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JOURNAL CLUB

Article Summary by: James Woodrow, MD

ARTICLE

Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate to Very Severe COPD (ETHOS Trial) N England J Med 2020; 383:35-48. https://www.nejm.org/doi/full/10.1056/NEJMoa1916046.

CLINICAL QUESTION

Which COPD patients benefit from triple inhaled therapy?

SUMMARY

This was an international randomized, double blind, parallel group trial. Subjects had symptomatic COPD defined by CAT score ≥ 10, FEV1/FVC < 70%, and Post Bronchodilator FEV1 25-65% predicted with at least a ten pack year smoking history. A history of exacerbations within the preceding year despite the use of at least two inhaled maintenance therapies, was required. Only one exacerbation was required if FEV1 was < 50%. Two moderate or one severe exacerbation was acceptable if FEV1>50%. Study drugs included high dose budesonide (HD-ICS), low dose budesonide (LD-ICS), glycopyrrolate (LAMA), and formoterol (LABA). Subjects were randomized into one of four groups: HD-ICS/LAMA/LABA; LD-ICS/LAMA/LABA; LAMA/LABA; and ICS/LABA. The primary end point of annual rate of exacerbation (moderate to severe). Data were collected over a 52-week period.

A total of 8573 patients underwent randomization and received a study drug. Annual rate of exacerbations was lower for both HD-ICS/LAMA/LABA and LD-ICS/LAMA/LABA (triple therapy) groups compared to either ICS/LABA or LAMA/LABA (dual therapy) groups. There was no difference between the high versus low dose triple therapy groups. The high dose triple therapy group outperformed dual therapy groups with regard to secondary endpoints including time to first exacerbation, rate of severe exacerbations, and mortality. Comparison between low dose ICS triple therapy groups and dual therapy groups with regard to these secondary endpoints was more equivocal. Incidence of pneumonia was 3.5-4.5% among subjects whose regimen included an ICS whereas incidence among patient receiving only bronchodilators was 2.3%. Benefits of triple therapy versus LAMA/LABA were significant regardless of eosinophil count (over/under 150cell/mcl) but the benefit was more pronounced in the higher eosinophils group.

Comparison	Reduction in annual rate of exacerbations
HD triple v. LABA/LAMA	24%
LD triple v LABA/LAMA	25%
HD triple v. ICS/LABA	13%
LD triple v. ICS/LABA	14%

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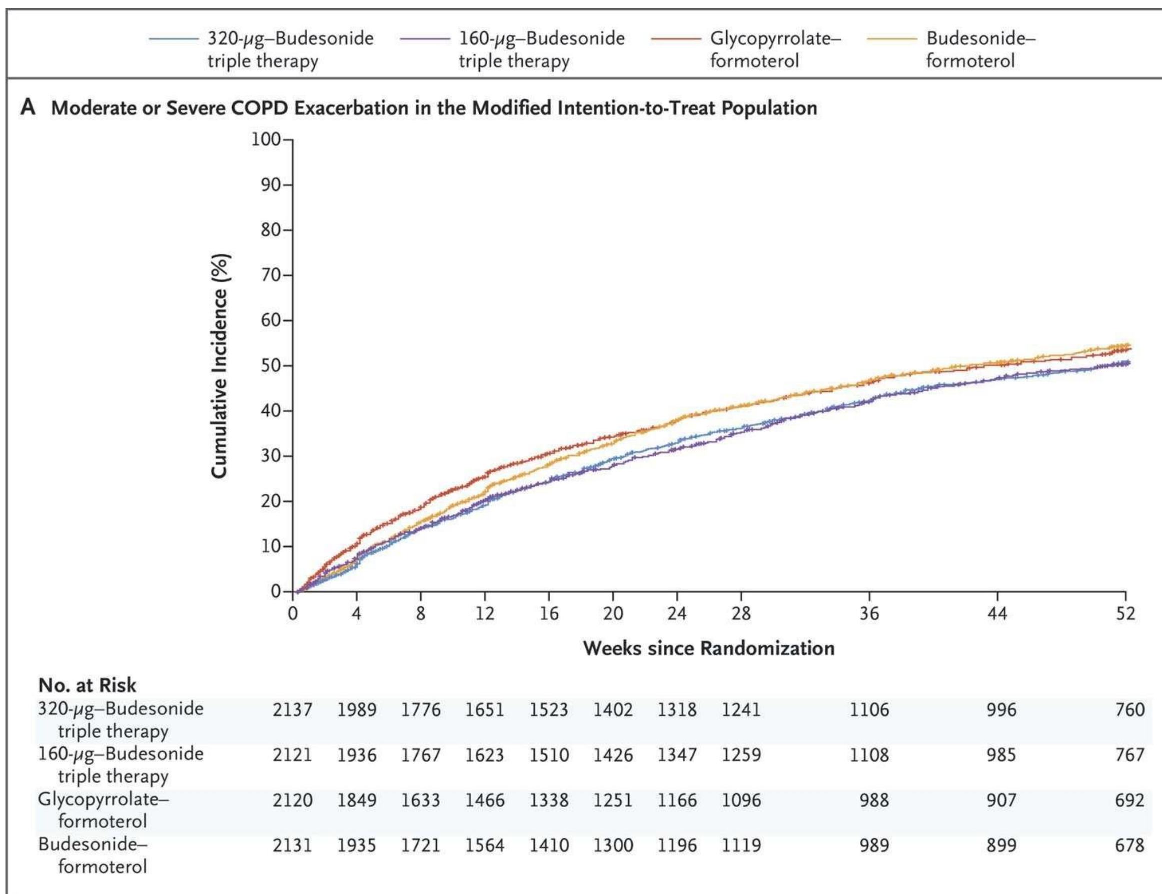

GROUP OPINION

COPD clinic providers discussed this and prior studies (IMPACT, TRILOGY, TRIBUTE Trials) that show a benefit of triple over dual therapy for COPD patients in terms of exacerbation prevention. There was consensus that patients who continue to have exacerbations despite two maintenance controller medications should be started on triple therapy regardless of peripheral eosinophil count. There was not consensus regarding high versus low ICS dose. Secondary endpoints in the current study seem to favor high dose budesonide but the whole of the evidence is not definitive. There was also consensus that discontinuation of ICS should be considered after a year without exacerbations. The ultimate decision to withdraw the ICS should be made based on exacerbation severity, peripheral eosinophilia, risk of pneumonia, and patient preference / shared decision making.

On behalf of the COPD Physicians: Ronald Balkissoon, MD; Russell Bowler, MD, PhD; James Crapo, MD; James Finigan, MD; Anthony Gerber, MD, PhD; Nir Goldstein, MD; Ann Granchelli, MD; Vamsi Guntur, MD; Patrick Hume, MD; Gabriel Lockhart, MD; Steven Lommatzsch, MD; Barry Make, MD; Irina Petrache, MD; Robert Sandhaus, MD, PhD; Karina Serban, MD; Amgen Sergew, MD; James Woodrow, MD

COPD Journal Club dates and times njhealth.org/COPDJournalClub

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