With DES
Oral Antiplatelet Agents
Are Needed for 6 Months ??

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한 규 록

Why antiplatelet agents

are needed with stents ?

Coronary Stent

- Positive
  - Treat Dissection
  - Prevent Acute Closure
  - Reduce Restenosis
- Negative
  - *Stent Thrombosis*
  - In-Stent Restenosis
  - High Costs

Thrombosis after Stenting

Intravascular Stents to Prevent Occlusion and Restenosis after Transluminal Angioplasty.

(U Sigwart N Engl J Med 1987;316:701-706)

- 24 Coronary stents in 19 patients
- 3 Thrombotic occlusions (16%)
  - 1 asymptomatic
  - 1 managed with thrombolysis
  - 1 died after bypass surgery

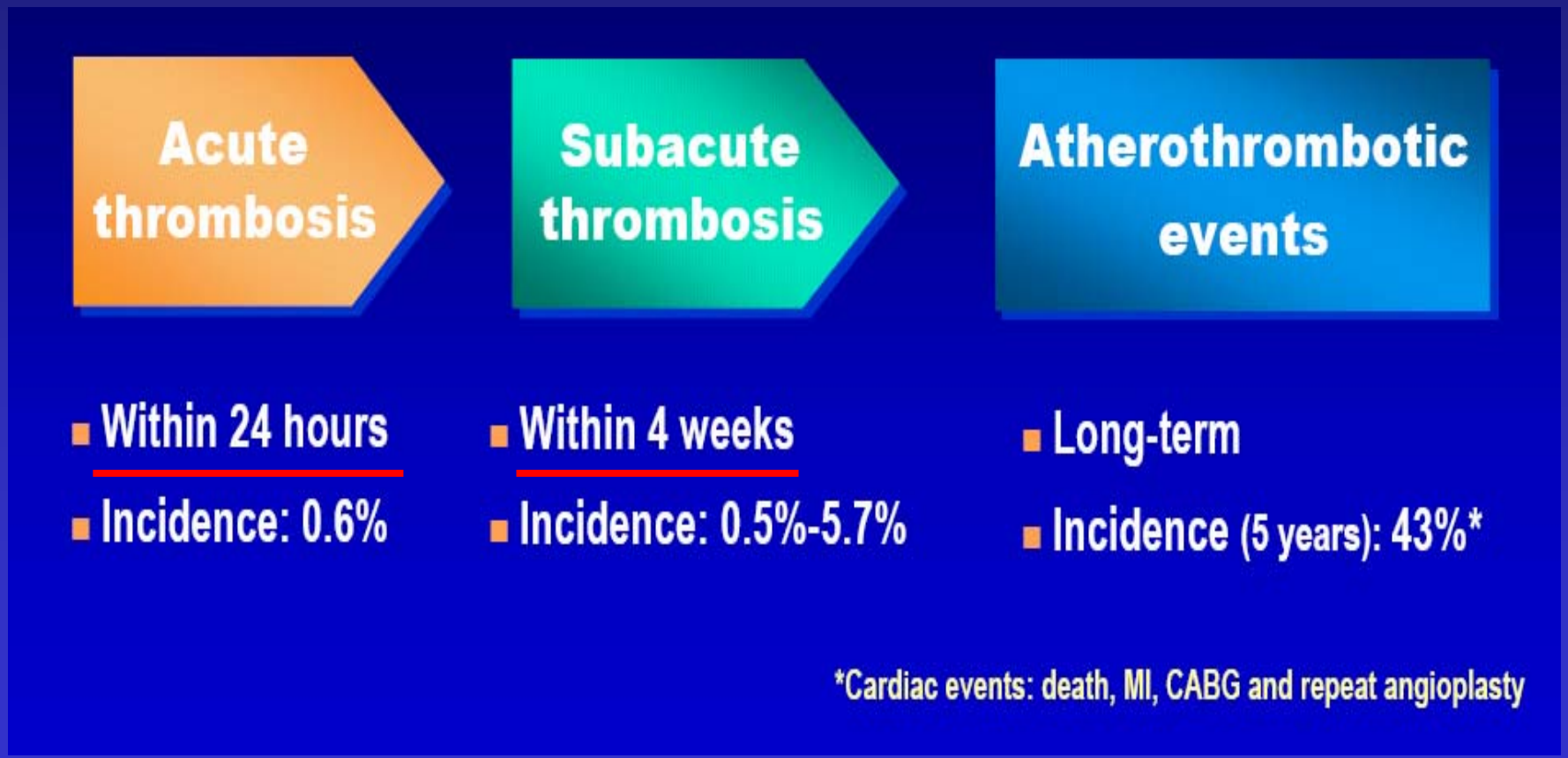
Thrombosis after Stenting

Angiographic Follow-up after Placement of a Self-Expanding Coronary-Artery Stent.

(PW Serruys N Engl J Med 1991;324:13-17)

- 117 Coronary stents in 105 patients
- Angiogram F/U at 1 month
- Complete occlusion in 27stents/25pts (24%)
  : 21 occlusions within first 14 days

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



Anti-thrombotic Regimen with Stenting

A Comparison of Balloon-Expandable-Stent Implantation with Balloon Angioplasty in Patients with Coronary Artery Disease.

(PW Serruys N Engl J Med 1994;331:489-495)

- *BENESTENT study*
  - Aspirin 250-500 mg daily
    Dipyridamole 75 mg three times a day (6 mos)
    Heparin 10,000 U bolus, repeated if necessary
    Dextran 1000 ml continuous infusion
    Warfarin (INR 2.5~3.5 , 3 mos)

Anti-thrombotic Regimen with Stenting

BENESTENT Study

(PW Serruys N Engl J Med 1994;331:489-495)

	Acute & Subacute Thrombosis	Bleeding & Vascular Cx.
Stent	3.5 %	13.5 % *(p<0.001)*
Balloon	2.7 %	3.1 %

Anti-thrombotic Regimen with Stenting

A Randomized Comparison of Antiplatelet and Anticoagulation Therapy after the Placement of Coronary-Artery Stents.

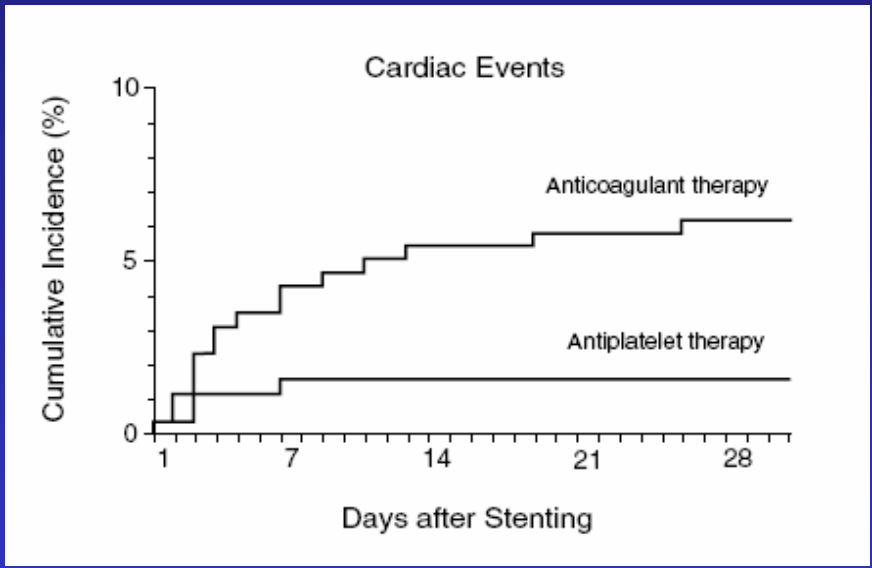
(A Schoemig N Engl J Med 1996;334:1084-1089)

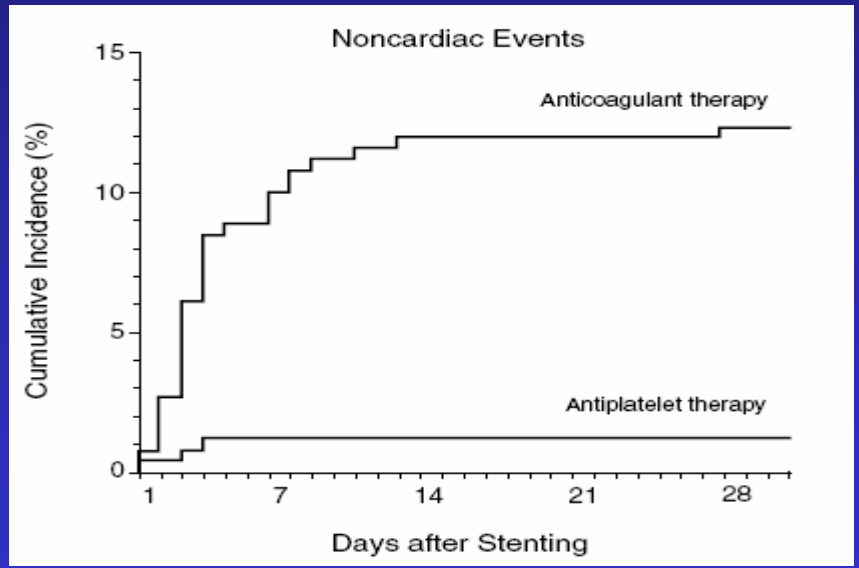
- *ISAR trial (Intracoronary Stenting & Antithrombotic Regimen)*
  - Anticoagulation Tx : Heparin + Coumadine + Aspirin
  - Anti-platelet Tx : Ticlopidine + Aspirin

Anti-thrombotic Regimen with Stenting

ISAR trial

(A Schoemig N Engl J Med 1996;334:1084-1089)





Cardiac Event
: Death, MI, TVR

Noncardiac Event
: CVA, Bleeding, Vascular Cx.

Anti-thrombotic Regimen with Stenting

A Clinical Trial Comparing Three Antithrombotic-Drug Regimens after Coronary-Artery Stenting.

(MB Leon N Engl J Med 1998;339:1665-1671)

- *STARS trial (Stent Anticoagulation Restenosis Study)*

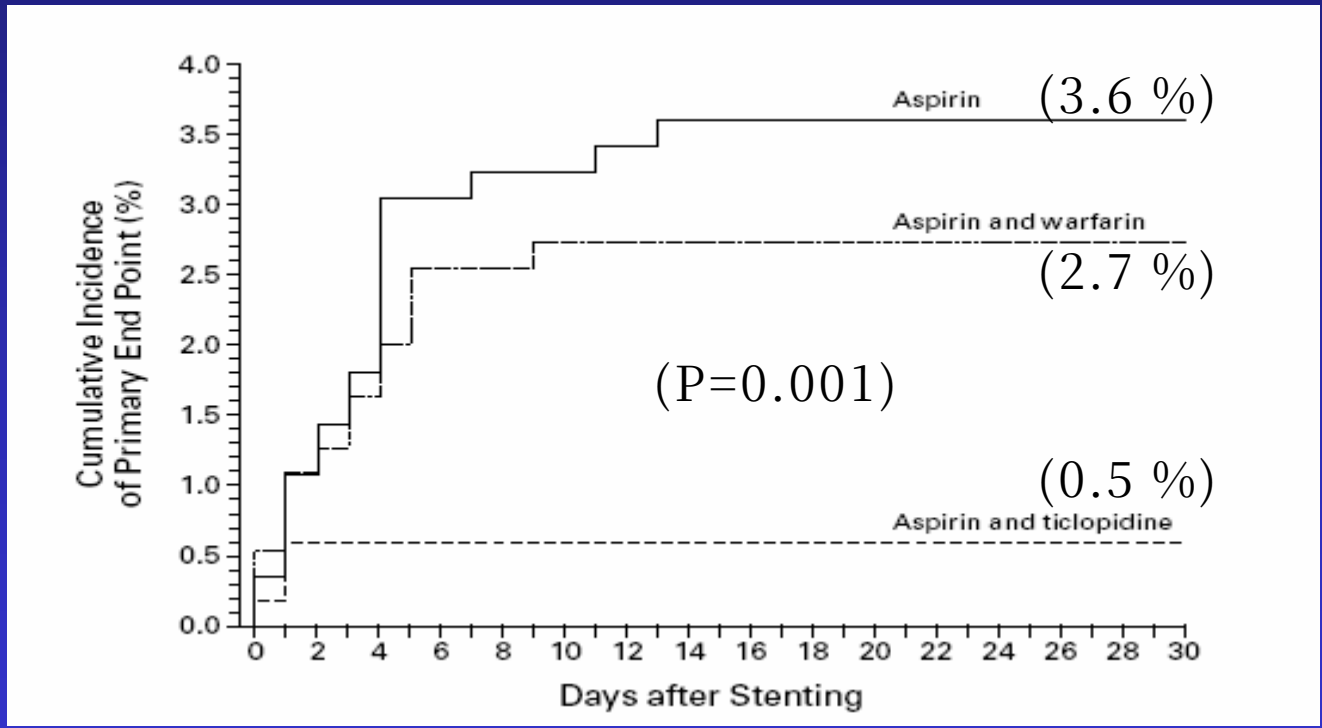
(1653 pts from 50 centers)

- Aspirin alone (325 mg)
- Aspirin + Wafarin (INR 2.0-2.5)
- Aspirin + Ticlopidine (250 mg po bid)

Anti-thrombotic Regimen with Stenting

STARS trial

(MB Leon N Engl J Med 1998;339:1665-1671)



Primary End Point
: Death, MI, TLR, Thrombosis

Anti-thrombotic Regimen with Stenting

ACC/AHA Guidelines

for Percutaneous Coronary Intervention

(SC Smith J Am Coll Cardiol 2001;37:2239i-lxvi)

❖ Combination Antiplatelet Regimen in Stenting

- Aspirin 80-325 mg, at least 2H before PCI
- Clopidogrel / Ticlopidine at least 72H before PCI

➢ Ticlopidine ： recommend shorter duration(10-14 days)

➢ Clopidogrel ： Pre-Tx / Loading dose 300mg

AHA Scientific Statement

Percutaneous Coronary Intervention &

Adjunctive Pharmacotherapy in Women

(AJ Lansky Circulation 2005;111:940-953)

- Clopidogrel 300-600 mg load / 75 mg

  : should be continued for at least 2-4 weeks after BMS

  for 3 mos after Sirolimus-ES

  for 6 mos after Paclitaxel-ES

Stent Thrombosis

Multiple Factors!!

Technical Issues

Patient / Lesion Triage

Pharmacologic Therapy

Stent Thrombogenicity

*Material
*Designs (open vs. closed cell)
*Surface coating
*Adjunctive therapeutic agents (Drug, radiation)

Bio-Compatibility

Patient / Lesion Factors

*Vessel size, lesion length
*Acute coronary syndrome, unstable angina
*Plaque characteristics
*Intrinsic platelet / coagulation activity
*Left ventricular ejection fraction / CHF

•Multiple stents
•Stent length

•Coronary Blood flow

Procedure Related Factors

*Morphometric abnormalities (underexpansion)
*Morphologic abnormalities (dissection, incomplete apposition, Thrombus, tissue protrusion
*Mechanical vessel injury
* Anti-thrombotic therapy

Procedural Optimization

Embolic Protection

Drug-Eluting Stents Approved by the FDA

FDA U.S. Food and Drug Administration — Department of Health and Human Services

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FDA News

FOR IMMEDIATE RELEASE
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Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Approves Drug-Eluting Stent for Clogged Heart Arteries

The Food and Drug Administration today approved the first drug-eluting stent for angioplasty procedures to open clogged coronary arteries. In most cases, a stent is left permanently in the artery to keep the vessel open after angioplasty. The new stent slowly releases a drug, and has been shown in clinical studies to significantly reduce the rate of re-blockage that occurs with existing stents.

Do Cypher™ Stents Cause Thrombosis?

THE NEW YORK TIMES, WEDNESDAY, JULY 9, 2003

Warning on Artery Stent Cites Some Cases of Clots

By MELODY PETERSEN

Johnson & Johnson sent a letter to doctors on Monday night advising them about rare cases of life-threatening blood clots linked to its new drug-coated stent, a fast-selling device used to keep blood flowing through the arteries.

The Food and Drug Administration said yesterday that it had received 47 reports of blood-clotting, or thrombosis, that occurred at the time the company's stent was implanted or within a few days. Regulators said five patients had died.

More than 50,000 patients have received the Cypher stent since it was approved in April. The stent is a tiny metal scaffold that props open an artery. Unlike other stents, Johnson & Johnson's device emits a drug to reduce the chance that the artery will clog again.

The F.D.A. said it was reviewing the reports and working with the company to determine what was causing the blood clots. "It is unclear what effect the Cypher stent has on thrombosis risk," regulators said yesterday.

Martin E. Schildhouse, global director for corporate communications at the Cordis Corporation, a subsidiary of Johnson & Johnson, said some of the problems were caused by doctors improperly using the stent and not by the device itself.

"At this point, you can't draw the conclusion that it is because of the Cypher stent that you are seeing these events," Mr. Schildhouse said.

Two patients died after receiving the Cypher stent at St. Francis Hospital in Roslyn, N.Y., said Dr. Lawrence A. Reduto, the hospital's executive vice president for medical affairs. He said it was not clear that the stent had caused the deaths.

Dr. Reduto said that the overall incidence of thrombosis with the Cypher stent appeared to be no greater than that associated with stents that had not been coated with a drug.

Five deaths are reported in patients who got a Johnson & Johnson product.

"I think we saw an abnormality," Dr. Reduto said.

Mr. Schildhouse said the company had agreed with the F.D.A. that the letter should be sent to advise doctors about the problem and remind them of the proper technique to use in implanting the Cypher sent.

In the company's letter, Dr. Dennis Donohoe, vice president for therapeutics and clinical research at Cordis, said that some of the problems might have been caused when doctors used a stent that was too small for the patient's artery.

Because of high demand for the stent, the company has been unable to manufacture enough to fill doctors' orders and has focused on making the two smallest versions. Dr. Donohoe said that the company had recently begun to ship a larger version.

Dr. Donohoe also wrote that some patients might not have taken the proper amounts of medications that help keep blood from clotting.

He also advised doctors not to use the drug-coated stent in patients with conditions that the device was not approved for, including restenosis, or a renarrowing of the artery where a stent procedure has already taken place.

Michael N. Weinstein, a medical device industry analyst at J. P. Morgan, said he did not think the reports of thrombosis would hurt sales of the Cypher stent. He said the problem had been aggravated by Johnson & Johnson's failure to supply all the appropriate sizes of device.

"Cardiologists are, as a result, 'using what they have,' and at times trying to deploy undersized stents into larger vessels, or in some cases using too many stents in a single vessel," Mr. Weinstein wrote in a recent research report after talking to numerous physicians.

Mr. Weinstein estimates that the company's sales of the Cypher stent will be $1.57 billion this year and $2.1 billion next year.

Shares of Johnson & Johnson fell 50 cents yesterday, to $52.48.

Bloomberg News

The Cypher stent, made by Johnson & Johnson, is coated with a drug meant to prevent arteries from clogging again.

FDA Public Health Web Notification: Information for Physicians on Sub-acute Thromboses (SAT) and Hypersensitivity Reactions with Use of the Cordis CYPHER™ Coronary Stent

What information is being reported?

We have received numerous reports of adverse events for the CYPHER™ stent through our MDR system, which is subject to significant underreporting. As of October 20, 2003, we have received more than 290 reports (>260 US and >25 Outside US) involving sub-acute (occurring between 24-hours and 30 days post-procedure) thrombosis (SAT) associated with the CYPHER™ stent. More than 60 reports of SATs were associated with patient death and the remaining reports were associated with patient injury requiring medical or surgical intervention. Also, we have received more than 50 reports, including some deaths, that Cordis considers possible hypersensitivity reactions. The symptoms reported include: pain, rash, respiratory alterations, hives, itching, fever, and blood pressure changes. ***We do not have sufficient data to establish rates for these events, nor can we determine whether these rates are different from those experienced with bare metal stents.*** As of October 10, 2003, Cordis reports that more then 450,000 units have been distributed worldwide (>260,000 US and >180,000 Outside US).

FDA Public Health Web Notification

- October 20, 2003
- > 290 reports involving SAT
  associated with Cypher
- > 450,000 units of Cypher
  were distributed worldwide

- Stent Thrombosis Rate = 290/450,000 (0.06%)

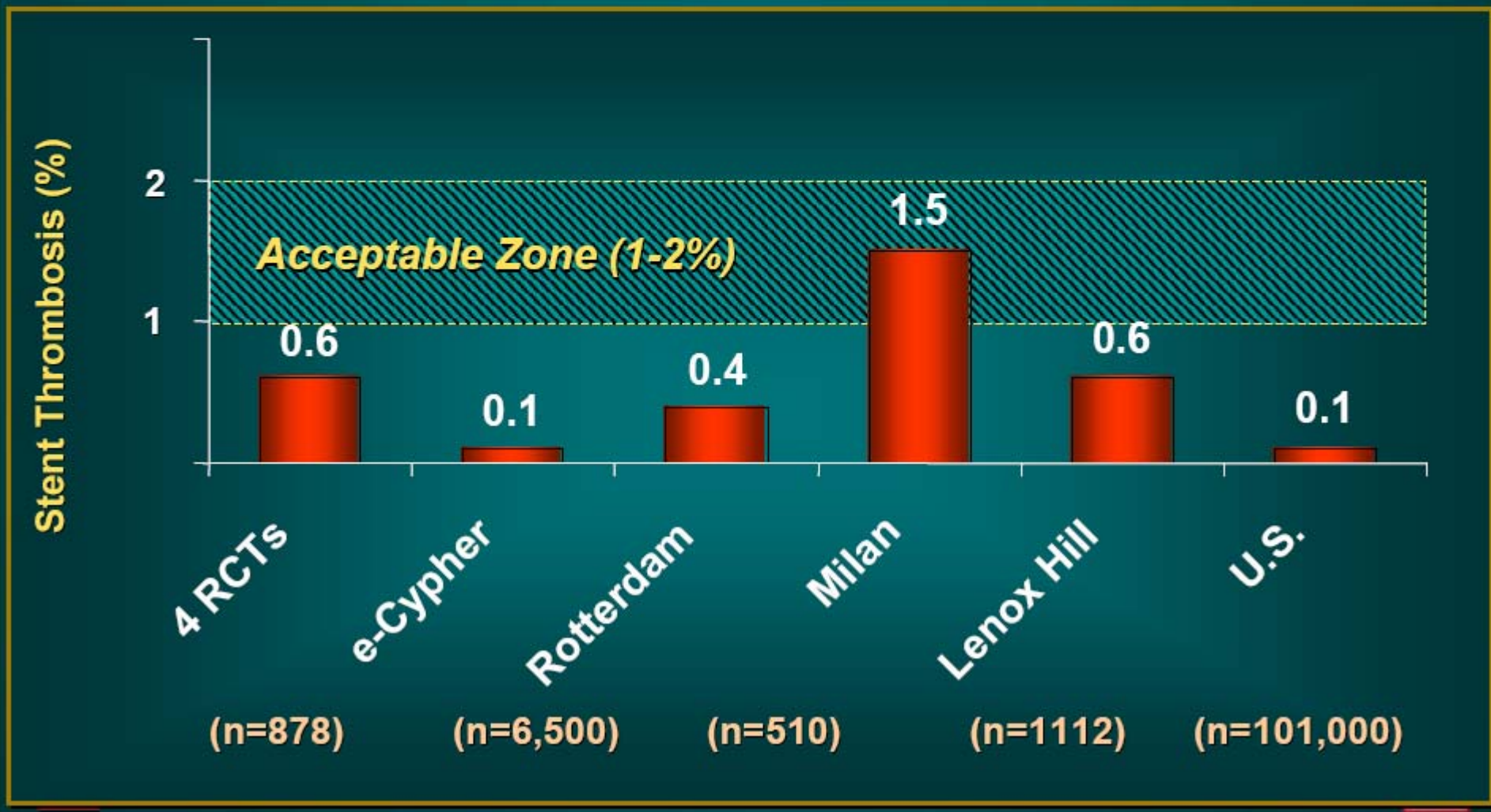
FDA Public Health Web Notification:
Information for Physicians on
Sub-acute Thromboses (SAT) and Hypersensitivity Reactions with Use of the Cordis CYPHER™ Coronary Stent

pressure changes. *We do not have sufficient data to establish rates for these events, nor can we determine whether these rates are different from those experienced with bare metal stents.* As of October 10, 2003, Cordis

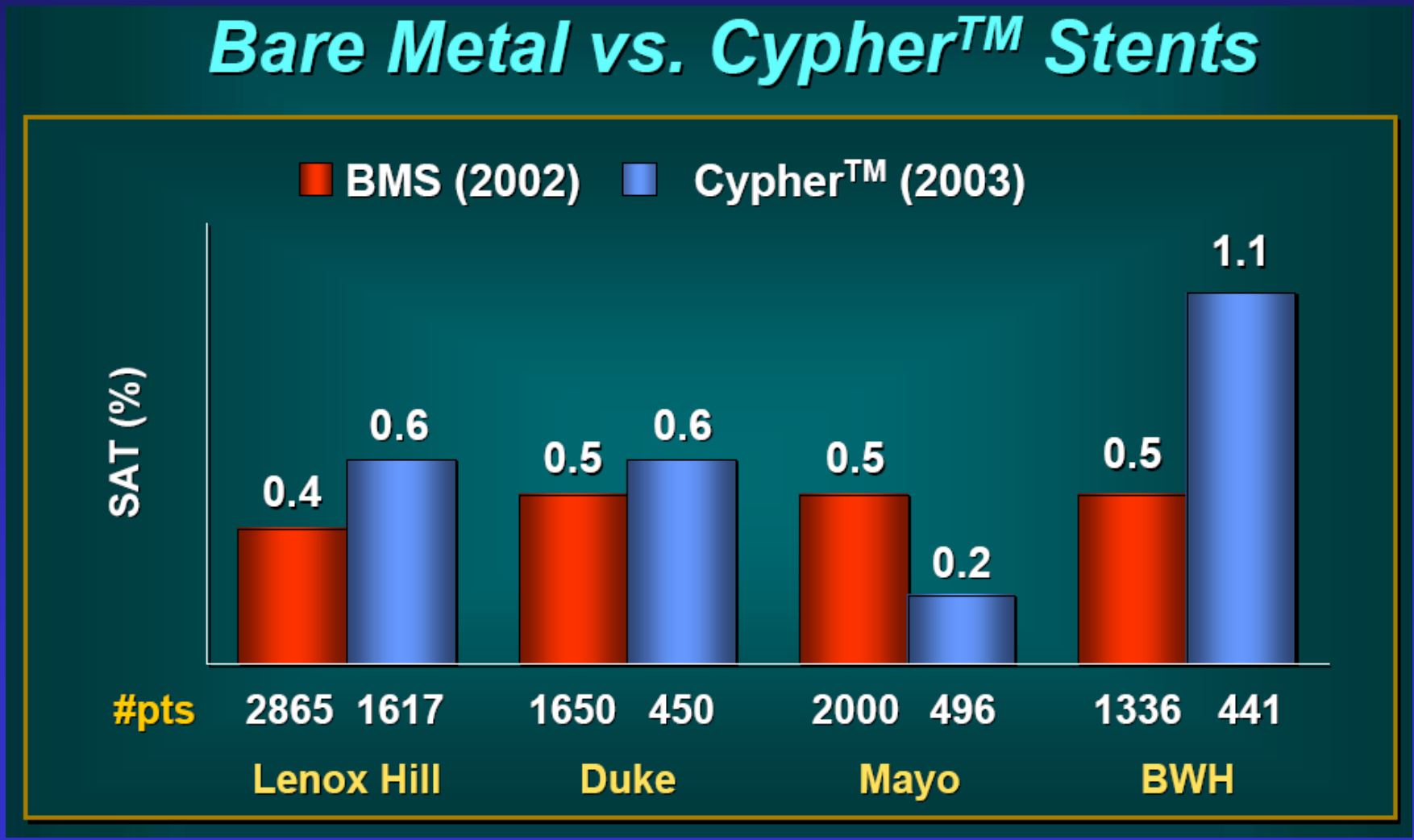
Cypher™ Stent Thrombosis

All Available Data

(total = 110,335 patients)



Subacute Thrombosis



RAVEL: Study Design

237 patients with single de novo lesions in native coronar
and 2.5 to 3.5 mm in diameter, randomized trial in Euro

Aspirin
100 mg 12H before PCI
100 mg once daily

Clopidogrel
300 mg 48H before PCI
75 mg once daily

Uncoated BX Velocity Stent (n=118)
+
Clopidogrel for 2 months

BX Velocity Stent Coated with Sirolimus (n=120)
+
Clopidogrel for 2 months

Major Adverse Cardiac Events (MACE) (Death / MI / Urgent TVR)

No Stent Thrombosis
at 6 months

SIRIUS Study

❖ Oral Anti-Platelet Regimen

- Aspirin 325 mg daily
- Clopidogrel 300-375 mg loading

75 mg daily for 3 months

❖ Stent Thrombosis

- No Acute stent thrombosis
- Subacute stent thrombosis : 1 case in each group
- Late stent thrombosis : 1 case in SES group

3 cases in BMS group

C-SIRIUS & E-SIRIUS

❖ Stent Thrombosis

- C – SIRIUS (Clopidogrel for 2 months)

  → Stent thrombosis in 1 pt (2%) in each arms

- E – SIRIUS (Clopidogrel / Ticlopidine for 2 months)

  → Subacute thrombosis in 2 pts (1.1%) in SES

  at 5 & 10 days

  No Late stent thrombosis

Antiplatelet Regimen in TAXUS Trials

	Aspirin daily	Clopidogrel Loading	Clopidogrel 75 mg daily
TAXUS I (3 Centers)	> 80 mg	300 mg	6 mos
TAXUS II (38 Euro Centers)	75 mg	300 mg	6 mos (or Ticlopidine)
TAXUS III (2 Centers)	> 75 mg	300 mg	6 mos
TAXUS IV (73 US Centers)	325 mg	300 mg	6 mos

Stent Thrombosis Rate in TAXUS Trials

	Stent Thrombosis
TAXUS I (3 Centers)	6 M F/U - 0% 2 Y F/U – 0%
TAXUS II (38 Euro Centers)	6 M F/U - 0.8% 12 M F/U – 1.5%
TAXUS III (2 Centers)	6 M F/U - 0% 12 M F/U - 0%
TAXUS IV (73 US Centers)	9 M F/U – 0.6% 12 M F/U – 0.6%

Stent Thrombosis after DES & BMS

A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eliting stents.

(MN Babapulle Lancet 2004;364:583-591)

- ❖ Meta-Analysis of 11 Eligeble RCTs with DES
- ❖ Compared with BMS
- Effective at Decreasing Rates of Restenosis
- No Evidence to Decrease Mortality & MI Rates
- No Difference in the Rate of Stent Thrombosis

AHA Scientific Statement

Percutaneous Coronary Intervention &

Adjunctive Pharmacotherapy in Women

(AJ Lansky Circulation 2005;111:940-953)

- Clopidogrel 300-600 mg load / 75 mg

  : should be continued for at least 2-4 weeks after BMS

  for 3 mos after Sirolimus-ES

  for 6 mos after Paclitaxel-ES

Paclitaxel-Eluting Stent

Taxus Stent (TAXUS I)

: to evaluate the safety of the Slow-Release polymer-coated NIR stent

85 μg of paclitaxel (1.0 μg / mm^2 of stent)

Release Kinetics

- About 80% of the drug is released within the first 1-3 days

Sirolimus-Eluting Stent

Cypher Stent

: 5-μm-thick layer of nonerodable polymer
on the BX Velocity stent

140 μg Sirolimus / cm^2 of stent

Release Kinetics

- Fast-Release : < 15-day drug release
- **Slow-Release** : > 28-day drug release
- About 80% of the drug is released within 30 days

After Stenting ...

- Complete Re-Endothelialization

  occurs within 2-4 weeks

- After Completing the Elution,

  DES would convert itself into a BMS.

- Theoretically,

  Anti-Platelet Coverage more than 2 Months

  Would Be Enough !!!

PCI-CURE Study

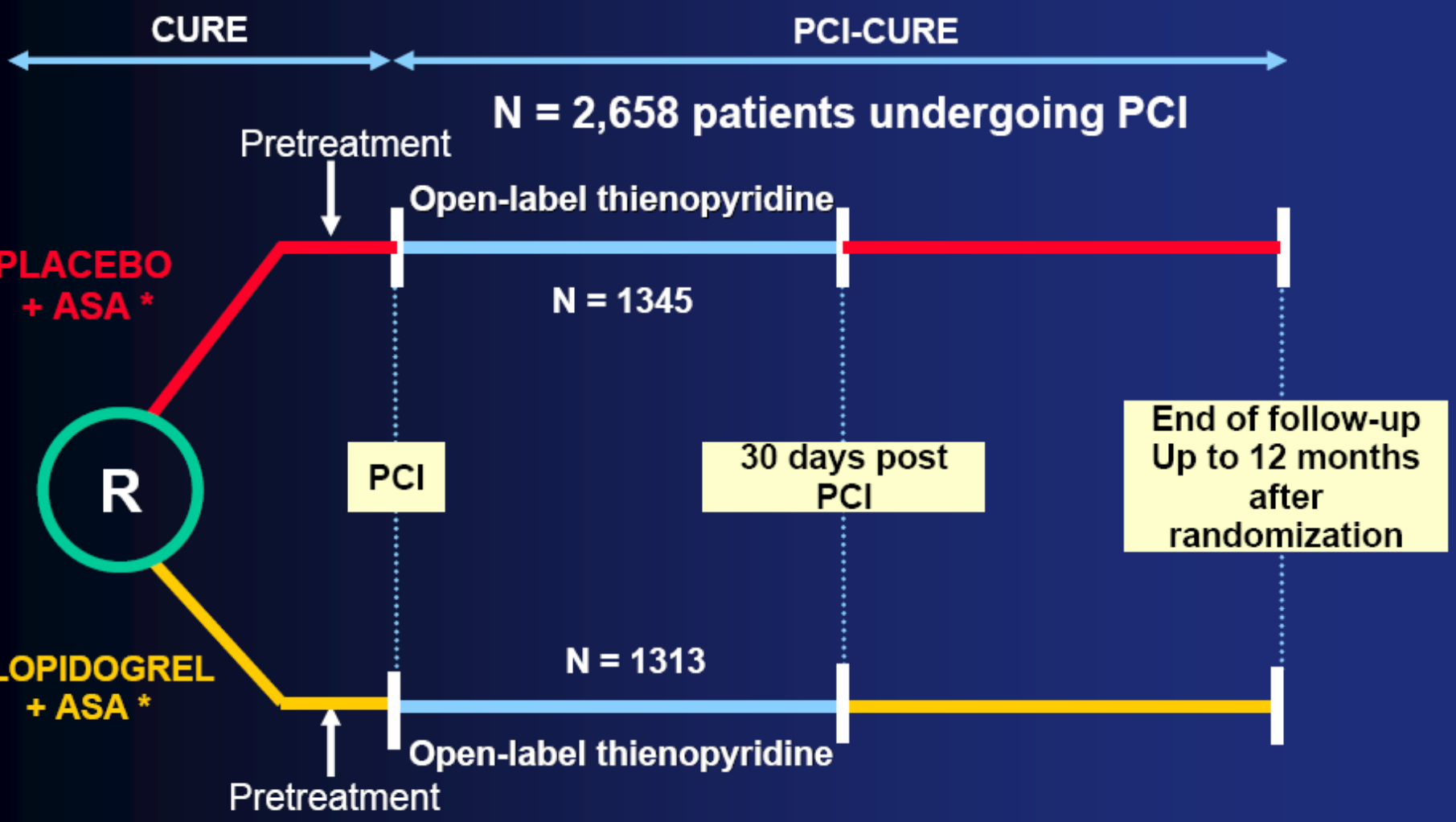
Effects of Pretreatment with Clopidogrel and Aspirin Followed by Long-Term Therapy in Patients Undergoing Percutaneous Coronary Intervention: The PCI-CURE Study.

(SR Mehta Lancet 2001;358:572-33)

- 2658 pts with NSTE ACS undergoing PCI in CURE
- Clopidogrel group
  : Preteratment for 10 days
  Thienopyridine for 4 weeks & a mean of 8 months
- Placebo group
  : Thienopyridine for 4 weeks

PCI-CURE

Study Design



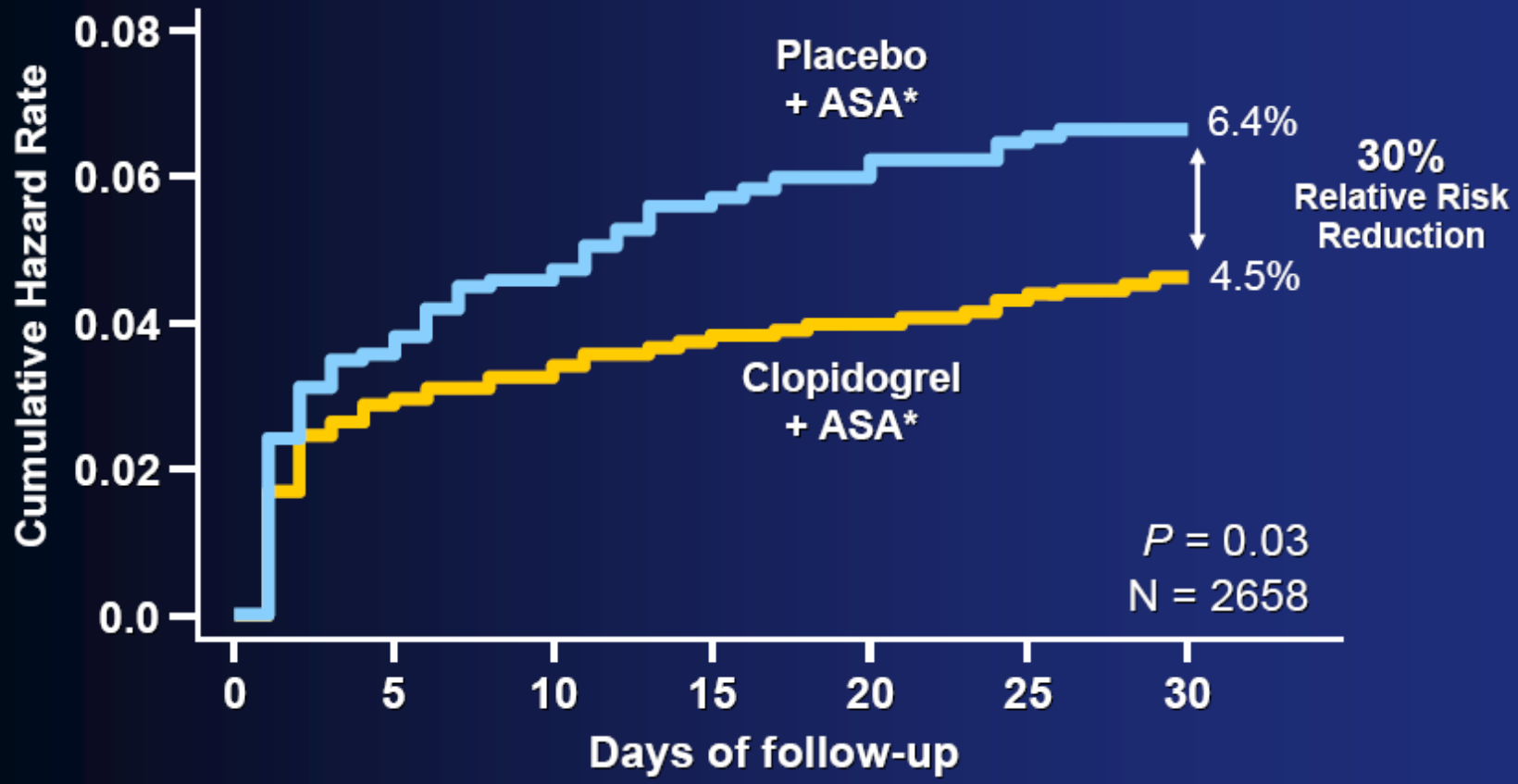
* In addition to other standard therapies.

Mehta et al for the CURE Investigators. *Lancet.* 2001;358:527-533.

PCI-CURE

Effects of Pre-treatment: 30 day results

Composite of MI, urgent revascularization or cardiovascular death



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(SR Mehta Lancet 2001;358:572-33)

- Primary Endpoint – MACE within 30 days of PCI
- Clopidogrel group: 4.5% (vs 6.4% in Cotrol, p=0.03)
- No significant advantage after the first 4 weeks

(P Eriksson Eur Heart J 2004;25:720-2)

- Pre-Treatment Effect

From TCT 2003

The basic "tips and tricks" for DES implantation: What every interventionalist should know

Martin B. Leon, MD

Transcatheter Cardiovascular Therapeutics 2003
Washington, DC; Sept 15-19, 2003

DES – Tips and Tricks

Anti-Thrombotic Regimen

- Pre-Procedure
  - ASA 325 mg daily
  - Clopidogrel 300-600 mg loading dose and 75 mg daily
- Intra-Procedure
  - Heparin (to maintain ACT >250 secs) OR bivalirudin
  - IIb/IIIa platelet inhibitors at operator discretion
- Post-Procedure
  - ASA 325 mg daily
  - Clopidogrel 75 mg daily for at least 3 months

AHA Scientific Statement

Percutaneous Coronary Intervention &
Adjunctive Pharmacotherapy in Women

(AJ Lansky Circulation 2005;111:940-953)

- Aspirin
  : Exact dose after DES has not been determined
- Clopidogrel 300-600 mg load / 75 mg
  : should be continued for at least 2-4 weeks after BMS
  for 3 mo for Sirolimus-ES
  for 6 mo for Paclitaxel-ES

Many recommendations prefer
longer (for 2-6 mos) than
former (for 2-4 wks as in BMS)
in antiplatelet regimen after DES.

→This is empirical
due to theoretical concerns.
There are no solid data favoring longer Tx.

There is no concrete evidence that

longer (for 6 mos) is better than

shorter (for 2-3 mos)

in antiplatelet regimen after DES !!!

All the Drugs

Can be Poison

If Not Used Properly !!!

After implantation of DES,

are the oral antiplatelet agents

always needed for longer (6 mos) ?

The answer is NO !!!

Remember

Voltaire’s bright reflection:

“The best may be

the enemy of the good”.

子曰過猶不及

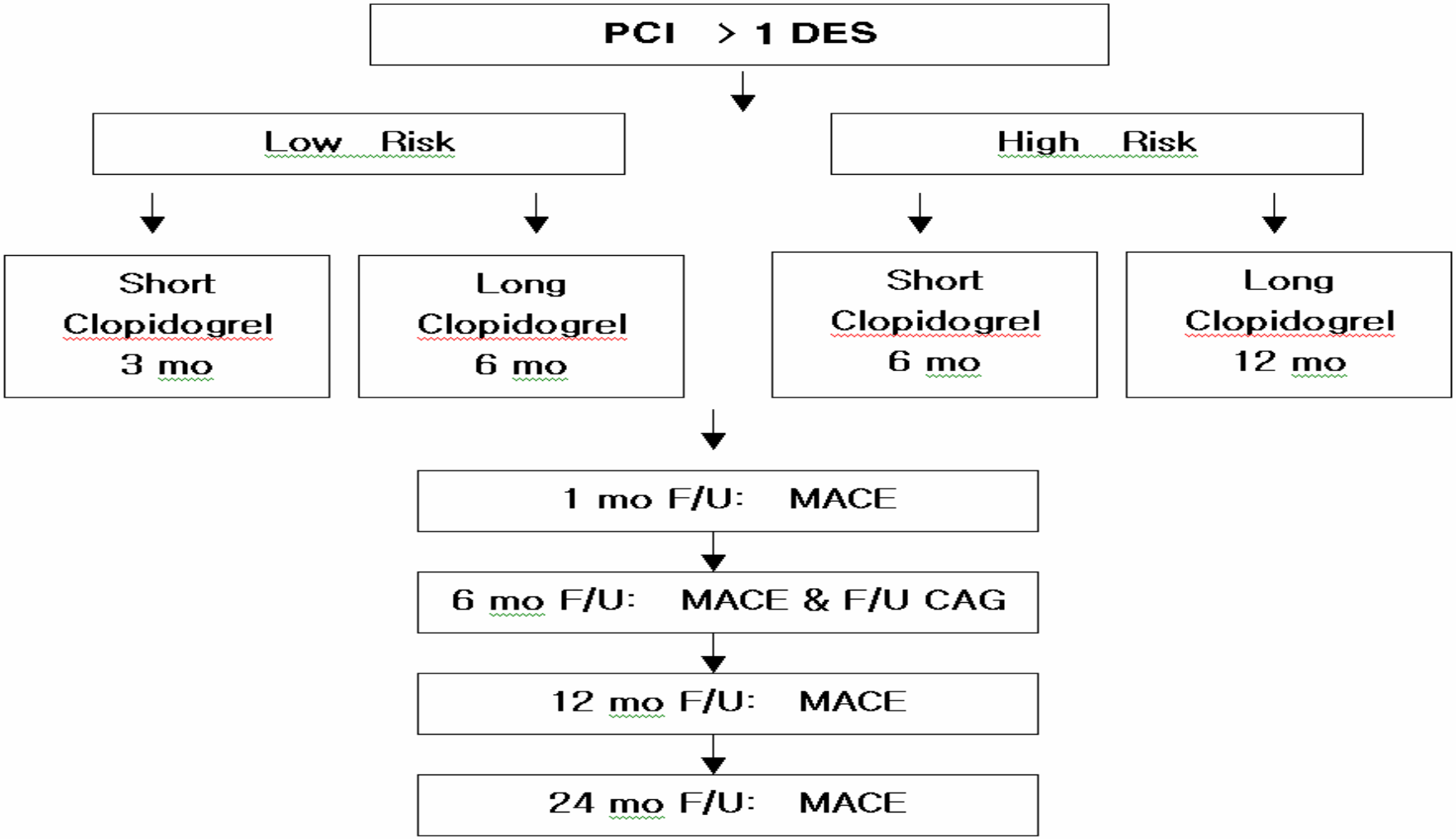
道以中庸爲至賢知者之過雖善勝於愚不肖之不及然其失中則一也

民曰中庸之爲德也其至矣乎

及均也蓋之毫釐繆以千里故聖人之教抑其過引其不及歸於中道而已

REDUCE Study

(REasonable DUration of Clopidogrel in the Era of DES)



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