Pharmacologic Management of COPD: An Official American Thoracic Society Clinical Practice Guideline

ONLINE SUPPLEMENT

**Note that tables and figures associated with the evidence synthesis are not included in this online supplement. They are included in systematic reviews that will be independently published:*

1. *Mammen MJ, Pai V, Aaron SD, Nici L, Alexander PE. Dual LABA/LAMA therapy versus LABA or LAMA monotherapy for symptomatic COPD: A systematic review and meta-analysis. Undergoing peer review.*

2. *Mammen MJ, Lloyd DR, Kumar S, Ahmed AS, Pai V, Kunadharaju R, Gupta S, Aaron SD, Nici L, Alexander PE. Triple Therapy with inhaled corticosteroids and long acting bronchodilators versus dual or monotherapy with long acting bronchodilators without inhaled corticosteroids for symptomatic COPD: A systematic review and meta-analysis. Undergoing peer review.*

3. *Mammen MJ, Kumar S, Ahmed AS, Lloyd DR, Pai V, Kunadharaju R, Aaron SD, Nici L, Alexander PE. Withdrawal of Inhaled Corticosteroids for patients with COPD on triple therapy: A systematic review and meta-analysis. Undergoing peer review.*

4. *Mammen MJ, Lloyd DR, Ahmed AS, Pai V, Kunadharaju R, Alhazzani W, Nici L, Aaron SD, Alexander PE. The use of inhaled corticosteroids in addition to long-acting bronchodilators in COPD with blood eosinophilia: A systematic review and meta-analysis: A systematic review and meta-analysis. Undergoing peer review.*

5. *Mammen MJ, Charbek E, Hasan SN, Adamson K, Ahmed AS, Shehata M, Gupta S, Kalanadhabhatta N, Alhazzani W, Aaron SD, Nici L, Alexander PE. Chronic oral steroids use for in COPD with frequent exacerbations: A systematic review and meta-analysis. Undergoing peer review.*

6. *Charbek E, Aaron SD, Nici L, Alexander PE, Mammen MJ. Effects and Safety of Opioids on Dyspnea in Patient with COPD: A systematic review and meta-analysis. Undergoing peer review.*

DETAILED METHODS DESCRIPTION

Group composition

The Task Force co-chairs (LN and SA) were selected by the American Thoracic Society (ATS) to lead this COPD treatment guideline. These experts functioned in all aspects of the guideline project management and played a direct leadership role in selecting the panelists, which included clinicians and researchers with experience in COPD.

The methodologist team consisted of lead consultant methodologist (PEA) and ATS guideline scholars (MJM, EC). The methodology team worked with the expert medical librarian in commissioning the literature search. The methodology team then led teams of screeners and abstractors (working independently and in pairs) to identify and collect available evidence to perform the necessary systematic reviews and meta-analyses for evidence syntheses. The methodology team constructed the evidence tables and ensured compliance with all the methodological requirements. The co-chairs and panelists held several high-level meetings along with several communications via email to discuss the evidence and formulate the recommendations.

Formulation of PICO questions

The ATS expert panel members were asked to compile a list of clinical questions that they felt were important and relevant to pharmacological treatment of COPD from patient perspective. The questions were discussed within the panel and rephrased by the methods team using the PICO (Population, Intervention, Comparator, and Outcomes) format. [A] Consensus debate and Panelist voting (using a modified Delphi approach) were used to determine the final treatment questions from those initially proposed by the panel. A final six questions were judged by the panel to be of top priority in COPD treatment.

Rating importance of the outcomes

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[B] approach to guideline development was used to rate the certainty/quality of evidence and to derive strength and direction of recommendation. As per the GRADE approach, final recommendations decision making involves a balance between health benefits (desirable outcomes) and harms (undesirable outcomes). Thus, the systematic reviews that underpinned the recommendations considered a comprehensive range of patient-important outcomes. As such, the focus was not only on desirable outcomes but also the undesirable ones (harms) linked to interventions. The panel compiled a list of patient-important outcomes that were important to clinical decision making and particularly important to patients., and not necessarily on what outcomes are measured and for which evidence is available.

The panel worked with the co-chairs and methods team to initially identify the patient-important outcomes that they considered relevant to each of the six questions, regardless of whether the evidence was known to be available. Once a list was compiled for each question, the panel then rated the relative importance of outcomes using a 9-point Likert scale, [E] whereby a rating of 1–3 was assigned to outcomes of low importance for clinical decision-making, 4–6 assigned to outcomes important for clinical decision-making and 7–9 assigned to outcomes critically important for clinical decision-making). A teleconference ensued during which the ratings were discussed and changes made. At the end of the exercise, all outcomes were categorized as "not important", "important" or "critical" for clinical decision-making.

Subgroup considerations

In formulating the questions in PICO format, panelists worked with the methods team to devise any important sub-groups a priori. A priori delineation of sub-groups ensure that any future heterogeneity/inconsistency could be elucidated by sub-group analysis where data/evidence would allow.

Literature searches

We enlisted the assistance of a trained medical librarian contracted by ATS. The literature searches involved complex search strategies that queried Medline, Embase and the Cochrane Library (CENTRAL for trials and the systematic reviews database) from 1990 to August 2018. Searches were updated to January 2019 where possible using PubMed and reference lists as well as any relevant publication that was deemed eligible by the panel and screened for eligibility by the methods team. All publication types were included in the searching except for case report/case series, letters/editorials/narrative reviews, and abstracts. The search focused on studies conducted in humans and in the English language. See Appendix for the search strategy by queried database.

Study selection

We arrived at the final set of manuscripts to inform each PICO question based on four important steps: i) titles and abstract screening (a preliminary screen review of all titles and abstracts to determine which studies are potentially eligible) ii) full-text screening (a more in-depth review of the full text for all included studies from the title/abstract phase to establish final eligibility for the review) iii) data abstraction and iv) risk of bias/internal validity of study estimates (note, step iii) and iv) are done at the same time by reviewers. For steps i) and ii) the methodology team screened the titles and abstracts (TA) of the uncovered citations and excluded studies on the basis of the pre-

defined study selection criteria that was specific to each of the six study PICOs. Only studies that were deemed eligible (or were judged 'unsure' by screeners) went on to the full-text (FT) phase. At the TA and FT phase of screening, screening was performed in duplicate and independently by pairs of screeners with consensus debate to settle disagreements and 3rd party adjudication when/if needed. At the FT phase, the full studies were retrieved so that the screeners could read the study in entirety to make a definitive decision on whether a study would be retained to inform the respective PICO. Screeners were also required to screen the reference lists from systematic reviews to ensure that the literature search did not miss relevant studies. Panel members were asked to be alert to any recently published studies or any studies that they thought were relevant to a particular PICO and that may have been missed in the electronic database search or TA and FT screen steps.

Data abstraction and study risk of bias

The methodology team trained pairs of abstractors on how to retrieve the relevant evidence as well as perform risk of bias assessment. The methodology team also played a role in this step to ensure quality assurance and to gain a certain level of comfort with the evidence for down-stream analytical purposes. Both iii) and IV) steps were performed in duplicate and independently using consensus debate and 3rd party adjudication. Data abstraction focused on study demographic type data as well as study methods and PICO elements. The primary focus was on the patient-important outcome data which would permit either a narrative qualitative analysis or a quantitative synthesis of the evidence when possible. The assessment of the risk of bias in included studies utilized the Cochrane Risk of Bias tool[F] for randomized controlled trials (focusing on flaws in the design, conduct and analysis of randomized clinical trials) or the Guyatt Busse tool[G] for non-randomized studies (with a focus on assessing the role of residual confounding, co-interventions, and selection bias). While routine convention has been for the assessor to assign a risk of bias as 'yes', 'no' or 'unsure', we adopted the approach of 'yes', 'probably yes', 'probably no', and 'no' to mitigate the elevated 'unsure' responses in such exercises. The aim of the ATS methods team was to focus on the more rigorous studies as these would more than likely yield accurate results.

Evidence synthesis

Pooling (meta-analysis) of the abstracted study evidence e.g. study characteristics, types of participants, interventions, outcomes measured, and the results were considered by the methods teams with the aim to pool studies that were homogeneous. If the study data were amenable to pooling, then the effects were estimated via meta-analysis using Review Manager (version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark).[H] For the meta-analyses per PICO, the random effects model was utilized unless otherwise specified. Dichotomous outcomes were reported as relative risks (RR), odds-ratios (OR), or risk difference (RD) and continuous outcomes were reported as mean differences (MD) unless otherwise specified. We used the standardized mean difference (SMD) instead of mean difference (MD) for continuous outcomes in instances when we judged the measurement tools to be variable, thus the decision to standardize the measurements using the pooled standard-deviations as the denominators. We accepted that the cross-over analyses were optimally done in the reported trials and combined results with the parallel-arm evidence using the generic inverse variance approach in Review Manager software (mean difference and SE derived from the 95% confidence interval).We computed the absolute anticipated treatment effect (absolute risk difference/absolute risk effect) based on the baseline risk multiplied by the pooled relative-risk. We chose our baseline risk to be the control group event rate. The methodology team appraised the certainty/quality of evidence using the GRADE approach via GRADEpro [J] (McMaster University, Hamilton, ON, Canada) developing evidence tables that summarised the findings for each outcome and the rationale for the certainty/quality of evidence appraisal.

A statistically significant result and change may not be indicative of a clinically meaningful or important change for physicians and importantly, for their patients to understand. We were therefore mindful of the role of minimally important differences (MID)[K] or minimum clinically important difference (MCID) as the threshold that patients would better interpret and consider as important to decision making and would consider changing the treatment

option. The challenge is that MID thresholds or cut-points for clinically important changes are typically sparsely reported. [L-N]

Formulating and grading recommendations using GRADE methods

Following the meta-analytical pooling, the GRADE evidence tables per PICO question were developed by the methods team and shared with the co-chairs and panel members for review. Using an iterative consensus process conducted face to face, and via teleconference, final evidence and GRADE certainty ratings were presented to the complete panel for concurrence and recommendations were formulated. This iterative process continued until the panel members and co-chairs agreed on the final text/content of the recommendations (along with the certainty rating and strength/direction of recommendation).

GRADE rates the certainty (also known as quality or confidence) in effect estimates for benefits and harms as high, moderate, low or very low [B-D, O] and the overall certainty is based on the lowest confidence of the outcomes critical for decision making. Recommendations are classified as strong (desirable consequences clearly do or do not outweigh undesirable consequences) or conditional (the balance of desirable and undesirable consequences is less certain).[P] Alternative designations are conditional, discretionary, or contingent recommendations.

A strong recommendation was made for an intervention when, following deliberations, the panel was certain that the desirable consequences of the intervention outweigh the undesirable consequences, likewise a strong recommendation would have been made against a proposed intervention if the panel was certain that the undesirable consequences of the intervention outweigh the desirable consequences. A strong recommendation indicates that almost all well-informed patients would choose to have or not to have the intervention. A conditional recommendation was made for an intervention when the panel was uncertain whether the desirable consequences of the intervention outweigh the undesirable consequences, likewise a conditional recommendation would have been made against a proposed intervention if the panel was uncertain that the undesirable consequences of the intervention outweigh the desirable consequences. Reasons for a conditional recommendation and thus uncertainty included low or very low quality of evidence, or the desirable and undesirable consequences being finely balanced, with underlying values and preferences playing an important role.

GRADE guidance requires the certainty/quality of evidence is rated per outcome in an evidence table based on the body of evidence informing the outcome. The overall certainty of the evidence for a recommendation is based on the lowest certainty from among the critical outcomes in the GRADE evidence table..

Values and preference considerations

Optimally, guidelines should have patient representatives informing the values and preference (VPs) considerations or if not available, be supported by literature evidence. A reasonable alternative, used by our panel, was to infer patient VPs via input from the panel clinicians who interact with patients in clinical decision making.

From evidence to recommendations using an evidence-to-decision (EtD) framework

The panel, with the input from the co-chairs and methods team, used the structured, explicit, and transparent GRADE EtD framework [A15] to move from evidence to recommendations for all six guideline questions. The following four GRADE criteria were used to guide the approach to each PICO question: i) overall certainty of evidence ii) the balancing of the benefits (desirable outcomes) and harms (undesirable outcomes) to establish net benefit (or harm) iii) patient values and preferences and iv) other considerations such as costs, cost-effectiveness, burden of use to patients, resources, feasibility, acceptability, implementation, and health-equality.

Conflict of Interest management and disclosure

Ms. Kimberly Lawrence and Dr. Kevin Wilson assisted the co-chairs, methods team, and panel in logistics and conflict of interest (COI) Management. All prospective panelists were required to disclose any actual, potential, or perceived COI prior to being placed on the panel. Both co-chairs and at least 50% of the panel were required to be free from conflicts of interest. Individuals with potential conflicts of interest could take part in the discussions about the evidence but could not participate in the formulation of recommendations.

Manuscript preparation

The initial draft of the manuscript was prepared by the co-chairs and methodology team. The panel members were then invited to contribute expert content, which was collated and edited by the co-chairs. The final guideline manuscript draft was reviewed, edited and approved by all panel members prior to submission.

References

https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf

A. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing question and deciding on important outcomes. ***J Clin Epidemiol*** **2011; 64: 395–400.**

B. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. ***J Clin Epidemiol.*** ***2011*** **Apr;64(4):383-94. doi: 10.1016/j.jclinepi.2010.04.026. Epub 2010 Dec 31.**

C. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. ***BMJ.*** **2008; 336(7650):924-6.**

D. Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, Rind D, Montori V, Brito Campana JP, Norris S, Elbarbary M, Post P, Nasser M,Shukla V, Jaeschke R, Brozek J, Djulbegovic B, Guyatt G. GRADE guidelines 15: Going from evidence to recommendation-determinants of a recommendation's directionand strength. ***J Clin Epidemiol.*** **2013 pii: S0895-4356(13)00054-1. doi: 10.1016/j.jclinepi.2013.02.003.**

E. Likert scales. url: https://www.simplypsychology.org/likert-scale.html (accessed on July 3rd 2019).

F. Cochrane Risk of Bias Tool. url: http://handbook-5-1.cochrane.org/chapter_8/8_5_the_cochrane_collaborations_tool_for_assessing_risk_of_bias.htm (accessed on July 4th 2019).

G. Risk of Bias in cohort studies. CLARITY Group at McMaster university. url: https://www.evidencepartners.com/wp-content/uploads/2017/09/Tool-to-Assess-Risk-of-Bias-in-Cohort-Studies.pdf (accessed on July 3rd 2019) and Evidence Partners. url: https://www.evidencepartners.com/resources/methodological-resources/

H. RevMan 5. Cochrane. url: https://community.cochrane.org/help/tools-and-software/revman-5 (accessed on July 4th 2019).

I. Schunemann HJ, Jaeschke R, Cook DJ, et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. ***Am J Respir Crit Care Med*** **2006; 174: 605–614.**

J. GRADEpro. McMaster University. url: https://gradepro.org/ (accessed on July 3rd 2019).

K. Houchen-Wolloff L, Evans RA. Unravelling the mystery of the 'minimum important difference' using practical outcome measures in chronic respiratory disease. ***Chron Respir Dis.*** **2019 Jan-Dec; 16:1479973118816491. doi: 10.1177/1479973118816491.**

L. Wedzicha JA Ers Co-Chair, Miravitlles M, Hurst JR, Calverley PM, Albert RK, Anzueto A, Criner GJ, Papi A, Rabe KF, Rigau D, Sliwinski P, Tonia T, Vestbo J, Wilson KC, Krishnan JA Ats Co-Chair. Management of COPD exacerbations: an European Respiratory Society/American Thoracic Society guideline. ***Eur Respir J.*** **2017 Mar 15;49(3). pii: 1600791. doi: 10.1183/13993003.00791-2016. Print 2017 Mar.**

M. National Institute for Health and Clinical Excellence. Chronic obstructive pulmonary disease: management of chronic pulmonary obstructive disease in adults in primary and secondary care (partial update). London, National Clinical Guideline Centre, 2004.

N. Jones PW, Beeh KM, Chapman KR, et al. Minimal clinically important differences in pharmacological trials. ***Am J Respir Crit Care Med*** **2014; 189: 250–255.**

O. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. ***J Clin Epidemiol.*** **2011; 64(4):401-6. doi: 10.1016/j.jclinepi.2010.07.015. Epub 2011 Jan 5.**

P. Brozek JL, Akl EA, Alonso-Coello P, Lang D, Jaeschke R, Williams JW, Phillips B, Lelgemann M, Lethaby A, Bousquet J, Guyatt GH, Schünemann HJ; GRADEWorking Group. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. ***Allergy.*** **2009;64(5):669-77. doi: 10.1111/j.1398-9995.2009.01973.x.**

Q. Celli B, Crater G, Kilbride S, Mehta R, Tabberer M, Kalberg CJ, Church A. Once-daily umeclidinium/vilanterol 125/25 mcg in COPD: a randomized, controlled study. ***Chest.*** **2014 May;145(5):981-991. doi: 10.1378/chest.13-1579.**

R. Tashkin DP, Donohue JF, Mahler DA, Huang H, Goodwin E, Schaefer K, Hanrahan JP, Andrews WT. Effects of arformoterol twice daily, tiotropium once daily, and their combination in patients with COPD. ***Respir Med.*** **2009 Apr;103(4):516-24. doi: 10.1016/j.rmed.2008.12.014. Epub 2009 Feb 8.**

S. Mahler DA, Kerwin E, Ayers T, FowlerTaylor A, Maitra S, Thach C, Lloyd M, Patalano F, Banerji D. FLIGHT1 and FLIGHT2: Efficacy and Safety of QVA149 (Indacaterol/Glycopyrrolate) versus Its Monocomponents and Plac ebo in Patients with Chronic ObstructivePulmonary Disease. ***Am J Respir Crit Care Med.*** **2015 Nov 1;192(9):1068-79. doi: 10.1164/rccm.201505-1048OC.**

T. Maltais F, Singh S, Donald AC, Crater G, Church A, Goh AH, Riley JH. Effects of a combination of umeclidinium/vilanterol on exercise endurance in patientswith chronic obstructive pulmonary disease: two randomized, double-blind clinical trials. ***Ther Adv Respir Dis.*** **2014 Dec;8(6):169-81. doi: 10.1177/1753465814559209.**

U. D'Urzo A, Rennard S, Kerwin E, Donohue JF, Lei A, Molins E, Leselbaum A. A randomised double-blind, placebo-controlled, long-term extension study of the efficacy, safety and tolerability of fixed-dose combinations of aclidinium/formoterol or monotherapy in the treatment of chronic obstructive pulmonary disease. ***Respir Med.*** **2017 Apr; 125:39-48. doi: 10.1016/j.rmed.2017.02.008. Epub 2017 Feb 16.**

V. Singh D, Jones PW, Bateman ED, Korn S, Serra C, Molins E, Caracta C, Gil EG, Leselbaum A. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-

dose combinationscompared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. ***BMC Pulm Med.*** **2014 Nov 18;14:178. doi: 10.1186/1471-2466-14-178.**

W. Martinez FJ, Rabe KF, Ferguson GT, Fabbri LM, Rennard S, Feldman GJ, Sethi S, Spangenthal S, Gottschlich GM, Rodriguez-Roisin R, Arora S, Siler TM, Siddiqui S, Darken P, Fischer T, Maes A, Golden M, Orevillo C, Reisner C. Efficacy and Safety of Glycopyrrolate/Formoterol Metered Dose Inhaler FormulatedUsing Co-Suspension Delivery Technology in Patients With COPD. ***Chest.*** **2017 Feb;151(2):340-357. doi: 10.1016/j.chest.2016.11.028. Epub 2016 Dec 1.**

X. Hanania NA, Tashkin DP, Kerwin EM, Donohue JF, Denenberg M, O'Donnell DE, Quinn D, Siddiqui S, Orevillo C, Maes A, Reisner C. Long-term safety and efficacy of glycopyrrolate/formoterol metered dose inhaler using novel Co-Suspension™ Delivery Technology in patients with chronic obstructive pulmonary disease. ***Respir Med.*** **2017 May; 126:105-115. doi: 10.1016/j.rmed.2017.03.015. Epub 2017 Mar 12.**

Y. Donohue JF, Soong W, Wu X, Shrestha P, Lei A. Long-term safety of aclidinium bromide/formoterol fumarate fixed-dose combination: Results of a randomized 1-year trial in patients with COPD. ***Respir Med.*** **2016 Jul; 116:41-8. doi: 10.1016/j.rmed.2016.05.007. Epub 2016 May 7.**

Z. Maleki-Yazdi MR, Kaelin T, Richard N, Zvarich M, Church A.
Efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary dise ase: results of a 24-week, randomized, controlled trial. ***Respir Med.*** **2014 Dec;108(12):1752-60.**

A1. Singh D, Ferguson GT, Bolitschek J, Grönke L, Hallmann C, Bennett N, Abrahams R, Schmidt O, Bjermer L. Tiotropium + olodaterol shows clinically meaningful improvements in quality of life. ***Respir Med.*** **2015 Oct;109(10):1312-9. doi: 10.1016/j.rmed.2015.08.002. Epub 2015 Aug 12.**

A2. Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G, Fležar M, Hébert J, McGarvey L, Pizzichini E, Reid J, Veale A, Grönke L, Hamilton A, Korducki L, Tetzlaff K, Waitere-Wijker S, Watz H, Bateman E.
Tiotropium and olodaterol fixeddose combination versus mono-components in COPD (GOLD 2-4). ***Eur Respir J.*** **2015 Apr;45(4):969-79. doi: 10.1183/09031936.00136014. Epub 2015 Jan 8.**

A3. Bateman ED, Ferguson GT, Barnes N, Gallagher N, Green Y, Henley M, Banerji D.
Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. ***Eur Respir J.*** **2013 Dec;42(6):1484-94. doi: 10.1183/09031936.00200212. Epub 2013 May 30.**

A4. Wedzicha JA, Decramer M, Ficker JH, Niewoehner DE, Sandström T, Taylor AF, D'Andrea P, Arrasate C[6], Chen H, Banerji D. Analysis of chronic obstructive pulmonary disease exacerbations with the dualbronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. ***Lancet Respir Med.*** **2013 May;1(3):199-209. doi: 10.1016/S2213-2600(13)70052-3. Epub 2013 Apr 23.**

A5. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, Balter M, O'Donnell D, McIvor A, Sharma S, Bishop G, Anthony J, Cowie R, Field S, Hirsch A, Hernandez P, Rivington R, Road J, Hoffstein V, Hodder R, Marciniuk D, McCormack D, Fox G, Cox G, Prins HB, Ford G, Bleskie D, Doucette S, Mayers I, Chapman K, Zamel N, FitzGerald M; Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium.
Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. ***Ann Intern Med.*** **2007 Apr 17;146(8):545-55. Epub 2007 Feb 19.**

A6. Kerwin EM, Kalberg CJ, Galkin DV, Zhu CQ, Church A, Riley JH, Fahy WA. Umeclidinium/vilanterol as step-up therapy from tiotropium in patients with moderateCOPD: a randomized, parallel-group, 12-week study. ***Int J Chron Obstruct Pulmon Dis.*** **2017 Feb 24;12:745-755. doi: 10.2147/COPD.S119032. eCollection 2017.**

A7. Ferguson GT, Taylor AF, Thach C, Wang Q, Schubert-Tennigkeit AA, Patalano F, Banerji D. Long-Term Maintenance Bronchodilation With Indacaterol/Glycopyrrolate VersusIndacaterol in Moderate-to-Severe COPD Patients: The FLIGHT 3 Study. ***Chronic Obstr Pulm Dis.*** **2016 Aug 18;3(4):716-728. doi: 10.15326/jcopdf.3.4.2016.0131.**

A8. Donohue JF, Maleki-Yazdi MR, Kilbride S, Mehta R, Kalberg C, Church A. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. ***Respir Med.*** **2013 Oct;107(10):1538-46. doi: 10.1016/j.rmed.2013.06.001. Epub 2013 Jul 2.**

A9. Vogelmeier C, Kardos P, Harari S, Gans SJ, Stenglein S, Thirlwell J. Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6-month study. ***Respir Med.*** **2008 Nov;102(11):1511-20. doi: 10.1016/j.rmed.2008.07.020. Epub 2008 Sep 19.**

A10. ZuWallack R, Allen L, Hernandez G, Ting N, Abrahams R. Efficacy and safety of combining olodaterol Respimat(®) and tiotropium HandiHaler(®) in patients with COPD: results of two randomized, double-blind, active-controlled studies. ***Int J Chron Obstruct Pulmon Dis.*** **2014 Oct 14;9:1133-44. doi: 10.2147/COPD.S72482. eCollection 2014.**

A11. Vincken W, Aumann J, Chen H, Henley M, McBryan D, Goyal P. Efficacy and safety of coadministration of once-daily indacaterol and glycopyrroniumversus indacaterol alone in COPD patients: the GLOW6 study. ***Int J Chron Obstruct Pulmon Dis.*** **2014 Feb 24;9:215-28. doi: 10.2147/COPD.S51592. eCollection 2014.**

A12. Calverley PMA, Anzueto AR, Carter K, Grönke L, Hallmann C, Jenkins C, Wedzicha J, Rabe KF. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial. ***Lancet Respir Med.*** **2018 May;6(5):337-344. doi: 10.1016/S2213-2600(18)30102-4. Epub 2018 Apr 5.**

A13. Decramer M, Anzueto A, Kerwin E, Kaelin T, Richard N, Crater G, Tabberer M, Harris S, Church A. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. ***Lancet Respir Med.*** **2014 Jun;2(6):472-86. doi: 10.1016/S2213-2600(14)70065-7. Epub 2014 May 14.**

A14. Mahler DA, D'Urzo A, Bateman ED, Ozkan SA, White T, Peckitt C, Lassen C, Kramer B; INTRUST-1 and INTRUST-2 study investigators. Concurrent use of indacaterol plus tiotropium in patients with COPD provides superiorbronchodilation compared with tiotropium alone: a randomised, double-blind comparison. ***Thorax.*** **2012 Sep;67(9):781-8. Epub 2012 Apr 27.**

A15. Li SA, Alexander PE, Reljic T, Cuker A, Nieuwlaat R, Wiercioch W, Guyatt G, Schünemann HJ, Djulbegovic B. Evidence to Decision framework provides a structured "roadmap" for making GRADE guidelines recommendations. ***J Clin Epidemiol.*** **2018 Dec;104:103-112. doi: 10.1016/j.jclinepi.2018.09.007. Epub 2018 Sep 22.**