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ORIGINAL ARTICLE
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Impact of chronic obstructive pulmonary disease and dyspnoea on clinical outcomes in ticagrelor treated patients undergoing percutaneous coronary intervention in the randomized GLOBAL LEADERS trial

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Aims To evaluate long-term safety and efficacy of ticagrelor monotherapy in patients undergoing percutaneous coronary interventions (PCIs) in relation to chronic obstructive pulmonary disease (COPD) at baseline and the occurrence of dyspnoea reported as adverse event (AE) that may lead to treatment non-adherence.

Methods and results This is a non-prespecified, *post hoc* analysis of the randomized GLOBAL LEADERS trial ($n = 15\,991$), comparing the experimental strategy of 23-month ticagrelor monotherapy following 1-month dual antiplatelet therapy (DAPT) after PCI with the reference strategy of 12-month DAPT followed by 12-month aspirin monotherapy. Impact of COPD and dyspnoea AE (as a time-dependent covariate) on clinical outcomes was evaluated up to 2 years. The primary endpoint was a 2-year all-cause mortality or non-fatal, centrally adjudicated, new Q-wave myocardial infarction. The presence of COPD ($n = 832$) was the strongest clinical predictor of 2-year all-cause mortality after PCI [hazard ratio (HR) 2.84; 95% confidence interval (CI) 2.21–3.66; *P* adjusted = 0.001] in this cohort ($n = 15\,991$).

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No differential treatment effects on 2-year clinical outcomes were found in patients with and without COPD (primary endpoint: HR 0.88; 95% CI 0.58–1.35; $P = 0.562$; P int = 0.952). Overall, at 2 years dyspnoea was reported as an AE in 2101 patients, more frequently among COPD patients, irrespective of treatment allocation (27.2% in experimental arm vs. 14.5% in reference arm, $P = 0.001$). Its occurrence was not associated with a higher rate of the primary endpoint (P adjusted = 0.640) in the experimental vs. the reference arm.

Conclusion In this exploratory analysis, COPD negatively impacted long-term prognosis after PCI. Despite higher incidence of dyspnoea in the experimental arm, in particular among COPD patients, the safety of the experimental treatment strategy appeared not to be affected.

Clinical trial registration unique identifier NCT01813435.

Keywords Percutaneous coronary intervention • Ticagrelor • Chronic obstructive pulmonary disease • Dyspnoea adverse event • Aspirin-free antiplatelet strategies after percutaneous coronary intervention

Introduction

Patients with coronary artery disease (CAD) and chronic obstructive pulmonary disease (COPD) represent a population at increased risk for adverse clinical events, periprocedural complications, comorbidities, and polypharmacy.[1–3] In PLATO, dual antiplatelet therapy (DAPT) consisting of ticagrelor and aspirin reduced the composite primary endpoint of cardiovascular death, myocardial infarction (MI), or stroke in patients with acute coronary syndromes (ACS), compared with clopidogrel and aspirin. However, ticagrelor increased the incidence of dyspnoea, which may lead clinicians to withhold ticagrelor from COPD patients.[4] In ACS patients with COPD, the absolute risk of ischaemic events at 1 year was reduced with ticagrelor vs. clopidogrel, without significantly increasing the risk of major bleeding events.[5] In stable CAD patients with COPD, ticagrelor has not yet been specifically evaluated, neither as a part of DAPT nor as a single antiplatelet agent.[6,7]

Chronic obstructive pulmonary disease has been recognized as a condition associated with an altered platelet function which may affect the efficacy of adjunctive antiplatelet regimen after percutaneous coronary interventions (PCIs), including the recently advocated aspirin-free antiplatelet strategies.[8]

While GLOBAL LEADERS did not demonstrate any safety signal associated with ticagrelor monotherapy use, as indicated by the close to unity upper boundary of confidence interval (CI) of the primary endpoint,[9] the risk-to-benefit balance may substantially differ among patients with concomitant COPD and patients experiencing dyspnoea that might lead to lower treatment adherence.

Therefore, it is of interest to evaluate the impact of COPD on long-term clinical outcomes after PCI in a contemporary large-scale all-comers randomized clinical trial, and to assess the efficacy and safety of ticagrelor monotherapy in these patients in relation to COPD status at baseline and occurrence of an important drug-related adverse effect of ticagrelor—dyspnoea.

Methods

Patient population

The GLOBAL LEADERS (ClinicalTrials.gov, identifier: NCT01813435) was an investigator-initiated, prospective, randomized, multicentre, multinational, open-label trial comparing two strategies of antiplatelet treatment in a large all-comers population scheduled for PCI.[9] A total of 15 991 patients with either stable CAD or ACS were randomly allocated either to an experimental strategy of 1 month aspirin and ticagrelor, followed by 23 months ticagrelor alone, or to the reference strategy with 1 year DAPT consisting of 75–100 mg aspirin daily in combination with either 75 mg clopidogrel daily (for patients with stable CAD) or 90 mg ticagrelor twice daily (for patients with ACS), followed by 75–100 mg aspirin alone for 12 months.[10] Detailed inclusion, exclusion criteria and study procedures were described previously and are presented in the Supplementary material online, *Appendix*.[10] The trial was performed in compliance with the ethical principles of the Declaration of Helsinki, the International Conference of Harmonization, and Good Clinical Practice. All participants provided written informed consent at the time of enrolment.

In the present *post hoc* analysis, we report the clinical outcome of patients undergoing PCI in relation to COPD status (documented at baseline) and the occurrence of dyspnoea adverse event (AE) during the 2-year follow-up. In addition, exploratory landmark analyses for assessing onset of dyspnoea were performed at 30 days, since ticagrelor-related dyspnoea predominantly occurs within the first 30 days of treatment, between 31 and 365 days, when ticagrelor-related dyspnoea occasionally occurs, and between 366 and 730 days, when other reasons for dyspnoea such as heart failure are more likely explanations.[11,12] Chronic obstructive pulmonary disease was defined as a chronic lung disease requiring a long-term use of bronchodilators or steroids, as defined in the EuroSCORE (Supplementary material online, *Appendix*).

Adherence was assessed by direct pill counts and self-reporting.[9,10] Patient was considered adherent in case there was no evidence of randomized treatment discontinuation prior to follow-up visits scheduled at 30 days, 3, 6, 12, 18, and 24 months after the index procedure[9,10] (Supplementary material online, *Appendix*). Revascularizations and

per-protocol restart of DAPT allowed: (i) ticagrelor and aspirin for 30 days in the experimental treatment strategy group, (ii) DAPT with ticagrelor and aspirin (ACS, stable CAD patients already on ticagrelor or prasugrel), clopidogrel and aspirin (stable CAD) for 365 days in the standard treatment strategy group.[1]

Study endpoints

The primary endpoint comprised a composite of all-cause death or ECG-core-lab adjudicated, new Q-wave MI up to 2 years after the index procedure.[9,13,14] Deaths from any cause were ascertained without adjudication. Q-wave MI was defined according to the Minnesota classification.[13,14] The key safety endpoint was site reported Bleeding Academic Research Consortium (BARC)-defined bleeding type 3 or 5. Additional secondary endpoints reported by investigators have been detailed in the Supplementary material online, *Appendix*.

The trial was monitored for event underreporting and event definition consistency; no independent central event adjudication was planned.[9]

Statistical analysis

Kaplan–Meier method was used to estimate the cumulative rates of events and the log-rank test was applied to compare the risk for clinical endpoints between groups.

A hazard ratio (HR) was reported with 95% CIs based on the univariable and multivariable Cox regression model.

The analyses of the primary endpoint and the secondary endpoints with tests for treatment-by-COPD status interaction were performed.

Cox proportional hazards survival model, including factors for randomized treatment and incidence of dyspnoea event as a time-dependent covariate, were performed with adjustment to account for differences in relevant clinical variables between treatment groups.

In addition, as analysis of the prognostic impact of dyspnoea may be confounded due to the fact that ticagrelor-related dyspnoea reportedly occurs predominantly within the first 30 days of treatment[11,12] and there might be a potential overlap between factors contributing to the development of dyspnoea and clinical events, landmark analyses were performed for clinical outcomes from 31 days onwards in those patients who reported dyspnoea in the first 30 days following randomization.[11,12]

Finally, exploratory univariable and multivariable analyses were performed to compare the impact of COPD and other baseline characteristics on 2-year mortality, dyspnoea occurrence and treatment adherence.

The adjustment variables were selected based on previous knowledge and literature, i.e. the variables with clinically relevant influence on the dependent variable were included in the model.[5,12] In addition, variables with *P*-values <0.10 by univariable analyses were added to the model.

Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR), and compared with a standard *t*-test (normally-distributed continuous data), or Wilcoxon rank-sum test. Categorical variables were presented as counts and percentages and compared using the Pearson's χ^2 or exact test, as appropriate.

All analyses were performed following the intention-to treat definition using the SPSS Software (SPSS 25, IBM, Chicago, IL, USA). A two-sided *P*-value of 0.05 was considered statistically significant.

Results

Between 1 July 2013 and 9 November 2015, the GLOBAL LEADERS study enrolled and randomized 15 991 patients.[9] After 23 patients withdrew consent and formally requested their data deletion, there were data from 7980 patients in the experimental group and 7988 in the reference group available for analysis[9] (Supplementary material online, *Figure S1*).

There were 832 (5.2%) of patients identified with a history of COPD at enrolment (*Table 1* and Supplementary material online, *Table S1*). Patients with COPD were older, more often presented with stable CAD, more often had comorbidities such as diabetes, hypertension, peripheral vascular disease, previous major bleeding, impaired renal function, prior stroke, MI, or coronary artery bypass grafting and were more frequently smokers, compared with non-COPD individuals (*Table 1*).

Chronic obstructive pulmonary disease was associated with higher rate of the primary endpoint (10.5% vs. 3.7%, HR 2.41, 95% CI 1.92–3.03, P_{adj} = 0.001), all-cause mortality, any type of stroke, BARC 3 type bleeding, and BARC 3 or 5 type bleeding (*Table 2*). Chronic obstructive pulmonary disease was identified as one of the most determinant predictors of 2-year mortality (HR 2.82, 95% CI 2.20–3.62, P_{adj} = 0.001) in the overall GLOBAL LEADERS study (Supplementary material online, *Table S2*).

Randomized treatment safety and efficacy in chronic obstructive pulmonary disease and non-chronic obstructive pulmonary disease patients

Among patients with COPD, the primary endpoint occurred in 9.8% of patients in the experimental group and in 11.1% of patients in the reference group (HR 0.88, 95% CI 0.58–1.35, P = 0.562, P_{int} = 0.952) (*Table 3*).

In patients with COPD allocated to the experimental arm, the rates of all-cause death, stroke, MI, definite stent thrombosis, and BARC 3 or 5 type bleeding were not statistically different, when compared with patients treated according to the reference treatment strategy (*Table 3*, *Figure 1*).

Treatment adherence in chronic obstructive pulmonary disease and non-chronic obstructive pulmonary disease patients

Patients with COPD presented consistently lower rates of treatment adherence, compared with patients without COPD (*Table 4*), that were lower in the experimental vs. the reference treatment arm (Supplementary material online, *Table S3*). By multivariable analysis, positive COPD status at baseline was identified as one of the most determinant negative predictors of adherence to randomized treatment at 1 and 2 years after PCI (Supplementary material online, *Table S4*).

Dyspnoea adverse event

In overall GLOBAL LEADERS cohort, up to 2 years dyspnoea was reported as AE in 2101 patients. Chronic obstructive pulmonary disease was identified as a significant predictor of this AE (Supplementary material online, *Tables S5* and *S6*).

Dyspnoea had been reported as AE more frequently among COPD patients irrespective of treatment allocation (*Figure 2*). Among those with a dyspnoea AE, median time from randomization

to first dyspnoea occurrence was 32 days in COPD patients ($n = 169$) and 34 days in non-COPD ($n = 1942$) ($P = 0.672$).

Analyses at the prespecified time intervals: at 30 days and 1 year indicated higher incidence of dyspnoea in the experimental group within the first month (in COPD: 13.1% vs. 6.2%, $P = 0.001$; in non-COPD: 7.4% vs. 4.2%, $P = 0.001$) and within the first year (in COPD: 23.8% vs. 11.5%, $P = 0.001$; in non-COPD: 14.4% vs. 8.6%, $P = 0.001$), but not during the second year after treatment initiation, when compared with the reference group (Supplementary material online, *Figure S2*).

Table 1 Baseline characteristics in patients with and without COPD

	No COPD (*N* = 15 136) *N* (%)	COPD (*N* = 832) *N* (%)	*P*-value
Age (years) (±SD)	64.4 (±10.4)	67.9 (±8.85)	0.001
Weight (kg) (±SD)	82.6 (±15.5)	82.3 (±16.7)	0.588
BMI (kg/m^2) (±SD)	28.18 (±4.56)	28.34 (±5.19)	0.351
Female gender	3510 (23.2)	204 (24.5)	0.377
Stable CAD	8004 (52.9)	477 (57.3)	0.012
UA	1914 (12.6)	108 (13.0)	0.777
NSTEMI	3201 (21.1)	172 (20.7)	0.744
STEMI	2017 (13.3)	75 (9.0)	0.001
Diabetes	3785 (25.0)	253 (30.4)	0.001
Diabetes on insulin	1135 (7.5)	88 (10.6)	0.001
Hypertension	11 067 (73.4)	648 (78.4)	0.001
Hypercholesterolaemia	10 197 (69.6)	571 (69.8)	0.910
Currently smoking	3883 (25.7)	286 (34.4)	0.001
Peripheral vascular disease	891 (5.9)	114 (14.0)	0.001
Previous major bleeding	85 (0.6)	13 (1.6)	0.001
Impaired renal function	2031 (13.5)	159 (19.2)	0.001
Previous stroke	388 (2.6)	33 (4.0)	0.013
Previous MI	3490 (23.1)	220 (26.6)	0.021
Previous PCI	4933 (32.6)	288 (34.7)	0.204
Previous CABG	870 (5.8)	73 (8.8)	0.033

BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

Dyspnoea and clinical outcomes in chronic obstructive pulmonary disease and non-chronic obstructive pulmonary disease patients

Multivariable adjusted HRs for experimental vs. reference treatment strategy were not significantly different in dyspnoeic and non-dyspnoeic patients in overall population (Supplementary material online, *Table S7*) and in patients with COPD (*Table 5*).

The occurrence of dyspnoea in COPD patients in the experimental group was not associated with a higher risk of primary endpoint ($P_{adj} = 0.452$), BARC 3 or 5 bleeding ($P_{adj} = 0.097$) when compared with the reference treatment group.

By landmark analysis at 30 days in the subgroup of patients with dyspnoea AE reported within 30 days from treatment initiation, no significant differences in the treatment effects were found with regard to the rates of the primary endpoint, BARC 3 and 5 type bleeding and other outcome variables beyond 1 month up to 2 years after PCI in the overall GLOBAL LEADERS study (Supplementary material online, *Table S8*) and specifically in COPD and non-COPD patients (Supplementary material online, *Table S9*).

Discussion

This is the first study on the long-term safety and efficacy of ticagrelor, either as monotherapy following short 1-month DAPT or as part of 12-month DAPT after PCI, that evaluated the impact of dyspnoea—a well-known drug adverse effect that may occasionally trigger treatment discontinuation.

Table 2 Two-year clinical outcomes of coronary artery disease patients undergoing PCI in relation to COPD status

	No COPD (*N* = 15 136)	COPD (*N* = 832)	Unadjusted		Adjusted	
	N (%)	*N* (%)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Primary endpoint	566 (3.7)	87 (10.5)	2.89 (2.31–3.62)	0.001	2.41 (1.92–3.03)	0.001
All-cause death	401 (2.6)	76 (9.1)	3.55 (2.78–4.54)	0.001	2.82 (2.20–3.62)	0.001
New Q-wave MI	173 (1.1)	13 (1.6)	1.42 (0.81–2.49)	0.227	1.34 (0.76–2.36)	0.318
Stroke[a]	144 (1.0)	18 (2.2)	2.35 (1.44–3.84)	0.001	2.08 (1.26–3.41)	0.004
MI (site-reported)	465 (3.1)	33 (4.0)	1.33 (0.94–1.90)	0.111	1.16 (0.82–1.66)	0.402
Any revascularization	1458 (9.6)	74 (8.9)	0.94 (0.75–1.20)	0.640	0.88 (0.70–1.12)	0.305
Definite ST	124 (0.8)	4 (0.5)	0.60 (0.22–1.62)	0.312	0.55 (0.20–1.49)	0.237
BARC 3	276 (1.8)	33 (4.0)	2.25 (1.57–3.23)	0.001	1.99 (1.38–2.87)	0.001
BARC 5	40 (0.3)	6 (0.7)	2.80 (1.18–6.61)	0.019	2.34 (0.98–5.60)	0.055
BARC 3 or 5	296 (2.0)	36 (4.3)	2.29 (1.62–3.24)	0.001	2.02 (1.42–2.87)	0.001

Adjusted for the following variables: age, gender, clinical presentation, diabetes, hypertension, smoking history, previous cardiovascular disease, history of previous major bleeding, impaired renal function, previous MI, stroke, CABG, and the randomized treatment strategy.
BARC, Bleeding Academic Research Consortium; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; ST, stent thrombosis.
[a]Not including TIA.

Table 3 Two-year clinical outcomes in coronary artery disease patients with and with COPD categorized according to the treatment strategy

	No COPD (*N* = 15 136)				COPD (*N* = 832)				*P* for interaction
	Reference (*n* = 7563) *N* (%)	Experimental (*n* = 7573) *N* (%)	HR (95% CI)	*P*-value	Reference (*n* = 425) *N* (%)	Experimental (*n* = 407) *N* (%)	HR (95% CI)	*P*-value	
Primary endpoint	302 (4.0)	264 (3.5)	0.87 (0.74–1.03)	0.099	47 (11.1)	40 (9.8)	0.88 (0.58–1.35)	0.562	0.952
All-cause death	212 (2.8)	189 (2.5)	0.89 (0.73–1.08)	0.240	41 (9.6)	35 (8.6)	0.89 (0.57–1.39)	0.604	0.996
New Q-wave MI	95 (1.3)	78 (1.0)	0.82 (0.61–1.11)	0.189	8 (1.9)	5 (1.2)	0.65 (0.21–1.98)	0.446	0.689
Stroke[a]	71 (0.9)	73 (1.0)	1.03 (0.74–1.43)	0.857	11 (2.6)	7 (1.7)	0.66 (0.26–1.71)	0.393	0.386
MI (site-reported)	234 (3.1)	231 (3.1)	0.99 (0.83–1.19)	0.911	16 (3.8)	17 (4.2)	1.13 (0.57–2.24)	0.722	0.710
Any revascularization	750 (10.0)	708 (9.4)	0.94 (0.85–1.05)	0.260	43 (10.4)	31 (7.9)	0.75 (0.47–1.19)	0.217	0.341
Definite ST	62 (0.8)	62 (0.8)	1.00 (0.70–1.42)	0.992	2 (0.5)	2 (0.5)	1.05 (0.15–7.47)	0.960	0.963
BARC 3	139 (1.8)	137 (1.8)	0.99 (0.78–1.25)	0.913	20 (4.7)	13 (3.2)	0.68 (0.34–1.37)	0.278	0.320
BARC 5	20 (0.3)	20 (0.3)	1.00 (0.54–1.86)	0.996	4 (0.9)	2 (0.5)	0.53 (0.10–2.87)	0.457	0.482
BARC 3 or 5	147 (1.9)	149 (2.0)	1.02 (0.81–1.28)	0.898	22 (5.2)	14 (3.4)	0.67 (0.34–1.30)	0.232	0.241

The *P*-value for interaction for the various endpoints derives from the dichotomized analysis according to chronic obstructive pulmonary disease (COPD) at baseline. The primary endpoint was a composite of 2-year all-cause mortality or non-fatal, centrally adjudicated, new Q-wave myocardial infarction (MI).
BARC, Bleeding Academic Research Consortium; 95% CI, 95% confidence interval; HR, hazard ratio; ST, stent thrombosis.
[a]Not including TIA.

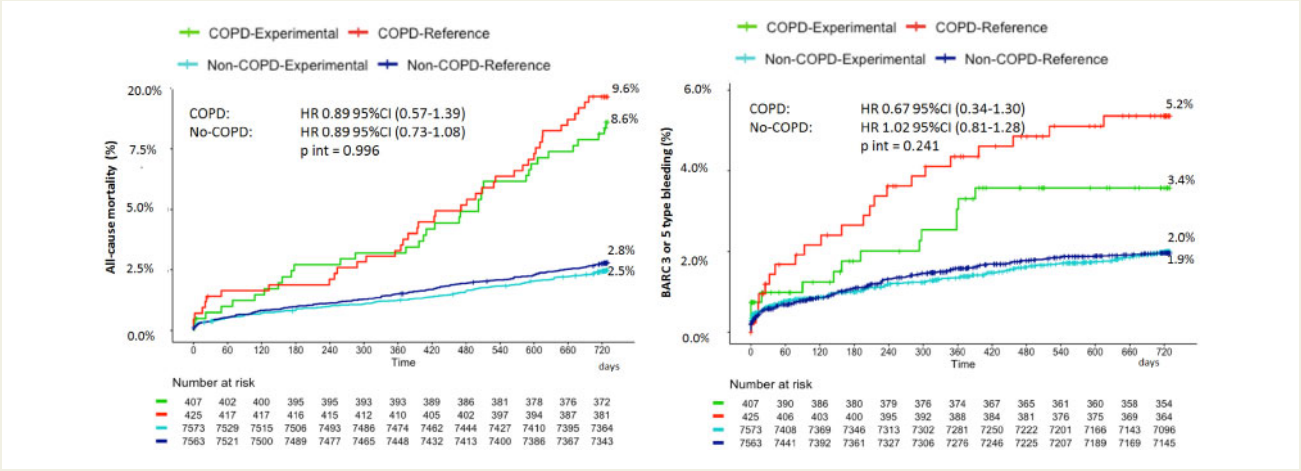


Figure 1 Kaplan–Meier curves for 2-year all-cause mortality (*A*) and Bleeding Academic Research Consortium defined bleeding type 3 or 5 (*B*) categorized according to chronic obstructive pulmonary disease status and randomized treatment strategy. BARC, Bleeding Academic Research Consortium; 95% CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio.

The highest HR of 2-year all-cause mortality identified for baseline COPD status in this contemporary PCI cohort—when compared with other clinical variables—emphasizes the rationale to verify whether the safety of ticagrelor monotherapy (after 1 month of dual therapy with aspirin) observed for overall population is also valid in case of particularly susceptible COPD patients.

The salient findings of the present study can be summarized as follows:

i. Chronic obstructive pulmonary disease represents an important factor negatively impacting prognosis after PCI that was associated with an increased rate of primary endpoint, all-cause mortality, stroke, and bleeding at 2 years in patients with CAD undergoing PCI.
ii. Ticagrelor monotherapy after 1 month of DAPT was safe and associated with similar rate of primary endpoint, stroke, and bleeding events when compared with 12-month DAPT in COPD and non-COPD patients undergoing PCI.
iii. In patients with COPD undergoing PCI, ticagrelor monotherapy after 1 month of DAPT was associated with a higher risk of dyspnoea, compared with the reference DAPT. Dyspnoea occurred mainly within the first months following treatment initiation; there was no significant excess of dyspnoea in the experimental group during the second year of observation.

Table 4 Adherence to randomized treatment in patients with and without COPD

	No COPD (n = 15 136)	COPD (n = 832)	P-value
Discharge	97.5 (14 719/15 099)	95.6 (789/825)	0.001
Follow up 1 month	96.4 (14 219/14 748)	95.4 (750/786)	0.147
Follow up 3 months	90.1 (13 112/14 556)	85.1 (655/770)	0.001
Follow up 6 months	88.7 (12 813/14 442)	82.1 (628/765)	0.001
Follow up 12 months	85.9 (12 318/14 338)	77.6 (578/745)	0.001
Follow up 18 months	85.7 (12 083/14 101)	77.5 (557/719)	0.001
Follow up 24 months	85.7 (12 233/14 268)	77.7 (558/718)	0.001

Data are shown as % (n/N).
The drug counts at the 1 month, 1 year, and 2-year time points reflect patient adherence before the protocol mandated change in antiplatelet regimen. Revascularizations and per-protocol restart of DAPT allowed: (i) ticagrelor and aspirin for 30 days in the experimental treatment strategy group, (ii) dual antiplatelet therapy with ticagrelor and aspirin (acute coronary syndrome, stable coronary artery disease patients already on ticagrelor or prasugrel), clopidogrel and aspirin (stable coronary artery disease patients) for 365 days in the standard treatment strategy group.
P-value derived from χ^2 test.

iv. Although the occurrence of dyspnoea up to 2 years could underlie the lower treatment adherence in COPD subset, it was not associated with any differential treatment effect for the experimental versus reference treatment strategy, among patients with COPD and without COPD.

Chronic obstructive pulmonary disease and prognosis after percutaneous coronary intervention

Chronic obstructive pulmonary disease has been reported to occur approximately in 7–15% of patients with CAD and has been associated with higher rates of adverse clinical events,[1–3,15] though results of studies and meta-analyses evaluating its impact on the long-term events remained highly heterogenous.[1,15–17] In the present investigation, with the information on COPD status at baseline available in 100% of patients, this condition was identified in 5.2% of enrolled patients who presented a three-fold higher mortality at 2 years after PCI. This emphasizes the magnitude of adverse impact of COPD on prognosis and further highlights the relevance of attempts to develop more effective and safe treatment strategies for this challenging patient subgroup, demonstrated to be prescribed secondary prevention therapies less frequently than non-COPD individuals.[18]

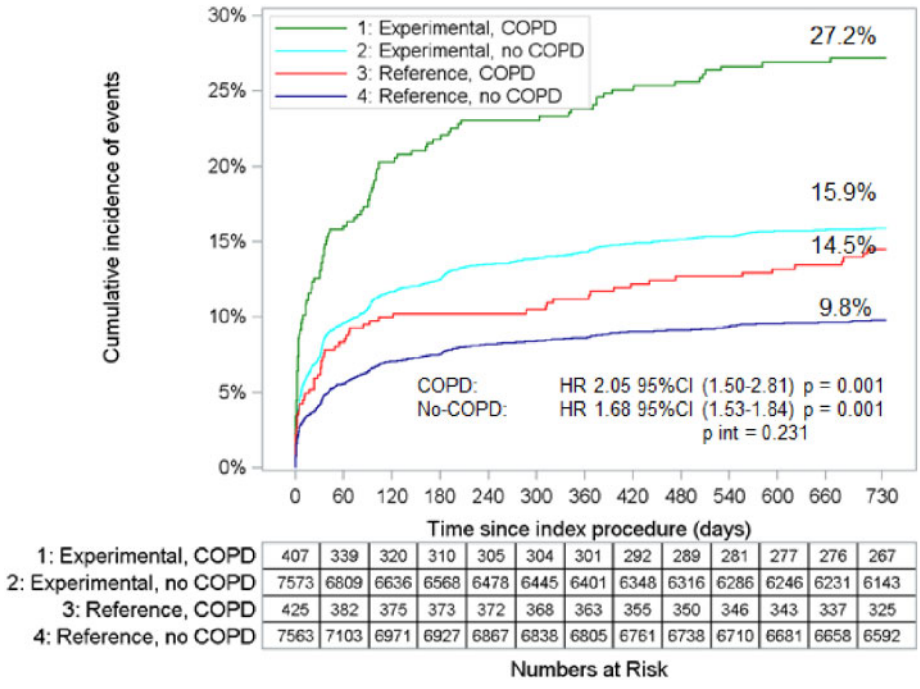
Nevertheless, the clinical—EuroSCORE based—definition of COPD applied in this trial, without performing specific pulmonary tests, could have at least partially underlie the lower prevalence of COPD in this cohort compared with some previous studies[1,15–17]; some under-diagnosis and preselection of patients with more severe disease cannot be excluded in our investigation. Previous reports suggested common under-diagnosis of COPD in patients with CAD.[15] The possibility that the analysed COPD population may represent a more clinically evident and severe COPD phenotype needs to be considered when interpreting the almost three-fold higher 2-year mortality after PCI in COPD patients in this study; previously described relationship between COPD severity and mortality risk could have affected the association between COPD status and all-cause mortality in our cohort.[19] Nevertheless, COPD definition used in GLOBAL LEADERS has been extensively adopted previously.[1,5] In addition, it may also reflect the actual clinical daily practice, where screening for lung diseases with pulmonary function testing in patients undergoing PCI is not a routine approach.

An intriguing observation in this study is also a two-fold higher risk of stroke observed among COPD patients, which corresponds with the recent studies suggesting that COPD may be a risk factor for stroke.[20,21] A systematic review by Morgan *et al.*,[20] found that COPD was associated with a higher incidence of stroke, even after adjustment for smoking status. The possible mechanisms underlying this association might involve systemic inflammation, hypoxia, hypercapnia, oxidative stress, and sympathetic activation that have been described in pathophysiology and prognosis of both COPD and stroke.[21] Another explanation could be related to overlapping risk factors for COPD and stroke; atherosclerosis frequently coexists with COPD, affecting both coronary and cerebral arteries.[22–24] In addition, COPD has been associated with increased arterial stiffness, independently of smoking status, and this abnormality was not explained by systemic endothelial dysfunction.[20] The *neuro-pneumonology* is gaining an increasing scientific interest nowadays.[20]

Chronic obstructive pulmonary disease and experimental treatment strategy

The findings of no evidence of differential safety and efficacy of ticagrelor monotherapy after 1-month vs. 12-month DAPT in patients with CAD and COPD are noteworthy; indeed, a higher incidence of dyspnoea in ticagrelor-treated patients within the PLATO study and previously released reports from European Medicines Agency that suggest an increased caution while prescribing ticagrelor to COPD subjects could have prompted clinicians to avoid this antiplatelet agent among patients with comorbidity of CAD and COPD.[25] Of note, although we analysed the COPD subgroup in the large contemporary PCI cohort, the study did not have a sufficient power to definitely assess differential treatment effects in COPD patients. Thus, our findings should be viewed as only hypothesis-generating and require confirmation in larger, prospective trials.

Interestingly, in overall cohort, COPD was identified to be associated with increased risk of BARC 3 or 5 type bleedings up to 2 years post-PCI. However, the experimental strategy including 23-month monotherapy with potent P2Y12 antagonist was found not to be



1: Experimental, COPD	407	339	320	310	305	304	301	292	289	281	277	276	267
2: Experimental, no COPD	7573	6809	6636	6568	6478	6445	6401	6348	6316	6286	6246	6231	6143
3: Reference, COPD	425	382	375	373	372	368	363	355	350	346	343	337	325
4: Reference, no COPD	7563	7103	6971	6927	6867	6838	6805	6761	6738	6710	6681	6658	6592

Figure 2 The occurrence of the first dyspnoea reported as an adverse event up to 2 years categorized according to chronic obstructive pulmonary disease status and randomized treatment strategy. 95% CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio. Kaplan–Meier estimates are reported (%).

associated with increased rate of bleeding complications (either in ACS or in stable CAD patients), among COPD patients undergoing PCI. This corresponds with the recent reports suggesting altered platelet function in CAD patients in the presence of COPD comorbidity.[8] Nevertheless, lower treatment adherence in the experimental arm needs also to be considered when interpreting the bleeding rates in our study.

Impact of dyspnoea

In line with prior reports, dyspnoea during ticagrelor therapy occurred mainly within the first months from treatment onset, nevertheless, a higher risk of dyspnoea was observed also beyond the first month of treatment up to 2 years of follow-up.[5,11] Although dyspnoea from any cause occurred more frequently in ticagrelor-treated patients, in particular among COPD patients, it was not *per se* associated with impaired prognosis. This observation may speak for the benign nature of ticagrelor-related dyspnoea compared with other causes of dyspnoea such as heart failure and cardiac ischemia. These findings are in line with the clinical outcomes in dyspnoeic and non-dyspnoeic ACS patients treated with ticagrelor DAPT reported in the PLATO study.[12]

Based on previously demonstrated favourable benefit-risk profile supporting the use of ticagrelor in patients with ACS and concomitant COPD,[5] and lack of significant safety signal found in the present investigation, it appears that the discomfort of ticagrelor-related dyspnoea should not *a priori* hinder its selective adoption in this patient subset. Nevertheless, the observed lower adherence in COPD patients warrants watchful post-discharge compliance monitoring. Knowledge of the anticipated adverse effects is important for developing optimal educational programmes.[26] Chronic obstructive pulmonary disease patient subset could represent a target population for recently developed systems aimed to improve the use of secondary prevention via tools to remind about medications, and, in particular, educate healthcare professionals and patients, i.e. about the benign nature of drug-related dyspnoea,[12,27] before switch to another medication. Such approach has been already specifically demonstrated to be effective after ACS.[26]

Strengths and limitations of the study

Here, we report a subgroup analysis from the largest so far trial comparing two antiplatelet treatment strategy (including a potent P2Y12 antagonist) with randomization at time of PCI, addressing the clinically relevant drug adverse effect—dyspnoea. However, the following limitations have to be considered.

GLOBAL LEADERS was neutral in the primary endpoint analysis in the overall population and the presented secondary analysis, like the parent trial, was not powered to detect between-group differences in clinical outcomes. Secondly, no adjustments were made for multiple comparisons, and therefore all presented results should be viewed as only hypothesis-generating.

In addition, this study is a *post hoc* analysis that was not prespecified in the original trial design. While a specific study on new antiplatelet strategies dedicated strictly to patients with CAD and COPD might be considered somewhat unlikely to be undertaken by independent research organizations or sponsors, based on the presented findings we would strongly advocate that future cardiovascular trial included more specific questions in their eCRF forms

Table 5 Exploratory analyses of 2-year clinical outcomes in patients with and without COPD categorized according to the occurrence of dyspnoea up to 2 years and the treatment strategy

	No COPD (n = 15 136)					COPD (n = 832)				
	After dyspnoea[a]		Without dyspnoea			After dyspnoea[a]		Without dyspnoea		
	HR (Exp vs. Ref) 95% CI	*P* adj	HR (Exp vs. Ref) 95% CI	*P* adj	*P* int	HR (Exp vs. Ref) 95% CI	*P* adj	HR (Exp vs. Ref) 95% CI	*P* adj	*P* int
Primary endpoint	0.95 (0.56–1.62)	0.855	0.88 (0.74–1.05)	0.150	0.867	0.67 (0.24–1.90)	0.452	0.96 (0.59–1.55)	0.860	0.418
BARC 3/5	0.67 (0.36–1.25)	0.206	1.09 (0.85–1.39)	0.516	0.345	0.28 (0.06–1.25)	0.097	0.64 (0.29–1.40)	0.262	0.743

BARC, Bleeding Academic Research Consortium; COPD, chronic obstructive pulmonary disease; Exp, experimental; Ref, reference.
HRs and *P*-values are from Cox proportional hazards model with explanatory variable for treatment group, occurrence of first dyspnoea as an adverse event (as a time-dependent covariate), and treatment-dyspnoea interaction and adjusted, for age, body mass index, gender, clinical presentation, diabetes on insulin, hypertension, peripheral vascular disease, previous major bleeding history, impaired renal function, impaired left ventricular ejection fraction <40%, previous myocardial infarction, and previous coronary artery bypass grafting.
[a]Dyspnoea as an adverse event occurred in 169 patients with COPD at baseline (n = 832), and in 1932 patients without COPD at baseline (n = 15 136).

addressing the diagnosis and severity of respiratory disorders such as COPD. This could facilitate addressing the remaining large evidence gap with regard to optimal potency and treatment scheme in this patient subset. GLOBAL LEADERS studied ticagrelor at a dose of 90-mg twice daily and the lower dose of 60-mg twice daily may be better tolerated whilst retaining a high level of platelet inhibition, a hypothesis which could warrant further investigation.[28,29] In the GLOBAL LEADERS trial, investigator reporting was used without central adjudication for secondary outcomes. Thus, bias and random event misclassification cannot be excluded. This limitation needs to be considered in particular when interpreting bleeding event rates. Nevertheless, the trial was monitored for event definition consistency and event under-reporting, with as many as seven on-site monitoring visits done at individual sites and one-fifth of clinical events checked based on the source documentation.[9] Use of site-reported endpoints is a valid method in clinical research, especially involving large cohorts, and well-defined and restricted categories within a classification, such as BARC-defined bleeding type 3 to 5 when compared with type 1 and 2, are anticipated to provide higher concordance among sites and a central clinical event adjudication committee, as well as higher reproducibility.

Finally, the randomization in GLOBAL LEADERS was not stratified for presence of COPD at baseline. Nevertheless, in the present analysis, the baseline characteristics of COPD subgroups categorized according to the treatment were balanced.

Conclusions

In this contemporary, large-scale, randomized trial, COPD was identified as the most significant clinical factor negatively impacting long-term prognosis after PCI. Among patients with CAD with COPD vs. those without COPD, ticagrelor monotherapy (after 1 month of ticagrelor and aspirin) was associated with similar rates of the primary endpoint of all-cause mortality or new Q-wave MI in the long-term follow-up, when compared with 12-month DAPT followed by 12-month aspirin monotherapy. Although dyspnoea was more frequent in the experimental arm, in particular among COPD patients treated with ticagrelor, the efficacy or safety appeared not to be affected. Judicious interpretation of these results is needed given the *post hoc* nature of this subanalysis.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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