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ORIGINAL ARTICLE

Effect of Triple Therapy on Cardiovascular and Severe Cardiopulmonary Events in Chronic Obstructive Pulmonary Disease

A *Post Hoc* Analysis of a Randomized, Double-Blind, Phase 3 Clinical Trial (ETHOS)

Dave Singh[1], Fernando J. Martinez[2], John R. Hurst[3], MeiLan K. Han[4], Chris P. Gale[5,6,7], Martin Fredriksson[8], Dobrawa Kisielewicz[9], Alec Mushunje[10], Charlotta Movitz[8], Nikki Ojili[11], Himanshu Parikh[11], Niki Arya[12], Karin Bowen[11], and Mehul Patel[10]

[1]Medicines Evaluation Unit, University of Manchester, Manchester University NHS Foundation Hospitals Trust, Manchester, United Kingdom; [2]Division of Pulmonary, Allergy, and Critical Care Medicine, University of Massachusetts Chan, Worcester, Massachusetts; [3]UCL Respiratory, University College London, London, United Kingdom; [4]Division of Pulmonary and Critical Care, University of Michigan, Ann Arbor, Michigan; [5]Leeds Institute for Data Analytics, University of Leeds, Leeds, United Kingdom; [6]Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, United Kingdom; [7]Department of Cardiology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; [8]AstraZeneca, Gothenburg, Sweden; [9]AstraZeneca, Barcelona, Spain; [10]AstraZeneca, Cambridge, United Kingdom; [11]AstraZeneca, Gaithersburg, Maryland; and [12]AstraZeneca, Durham, North Carolina

ORCID IDs: 0000-0001-8918-7075 (D.S.); 0000-0002-2412-3182 (F.J.M.); 0000-0002-7246-6040 (J.R.H.); 0000-0002-9095-4419 (M.K.H.); 0000-0003-4732-382X (C.P.G.); 0000-0003-0435-858X (M.P.).

Abstract

Rationale: Chronic obstructive pulmonary disease (COPD) is associated with an increased risk of cardiovascular and cardiopulmonary events. In the phase III, 52-week ETHOS trial (NCT02465567), triple therapy with budesonide/glycopyrrolate/formoterol fumarate (BGF) reduced rates of moderate/severe exacerbations and all-cause mortality compared with dual therapy with glycopyrrolate/formoterol fumarate (GFF) or budesonide/formoterol fumarate (BFF). However, the effect of BGF on cardiovascular events versus GFF remains unevaluated. Furthermore, the effect of BGF on time to first severe exacerbation has not been reported.

Objectives: To assess the effects of BGF 320/18/9.6 μg (BGF 320) and other inhaled corticosteroid–containing arms on cardiovascular and severe cardiopulmonary endpoints versus GFF in patients with COPD from the ETHOS trial.

Methods: Patients with moderate to very severe COPD and a history of exacerbations were randomized to twice-daily BGF 320, BGF 160/18/9.6 μg, BFF 320/9.6 μg, or GFF 18/9.6 μg (GFF). Time to first severe COPD exacerbation was a prespecified endpoint; *post hoc* cardiovascular and severe cardiopulmonary endpoints included time to first major adverse cardiac event, time to first cardiovascular adverse event (AE) of special interest, time to first cardiac AE, and time to the composite endpoint of first severe cardiopulmonary event.

Measurements and Main Results: BGF 320 reduced the rate of first occurrence (hazard ratio [95% confidence interval]) of cardiovascular and severe cardiopulmonary events versus GFF, including for time to first cardiovascular adverse event of special interest (0.63 [0.48, 0.82]), cardiac AE (0.60 [0.48, 0.76]), and severe cardiopulmonary event (0.80 [0.67, 0.95]).

Conclusions: BGF had a benefit on cardiovascular endpoints and severe cardiopulmonary events versus GFF in patients with moderate to very severe COPD.

Keywords: cardiovascular; budesonide/glycopyrrolate/formoterol fumarate; hospitalization; mortality

(Received in original form December 19, 2023; accepted in final form August 28, 2024)

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The ETHOS study was supported by AstraZeneca. The sponsor was involved in the study design; the collection, analysis, and interpretation of data; the writing of the report; and in the decision to submit the article for publication. Medical writing support for development of the manuscript was funded by AstraZeneca.

Author Contributions: All authors made a significant contribution to the work reported. D.S., F.J.M., J.R.H., and M.K.H. contributed to the study conception or design and data interpretation. C.P.G. contributed to the data interpretation. M.F., A.M., C.M., and H.P. contributed to data analysis and interpretation. K.B., N.A., and M.P. contributed to the study conception or design and data analysis and interpretation. All authors 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.

Am J Respir Crit Care Med Vol 211, Iss 2, pp 205–214, Feb 2025
Copyright © 2025 by the American Thoracic Society
Originally Published in Press as DOI: 10.1164/rccm.202312-2311OC on August 30, 2024
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: People living with chronic obstructive pulmonary disease (COPD) are at increased risk of adverse cardiovascular and pulmonary events, particularly after an exacerbation of COPD. Although twice-daily budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 μg (BGF 320) reduced the risk of moderate or severe exacerbations and all-cause mortality in the ETHOS study, the benefit of triple therapy on cardiovascular and severe cardiopulmonary outcomes is yet to be determined.

What This Study Adds to the Field: This analysis of ETHOS assessed the impact of BGF 320 relative to glycopyrrolate/formoterol fumarate 18/9.6 μg (GFF) across a broad spectrum of prespecified and *post hoc* analyses of cardiovascular and severe cardiopulmonary endpoints. BGF 320 is associated with a benefit across a range of cardiovascular endpoints and further indicated a benefit of BGF 320 on severe cardiopulmonary outcomes compared with GFF in the ETHOS study population. These findings indicate that the benefit of BGF 320 may be mediated through both cardiovascular and pulmonary mechanisms and highlights the need to include cardiovascular endpoints, and cardiopulmonary outcomes as primary endpoints, in randomized clinical trials for COPD.

People living with chronic obstructive pulmonary disease (COPD) are at increased risk of cardiovascular events, such as myocardial infarction (MI) (1–3), heart failure (3, 4), arrythmia (3, 5), and cardiovascular-related mortality (6), particularly after a COPD exacerbation. Cardiovascular-related death is a major cause of mortality in people living with COPD (7, 8), emphasizing the importance of evaluating and managing cardiovascular risk in COPD. Because more frequent and severe COPD exacerbations are associated with an increased risk of further exacerbations and COPD-related death (6), and given that the cardiovascular and pulmonary systems are physiologically and pathologically linked (9), evaluating patients with COPD by way of combined cardiopulmonary risk through the assessment of both cardiovascular-related and pulmonary-related clinical events may better elucidate treatment effects and disease mechanisms.

Optimized management of COPD has the potential to decrease the risk of both cardiovascular and cardiopulmonary events and thus to reduce premature mortality. Risk prevention by escalation of treatment to triple therapy with an inhaled corticosteroid (ICS), a long-acting muscarinic antagonist (LAMA), and a long-acting β_2-agonist (LABA) is recommended by the Global Initiative for Chronic Obstructive Lung Disease for patients who continue to experience exacerbations while being treated with mono- or dual bronchodilator therapy (10), with higher blood eosinophil counts (i.e., $\geqslant$100 cells/μl) identifying patients most likely to benefit from the addition of ICS (11).

In the phase III, 52-week ETHOS study (NCT02465567), treatment with the fixed-dose ICS/LAMA/LABA triple therapy of budesonide/glycopyrrolate/formoterol fumarate (BGF) at two ICS doses (320 or 160 μg) reduced the rate of moderate or severe COPD exacerbations compared with dual therapy with glycopyrrolate/formoterol fumarate (GFF) or budesonide/formoterol fumarate (BFF) (12). A subsequent analysis of ETHOS reported reductions in the risk of all-cause mortality in patients treated with BGF 320/18/9.6 μg compared with GFF 18/9.6 μg dual therapy (13). Of the 156 adjudicated deaths across all treatment groups in ETHOS, 67 (42.9%) were attributed to cardiovascular causes, and 34 (21.8%) were attributed to respiratory causes (13). Moreover, there were fewer deaths of cardiovascular causes in all of the ICS-containing treatment groups (BGF 320, BGF 160, or BFF) compared with the LAMA/LABA group (GFF) (13).

Given the interaction between cardiovascular and pulmonary physiology and the associations between cardiovascular and pulmonary events in COPD (2, 14), the present prespecified and *post hoc* analyses of ETHOS aimed to investigate the direction and magnitude of the effects of BGF compared with GFF on both cardiovascular and severe cardiopulmonary endpoints. Cardiovascular event composites, including major adverse cardiac events (MACEs), cardiovascular adverse events (AEs) of special interest (CVAESI), and cardiac AEs, were explored. Given the relevance of severe COPD exacerbations in a clinical context, the effect of BGF versus GFF on time to first severe COPD exacerbation is also reported for the first time, to our knowledge. Subsequently, a composite measure of severe cardiopulmonary events, which was designed to describe the combined cardiopulmonary risk in patients with COPD, was investigated. Some of the results of these analyses were reported in a poster presented at the 2024 American Thoracic Society International Conference (15).

Methods

Ethical Approval

All patients provided written informed consent before screening. The study protocol and informed consent forms were approved by an appropriate institutional review board, independent ethics committee, or health authority, and an independent data monitoring and clinical endpoint committee reviewed safety data throughout the study. A complete listing of institutional review

Data underlying the findings described in this article may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli can be requested through Vivli at https://search.vivli.org/enquiries/. The AstraZeneca Vivli member page is also available, outlining further details: https://vivli.org/ourmember/astrazeneca/.

Correspondence and requests for reprints should be addressed to Mehul Patel, B.Sc., M.B. B.S., Ph.D., AstraZeneca, Academy House, 136 Hills Road, Cambridge CB2 8PA, UK. E-mail: mehul.patel1@astrazeneca.com.

This article has a related editorial.

A data supplement for this article is available via the Supplements tab at the top of the online article.

boards and ethics committees was published previously (16).

Study Design

ETHOS was a 52-week, randomized, double-blind, parallel-group, multinational phase III study in people with moderate to very severe COPD and a history of exacerbations (12, 17). Patients were randomized 1:1:1:1 to twice-daily BGF 320/18/9.6 μg (BGF 320) or 160/18/9.6 μg (BGF 160), BFF 320/9.6 μg (BFF), or GFF 18/9.6 μg (GFF). The study design and protocol were previously published (12, 17).

Endpoints

Post hoc analyses examined cardiovascular endpoints of time to first MACE, time to first CVAESI, and time to first cardiac AE, and further analyses assessed the prespecified efficacy endpoint of time to first severe exacerbation. The composite endpoint of severe cardiopulmonary event included MACE, severe exacerbations, and deaths of a nonmalignant respiratory cause (which excludes death of a severe exacerbation) to evaluate both cardiovascular and pulmonary events. A composite endpoint comprising CVAESI leading to hospitalization or death, all-cause mortality, COPD exacerbation leading to hospitalization, or hospitalization for pneumonia was also assessed.

The definitions of each endpoint are described in Table 1. In brief, MACE was defined in the study protocol as a cardiovascular death, nonfatal MI, or nonfatal stroke; the adjudication of potential MACE is described in the data supplement. Severe COPD exacerbations were defined as those resulting in hospitalization or death. Severe cardiopulmonary event was a composite endpoint defined as a MACE, severe COPD exacerbation, or death of a nonmalignant respiratory cause. Occurrences of death in this endpoint were cardiovascular related in MACE, respiratory related for severe exacerbation, or nonmalignant respiratory related excluding those resulting from a severe exacerbation.

The definition of CVAESI was prespecified in the study protocol on the basis of potentially relevant effects of ICS, LABA, and LAMA use; Medical Dictionary for Regulatory Activities (MedDRA) terms specified as CVAESI are reported in Table E1 in the data supplement. Cardiac AEs were defined as any AE in the MedDRA Cardiac Disorders System Organ Class.

Statistical Analyses

All analyses except for MACE by blood eosinophil count were conducted using on-treatment data from the modified intention-to-treat (mITT) population in line with the primary ETHOS publication (12). The analysis populations are defined in the data supplement.

Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox regression to compare ICS-containing therapies (BGF 320, BGF 160, or BFF) with GFF. All time-to-event analyses were adjusted for the following covariates: treatment, baseline post-bronchodilator percent FEV_1 predicted normal, log baseline blood eosinophil count, COPD exacerbation history (one, two or more) in the last 12 months, region, and ICS use at screening (yes, no). Across all time-to-event analyses, the proportional hazards assumption appeared to hold because the treatment × time interaction was not significant in the statistical models. Even so, the study may have been underpowered to detect this interaction for some analyses. Information on type I error control is described in the data supplement. Kaplan-Meier curves examined time to first MACE and time to first severe cardiopulmonary event with BGF 320, BGF 160, BFF, and GFF.

Subgroup analyses assessed time to first MACE and time to first CVAESI among patients with baseline blood eosinophil counts ⩾100 cells/μl and with or without prior established cardiovascular disease. In addition, the incidence of MACE was assessed by baseline blood eosinophil count using a generalized additive model in the safety population.

Table 1. Endpoint Definitions

Endpoint	Definition
MACE	Cardiovascular death, nonfatal MI, or nonfatal stroke*
Severe COPD exacerbation	COPD exacerbation resulting in hospitalization or death
Severe cardiopulmonary event	MACE, severe COPD exacerbation, or death of a nonmalignant respiratory cause
CVAESI	Prespecified in the study protocol on the basis of potentially relevant effects of ICS, LABA, and LAMA use†
Cardiac AE	Any AE in the MedDRA Cardiac Disorders System Organ Class

Definition of abbreviations: AE = adverse event; COPD = chronic obstructive pulmonary disease; CVAESI = cardiovascular adverse event of special interest; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; MACE = major adverse cardiac event; MedDRA = Medical Dictionary for Regulatory Activities. MI = myocardial infarction.
*Adjudication of potential MACE is described in the data supplement.
†MedDRA terms specified as CVAESI are reported in Table E1.

Results

Study Population

The baseline characteristics of the ETHOS population were described previously (12). A total of 8,588 patients were randomized, and 8,573 received treatment, of whom 8,529 had a postrandomization safety assessment and were included in the safety population, whereas the ITT and mITT populations comprised 8,509 patients each.

Cardiovascular risk factors were comparable across treatment groups (Table 2). In the safety population, approximately 70% of patients in each treatment group had at least one cardiovascular risk factor, with the most frequent risk factors being hypertension (58.9%), high total cholesterol (35.7%; *see* Table E2 for total cholesterol range definitions), and diabetes mellitus (17.5%); the proportion of patients with a history of angina and prior MI were 7.4% and 7.1%, respectively. In the mITT population, baseline smoking status and pack-years smoked, number of exacerbations in the previous year, and ICS use at screening were similar between treatment groups (Table 3). The proportion of patients with MACE, CVAESI, cardiac AE, severe exacerbation, and severe cardiopulmonary events are reported in Table 4.

Demographic and clinical characteristics and cardiovascular risk factor history for patients with or without a MACE are reported in Tables E3 and E4, respectively.

Table 2. History of Cardiovascular Risk Factors Reported in ⩾2% of Patients in Any Treatment Group (Safety Population)*

	BGF 320 (*n* = 2,144)	BGF 160 (*n* = 2,124)	BFF (*n* = 2,136)	GFF (*n* = 2,125)	All Patients (*N* = 8,529)
Any cardiovascular risk factor of interest, *n* (%)	1,511 (70.5)	1,505 (70.9)	1,513 (70.8)	1,492 (70.2)	6,021 (70.6)
Hypertension	1,272 (59.3)	1,252 (58.9)	1,251 (58.6)	1,250 (58.8)	5,025 (58.9)
High total cholesterol†	769 (35.9)	769 (36.2)	761 (35.6)	744 (35.0)	3,043 (35.7)
Diabetes	398 (18.6)	400 (18.8)	358 (16.8)	339 (16.0)	1,495 (17.5)
Type 2 diabetes	380 (17.7)	384 (18.1)	350 (16.4)	335 (15.8)	1,449 (17.0)
Angina	162 (7.6)	154 (7.3)	165 (7.7)	147 (6.9)	628 (7.4)
Myocardial infarction	142 (6.6)	166 (7.8)	158 (7.4)	138 (6.5)	604 (7.1)
Peripheral vascular disease	162 (7.6)	151 (7.1)	116 (5.4)	137 (6.4)	566 (6.6)
Atrial fibrillation	121 (5.6)	92 (4.3)	87 (4.1)	89 (4.2)	389 (4.6)
Stroke	71 (3.3)	54 (2.5)	65 (3.0)	51 (2.4)	241 (2.8)
Transient ischemic attack	40 (1.9)	47 (2.2)	36 (1.7)	52 (2.4)	175 (2.1)

Definition of abbreviations: BFF = budesonide/formoterol fumarate 320/9.6 μg; BGF 160 = budesonide/glycopyrrolate/formoterol fumarate 160/18/9.6 μg; BGF 320 = budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 μg; GFF = glycopyrrolate/formoterol fumarate 18/9.6 μg.
*Adapted from Table E1 of Martinez *et al.* (13), licensed under CC BY 4.0 (Creative Commons—Attribution 4.0 International—CC BY 4.0), with addition of data for type 2 diabetes.
†Cholesterol range definitions are reported in Table E2.

Demographic and clinical characteristics for patients with or without a CVAESI are reported in Table E5.

Time to First MACE

Relative to GFF, reductions in the rate of first occurrence of MACE were 35% (HR [95% CI], 0.65 [0.41, 1.03]) with BGF 320, 38% (HR [95% CI], 0.62 [0.39, 0.99]) with BGF 160, and 50% (HR [95% CI], 0.50 [0.30, 0.83]) with BFF (Figure 1). Although the effect size for BGF 320 versus GFF was similar in magnitude to the effect size for BGF 160 versus GFF, the treatment effect for BGF 320 versus GFF was not nominally significant (Figure 1). These results are supported by Kaplan-Meier curves (Figure E1). HRs for MACE among patients with baseline blood eosinophil counts ⩾100 cells/μl and with or without prior cardiovascular disease are reported in Table E6. The event rate of MACE was lower in patients treated with BGF 320, BGF 160, and BFF versus GFF, with the benefit of BGF 320 versus GFF increasing with baseline eosinophil count (Figure E2).

Time to First CVAESI and Time to First Cardiac AE

Relative to GFF, the rate of first occurrence of CVAESI was reduced by 37% (HR [95% CI], 0.63 [0.48, 0.82]) with BGF 320, and findings were similar for BGF 160 and BFF (Figure 2). Subgroup analyses for CVAESI among patients with blood eosinophil counts ⩾100 cells/μl and with or without prior cardiovascular disease are reported in Table E7. BGF 320 reduced the rate of first occurrence of cardiac AE by 40% (HR [95% CI], 0.60 [0.48, 0.76]) versus GFF, with similar findings for BGF 160 and BFF versus GFF (Figure 2).

Time to First Severe COPD Exacerbation

The reduction in the rate of first occurrence of severe COPD exacerbations for BGF 320 versus GFF was 14% (HR [95% CI], 0.86 [0.71, 1.03]), although it was not nominally significant. Findings were similar for BGF 160 versus GFF (Figure 1).

Time to First Severe Cardiopulmonary Event

A reduction in the rate of first occurrence of a severe cardiopulmonary event was observed in patients treated with BGF 320

Table 3. Baseline Smoking Status, ICS Use at Screening and Exacerbation History (Modified Intention-to-Treat Population)

	BGF 320 (*n* = 2,137)	BGF 160 (*n* = 2,121)	BFF (*n* = 2,131)	GFF (*n* = 2,120)	All Patients (*N* = 8,509)
Current smoker, *n* (%)	910 (42.6)	865 (40.8)	864 (40.5)	856 (40.4)	3,495 (41.1)
Pack-years of smoking history, mean (SD)	47.0 (25.1)	47.9 (25.8)	47.1 (26.3)	48.4 (26.5)	47.6 (25.9)
ICS use at screening, *n* (%)	1,706 (79.8)	1,729 (81.5)	1,704 (80.0)	1,707 (80.5)	6,846 (80.5)
Number of exacerbations* in previous year					
Mean (SD)	1.7 (0.8)	1.7 (0.9)	1.7 (0.9)	1.7 (0.8)	1.7 (0.8)
0 exacerbations, *n* (%)	2 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)	8 (0.1)
1 exacerbation, *n* (%)	940 (44.0)	932 (43.9)	912 (42.8)	907 (42.8)	3,691 (43.4)
2 exacerbations, *n* (%)	974 (45.6)	960 (45.3)	977 (45.8)	990 (46.7)	3,901 (45.8)
⩾2 exacerbations, *n* (%)	1,195 (55.9)	1,187 (56.0)	1,217 (57.1)	1,211 (57.1)	4,810 (56.5)
⩾3 exacerbations, *n* (%)	221 (10.3)	227 (10.7)	240 (11.3)	221 (10.4)	909 (10.7)

Definition of abbreviations: BFF = budesonide/formoterol fumarate 320/9.6 μg; BGF 160 = budesonide/glycopyrrolate/formoterol fumarate 160/18/9.6 μg; BGF 320 = budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 μg; GFF = glycopyrrolate/formoterol fumarate 18/9.6 μg; ICS = inhaled corticosteroid; SD = standard deviation.
*Moderate or severe exacerbations per patient.

Table 4. MACE, CVAESIs, Cardiac AEs, Severe Exacerbations, and Severe Cardiopulmonary Events (Modified Intention-to-Treat Population)

	BGF 320 (*n* = 2,137)	BGF 160 (*n* = 2,121)	BFF (*n* = 2,131)	GFF (*n* = 2,120)
Patients with MACE, *n* (%)	31 (1.5)	30 (1.4)	23 (1.1)	44 (2.1)
Percentage of patients with MACE (95% CI) within:				
3 mo	0.4 (0.2, 0.8)	0.4 (0.2, 0.8)	0.3 (0.1, 0.7)	0.9 (0.6, 1.5)
6 mo	0.8 (0.5, 1.3)	0.9 (0.6, 1.4)	0.5 (0.3, 0.9)	1.1 (0.7, 1.7)
9 mo	1.4 (1.0, 2.0)	1.2 (0.8, 1.8)	0.8 (0.5, 1.3)	1.8 (1.3, 2.6)
Patients with CVAESI, *n* (%)	93 (4.4)	109 (5.1)	93 (4.4)	136 (6.4)
Percentage of patients with CVAESI (95% CI) within:				
3 mo	1.3 (0.9, 1.8)	1.3 (0.9, 1.9)	1.2 (0.8, 1.8)	2.2 (1.7, 3.0)
6 mo	2.6 (2.0, 3.4)	3.0 (2.4, 3.9)	2.5 (1.9, 3.3)	4.3 (3.5, 5.3)
9 mo	4.0 (3.2, 5.0)	4.4 (3.6, 5.5)	3.5 (2.8, 4.5)	5.6 (4.7, 6.8)
Patients with cardiac AE, *n* (%)	125 (5.8)	136 (6.4)	128 (6.0)	189 (8.9)
Percentage of patients with cardiac AE (95% CI) within:				
3 mo	1.5 (1.1, 2.2)	1.6 (1.2, 2.3)	1.4 (1.0, 2.0)	3.1 (2.4, 3.9)
6 mo	3.2 (2.5, 4.1)	3.6 (2.9, 4.5)	2.9 (2.3, 3.8)	5.9 (4.9, 7.0)
9 mo	5.2 (4.3, 6.2)	5.3 (4.4, 6.4)	4.8 (3.9, 5.9)	7.8 (6.7, 9.1)
Patients with severe exacerbation, *n* (%)	219 (10.2)	243 (11.5)	261 (12.2)	239 (11.3)
Percentage of patients with severe exacerbation (95% CI) within:				
3 mo	3.1 (2.4, 3.9)	4.1 (3.4, 5.1)	4.3 (3.5, 5.3)	4.6 (3.8, 5.6)
6 mo	6.3 (5.3, 7.4)	6.9 (5.9, 8.1)	8.1 (7.0, 9.4)	8.1 (7.0, 9.5)
9 mo	9.1 (7.9, 10.5)	9.9 (8.6, 11.3)	11.4 (10.1, 13.0)	10.8 (9.5, 12.3)
Patients with severe cardiopulmonary event, *n* (%)	240 (11.2)	270 (12.7)	279 (13.1)	279 (13.2)
Percentage of patients with severe cardiopulmonary event (95% CI) within:				
3 mo	3.4 (2.7, 4.3)	4.5 (3.7, 5.5)	4.6 (3.8, 5.6)	5.3 (4.4, 6.4)
6 mo	6.9 (5.8, 8.1)	7.7 (6.7, 9.0)	8.6 (7.5, 10.0)	9.1 (7.9, 10.5)
9 mo	10.2 (9.0, 11.6)	11.0 (9.7, 12.4)	12.1 (10.7, 13.6)	12.5 (11.0, 14.0)

Definition of abbreviations: AE = adverse event; BFF = budesonide/formoterol fumarate 320/9.6 μg; BGF 160 = budesonide/glycopyrrolate/formoterol fumarate 160/18/9.6 μg; BGF 320 = budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 μg; CI = confidence interval; CVAESI = cardiovascular adverse event of special interest; GFF = glycopyrrolate/formoterol fumarate 18/9.6 μg; MACE = major adverse cardiac event.

versus GFF (HR [95% CI], 0.80 [0.67, 0.95]), but not with BFF versus GFF (Figure 1), supported by Kaplan-Meier curves (Figure 3). Similar findings were observed for the rate of first occurrence of a CVAESI leading to hospitalization or death, all-cause mortality, exacerbation leading to hospitalization, or hospitalization for pneumonia (Figure E3). Numbers of first events within severe cardiopulmonary event components are reported in Table E8.

Discussion

This analysis of prespecified and *post hoc* endpoints from ETHOS found that BGF 320 has a consistent beneficial effect on cardiovascular and severe cardiopulmonary endpoints compared with GFF in patients with moderate to very severe COPD, with evidence for reductions in the rate of first occurrence of a broad spectrum of cardiovascular events, including CVAESI and cardiac AEs. Moreover, clinical benefits with BGF 320 versus GFF were observed for time to severe cardiopulmonary events. Although HRs for BGF 320 versus GFF for the rate of first occurrence of MACE and first severe COPD exacerbation were in the same direction, they were not nominally significant.

These findings are consistent with, and extend, the previously reported treatment effect of BGF 320 on all-cause mortality (13). Importantly, we note that the relative effect of treatment with BGF 320 on the rate of a first occurrence of a CVAESI or cardiac AE was substantially greater than that for a severe COPD exacerbation, indicating that part of the broader benefit of BGF 320 is likely mediated through a cardiopulmonary axis. Interestingly, with BGF 320, the magnitude of the reduction in the rate of first occurrence of cardiovascular events was comparable with the previously reported reduction in rates of all-cause mortality (13). It was substantially greater than the reduction in the rate of first occurrence of a severe COPD exacerbation, despite the fewer reported cardiovascular events compared with respiratory events in this study, which is not surprising, given that ETHOS was designed primarily to evaluate respiratory events. In addition, despite a lower number of severe exacerbations versus moderate/severe exacerbations in the ETHOS population, the treatment effect of BGF 320 on the rate of first occurrence of severe exacerbations was comparable with those previously reported for moderate/severe exacerbations (HR [95% CI], 0.88 [0.81, 0.96]) (12), which was the basis for the primary endpoint in the ETHOS study.

Rate reductions for first occurrence of MACEs, CVAESI, and cardiac AEs were also observed in patients treated with BGF 160 relative to GFF but were not observed for severe cardiopulmonary events. The lower treatment effect with BGF 160 on severe cardiopulmonary events is potentially unsurprising, given that BGF 160 had a lower observed effect on all-cause mortality in prior analyses of ETHOS (13). A potential dose–response effect for some ICS-mediated treatment effects, including those not directly

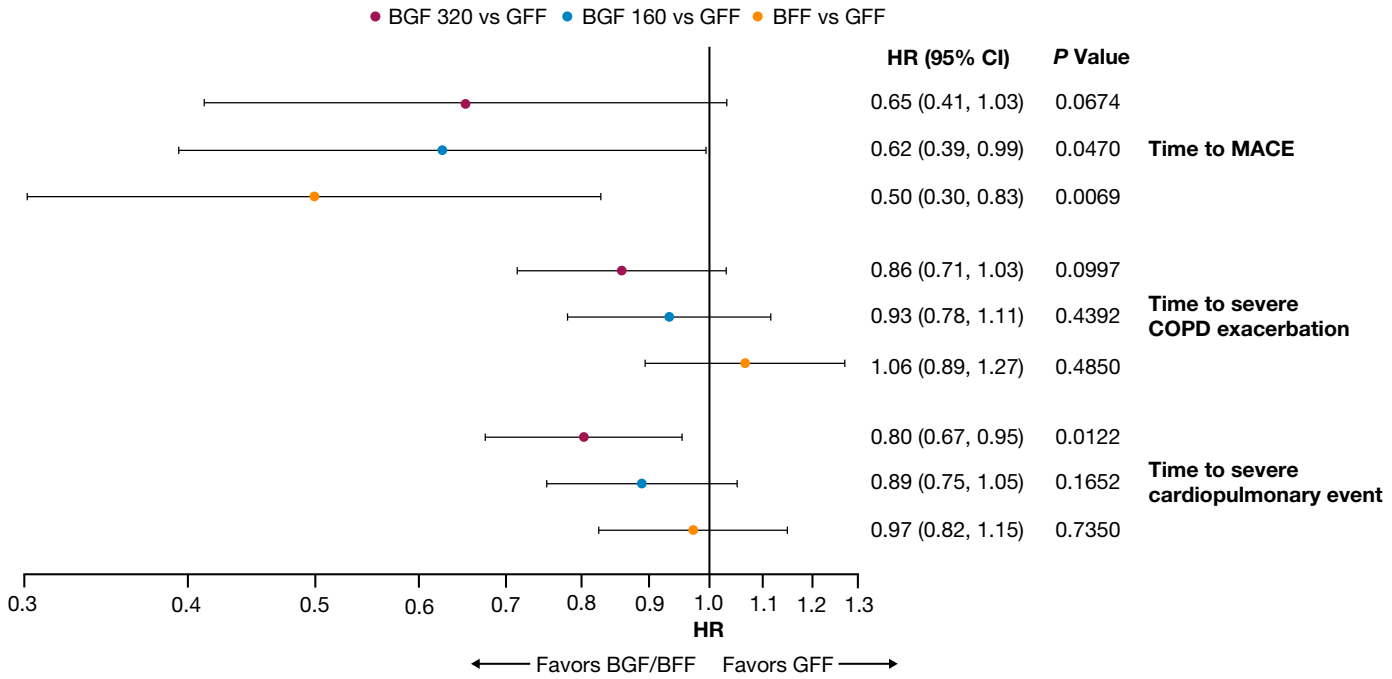


Figure 1. Hazard ratios (HRs) for time to severe cardiopulmonary events with BGF 320, BGF 160, and BFF versus GFF (modified intention-to-treat population). HRs and 95% CIs were calculated using Cox regression; *P* values are nominal and unadjusted for multiplicity. BFF = budesonide/formoterol fumarate 320/9.6 μg; BGF 160 = budesonide/glycopyrrolate/formoterol fumarate 160/18/9.6 μg; BGF 320 = budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 μg; CI = confidence interval; COPD = chronic obstructive pulmonary disease; GFF = glycopyrrolate/formoterol fumarate 18/9.6 μg; MACE = major adverse cardiac event. Adapted by permission from reference 15.

mediated by exacerbations (e.g., the effect of ICS on the pulmonary vasculature [18]), may have further contributed to the difference in treatment effects between BGF 320 and BGF 160 versus GFF.

Reductions in cardiovascular events are clinically important and relevant to patients. Cardiovascular events such as MI, heart failure, and stroke are costly with respect to quality of life, healthcare expenditure, and—if not associated with subsequent fatal events—are inevitably associated with further healthcare resource use and morbidity (19–27). People living with COPD, particularly those who experience

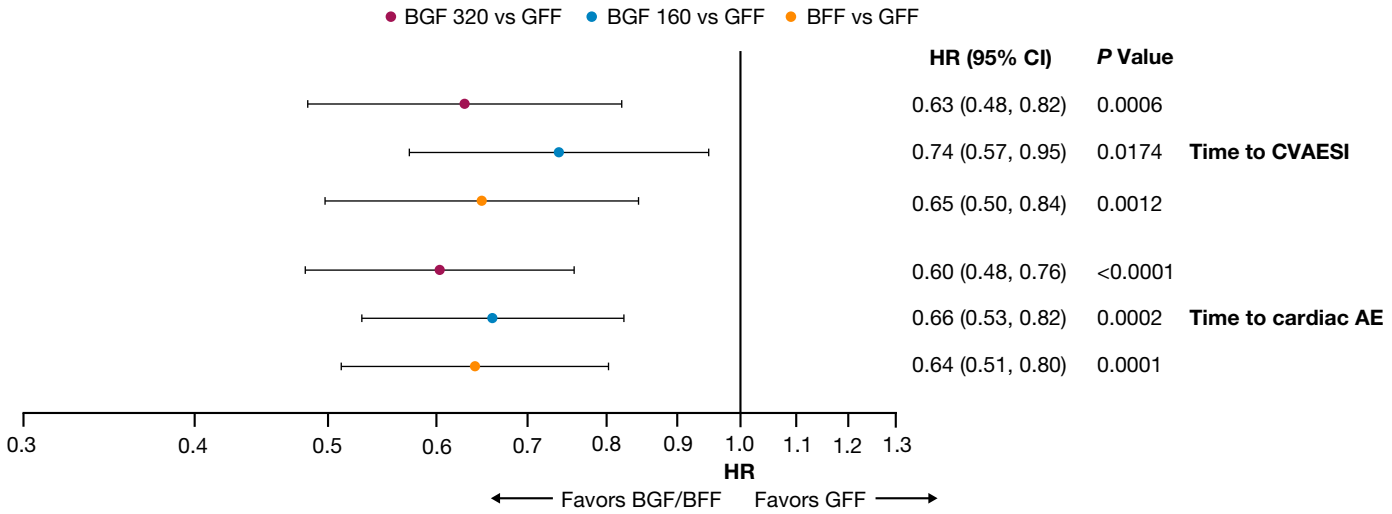
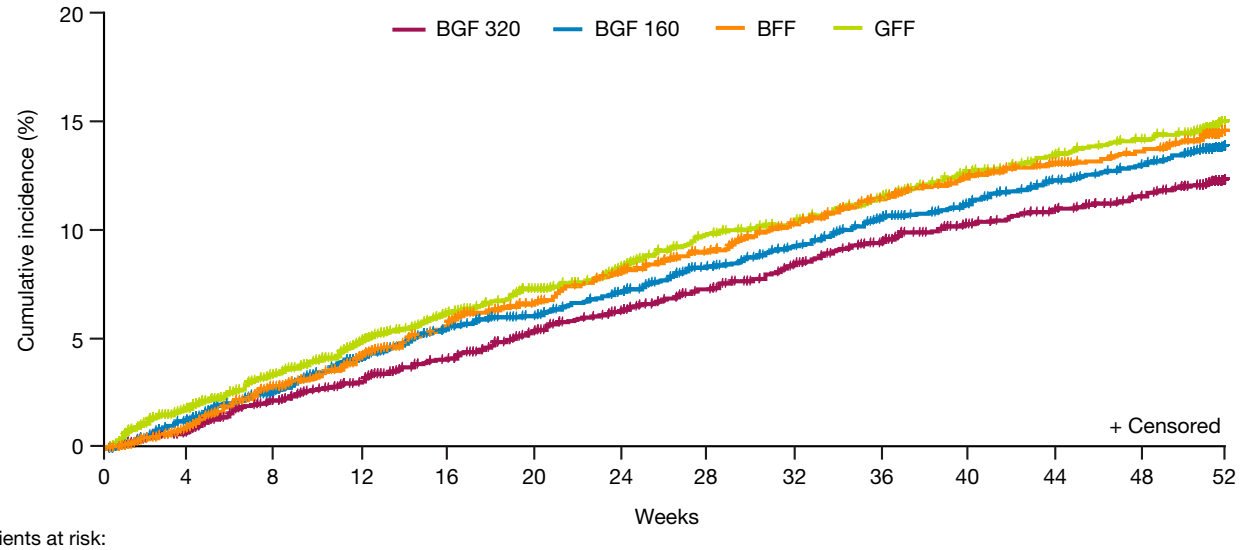


Figure 2. Hazard ratios (HRs) for time to first CVAESI and cardiac AE with BGF 320, BGF 160, and BFF versus GFF (modified intention-to-treat population). HRs and 95% CIs were calculated using Cox regression; *P* values are nominal and unadjusted for multiplicity. AE = adverse event; BFF = budesonide/formoterol fumarate 320/9.6 μg; BGF 160 = budesonide/glycopyrrolate/formoterol fumarate 160/18/9.6 μg; BGF 320 = budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 μg; CI = confidence interval; CVAESI = cardiovascular adverse event of special interest; GFF = glycopyrrolate/formoterol fumarate 18/9.6 μg. Adapted by permission from reference 15.



Patients at risk:

BGF 320	2137	2084	2006	1958	1905	1849	1808	1762	1724	1685	1636	1608	1576	1296
BGF 160	2121	2056	1990	1932	1872	1834	1798	1750	1712	1673	1638	1601	1576	1271
BFF	2131	2051	1957	1886	1817	1770	1730	1686	1641	1597	1561	1533	1508	1217
GFF	2120	2015	1903	1827	1753	1704	1658	1602	1579	1549	1511	1484	1458	1182

Figure 3. Kaplan-Meier curves for time to severe cardiopulmonary event (defined as a major adverse cardiac event, severe chronic obstructive pulmonary disease exacerbation, or death of a nonmalignant respiratory cause) with BGF 320, BGF 160, BFF, and GFF (modified intention-to-treat population). BFF = budesonide/formoterol fumarate 320/9.6 μg; BGF 160 = budesonide/glycopyrrolate/formoterol fumarate 160/18/9.6 μg; BGF 320 = budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 μg; GFF = glycopyrrolate/formoterol fumarate 18/9.6 μg. Adapted by permission from reference 15.

ongoing exacerbations, are at elevated risk of both cardiovascular and pulmonary events, including cardiopulmonary-related death (1, 2, 4–6, 28, 29), which is a leading cause of mortality in COPD (7, 8). Indeed, people living with COPD who have comorbid heart disease are at increased risk of all-cause, cardiovascular-related, and other-cause hospitalization in addition to an increased number of days hospitalized per year (30). In ETHOS, a greater proportion of deaths was adjudicated to be of cardiovascular causes (0.8%) compared with respiratory causes (0.4%) (13). Therefore, reducing risk of cardiovascular and cardiopulmonary events is crucial in minimizing the burden of COPD on patients and healthcare systems. To improve the outcomes of people living with COPD, it is clinically appropriate that composites of cardiopulmonary events are defined and tested such that future interventions may be robustly assessed.

For BFF versus GFF, reductions in the rate of first occurrence of some cardiovascular endpoints, including MACE, CVAESI, and cardiac AE, were observed. However, the reduction in the rate of first occurrence of severe cardiopulmonary events versus GFF was most pronounced or evident only in patients treated with BGF 320 and not BFF. The composite measure of severe cardiopulmonary event evaluates the interrelated and combined cardiovascular and respiratory involvement in COPD by incorporating MACE, severe COPD exacerbations (i.e., those leading to hospitalization or death), or death of a nonmalignant respiratory cause. Given that COPD exacerbations are a strong predictor of mortality risk (6), and because people living with COPD are at increased risk of cardiopulmonary-related death (7), it is perhaps not surprising that the reductions in the rate of severe cardiopulmonary events for BGF 320 versus GFF are likewise observed for risk of all-cause mortality (13).

A recent *post hoc* analysis of the IMPACT study reported a reduction in the rate of first occurrence of a composite cardiopulmonary endpoint consisting of severe COPD exacerbation, CVAESI leading to hospitalization or death, serious pneumonia AE of special interest, and all-cause mortality in people living with moderate to severe COPD treated with the ICS/LAMA/LABA fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) versus the LAMA/LABA UMEC/VI (31). However, that analysis reported no reduction in the rate of first occurrence of CVAESI with FF/UMEC/VI versus UMEC/VI. In contrast, the current analyses of ETHOS evaluate a range of cardiopulmonary endpoints and report a reduction in the rate of first occurrence of CVAESI with BGF 320 versus GFF. For comparison with the *post hoc* analyses of IMPACT, an additional analysis of ETHOS was conducted using a comparable composite outcome, which produced results consistent with the findings of the other analyses in ETHOS, with a 19% reduction in the rate of first occurrence of a serious CVAESI leading to hospitalization or death, all-cause mortality, exacerbation leading to hospitalization, or hospitalization for pneumonia for BGF 320 versus GFF.

COPD exacerbations are characterized by worsening airflow obstruction, lung hyperinflation, and airway and systemic inflammation (32, 33), but LAMA/LABA therapy (which forms two of the components of BGF) may decrease airway resistance and reduce lung hyperinflation, resulting in improved inspiratory capacity, reduced residual volume, and potentially improved cardiac function (34, 35). Benefits to lung function have also been observed with ICS, including reduced lung hyperinflation, which may mediate similar benefits to LAMA/LABA therapy beyond simply reducing

exacerbations (36–39). Indeed, decreasing lung hyperinflation improves respiratory mechanics, potentially leading to improved cardioventilatory coupling and increased peripheral oxygen delivery (40, 41). Finally, it has been proposed that bronchodilators with or without ICS may improve ventilation-perfusion mismatching (42–44) and that ICS may reduce airway and systemic inflammation in COPD (45). However, the potential mechanisms behind the association between COPD and cardiovascular disease are unclear. There is a potential for a dose–response effect of ICS on severe cardiopulmonary events, as observed in the present study, and previously all-cause mortality, as observed in a prior analysis of ETHOS (13), despite no significant difference in rates of moderate/severe exacerbations between BGF 320 and BGF 160 relative to GFF (12). As such, the potential effects of ICS, including on pulmonary vasculature, must be considered (18).

This study highlights the importance of identifying, monitoring, and treating both cardiovascular and respiratory events in COPD, which is an important insight, given that cardiovascular events may be underreported in COPD-designated studies. A strength of these analyses is that ETHOS was a clinical trial of an investigational medical product and, as such, was designed to robustly capture AEs, allowing the analysis of CVAESI beyond what may be possible in retrospective observational studies that are not designed to capture all relevant AEs.

Limitations

The limitations of this study must be acknowledged. Although the present findings highlight the potentially protective role of triple therapy with BGF versus dual bronchodilator therapy with GFF on cardiovascular and severe cardiopulmonary events in patients with moderate to very severe COPD and a history of exacerbations, the potential for dual bronchodilator therapy to increase rates of cardiopulmonary events should be considered. One nested case-control study reported significant increases in cardiovascular disease risk in patients with COPD who received LAMA, LABA, or LAMA/LABA for the first time in the prior year (46). A meta-analysis published in 2023 reported a 42% higher risk of MACE in patients with COPD treated with LAMA/LABA compared with LABA/ICS, but risk of MACE was not significantly higher in patients treated with LAMA/LABA than in those treated with LAMA or LABA alone, indicating a potentially beneficial effect of ICS on MACE (47). In contrast, a population cohort study reported no significant increase in the risk of composite or individual cardiovascular events in patients with COPD treated with LAMA/LABA versus LABA/ICS (48). Importantly, in two studies (PINNACLE-1 and PINNACLE-2) that evaluated the efficacy and safety of GFF versus its monocomponents in a population of patients with less severe COPD than the ETHOS population, the incidence of CVAESI was low and similar across treatments, and no clinically important differences were observed between treatments in the 24-hour Holter substudy of PINNACLE-2 (49). Of the few deaths reported in the PINNACLE studies, none were considered related to the study drug (49). ETHOS was a study in which patients with severe cardiovascular disease were excluded, and only patients with a history of moderate or severe exacerbations in the last 12 months were included, among other selection criteria. As such, the generalizability of the present findings may be limited to a subset of the overall COPD population who have a recent history of exacerbations and a relatively lower risk of cardiovascular events than patients with similarly severe COPD in clinical practice. Long-term placebo-controlled trials are considered unethical, given the observed benefits of ICS and bronchodilators in patients with COPD at risk of exacerbations; however, additional studies are warranted to determine the applicability of the present findings to the wider COPD population and to further evaluate the protective effect of BGF in patients at risk of cardiovascular and severe cardiopulmonary events.

The greater reductions in the rate of first occurrence of CVAESI, cardiac AE, and MACE relative to severe exacerbations must be considered in the context of differing sample sizes because of the differing frequency of events. The present analyses were conducted *post hoc*, were not powered to demonstrate a treatment effect for the reported endpoints, and were not adjusted for multiplicity; therefore, they should be considered exploratory in nature. Because of the low incidence of MACE in ETHOS ($n = 128$), CVAESI ($n = 431$) and cardiac AE ($n = 578$) were included as additional cardiovascular outcomes, allowing greater precision due to their higher incidence. The relative effect of BGF versus GFF on cardiac AE and CVAESI was comparable to, and thus supportive of, the effect of BGF on MACE.

Finally, given that the majority of patients in ETHOS used ICS before screening, most patients randomized to GFF discontinued ICS use at randomization, which may have resulted in increased rates of severe cardiopulmonary events, such as exacerbations (50). However, the effects of ICS withdrawal are mixed and vary according to a number of factors (51, 52). All time-to-event analyses included in this study were adjusted for ICS use at screening, and previously reported sensitivity analyses for time to severe exacerbation by prior ICS use did not substantially alter the benefit of BGF 320 versus GFF (53). Therefore, ICS withdrawal likely did not contribute to the results observed in this study.

Conclusions

These analyses of the ETHOS study indicate that BGF triple therapy is associated with reductions in the rate of first occurrence of cardiovascular and severe cardiopulmonary events compared with GFF dual therapy across an array of clinically relevant endpoints, including CVAESI, cardiac AEs, and the composite measure of severe cardiopulmonary events, in people living with moderate to very severe COPD and a history of COPD exacerbations. Given that cardiovascular and severe cardiopulmonary events are a major burden in COPD, these data highlight the importance of including cardiovascular and cardiopulmonary events as key endpoints in clinical trials for COPD; monitoring and preventing both cardiovascular and respiratory events are crucial to supporting positive outcomes in people living with COPD. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: D.S. is supported by the National Institute for Health Research Manchester Biomedical Research Centre. Medical writing support, under the guidance of the authors, was provided by Daniel Spindlow, M.Sc., CMC Connect, a division of IPG Health Medical Communications, funded by AstraZeneca, in accordance with Good Publication Practice (GPP 2022) guidelines (54).

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