KOPRE CAD/DM & Stent Study

(**KO**rea **PRE**grel multicenter Clinical Study for patients with **CAD/DM** & **Stent** Implantation)

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Contents

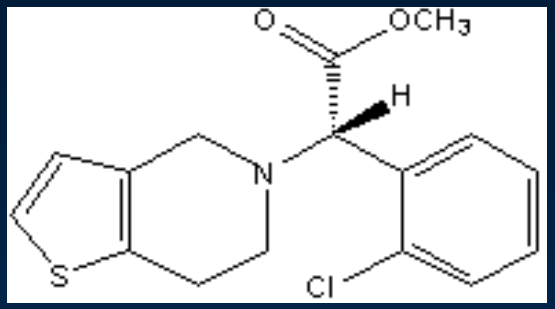
- **Introduction of Pregrel® (Clopidogrel Resinate)**
- KOPRE CAD/DM Study
- KOPRE Stent Study

Clopidogrel is unstable !!

Viscous semi-solid form

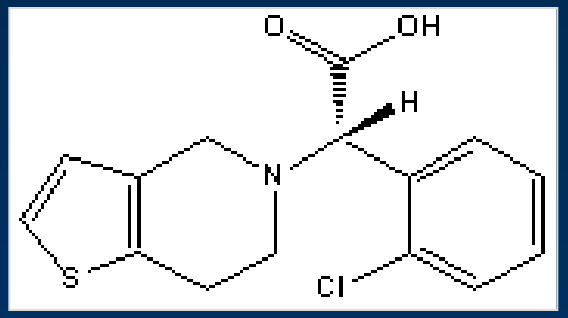
Solubility : < 5 ug/mL

Stability : unstable



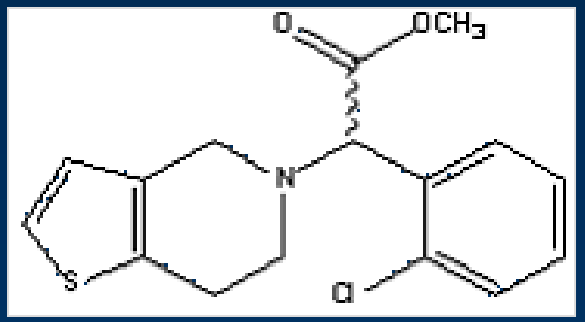
Clopidogrel

(S-enantiomer)



Impurity A

Hydrolysis metabolite



Impurity C

Racemic form

(S + R-enantiomer)

Unknown Impurities

Degradation of Clopidogrel

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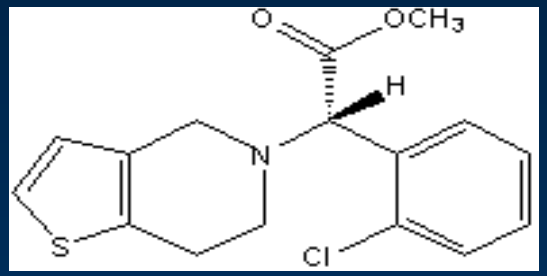
Initial, 40°C

3 days, 40°C

7 days, 40°C

Salt Screening



Acetate
Aspartate
Citrate
Edatate
Glutamate
Glycolate
Glucuronate
Malate
Propionate
Phosphate
Metaphosphate
Polyphosphate
Metabisulfate
Hydrochlorate
Tartrate

Sulfate (Bisulfate) – Sanofi
Besylate – Helm, Cadila

Clopidogrel does not easily form stable and solid salts with conventional acids, FDA approved acids for salts.

It has been stabilized and solidified with **sulfate or sulfonate** group.

New Polymeric Salt form of Clopidogrel

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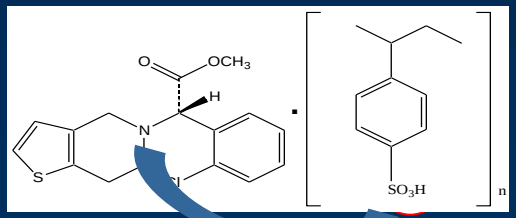
Drug load : about 50%(48~53%)

Stability : stable

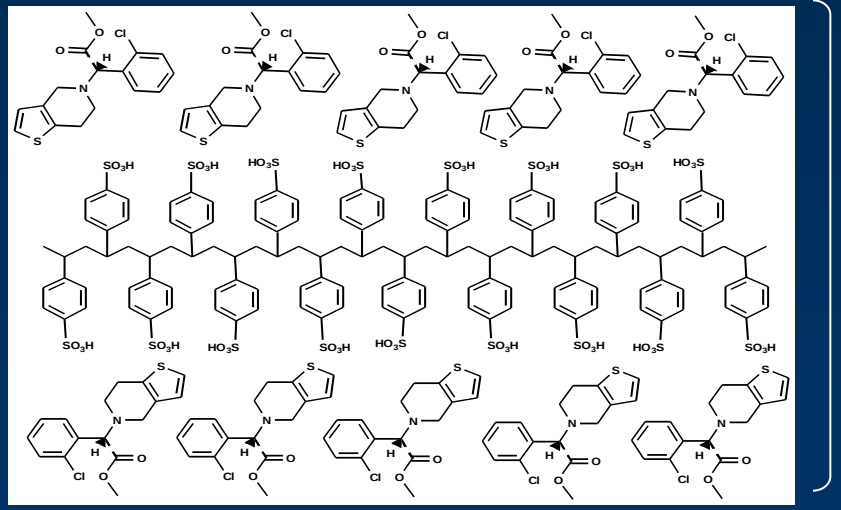
Clopidogrel Resinate

(A)



Stable Salt Formation

(B)



Chemical structure of clopidogrel resinate

Preliminary Stability

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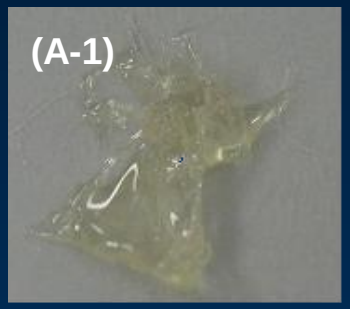
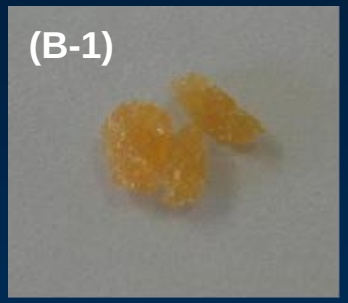
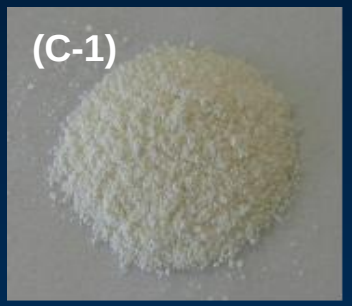
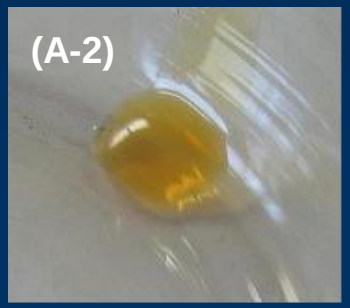
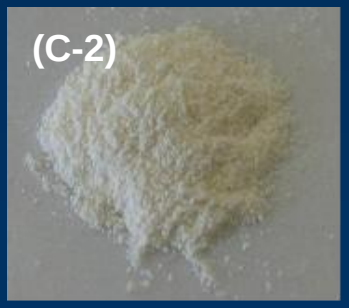
	Clopidogrel-free Base	Clopidogrel-resin Physical mixture	Clopidogrel resinate
Appearance	 (A-1)	 (B-1)	 (C-1)
Assay	98.63%	95.43%	99.18%
Total Impurities	0.39%	0.87%	0.28%

40°C, 75% relative humidity

1 week

Appearance	 (A-2)	 (B-2)	 (C-2)
Assay	92.21%	92.32%	99.61%
Total Impurities	5.87%	3.66%	0.29%

Physical Stability

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Clopidogrel resinate (Pregrel ®)

2 weeks, open condition

Clopidogrel bisulfate (Plavix ®)

2 weeks, open condition

Ref) The efficacy and safety of Clopidogrel Resinate as A Novel Polymeric Salt Form of Clopidogrel, Arch Pharm Res Vol 31, No 2, 250-258, 2008

Chemical Stability

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Product	Assay (%)	Hydrolysis product (%)		R-enantiomer (%)		Total impurities (%)		Company
		Initial	3 months[b)]	Initial	3 months	Initial	3 months	
Pregrel®	**102.5**	**0.07**	**0.19**	**0.27**	**0.32**	**0.48**	**1.22**	**ChongKunDang Pharm.**
Plavix®	97.9	0.04	0.31	0.25	0.35	0.61	1.75	Sanofi-Synthelabo
Plagil®	95.1	0.45	0.46	1.09	1.14	1.76	3.29	Dr. Reddy's Lab.
Clodrel®	88.7	0.85	1.36	2.24	3.61	3.55	5.55	Unichem Lab.
Orawis®	95.6	0.67	1.36	1.57	3.30	1.52	5.21	Merck
Noklot®	91.6	0.86	1.35	1.71	2.71	2.97	4.85	Zydus Medica
Clopigrel®	91.6	0.15	1.40	5.68	6.12	6.65	9.71	USV Ltd.
Preva®	93.3	0.57	2.54	1.97	5.30	3.07	10.84	Intas Pharm.
Clavix®	93.6	1.46	2.06	0.67	6.50	3.13	11.21	Intas Suprima
Clopilet®	91.3	<0.01	0.45	0.87	1.26	4.48	5.17	Sun Pharm.
Stomix®	86.5	0.07	0.70	3.41	3.63	8.87	9.17	Nicholas Piramal
Cloplat 75®	95.9	1.36	2.47	3.20	3.56	5.99	8.53	IPCA Lab.
Deplatt®	96.7	0.08	0.08	0.95	1.03	1.68	2.54	Torrent Pharm.
Ceruvin®	96.1	0.23	0.41	1.50	1.55	2.50	3.46	Stancare/Reddy
Cloplatic®	90.3	1.47	2.20	1.93	3.70	5.88	9.08	Haymann
Plagrel®	102.3	0.21	0.26	0.79	0.80	1.78	1.90	Servimedic
Nefazan®	96.4	0.07	0.07	0.93	0.98	1.28	1.91	Lab. Phoenix
Talcom®	94.5	0.04	0.08	1.11	1.68	2.46	3.43	Shenzen Salubris
Clopifran®	95.3	0.07	0.07	1.13	4.65	3.90	5.60	Lab. Lufra Farnacis
Clopigrel®	97.7	0.17	1.78	1.03	3.66	2.59	7.40	Noas Farma

Generic Drugs

Ref> Analysis of Purity in 19 drug product tablets containing clopidogrel, Journal of pharmaceutical and biomedical analysis, 34(2004)341-348

KoPre-Study

Selective Permeability in Pregrel

Permeation constant of Clopidogrel and resinate across Caco-2 cell monolayers from apical(A) to basolateral(B) side.

	P_{app} (cm/sec), apical to basal	
	P_{app} of Clopidogrel	P_{app} of Salts
Clopidogrel resinate	**13.5 x 10^{-6} cm/sec**	**0.0 x 10^{-6} cm/sec**
Clopidogrel bisulfate	**12.7 x 10^{-6} cm/sec**	**26.6 x 10^{-6} cm/sec**
Clopidogrel besylate	**11.9 x 10^{-6} cm/sec**	**8.0 x 10^{-6} cm/sec**
Clopidogrel napadisylate	**14.9 x 10^{-6} cm/sec**	**7.8 x 10^{-6} cm/sec**

* The correlation between the permeability coefficient (P_{app}) across Caco-2 cell monolayer and the oral bioavailability (F) in the intestinal tract.

P_{app} (permeability coefficient, cm/sec)	F (oral bioavailability, %)
< 1.0 x 10^{-6}	< 10%
1.0 x 10^{-6} ~ 10.0 x 10^{-6}	10% ~ 90%
> 10.0 x 10^{-6}	> 90 %

Beauty of Polymeric salt of Clopidogrel PREGREL® Tablet

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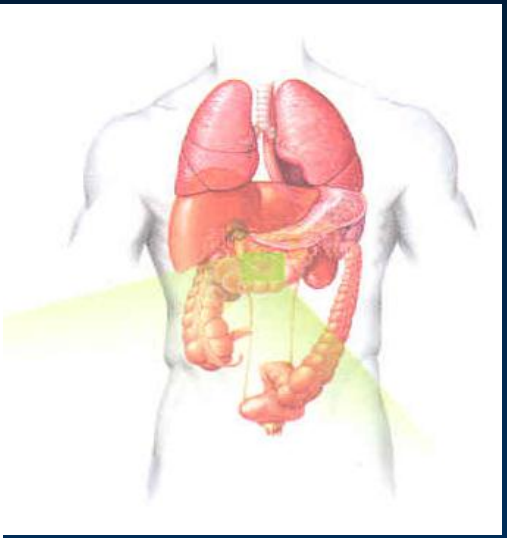
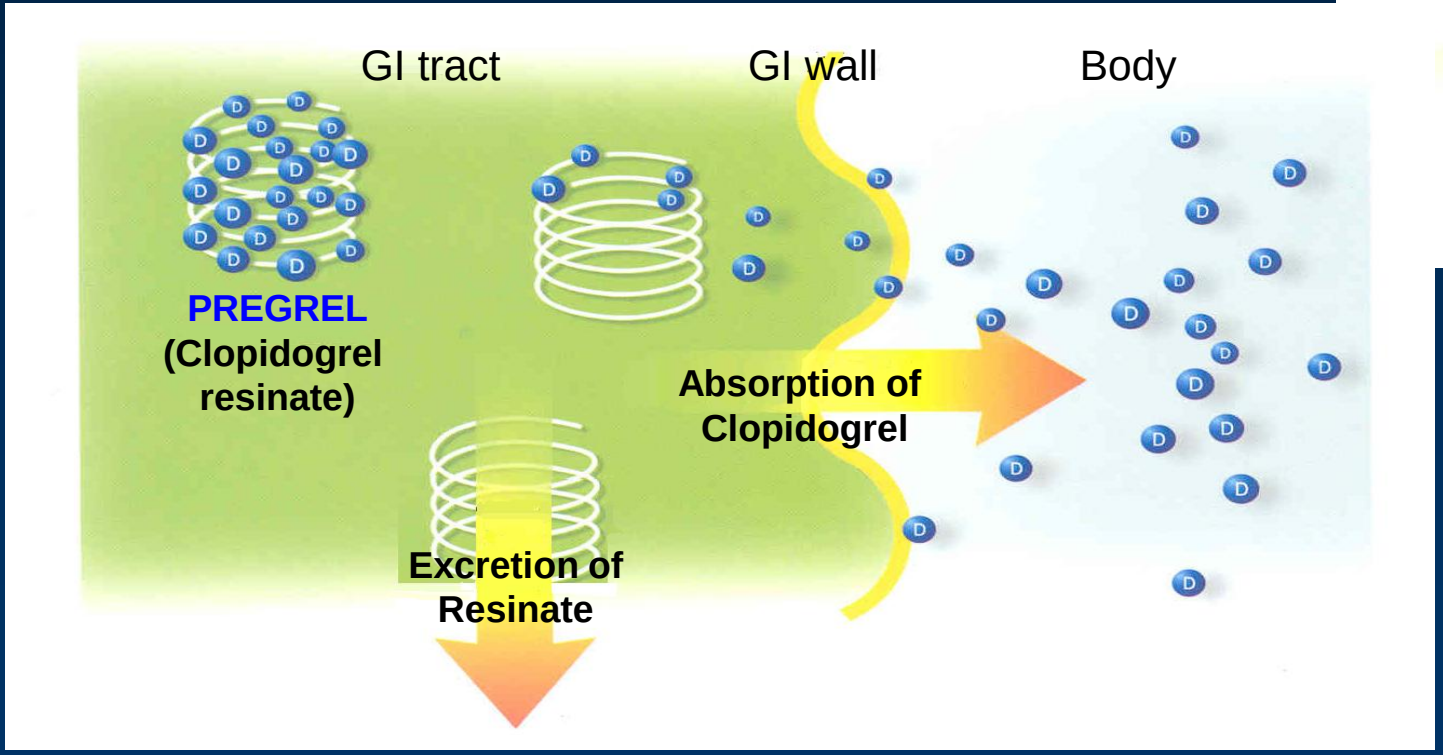
- Resinate is not absorbed from the gastrointestinal (GI) tract, and carries the active drug (clopidogrel) into the body.





Toxicity in animal experiment

Safety Study of Clopidogrel Resinate

A. Single-dose study
B. Dose range-finding study (4 weeks)
C. Multiple-dose study (13 weeks)
D. Toxicokinetics in multiple-dosing (13 weeks)
E. Mutagenicity

Comparative toxicity : oral lethal dose, 50%

API *	LD_{50} ** (Rat)	
	Male	Female
Clopidogrel Resinate	**> 2,000 mg/kg**	**> 2,000 mg/kg**
Clopidogrel Bisulfate	**1,800 mg/kg**	**2,000 mg/kg**

[Reference] GLP toxicity study report of Clopidogrel resinate
* API: Active Pharmaceutical Ingredient
**LD_{50}: The amount of a chemical that is lethal to one-half (50%) of the experimental animals orally exposed to it

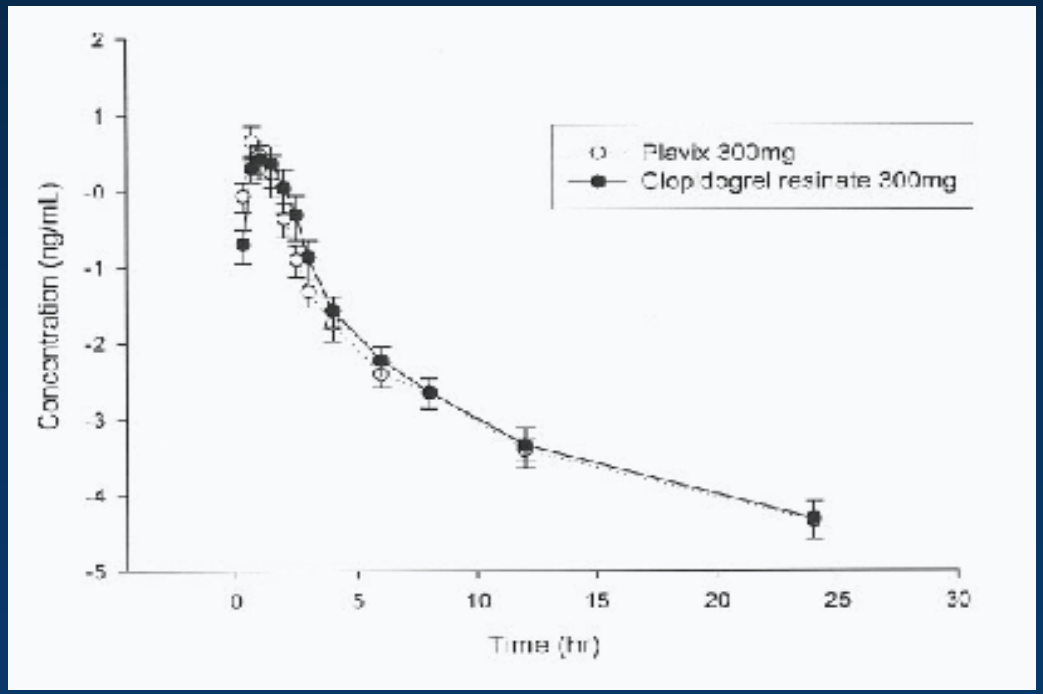
Phase I :Pharmacokinetics profiles

KoPre-Study

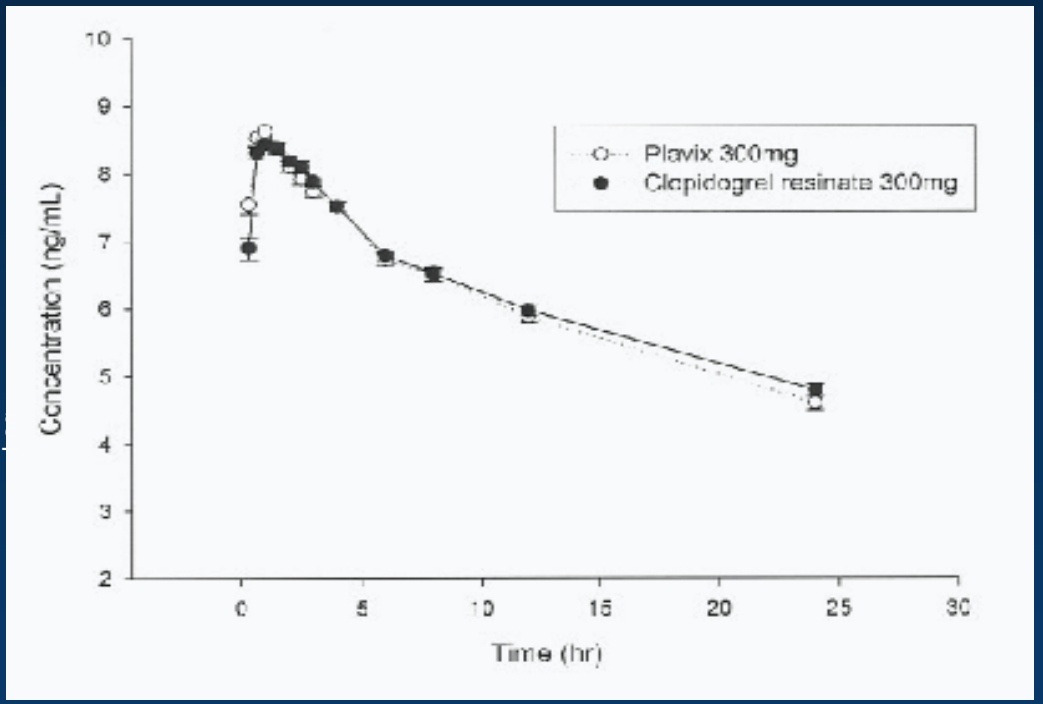
Healthy volunteers

Center : Asan medical center
Subject: 48, cross-over

PK profiles of Clopidogrel (Parent drug)



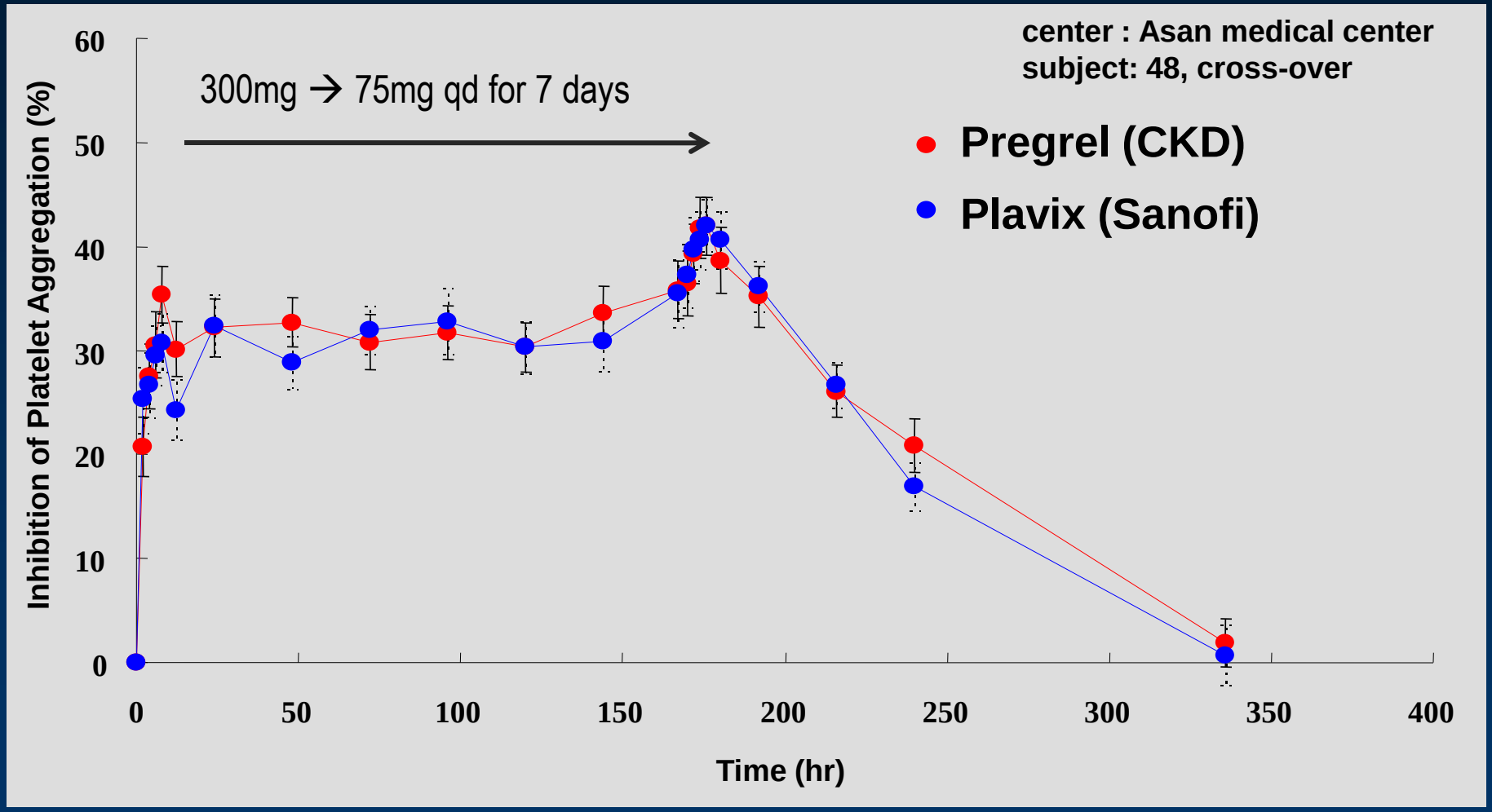
PK profiles of 1st Clopidogrel Metabolite



Phase I : Pharmacodynamics profiles

KoPre-Study

Healthy volunteers



KOPRE-CAD/DM Study in 10 Centers

Background

- Clopidogrel generic drugs
  - PK/PD studies : healthy volunteers
  - Not evaluated in the real-world CAD or DM patients in Korea

- Aim of this study
  - To validate the ADP blocking activity of clopidogrel resinate (Pregrel®) in the real-world pts
  - To compare the antiplatlet activity of clopidogrel resinate (Pregrel®) with clopidogrel bisulfate (Plavix®)

Study Design

- Double-blind, randomized, prospective multicenter trial
- Coronary Artery Disease(CAD) or CAD equivalent patient
- Treatment
  - Pregrel+Aspirin vs. Plavix+Aspirin vs. Placebo+Aspirin
  - 4 weeks
- Primary endpoint
  - VerifyNow ™ P2Y12 assay % inhibition
- Secondary endpoint
  - Safety profile, hs-CRP, lipid profile change in atorvastatin users

KoPre-Study

Participating 10 Centers in Korea

Site	Principle Investigator
Ajou University Medical center	Tahk, Seung Jea
Seoul ST. Mary's Hospital	Seung, Kie Bae
Gyeongsang Natinal University Hospital	Kwak, Chung Hwan
Kyung Hee University Medical Center	Kim, kwon Sam
Korea University Anam Hospital	Hong, Soon Jun
Dong-A Medical center	Park, Tae Ho
Boramae Hospital	Kim, Sang Hyun
Seoul National University Hospital	Kim, Hyo Soo
Cheju National University Hospital	Joo, seung Jae
Hallym University Medical Center	Choi, young Jin

Inclusion Criteria

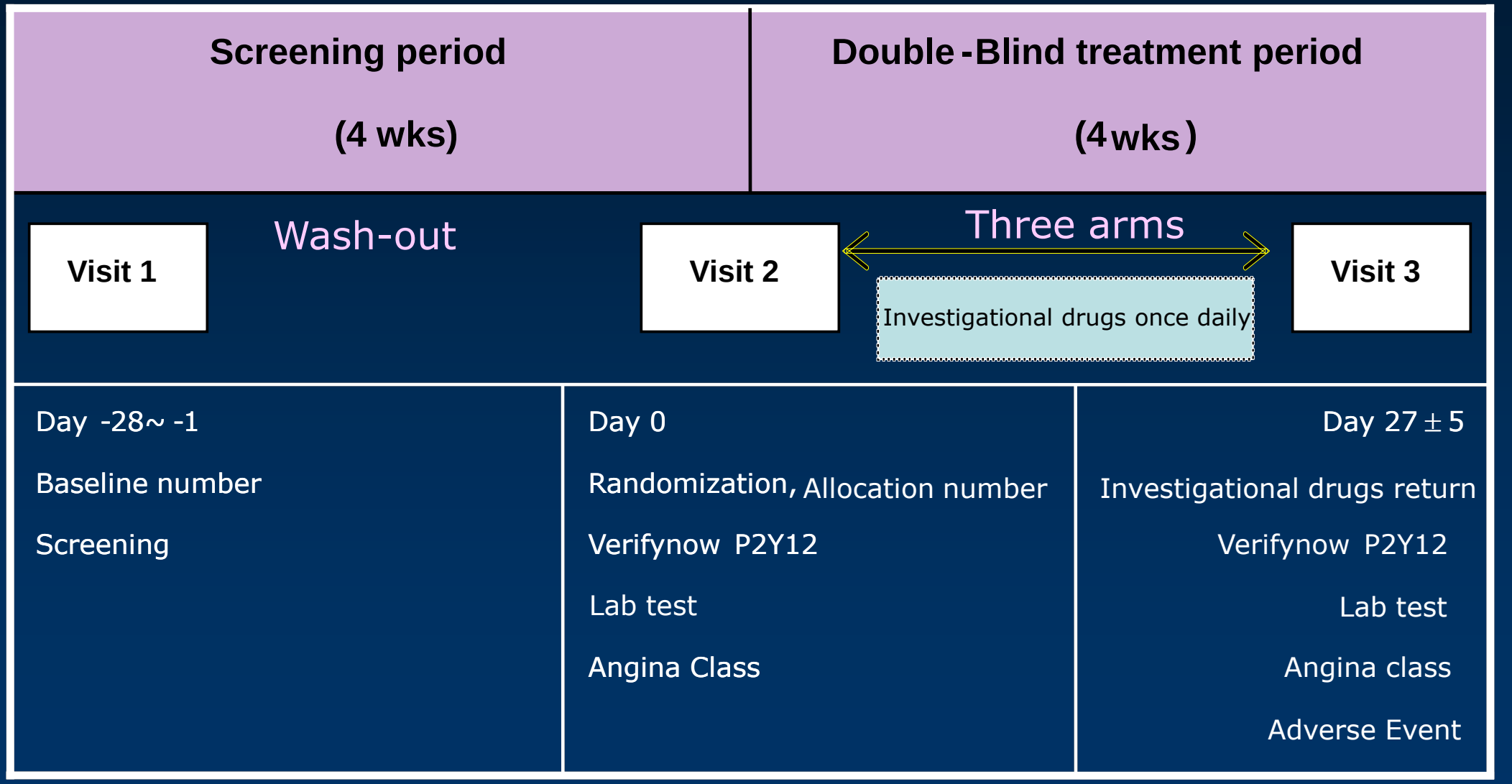
- Coronary Artery Disease or CAD equivalent patients
  - Coronary Artery Disease
    - Dectected any Atheroscleotic plaque by Coronary CT or Angiography
      or
    - Positive stress test
    - History of PCI or CABG (>1yr)
  - Diabetes Mellitus
  - Carotid atheroscleotic plaque
  - Pheripheral Artery disease including cerebrovascular disease
- Age : 20~85yrs
- Able to give informed consent

Exclusion Criteria

- History of PCI within 1 year of entry into the study
- Concomitant use of antiplatelet agents such as clopidogrel, cilostazol
  - **Washout period**
- Concomitant use of anticoagulants
- Chronic alcoholism
- Hypersensitivity to aspirin or clopidogrel
- History of gastrointestinal bleeding or intracranial hemorrhage bleeding
- Blood coagulation disorders, uncontrolled severe hypertension
- History of severe bleeding, active bleeding
- Pregnancy or breast feeding

KoPre-Study

Flow Chart of KoPre-CAD/DM trial



KoPre-Study

Hypothesis & allocation of patients

- Pregrel+aspirin / Plavix+aspirin

  superior to aspirin in the inhibition of ADP receptor

- Pregrel+aspirin non-inferior to Plavix+aspirin

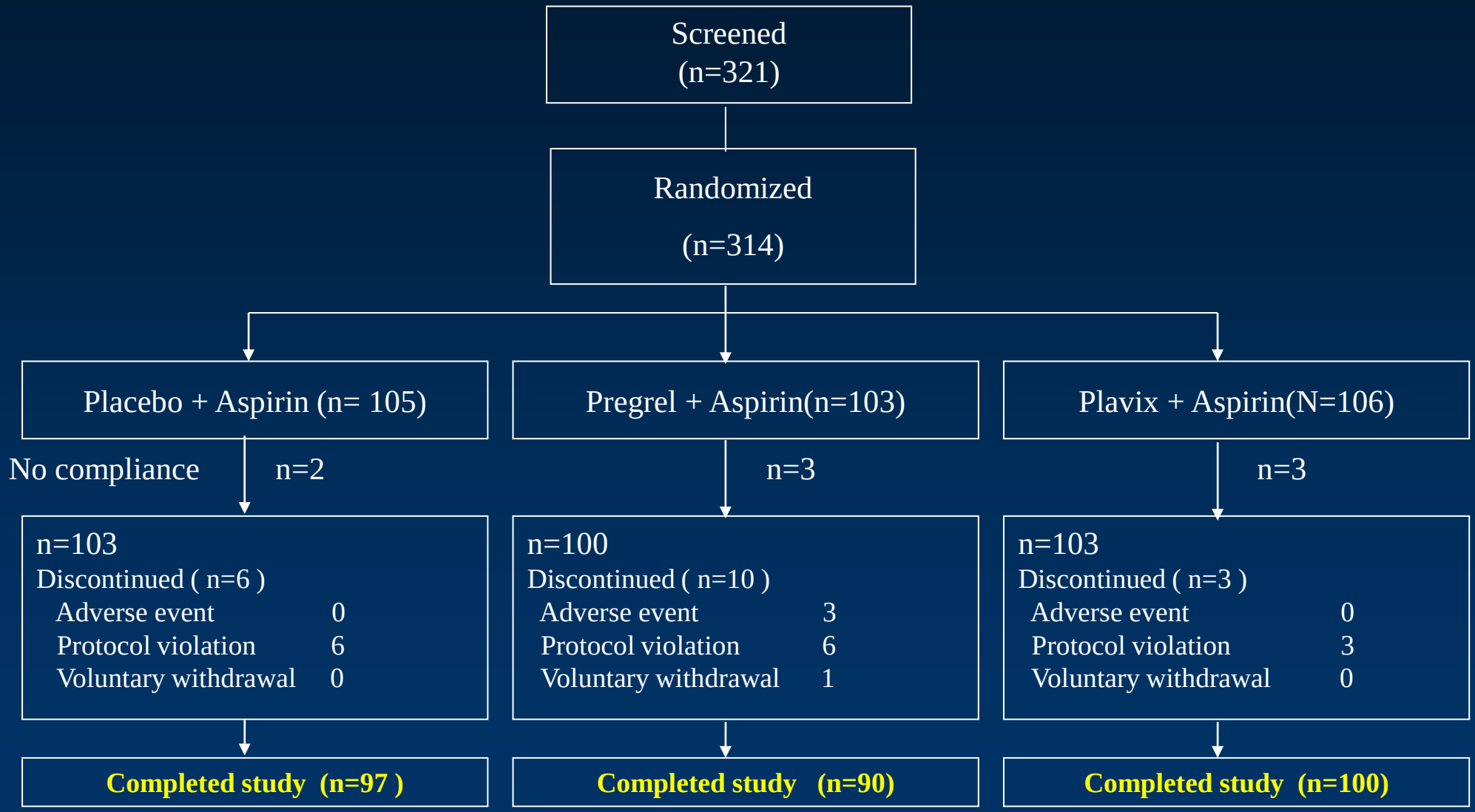
****

- N= 330 pts (including 10% drop out)
- Stratification by DM (40% for each group)
- Statin : atorvastatin exclusively

Results

KoPre-Study

Patient distribution



Baseline Characteristics of patients

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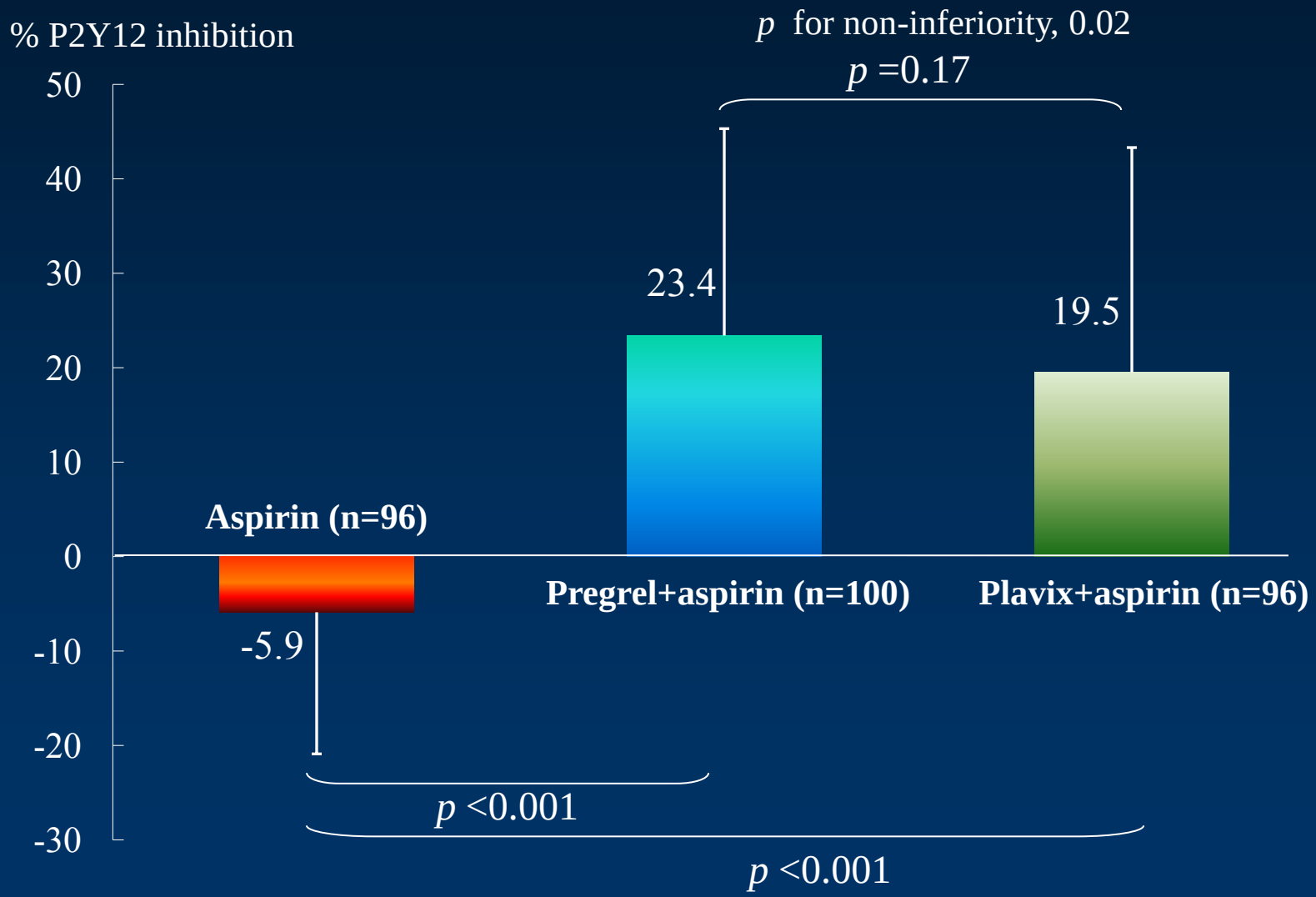
Characterristics	Aspirin (n=103)	Pregrel + Aspirin (n=100)	Plavix + Aspirin (n=103)	*p*
Age y, Mean (SD)	62.1 ± 9.7	62.1 ± 8.1	62.7 ± 8.9	0.82
Male, n (%)	65 (63.1)	68 (68.0)	62 (60.2)	0.51
Diabetes mellitus, n (%)	41 (39.8)	40 (40.0)	41 (39.8)	1.0
Hypertension, n (%)	87 (84.5)	91 (91.0)	85 (82.5)	0.19
Hyperlipidemia, n (%)	37 (35.9)	29 (29.0)	40 (38.8)	0.32
History of CHD, n (%)	88 (85.4)	73 (73.0)	91 (88.3)	0.01
History of PCI	40 (38.8)	37 (37.0)	47 (45.6)	0.42
History of carotid artery disease, n (%)	5 (4.9)	4 (4.0)	3 (2.9)	0.82
History of peripheral artery disease, n (%)	7 (6.8)	5 (5.0)	6 (5.8)	0.86
Current Smoker	19 (18.5)	23 (23.0)	16 (15.5)	0.41

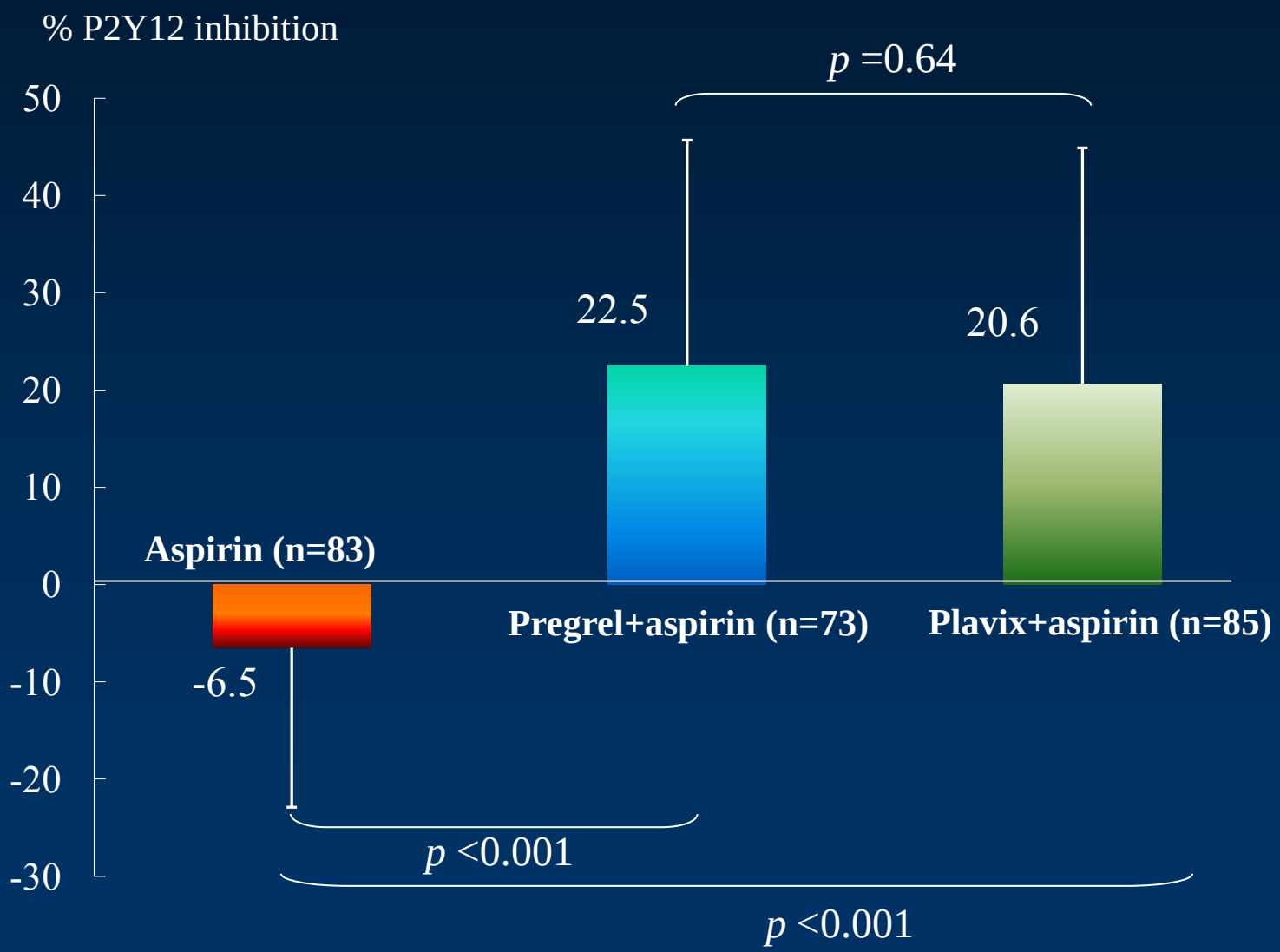
$P2Y_{12}$ receptor inhibition among three groups : All Patients

KoPre-Study



Subgroup analysis : CHD patients

KoPre-Study



Subgroup analysis : DM patients

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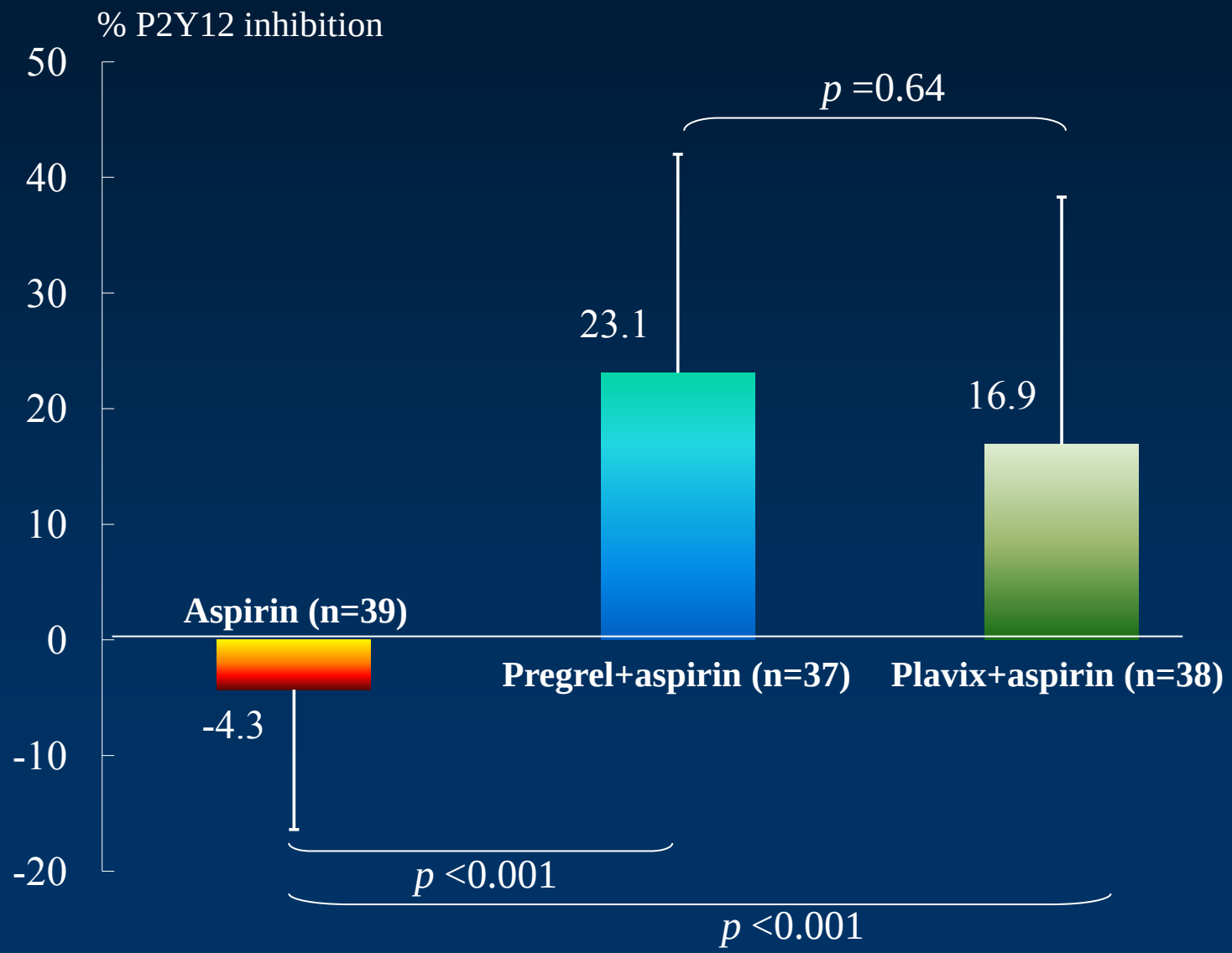
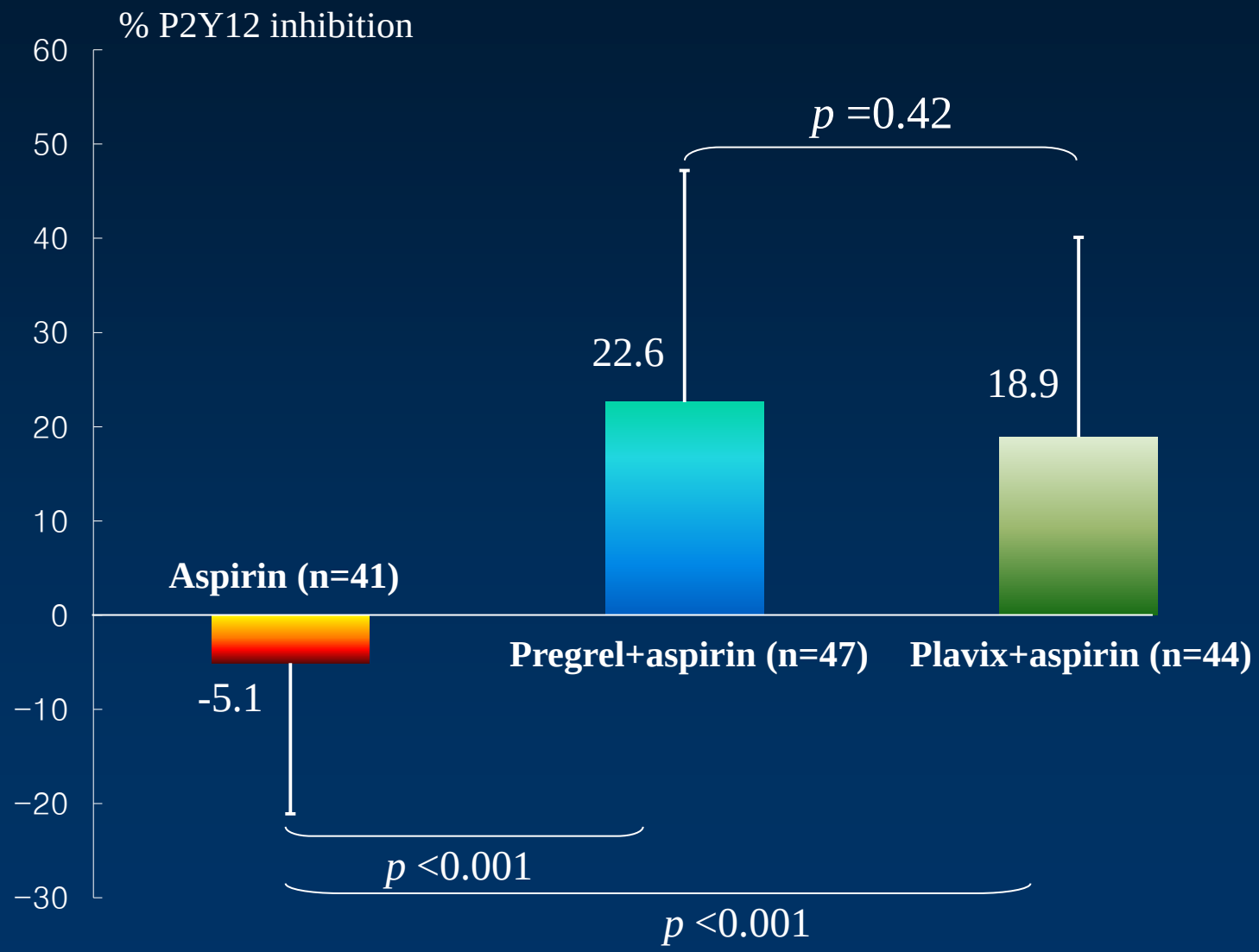


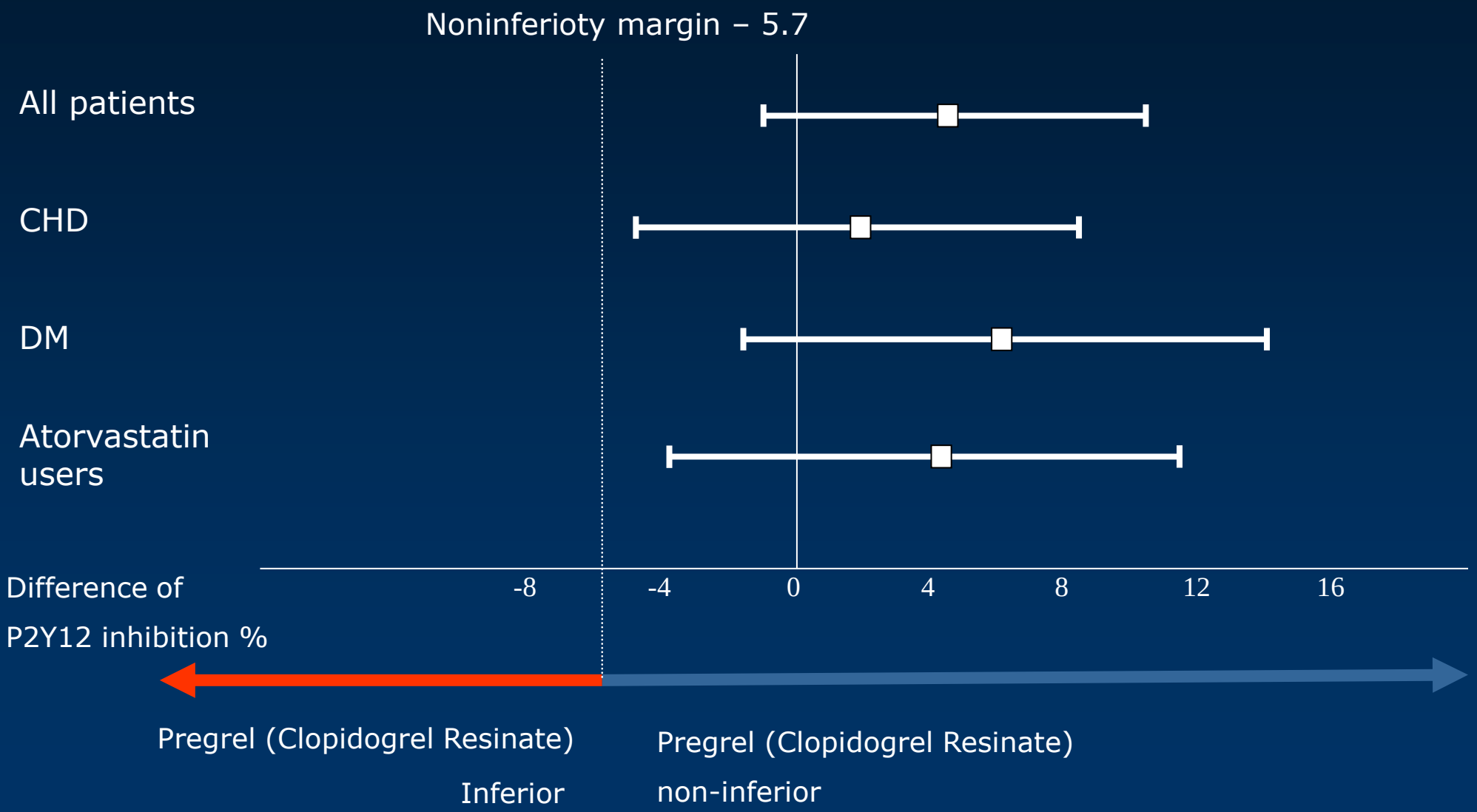
Subgroup analysis : Atorvastatin Users

KoPre-Study



Non-inferiority comparison of Pregrel & Plavix
: by the difference of %P2Y12 inhibition

KoPre-Study



Adverse Events during the study

KoPre-Study

Category	Aspirin (n=103)	Pregrel+Aspirin (n=100)	Plavix+aspirin (n=103)	*P*
All adverse events	34 (33.0)	26 (26.0)	24 (23.3)	0.27
Serious adverse events	1 (0.97)	3 (3.0)	1 (1.0)	0.42
Serious drug-related AEs	0	1 (1.0)	0	0.36

KOPRE-CAD/DM Conclusion

- Clopidogrel resinate in CHD/ CHD equivalents
  - Non-inferior antiplatelet effect to original form of clopidogrel bisulfate
  - Similar safety profile to negative control

- Safe substitute for clopidogrel bisulfate in atherosclerotic vascular disease

KOPRE-Stent Study in 4 Centers

Background

- Pharmacokinetics & Pharmacodynamics Study
  - Healthy volunteers

- KOPRE CAD/DM Study
  - Clopidogrel resinate can be substituted for Clopidogrel bisulfate and prescribed safely in stable OPD patients with CAD/DM

- **KOPRE Stent Study**
  - **To validate the efficacy of Pregrel in CAD patients undergoing stent implantation**

Aim of this study

- To validate the ADP blocking activity of Clopidogrel Resinate (Pregrel®) in patients with stent implantation

- To evaluate the death, MACE, safety of Pregrel® group comparing with Plavix® group for 4 weeks

Study Design

KoPre-Study

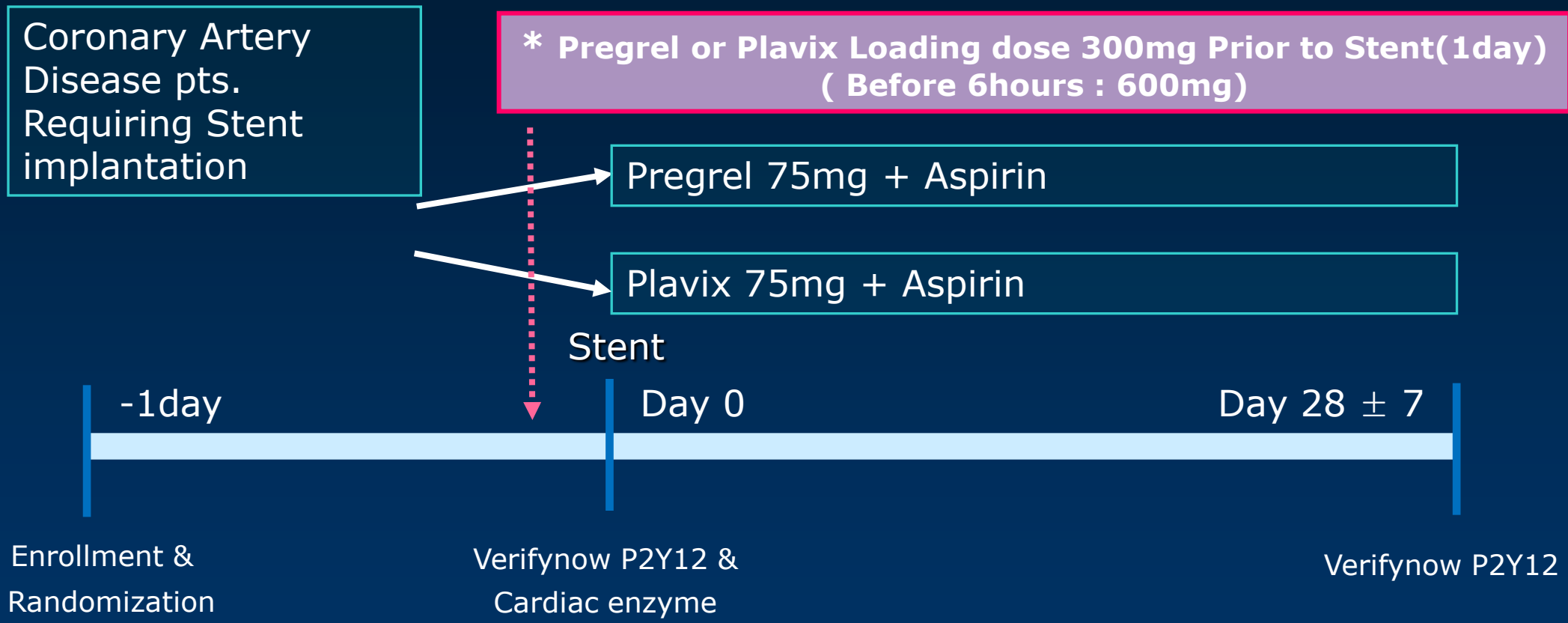
- A randomized, open-label, comparative, parallel group
- Treatment
  - **Pregrel** + Aspirin vs **Plavix** + Aspirin
- Primary endpoint
  - VerifyNow ™ P2Y12 assay % inhibition
- Secondary endpoint
  - MACE, Safety Profile, Cardiac Enzyme

Inclusion Criteria

- Coronary Artery Disease patients
  requiring Stent Implantation
- Age : 20~85yrs
- Able to give informed consent

Study Flow Chart

KoPre-Study



KoPre-Study

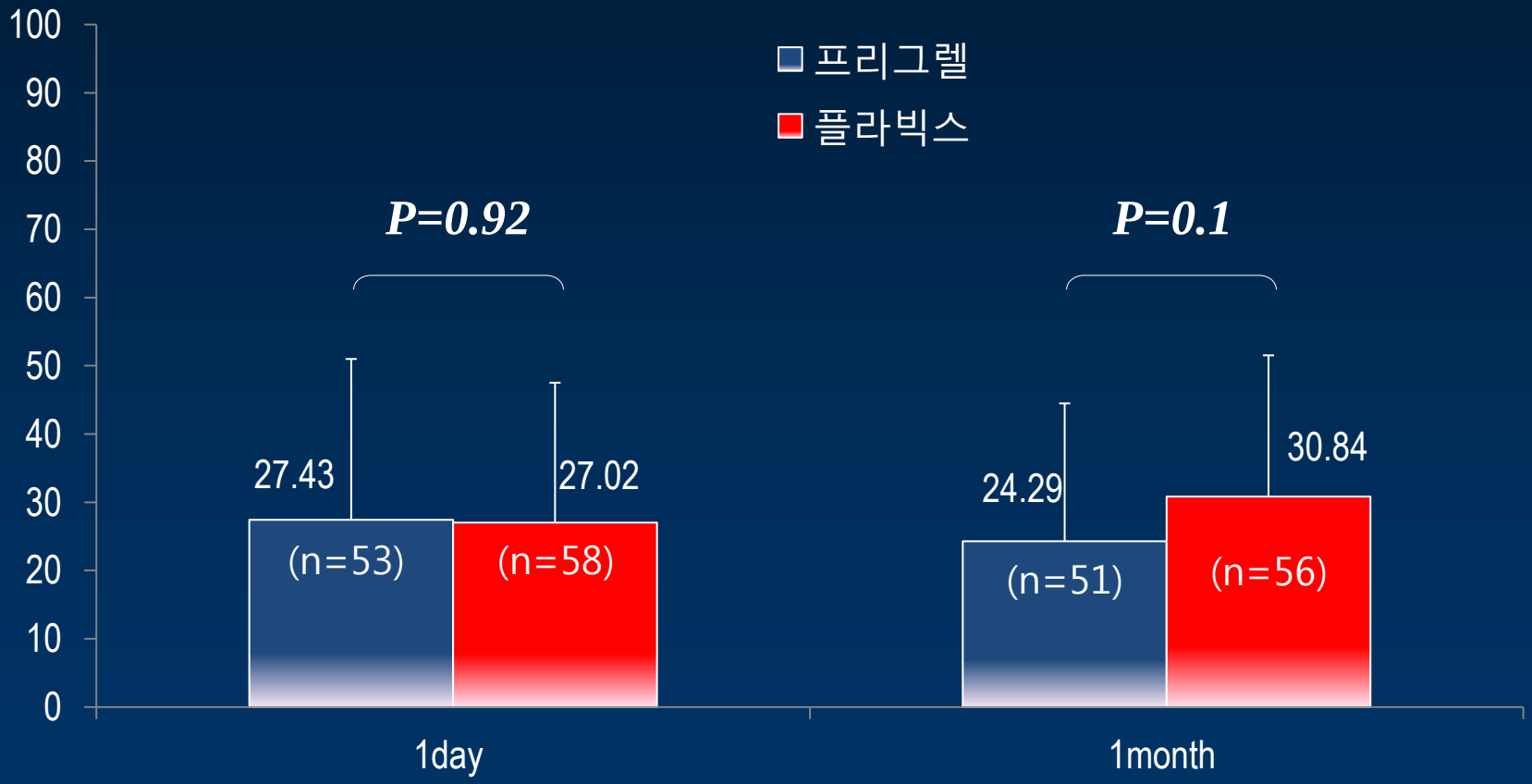
Participating 4 Centers in Korea

Site	Principle Investigator
Kyung Hee Hospital at Kangdong	Kim, Chong Jin
Konyang University Hospital	Bae Jang Ho
Daegu Catholic Uni. Medical Center	Kim, Kee Sik
Seoul National University Hospital	Kim, Hyo Soo

Results

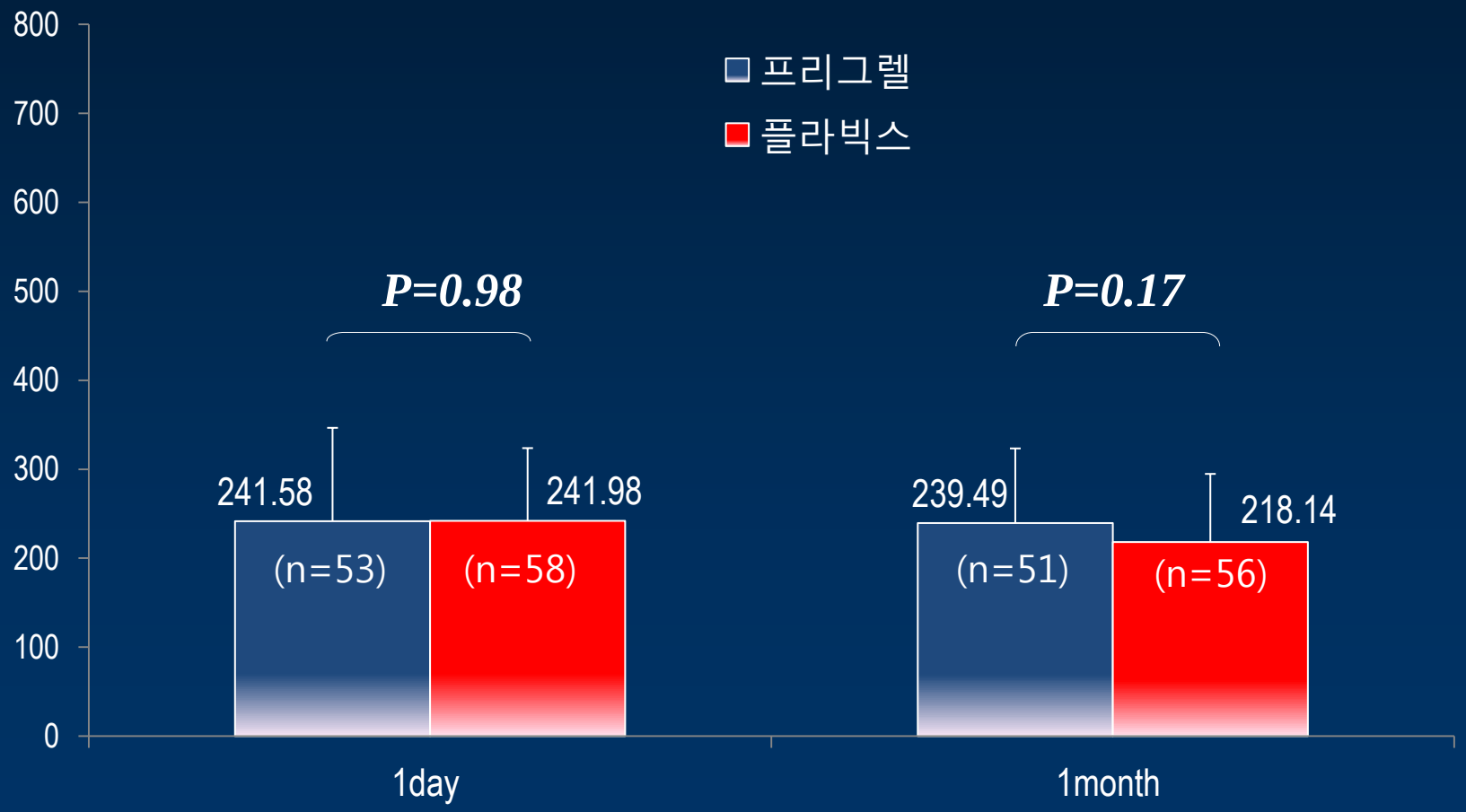
VerifyNow P2Y12 % inhibition

KoPre-Study



VerifyNow PRU

KoPre-Study



Adverse Event

KoPre-Study

Category	Pregrel (n=54)	Plavix (n=59)	*P*
All AEs	16 (29.6)	18 (30.5)	0.92
Serious AEs	0 (0.0)	2 (3.4)	0.50
Drug-related AEs	0 (0.0)	0 (0.0)	
MACE	0 (0.0)	0 (0.0)	

Conclusion

- Clopidogrel resinate in patients with PCI
  - No difference in efficacy & safety between Pregrel® and Plavix®
- Safe substitute for clopidogrel bisulfate in CAD patients undergoing stent implantation

Comparison of Price

	Price (₩)	Daily cost	Monthly cost	Yearly cost	%
Plavix	2,014	2,014	60,420	735,110	219
Generic A	1,733	1,733	51,990	632,545	189
Pregrel	**919**	**919**	**27,570**	**335,435**	**100**

All that glitters is NOT gold.....