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Acute Coronary Syndrome

The Impact of FEV1/FVC Ratio on the Clinical Outcomes in Acute Coronary Syndrome Patients Treated with Dual Anti-Platelet Agents

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Background: Few studies have investigated the clinical efficacy and pulmonary side effects of different P2Y12 inhibitors in acute coronary syndrome (ACS) patients. The aim of this study was to explore the impact of forced expiratory volume in 1 second over forced vital capacity (FEV1/FVC) ratio on the clinical outcomes in ACS patients treated with dual antiplatelet therapy after percutaneous coronary intervention (PCI).

Methods: ACS patients who underwent PCI, had documented pre-existing spirometry tests, and received aspirin with either ticagrelor or clopidogrel were enrolled for retrospective analysis.

Results: Of the enrolled ACS patients, 275 and 247 received ticagrelor and clopidogrel, respectively. The incidence of wheeze was significantly higher in the ticagrelor group compared to the clopidogrel group within 360 days (14.91% vs. 8.09%, p = 0.016). Multivariable analysis revealed that ticagrelor treatment, as compared to clopidogrel treatment, independently predicted 1-year hospitalization for acute exacerbation (AE) of obstructive airway disease (hazard ratio: 3.44; 95% confidence interval: 1.92 to 6.15; p < 0.01). The receiver operating characteristic curve indicated that an FEV1/FVC ratio of 63.85% had the highest sensitivity and specificity for predicting the incidence of AE of obstructive airway disease within 1 year (p < 0.001). The 1-year hospitalization rate for AE of obstructive airway disease was significantly higher in the ticagrelor group when the FEV1/FVC ratio was < 63%.

Conclusions: This study demonstrated higher incidence of wheeze and hospitalization for AE of obstructive airway disease in ACS patients treated with ticagrelor compared to clopidogrel. Furthermore, the FEV1/FVC ratio ≤ 63% in the ACS patients predicted hospitalization for AE of obstructive airway disease in 1 year.

Key Words: Acute coronary syndrome • Chronic obstructive pulmonary disease • Clopidogrel • FEV1/FVC ratio • Ticagrelor

INTRODUCTION

Acute coronary syndrome (ACS) is the leading cause of mortality and hospitalization in developed nations.[1]

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitors
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AE	Acute exacerbation
ARB	Angiotensin II receptor blockers
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DAPT	Dual antiplatelet therapy
ED	Emergency department
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HR	Hazard ratio
MACCEs	Major adverse cardiac and cerebrovascular events
PCI	Percutaneous coronary intervention
PLATO	Platelet Inhibition and Patient Outcomes

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Platelet activation, adhesion, and aggregation are associated with atherothrombosis and overall clinical outcomes in ACS patients. Sufficient platelet inhibition is important for preventing thrombus formation and related ischemic events.[2,3] A combination of a P2Y12 inhibitor and aspirin as dual antiplatelet therapy (DAPT) is crucial for treating ACS.[3,4] Underlying chronic obstructive pulmonary disease (COPD) is associated with adverse clinical events in ACS patients.[5] COPD is a significant and growing cause of mortality and morbidity worldwide. Aging of the global population and the continued use of tobacco are thought to be responsible for the growing burden of COPD and ACS.[1,6] Moreover, the incidence of COPD is higher in ACS patients, which makes simultaneous treatment for both diseases common in clinical practice.[5] However, standard medications recommended in established guidelines such as beta-blockers may exacerbate the symptoms of COPD,[7] and acute exacerbations of COPD may be associated with increased risks of myocardial infarction and major adverse cardiac events.[5,8]

The multicenter, double-blinded and randomized phase III Platelet Inhibition and Patient Outcomes (PLATO) trial reported that antithrombotic therapy with ticagrelor after percutaneous coronary intervention (PCI) achieved a 16% lower relative risk of major adverse cardiac and cerebrovascular events (MACCEs) and a 22% lower relative risk of all-cause mortality compared to antithrombotic therapy with clopidogrel.[9] Importantly, ticagrelor, which inhibits the re-uptake of adenosine diphosphate (ADP), resulted in a significantly higher incidence of dyspnea in the PLATO trial.[9] Further studies have raised concerns that the high baseline cardiovascular disease burden in COPD patients may limit their response to antiplatelet therapy.[10] Nevertheless, few studies have explored spirometry test results in patients who receive antiplatelet therapy for ACS after revascularization and the association with clinical outcomes. Therefore, the present study sought to compare 1-year pulmonary and cardiovascular outcomes between ACS patients who received ticagrelor or clopidogrel as one component of DAPT after ACS and revascularization.

METHODS

This retrospective cohort study was performed by reviewing medical records of patients with documented obstructive airway disease or COPD and ACS who had been treated with clopidogrel or ticagrelor at a single medical center in southern Taiwan.

Patient population

We reviewed the relevant medical records including admission/progress/discharge notes in either an in-hospital or outpatient setting, reports of coronary interventions and results of spirometry, as well as medical prescriptions over a 1-year period after the index PCI. We recruited patients who received spirometry tests to evaluate pulmonary function prior to the index PCI.

Inclusion and exclusion criteria

This study included patients over 18 years old who underwent revascularization with PCI with stent implantation for ACS and received P2Y12 inhibitors, either clopidogrel or ticagrelor, and aspirin as antiplatelet therapy at Kaohsiung Chang Gung Memorial Hospital from January 1, 2015 to September 1, 2019. The exclusion criteria were mortality during in-hospital care and unavailability of the required clinical data (e.g., patients transferred to a different hospital and patients whose prescriptions had been filled at a different clinic).

Definition of clinical symptoms and follow-up

All included patients were managed with regular clinical follow-up and prescription refills every 1 to 3 months. The patients were evaluated for their symptoms and signs, if present, and any discomfort related to cardiovascular or pulmonary function by experienced specialists during 1 year of follow-up. Dyspnea was defined as subjective breathing discomfort and respiratory distress consisting of distinct sensations noted by inspection or other objective evidence, while wheeze was defined as a high- or low-pitched respiratory sound during inspiratory and/or expiratory phase on auscultation, suggestive of peripheral or central airway narrowing or airflow limitation.[28,29] During follow-up, the in-charge cardiologist and pulmonologist asked the patients about their symptoms and performed physical examinations, and then documented wheeze or dyspnea in the medical records. Additionally, symptoms of wheeze and dyspnea recognized by emergency department (ED) physicians were also recorded, as patients often visit the ED due to exacerba-

tions of these symptoms. Wheezing cases and dyspnea cases were identified based on the presence of these symptoms during the medical record review.

Clinical outcomes

The clinical outcomes comprised of cardiovascular mortality, MACCEs, hospitalization for acute exacerbation (AE) of obstructive airway disease and hospitalization for bleeding events during the 1-year period after the index hospitalization. MACCEs were defined as the composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular mortality. Cardiovascular mortality was defined as death related to myocardial infarction, cardiac arrhythmia, or heart failure. Obstructive airway disease was defined and characterized by a progressive and not fully reversible airflow obstruction, airway inflammation and exposure to noxious particles or gases (e.g. cigarette smoking), including COPD, asthma and bronchitis. The diagnosis of COPD was based on the 2020 report of the Global Initiative for Chronic Obstructive Lung Disease criteria. A ratio of forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) < 70% with symptoms of cough and sputum production was diagnosed as COPD.[6] Adjudications of the end-points including cardiovascular mortality, MACCEs, hospitalization for AE of obstructive airway disease or for bleeding events were based on hospitalization via the ED, and if the diagnosis was present in the discharge summary and confirmed by cardiologists and pulmonologists.

Statistics

All quantitative variables are presented either as the mean ± standard deviation or as counts (percentages). Group differences were tested using the independent t-test for continuous variables and the chi-square test for categorical variables. All-cause mortality, cardiovascular mortality, MACCEs, hospitalization for acute exacerbation of obstructive airway disease, and hospitalization for bleeding events were evaluated using the Kaplan-Meier method, and group differences were compared using the log-rank test. To identify factors affecting 1-year all-cause mortality, MACCEs, and hospitalization for acute exacerbation of obstructive airway disease, univariate Cox regression was first performed on all baseline variables; those with $p < 0.1$ in the univariate analysis were put into multivariable regression analysis with a backward stepwise method. The results of the model are reported as hazard ratio (HR) and 95% confidence interval (CI).

All reported p values were based on two-sided tests and were compared to a significance level of 5%. Differences with $p < 0.05$ were considered statistically significant for all tests. Statistical analyses were performed using SPSS for Windows (version 22.0; IBM Corporation, Armonk, NY, USA). This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved for human research by the Institutional Review Committee of the Chang Gung Medical Foundation (IRB number: 202001471B0). To control the false discovery rate and adjust for multiple comparisons, we used the Benjamini-Hochberg method to identify p values between different subgroups.[30]

RESULTS

Baseline characteristics of the patients

A total of 5,035 patients who received PCI and P2Y12 inhibitor therapy for ACS between January 1, 2015 and September 1, 2019 were screened for eligibility. Among these patients, 522 (10.4%) had received spirometry tests before the index ACS event and were enrolled in this study. Table 1 shows the baseline characteristics of the study population. Of the 522 enrolled patients, 247 had been treated with clopidogrel, and 275 had been treated with ticagrelor. The median age was 68.1 ± 11.7 years and 71.1 ± 10.1 years in the ticagrelor and clopidogrel groups, respectively ($p = 0.12$). The ticagrelor group had a significantly higher percentage of males (82.9% vs. 70.0%, $p < 0.01$) and a significantly higher rate of cigarette smoking (60.7% vs. 38.5%, $p < 0.01$) compared to the clopidogrel group. Comparisons of other demographic and clinical characteristics between the two groups showed that the ticagrelor group used a significantly higher percentage of statins (84.0% vs. 72.1%, $p < 0.01$), and angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers (ACEI/ARB) (77.1% vs. 66.0%, $p < 0.01$), whereas the clopidogrel group had a significantly higher percentage of hypertension (82.2% vs. 73.1%, $p = 0.01$), end-stage renal disease (ESRD, 30.4% vs. 19.3%, $p < 0.01$), atrial fibrillation (AF, 24.3% vs. 9.8%, p <

Table 1. Demography of study population

	Clopidogrel (n = 247)	Ticagrelor (n = 275)	p value
Male (%)	173 (70.0)	228 (82.9)	< 0.01
Age (year)	71.1 ± 10.1	68.1 ± 11.7	0.12
Body weight (kg)	66.5 ± 12.7	70.6 ± 13.3	0.61
Smoking (%)	95 (38.5)	167 (60.7)	< 0.01
EGFR (mL/min/1.73 m^2)	44.5 ± 33.7	54 ± 32.9	0.18
Past history of diseases			
Hypertension (%)	203 (82.2)	201 (73.1)	0.01
DM (%)	151 (61.1)	146 (53.1)	0.07
Dyslipidemia (%)	124 (50.6)	154 (56.0)	0.25
ESRD (%)	75 (30.4)	53 (19.3)	< 0.01
AF (%)	60 (24.3)	27 (9.8)	< 0.01
Peptic ulcer (%)	80 (32.4)	52 (18.9)	< 0.01
COPD (%)	42 (17.0)	53 (19.3)	0.57
Asthma (%)	25 (10.1)	25 (9.1)	0.76
Cardiovascular parameters			
LM CAD (%)	48 (19.4)	54 (19.6)	0.95
Multi-vessel CAD (%)	192 (77.7)	220 (80.0)	0.46
Stent type			0.78
BMS (%)	76 (30.8)	90 (32.7)	
DES (%)	170 (68.8)	183 (66.5)	
Killip classification			0.54
Killip 1 (%)	138 (55.9)	145 (52.7)	
Killip 2 (%)	36 (14.6)	64 (23.3)	
Killip 3 (%)	55 (22.3)	42 (15.3)	
Killip 4 (%)	18 (7.2)	24 (8.7)	
LVEF			0.47
< 40%	148 (59.9)	186 (67.6)	
40-50%	45 (18.2)	34 (12.4)	
> 50%	54 (21.9)	55 (20.0)	
Spirometry parameters			
Time interval between spirometry test and ACS (days)	116.8 ± 61.7	117.2 ± 78.9	0.65
FEV1/FVC (%)	70.7 ± 9.8	70.1 ± 9.7	0.86
FEV1 (liters)	2.64 ± 0.48	2.59 ± 0.43	0.66
FVC (liters)	3.75 ± 0.63	3.69 ± 0.55	0.69
Medication at discharge (%)			
Oral prednisolone	45 (18.2)	24 (8.7)	< 0.01
Tiotropium	26 (10.5)	34 (12.4)	0.58
LABA	51 (20.6)	54 (19.6)	0.82
Theophylline	70 (28.7)	66 (24.3)	0.30
Statin	178 (72.1)	231 (84.0)	< 0.01
Beta-blocker	182 (73.7)	221 (80.0)	0.07
ACEI/ARB	163 (66.0)	212 (77.1)	< 0.01

ACEI, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; BMS, bare metal stent; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DES, drug eluting stent; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; LABA, long-acting beta-agonist; LVEF, left ventricular ejection fraction; LM, left main.

0.01), peptic ulcer (32.4% vs. 18.9%, p < 0.01), and oral prednisolone use (18.2% vs. 8.7%, p < 0.01). There were no significant differences in FEV1, FCV and the FEV1/FVC ratio. These results indicated that physicians may choose a specific P2Y12 agent based on the co-morbidities of the patients in real-word practice.

The incidence of wheeze and dyspnea in the patients treated with different P2Y12 inhibitors

To understand whether ticagrelor was associated

with dyspnea or wheeze, we reviewed all included patients within 1 year after the index PCI, and the results are illustrated in Figure 1. Although the ticagrelor group had non-significantly higher incidence rates of dyspnea within 90 days (9.45% vs. 5.67%, p = 0.104) and 360 days (18.82% vs. 14.17%, p = 0.257), the incidence of wheeze was significantly higher in the ticagrelor group than in the clopidogrel group within 90 days (8.36% vs. 1.21%, p = 0.001) and 360 days (14.91% vs. 8.09%, p = 0.016). These results indicated that the prescription of ticagrelor in the ACS patients, as compared to those who received clopidogrel, was associated with a higher incidence of wheeze.

Risk factors predicting 1-year outcomes

Since the two groups differed in baseline characteristics, regression analysis was performed to identify independent risk factors. Table 2 shows the results of univariate and multivariable analyses to identify predictors of 1-year hospitalization for AE of obstructive airway dis-

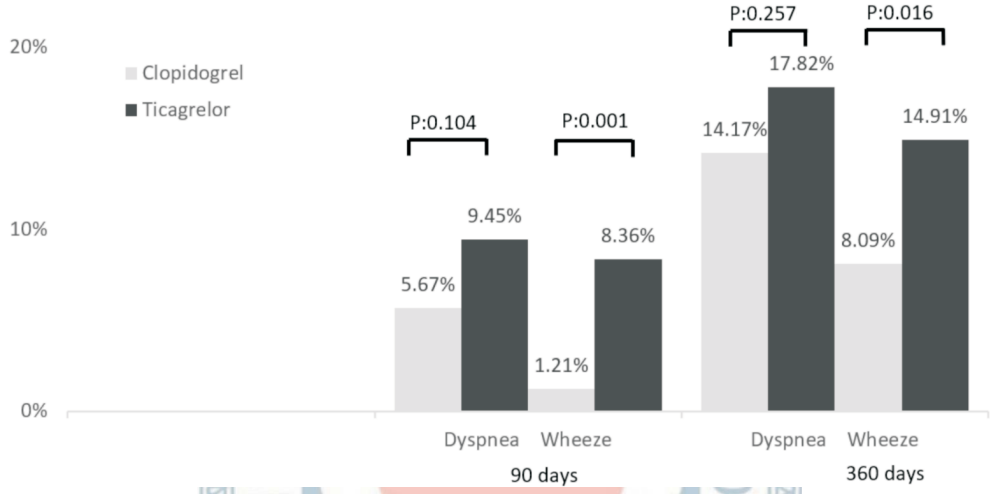


Figure 1. *The incidence of dyspnea and wheezing during 1-year follow-up. The figure shows the incidence of dyspnea and wheeze within 90 days and 360 days between clopidogrel group (gray column) and ticagrelor group (black column).*

Table 2. Univariate and multivariate analysis to predict 1-year hospitalization for acute exacerbation of obstructive airway disease

Variable	Univariate			Multivariable		
	HR	95% CI	p	HR	95% CI	p
Ticagrelor vs. clopidogrel*	2.11	1.21-3.69	< 0.01	3.44	1.92-6.15	< 0.01
Age (year)	1.05	1.02-1.08	< 0.01	1.03	1.01-1.07	< 0.01
Female	1.17	0.65-2.11	0.59			
BW (kg)	0.99	0.97-1.01	0.44			
Smoking	1.25	0.75-2.11	0.38			
History of COPD	5.44	3.21-7.40	< 0.01	3.74	2.32-5.88	< 0.01
History of asthma	1.45	0.88-3.43	0.77			
AF	1.14	0.59-2.20	0.68			
LVEF < 40%	1.33	0.73-2.39	0.34			
Oral prednisolone*	4.14	2.42-7.08	< 0.01	2.70	1.53-4.91	< 0.01
LABA*	2.35	1.38-4.02	< 0.01			
Theophylline*	1.97	1.18-3.28	< 0.01			
Beta-blockers*	1.02	0.55-1.89	0.94			
ACEI/ARB*	0.68	0.40-1.17	0.16			
FEV1/FVC (%)	0.94	0.91-0.96	< 0.01	0.95	0.92-0.97	< 0.01

ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; BW, body weight; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; HR, hazard ratio; LABA, long-acting beta-agonist; LVEF, let ventricle ejection fraction.
* Medications prescribed at discharge.

ease in the study population. The multivariable analysis results indicated that ticagrelor treatment, compared to clopidogrel treatment, independently predicted 1-year hospitalization for AE of obstructive airway disease (HR: 3.48; 95% CI: 1.92 to 6.11; p < 0.01). Furthermore, the HR for COPD AE history was 3.74 (95% CI: 2.32 to 5.88; p < 0.01). Additionally, advanced age, underlying COPD, oral prednisolone use and the lower FEV1/FVC ratio were also significantly associated with 1-year hospitalization for AE of obstructive airway disease in multivariable analysis. Supplementary Tables 1 and 2 show the results of univariate and multivariable analyses performed to identify the predictors of the 1-year incidence of MACCEs and all-cause mortality in the study population, respectively. The results showed that the FEV1/FVC ratio, COPD/asthma history, and hospitalization for obstructive airway disease in 1 year were not independent predictors of 1-year MACCEs or all-cause mortality in this patient cohort.

ROC curve analysis to identify the cut-off point for FEV1/FVC ratio in predicting 1-year outcomes

Since the FEV1/FVC ratio was significantly associated with 1-year hospitalization for AE of obstructive airway disease in multivariable analysis, a receiver operating characteristic (ROC) curve (Figure 2) was used to identify the best cut-off point for predicting 1-year hospitalization for AE of obstructive airway disease. An FEV1/FVC ratio of 63.85% had the highest sensitivity (45.9%) and specificity (82.21%) in predicting AE within a 1-year period. The area under the curve was 0.663, with a p value < 0.001.

Subgroup analysis of 1-year outcomes by the Kaplan-Meier method

Clinical outcomes were presented as survival curves constructed using the Kaplan-Meier method. The patients were classified into four groups: clopidogrel with FEV1/FVC ≥ 63% (n = 209 at baseline); ticagrelor with FEV1/FVC ≥ 63% (n = 225 at baseline); clopidogrel with FEV1/FVC < 63% (n = 38 at baseline); ticagrelor with FEV1/FVC < 63% (n = 50 at baseline). Figure 3A shows the results of subgroup analysis for the 1-year rate of hospitalization for AE of obstructive airway disease. The log-rank p-values were < 0.01 in comparisons of all four groups, 0.014 in comparisons between clopidogrel with FEV1/FVC < 63% and ticagrelor with FEV1/FVC < 63% groups, and < 0.01 in comparisons between ticagrelor with FEV1/FVC ≥ 63% and ticagrelor with FEV1/FVC < 63% groups. The 1-year hospitalization rate for AE of obstructive airway disease significantly differed between the clopidogrel with FEV1/FVC < 63% and ticagrelor with FEV1/FVC < 63% group, as well as between the ticagrelor with FEV1/FVC ≥ 63% and ticagrelor with FEV1/FVC < 63% groups. However, there was no significant difference between the clopidogrel with FEV1/FVC ≥ 63% and ticagrelor with FEV1/FVC ≥ 63% (p = 0.15) groups. We used the Benjamini-Hochberg procedure to control the false discovery rate and identify the adjusted p-values between different subgroups. The adjusted p-value was 0.028 in comparisons between the clopidogrel with FEV1/FVC < 63% and ticagrelor with FEV1/FVC < 63% groups, and < 0.01 in comparisons between the ticagrelor with FEV1/FVC ≥ 63% and ticagrelor with FEV1/FVC < 63% groups. The 1-year hospitalization rate for AE of obstructive airway disease significantly differed between the subgroups.

Figure 3B shows the results of subgroups analysis of 1-year survival of cardiovascular mortality, and no significant differences between all four groups and subgroups analysis were observed. Figure 3C and 3D show the results of subgroup analysis of 1-year survival of MACCEs

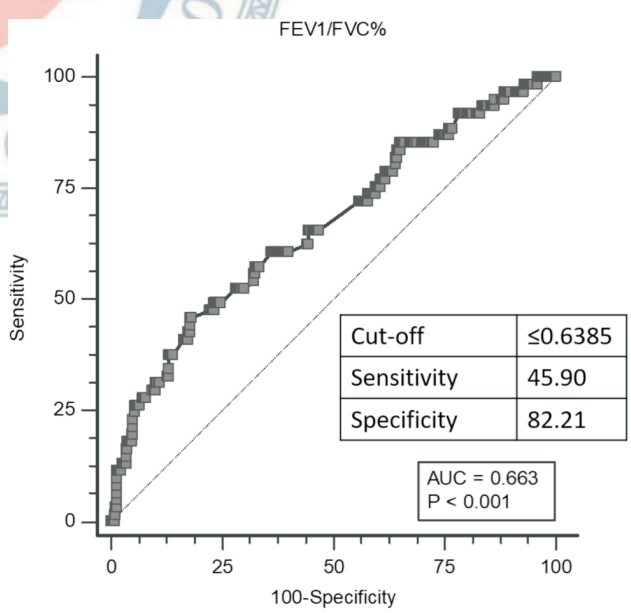
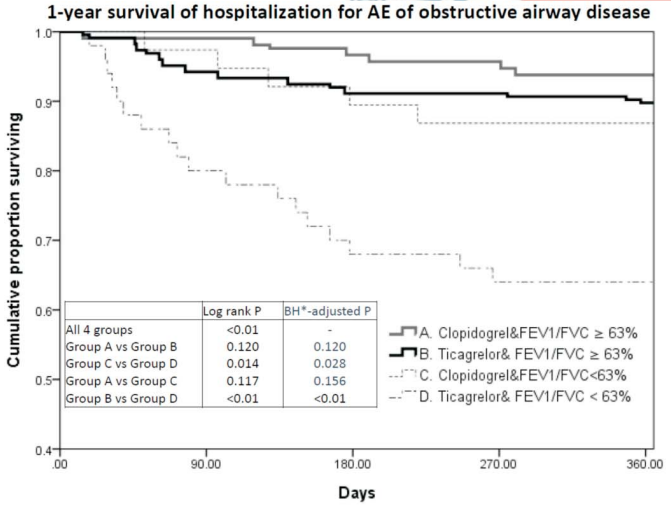


Figure 2. *The receiver operating characteristic curve of forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio for hospitalization for acute exacerbation of obstructive airway disease.*

and hospitalization for bleeding, respectively. No significant differences between all four groups and subgroups analysis were observed.

DISCUSSION

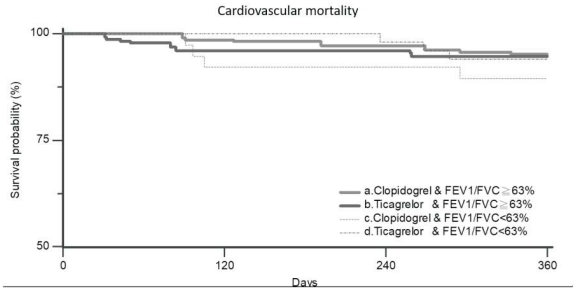
To our knowledge, the current study is the first to assess the impact of baseline pulmonary function in ACS patients treated with different P2Y12 inhibitors on pulmonary and cardiovascular outcomes in 1 year of follow-up. Our study demonstrated that both the use of ticagrelor as compared to clopidogrel and baseline FEV1/FCV independently predicted hospitalization for AE of obstructive airway disease but not cardiovascular events in 1 year. The best cut-off value for FEV1/FVC to predict



Number at risk	Day0	Day120	Day240	Day360	Event Free rate
a.Clopidogrel & FEV1/FVC ≧63%	209	205	300	196	90.78%
b.Ticagrelor & FEV1/FVC ≧63%	225	210	205	203	90.22%
c.Clopidogrel & FEV1/FVC <63%	38	36	33	33	86.84%
d.Ticagrelor & FEV1/FVC <63%	50	39	34	32	64.00%

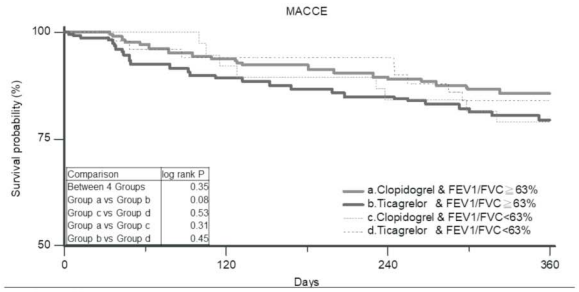
*: Benjamini-Hochberg Adjusted P value

A



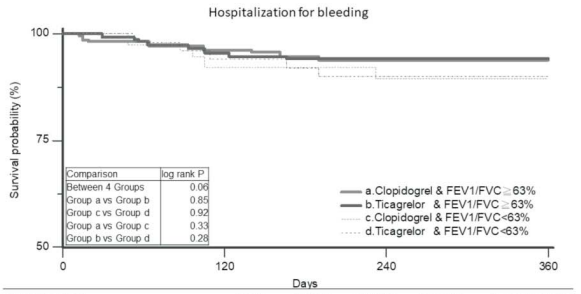
Number at risk	Day0	Day120	Day240	Day360	Event Free rate
a.Clopidogrel & FEV1/FVC ≧63%	209	206	203	199	95.22%
b.Ticagrelor & FEV1/FVC ≧63%	225	216	216	213	94.67%
c.Clopidogrel & FEV1/FVC <63%	38	35	35	34	89.47%
d.Ticagrelor & FEV1/FVC <63%	50	50	49	47	94.00%

B



Number at risk	Day0	Day120	Day240	Day360	Event Free rate
a.Clopidogrel & FEV1/FVC ≧63%	209	196	186	179	85.65%
b.Ticagrelor & FEV1/FVC ≧63%	225	201	191	179	79.56%
c.Clopidogrel & FEV1/FVC <63%	38	35	32	30	78.95%
d.Ticagrelor & FEV1/FVC <63%	50	47	47	42	84.00%

C



Number at risk	Day0	Day120	Day240	Day360	Event Free rate
a.Clopidogrel & FEV1/FVC ≧63%	209	210	196	196	93.78%
b.Ticagrelor & FEV1/FVC ≧63%	225	215	212	212	94.22%
c.Clopidogrel & FEV1/FVC <63%	38	35	34	34	89.47%
d.Ticagrelor & FEV1/FVC <63%	50	47	45	45	90.00%

D

Figure 3. *The Kaplan-Meier survival estimates of 1-year clinical outcomes stratified by P2Y12 therapy and forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC). Patients were grouped by treatment of ticagrelor or clopidogrel and FEV1/FCV ≥ 63% or < 63% into 4 groups: group A with clopidogrel and FEV1/FVC ≥ 63%; group B with ticagrelor and FEV1/FVC ≥ 63%; group C with clopidogrel and FEV1/FVC < 63%; and group D with ticagrelor and FEV1/FVC < 63%. The Kaplan-Meier survival estimates of 1-year hospitalization for AE of obstructive airway disease (A), cardiovascular mortality (B), Major adverse cardiac and cerebrovascular events (MACCE) (C), and hospitalization for bleeding events (D) were presented accordingly. The number at risk and the percentage of event-free survival of each group were showed in bottom of the panel. The log-rank p-values and Benjamini-Hochberg procedure adjusted p-values compared between groups demonstrated in the figures.*

hospitalization for AE of obstructive airway disease was ≤ 63.85%.

Obstructive airway disease is underdiagnosed in ACS patients

Although our study did not find that a history of COPD was associated with worse cardiovascular outcomes in the ACS patients, a previous study did show that nearly one quarter of their patients with ischemic heart disease who underwent PCI met the spirometry criteria for COPD, of whom 81.8% were undiagnosed.[11] Indeed, although all of the patients in this study received spirometry tests prior to the admission for ACS and nearly half of those had an FEV1/FCV ratio < 70%, only 27.1% in the clopidogrel group and 28.4% in ticagrelor group were diagnosed with either COPD or asthma. This raises concerns of the underdiagnosis of COPD or obstructive airway disease in ACS patients. Therefore, we suggest that spirometry should be arranged to exclude COPD and guide treatment whenever clinically suspected.

Special treatment considerations for ACS patients with obstructive pulmonary disease

Hospitalized patients with obstructive pulmonary disease exacerbations have been reported to have an increased risk of subsequent cardiovascular disease events, especially within the first 30 days after exacerbation.[12,24,25] Although the cardiovascular risk of concurrently using long-acting β2-agonists and anticholinergics in COPD patients may raise concerns, a recent claims database study derived from United Kingdom Clinical Practice Research Datalink demonstrated that long-acting bronchodilators in a real-world setting of treatment for COPD did not increase the risk of most cardiovascular events.[13,27] Notably, a study using data derived from the Taiwan National Health Insurance Research Database showed that the use of beta-blockers after ACS was associated with a reduced risk of mortality in patients with COPD, and did not increase the risk of COPD exacerbations.[14] However, another study of this database revealed that a lower proportion of patients with COPD received DAPT or beta-blockers for ACS than patients without COPD, and their clinical outcomes were inferior.[15] Undertreatment in patients with ACS and COPD is not rare. Importantly, the APPLE COPD-ICON2 trial showed that a platelet response to antiplatelet therapy with aspirin and ticagrelor was not observed in nearly one-third of COPD patients with no prior history of cardiovascular disease, suggesting the high prothrombotic status in COPD patients.[16,26] Further research is needed to determine the effect of antiplatelet therapy on cardiovascular morbidity and mortality in COPD patients.

Ticagrelor and bronchospasm

The ONSET/OFFSET trial prospectively demonstrated that, at 6 weeks of treatment, the incidence of dyspnea was significantly higher in the ticagrelor group compared to the clopidogrel group (38.6% vs. 9.3%, respectively; p < 0.001), although most cases of dyspnea in the ticagrelor group were mild and short-term, and ticagrelor was not associated with significant changes in FEV1/FCV.[17,23] Additionally, in the PLATO trial, despite the significantly higher incidence of dyspnea observed in the ticagrelor group (13.8%) compared to the clopidogrel group (7.8%),[9] ticagrelor-induced dyspnea was mild to moderate or transient during outpatient department follow-up, and tended to resolve either spontaneously or shortly after discontinuation of treatment.[18,19] Indeed, only a few patients discontinued ticagrelor because of dyspnea. In the present study, we found that ticagrelor was an independent predictor of hospitalization for AE of obstructive airway disease. In contrast, the PLATO study did not find that ticagrelor had more adverse effects on pulmonary function in comparison with clopidogrel.[20,21] A possible reason for this the difference may be that the patients recruited in our study had worse baseline pulmonary function than those in the PLATO trial. Therefore, wheeze may have been noted when using P2Y12 inhibitors such as ticagrelor or cangrelor. Whether P2Y12 inhibitors should be shifted to clopidogrel or prasugrel is an important issue, and further large scale studies are warranted to investigate this issue from the perspective of both pulmonary and cardiovascular outcomes.

Study implications

Established guidelines[4] suggest that ticagrelor is preferred to clopidogrel for patients with ACS together with aspirin as DAPT. Nevertheless, our study demonstrated that ticagrelor was associated with a higher incidence of wheeze and subsequent hospitalization for AE of obstructive airway disease. In COPD patients who are

treated with oral prednisolone and have a low FEV1/FCV ratio (e.g. < 63%), it is important for clinicians to closely monitor respiratory complications during follow-up. Additionally, ticagrelor is a powerful P2Y12 inhibitor with pleiotropic effects in the cardiovascular system in patents with stable coronary artery disease and COPD.[21,22] Given that the use of ticagrelor but not beta blockers was associated with hospitalization for AE of obstructive airway disease in our study, the prescription of ticagrelor on top of aspirin and β-1 selective beta blockers should be chosen cautiously in ACS patients with COPD.

Study limitations

Some limitations of this observational study should be noted. First, this was a retrospective study that analyzed patients treated at a single medical center, which may have introduced selection bias. Second, this study applied intention-to-treat analysis of P2Y12 receptor inhibitors prescribed at discharge; however, the treatment duration and medication switch were not taken into consideration. Third, only a few patients were treated with prasugrel, and therefore they were not included in the analysis. Fourth, patients with chronic bronchitis who suffered from wheeze in our population may have been classified and coded as COPD. Nevertheless, this study provides a sufficiently accurate reflection of the real-world experience.

CONCLUSIONS

This study demonstrated a higher incidence of wheeze and hospitalization for AE of obstructive airway disease in ACS patients treated with ticagrelor as compared to clopidogrel. Furthermore, FEV1/FVC ≤ 63.85% in ACS patients independently predicted hospitalization for AE of obstructive airway disease in 1 year. Our findings suggest that ticagrelor should be prescribed cautiously in ACS patients with low FEV1/FVC.

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DECLARATION OF CONFLICT OF INTEREST

All the authors have no conflict of interest related to the manuscript.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. Univariate and multivariable analysis to predict 1-year MACCE

Variable	Univariate			Multivariable		
	HR	95% CI	p	HR	95% CI	p
Ticagrelor vs. clopidogrel*	1.32	0.87-2.00	0.18			
Age (year)	0.98	0.97-1.01	0.19			
Female	1.43	0.91-2.24	0.11			
BW (kg)	0.99	0.98-1.01	0.86			
Smoking	0.81	0.53-1.22	0.31			
History of COPD	0.96	0.63-1.55	0.92			
History of asthma	0.95	0.66-2.73	0.95			
Hypertension	1.72	0.97-3.02	0.05			
DM	1.59	1.03-2.47	0.03			
LM vs. non-LM CAD	2.47	1.61-3.79	< 0.01	2.37	1.54-3.63	< 0.01
Multi-vessel CAD	1.11	0.67-1.83	0.67			
ESRD	2.36	1.55-3.57	< 0.01	2.25	1.48-3.41	< 0.01
AF	0.86	0.49-1.53	0.62			
LVEF < 40%	1.36	0.87-2.20	0.17			
Statin*	1.01	0.61-1.65	0.98			
Beta-blocker*	1.23	0.73-2.06	0.42			
ACEI/ARB*	1.17	0.73-1.88	0.50			
eGFR < 30 (mL/min/1.73 m^2)	2.25	1.49-3.39	< 0.01			
FEV1/FVC (%)	1.00	0.98-1.03	0.42			
Hospitalization for bleeding event in 1 year	2.04	1.05-3.93	0.03	2.03	1.05-3.92	0.03
Hospitalization for AE of obstructive airway disease in 1 year	0.84	0.42-1.68	0.63			

ACEI, angiotensin-converting enzyme inhibitors; AE, acute exacerbation; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; BW, body weight; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; LM, left main; LVEF, let ventricle ejection fraction.
* Medications prescribed at discharge.

Supplementary Table 2. Univariate and multivariable analysis to predict 1-year all-cause death

Variable	Univariate			Multivariable		
	HR	95% CI	p	HR	95% CI	p
Ticagrelor vs. clopidogrel	0.53	0.34-0.82	< 0.01			
Age (year)	1.03	1.01-1.06	< 0.01	1.03	1.01-1.05	< 0.01
Female	2.00	1.29-3.12	< 0.01	1.77	1.13-2.77	< 0.01
BW (kg)	0.99	0.98-1.01	0.99			
Smoking	0.59	0.38-0.92	0.02			
History of COPD	1.31	0.82-2.12	0.20			
History of asthma	1.62	0.55-3.12	0.40			
Hypertension	2.36	1.22-4.56	0.01			
DM	1.97	1.23-3.14	< 0.01			
LM vs. non-LM CAD	2.61	1.68-4.04	< 0.01	2.84	1.81-4.46	< 0.01
Multi-vessel CAD	2.15	1.25-3.72	< 0.01			
AF	2.55	1.62-4.04	< 0.01	2.08	1.31-3.31	< 0.01
ESRD	2.42	1.57-3.71	< 0.01	2.31	1.48-3.60	< 0.01
LVEF < 40%	1.62	1.01-2.58	0.42			
FEV1/FVC (%)	1.00	0.97-1.02	0.96			
Hospitalization for bleeding event in 1 year	3.51	2.01-6.14	< 0.01	3.10	1.73-5.55	< 0.01
Hospitalization for AE of obstructive airway disease in 1 year	1.59	0.89-2.82	0.11			

AE, acute exacerbation; AF, atrial fibrillation; BW, body weight; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ESRD, end stage renal disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; HTN, hypertension; LM, left main; LVEF, let ventricle ejection fraction.
[#] Past history of acute exacerbation recorded.