上海市心血管病研究所
复旦大学附属中山医院
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# A Prospective Randomized Multi-center Study of Antiplatelet using Cilostazol versus Ticlopidine Undergoing Coronary Artery Stenting

Junbo Ge, MD, FACC, FESC
Shanghai institute of Cardiovascular Diseases
Zhongshan Hospital, Fudan University
On behalf of RACTS investigators

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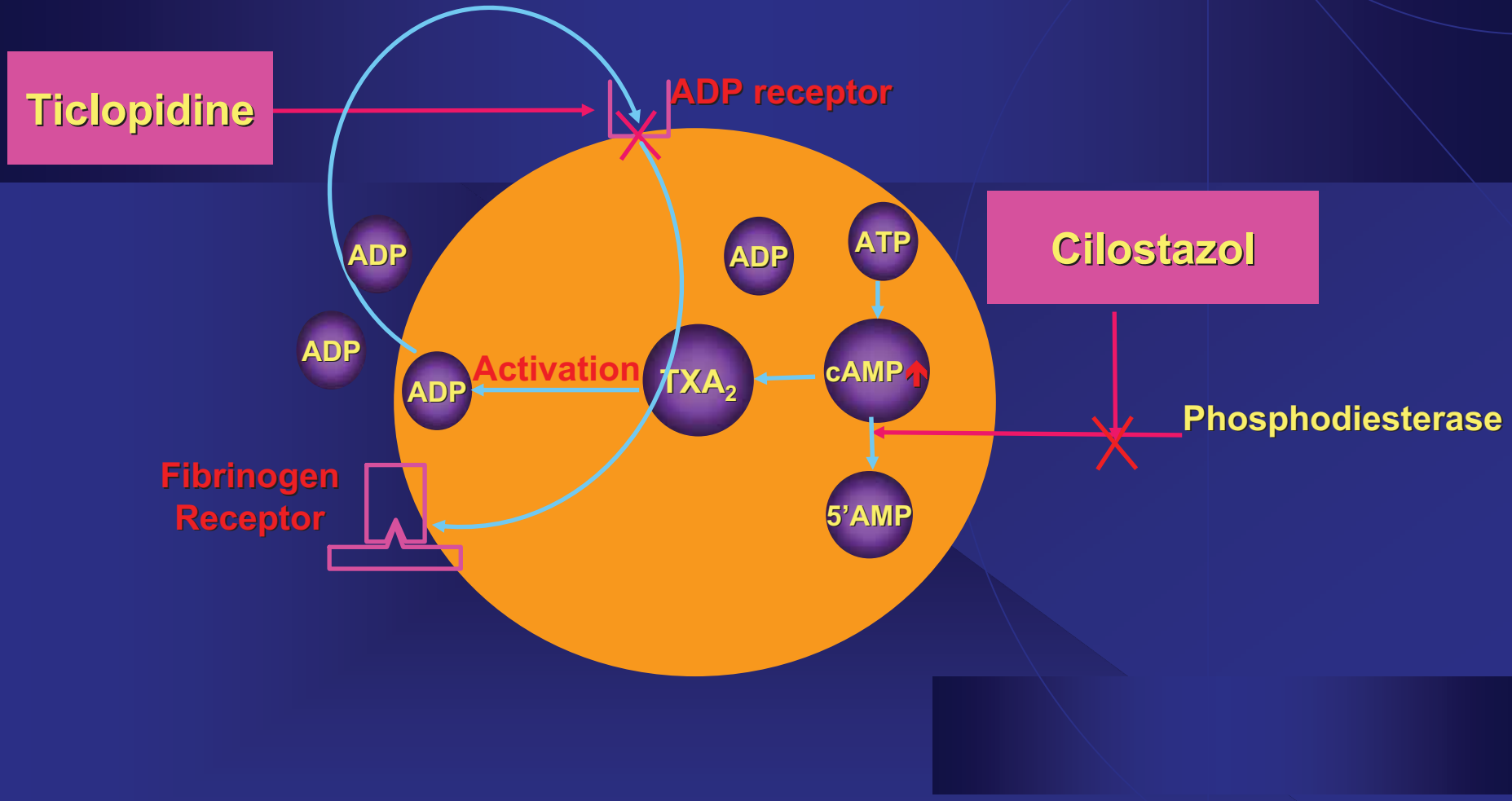
# Background

- Antiplatelet therapy is essential in PCI both in preventing thrombosis and restenosis. The currently used antiplatelet agents include aspirin, ADP inhibitor and GP IIb/IIIa antagonist.
- Cilostazol
  - Newly developed platelet aggregation inhibitor
  - Increases the intracellular concentration of cAMP by inhibiting phosphodiesterase III
  - Decrease neointimal proliferation
  - Decrease MACE and restenosis rate after PCI.

# Antiplatelet Agent Overview

- $TXA_2$ antagonists: Aspirin
- ADP receptor antagonists: Thienopyridine-Ticlopidine and Clopidogrel
- Phosphodiesterase inhibitors: Cilostazol and Dipyridamole
- Glycoprotein (GP) IIb/IIIa receptor antagonists: Eptifibatide, tirofiban and abciximab.
- Other: Thromboxane A2 receptor antagonists; Omega-3 fatty acids; thromboxane synthase inhibitors; Monoclonal antibodies; etc

# Mechanism of Antiplatelet Action of Ticlopidine in Comparison to Cilostazol




ADP = adenosine diphosphate, $TXA_2$ = thromboxane $A_2$

# RACTS-Purpose

To assess the safety and efficacy of cilostazol plus aspirin compared with conventional regimen using ticlopidine plus aspirin in patients undergoing coronary artery stenting.

# RACTS – Inclusion Criteria

- The patient is ≥18 ≤ 75 years old ;
- Symptomatic ischemic heart disease and/or evidence of myocardial ischemia ;
- Target lesion is ≤30mm in length ;
- Target lesion is ≥2.75mm and ≤ 4.0mm in diameter (QCA);
- The target lesions located in a native coronary artery which can be covered preferably by 1 stent (lesion ≤30 mm); two lesions in a vessel is allowed;
- Target lesion stenosis is >50% and <99%;
- No significant (>50%) stenosis proximal or distal to the target lesion that need to be treated during the procedure;

# RACTS – Exclusion Criteria

- MI within 120 hours ;
- Unprotected left main coronary disease with ≥50% stenosis;
- Unstable angina Braunwald Class III B and C
- In-stent restenosis
- Target lesion involves bifurcation
- LVEF ≤30%;
- Totally occluded vessel (TIMI 0)
- Prior stent within 5mm of the target lesion;
- Current treatment with Warfarin®
- Known allergies to aspirin, clopidogrel , ticlopidine, heparin, or stainless steel;

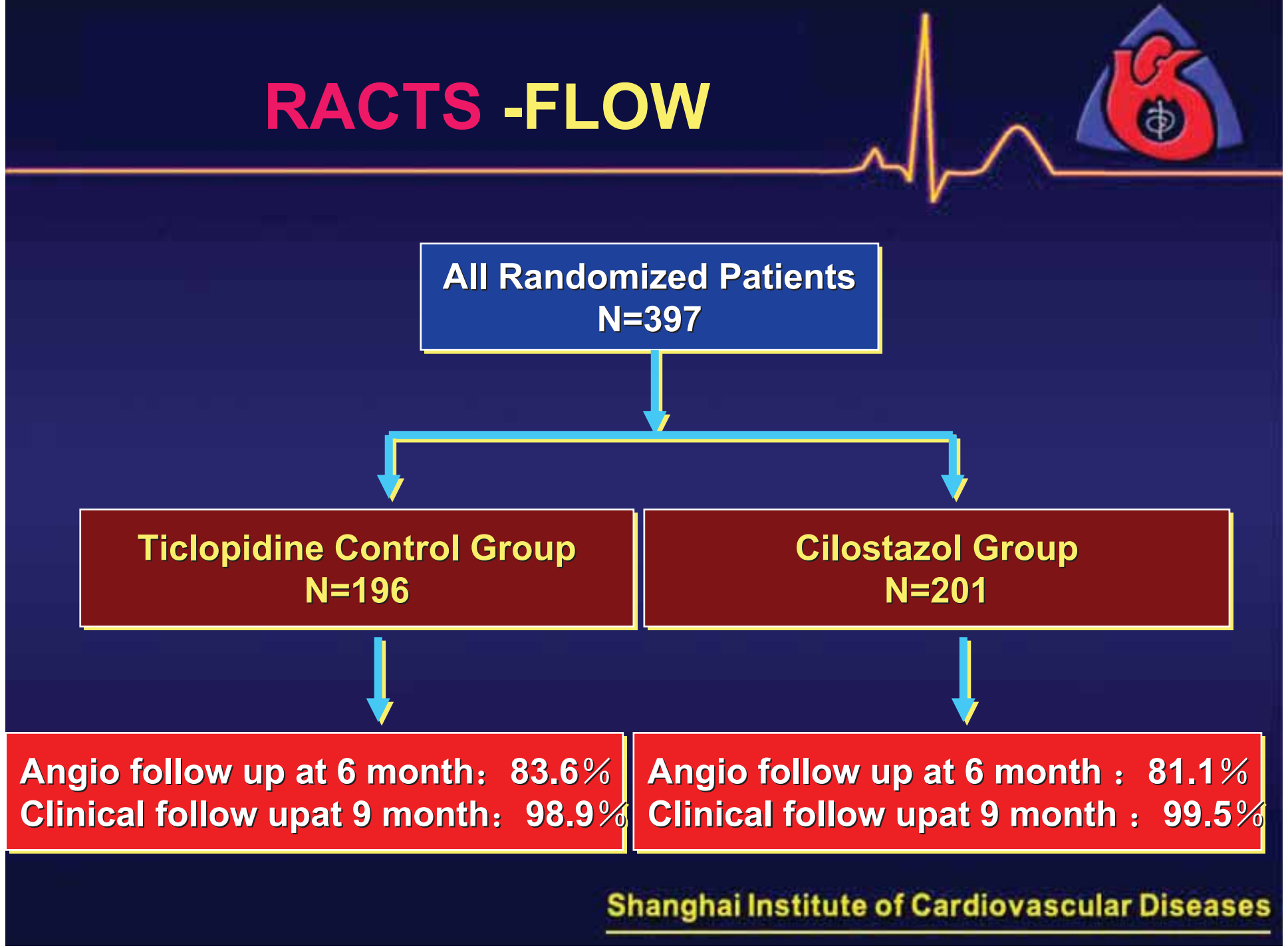
# RACTS -Endpoints

- **Primary Endpoint :** Restenosis rate and MLD after 6 months of procedure.
- **Secondary Endpoint:** Death, myocardial infarction, cerebrovascular event, stent thrombosis, target vessel revascularization (TVR), and bleeding complication at 9 months.
- **Drug related events:** Neutropenia, thrombocytopenia, liver dysfunction, etc., and early discontinuation of the study drug.

# RACTS –Study Design

| | |
|---|---|
| Study Design | Prospective, Randomized , Multi-center |
| Number of Patients | 397 |
| Patient Included | Patients undergoing coronary stenting for coronary stenosis |
| Study Drugs | Cilostazol 100mg twice daily for 6 months<br>Ticlopidine 250mg twice daily for 1 month |
| Concomitant Drugs | Aspirin 100mg once daily |
| Investigational Centers | 7 Medical Centers in P.R.China |

# RACTS -FLOW

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# RACTS

## - Baseline Demographic Characteristics

| | Cilostazol N=201 | Ticlopidine N=196 |
|---|---|---|
| Mean age(years) | 59.2±10.0 | 60.4± 9.9 |
| Male sex(%) | 83.6 | 79.1 |
| Diabetes Mellitus(%) | 11.4 | 12.2 |
| Hyperlipidemia(%) | 23.4 | 29.6 |
| Hypertension(%) | 55.7 | 60.2 |
| Prior MI(%) | 39.3 | 34.7 |
| Ever smoked/Current smoker(%) | 47.3 | 40.8 |
| Family history (%) | 13.9 | 10.2 |

ALL P>0.05

# RACTS
## - Concomitant Medications

| | Cilostazol(%) N=201 | Ticlopidine(%) N=196 |
|---|---|---|
| Nitrate | 85.5 | 81.6 |
| ACE inhibitor | 60.0 | 62.2 |
| Beta-blocker | 64.0 | 65.8 |
| Lipid-lowering agent(HMG-CoA) | 70.7 | 78.1 |
| Calcium-channel blocker | 34.7 | 38.4 |

ALL P>0.05

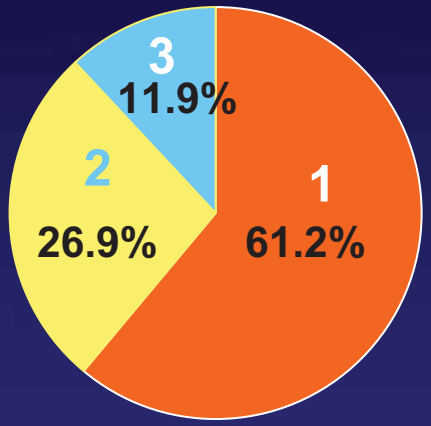
# RACTS
## - Stent Procedural Details

| | Cilostazol(%) N=201 | Ticlopidine(%) N=196 |
|---|---|---|
| Target Lesion Calcified | 24(9.6) | 21(9.1) |
| Diffuse target Lesion | 49(19.7) | 42(18.1) |
| Number of Stent Implant | 159(79.1) | 161(82.1) |
| 1 | 36(17.9) | 34(17.3) |
| 2 | 6(3.0) | 1(0.5) |
| 3 | | |

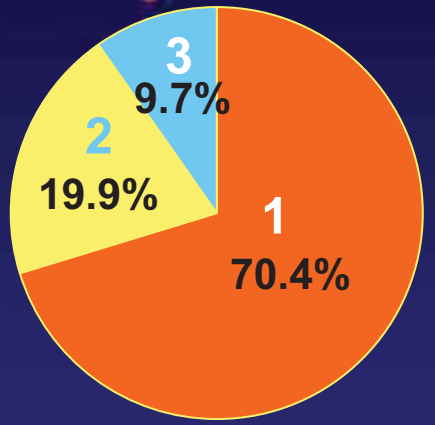
ALL P>0.05

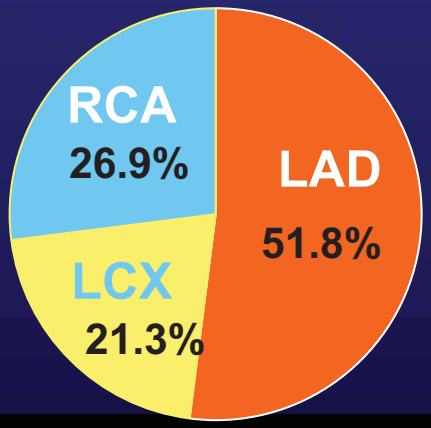
# RACTS

## - Baseline Angiographic Characteristics



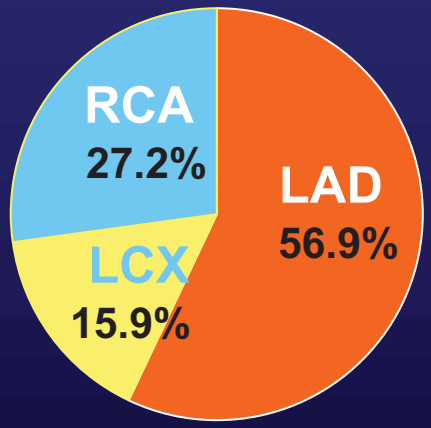

No. of diseased vessels, P=0.150




Cilostazol+Aspirin

Target Vessel location,P=0.301




Ticlopidine +Aspirin

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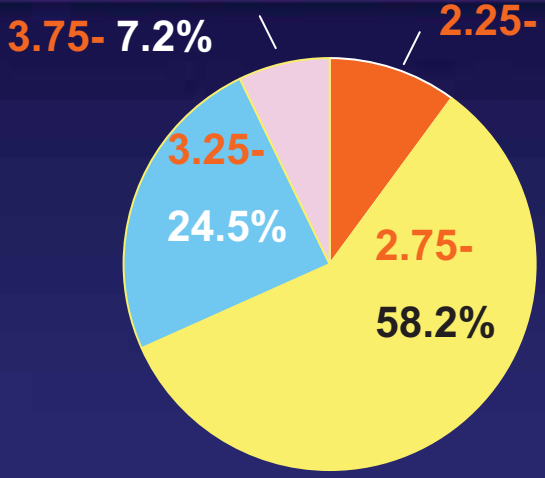
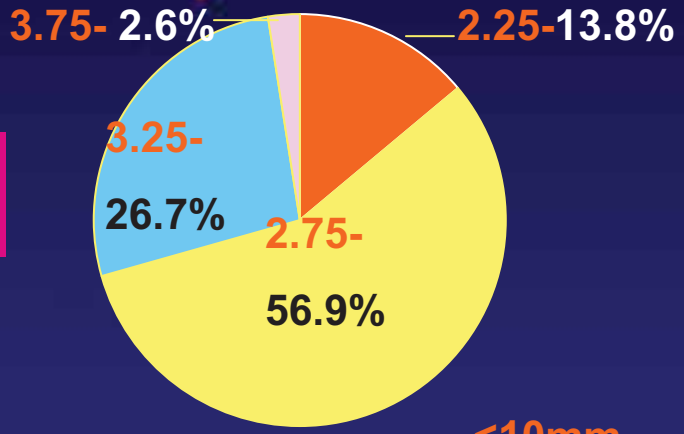
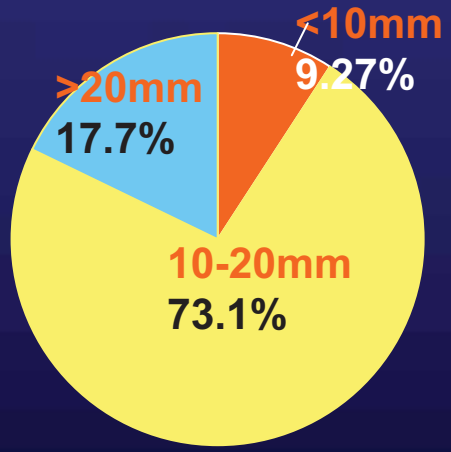
# RACTS

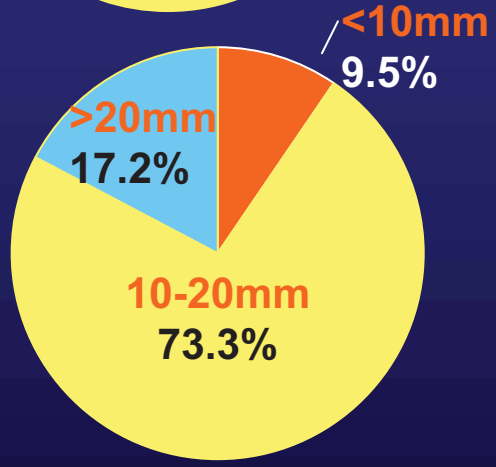
## - Baseline Angiographic Characteristics




**Reference diameter**
**P=0.076**




**Lesion length**
**P=0.990**

**Cilostazol+Aspirin**

**Ticlopidine +Aspirin**

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# RACTS
## - Angiographic Results at 6 months

| | Cilostazol N=163 | Ticlopidine N=164 | P |
|---|---|---|---|
| Minimal lumen diameter (mm) | | | |
| Before | 0.42±0.35 | 0.38±0.33 | 0.324 |
| After | 3.11±0.35 | 3.06±0.35 | 0.168 |
| Follow-up | 2.31±1.06 | 2.10±1.16 | 0.057 |
| Stenosis (%) | | | |
| Before | 76 ±11 | 77±11 | 0.342 |
| After | 5.6 ±6.4 | 4.9±7.2 | 0.142 |
| Follow-up | 34 ±25 | 38±30 | 0.190 |

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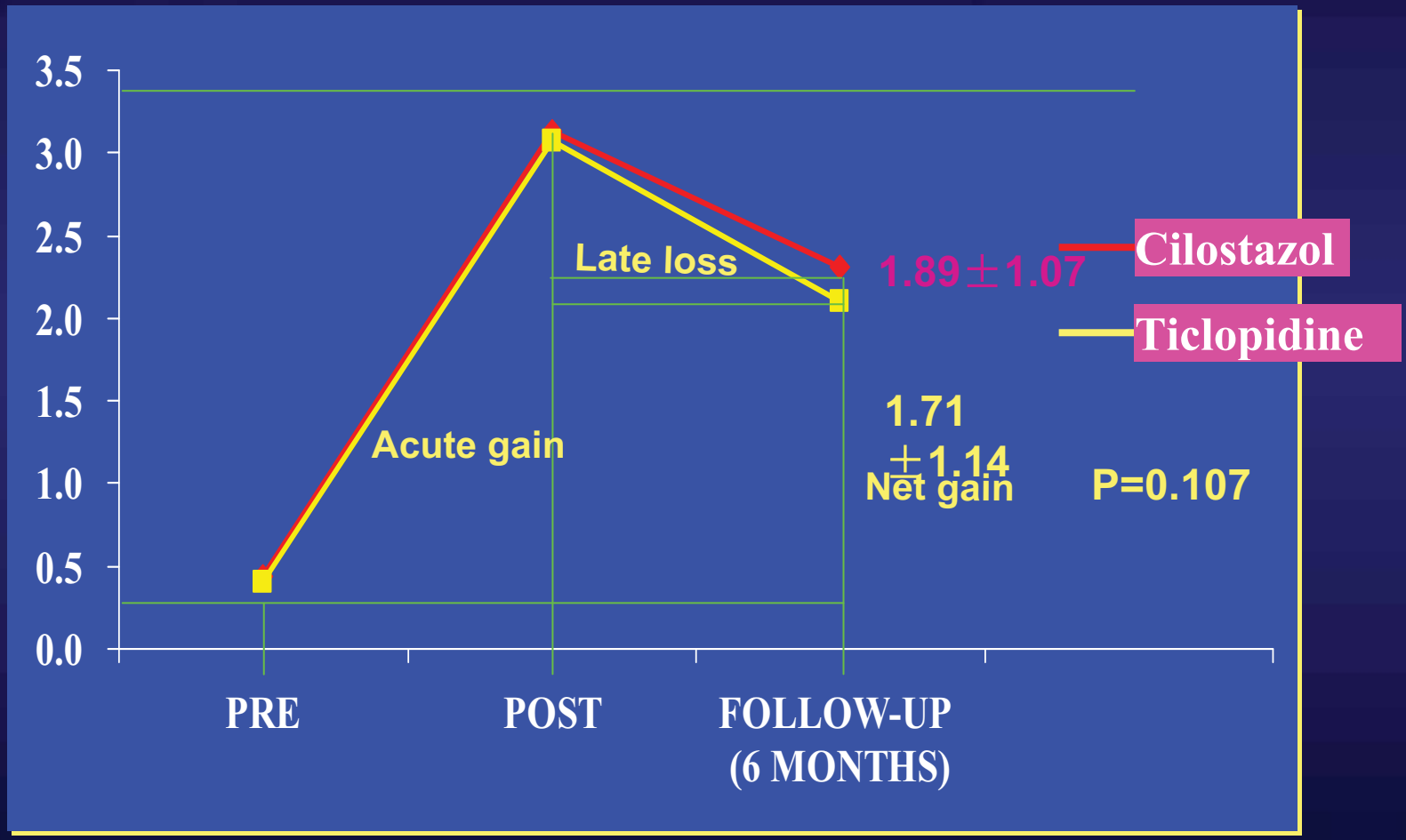
# RACTS
## - Angiographic Results at 6 months

| | Cilostazol N=163 | Ticlopidine N=164 | P |
|---|---|---|---|
| Acute lumen gain (mm) | 2.69±0.45 | 2.67±0.43 | 0.727 |
| Late lumen loss (mm) | 0.80±1.00 | 0.96±1.08 | 0.120 |
| Net lumen gain (mm) | 1.89±1.07 | 1.71±1.14 | 0.107 |
| Loss index (late loss/acute gain) | 0.30±0.39 | 0.36±0.41 | 0.125 |

# RACTS – QCA analysis




ALL P>0.05

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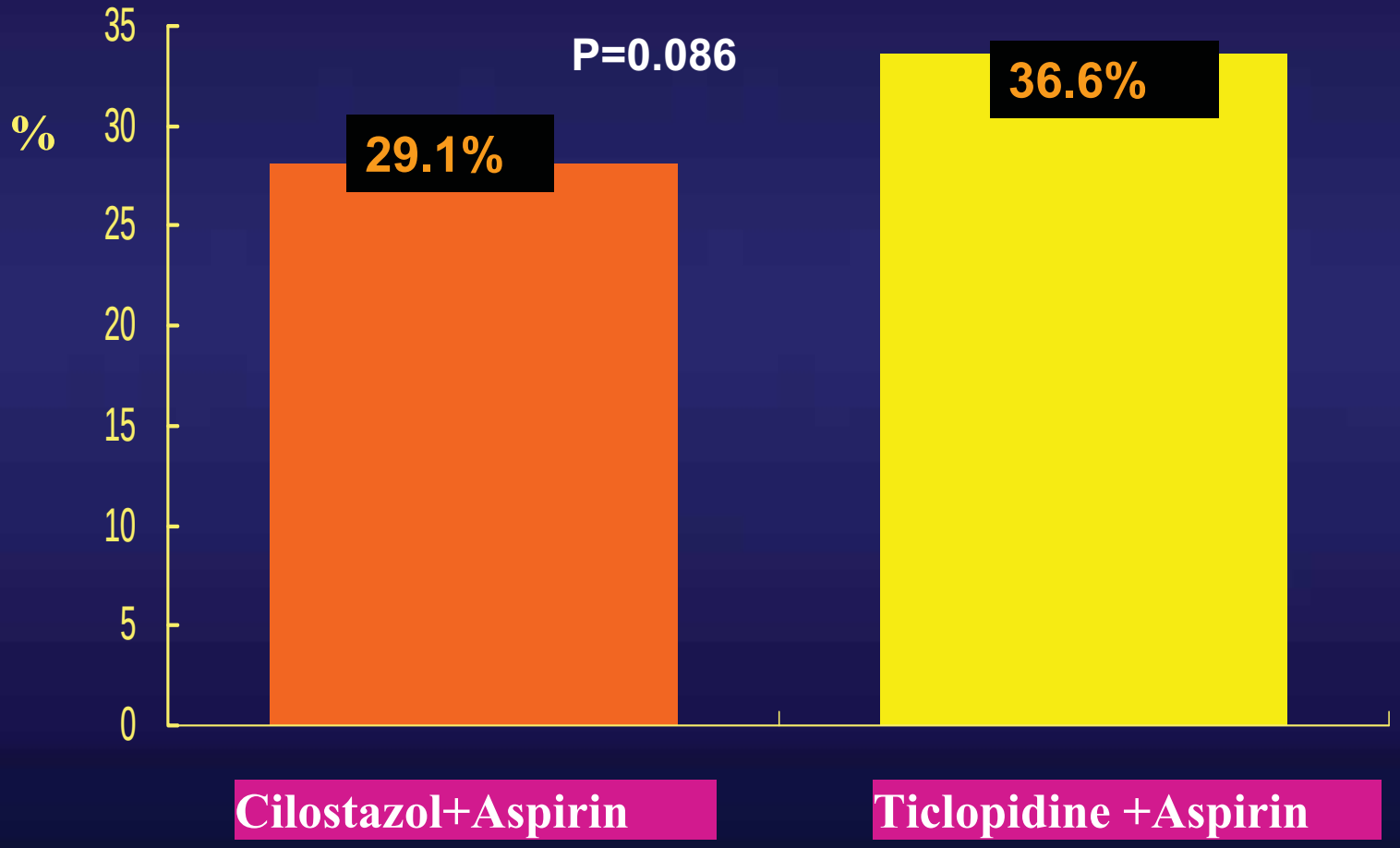
# RACTS
## - Angiographic Restenosis at 6 months

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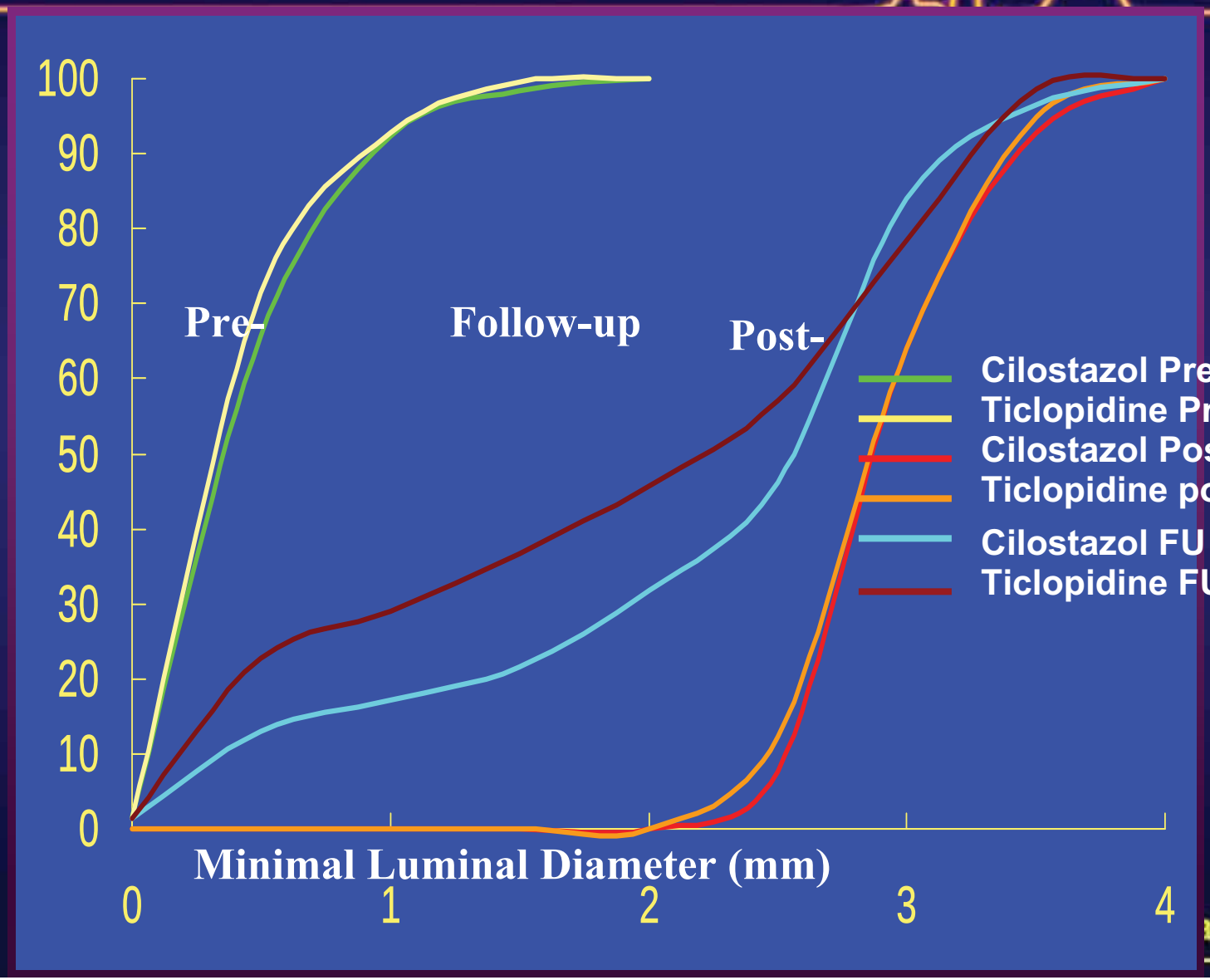
# RACTS

## -Cumulative Frequency Distribution Curves



# RACTS -Stent Thrombosis

| | Cilostazol N=201 | Ticlopidine N=196 |
|---|---|---|
| Acute(<24hour) | 0.5%(1) | 0 |
| Subacute(1~30days) | 0.5%(1) | 0.5%(1) |
| Late (>30days) | 0 | 0.5%(1) |
| Total | 1.0%(2) | 1.0%(2) |

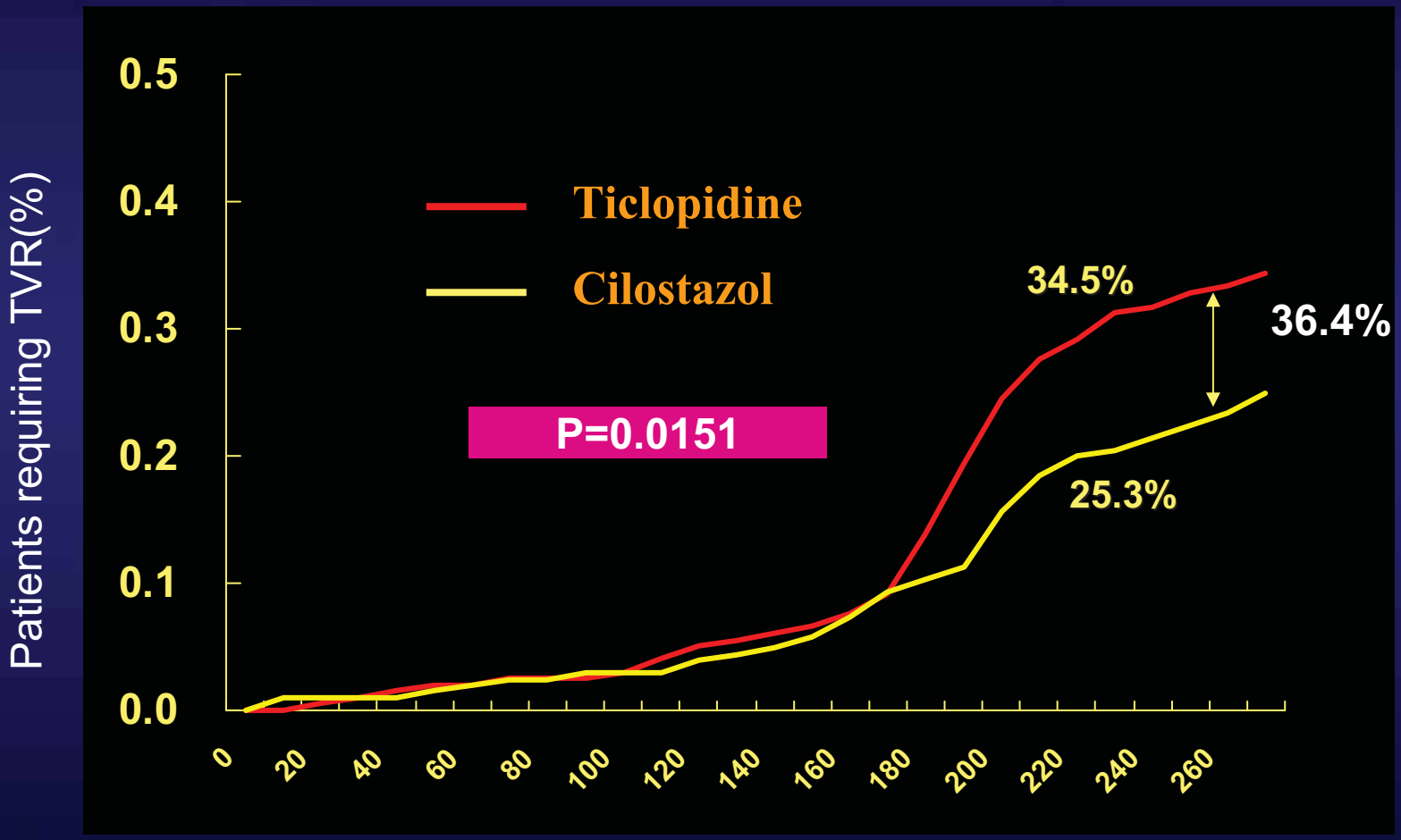
# RACTS

## - Clinical Events During 9 Months

| | Cilostazol N=201 | Ticlopidine N=196 |
|---|---|---|
| Death | 0(0.0) | 2(1.0) |
| Myocardial infraction | 2 (1.0) | 1(0.5) |
| Cerebrovascular thrombosis | 1(0.5) | 1(0.5) |
| Cerebrovascular Hemorrhage | 0 (0.0) | 1(0.5) |
| Coronary bypass surgery | 0 (0.0) | 0 (0.0) |
| TVR per patient* | 46（22.9） | 64（32.7） |
| TVR per vessel* | 50(25.3) | 67 (34.5) |

*P<0.05

# RACTS-Cumulative curve for TVR per patients during 9 months follow-up

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# RACTS- Safety

| | Cilostazol (%)N=201 | Ticlopidine (%)N=196 |
|---|---|---|
| Composite any of the below | 10(5.0) | 19(9.7) |
| Neutropenia | 0(0.0) | 2(1.0) |
| Thrombocytopenia | 0(0.0) | 0(0.0) |
| Skin rash | 4(2.0) | 6(3.1) |
| Minor bleeding complication | | |
| Hematuria | 0(0.0) | 1(0.5) |
| Gingival bleeding | 0(0.0) | 1(0.5) |
| Liver dysfunction | 2(1.0) | 5(2.6) |
| Headache(discontinuing drug) | 2(1.0) | 0(0.0) |
| Nausea | 2(1.0) | 4(2.0) |

ALL P>0.05

# RACTS-Conclusion

- Cilostazol has equivalent beneficial effects to ticlopidine in 6 month restenosis rate and the frequency of short-term MACE.
- Cilostazol significantly reduced the long-term TVR rates compared to ticlopidine(time course?).
- Cilostazol tended to have less side effect rate but more headache compared to ticlopidine.
- Cilostazol may be used as a complementary drug for antiplatelet therapy when patient is allergic to ADP inhibitors.