Personalising add-on treatment with inhaled corticosteroids in patients with chronic obstructive pulmonary disease: a benefit–harm modelling study

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Summary

Background Since the benefit–harm balance of adding inhaled corticosteroids to long-acting β2-agonists (LABA) and long-acting muscarinic antagonists (LAMA) for patients with chronic obstructive pulmonary disease is unclear, we evaluated this addition for a range of patient profiles.

Methods Analyses considered the effects of low-to-moderate doses of inhaled corticosteroids, LABA, and LAMA compared with LABA and LAMA alone, outcome incidences, and preference weights assigned to averted moderate-to-severe exacerbations (benefit) and severe pneumonia, candidiasis, and dysphonia (harm). Using exponential models, we estimated the preference weight-adjusted 2-year net clinical benefit (ie, benefits outweighing harms) indices. Exacerbation risk thresholds for triggering inhaled corticosteroids, LABA, and LAMA were established when the probability of a 2-year net clinical benefit reached 60%. We estimated the proportion of patients benefiting from added inhaled corticosteroids using an externally validated prediction model for acute exacerbations in primary care.

Findings Adding low-to-moderate dose inhaled corticosteroids to LABA and LAMA provided a net clinical benefit in patients with a 2-year baseline exacerbation risk of 54–83%. Low-dose inhaled corticosteroids showed a net clinical benefit if the baseline risk was 40–91%, but not at higher doses. The benefit was modified by blood eosinophil count (BEC) and age. Although no net benefit was associated with a BEC of less than 150 cells per µL, patients with a BEC of 150 cells per µL or more had a net benefit from low-dose inhaled corticosteroids with a 2-year exacerbation risk of 32–95% in those aged 40–79 years and 41–93% in those older than 80 years. A moderate dose of inhaled corticosteroids showed a net benefit in patients younger than 80 years with a BEC of 150 cells per µL or more at 52–86% 2-year exacerbation risk. Depending on the subgroups, the proportion of patients with a net benefit from added inhaled corticosteroids ranged from 0 to 68%.

Interpretation The net clinical benefit of adding different inhaled corticosteroid doses to LABA and LAMA varies greatly with exacerbation risk, BEC, and age. Personalised treatment decisions based on these factors and predicted exacerbation risks might reduce overtreatment and undertreatment with inhaled corticosteroids.

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Introduction

Inhaled corticosteroids are commonly used in combination with long-acting β2-agonists (LABA) and long-acting muscarinic antagonists (LAMA) to prevent moderate-to-severe exacerbations in patients with chronic obstructive pulmonary disease (COPD).1 The 2020 American Thoracic Society (ATS) evidence-based guideline on COPD drug treatments issued a conditional recommendation to add inhaled corticosteroids to LABA and LAMA in patients with a history of one or more exacerbations in the past year, requiring antibiotics or oral steroids, or admission to and treatment in hospital.1 With a conditional recommendation, clinicians are advised not to pursue a treat-all strategy but seek a treatment decision that is consistent with the patient’s characteristics, values, and preferences. This decision can be challenging because of the interplay of several factors contributing to the risk of exacerbations, harm outcomes, and patient preferences.1,4 Processing all relevant factors might be cognitively overwhelming for both patients and clinicians, and unless a more systematic approach is taken, there is a risk of overtreatment or undertreatment with inhaled corticosteroids.

To the best of our knowledge, a systematic and quantitative benefit–harm assessment of inhaled corticosteroids, LABA, and LAMA has never been done. We consider it is an ideal time to do so, since additional evidence has become available from recent (published since 2018) randomised controlled trials (RCTs) and observational studies on the benefit and harm of added inhaled corticosteroids, but also on the treatment-modifying effect of blood eosinophil counts (BEC).2,4,7 Therefore, our study aimed to: (1) quantitatively assess the net clinical benefit of triple therapy with inhaled corticosteroids, LABA, and LAMA compared with dual
therapy with LABA and LAMA for the prevention of moderate-to-severe exacerbations against the harms of severe pneumonia, oropharyngeal candidiasis, and dysphonia; (2) establish the exacerbation risk thresholds, above which the benefits outweigh the harms; and (3) assess the influence of risk thresholds by estimating the proportion of patients who benefit from adding inhaled corticosteroids to their treatment.

Methods

Study design and participants

The target population of this modelling study was patients with COPD at risk of moderate-to-severe exacerbations. Triple therapy with inhaled corticosteroids, LABA, and LAMA was compared with dual therapy with LABA and LAMA. Low (<500 μg fluticasone-equivalent) to moderate (500 to <1000 μg fluticasone-equivalent) inhaled corticosteroid doses combined and stratified as low, moderate, and high (1000 μg or more) daily doses were considered, with high doses considered in a sensitivity analysis.

Benefit and harm outcomes

In the main analysis, we considered the benefit in terms of a reduced risk of moderate-to-severe exacerbations and the harm due to increased risk of severe pneumonia, oropharyngeal candidiasis, and dysphonia (and skin bruising in high doses only). We used an event-based definition of exacerbations as those for which patients required an unscheduled doctor or emergency room visit requiring oral antibiotic or corticosteroid therapy (moderate) or a hospital admission (severe). We defined severe pneumonia as requiring a hospital admission. Outcomes described in observational studies but not reported in RCTs, such as the onset or progression of diabetes, cataract, and fractures, were included in a sensitivity analysis. All-cause mortality was considered a competing risk.

Data sources

Relative effect estimates

We reviewed the availability and examined the applicability of treatment effect estimates for the chosen outcomes. We considered the systematic review by Nici and colleagues, which served as an evidence base for the ATS guideline, to provide the most up-to-date and valid estimates for moderate-to-severe exacerbations and severe pneumonia sourced from RCTs—namely IMPACT, KRONOS, Aaron and colleagues, and TRIBUTE. This particular review did not comprise all outcomes chosen a priori. We thus reviewed eight RCTs and summarised estimates using a pairwise meta-analysis, particularly for oropharyngeal candidiasis, dysphonia, and skin bruising, to inform our study. Although the main sources of estimates were RCTs, we also included estimates from observational data in sensitivity analyses, mainly on the harm outcomes of candidiasis and severe pneumonia, for which RCTs are often underpowered (table 1, appendix pp 3–4).

Research in context

Evidence before this study

We searched PubMed on April 4, 2021 for studies published in English using the search terms "inhaled corticosteroids", "ICS", "fluticasone", "budesonide", "beclometasone", "flunisolide", "benefit–harm", "risk–benefit", "cost-effectiveness", "COPD", and "chronic obstructive pulmonary disease". The search resulted in 89 publications. Of these, 56 were cost-effectiveness analyses and 29 were systematic reviews or other types of studies. Although many of the cost-effectiveness analyses were on other forms of long-acting bronchodilator and inhaled corticosteroid combinations, two analyses were on triple therapy with inhaled corticosteroids, long-acting β-agonists (LABA), and long-acting muscarinic antagonists (LAMA) versus dual therapy with LABA and LAMA. Both cost-effectiveness analyses measured quality-adjusted life-years, cost per quality-adjusted life-year, or cost per exacerbation avoided. They did not stratify the outcomes by patient risk spectrum or other granular patient subgroups that would help for personalised treatment decisions. We also found four studies related to benefit–harm assessments. All four were reviews of benefits and harm outcomes, but none of the studies did a quantitative benefit–harm assessment of adding inhaled corticosteroids to LABA and LAMA.

Added value of this study

This is the first study to quantitatively estimate the benefit–harm balance of low-to-moderate doses of inhaled corticosteroids combined with LABA and LAMA, and to identify predictors of net clinical benefit. Identified predictors included the 2-year risk of exacerbations, blood eosinophil counts, and age. On the basis of these predictors and a prognostic model for exacerbations that we additionally validated in a two-country cohort of patients with chronic obstructive pulmonary disease, the proportion of patients who would benefit from inhaled corticosteroids, LABA, and LAMA triple therapy was 68% in the best-case scenario of subgroup combinations.

Implications of all the available evidence

The absence of a personalised approach for adding inhaled corticosteroids to LABA and LAMA probably leads to overtreatment and undertreatment with inhaled corticosteroids. The predictors of the net clinical benefit identified here together with a model for predicting the risk of exacerbations of individuals help to personalise the decision to initiate additional inhaled corticosteroids therapy, thereby increasing the benefit and reducing overtreatment or undertreatment in patients with chronic obstructive pulmonary disease.
Baseline incidence of events

Event incidences in the population with COPD given LABA and LAMA only were used as the baseline to extrapolate the absolute effects of inhaled corticosteroids, LABA, and LAMA. Most recommendations for inhaled corticosteroids depend on the risk of exacerbations. Instead of taking a single average risk, we thus considered all possible 2-year risks that individual patients might have (ie, from 0 to 100%). However, we took the average risks for severe pneumonia, oropharyngeal candidiasis, and all-cause mortality from large population-based COPD studies and dysphonia from the control groups of RCTs, because no observational data on these outcomes were available (table 2, appendix pp 5–7).

Preference weights

The preference weights represent the relative importance (or seriousness) of outcomes, for which a higher value means that patients have a stronger preference to avoid the outcome. Empirically established preference weights, for example by preference-elicitation surveys,
extensively elsewhere, but we have also included some details in the appendix (p 8). In brief, we assumed that the risk of having events related to inhaled corticosteroids was constant over a 2-year period. Cumulative risk of having a benefit or harm event was calculated with a probabilistic exponential model in a theoretical cohort of 1000 patients with COPD given LABA and LAMA. The cumulative risk of the outcomes was again calculated for the same cohort size receiving inhaled corticosteroids, LABA, and LAMA. The risk difference of the outcomes was then calculated from the aforementioned two estimations of cumulative risk with and without inhaled corticosteroids and individually weighted on the basis of patient preferences towards the outcomes. The weighted risk differences of the outcomes were interpreted as a net–harm balance index or a net clinical benefit. The index shows whether the benefits outweighed the harms (positive index) or vice versa (negative index), or whether neither benefits nor harms outweighed the other (index equals zero). The analysis was done stochastically with 100 000 repetitions accounting for the statistical uncertainty of the input estimates to generate a distribution of the net clinical benefit. From the distribution, we calculated the probability that patients given inhaled corticosteroids, LABA, and LAMA would have a net benefit compared with those given LABA and LAMA. Triple therapy was considered to be net beneficial when the probability of net benefit was 60% or above. Thus, the 2-year baseline risk of exacerbations corresponding to the 60% probability was defined as the risk threshold, above which the benefits of triple therapy outweigh its harms. We chose 60% (instead of 50%, a threshold at which expected incremental net benefit is zero) since, when taking a more intensive treatment, it is sensible to be slightly risk averse. We defined more than 40% to less than 60% as an uncertainty zone in which decisions needed to be made with greater caution. Probabilities of less than 40% were interpreted as a net harm. We did the benefit–harm analysis according to age, sex, and BEC, and stratified by inhaled corticosteroids type and dose, when data allowed.

Finally, we calculated the proportion of patients in the Dutch and Swiss primary care COPD cohort (International Collaborative Effort on Chronic Obstructive Lung Disease: Exacerbation Risk Index Cohorts [ICE COLD ERIC]) that would benefit from triple therapy.

This calculation required a prediction model for exacerbations to estimate the 2-year risk for each patient and to see whether the risk is more than the thresholds of a net benefit. The model by Bertens and colleagues is one of few that allows for estimating the risk of exacerbations in primary care settings. Since we needed to ensure that this model worked well in patients of the ICE COLD ERIC cohort, we first did an external validation of the prediction model, in which we identified the need for a minor

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Figure 1: Probability of a net clinical benefit across a 2-year baseline risk of exacerbations

The horizontal line indicates a 60% predefined probability threshold for a net clinical benefit. (A) Low-to-moderate inhaled corticosteroid dose. (B) Low (<500 μg), moderate (500 to <1000 μg), and high (≥1000 μg) daily doses of inhaled corticosteroids. Doses are adjusted to be equivalent to fluticasone-equivalent doses. (C) Blood eosinophils counts (≥150 cells µL and <150 cells µL) by low (<500 μg) or moderate (500 to <1000 μg) doses of inhaled corticosteroids. Doses are adjusted to be equivalent to fluticasone-equivalent doses. (D) 40–59, 60–79, and ≥80 years treated with low-to-moderate inhaled corticosteroid dose.

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Statistical analysis

A 2-year horizon was used to estimate the cumulative risk of benefit and harm outcomes in patients with COPD. We used the modelling approach by Gail and colleagues, which has been applied in various preventive and therapeutic treatments. The model is described extensively elsewhere, but we have also included some details in the appendix (p 8). In brief, we assumed that the risk of having events related to inhaled corticosteroids was constant over a 2-year period. Cumulative risk of having a benefit or harm event was calculated with a probabilistic exponential model in a theoretical cohort of 1000 patients with COPD given LABA and LAMA. The cumulative risk of the outcomes was again calculated for the same cohort size receiving inhaled corticosteroids, LABA, and LAMA. The risk difference of the outcomes was then calculated from the aforementioned two estimations of cumulative risk with and without inhaled corticosteroids and individually weighted on the basis of patient preferences towards the outcomes. The weighted risk differences of the outcomes were interpreted as a net–harm balance index or a net clinical benefit. The index shows whether the benefits outweighed the harms (positive index) or vice versa (negative index), or whether neither benefits nor harms outweighed the other (index equals zero). The analysis was done stochastically with 100 000 repetitions accounting for the statistical uncertainty of the input estimates to generate a distribution of the net clinical benefit. From the distribution, we calculated the probability that patients given inhaled corticosteroids, LABA, and LAMA would have a net benefit compared with those given LABA and LAMA. Triple therapy was considered to be net beneficial when the probability of net benefit was 60% or above. Thus, the 2-year baseline risk of exacerbations corresponding to the 60% probability was defined as the risk threshold, above which the benefits of triple therapy outweigh its harms. We chose 60% (instead of 50%, a threshold at which expected incremental net benefit is zero) since, when taking a more intensive treatment, it is sensible to be slightly risk averse. We defined more than 40% to less than 60% as an uncertainty zone in which decisions needed to be made with greater caution. Probabilities of less than 40% were interpreted as a net harm. We did the benefit–harm analysis according to age, sex, and BEC, and stratified by inhaled corticosteroids type and dose, when data allowed.

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model update (appendix), and subsequently estimated the proportion of patients with COPD who would benefit from the additional inhaled corticosteroids (appendix p 10). All analyses were done in R (version 4.0.2).

Sensitivity analysis
We examined the sensitivity of the net clinical benefit to different preference weights and to baseline incidences for the harm outcomes. We also assessed the effect of estimates from observational data on harm outcomes and types of inhaled corticosteroids, as well as the outcomes of additional harms (particularly diabetes and fracture).

This study was done in accordance with the consolidated standards of reporting quantitative benefit-risk models applied to vaccines guidelines.32

Role of the funding source
There was no funding source for this study.

Results
Figure 1A shows the probability that a patient has a net clinical benefit as a function of their 2-year predicted risk of at least one moderate-to-severe exacerbation (appendix p II). Weighing the risk of avoided exacerbations against the excess risk of harmful outcomes on

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### Table 3: Net clinical benefit and predicted risk of exacerbation over 2 years by 2-year baseline risk of moderate-to-severe exacerbations

| No ICS use | ICS use | RD | Weighted RD | Probability (%) of a net clinical benefit | Cumulative % of patients in the ICE COLD ERIC cohort whose 2-year predicted risk is less than or equal to the probability of net benefit (n=404) |
|-----------|---------|----|-------------|-----------------------------------------|--------------------------------------------------------------------------------------------------|
| 0%        | 0 (0 to 0) | 0 (0 to 0) | 0 (0 to 0) | -23 (-45 to -8) | 3.13 | 0 (0) |
| 4%        | 38 (35 to 42) | 27 (22 to 34) | -11 (-16.5 to -5) | -20 (-42 to -5) | 4.87 | 0 (0) |
| 8%        | 77 (70 to 85) | 55 (45 to 68) | -22 (-31 to -11) | -17 (-40 to -1) | 7.84 | 0 (0) |
| 12%       | 135 (105 to 127) | 83 (68 to 102) | -32 (-47 to -15) | -9 (-13 to -4) | 12.49 | 1 (0) |
| 16%       | 154 (141 to 168) | 112 (92 to 136) | -42 (-61 to -20) | -12 (-17 to -6) | 18.57 | 13 (0.03) |
| 20%       | 192 (176 to 210) | 141 (116 to 171) | -52 (-75 to -25) | -14 (-21 to -7) | 25.18 | 73 (0.18) |
| 24%       | 231 (212 to 252) | 170 (140 to 206) | -61 (-89 to -29) | -17 (-24 to -8) | 31.67 | 114 (0.28) |
| 28%       | 270 (248 to 293) | 200 (166 to 241) | -70 (-102 to -33) | -19 (-28 to -9) | 37.61 | 174 (0.43) |
| 32%       | 308 (284 to 334) | 231 (191 to 276) | -78 (-114 to -37) | -21 (-31 to -10) | 42.79 | 243 (0.6) |
| 36%       | 347 (320 to 375) | 261 (218 to 312) | -86 (-126 to -42) | -24 (-35 to -11) | 47.34 | 264 (0.65) |
| 40%       | 386 (357 to 416) | 293 (245 to 348) | -93 (-133 to -44) | -25 (-38 to -12) | 51.13 | 273 (0.67) |
| 44%       | 424 (394 to 456) | 325 (273 to 384) | -99 (-147 to -47) | -27 (-40 to -13) | 54.44 | 276 (0.68) |
| 48%       | 463 (431 to 496) | 358 (302 to 421) | -105 (-156 to -59) | -29 (-43 to -13) | 57.05 | 278 (0.68) |
| 52%       | 502 (469 to 536) | 392 (332 to 458) | -110 (-165 to -51) | -30 (-45 to -14) | 59.22 | 284 (0.7) |
| 56%       | 541 (507 to 576) | 426 (363 to 496) | -115 (-172 to -53) | -32 (-47 to -15) | 60.91 | 290 (0.71) |
| 60%       | 580 (545 to 615) | 462 (395 to 534) | -118 (-179 to -54) | -33 (-49 to -15) | 62.21 | 292 (0.72) |
| 64%       | 619 (584 to 655) | 498 (429 to 572) | -122 (-187 to -55) | -34 (-51 to -15) | 63.55 | 301 (0.74) |
| 68%       | 658 (623 to 693) | 536 (464 to 611) | -127 (-184 to -55) | -35 (-50 to -15) | 64.88 | 303 (0.74) |
| 72%       | 698 (663 to 732) | 575 (501 to 651) | -128 (-189 to -54) | -36 (-52 to -15) | 66.13 | 315 (0.75) |
| 76%       | 737 (703 to 770) | 616 (541 to 692) | -130 (-191 to -53) | -37 (-55 to -15) | 67.49 | 324 (0.76) |
| 80%       | 777 (744 to 807) | 659 (584 to 734) | -131 (-195 to -53) | -38 (-58 to -15) | 68.84 | 334 (0.77) |
| 84%       | 817 (787 to 844) | 705 (630 to 776) | -131 (-197 to -47) | -39 (-61 to -13) | 70.59 | 346 (0.78) |
| 88%       | 857 (830 to 881) | 755 (683 to 821) | -132 (-196 to -42) | -39 (-63 to -12) | 72.02 | 357 (0.79) |
| 92%       | 897 (876 to 917) | 810 (743 to 886) | -132 (-196 to -42) | -40 (-71 to -10) | 74.04 | 368 (0.80) |
| 96%       | 940 (925 to 952) | 875 (820 to 919) | -133 (-197 to -42) | -40 (-75 to -7) | 75.35 | 379 (0.81) |
| 100%      | 974 (967 to 979) | 942 (907 to 965) | -134 (-198 to -42) | -41 (-81 to -3) | 76.68 | 390 (0.82) |

Event risks with or without inhaled corticosteroids, long-acting β₂-agonists, and long-acting muscarinic antagonists triple therapy were estimated using an exponential model assuming constant exacerbation risk over 2 years, as explained in the methods. The difference of the outcome risks was calculated after adjustment for the preference weights of the individual outcomes. This was done stochastically to generate a distribution of the benefit-harm indices, from which the probability of a net clinical benefit was calculated. ICS=inhaled corticosteroid. RD=risk difference. *Proportion of patients from the Dutch and Swiss Chronic obstructive pulmonary disease cohort (ICE COLD ERIC) with 2-year predicted risk x the probability of net benefit.
the same scale, low-to-moderate doses of inhaled corticosteroids with LABA and LAMA showed a net clinical benefit in patients with a 2-year baseline risk of exacerbations between 54% and 83%. The rate of incremental net benefit increased at a decreasing rate up to the 2-year baseline risk of 72% and began to decrease. The proportion of patients in ICE COLD ERIC cohort with a baseline risk between the thresholds was 30%.

Tables 3 and 4 show a summary of a net clinical benefit and the expected events of each benefit and harm outcome. For example, consider 1000 patients with a predicted 2-year exacerbation risk of 28% given inhaled corticosteroids, LABA, and LAMA for 2 years. On average, 70 moderate-to-severe exacerbations would be averted compared with patients given LABA and LAMA only, but the patients would have an excess 21 cases of severe pneumonia, 86 of oropharyngeal candidiasis, and 36 of dysphonia. Applying the preference weights, this corresponds to avoiding 19 fatal-equivalent exacerbations, at the cost of 23 fatal-equivalent harm events per 1000 patients (ten pneumonia, nine oropharyngeal candidiasis, and four dysphonia; tables 3 and 4). This shows that patients with a 28% 2-year exacerbation risk are less likely to have a net clinical benefit from inhaled corticosteroids, LABA, and LAMA.

### Table 3: Predicted risk of harm outcomes over 2 years by 2-year baseline risk of moderate-to-severe exacerbations

| Event                  | No ICS use (RD) | ICS use (RD) | Weighted RD (RD) |
|------------------------|-----------------|--------------|------------------|
| Severe pneumonia       | 56 (43–72)      | 77 (52–114)  | 21 (1–50)        |
| Oropharyngeal candidiasis | 51 (45–58)      | 137 (84–217) | 86 (34–164)      |
| Dysphonia              | 19 (9–43)       | 56 (20–149)  | 36 (9–113)       |

Events per 1000 patients (2.5th and 97.5th percentiles). Event risks with or without inhaled corticosteroids, long-acting β2-agonists, and long-acting muscarinic antagonists triple therapy were estimated using an exponential model assuming constant exacerbation risk over 2 years. The difference of the outcome risks was calculated after adjustment for the preference weights of the individual outcomes. This was done stochastically to generate a distribution of the benefit–harm indices, from which the probability of a net clinical benefit was calculated. ICS=inhaled corticosteroid. RD=risk difference.

### Table 4: Predicted risk of harm outcomes over 2 years by 2-year baseline risk of moderate-to-severe exacerbations

| Event                  | No ICS use (2.5th and 97.5th centiles) | ICS use (2.5th and 97.5th centiles) | Weighted RD (2.5th and 97.5th centiles) |
|------------------------|----------------------------------------|-------------------------------------|----------------------------------------|
| Severe pneumonia       | 56 (43–72)                             | 77 (52–114)                         | 21 (1–50)                              |
| Oropharyngeal candidiasis | 51 (45–58)                             | 137 (84–217)                        | 86 (34–164)                            |
| Dysphonia              | 19 (9–43)                              | 56 (20–149)                         | 36 (9–113)                            |

### Figure 2: Summary of thresholds for a net clinical benefit of inhaled corticosteroids, LABA, and LAMA in patients with chronic obstructive pulmonary disease

BEC=baseline eosinophil count. LABA=long-acting β2-agonists. LAMA=long-acting muscarinic antagonists. *Proportion of patients who have a 2-year risk of exacerbations of more than or equal to the thresholds calculated in this study. †Proportion of patients who have had one or more exacerbations in the past year. ‡Average 2-year risk of exacerbations estimated using a prediction model by Bertens and colleagues. 10
corticosteroids, compared with those at a higher risk of exacerbations. For example, patients with a 68% 2-year exacerbation risk would expect to avoid 34 fatal-equivalent exacerbations in 1000 patients, while having a similar harm risk as above (23 fatal-equivalent harm events), and thus more benefits than harms. For this scenario, the risk without inhaled corticosteroids for harm outcomes was assumed to be the same regardless of an increased risk of exacerbations.

Dose and patient subgroups, including baseline exacerbation risk, BEC, and age, were important predictors of net benefit each independently, and even more so in combination. Low doses of inhaled corticosteroids showed a net clinical benefit at a 2-year exacerbation risk between 40% and 91% but not at higher doses, regardless of higher baseline risks (figure 1B). The benefit for patients with a BEC of less than 150 cells per µL was unlikely to outweigh harms at low and moderate, and at all exacerbation risks (figure 1C). Patients with baseline BEC of 150 cells per µL or more were more likely to have a net clinical benefit from low-to-moderate inhaled corticosteroid dose at 41–91% 2-year risk of exacerbations. Stratified by dose, patients with a BEC of 150 cells per µL or more would have a net clinical benefit from a low dose of inhaled corticosteroids at 32–95% baseline exacerbation risk in those aged 40–79 years and a 41–93% risk in those older than 80 years. Moderate-dose inhaled corticosteroids were also associated with a net benefit at baseline risks of 52–86% only in patients younger than 80 years with a BEC of 150 cells per µL or more. The thresholds for all subgroups are presented in the appendix (p 12).

Age affected the net clinical benefit of inhaled corticosteroids independent of BEC as a function of difference in the risk of severe pneumonia, which offset the benefit of inhaled corticosteroids. Other harm risks might also play a role, but no age-specific baseline risks were available. The net clinical benefit at a low-to-moderate dose of inhaled corticosteroids was a 2-year baseline risk of 50–84% only in patients younger than 80 years (figure 1D). The lower risk of severe pneumonia in men also led to a more favourable–harm balance index for men than for women, with a net benefit shown as a 2-year baseline risk of 51–85% for men and 62–76% for women (appendix p 13).

The proportion of patients with COPD in the ICE COLD ERIC cohort who would benefit from inhaled corticosteroid, LABA, and LAMA triple therapy based on the calculated thresholds ranged from 0 to 68%, depending on the subgroup and inhaled corticosteroid dose. Approximately 48% of primary care patients in the cohort would benefit from a low dose of inhaled corticosteroids. Of patients with a BEC of 150 cells per µL or more given a low dose of inhaled corticosteroids, 154 (68%) of 227 would benefit, whereas no patients with a BEC of less than 150 cells per µL would. The benefit of inhaled corticosteroids can be optimised by taking combinations of subgroups to some patients who would more likely benefit from inhaled corticosteroids (figure 2).

We extended the analysis to include additional data from observational data, particularly on harm outcomes. Data combined from RCTs and observational studies showed a net clinical benefit from low-to-moderate inhaled corticosteroid doses at a baseline exacerbation risk between 68% and 72% (27–96% for low-dose inhaled corticosteroids), which corroborated the main results based on RCT data. In the analysis by inhaled corticosteroid types, the net clinical benefit differed between budesonide and fluticasone therapies, with thresholds of 40–91% for fluticasone and 23–97% (low dose) and 47–87% (moderate dose) for budesonide (appendix p 14).

In a further analysis to assess the effect of the perceived importance of exacerbations, we found that each 2% increase in its preference weight had a visible effect on the net clinical benefit in favour of the inhaled corticosteroid, LABA, and LAMA triple therapy. For example, when patients considered avoiding exacerbations as the most important treatment goal (ie, a preference close to 1-0), even patients with an exacerbation risk of 14% would have a net clinical benefit from the triple therapy (figure 3A).
Since we used average rate of severe pneumonia from real-world data in the main model, in a sensitivity analysis we tested other baseline incidences for severe pneumonia to consider other possible rates. The results showed a notable effect on the net clinical benefit. Low-to-moderate doses of inhaled corticosteroids provided a net clinical benefit only if the incidence for severe pneumonia was less than 35 per 1000 person-years (figure 3B).

The inclusion of all potential harms—eg, diabetes and fracture—had only a slight effect on the benefit–harm balance (figure 3C). In another analysis with equal preference weights of all outcomes, the results showed an unfavourable benefit–harm balance of the triple therapy (figure 3D).

Figure 2 provides a heuristic summary of the thresholds, focusing on the most important determinant factors and excluding other factors that would have little or no effect on treatment decisions. Low doses of inhaled corticosteroids were generally preferable. BEC and age were important predictors of the net clinical benefit that would help to select patients with COPD for recommendation of inhaled corticosteroid, LABA, and LAMA triple therapy. On the basis of this algorithm, we calculated the proportion of primary care patients in the ICE COLD ERIC cohort who would benefit from adding inhaled corticosteroids, using the calculated thresholds and the ATS guideline. The overall proportion of patients who would have a net clinical benefit was 37% with the thresholds and 33% with the ATS guideline. However, the proportion of those who would benefit was highly variable according to the inhaled corticosteroid dose and patient factors, which was 68% in the best scenario (ie, for patients aged 40–79 years with a baseline exacerbation risk of 32–95% and a BEC of 150 cells per µL or more given low-dose inhaled corticosteroids). However, the proportions were qualitatively similar between the subgroups and different inhaled corticosteroid doses using the ATS recommendation.

**Discussion**

This quantitative benefit–harm assessment showed that inhaled corticosteroid, LABA, and LAMA triple therapy was more likely to yield a net clinical benefit for patients with COPD with a 2-year moderate-to-severe exacerbation risk between 54% and 83% than was LABA and LAMA dual therapy. However, the net clinical benefit differed by inhaled corticosteroid dose and between patient characteristics, such as baseline exacerbation risk, BEC, and age, yielding opportunities for personalised decision making.

The 2020 ATS guideline is not based on a quantitative benefit–harm assessment and was not based on predicted risk for exacerbations. As a proxy for an increased exacerbation risk, the ATS guideline referred to one or more exacerbations in the previous year to recommend patients for inhaled corticosteroid, LABA, and LAMA triple therapy. This guideline corresponded to a 71% average expected risk over 2 years (figure 2), as calculated from the ICE COLD ERIC cohort based on the prediction model that we validated. This risk value was within our calculated thresholds. The overall proportion of patients who would benefit from the added inhaled corticosteroids was also similar between the ATS and thresholds approaches. However, granulating the recommendations according to patient characteristics showed greater differences between the two approaches. Although the net clinical benefit for low doses of inhaled corticosteroids based on our calculated thresholds was driven primarily by a higher baseline BEC and a younger age, the ATS approach was equally applicable to all patients. For example, the proportion of patients who would benefit from inhaled corticosteroids in those with a BEC of 150 cells per µL or more and less than 150 cells per µL was similar at 34% using the ATS guideline, whereas the average 2-year exacerbation risk was greatly different, at 71% for those with a BEC of 150 cells per µL or more and 46% for those with a BEC of less than 150 cells per µL (figure 2). These results could lead to treatment misclassification, resulting in undertreatment in patients with more eosinophil counts and overtreatment in those with fewer.

Exacerbation history might not guide treatment decisions well and therefore predicted exacerbation risk, baseline BEC, and age would better personalise the treatment decision for low and moderate doses of inhaled corticosteroids added to LABA and LAMA. Baseline BEC is an important predictor of response to inhaled corticosteroid treatment, as shown in ETHOS, a meta-analysis of several RCTs, INCONTROL, and other meta-analyses. The Global Initiative for Chronic Obstructive Disease guidelines also recommend inhaled corticosteroids in patients with an increased BEC. But even for patients with a higher BEC, a one-size-fits-all strategy is not appropriate, since the baseline exacerbation risk still needs to be considered, as we showed in this study. In the ICE COLD ERIC cohort, 57% of patients had a BEC of 150 cells per µL or more, but only 68% of these patients would be recommended for triple therapy on the basis of our calculated thresholds. In terms of age, the benefits of additional inhaled corticosteroids were generally more favourable for younger people than for older people, because of the higher baseline risks of harm outcomes in older patients that counterbalance the potential benefit of inhaled corticosteroids.

The net benefit of inhaled corticosteroids was also dose dependent. The lower the dose, the more favourable the benefit–harm balance. This effect was because of the dose-related excess risk of harm outcomes. Increasing the dose of inhaled corticosteroids confers little additional benefit in terms of reducing exacerbations, but substantially increases harm risks. As such, as shown in this analysis, reducing the inhaled
corticosteroid dose appears to be a preferable therapeutic option for many patients with COPD.

In most results, the rate of incremental net benefit or marginal net benefit was not linear. Rather, it increased at a decreasing rate over a range of exacerbation risks, depending on the subgroups, and subsequently decreased. The expected exacerbation risk over the 2-year horizon increased in patients given the triple and dual therapies, but the difference in cumulative risk decreased over time. These results are attributed to the model property that the cumulative risk of events over a restricted time horizon cannot exceed 100%, regardless of higher baseline risks.

The diminishing benefit at high exacerbation risks could thus be interpreted analogously to the law of diminishing marginal utility, but here, net clinical benefit, rather than utility. However, this finding could change if the risk of harm outcomes (such as pneumonia) are not the same across the exacerbation risk spectrum.

Although we did a rigorous analysis to assess the benefit–harm balance of triple therapy with a transparent model, the study was not without its limitations. The findings could be more highly stratified than we presented. Data were not available for important factors, such as body-mass index, smoking, or the method of inhaled corticosteroid delivery. In addition, the model presented. Data were not available for important factors, and the findings could be more highly stratified than we model, the study was not without its limitations. The benefit–harm balance of triple therapy with a transparent model for predicting exacerbation risk, BEC stability, treatment compliance, the recurrence of outcome events and their distribution over time, and the benefit and harm outcomes of treatments that might be prescribed for inhaled corticosteroid-related harms. We did not elicit preferences from the patients, but took generic weights that were applied in other decision problems. However, it should be noted that average estimates from preference surveys might not always be relevant. Preference could be patient-dependent because of differences in treatment goals between individuals in terms of social, psychological, and functional health. In such cases, decision aids could be of great help to better personalise decisions, instead of taking average estimates, for which individual patient preferences could be considered and individual risks could be estimated using predictive models (eg, Bertens and colleagues and ACCEPT).

This study shows that the benefit–harm balance of LABA and LAMA varies greatly according to the 2-year risk of baseline exacerbations, BEC, age, and inhaled corticosteroid dose, on the basis of which more granular treatment decisions are needed. With the use of these factors and a model for predicting exacerbation risk, the uncertainty about when to prescribe inhaled corticosteroids and at what dose can be substantially reduced, and overtreatment and undertreatment with inhaled corticosteroids minimised.

Contributors
All authors contributed substantially to the content and writing of this article. HGY and MAP conceptualised the study. HGY collected the data and MAP, DM, GR, MS, and JB accessed and verified the data. HGY did the benefit–harm analysis. JB validated the COPD prediction model. MAP, DM, GR, and MS reviewed the analysis and results. HGY drafted the manuscript. All authors reviewed and edited the manuscript, and approved the final version.

Declaration of interests
We declare no competing interests.

Data sharing
Extracted data are available within the publication and its appendix. Codes can be accessed from the corresponding author upon request with a signed data access agreement.

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