06-Mar-2023 (start of R1) and 13-Jul-2023 (completion of R3). All panelists completed the online survey in R1 and R2 (response rate: 100%), while all but one (96.3%) completed the survey in R3. The flow chart for the survey rounds is presented in Figure 3. Further information on survey rounds, timelines and response rates are presented in detail on the online supplement (Table 2 in the online supplementary material and Supplementary Figure 1).

In R1, 44.4% (24/54) of all statements across all domains reached consensus, with the remaining 55.6% (30/54) progressing to R2. After completion of R2, 77.8% (42/54) of all statements had reached consensus, one of which (statement 12c) achieved consensus but with uncertain rating (median: 5) and thus progressed to R3, along with the remaining 12 statements (22.2%; 12/54) that failed to achieve consensus. Finally, after completion of R3, the rate of consensus achievement increased to 83.3% (45/54), which was highest in Domain C (100%) and lowest in Domain B (63.6%). Detailed and synoptic summary on statistics and indexes per statement are provided in Tables 3 and 4 in the online supplementary material.

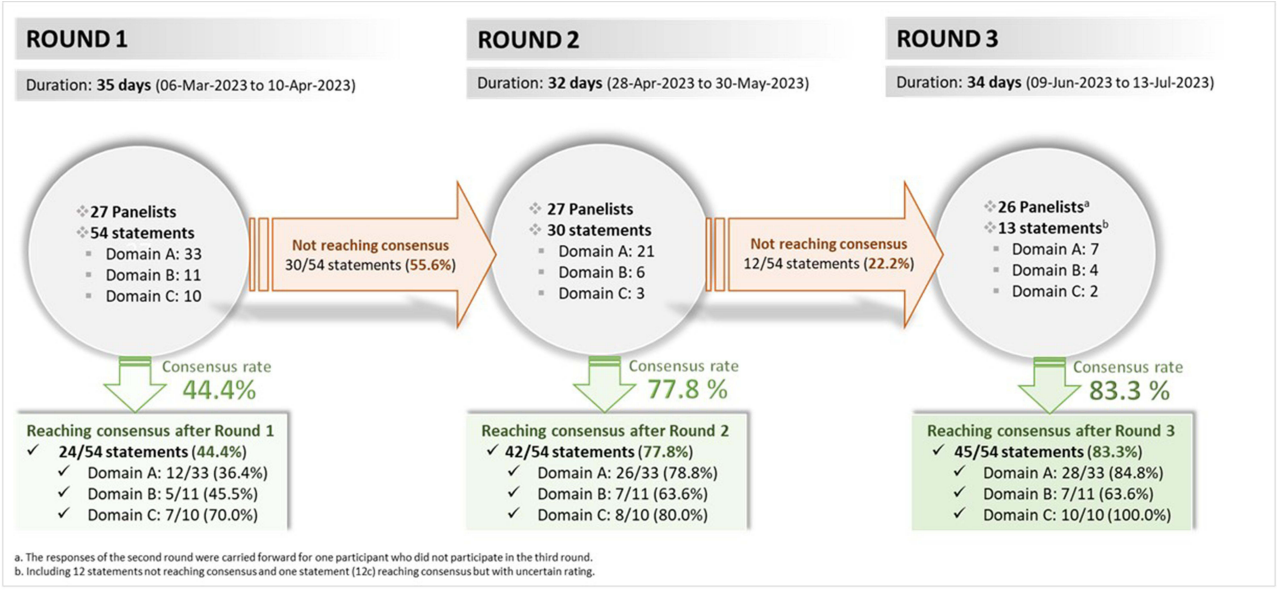

Figure 3 Survey round flow chart.

The frequencies of the expert panel ratings per domain and statement over the 3 successive rounds are displayed in Figure 4, the final consensus rate per domain and statement is presented in Figure 5, the detailed rating frequencies and metrics per statement across all domains in Supplementary Figure 2, whereas a summary of the appropriateness of therapeutic choice per statement is presented in Figure 6.

Figure 4 Frequencies of expert panel ratings per domain and statement over the 3 successive rounds.

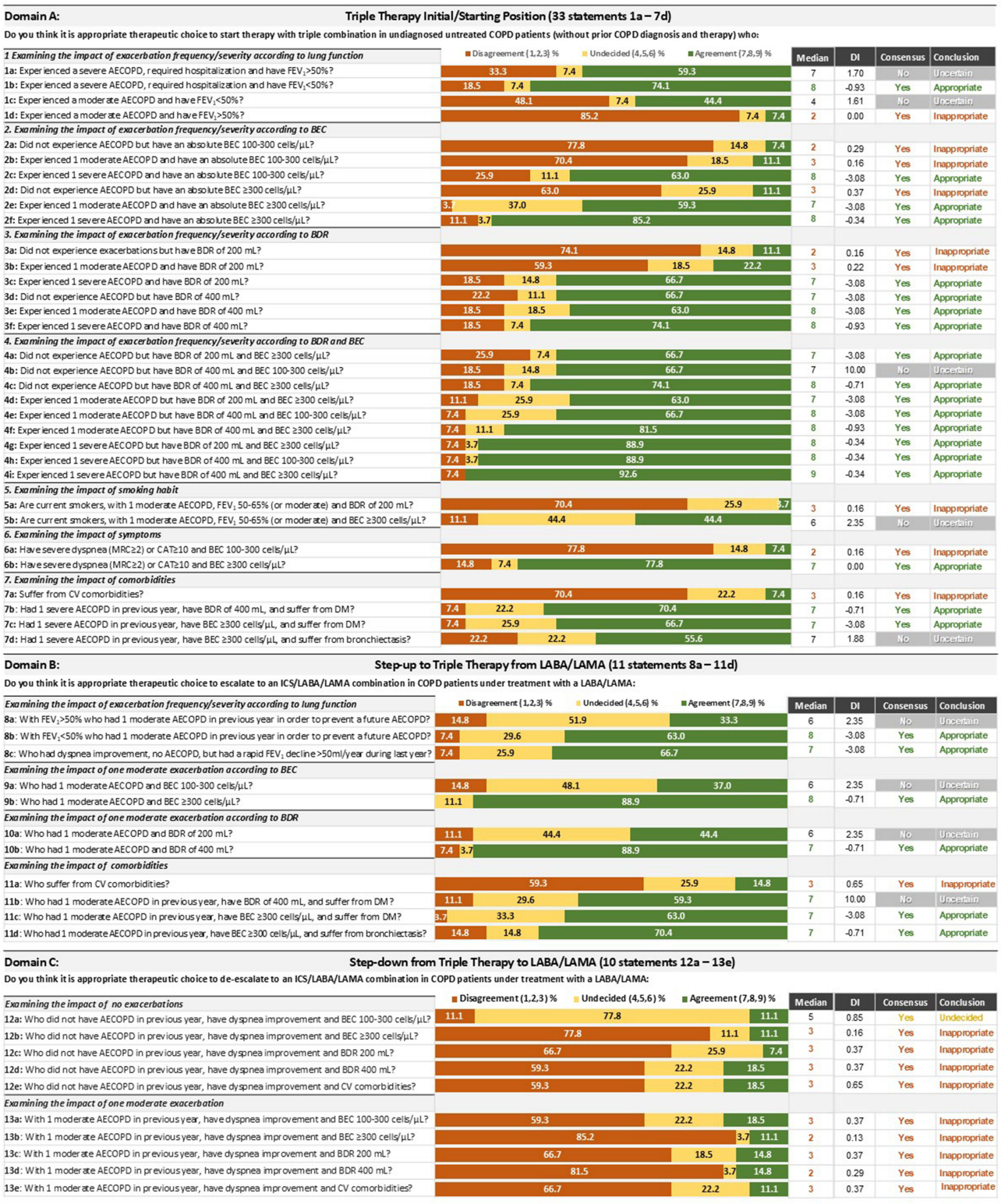

Figure 5 Final consensus rate per domain and statement.

Domain A Triple Therapy Initial/Starting Position

Among statements of this domain, 63.6% (21/33) and 21.2% (7/33) progressed to R2 and R3, respectively, with 84.8% (28/33) finally reaching consensus (Figures 4–6).

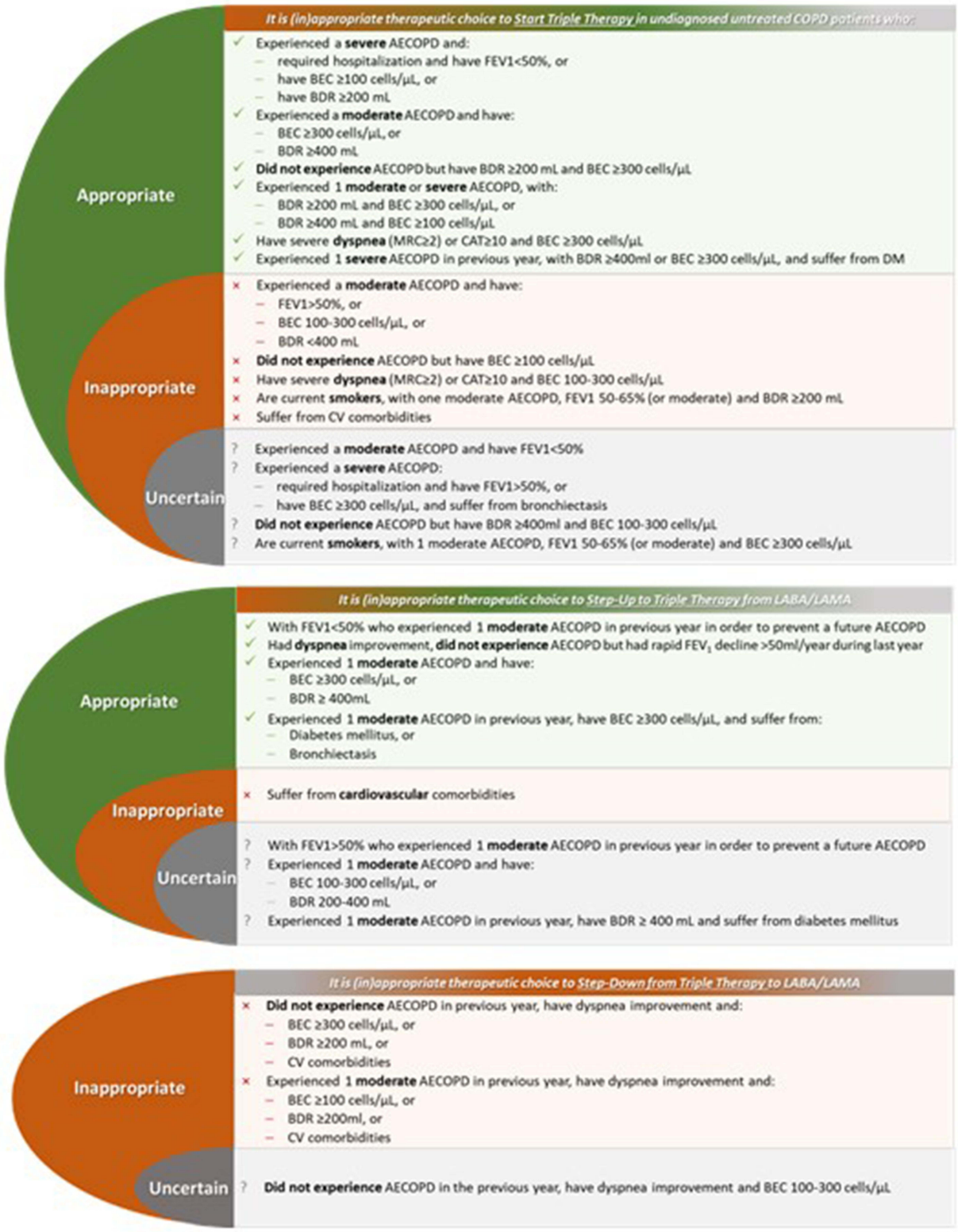

Figure 6 Appropriateness of therapeutic choice per domain and statement.

Impact of Exacerbation Frequency/Severity According to Lung Function

The rate of consensus was low (50%; 2/4) in the subdomain examining the impact of exacerbation frequency/severity according to lung function, with 3 of the 4 statements advancing to R2 and 2 statements (1a, 1c) to R3, both failing to reach consensus. The latter mirror panelists' divergence in terms of the appropriateness of triple therapy initiation in patients who have experienced a severe AECOPD requiring hospitalization and have FEV_1 >50% as well as in those with a moderate AECOPD and FEV_1 <50%. Conversely, panellists agreed that triple therapy initiation is an appropriate option for patients with a severe AECOPD requiring hospitalization and FEV_1 <50% (1b), whereas it is considered inappropriate for those with a moderate AECOPD and FEV_1 >50% (1d) (Figures 4–6).

Impact of Exacerbation Frequency/Severity According to BEC and/or BDR

The rate of consensus was the highest (95.2%; 20/21) among the 21 statements of the 3 subdomains examining the impact of exacerbation frequency/severity according to BEC, BDR and both BEC and BDR, with around half of the statements (11/21) progressing to R2 and two (2/21) to R3; the only statement not ultimately reaching consensus was 4b which examines the appropriateness of triple therapy initiation in patients without AECOPD but with a BDR ≥400 mL and BEC 100–300 cells/μL.

Among the 20 statements reaching consensus, 15 reflect panelists' agreement on the appropriateness of triple therapy initiation in the following patient profiles: in those having experienced one severe AECOPD with BEC ≥100 cells/μL (2c, 2f) or BDR ≥200mL (3c, 3f); in those having experienced one moderate AECOPD with BEC ≥300 cells/μL (2e) or BDR ≥400mL (3e); in those having experienced one moderate or severe AECOPD with both BEC ≥100 cells/μL and BDR ≥400mL (4h, 4i, 4e, 4f) or with both BEC ≥300 cells/μL and BDR ≥200mL (4d, 4g); and in patients without AECOPD but with both BDR ≥200mL and BEC ≥300 cells/μL (3d, 4a, 4c). It is worth mentioning that 5 of the above 15 statements (2f, 3f, 4g, 4h, 4i) were highly endorsed (ie, with strongly agreement rating of 9) by more than one-third of panelists (Supplementary Figure 2).

The remaining 5 consensus statements indicate panelists' agreement on the inappropriateness of triple therapy initiation in patients without AECOPD and either BEC ≥100 cells/μL (2a, 2d) or BDR of 200mL (3a), as well as in those with one moderate AECOPD and either BEC 100–300 cells/μL (2b) or BDR of 200mL (3b) (Figures 4–6).

Impact of Smoking Habit

Regarding the 2 statements addressing the impact of smoking habit on the decision-making for triple therapy initiation, both proceeded to R2 and one statement to R3 which eventually did not reach consensus. Specifically, panelists agreed against initiating triple therapy in current smokers with one moderate AECOPD, FEV_1 50–65% (or moderate) and BDR of 200 mL (5a), whereas their collective opinion was inconclusive when considering the above patient profile but with BEC ≥300 cells/μL (5b) instead of BDR (Figures 4–6).

The Impact of Symptoms

Pertaining to the 2 statements exploring the impact of symptoms, both were moved to R2, and one to R3 reaching consensus. When considering patients with severe dyspnea (MRC ≥ 2) or CAT ≥10, expert panelists voted in favor of initiating triple therapy when BEC is ≥300 cells/μL (6b), whereas they voted against this therapeutic approach when BEC is 100–300 cells/μL (6a) (Figures 4–6).

Impact of Comorbidities

Concerning the subdomain examining the impact of comorbidities, 3 of the 4 statements advanced to R2, and one statement to R3 which eventually failed to attain consensus; the latter with inconclusive outcome concerns patients with one severe AECOPD in the previous year, who have BEC ≥300 cells/μL, and suffer from bronchiectasis (7d). Of the 3 consensus statements, 2 pertain to patients with Diabetes Mellitus (DM) who have experienced one severe AECOPD in the previous year and have either BDR ≥400 mL (7b) or BEC ≥300 cells/μL (7c); in both patient profiles, triple therapy initiation was endorsed as an appropriate therapeutic option by the expert panel. On the contrary, the panelists voted against initiating triple therapy initiation in patients with CV comorbidities (7a) (Figures 4–6).

Domain B: Escalation to Triple Therapy from LABA/LAMA

This domain generated the lowest rate of consensus (63.6%) among panelists, with more than half of the statements advancing to R2 (54.5%; 6/11), and 4 statements (36.4%; 4/11) to R3, failing eventually to reach consensus (8a, 9a, 10a, 11b). All statements with inconclusive voting refer to patients who have experienced one moderate AECOPD in the previous year with any of the following: FEV_1>50% to prevent a future AECOPD (8a); BEC 100–300 cells/mL (9a); BDR 200–400 mL (10a); and BDR ≥400 mL and concurrent DM (11b).

Among the 7 consensus statements, escalation to triple therapy was voted as an appropriate therapeutic option in all described patient profiles (8b, 8c, 9b, 10b, 11c, 11d), except for those with CV comorbidities (11a) (Figures 4–6).

Domain C: De-Escalation from Triple Therapy to LABA/LAMA

The rate of consensus was highest in this domain, with only 3 statements (30.0%; 3/10) progressing to R2 and 2 statements to R3 (20.0%; 2/10), both reaching consensus; nevertheless, one of the latter statements (12a; pertaining to patients without AECOPD in the previous year, with dyspnea improvement and BEC 100–300 cells/μL) although achieved consensus, had a median score falling within the neutral/undecided category.

Among all remaining consensus statements (n=9), de-escalation from triple therapy was endorsed as inappropriate in all described patient profiles, and specifically: in patients without AECOPD in the previous year, who have dyspnea improvement and any of the following: BEC ≥300 cells/mL (12b), BDR ≥200 mL (12c, 12d), or CV comorbidities (12e); and in those with one moderate AECOPD in the previous year, who have dyspnea improvement and any of the following: BEC ≥100 cells/mL (13a, 13b), BDR ≥200 mL (13c, 13d), or CV comorbidities (13e) (Figures 4–6).

Finally, consensus results per survey domain and statement are provided in Table 5 in the online supplementary material.

Discussion

According to the GOLD consensus, triple therapy is indicated as an initial treatment only for patients who have concomitant asthma or are frequent exacerbators and have a BEC over 300 cells/μL without taking into account the BDR or the obstruction severity.[1] The panel, however, agreed that patients who had experienced one severe exacerbation in the previous year and thus are considered to be at increased exacerbation risk should receive triple therapy as initial treatment in the case that they have significant BDR. Previous studies have shown that treatment with ICS in COPD patients who had BDR resulted in clinical and functional improvements,[24,25] although the significance of BDR in the natural course of the disease is debated.[26] Furthermore, the panelists agreed that COPD patients with a history of one severe exacerbation in the previous year should be initially treated with triple therapy in the case that they have a BEC over 100 cells/μL, a number which is lower compared to that suggested by the GOLD recommendations.[1] However, it is a fact that there is a significant reduction of clinically important deterioration and an exacerbation reduction in COPD patients receiving ICS which is eosinophil dependent and accounts for a much lower number of blood eosinophils in most studies which approximates the number of 100 eosinophils chosen by the panelists.[3,5,27,28] Furthermore, in the cases that patients had a history of one moderate exacerbation, panelists considered that triple therapy as initial treatment is appropriate in cases with either very high BEC (≥300 cells/μL) or significant BDR (≥400mL). Although in our study it has been stated that all cases represented patients without concomitant asthma, the presence of very high eosinophil count or large BDR (defined as ≥400mL) have been considered as factors that could lead to the suspicion of the presence of undiagnosed comorbid asthma which probably is the reason for the agreement of panelists regarding the use of triple therapy as initial treatment.[29]

On the contrary, the panel agreed that triple therapy as initial treatment is inappropriate for COPD patients with no exacerbation history when they have BDR of 200mL, irrespective BEC count probably due to existing evidence suggesting that the number of blood eosinophils seems to affect future exacerbation rate in patients receiving ICS, mainly when there is history of previous exacerbations.[30,31] However, it has been agreed that patients with no exacerbation history should receive triple therapy as an initial treatment if they have BDR of 200mL and BEC >300 cells/μL. Probably, the panelists considered the fact that less than one-third of the exacerbations are usually reported[32] (but even unreported exacerbations have a significant impact on health status)[32] and were based on the fact that the coexistence of a positive BDR and high eosinophils could be predictors of ICS response in these patients as mentioned

above. Moreover, BEC has been shown to be correlated to exacerbation frequency in COPD,[33–35] thus it is reasonable that the presence of increased BEC in combination with significant BDR has led to the agreement that the patient should receive initial treatment with triple therapy.

Although the GOLD recommendations do not take into account the severity of airway obstruction for the choice of initial treatment for COPD,[1] there is evidence showing that patients with more severe airflow obstruction are at increased risk of exacerbations while previous exacerbations seem to predispose in future exacerbations.[36] Probably based on aforementioned evidence panelists also agreed that the use of triple therapy as initial COPD treatment is appropriate for patients with one severe exacerbation and severe and very severe airway obstruction while it has been considered as inappropriate for patients with a history of one moderate exacerbation and not severe airway obstruction or lower numbers of blood eosinophils (100–300 cells/μL) or BDR of 200mL. Finally, the use of triple therapy as an initial treatment has been considered as inappropriate in patients with no exacerbation history and no significant BDR irrespective of BEC count as well as in highly symptomatic patients with BEC 100–300 cells/μL.

Smoking has not only been recognized as a cause of developing COPD[37–39] but also as a factor which leads to lower steroid sensitivity since it has been shown that COPD patients who are current smokers benefit less from ICS regarding lung function improvement and exacerbation rates compared to ex-smokers.[40,41] This steroid insensitivity which is also observed in everyday clinical practice is probably the reason why panelists have agreed that the administration of triple therapy as an initial COPD treatment is inappropriate in current smokers despite the history of one moderate AECOPD and moderate airflow obstruction even if they have a positive BDR test. Finally, the panel agreed that symptomatic patients should receive triple therapy as initial treatment if they have increased blood eosinophils. Taking into account existing evidence that the number of blood eosinophils is associated with increased exacerbation rate[34,42,43] as do severe symptoms[44–47] probably has led the panelists to vote for triple therapy as initial treatment for these patients.

Although ICS is known to worsen DM control,[48] panelists agreed that patients with comorbid DM should receive triple therapy as initial treatment if they had a history of one severe exacerbation in the previous year and very high BEC or very high BDR again considering that these two characteristics are putting the patient at increased risk for future exacerbations as stated above.

Despite the current evidence showing that ICS might protect from the occurrence of CV events in COPD patients with CV comorbidities,[49–51] panelists have agreed that the use of triple therapy as initial COPD treatment would be inappropriate based on the presence of CV comorbidities per se if there were no additional characteristics to support its use. Further studies are needed in order to support the possible protective role of triple therapy for the prevention of adverse CV events in COPD patients.

Regarding escalating therapy from dual bronchodilation to triple therapy, the panelists agreed that it was appropriate for patients with one moderate exacerbation who had severe or very severe airflow obstruction or had BDR ≥400mL or BEC≥300 cells/μL. Again it has to be mentioned that airflow limitation is known to be a predictor of future exacerbations[36] and probably experts believed that these patients should increase their therapy to be protected. Furthermore, the presence of either significant BDR or increased BEC are recognized factors for future exacerbations as mentioned earlier in this manuscript and probably the existence of this evidence has resulted in this decision from the panelists regarding escalation of therapy. Interestingly, panelists have agreed that escalation from dual bronchodilation to triple therapy is appropriate in patients with one moderate exacerbation in the previous year and BEC≥300 cells/μL regardless the presence of DM or bronchiectasis. Finally, panelists agreed that patients on dual bronchodilation who experience rapid lung function decline (ie, FEV_1 decline > 50mL/year) should escalate to triple therapy even if in the case of symptom improvement and absence of exacerbations during the last year. Previous studies have shown that discontinuation of ICS from patients previously receiving triple therapy resulted in symptom deterioration and increased lung function decline despite the absence of any effect on exacerbation frequency.[52]

Although the presence of DM and bronchiectasis did not affect the decision of the panelists to escalate from dual bronchodilation to triple therapy in the presence of other characteristics which could lead to clinical benefit, again the presence of CV comorbidities per se was not a factor which would affect the decision of escalating therapy despite the existence of evidence showing a benefit from their use.[49–51] Further studies are probably needed to clarify, whereas triple therapy has beneficial effects to prevent adverse CV events in COPD patients suffering from CV comorbidities.

The panelists agreed that in patients with high BEC or high BDR or CV comorbidity who had symptom improvement with triple therapy, de-escalation from triple therapy to dual bronchodilation was inappropriate regardless of the absence of any exacerbation or the presence of one moderate in the previous year. Probably, existing evidence on the role of increased BEC and high BDR as analyzed previously has resulted in this agreement.

Our study has several limitations. First, this is a national and not international consensus since the expert panelists were chosen from one single country (Greece) which might reflect the clinical practice in this specific area. Although an international consensus would be much more valuable and generalizable, the very careful choice of the panelists who were asked to consider not only their personal clinical experience but also all available evidence to their knowledge, increases the validity of the results. Nevertheless, the areas of agreement are merely panelist agreements, and although some evidence supports these points, many of these areas remain controversial. Another limitation of this study, is that panelists could not provide any explanation on their answers since no free text entering was possible. Finally, it is a fact that the use of ICS/LABA has not been included in the questionnaire since according to the latest GOLD recommendations ICS should be added in COPD patients only on the top of dual bronchodilation.

Conclusion

This Delphi consensus study has provided expert consensus statements on the use of triple therapy in patients with COPD. Many of these consensus statements are not included in the COPD recommendations, although they may be used to help physicians to optimize management of COPD patients. This Delphi consensus, although conducted in only one country, covers three important domains of the use of triple therapy, its use as an initial COPD treatment in previously untreated patients, the escalation from dual bronchodilation and finally the de-escalation from triple therapy to dual bronchodilation. It seems that consensus was mostly based on an effort to provide the best treatment related to disease improvement and at the same time to reduce ICS use where there is no definite benefit. Although consensus was generated in several statements, still many remain controversial highlighting the fact that still there are many unanswered questions regarding the exact use of triple therapy in COPD treatment. Thus, there is a great need for further research to answer these uncertain statements in order to help the development of future evidence-based guidelines for COPD management.

Take Home Message

In this Delphi consensus project, experts agreed that several patient characteristics which are not included in the current GOLD recommendations (such as moderate exacerbations, comorbidities and bronchodilation reversibility) should be taken into account when considering the use of triple therapy in COPD.

Data Sharing Statement

The study protocol is available in the supplementary file. Calculation method for disagreement index (DI) is presented in Supplementary Figure 3. Study data are also presented in the supplementary file.

Ethics Approval and Consent to Participate

All participants have provided a consent to participate in the study.

Consent for Publication

All authors have read and approved the final version of the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Collaborators

The triple therapy for COPD Delphi expert panel members who have contributed to this study.

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