Prevention of Coronary Stent Thrombosis and Restenosis

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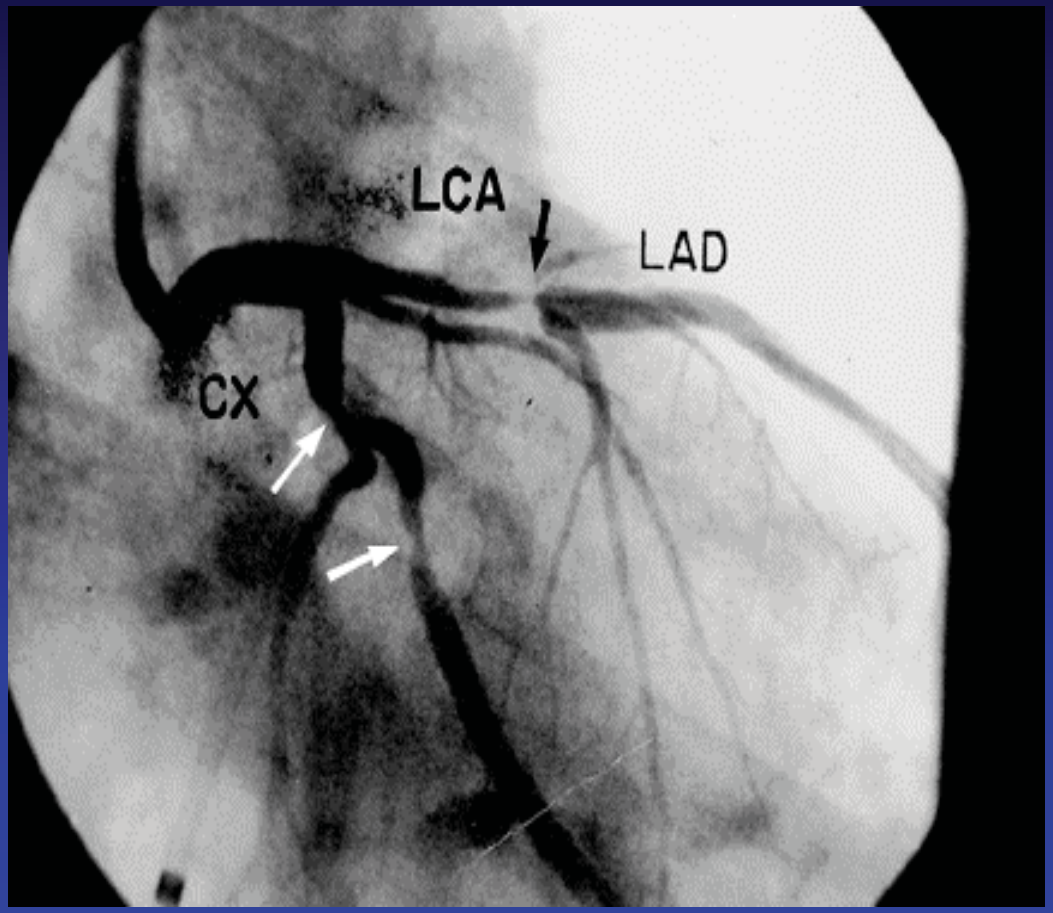
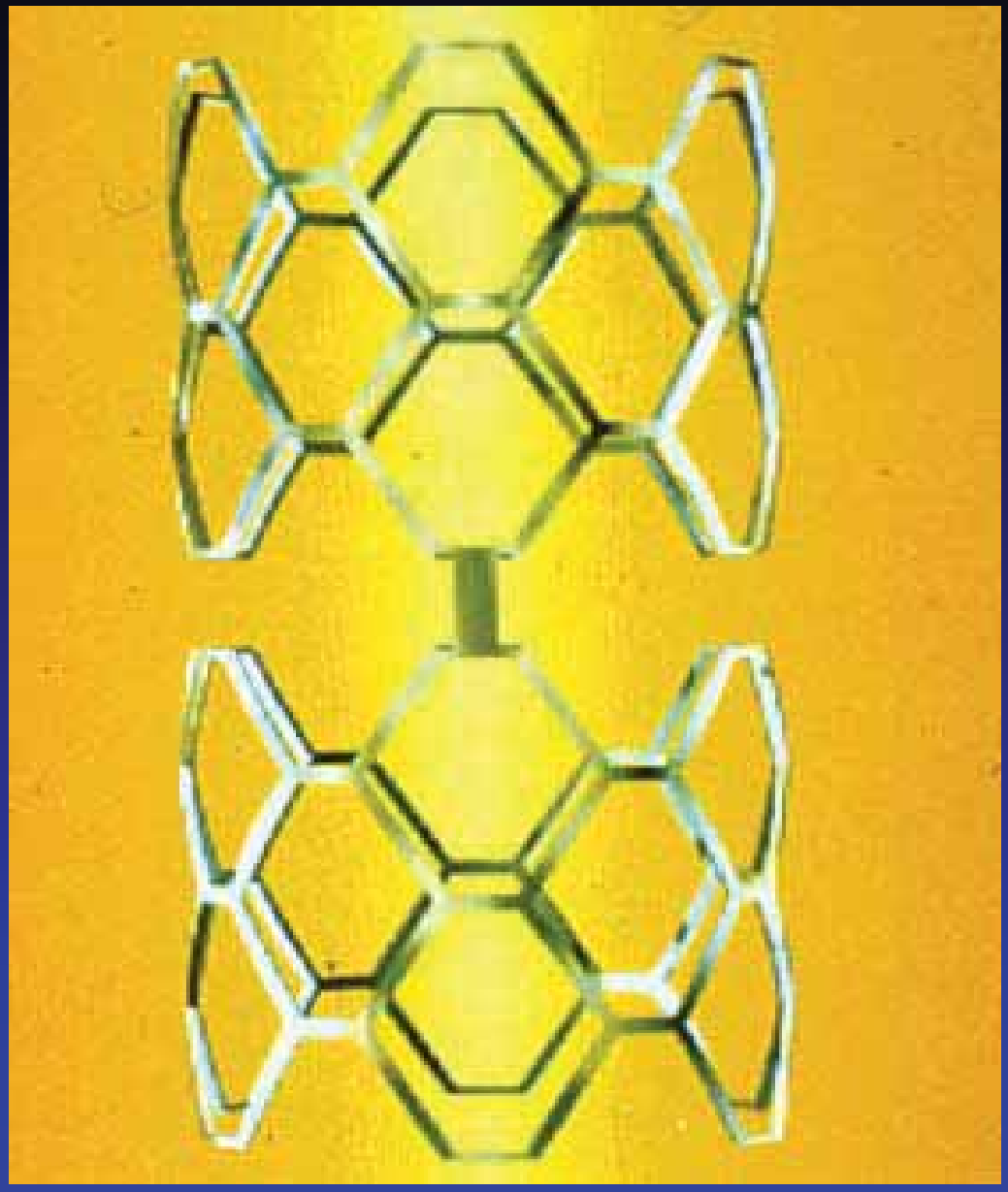
9/12/03

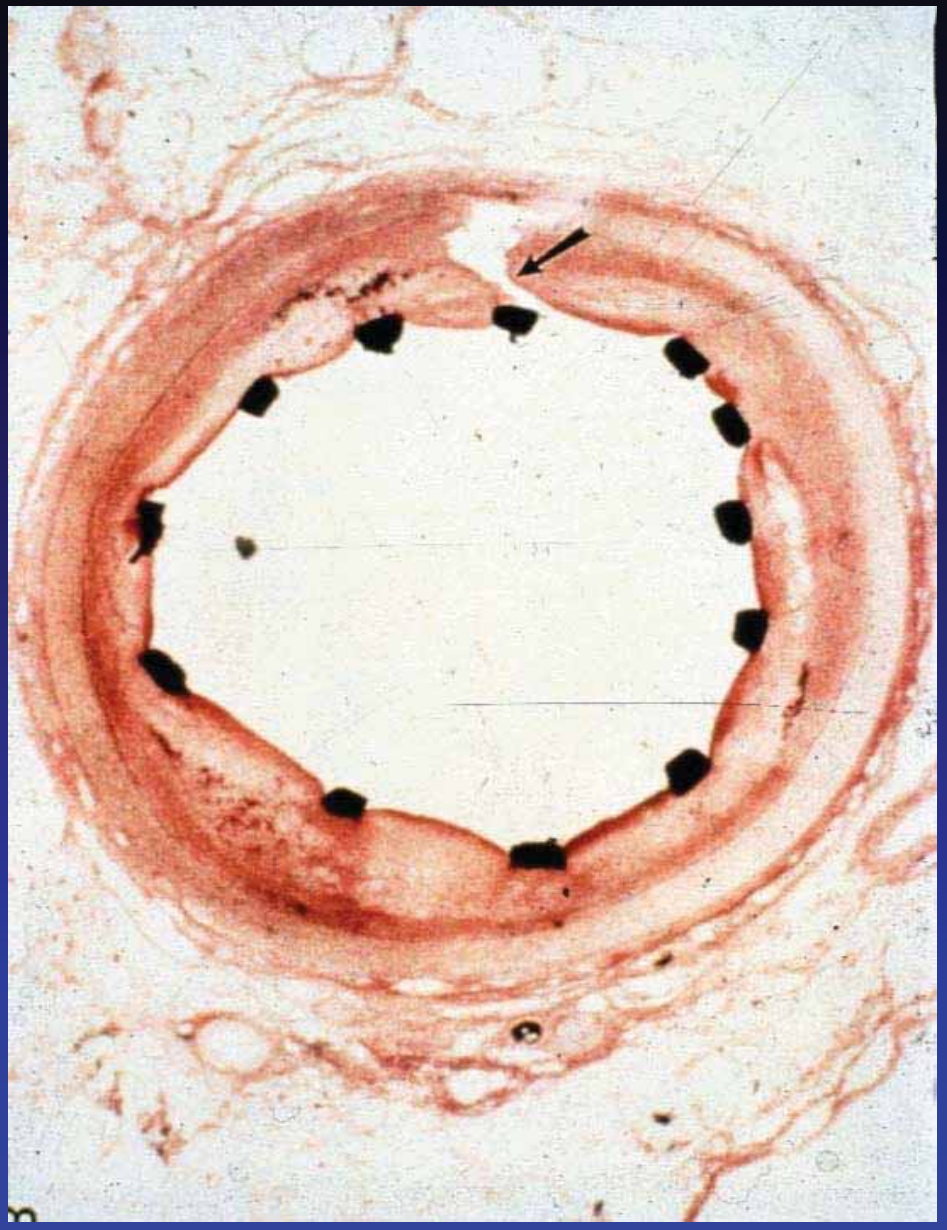
Coronary Artery Disease :

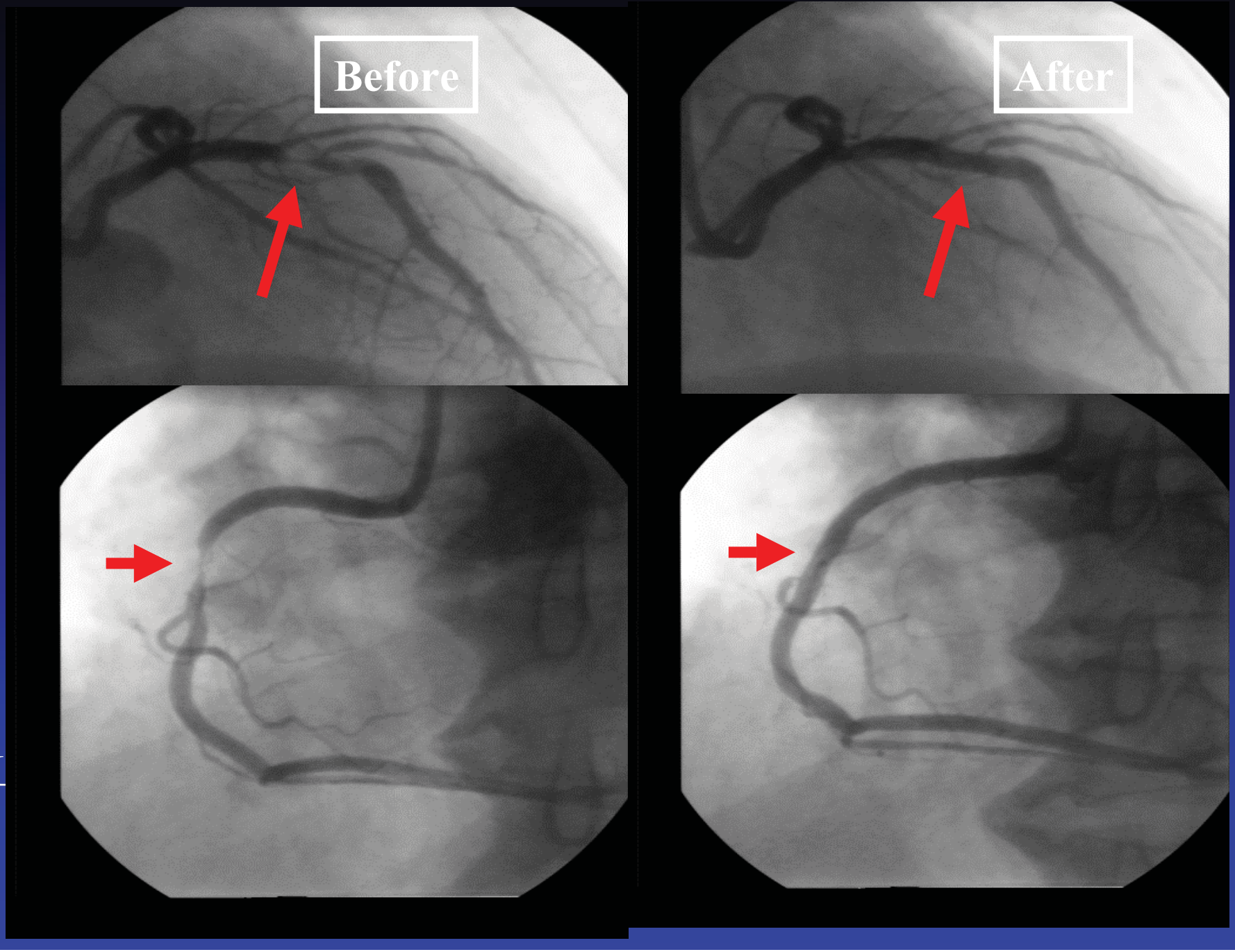


Percutaneous Coronary Intervention (PCI)

- Balloon Angioplasty
- Atherectomy
- Stenting



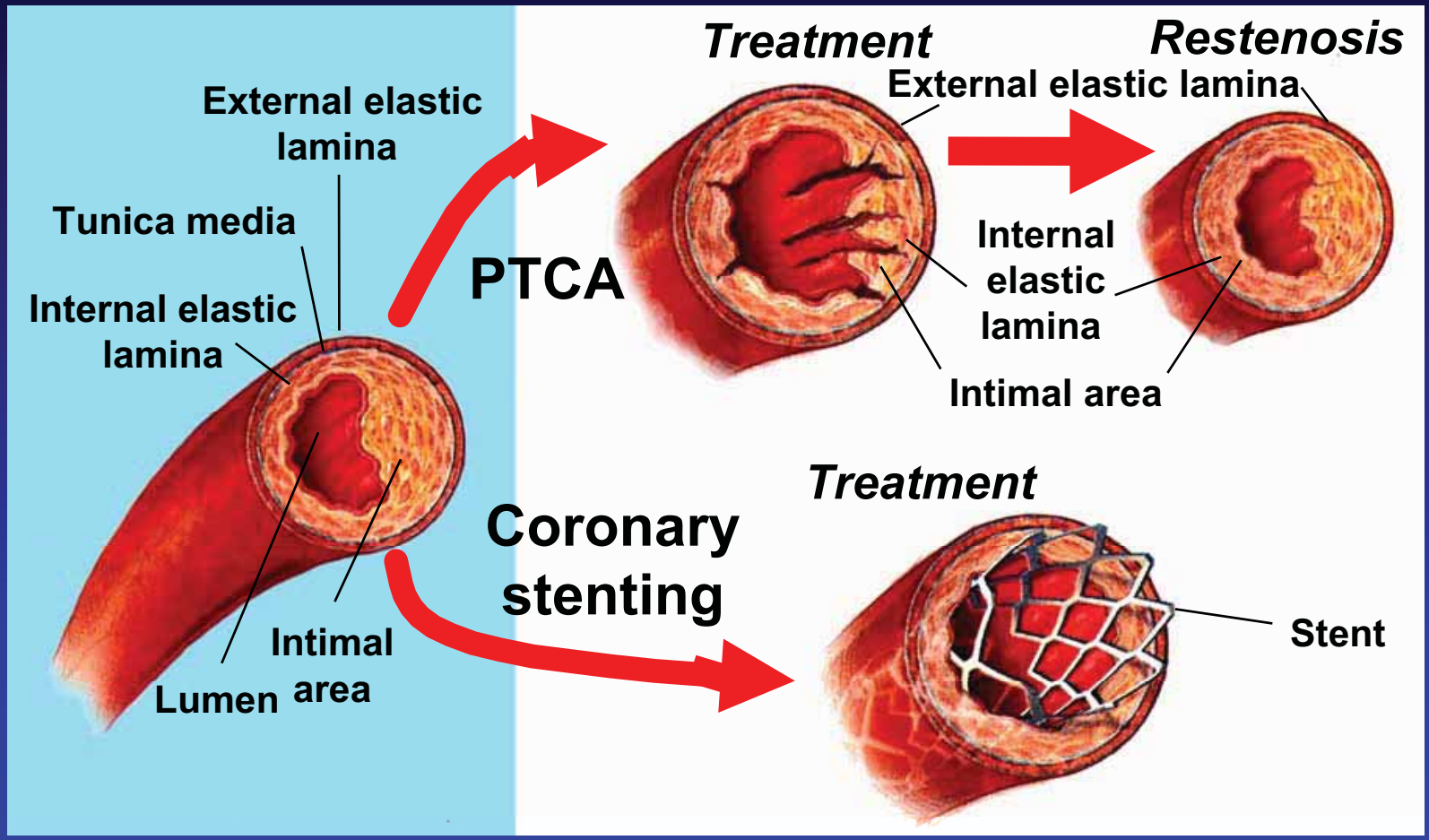



Before
After

Coronary Stenting vs Conventional PTCA

- Percutaneous transluminal coronary angioplasty (PTCA) has been established as a safe and effective therapeutic modality.
- More recently, coronary stent implantation has been the preferred therapy because of the additional benefits such as
  - Prevention of abrupt reocclusion
  - Lower rates of restenosis
  - Less frequent need for repeat revascularization of the original lesion

Lower Rate of Restenosis with Stenting
(6 month follow-up)



Coronary Stent

- Bail-out device
- Anti-restenosis device

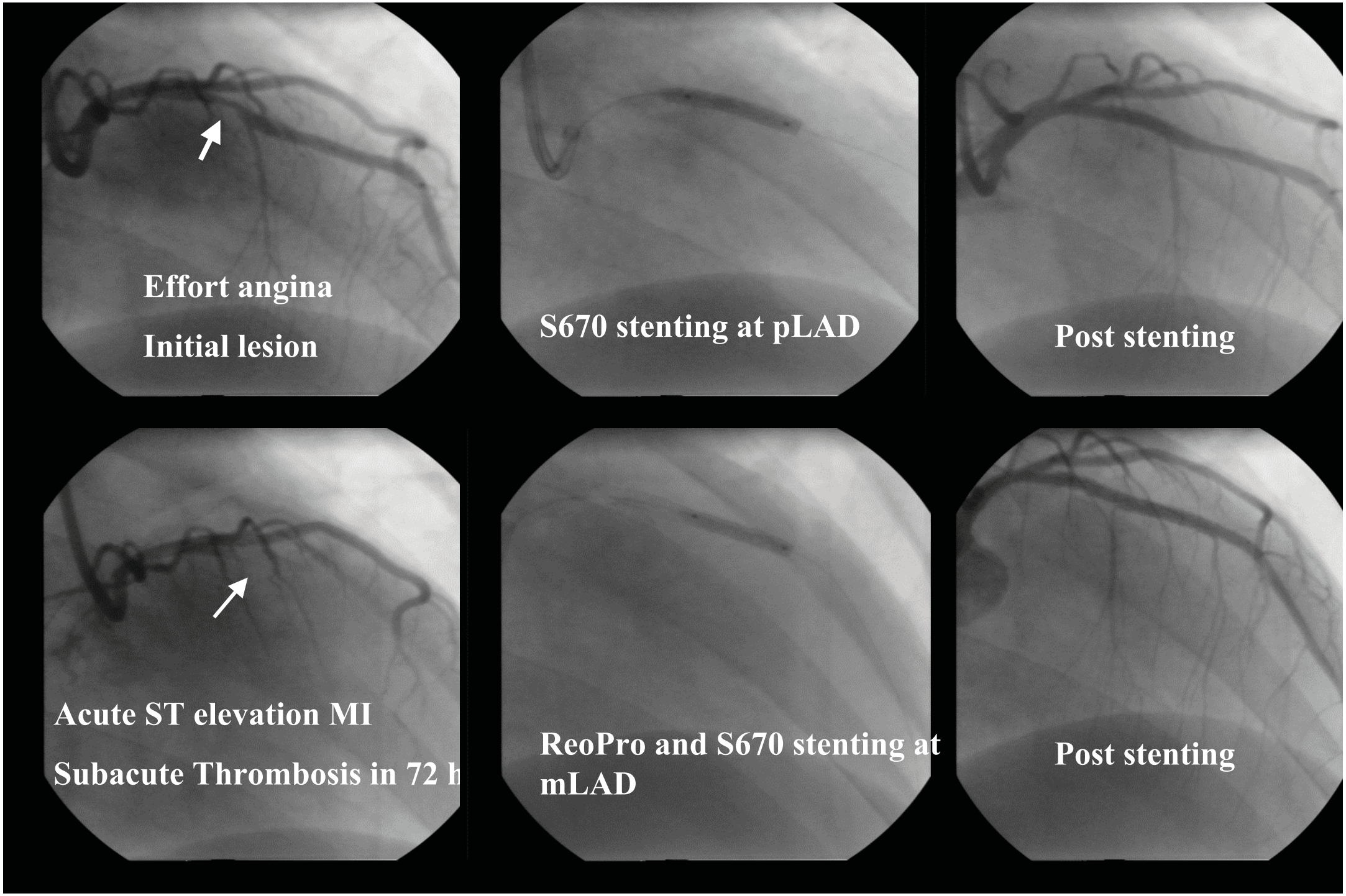
- Stent thrombosis
- In-stent restenosis
- Additional cost
- Efficacy not proven in lesions with complex morphologies

Time scale of coronary stent thrombosis and long-term risk

Stent thrombosis may occur as a direct result of endothelial injury or disruption of the coronary lesion

Acute thrombosis	Subacute thrombosis	Atherothrombotic events
Within 24 hours	Within 4 weeks	Long-term
Incidence: 0.6%	Incidence: 0.5%-5.7%	Incidence (5 years): 43%*

*Cardiac events: death, MI, CABG and repeat angioplasty


Effort angina
Initial lesion
S670 stenting at pLAD
Post stenting
Acute ST elevation MI
Subacute Thrombosis in 72 h
ReoPro and S670 stenting at mLAD
Post stenting

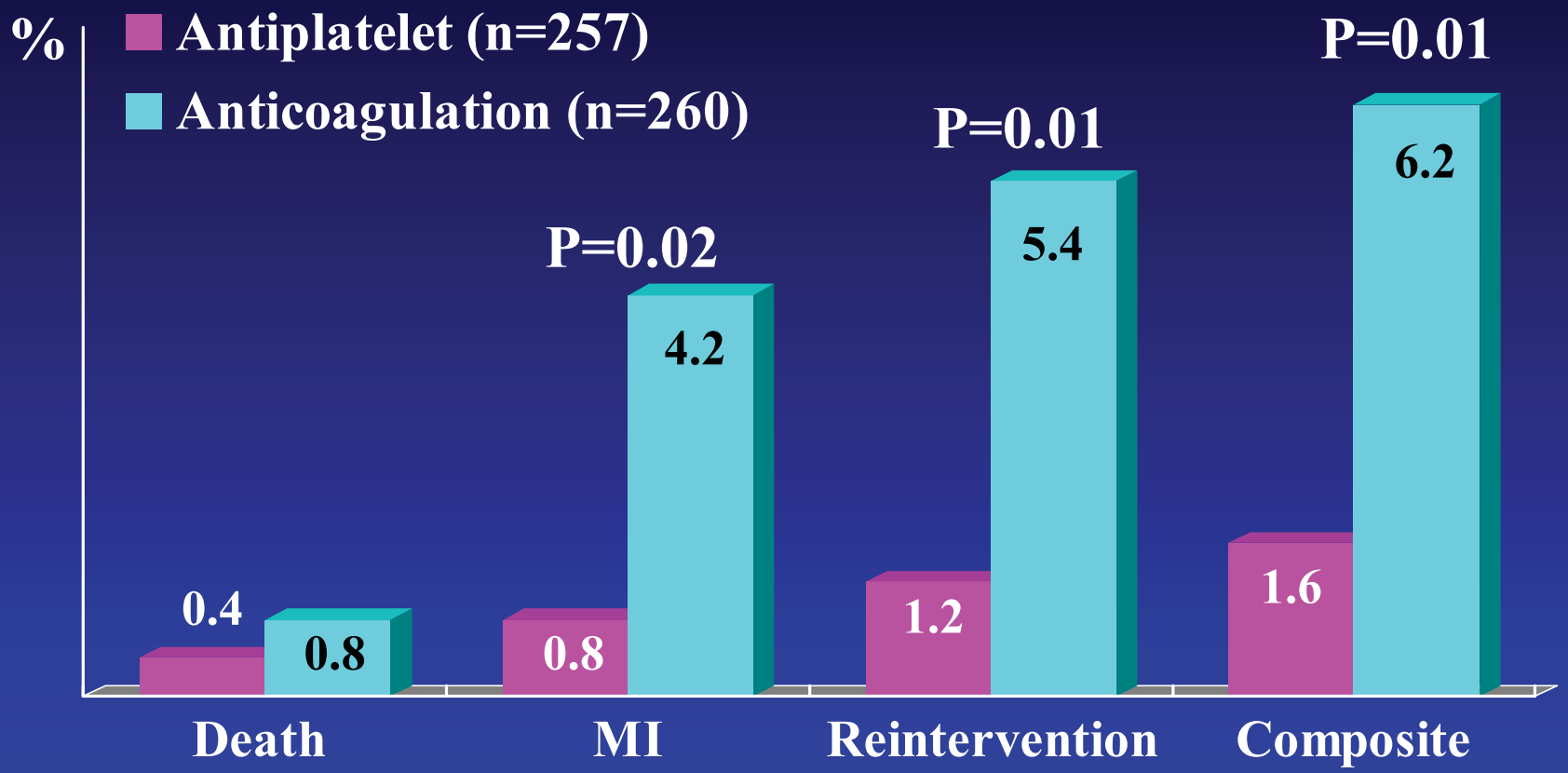
Clinical Consequences of Stent Thrombosis

- Short-term mortality rate; up to 20 - 25%
- Major myocardial infarction in 60 – 70%
- Additional hospital cost; 11,000 USD per patient excluding indirect costs related to stent thrombosis

Anticoagulation regimens in prevention of stent thrombosis

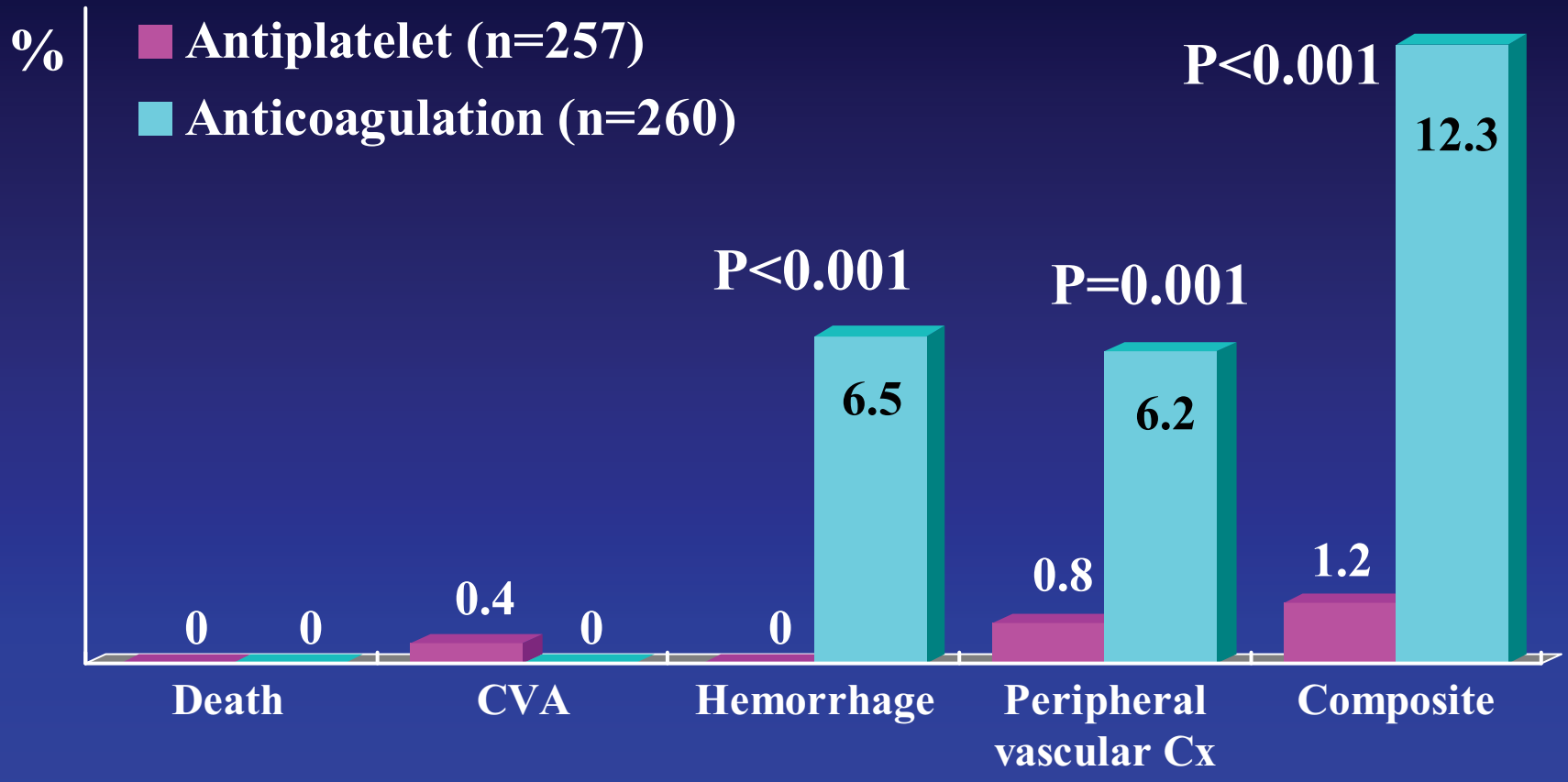
- **Aggressive anticoagulant regimens consisted of multiple agents, e.g. warfarin, heparin, LMW heparin**
- **Drawbacks of early regimens**
  - ***Not optimally effective against stent thrombosis***
  - ***Significant risk of bleeding complications***
  - ***Long-term management required to stabilize oral anticoagulant dose***

ISAR: Primary Cardiac End Point



Schömig A, N Engl J Med 1996;334:1084-9

ISAR: Primary Noncardiac End Point



Schömig A, N Engl J Med 1996;334:1084-9

FANTASTIC Study

(Full Anticoagulation versus Aspirin and Ticlopidine)

Randomized, multicenter trial

- Conventional anticoagulation (n=236)
- Antiplatelet therapy (n=249)

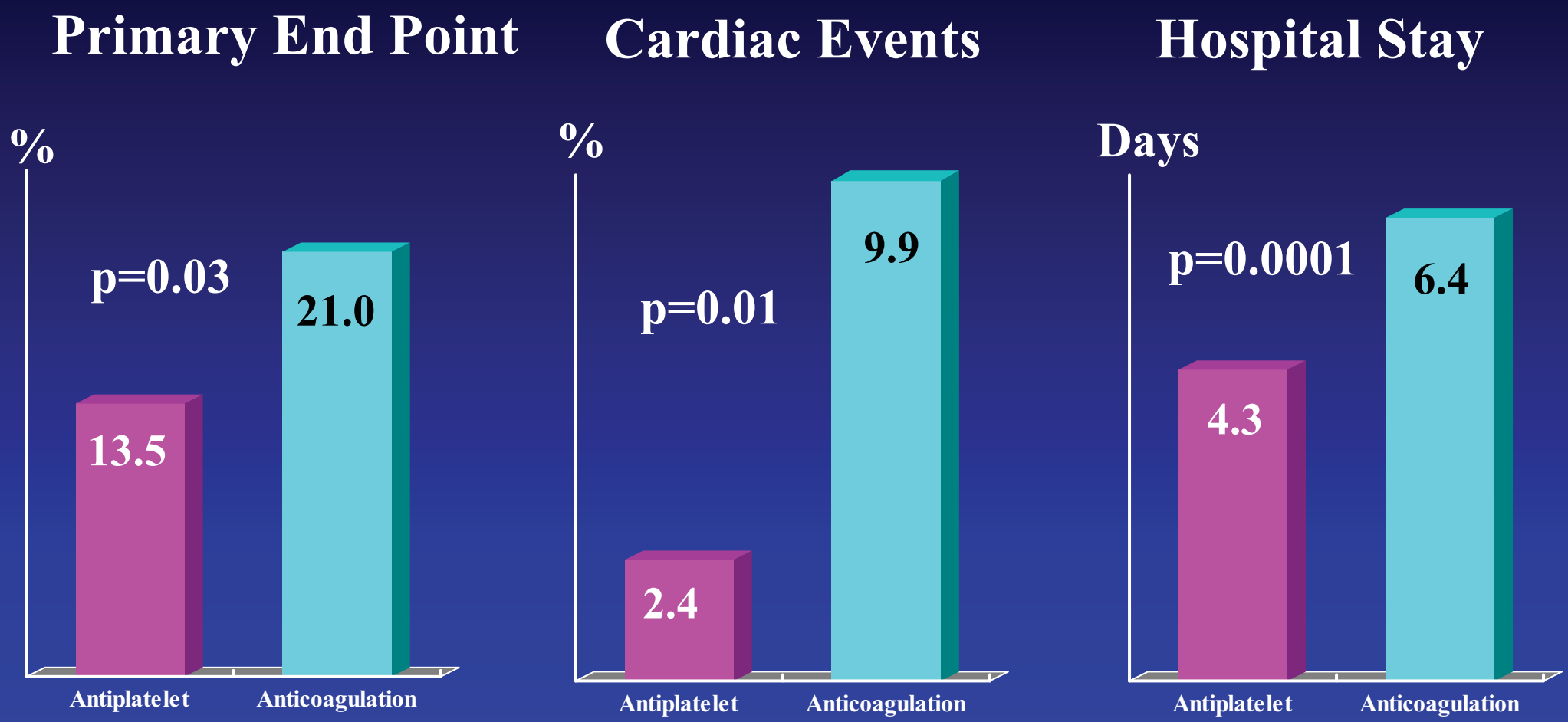
Primary End Point: Bleeding or peripheral vascular complications

Secondary End Point: Cardiac events and duration of hospitalization

Stent: Wiktor stent (Elective 58%, Unplanned 42%)

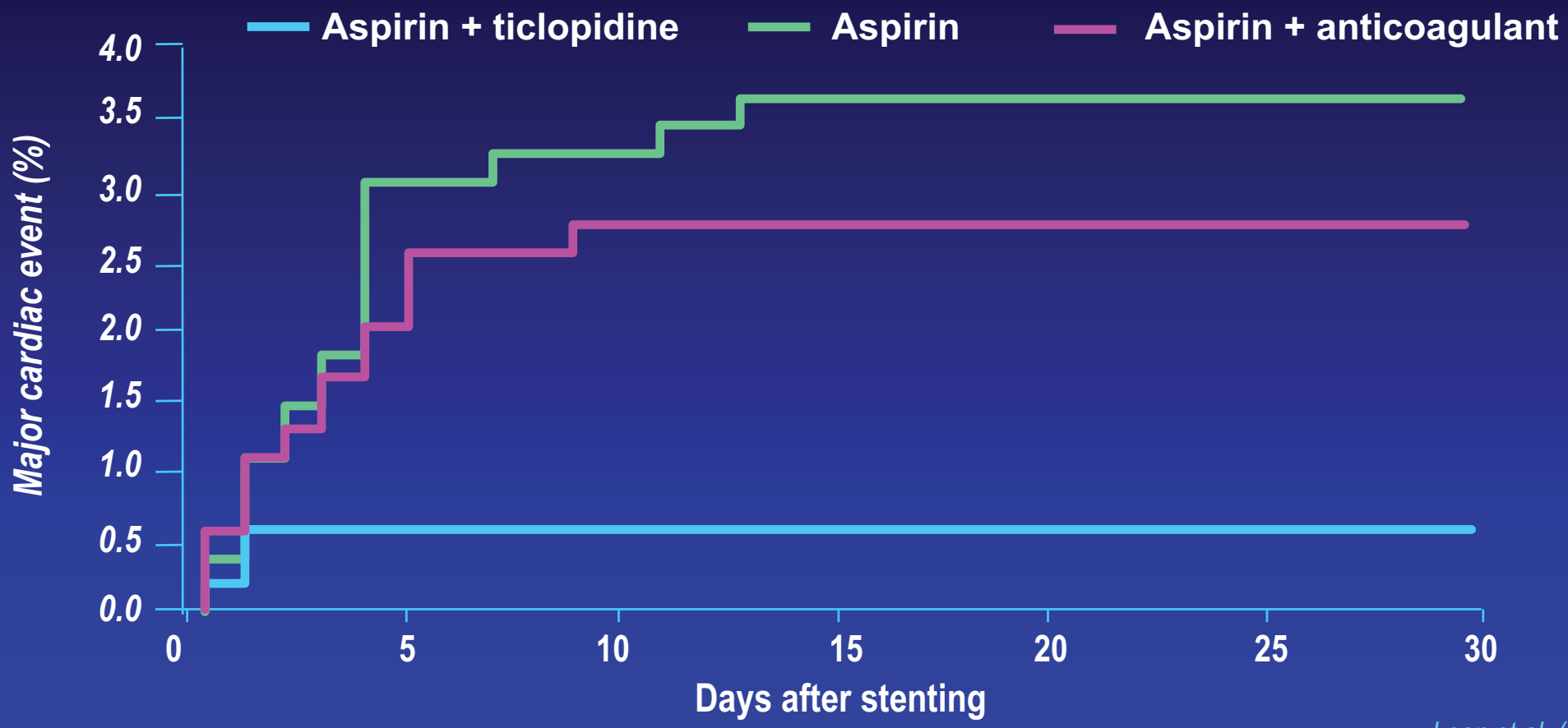
Bertrand ME, Circulation 1998;98:1597-1603

FANTASTIC Study: Results



ADP receptor antagonist therapy

The optimal combination therapy



Leon et al. (1998)

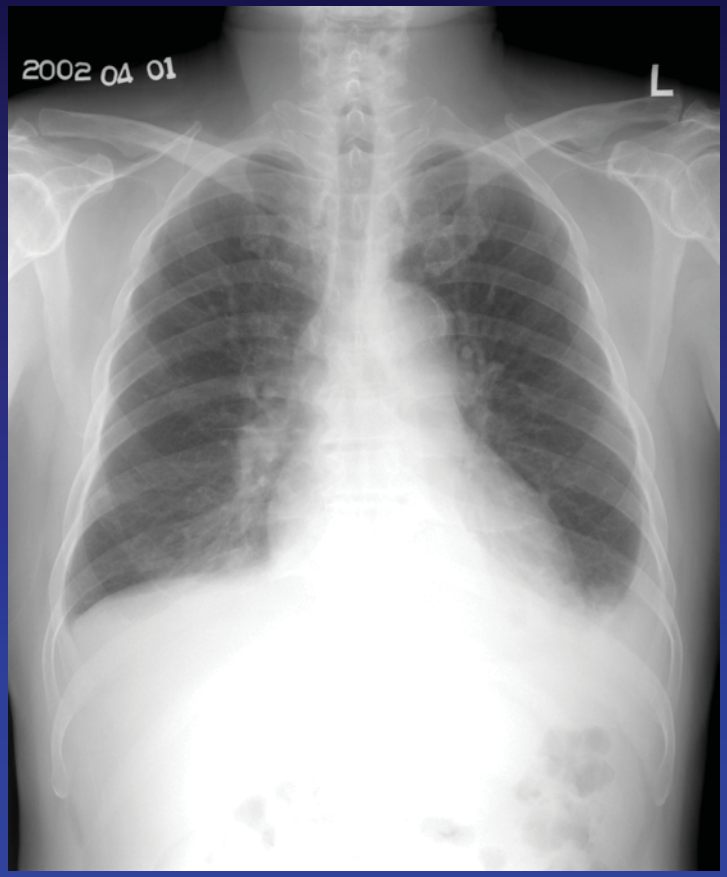
Issues with ticlopidine in stenting

- **Delayed onset of action *(250 mg b.i.d.)***
  - **Antiplatelet effect not seen until day 3-4[1]**
- **Tolerability / Safety**
  - **Gastrointestinal side effects**
  - **Rash**
  - **Diarrhea**
  - **Rare but severe hematological side effects [2 - 3]**

[1] Schuhlen et al. (1998a), [2] Moses (1998), [3] Feldman et al. (1998)

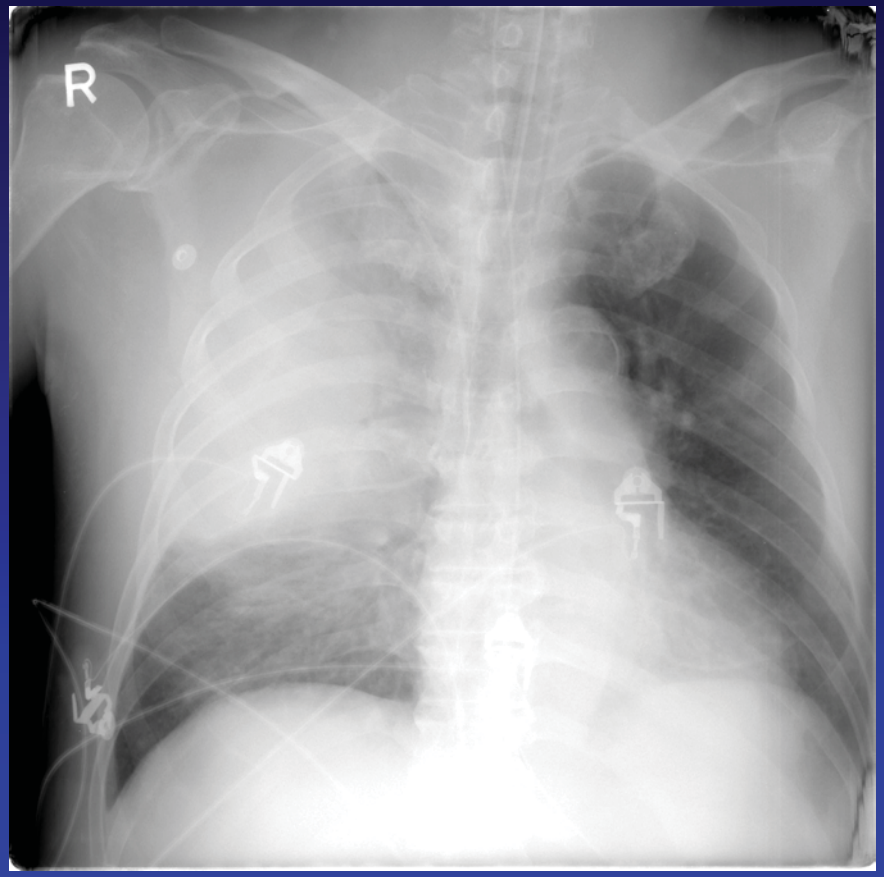
Ticlopidine-induced Leukopenia

Before stenting



WBC: 6,000/mm^3

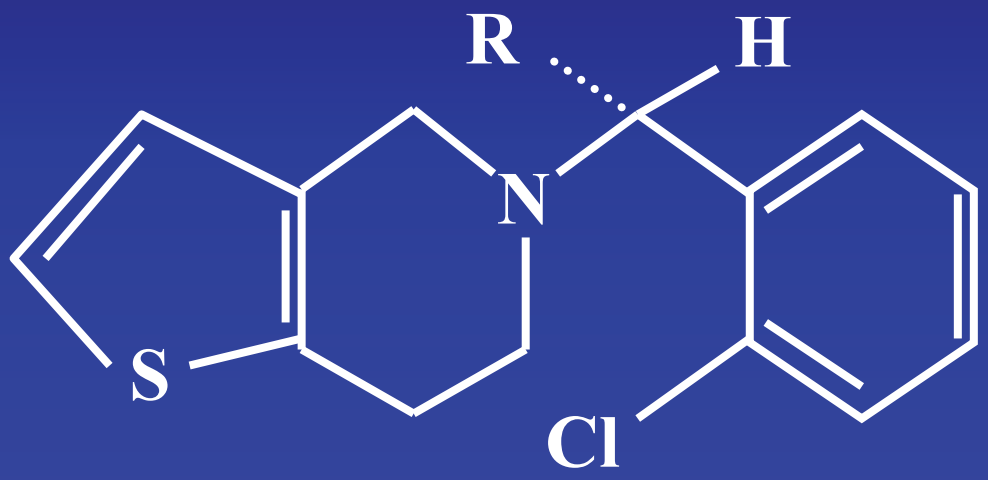
Two weeks after stenting



WBC: 200/mm^3

Clopidogrel

- Clopidogrel blocks ADP-mediated platelet activation, thereby affecting ADP-dependent activation of the GP IIb/IIIa complex
- Its activity is greater than that of ticlopidine in animal thrombosis models



R=H Ticlopidine

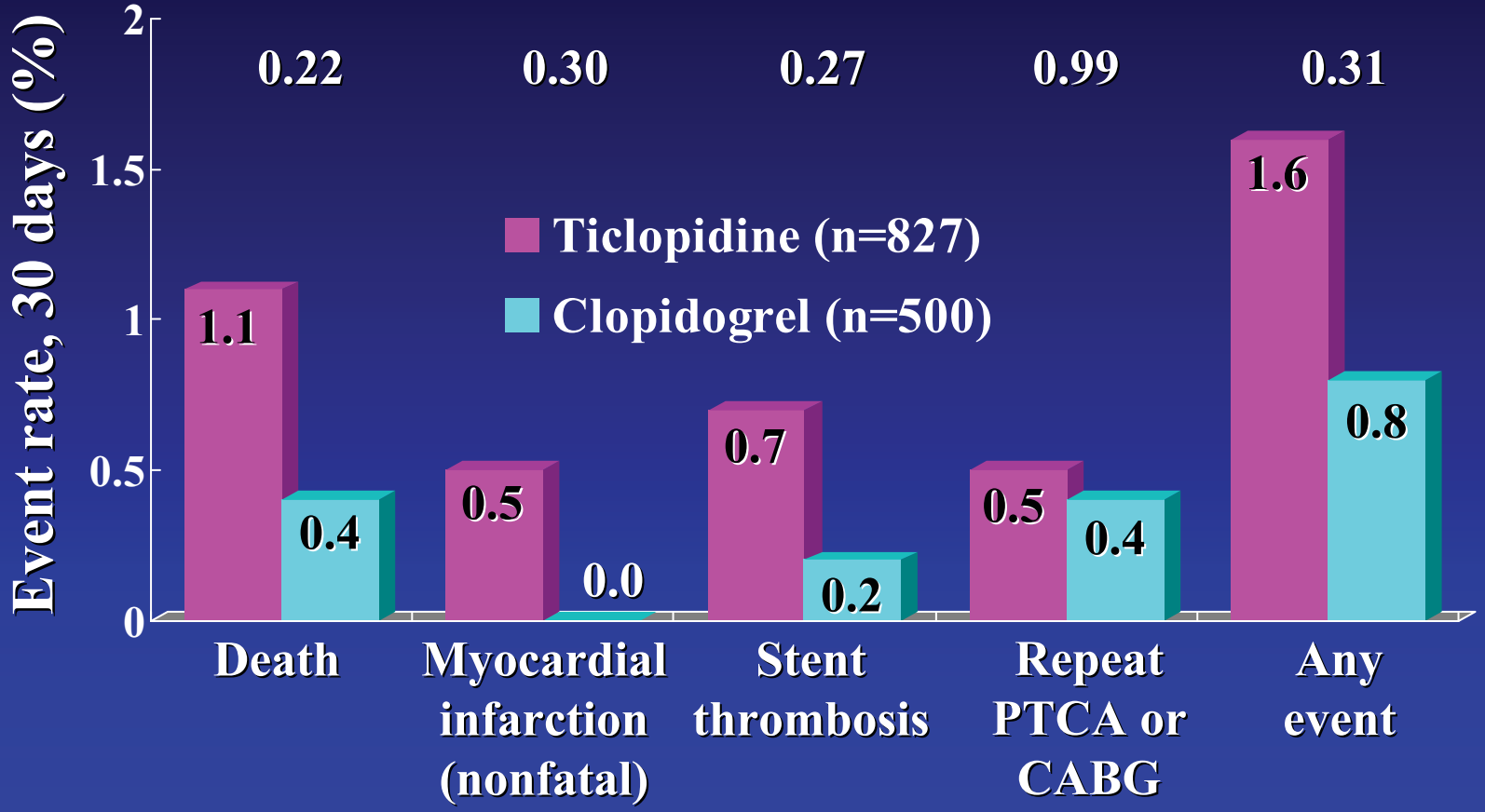
R=CO_2CH_3 Clopidogrel

Clopidogrel as Adjunctive Antiplatelet Therapy During Coronary Stenting

30-Day Events	Clopidogrel	Ticlopidine	P
Acute Stent Thrombosis	3 (0.6%)	0	0.39
Subacute Stent Thrombosis	1 (0.2%)	2 (0.3%)	0.99
Death	5 (0.9%)	2 (0.6%)	0.54
Q-MI	2 (0.4%)	0	0.65
Urgent PCI	1 (0.2%)	0	0.99
Urgent CABG	2 (0.4%)	1 (0.3%)	0.76
MACE	11 (2.1%)	3 (1.4%)	0.57

Mishrel GJ. JACC 1999;34:1884

Clopidogrel as Adjunctive Antiplatelet Therapy During Coronary Stenting



Berger PB. JACC 1999;34:1891

Is Clopidogrel Superior to Ticlopidine for the Prevention of Stent Thrombosis ?

Results of a U.S. Multicenter Study (Nested case control study, 197 patients with stent thrombosis vs. control)

Independent Predictors of SST	Multivariate OR	95% CI	P-value
Platelet count (per 100*k*)	2.4	1.6 – 3.6	<0.001
Acute MI indication	4.6	1.9 – 10.0	0.001
Length of stent (per 10mm)	1.3	1.1 – 1.5	0.006
Coil or self-expanding stent	3.0	1.2 – 7.5	0.018
Pre-procedural thrombus	1.9	1.2 – 3.2	0.011
Clopidogrel	2.1	1.2 – 3.7	0.006

AHA 2001

Cilostazol

- Cilostazol is a potent antiplatelet agents that selectively inhibits phosphodiesterase III
- Previous studies suggested that cilostazol had similar antiplatelet effects with less serious adverse effects, as compared with ticlopidine

Ochiai M, Am J Cardiol 1997;79:1471-74

Dawson DL, Circulation 1998;98:678-86

A Randomized Comparison of Cilostazol vs Ticlopidine Therapy After Stent Implantation

AMC Experiences

Park SW. Am J Cardiol 1999;84:511

Clinical Events

	Ticlopidine (n=243)	Cilostazol (n=247)
Angiographic events		
Acute stent thrombosis	1(0.4%)	0 (0%)
Subacute stent thrombosis	0(0)	2 (0.9%)
Clinical events		
Death	0(0)	0 (0)
Myocardial infarction	1(0.4)	2 (0.8)
TLR	2(0.8)	1 (0.4)
CVA	1(0.4)	0 (0)
Other major bleeding	2(0.8)	2 (0.8)

Drug Adverse Effects

	Ticlopidine (n=243)	Cilostazol (n=247)
Leukopenia	3(1.2%)	0(0%)
Thrombocytopenia	1(0.4)	0(0)
Gastritis	5(2.1)	8(3.2)
Skin rash	7(2.9)	5(2.0)
Elevated transaminase	1(0.4)	0(0)

Leukopenia($<1,000/mm^3$)
Thrombocytopenia($<20,000/mm^3$)

Conclusion

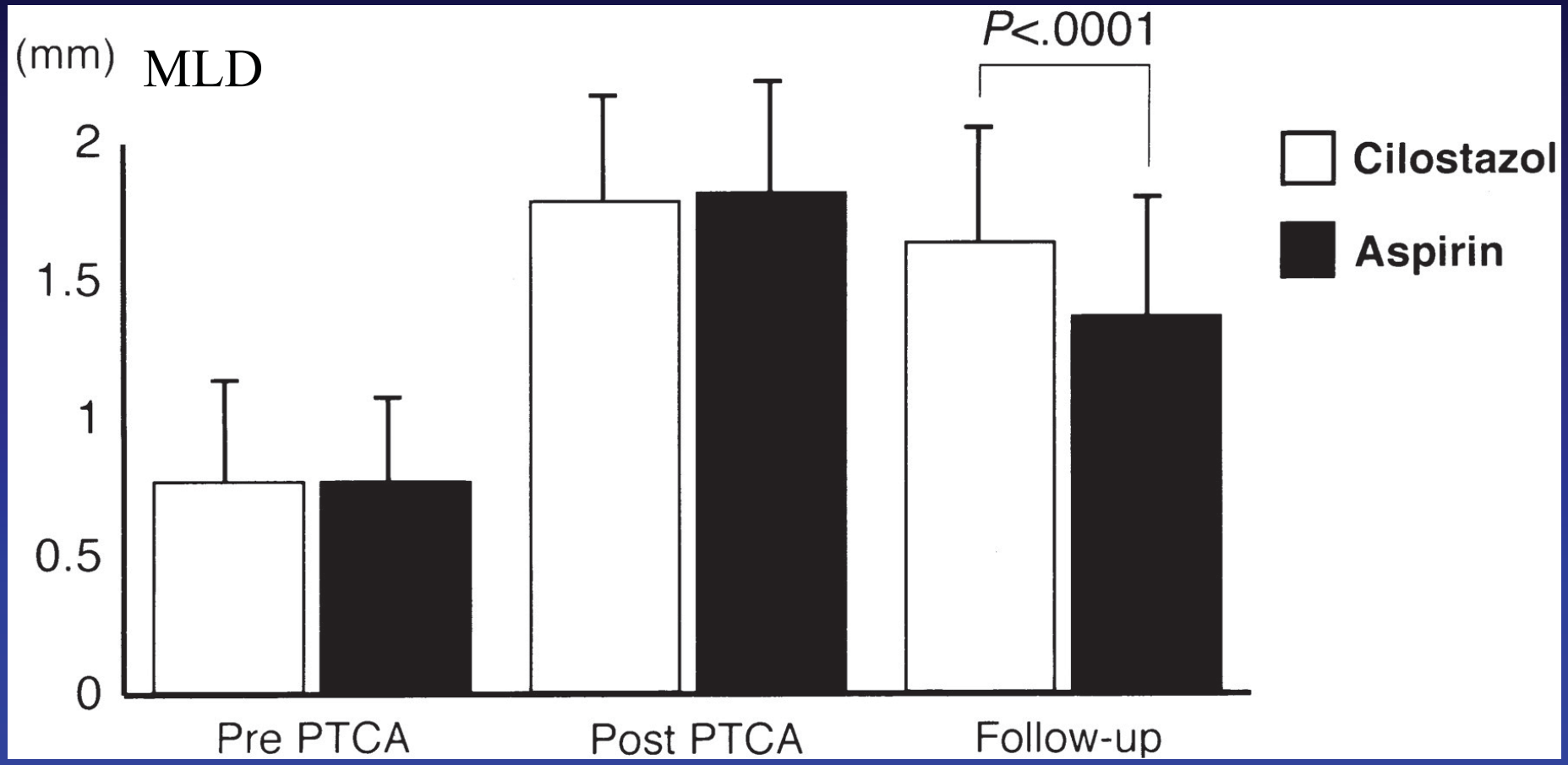
Aspirin plus cilostazol is an effective antithrombotic regimen in prevention of stent thrombosis, comparable to aspirin plus ticlopidine after elective coronary stenting.

Park SW. Am J Cardiol 1999;84:511

In-Stent Restenosis

- A major clinical problem limiting the long-term efficacy of coronary stenting
- The mechanism of restenosis after stenting is principally neointimal hyperplasia

Impact of Cilostazol on Restenosis after PTCA: Angiographic Results



Tsuchikane E. Circulation 1999;100:21

Effects of Cilostazol on Angiographic Restenosis after Coronary Stent Placement

Hypothesis

Cilostazol may reduce neointima accumulation within the stent, and subsequently lead to reduction of the restenosis rate after coronary stenting

Park SW. Am J Cardiol 2000;86:499

Methods

- 409 consecutive patients (494 lesions) scheduled for elective coronary stenting were included for this study

- All eligible patients were randomly assigned to either aspirin plus ticlopidine (group I) or aspirin plus cilostazol (group II)

Endpoints

- **Primary endpoint : the binary angiographic restenosis (diameter stenosis > 50%) at 6-month follow-up**
- **Secondary endpoints : composite end point defined as event-free survival (death, myocardial infarction and target lesion revascularization) during the follow-up**

QCA Data

	Ticlopidine (n=240)	Cilostazol (n=254)
Ref size, mm	3.24 ± 0.51	3.31 ± 0.51
MLD		
Baseline	0.67 ± 0.44	0.72 ± 0.45
Final	3.24 ± 0.55	3.25 ± 0.49
Follow-up	1.93 ± 0.87	2.12 ± 0.74*

*P <0.05

Late Clinical Events (30 days - 6 months)

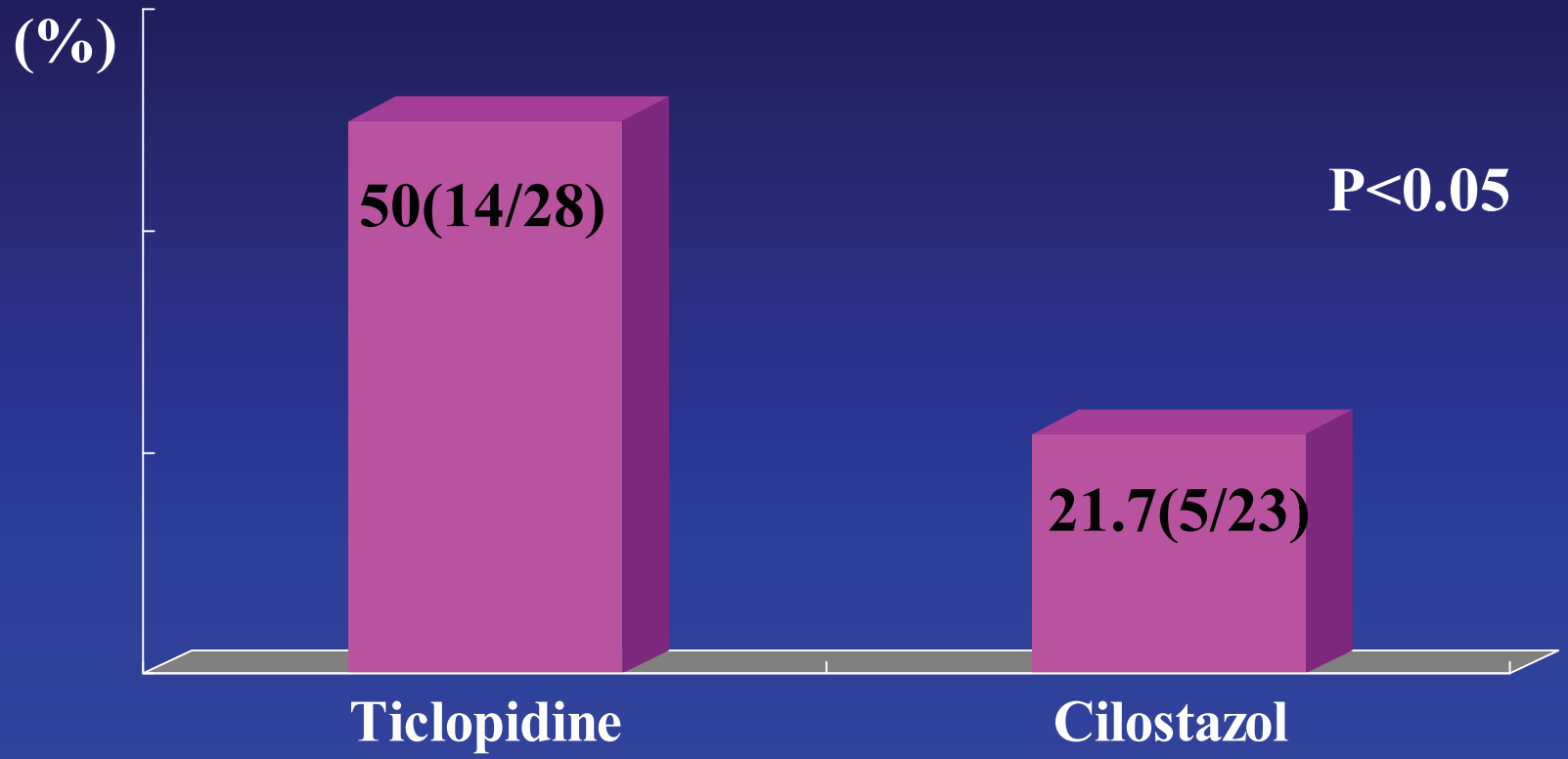
	Ticlopidine (n=201)	Cilostazol (n=208)
Death	6(3%)	2(1%)
Cardiac	4	2
Non-cardiac	2	0
Q-wave MI	0	0
CVA	0	0

Angiographic Restenosis

	Ticlopidine (n=240)	Cilostazol (n=254)
Follow-up	184/233(77%)	196/251(77%)
Restenosis	50/184(27)	45/196(22.9)
TLR	13(5)	11(4)

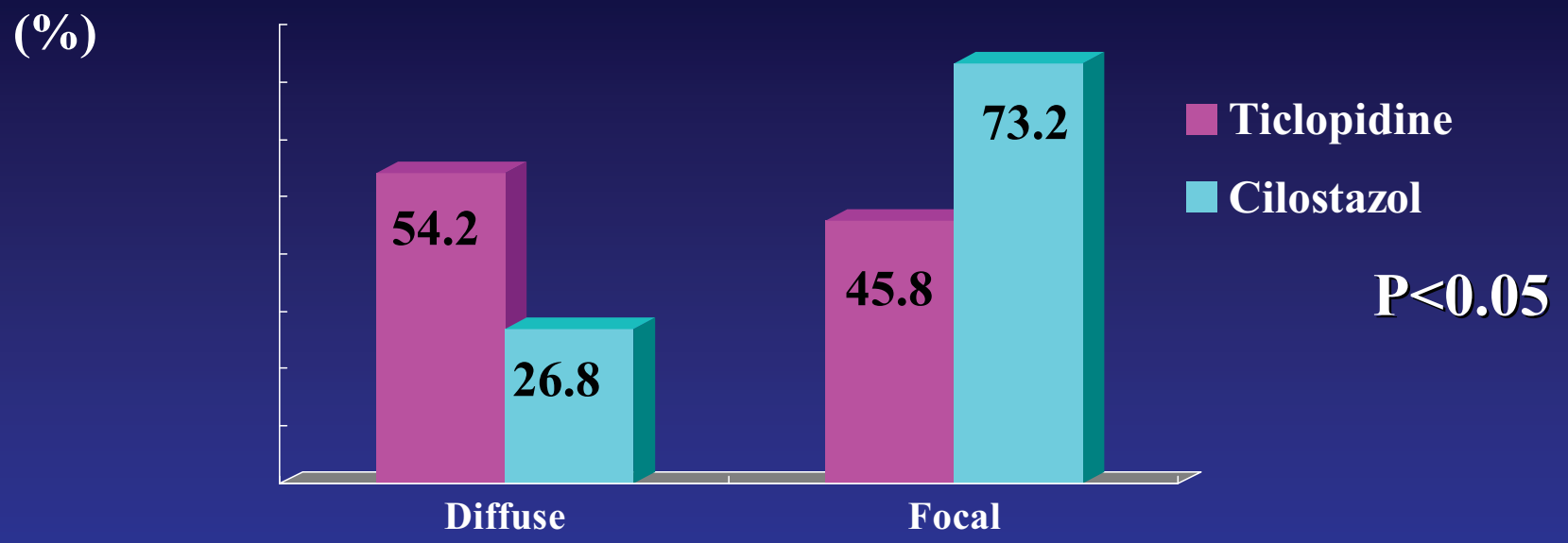
p= NS

Restenosis Rate in Diabetic Patients



AMC, 2000

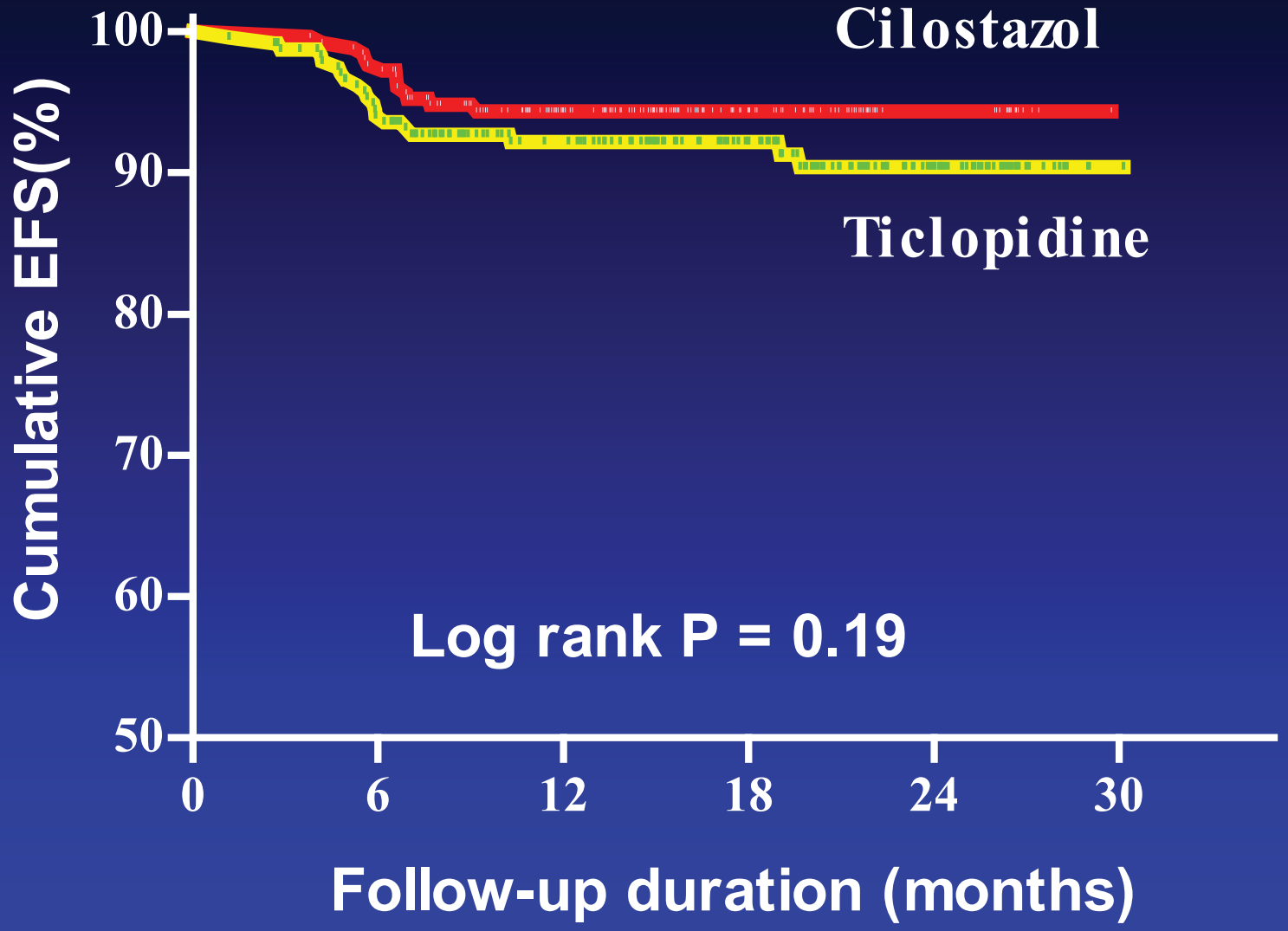
Patterns of In-Stent Restenosis



Mean length of in-stent restenosis

Ticlopidine 13.8 ± 11.7 mm
Cilostazol 9.0 ± 5.4 mm
P<0.05

AMC, 2000


Cilostazol
Ticlopidine
Cumulative EFS(%)
100
90
80
70
60
50
Log rank P = 0.19
0
6
12
18
24
30
Follow-up duration (months)

Conclusions(I)

Aspirin plus cilostazol appears to be an effective antithrombotic regimen with comparable results to aspirin plus ticlopidine

Conclusions(II)

Aspirin plus cilostazol does not seem to reduce the overall angiographic restenosis rate after elective coronary stenting

Conclusions(III)

- Administration of cilostazol after coronary stenting could reduce the angiographic restenosis rate in diabetic patients and modify the pattern of in-stent restenosis more favorably.
- This anti-restenotic efficacy of cilostazol warrants further investigation in the large number of patients.

Park SW. Am J Cardiol 2000;86:499

Cilostazol versus Clopidogrel After Coronary Stenting

AMC data, 2003

METHODS

Prospective randomization

From June, 2002 to July, 2003

Patients(n=651) who underwent stenting

- Cilostazol (n=325, 477 lesions)
- Clopidogrel (n=326, 495 lesions)

  in addition to aspirin 200 mg

Study drug Medication

- Loading dose ; *after stenting*
  - Cilostazol 200mg
  - Clopidogrel 300mg
- Study drugs for one month
  - Cilostazol 100mg BID
  - Clopidogrel 75mg QD

Exclusion Criteria

- Left main stenting
- Bypass graft stenting
- Radiation therapy
- Drug eluting stenting
- Poor LV function (EF<30%)
- Hematological disease
  Neutropenia (<3000/mm3)
  Thrombocytopenia (<100,000/mm3)
- Hepatic dysfunction
- Renal dysfunction (Cr>3.0mg/dl)
- Contraindication to aspirin, clopidogrel or cilostazol

Primary Endpoint

Within 30 days after stenting

Subacute stent thrombosis

Major adverse cardiac events

- Death
- Myocardial infarction
- Repeat intervention

Secondary Endpoint

Any events requiring termination of study drugs during treatment period

- Major bleeding
- Neutropenia (<1500/mm^3)
- Thrombocytopenia (<100,000/mm3)
- Skin rash,
- Liver dysfunction, and GI trouble

Baseline Characteristics

	Cilostazol (n=325)	Clopidogrel (n=326)	*p*
Age,yrs	59±10	60±11	NS
Men	71.4%	69.3%	NS
Diabetes	24.2%	23.4%	NS
Hypertension	45.5%	45.9%	NS
Prior MI	15.1%	12.9%	NS
Hypercholesterol	29.6%	30.4%	NS

Baseline Characteristics

	Cilostazol (n=325)	Clopidogrel (n=326)	*p*
Clinical Dx			NS
Stable	39.0%	40.4%	
Unstable	32.0%	32.8%	
AMI	29.0%	26.8%	
1° Stenting	12.9%	12.6%	NS
LVEF(%)	58±8	58±9	NS

Angiographic Characteristics

	Cilostazol (n=477)	Clopidogrel (n=495)	*p*
Stented site			NS
LAD	39.0%	40.4%	
LCX	32.0%	32.8%	
RCA	29.0%	26.8%	
AHA/ACC type			NS
A	12.5%	11.3%	
B1	30.5%	31.2%	
B2	22.7%	21.9%	
C	34.3%	35.6%	

Angiographic characteristics

	Cilostazol (n=477)	Clopidogrel (n=495)	*p*
Small vessel(<3.0 mm)	35.7%	38.1%	NS
Long lesion(≥20 mm)	29.7%	35.6%	NS
Chronic total occlusion	6.4%	5.7%	NS
Long stent(≥ 20 mm)	40.1%	43.2%	NS
Multi-vessel stenting	57.2%	60.6%	NS

Angiographic characteristics

	Cilostazol (n=477)	Clopidogrel (n=495)	*p*
Reference diameter(mm)	3.2±0.6	3.2±0.5	NS
MLD(mm)			
Baseline	0.8±0.6	0.7±0.5	NS
Final	3.1±0.6	3.0±0.6	NS
Balloon artery ratio	1.1±0.1	1.1±0.1	NS
Maximal pressure(atm)	13±4	13±2	NS

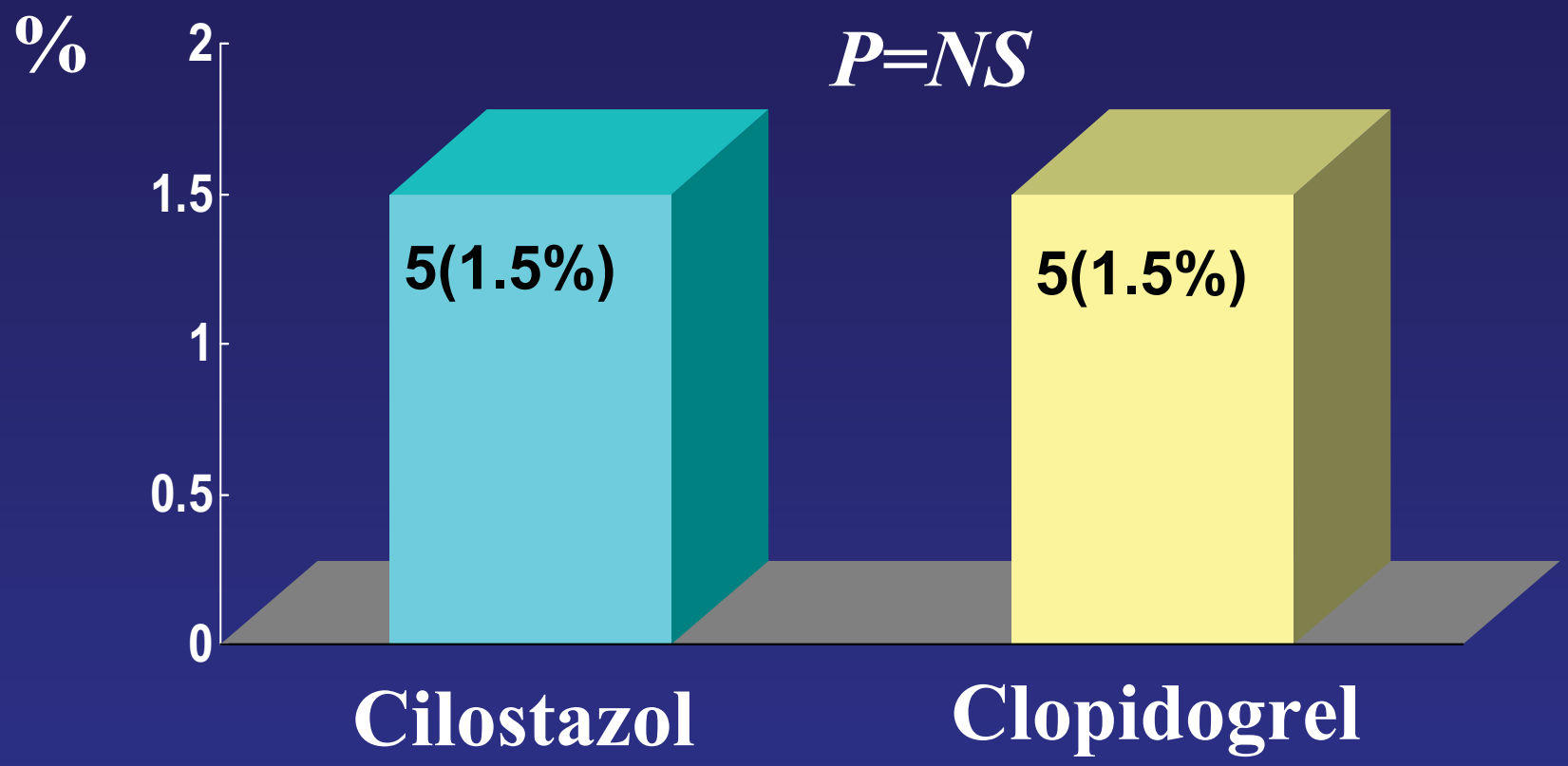
Major Cardiac Events

	Cilostazol (n=325)	Clopidogrel (n=326)	*p*
Acute ST	1 (0.3%)	2 (0.6%)	NS
Subacute ST	2 (0.6%)	2 (0.6%)	NS
MI	3 (0.9%)	4 (0.9%)	NS
TLR	3 (0.9%)	4 (0.9%)	NS
Death	2 (0.6%)	2 (0.6%)	NS

ST; stent thrombosis

Primary Endpoint

Subacute thrombosis & MACE



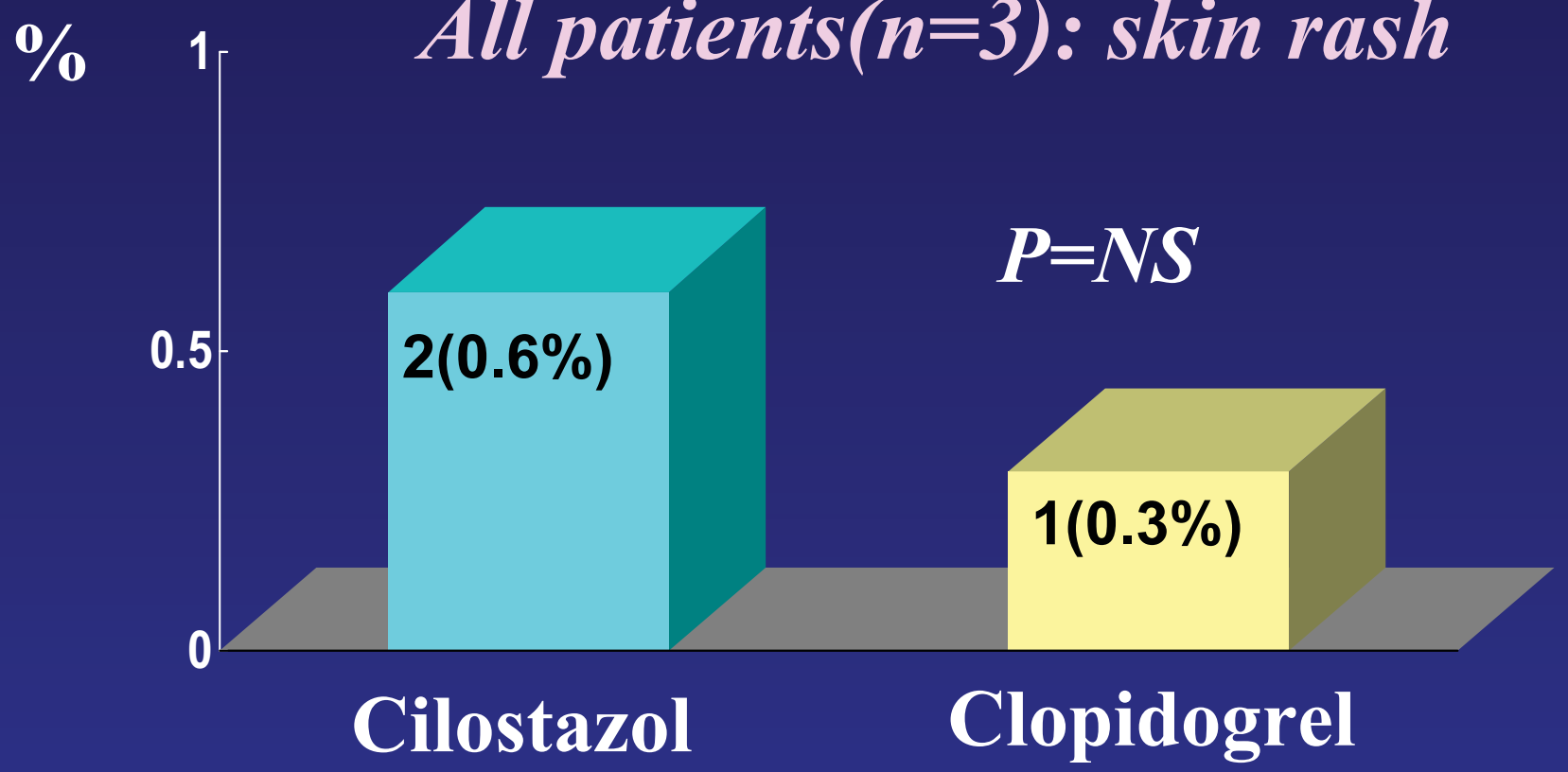
Noncardiac Events

	Cilostazol (n=325)	Clopidogrel (n=326)	*p*
Major bleeding*	2 (0.6%)	1 (0.3%)	NS
Adverse side effect			
Leukopenia	0	0	NS
Thrombocytopenia	0	0	NS
Elevated LFT	0	0	NS
GI trouble	10 (3.1%)	2(0.6%)	0.02
Skin rash	7 (2.2%)	3 (0.9%)	NS
Overall events	19 (5.8%)	6 (1.8%)	0.008

* Vascular access site bleeding (n=2), Ulcer bleeding(n=1)

Secondary Endpoint

Cessation of study drug (<1 Mo)



CONCLUSION

Preliminary results of this ongoing study show that the regimen with *cilostazol and aspirin* appears to be safe and as effective as *clopidogrel and aspirin* in preventing thrombotic complication after coronary stenting.

Triple Antiplatelet Therapy

Triple antiplatelet regimen for complex lesions or high risk group of thrombotic complication

- **Aspirin indefinitely**
- **Clopidogrel 75 mg QD for 1 month (300mg loading)**
- **Cilostazol 100mg BID for 1 month (200mg loading)**

Triple Antiplatelet Therapy

Treatment of Diffuse In-Stent Restenosis With Rotational Atherectomy Followed by Radiation Therapy With a Rhenium-188–MAG_3-Filled Balloon (R4 Registry)

SW Park et al. J Am Coll Cardiol 2001;38:631-637

We've learned that triple antiplatelet regimen would be safe and effective from the brachytherapy study (R4 Registry, n=50) ; no stent thrombosis or late thrombotic occlusion

Patients Characteristics

	N=555
Left main stenting	101
Radiation therapy	68
Drug eluting stenting	308
Bypass graft stenting	2
Poor TIMI flow after stenting	15
Stent inapposition on IVUS	5
Others	56

Major Cardiac Events

	N=555
Acute stent thrombosis	0 (0)
Subacute stent thrombosis	1 (0.2%)
Major adverse cardiac event	
Myocardial infarction	2 (0.4%)
Repeat intervention	1 (0.2%)
Cardiac Death	2 (0.4%)
Overall events	4 (0.8%)

Noncardiac Events

	N=555
Major bleeding	1 (0.2%)
Adverse side effect	
Leukopenia	0
Thrombocytopenia	1(0.2%)
Elevated LFT	0
GI trouble	5(0.9%)
Skin rash	11(2.0%)
Overall events	18(3.2%)

CONCLUSION

Triple antiplatelet therapy appears to be safe and effective in preventing subacute stent thrombosis.

Cilostazol in PCI

- “Aspirin plus Cilostazol” regimen has been used after coronary stenting with stent thrombosis rate of 1 % or less (comparable with ticlopidine or clopidogrel).
- Cilostazol has been demonstrated to have beneficial effect in reducing late restenosis in diabetic patients.
- Cilostazol is effective in patients with PVD.
- Triple antiplatelet therapy may be safe and effective in high-risk patients.
- With drug-eluting stenting or brachytherapy, “Aspirin plus Cilostazol” regimen needs to be