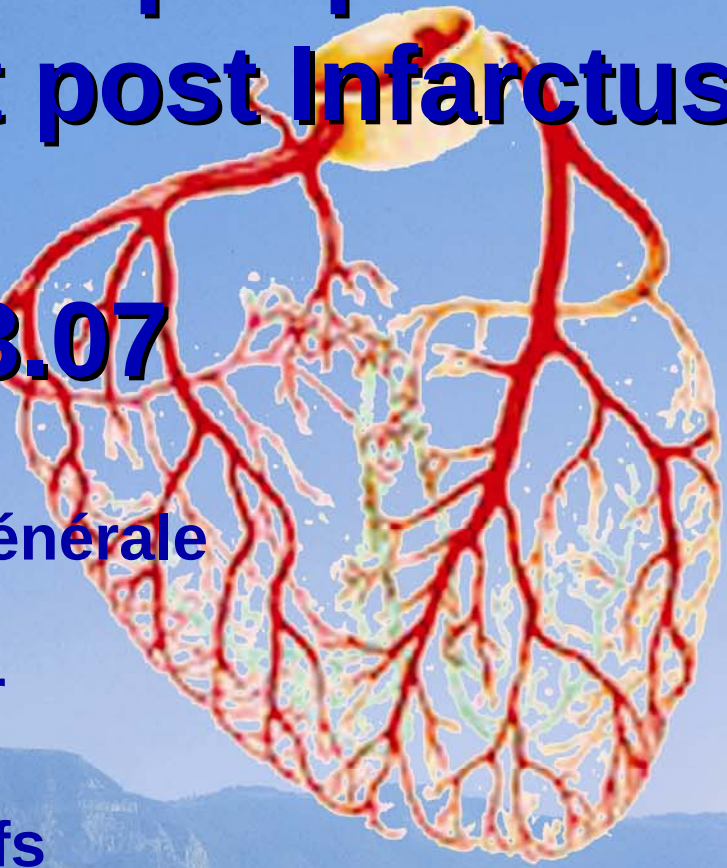
Les traitements antiplaquettaires et anticoagulant post Infarctus



26.03.07

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Faculté de médecine
Université de Genève

Hôpitaux Universitaires de Genève

M. J. T. 68 ans (I)

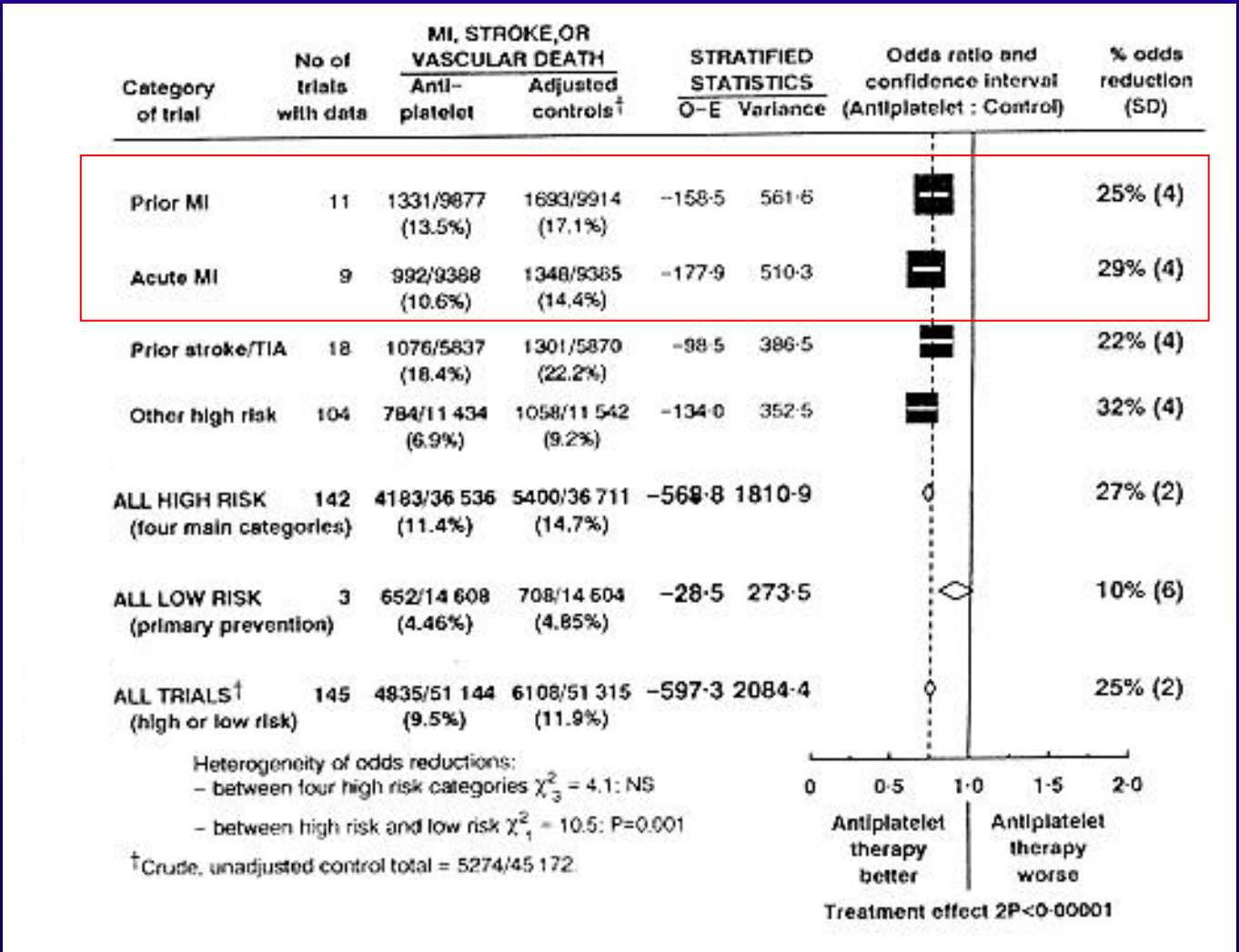
- Patient hospitalisé pour des DRS typiques inaugurales 7/10
- AP: HTA, diabète de type II
- Dx ECG: STEMI antérieur
- Coronarographie:
  - Occlusion de l'IVA proximale
  - Irrégularités des autres vaisseaux
- Intervention: PTCA de l'IVA avec mise en place d'un stent à élution (sirolimus)

M. J. T. 68 ans (I)

- Quel traitement anti-agrégant faut-il lui donner?
  - Aspirine?
  - Clopidogrel?
  - Les deux?
  - Pour combien de temps?
  - L’attitude serait-elle la même si on lui avait mis un stent simple (« bare-metal stent »)?

Aspirine

Aspirin prevention for CV events



Category of trial	No of trials with data	MI, STROKE, OR VASCULAR DEATH: Anti-platelet	MI, STROKE, OR VASCULAR DEATH: Adjusted controls†	STRATIFIED STATISTICS: O−E	STRATIFIED STATISTICS: Variance	% odds reduction (SD)
Prior MI	11	1331/9877 (13.5%)	1693/9914 (17.1%)	−158·5	561·6	25% (4)
Acute MI	9	992/9388 (10.6%)	1348/9385 (14.4%)	−177·9	510·3	29% (4)
Prior stroke/TIA	18	1076/5837 (18.4%)	1301/5870 (22.2%)	−98·5	386·5	22% (4)
Other high risk	104	784/11 434 (6.9%)	1058/11 542 (9.2%)	−134·0	352·5	32% (4)
ALL HIGH RISK (four main categories)	142	4183/36 536 (11.4%)	5400/36 711 (14.7%)	−568·8	1810·9	27% (2)
ALL LOW RISK (primary prevention)	3	652/14 608 (4.46%)	708/14 604 (4.85%)	−28·5	273·5	10% (6)
ALL TRIALS† (high or low risk)	145	4935/51 144 (9.5%)	6108/51 315 (11.9%)	−597·3	2084·4	25% (2)

Odds ratio and confidence interval (Antiplatelet : Control)

Heterogeneity of odds reductions:
- between four high risk categories $\chi^2_3 = 4.1$: NS
- between high risk and low risk $\chi^2_1 = 10.5$: P=0.001

†Crude, unadjusted control total = 5274/45 172

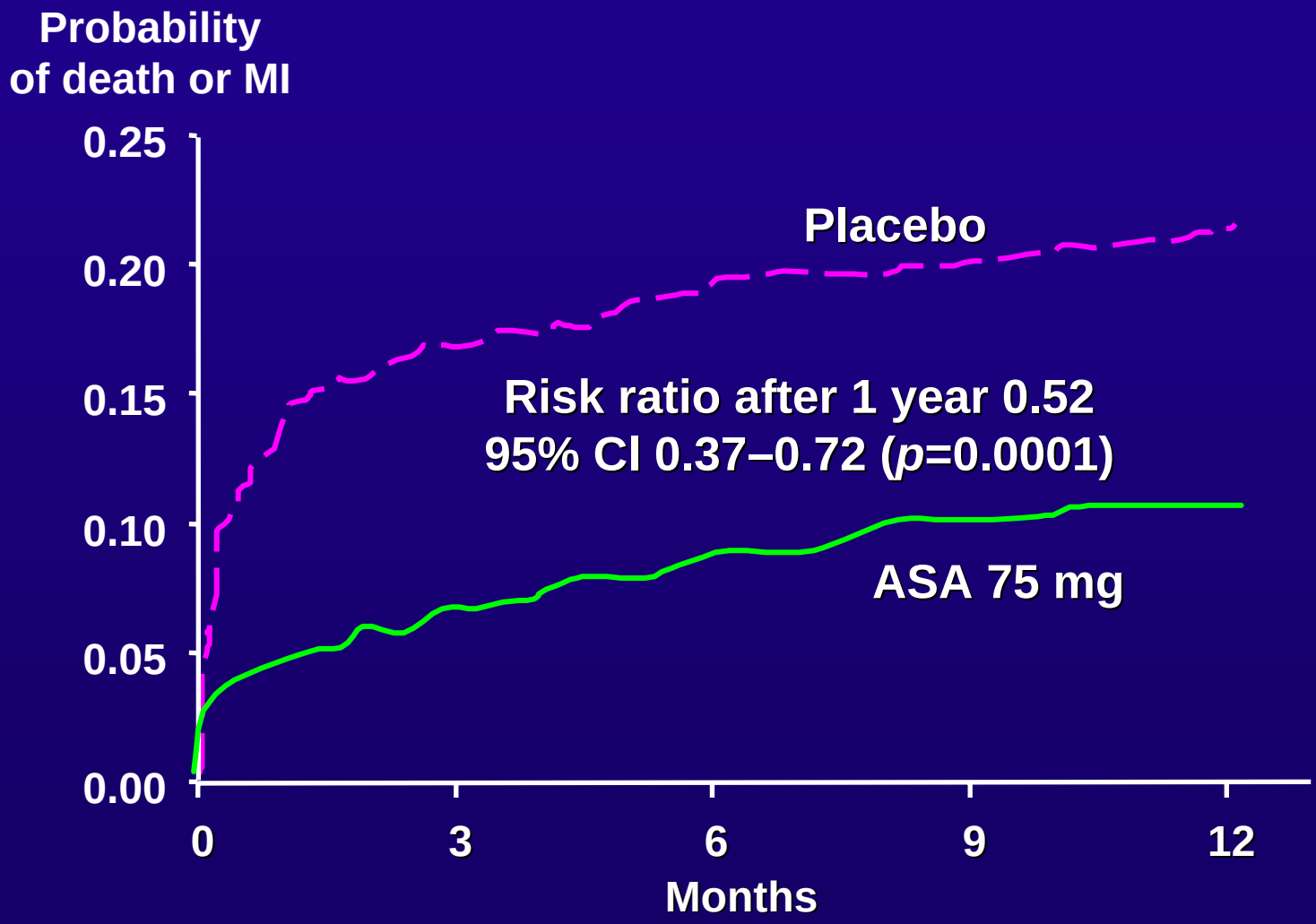
0 0·5 1·0 1·5 2·0

Antiplatelet therapy better | Antiplatelet therapy worse

Treatment effect 2P<0·00001

BMJ 1994;308:81-106

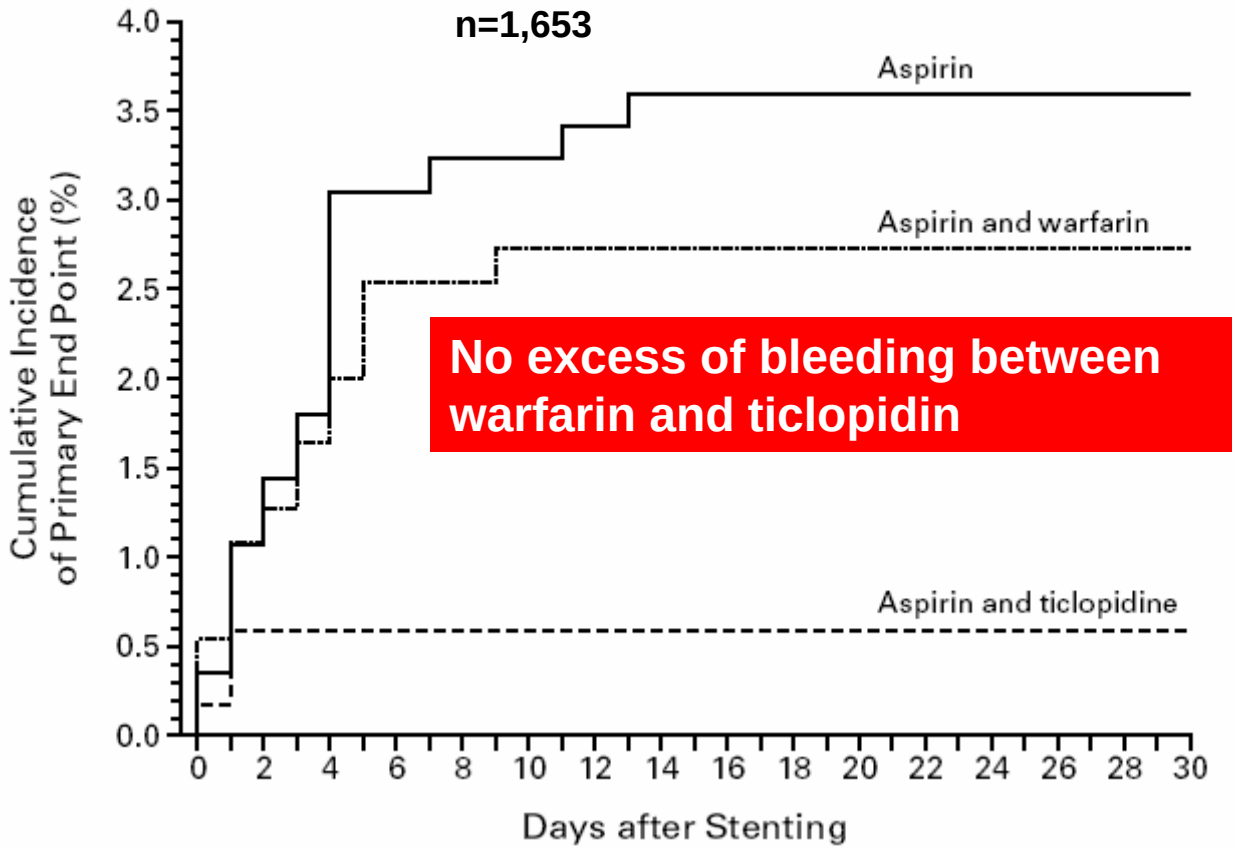
Long-term Efficacy of ASA in Reducing Death or MI in Patients with Unstable Angina



Wallentin LC. JACC 1991;18:1587

Aspirine + Thienopyridines or Aspirine + Warfarin following stenting

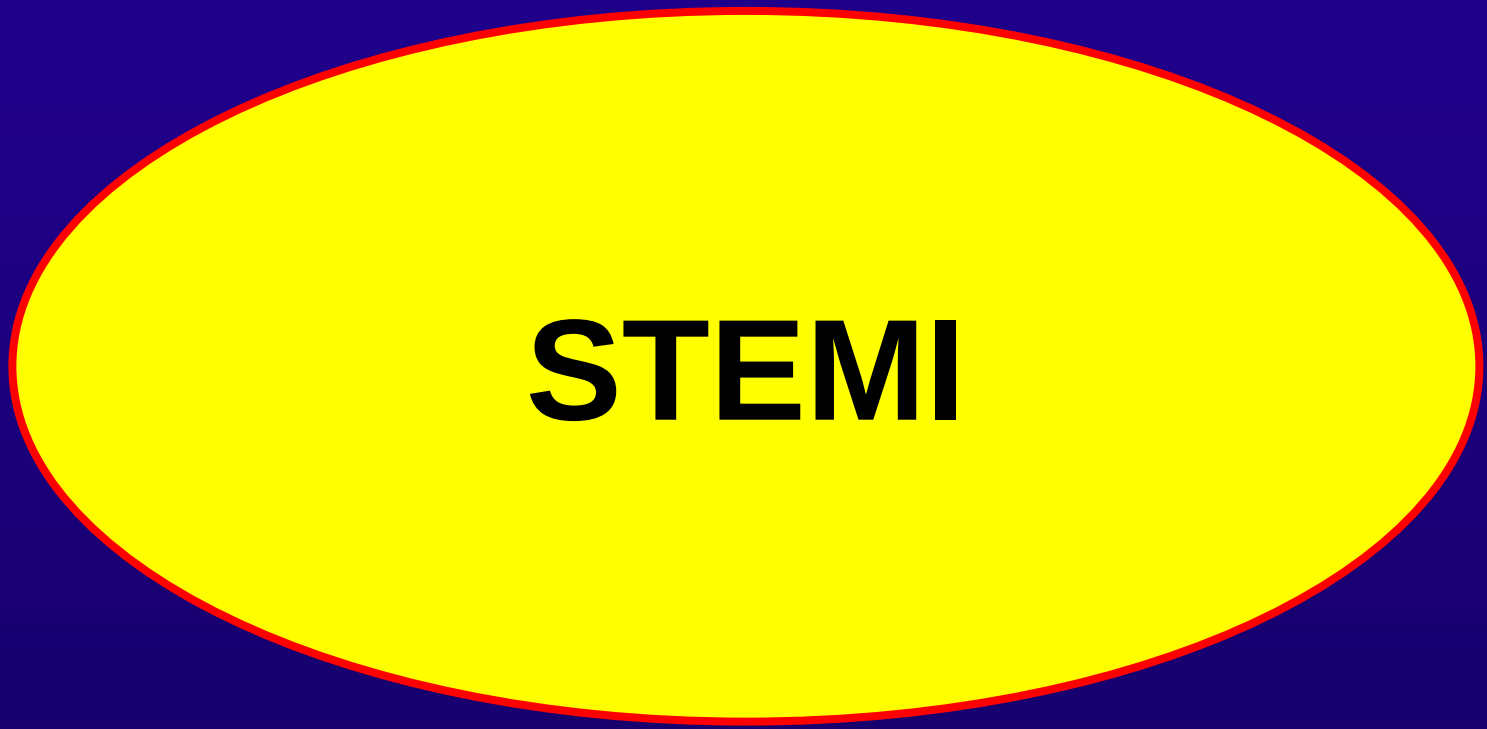
Death, revascularization of the target lesion, angiographically evident thrombosis, or MI within 30 days



No excess of bleeding between warfarin and ticlopidin

Leon MB. N Engl J Med 1998;339:1665

Clopidogrel

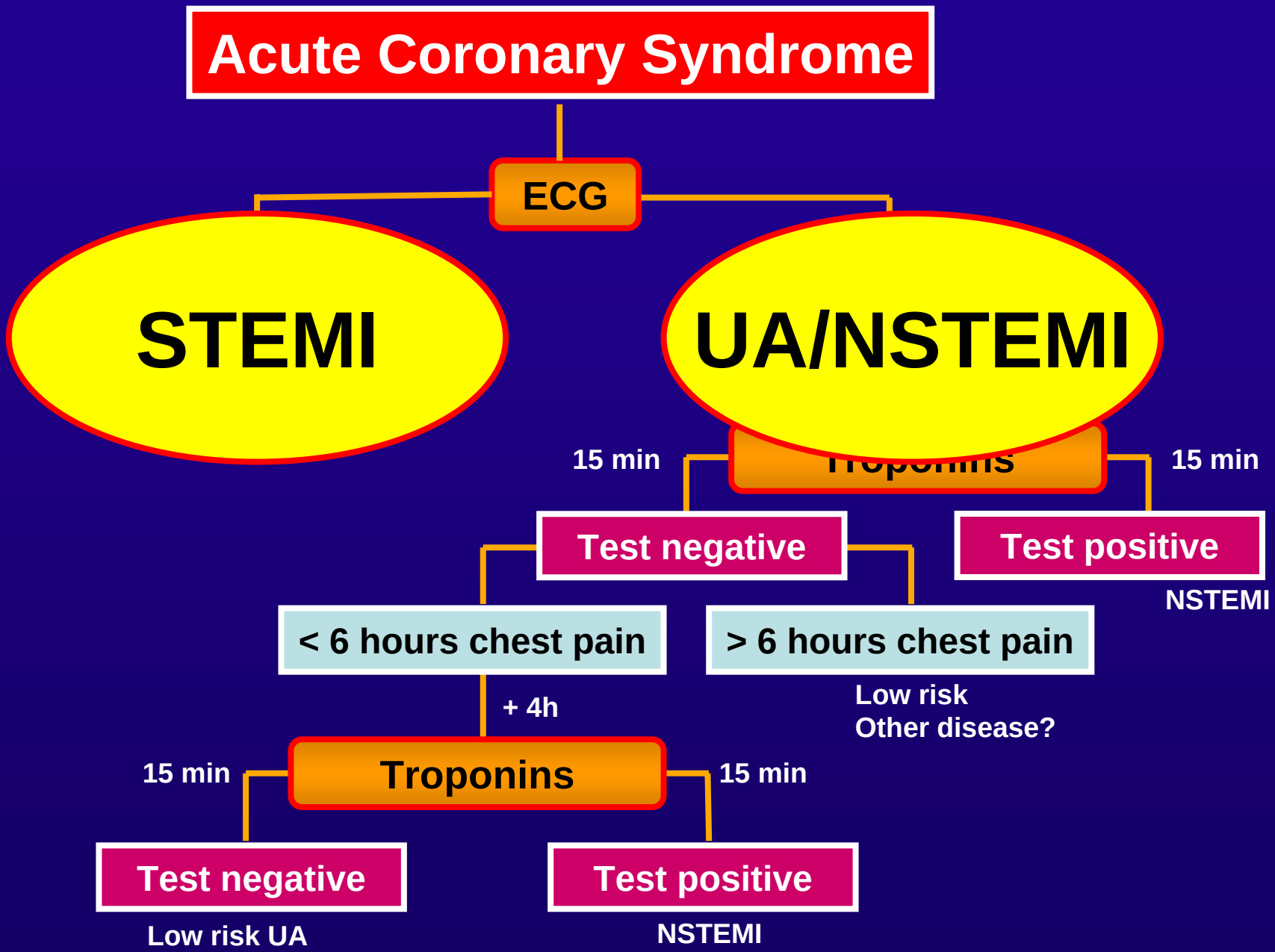

STEMI

European Heart Journal (2003) 24, 28–66

segment elevation.[193] No data are available regarding the routine use of clopidogrel in addition to aspirin following reperfusion therapy. In patients who do not tolerate aspirin, clopidogrel is a good alternative antiplatelet therapy.[194]

Christian Thygesen, S. Richard Underwood, Alec Vahanian, Freek W.A. Verheugt, William Wijns

Received 6 August 2002; accepted 7 August 2002



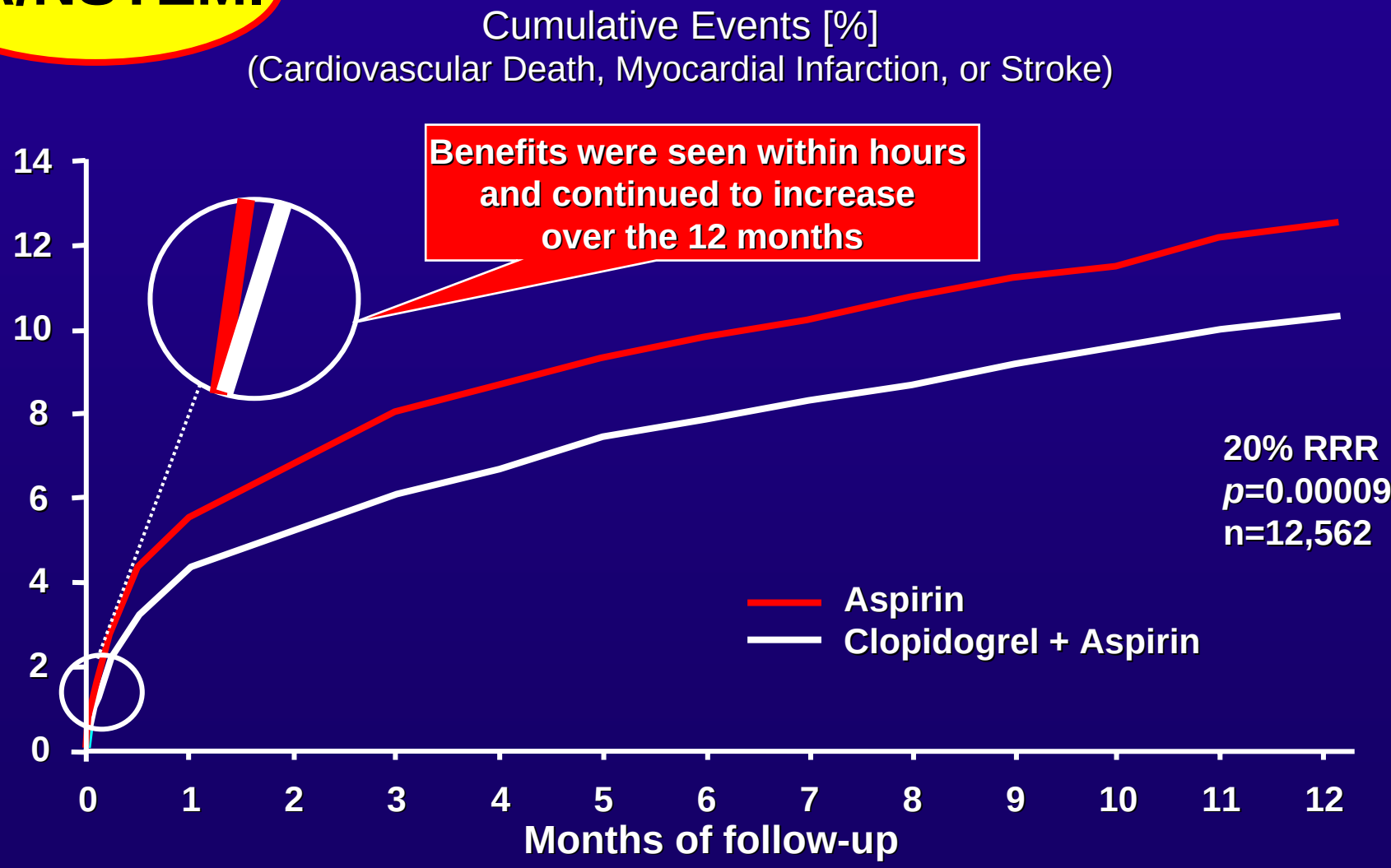
Circulation. 2000;102:118

Clopidogrel dans les STEMI: 1) leçon des NSTEMI

NSTEMI

CURE: Early & Long-Term Benefits of Clopidogrel

UA/NSTEMI



N Eng J Med 2001;345:494

CURE: Safety of Clopidogrel

UA/NSTEMI

n° (%)	Clopidogrel	Placebo	Relative risk	p value
Major				0.001
Life threatening	135 (2.2)	112 (1.8)	1.21 (0.95–1.56)	0.13
Minor bleeding	322 (5.1)	153 (2.4)	2.12 (1.75–2.56)	<0.001

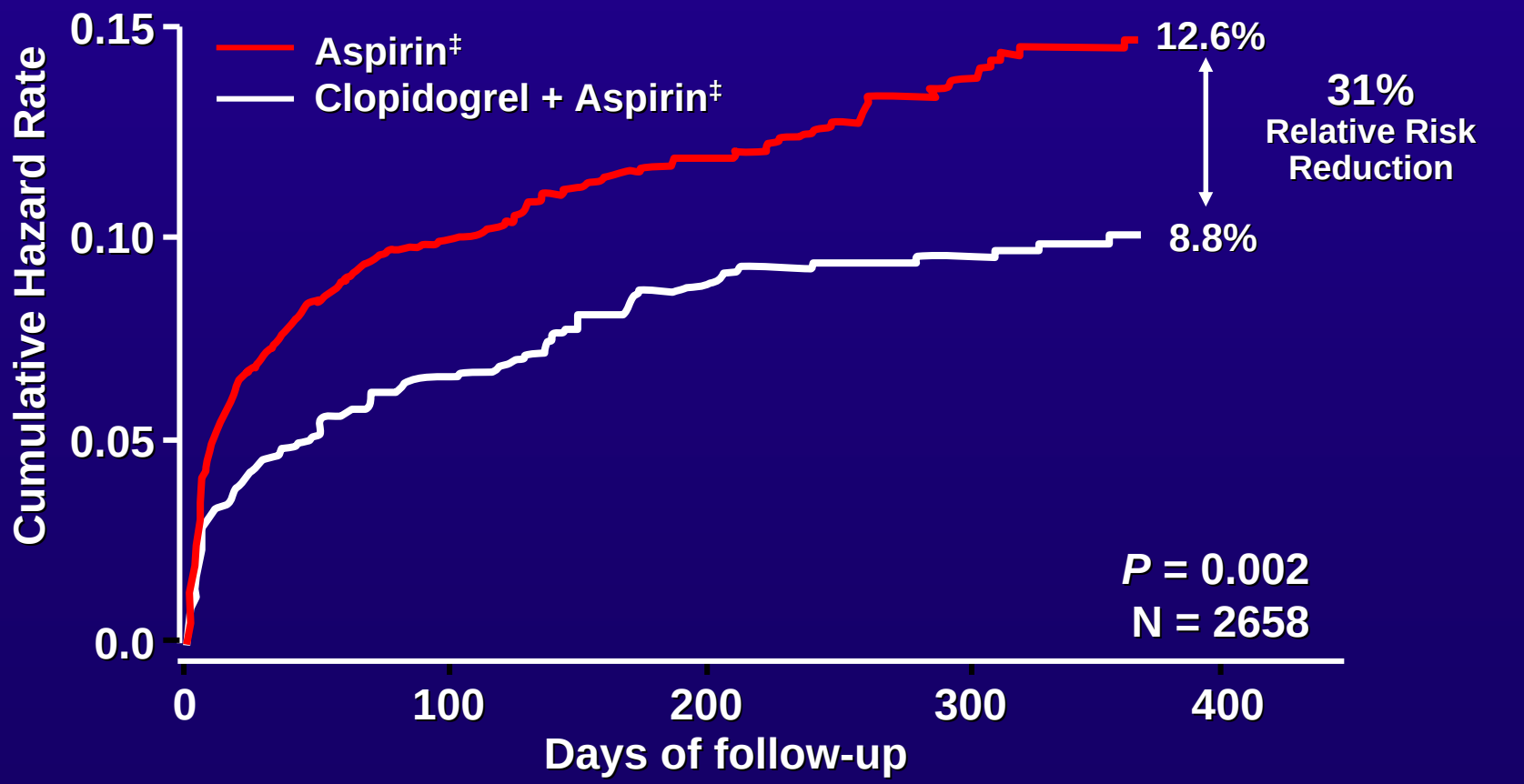
No excess of death, hemorrhagic stroke or need for hemodynamic support

N Eng J Med 2001;345:494

PCI-CURE – Long-Term Efficacy of Clopidogrel

UA/NSTEMI

Composite of CV-death or MI from randomization to end of follow-up†



†up to 12 months
‡plus standard therapies

Mehta et al. Lancet. 2001;358:527-533

PCI-CURE: Safety of Clopidogrel

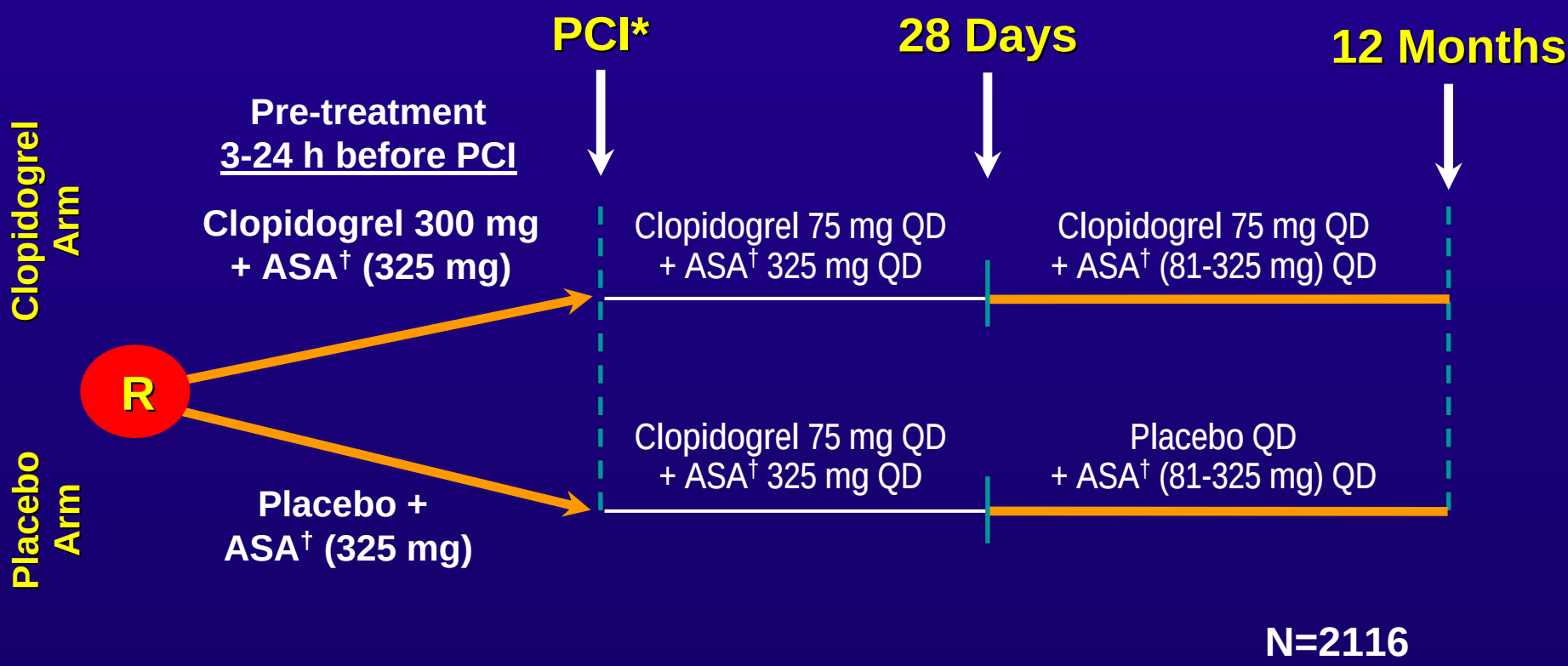
UA/NSTEMI

n° (%)	Clopidogrel + Aspirin (n=1313)	Aspirin (n=1345)	Relative risk (95% CI)	p value
Major bleeding	36 (2.7)	33 (2.5)	1.12 (0.70–1.78)	0.64
Life threatening	16 (1.2)	18 (1.3)	0.91 (0.47–1.78)	0.78
Minor bleeding	46 (3.5)	28 (2.1)	1.06 (0.63–1.79)	0.03

Mehta et al. Lancet. 2001;358:527-533

CREDO: Study Design

Elective PCI



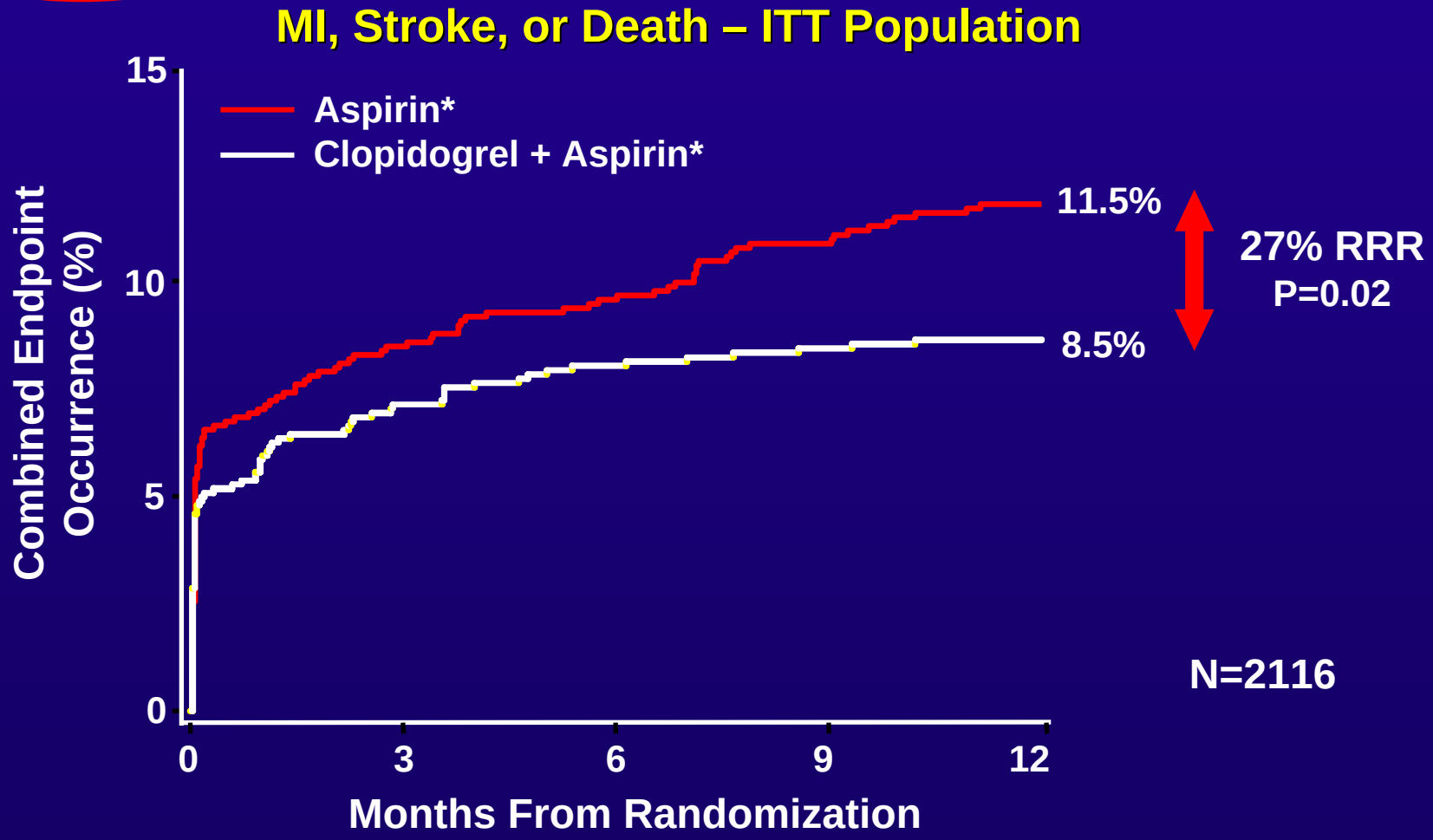
N=2116

† Plus other standard therapies
* Both groups received clopidogrel 75 mg + ASA 325 mg at time of procedure

Steinhubl S. JAMA. 2002;Vol 288,No 19:2411

CREDO : Long-Term (1 Year) Benefits of Clopidogrel in PCI Patients

Elective PCI



* Plus other standard therapies

Steinhubl S. JAMA. 2002;Vol 288,No 19:2411

CREDO - Safety : Clopidogrel vs Aspirin

Elective PCI

n° (%)	Clopidogrel + Aspirin (n=1053)	Aspirin (n=1063)	p value
28 days			
Major bleeding	50 (4.7)	38 (3.6)	0.19
Minor bleeding	33 (3.1)	24 (2.3)	0.23
1 year			
Major bleeding	93 (8.8)	71 (6.7)	0.07
Minor bleeding	56 (5.3)	59 (5.6)	0.84

Steinhubl S. JAMA. 2002;Vol 288,No 19:2411

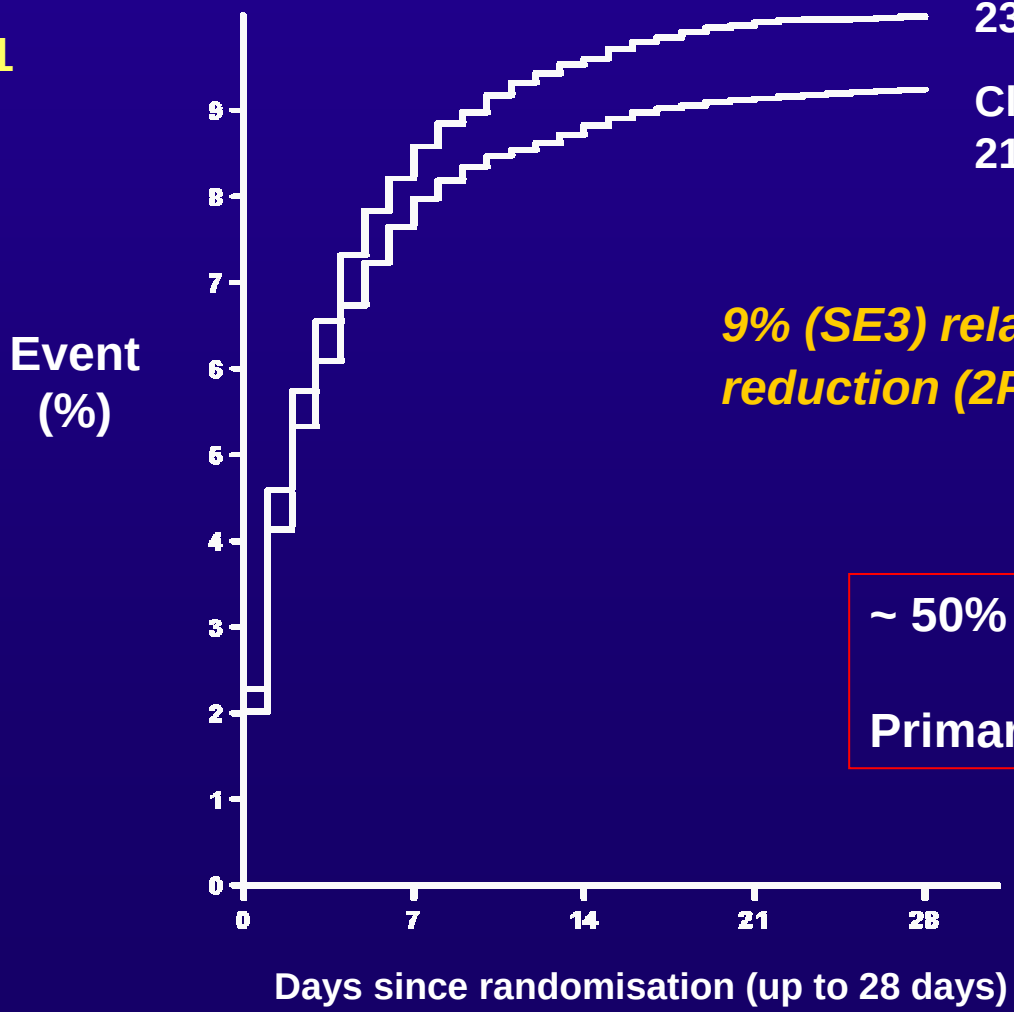
Clopidogrel dans les STEMI: 2) Une étude récente

STEMI

COMMIT: Effects of CLOPIDOGREL on Death, Re-MI or Stroke

STEMI

n=45’851



Placebo + ASA:
2311 events (10.1%)

Clopidogrel + ASA:
2125 events (9.3%)

9% (SE3) relative risk reduction (2P=0.002)

~ 50% thrombolysis

Primary PCI excluded

Lancet 2005; 366: 1607

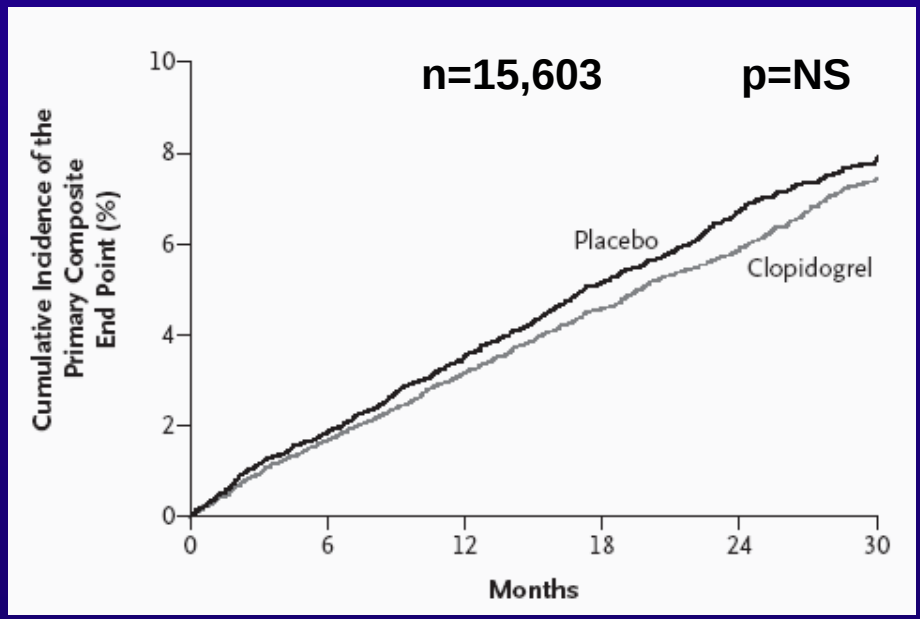
COMMIT : Safety

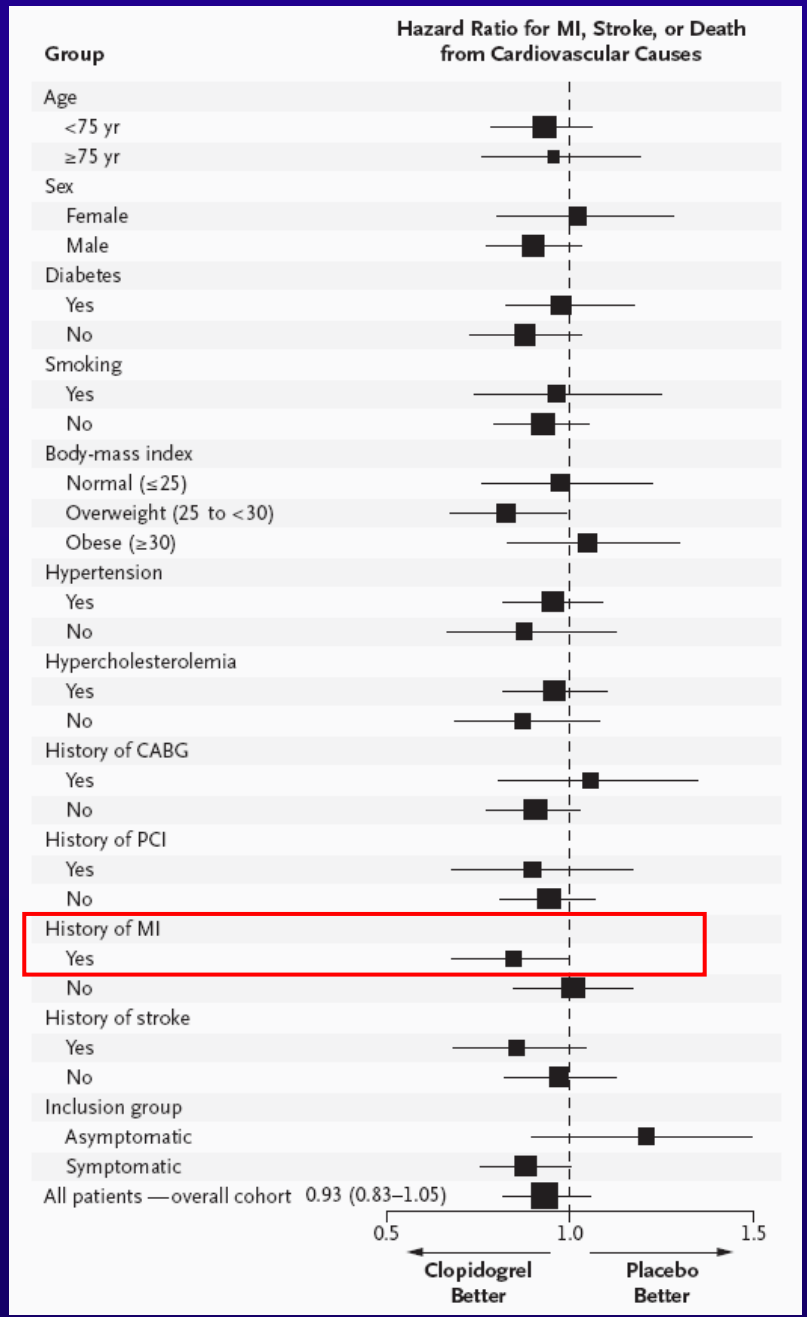
STEMI

Bleeding	Clopidogrel (%)	Placebo (%)	Excess per 1000	p
Any major bleeding	0.58	0.55	0.4	0.59

Lancet 2005; 366: 1607

Charisma trial





N Engl J Med 2006;354:1706

Safety end points: Clopidogrel vs Aspirin – Charisma trial

Bleeding

n° (%)	Clopidogrel (n=7802)	Placebo (n=7801)	Relative risk (95% CI)	p value
Severe bleeding	130 (1.7)	104 (1.3)	1.25 (0.97–1.61)	0.09
Fatal bleeding	26 (0.3)	17 (0.2)	1.53 (0.83–2.82)	0.17
Intrac hemorrhage	26 (0.3)	27 (0.3)	0.96 (0.56–1.65)	0.89
Moderate bleeding	164 (2.1)	101 (1.3)	1.62 (1.27–2.08)	<0.001

Bhatt, DL. N Engl J Med 2006;354:1706

ACS (STEMI and NSTEMI) : Summary of antiplatelet and anticoagulant Rx

	1st 24 h	During Hosp	Hosp DC + Long Term
Aspirin	162-325 mg chewed or iv	75-162 mg/d p.o.	75-162 mg/d p.o.
Clopidogrel	600 mg p.o.	75mg/d p.o.	75mg/d p.o. 9-12 months or longer
UFH / HBPM*	Full dose	To PCI or 48h post Thrombolysis	
IIbIIIa inhib	ABCX, Tirofiban, Eptifibatide		

* Excluding primary PCI

M. J. T. 68 ans (II)

- Le patient ayant fait appel tardivement, l'angioplastie a été faite après 8h de DRS
- Troponines: pic à 35
- ECG:
  - persistance d'un susdécalage antérieur
- Echocardiographie:
  - Akinésie apicale étendue. Suspicion de thrombus

M. J. T. 68 ans (II)

- Faut-il ajouter un traitement anticoagulant?
- Pour combien de temps?
- Faut-il refaire un écho cardiaque de contrôle? Si oui, quand?
- Quel est le risque hémorragique lié à l’association clopidogrel-aspirine-AVK?

Patients at increased risk for thromboembolism

- Left ventricular thrombus or aneurysm
- Left ventricular ejection fraction below 30 percent with or without heart failure
- Chronic atrial fibrillation

Left ventricular thrombus

- Anterior MI with severe apical left ventricular dysfunction are at high risk : 46% thrombus.

- Inferior AMI or in anterior MI without severe apical apical-wall-motion abnormality are at low risk : no thrombus.

Asinger RW. N Engl J Med 1981;305:297

LV Thrombus and Embolic events

- Embolization post AMI in patients with proven thrombus: 36 % versus 7 %, p<0.05.

  Stratton JR; Circulation 1982;66:156

- Late thromboembolism (6-15 months follow up):
  1 % with anticoagulation vs 13 % without anticoagulation.

  Sherman, DG; Chest 1999;95:140S

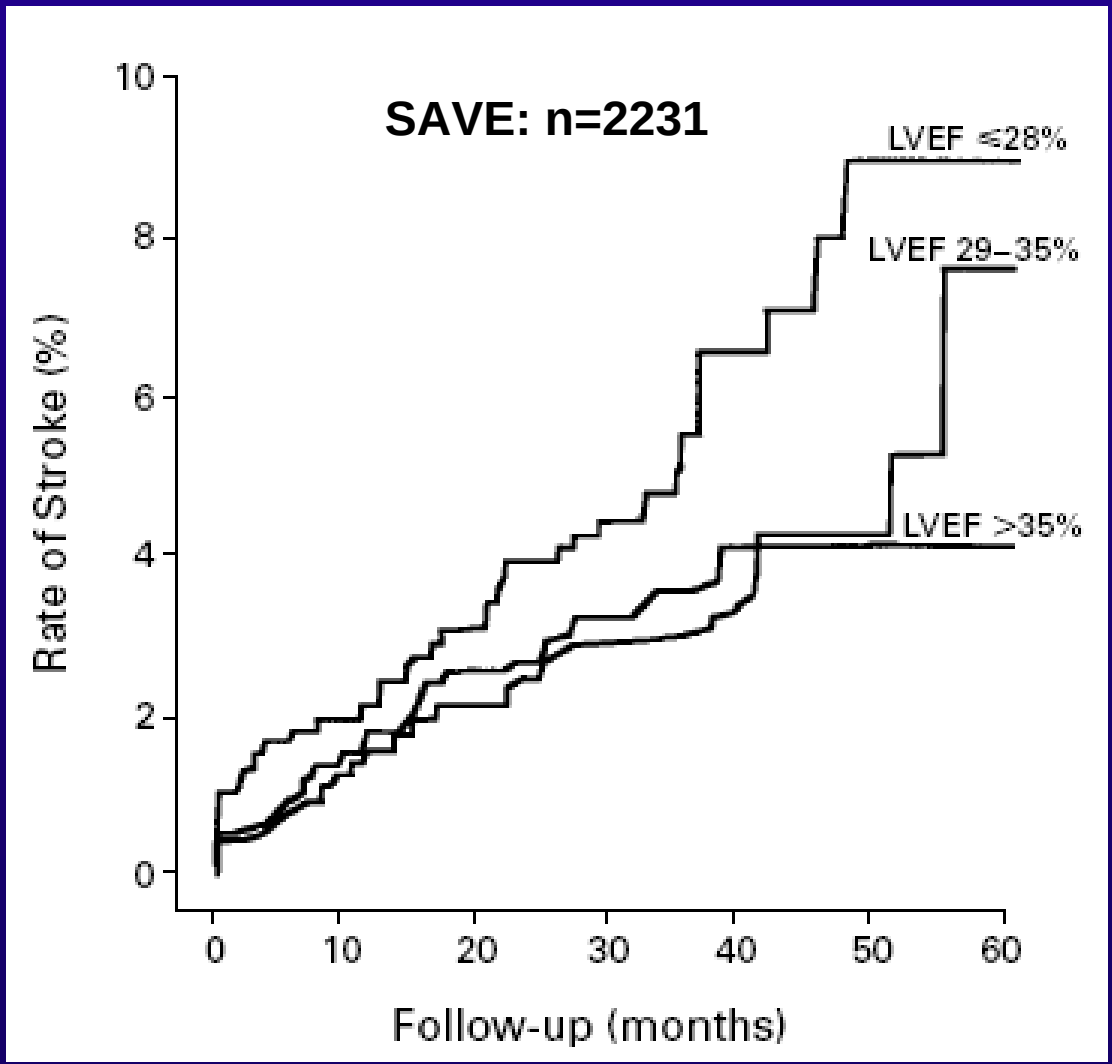
- Positive TTE for LV thrombus:
  - sensitivity 95%
  - specificity 83%

- Positive TTE for LV thrombus: PPV 86%

- Equivocal TTE for LV thrombus: PPV 29%

Stratton JR; Circulation 1982;66:156

Left ventricular dysfunction and Embolic events



Loh, E. N Engl J Med 1997;336:251

Aspirin, Clopidogrel and anticoagulant therapy : safety concern

- Triple antithrombotic therapy in 66 patients:
  - 9.2% Bleeding, 2 patients required a blood transfusion *Orford, JL. Am Heart J 2004;147:463*

- Triple antithrombotic therapy vs dual antiplatelet therapy (n=214):
  - major bleeding (6.6% vs. 0%; p = 0.03)
  - minor bleeding (14.9% vs. 3.8%; p = 0.01)

Khurram, Z. J Invasive Cardiol. 2006;18:162

M. J. T. 68 ans (II)

- Faut-il ajouter un traitement anticoagulant? OUI
- Pour combien de temps? 3 mois
- Faut-il refaire un écho cardiaque de contrôle? Si oui, quand? À 3 mois
- Quel est le risque hémorragique lié à l'association clopidogrel-aspirine-AVK?

  ~7%

M. J. T. 68 ans (III)

- Echocardiographie de contrôle à 3 mois: pas de thrombus apical, donc:
  - stop Sintrom
  - Poursuite clopidogrel-aspirine (drug-eluting stent)
- 1 mois plus tard, plusieurs épisodes de douleurs abdominales aspécifiques
- Echographie abdominale: lithiase vésiculaire

M. J. T. 68 ans (III)

- Le patient désire à tout prix se faire opérer
- Faut-il
  - Procéder à l'intervention sans autre?
  - Stopper le clopidogrel et l'aspirine et opérer?
  - Stopper le clopidogrel ou l'aspirine et opérer? Lequel?
  - Convaincre le patient de surseoir à l'intervention? Combien de temps?

Surgery early post stenting

↑↑ **Risk of death because of:**

- **Thrombotic complications**
- **Hemorrhagic complications**

Catastrophic Outcomes of Noncardiac Surgery Soon After Coronary Stenting

Grzegorz L. Kałuża, MD, PHD, Jane Joseph, Joseph R. Lee, MD, Michael E. Raizner, MD, Albert E. Raizner, MD, FACC

Houston, Texas

40 patients underwent surgery 1 to 39 days after coronary stent placement (average 13 days).

- 8 out of 40 patients (20%) died:
  - 6 MI
  - 2 major bleeding complications

- Stent thrombosis was presumed to be the cause of all of the MIs.

- All deaths and MIs (7 MIs) as well as 8 of 11 bleeding episodes occurred in patients who underwent surgery in less than two weeks after coronary stent placement.

- Mortality rate among 25 patients operated within this two-week timeframe was 32%.

J Am Coll Cardiol 2000;35:1288

Clinical Outcome of Patients Undergoing Non-Cardiac Surgery in the Two Months Following Coronary Stenting

Stephanie H. Wilson, MBBS, FRACP,* Panayotis Fasseas, MD,† James L. Orford, MBCHB, MPH,‡ Ryan J. Lennon, MS,§ Terese Horlocker, MD,‖ Nina E. Charnoff, MD,‖ Steven Melby, RN,¶ Peter B. Berger, MD, FACC¶

Darlinghurst, Australia; Milwaukee, Wisconsin; Surrey, England; and Rochester, Minnesota

207 patients underwent surgery within 2 months after coronary stent placement:

- 8 out of 207 patients (4.0%) died or suffered a myocardial infarction or stent thrombosis.
- All 8 patients were among the 168 patients undergoing surgery within six weeks after stent placement
- No events occurred in the 39 patients undergoing surgery seven to nine weeks after stent placement.

J Am Coll Cardiol 2003;42:234

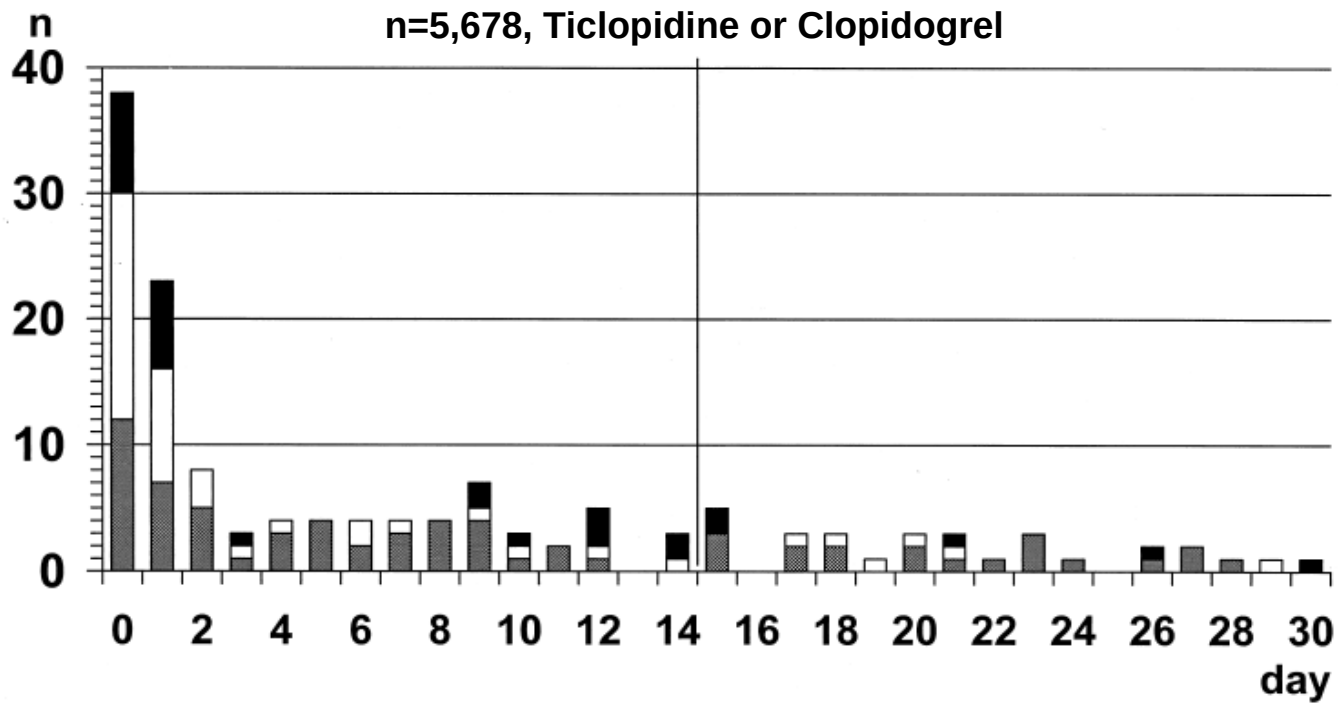
Angioplasty alone before major noncardiac surgery

194 patients who underwent angioplasty a median of 11 days (3-49) prior to major noncardiac surgery.

- 13.4 % Cardiac morbidity (angina, heart failure, or arrhythmia).
- 0.5 % death or MI.

Gottlieb A. J Cardiothorac Vasc Anesth 1998;12:501

BMS Thrombosis: early post PCI

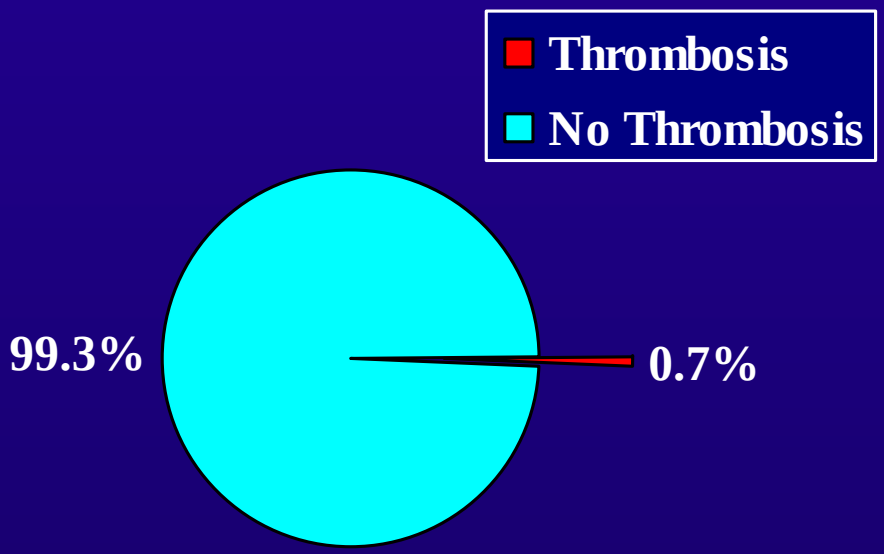


Temporal distribution of all events. There were 112 events (2.0%) that occurred during the first 14 days and 30 events during days 15 to 30 (0.5%). Events per day are illustrated in a hierarchial order: **hatched box** = death; **white box** = nonfatal myocardial infarction; **black box** = occlusion.

Schulen H. J Am Coll Cardiol 2001;37:2066

Angiographic Stent Thrombosis

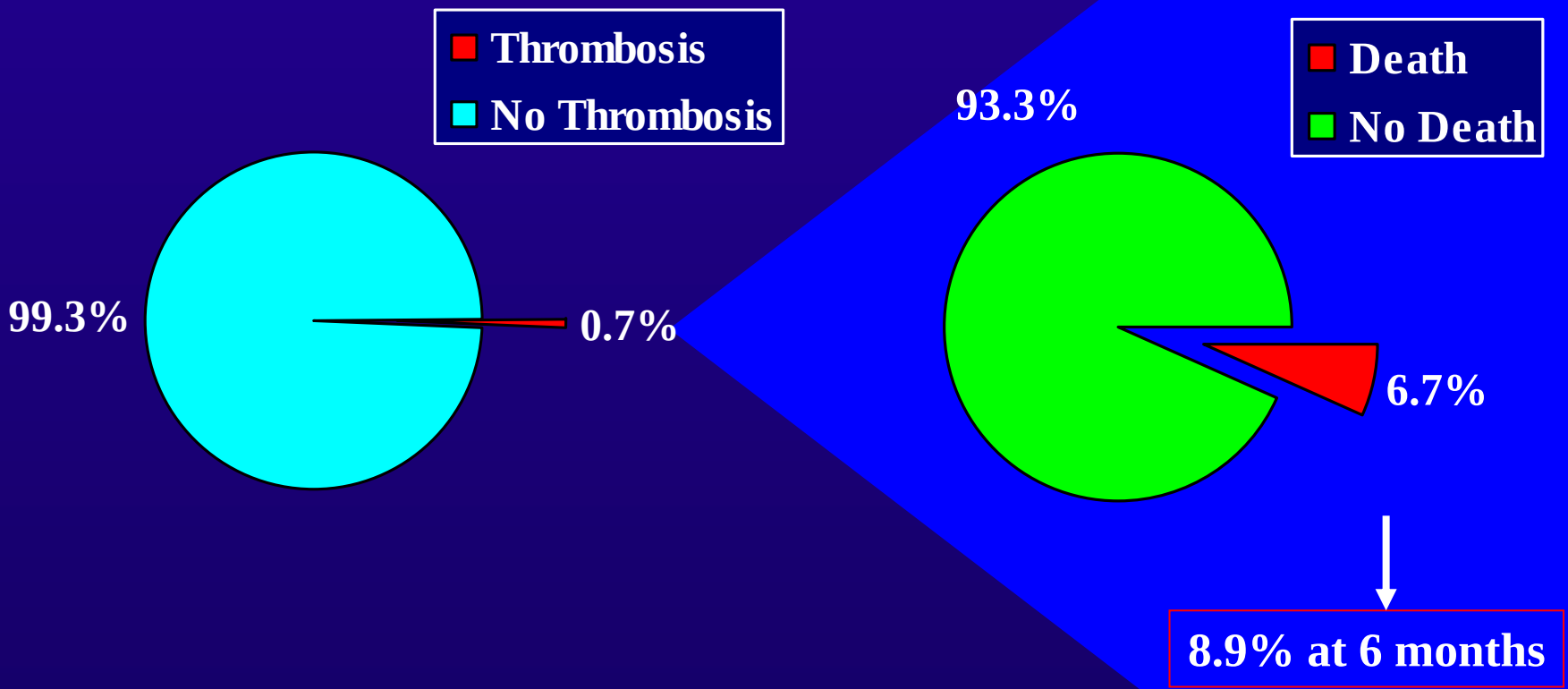
30 days outcome



Cutlip, DE. Circulation.2001;103:1967

Angiographic Stent Thrombosis

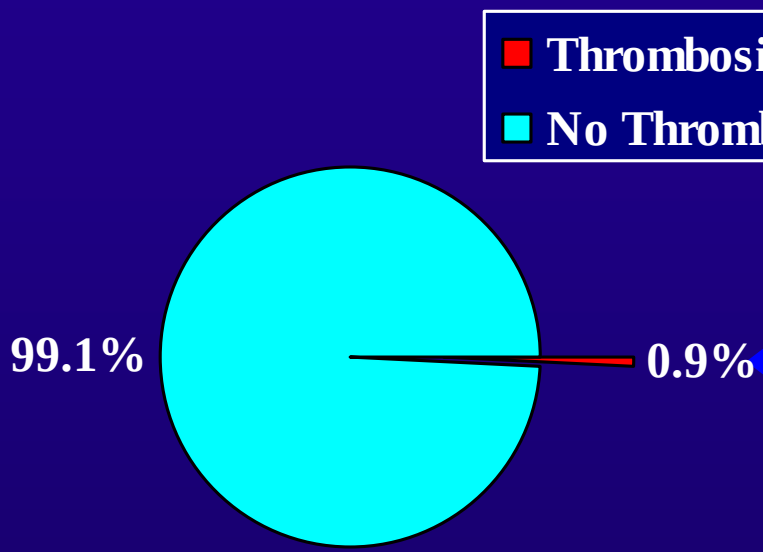
30 days outcome

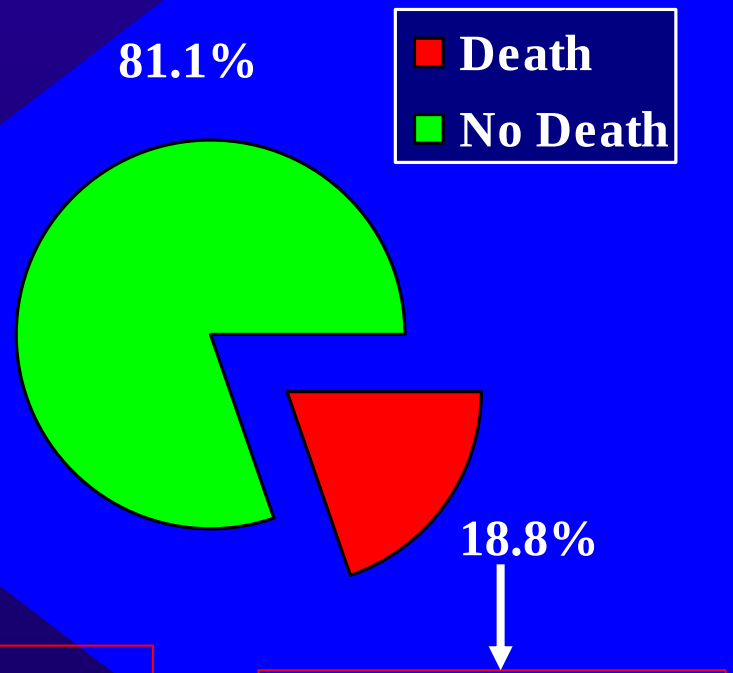


Cutlip, DE. Circulation.2001;103:1967

Clinical Stent Thrombosis

30 days outcome





20.6% at 6 months

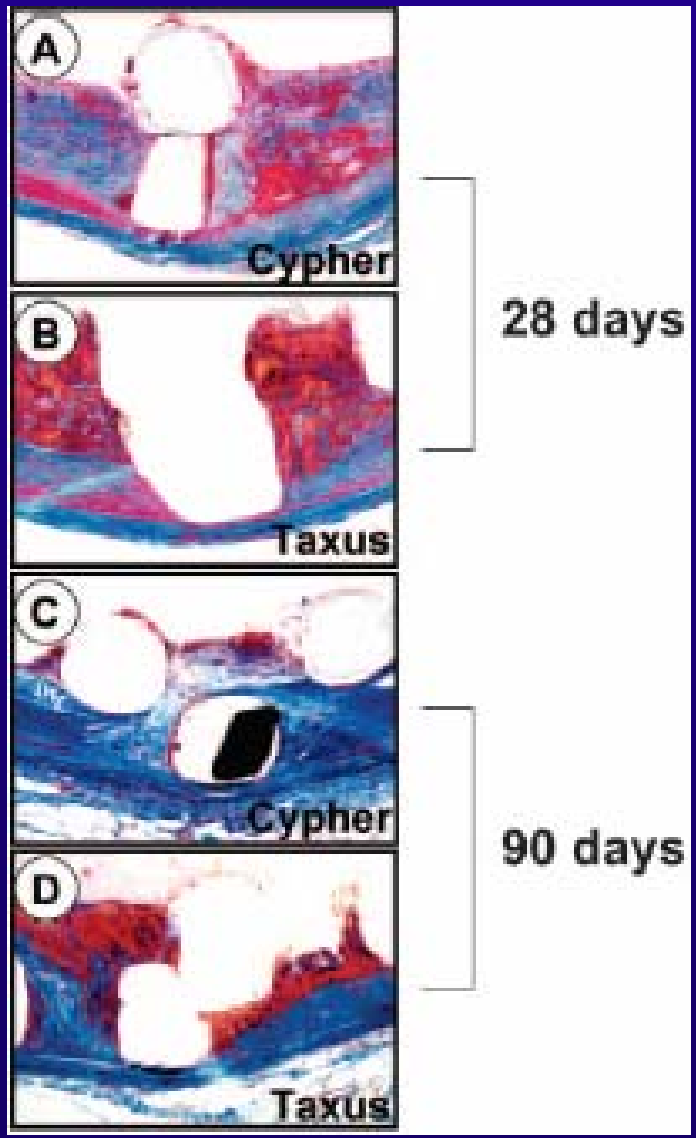
Clinical stent thrombosis :

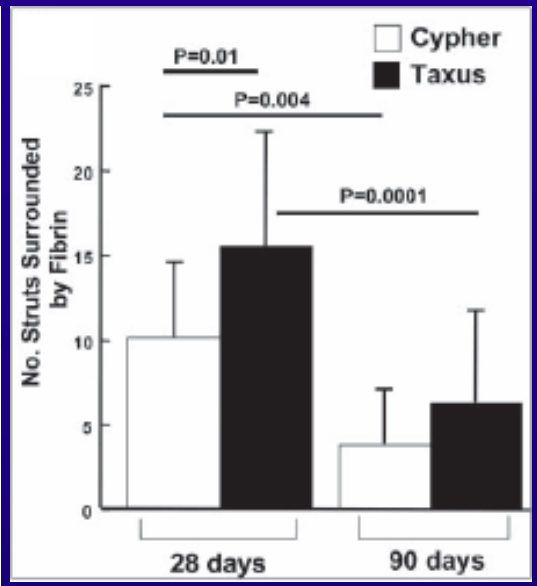
- Angiographic documentation of stent occlusion,
- Unexplained sudden death,
- Myocardial infarction, or
- Urgent TLR within 30 days of the procedure.

Cutlip, DE. Circulation.2001;103:1967

Concern about DES :

Fibrin deposition and persistent inflammation





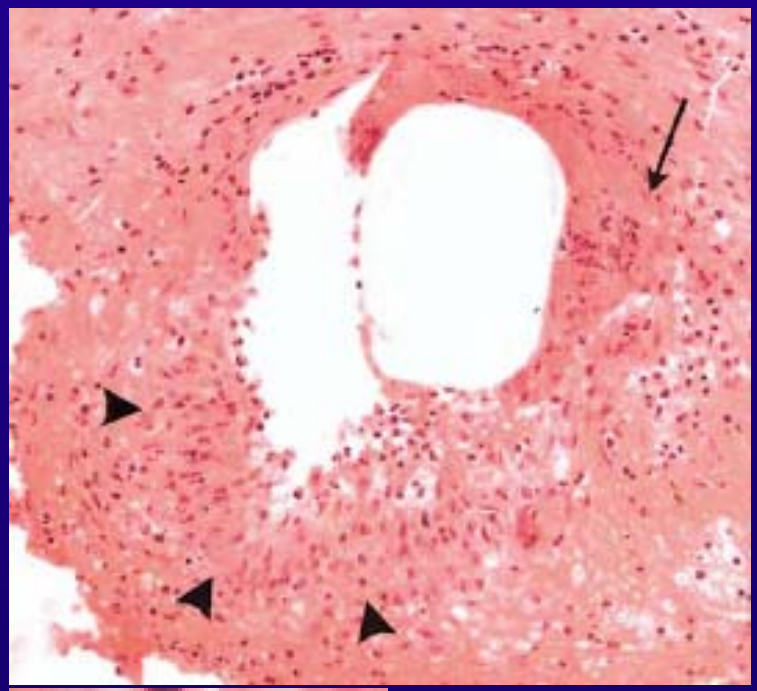
Finn AV. Circulation. 2005;112:270

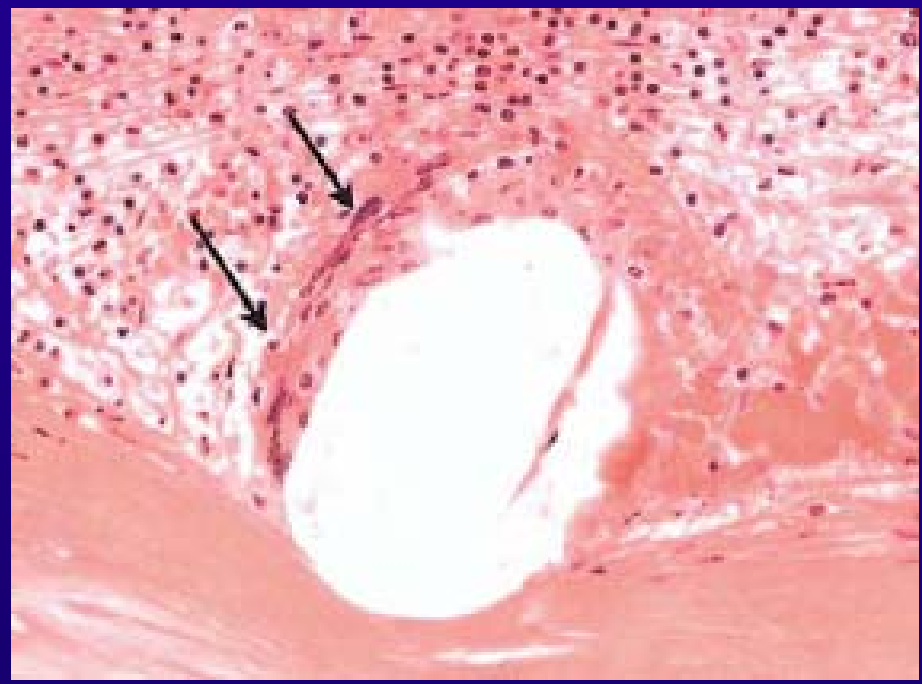
Virmani R. Circulation. 2002;106:2649

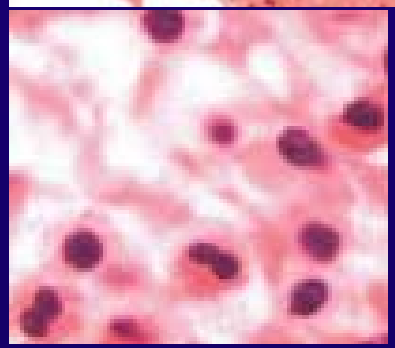
Paclitaxel Eluting In-Stent Restenosis at 12 months

CD 68: Monocytes, macrophages. CD 45: Lymphocytes

Hypersensitivity Reactions to Drug-Eluting Stents



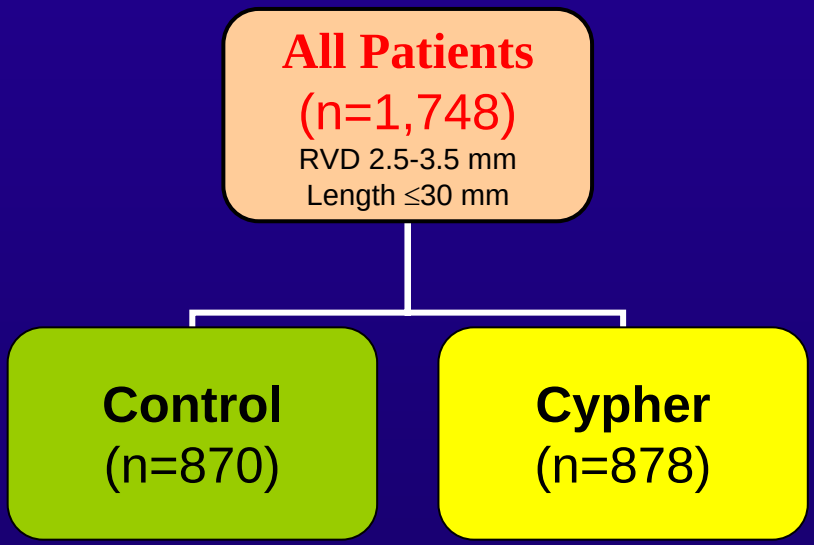




Four autopsies confirmed intrastent eosinophilic inflammation, thrombosis, and lack of intimal healing

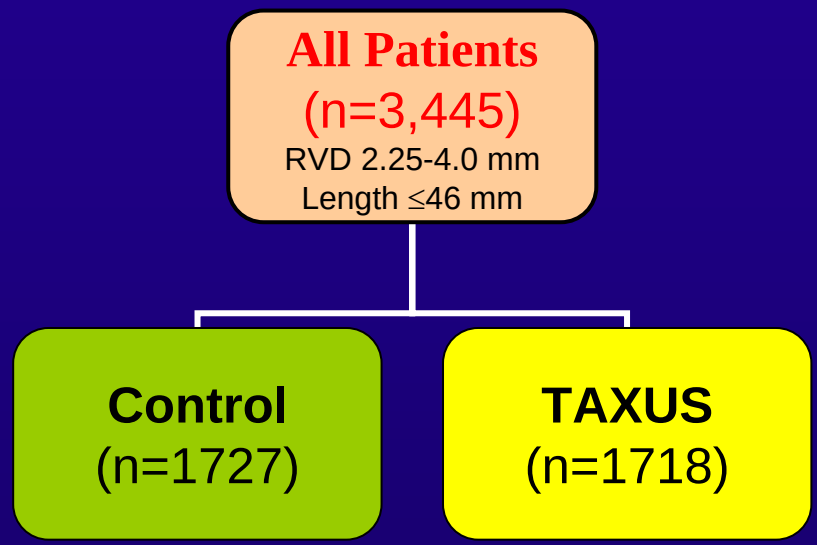
Nebecker JR. J Am Coll Cardiol 2006;47:175

Analysis of All Patients RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS



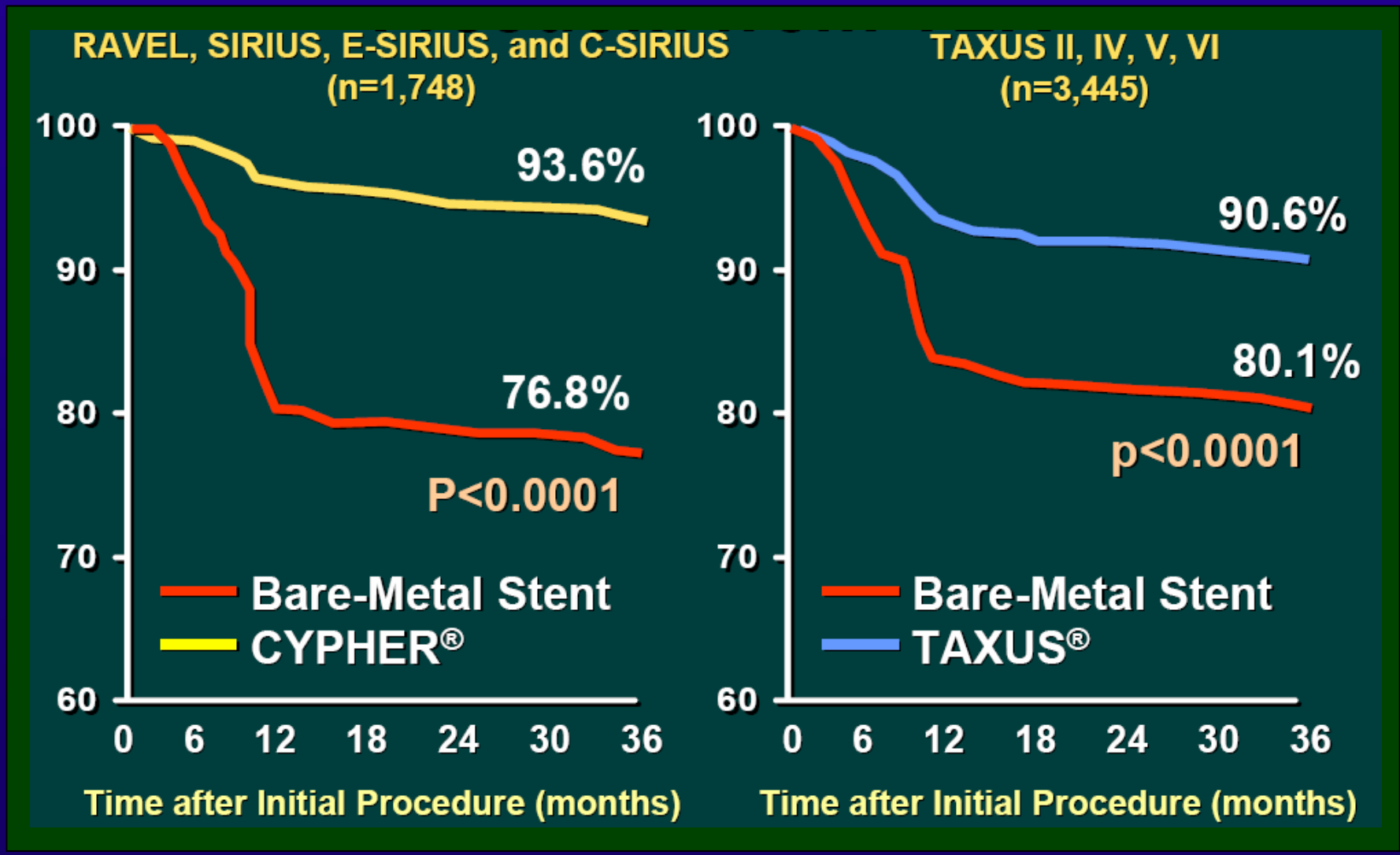
NEJM. 2002;346:1773
NEJM. 2003;349:1315
Lancet. 2003;362:1093
JACC. 2004;43:1110

Analysis of All Patients TAXUS II, IV, V, VI



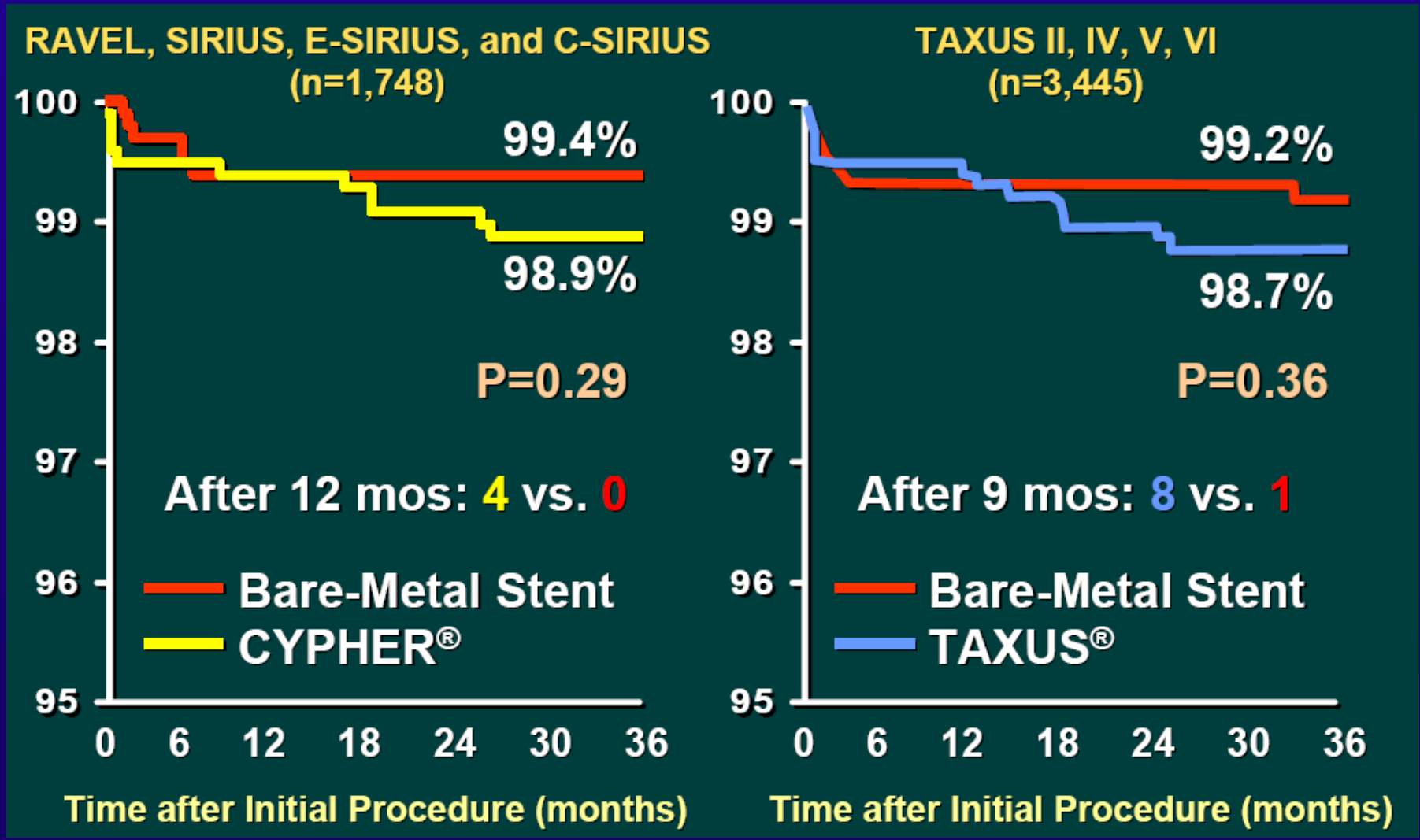
Circulation. 2003;108:788
NEJM. 2004;350:221
JAMA. 2005;294:1215
Circulation. 2005;112:3306

Freedom from TLR



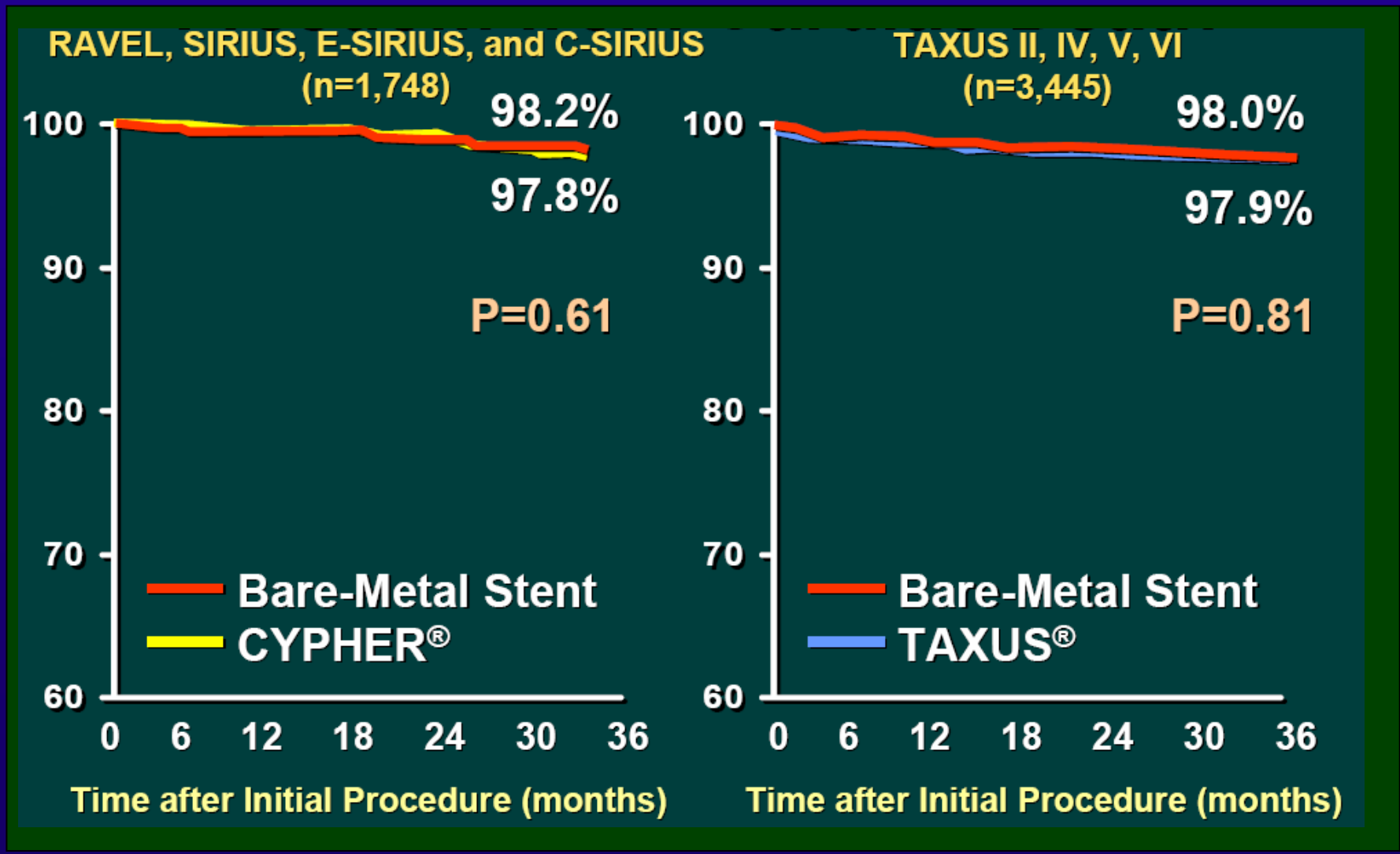
Stone G. ACC 2006

Freedom from Stent Thrombosis



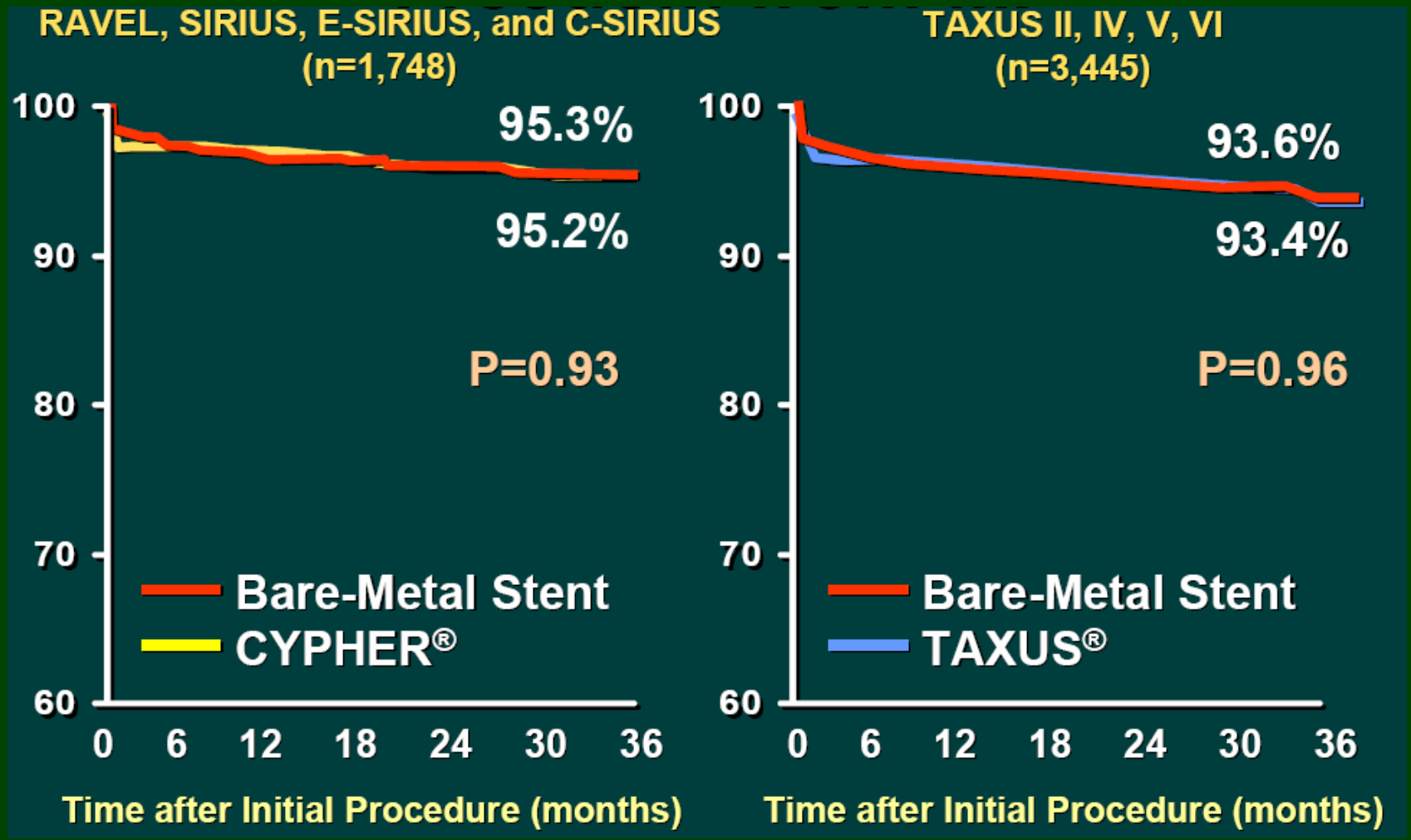
Stone G. ACC 2006

Freedom from Cardiac Death



Stone G. ACC 2006

Freedom from MI



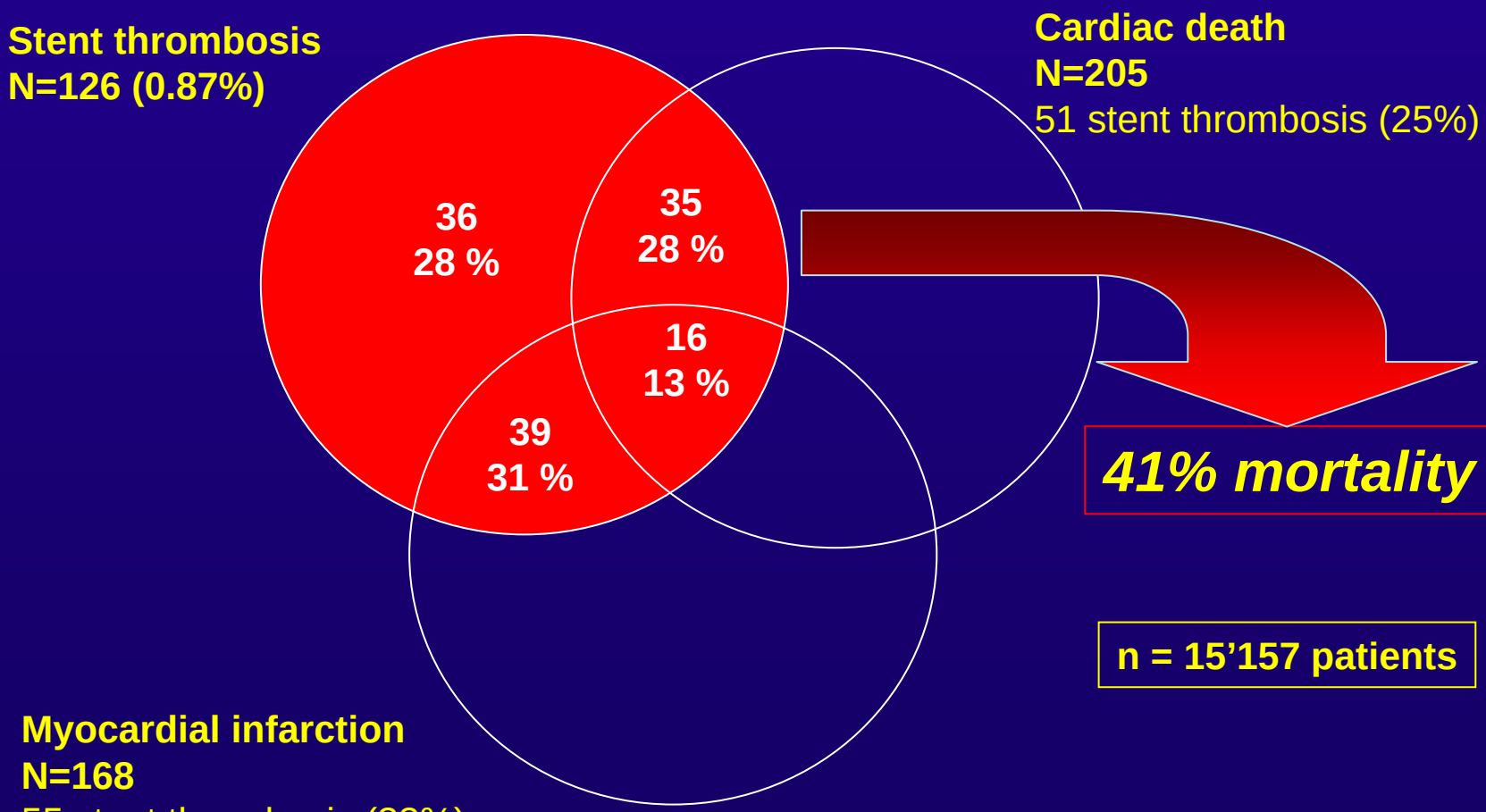
Stone G. ACC 2006

Predictors of stent thrombosis

- Advanced age
- Non compliance
- Diabetes
- Acute coronary syndrome
- Renal failure
- Low LVEF
- Bifurcation lesions
- Calcifications
- Chronic total occlusions
- Stenting of multivessels (multiple stents)
- Total stent length

Stent thrombosis in real life: e-Cypher registry

Late thrombosis 0.19%. 12-months actuarial incidence of stent thrombosis 0.87%

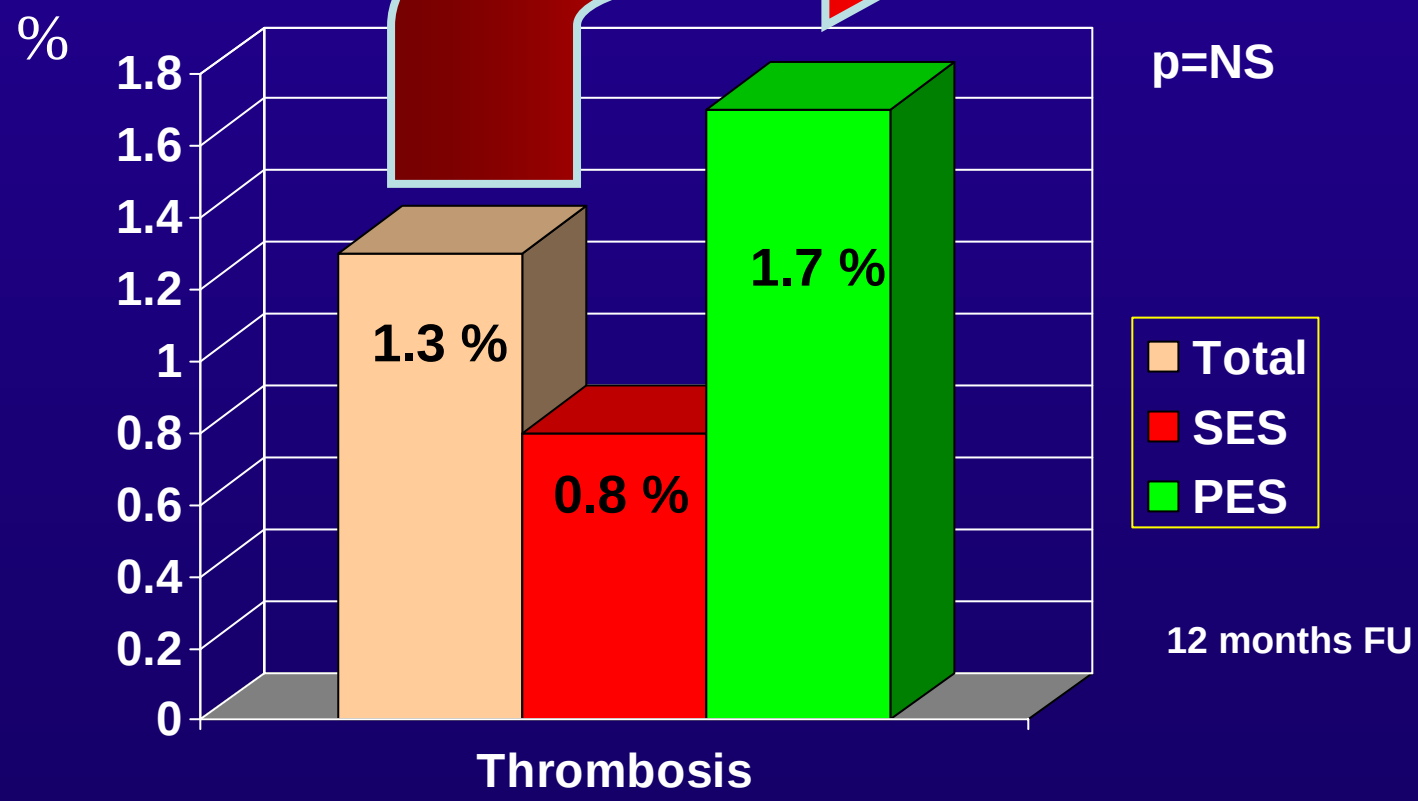


Urban P. Circulation. 2006;113:1434

Incidence of Stent Thrombosis in real-world

N=2229 consecutive pts

Mortality : 45%



Clopidogrel or Ticlopidine : 3 months for SES, 6 months for PES

Iakovou I. JAMA. 2005;293:2126

- 4 Cases of angio-proven stent thrombosis in AMI
  - 2 Paclitaxel Eluting Stent: 343 and 442 days following PCI
  - 2 Sirolimus Eluting Stents: 335 and 375 days following PCI

⇒ **All cases arose soon after antiplatelet therapy cessation**

Aspirin Withdrawal: a risk factor for Early and Late Bare Metal Stent Thrombosis

- 383 patients with known CAD were hospitalized for ACS:
  - 51 (13.3%) of these ACSs occurred within 1 month after aspirin withdrawal.

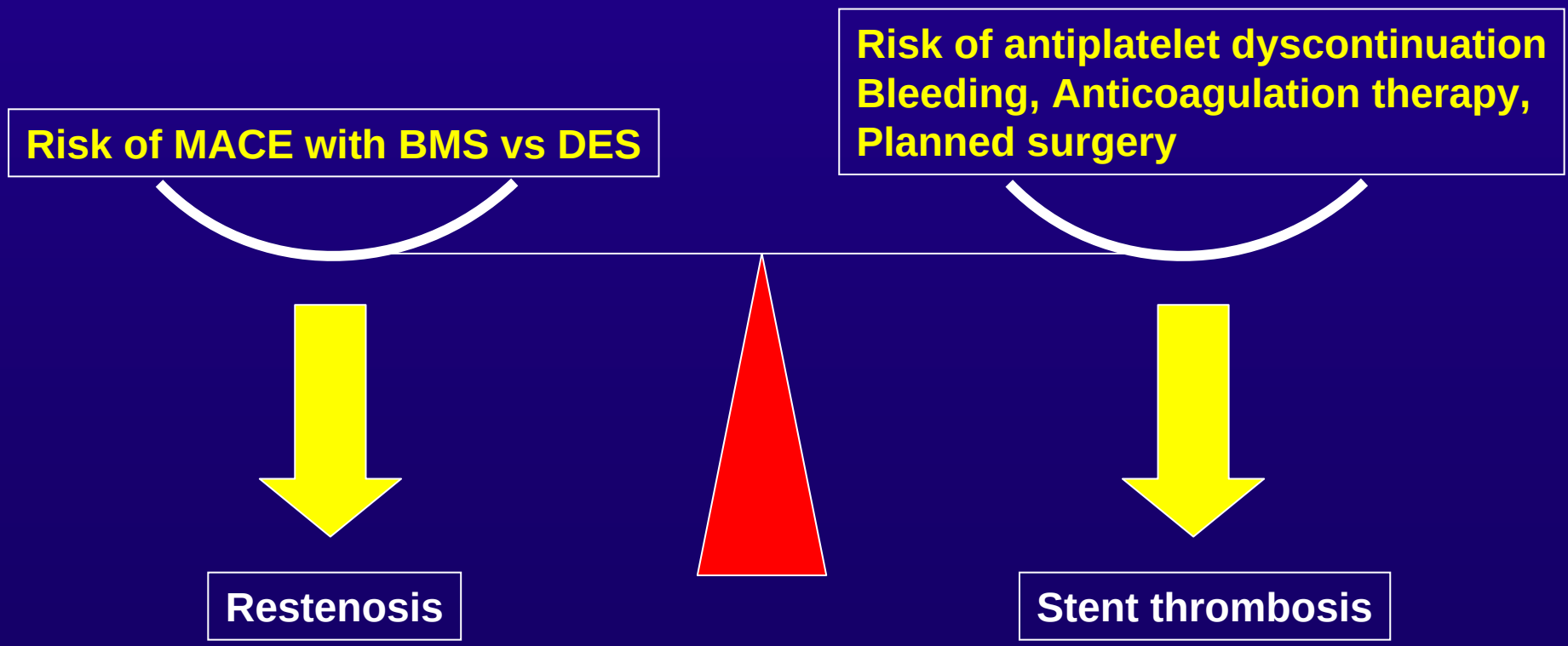
	Aspirin Withdrawal n = 51	No Aspirin Withdrawal n = 332
Non–ST-segment elevation coronary syndrome	31 (61%)	271 (82%)
ST-segment elevation coronary syndrome	20 (39%)	61 (18%)

Data are presented as n (%). $p < 0.001$.

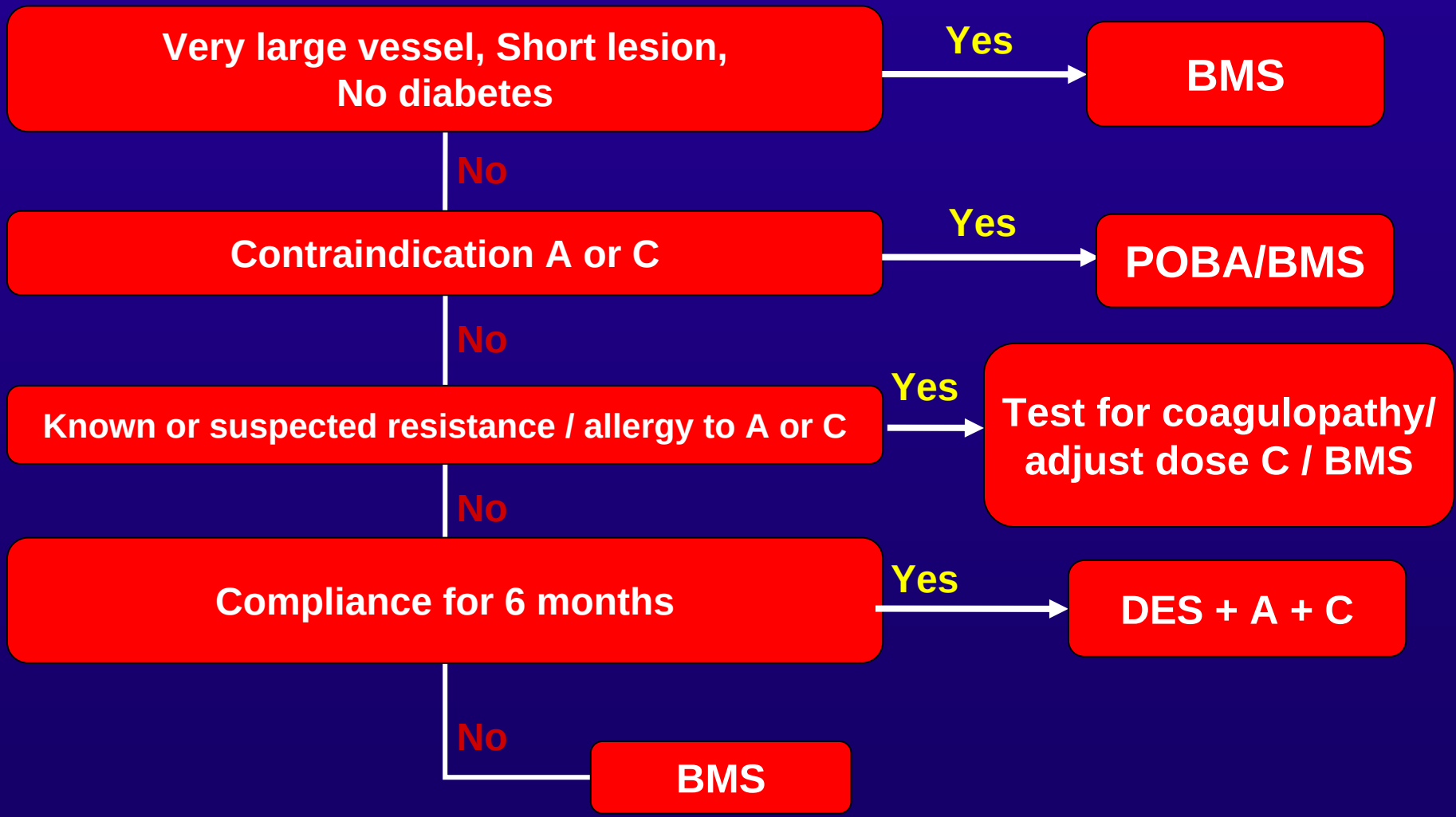
  - **10 pts (20%) had a thrombosis of Bare Metal Stent implanted on average 15.5±6.5 months previously.**

Ferrari E. J Am Coll Cardiol 2005;45:456

DES in 2006


Risk of MACE with BMS vs DES
Risk of antiplatelet dyscontinuation
Bleeding, Anticoagulation therapy,
Planned surgery
Restenosis
Stent thrombosis

Indication of BMS or DES



Recommandations for Clopidogrel as adjunctive medication for PCI The Task force of the ESC

Indication	Duration	Level of evidence
• Bare metal stents	3-4 weeks	IA
• Brachytherapy	12 months	IC
• Drug eluting stents	6-12 months	IC
• NSTE-ACS	9-12 months	IB

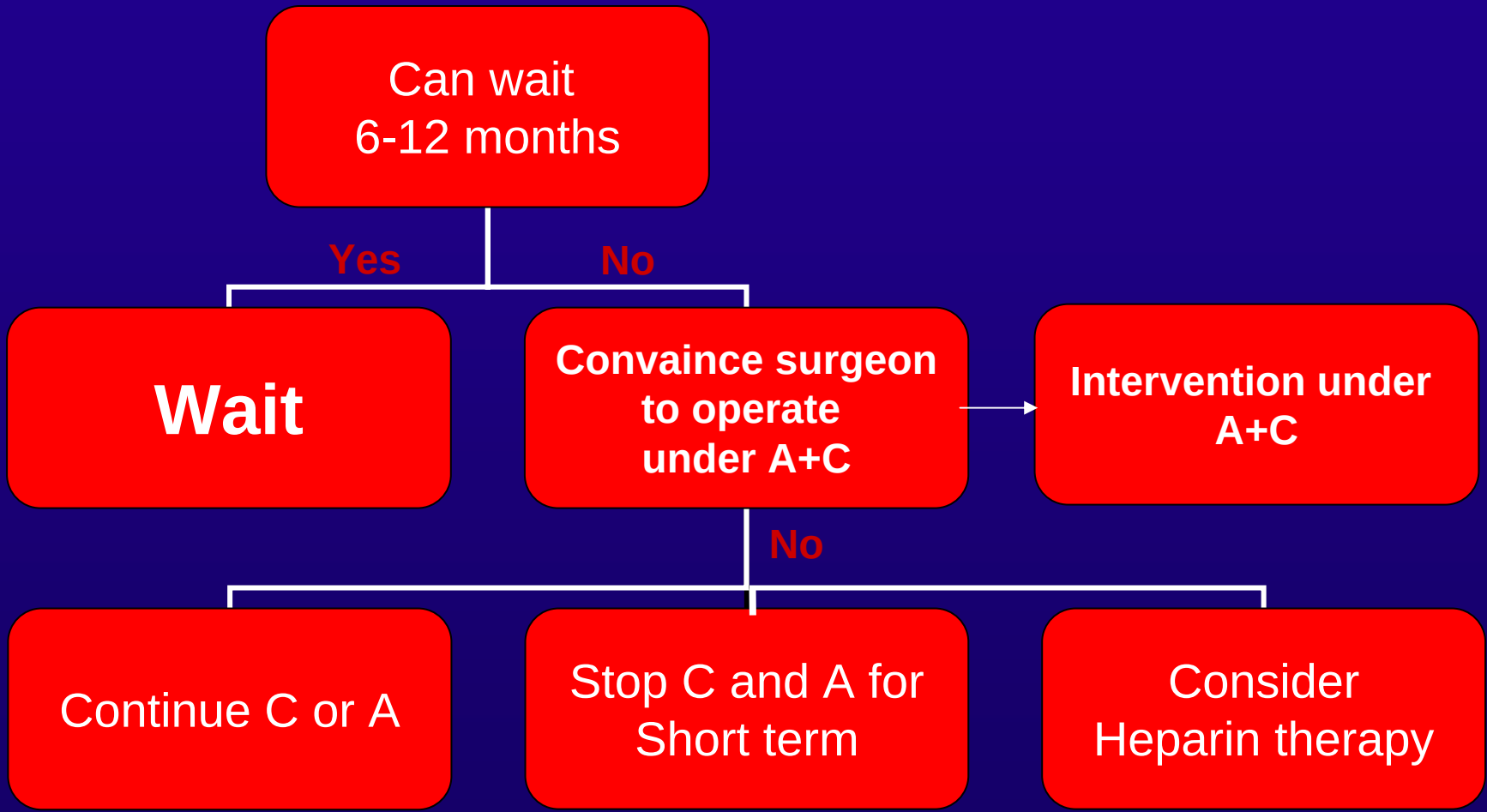
Loading dose 300mg if >12 hours before BMS or DES stenting or 600mg

Eur Heart J March 29, 2005

Clopidogrel after Bare Metal Stents vs Drug Eluting Stents implantation

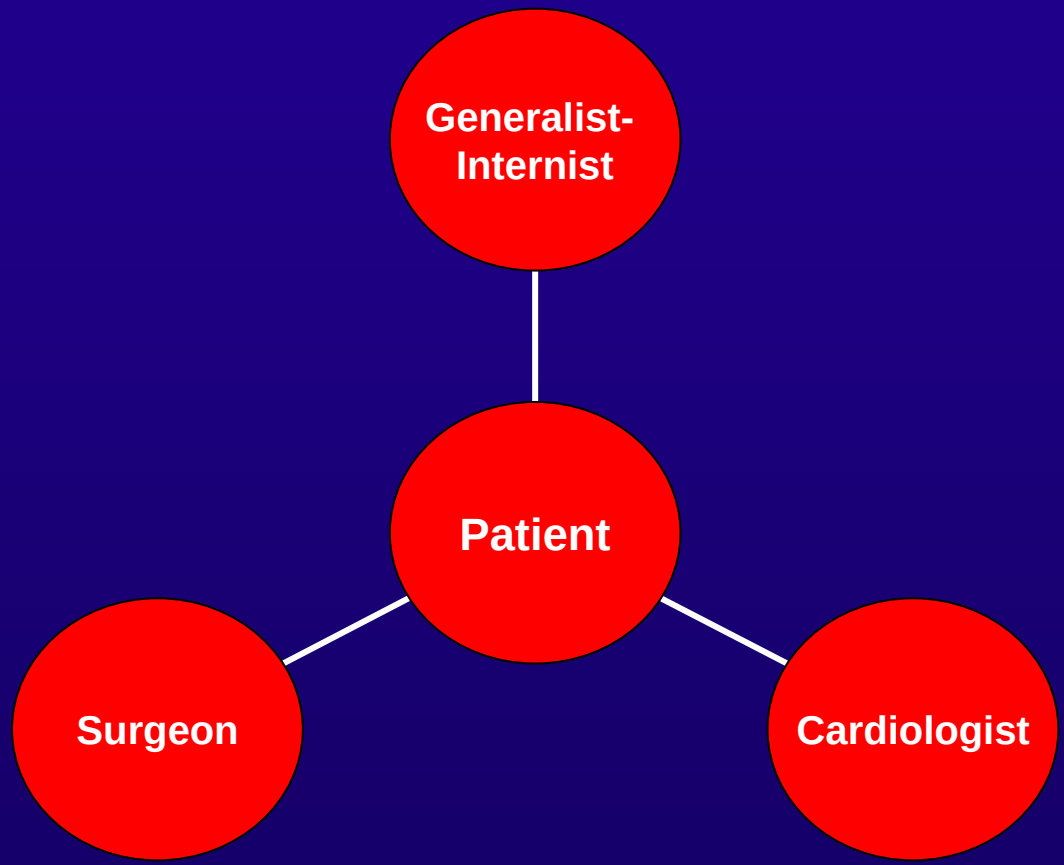
- All DES : FDA expert consensus at least 12 months treatment except for patients with increased risk of bleeding (6 months).
- Elective BMS implantation : 4 weeks treatment.
- BMS in ACS : 9-12 months treatment except for patients with increased risk of bleeding (4 weeks).

Strategy before surgery in DES era

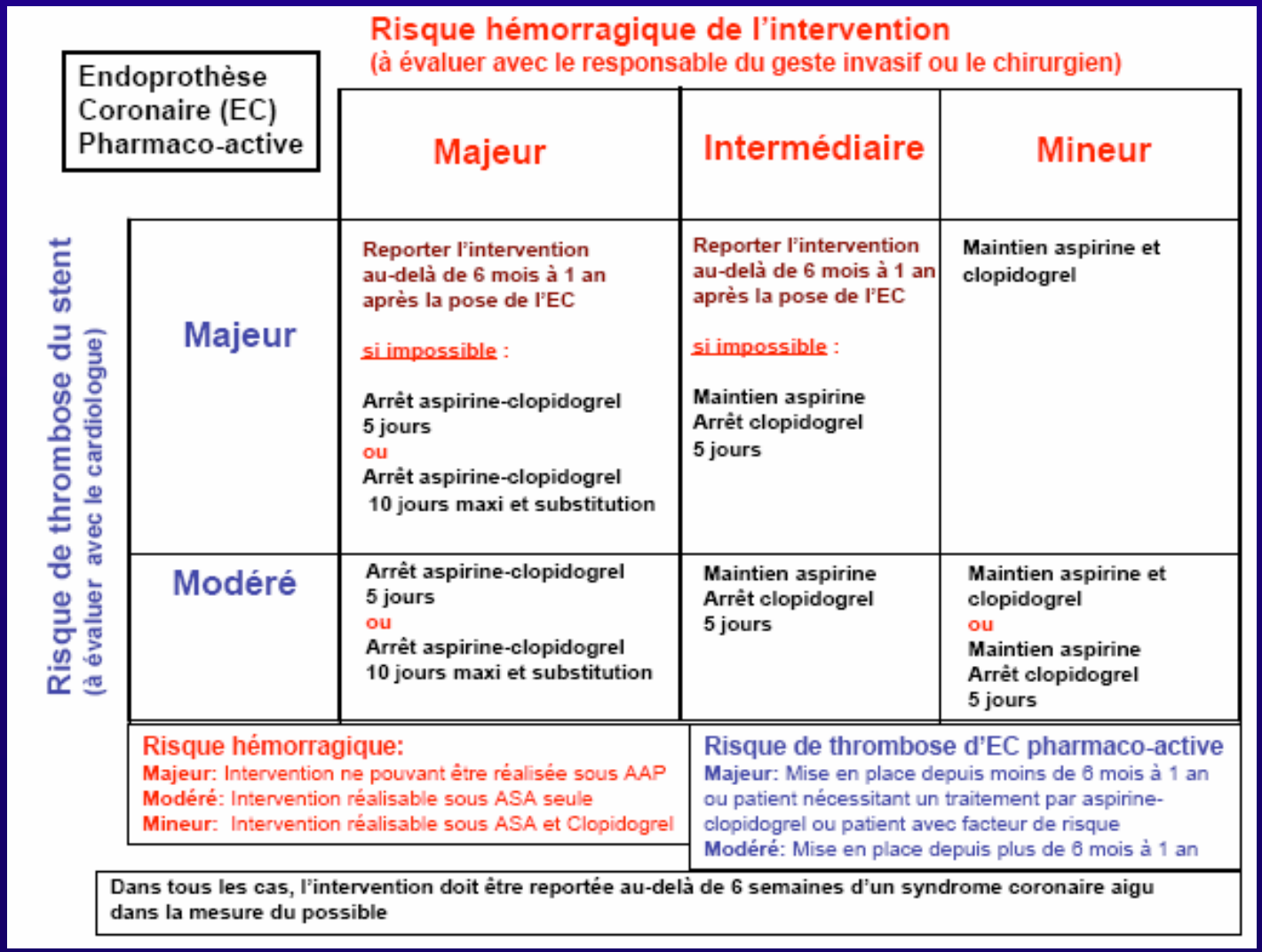


Strategy before surgery

Team



DES et chirurgie non cardiaque



Risque hémorragique de l'intervention
(à évaluer avec le responsable du geste invasif ou le chirurgien)

Endoprothèse Coronaire (EC) Pharmaco-active	Majeur	Intermédiaire	Mineur
Risque de thrombose du stent (à évaluer avec le cardiologue) **Majeur**	Reporter l'intervention au-delà de 6 mois à 1 an après la pose de l'EC si impossible : Arrêt aspirine-clopidogrel 5 jours ou Arrêt aspirine-clopidogrel 10 jours maxi et substitution	Reporter l'intervention au-delà de 6 mois à 1 an après la pose de l'EC si impossible : Maintien aspirine Arrêt clopidogrel 5 jours	Maintien aspirine et clopidogrel
Modéré	Arrêt aspirine-clopidogrel 5 jours ou Arrêt aspirine-clopidogrel 10 jours maxi et substitution	Maintien aspirine Arrêt clopidogrel 5 jours	Maintien aspirine et clopidogrel ou Maintien aspirine Arrêt clopidogrel 5 jours

Risque hémorragique:
Majeur: Intervention ne pouvant être réalisée sous AAP
Modéré: Intervention réalisable sous ASA seule
Mineur: Intervention réalisable sous ASA et Clopidogrel

Risque de thrombose d'EC pharmaco-active
Majeur: Mise en place depuis moins de 6 mois à 1 an ou patient nécessitant un traitement par aspirine-clopidogrel ou patient avec facteur de risque
Modéré: Mise en place depuis plus de 6 mois à 1 an

Dans tous les cas, l'intervention doit être reportée au-delà de 6 semaines d'un syndrome coronaire aigu dans la mesure du possible

M. J. T. 68 ans (III)

- Le patient désire à tout prix se faire opérer
- Faut-il
  - ~~Procéder à l'intervention sans autre?~~
  - ~~Stopper le clopidogrel et l'aspirine et opérer?~~
  - ~~Stopper le clopidogrel ou l'aspirine et opérer? Lequel?~~
  - Convaincre le patient de surseoir à l'intervention? Combien de temps?

6 mois après l'implantation du stent

M. J. T. 68 ans (IV)

- Vous avez convaincu le patient de surseoir à la cholécystectomie
- Avec des conseils diététiques et une reprise de l'activité physique, il n'a plus eu de douleurs abdominales
- Lors d'un contrôle de routine, vous découvrez un pouls irrégulier env. 80/min
- Status: pas de signe d'IC

M. J. T. 68 ans (IV)

- ECG: FA spontanément lente
- Holter: FA permanente avec réponse ventriculaire entre 60 et 100/min
- Echo cardiaque: oreillette dilatée (diamètre 5,6 cm)
- Vous débutez le Sintrom
  - Que faites-vous avec le traitement anti-agrégant?

M. J. T. 68 ans (IV)

- ECG: FA spontanément lente
- Holter: FA permanente avec réponse ventriculaire entre 60 et 100/min
- Echo cardiaque: oreillette dilatée (diamètre 5,6 cm)
- Vous débutez le Sintrom
  - Que faites-vous avec le traitement anti-agrégant? Introduction de Sintrom et arrêt du Clopidogrel 6 mois après l'implantation du stent


Merci