

# Association of Chronic Obstructive Pulmonary Disease with Morbidity and Mortality in Patients with Peripheral Artery Disease: Insights from the EUCLID Trial

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**Background:** Patients with chronic obstructive pulmonary disease (COPD) are at increased risk of developing lower extremity peripheral artery disease (PAD) and suffering PAD-related morbidity and mortality. However, the effect and burden of COPD on patients with PAD is less well defined. This post hoc analysis from EUCLID aimed to analyze the risk of major adverse cardiovascular events (MACE) and major adverse limb events (MALE) in patients with PAD and concomitant COPD compared with those without COPD, and to describe the adverse events specific to patients with COPD.

**Methods:** EUCLID randomized 13,885 patients with symptomatic PAD to monotherapy with either ticagrelor or clopidogrel for the prevention of MACE. In this analysis, MACE, MALE, mortality, and adverse events were compared between groups with and without COPD using unadjusted and adjusted Cox proportional hazards model.

**Results:** Of the 13,883 patients with COPD status available at baseline, 11% (n=1538) had COPD. Patients with COPD had a higher risk of MACE (6.02 vs 4.29 events/100 patient-years; p<0.001) due to a significantly higher risk of myocardial infarction (MI) (3.55 vs 1.85 events/100 patient-years; p<0.001) when compared with patients without COPD. These risks persisted after adjustment (MACE: adjusted hazard ratio (aHR) 1.30, 95% confidence interval [CI] 1.11–1.52; p<0.001; MI: aHR 1.45, 95% CI 1.18–1.77; p<0.001). However, patients with COPD did not have an increased risk of MALE or major bleeding. Patients with COPD were more frequently hospitalized for dyspnea and pneumonia (2.66 vs 0.9 events/100 patient-years; aHR 2.77, 95% CI 2.12–3.63; p<0.001) and more frequently discontinued study drug prematurely (19.36 vs 12.54 events/100 patient-years; p<0.001; aHR 1.34, 95% CI 1.22–1.47; p<0.001).

**Conclusion:** In patients with comorbid PAD and COPD, the risks of MACE, respiratory-related adverse events, and premature study drug discontinuation were higher when compared with patients without COPD.

**Registration:** ClinicalTrials.gov: NCT01732822.

**Keywords:** peripheral artery disease, chronic obstructive pulmonary disease, major adverse cardiovascular events

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide.<sup>1</sup> Due to shared risk factors, particularly cigarette smoking, patients with COPD are at increased risk of developing cardiovascular disease.<sup>2–4</sup> In patients with known COPD, peripheral artery disease (PAD) is more prevalent

than in age-matched patients without COPD, affecting 8.8% of a cohort of patients with COPD with a mean age of 65 compared with 1.8% of those without COPD.<sup>5</sup> In prospective studies of patients with COPD, a diagnosis of PAD was associated with lower exercise tolerance, a higher incidence of major adverse cardiovascular events (MACE), and higher all-cause mortality.<sup>6–8</sup>

In contrast, the prevalence of COPD among patients with PAD, as well as the added risk of MACE, major adverse limb events (MALE), and respiratory events associated with COPD, are less well defined. Understanding the additional burden associated with COPD concomitant with PAD has both clinical and research implications, including understanding the increased cardiovascular and limb risk, as well as adherence to medications, that may improve trial planning and patient management in this population. The EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) study was a large cardiovascular outcomes trial in patients with symptomatic PAD that compared monotherapy between ticagrelor and clopidogrel, and it affords an opportunity to study the natural history of patients with PAD.<sup>9</sup> Of note, ticagrelor carries the unique side effect of dyspnea, which may disproportionately affect medication adherence, and therefore clinical outcomes, among this cohort of patients with COPD.<sup>9</sup> The primary aim of this analysis was to compare the occurrence of MACE and MALE in patients with PAD with and without concomitant COPD. The secondary aims were to compare all-cause mortality, Thrombolysis in Myocardial Infarction (TIMI) major bleeding, serious adverse events (all-cause and respiratory-related hospitalizations, premature study drug discontinuation), and non-serious adverse events (dyspnea, pneumonia, and malignancy) between groups in order to characterize the added burden of hospitalizations and adverse events associated with COPD. We hypothesized that patients with PAD and COPD have higher rates of MACE and MALE, are hospitalized for respiratory causes more often, prematurely discontinue study drug more frequently, and have dyspnea, pneumonia, and malignancy more often.

## Methods

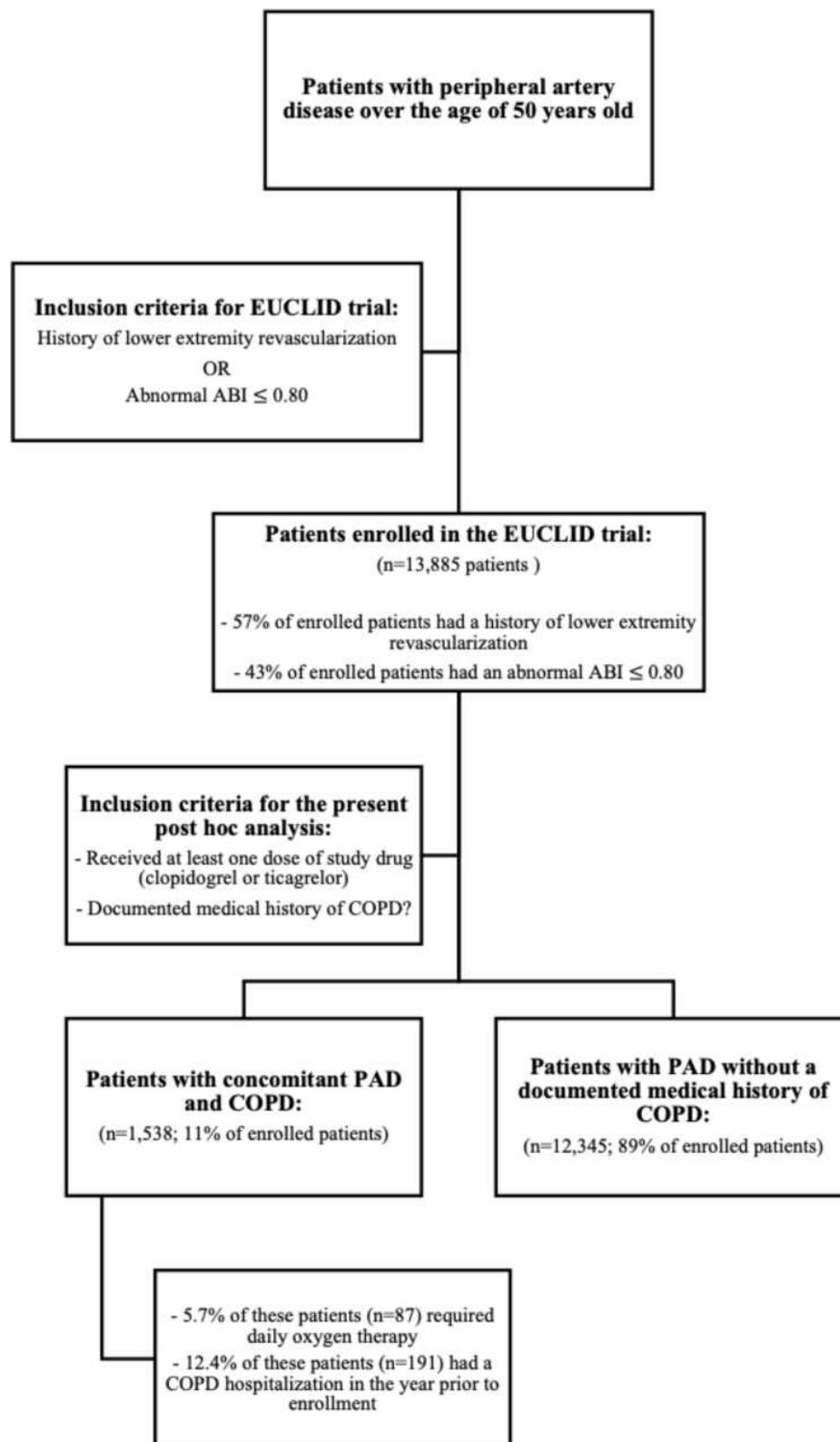
### Study Design and Participants

Details of the EUCLID study design have been previously published.<sup>9,10</sup> In brief, EUCLID was a multi-center, double-blind, active-comparator randomized controlled trial of 13,885 patients aged 50 years or older with lower

extremity PAD comparing monotherapy with either ticagrelor (90 mg twice daily) or clopidogrel (75 mg once daily) in a 1:1 fashion. Enrollment criteria included either a history of lower extremity revascularization or an abnormal ankle-brachial index (ABI)  $\leq 0.80$ . The presence or absence of COPD was assessed at the enrolling study visit on the basis of the documented medical history. For patients with a documented medical history of COPD, further data regarding the patients' supplemental oxygen requirement and previous COPD-related hospitalizations was obtained (Figure 1). Information on COPD severity (i.e., Global Initiative for Obstructive Lung Disease [GOLD] criteria and pulmonary function testing) was not ascertained at any point in the study. The study was approved by all local Ethics Committees and Institutional Review Boards (Appendix Table I).

## Outcomes

The primary efficacy and safety endpoints in EUCLID were MACE (a composite of cardiovascular death, myocardial infarction, or ischemic stroke) and major bleeding according to TIMI criteria. For the present analysis, our primary efficacy outcomes were MACE and MALE (a composite of hospitalization for acute limb ischemia or major lower extremity amputation). Secondary endpoints of interest were all-cause mortality, serious adverse events (all-cause hospitalization, hospitalization for dyspnea or pneumonia, and premature study drug discontinuation), and non-serious adverse events of special interest (dyspnea, pneumonia, malignancy, and any respiratory-related adverse event). Serious adverse events were defined as adverse events resulting in death or hospitalization. Each endpoint and adverse event was collected via the case report form at every clinic visit. The efficacy and safety endpoints of myocardial infarction (MI), cardiovascular death, stroke, acute limb ischemia, and bleeding were adjudicated according to the EUCLID Clinical Endpoints Classification Charter by board-certified cardiologists or neurologists, depending on the event type. Adverse events were systematically collected in all participants in the EUCLID trial. Those adverse events that were serious, including hospitalizations and events that led to study drug discontinuation, were reviewed by the Duke Clinical Research Institute Safety Surveillance Group, and these adverse events were cross-referenced with the Clinical Endpoints Classification database to ensure that clinical endpoints were not double counted.



**Figure 1** Inclusion criteria for EUCLID trial. This figure highlights the inclusion criteria of patients for both the EUCLID trial and this COPD-focused post hoc analysis of the EUCLID trial.

## Statistical Analysis

The analytic cohort included all patients randomized in EUCLID who received at least one dose of study drug and had information on COPD status at baseline ( $n=13,883$ ). For baseline characteristics, continuous variables were reported as medians with associated 25th and 75th percentiles and were compared between patients with and without COPD using the Wilcoxon rank sum test. Categorical variables were reported as counts with percentages and were assessed using the chi-square test.

The efficacy and safety outcomes (MACE, MALE, bleeding, and all-cause mortality) and serious adverse events (all-cause and respiratory-related hospitalizations and premature study drug discontinuation) were evaluated as time-to-event outcomes. Incidence rates were calculated as the number of events per 100 patient-years of follow-up. The unique number of patients who experienced non-serious adverse events and the mean and median number of adverse events per patient are reported by COPD status.

The relationships between baseline COPD and efficacy and safety outcomes and serious adverse events were examined using unadjusted and adjusted Cox proportional hazards models. The models were adjusted for randomized treatment and differing sets of baseline clinical characteristics including age, sex, weight, body mass index, tobacco use, prior medical history, medications, limb symptoms at study entry, and prior revascularizations/amputations ([Appendix Table II](#)). The proportional hazards assumption was assessed using weighted Schoenfeld residuals and no major violations were found. The linearity assumption for continuous adjustment variables was also examined, and natural cubic splines were used when necessary. Hazard ratios (HR) with 95% confidence intervals (CI) comparing patients with COPD with those without COPD at baseline and the associated p-values are presented. The analysis of non-serious adverse events did not undergo adjustment.

To evaluate the interaction between treatment arm and COPD, the unadjusted Cox proportional hazards models from above were additionally fit with randomized treatment and the interaction between treatment and COPD status. HRs with 95% CIs comparing ticagrelor with clopidogrel for those with and without COPD are presented with interaction p-values.

All analyses were performed by the Duke Clinical Research Institute (Durham, NC) using SAS version 9.4 (SAS Institute, Inc. Cary, NC).

## Results

### Study Population and Clinical Characteristics

Of the 13,883 patients enrolled in EUCLID who received at least one dose of study drug and had COPD status available, a total of 1538 patients (11%) had COPD at baseline ([Table 1](#)). Patients with COPD were similarly distributed between the ticagrelor (50.9% [ $n=783$ ]) and clopidogrel (49.1% [ $n=755$ ]) treatment groups. Of those with COPD, 5.7% ( $n=87$ ) required daily oxygen therapy and 12.4% ( $n=191$ ) had a COPD hospitalization in the year prior to enrollment. Patients with baseline COPD were older than those without COPD (median 67 vs 66 years,  $p<0.001$ ), weighed more (median 78 kg vs 76kg,  $p=0.012$ ), and were more likely to be current or former smokers (92.5% vs 76.6%,  $p<0.001$ ). Patients with COPD more frequently had a history of transient ischemic attack (TIA) (5.3% vs 3.4%), carotid artery disease (26.6% vs 18.3%), coronary artery disease (CAD) (35.6% vs 28.2%), MI (21.4% vs 17.8%), hypertension (83.4% vs 77.6%), hyperlipidemia (82.3% vs 74.6%), and prior malignancy (12.9% vs 7.3%) compared with patients without COPD (all p-values  $<0.001$ ). Interestingly, patients with PAD and COPD had lower rates of diabetes when compared with those without COPD (32.6% vs 39.2%,  $p<0.001$ ).

Patients with PAD and COPD had a higher rate of statin (77.5% vs 72.8%,  $p<0.001$ ) and antiplatelet use prior to study entry, specifically aspirin (71.3% vs 66.2%,  $p<0.001$ ) and clopidogrel (39.4% vs 31.3%,  $p<0.001$ ). Patients with PAD and COPD had more frequently undergone a previous lower extremity revascularization (63.6% vs 55.9%,  $p<0.001$ ) and experienced more severe limb symptoms (severe claudication and ischemic rest pain) at study entry when compared with the remaining study population.

### Unadjusted Outcomes

#### Efficacy and Safety Outcomes

The risk of occurrence of the primary composite endpoint (cardiovascular death, MI, or ischemic stroke) is shown in [Figure 2](#) and [Appendix Figure I](#). There was a significantly higher risk of MACE in patients with PAD and COPD compared with those without COPD (6.02 vs 4.29 events/100 patient-years,  $p<0.001$ ). This was primarily driven by a higher occurrence of MI (3.55 vs 1.85 events/100 patient-years,  $p<0.001$ ), with no statistically significant difference in the number of

**Table I** Baseline Clinical Characteristics by COPD at Baseline

	<b>COPD (N=1538)</b>	<b>No COPD (N=12,345)</b>	<b>P-value</b>
Age, (median, IQR), yrs	67, 62–73	66, 60–72	<0.001
Female, no. (%)	438 (28.5%)	3450 (27.9%)	0.661
Weight, (median, IQR), kg	78, 66–91	76, 66–88	0.012
BMI (mean, IQR)	27, 24–31	27, 24–30	0.309
Chronic lung disease characteristics, no. (%)			
Required daily, long-term oxygen therapy	87 (5.7%)		
Hospitalization in the last year	191 (12.4%)		
Inclusion criteria for randomization, no. (%)			<0.001
Previous revascularization	978 (63.6%)	6896 (55.9%)	
ABI criteria	560 (36.4%)	5449 (44.1%)	
ABI values based on inclusion criteria, mean (SD)			
Previous revascularization	0.79 (0.22)	0.78 (0.23)	0.033
ABI criteria	0.63 (0.13)	0.63 (0.15)	0.117
Limb symptoms at baseline, no. (%)			<0.001
Asymptomatic	239 (15.5%)	2362 (19.1%)	
Mild or moderate claudication	762 (49.5%)	6648 (53.9%)	
Severe claudication	470 (30.6%)	2758 (22.3%)	
Ischemic rest pain	49 (3.2%)	329 (2.7%)	
Minor tissue loss	12 (0.8%)	195 (1.6%)	
Major tissue loss	6 (0.4%)	52 (0.4%)	
Major amputation above the ankle, no. (%)	28 (1.8%)	311 (2.5%)	0.092
Minor amputation, no. (%)	32 (2.1%)	573 (4.7%)	<0.001
Tobacco use, no. (%)			<0.001
Current	665 (43.6%)	3624 (29.5%)	
Former	746 (48.9%)	5784 (47.1%)	
Never	115 (7.5%)	2869 (23.4%)	
Prior medical history, no. (%)			
Stroke	128 (8.3%)	1015 (8.2%)	0.892
Transient ischemic attack	82 (5.3%)	425 (3.4%)	<0.001
Coronary artery disease	548 (35.6%)	3484 (28.2%)	<0.001
Myocardial infarction	329 (21.4%)	2193 (17.8%)	<0.001
Carotid stenosis or carotid revascularization	394 (26.6%)	2133 (18.3%)	<0.001
Diabetes mellitus type I or II	502 (32.6%)	4843 (39.2%)	<0.001
Hypertension	1282 (83.4%)	9575 (77.6%)	<0.001
Hyperlipidemia	1266 (82.3%)	9214 (74.6%)	<0.001
History of cancer	198 (12.9%)	900 (7.3%)	<0.001
Medications before randomization, no. (%)			
Aspirin	1097 (71.3%)	8174 (66.2%)	<0.001
Clopidogrel	606 (39.4%)	3867 (31.3%)	<0.001
Statin	1192 (77.5%)	8989 (72.8%)	<0.001
ACE inhibitor	632 (41.1%)	5003 (40.5%)	0.670
Angiotensin-receptor blocker	415 (27.0%)	3073 (24.9%)	0.075
Cilostazol	183 (11.9%)	1912 (15.5%)	<0.001

(Continued)

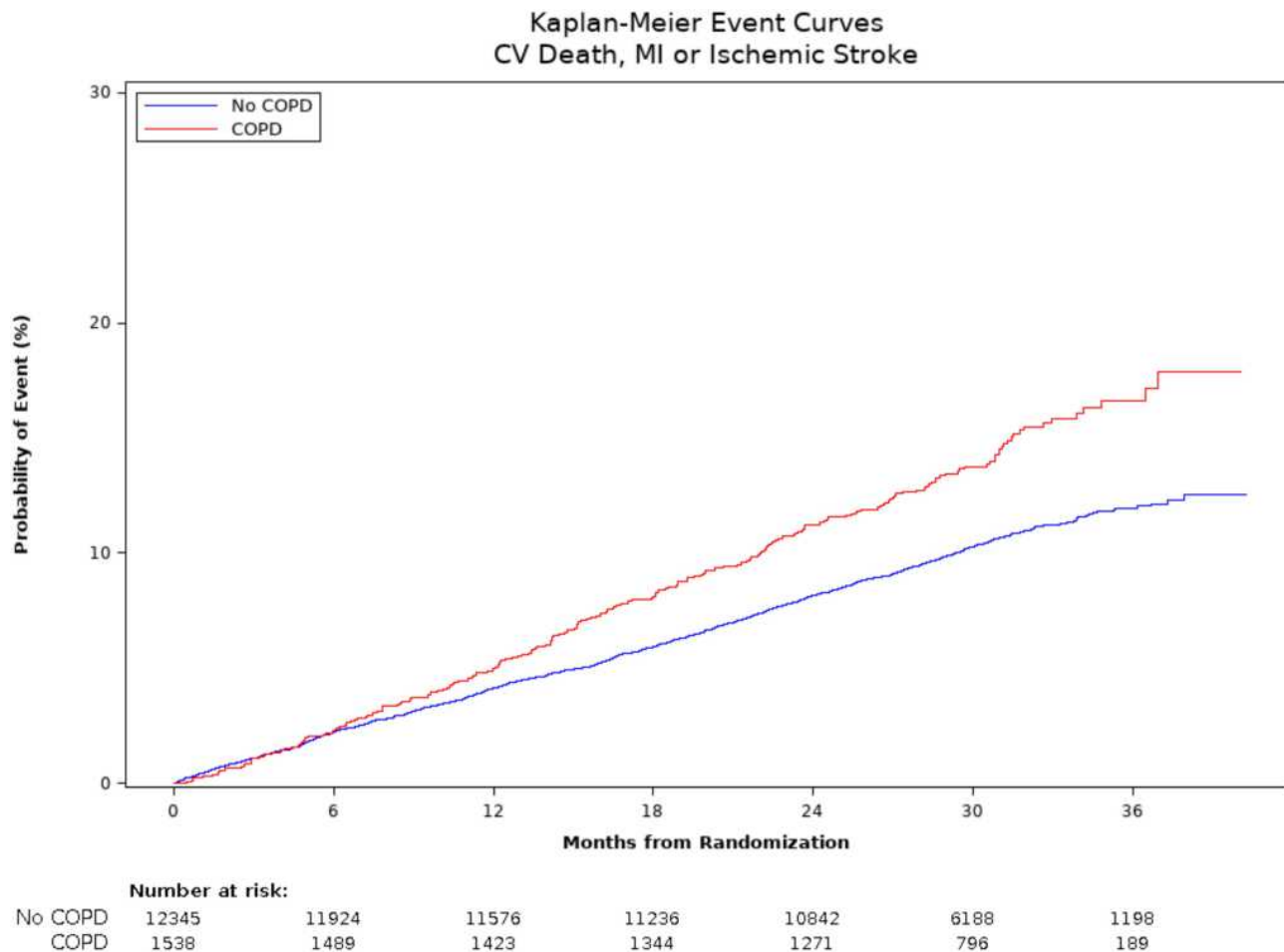
**Table 1** (Continued).

	COPD (N=1538)	No COPD (N=12,345)	P-value
Randomized treatment assignment, no. (%)			0.405
Clopidogrel 75 mg once daily	755 (49.1%)	6199 (50.2%)	
Ticagrelor 90 mg twice daily	783 (50.9%)	6146 (49.8%)	

**Abbreviations:** ABL, ankle-brachial index; ACE, angiotensin-converting enzyme; BMI, body mass index; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

cardiovascular deaths (2.35 vs 2.01 events/100 patient-years,  $p=0.059$ ) or ischemic strokes (0.85 vs 0.89 events/100 patient-years,  $p=0.691$ ). Specifically, 50.0% ( $n=65$ ) of the MIs experienced by patients with concomitant PAD and COPD were type 1 and 43.8% ( $n=57$ ) were type 2, compared with 61.5% ( $n=340$ ) type 1 and 32.4% ( $n=179$ ) type 2 MIs in patients without COPD. After excluding type 2 MI from the endpoint definitions, the higher risk of MACE in patients with PAD and COPD compared with those without COPD persisted

(4.78 vs 3.79 events/100 patient-years,  $p=0.004$ ), as did risk of MI (2.05 vs 1.28 events/100 patient-years,  $p<0.001$ ). The occurrence of MACE was 1.10 events per 100 patient-years in patients with COPD and 1.19 events per 100 patient-years in patients without COPD ( $p=0.54$ ). Patients with COPD did not have any increase in major bleeding (0.90 vs 0.74 events/100 patient-years,  $p=0.34$ ), but did have higher all-cause mortality (5.01 vs 3.46 events/100 patient-years,  $p<0.001$ ) compared with those without COPD.



**Figure 2** Kaplan-Meier plot of primary endpoint by history of COPD. The rate of occurrence of the primary endpoint (composite of cardiovascular death, myocardial infarction and ischemic stroke) is greater in patients with a history of COPD, compared to PAD patients without baseline COPD.

## Serious Adverse Events

All-cause hospitalizations were significantly higher among patients with COPD when compared with patients without COPD (33.30 vs 21.53 events/100 patient-years,  $p<0.001$ ). Specifically, patients with PAD and COPD were hospitalized for dyspnea and pneumonia more frequently when compared with patients without COPD (2.66 vs 0.90 events/100 patient-years,  $p<0.001$ ). Patients with COPD had a significantly greater rate of premature study drug discontinuation (19.36 vs 12.54 events/100 patient-years,  $p<0.001$ ) than those without COPD. Table 2 further specifies serious adverse events by history of COPD.

## Non-Serious Adverse Events

Table 3 details the non-serious adverse events by history of COPD. The frequency of all adverse events and respiratory-related adverse events was higher in patients with PAD and COPD compared with those without COPD. Among patients with baseline COPD, more patients experienced at least one respiratory-related adverse event than patients without baseline COPD (22.8% vs 8.9%). However, the number of respiratory-related adverse events experienced per patient was similar between the two groups (mean 1.4 vs 1.2 adverse events per patient).

**Table 2** Serious Adverse Events by History of COPD

	<b>COPD (N=1538)</b>	<b>No COPD (N=12,345)</b>
Hospitalization for any SAE Unique N Mean (SD) PP*	538 (35.2%) 2.0 (1.5)	2780 (22.6%) 1.6 (1.2)
Hospitalization for any respiratory SAE Unique N Mean (SD) PP*	144 (9.4%) 1.4 (0.8)	211 (1.7%) 1.2 (0.6)
Hospitalization for dyspnea Unique N Mean (SD) PP*	6 (0.4%) 1.0 (0.0)	9 (0.1%) 1.2 (0.4)
Hospitalization for pneumonia Unique N Mean (SD) PP*	75 (4.9%) 1.1 (0.4)	230 (1.9%) 1.0 (0.2)
Hospitalization for malignancy Unique N Mean (SD) PP*	62 (4.1%) 1.0 (0.1)	385 (3.1%) 1.1 (0.2)

**Note:** \*Per patient with at least 1 adverse event of that type.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; SAE, serious adverse event; SD, standard deviation.

**Table 3** Adverse Events by History of COPD

	<b>COPD (N=1538)</b>	<b>No COPD (N=12,345)</b>
Any adverse event Unique N Mean (SD) PP*	868 (56.7%) 2.5 (2.2)	5031 (40.9%) 2.1 (2.2)
Respiratory <sup>†</sup> adverse event Unique N Mean (SD) PP*	349 (22.8%) 1.4 (0.8)	1090 (8.9%) 1.2 (0.5)
Dyspnea Unique N Mean (SD) PP*	224 (14.6%) 1.2 (0.5)	870 (7.1%) 1.2 (0.5)
Pneumonia Unique N Mean (SD) PP*	103 (6.7%) 1.2 (0.5)	352 (2.9%) 1.1 (0.4)
Malignancy Unique N Mean (SD) PP*	93 (6.1%) 1.2 (0.5)	527 (4.3%) 1.1 (0.3)

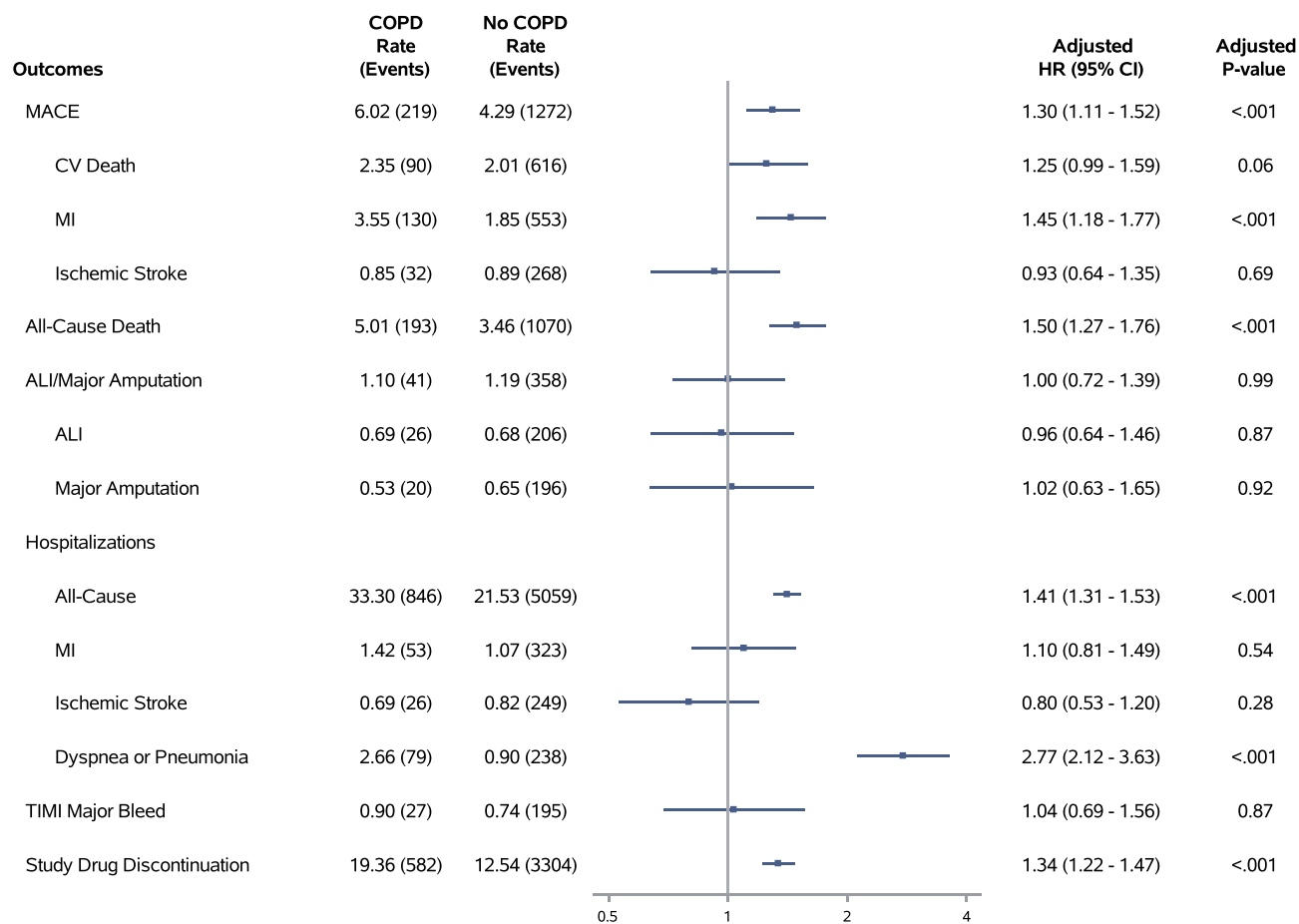
**Notes:** \*Per patient with at least 1 adverse event of that type. <sup>†</sup>Respiratory defined by the respiratory, thoracic and mediastinal body system.

When examining specific adverse events of interest, patients with PAD and COPD were more likely to report dyspnea (14.6% vs 7.1%), pneumonia (6.7% vs 2.9%), and malignancy (6.1% vs 4.3%) when compared with patients without baseline COPD. Patients with PAD and COPD were also more likely to require hospitalization for a serious adverse event (35.2% vs 22.6%) than those without COPD.

## Adjusted Outcomes

### Efficacy and Safety Outcomes

Figure 3 details the risk of occurrence of the efficacy and safety endpoints after adjustment for baseline characteristics. The adjusted hazard ratio (aHR) for MACE was 1.30 (95% CI 1.11–1.52,  $p<0.001$ ) and for MI was 1.45 (95% CI 1.18–1.77,  $p<0.001$ ). After excluding type 2 MI, the aHR for MACE was 1.21 (95% CI 1.02–1.43,  $p=0.030$ ) and for MI was 1.26 (95% CI 0.97–1.62,  $p=0.083$ ). Patients with PAD and COPD did not have a higher risk of adverse limb events (aHR 0.98, 95% CI 0.71–1.37,  $p=0.92$ ) than those without COPD. Patients with PAD and COPD had a higher risk of all-cause mortality (aHR 1.50, 95% CI: 1.27–1.76,  $p<0.001$ ) compared with those without COPD. However, there was no increased risk of bleeding observed in patients with PAD and COPD when compared with patients without baseline COPD (aHR



**Figure 3** Association between baseline COPD and clinical outcomes. This forest plot highlights the primary efficacy outcomes (MACE and MACE), secondary endpoints of interest (all-cause mortality), safety endpoints (TIMI major bleed), and serious adverse events (all-cause hospitalizations, hospitalization for dyspnea or pneumonia, premature study drug discontinuation).

1.04, 95% CI 0.69–1.56,  $p=0.866$ ), and there was no interaction between COPD status and response to ticagrelor for any clinical outcome.

### Serious Adverse Events

Patients with COPD were at higher risk of all-cause hospitalization (aHR 1.41, 95% CI 1.31–1.53,  $p<0.001$ ) after adjustment, and specifically at risk of hospitalization for dyspnea and pneumonia (aHR 2.77, 95% CI 2.12–3.63,  $p<0.001$ ) compared with those without COPD. Patients with PAD and COPD were more likely to prematurely discontinue their assigned study drug when compared with patients without baseline COPD, regardless of whether it was ticagrelor or clopidogrel (19.36 vs 12.54 discontinuations/100 patient-years; aHR 1.34, 95% CI 1.22–1.47,  $p<0.001$ ). In patients with PAD both with and without COPD, there was an increased risk of premature study drug discontinuation with ticagrelor compared with clopidogrel (PAD with COPD: aHR 1.22, 95% CI

1.04–1.44; PAD without COPD: aHR 1.21, 95% CI 1.13–1.30). However, there was no significant difference in the hazard ratios comparing ticagrelor with clopidogrel discontinuation between patients with and without COPD (interaction  $p=0.913$ ).

### Discussion

We evaluated the past medical history, clinical outcomes and adverse events in patients with concomitant PAD and COPD using data from the EUCLID study, yielding four major findings. First, patients with PAD and COPD had more comorbidities at baseline and had more severe PAD at the time of study entry than those without COPD. Second, patients with PAD and COPD had a higher risk of MACE (primarily driven by a significantly higher rate of MI) and a higher risk of all-cause mortality and all-cause hospitalization, findings that persisted after adjustment for baseline characteristics. Third, patients with PAD and COPD did not have a higher risk of MALE compared



with patients with PAD without COPD, despite more severe PAD at baseline. Finally, patients with PAD and COPD more frequently experienced respiratory-related serious adverse events, including respiratory-related hospitalizations, and were more likely to discontinue the study drug prematurely, regardless of whether it was ticagrelor or clopidogrel.

The few prior studies of patients with concomitant PAD and COPD have focused on mortality, which they reported was higher in this population, consistent with our data.<sup>11,12</sup> Our analysis adds depth and nuance to these findings, showing that the increase in all-cause mortality is not due to cardiovascular mortality, while patients with COPD are also at significantly greater risk of other clinically-important events. Patients with COPD in addition to PAD carry an increased risk of MACE driven by significantly higher risks of MI, specifically type 2 MI, as well as increased risks of all-cause and respiratory-related hospitalizations. Patients with PAD who were hospitalized for acute pulmonary events have been shown to be at increased risk of MACE following the hospitalization, and the same has been observed in patients both with and without COPD.<sup>13–16</sup> This is hypothesized to be due to the inflammatory state associated with pulmonary hospitalizations.<sup>13,15,16</sup> It is possible that the increased risk of MI we observed in EUCLID participants with PAD and COPD is attributable to the more frequent respiratory-related adverse events experienced by the patients with PAD and baseline COPD. Furthermore, these pulmonary exacerbations may lead to hypoxia, creating an imbalance between myocardial oxygen demand and delivery and an increased frequency of type 2 MI seen in patients with concomitant PAD and COPD when compared with patients without COPD.<sup>17</sup> Although a higher frequency of type 2 MI is expected in patients with COPD, our data shows persistence of the higher risk of MACE in patients with concomitant PAD and COPD even after exclusion of type 2 MI from the primary endpoints, suggesting that type 2 MI may not be the sole cause of increased mortality in this population. Interestingly, while MALE is also associated with pro-inflammatory states such as those that might be experienced during COPD exacerbations, there was no increased risk for MALE in patients with COPD.

This study provides new information on adverse events unique to patients with concomitant PAD and COPD. One noteworthy observation was an increased rate of premature study drug discontinuation in patients with PAD and

COPD, with a higher risk of discontinuing ticagrelor compared with clopidogrel in patients both with and without COPD. Ticagrelor carries the unique side effect of dyspnea, which may be particularly problematic for patients with COPD.<sup>9</sup> In a meta-analysis of four randomized clinical trials of ticagrelor, including EUCLID, premature ticagrelor discontinuation was seen in 25% of patients, and the highest risk of discontinuation was among patients who experienced dyspnea, a more common adverse event in patients with PAD and COPD compared with those without COPD.<sup>18</sup> Ticagrelor-related dyspnea may compound COPD-related dyspnea, complicating clinicians' efforts to monitor patients with COPD for cardiac and pulmonary dysfunction.

While establishing worse clinical outcomes and a higher rate of adverse events for patients with concomitant PAD and COPD, these findings also demonstrate the need for further research in this area. For instance, given the association between pulmonary hospitalizations and cardiovascular events, as well as the possibility of undiagnosed COPD among patients with PAD (given the overlapping risk factors), evaluation of enhanced monitoring strategies for cardiovascular events following pulmonary hospitalizations in patients with PAD should be considered. While the higher risk of MACE within this population was driven solely by a significantly higher risk of MI, there is a dearth of evidence about the causes of non-cardiovascular death within this population. Additionally, further clarification is needed regarding the causes of premature study drug discontinuation, which may be attributable to dyspnea or to decreased medication adherence associated with polypharmacy, hospitalizations, and increasing COPD symptoms in this population.<sup>19,20</sup>

There were limitations to this analysis. First, this was a post hoc analysis of a subgroup of patients that represented 5% of the overall study population. While this analysis focused only on patients with symptomatic PAD, COPD is more prevalent among patients with asymptomatic PAD, a group not included in this study.<sup>7,12</sup> Second, discrete data on COPD severity (i.e., GOLD criteria, pulmonary function testing results, medications for COPD) were not ascertained at any point in the study, thereby making it difficult to correlate severity of baseline COPD with clinical outcomes. We relied on investigator reported history of COPD rather than any formal testing at time of enrollment. As a result, we may have failed to capture undiagnosed or less severe cases of COPD in the PAD alone group, as well as overreported cases of COPD in the COPD and PAD

group due to misclassification of other lung diseases such as asthma.<sup>21</sup> Additionally, other comorbid chronic conditions in patients with COPD, such as heart failure, a highly possible alternative diagnosis in the EUCLID cohort, may be misdiagnosed as a COPD exacerbation.<sup>22</sup> This may provide a falsely elevated rate of respiratory-related adverse events. Third, we were not able to ascertain whether the rate of ticagrelor discontinuation among patients with PAD and COPD for the reason of dyspnea was higher than in patients without COPD. Therefore, it is unclear if the decreased pulmonary reserve in patients with COPD was driving the increased risk of premature study drug discontinuation within that subgroup.

## Conclusions

In patients with PAD and baseline COPD, the risk of major adverse cardiovascular events, all-cause mortality, all-cause hospitalizations, and respiratory-related adverse events was higher when compared with patients with PAD without COPD. Surprisingly, the rate of major adverse limb events was similar between patients with PAD with and without COPD. Patients with COPD were also more likely to discontinue study medication (either ticagrelor or clopidogrel) when compared with patients without COPD; however, after adjustment, the rate of discontinuation of ticagrelor was similar in patients with and without COPD. The results from this study suggest that the increased risk of multiple respiratory- and non-respiratory-related clinical events among patients with both COPD and PAD warrant increased efforts to investigate and prevent cardiovascular and respiratory events in this population.

## Data Sharing Statement

The authors do not plan to share individual deidentified participant data at this time.

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## Disclosure

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