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Exacerbations of Chronic Obstructive Pulmonary Disease and Cardiac Events

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Original Research

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

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<u>At a Glance Commentary</u>

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

1

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).

21 **Conclusions:** In COPD patients with CVD or risk factors for CVD, exacerbations confer an

22 increased risk of subsequent CVD events, especially in hospitalized patients and within the

23 first 30 days post-exacerbation. Patients and clinicians should have heightened vigilance for

24 early CVD events following AECOPD.

25 **Trial Registration:** ClinicalTrials.gov NCT01313676

31

32

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]

53 The Study to Understand Mortality and MorbidITy (SUMMIT) trial was an international,

54 multicenter trial of patients with COPD and either a history of CVD or heightened risk for CVD.

55 SUMMIT assessed the impact of inhaler treatments on mortality and rigorously adjudicated

56 CVD events, therefore reducing the risk of ascertainment bias and providing more accurate

57 estimates of risk. We hypothesized that time periods following AECOPD would be associated

58 with higher risk for CVD events compared with time periods free of AECOPD.

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

60 **<u>METHODS</u>**

61 A detailed description of our methods is included with the **<u>Online Supplement</u>**. In brief, we

62 performed a post-hoc cohort analysis using data in SUMMIT, a double-blind, parallel group,

63 placebo-controlled, randomized trial conducted at 1,368 centers in 43 countries between 2011

64 and 2015. Details of the study design and main results are published.[20,21] Participants

65 (n=16,485) were randomly assigned to receive either inhaled placebo, fluticasone furoate,

66 vilanterol, or the combination of fluticasone furoate and vilanterol. The study showed no

67 significant differences in risk of death or cardiovascular events between the four arms of the

68 trial.

69 Participants were current or former smokers with at least a 10-pack-year smoking history, aged

70 40–80 years with a ratio of forced expiratory volume in 1 s to forced vital capacity (FEV_1/FVC)

71 ≤70%, FEV_1 50%-70% of predicted, and a modified Medical Research Council dyspnea scale

72 score of ≥2. Participants 40-59 years old were required to have a history of CVD, defined as

73 coronary artery disease, peripheral arterial disease, stroke, myocardial infarction, or diabetes

74 mellitus with target organ disease. Participants 60-80 years old could have either a history of

75 CVD or increased risk for CVD, defined as receiving medication for two or more of the

76 following: hypercholesterolemia, hypertension, diabetes mellitus, or peripheral arterial disease.

77 Exclusion criteria included respiratory disorders other than COPD, lung reduction surgery,

78 receiving long-term oxygen, chronic oral corticosteroid therapy, severe heart failure (New York

79 Heart Association Class IV or ejection fraction <30%), life expectancy less than three years,

80 and end-stage chronic renal disease.

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

82 were assessed.

83 Statistical analysis

84 We used Cox proportional hazards models with time-dependent 'period' covariates, where the

85 hazard for a CVD event was compared between the period prior to AECOPD ('baseline' in our

86 tables) and following AECOPD (~~Online Supplement~~ **Figure S1)**. AECOPD was defined as an

87 increase in respiratory symptoms requiring treatment with antibiotics, systemic corticosteroids

88 and/or hospitalization. Our primary outcome was a composite CVD outcome that included

89 cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischemic

90 attack. A clinical endpoint committee (CEC) **used data from medical records, witness**

91 **interviews, autopsy reports, and death certificates to** adjudicate~~d~~ all CVD events using

92 **standardized guidelines.**[22,23] ~~medical records, witness interviews, autopsy reports, and death~~

93 ~~certificates.~~

5

94 We excluded events where AECOPD and CVD were reported on the same day, as we were

95 unable to determine which event happened first. We analyzed the hazard of post-AECOPD

96 CVD events at 1-30 days, 31-90 days, 91 days-1 year, and >1 year following AECOPD events.

97 Covariates are detailed in our table legends. In cases where participants experienced more

98 than one AECOPD, only the first was used. Data were censored after the first CVD event.

99 Secondary analyses focused on: 1) only hospitalized AECOPDs, 2) only myocardial

100 infarctions, 3) comparison of those with established CVD versus those with only increased

101 CVD risk, 4) restriction to each of the four arms of the trial, and 5) restriction to only those who

102 experienced an AECOPD event during the study.

103

104 **RESULTS**

105 Among the 16,485 participants in SUMMIT, 75% were male, 47% were current smokers, mean

106 body mass index (BMI) was 28 kg/m^2 and 39% had a history of one or more AECOPD events

107 in the year prior to enrolment **(Table 1)**.

108 Median participant on-treatment follow up time was 1.5 years with a total of 26,946 patient

109 years of follow-up. During follow-up, 4,704 participants had at least one AECOPD and 688 had

110 at least one adjudicated CVD event. The first CVD event was CV death in 271, myocardial

111 infarction in 173, stroke in 127, unstable angina in 83, and transient ischemic attack in 34.

112   Depending on the particular analysis, between 0 to 9 participants were excluded due to

113   reporting CVD and AECOPD on the same day.

114   A total of 487 participants experienced a CVD event during the baseline period (487 events in

115   21,624 patient years is 2.3 per 100 patient-years). Between days 1 to 30 following AECOPD,

116   32 participants experienced a CVD event (8.8 per 100 patient-years); 29 participants had a

117   CVD event between days 31 to 90 (4.4 per 100 patient-years); 91 participants had a CVD

118   event between day 91 to 1 year (4.0 per 100 patient-years) and 41 participants had a CVD

119   event after 1 year (2.4 per 100 patient-years). Compared with pre-AECOPD baseline periods,

120   the hazard of CVD events following AECOPD was increased, particularly in the first 30 days

121   following AECOPD (HR 3.8; 95%CI: 2.7 to 5.5), though it remained increased between 31

122   days - 90 days and 91 days - 1 year, and was no longer increased beyond 1 year following

123   AECOPD (**Table 2** and **Figure 1 2**).

124   In a further analysis, we restricted the AECOPD events to only hospitalized AECOPD events

125   and considered participants who had a non-hospitalized AECOPD to remain in the baseline

126   period. A total of 605 participants experienced a CVD event during the baseline period (2.4 per

127   100 patient-years). Between days 1 to 30 following hospitalized AECOPD, 24 participants

128   experienced a CVD event (26.7 per 100 patient-years); 15 participants had a CVD event

129   between days 31 to 90 (9.9 per 100 patient-years); 24 participants had a CVD event between

130   day 91 to 1 year (4.9 per 100 patient-years) and 11 participants had a CVD event after 1 year

131   (3.3 per 100 patient-years). In this case, the post-AECOPD hazard for CVD events was again

132   particularly increased in the first 30 days following hospitalized AECOPD (HR 9.9; 95%CI: 6.6

133 to 14.9), remained increased between 31 days - 90 days and 91 days - 1 year, but was not

134 increased beyond one year following hospitalized AECOPD (**Table 2** and **Figure ~~1~~ 2**).

135 Analyses restricted only to those who experienced an AECOPD event during the study

136 (n=4,629 with all covariates) showed that the hazard for CVD following AECOPD was again

137 particularly increased in the first 30 days following AECOPD (HR 6.4; 95% CI: 4.1 to 10.2). The

138 hazard was attenuated, but still significant, between 31 days - 1 year following AECOPD, and

139 remained slightly elevated >1 year after AECOPD (**Table 3**).

140 Analyses restricted to only myocardial infarction events (i.e., excluding other non-myocardial

141 infarction CVD events) showed similar results, with a substantially increased risk of myocardial

142 infarction in the first 30 days following AECOPD, a lower, but still significant, risk between 31

143 days - 1 year, and no significant increased risk beyond 1 year (**Online Supplement, Table**

144 **S1**).

145 Analyses stratified by whether participants entered the study with a history of established CVD

146 or CVD risk are shown in **Online Supplement, Table S2**. The hazard ratio for experiencing a

147 CVD event following AECOPD was again most pronounced in the first 30 days following

148 AECOPD, regardless of whether participants entered the study with established CVD or CVD

149 risk. Among those with established CVD, the younger and older age groups had similar 95%

150 CI bounds for the hazard ratios at each time period post-AECOPD, but there were very few

151 CVD events, so these estimates may not be reliable.

152 Lastly, we analyzed the hazard for CVD following AECOPD separately in each of the four

153 original trial arms of the parent SUMMIT study. Results were again similar to that observed in

154 our other analyses, with each arm demonstrating hazard ratios that were particularly increased

155 in the first 30 days following AECOPD, remained increased between 31 days - 1 year, and

156 were no longer significant beyond 1 year following AECOPD (**Online Supplement, Table S3**).

157

158 **DISCUSSION**

159 This analysis of prospectively collected data from a multi-center, international study of patients

160 with moderately severe COPD and rigorously adjudicated CVD events supports the notion that

161 AECOPD increases the risk for subsequent CVD events, especially in the first 30 days

162 following an AECOPD. Moreover, the observed effect size was substantial, with a 4-fold

163 increased hazard for CVD events following AECOPD, and a 10-fold increase in those

164 hospitalized with AECOPD. These results suggest that clinicians and patients need to be

165 vigilant for the occurrence of CVD events following AECOPD, especially in those hospitalized

166 with AECOPD.

167 Our findings are notable for remarkable consistency among the primary analysis and the

168 multiple secondary analyses regarding the particularly high CVD risk in the first 30 days

169 following AECOPD, whether we analyzed all AECOPD events, hospitalized AECOPD events,

170 myocardial infarctions only, or stratified by age and established CVD versus CVD risk. Our

171 sample of over 16,000 study participants is one of the largest prospective COPD studies

9

172 ~~conducted to date and the multi-center, multi-national design~~ **enrolled from multiples sites**

173 **and countries** increases the generalizability to patients seen in varying clinical settings. Our

174 findings are further strengthened by the blinded adjudication of CVD events. This adjudication

175 provides us with a high degree of confidence regarding the validity of the CVD events.

176 Our findings validate preliminary observations in the Understanding Potential Long-term

177 Impacts on Function with Tiotropium (UPLIFT) trial, where AECOPD was associated with a

178 higher risk of cardiovascular SAEs in both the first 30 and first 180 days post-AECOPD, with

179 higher risk in the first 30 days.[18] CVD event data in UPLIFT consisted of only serious adverse

180 event (SAE) reporting data without detailed adjudication, and the analysis did not include

181 adjustment for multiple potential confounders. Unlike SUMMIT, UPLIFT did not specifically

182 select for COPD patients at risk for CVD, but in both UPLIFT and our SUMMIT results,

183 associations between AECOPD and CVD were present whether patients entered the studies

184 with a history of previously diagnosed CVD or not.

185 Our findings also build upon a previous study of AECOPD and CVD relationships using

186 administrative data in England and Wales. Among those with administrative codes for

187 physician-diagnosed COPD (not necessarily confirmed by spirometry), prescriptions for oral

188 antibiotics and corticosteroids (considered a surrogate marker of AECOPD) were associated

189 with a higher risk for subsequent myocardial infarctions and stroke.[17] These associations were

190 dependent on the outcomes and time-period examined. For example, the increased risk for

191 myocardial infarction was only observed for five days following a prescription for both

192 antibiotics and steroids—there was no association with antibiotics alone, steroids alone, or

193 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.

238

<u>CONCLUSION</u>

240   In COPD patients with CVD or risk factors for CVD, exacerbations confer an increased risk of

241   subsequent CVD events, especially in hospitalized patients and within the first 30 days post-

242   exacerbation. Patients and clinicians should have heightened vigilance for early CVD events in

243   this patient group following AECOPD.

244

265   Ingelheim, Centocor, Gilead Sciences, Genentech, Ikaria, Kadmon, Nycomed/Takeda, Pfizer,

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273   member for GlaxoSmithKline, has received speaker fees from GlaxoSmithKline, and has

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275   JV has received consultancy and speaker fees from GlaxoSmithKline, AstraZeneca, Chiesi,

276   Boehringer Ingelheim, and Novartis.

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

278   DENiewoehner has received consultancy fees from GlaxoSmithKline, Boehringer Ingelheim,

279   and Forrest Research.

280   BH was a previous employee of GlaxoSmithKline, holds shares in the company and is an

281   employee of Veramed who are contracted to perform statistical analyses for GlaxoSmithKline.

282   KMK and AAP declare no conflicts of interest.

283

284   <u>Disclaimer:</u> The views expressed in this article are those of the authors and do not reflect the

285   views of the United States Government, the Department of Veterans Affairs, the funders, the

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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**).

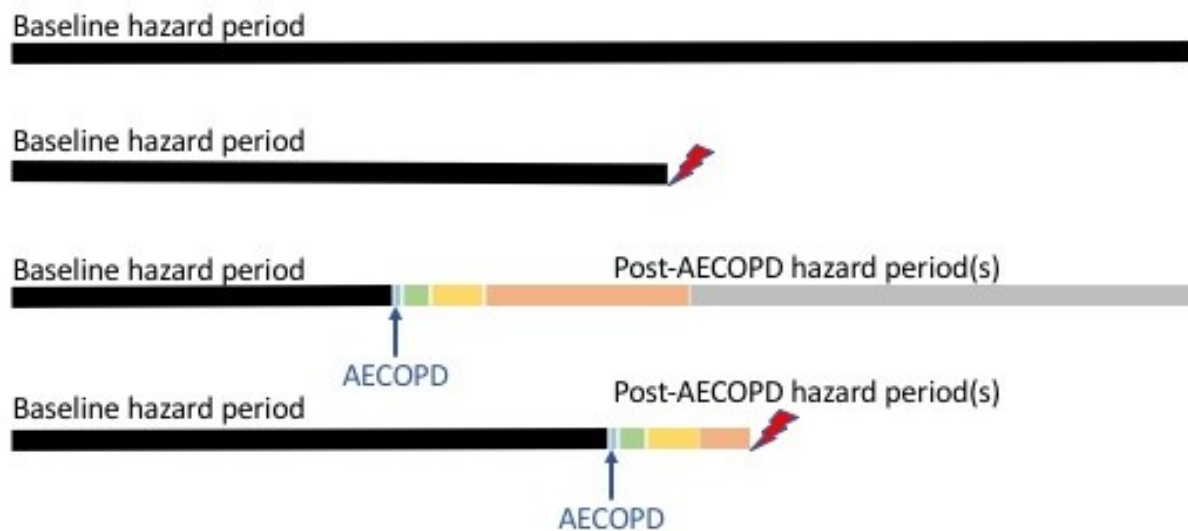**Figure ~~1~~ 2**. Hazard ratios (95% confidence intervals) for cardiovascular disease (cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischemic attack) following an acute exacerbation of chronic obstructive pulmonary disease.
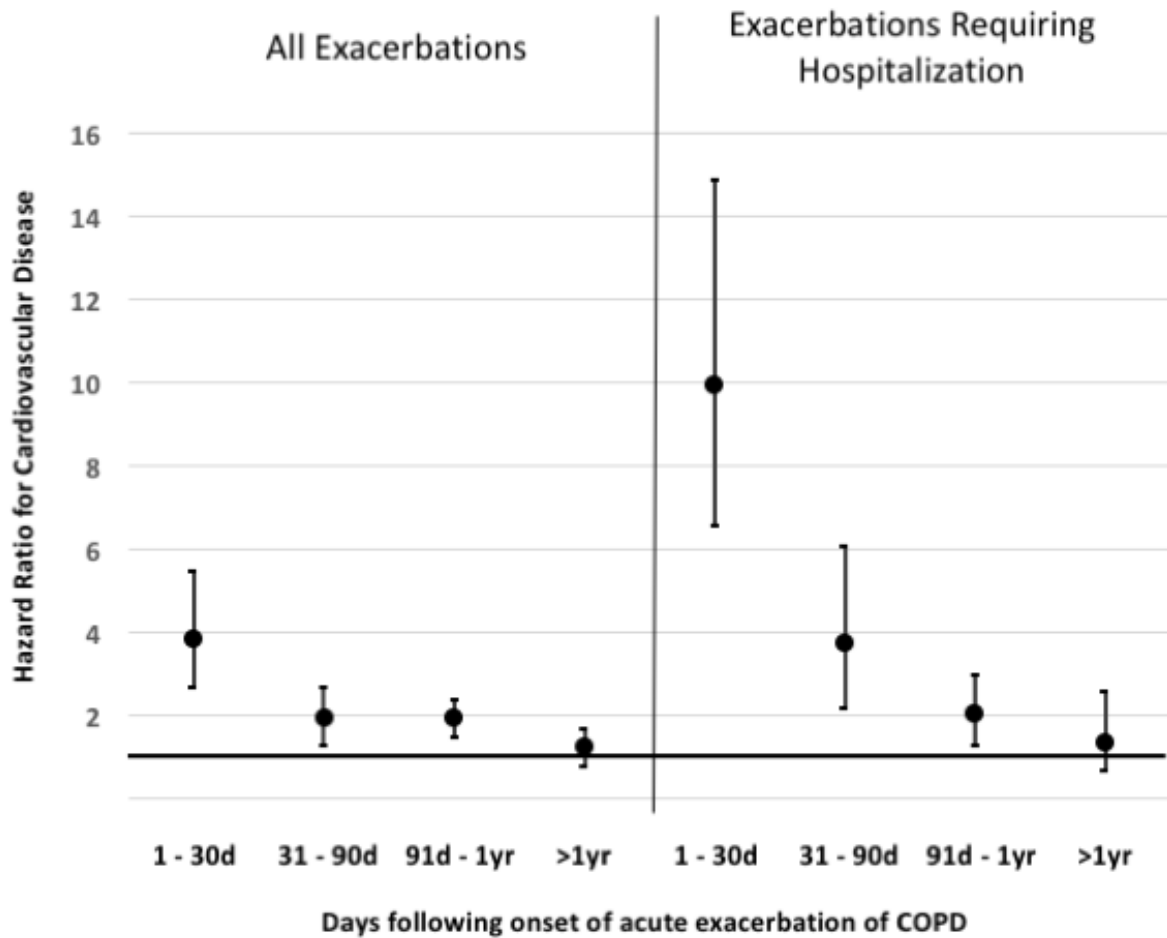
Table 1. Study participant characteristics. Reported as mean (SD) or n (%).

	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.