La doppia antiaggregazione del paziente trattato con stent coronarico

dott. Francesco Abbadessa

Azienda Ospedaliera Universitaria San Martino

Genova

Clinical Forum Genova 8 maggio 2007

Stent e doppia antiaggregazione : da oltre 10 anni

Colombo A, Hall P, Nakamura S, Almagor Y, Maiello L, Martini G, Gaglione A, Goldberg SL, Tobis JM.

Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance.

Circulation 1995; 91: 1676-1688.

Schomig A, Neumann FJ, Kastrati A.

A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents.

N Engl J Med 1996; 334: 1084.

Stent coronarici : duplice terapia antiaggregante

- Aspirina
- Tienopiridina (ticlopidina - clopidogrel)

Razionale

Il doppio trattamento antiaggregante è indispensabile per la necessità di contrastare l'attivazione piastrinica provocata da:

- danno endoteliale (trauma vasale)
- presenza di corpo estraneo (maglie dello stent)

Obiettivo della duplice terapia antiaggregante

Evitare la trombosi dello stent

nella fase iniziale in cui non si è ancora completata l'endotelizzazione

Nonostante l'uso consolidato, recentemente sono emersi diversi problemi

La trombosi degli stent continua a verificarsi : ~ 0.6 % /anno

Problemi attuali : dosi, durata del trattamento, resistenza, misurazione dell'attività antiaggregante

Una parte delle indicazioni in uso è basata su documenti di consenso in assenza di chiare evidenze cliniche

Principali aspetti controversi

- **dose ASA ed interazione con altri FANS**

- **Clopidogrel:** durata del trattamento e prevenzione della sospensione precoce

- **Stent medicati:** trombosi tardiva

ACC/AHA/SCAI Practice Guideline

ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention—Summary Article

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention)

Aspirin dose : load

Class I

1. Patients already taking daily chronic aspirin therapy should take 75 to 325 mg of aspirin before the PCI procedure is performed. *(Level of Evidence: A)*

A daily dose of 75 mg of aspirin has been shown to result in improved cardiovascular outcomes similar to daily doses of 325 mg but with fewer bleeding complications (67–69).

2. Patients not already taking daily chronic aspirin therapy should be given 300 to 325 mg of aspirin at least 2 hours and preferably 24 hours before the PCI procedure is performed. *(Level of Evidence: C)*

Higher doses of aspirin are recommended for patients not already taking aspirin therapy immediately before PCI procedures.

Circulation - January 3/10, 2006

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Aspirin dose : stent

3. After the PCI procedure, in patients with neither aspirin resistance, allergy, nor increased risk of bleeding, aspirin 325 mg daily should be given for at least 1 month after bare-metal stent implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which daily chronic aspirin use should be continued indefinitely at a dose of 75 to 162 mg. *(Level of Evidence: B)*

Circulation - January 3/10, 2006

ESC GUIDELINES

To improve the quality of clinical practice and patient care in Europe

European Heart Journal (2005) **26**, 804–847
doi:10.1093/eurheartj/ehi138

EUROPEAN SOCIETY OF CARDIOLOGY®

For the first time !

ESC Guidelines

Guidelines for Percutaneous Coronary Interventions

The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology

European Heart Journal - March 15, 2005

Adjunctive Medications for PCI: (1)

Acetylsalicylic Acid (ASA), Ticlopidine and Clopidogrel

- The "double" antiplatelet therapy with ASA and clopidogrel is standard for the pre-treatment of patients with stable CAD undergoing PCI – with or without planned stent implantation.
- After implantation of a bare metal stent, clopidogrel must be continued for 3-4 weeks and ASA life-long.
- In patients presenting with NSTE-ACS, ASA and, if clinically justifiable, immediate administration of clopidogrel, is the basic standard antiplatelet regimen.
- After the acute phase, the continuation of 100 mg/d ASA + clopidogrel 75mg/d over 9-12 months is beneficial.

What dose of aspirin is best ?

- Currently available doses of ASA used in CV disease have no basis in their antiplatelet efficacy

- While there are no clinical data supporting increased efficacy with daily ASA doses > 75 mg, there are suggestive data of increased harm

Steven Steinhubl at ACC 2007

Just married

Moglie:

Xia Shujuan, 29 a

h: **1.68 m**

Marito:

Bao Xishun 56 a

h: **2.36 m**

Chifeng, Mongolia

Marzo 2007

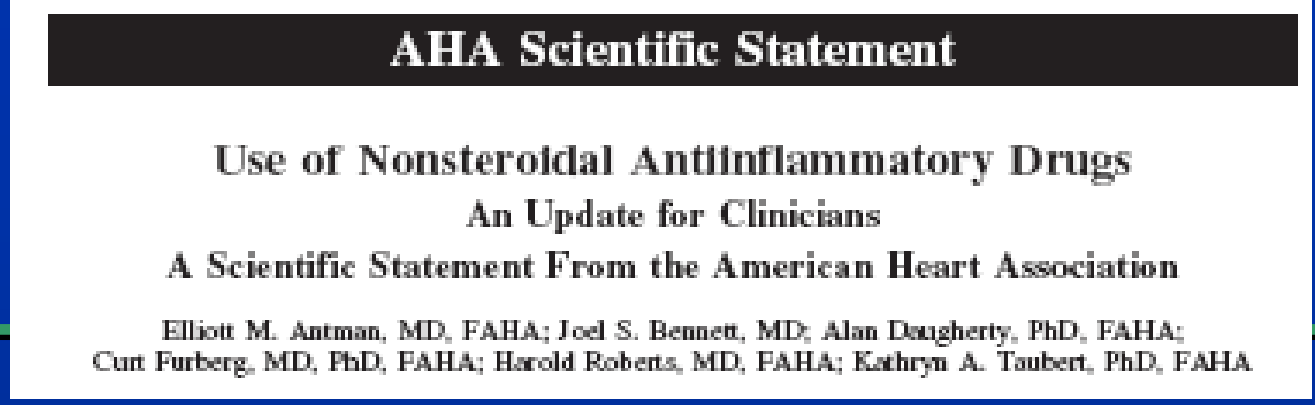
E’ sufficiente un’ uguale dose di ASA per questi due adulti ?

Oasis – 7

on going

- ~ 13 000 ACS pts (NSTEMI) planned for early PCI within 24 h

- **ASA** : low dose, 75-100, vs high dose, 325 mg
- **Clopidogrel** : low dose, 300, vs high dose, 600 mg



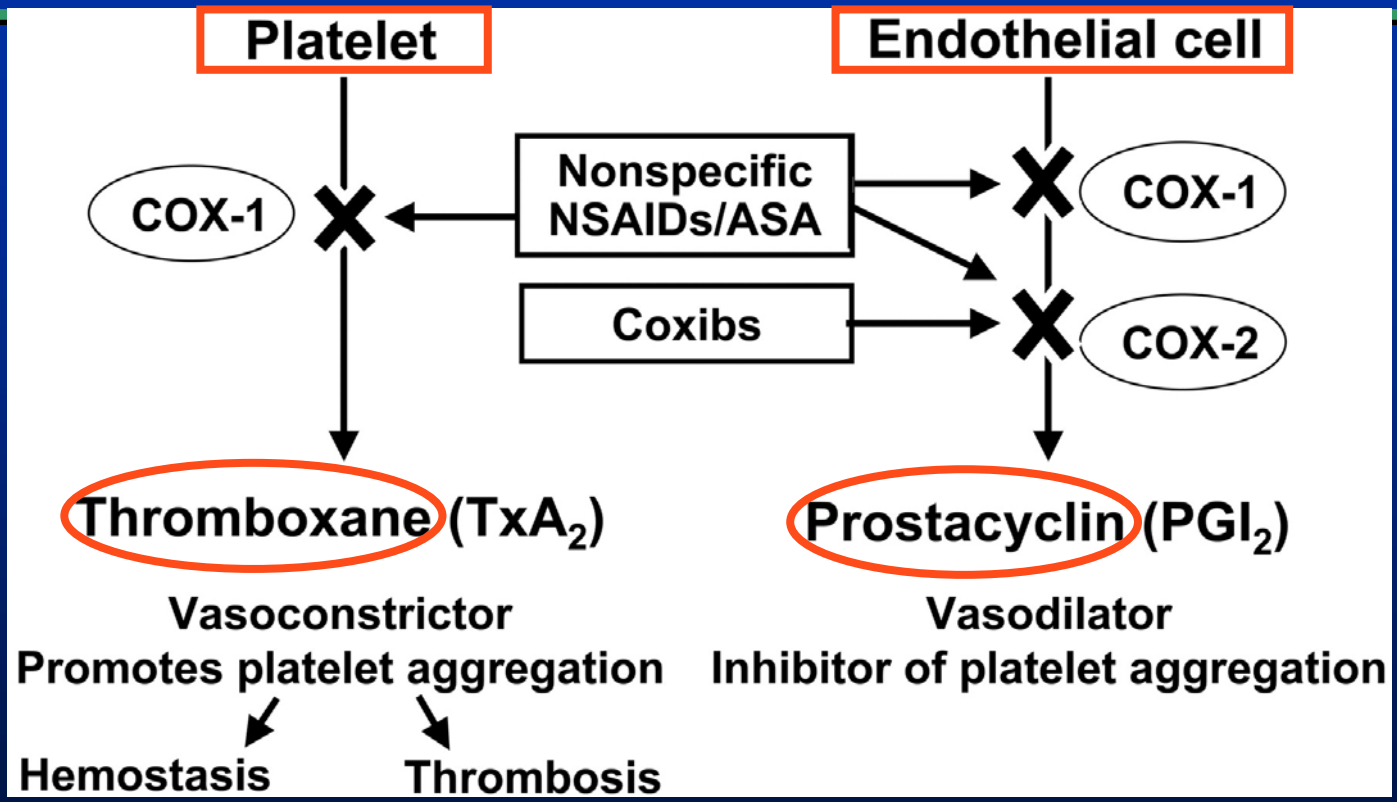
Interazione ASA – altri FANS

Ridotta azione dell'ASA per competizione sfavorevole rispetto ad altri FANS sulla inibizione delle ciclossigenasi COX1 :

aumentato rischio trombotico

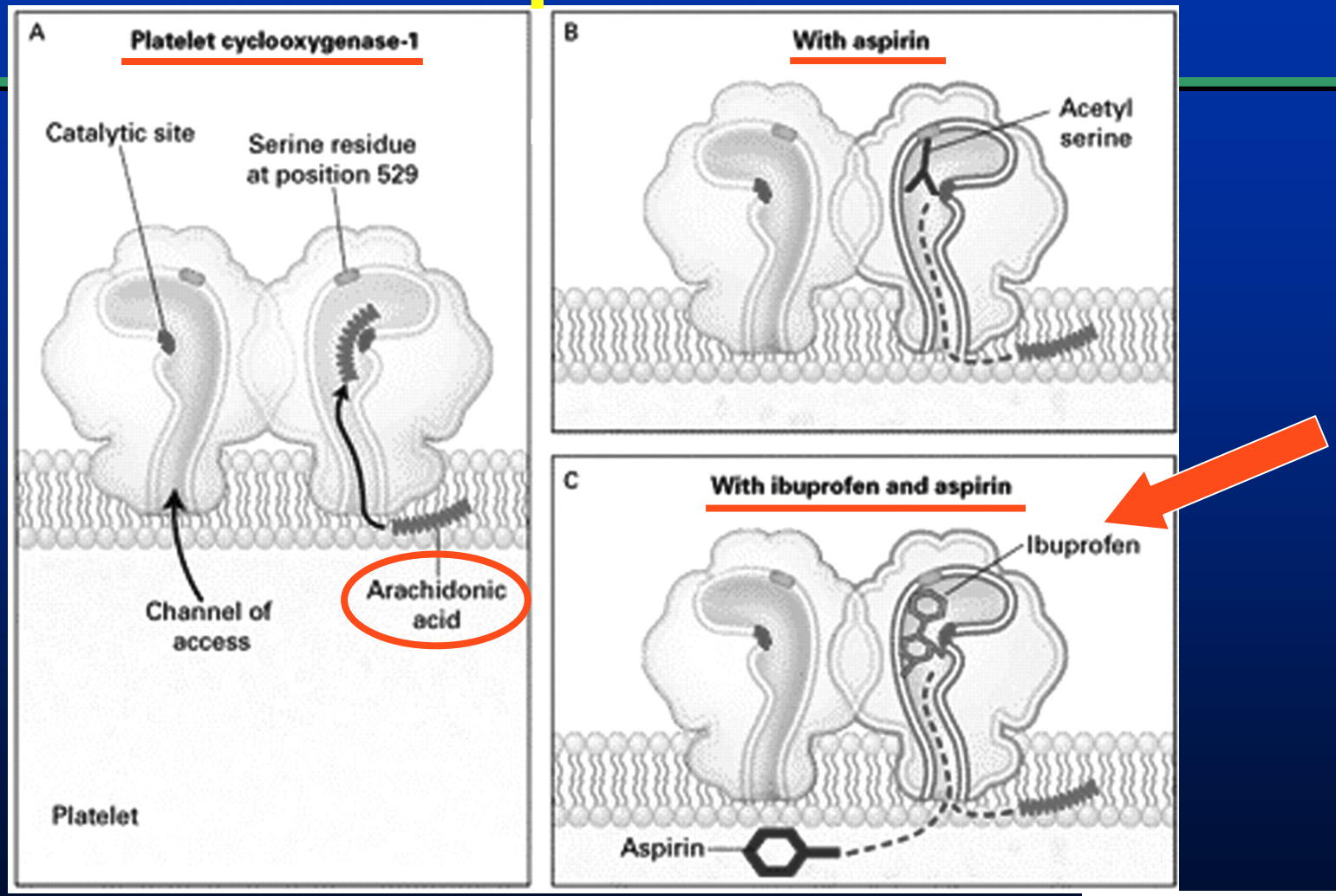
Circulation March 27, 2007 published online February 26, 2007, in *Circulation*

Meccanismo di azione ASA & altri FANS



Bates, E. R. et al. Circulation 2005;111:e267-e271

Competizione di ASA e ibuprofene su COX-1 piastrinica



Bates, E. R. et al. Circulation 2005;111:e267-e271

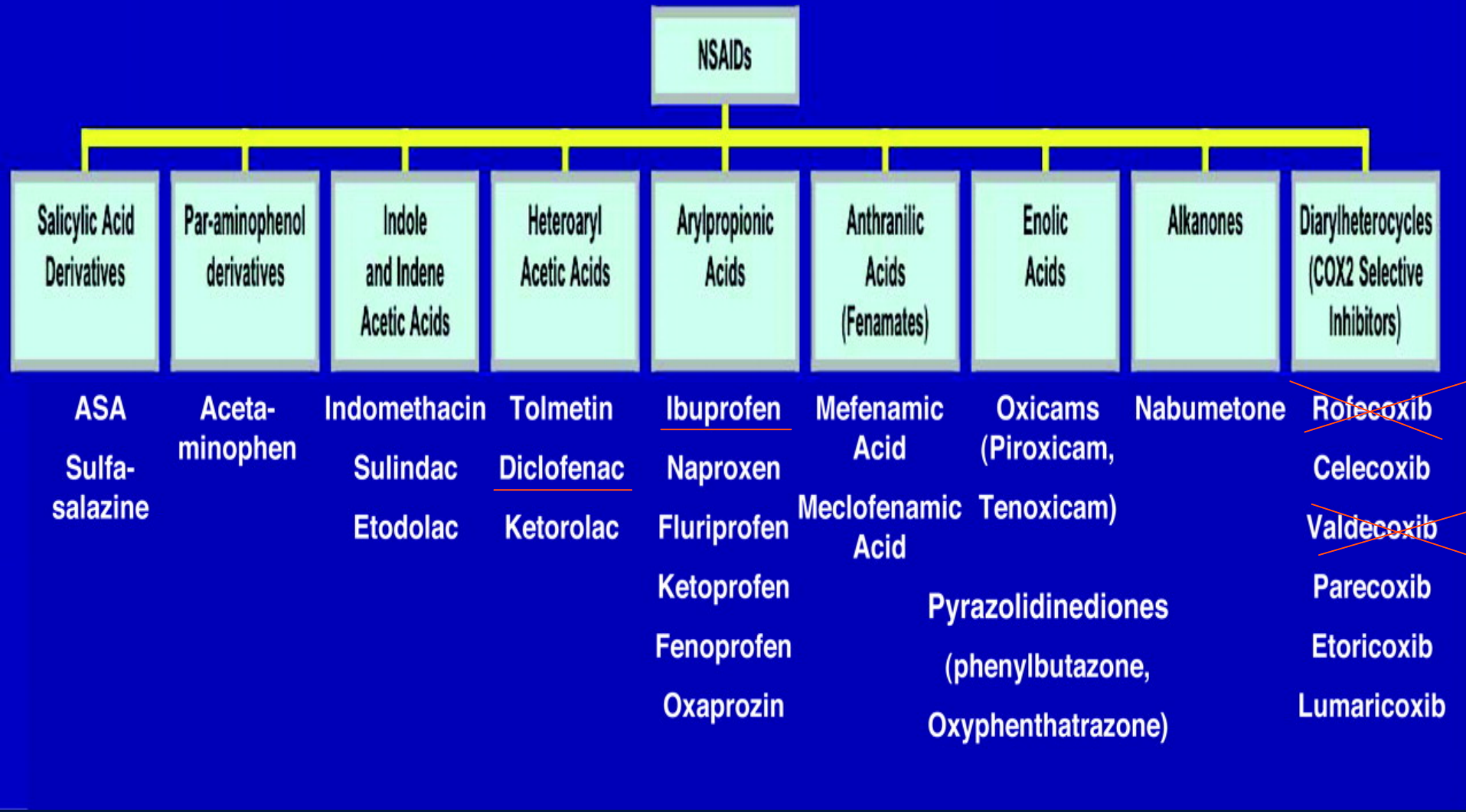
Composite cardiovascular outcomes in the ibuprofen substudy of high-risk patients
TARGET study

Composite cardiovascular outcomes*	Lumiracoxib	Ibuprofen	p
No aspirin (%)	0.92	0.80	NS
Low-dose aspirin (%)	0.25	2.14	0.03
Overall (%)	0.56	1.61	0.05

***Composite end point includes nonfatal and silent MI, stroke, and cardiovascular death**

"We think that ibuprofen should be avoided in high-risk cardiovascular patients. Secondly, we think all NSAIDs should be given at their lowest dose and at the least frequency."

Farkouh ME et al. *Ann Rheum Dis* 2007; published online before print April 5, 2007



Antman, E. M. et al. Circulation 2007;115:1634-1642

Circulation

Black box warning for NSAIDs

Diclofenac sodium enteric-coated tablets

Tablets of 25 mg, 50 mg, and 75 mg

Rx only

Prescribing information

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS.)

- Voltaren® (diclofenac sodium enteric-coated tablets) is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

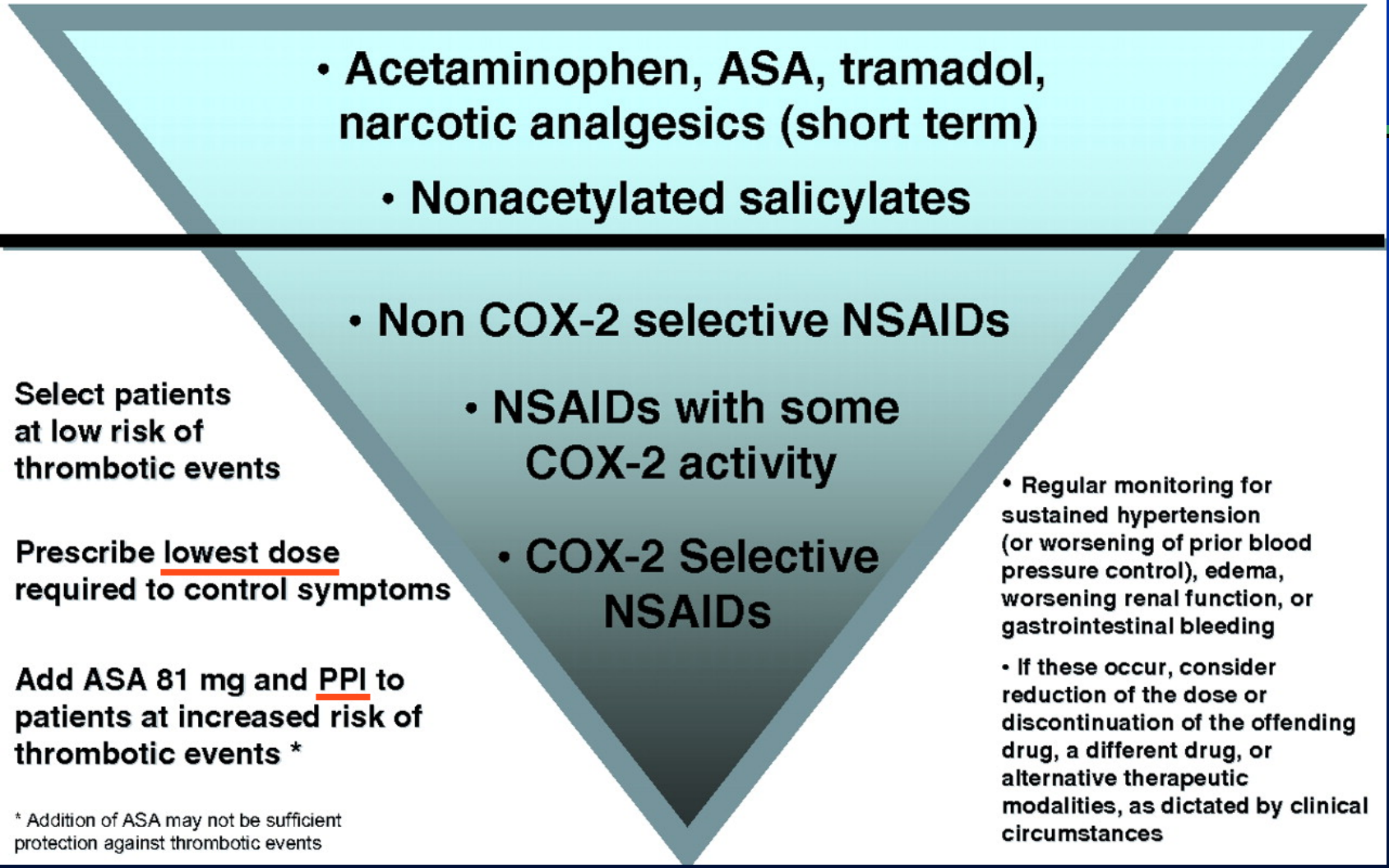
Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (See WARNINGS).

Antman, E. M. et al. Circulation 2007;115:1634-1642

Circulation

Stepped Care Approach to Pharmacologic Therapy for Musculoskeletal Symptoms With Known Cardiovascular Disease or Risk Factors for Ischemic Heart Disease



Antman, E. M. et al. Circulation 2007;115:1634-1642

Circulation

March 27, 2007

Interazioni ASA – altri FANS

- Evitare la somministrazione contemporanea di Ibuprofene (es. Brufen)
- Preferire paracetamolo o naproxene (es. Naprosyn)
- Brevi periodi di trattamento a basse dosi
- Controindicazione per i COX 2 selettivi (EMEA, AIFA)

E' in corso lo studio Precision (20 000 pts) per valutare l'interazione tra ASA e FANS in pts con coronaropatia

Tienopiridine

Meccanismo di azione:

blocco del recettore piastrinico dell'ADP (P2Y12)

- I^ generazione : ticlopidina (ridotto profilo di sicurezza)
- II^ generazione : clopidogrel (attuale standard)
- III^ generazione : inibitori sperimentali del recettore $P2Y_{12}$
  - prasugrel (Triton TIMI 38) ~ 14 000 pts
  - cangrelor iv (Champion PCI)
  - AZD6140 (Plato) ~ 18 000 pts

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Clopidogrel

4. A loading dose of clopidogrel should be administered before PCI is performed. *(Level of Evidence: A)* An oral loading dose of 300 mg, administered at least 6 hours before the procedure, has the best established evidence of efficacy. *(Level of Evidence: B)*

5. In patients who have undergone PCI, clopidogrel 75 mg daily should be given for at least 1 month after bare-metal stent implantation (unless the patient is at increased risk for bleeding; then it should be given for a minimum of 2 weeks), 3 months after sirolimus stent implantation, and 6 months after paclitaxel stent implantation, and ideally up to 12 months in patients who are not at high risk of bleeding. *(Level of Evidence: B)*

Adjunctive Medications for PCI : (2)

Acetylsalicylic Acid (ASA), Ticlopidine and Clopidogrel

- ASA should be given i.v. to all patients with STEMI as soon as possible after the diagnosis is established - if clinically justifiable.
- With the concept of primary PCI and primary stenting in STEMI, clopidogrel will be additionally administered in these patients, preferably with a loading dose of 600 mg.
- After drug-eluting stents clopidogrel should be administered in addition to ASA for for 6-12 months to avoid late vessel thrombosis.

Table 8 Recommendations for clopidogrel as adjunctive medication for PCI

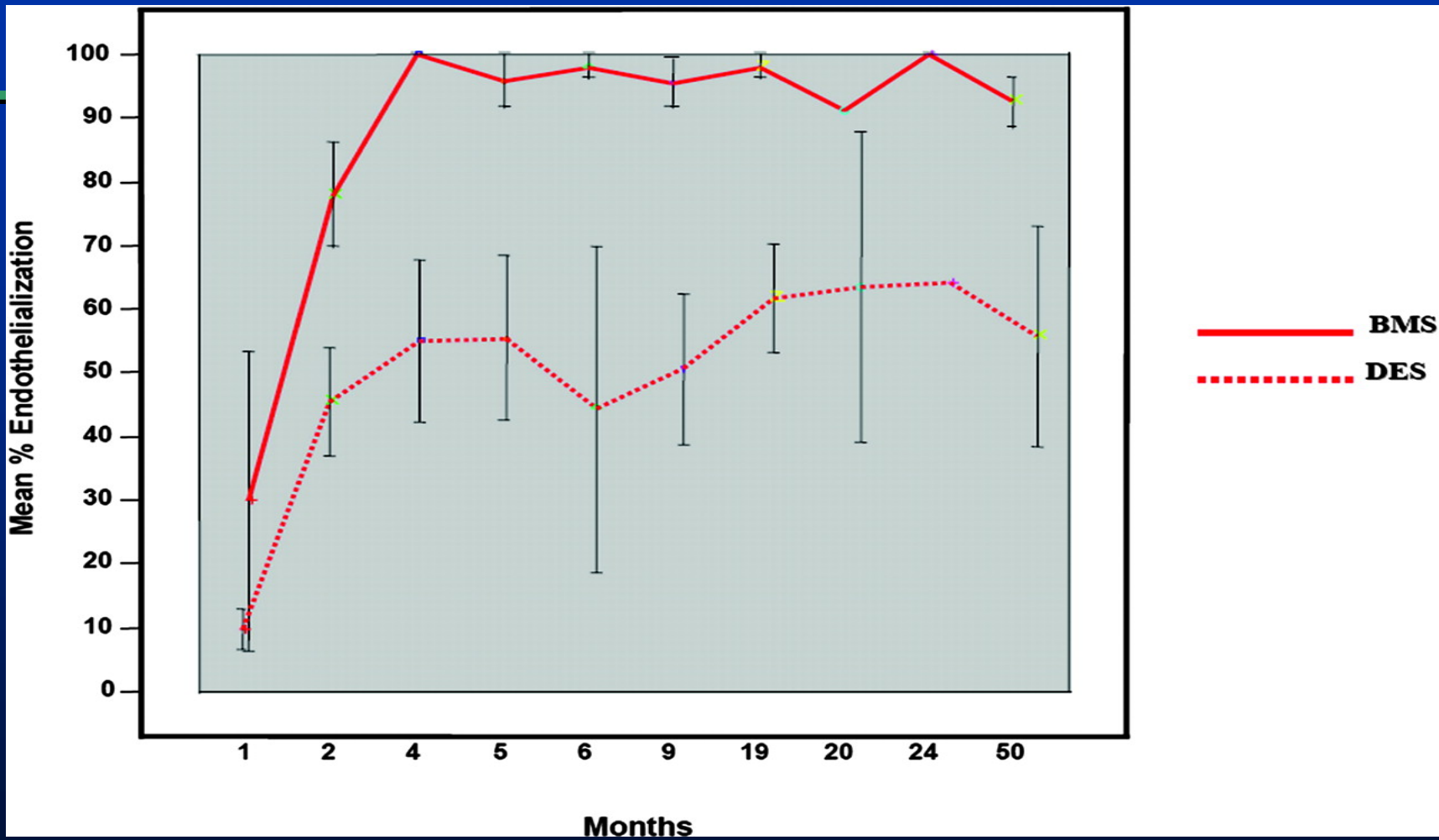
Indication	Initiation and duration	Classes of recommendations and levels of evidence	Randomized studies for levels A or B
Pre-treatment of planned PCI in stable CAD	Loading dose of 300 mg at least 6 h before PCI, ideally the day before	I C	–
Pre-treatment for primary PCI in STEMI or immediate PCI in NSTE-ACS or ad hoc PCI in stable CAD	Loading dose of 600 mg, immediately after first medical contact, if clinically justifiable	I C	–
After all bare metal stent procedures	3–4 weeks	I A	CLASSICS TOPPS Bad Krozingen
After vascular brachytherapy	12 months	I C	–
After drug-eluting stents	6–12 months	I C	–
After NSTE-ACS	Prolonged for 9–12 months	I B	CURE

Durata del trattamento: fino alla completa endotelizzazione degli stent ?

L'endotelizzazione degli stent richiede un tempo variabile:

- Stent tradizionali: almeno 30 gg
- Stent medicati : diversi mesi

Temporal sequence of re-endothelialization in BMS and DES



Luscher, T. F. et al. Circulation 2007;115:1051-1058

Circulation

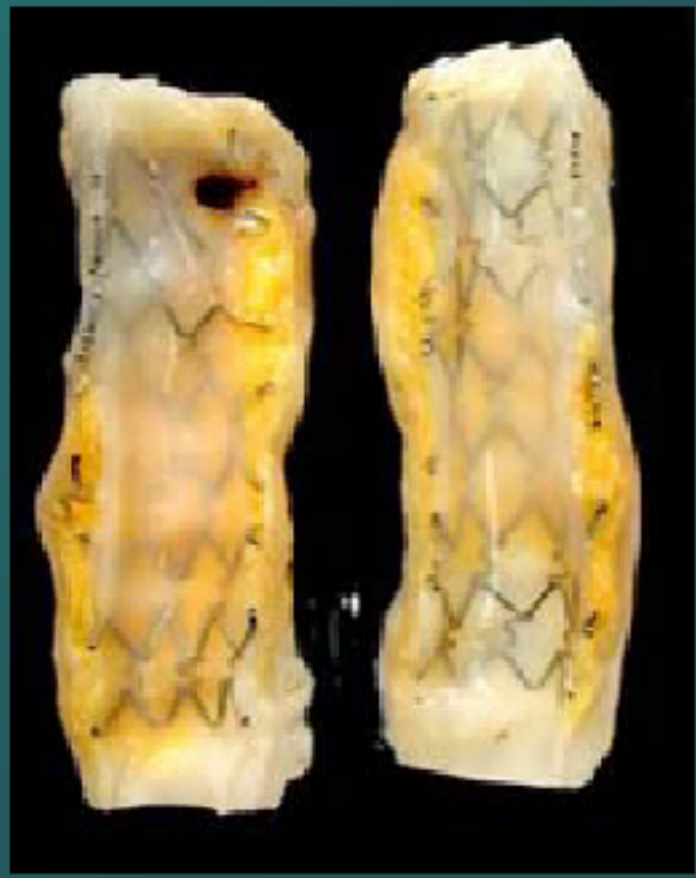
What is the Purpose of a Drug-eluting Stent?

- To eliminate excess the neointimal proliferation that occurs with bare metal stents compared to balloon angioplasty

Restenosis 20-30%

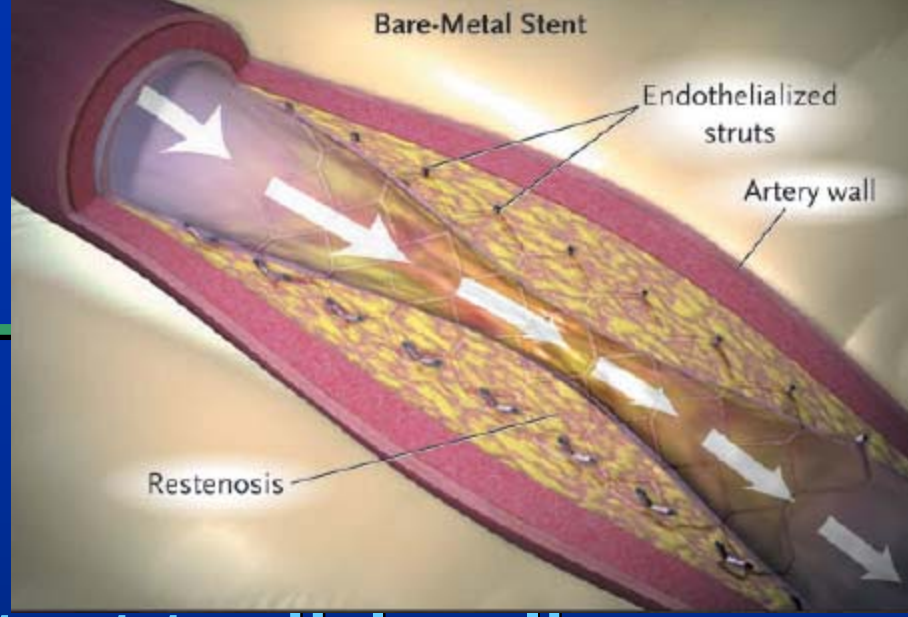
Pathology Findings - Sirolimus-Eluting Stents from Different Coronary Arteries in the Same Patient (delayed healing)

BMS 24 Months after Deployment



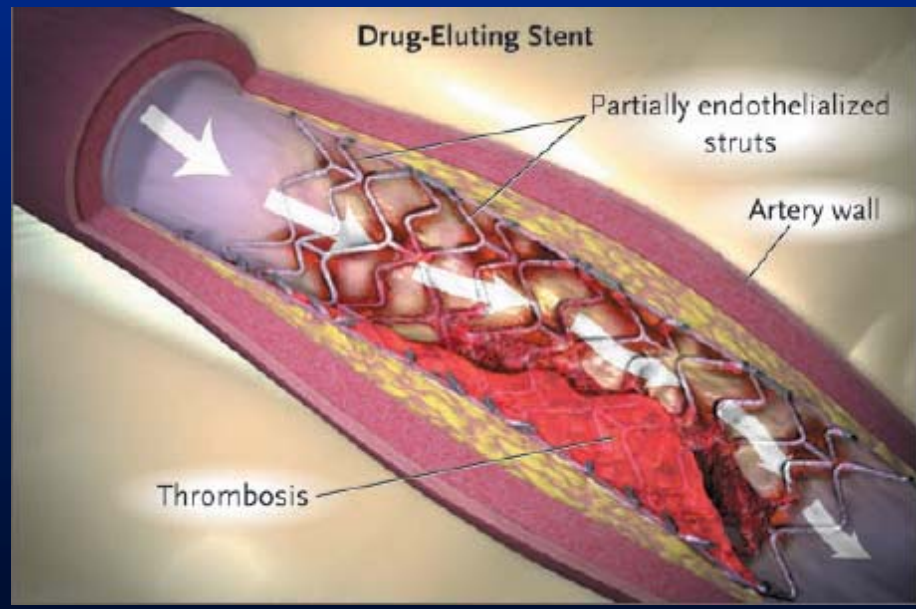
Cypher 16 Months after Deployment

Problemi con gli stent



- **Ristenosi :**

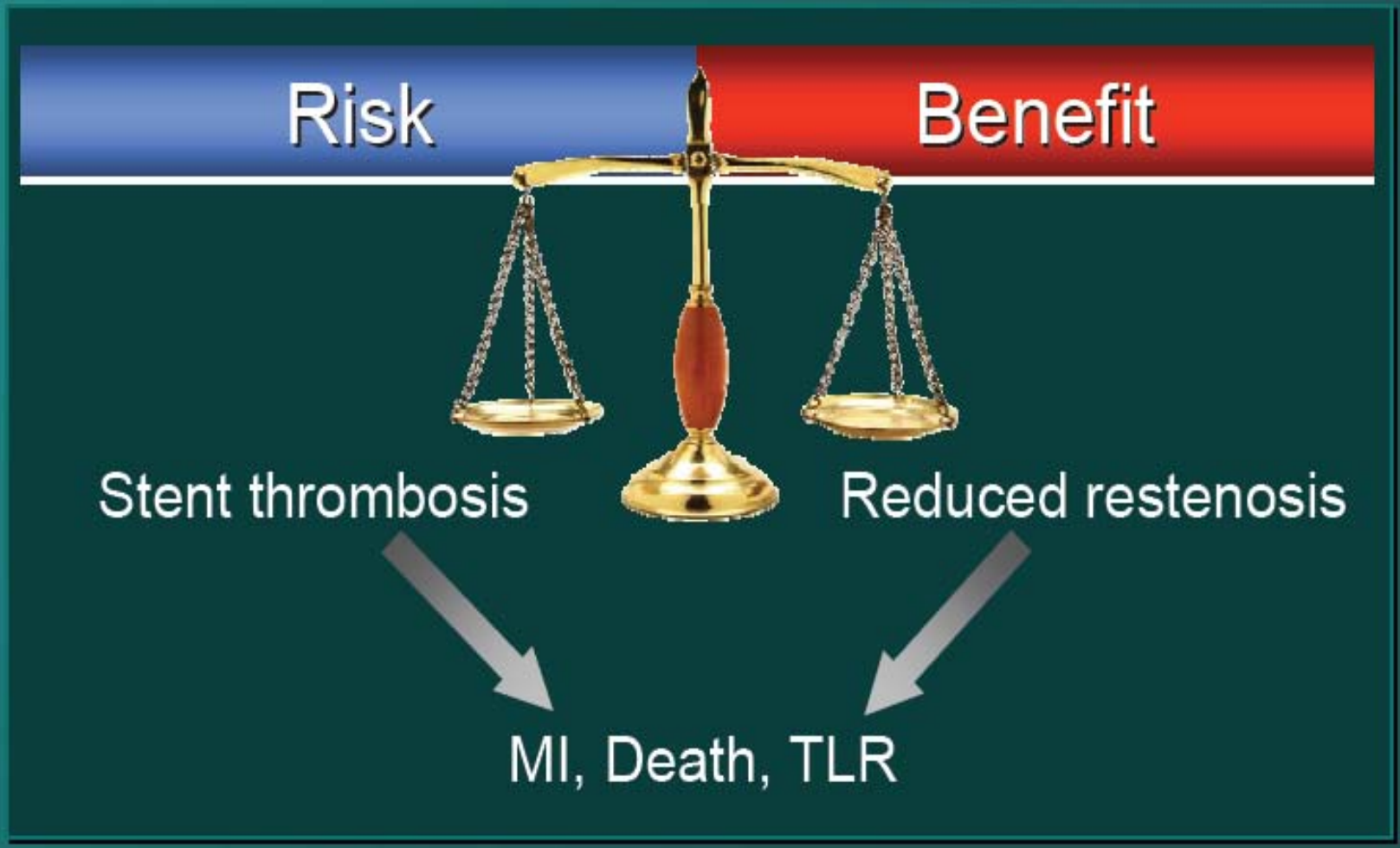
  Tallone d'Achille degli stent tradizionali:



- **Trombosi tardiva :**

  Spada di Damocle degli stent medicati:

The DES Scale



History of stents

Early 1990s: Bare-metal stents were first used

2003: Cypher (sirolimus-eluting) stent introduced in the US

2004: Taxus (paclitaxel) stent introduced

There are currently ~6 million people with drug-eluting stents

Average costs:

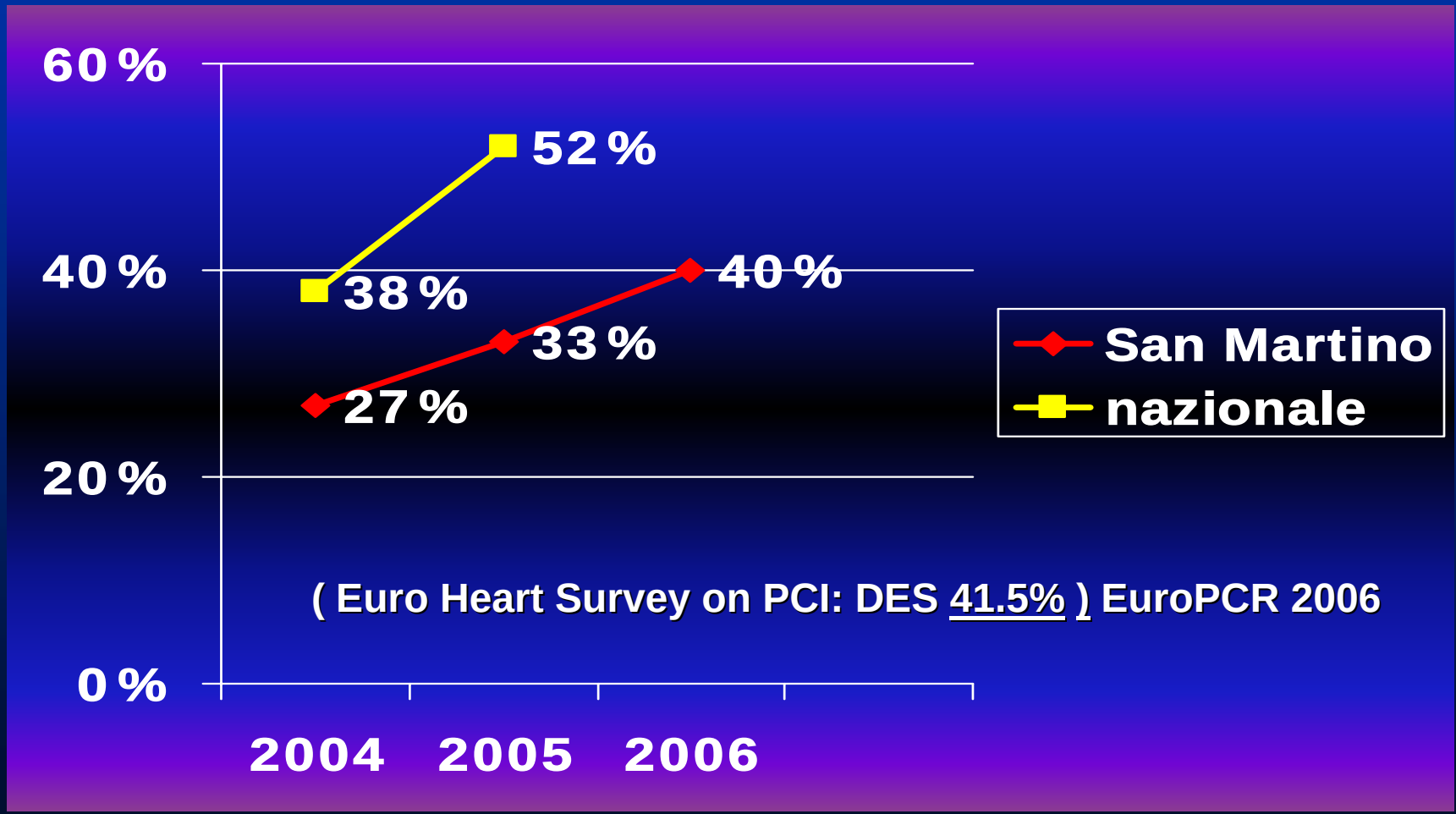
- **Drug-eluting stent: >$2000**
- **Bare-metal stent: $800**

Fuster

U.S. Penetration of DES

Cypher approved April 2003 and Taxus approved March 2004

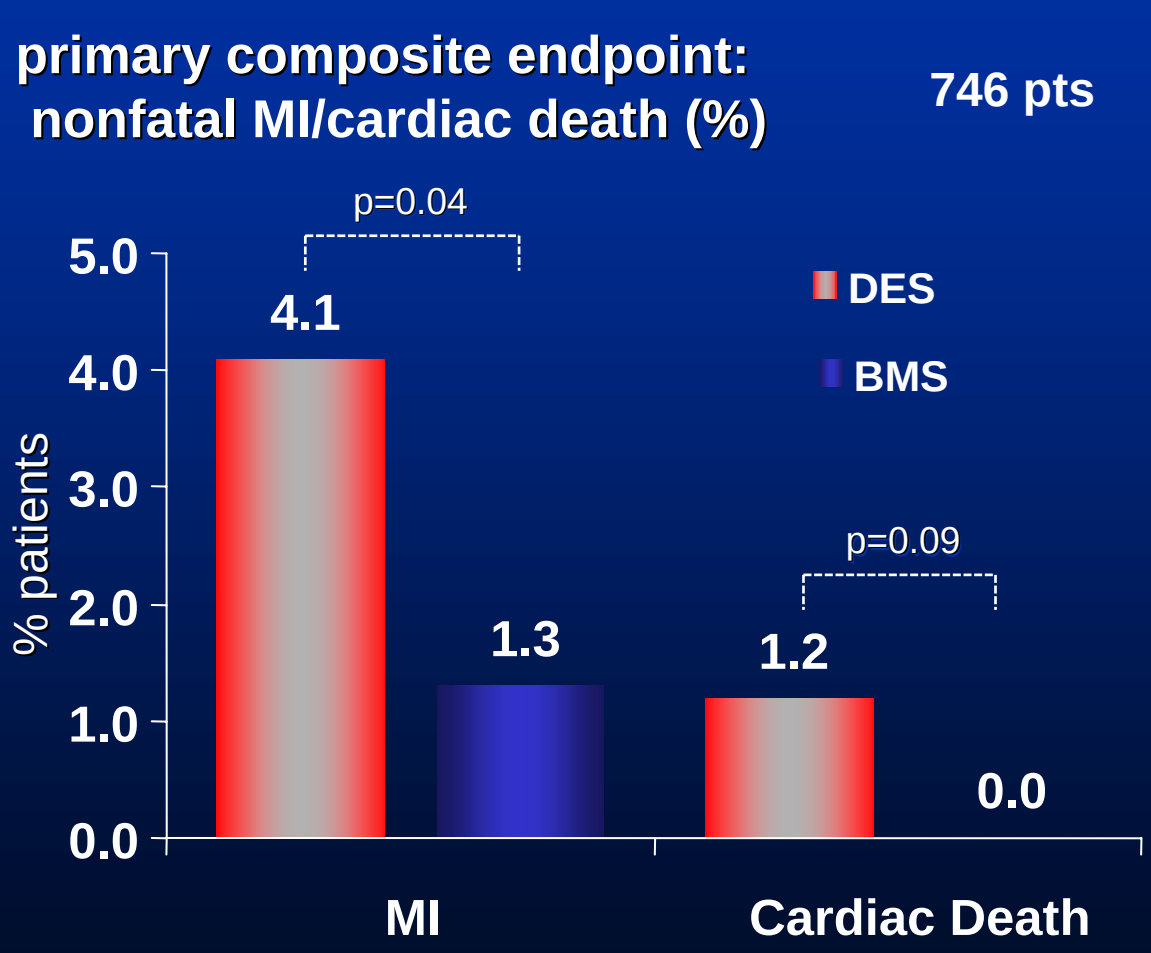
Quota DES nazionale, europea e nel nostro reparto



Dati SICI-GISE

BASKET LATE Trial: Late Events (7 to 18 months)

Presented at ACC March 2006



- Non-fatal MI was higher in the DES group compared with the BMS group (4.1% vs. 1.3%, p=0.04).
- Also, cardiac death trended higher in the DES group than in the BMS group (1.2% vs. 0%, p=0.09).

Pfisterer M. J Am Coll Cardiol ; Dec 19, 2006

THE WALL STR

WSJ.com THURSDAY, JUNE 22, 2006 - VO

Concerns Prompt Some Hospitals To Pare Use of Drug-Coated Stents

By Sylvia Pagán Westphal

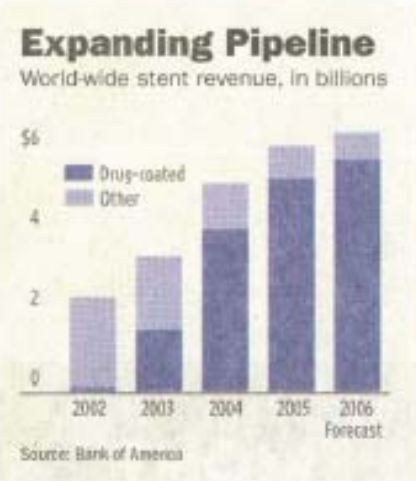
Rising concern over potentially deadly blood clots has led some cardiac centers to cut back on use of drug-coated stents—tiny, wire-mesh tubes that have propped open the arteries of more than three million heart patients since their introduction in 2003.

The moves come as a growing number of studies question the effectiveness and safety of the stents, which are coated with drugs to prevent arterial scarring. They have quickly become by far the most common form of stent in use, generating $5.3 billion in sales last year in a field dominated by Boston Scientific Corp. and Johnson & Johnson.

Hospitals aren't drastically curbing use of coated stents, and there's no indication yet of an overall decline in sales of them. But some leading hospitals have started substituting uncoated, bare-metal stents in some patients.

Moreover, the debate over the safety of drug-coated stents could signal turmoil in the booming industry. Drug-coated stents, which cost about $2,300 apiece, are far more profitable than the uncoated variety, which sell for about $700.

The new research also raises questions of long-term risks for patients who already have the devices. A recent Swiss study found 3.3 more heart attacks and deaths per 100 patients with drug-coated stents than with the uncoated, bare-metal ones, beginning six months after implantation and ending a year later. The heart attacks and deaths were mostly attributed to blood clots.



Stents are designed to keep arteries open after they are cleared of fatty deposits. The idea is to prevent a future heart attack and avoid more risky heart-bypass surgery. Millions of heart patients have received stents since they won federal approval in the early 1990s.

But stents can trigger the growth of scar tissue that gradually narrows the artery again, a condition called restenosis. This rarely leads to deaths from heart attacks, but can affect a patient's quality of life by causing chest pain. If restenosis progresses, a patient must get the area opened up again—a process called "revascularization."

Drug-coated stents were designed to combat restenosis and reduce the need

Please Turn to Page A15, Column 1

…the debate over the safety of drug-coated stents could signal turmoil in the booming industry.

Stent: fatturato 2006

~ 6 miliardi di $

TUESDAY

ESC Congress News

WORLD HEART FEDERATION

World Congress of Cardiology 2006

The unique meeting of the European Society of Cardiology Congress 2006 and the World Heart Federation's XVth World Congress of Cardiology

Do drug-eluting stents increase deaths?

TWO SEPARATE, independent meta-analyses, presented in Hot Line session I, suggest drug-eluting stents (DES) may increase death, Q-wave myocardial infarction (clinical surrogates of in-stent thrombosis) and cancer deaths, bringing the long-term safety of DES firmly into the spotlight. Discussant Salim Yusuf (McMaster University, Canada) hailed the data as one of the most important presentations to come out of this year's meeting.

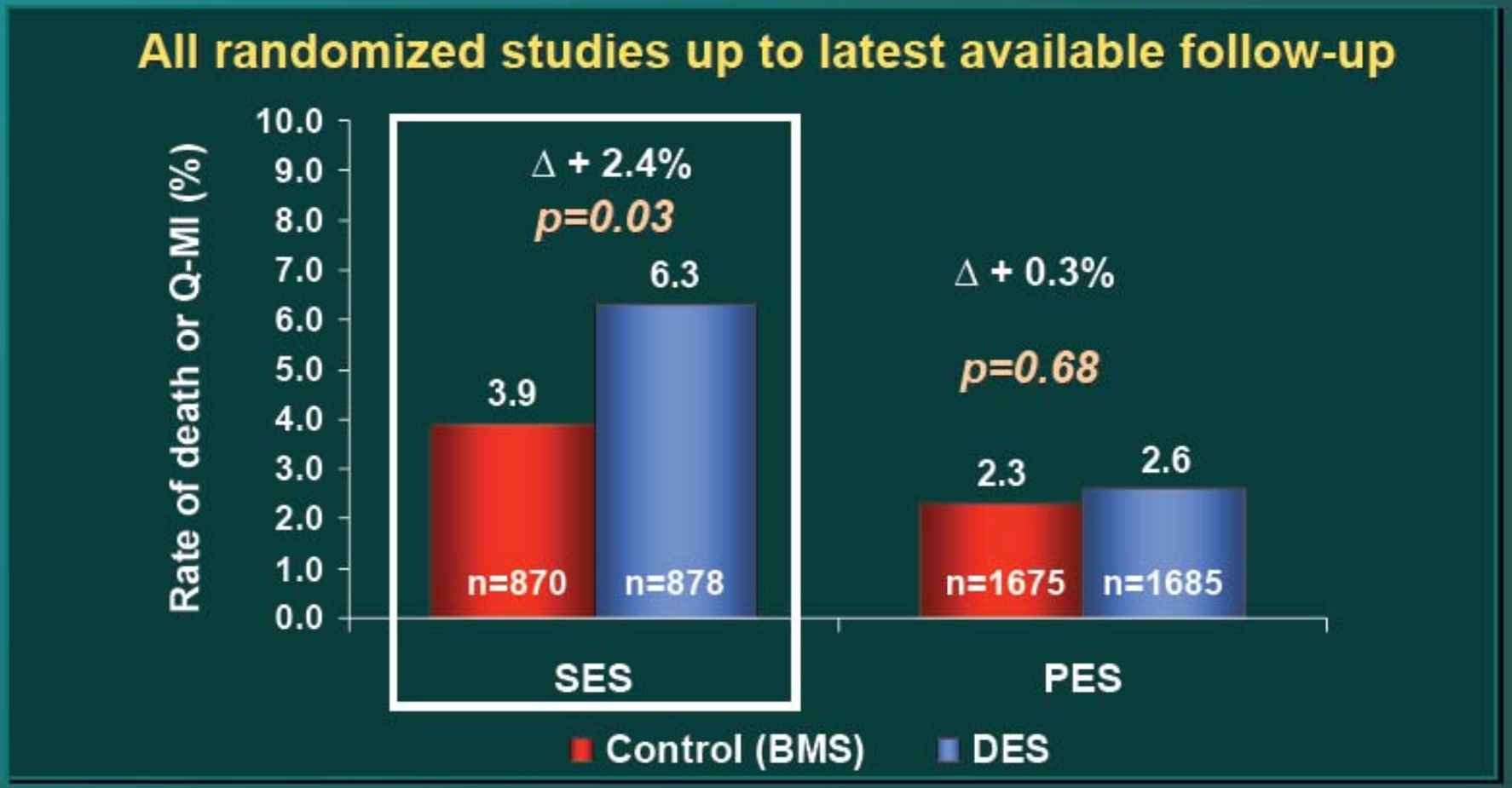
"Six million people in the world have been implanted with DES, yet their long-term safety and efficacy is unknown," said Yusuf. "I've a feeling the data we're seeing today is only the tip of the iceberg. We need to encourage more public access to the data."

obtain this data from the manufacturer," said Nordmann. He speculated that the increase in cancer might be due to a rapid impairment of the immune system.

Yusuf widened the debate to include percutaneous coronary intervention (PCI). "The overuse of PCI is an insidious change in the culture of cardiology that needs to be reversed," he said. The use of PCI was established in MI, high-risk unstable angina and cardiogenic shock. However, its use in stable disease was a totally different question.

"There's no beneficial influence on mortality – PCI does nothing to prevent heart attack. All we are doing is providing short-term relief of chest pain. It's not re-stenosis that kills but the

Incidence of Serious Adverse Events (Death or MI)



Camenzind E, ESC 2006, Oral Presentation #992

Forte impatto mediatico e preoccupazione per i DES

FDA meeting on DES
Dec 7-8, 2006

As many as 40 different presentations of data from around the world

Day 1

- **On-label** indications for drug-eluting stents, which are fairly restrictive

Day 2

- **Off-label** indications, which are the dominant uses (more complex lesions, ACS, diabetes)

  ~ 60%–70% of DES are used for off-label indications

United States and European Collaboration Academia, Industry and Regulatory

Academic Research Consortium - ARC

US Investigators

- Harvard Clinical Research Institute
- Cardiovascular Research Foundation
- Duke Clinical Research Institute

European Investigators

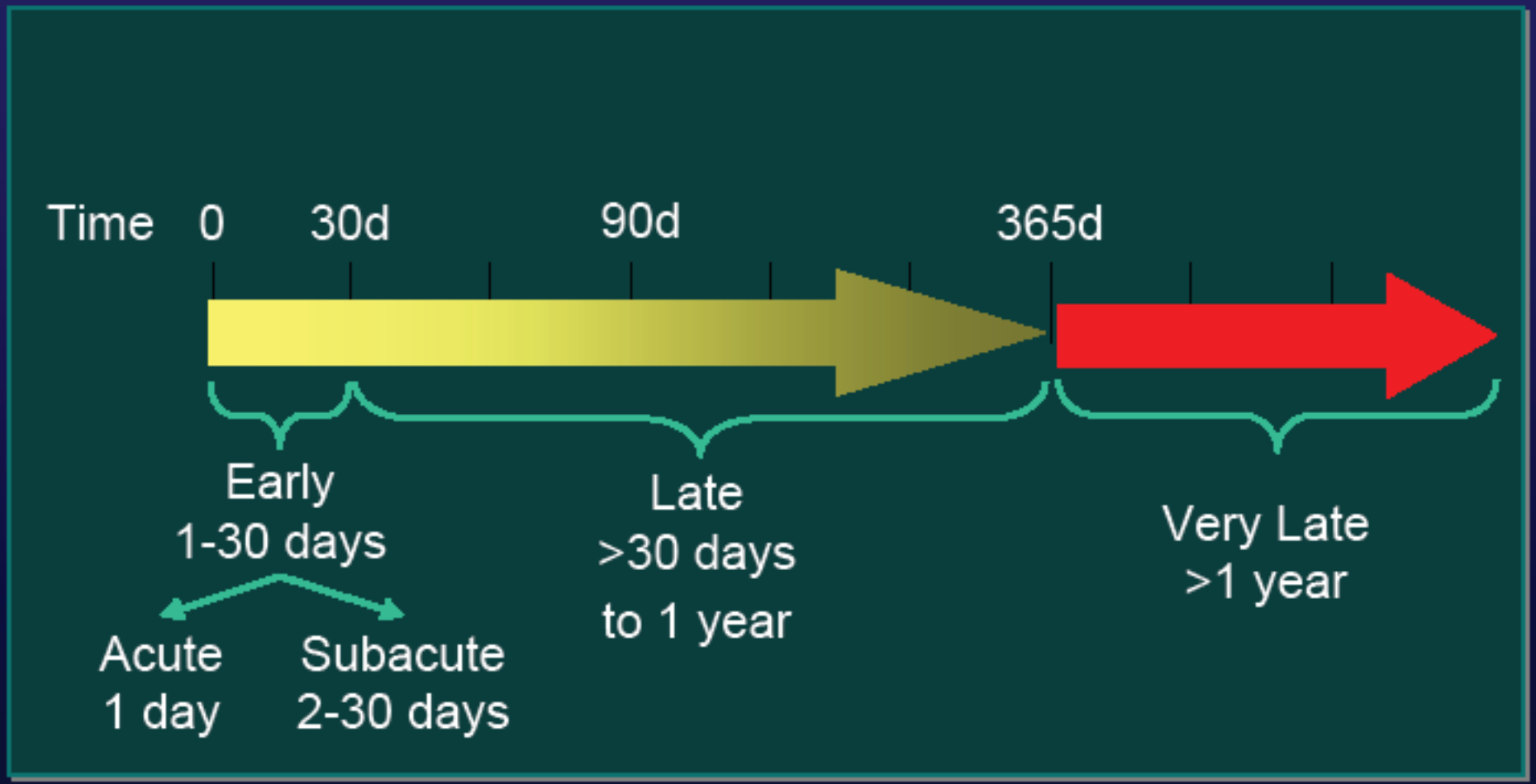
- Cardialysis
- Bern, Switzerland
- Paris, France

Industry

FDA

Washington, DC	March 2006
Dublin, Ireland	July 2006

Stent Thrombosis
Time Frame Classification



DHHS/FDA

Stent Thrombosis Proposed Standard Definitions Levels of Certainty

- Definite/Confirmed
  - Acute coronary syndrome AND
  - Angiographic confirmation of thrombus or occlusion

    OR
  - Pathologic confirmation of acute thrombosis
- Probable
  - Unexplained death within 30 days
  - Target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion
- Possible
  - Unexplained death after 30 days

FDA meeting on DES
Dec 7-8, 2006

Day 1: FDA Panel Accepts Stent Thrombosis But Rejects Increased Death/MI Risk for On-Label DES Use

- **For the low-risk population included in randomized trials, the overall data looked favorable**

Topol

the heart.org:
Thumbs up / Thumbs down – Dec 22, 2006

FDA meeting on DES
Dec 7-8, 2006

Day 2: FDA panel warns against increased risk of death/MI, stent thrombosis with off-label DES use

Dual antiplatelet therapy for 12 months,regardless of label

(following AHA/ACC indications)

In pratica non sono emersi elementi tali da comportare l'assunzione di provvedimenti restrittivi per i DES

No data for on- or off-label patients

The AHA/ACC recommends dual antiplatelet therapy for one year after a drug-eluting stent, regardless of label

"I don't know where that came from because I'm not aware of any data to substantiate that."

12 months of clopidogrel:

Arbitrary cut-off

Topol

Comunicazione del GISE

Società Italiana di Cardiologia Invasiva

Piazza IV Novembre, 4 20124 Milano, Tel. 02-67165612; Fax 02-67165266 Email: gisemail@tin.it

18 Dicembre 2006

Cari Colleghi,

come certamente saprete, si e' riunito recentemente l'FDA "Circulatory Systems Devices Advisory Panel" per cercare di rispondere a quesiti riguardanti l'efficacia e la sicurezza degli stent a rilascio di farmaco (DES). La verifica dei dati e il dibattito tra i panelist ha portato alla conclusione che per quanto riguarda le indicazioni "on label" , cioè quelle studiate nei grandi trial (e che nelle "Guidelines for PCI" della Società Europea di Cardiologia del 2005 sono indicazioni in classe I B) non vi e' una incidenza di eventi avversi (decesso, infarto) a distanza superiore a quella osservata utilizzando gli stent tradizionali (BMS). Constatiamo che se lo stesso rigore metodologico di queste analisi fosse stato applicato anche a quelle presentate al recente Congresso Mondiale di Barcellona , si sarebbe evitato di diffondere sconcerto tra gli operatori e panico tra i pazienti, alimentati anche da dichiarazioni avventate , amplificate dalla cassa di risonanza dei media , di qualche "cardiologo esperto" non interventista.

Per quanto riguarda l'utilizzo "off label" dei DES (indicato in classe IIa C nelle "Guidelines" della Società Europea di Cardiologia) l'assenza di ampi studi randomizzati di confronto sia con i BMS che con strategie di rivascolarizzazione chirurgica , rende più difficile un'analisi accurata e conclusioni certe. Tuttavia alcuni ampi registri segnalerebbero per i DES un rischio modesto , ma significativo , di trombosi tardiva. Per queste indicazioni consigliamo perciò di valutare il "rischio-beneficio" delle procedure fornendo una informazione adeguata sulla base delle evidenze della letteratura e della esperienza personale.

Ogni anno decine di migliaia di pazienti in Italia vengono trattati efficacemente, spesso in condizioni di estrema urgenza, da cardiologi emodinamisti pronti ad intervenire ad ogni ora del giorno e della notte, con risultati superiori rispetto a quelli forniti dalle terapie farmacologiche alternative. Consci di questo, guardiamo con fiducia al futuro, attenti alle verifiche provenienti dallo sviluppo delle conoscenze.

Il GISE non mancherà di offrire il suo contributo in proposito.

In nome e per conto del Consiglio Direttivo GISE

Stefano De Servi
Presidente SICI-GISE

Per quanto riguarda l'utilizzo "off label" dei DES (indicato in classe IIa C nelle "Guidelines" della Società Europea di Cardiologia) …

consigliamo di valutare il "rischio-beneficio" delle procedure

18 dicembre 2006

Impiego dei DES

- L'uso estensivo dei DES appare ingiustificato
- È più appropriato un uso selettivo
- Nel nostro centro la percentuale delle procedure con DES è intorno al 40 % di quelle con stent, inferiore alla media nazionale ed europea, in relazione ad una maggior selezione dei pz

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 8, 2007 VOL. 356 NO. 10

Trombosi tardiva dei DES

8 articoli

- **Di cui 5 originali**
  - **4 meta-analisi + registro svedese SCAAR**
- **1 editoriale e 2 commenti**

- **Tutti i pts trattati con stent in Svezia negli anni 2003-2004: 6 033 DES, 13 738 BMS**
- **Leggero maggior rischio con i DES**

Dopo l'analisi di questi dati, la percentuale di utilizzo dei DES, in Svezia, è scesa al 30%

Presentato al TCT 2006

New England Journal of Medicine – March 8, 2007

Circulation

Stent Thrombosis Late After Implantation of First-Generation Drug-Eluting Stents

A Cause for Concern

Edoardo Camenzind, MD; P. Gabriel Steg, MD; William Wijns, MD

Are drug-eluting stents associated with a higher rate of late thrombosis than bare metal stents?

Late Stent Thrombosis

A Nuisance in Both Bare Metal and Drug-Eluting Stents

Patrick W. Serruys, MD, PhD; Joost Daemen, MD

Circulation - March 20, 2007

Patient compliance

Up to 20% of people are not going to take their clopidogrel

- **Because of an upcoming surgical procedure**
- **Because of social circumstances**

"I see no excuse for putting a drug-eluting stent in a person like that, and I think it has to be stopped."

Califf

Unforeseen surgery

The problem arises when surgery is unforeseen

When you know a patient is not going to be compliant or has an upcoming major operation, it's straightforward

Topol

Sospensione prematura di tienopiridine e trombosi di stent

La **sospensione prematura** (< 12 mesi) di clopidogrel rappresenta la **principale causa indipendente** di trombosi di stent nelle analisi multivariate

Cause di precoce sospensione:

- Costo del farmaco (~2 €/die)
- Disposizione di un medico o dentista per chirurgia
- Inadeguata informazione e comprensione

Prevenzione della sospensione prematura della doppia terapia antiaggregante

AHA/ACC/SCAI/ACS/ADA Science Advisory

Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients With Coronary Artery Stents

A Science Advisory From the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, With Representation From the American College of Physicians*

Cindy L. Grines, MD, FACC; Robert O. Bonow, MD, FAHA, FACC; Donald E. Casey, Jr, MD, MPH, MBA, FACP; Timothy J. Gardner, MD, FAHA, FACC, FACS; Peter B. Lockhart, DDS, FDS RCSEd; David J. Moliterno, MD, FAHA, FSCAI, FACC; Patrick O'Gara, MD, FAHA, FACC; Patrick Whitlow, MD, FAHA, FACC

Abstract—Dual antiplatelet therapy with aspirin and a thienopyridine has been shown to reduce cardiac events after coronary stenting. However, many patients and healthcare providers prematurely discontinue dual antiplatelet therapy, which greatly increases the risk of stent thrombosis, myocardial infarction, and death. This advisory stresses the importance of 12 months of dual antiplatelet therapy after placement of a drug-eluting stent and educating the patient and healthcare providers about hazards of premature discontinuation. It also recommends postponing elective surgery for 1 year, and if surgery cannot be deferred, considering the continuation of aspirin during the perioperative period in high-risk patients with drug-eluting stents. (*Circulation*. 2007;115:813-818.)

Circulation February 13, 2007

AHA/ACC/SCAI/ACS/ADA Science Advisory

Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients With Coronary Artery Stents

1. Physicians should discuss the need for dual antiplatelet therapy with the patient prior to stent implantation and "strongly consider" using a bare-metal stent in **patients not expected to comply with 12 months of thienopyridine** therapy, **for whatever reasons**.

2. In patients who are likely to require **surgery within 12 months** of receiving a stent, a bare-metal stent or balloon angioplasty with provisional stenting should be considered.

3. Before hospital discharge, healthcare professionals must do a better job of **educating patients** about the reasons for taking the dual antiplatelet therapy and the risks for stopping it early.

4. Patients must be instructed to **contact their cardiologist** before stopping any antiplatelet therapy, even if instructed to do so by another healthcare professional.

Circulation February 13, 2007

AHA/ACC/SCAI/ACS/ADA Science Advisory

Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients With Coronary Artery Stents

5. Healthcare providers who perform invasive or surgical procedures must be made aware of the "potentially catastrophic" risks of stopping thienopyridine therapy prematurely and should contact the patient's cardiologist if needed.

6. **Elective procedures** that entail bleeding risk **should be delayed** until a month after the ideal course of dual antiplatelet therapy (12 months post DES implantation; one month post bare-metal-stent implantation).

7. DES recipients requiring urgent procedures should **continue on aspirin** "if at all possible," with thienopyridine restarted as soon post procedure as possible.

8. Healthcare workers, insurers, policy-makers, and drug companies should ensure that patients are not stopping therapy due to **prohibitive drug costs**.

Circulation February 13, 2007

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Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients With Coronary Artery Stents

- **Dopo impianto di DES, la semplice prescrizione di aspirina e clopidogrel non è sufficiente per ottenere una buona adesione del pz al trattamento**
- **Occorre motivare il pz, discutendo le possibili conseguenze della sospensione precoce della terapia ed adeguando le informazioni al livello di comprensione del pz**
- **La relazione clinica dovrebbe evidenziare l'importanza del doppio trattamento antiaggregante e precisare l'indicazione ad una consulenza cardiologica nel caso di eventuali modifiche (chirurgia, patologia gastro-intestinale)**

Nuova normativa SSN

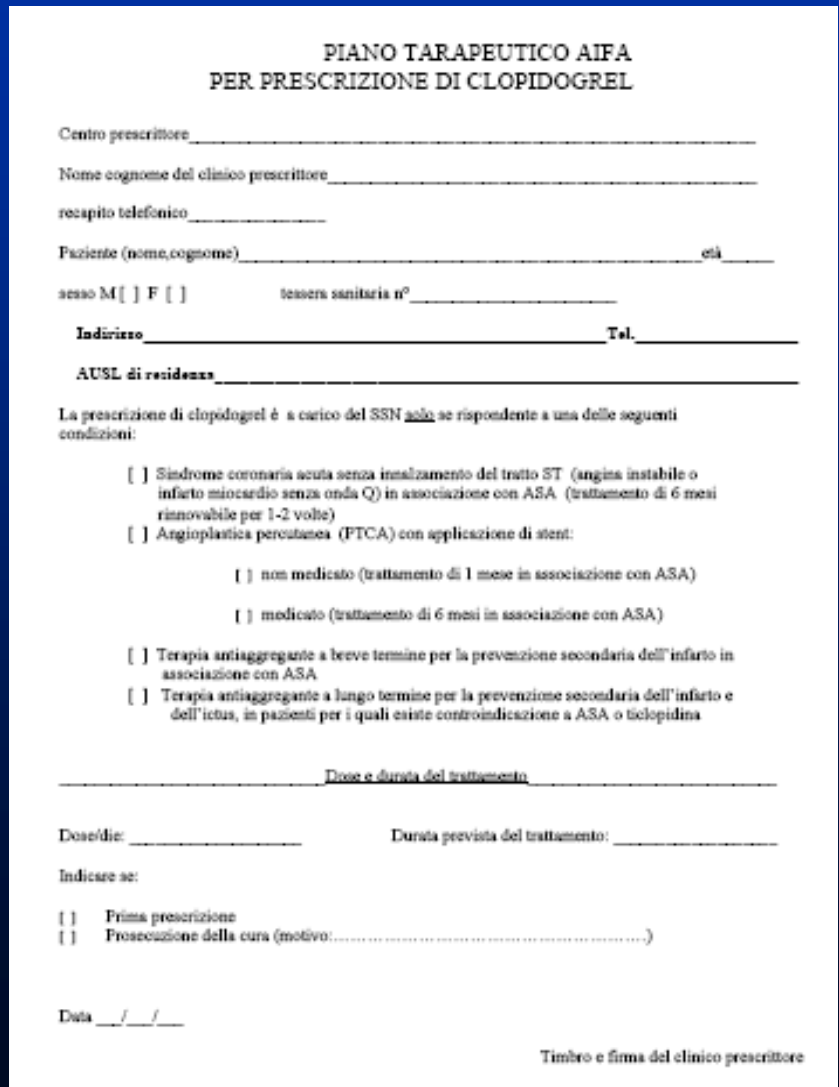
ticlopidina - clopidogrel

Gazzetta Ufficiale 10-01-07

Le note 9 e 9 bis sono abolite.

La prescrizione del clopidogrel a carico del SSN è vincolata all'adozione del piano terapeutico AIFA

e alla presenza di alcune (4) condizioni cliniche



PIANO TARAPEUTICO AIFA
PER PRESCRIZIONE DI CLOPIDOGREL

Centro prescrittore_____

Nome cognome del clinico prescrittore_____

recapito telefonico_____

Paziente (nome,cognome)_____età_____

sesso M [ ] F [ ] tessera sanitaria n°_____

Indirizzo_____**Tel.**_____

AUSL di residenza_____

La prescrizione di clopidogrel è a carico del SSN solo se rispondente a una delle seguenti condizioni:

[ ] Sindrome coronaria acuta senza innalzamento del tratto ST (angina instabile o infarto miocardio senza onda Q) in associazione con ASA (trattamento di 6 mesi rinnovabile per 1-2 volte)
[ ] Angioplastica percutanea (PTCA) con applicazione di stent:

[ ] non medicato (trattamento di 1 mese in associazione con ASA)

[ ] medicato (trattamento di 6 mesi in associazione con ASA)

[ ] Terapia antiaggregante a breve termine per la prevenzione secondaria dell'infarto in associazione con ASA
[ ] Terapia antiaggregante a lungo termine per la prevenzione secondaria dell'infarto e dell'ictus, in pazienti per i quali esiste controindicazione a ASA o ticlopidina

Dose e durata del trattamento

Dose/die: _____ Durata prevista del trattamento: _____

Indicare se:

[ ] Prima prescrizione
[ ] Prosecuzione della cura (motivo:.....)

Data __/__/__

Timbro e firma del clinico prescrittore

PIANO TERAPEUTICO AIFA PER PRESCRIZIONE DI CLOPIDOGREL

- **ACS NSTEMI** in associazione con ASA - 6 mesi rinnovabile per 1-2 volte (Yusuf 2001, PCI - CURE)
- **PCI + stent**: (PCI - CURE, AHA/ACC guide-lines)

  - non DES - 1 mese in associazione con ASA

  - DES - 6 mesi in associazione con ASA

- **Terapia antiaggregante a breve termine** per la prevenzione secondaria dell'infarto in associazione con ASA (COMMIT, CLARITY-TIMI 28)
- **Terapia antiaggregante a lungo termine** per la prevenzione secondaria dell'infarto e dell'ictus, in pazienti per i quali esiste controindicazione a ASA o ticlopidina (CAPRIE)

PIANO TERAPEUTICO AIFA PER PRESCRIZIONE DI CLOPIDOGREL

PCI + stent :

- **non medicato**

  trattamento di 1 mese in associazione con ASA

- **medicato**

  trattamento di 6 mesi in associazione con ASA

Nonostante l'estensione della prescrivibilità a carico del SSN, una quota di pazienti (DES) per i quali il trattamento è indicato per 12 mesi, rimane esclusa e deve provvedere a proprie spese

Protocollo gestionale di reparto

U.O. Cardiologia

San Martino

Terapia antiaggregante orale nei pz trattati con stent coronarici

Aspirina

- carico di almeno 300 mg
- 75 mg/die a tempo indeterminato

Clopidogrel

- Carico di almeno 300 mg , minimo 6 h prima della procedura (pre-trattamento in tutti i pz candidati a PCI)
- 75 mg/die per un mese negli stent tradizionali
- Per almeno un anno negli stent medicati

Gastroprotezione: inibitori pompa protonica

Evitare l'associazione con FANS in genere, soprattutto ibuprofene e COX2 selettivi ; se necessario preferire paracetamolo e naproxene.

Anticoagulanti orali:

nei pz in trattamento con anticoagulanti orali viene evitato l'impianto di stent medicati. Con gli stent tradizionali utilizzare la triplice terapia con anticoagulante, ASA e clopidogrel per un mese, poi continuare con anticoagulante e ASA.

Prevenzione della sospensione precoce: adeguata informazione
spiegazioni al paziente
informazioni per i medici nella relazione clinica

Esempio di avviso evidenziato:

Attenzione: E' necessario proseguire il doppio trattamento antiaggregante piastrinico, con aspirina e Plavix, per il tempo indicato. La sospensione precoce di questo trattamento espone il paziente al rischio di infarto miocardico. Eventuali modifiche dovranno essere concordate con un cardiologo.

Rinviare gli interventi elettivi: un mese per gli stent tradizionali, un anno per quelli medicati.

In caso di chirurgia imprevista, indicare la temporanea sospensione del solo clopidogrel e solo per il tempo strettamente necessario. Non sospendere l'aspirina.

Antiaggreganti con i DES

- Aspirina
  - carico di almeno 300 mg
  - 75 mg/die a tempo indeterminato
- Clopidogrel
  - Carico di almeno 300 mg
  - 75 mg/die per almeno un anno
- Gastroprotezione: inibitori pompa protonica
- Evitare l'associazione con FANS, soprattutto ibuprofene e COX2 selettivi

Prevenzione della sospensione precoce: adeguata informazione

In caso di chirurgia imprevista, indicare la temporanea sospensione di uno solo dei due antiaggreganti (clopidogrel)