

ORIGINAL ARTICLE

Post-Percutaneous Transluminal Coronary Angioplasty Acute Dyspnea in Acute Coronary Syndrome Patients: Ticagrelor Versus Clopidogrel at Tertiary Cardiac Center: A Cross-Sectional Study

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ABSTRACT

Objective: To compare the frequency of new-onset acute dyspnea in acute coronary syndrome patients undergoing percutaneous transluminal coronary (PTCA) receiving ticagrelor versus clopidogrel.

Study Design: Quasi-experimental study.

Place and Duration of Study: This study was conducted at the Department of Adult Cardiology, Armed Forces Institute of Cardiology/National Institute of Heart Diseases (AFIC/NIHD), Rawalpindi, Pakistan, from 30th September 2025 to 30th March 2026.

Methods: A total of 198 male patients aged 50–75 years who underwent percutaneous transluminal coronary angioplasty (PTCA) for acute coronary syndrome (ACS) were enrolled and allocated into two groups: experimental group (N=99) received ticagrelor plus aspirin, and control group (N=99) received clopidogrel plus aspirin. Post-procedural dyspnea was assessed as the primary outcome within 8–24 hours post-procedure using the Modified Borg Acute Dyspnea Scale (0–4), with follow-up evaluations at one, two, and three months.

Results: A total of 198 male patients with ACS who underwent PTCA were included in the study. Mean patient age was 67.41±3.83 years. Dyslipidemia was the most common comorbidity, present in 140 patients (70.7%), followed by smoking in 111 (56.1%), diabetes mellitus in 104 (52.5%), and hypertension in 86 (43.4%). In-hospital dyspnea was significantly more frequent with ticagrelor (57.6%) than with clopidogrel (12.1%) ($P<0.001$). Dyspnea frequency declined progressively in both groups across follow-ups; at three months, only 3.0% of ticagrelor and 1.0% of clopidogrel patients remained symptomatic. A significant within-group decline was observed in both groups over the follow-up period ($P<0.001$).

Conclusion: Ticagrelor was associated with a significantly higher incidence of dyspnea compared with clopidogrel among patients with acute coronary syndrome undergoing PTCA, particularly during the in-hospital period. Most episodes were mild and self-limiting, supporting continued use given its established cardiovascular benefits.

Keywords: *Acute Coronary Syndrome, Clopidogrel, Dyspnea, Percutaneous Transluminal Coronary Angioplasty, Ticagrelor.*

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Introduction

Acute coronary syndromes (ACS) represent a range of conditions characterized by clinical symptom changes, with/without ECG changes and elevations in cardiac troponin (cTn).¹ Percutaneous transluminal coronary angioplasty (PTCA) with stent insertion remains the standard interventional treatment. According to American Heart Association (AHA) guidelines, patients undergoing PTCA are advised to receive dual antiplatelet therapy (DAPT)

for at least 12 months, typically comprising aspirin and a P2Y₁₂ receptor antagonist such as clopidogrel.²

However, there are certain limitations associated with Clopidogrel, which include being a prodrug with delayed onset, different inter-patient response, and irreversible platelet inhibition.³ A novel cyclopentyltriazolopyrimidine and reversible oral P2Y₁₂ receptor antagonist is the Ticagrelor, which offers a more rapid onset, higher potency, and reduced variability. After FDA approval in 2011, ticagrelor entered the research era and has demonstrated superior efficacy in several clinical trials, notably PLATO, TREAT, and Prague-18.⁴⁻⁶

Irrespective of these advantages, ticagrelor use has been linked to dyspnea, an adverse effect that may cause poor treatment adherence and impaired quality of life. Two main hypotheses explain this phenomenon. The first, the adenosine hypothesis, proposes that ticagrelor prevents cellular uptake of adenosine by blocking equilibrative nucleoside transporters (ENT1 and ENT2), thereby prolonging the extracellular adenosine half-life. Adenosine interacts with airway P1 receptors, then stimulates vagal C fibers, causing bronchoconstriction and the sensation of dyspnea.^{7,8} The second hypothesis suggests that inhibition of P2Y₁₂ receptors on neurons and glial cells boosts vagal C-fiber signaling and activates central chemoreflex pathways, thereby producing dyspnea.^{9,10}

Dyspnea following PTCA is clinically significant, as it influences both patient compliance with DAPT and long-term outcomes. Although ticagrelor has shown superior protection against thrombotic events compared to clopidogrel, its association with dyspnea limits its widespread use. Existing evidence primarily focuses on efficacy and safety comparisons, while limited data address post-PTCA dyspnea specifically in ACS patients. This study aimed to fill this gap by comparing the incidence and severity of dyspnea in ACS patients receiving ticagrelor versus clopidogrel following PTCA.

Methods

This quasi-experimental study was conducted at the Department of Adult Cardiology, Armed Forces Institute of Cardiology/National Institute of Heart Diseases (AFIC/NIHD), Rawalpindi, Pakistan, from 30th September 2025 to 30th March 2026, after

obtaining approval from the Institutional Ethical Review Board of AFIC, vide letter no: 9/2/R&D/2025/338, dated: 20th Feb 2025, and the CPSP research department. The study duration was six months. A non-probability consecutive sampling technique with non-random participant allocation was employed.

An online WHO sample size calculator was used for sample size calculation and got 89 in the experimental group and 89 in the control group, with reference to the population proportion experiencing dyspnea in the ticagrelor versus clopidogrel groups (26.3% vs. 13.6%), using a power of 80% and a margin of error of 5%. A total of 198 patients were ultimately enrolled.¹¹

Eligible participants were male patients aged 50–75 years who were planned for a 12-month course of DAPT, including ticagrelor. Only brand formulations Anplag (ticagrelor), Loprin (aspirin), and Lowplat (clopidogrel) were used. Patients were excluded if they had a history of dyspnea before or during the procedure, severe comorbid conditions (e.g., stage IV cancer or significant organ dysfunction), respiratory diseases (asthma, COPD, or COVID-19 during ACS), previous or new-onset NYHA class III or IV heart failure, warfarin use, or anemia.

Upon presentation with ACS, informed consent was obtained, and a detailed medical history was recorded. Baseline investigations were performed, including ECG and laboratory tests (CBC, RFTs, LFTs, PFTs, electrolytes, and high-sensitivity troponin-I). Following ACS confirmation, patients underwent PTCA within 60 minutes of arrival.

Post-PTCA, Group 1 (experimental) received ticagrelor 90 mg twice daily with aspirin 75 mg once daily, following a loading dose of ticagrelor 180 mg immediately after PTCA. Group 2 (control) received clopidogrel 75 mg every 8 hours with aspirin 150 mg once daily. After four weeks, maintenance DAPT was prescribed: Group 1 received ticagrelor 60 mg twice daily with aspirin 75 mg once daily, while Group 2 received clopidogrel 75 mg once daily with aspirin 75 mg once daily.

The study outcome was the occurrence and severity of dyspnea within 8–24 hours post-PTCA, assessed using the Modified Borg Acute Dyspnea Scale, with ratings from 0 (no dyspnea) to 4 (very severe dyspnea).¹² In-hospital dyspnea was assessed at 8,

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Quasi-Experimental Study | AFIC/NIHD, Rawalpindi



Study Population

Inclusion Criteria

- Male patients aged 50–75 years
- ACS confirmed by symptoms + ECG + hs-Troponin-I
- Planned for 12-month DAPT including ticagrelor
- Brand formulations only: Anplag (ticagrelor), Loprin (aspirin), Lowplat (clopidogrel)



Exclusion Criteria

- History of dyspnea before or during the procedure
- Comorbid (stage IV cancer, significant organ dysfunction)
- Respiratory diseases: asthma, COPD, or COVID-19 during ACS
- Prior or new-onset NYHA class III or IV heart failure
- Warfarin use
- Anaemia



Enrolment

Total enrolled: N = 198 male patients

Non-probability consecutive sampling | non-random allocation



Baseline Assessment (pre-PTCA)

Informed consent obtained | Detailed medical history recorded

ACS confirmed → PTCA performed within 60 minutes of arrival



Experimental Group — Ticagrelor

N = 99



Control Group — Clopidogrel

N = 99



Outcome: Occurrence and severity of dyspnea within 8–24 hours post-PTCA



Follow-up Schedule (3 Months)

Dyspnea reassessment (Modified Borg Scale) | Telephone reminder



Statistical Analysis

Software: SPSS Version 23

- Categorical data → N (%)
- Quantitative data → Mean ± Standard deviation
- Between-group dyspnea frequency → Chi-Square/Fisher's exact test
- Continuous variables → Independent t-test

Statistical significance: $P < 0.05$

Fig.1: Flow diagram showing selection of eligible study participants

12, and 24 hours post-ticagrelor loading dose. Follow-up evaluations were scheduled every four weeks for three months, with additional telephone reminders (Figure 1).

Data were analyzed using Statistical Package for the Social Sciences version 23. Categorical data were presented as frequencies and percentages, and quantitative data as mean±standard deviation. Chi-Square was applied to compare dyspnea frequency across study groups. Cochran's Q test was used to assess within-group change in the frequency of dyspnea across follow-up time points. An independent t-test was applied for continuous variables. Binary logistic regression was applied to find out the predictors of dyspnea. Results were considered statistically significant at $P<0.05$.

Results

A total of 198 male patients with ACS who underwent PTCA were included in the study. Mean patient age was 67.41 ± 3.83 years. Dyslipidemia was the most common comorbidity, present in 140 patients (70.7%), followed by smoking in 111 (56.1%), diabetes mellitus in 104 (52.5%), and hypertension in 86 (43.4%). The majority of patients presented with STEMI 168(84.8%), while NSTEMI was less frequent, 30 (15.2%) (Table 1).

In-hospital dyspnea was reported in 69 (34.8%) patients overall, representing the most prominent finding. The frequency declined progressively, affecting 23 (11.6%) patients at one month, 8 (4%) at two months, and only 4 (2%) at three months (Figure 2).

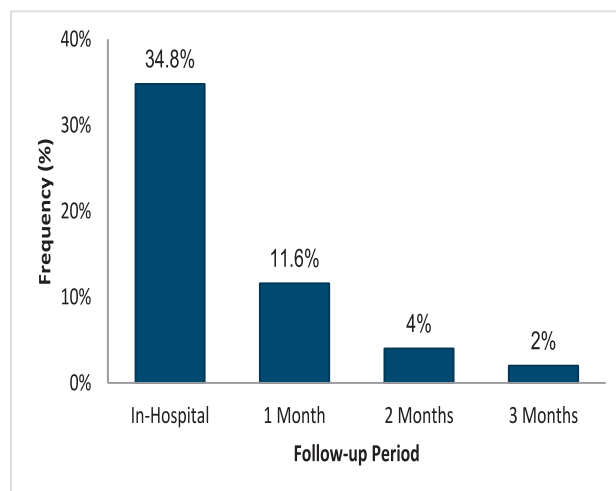


Fig.2: Dyspnea Across Follow-up Periods in study population (N=198)

Dyslipidemia was significantly more prevalent in the ticagrelor group 83 (83.8%) compared to the clopidogrel group 57 (57.6%) ($P<0.001$). Smoking was more frequent in clopidogrel-treated patients 76 (76.8%) than in ticagrelor users 35 (35.4%) ($P<0.001$). STEMI was significantly more common among clopidogrel recipients 94, 94.9%) compared to ticagrelor 74 (74.7%), while NSTEMI was more frequent in ticagrelor users (25.3% vs. 5.1%) ($P<0.001$) (Table 2).

In-hospital dyspnea was markedly higher in the ticagrelor group, 57 (57.6%), compared to clopidogrel, 12 (12.1%) ($P<0.001$). At one-month follow-up, dyspnea was reported in 9 (9.1%) on clopidogrel and 14 (14.1%) on ticagrelor, with no significant difference ($P=0.267$). At two-month follow-up, occurrence was similar (3.0% vs. 5.1%; $P=0.470$). At three months, persistent dyspnea was reported in 1 (1.0%) clopidogrel patient compared to 3 (3.0%) ticagrelor patients ($P=0.312$). A significant decline in dyspnea frequency was noted within both groups across follow-ups ($P<0.001$, Cochran's Q test) (Table 3).

On univariable analysis, treatment group (Ticagrelor vs. Clopidogrel; uOR 9.84, 95% CI 4.77–20.28, $P<0.001$), hypertension (uOR 0.36, 95% CI 0.19–0.68, $P=0.003$), diabetes mellitus (uOR 2.98, 95% CI 1.60–5.53, $P<0.001$), smoking status (uOR 0.50, 95% CI 0.28–0.90, $P=0.022$), and ACS type — NSTEMI vs. STEMI (uOR 0.52, 95% CI 0.21–1.28, $P=0.156$) met the threshold of $P\leq0.25$.

Four variables were identified as independent predictors of in-hospital dyspnea in multivariable logistic regression (P -value cut-off ≤0.05). The most prominent predictor was Ticagrelor use; in-hospital dyspnea was significantly associated with Ticagrelor use (aOR 14.39, 95% CI 5.84–35.44, $P<0.001$) compared to Clopidogrel. Nearly three times greater odds of in-hospital dyspnea were associated with diabetes mellitus alone (aOR 2.82, 95% CI 1.34–5.97, $P=0.007$). On the other hand, there was a statistically significant decrease in the odds of in-hospital dyspnea associated with hypertension (aOR 0.42, 95% CI 0.20–0.91, $P=0.027$), meaning that this symptom is less likely to occur during hospitalization in people with hypertension. Likewise, the odds of in-hospital dyspnea were significantly lower with NSTEMI than with STEMI (aOR 0.21, 95% CI

Table 1: Baseline characteristics of study subjects (N=198)

Variables	Median (IQR)
Age (years)	68.0 (64.0-70.0)
	Frequency (%)
Dyslipidemia	140 (70.7%)
Hypertension	86 (43.4%)
Diabetes Mellitus	104 (52.5%)
Smoker	111 (56.1%)
ACS Type	
STEMI	168 (84.8%)
NSTEMI	30 (15.2%)

ACS=Acute Coronary Syndrome; STEMI=ST-Elevation Myocardial Infarction; NSTEMI=Non-ST-Elevation Myocardial Infarction

Table 2: Association of comorbidities and ACS type with study groups (N=198)

Variables	Clopidogrel (N=99)	Ticagrelor (N=99)	t-test value	P-value
	Median (IQR)			
Age (years)	68 (64-70)	68 (65-71)	-	0.480
	Frequency (%)			
Dyslipidemia	57 (57.6%)	83 (83.8%)	16.48	<0.001
Hypertension	50 (50.5%)	36 (36.4%)	4.06	0.13
Diabetes Mellitus	50 (50.5%)	54 (54.5%)	0.32	0.56
Smoker	76 (76.8%)	35 (35.4%)	34.46	<0.001
ACS Type				
STEMI	94 (94.9%)	74 (74.7%)	15.71	<0.001
NSTEMI	5 (5.1%)	25 (25.3%)		

ACS=Acute Coronary Syndrome; STEMI=ST-Elevation Myocardial Infarction; NSTEMI=Non-ST-Elevation Myocardial Infarction; SD=Standard Deviation

Table 3: Comparison of dyspnea occurrence in ticagrelor versus clopidogrel-treated patients (N=198)

Variables	Clopidogrel (N=99)	Ticagrelor (N=99)	t-test value	P-value
In-hospital Dyspnea	12 (12.1%)	57 (57.6%)	45.04	<0.001
Dyspnea at 1 st Month	9 (9.1%)	14 (14.1%)	1.23	0.267
Dyspnea at 2 nd Month	3 (3.0%)	5 (5.1%)	0.52	0.470
Dyspnea at 3 rd Month	1 (1.0%)	3 (3.0%)	1.02	0.312
P-Value (Cochran's Q test)	<0.001	<0.001	-	-

Table 4: Predictors of In-Hospital Dyspnea in Acute Coronary Syndrome Patients (N=198)

Variable	Univariable Analysis			Multivariable Analysis		
	uOR	95% CI	P-value	aOR	95% CI	P-value
Group (Ticagrelor vs. Clopidogrel)	9.84	4.77–20.28	<0.001	14.39	5.84–35.44	<0.001
Age (years)	5.47	0.91–1.06	0.684	1.02	0.93–1.12	0.705
Dyslipidemia	1.60	0.82–3.12	0.169	0.96	0.39–2.34	0.927
Hypertension	0.36	0.19–0.68	0.003	0.42	0.20–0.91	0.027
Diabetes Mellitus	2.98	1.60–5.53	<0.001	2.82	1.34–5.97	0.007
Smoker	0.50	0.28–0.90	0.022	1.08	0.47–2.48	0.848
ACS type (NSTEMI vs. STEMI)	0.52	0.21–1.28	0.156	0.21	0.07–0.62	0.005

uOR = Unadjusted Odds Ratio; aOR = Adjusted Odds Ratio; CI = Confidence Interval; ACS = Acute Coronary Syndrome; STEMI = ST-Elevation Myocardial Infarction; NSTEMI = Non-ST-Elevation Myocardial Infarction

0.07–0.62, $P=0.005$), indicating that NSTEMI is more hemodynamically unstable and has a higher symptom burden. On univariable analysis, smoking was nominally significant (uOR 0.50, 95% CI 0.28–0.90, $P=0.022$), but this did not remain significant after the covariates were adjusted for (aOR 1.08, 95% CI 0.47–2.48, $P=0.848$) as demonstrated in Table 4.

Discussion

The present study evaluated the occurrence of post-PTCA acute dyspnea in ACS patients receiving ticagrelor versus clopidogrel. In-hospital dyspnea was significantly more frequent with ticagrelor (57.6%) than with clopidogrel (12.1%), although the overall frequency declined progressively in both groups during subsequent follow-ups. By the third month, only 1.0% of clopidogrel and 3.0% of ticagrelor patients continued to report dyspnea, confirming that most episodes were transient and self-limiting. Notable baseline differences included higher dyslipidemia prevalence in the ticagrelor group and higher smoking rates and STEMI frequency in the clopidogrel group.

Our findings are consistent with prior evidence demonstrating an increased risk of dyspnea with ticagrelor. A meta-analysis of 25 randomized controlled trials involving 63,484 patients reported a significantly higher risk of dyspnea with ticagrelor versus clopidogrel (RR 2.65, 95% CI 1.87–3.76), with this association persisting across short- and long-term follow-up periods.¹³ Similarly, You SC et al. reported dyspnea rates of 27.3% with ticagrelor compared to 22.6% with clopidogrel, with a summary hazard ratio of 1.21 (95% CI 1.17–1.26; $P<0.001$).¹⁴ The PLATO trial demonstrated a higher incidence of dyspnea in the ticagrelor group (13.8%) compared to clopidogrel (7.8%).¹⁵ While the absolute in-hospital dyspnea frequency in our study exceeded these large trial figures, the overall pattern aligns closely. The disparity likely reflects our active capture of all inpatient episodes, including mild and transient symptoms that are often underreported in large multicenter trials.

Previous studies have also described important characteristics of ticagrelor-induced dyspnea: symptoms typically occur early after drug initiation,^{16–18} are often mild to moderate in intensity, and in most cases resolve spontaneously without

requiring drug discontinuation. Zhang N et al. similarly emphasized that dyspnea is an important adverse effect of third-generation oral P2Y₁₂ inhibitors, with findings consistent with those of PLATO and other trials.^{13,15} Despite this drawback, ticagrelor remains preferred over clopidogrel in ACS due to its superior efficacy in reducing cardiovascular events, more rapid onset and offset of action, and significant reductions in stent thrombosis and ischemic outcomes. On the basis of PLATO, international guidelines now recommend ticagrelor as first-line therapy in ACS.^{19–20}

This study has certain limitations. First, it was a single-center study with a relatively small sample size, limiting generalizability. Second, the assessment of dyspnea relied on clinical observation and patient self-report without standardized objective pulmonary function testing, raising the possibility of subjective bias. Third, confounding factors such as pre-existing respiratory conditions, left ventricular dysfunction, and heart failure could not be fully adjusted for. Finally, the three-month follow-up period restricted our ability to assess long-term persistence or recurrence of dyspnea. Larger multicenter studies with longer follow-up and standardized outcome measures are needed to validate these findings.

Conclusion

Ticagrelor was associated with a significantly higher incidence of acute dyspnea than clopidogrel in ACS patients undergoing PTCA, particularly during the in-hospital phase, though most cases were transient and self-limiting. These findings underscore the need for patient counselling and close monitoring, while reaffirming that the cardiovascular benefits of ticagrelor outweigh its respiratory side effects.

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Author Contributions

TA: Conception, design of the work, and approval for final submission

QZB: Manuscript writing for methodology design, investigation, and approval for final submission

MBS: Data acquisition, curation, statistical analysis, and approval for final submission

HM: Validation of data, interpretation, write-up of results, and approval for final submission

HA: Revising, editing, supervising for intellectual content, and approval for final submission

JK: Writing the original draft, proofreading, and approval for final submission

TA is the nominated guarantor and takes full responsibility for the overall content and integrity of the work

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