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Evaluation of Rabeprazole for Gastrointestinal Protection in Acute Coronary Syndrome Patients Treated with Aspirin and Ticagrelor: A Pilot Study

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Purpose: Patients with acute coronary syndrome (ACS) on ticagrelor-based dual antiplatelet therapy (DAPT) have an increased risk of gastrointestinal (GI) bleeding. However, evidence supporting the protective role of proton pump inhibitors against DAPT-induced gastric mucosal injury remains limited.

Materials and Methods: This was a single-center, prospective, open-label, observational trial enrolling patients with ACS who were treated with DAPT, specifically aspirin and ticagrelor, following percutaneous coronary intervention in South Korea. Participants received 20 mg rabeprazole once daily for 8 weeks. The primary outcome was the proportion of patients exhibiting a modified Lanza score (MLS) of 0–5 on upper endoscopy at 8 weeks compared to baseline endoscopy results. The secondary outcomes included GI symptom scores and safety assessments.

Results: Among the 50 patients included in the per-protocol analysis, the median MLS at baseline and 8 weeks was 2.0 (1.0–2.0) and 2.0 (1.0–2.0), respectively, with no significant change (p=0.69). Similarly, in patients at high-risk for GI bleeding (76.0%, 38/50), there was no significant difference in MLS after 8 weeks of treatment with rabeprazole compared to the baseline MLS, consistent with the results of the overall study population. GI symptom scores, including the Nepean Dyspepsia Index-Korean, Gastroesophageal Reflux Disease (GERD) Questionnaire, and GERD Health-Related Quality of Life Questionnaires, showed no significant changes from baseline in the overall cohort and high-risk groups. No major bleeding or adverse cardiac events were observed.

Conclusion: In this pilot study, rabeprazole was associated with maintained gastric mucosal integrity in patients with ACS receiving ticagrelor-based DAPT.

Key Words: Rabeprazole, ticagrelor, acute coronary syndrome, gastric mucosa, gastrointestinal hemorrhage

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INTRODUCTION

Dual antiplatelet therapy (DAPT), which combines aspirin with a $P2Y_{12}$ inhibitor such as clopidogrel, ticagrelor, or prasugrel, is the first-line treatment for the prevention of ischemic events in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary interventions (PCI).[1-3] Clopidogrel is an inactive prodrug that requires hepatic activation by cytochrome P450 (CYP) enzymes, including CYP2C19, to become effective.[4] However, its delayed onset, modest platelet inhibition, and variability in response to genetic polymorphisms and drug interactions limit its efficacy.[5] In contrast, ticagrelor and prasugrel are potent $P2Y_{12}$ inhibitors that act directly, achieving a rapid onset and peak plasma concentrations within a few hours.[6,7] These agents provide more consistent and potent platelet inhibition than clopidogrel.[8,9] Therefore, current guidelines recommend 1-year of DAPT treatment with aspirin and a potent $P2Y_{12}$ inhibitor for patients with ACS undergoing PCI, unless contraindicated.[1,2]

The inhibition of platelet adhesion and aggregation following PCI reduces the risk of myocardial infarction but increases the risk of bleeding. This bleeding most commonly occurs in the gastrointestinal (GI) tract,[10-12] and GI bleeding is a significant potential adverse event of DAPT,[13] occurring at particularly high rates in the Asian population.[14,15] Additionally, higher overall bleeding rates have been reported with potent $P2Y_{12}$ inhibitors than with clopidogrel.[16,17] Therefore, proton pump inhibitors (PPIs) are recommended to reduce the risk of GI bleeding in these patients.[18,19] However, there is concern that PPIs may inhibit CYP2C19, potentially compromising the effectiveness of $P2Y_{12}$ inhibitors due to drug–drug interactions.[20,21] Although this interaction is less concerning with ticagrelor and prasugrel, concern remains about whether certain PPIs are preferable in patients receiving DAPT.

Rabeprazole is a fast-acting and potent PPI that provides sustained acid suppression and 24-hour symptom relief, particularly in patients with Gastroesophageal Reflux Disease (GERD).[22] Unlike conventional PPIs, it undergoes a balanced metabolism involving both CYP450-mediated and nonenzymatic pathways, which minimizes the impact of CYP2C19 genetic polymorphisms on drug clearance and efficacy. Its reduced dependence on CYP2C19 and CYP3A4 decreases variability in acid suppression among patients. Additionally, rabeprazole exhibits no clinically significant drug–drug interactions, making it a more stable and reliable option for managing acid-related disorders in genetically diverse populations.[23]

However, research on the effectiveness and safety of third-generation PPIs, such as rabeprazole, in patients receiving $P2Y_{12}$ inhibitors remains limited. Furthermore, no studies have examined the role of rabeprazole in preventing mucosal damage in patients taking potent $P2Y_{12}$ inhibitors. Considering the potential advantages of rabeprazole in terms of metabolic stability and reduced risk of drug interactions, further investigation is required. Therefore, this study aims to evaluate the preventive effect and safety of rabeprazole in mitigating mucosal injury in patients undergoing ticagrelor-based DAPT following PCI for ACS.

MATERIALS AND METHODS

Study design

This investigator-initiated, single-center, prospective, open-label, observational trial was conducted to assess the efficacy and safety of rabeprazole administered once daily for 8 weeks in patients with ACS receiving DAPT consisting of ticagrelor and aspirin, along with rabeprazole, following PCI with stent implantation. The study was conducted at Yongin Severance Hospital in South Korea from July 2023 to September 2024. The study protocol received approval from the Institutional Review Board of Yongin Severance Hospital (approval number: 9-2023-0010), and the study was registered at cris.nih.go.kr (KCT0008344). Written informed consent was obtained from all patients prior to enrollment in this study.

Patient population

PCI was performed in accordance with standard techniques and current guidelines.[24,25] Patients who received DAPT with ticagrelor (90 mg twice daily) and aspirin (100 mg once daily) following the loading dose—unless they were already on these medications—were screened for inclusion in this study. All patients underwent upper endoscopy within 7 days of PCI. Detailed inclusion and exclusion criteria are provided in Supplementary Table 1 (only online). High-risk patients for GI bleeding were defined as those aged ≥65 years; those taking nonsteroidal anti-inflammatory drugs or corticosteroids; and those with a history of peptic ulcer or GI bleeding, *H. pylori* IgG positivity, chronic kidney disease stage ≥3 (defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2), hemoglobin <13 g/dL, platelet count <100000/μL, or a history of cerebrovascular accident.[26,27]

Study protocol

Patients who met the inclusion criteria completed the Nepean Dyspepsia Index-Korean (NDI-K), GERD Questionnaire (GERD-Q), and GERD Health-Related Quality of Life (GERD-HRQL) questionnaires. These validated instruments are widely used to assess symptomatic outcomes and therapeutic effects.[28,29] All patients received 20 mg rabeprazole once daily before breakfast for a duration of 8 weeks. Upper endoscopy was performed at baseline and at 8 weeks to evaluate the degree of gastric mucosal injury, which was assessed using the modified Lanza score (MLS) (Supplementary Table 2, only online). Patients were excluded from the study if baseline endoscopy revealed active peptic ulcers, cancer, or gastroduodenal bleeding. The 8-week follow-up period was pragmatically

determined, as upper endoscopy under continued DAPT is categorized as a low-risk procedure.[30] In addition, rabeprazole can be prescribed for up to 8 weeks under the current national reimbursement policy in South Korea. At 8 weeks, the patients completed a GI questionnaire using the NDI-K, GERD-Q, and GERD-HRQL assessments. Medication compliance and adverse events related to rabeprazole were also evaluated. Following the 8-week period, patients returned any remaining study medication, and compliance was assessed by the investigator based on the quantity of unused study drugs. All returned medications were documented and sent back to the pharmacist for proper handling. Furthermore, clinical outcomes—including GI events, major cardiovascular events, and bleeding outcomes—were assessed during the follow-up period.

Endpoints

The primary outcome was measured by the proportion of patients with an MLS of 0–5 on upper endoscopy after 8 weeks of rabeprazole treatment, compared to scores from baseline endoscopy. Secondary outcomes included GI symptom scores measured using the NDI-K, GERD-HRQL, and GERD-Q. Safety was evaluated through treatment-emergent adverse events (TEAEs) at week 8, along with physical examinations, vital signs, and laboratory results. Additional assessments included the incidence of GI bleeding and Bleeding Academic Research Consortium types 2, 3, and 5 bleeding. Major adverse cardiac events, defined as a composite of cardiovascular death, myocardial infarction, coronary revascularization, and stroke, were also evaluated over the 8-week period. The definitions of the clinical outcomes are provided in Supplementary Table 3 (only online).

Statistical analysis

Data are presented as mean±standard deviation or median (interquartile range) for continuous variables and as frequency (percentage) for categorical variables. The 95% confidence intervals (CIs) for the means of continuous variables and percentages of categorical variables were calculated using t-tests and Clopper–Pearson (exact) methods, respectively. The Wilcoxon signed-rank test was applied to continuous MLS scores, and chi-square tests were used to analyze categorical classifications. GI symptom scores were compared between baseline and week 8 using paired t-tests. A Sankey diagram was employed to illustrate the flow of changes from baseline to 8 weeks for the MLS. Although patients with drug adherence <80% were excluded from the per-protocol (PP) analysis, all patients met the ≥80% threshold and were therefore included. For the MLS, sensitivity analyses were conducted for patients with high risk of bleeding. Statistical significance was set at $p<0.05$ (two-sided). All statistical analyses were performed using R software (version 4.2.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

A total of 64 patients were screened, and 59 were enrolled. Five patients were excluded because of active gastric or duodenal ulcers. After excluding nine patients who withdrew from the study or had poor drug adherence, the PP analysis included 50 patients (Fig. 1). Patient characteristics are summarized in Table 1. The mean age of the patients was 59.34 years, and 82.0% were male. The high-risk group for GI bleeding comprised 38 patients (76.0%). The procedural characteristics of PCI for ACS are presented in Supplementary Table 4 (only online).

Efficacy analysis

Baseline upper endoscopy was performed 2 days (interquartile range: 2–3 days) after PCI. The median MLS at baseline and after 8 weeks were 2.0 (1.0–2.0) and 2.0 (1.0–2.0), respectively, with no significant change ($p=0.69$) (Table 2). There was no significant change in MLS following 8 weeks of rabeprazole administration in patients receiving DAPT after PCI ($p=0.81$) (Fig. 2). Similarly, no significant changes were observed in the high-risk group for GI bleeding ($p=0.82$) (Supplementary Table 5 and Supplementary Fig. 1, only onlie). The intention-to-treat analysis, which included all patients, showed no significant change in MLS after 8 weeks of treatment (Supplementary Table 6 and Supplementary Fig. 2, only online). GI symptoms demonstrated no significant changes between baseline and week 8 (baseline vs. 8 weeks; NDI-K: 3.12±4.14 vs. 2.42±3.85, $p=0.30$; GERD-HRQL: 1.88±1.12 vs. 1.68±0.94,

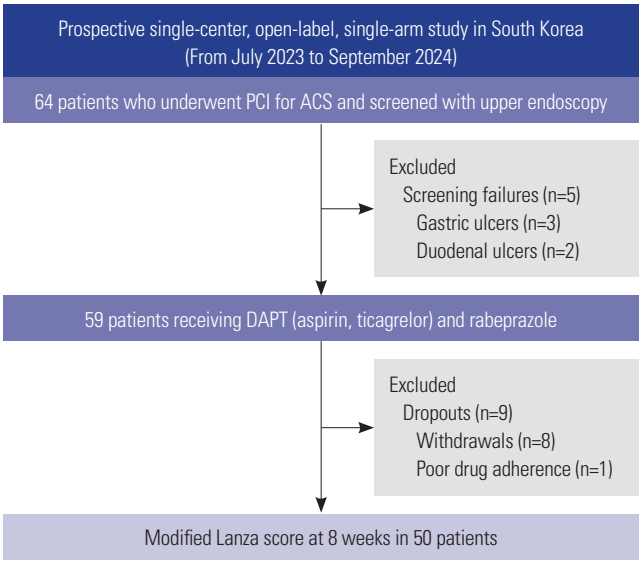

Fig. 1. Study flowchart. A total of 64 patients were screened; 5 were excluded due to active gastric or duodenal ulcers. Of the 59 enrolled patients, 9 were excluded from the per-protocol analysis due to study withdrawal or poor drug adherence, resulting in 50 patients included in the final analysis. ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

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Table 1. Baseline Characteristics of the Study Population

Variables	All (n=50)	95% CI*
Demographics		
Age (yr)	59.34±9.78	56.6–62.1
Male	41 (82.0)	68.6–91.4
Height (cm)	168.20±7.75	166.0–170.4
Weight (kg)	72.75±11.75	69.4–76.1
Body mass index (kg/m^2)	25.60±2.99	24.8–26.5
Comorbidities		
Hypertension	25 (50.0)	35.5–64.5
Diabetes mellitus	11 (22.0)	11.5–36.0
Dyslipidemia	23 (46.0)	31.8–60.7
Chronic kidney disease (≥stage 3)†	1 (2.0)	0.1–10.6
Current smoking status	23 (46.0)	31.8–60.7
Current alcohol consumption	24 (48.0)	33.7–62.6
Positive for *Helicobacter pylori*	22 (44.0)	30.0–58.7
Medications		
NSAIDs	14 (28.0)	16.2–42.5
Corticosteroids	1 (2.0)	0.1–10.6
GI history		
Peptic ulcer	0 (0.0)	0.0–7.1
GI bleeding	3 (6.0)	1.3–16.5
Cardiovascular history		
Prior PCI	5 (10.0)	3.3–21.8
Prior myocardial infarction	1 (2.0)	0.1–10.6
Prior cerebrovascular accident	1 (2.0)	0.1–10.6
Peripheral artery disease	1 (2.0)	0.1–10.6
Congestive heart failure	5 (10.0)	3.3–21.8
Clinical manifestations of ACS		
Unstable angina	14 (28.0)	16.2–42.5
NSTEMI	19 (38.0)	24.7–52.8
STEMI	17 (34.0)	21.2–48.8
Left ventricular ejection fraction, %	53.14±8.50	50.7–55.6
Peri-procedural medications		
Aspirin	50 (100)	92.9–100.0
Ticagrelor	50 (100)	92.9–100.0
Oral anticoagulation	0 (0.0)	0.0–7.1
ACEi or ARB	11 (22.0)	11.5–36.0
Beta-blocker	18 (36.0)	22.9–50.8
Calcium channel blocker	0 (0.0)	0.0–7.1
Statin	49 (98.0)	89.4–99.9
Laboratory findings		
Hemoglobin (g/dL)	14.02±1.40	13.6–14.4
Platelet count (10^3/μL)	218.90±62.72	201.1–236.7
Serum creatinine (mg/dL)	0.85±0.18	0.8–0.9
Serum C-reactive protein (mg/L)	8.06±20.09	2.4–13.8
Prothrombin time (INR)	0.94±0.05	0.93–0.96
aPTT (sec)	30.22±9.83	27.4–33.0

ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; aPTT, activated partial thromboplastin time; CI, confidence interval; GI, gastrointestinal; INR, international normalized ratio; NSAIDs, nonsteroidal anti-inflammatory drug; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.
Variables are expressed as mean±SD or n (%).
*95% CI calculated using the Clopper–Pearson exact method for categorical variables and the t-distribution for continuous variables; †Chronic kidney disease (≥stage 3) was defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2.

p=0.22; GERD-Q: 6.06±1.22 vs. 5.84±0.55, *p*=0.21) (Fig. 3 and Supplementary Table 7, only online). Furthermore, no significant changes were observed in the high-risk group for GI bleeding (baseline vs. 8 weeks; NDI-K: 3.32±4.32 vs. 2.50±3.89, *p*=0.33; GERD-HRQL: 1.76±0.97 vs. 1.61±0.89, *p*=0.38; GERD-Q: 6.08±1.40 vs. 5.87±0.41, *p*=0.33) (Supplementary Fig. 3, only online).

Safety analysis

The incidence of adverse events was 6% (3/50) among the 50 patients in the safety analysis set, while the incidence of TEAE was 2% (1/50) (Supplementary Table 8, only online). No serious TEAEs or deaths occurred during the study period. One serious adverse event, unrelated to the study drug, was reported: anaphylactic shock induced by contrast media administered for cardiac magnetic resonance imaging, which fully resolved without sequelae.

Regarding clinical outcomes at 8 weeks, no serious GI events, major adverse cardiac events, or bleeding events were observed throughout the study (Supplementary Table 9, only online).

DISCUSSION

This pilot study observed preserved gastric mucosal integrity after 8 weeks of rabeprazole [median MLS: 2.0 (1.0–2.0) at baseline vs. 2.0 (1.0–2.0) at 8 weeks] and alleviated GI symptoms, as measured by the NDI-K, GERD-HRQL, and GERD-Q, in patients with ACS receiving ticagrelor-based DAPT, including those at high risk for GI bleeding. Furthermore, no serious TEAEs, cardiovascular adverse events, including mortality, or bleeding events were reported.

Although DAPT has been widely utilized due to its effectiveness in preventing thrombotic events in patients with ischemic heart disease undergoing PCI,[1,2,31] antiplatelet therapy carries a substantial risk of GI bleeding, which can be elevated by as much as 7.4-fold with DAPT.[32] Furthermore, the enhanced antiplatelet efficacy of potent $P2Y_{12}$ inhibitors exacerbates concerns regarding bleeding adverse events.[33,34] A recent meta-analysis demonstrated that potent $P2Y_{12}$ inhibitors significantly increased the risk of major bleeding compared to clopidogrel, with an odds ratio of 1.24 (95% CI: 1.15–1.33).[33] Another meta-analysis reported that these potent $P2Y_{12}$ inhibitors were associated with an increased risk of GI bleeding compared to clopidogrel, with a risk ratio of 1.28 (95% CI: 1.13–1.46).[35]

To mitigate the risk of GI bleeding associated with antiplatelet therapy, numerous studies have investigated the concurrent use of PPIs with DAPT. The COGENT (Clopidogrel and the Optimization of Gastrointestinal Events Trial) study is the only large, multi-center, international, double-blind Phase 3 randomized controlled trial (RCT) that demonstrated that the concurrent administration of PPIs and DAPT significantly reduces upper GI bleeding, erosions, and ulcers without increas-

Table 2. Comparison of Endoscopic Characteristics at Baseline and 8 Weeks Assessed by the MLS

Grade of MLS	Variables	Baseline	At 8 weeks	*p*	*p*†
0	No visible erosion/hemorrhage	4 (8.0)	6 (12.0)	0.68	
1	Mucosal hemorrhage only	17 (34.0)	15 (30.0)	0.77	
2	One or two erosions	21 (42.0)	21 (42.0)	>0.99	0.81
3	Numerous (3–10) areas of erosions	7 (14.0)	8 (16.0)	>0.99	
4	Large number (>10) of erosions	1 (2.0)	0 (0)	>0.99	
Median MLS score		**Baseline**	**At 8 weeks**	***p****	
Overall patients		2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.69	
Patients with high GI bleeding risk		2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.38	

MLS, modified Lanza score, GI, gastrointestinal.
Variables are expressed as n (%) or median (Q1–Q3).
**p* values were calculated using the Wilcoxon signed-rank test; †*p* values were calculated using the chi-square test.

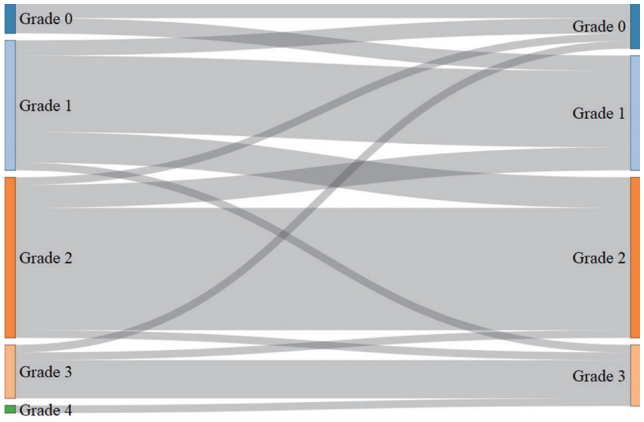

Fig. 2. Changes of MLS between baseline and 8 weeks after rabeprazole treatment. Change in MLS after 8 weeks of rabeprazole treatment in patients receiving dual antiplatelet therapy following percutaneous coronary intervention. Each flow in the Sankey diagram represents the number of participants transitioning between MLS grades from baseline to follow-up, with the width proportional to the number of participants. No significant change in MLS was observed (p=0.81, assessed by chi-square test). MLS, modified Lanza score; Grade 0, no visible erosion/hemorrhage; Grade 1, mucosal hemorrhage only; Grade 2, one or two erosions; Grade 3, numerous (3–10) areas of erosions; Grade 4, large number (>10) of erosions.

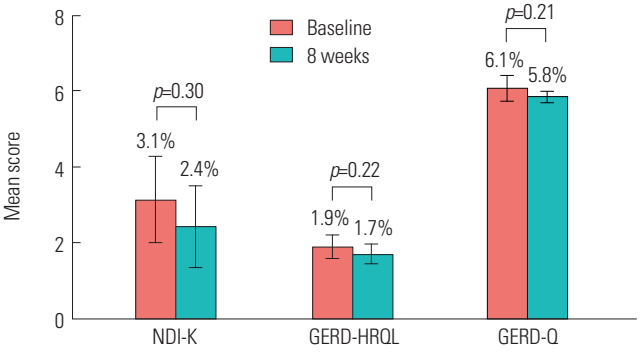

Fig. 3. Changes of NDI-K, GERD-HRQL, and GERD-Q scores between baseline and 8 weeks after rabeprazole treatment. Comparison of gastrointestinal symptom scores at baseline and after 8 weeks of rabeprazole treatment. No significant differences were observed in any of the symptom indices. NDI-K, Nepean Dyspepsia Index-Korean; GERD-Q, Gastroesophageal Reflux Disease Questionnaire; GERD-HRQL, GERD-Health-Related Quality of Life Questionnaire.

ing adverse events. The rate of overt upper GI bleeding with the concomitant therapy of clopidogrel plus omeprazole was lower than that with clopidogrel plus placebo, yielding a hazard ratio of 0.13 (95% CI, 0.03–0.56; p=0.001).[36] Reflecting this evidence, both the 2023 European and American guidelines strongly advocate for this combination as a preventive measure.[37,38] However, because clopidogrel is metabolized by CYP450 liver enzymes and some PPIs inhibit CYP450, the concurrent use of clopidogrel and PPIs may reduce the overall efficacy of clopidogrel.[20,21] Subsequent observational studies have suggested an association between PPIs and clopidogrel, indicating a significantly increased risk of recurrent myocardial infarction due to CYP450 inhibition.[39] Therefore, the use of PPIs raises concerns about potential drug–drug interactions that could diminish the effectiveness of $P2Y_{12}$ inhibitors, including potent $P2Y_{12}$ inhibitors that carry a significant risk of upper GI bleeding.

Rabeprazole, a third-generation PPI, is primarily metabolized through a nonenzymatic pathway, with minor involvement of CYP2C19. It is less reliant on CYP2C19 for metabolism, offering a safer and potentially more effective option for preventing GI adverse events.[40] A randomized crossover study demonstrated that rabeprazole significantly reduced gastric damage and hemorrhage induced by dual therapy with low-dose aspirin and clopidogrel.[41] However, research on the protective effects of rabeprazole against gastric mucosal damage in patients receiving DAPT after PCI for ACS remains limited, with few studies specifically addressing the prevention of gastric mucosal injury in this population. The present study indicates that rabeprazole may have contributed to maintaining gastric mucosal integrity in patients undergoing ticagrelor-based DAPT. Recently, potassium-competitive acid blockers, including tegoprazan and fexuprazan, have emerged as alternatives to PPIs, providing faster onset and more potent acid suppression.[42,43] Further investigations are warranted to clarify their efficacy and safety in this clinical setting.

This study had several strengths. First, it uniquely demonstrates the mucoprotective effect of rabeprazole in patients with ACS who were treated with potent $P2Y_{12}$ inhibitors without serious adverse events, including death. Second, upper endos-

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copy was performed at baseline and 8 weeks in patients with ACS to directly evaluate mucosal injury and assess the mucosal protective effect of rabeprazole in individuals using potent $P2Y_{12}$ inhibitors. Third, we employed various questionnaires and clinical evaluations to assess treatment impact, providing a comprehensive view of patient outcomes. Finally, this study focused on potent $P2Y_{12}$ inhibitors, which are associated with a higher risk of GI bleeding than clopidogrel.

This study had some limitations. First, this was a single-arm pilot study without a control group because of ethical and regulatory considerations; therefore, the results should be interpreted with caution. Second, this was a single-center, observational study with a small sample size, which may restrict the generalizability of the results. Third, the interval for upper endoscopy was relatively short, with only 8 weeks of follow-up. This duration was pragmatically chosen in accordance with current guideline, which classifies diagnostic endoscopy under continued DAPT as a low risk procedure, and with the national reimbursement policy that allows rabeprazole prescription for up to 8 weeks. Nevertheless, the degree of mucosal injury may fluctuate over longer follow-up period. Therefore, further studies with longer durations and larger cohorts are necessary to comprehensively evaluate the long-term effects of rabeprazole. Fourth, the pre-specified primary endpoint, the proportion of patients with an MLS of 0–5, was non-informative because all patients fell within this range by definition. Therefore, interpretation of mucosal outcomes was based primarily on within-patient changes in MLS and transitions between MLS grades as exploratory measures. Fifth, *H. pylori* infection, which is associated with the development of gastric mucosal inflammation and/or progression of gastric mucosal atrophy, was assessed using serum anti-*H. pylori* IgG antibody. However, this method cannot distinguish between past and current infections, which renders the evaluation incomplete. Finally, although the impact of rabeprazole on CYP2C19 metabolism is minimal, the study did not assess the CYP2C19 genotype of participants, limiting the ability to characterize outcomes in homogeneous extensive metabolizers.

In conclusion, this pilot study observed maintained mucosal integrity without safety concerns in patients with ACS receiving rabeprazole with ticagrelor-based DAPT. These findings suggest that rabeprazole may be a feasible option for GI protection in this patient population, although large-scale, long-term RCTs are warranted to validate its potential benefits and establish definitive clinical recommendations.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request from the corresponding authors.

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AUTHOR CONTRIBUTIONS

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