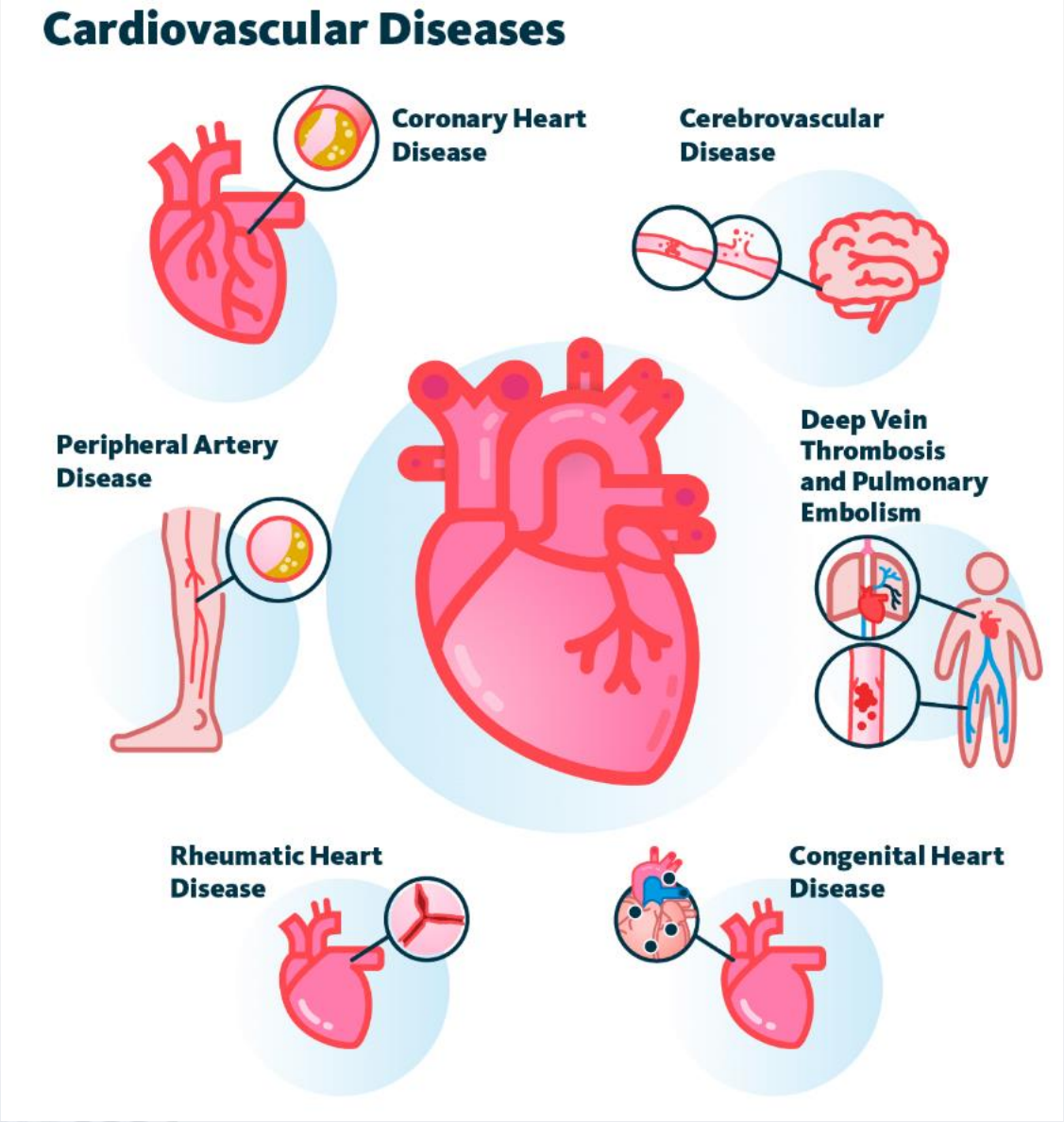
Potassium-Competitive Acid Blocker versus pROton-Pump Inhibitor for GastroproTECTion Strategies In Patients at High Gastro-Intestinal Bleeding Risk Receiving Antithrombotic Therapy

PROTECT-HBR Trial

Jinho Lee, MD, PhD

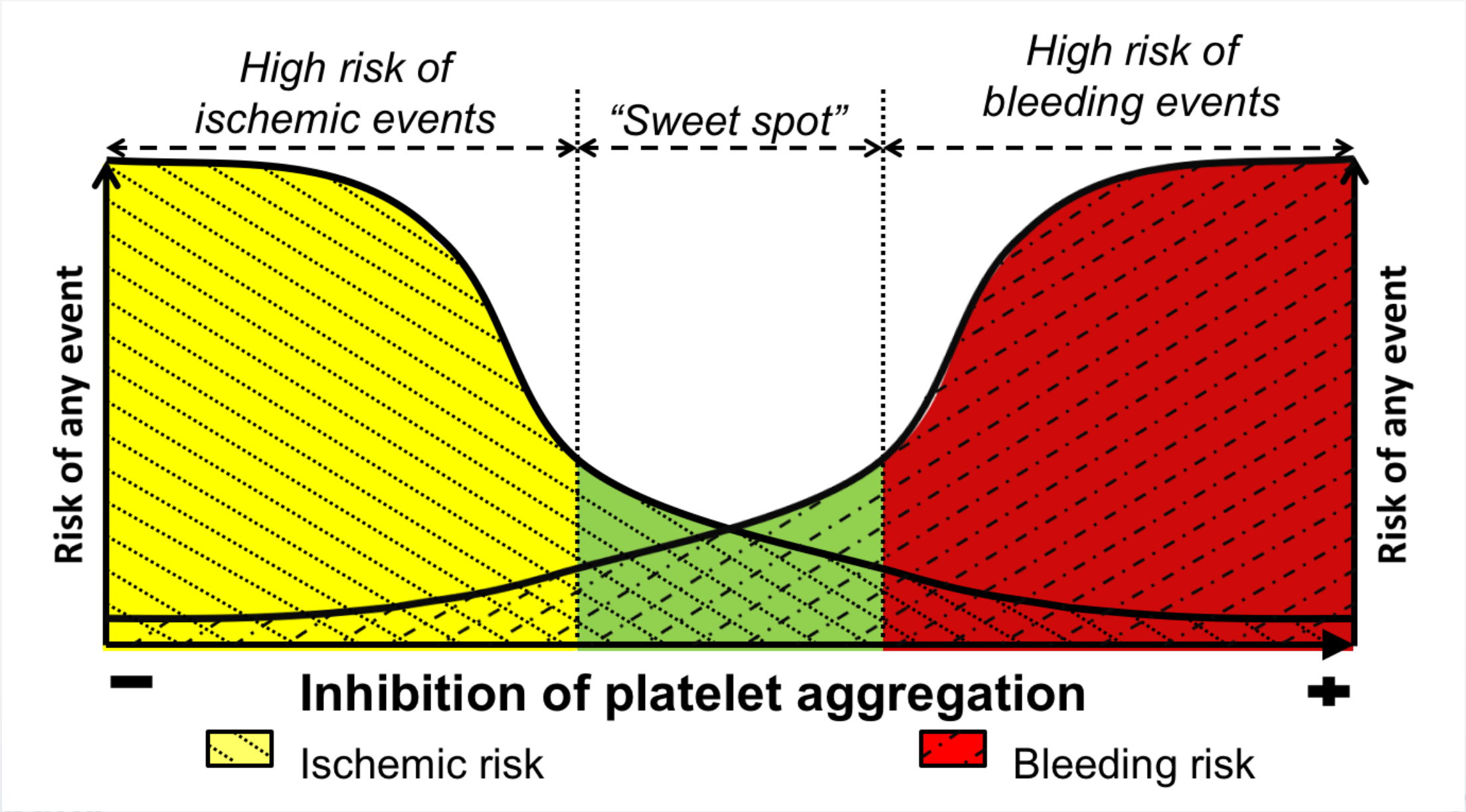
Assistant Professor

Department of Cardiology, Kyung Hee University Hospital, Seoul, Korea



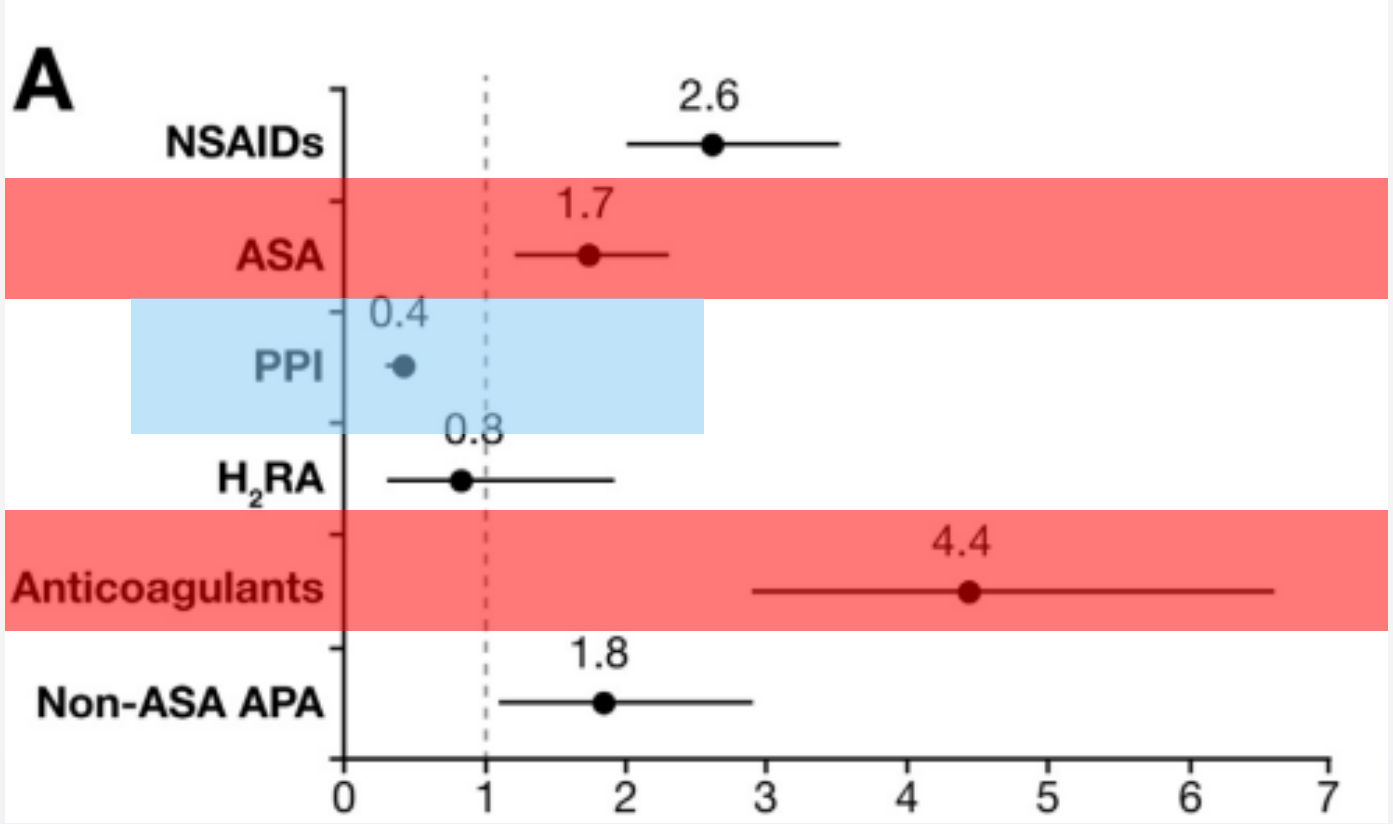
Long-term Antithrombotic Therapy

Finding the SWEET SPOT



Ferreiro & Angiolillo. Thromb aemost 2010

Upper GI Bleeding

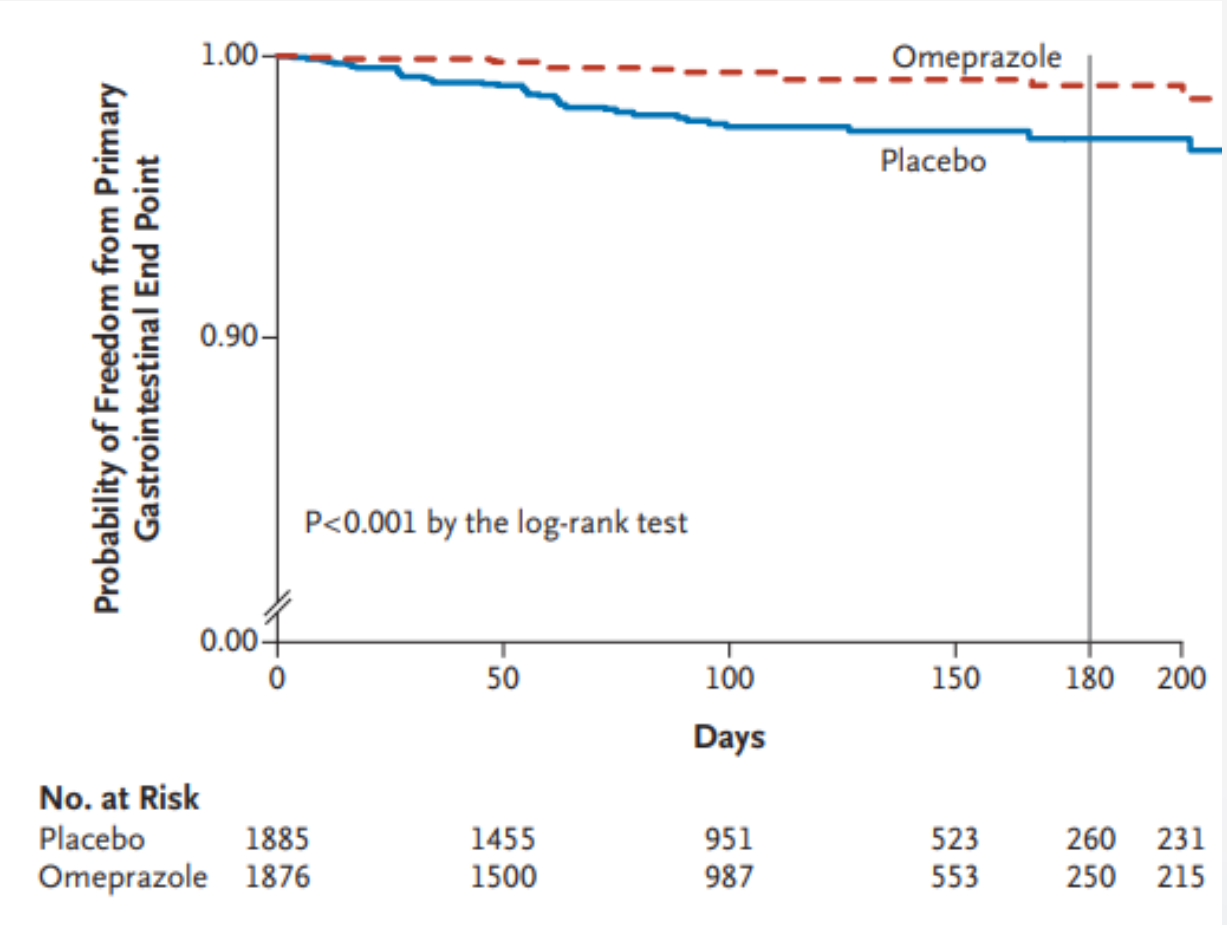


Antiplatelet & Anticoagulants ↑

Proton Pump Inhibitor ↓

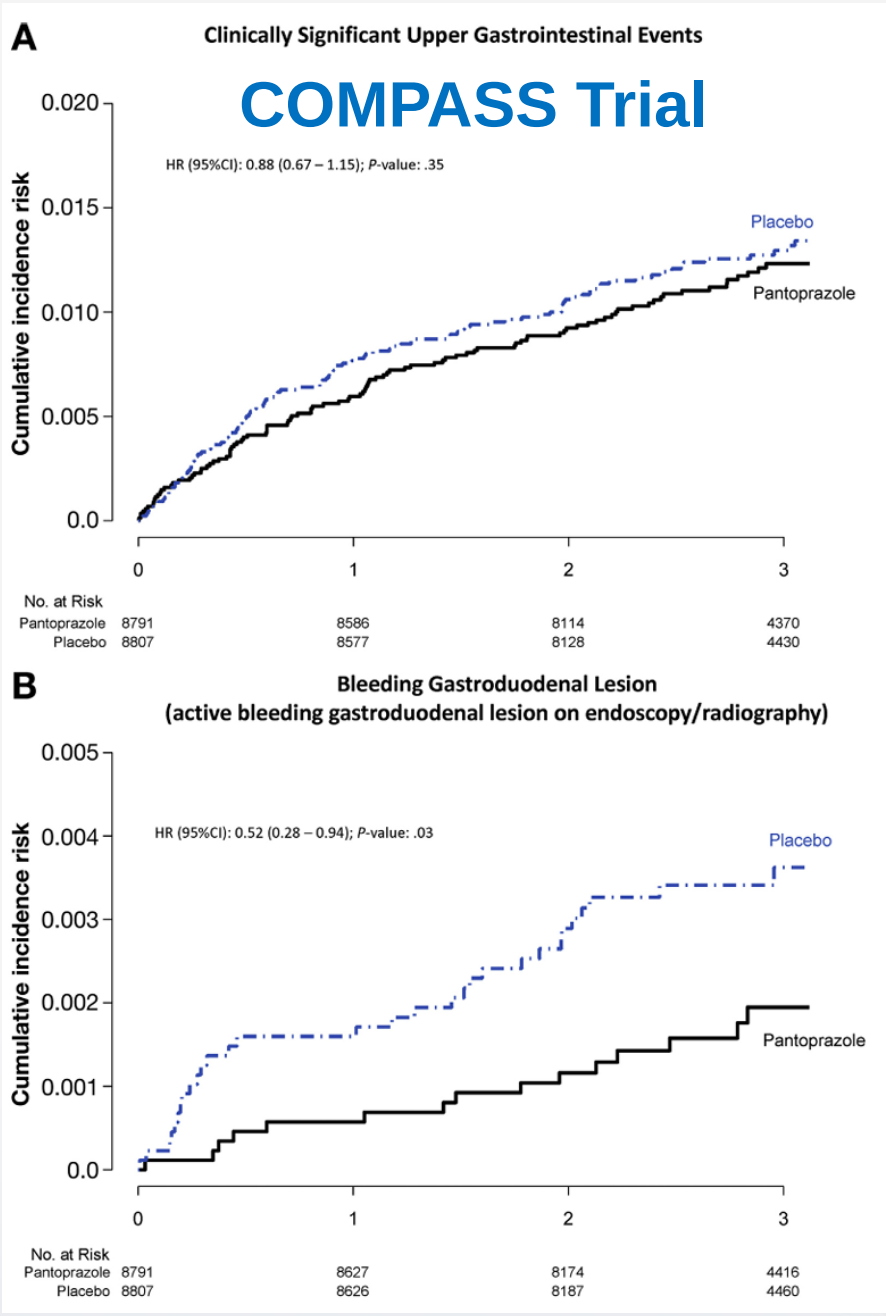
Lanas, Ángel et al. *Clinical gastroenterology and hepatology* vol. 13,5 (2015): 906-12.e2.

COGENT Trial



Bhatt, Deepak L et al. *N Engl J Med. 2010;363(20):* 1909-17.

COMPASS Trial



Moayyedi P et al.Gastroenterology. 2019;157(2):403-412.e5.

- **Concomitant use of a proton pump inhibitor** is recommended in patients receiving **aspirin monotherapy, DAPT, or OAC monotherapy** who are at **high risk of gastrointestinal bleeding**

Concerns of PPI

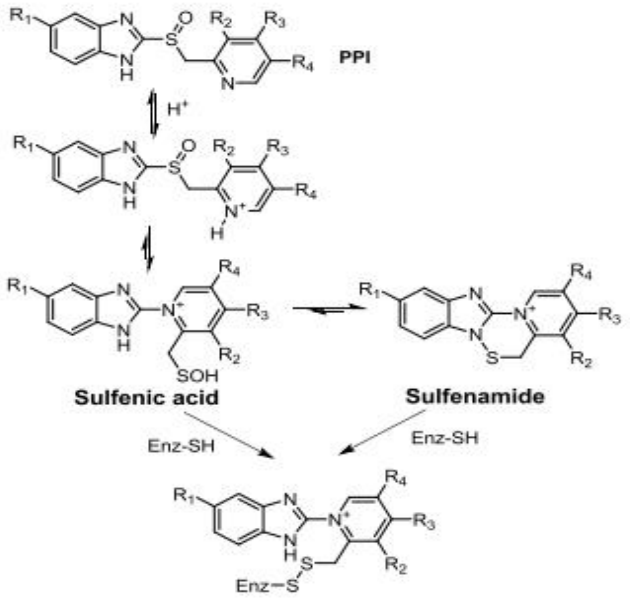
- **Adverse Effect**
  - Hypomagnesaemia, osteoporosis, bone fracture, pneumonia, small intestinal bacterial overgrowth, spontaneous bacterial peritonitis, clostridium difficile-associated diarrhea, myocardial infarction, liver disease, chronic kidney disease, microscopic colitis, cognitive decline, dementia, or GI malignancies

- **Pharmacologic limitations**
  - Delay onset of action, incomplete acid suppression,
  - Need for ingestion before a meal to achieve maximum efficacy

- **Significant drug-drug interaction** especially for clopidogrel mediated by cytochrome P-450

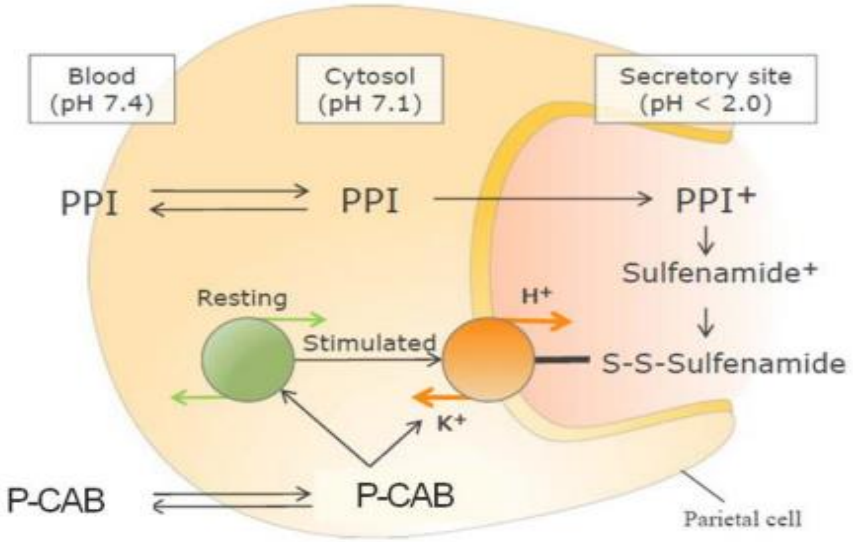
PPIs

- **Conversion** to a reactive form
- Irreversible binding to the external surface of acid pump
- **Need to stimulate** proton pump



P-CAB

- **Directly** binds to K+ Binding domain at resting and stimulated state
- Reversible binding
- **No need** to stimulate proton pump

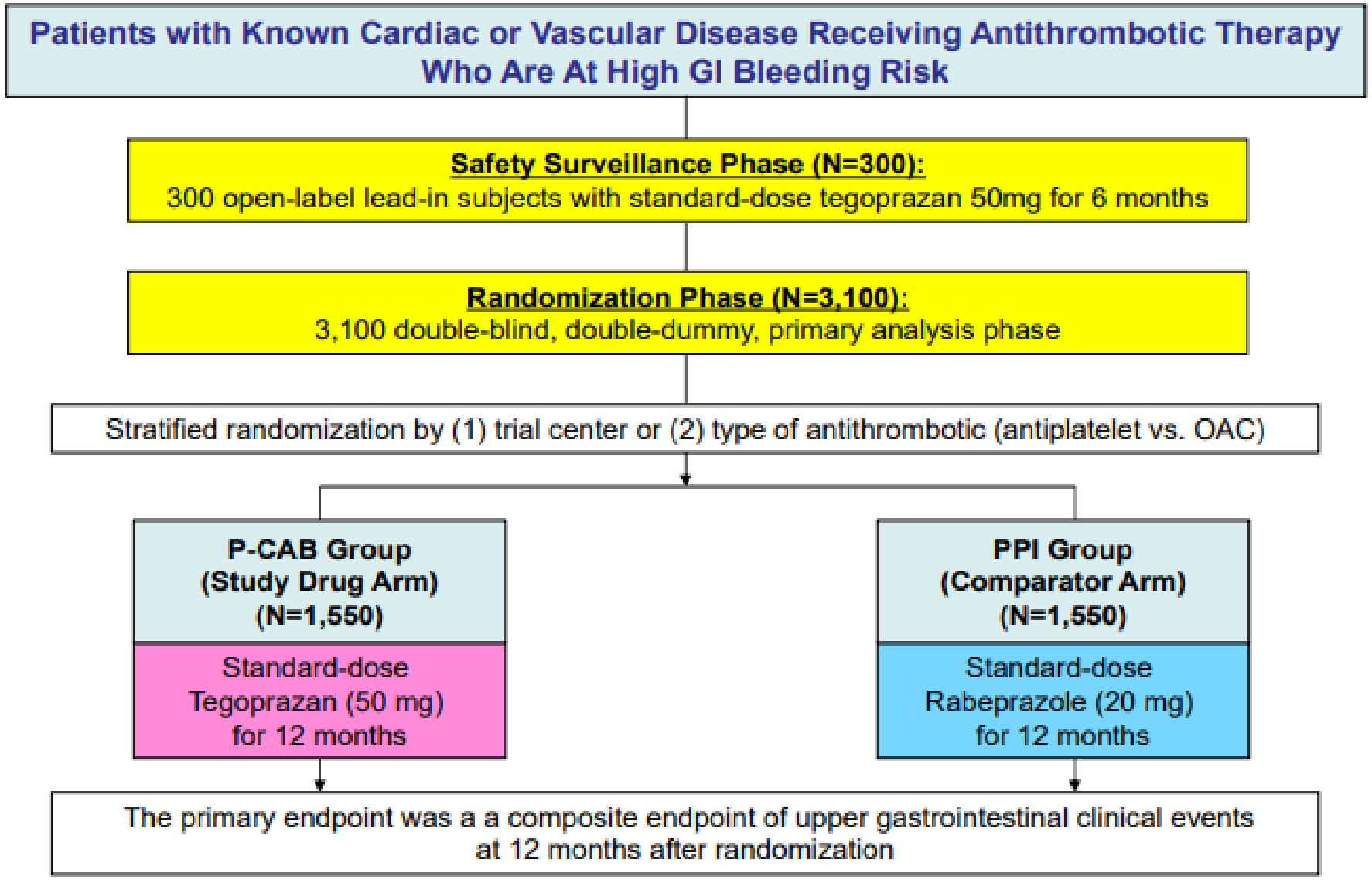


Hypothesis

- **P-CAB** would be **noninferior** to **PPI** with respect to the rate of the primary composite end point of GI events at 12 months.

Potassium-Competitive Acid Blocker versus p***RO***ton-Pump Inhibitor
for Gastropro***TECT***ion Strategies In Patients at ***H***igh Gastro-Intestinal ***B***leeding ***R***isk Receiving
Antiplatelet or Oral Anticoagulant Therapy

PROTECT-HBR Trial



Study Design

- Multi-center, randomized, double-blind,
- Active controlled, parallel-group, phase IV study

- **Stratification:**
  - Participating center

  - Type of antithrombotic drug (Antiplatelet or OAC)

(Patients receiving concomitant use of antiplatelet drugs and OAC are regarded as those receiving OAC)

- **Interventions:**
- Tegoprazan Group :
  - Tegoprazan 50mg once daily + Rabeprazole 20mg placebo once daily
- Rabeprazole Group :
- - Rabeprazole 20mg once daily + Tegoprazan 50mg placebo once daily

Sample Size Estimation

- Non-inferiority trial design
- % of primary endpoint : 4% in the PPI group base on result from COGENT, COMPASS Trial

- Non-inferiority margin of a hazard ratio of 1.40 or less

- Dropout rate : 5%
- Power = 80%; alpha-level = 0.05
- Final N = 3100 (1550 vs. 1550)

Study Endpoint

- **Primary efficacy Endpoint**

  - Composite endpoint of upper GI clinical events

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

Secondary Endpoint

1. Each component of the primary efficacy end point;
2. Time from randomization to discontinuation of study medication attributed to gastrointestinal 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, non-fatal myocardial infarction, or non-fatal stroke);
5. Each component of composite cardiovascular end point;
6. Any coronary or peripheral revascularization;
7. All-cause mortality

Inclusion Criteria

- **Patients 19 years of age or older**
- **Chronic use of antithrombotic drugs**
  (either antiplatelets, OAC, and its combinations)
- **Cardiac and Vascular disease**
  - Coronary artery disease
    : stable or unstable angina, acute coronary syndrome, a history of MI, or any coronary revascularization
  - Cerebrovascular disease (Stroke or TIA)
  - Peripheral arterial disease
  - Atrial fibrillation
  - Valvular heart disease requiring intervention (TAVR, TEER)

Inclusion Criteria

- **Definition** of patients who are at high risk of gastrointestinal bleeding
    1. Age ≥65 years
    2. Concomitant use of OAC and any antiplatelet therapy (mono or DAPT) (i.e., DAT or TAT)
    3. Long-term use of oral NSAIDs (non-steroidal anti-inflammatory drugs) or steroids or high-dose NSAID therapy even during a relatively short-term period.
    4. History of prior GI bleeding events at any time
    5. History of a previously complicated ulcer
    6. History of peptic ulcer disease or a previously uncomplicated ulcer
    7. Documented Helicobacter pylori infection

- coronary artery disease
  - stable or unstable angina, acute coronary syndrome, a history of myocardial infarction, or any coronary revascularization
- documented cerebrovascular disease
  - stroke or transient ischemic attack
- known peripheral arterial disease or a history of peripheral arterial revascularization
- atrial fibrillation
- valvular heart disease requiring interventions
  - transcatheter aortic-valve replacement or transcatheter mitral-valve repair

cardiac and vascular disease

- aspirin monotherapy
- DAPT
  - dual antiplatelet therapy; aspirin plus any P2Y12 inhibitors
- DAT
  - dual antithrombotic therapy; antiplatelet drug plus OAC
- TAT
  - triple antithrombotic therapy; DAPT plus OAC
- OAC monotherapy
  - warfarin or direct oral anticoagulants

chronic use of antithrombotic drugs

A. Age ≥65 years
B. Concomitant use of OAC and any antiplatelet therapy (mono or DAPT) (i.e., DAT or TAT)
C. Long-term use of oral NSAIDs (non-steroidal anti-inflammatory drugs) or steroids or high-dose NSAID therapy even during a relatively short-term period.
D. History of prior GI bleeding events at any time
E. History of a previously complicated ulcer
F. History of peptic ulcer disease or a previously uncomplicated ulcer
G. Documented Helicobacter pylori infection

increased risk of gastrointestinal bleeding

20240202 added

Exclusion Criteria

- **Active Bleeding** at the time of inclusion

  or history of hereditary or acquired hemostatic disorder

- **Any clinical contraindication** to using of antithrombotic therapies

  (antiplatelet agents or OAC)

- **Concurrent use of PPI or P-CAB** within **4 weeks before randomization**

- **Hemodynamically unstable conditions** at the time of inclusion

  : Cardiogenic shock, refractory ventricular arrhythmia, or congestive heart failutre (NYHA Class IV)

Exclusion Criteria

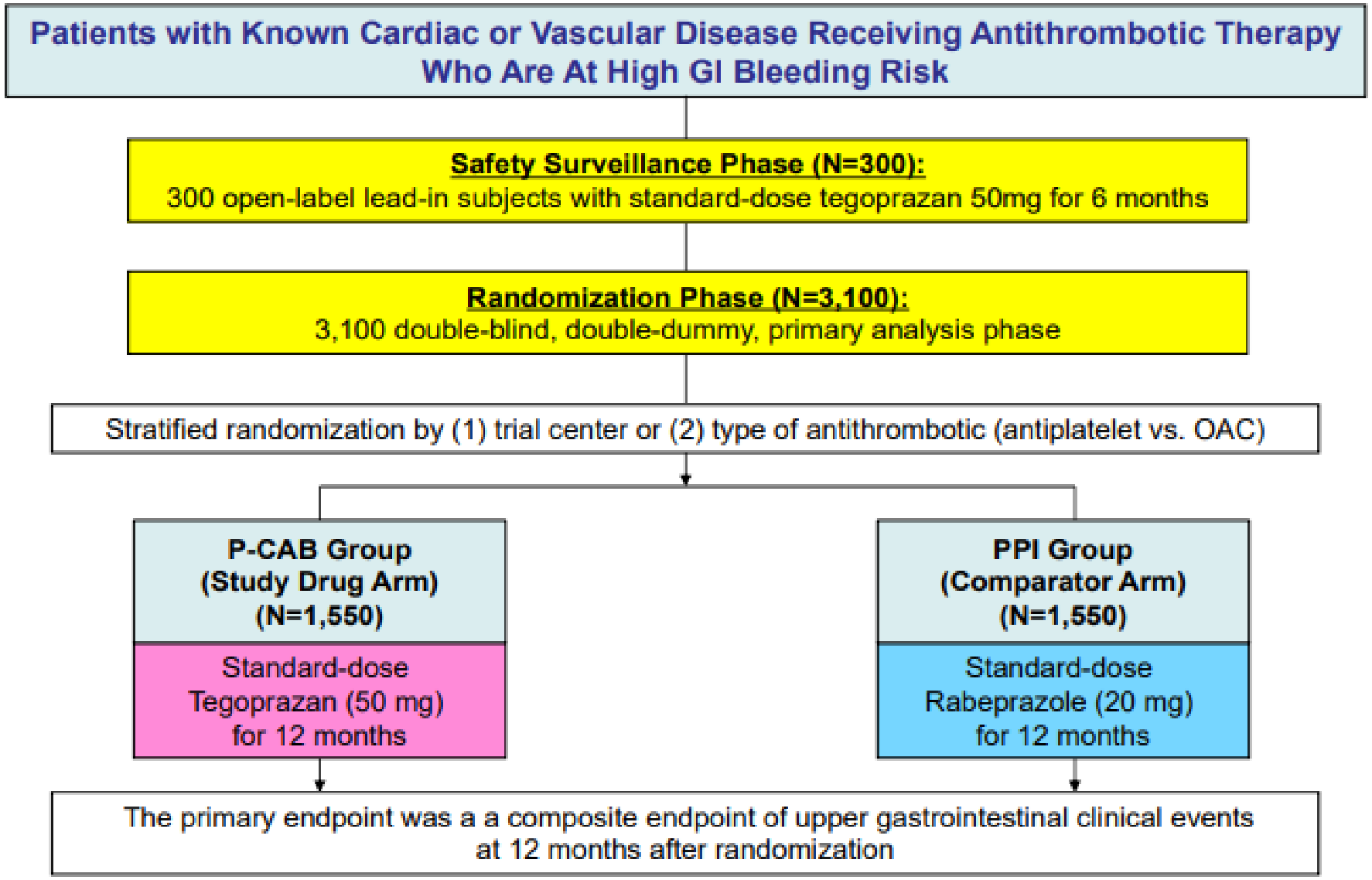
- Baseline severe anemia (Hgb < 8 g/dl at baseline) or transfusion within 4 weeks before randomization
- Baseline severe thrombocytopenia (platelet count <50,000/mm$^{3)}$
- Renal failure dependent on dialysis or severe renal insufficiency (Cr <15ml/min)
- Severe chronic liver disease

Exclusion Criteria

- **Hypersensitivity** or contraindication to PPI, P-CAB
- Use of Clarithromycin and **hypersensitivity to macrolide antibiotics** for Helicobacter pylori eradication
- Concomitant use of clarithromycin with **terfenadine, cisapride, astemizole, or pimozide** for Helicobacter pylori eradication
- Systemic treatment with strong CYP 3A4 and p-glycoprotein (P-GP) inhibitors (e.g., systemic azole antimycotics, such as ketoconazole, and human immunodeficiency virus [HIV]-protease inhibitors, such as ritonavir)
- Patients who take atazanavir, nelfinavir, or rilpivirine-containing products (see **Drug-Drug interaction** section)
- 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 [UNL**] or any other condition that, in the opinion of the Investigator, precludes participation in the study
- Any known or suspected **malignancy**
- Subjects with non-cardiac co-morbidities with a life expectancy of less than 12 months
- Subjects with active treatment for H-pylori infection

Potassium-Competitive Acid Blocker versus p***RO***ton-Pump Inhibitor
for Gastropro***TECT***ion Strategies In Patients at ***H***igh Gastro-Intestinal ***B***leeding ***R***isk Receiving
Antiplatelet or Oral Anticoagulant Therapy

PROTECT-HBR Trial



Participating Center

No.	Participating Centers	P.I.	Contact (E-mail(
1	서울아산병원	박덕우	dwpark3995@gmail.com
2	강릉아산병원	박한빛	phb8012@gmail.com
3	동아대학교병원	김무현	kmh60@damc.or.kr
4	부산대학교병원	이한철	glaraone@hanmail.net
5	세종병원	최영진	cyjheart@gmail.com
6	인제대학교 일산백병원	권성욱	mdksu@paik.ac.kr
7	강원대학교병원	이봉기	mdbklee@kangwon.ac.kr
8	경희의료원	김원	mylovekw@daum.net
9	광주기독병원	이승욱	cardiosu@hanmail.net
10	순천향대학교 천안병원	이세환	swlee@schmc.ac.kr
11	양산 부산대학교병원	천민구	chonmingu@gmail.com
12	인제대학교 부산백병원	양태현	yangthmd@naver.com
13			
14			
15			
16	가톨릭대학교 서울성모병원	황명희	hbhmac@naver.com
17	가톨릭대학교 은평성모병원	김범준	bjheart@catholic.ac.kr
18	영남대학교병원	김웅	woongwa@yu.ac.kr
19	전남대학교병원	홍영준	hyj200@hanmail.net
20	차의과학대학교 분당차병원	김원장	mdwjkim@gmail.com
21	충북대학교병원	배장환	drcorazon@hanmail.net
22	분당서울대학교병원	서정원	suhjw1@gmail.com
23	전북대학교병원	이상록	medorche@jbnu.ac.kr
24	충남대학교병원	최시완	siwanc@cnu.ac.kr
25	강동경희대학교병원	진은선	eunsun.marcella@gmail.com
26	강북삼성병원	이종영	jyleeheart@naver.com, shsh96.lee@samsung.com
27	건국대학교병원	권창희	vertex_77@naver.com
28	동국대학교 일산병원	김유리	yul@dumc.or.kr
29	서울대학교병원	최의근	choiek417@gmail.com
30	중앙보훈병원	황진경	dangtong@naver.com
31	한림대학교 성심병원	박경하	pkhmd@naver.com
32	수원성빈센트	허성호	hhhsungho@naver.com

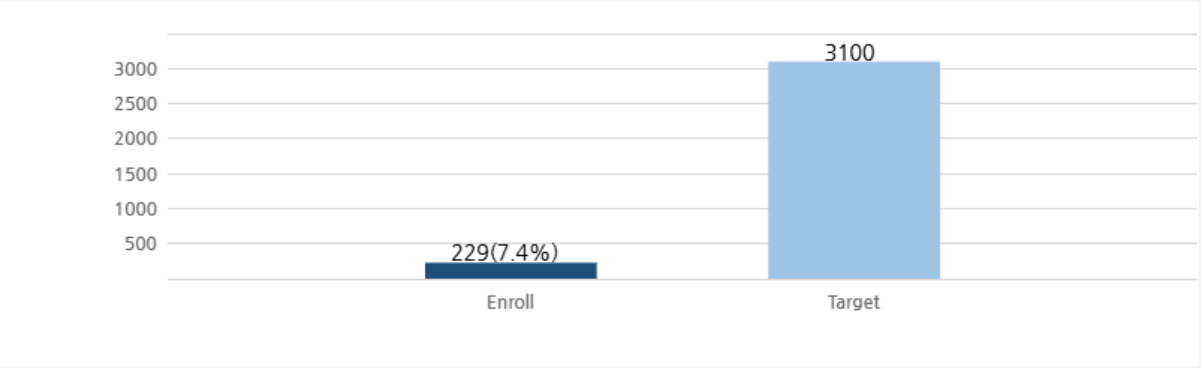
43 Participating Center in South Korea

21	충북대학교병원	배장환	drcorazon@hanmail.net
22	분당서울대학교병원	서정원	suhjw1@gmail.com
23	전북대학교병원	이상록	medorche@jbnu.ac.kr
24	충남대학교병원	최시완	siwanc@cnu.ac.kr
25	강동경희대학교병원	진은선	eunsun.marcella@gmail.com
26	강북삼성병원	이종영	jyleeheart@naver.com, shsh96.lee@samsung.com
27	건국대학교병원	권창희	vertex_77@naver.com
28	동국대학교 일산병원	김유리	yul@dumc.or.kr
29	서울대학교병원	최의근	choiek417@gmail.com
			aver.com
			er.com
			naver.com

33	울산병원	신은석	sesim1989@gmail.com
34	조선의대	김현국	sale38@hanmail.net
35	경상의대	박용휘	angio2000@hanmail.net
36	이화의대서울병원	장우진	wj78914@gmail.com
37	한양대학교	임영효	mdoim@hanyang.ac.kr
38	단국대학교	임성훈	shlimd@gmail.com
39	고대안암병원	홍순준	psyche94@gmail.com
40	보라매병원	김상현	shkimmd@snu.ac.kr
41	한양대구리병원	박환철	pigpooh76@hanmail.net
42	중앙대병원	이왕수	wslee1227@cau.ac.kr
43	삼성창원병원	박용환	hippomac@hanmail.net

PROTECT-HBR Trial Status

Current Enrollment Status (7.4%)



Monthly Enrollment Status