New Insights Into the Use of Clopidogrel

: Duration of Dual Antiplatelet Therapy with Next Generation DES

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구 분	세부 인정기준 및 방법
항혈전 치료제 (경구용 Heparinoid 제제 및 경구용 항혈소판제)	**아래와 같은 기준으로 투여 시 요양급여를 인정하며, 허가사항 범위지만 동 인정기준 이외에 투여한 경우에는 약값 전액을 환자가 부담토록 함.** 가. 각 약제는 대상 질환의 허가사항 범위 내에서 투여하되 심혈관 질환·뇌혈관 질환·말초동맥성 질환의 혈전예방 및 치료를 위해서는 Aspirin을 우선 투여하고 Aspirin에 효과 없거나(사용 중 심혈관 질환・뇌혈관 질환・말초동맥성 질환이 발생한 경우), Aspirin을 사용할 수 없는 경우〔알러지, 저항성(resistance) 또는 심한 부작용(위장관 출혈 등)〕및 심혈관 질환 또는 뇌혈관 질환 발병환자의 재발방지(2차 예방)를 위해서는 해당질환에 허가받은 항혈전제 ※1종을 인정함. 나. 심혈관 질환·뇌혈관 질환·말초동맥성 질환 중 ST분절 상승 심근경색증, 급성관상동맥증후군, 재발성 뇌졸중, 중증 뇌졸중, Stent 삽입환자(심혈관 질환・뇌혈관 질환・말초동맥성 질환)와 같은 고위험군에는 항혈전제 단독요법 뿐만 아니라 병용요법(2제요법)으로 투여시 급여를 인정함. **- 병용요법(2제요법)의 급여인정 기간은 1년 이내로 하되, 1년 이상 투여가 필요한 경우 진료담당의사의 투여소견서를 참조하여 사례별로 인정. 병용요법 급여인정 기간 이후에는 항혈전제 단독요법으로 전환하여야 함.** - 병용요법(2제요법)은 병용약물 중 고가의 항혈전제 1종만 급여인정함(투약비용이 저렴한 약제의 약값은 전액 환자가 부담). 단, Aspirin을 포함한 병용요법의 경우에는 모두 급여를 인정함. 다. 관상동맥 스텐트 시술 후 당뇨병 환자의 재협착 방지를 위한 경우, 재협착 병변환자 또는 다혈관 협착으로 다수의 스텐트를 시술(multiple-stenting)한 환자의 경우에는 상기 "나"에 의한 요법뿐만 아니라 Aspirin+ Clopidogrel+Cilostazol 3제 요법도 급여를 인정 - Aspirin+Clopidogrel+Cilostazol 3제요법의 급여인정 기간은 1년 이내로(3제요법 중 Cilostazol은 6개월까지만 급여인정)하되, 1년 이상 투여가 필요한 경우 진료담당의사의 투여소견서를 참조하여 사례별로 인정. 병용요법 급여인정 기간 이후에는 항혈전제 단독요법으로 전환하여야 함.

What is the Optimal Duration of Dual Anti-Platelet Therapy after PCI?

Optimal Duration of DAPT

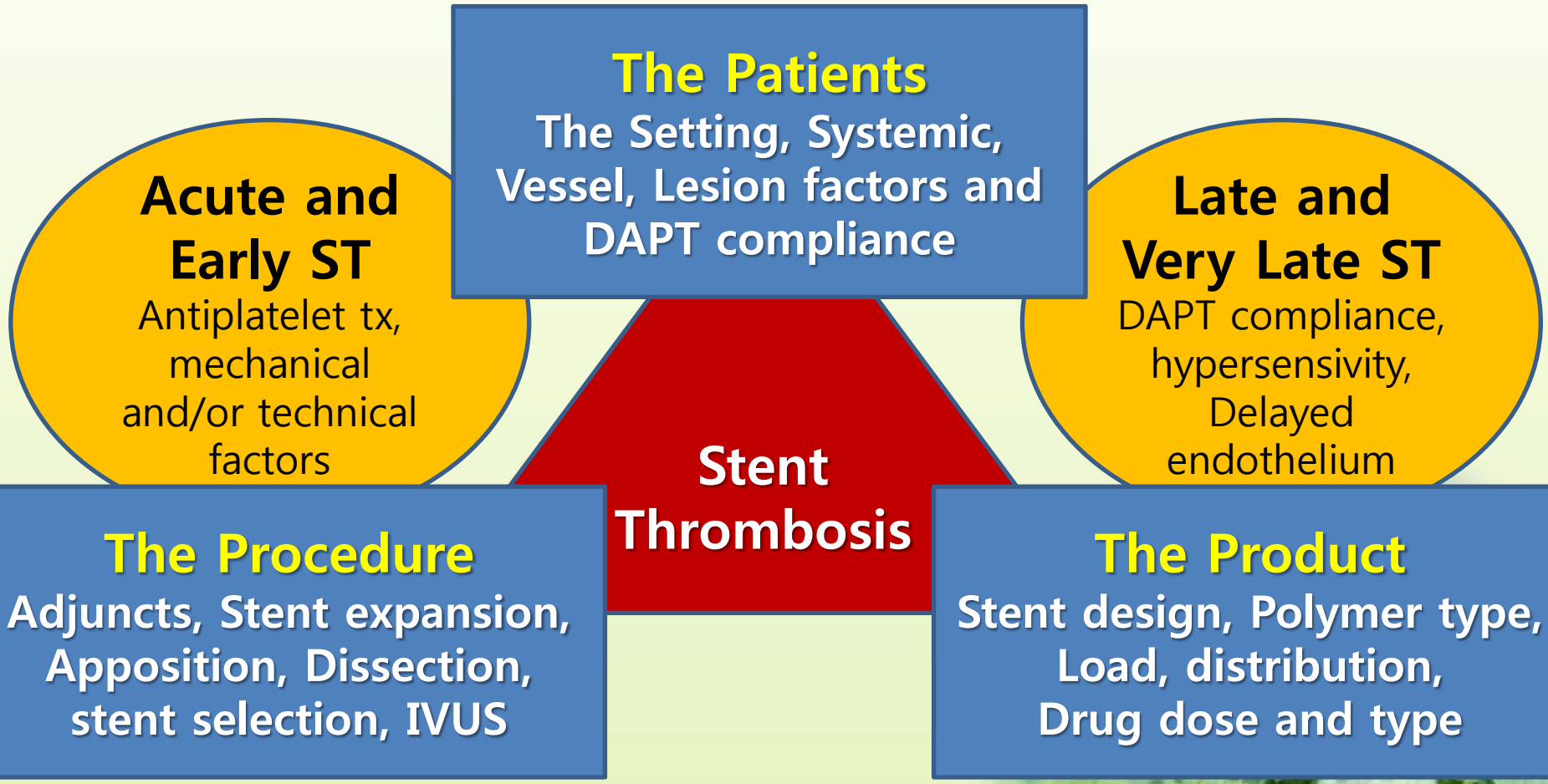
- ✓ **Optimal duration of antiplatelet therapy after PCI is still unclear.**

- ✓ **It can only be determined by means of a large, randomized controlled study with long-term follow up.**

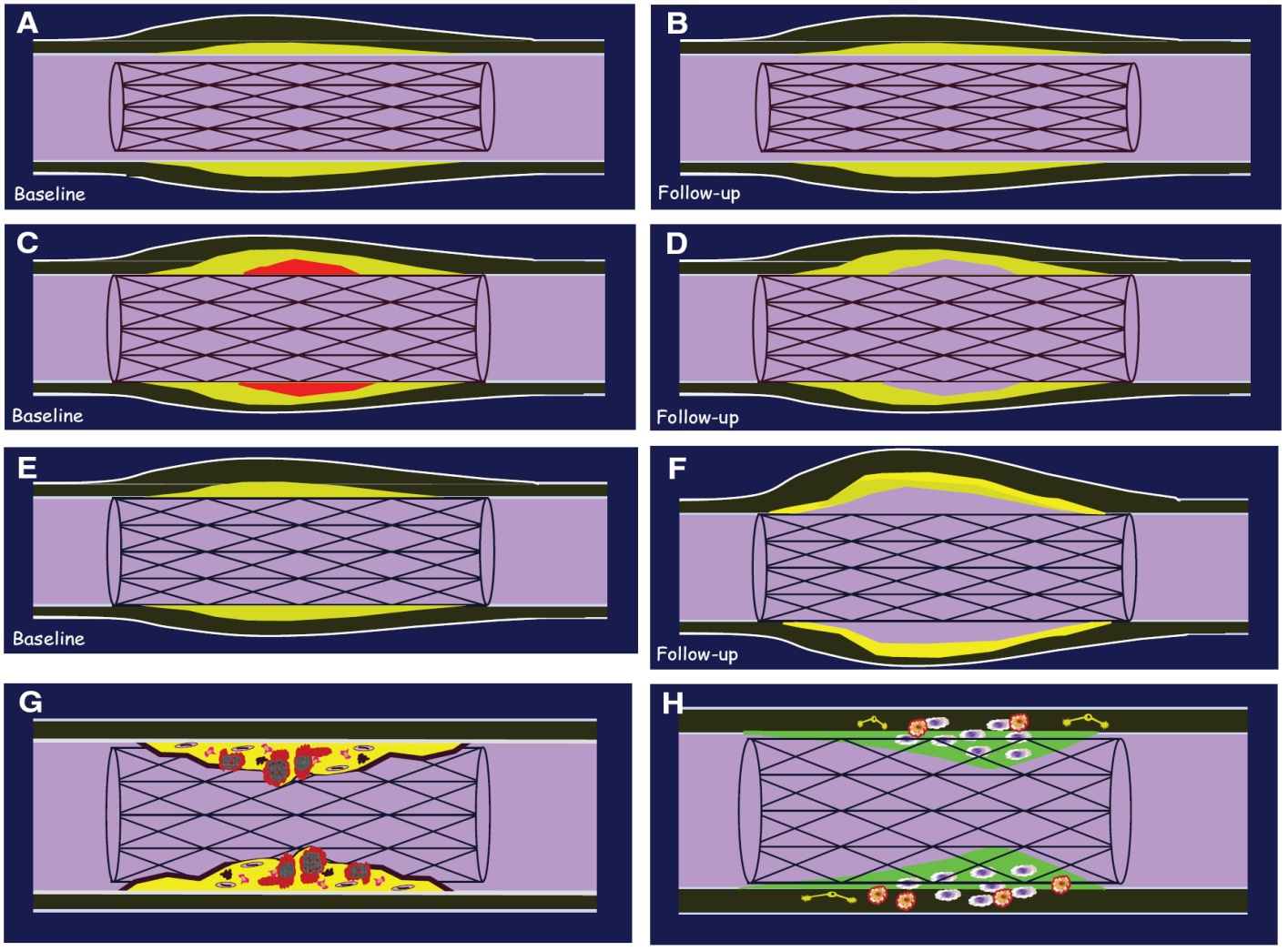
Stent Thrombosis

Stent Thrombosis

The Patient, Procedure and Product Interplay

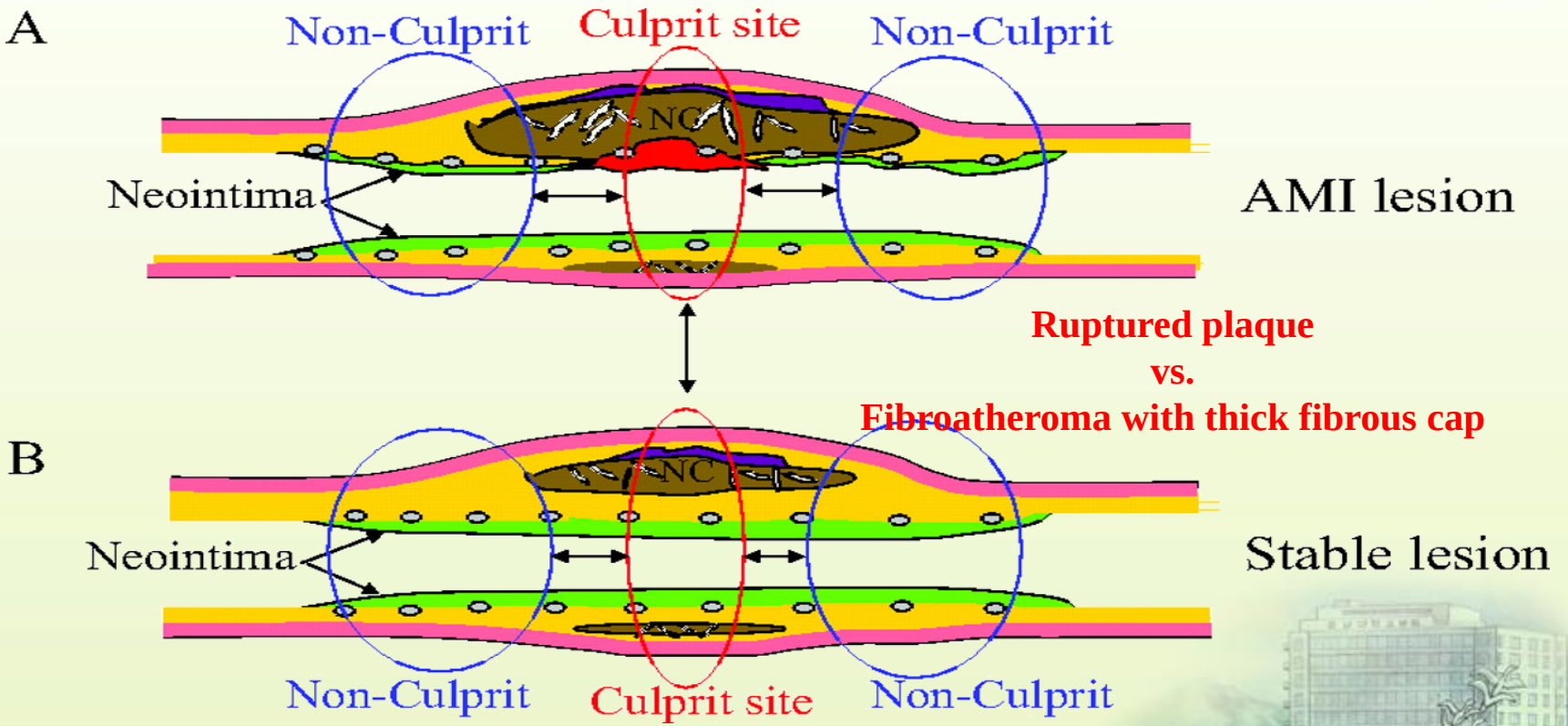


Proposed Mechanisms Leading to Late and Very Late Stent Thrombosis



Colombo and Gerber. *Circ Cardiovasc Intervent.* 2008;1:226-232.

Pattern of healing at AMI culprit/vulnerable sites vs. Stable plaque following DES deployment



Conclusions—Vessel healing at the culprit site in AMI patients treated with DES is substantially delayed compared with the culprit site in patients receiving DES for stable angina, emphasizing the importance of underlying plaque morphology in the arterial response to DES. Our data suggest an increased risk of thrombotic complications in patients treated with DES for AMI. (***Circulation***. 2008;118:1138-1145.)

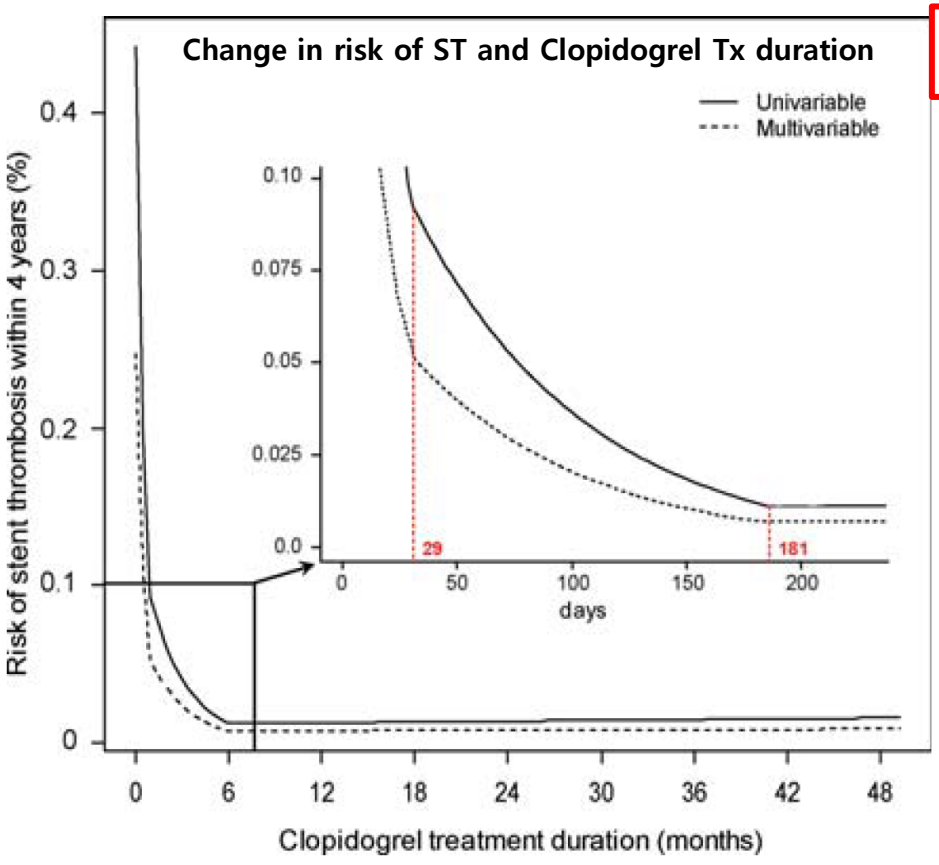
Nakazawa G. et al. *Circulation* 2008;118:1138-1145.

Dual Anti-Platelet Therapy and 1st and 2nd Generation DES

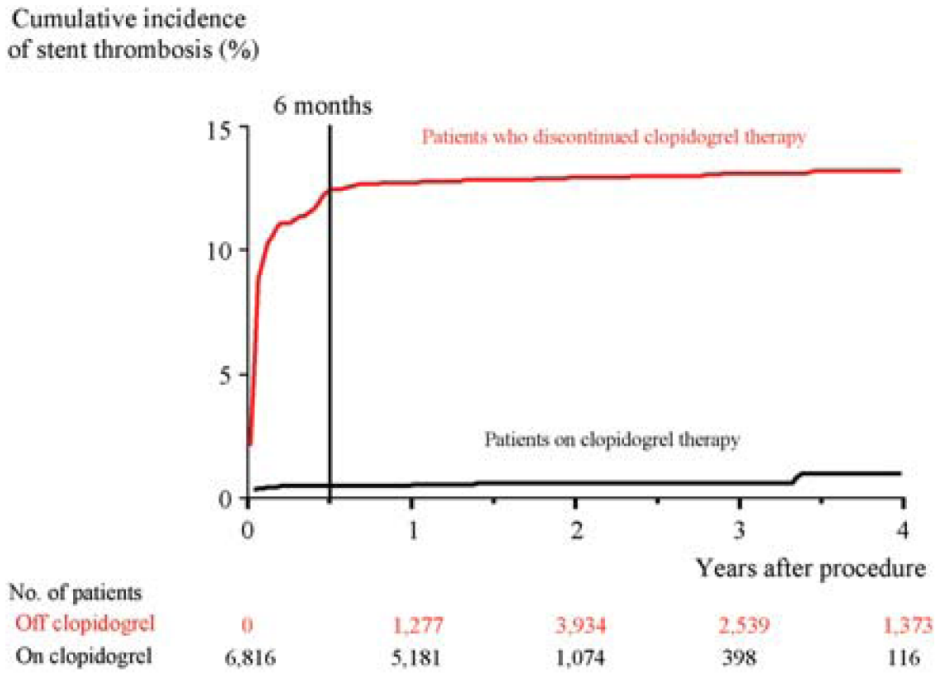
Stent Thrombosis after DES: Relation to Discontinuation of Clopidogrel

6816 consecutive patients with DES followed for 4 years
Stent thrombosis in 1.2%; MI 89% and death 42%

Median time to ST after stopping clopidogrel: <6 mos: 9 days (IQR 5.5–22.5), >6 mos: 104.3 days (IQR 7.4–294.8)



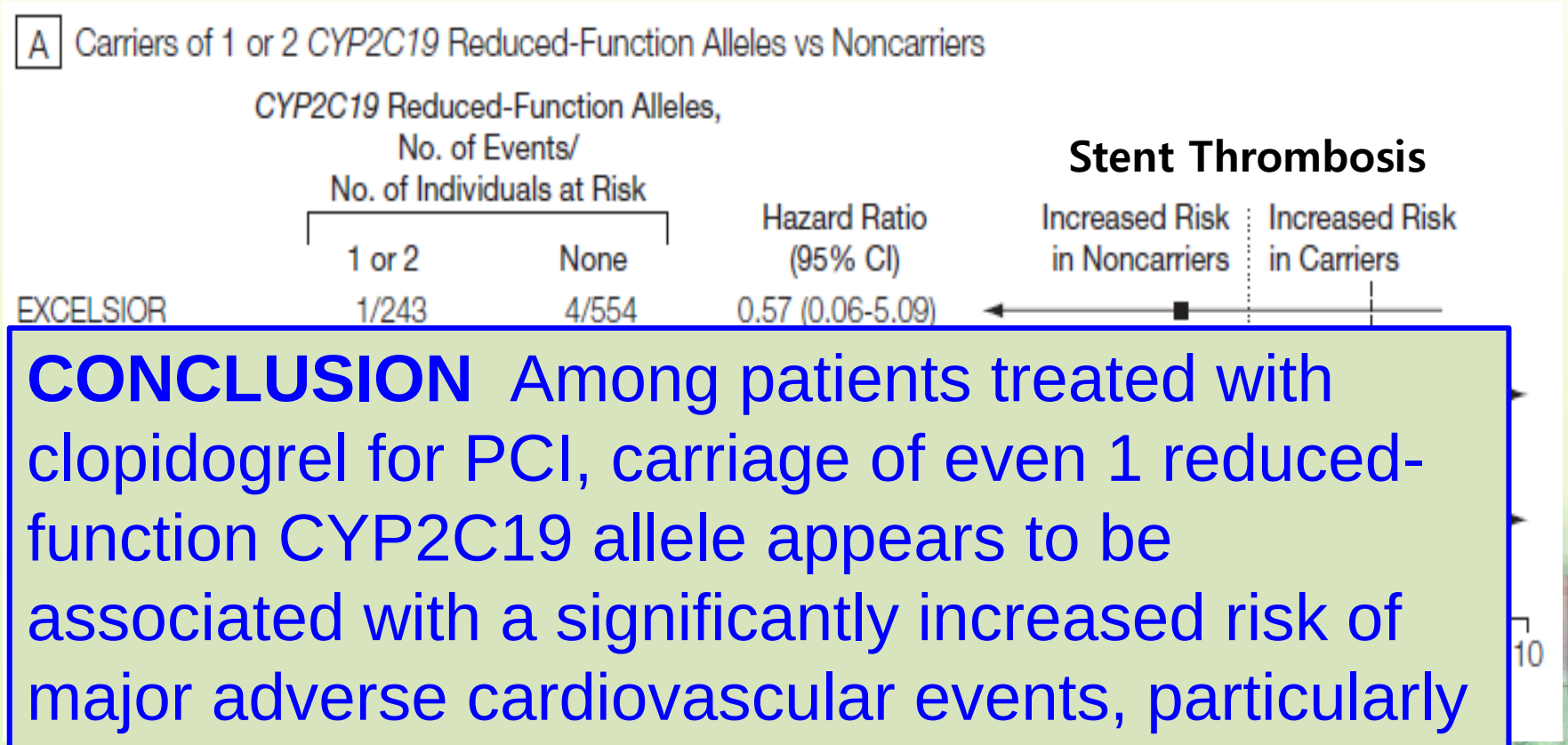
The increase in the cumulative incidence of ST was low in patients who discontinued clopidogrel beyond 6 months of therapy.



Schulz S et al. *Eur Heart J* 2009;30:2714-21.

Reduced-Function CYP2C19 Genotype and Risk of ST with Clopidogrel: A Meta-Analysis

9,685 patients with PCI – 84 pts with stent thrombosis
: 72% non-carriers, 26% 1 reduced function allele, 2% 2 reduced function allele



CONCLUSION Among patients treated with clopidogrel for PCI, carriage of even 1 reduced-function CYP2C19 allele appears to be associated with a significantly increased risk of major adverse cardiovascular events, particularly stent thrombosis.

21-30.

REAL-LATE and ZEST-LATE Study Patients

REAL-LATE

N=1,625
Broader population of patients who had received any DES

ZEST-LATE

N=1,357
Patients who had participated in ZEST trial

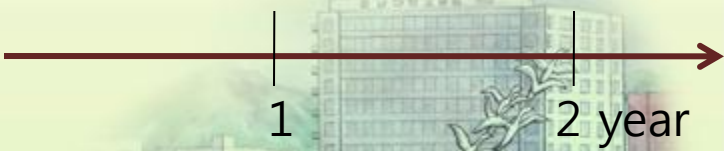
N=2,701

Patients who were free of MACCE with dual antiplatelet therapy for at least a 12 month after DES implantation

R

N=1,357
Clopidogrel + Aspirin

N=1,344
Aspirin Alone



From July 2007 through September 2008

Clinical follow-up every 6 months
Composite of MI or Death from cardiac causes

REAL-LATE and ZEST-LATE

Outcome	Total No. of Events		Cumulative Event Rate at 12 Mo		Cumulative Event Rate at 24 Mo		Hazard Ratio (95% CI)†	P Value
	Clopidogrel +Aspirin	Aspirin Alone	Clopidogrel +Aspirin	Aspirin Alone	Clopidogrel +Aspirin	Aspirin Alone		
Primary end point: MI or death from cardiac causes	20	12	0.7	0.5	1.8	1.2	1.65 (0.80–3.36)	0.17
Secondary end points								
Death from any cause	20	13	0.5	0.5	1.6	1.4	1.52 (0.75–3.50)	0.24
MI	10	7	0.4	0.3	0.8	0.7	1.41 (0.54–3.71)	0.49
Stroke	9	4	0.3	0.3	1.0	0.3	2.22 (0.68–7.20)	0.19
Stent thrombosis, definite	5	4	0.2	0.1	0.4	0.4	1.23 (0.33–4.58)	0.76
Repeat revascularization	36	26	1.7	1.1	3.1	2.4	1.37 (0.83–2.27)	0.22
MI or death from any cause	27	17	0.8	0.8	2.3	1.7	1.57 (0.85–2.88)	0.15
MI, stroke, or death from any cause	35	20	1.1	1.1	3.2	1.8	1.73 (0.99–3.00)	0.05
MI, stroke, or death from cardiac causes	28	15	1.0	0.8	2.7	1.3	1.84 (0.99–3.45)	0.06
Major bleeding, according to TIMI criteria‡	3	1	0.2	0.1	0.2	0.1	2.96 (0.31–28.46)	0.35

Park SJ et al. *N Engl J Med* 2010;362:1374-82.

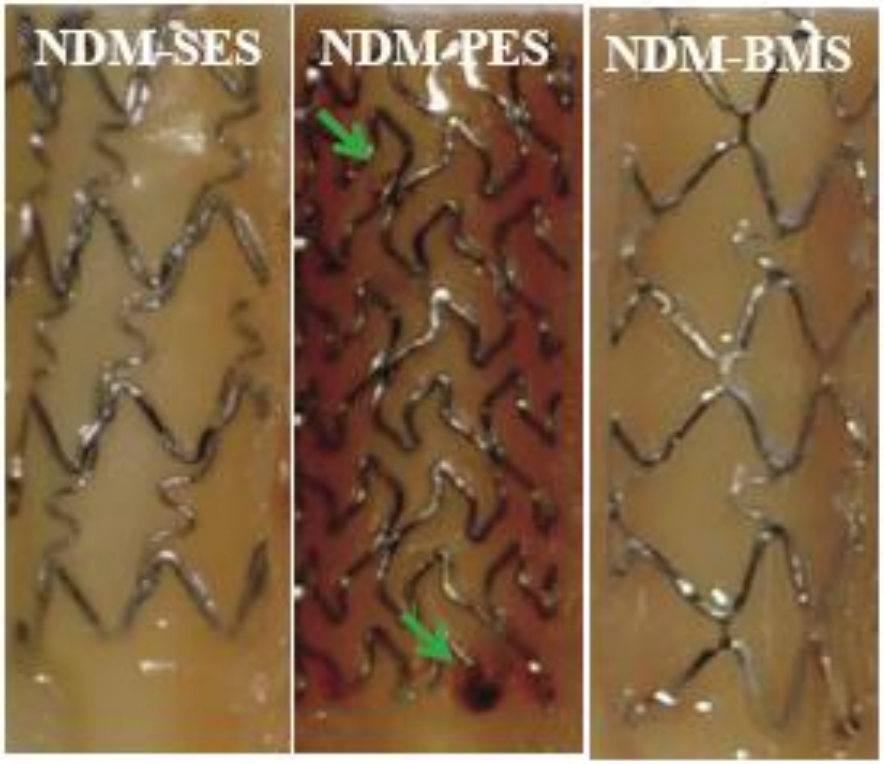
Prolonged Double Antiplatelet Therapy in a Cohort of "De Novo" Diabeteic Patients Treated With Drug-Eluting Stent Implantation

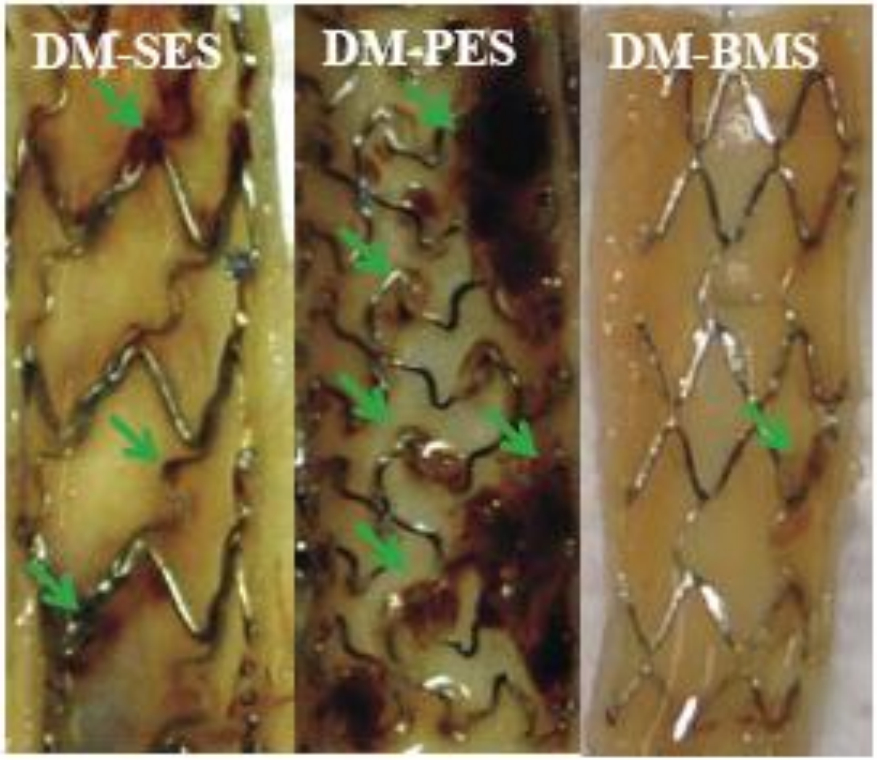
Nadia Mollichelli, MD[a,†], Nuccia Morici, MD[b,†], Federico Ambrogi, PhD[c], Azeem Latib, MD[a,d], Patrizia Boracchi, PhD[c], Cosmo Godino, MD[a,d], Luca Ferri, MD[a], Alfonso Ielasi, MD[a], Alaide Chieffo, MD[a,d], Matteo Montorfano, MD[a], and Antonio Colombo, MD[a,d,*]

Diabetes mellitus (DM) accounts for >25% of all percutaneous coronary interventions. In patients with DM, drug-eluting stent implantation is associated with a reduced risk of restenosis and target lesion revascularization. However, concern has been raised about the incidence of late and very late stent thrombosis and the increased mortality rate, mostly after thienopyridine withdrawal. We evaluated the long-term prognostic effect of thienopyridine discontinuation after drug-eluting stent implantation on the subsequent occurrence of stent thrombosis and all-cause death among a cohort of high-risk "de novo" diabetic patients. From May 2002 to December 2005, 542 consecutive patients with DM underwent drug-eluting stent implantation at 2 hospitals in Milan, Italy. For study purposes, only the 217 patients who had not previously undergone percutaneous or surgical revascularization were considered in the final analysis. The follow-up time was curtailed at 3.5 years. Detailed information about dual antiplatelet therapy (DAT) were collected for all patients included. Of the 217 patients, 15 died (6.9%); in 9 cases, the cause of death was cardiac (4.1%). The incidence of cumulative stent thrombosis was 4.6% (10 patients); 3 stent thromboses were early (1.38%), 5 late (2.3%), and only 2 were very late (0.9%). Of the 10 cases of stent thrombosis, 5 were definite and 5 were probable. Most (80%) of the stent thromboses occurred within the first 6 months during DAT. The median duration of DAT was 420 days (interquartile range 350 to 859). DAT discontinuation was the only independent predictor of the follow-up events (hazard ratio 20.42, 95% confidence interval 4.99 to 83.62). In conclusion, DM remains an independent adverse factor on clinical outcome. In this setting, prolonged DAT, even beyond that recommended in the guidelines, might be beneficial. (Am J Cardiol 2010;105:1395–1401)

Clopidogrel or ticlopidine for 3 M (SES) and 6 M (PES)

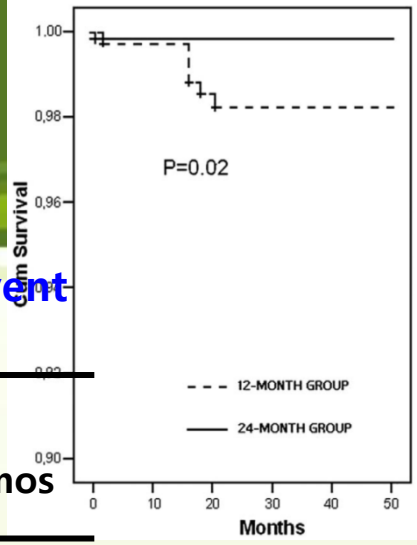
Origin of Restenosis after Drug-Eluting Stent Implantation in Hyperglycemia is Inflammatory Cells and Thrombus





Kwon et al. J Atheroscler Thromb, 2011

Two-Year ClOpidOgrel Need registry



A 2-year dual antiplatelet regimen with aspirin and clopidogre can prevent the occurrenc of very late stent thrombosis after PCI with DES.

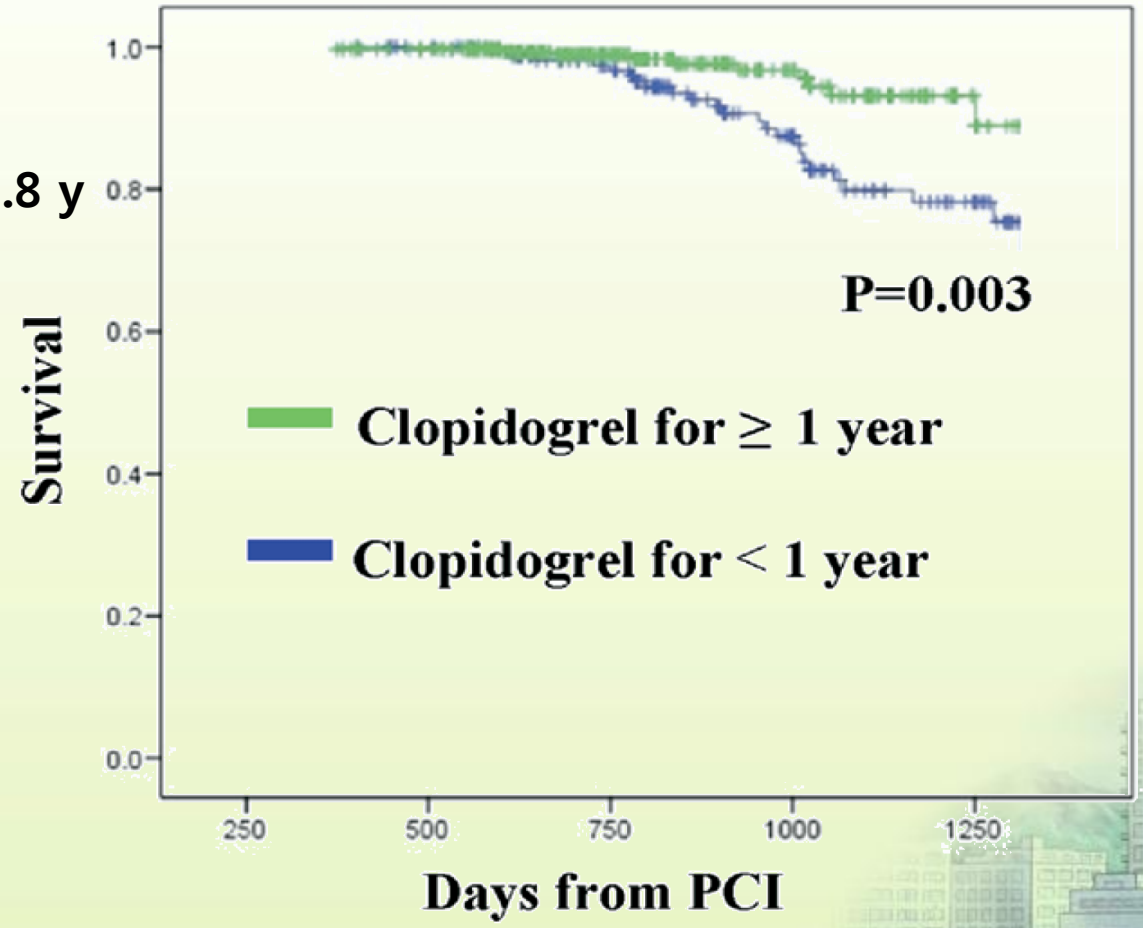
Variable	BMS (n=450)	DES		P-value 12 vs 24 mos
		12 Mos (n=173)	24 Mos (n=274)	
Clinical events				
Cardiac death	12 (3%)	4 (2%)	5 (2%)	0.74
TLR	81 (18%)†	6 (3%)	8 (3%)	0.78
TVR	68 (15%)†	10 (6%)	10 (4%)	0.35
MI	9 (2%)	3 (2%)	1 (0.4%)	0.30
Stent thrombosis				
Acute	1 (0.2%)	0	0	-
Subacutet	1 (0.2%)	1 (0.6%)	1 (0.4%)	-
Late	1 (0.2%)	0	0	-
Very late	0	4 (2%)*	0	0.03
All thromboses	3 (0.7%)	5 (3%)*	1 (0.4%)	0.02

† p <0.05, BMS vs. 12-month DES group.
* p <0.05, BMS vs. 12- and 24-month DES groups.

Tanzilli G et al. *Am J Cardiol* 2009;104:1357-61.

Impact of Long-Term Clopidgorel Use after PCI on mortality

N=530
ACS: 57%
DES: 85%
Mean FU 2.4±0.8 y



The use of clopidogrel ≥1 year after PCI was associated with lower mortality.

Banerjee S et al. *Am J Cardiol* 2008;102:1159-62.

2009 Joint STEMI/PCI Focused Update Recommendations

Class I Recommandation for the Use of Thienopyridines

1. A loading dose of thienopyridine is recommended for STEMI patients for whom PCI is planned. Regimens should be 1 of the following:
   a. At least 300 to 600 mg of clopidogrel† should be given as early as possible before or at the time of primary or nonprimary PCI. (*Level of Evidence: C*)
   b. Prasugrel 60 mg should be given as soon as possible for primary PCI.[26,27] (*Level of Evidence: B*)
   c. For STEMI patients undergoing **nonprimary** PCI, the following regimens are recommended:
      (i) If the patient has received fibrinolytic therapy and has been given clopidogrel, clopidogrel should be continued as the thienopyridine of choice (*Level of Evidence: C*);
      (ii) If the patient has received fibrinolytic therapy without a thienopyridine, a loading dose of 300 to 600 mg‡ of clopidogrel should be given as the thienopyridine of choice (*Level of Evidence: C*);
      (iii) If the patient did not receive fibrinolytic therapy, either a loading dose of 300 to 600 mg of clopidogrel should be given or, once the coronary anatomy is known and PCI is planned, a loading dose of 60 mg of prasugrel should be given promptly and no later than 1 hour after the PCI.[26,27] (*Level of Evidence: B*)

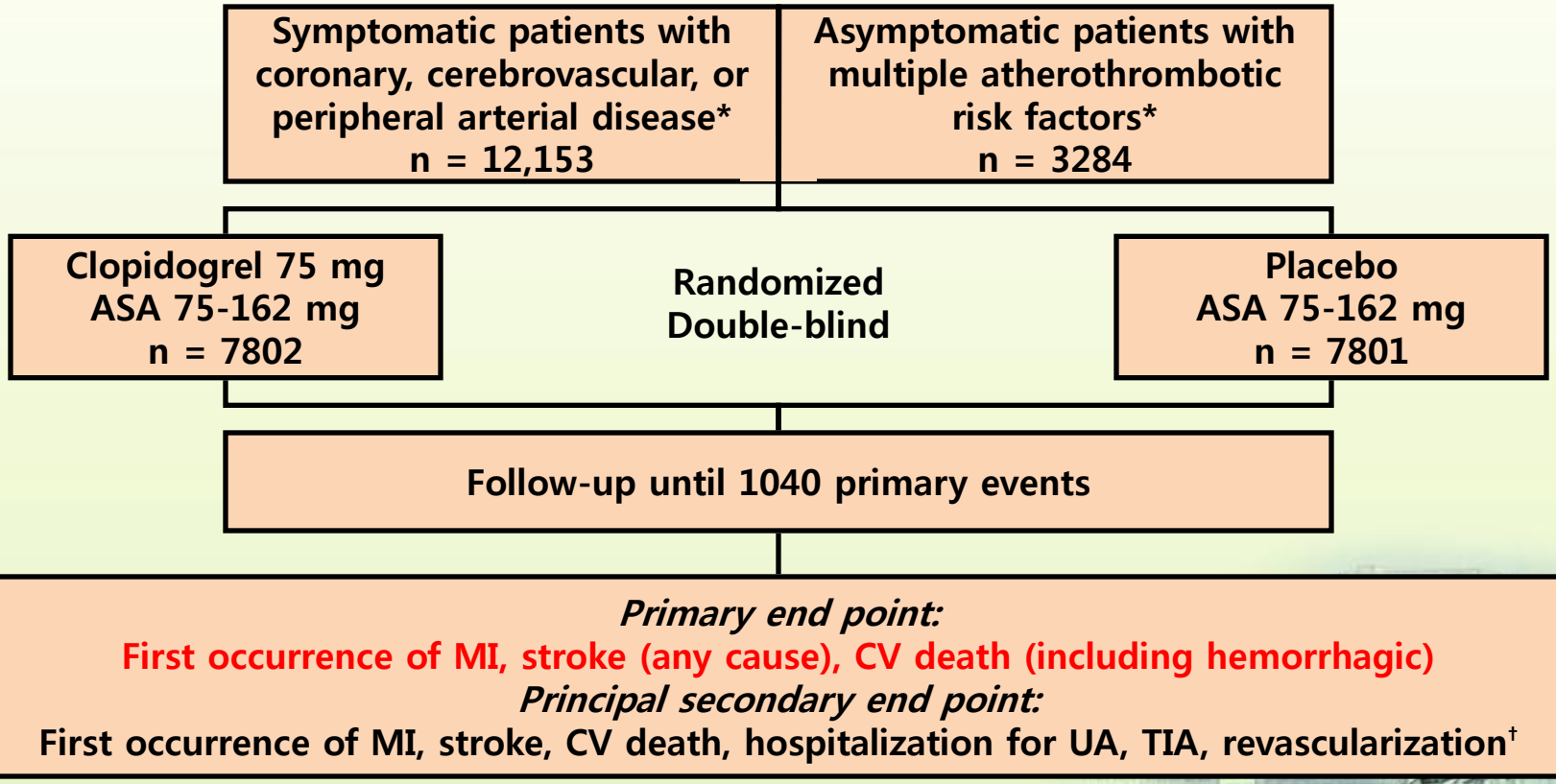
2. The duration of thienopyridine therapy should be as follows:
   a. In patients receiving a stent (BMS or drug-eluting stent [DES]) during PCI for ACS, clopidogrel 75 mg daily†[27–29] (*Level of Evidence: B*) or prasugrel 10 mg daily§[27] (*Level of Evidence: B*) should be given for at least 12 months;
   b. If the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered. (*Level of Evidence: C*)

3. In patients taking a thienopyridine in whom CABG is planned and can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect. (*Level of Evidence: C*) The period of withdrawal should be at least 5 days in patients receiving clopidogrel[2,30] (*Level of Evidence: B*) and at least 7 days in patients receiving prasugrel†[27] (*Level of Evidence: C*), unless the need for revascularization and/or the net benefit of the thienopyridine outweighs the potential risks of excess bleeding.[31] (*Level of Evidence: C*)

Kushner et al. *Circulation* 2009;120:2271-2306

CHARISMA: Study design

N = 15,603



*n = 166 not in either category, but included in overall analysis

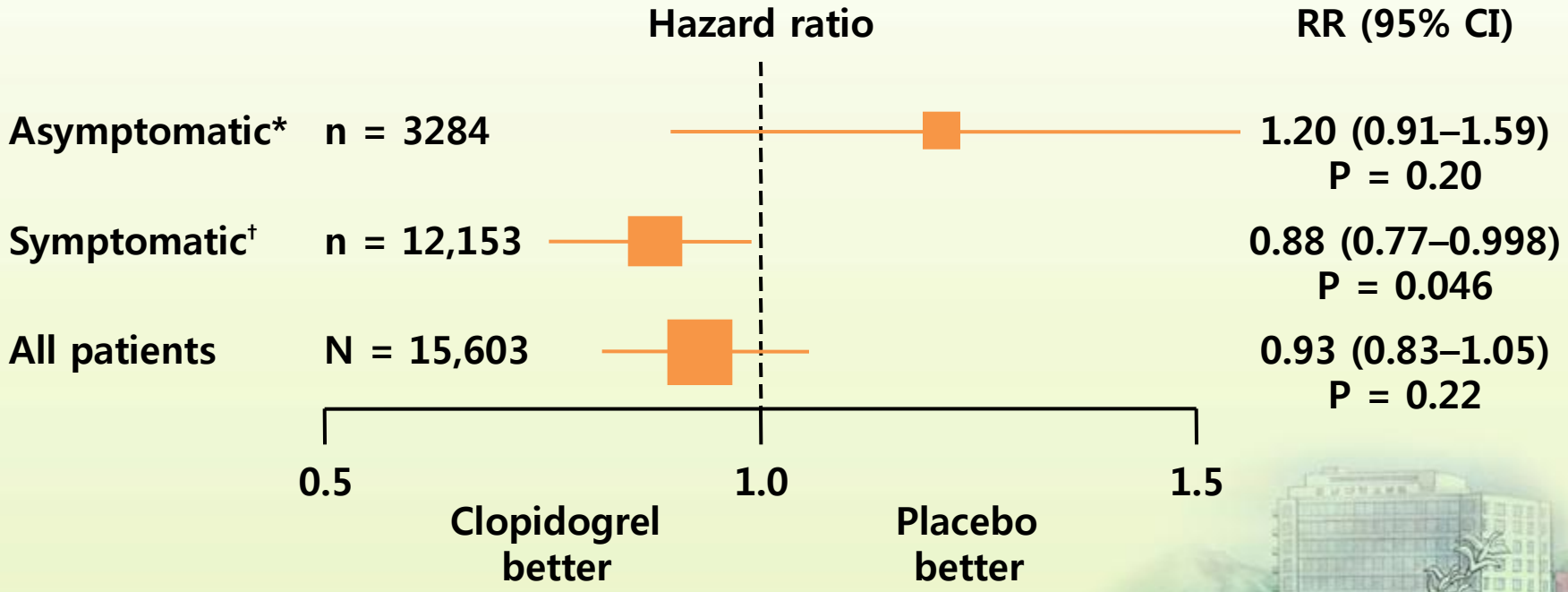
†Coronary, cerebral, or peripheral

Bhatt DL et al. *Am Heart J.* 2004;148:263-8.

Bhatt DL et al. *N Engl J Med.* 2006;354:1706-17.

CHARISMA: Treatment effect by inclusion criteria

MI, stroke, CV death



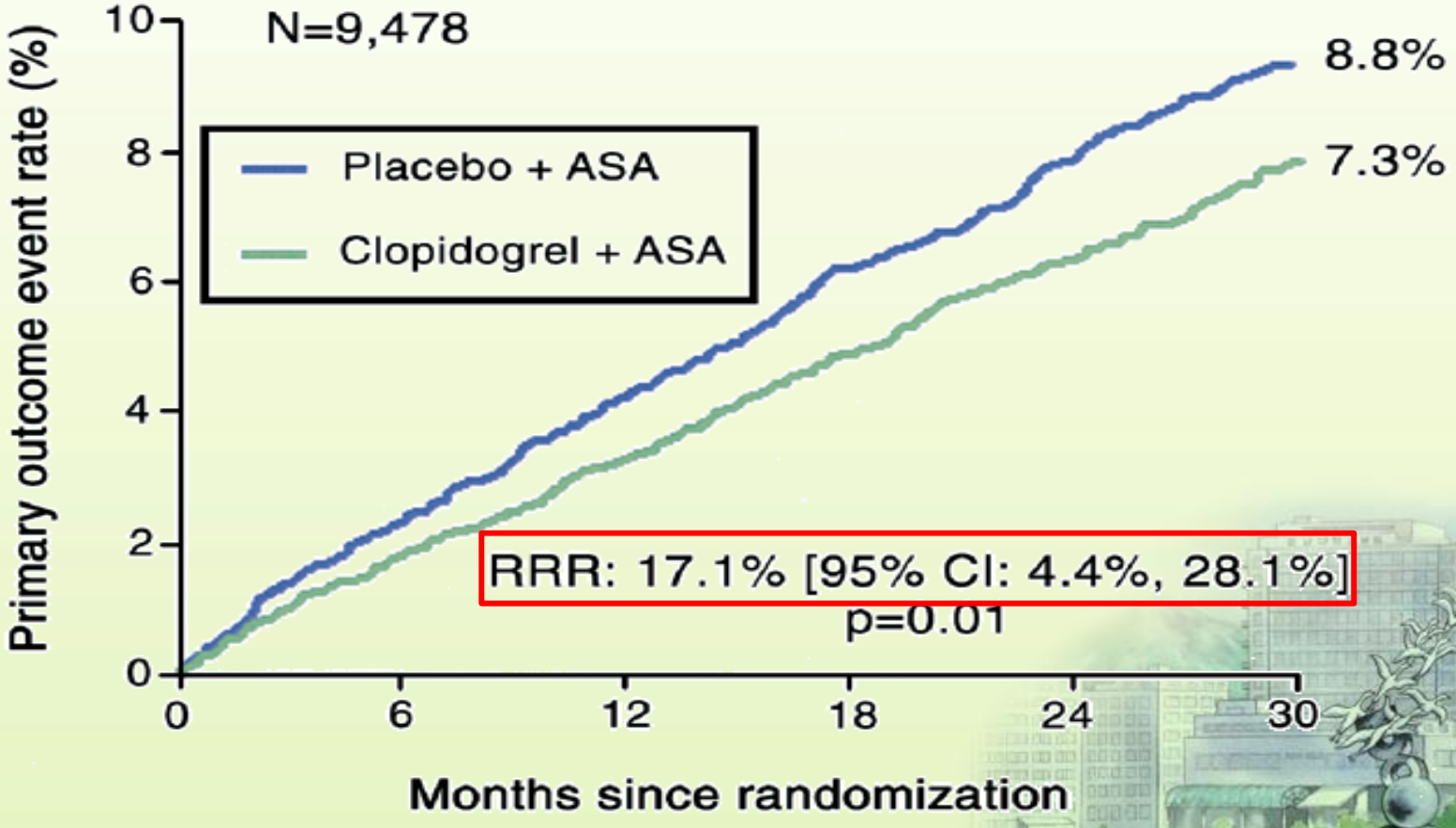
*Multiple atherothrombotic risk factors
†Documented coronary, cerebrovascular, or peripheral arterial disease

Bhatt DL et al. *N Engl J Med.* 2006;354:1706-17.

CHARISMA: Pts with Established CV disease

Prior MI, ischemic stroke or symptomatic PAD; N = 9,478

Primary end point of CV death, MI or stroke (median F/U 27 months)



Bhatt DL et al. *J Am Coll Cardiol* 2007;49:1982-8.

2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With UA/NSTEMI (Updating the 2007 Guideline)

Table 2. Recommendations for Antiplatelet Therapy

2007 Recommendations	2011 Focused Update Recommendations	Comments
Class I		
ASA should be administered to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients not known to be intolerant of that medication. *(Level of Evidence: A)* (Figs. 7 and 8; Box A)	1. ASA* should be administered to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients who tolerate it (3–10). *(Level of Evidence: A)*	Modified recommendation (changed wording for clarity).
Clopidogrel (loading dose followed by daily maintenance dose) should be administered to UA/NSTEMI patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance. *(Level of Evidence: A)* (Figs. 7 and 8; Box A)	2. Clopidogrel (loading dose followed by daily maintenance dose) should be administered to UA/NSTEMI patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance (11–13). *(Level of Evidence: B)*	Modified recommendation (level of evidence changed from A to B because trials do not address the specific subgroups in this recommendation).
In UA/NSTEMI patients with a history of gastrointestinal bleeding, when ASA and clopidogrel are administered alone or in combination, drugs to minimize the risk of recurrent gastrointestinal bleeding (e.g., PPI), should be prescribed		Deleted recommendation (see ACCF/ACG/AHA PPI expert consensus document [14]).

7. The duration and maintenance dose of thienopyridine therapy should be as follows:
   a. In UA/NSTEMI patients undergoing PCI, clopidogrel 75 mg daily (17) or prasugrel† 10 mg daily (22) should be given for at least 12 months (13,17). *(Level of Evidence: B)*
   b. If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by thienopyridine therapy, earlier discontinuation should be considered. *(Level of Evidence: C)*

(*Continued*)

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Coronary Responses and Differential Mechanisms of Late Stent Thrombosis Attributed to First-Generation Sirolimus- and Paclitaxel-Eluting Stents

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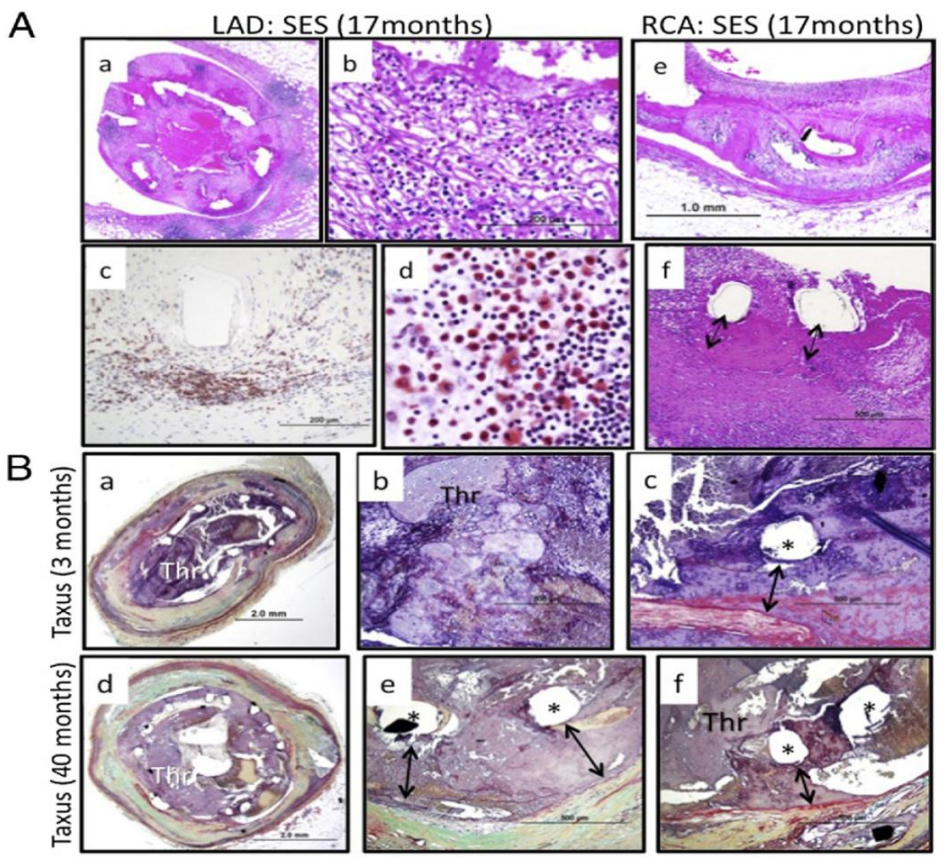
Gaithersburg, Maryland; and Atlanta, Georgia

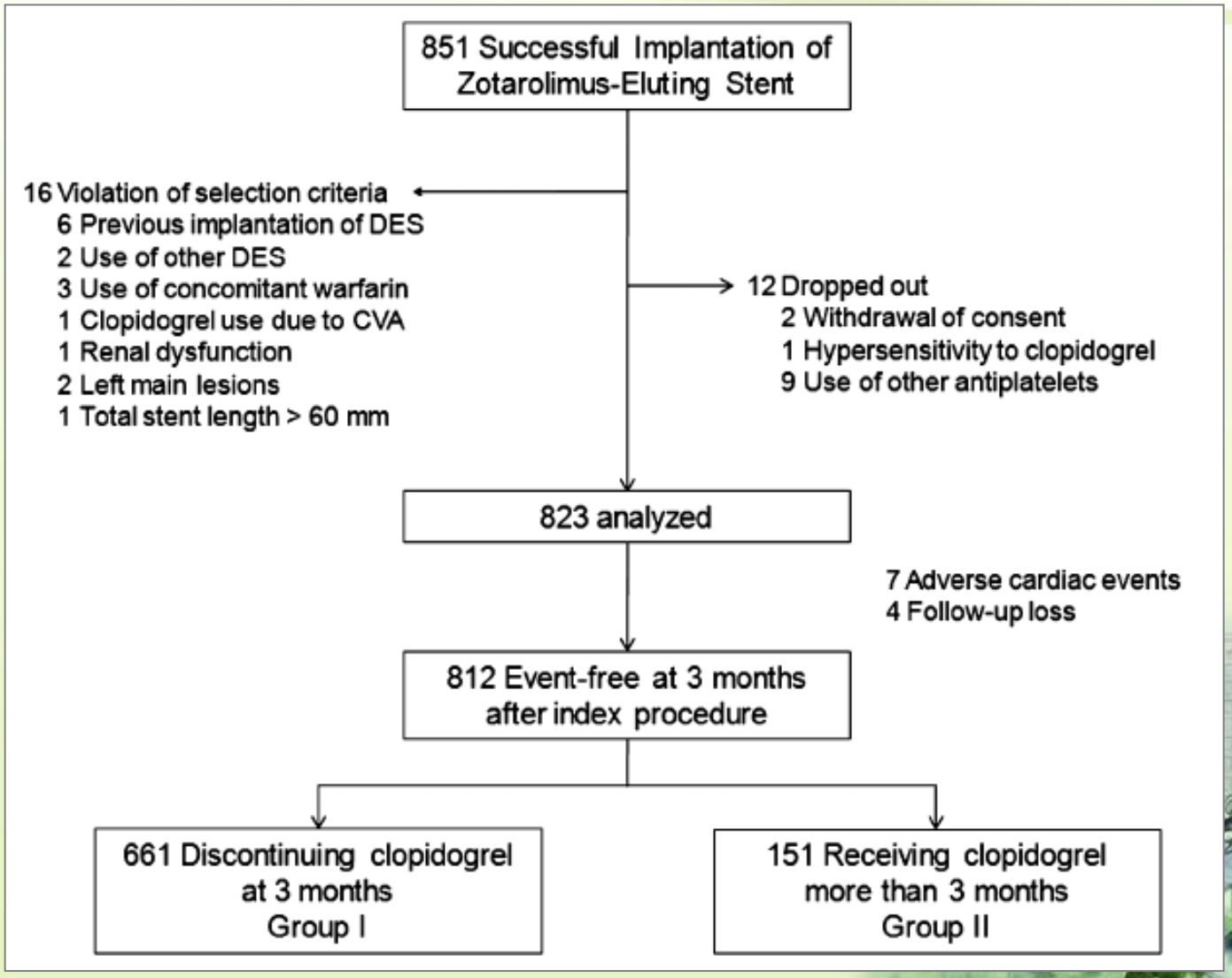
174 autopsies with DES – 127 patients (73%) died > 30 days after PCI
Underlying Causes of Thrombosis of DES

Underlying Causes of Thrombosis in First-Generation DES

Late thrombosis (≥30 days), n	SES (16)	PES (25)	P Value
AMI, penetration of necrotic core	5	5	0.47
Bifurcation	1	9	0.06
Long/overlapping stents	0	2	0.50
Underexpansion	1	1	1.00
Isolated uncovered struts	2	1	0.55
Localized hypersensitivity reaction	7	0	0.0005
Malapposition from excessive to fibrin	0	7	0.03

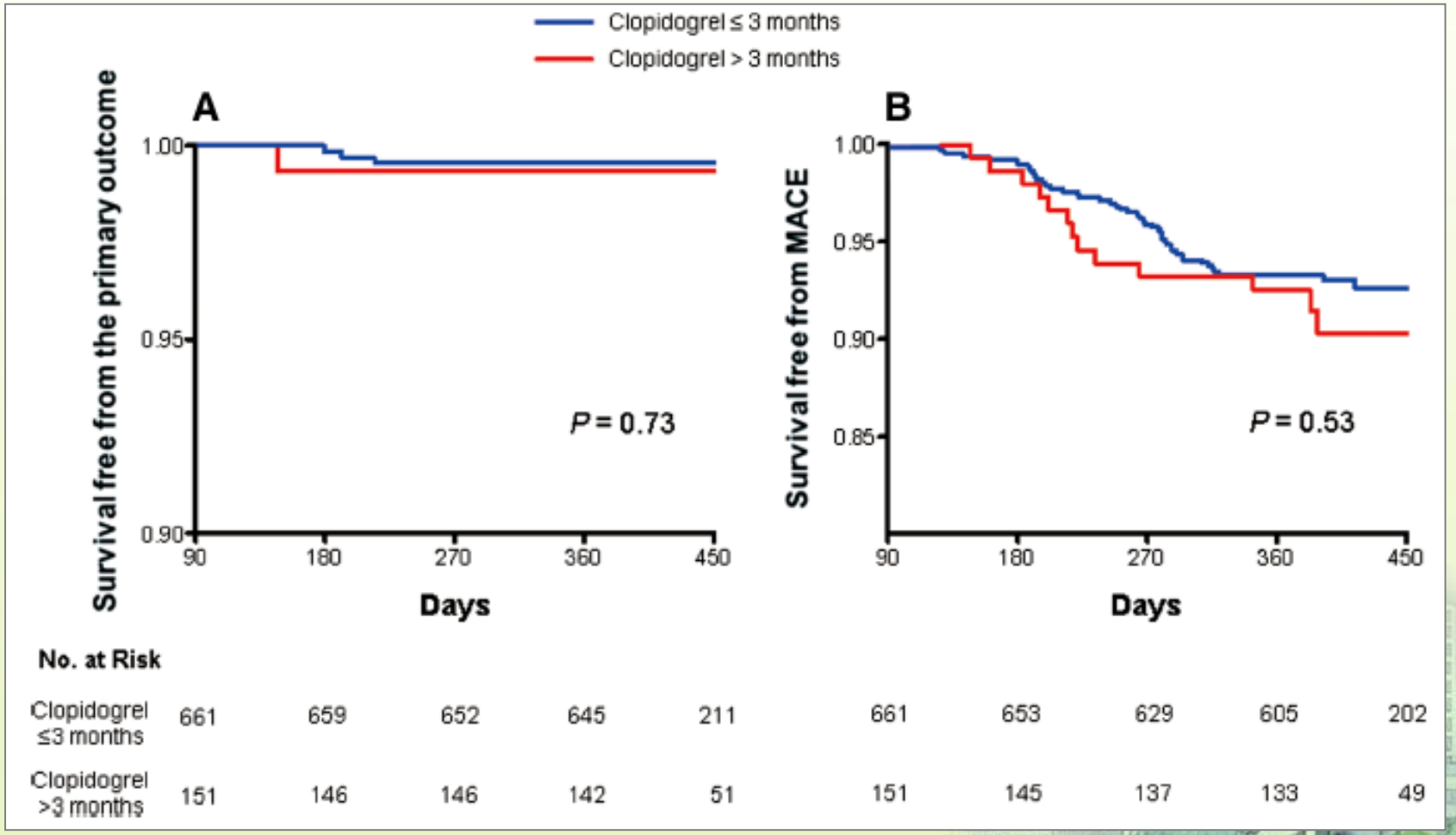


Three-Month Dual Antiplatelet Therapy After Implantation of Zotarolimus-Eluting Stents



Han et al. Cir J 2010;74:2314 – 2321

Three-Month Dual Antiplatelet Therapy After Implantation of Zotarolimus-Eluting Stents



Han et al. Cir J 2010;74:2314 – 2321

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EXPEDITED PUBLICATION

Clinical Evaluation of the Resolute Zotarolimus-Eluting Coronary Stent System in the Treatment of De Novo Lesions in Native Coronary Arteries

The RESOLUTE US Clinical Trial

Alan C. Yeung, MD,* Martin B. Leon, MD,‡ Ash Jain, MD,† Thaddeus R. Tolleson, MD,§ Douglas J. Spriggs, MD,‖ Brent T. Mc Laurin, MD,¶ Jeffrey J. Popma, MD,# Peter J. Fitzgerald, MD,* Donald E. Cutlip, MD,** Joseph M. Massaro, PHD,†† Laura Mauri, MD, MSC,‡‡ on behalf of the RESOLUTE US Investigators

Palo Alto and Fremont, California; New York, New York; Tyler, Texas; Clearwater, Florida; Anderson, South Carolina; and Boston, Massachusetts

Overall, 1,402 patients were enrolled with a mean reference vessel diameter of 2.59±0.47 mm and diabetes prevalence of 34.4%.

- ✓ The overall rate of ST was 0.1% (2 of 1,376), and dual antiplatelet use was 97.0% at 30 days and 93.3% at 12 months.
- ✓ Definite or probable ST was observed only among patients treated with 2.25-mm stents.

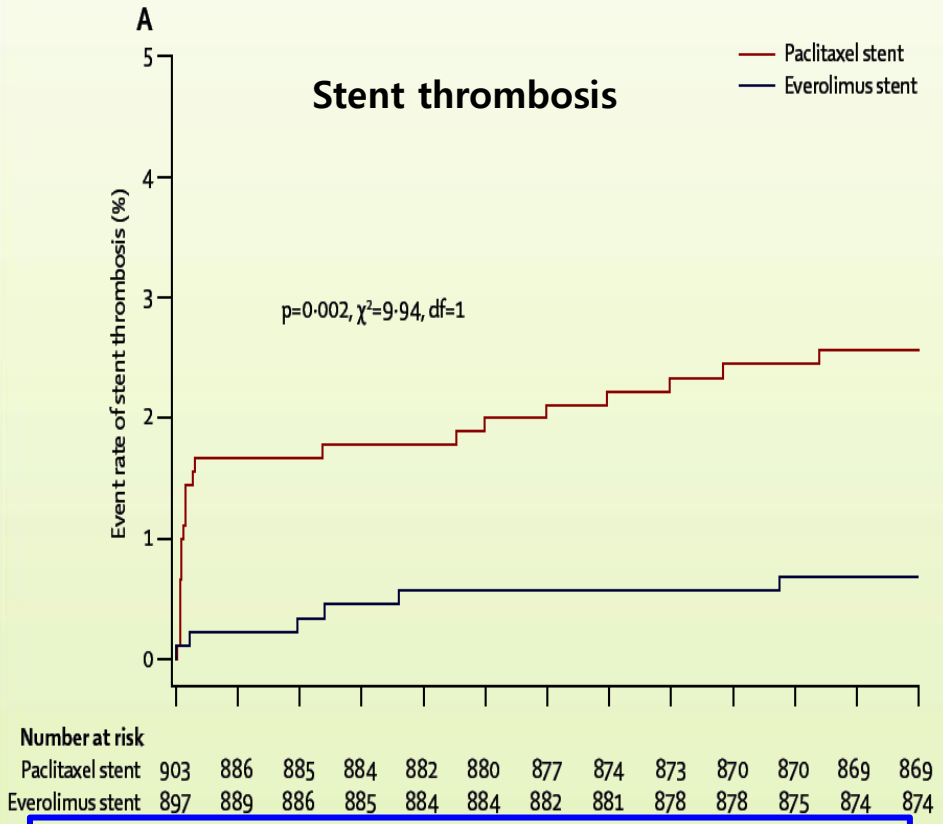
This included 1 patient with definite ST who presented with MI and angiographically confirmed ST on day 32 despite dual antiplatelet therapy, and 1 patient with probable ST who was not discharged on aspirin and died of presumed cardiac causes on day 5.

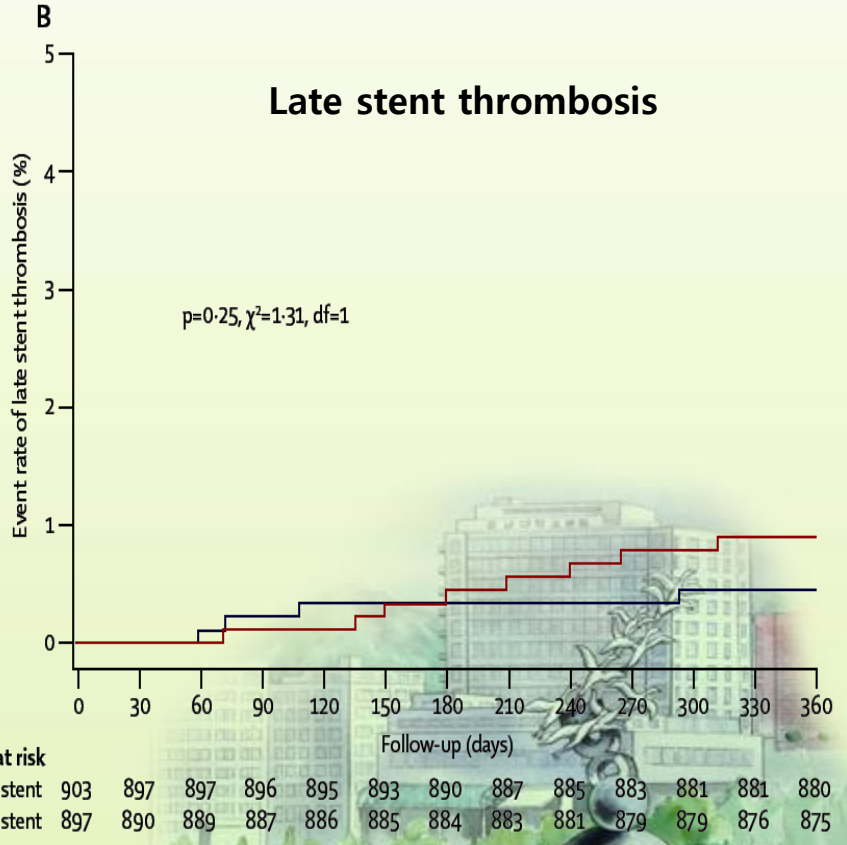
Outcome	30 Days (n = 1,398)	12 Months (n = 1,376)
TLF	1.4% (20)	4.7% (65)
Death	0.1% (1)	1.3% (18)
Cardiac	0.1% (1)	0.7% (9)
Noncardiac	0.0% (0)	0.7% (9)
Myocardial Infarction	1.2% (17)	1.4% (19)
Q-wave	0.1% (1)	0.1% (2)
Non-Q-wave	1.1% (16)	1.2% (17)
Clinically-driven TLR	0.1% (2)	2.8% (39)
Clinically-driven TVR	0.4% (5)	4.6% (63)
Stent thrombosis (ARC definite + probable)	0.1% (1)	0.1% (2)
Early (≤30 days)	0.1% (1)	0.1% (1)*
Late (>30 and ≤360 days)	n/a	0.1% (1)†

Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial

Elvin Kedhi, Kaiyum Sheik Joesoef, Eugene McFadden, Jochem Wassing, Carlos van Mieghem, Dick Goedhart, Pieter Cornelis Smits

Randomly assigned 1800 consecutive patients (aged 18–85 years) undergoing percutaneous coronary intervention at one centre to treatment with everolimus-eluting or paclitaxel-eluting stents.





Recommanded DAPT : at least 12 months
91/92% at 1 M, 91/91% at 6 M, 70/70% at 1 Y

Kedhi E et al. *Lacet 2010*;375:201-9.

The NEW ENGLAND JOURNAL of MEDICINE

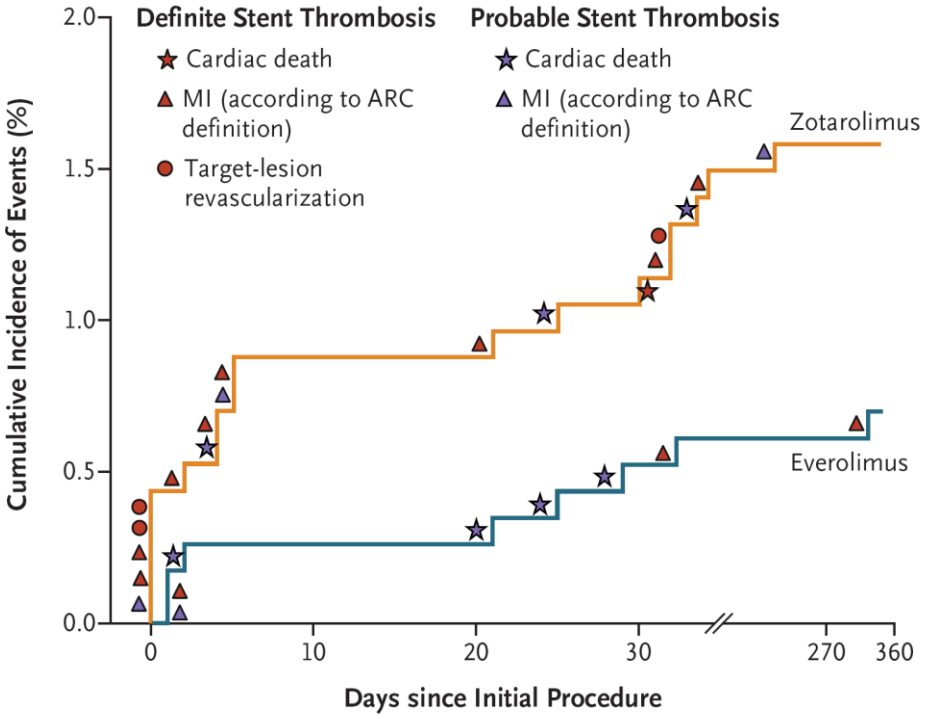
ORIGINAL ARTICLE

Comparison of Zotarolimus-Eluting and Everolimus-Eluting Coronary Stents

Patrick W. Serruys, M.D., Ph.D., Sigmund Silber, M.D., Ph.D., Scot Garg, M.B., Ch.B., M.R.C.P., Robert Jan van Geuns, M.D., Ph.D., Gert Richardt, M.D., Pawel E. Buszman, M.D., Ph.D., Henning Kelbæk, M.D., Adrianus Johannes van Boven, M.D., Ph.D., Sjoerd H. Hofma, M.D., Ph.D., Axel Linke, M.D., Ph.D., Volker Klauss, M.D., Ph.D., William Wijns, M.D., Ph.D., Carlos Macaya, M.D., Ph.D., Philippe Garot, M.D., Carlo DiMario, M.D., Ph.D., Ganesh Manoharan, M.B., B.Ch., M.D., F.R.C.P., Ran Kornowski, M.D., Thomas Ischinger, M.D., Ph.D., Antonio Bartorelli, M.D., Jacintha Ronden, Ph.D., Marco Bressers, M.Sc., Pierre Gobbens, B.Sc., Manuela Negoita, M.D., Frank van Leeuwen, M.D., and Stephan Windecker, M.D.

Randomly assigned 2292 patients treated with ZES or EES

	ZES (N=1119)	EES (N=1126)	Difference (95% CI)	p value
Definte stent thrombosis				
All patients	13 (1.2)	3 (0.3)	0.9 (0.2 to 1.6)	0.01
Acute (0-1 day)	4 (0.4)	1 (0.1)	0.3 (-0.1 to 0.7)	0.22
Subacute (2-30 days)	5 (0.4)	0	0.4 (0.1 to 0.8)	0.03
Late (31-360 days)	5 (0.4)	2 (0.2)	0.3 (-0.2 to 0.7)	0.29
Stent thrombosis (0-360 days)				
Possible	9 (0.8)	9 (0.8)	0.0 (-0.7 to 0.7)	1.00
Definite or probable	18 (1.6)	8 (0.7)	0.9 (0.0 to 1.8)	0.05
Definite, probable or possible	26 (2.3)	17 (1.5)	0.8 (-0.3 to 1.9)	0.17



Recommanded DAPT : at least 6 months

Serruys PW et al. *N Engl J Med* 2010;363:136-468.

EXCELLENT Outcomes Regardless of Antiplatelet Therapy Duration after DES

Purpose: To compare the efficacy and safety of 6 months versus 12 months duration of dual antiplatelet therapy (DAT) after implantation of a drug-eluting stent.
Study design: Open-label multicenter non-inferiority trial with a 2×2 factorial design, including 1443 patients with coronary artery disease, randomly assigned to 6 or 12 months of DAT and either an everolimus-eluting or a sirolimus-eluting stent.

Result: 6-month DAT was non-inferior to 12-month DAT with regards to the primary endpoint, 12-month target-vessel failure (a composite of cardiovascular death, myocardial infarction [MI], and clinically driven target-vessel revascularization). Other secondary endpoints, including a safety endpoint (a composite of death, MI, cerebrovascular accident, stent thrombosis, and TIMI major bleeding) and a composite of major adverse cardiac and cerebrovascular events (MACCE), did not differ between the 2 groups.

	6-month DAT (n=716)	12-month DAT (n=712)	Hazard ratio (95% CI)	p value
Primary endpoint Target-vessel failure[a]	4.7%	4.4%	1.17 (0.73–1.89)	NS
Secondary endpoints				
Safety endpoint[b]	3.4%	3.1%	1.13 (0.64–1.99)	NS
Cardiac death	0.3%	0.4%	0.58 (0.10–3.23)	NS
Myocardial infarction	1.8%	1.1%	1.62 (0.67–3.93	NS
Stent thrombosis[c]	0.8%	0.4%	1.68 (0.47–6.06)	NS
TIMI major bleeding[d]	0.3%	0.6%	0.50 (0.09–2.71)	NS
MACCE[e]	7.5%	8.4%	0.98 (0.68–1.40)	NS

Conclusion: **6-month DAT is non-inferior to 12-month DAT with regards to the risk of target-vessel failure at 12 months after DES implantation. A larger-scale randomized controlled trial is required to test the impact of shorter duration of clopidogrel therapy on the hard endpoints of death, MI, and stent thrombosis.**

a, target-vessel failure (a composite of cardiovascular death, MI and clinically driven target-vessel revascularization) ; b, a composite of death, MI, cerebrovascular accident, stent thrombosis, and TIMI major bleeding; c, definite or probable stent thrombosis by ARC definition; d, overt clinical bleeding with a drop of hemoglobin of >5 g/dl or hematocrit of >15%; e, a composite of death, MI, stent thrombosis, cerebrovascular accident, and TIMI major bleeding.

Gwon H-C. Presented . ACC 2011 Scientific Sessions. Abstract, LBCT

How to Prevent Stent Thrombosis by Optimizing Stent Selection

- ✓ Newer generation DES appear to be associated with fewer LST and VLST events
- ✓ Whether this is consequent upon DES design, drug and polymer improvements or in part coincident with technical and procedural improvements is unclear
- ✓ Some existing DES features, open cell, side-branch access, flexibility, radial strength may provide differential advantages in certain vessel and lesion types
- ✓ Almost universal move to minimize drug and polymer load

ACC/i2 Summit 2011.

Dual Anti-Platelet Therapy and New DES

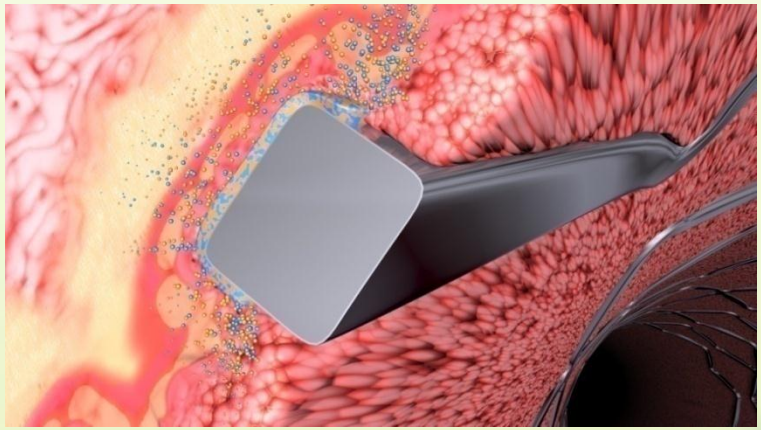
- ✓ Biodegradable Polymer Coating DES
- ✓ Endothelial Progenitor Cell (EPC) Capture Stents
- ✓ Bioabsorbable Stents

Biolimus-Eluting Stents: BioMatrix™

ABLUMINAL COATING
Improved healing
More targeted tissue release
Less systemic exposure

BIOLIMUS A9™ DRUG
Biosensors' proprietary rapamycin derivative
Highest lypophilic profile of all common limus drugs

BIODEGRADABLE PLA
Co-released with BA9™
Fully biodegrades from the stent in 6 months



S-STENT™ PLATFORM
Superior side branch access without compromising radial strength (Data on file at BSI)

Designed for Improved Healing and Long-term Safety

1. Drug and Polymer is gone after 6-9 months
2. Leaving behind a Bare Metal Stent (BMS)
3. BMS is safer for those patients who are not compliant of Dual Anti-Platelet Therapy.

Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial

Stephan Windecker, Patrick W Serruys, Simon Wandel, Pawel Buszman, Stanislaw Trznadel, Axel Linke, Karsten Lenk, Thomas Ischinger, Volker Klauss, Franz Eberli, Roberto Corti, William Wijns, Marie-Claude Morice, Carlo di Mario, Simon Davies, Robert-Jan van Geuns, Pedro Eerdmans, Gerrit-Anne van Es, Bernhard Meier, Peter Jüni

Recommanded DAPT : at least 12 months

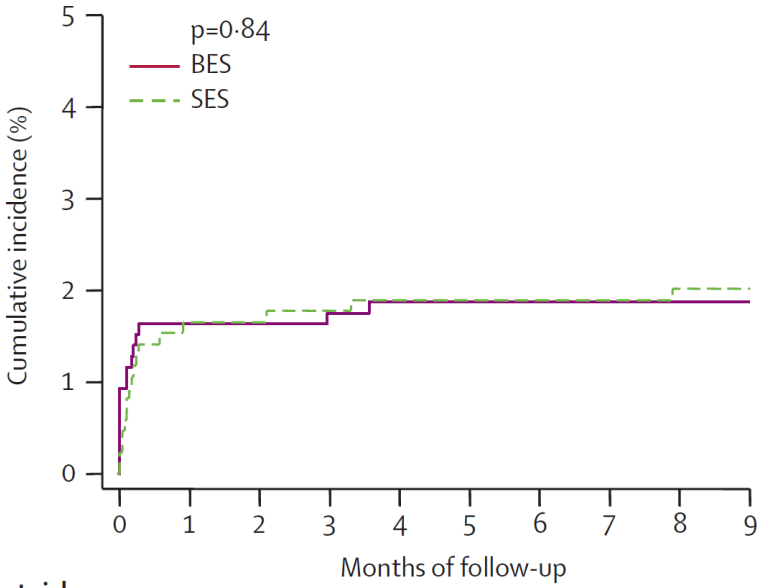
Summary

Background A novel sten … able polymer showed promising results in pre … is-eluting stent (with biodegradable polymer) w …

Methods We undertook a … centres. 1707 patients aged 18 years or older … romes were centrally randomised by a compu … is-eluting (n=857) or sirolimus-eluting (n=850) … ocardial infarction, or clinically-indicated target … to treat. 427 patients were randomly allocated … as principal outcome measure at 9 months. Th …

Findings We analysed all … olimus-eluting stents for the primary endpoint … ·64–1·19], p for non-inferiority=0·003, p for su … for superiority=0·22), myocardial infarction (4 … ssel revascularisation (38 [4·4%] *vs* 47 [5·5%], … olimus-eluting group and 167 (78%) in the siro … olimus-eluting stents were non-inferior to siro … *vs* 23·3%, difference −2·2% [95% CI −6·0 to 1·

Definite ST



Number at risk

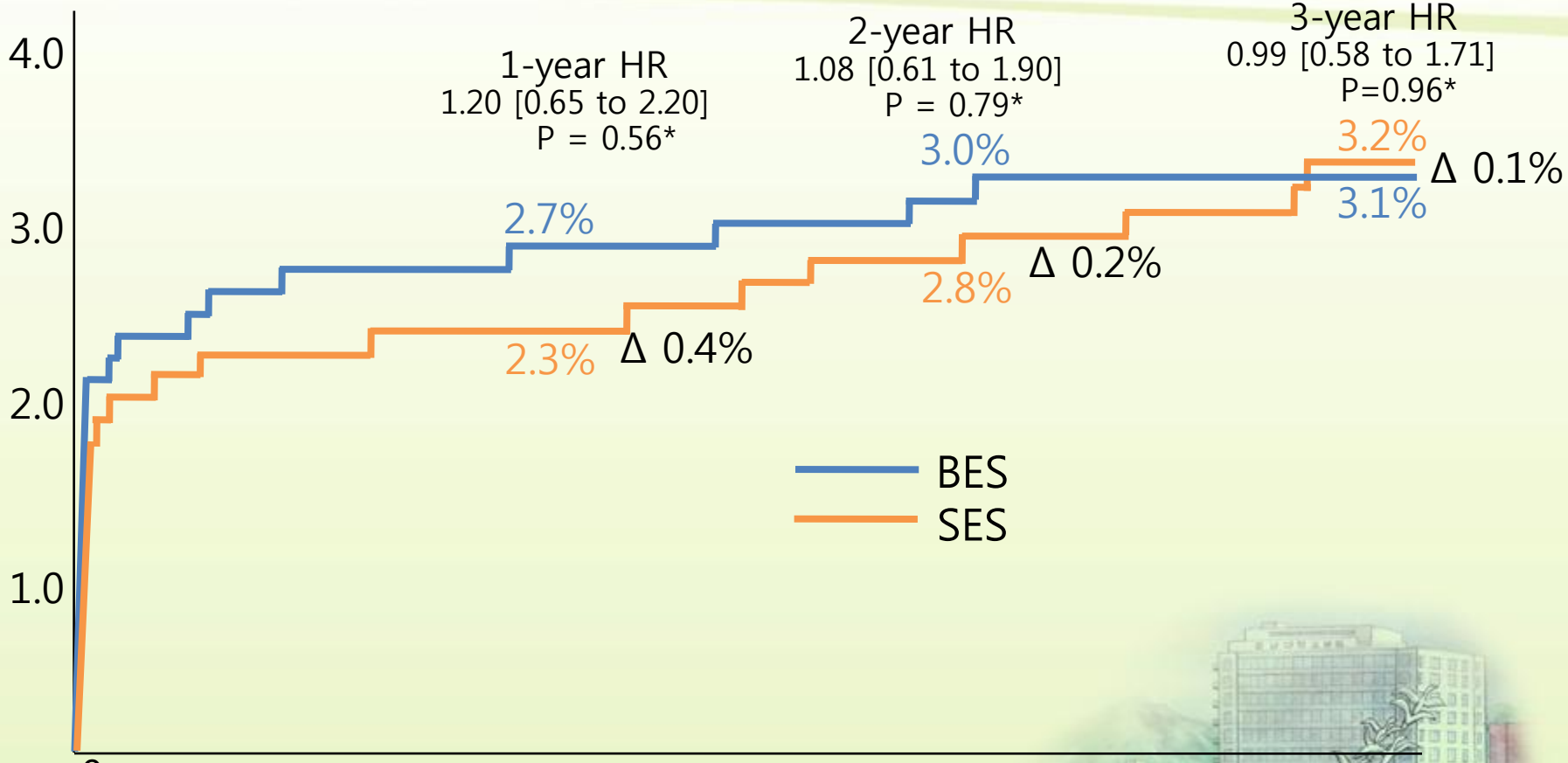
BES	857	833	826	825	824	821	818	817	816	808
SES	850	822	818	816	815	815	813	806	803	799

Interpretation Our results suggest that a stent eluting biolimus from a biodegradable polymer represents a safe and effective alternative to a stent eluting sirolimus from a durable polymer in patients with chronic stable coronary artery disease or acute coronary syndromes.

Lancet 2008; 372: 1163–73
Published Online September 1, 2008
DOI:10.1016/S0140-6736(08)61244-1
See Comment page 1126

Department of Cardiology, Bern University Hospital, Bern, Switzerland (Prof S Windecker MD, Prof B Meier MD); CTU Bern, Bern University Hospital, Bern, Switzerland (S Windecker, S Wandel MSc, P Jüni MD); Thoraxcentre, Erasmus University, Rotterdam, Netherlands (Prof P W Serruys MD, R-J van Geuns MD); Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland (S Wandel, P Jüni); Medical University of Silesia, Katowice, Poland (Prof P Buszman MD, S Trznadel MD); Herzzentrum Leipzig, Leipzig, Germany (A Linke MD, K Lenk MD); Department of Cardiology,

Definite/Probable ST through 3 years FU in LEADERS



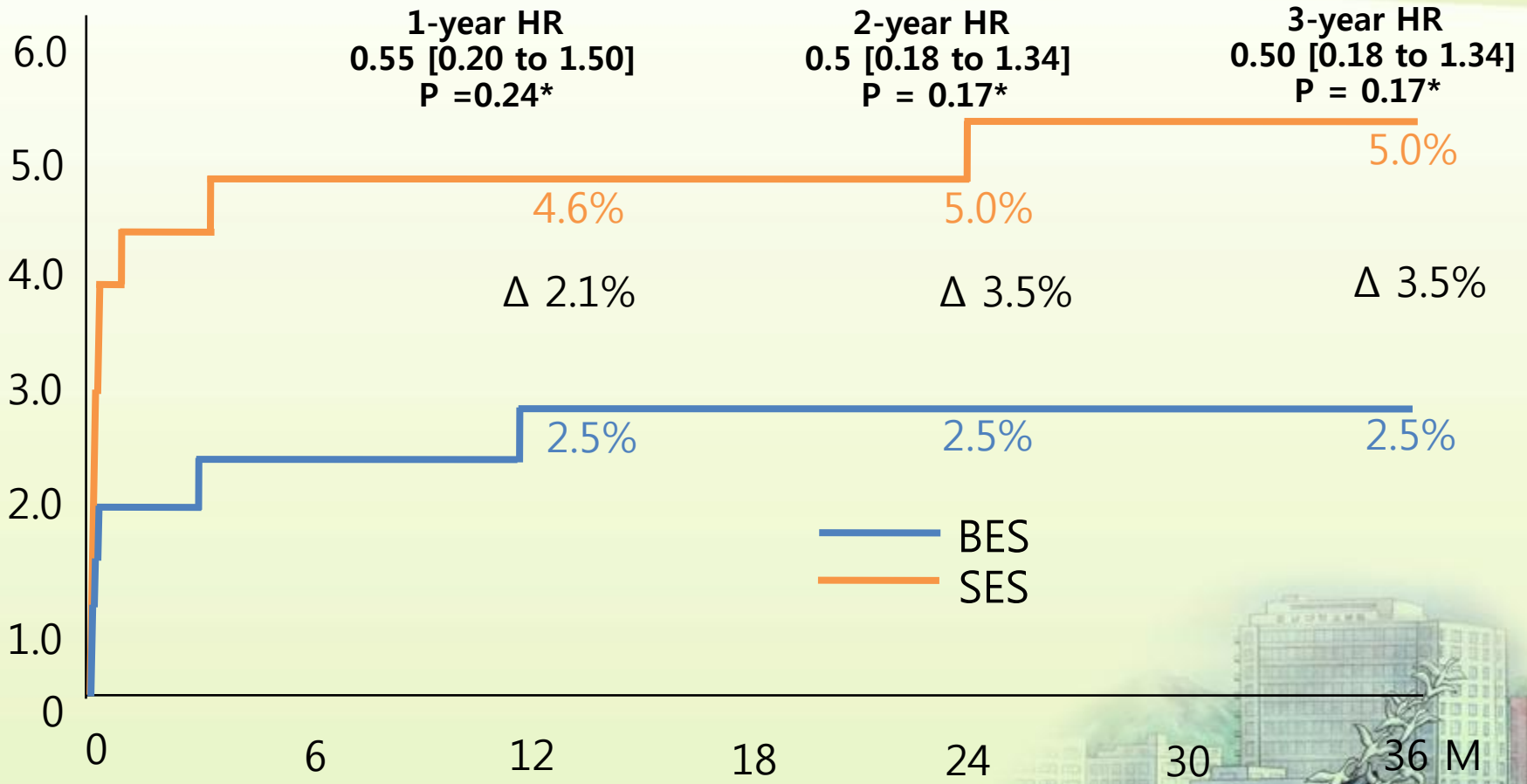
Number at risk

BES	857	848	806	795	785	772	730
SES	850	842	801	792	779	758	715

*P values for superiority

Serruy PW TCT 2010

Definite ST in High Syntax Score (>16)



Number at risk

BES	239	236	223	220	217	215	209
SES	222	217	196	194	190	183	169

*P values for superiority

Serruy PW TCT 2010

ESTIMATE-BES

- **PI: Moo Hyun Kim**
- **DAPT: 6 months vs. 12 months**
- **n=1,060 CAD pts except AMI**

Randomized Comparison of the Nobori Biolimus A9-Eluting Coronary Stent With the Taxus Liberté Paclitaxel-Eluting Coronary Stent in Patients With Stenosis in Native Coronary Arteries

The NOBORI 1 Trial—Phase 2

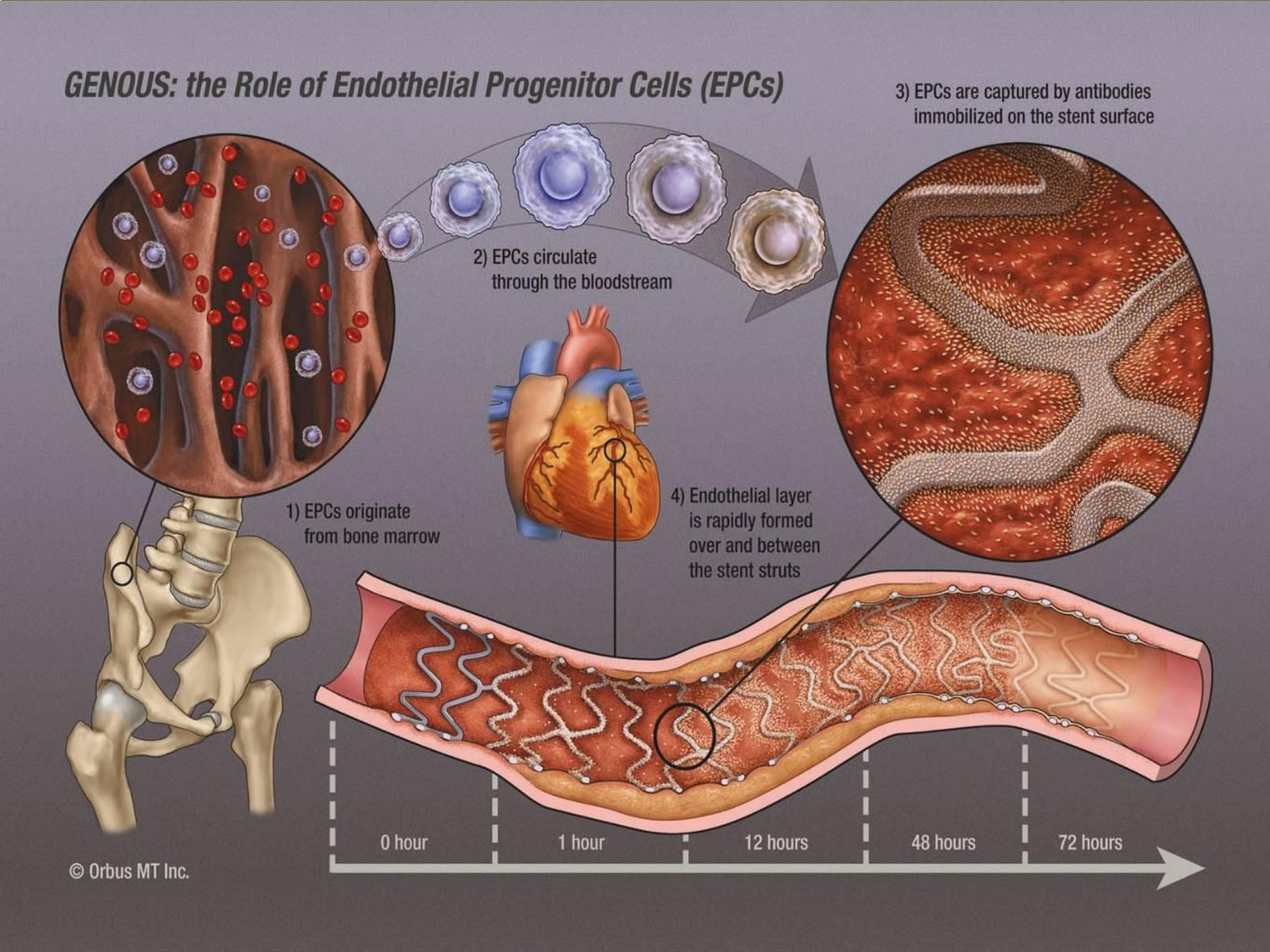
Bernard Chevalier, MI
Gerhard Schuler,
Karl E. Haupt
Didier Carrie, MD, PI
Dragica Paunovic, MI
D; Eulogio Garcia, MD;
Koolen, MD, PhD;
e Morice, MD;
D; Danny Detiege, MS;
1 Clinical Investigators

Background—The newly dev
antiproliferative agent Biol
Methods and Results—We co
and the paclitaxel-eluting st
and Australia. Patients wi
enrollment. The primary e
quantitative coronary angic
intravascular ultrasound pa
adverse cardiac events con
in-stent late loss was signif
0.32±0.50 mm) reaching
($P<0.001$) and the second
reduction in binary restenc
detected by intravascular u
cardiac events rate was 4.6
in the Nobori arm and 4.4
Conclusions—The NOBORI
olymer, polylactic acid, and the
ng neointima formation.
iolimus A9-eluting stent Nobori
s) at 29 centers in Europe, Asia,
y arteries were considered for
dary end points included other
te of restenosis as well as key
bosis and composite of major
scularization. At 9 months, the
s group (0.11±0.30 mm versus
ent versus Taxus Liberté stent
as confirmed by a significant
neointimal volume obstruction,
($P=0.01$). The major adverse
e stent thrombosis rate was 0%
riority of the Nobori Biolimus
A9-eluting stent versus the Taxus Liberté stent in reducing neointimal proliferation. Both stents showed a low major adverse cardiac events rate in the studied population. (***Circ Cardiovasc Intervent.* 2009;2:188-195.**)

Table 4. Clinical Outcomes at 300 Days

	Nobori Stent Group (N=153)		Taxus Stent Group (N=90)	
All Events	N	%	N	%
Death	2	1.3	3	3.3
Cardiac death	1	0.7	1	1.1
MI	6	3.9	5	5.6
Q-wave	1	0.7	3	3.3
Non–Q-wave	5	3.3	2	2.2
TLR	2	1.3	6	6.7
Percutaneous	2	1.3	5	5.6
Surgical	0	0.0	1	1.1
Clinically indicated TLR	0	0.0	2	2.2
Percutaneous	0	0.0	2	2.2
Surgical	0	0.0	0	0.0
TVR	4	2.6	0	0.0
Percutaneous	4	2.6	0	0.0
Surgical	0	0.0	0	0.0
Clinically indicated TVR	3	2.0	0	0.0
Percutaneous	3	2.0	0	0.0
Surgical	0	0.0	0	0.0
MACE	7	4.6	5	5.6
Stent thrombosis	0	0.0	4*	4.4
Acute	0	0.0	3	3.3
Subacute	0	0.0	2	2.2
Late	0	0.0	0	0.0

Recommanded DAPT : at least 6 months


GENOUS: the Role of Endothelial Progenitor Cells (EPCs)
3) EPCs are captured by antibodies immobilized on the stent surface
2) EPCs circulate through the bloodstream
1) EPCs originate from bone marrow
4) Endothelial layer is rapidly formed over and between the stent struts
0 hour
1 hour
12 hours
48 hours
72 hours
© Orbus MT Inc.

Benefits of EPC Capture Stents (Genous)

Benefit 1: Protects Against Thrombus

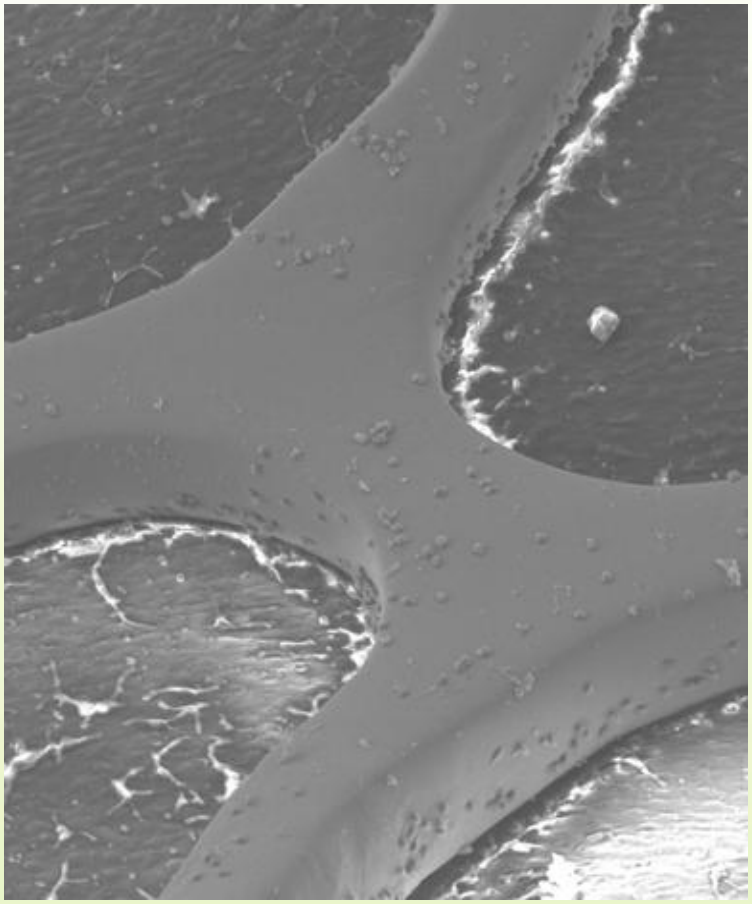
Genous establishes functional endothelium. **No long term anti-platelet therapy is required.**

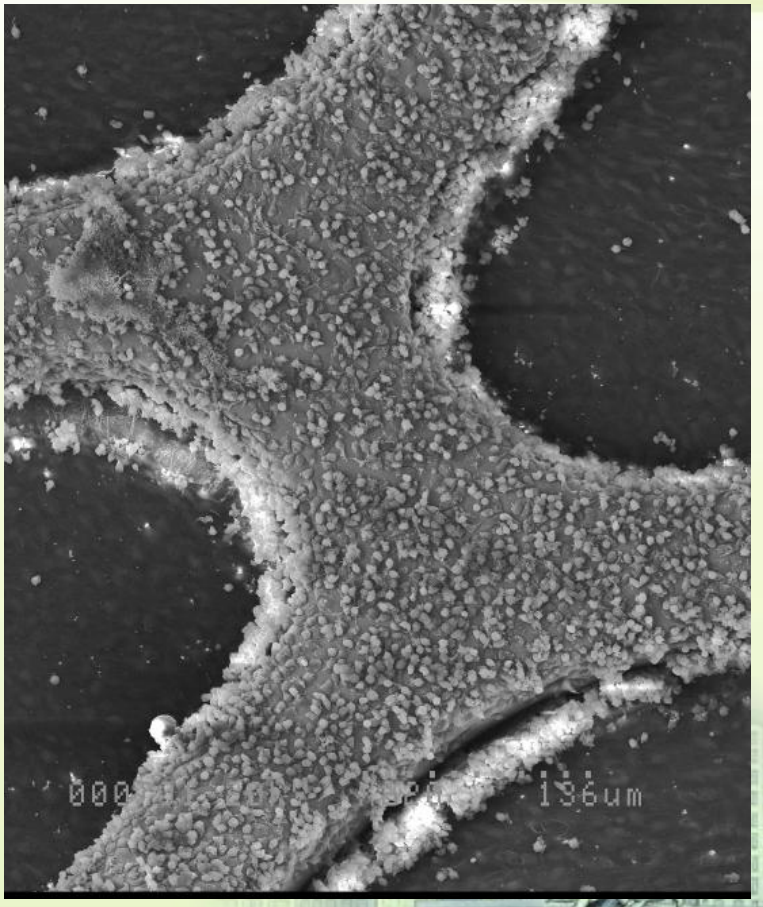
Benefit 2: Minimizes Restenosis

Genous establishes healthy endothelium which expresses vasoactive compounds, such as nitric oxide, which modulates neo-intimal hyperplasia and thus restenosis.

- **No polymer – polymers can cause inflammation due to hypersensivity**
- **Antibody is covalently bonded, extremely strong bond**
  - **won't scrape off as stent is deployed**
  - **it is more important to have antibodies on the inside of the stent, which is protected by the balloon**

Porcine Implants at One Hour



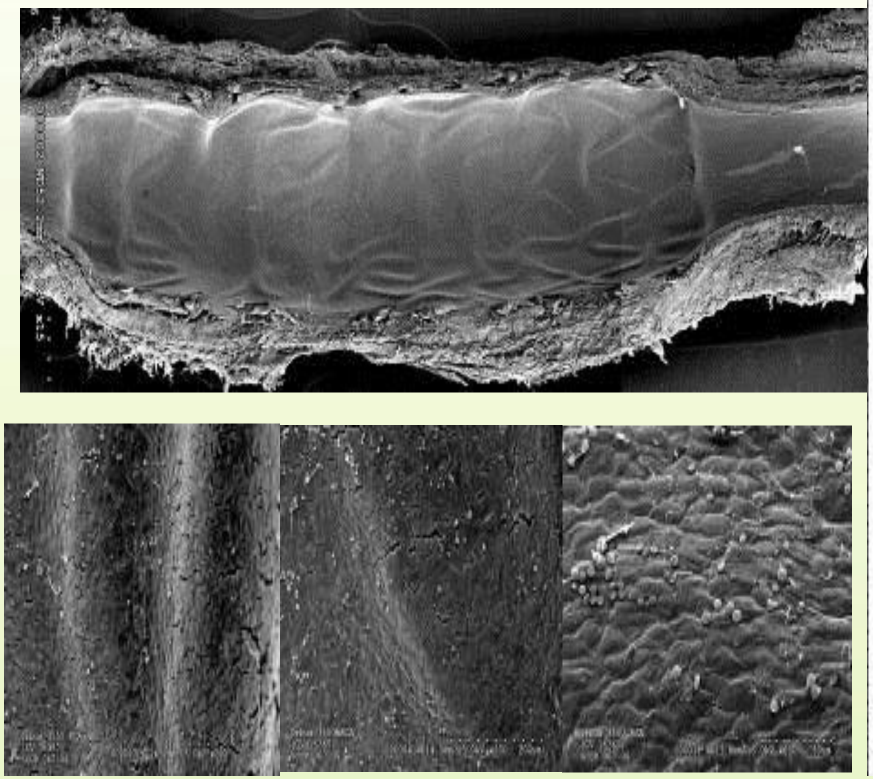


Bare metal stent with no cell coverage

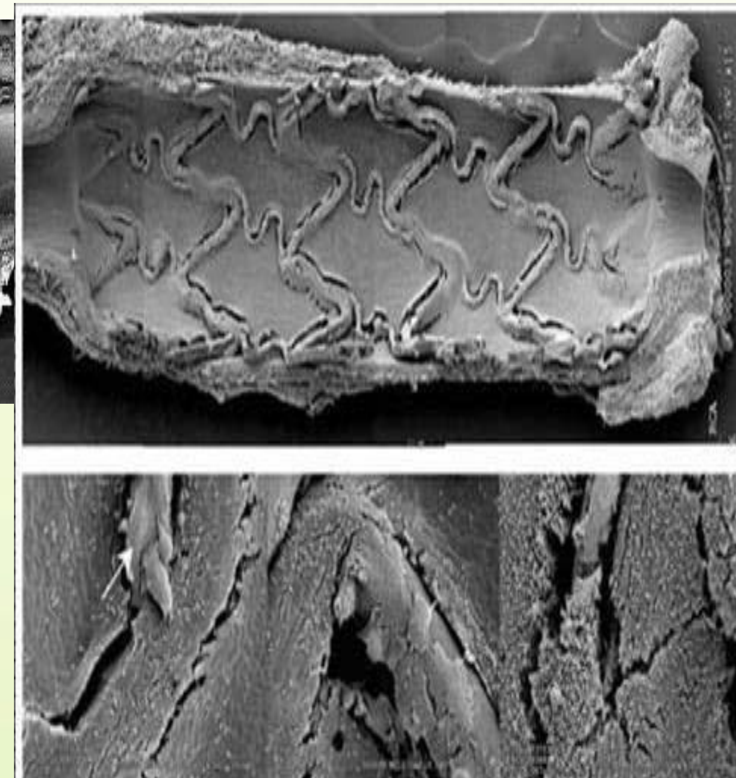
Genous stent with cell capture

Kutryk – unpublished data

Porcine Implants at 14 Days



Complete Healing in Genous

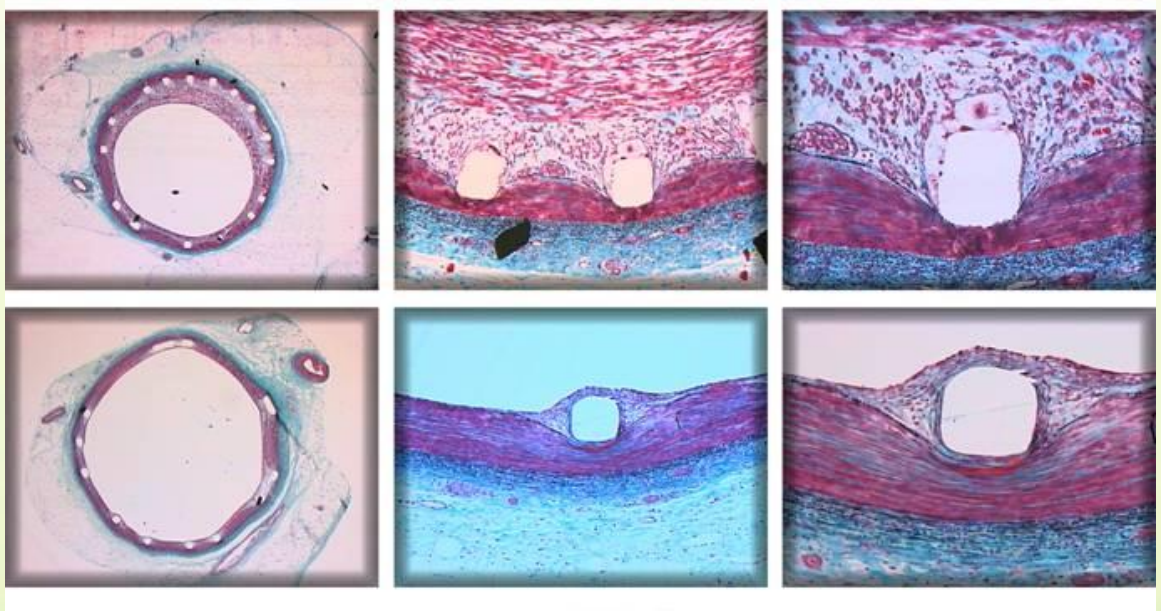


Delayed Healing in BMS

Pictures courtesy Virmani, Leon

28 Day Histology – Porcine

BMS stent



Typical neo-intimal response to stent injury with evidence of immature intima and remaining active fibrin.

Complete healing with mature neo-intima.

Genous

EuroIntervention

Clinical results after coronary stenting with the Genous™ Bio-engineered R stent™: 12-month outcomes of the e-HEALING (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth) worldwide registry

Sigmund Silber[1§], MD, PhD; Peter Damman[2§], MD; Margo Klomp[2], MD; Marcel A. Beijk[2], MD; Manfred Grisold[3], MD; Expedito E. Ribeiro[4], MD, PhD; Harry Suryapranata[5], MD, PhD; Jaroslaw Wójcik[6], MD, PhD; Kui Hian Sim[7], MD, PhD; Jan G.P. Tijssen[2], PhD, MPH; Robbert J. de Winter[2*], MD, PhD
on behalf of the e-HEALING investigators

Table 3. Adherence to dual anti-platelet therapy.

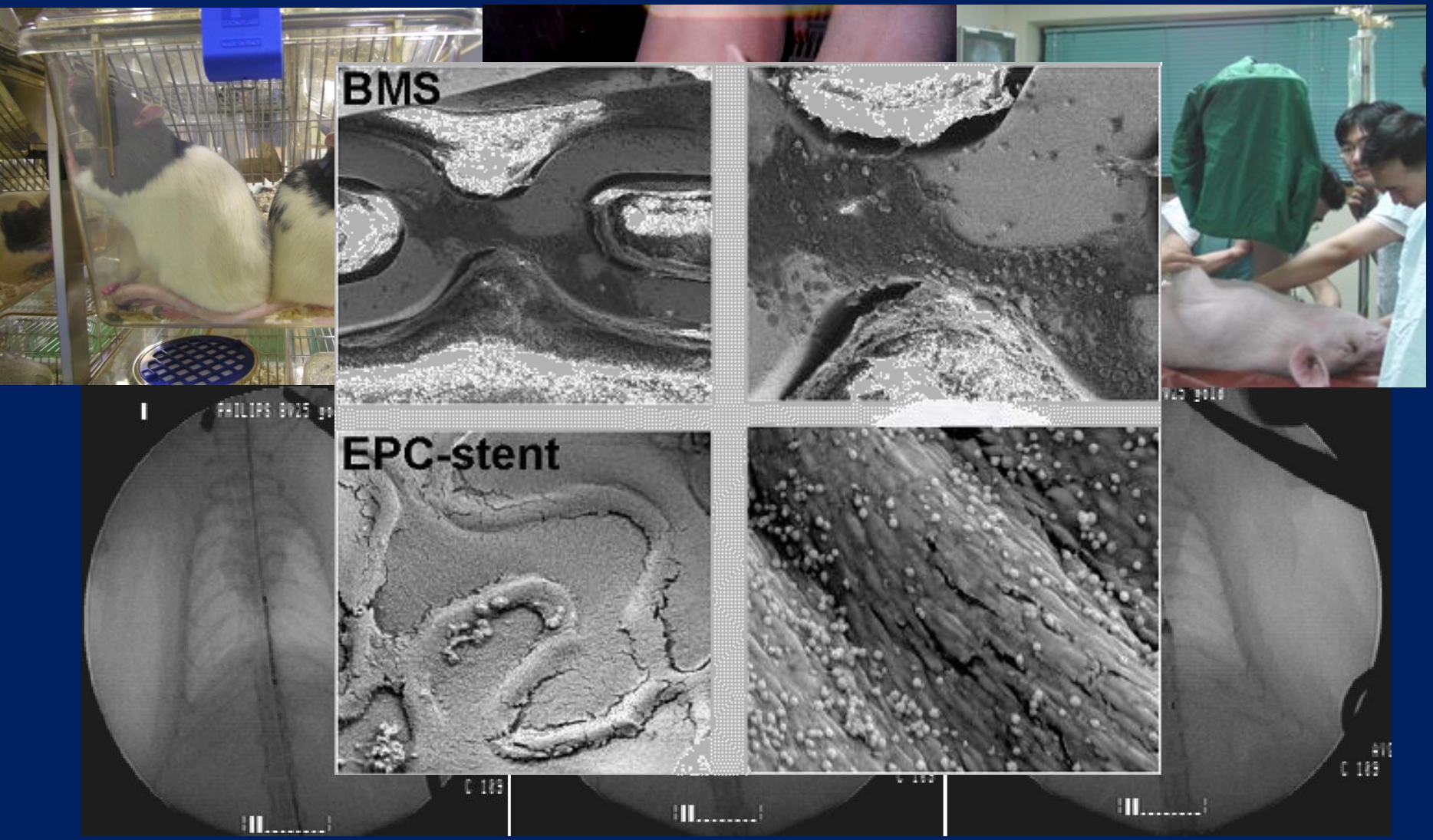
	no. / total no. (%)	
At 30-day visit		
DAPT	4103 / 4939	(83.1%)
DAPT stopped	640 / 4939	(13.0%)
Deceased	32 / 4939	(0.6%)
Unknown	164 / 4939	(3.3%)
At 6-month visit		
DAPT	2915 / 4939	(59.0%)
DAPT stopped	1626 / 4939	(32.9%)
Deceased	76 / 4939	(1.5%)
Unknown	322 / 4939	(6.5%)
At 12-month visit		
DAPT	1692 / 4939	(34.3%)
DAPT stopped	1187 / 4939	(24.0%)
Deceased	111 / 4939	(2.2%)
Unknown	1949 / 4939	(39.5%)

Recommanded DAPT : at least 1 month

Table 4. Twelve-month clinical outcomes.

Outcome	No. (%)*	
Main composite outcome		
Target vessel failure*	401	(8.4%)
Individual outcomes		
Death	111	(2.3%)
Cardiac death	80	(1.7%)
Myocardial infarction	93	(1.9%)
Q-wave MI	17	(0.4%)
Non-Q-wave MI	77	(1.6%)
Clinically indicated target lesion revascularisation	266	(5.7%)
PCI	245	(5.2%)
CABG	30	(0.6%)
Target vessel revascularisation	304	(6.5%)
PCI	272	(5.8%)
CABG	42	(0.9%)
Composite outcomes		
Device oriented: cardiac death, target vessel MI, TLR	371	(7.8%)
Patient oriented: death, MI, any revascularisation	574	(12.0%)
Cardiac death, MI, TLR	379	(7.9%)
Death or MI	190	(3.9%)
Cardiac death or MI	161	(3.3%)

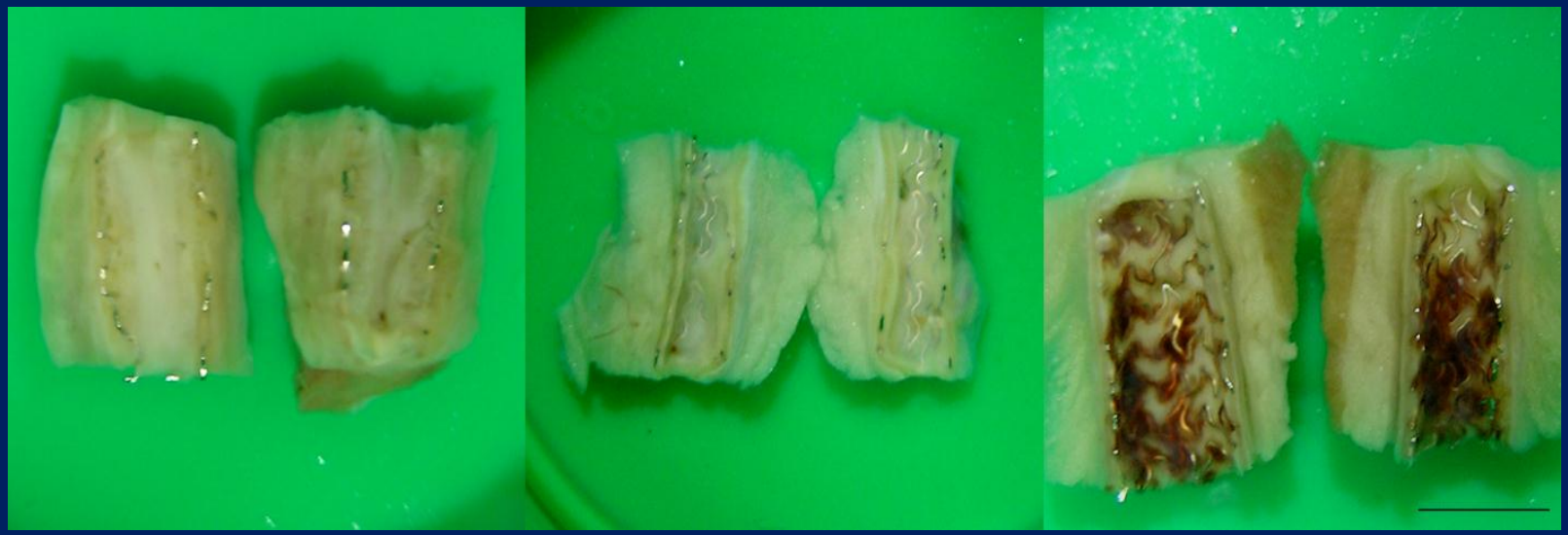
EPC-Capturing Aptamer Stent



CNUH data. 2009 ACC. Tissue Eng Regen Med 2009;6:555-61

EPC-Capturing Aptamer Stent

Aptamer | Cobalt-chromium | Taxus



Re-endothelialization score = 3.6; 3.4; 1.3
(complete: 4, ~75%: 3, ~50%: 2, ~25%: 1, ~0%)
Thrombus appearance rate = 16.7 %; 0%; 66.7%

CNUH data. 2009 ACC. Tissue Eng Regen Med 2009;6:555-61

Genous stent clinical trial in Korean AMI pts

- **Genous-STEMI:** **[STEMI pts (n=1,000), PI: Seung Jung Park, DAT – 1 month)**

- **GREAT study:** **[NSTEMI pts (n= 1,000), PI: Youngkeun Ahn, DAT - 3 months)**

Bioresorbable Scaffold – Rationale and Goals

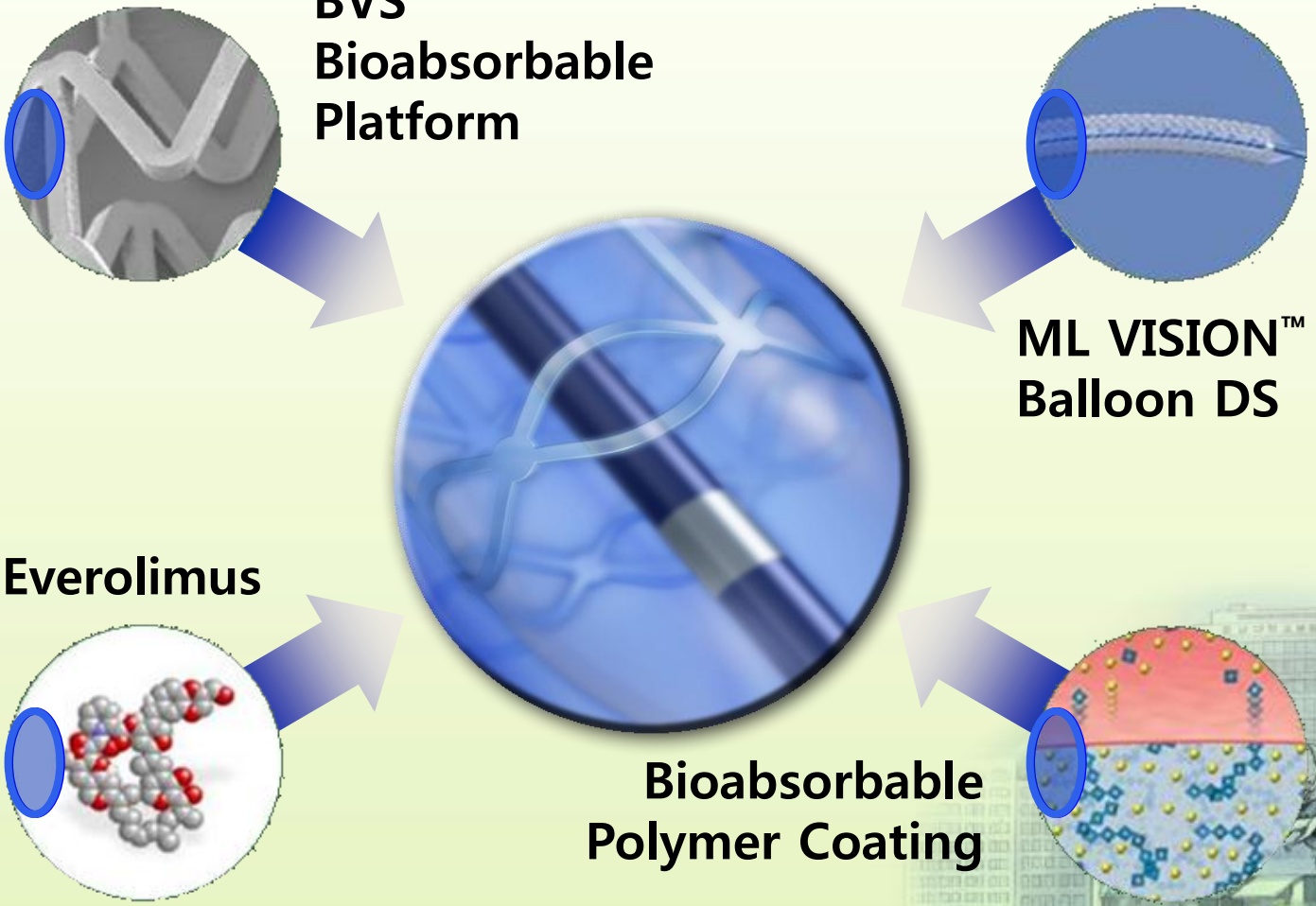
Vessel scaffolding is only needed transiently

- ✓ Revascularize the vessel like a metallic DES, then resorb naturally into the body.
- ✓ Leave no permanent metallic implant.
  - ✓ No permanent scaffold – restores natural vascular response to physiological stimuli and potentially permits late lumen expansion.
  - ✓ No stimulus for chronic inflammation – potentially reduces the need for long-term dual antiplatelet therapy.
  - ✓ Future re-intervention (PCI and CABG) is facilitated.
- ✓ Provide compatibility with non-invasive diagnostic imaging (MR/CT), allowing non-invasive follow-up.

Bioabsorbable Stent Program

Igaki-Tamai		PLA
BVS		PLA
REVA		Tyrosine-Policarbonate
BIT		PAE-Salicylate
Biotronik		Magnesium

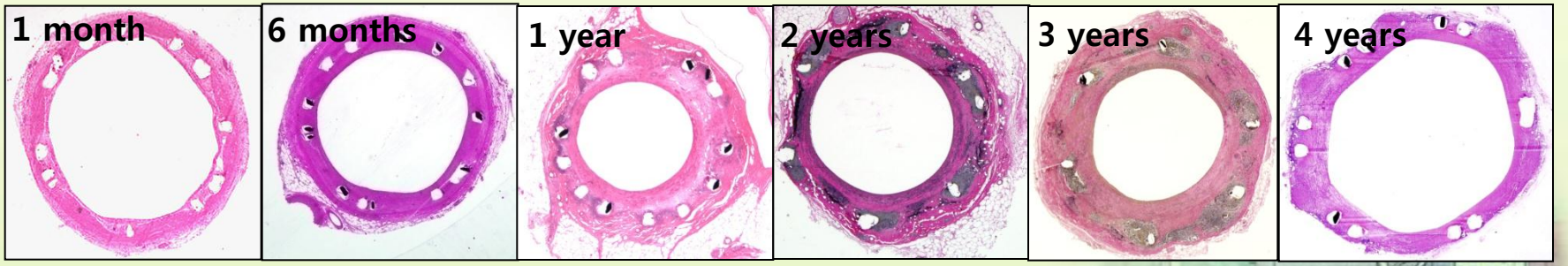
Abbott Vascular BVS Everolimus Eluting Device



Porcine Coronary Artery Safety Study: Representative Photomicrographs (2x)

BVS Cohort A

CYPHER



Photos taken by and on file at Abbott Vascular.

A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods

Patrick W Serruys, John A Ormiston, Yoshinobu Onuma, Evelyn Regar, Nieves Gonzalo, Hector M Garcia-Garcia, Koen Nieman, Nico Bruining, Cécile Dorange, Karine Miquel-Hébert, Susan Veldhof, Mark Webster, Leif Thuesen, Dariusz Dudek

Summary

Background Drug-eluting metallic coronary stents predispose to late stent thrombosis, prevent late lumen vessel enlargement, hinder surgical revascularisation, and impair imaging with multislice CT. We assessed the safety of the bioabsorbable everolimus-eluting stent (BVS)

Methods 30 patie… with multiple imaging …ters (virtual histology, …

Findings Clinical … ischaemia-driven … tion (non-Q wave). 18-… . At 2-year angiograph… iffer from the findings … nths and 2 years was d… ions presented no disce… ing; the remaining app… cent coronary artery in …

	6 months (n=30)	12 months (n=29)*	18 months (n=29)*	2 years (n=28)†
Cardiac death	0%	0%	0%	0%
MI	3·3% (1)‡	3·4% (1)‡	3·4% (1)‡	3·6% (1)‡
Q-wave MI	0%	0%	0%	0%
Non-Q-wave MI	3·3% (1)‡	3·4% (1)‡	3·4% (1)‡	3·6% (1)‡
Ischaemia-driven TLR	0%	0%	0%	0%
By PCI	0%	0%	0%	0%
By CABG	0%	0%	0%	0%
Ischaemia-driven MACE (cardiac death, MI, or ischaemia-driven TLR)	3·3% (1)‡	3·4% (1)‡	3·4% (1)‡	3·6% (1)‡
Stent thrombosis	0%	0%	0%	0%

Interpretation At 2 years after implantation the stent was bioabsorbed, had vasomotion restored and restenosis prevented, and was clinically safe, suggesting freedom from late thrombosis. Late luminal enlargement due to plaque reduction without vessel remodelling needs confirmation.

Lancet 2009; 373: 897–910

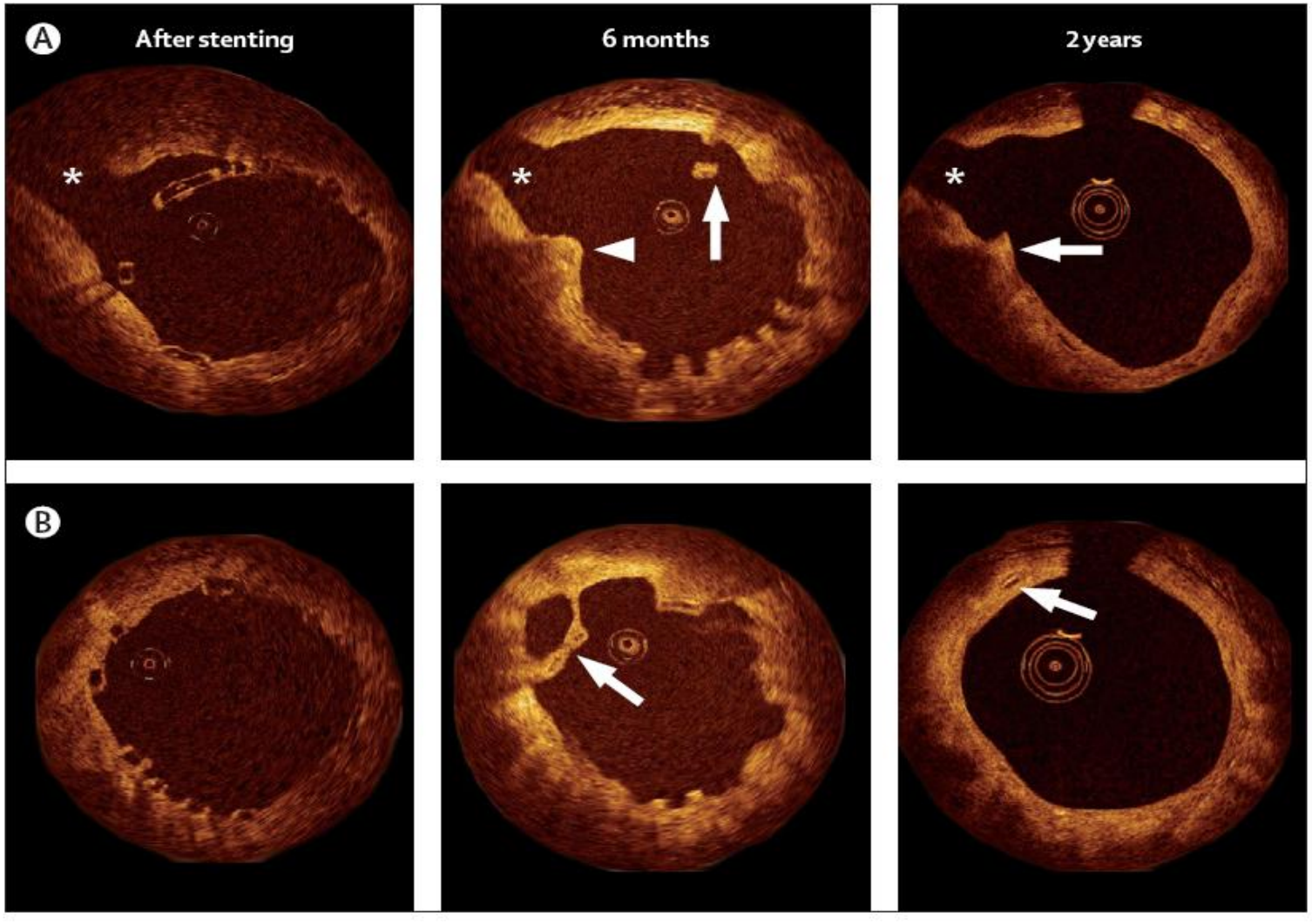
See Comment page 869

See Perspectives page 887

Thorax Center (Prof P W Serruys MD, Y Onuma MD, E Regar MD, N Gonzalo MD, K Nieman MD, N Bruining PhD) **and Department of Radiology** (K Nieman MD), **Erasmus Medical Center, Rotterdam, Netherlands; Auckland City Hospital, Auckland, New Zealand** (Prof J A Ormiston MB, M Webster MB); **Cardialysis BV, Rotterdam, Netherlands** (H M Garcia-Garcia MD); **Abbott Vascular, Diegem, Belgium** (C Dorange MSc, K Miquel-Hébert PhD, S Veldhof RN); **Skejby Sygehus, Aarhus University Hospital, Skejby, Denmark** (L Thuesen MD); **and Jagiellonian University, Krakow, Poland** (D Dudek MD)

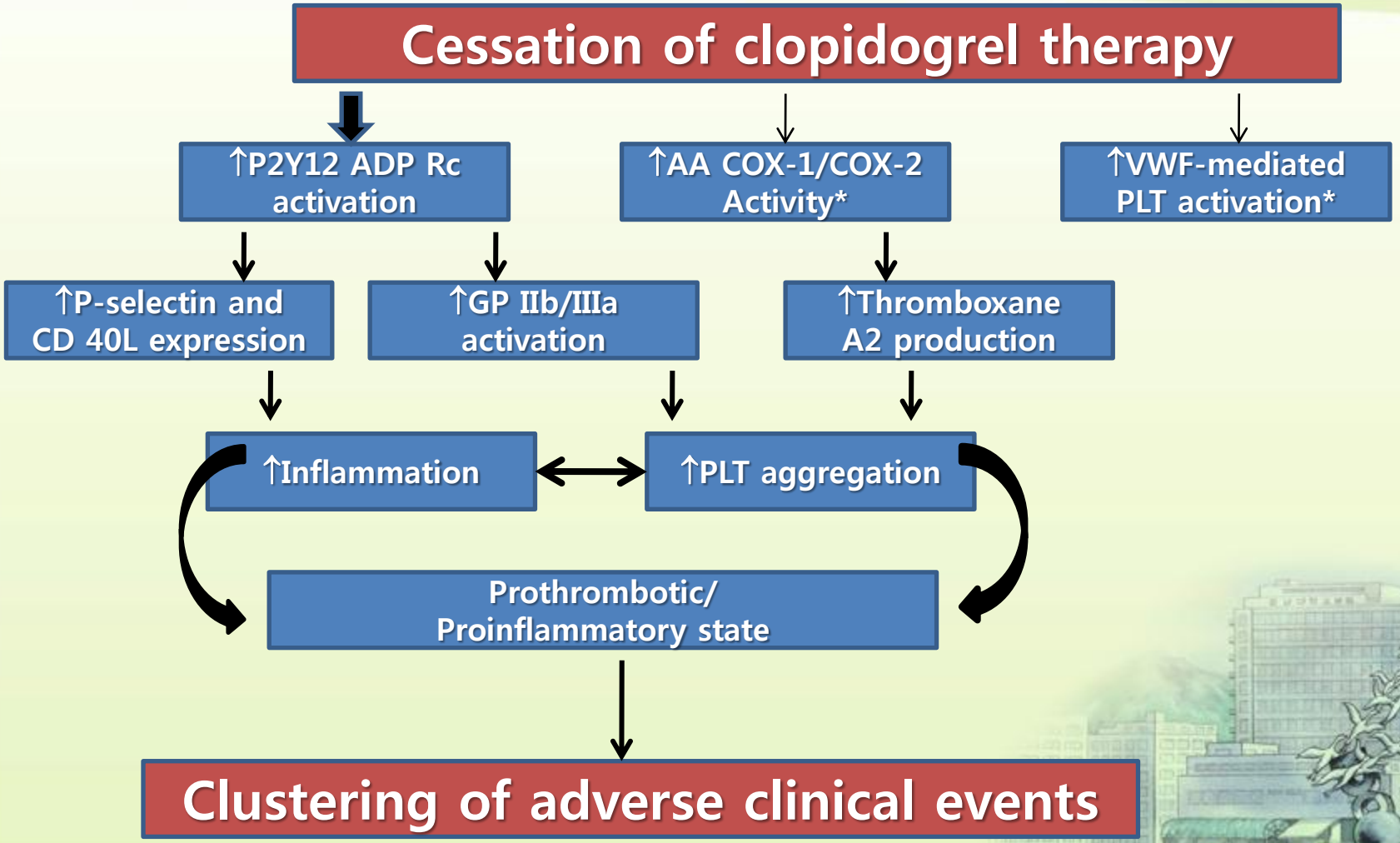
Recommanded DAPT : a minimum of 6 months

Serial assessment of stent struts by OCT



Serruys PW et al. *Lancet* 2009;373:897-910.

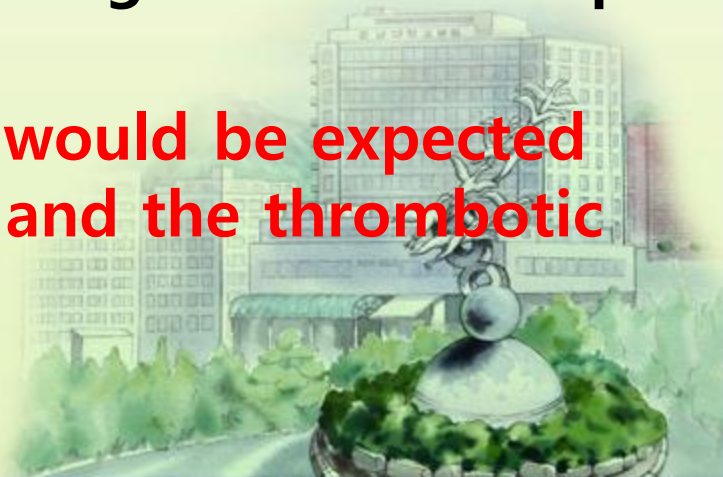
Clopidogrel withdrawal: Is there a "rebound phenomenon?



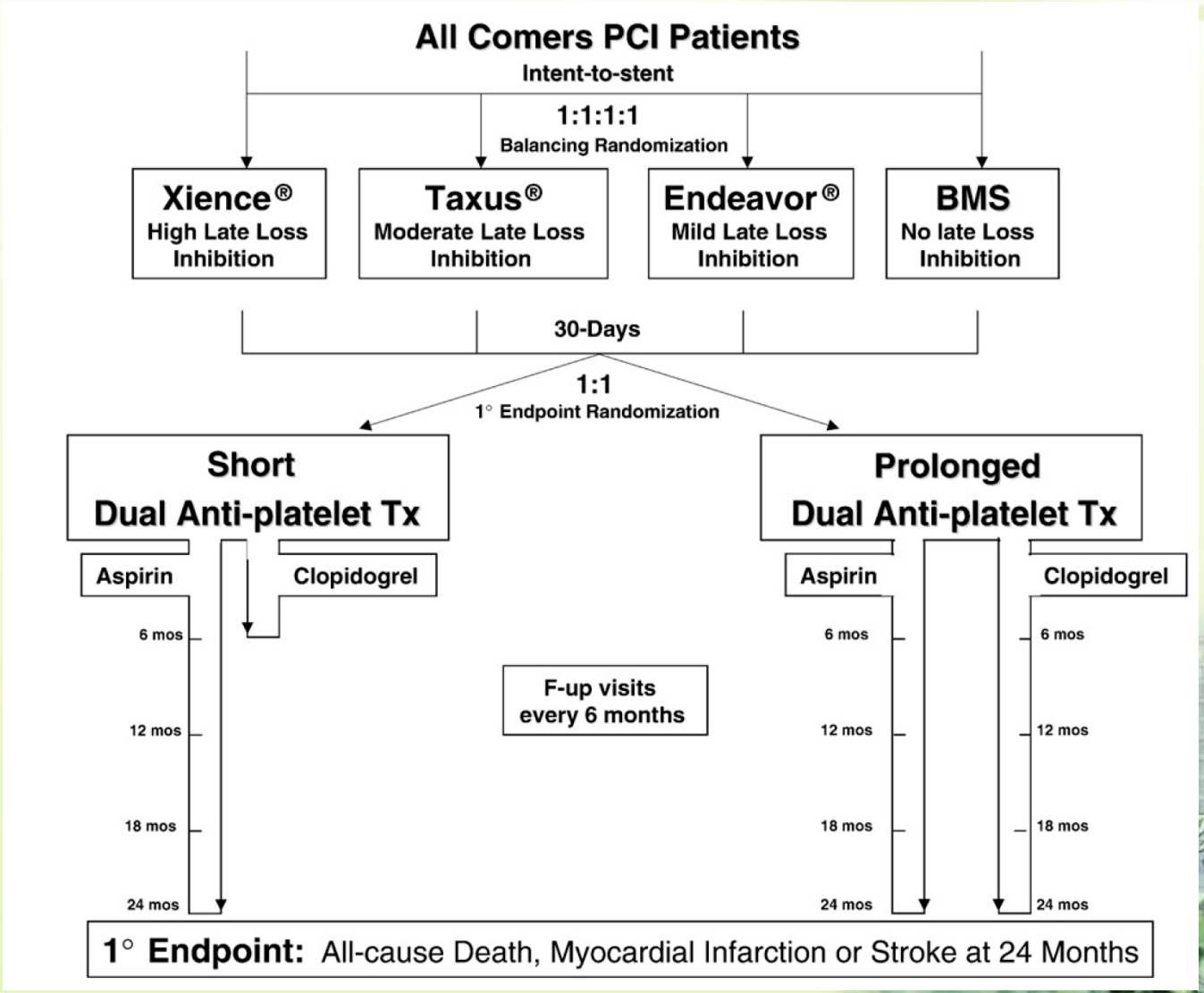
Sambu et al. Thromb Haemost 2011;105:211 – 20

Summary

- ✓ Optimal duration of antiplatelet therapy after PCI is still unclear.
- ✓ Duration of DAP therapy should be longer in higher-risk patients such as patients with ACS, DM and susceptible to stent thrombosis.
- ✓ It can only be determined by means of a large, randomized controlled study with long-term follow up.
- ✓ New DES and antiplatelet agents would be expected to decrease the duration of DAPT and the thrombotic events.



PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia study (PRODIGY)



Valgimigli M et al. *AHJ* 2010;160:804-811

Dual Antiplatelet Therapy Study

12 mos.

18 mos.

DES n = 15,245

BMS n = 5,400

All patients on aspirin +open-label thienopyridine therapy for 12 months

1:1 Randomization at month 12

50% of patients continue on Dual Antiplatelet Therapy

50% of patients receive aspirin + placebo

Results not expected until 2014!

Total 33 month patient evaluation including additional 3-month follow-up

Mauri L et al. *Am Heart J.* 2010;160:1035-41.

티타늄 산화물 박막코팅을 이용한 유전자 전달 스텐트 및 그 제조방법

관 인 생 략

출 원 번 호 통 지 서

출 원 일 자	2010.12.13
특 기 사 항	심사청구(유) 공개신청(무)
출 원 번 호	10-2010-0127251 (접수번호 1-1-2010-0820966-17)
출원인 명칭	전남대학교병원(2-2000-050586-2)
대 리 인 성 명	김종일(9-2003-000372-1)
발 명 자 성 명	안영근 권진숙 정명호 송선정 조동연
발 명 의 명 칭	티타늄 산화물 박막코팅을 이용한 유전자 전달 스텐트 및 그 제조 방법

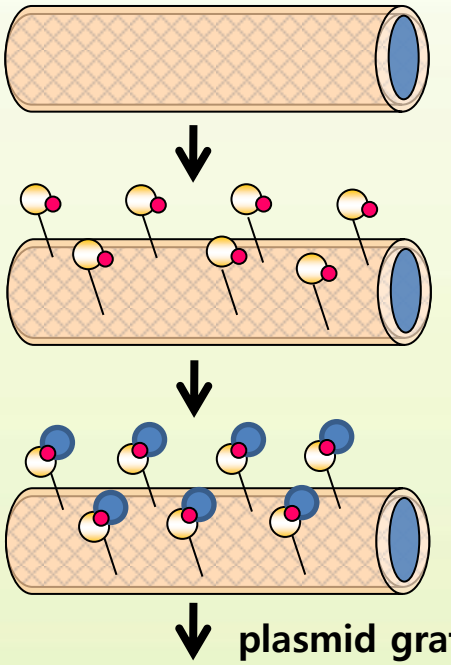
C O P Y

특 허 청 장

산화 티타늄 박막 코팅 후 항염증 및 항혈전 약물을 부착시킨 금속 표면에 다시 세포의 성장을 조절하는 유전자를 부착시켜서 염증반응 및 세포 성장 조절을 통하여 스텐트 내 혈관재협착 방지를 목적으로 함

티타늄 산화물 박막코팅을 이용한 유전자 전달 스텐트 및 그 제조방법

-유전자 전달 스텐트의 제작 모식도: 티타늄 산화물 박막코팅 후 항혈전 및 항산화 약물을 결합시키고 다시 유효한 유전자를 부착



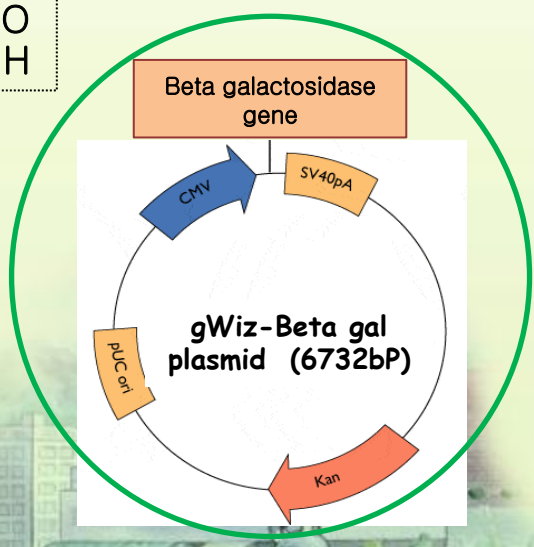
TiO_2 thin film coating

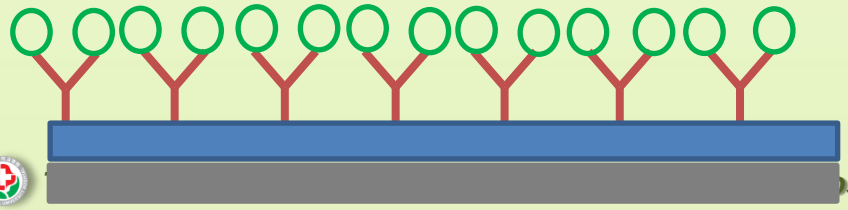
H_2O modification by H_2O plasma

: O
: H

drug grafting

plasmid grafting





Plasmid

Drug (Abciximab or Heparin, ALA, sirolimus, paclitaxel)

TiO_2 thin film

Metal

Thank your for your attention !