Beta-blocker Therapy and Clinical Outcomes in Patients with Moderate COPD and Heightened Cardiovascular Risk

Original Research

Exacerbations of chronic obstructive pulmonary disease and cardiac events: a cohort analysis

Authors:

Ken M. Kunisaki, MD, MS[1,2]
Mark T. Dransfield, MD[3,4]
Julie A. Anderson, BSc, MA, MBA[5]
Robert D. Brook, MD[6]
Peter M.A. Calverley, MBChBDSc[7]
Bartolome R. Celli, MD[8]
Courtney Crim, MD[9]
Benjamin F. Hartley, MMath[10]
Fernando J. Martinez, MD, MS[11]
David E. Newby, PhD, DM, DSc[12]
Alexa A. Pragman, MD, PhD[1,2]
Jørgen Vestbo, DMSc[13]
Julie C. Yates, MS[9]
Dennis E. Niewoehner, MD[1,2]
on behalf of the SUMMIT Investigators

1: Minneapolis Veterans Affairs Health Care System, Minneapolis, USA
2: University of Minnesota, Minneapolis, USA
3: Lung Health Center, University of Alabama at Birmingham, Birmingham, USA
4: Birmingham VA Medical Center, Birmingham, USA
5: GlaxoSmithKline, Stockley Park, UK
6: University of Michigan, Ann Arbor, USA
7: University of Liverpool, Liverpool, UK
8: Brigham and Women's Hospital, Boston, USA
9: GlaxoSmithKline, Research Triangle Park, USA
10: Veramed Ltd, Twickenham, UK
11: Weill Cornell Medical College of Cornell University, New York, USA
12: University of Edinburgh, Edinburgh, UK
13: University of Manchester, Manchester, UK

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Corresponding author(s):
Ken Kunisaki, MD, MS
Associate Professor of Medicine
Minneapolis VA Health Care System
Pulmonary, Critical Care, and Sleep (111N)
One Veterans Drive
Minneapolis, MN, USA, 55417
+1 (612) 467-4400; office
+1 (612) 727-5634; fax
kunis001@umn.edu

Author contributions:

Conceived the current analysis: KMK, DENiewoehner
Designed the analysis: KMK, MTD, JAA, JCY, BFH, DENiewoehner
Obtained funding: n/a
Acquired the data: JAA, JCY, CC
Performed the primary statistical analyses: BFH, JAA
Drafted the manuscript: KMK
Provided critical input and revised the manuscript for important intellectual content and approved the final manuscript: All
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Short running title: COPD Exacerbations and Cardiac Events

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At a Glance Commentary

Scientific Knowledge on the Subject:

- Patients with COPD frequently experience cardiovascular disease (CVD).
- COPD exacerbations are associated with increased systemic inflammation, which is a risk factor for CVD.
- Preliminary data suggest that acute exacerbations of COPD (AECOPD) are associated with an increased risk of subsequent CVD events, but studies have relied on administrative data or non-adjudicated CVD event data.

What This Study Adds to the Field

- In this ~~large~~ cohort of 16,485 COPD patients with CVD or multiple CVD risk factors, exacerbations were followed by an increased risk of adjudicated CVD events, especially in hospitalized COPD patients and in the first 30 days following AECOPD.

Abstract

Rationale: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are common, associated with acute inflammation, and may increase subsequent cardiovascular disease (CVD) risk.

Objective: Determine if AECOPD events are associated with increased risk of subsequent CVD.

Methods: A secondary cohort analysis of the Study to Understand Mortality and MorbidITy (SUMMIT) trial, a convenience sample of current/former smokers with moderate COPD from 1,368 centers in 43 countries. All had CVD or increased CVD risk. AECOPD was defined as an increase in respiratory symptoms requiring treatment with antibiotics, systemic corticosteroids and/or hospitalization. CVD events were a composite outcome of cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischemic attack. All CVD events were adjudicated. Cox proportional hazards models compared the hazard for a CVD event prior to AECOPD versus following AECOPD.

Measurements and Main Results:

Among 16,485 participants in SUMMIT, 4,704 participants had at least one AECOPD and 688 had at least one CVD event. The hazard ratio (HR) for CVD events following AECOPD was increased, particularly in the first 30 days following AECOPD (HR 3.8; 95%CI: 2.7 to 5.5) and was elevated up to one year post-AECOPD. The 30-day HR following hospitalized AECOPD was more than two-fold greater (HR 9.9; 95%CI: 6.6 to 14.9).

Conclusions: In COPD patients with CVD or risk factors for CVD, exacerbations confer an increased risk of subsequent CVD events, especially in hospitalized patients and within the first 30 days post-exacerbation. Patients and clinicians should have heightened vigilance for early CVD events following AECOPD.

Trial Registration: ClinicalTrials.gov NCT01313676

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INTRODUCTION

Ischemic heart disease, stroke, and chronic obstructive pulmonary disease (COPD) are three leading causes of death globally.[1] These diseases share common risk factors such as older age and cigarette smoking, yet data suggest that COPD and lower lung function are independent risk factors for cardiovascular disease (CVD), even after adjustment for traditional CVD risk factors.[2-4]

The mechanisms by which COPD increases CVD risk are not clear, but patients with COPD often display abnormally high concentrations of circulating systemic inflammatory biomarkers such as C-reactive protein, interleukin-6, and fibrinogen[5]—biomarkers that predict CVD risk in the general population[6,7] and in COPD.[8] Acute exacerbations of COPD (AECOPD) are often associated with particularly high concentrations of these biomarkers[9] which can be slow to return to baseline.[10]

Additionally, many AECOPD events are triggered by infections,[11] and data have shown that infections (mostly respiratory, but also urinary and gastrointestinal) are associated with an increased risk for subsequent CVD events.[12-16] The reasons for this are not clear, but hypotheses have focused on infections as inducers of systemic inflammation and pro-coagulant pathways that subsequently lead to cardiovascular events.

Two previous studies have suggested that AECOPD increases risk for subsequent CVD, but both had significant methodologic limitations including use of administrative data to define COPD, AECOPD and CVD events[17] or use of non-adjudicated adverse event reporting data.[18]

The Study to Understand Mortality and MorbidITy (SUMMIT) trial was an international, multicenter trial of patients with COPD and either a history of CVD or heightened risk for CVD. SUMMIT assessed the impact of inhaler treatments on mortality and rigorously adjudicated CVD events, therefore reducing the risk of ascertainment bias and providing more accurate estimates of risk. We hypothesized that time periods following AECOPD would be associated with higher risk for CVD events compared with time periods free of AECOPD.

Some of the results of this study have been previously reported in the form of an abstract.[19]

METHODS

A detailed description of our methods is included with the **Online Supplement**. In brief, we performed a post-hoc cohort analysis using data in SUMMIT, a double-blind, parallel group, placebo-controlled, randomized trial conducted at 1,368 centers in 43 countries between 2011 and 2015. Details of the study design and main results are published.[20,21] Participants (n=16,485) were randomly assigned to receive either inhaled placebo, fluticasone furoate, vilanterol, or the combination of fluticasone furoate and vilanterol. The study showed no significant differences in risk of death or cardiovascular events between the four arms of the trial.

Participants were current or former smokers with at least a 10-pack-year smoking history, aged 40–80 years with a ratio of forced expiratory volume in 1 s to forced vital capacity (FEV_1/FVC) ≤70%, FEV_1 50%-70% of predicted, and a modified Medical Research Council dyspnea scale score of ≥2. Participants 40-59 years old were required to have a history of CVD, defined as coronary artery disease, peripheral arterial disease, stroke, myocardial infarction, or diabetes

mellitus with target organ disease. Participants 60-80 years old could have either a history of CVD or increased risk for CVD, defined as receiving medication for two or more of the following: hypercholesterolemia, hypertension, diabetes mellitus, or peripheral arterial disease.

Exclusion criteria included respiratory disorders other than COPD, lung reduction surgery, receiving long-term oxygen, chronic oral corticosteroid therapy, severe heart failure (New York Heart Association Class IV or ejection fraction <30%), life expectancy less than three years, and end-stage chronic renal disease.

Participants were seen every three months at which time data relating to AECOPD and CVD were assessed.

Statistical analysis

We used Cox proportional hazards models with time-dependent 'period' covariates, where the hazard for a CVD event was compared between the period prior to AECOPD ('baseline' in our tables) and following AECOPD (~~**Online Supplement**~~ **Figure ~~S~~1)**. AECOPD was defined as an increase in respiratory symptoms requiring treatment with antibiotics, systemic corticosteroids and/or hospitalization. Our primary outcome was a composite CVD outcome that included cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischemic attack. A clinical endpoint committee (CEC) **used data from medical records, witness interviews, autopsy reports, and death certificates to** adjudicate~~d~~ all CVD events using **standardized guidelines.**[22,23] ~~medical records, witness interviews, autopsy reports, and death certificates.~~

We excluded events where AECOPD and CVD were reported on the same day, as we were unable to determine which event happened first. We analyzed the hazard of post-AECOPD CVD events at 1-30 days, 31-90 days, 91 days-1 year, and >1 year following AECOPD events. Covariates are detailed in our table legends. In cases where participants experienced more than one AECOPD, only the first was used. Data were censored after the first CVD event.

Secondary analyses focused on: 1) only hospitalized AECOPDs, 2) only myocardial infarctions, 3) comparison of those with established CVD versus those with only increased CVD risk, 4) restriction to each of the four arms of the trial, and 5) restriction to only those who experienced an AECOPD event during the study.

RESULTS

Among the 16,485 participants in SUMMIT, 75% were male, 47% were current smokers, mean body mass index (BMI) was 28 kg/m^2 and 39% had a history of one or more AECOPD events in the year prior to enrolment **(Table 1)**.

Median participant on-treatment follow up time was 1.5 years with a total of 26,946 patient years of follow-up. During follow-up, 4,704 participants had at least one AECOPD and 688 had at least one adjudicated CVD event. The first CVD event was CV death in 271, myocardial infarction in 173, stroke in 127, unstable angina in 83, and transient ischemic attack in 34.

Depending on the particular analysis, between 0 to 9 participants were excluded due to reporting CVD and AECOPD on the same day.

A total of 487 participants experienced a CVD event during the baseline period (487 events in 21,624 patient years is 2.3 per 100 patient-years). Between days 1 to 30 following AECOPD, 32 participants experienced a CVD event (8.8 per 100 patient-years); 29 participants had a CVD event between days 31 to 90 (4.4 per 100 patient-years); 91 participants had a CVD event between day 91 to 1 year (4.0 per 100 patient-years) and 41 participants had a CVD event after 1 year (2.4 per 100 patient-years). Compared with pre-AECOPD baseline periods, the hazard of CVD events following AECOPD was increased, particularly in the first 30 days following AECOPD (HR 3.8; 95%CI: 2.7 to 5.5), though it remained increased between 31 days - 90 days and 91 days - 1 year, and was no longer increased beyond 1 year following AECOPD (**Table 2** and **Figure ~~1~~ 2**).

In a further analysis, we restricted the AECOPD events to only hospitalized AECOPD events and considered participants who had a non-hospitalized AECOPD to remain in the baseline period. A total of 605 participants experienced a CVD event during the baseline period (2.4 per 100 patient-years). Between days 1 to 30 following hospitalized AECOPD, 24 participants experienced a CVD event (26.7 per 100 patient-years); 15 participants had a CVD event between days 31 to 90 (9.9 per 100 patient-years); 24 participants had a CVD event between day 91 to 1 year (4.9 per 100 patient-years) and 11 participants had a CVD event after 1 year (3.3 per 100 patient-years). In this case, the post-AECOPD hazard for CVD events was again particularly increased in the first 30 days following hospitalized AECOPD (HR 9.9; 95%CI: 6.6

to 14.9), remained increased between 31 days - 90 days and 91 days - 1 year, but was not increased beyond one year following hospitalized AECOPD (**Table 2** and **Figure ~~1~~ 2**).

Analyses restricted only to those who experienced an AECOPD event during the study (n=4,629 with all covariates) showed that the hazard for CVD following AECOPD was again particularly increased in the first 30 days following AECOPD (HR 6.4; 95% CI: 4.1 to 10.2). The hazard was attenuated, but still significant, between 31 days - 1 year following AECOPD, and remained slightly elevated >1 year after AECOPD (**Table 3**).

Analyses restricted to only myocardial infarction events (i.e., excluding other non-myocardial infarction CVD events) showed similar results, with a substantially increased risk of myocardial infarction in the first 30 days following AECOPD, a lower, but still significant, risk between 31 days - 1 year, and no significant increased risk beyond 1 year (**Online Supplement, Table S1**).

Analyses stratified by whether participants entered the study with a history of established CVD or CVD risk are shown in **Online Supplement, Table S2**. The hazard ratio for experiencing a CVD event following AECOPD was again most pronounced in the first 30 days following AECOPD, regardless of whether participants entered the study with established CVD or CVD risk. Among those with established CVD, the younger and older age groups had similar 95% CI bounds for the hazard ratios at each time period post-AECOPD, but there were very few CVD events, so these estimates may not be reliable.

Lastly, we analyzed the hazard for CVD following AECOPD separately in each of the four original trial arms of the parent SUMMIT study. Results were again similar to that observed in our other analyses, with each arm demonstrating hazard ratios that were particularly increased in the first 30 days following AECOPD, remained increased between 31 days - 1 year, and were no longer significant beyond 1 year following AECOPD (**Online Supplement, Table S3**).

DISCUSSION

This analysis of prospectively collected data from a multi-center, international study of patients with moderately severe COPD and rigorously adjudicated CVD events supports the notion that AECOPD increases the risk for subsequent CVD events, especially in the first 30 days following an AECOPD. Moreover, the observed effect size was substantial, with a 4-fold increased hazard for CVD events following AECOPD, and a 10-fold increase in those hospitalized with AECOPD. These results suggest that clinicians and patients need to be vigilant for the occurrence of CVD events following AECOPD, especially in those hospitalized with AECOPD.

Our findings are notable for remarkable consistency among the primary analysis and the multiple secondary analyses regarding the particularly high CVD risk in the first 30 days following AECOPD, whether we analyzed all AECOPD events, hospitalized AECOPD events, myocardial infarctions only, or stratified by age and established CVD versus CVD risk. Our sample of over 16,000 study participants ~~is one of the largest prospective COPD studies~~

~~conducted to date and the multi-center, multi-national design~~ **enrolled from multiples sites and countries** increases the generalizability to patients seen in varying clinical settings. Our findings are further strengthened by the blinded adjudication of CVD events. This adjudication provides us with a high degree of confidence regarding the validity of the CVD events.

Our findings validate preliminary observations in the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial, where AECOPD was associated with a higher risk of cardiovascular SAEs in both the first 30 and first 180 days post-AECOPD, with higher risk in the first 30 days.[18] CVD event data in UPLIFT consisted of only serious adverse event (SAE) reporting data without detailed adjudication, and the analysis did not include adjustment for multiple potential confounders. Unlike SUMMIT, UPLIFT did not specifically select for COPD patients at risk for CVD, but in both UPLIFT and our SUMMIT results, associations between AECOPD and CVD were present whether patients entered the studies with a history of previously diagnosed CVD or not.

Our findings also build upon a previous study of AECOPD and CVD relationships using administrative data in England and Wales. Among those with administrative codes for physician-diagnosed COPD (not necessarily confirmed by spirometry), prescriptions for oral antibiotics and corticosteroids (considered a surrogate marker of AECOPD) were associated with a higher risk for subsequent myocardial infarctions and stroke.[17] These associations were dependent on the outcomes and time-period examined. For example, the increased risk for myocardial infarction was only observed for five days following a prescription for both antibiotics and steroids—there was no association with antibiotics alone, steroids alone, or beyond five days of the combination prescription. However, for stroke, the association was

194 significant up to 49 days after a prescription for a steroid or an antibiotic, but not the
195 combination steroid plus antibiotic. These complex observations may reflect the limitations of
196 administrative data, as compared with our study's strict criteria for spirometry confirmation of
197 COPD, prospective collection of pre-defined AECOPD and CVD data, and detailed
198 adjudication of CVD events.

199 AECOPD events are associated with elevated concentrations of circulating pro-inflammatory
200 biomarkers[24] that can be slow to return to baseline.[10] The high initial concentrations with slow
201 recovery might help explain why we observed the most risk for CVD in the first 30 days post-
202 AECOPD, but we continued to observe a statistically significant, albeit much smaller, risk up to
203 one year post-AECOPD. The prolonged duration of increased CVD risk is consistent with
204 studies that have shown that respiratory events such as pneumonia[13] and other respiratory
205 infections[14] are associated with prolonged CVD risk.

206 Inflammation might also explain why hospitalized AECOPD patients had a 30-day CVD risk
207 more than double that seen in those with less severe AECOPD. Hospitalized AECOPD
208 episodes are often associated with higher concentrations of circulating pro-inflammatory
209 biomarkers compared to AECOPD events treated outside of the hospital.[25] We did not
210 measure biomarkers in this study, so we were unable to determine the contribution of
211 inflammation to post-AECOPD CVD risk. We were also unable to test other potential
212 mechanisms such as AECOPD leading to hypoxemia, increased respiratory muscle work
213 diverting perfusion from the coronary circulation, induction of a pro-thrombotic state, increases
214 in blood pressure, or worsening adherence to non-respiratory medications.

From a therapeutic standpoint, our data suggest that the immediate post-AECOPD period is a window of heightened CVD susceptibility, and therefore future studies should test interventions in this period to reduce CVD risk. Possible interventions to test might include established CVD therapies (e.g. antiplatelet agents, statins, and/or beta blockers) and/or experimental CVD interventions (e.g. anti-inflammatory drugs).

Our study has several important limitations. SUMMIT participants were selected based on being at high CVD risk either due to pre-existing disease or having multiple risk factors for CVD. Although estimates of CVD prevalence in patients with COPD have ranged from 28% to 70%,[3] our findings may not apply to COPD patients without CVD or CVD risk factors. SUMMIT participation was also restricted to those with FEV_1 between 50%-70% of predicted, so we cannot generalize our findings to those with milder or more severe airflow limitation. Our follow-up time was also relatively short, at a median of 1.5 years. While data from our study and other studies suggest that most of the excess CVD risk occurs within the first year after AECOPD, we had limited power to study long-term event risk beyond one year. Lastly, although CVD events were adjudicated, AECOPD events were self-reported and not adjudicated. **Therefore, we cannot exclude the possibility that some AECOPD events were CVD events to begin with.** However, our AECOPD definition is that used by nearly every contemporary COPD trial and is a definition that has proven to be modifiable by treatments such as inhalers and oral medications.[26] Moreover, we found even stronger associations in hospitalized patients who ~~have presumably had~~ **typically undergo** more detailed assessments for other clinical etiologies of acute-onset dyspnea (e.g. pneumonia, myocardial infarction, pulmonary embolism) compared to outpatients. Therefore, we think misclassification of AECOPD is not likely.

CONCLUSION

In COPD patients with CVD or risk factors for CVD, exacerbations confer an increased risk of subsequent CVD events, especially in hospitalized patients and within the first 30 days post-exacerbation. Patients and clinicians should have heightened vigilance for early CVD events in this patient group following AECOPD.

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IRB approval: Institutional review board (IRB) approval was obtained at each of the 1,368 participating study centers prior to study initiation.

Declaration of interests:

MTD has received consultancy fees from GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, and Genentech, and has received research support from GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Novartis, Yungjin, PneumRx, Pulmonx, and Mereo.

RDB has received consultancy fees from GlaxoSmithKline.

PMAC has advised Boehringer Ingelheim, GSK, AstraZeneca and Takeda on the design and conduct of clinical trials and has spoken at meetings sponsored by these companies and by Novartis.

BRC has received consultancy fees from GlaxoSmithKline, is a board/advisory committee member for GlaxoSmithKline, AstraZeneca, and Boehringer Ingelheim, and has received research support from AstraZeneca.

FJM has received consultancy fees from Axon Communication, Johnson & Johnson, Bioscale, and Unity Biotechnology, is a board/advisory committee member for Bayer, Boehringer

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JV has received consultancy and speaker fees from GlaxoSmithKline, AstraZeneca, Chiesi, Boehringer Ingelheim, and Novartis.

JAA, CC, and JCY are employees of GlaxoSmithKline and hold shares in the company.

DENiewoehner has received consultancy fees from GlaxoSmithKline, Boehringer Ingelheim, and Forrest Research.

BH was a previous employee of GlaxoSmithKline, holds shares in the company and is an employee of Veramed who are contracted to perform statistical analyses for GlaxoSmithKline.

KMK and AAP declare no conflicts of interest.

Disclaimer: The views expressed in this article are those of the authors and do not reflect the views of the United States Government, the Department of Veterans Affairs, the funders, the sponsors, or any of the authors' affiliated academic institutions.

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Figure 1. Graphical representation of analytic method. All study participants with any follow-up time contribute to the analysis. Participants can have one of four possible patterns, as graphically shown below, from the top down: 1) No acute exacerbation of chronic obstructive pulmonary disease [AECOPD] (black bars) and no cardiovascular disease [CVD] events (as depicted by red bolts), 2) No AECOPD, but with CVD event, 3) AECOPD (as indicated by blue arrow/bar), but with no CVD event, and 4) AECOPD and CVD event. All participants with any follow-up time contribute to baseline hazard data for CVD events. Participants with AECOPD events contribute baseline hazard data for both baseline, exacerbation-free periods (black bars) and comparison data regarding post-AECOPD hazard data at 1-30 days after AECOPD (green bars), 31-90 days after AECOPD (yellow bars), 91 days-1 year after AECOPD (orange bars) and >1 year after AECOPD (grey bars). Data are censored at the time of a CVD event. Secondary analyses included: 1) only hospitalized AECOPD events, where participants who had a non-hospitalized AECOPD remained in the baseline period (**Table 2**), and 2) restriction to only the last two groups who experienced an AECOPD during the study (**Table 3**).

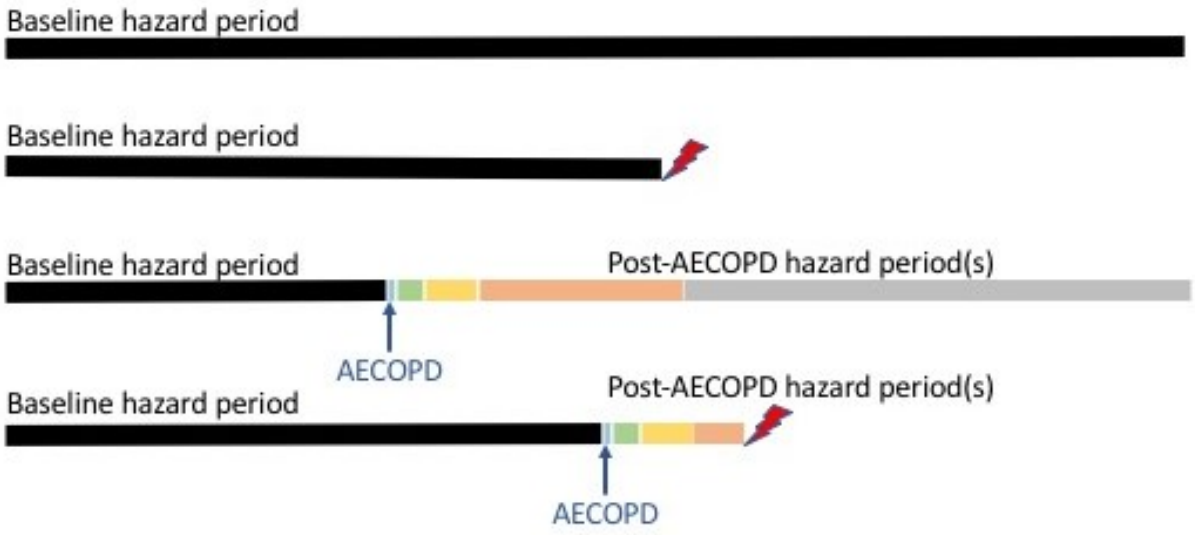

Figure ~~1~~ 2. Hazard ratios (95% confidence intervals) for cardiovascular disease (cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischemic attack) following an acute exacerbation of chronic obstructive pulmonary disease.

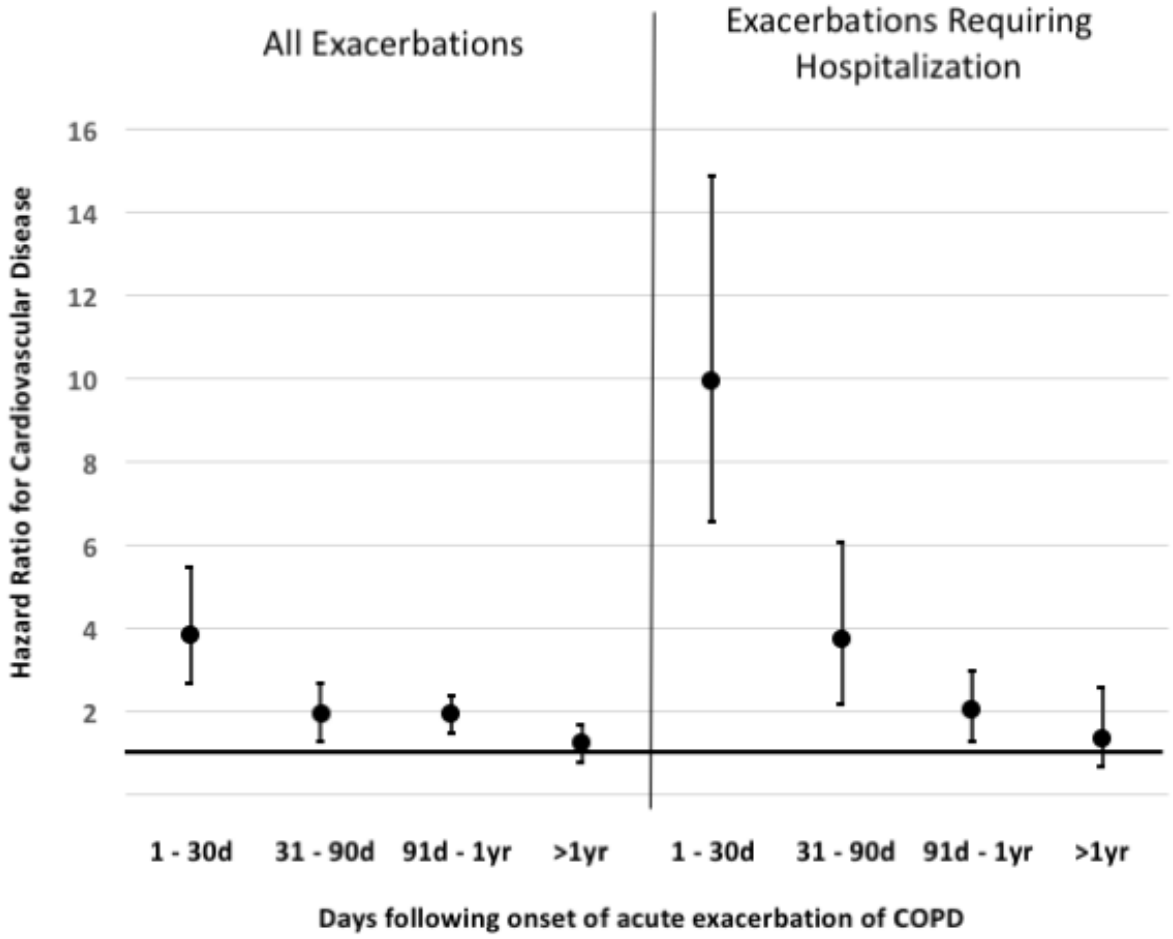

Table 1. Study participant characteristics. Reported as mean (SD) or n (%).

	Total (n = 16,485)
Age (years)	65 (8)
Female	4,196 (25%)
Race	
White	13,357 (81%)
Asian	2,724 (17%)
Other	404 (2%)
Body mass index (kg/m^2)	28 (6)
Current Smokers	7,678 (47%)
Smoking History (pack-years)	41 (24)
Systolic blood pressure, mmHg	135 (15)
Diastolic blood pressure, mmHg	80 (10)
Cardiac comorbidities	
Coronary artery disease	8,379 (51%)
Previous myocardial infarction	2,774 (17%)
Previous stroke	1,595 (10%)
Hypercholesterolemia	11,518 (70%)
Hypertension	14,851 (90%)
Diabetes mellitus	4,997 (30%)
Cardiac medications	
Antiplatelet	8,517 (52%)
Statin	10,721 (65%)
Beta-blocker	5,667 (34%)

Diuretic	6,148 (37%)
Post-Bronchodilator FEV_1 (L)	1.70 (0.40)
% Predicted post-bronchodilator FEV_1	59.7 (6.1)
Pre-study COPD inhaler therapy	
Long-acting β-agonist	5,769 (35%)
Long-acting muscarinic antagonist	2,550 (15%)
Inhaled corticosteroid	5,486 (33%)
Pre-study exacerbations in 12 months before study	
0	10,021 (61%)
1	4,020 (24%)
2+	2,444 (15%)

Abbreviations: COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in 1 second.

Table 2. Hazard ratios for cardiovascular disease (CVD) event (cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischemic attack) following an acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Analysis shown for all exacerbations (top) and for exacerbations requiring hospitalization (bottom).

Period	Number of Participants in Period	Observed Follow-up in Period (Patient-Years)	Number of Participants with adjudicated CVD event	Hazard Ratio (95% CI)
All Exacerbations				
Baseline, AECOPD-free	16,477	21,624	487	*-reference-*
1 – 30 days	4,639	363	32	3.8 (2.7 to 5.5)
31 days – 90 days	4,235	658	29	1.9 (1.3 to 2.7)
91 days – 1 year	3,779	2,267	91	1.9 (1.5 to 2.4)
>1 year	2,179	1,744	41	1.2 (0.8 to 1.7)
Exacerbations Requiring Hospitalization				
Baseline, AECOPD-free	16,476	25,595	605	*-reference-*
1 – 30 days	1,243	90	24	9.9 (6.6 to 14.9)
31 – 90 days	998	152	15	3.7 (2.2 to 6.1)
91 days – 1 year	862	487	24	2.0 (1.3 to 3.0)
>1 year	447	330	11	1.3 (0.7 to 2.6)

Covariates included: AECOPD period (baseline free of AECOPD or other post-AECOPD periods as in Figure 1), treatment assignment arm, age, sex, body mass index (BMI), region, race, ethnicity, ischemic and vascular indicators (e.g. previous treatment of coronary or vascular disease), cardiovascular disease/risk indicators (with CVD; with CV risk), smoking status, previous exacerbation history, and percent predicted post-bronchodilator FEV_1

8 participants were excluded from the 'All Exacerbations' analysis due to experiencing an AECOPD and CVD event on the same day; 9 were excluded from the 'Exacerbations Requiring Hospitalization' analysis due to experiencing an AECOPD and CVD event on the same day. 183 participants were excluded from the calculation of the Hazard Ratios in both analyses because they did not have all model covariates.

Table 3. Secondary analysis restricted to only those study participants who experienced an AECOPD event during the study. Hazard ratios for CVD events following an AECOPD. Due to small numbers in this restricted analysis, the post-AECOPD periods of 31-90 days and 90 days-1 year were combined.

Period	Number of Participants in Period	Observed Follow-up in Period (Patient-Years)	Number of Participants with adjudicated CVD event	Hazard Ratio (95% CI)
Baseline, AECOPD-free	4,696	3,695	55	*-reference-*
1 – 30 days	4,639	363	32	6.4 (4.1 to 10.2)
31 days – 1 year	4,235	2,926	120	3.0 (2.1 to 4.4)
>1 year	2,179	1,744	41	1.8 (1.1 to 3.1)

Covariates included: AECOPD period (baseline free of AECOPD or other post-AECOPD periods as in Figure 1), treatment assignment arm, age, sex, body mass index (BMI), region, race, ethnicity, ischemic and vascular indicators (e.g. previous treatment of coronary or vascular disease), cardiovascular disease/risk indicators (with CVD; with CV risk), smoking status, previous exacerbation history, and percent predicted post-bronchodilator FEV_1

8 participants were excluded due to experiencing an AECOPD and CVD event on the same day. 67 participants were excluded from the calculation of the Hazard Ratios because they did not have all model covariates.