Potassium-competitive acid blocker vs proton-pump inhibitor in patients receiving antithrombotic therapy who are at high risk for gastrointestinal bleeding: Rationale and design of the randomized PROTECT- HBR trial

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Background Concomitant use of proton pump inhibitor (PPI) is recommended in patients receiving chronic antithrombotic therapy who are at high risk of gastrointestinal (GI) bleeding. However, long-term safety and efficacy of chronic PPI use have been concerned. Potassium-competitive acid blocker (P-CAB) is a novel class of acid suppressants, providing more acid stability, rapid onset of action, less variability with CYP2C19 polymorphisms, and longer duration of action than PPI.

Design The PROTECT-HBR trial is a multicenter, randomized, double-blind, double-dummy, parallel-group clinical trial. Approximately 3320 patients with known cardiac or vascular disease receiving antithrombotic drugs (either antiplatelet or anticoagulant agents) and who are at high risk of GI bleeding will be randomized to P-CAB (tegoprazan 50mg once daily) or PPI (rabeprazole 20mg once daily) for up to 12 months. The primary endpoint is a composite outcome of upper GI clinical events, including overt or occult GI bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction, or perforation, at 12 months. Secondary endpoints also included cardiovascular events and safety outcomes.

Results As of December 2024, approximately 1460 patients were enrolled from 32 participating sites in South Korea. The complete enrollment is anticipated at the mid- or late-term of 2025, and the primary results will be available by 2027.

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Conclusion PROTECT-HBR is a large-scale, multicenter, clinical trial, which will provide a pivotal comparison of the efficacy and safety of novel P-CAB, tegoprazan with those of PPI, rabeprazole in patients with documented cardiac or vascular disease receiving chronic antithrombotic drugs and at high risk of GI bleeding.

Clinical Trial Registration Potassium-Competitive Acid Blocker versus pROton-Pump Inhibitor for GastroprotECTion Strategies In Patients at High GastroIntestinal Bleeding Risk Receiving Antithrombotic Therapy (PROTECT-HBR): NCT04416581. (Am Heart J 2025;287:50–60.)

Background

Gastrointestinal (GI) complications are an important and common problem associated with use of antithrombotic therapy, including antiplatelet agents and oral anticoagulants (OACs).[1-3] In particular, GI hemorrhage is the most common serious bleeding complication resulting from the use of long-term antithrombotic therapy.[4-6] Theoretically, aspirin blocks the production of tissue prostaglandins (and its associated gastroprotective effects) by inhibiting the cyclooxygenase enzyme, which increases susceptibility to direct gastroduodenal mucosal injury.[5] $P2Y_{12}$ inhibitors may impede the release of platelet-derived growth factors that contribute to angiogenesis and GI mucosal healing.[7] Although OACs do not directly affect the GI mucosa, warfarin is associated with GI bleeding risk due to its systemic anticoagulant effects through the inhibition of vitamin K-dependent clotting factors[8] and direct-acting oral anticoagulants (DOACs) may induce GI injury through a direct topical anticoagulant effect.[2] In particular, such antithrombotic therapy may substantially trigger GI bleeding in patients with increased bleeding risk, such as the elderly individuals, those with a history of GI bleeding or peptic ulcer disease, those with chronic use of steroids or nonsteroidal anti-inflammatory drugs (NSAIDs), or those receiving a combination of antithrombotic drugs.[7,9,10]

Proton-pump inhibitors (PPIs) may be effective in reducing the risk of such GI complications and bleeding in patients receiving various types of antithrombotic drugs. Therefore, clinical guidelines recommend the concomitant use of PPIs in patients receiving a single or combined antithrombotic therapy (antiplatelet drugs and/or OACs) who are at high risk of GI bleeding.[7,11-14] Although PPIs are commonly considered as the gold standard for gastroprotection in patients with high GI bleeding risk, there have been concerns regarding the long-term safety and efficacy of chronic PPI use, which include potential adverse effects such as hypomagnesemia, osteoporosis, pneumonia, enteric infection, and cognitive decline, as well as pharmacological limitations such as slow onset of action and incomplete acid suppression.[15,16] Furthermore, concerns have been raised about the potential for PPIs to blunt the efficacy of clopidogrel;[17,18] PPIs inhibit CYP2C19, particularly omeprazole and esomeprazole and thus can reduce exposure to clopidogrel's active metabolite.[19]

To mitigate these limitations of PPIs, potassium-competitive acid blockers (P-CABs) have emerged as a novel class of acid suppressants, promising significant potential to improve gastroprotection strategies.[20-22] P-CABs inhibit gastric H+ secretion through a competitive and reversible mechanism and have distinct characteristics from those of PPIs (Figure 1). Hence, P-CABs provide more rapid onset of action, sustained gastric pH control, acid stability with dosing independent of food consumption, less variability with CYP2C19 polymorphisms, and extended half-lives.[23,24] Given their distinct pharmacological advantages, P-CABs are gaining attention as a potential alternative to PPIs for an effective gastroprotection strategy in patients with increased risk of GI bleeding and receiving antithrombotic therapy.

In this context, the Potassium-Competitive Acid Blocker versus pROton-Pump Inhibitor for GastroprotECTion Strategies In Patients at High Gastrointestinal Bleeding Risk Receiving Antithrombotic Therapy (PROTECT-HBR) study is designed to test the hypothesis that a novel gastric acid suppressant, P-CAB (tegoprazan 50mg once daily), would be noninferior to standard PPI (rabeprazole 20mg once daily) for the prevention of major GI events in patients with known cardiac and vascular disease receiving antithrombotic therapy and who are at high GI bleeding risk. Tegoprazan (K-CAB, HK inno.N) was approved in South Korea in 2018 for the treatment of acid-related diseases (e.g., reflux esophagitis, gastric ulcer, duodenal ulcer, prevention of recurrence of gastric or duodenal ulcer, and adjunct to *Helicobacter pylori* eradication), with subsequent expansion of approvals to other countries.[25-27]

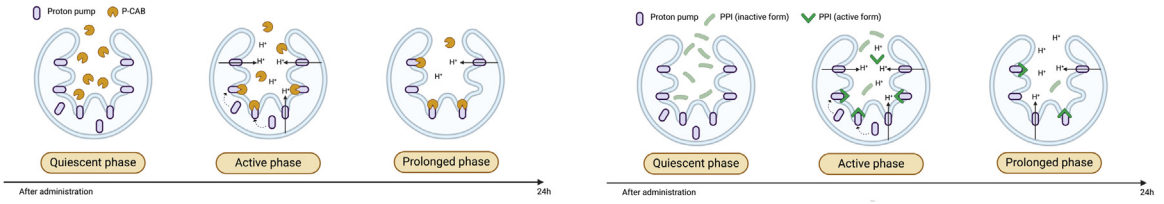
Methods

Trial design and objectives

The PROTECT-HBR (ClinicalTrials.gov unique identifier: NCT04416581) is a multicenter, randomized, double-blind, double-dummy, active comparator–controlled, parallel-group, clinical trial that compares the efficacy and safety of the novel P-CAB tegoprazan with those of the conventional PPI rabeprazole for gas-

Figure 1. Mode of action and characteristics between potassium-competitive acid blocker and proton-pump inhibitor. Potassium-competitive acid blocker (P-CAB) act directly without the need for conversion from a prodrug. They inhibit the proton pump (H+/K+-ATPase) regardless of its activation state. This reversible binding allows P-CABs to suppress newly synthesized proton pumps during the prolonged phase, ensuring sustained acid suppression over time. Proton pump inhibitor (PPI) remain inactive during the quiescent phase and must be converted to their active form after proton pump activation to bind effectively. Once activated, they bind irreversibly to the proton pump, providing initial acid suppression. However, during the prolonged phase, PPIs cannot target newly synthesized pumps, leading to diminished acid suppression over time. Abbreviations: P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor. Created in BioRender. Lee, J. (2025) https://BioRender.com/e35a290.

P-CAB	Characteristics	PPI
Ionic, reversible	**Binding**	Covalent, irreversible
Active and resting states	**H+/K+-ATPase inhibition**	Active state only
No	**Prodrug**	Yes
Yes	**Acid stability**	No
6 - 9 hours	**Half-life**	1 - 2 hours
1 day	**Maximal acid suppression (day)**	3 - 5 days
No	**Affected by CYP2C19 Polymorphism**	Yes
Independent of mealtimes	**Optimal dosing administration**	30-60 minutes before meals



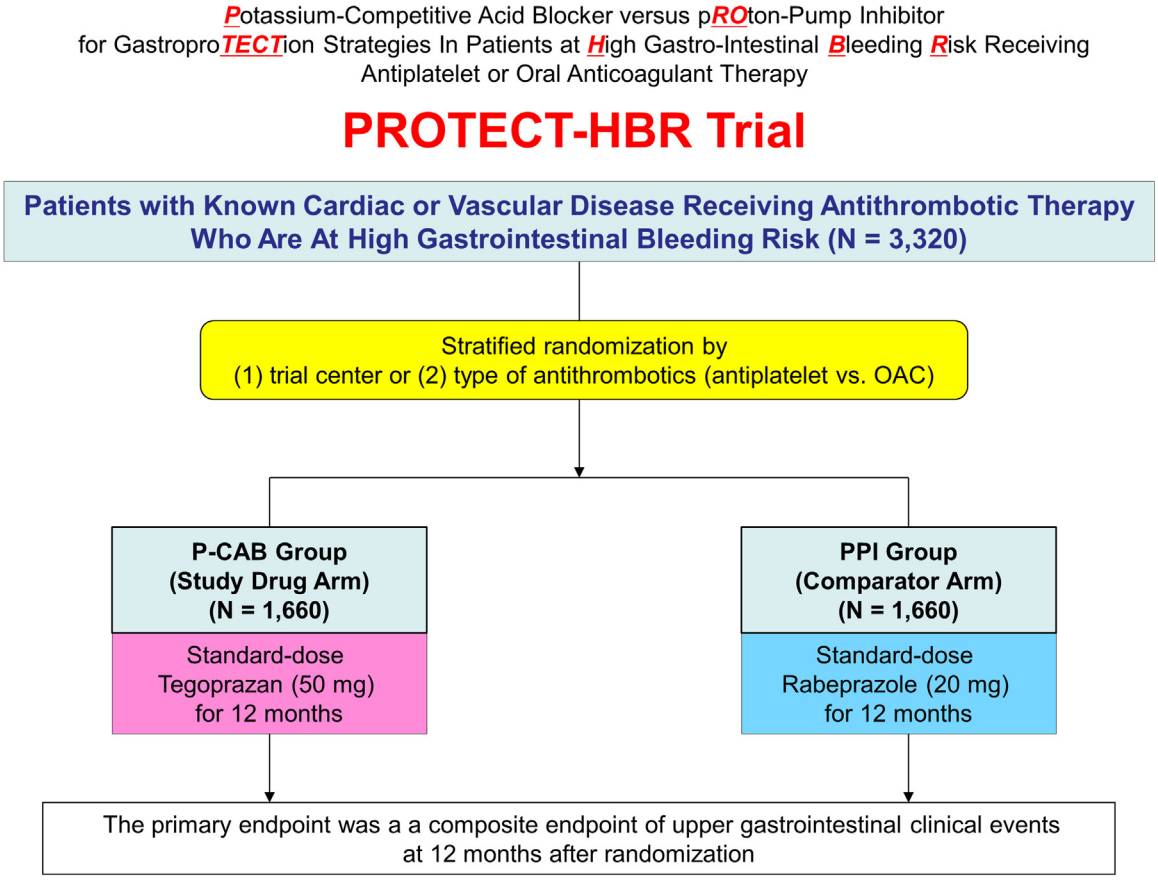
troprotection with concomitant use of antithrombotic agents. The primary objective is to test the hypothesis that tegoprazan (50mg once daily) will be noninferior to rabeprazole (20mg once daily) for the prevention of the primary composite of major GI events in patients with known cardiac and vascular disease receiving antithrombotic drugs (either antiplatelets, OACs, or its combinations) who are at an increased risk of upper GI bleeding (Figure 2). Rabeprazole 20 mg was selected as it is the widely recognized standard-dose PPI for acid-related disorders. Tegoprazan 50 mg has demonstrated comparable acid suppression and clinical efficacy to standard-dose PPIs in previous studies.[22,28]

Study population

Patients are eligible to participate in the PROTECT-HBR trial if they are aged ≥18 years, had known cardiac and vascular disease with a clinical indication for chronic antithrombotic therapy (either antiplatelet drugs, OACs, or its combinations), and had an increased risk of GI bleeding.

Documented cardiac or vascular disease requiring chronic antithrombotic therapy may include clinical conditions such as coronary artery disease (stable or unstable angina, acute coronary syndrome, a history of myocardial infarction [MI], or previous coronary revascularization, either percutaneous coronary intervention [PCI] or coronary-artery bypass grafting [CABG]), cerebrovascular disease (stroke or transient ischemic attack), peripheral arterial disease or a history of peripheral arterial revascularization, atrial fibrillation (AF), or valvular heart disease requiring interventions (transcatheter aortic-valve replacement or transcatheter mitral-valve repair). For trial enrollment, on the basis of clinical guidelines[11-14,29-32] and expert consensus documents,[33-35] patients are considered to be at high risk for GI bleeding if they had a least one or more criteria of the following characteristics; (1) old age of ≥65 years, (2) concomitant use of OACs and any antiplatelet therapy (mono or dual antiplatelet therapy [DAPT]) (i.e., dual antithrombotic therapy [DAT] or triple antithrombotic therapy [TAT]), (3) long-term use of oral NSAIDs or steroids, or high-dose NSAID therapy, (4) previous history of GI bleeding events, (5) previous history of a complicated ulcer, (6) a history of peptic ulcer disease or a previously uncomplicated ulcer, or (7) documented *Helicobacter pylori* infection. Treatment guidelines strongly recommend the concomitant use of PPIs in patients receiving aspirin monotherapy, DAPT, DAT, TAT, or OAC monotherapy who are at high risk of GI bleeding in order to reduce the risk of gastric bleed or GI events.[11-14,29] Based on these criteria, the use of $P2Y_{12}$ inhibitor monotherapy

Figure 2. Study schema of the PROTECT-HBR trial. Abbreviations: OAC, oral anticoagulant; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.



(i.e. clopidogrel, ticagrelor, or prasugrel) was not considered in trial enrollment.

Key exclusion criteria include active bleeding at the time of trial evaluation or a history of hereditary or acquired hemostatic disorder, concurrent use of PPIs or P-CABs within 4 weeks before randomization, severe anemia (hemoglobin <8 g/dL) or thrombocytopenia (platelet count <50,000/mm^3), contraindications to the study medications, and severe hepatic dysfunction or severe renal insufficiency. The full eligibility criteria are listed in Table 1. The trial was approved by the national regulatory authorities (Ministry of Food and Drug Safety [MFDS]) and ethics committees at the participating centers. The study will adhere fully to the ethical principles of the Declaration of Helsinki, including the requirement for each subject's informed consent before initiating any study procedure.

Randomization and trial procedures

Eligible patients are screened and receive randomization within 14 days after screening. After obtaining informed consent, eligible patients are randomly assigned, in a 1:1 ratio and by double-blinded, double-dummy manner, to receive either P-CAB therapy (tegoprazan 50 mg once daily with rabeprazole 20mg placebo once daily) or PPI therapy (rabeprazole 20mg once daily with tegoprazan 50 mg placebo once daily) for 12 months. Randomization is conducted by means of a central, interactive web-response system (IWRS) with randomly permuted blocks of 4 or 6, stratified according to the participating center and the type of antithrombotic therapy (antiplatelet drugs or OACs), wherein patients receiving concomitant use of antiplatelet drugs and OACs are regarded as subjects receiving OACs.

Blinded study medications are manufactured and supplied by the sponsor (HK inno.N, South Korea) to the participating sites. Adherence to study medications are monitored by means of drug dispensing and return for each patient; compliance of study treatment will be assessed by the return of all unused investigational products and empty packages at each visit. Patients who have taken study medications for ≥80% of days between each

Table 1. Inclusion and exclusion criteria

Inclusion criteria: the study subject must have met all of the following criteria to be eligible for trial enrollment:	
1.	Patients aged ≥18 years
2.	Patients with known cardiac and vascular disease* and receiving chronic use of antithrombotic drugs (either antiplatelet drug, OAC, or its combinations). *Documented cardiac or vascular disease that may necessitate chronic antithrombotic therapy may include clinical conditions such as coronary artery disease (stable or unstable angina, acute coronary syndrome, a history of MI, or previous coronary revascularization, either PCI or CABG), cerebrovascular disease (stroke or transient ischemic attack), peripheral arterial disease or a history of peripheral arterial revascularization, atrial fibrillation, or valvular heart disease requiring interventions (transcatheter aortic-valve replacement or transcatheter mitral-valve repair).
3.	Patients must have at least one of any features of high GI bleeding risk
3-1	old age ≥65 years
3-2	Concomitant use of OAC and any antiplatelet therapy (mono or DAPT) (i.e., DAT or TAT)
3-3	Long-term use of oral NSAIDs or steroids or high-dose NSAID therapy during a relatively short-term period.
3-4	History of previous GI bleeding events at any time
3-5	History of a previously complicated ulcer
3-6	History of peptic ulcer disease or a previously uncomplicated ulcer
3-7	Documented *Helicobacter pylori* infection
4.	The patient or guardian agrees to the study protocol and the schedule of clinical follow-up and provides informed, written consent, as approved by the appropriate institutional review board/ethical committee of the respective clinical site.
Exclusion criteria: Subjects were to be excluded from the study if any of the following criteria were met:	
1.	Active bleeding at the time of trial evaluation or a history of hereditary or acquired hemostatic disorder
2.	Any clinical contraindication to the use of antithrombotic therapies (antiplatelet agents or OAC)
3	Concurrent use of PPIs or P-CABs within 4 weeks before randomization
4.	Hemodynamically unstable conditions at the time of inclusion: cardiogenic shock at the time of randomization, refractory ventricular arrhythmias, or congestive heart failure (NYHA class IV).
5.	Baseline severe anemia (Hgb < 8g/dL) or transfusion within 4 weeks before randomization
6.	Baseline severe thrombocytopenia (platelet count <50,000/mm^3)
7.	Renal failure-dependent on dialysis or severe renal insufficiency (creatinine clearance <15 mL/min)
8.	Severe chronic liver disease (defined as variceal hemorrhage, ascites, hepatic encephalopathy, or jaundice)
9.	Hypersensitivity or contraindication to PPIs, P-CABs, any of the product components, or substituted benzimidazoles
10.	Use of clarithromycin and hypersensitivity to macrolide antibiotics for *Helicobacter pylori* eradication
11.	Concomitant use of clarithromycin with terfenadine, cisapride astemizole, or pimozide for *Helicobacter pylori* eradication
12.	Systemic treatment with strong CYP 3A4 and p-glycoprotein inhibitors (e.g., systemic azole antimycotics, such as ketoconazole, and human immunodeficiency virus [HIV]-protease inhibitors, such as ritonavir)
13.	Patients who take atazanavir, nelfinavir or rilpivirine-containing products
14.	Clinically significant laboratory abnormality at screening (estimated glomerular filtration rate (eGFR) < 15 mL/min or elevated liver enzyme [AST, ALT ALP, total bilirubin] > 3 times upper normal limit or any other condition that, in the opinion of the Investigator, precludes participation in the study
15.	Any known or suspected malignancy
16.	Patients with noncardiac comorbidities with life expectancy less than 12 months
17.	Patients receiving active treatment for *H-pylori* infection
18.	Women who are pregnant or breastfeeding or female subjects, premenopausal who are not surgically sterile, or if sexually active not practicing an effective method or birth control (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double barrier method, contraceptive patch, male partner sterilization) before entry and throughout the study; and, for those of childbearing potential, who have a positive pregnancy test at screening
19.	Participation in another clinical study within 12 months: However, where at least one or more conditions are satisfied, it could be an exception according to an investigator's discretion; ① Participated in the observational study with no anticipated effect on the safety and/or effectiveness evaluation of this trial ② Screening failed before any interventional factor is involved ③ Participated in academic trials such as strategic or medical device comparison studies conducted under standard therapy provided that there is no additional risk or a specific procedure to a subject and no interference between this trial and other studies

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CABG, coronary-artery bypass grafting; DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; NYHA, New York Heart Association; OAC, oral anticoagulant; P-CAB, potassium-competitive acid blocker; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; TAT, triple antithrombotic therapy.

visit are regarded as compliant. During the study period, if necessary, study patients are permitted to take rescue GI medications for upper GI distress at the discretion of the treating physicians (e.g., magnesium, aluminum, or calcium carbonate-based antacids). Any concomitant use of open-label PPIs or P-CABs is not allowed during the study period. Guideline-directed medical therapy and the management of risk factors for primary or secondary prevention for known cardiac or vascular disease are highly recommended for all study patients.

Study endpoints and follow-up

The primary efficacy endpoint is the time from randomization to the first occurrence of a composite end-

Table 2. Primary and secondary endpoints*

Primary endpoints

The primary efficacy endpoint is the time from randomization to the first occurrence of a composite endpoint of upper GI clinical events during 12 months (which is defined as the time from the first administration of a trial drug through 12 months of therapy after randomization).

(1) Overt upper GI bleeding (confirmed by means of upper endoscopy or CT scan)
(2) Overt upper GI bleeding of unknown origin
(3) Bleeding of presumed occult GI origin with documented decrease in hemoglobin level of ≥2 g/dL or decrease in hematocrit of ≥10% from baseline
(4) Symptomatic gastroduodenal ulcer (confirmed by means of endoscopy) without evidence of GI bleeding
(5) Persistent pain of presumed GI origin (duration ≥3 days) with. underlying multiple erosive disease (5 or more gastroduodenal erosions confirmed by means of endoscopy)
(6) Upper GI obstruction
(7) Upper GI perforation

Secondary endpoints

1. Each component of the primary efficacy endpoint
2. Time from randomization to discontinuation of study medication attributed to GI signs or symptoms
3. Gastroesophageal reflux disease, as evidenced by symptomatic endoscopically confirmed erosive esophagitis
4. Composite cardiovascular safety end point (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke)
5. Each component of the composite cardiovascular end point
6. Any coronary or peripheral revascularization
7. All-cause mortality
8. Any potential side effects of PPI or P-CAB

Abbreviations: CT, computed tomography; GI, gastrointestinal; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.
* Detailed definitions of clinical endpoints are available in the online Appendix Table 1.

point of upper GI clinical events during 12 months (which is defined as the time from the first administration of a trial drug through 12 months of therapy after randomization). Based on previous relevant trials,[36,37] primary GI composite events included (1) overt bleeding of upper GI origin (confirmed by endoscopy or computed tomography [CT] scan), (2) overt upper GI bleeding of unknown origin, (3) bleeding of presumed occult GI origin, (4) symptomatic gastroduodenal ulcer (confirmed by endoscopy), (5) persistent pain of presumed GI origin with underlying multiple gastroduodenal erosive disease, (6) upper GI obstruction, or (7) upper GI perforation. The secondary outcomes included individual components of the primary outcome; composite cardiovascular safety end point (death from cardiovascular causes, nonfatal MI, or nonfatal stroke) and its each component; gastroesophageal reflux disease (confirmed by endoscopy); any revascularization (either coronary or peripheral), death from any causes; and any potential side effect of PPIs or P-CABs. Detailed lists of the primary and secondary clinical endpoints are summarized in Table 2.

All serious events and primary or secondary outcomes are thoroughly monitored on-site. The investigators at each participating center should complete a dedicated electronic case report form (e-CRF) for all events and provide sufficient source documentation for independent central review. All adjudications of GI events will be confirmed by an independent committee of gastroenterologists who are unaware of the study-drug assignments. Adjudication of cardiovascular or other clinical events will be performed by an independent committee of cardiologists blinded to the study-drug assignments. Detailed information on definitions of each clinical event is indicated in Appendix Table 1.

After randomization, trial follow-up assessments will be conducted at baseline, 1 month, 6 months, 9 months, and 12 months with additional evaluations for routine clinical care scheduled as required. At each visit, all information regarding clinical events and concomitant GI or cardiovascular medications are systematically collected. Symptomatic GI events that may contribute to primary or secondary endpoints will be clinically evaluated according to protocol guidelines, including the requirement for upper endoscopy in patients whose GI symptoms meet criteria for persistence. Clinical indications for endoscopy are at the discretion of the treating physician. Cross-validation of survival status will be performed with the use of the Korean National Health Insurance database.[38,39] To investigate the potential risks associated with long-term use of PPIs or P-CABs, as recommended by the national regulatory authorities (MFDS, Korea), serum levels of gastrin, pepsinogen I and II, and magnesium will be systematically measured at baseline (before administration of study medications) and at 12-month follow-up. A serologic test for *H. pylori* infection (*H. pylori* Ab IgG) at baseline will also be performed in all enrolled patients.

Statistical methods

Sample size and power calculation

We hypothesized that the novel P-CAB strategy would be noninferior to the conventional PPI strategy with respect to the prespecified GI efficacy endpoint at 12 months after randomization. On the basis of previous trials of COGENT and COMPASS,[36,37] wherein patients

with high GI bleeding risk were excluded, as well as considering that the current trial exclusively enrolls patients with high GI bleeding risk and that the East Asian population is well-known to be more susceptible to an increased risk of GI bleeding than the Western population,[40-42] we assumed that 4.0% of the patients in the PPI group (standard-group) would have a primary GI endpoint at 12 months after randomization. With an upper boundary of less than 1.40 for the 95% confidence interval (CI) of the hazard ratio prespecified as indicating noninferiority and with a one-sided type 1 error of 2.5% significance level, we calculated that a total sample of 3,320 patients (1,660 patients per group) would be required to achieve 80% power to claim noninferiority. The final sample-size calculation is considered 10% of trial attrition rate (study drug noncompliance, withdrawal from the trial, or follow-up loss) and 4 years of the total study time including the first 3-year recruitment period. The noninferiority margin of a hazard ratio of 1.40 or less was agreed on by the study leadership of gastroenterologists and cardiologists as consistent with an interpretation of equipoise between the 2 treatment arms. If noninferiority regarding the primary outcome is established, a conditional test for superiority would be performed at a 2-sided alpha level of 0.05. A noninferiority log-rank test and the PASS 15 (NCSS, Kaysville, Utah, US) software are used for sample-size estimation.

Primary statistical analysis

Endpoint analyses are performed according to the intention-to-treat principle of all randomized patients as the time to the first event. Sensitivity analyses will be conducted in the as-treated population (patients analyzed by the treatment they actually received) and in the per-protocol population (patients analyzed according to their assigned treatment group only if they actually received their assigned treatment). Differences between treatment groups are evaluated using Student's t-test for continuous variables and the $\chi 2$ or Fisher's exact for categorical variables, as appropriate. Cumulative event curves are generated using the Kaplan–Meier method and compared with the log-rank test. Data from patients who had not had a primary end-point event between randomization and 12 months are censored at the time of death, the time of last known contact, or 365 days, whichever came first. Statistical comparisons of the 2 randomized groups are based on a time-to-first-event analysis using the Cox proportional hazards model. Relative risks are expressed as hazard ratios with associated 95% CIs and are derived from the Cox model. The proportional-hazards assumption was confirmed using Schoenfeld residuals and visual assessment of log(−log) plots. Absolute differences and 95% CIs for primary and key secondary end points at 12 months are calculated with Kaplan–Meier estimates and Greenwood standard errors.[43] To evaluate the consistency of results among clinically relevant subgroups, prespecified subgroup analyses will be conducted (e.g., age, sex, body-mass index, diabetes mellitus, renal function, status for *Helicobacter pylori* [positive or negative], type of cardiac or vascular disease [e.g., coronary artery disease, cerebrovascular disease, peripheral vascular disease, or AF], and type of antithrombotic therapy [e.g., antiplatelet agents or OACs]). For prespecified subgroup analyses, the interaction term between the randomized groups and key subgroups will be evaluated for the primary endpoint.

Trial data are held by the trial coordination center at Asan Medical Center. Analyses will be conducted by independent statistical analysts who are unaware of the randomized drug. The *P*-value for noninferiority is one-sided and calculated by use of the Farrington–Manning test. All other *P*-values are 2-sided and values $<.05$ are considered as statistically significant. No interim analyses of the primary and secondary outcomes will be performed; therefore, the alpha significance level in the final primary analysis was 0.05. The 95% CIs for the secondary outcomes are not adjusted for multiple comparisons; therefore, inferences drawn from these intervals may not be reproducible and should not be used to infer definitive treatment effects. All the analyses are conducted using the SAS (SAS Institute) or R (R Foundation for Statistical Computing) software.

Ethics and dissemination

The trial is being conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice guidelines, and applicable regulatory requirements. This trial is approved by National Institute of Food and Drug Safety Evaluation of Republic of Korea, MFDS (approval number: 33340). Also, the final protocol and patient informed consent have been approved by the appropriate ethics committees of all participating sites, and all the participants must provide written informed consent to confirm voluntary participation. The study results will be disseminated to the participants and the public, including at scientific meetings and publication of our research in peer-reviewed journals.

Present status

Between October 2023 and December 2024, approximately 1460 patients from 32 participating sites in South Korea were enrolled and randomized in the PROTECT-HBR trial. Complete enrollment is anticipated at the mid- or late-term of 2025, and the primary results of the PROTECT-HBR trial are expected to be available by early or mid-2027.

Discussion

The primary objective of PROTECT-HBR is to evaluate the efficacy and safety of a novel gastroprotective agent, P-CAB (tegoprazan 50mg once daily) as compared with

a standard PPI (rabeprazole 20mg once daily) for the protection of major GI clinical events in patients with known cardiac and vascular disease receiving chronic antithrombotic therapy and who are at high risk of GI bleeding. To our knowledge, PROTECT-HBR is the first large, multi-center, double-blind, double-dummy RCT to explore the potential role of P-CAB for a novel gastroprotection strategy in patients with high GI bleeding risk receiving antithrombotic drugs.

GI bleeding is an important potential complication of chronic antithrombotic therapy (either antiplatelet drugs or OACs), especially in patients with a high GI bleeding risk.[2-4,7,44,45] The risk of GI bleeding is particularly high in East Asian patients compared to other racial groups under similar treatment regimens.[35,42] Therefore, to minimize the GI bleeding risk associated with use of antithrombotic agents, several clinical practice guidelines uniformly recommend that gastroprotective agents (i.e., prophylactic use of PPIs) should be considered in most patients receiving antithrombotic agents at increased risk of GI bleeding.[7,11-14] In contrast, routine use of PPIs is not recommended for patients at a low risk of GI bleeding; therefore, only patients with a high GI bleeding risk are included in the PROTECT-HBR trial. Despite the recognized importance of gastroprotection in such high GI-bleeding risk patients, the efficacy of PPIs in reducing upper GI bleeding events in patients receiving antithrombotic therapy remains a subject of debate and limited evidence from RCTs exists. A prior small-sized trial revealed the usefulness of PPIs in preventing recurrent GI bleeding in patients who had ulcer complications related to chronic aspirin use.[46] A much larger-sized COGENT (Clopidogrel and the Optimization of Gastrointestinal Event Trial) trial demonstrated the effect of PPI (omeprazole) on a significant reduction of GI clinical events, including overt GI bleeding, in patients receiving DAPT of aspirin and clopidogrel.[36] In contrast, the COMPASS (Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease) trial failed to show the benefit of PPI (pantoprazole) in reducing upper GI events in patients receiving low-dose rivaroxaban with or without aspirin.[37] However, the study population of COGENT and COMPASS was not selected to represent high-risk patients. Such gastroprotective agents may be appropriate for patients at high risk of upper GI bleeding, who are the primary target population in the PROTECT-HBR trial, and the number needed to treat would most likely be lower for a patient population at a higher GI bleeding risk. Accordingly, a no-treatment arm was not included in the present trial, as withholding prophylactic acid suppression in this clearly high-risk population was deemed ethically and clinically inappropriate.

Although PPIs are considered as the standard of choice of gastroprotective agents in high-risk patients receiving antithrombotic therapy, PPIs have inherent pharmacological limitations, the safety issues related to long-term use, and possible drug interactions with antiplatelet agents.[15,16] In particular, prior studies of drug-drug interaction suggest that omeprazole and esomeprazole have the highest propensity for drug interaction with clopidogrel (i.e., potentially blunting the effect of clopidogrel), whereas pantoprazole and rabeprazole have the lowest propensity.[47] Therefore, any significant clinical interaction of PPI (rabeprazole) with clopidogrel would be minimal in the PROTECT-HBR. Given that pharmacodynamics and pharmacokinetics of P-CABs convey other potentially beneficial properties compared to PPI (e.g., acid-stable, not prodrugs, more rapid onset of action, and longer half-life),[23,48,49] P-CABs have strong potential utility in clinical practice across the spectrum of acid peptic disorders, including a viable alternative to PPI for the pharmacologic prophylaxis of upper GI events.[24,25] Similar to PPIs, P-CABs have recently demonstrated the utility for peptic ulcer prophylaxis indications in the setting of NSAID or aspirin use for high-risk patients.[50,51] Further research will be required to determine the optimal approach to reducing the risk of GI adverse events among high-risk patients receiving diverse antithrombotic drugs, for which prophylactic P-CABs could be a promising alternative to standard PPIs. Moreover, although the overall safety profile of P-CABs based on available evidence appears favorable and comparable with that of PPIs, longer-term safety data for P-CABs are warranted and emerging. In this clinical context, the PROTECT-HBR trial will provide more compelling evidence on the long-term effect of P-CABs, which will be crucial, particularly for expanding regulatory approval and indications in clinical practice.

Conclusion

PROTECT-HBR is the first large-scale, multi-center, randomized, double-blind, double-dummy, parallel-group, clinical trial to assesses the efficacy and safety of novel P-CAB (tegoprazan) compared with that of standard PPI (rabeprazole) in patients with known cardiac or vascular disease receiving antithrombotic agents and who are at high risk of GI bleeding. This trial will provide clinically relevant evidence regarding the potential role of P-CABs as an alternative to conventional PPIs for GI prophylaxis in prevention and reduction of GI complications or bleeding events in high-risk patients treated with antiplatelet drugs, OAC, or its combinations. The findings of PROTECT-HBR may help inform future clinical strategies for optimizing gastroprotection in this high-risk population.

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inno.N Co., Ltd (Seoul, Korea). The initial trial protocol was developed by the academic authors of the steering committee in collaboration with the sponsor. The sponsors play no role in the conduct of the trial, collection or analysis of the data, interpreting the trial results, or writing of the manuscript. Confidentiality agreements are in place between all the authors and the sponsor. The sponsor covers all costs associated with the trial, including the cost of the study medications and all tests for trial purposes that are not otherwise clinically indicated.

This trial is designed and led by the executive steering committee members. The steering committee is also responsible for the scientific content of the protocol, protocol implementation, presentation of results, and written manuscripts. An independent data safety monitoring board (DSMB) will be responsible for monitoring safety during the trial and thus periodically review the safety data according to a dedicated charter and make recommendations based on safety analyses, protocol deviation, and clinical follow-up reports. The DSMB members will not have a primary affiliation with the study sponsor or the principal investigator of the trial. The clinical event committee is in charge of developing specific criteria used to categorize the clinical endpoints in the trial. Under the guidance of the leading investigators, the Cardiovascular Clinical Research Center (Asan Institute for Education & Research, Asan Medical Center) assisted in the selection of the participating centers, supervision and monitoring of the centers, collection and storage of trial data, data analysis, interpretation of trial results, and preparation of the manuscript.

Conflict of interest

D-WP reports institutional research grants from HK inno.N Pharm, Daiichi-Sankyo, ChongKunDang Pharm, Daewoong Pharm, Abbott Vascular, Boston Scientific, Medtronic, and Edwards Lifescience. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Supplementary materials

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CRediT authorship contribution statement

Jinho Lee: Writing – review & editing, Writing – original draft. **Han-Su Park:** Writing – review & editing. **Junghoon Lee:** Writing – review & editing. **Kee Don Choi:** Writing – review & editing, Methodology. **Do-Yoon Kang:** Writing – review & editing, Conceptualization. **Jung-Min Ahn:** Writing – review & editing, Validation. **Weon Kim:** Investigation. **Jong-Young Lee:** Investigation. **Young-Hyo Lim:** Investigation. **Se Hun Kang:** Investigation. **Sung Uk Kwon:** Investigation. **Hanbit Park:** Investigation. **Eue-Keun Choi:** Investigation. **Soon Jun Hong:** Investigation. **Byeong-Keuk Kim:** Investigation. **Eun-Sun Jin:** Investigation. **Jin-Ok Jeong:** Investigation. **Chang-Wook Nam:** Investigation. **Wang Soo Lee:** Investigation. **Sang Min Kim:** Investigation. **Kyoung-Ha Park:** Investigation. **Sung-Ho Her:** Investigation. **Eun-Seok Shin:** Investigation. **Young Jin Choi:** Investigation. **Tae-Hyun Yang:** Investigation. **Sang-Hyun Kim:** Investigation. **Jung-Won Suh:** Investigation. **Hwan-Cheol Park:** Investigation. **Yong-Hoon Yoon:** Investigation. **Myeong-Ho Yoon:** Investigation. **Seung-Jung Park:** Supervision, Conceptualization. **Duk-Woo Park:** Writing – review & editing, Supervision, Formal analysis, Data curation, Conceptualization.

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