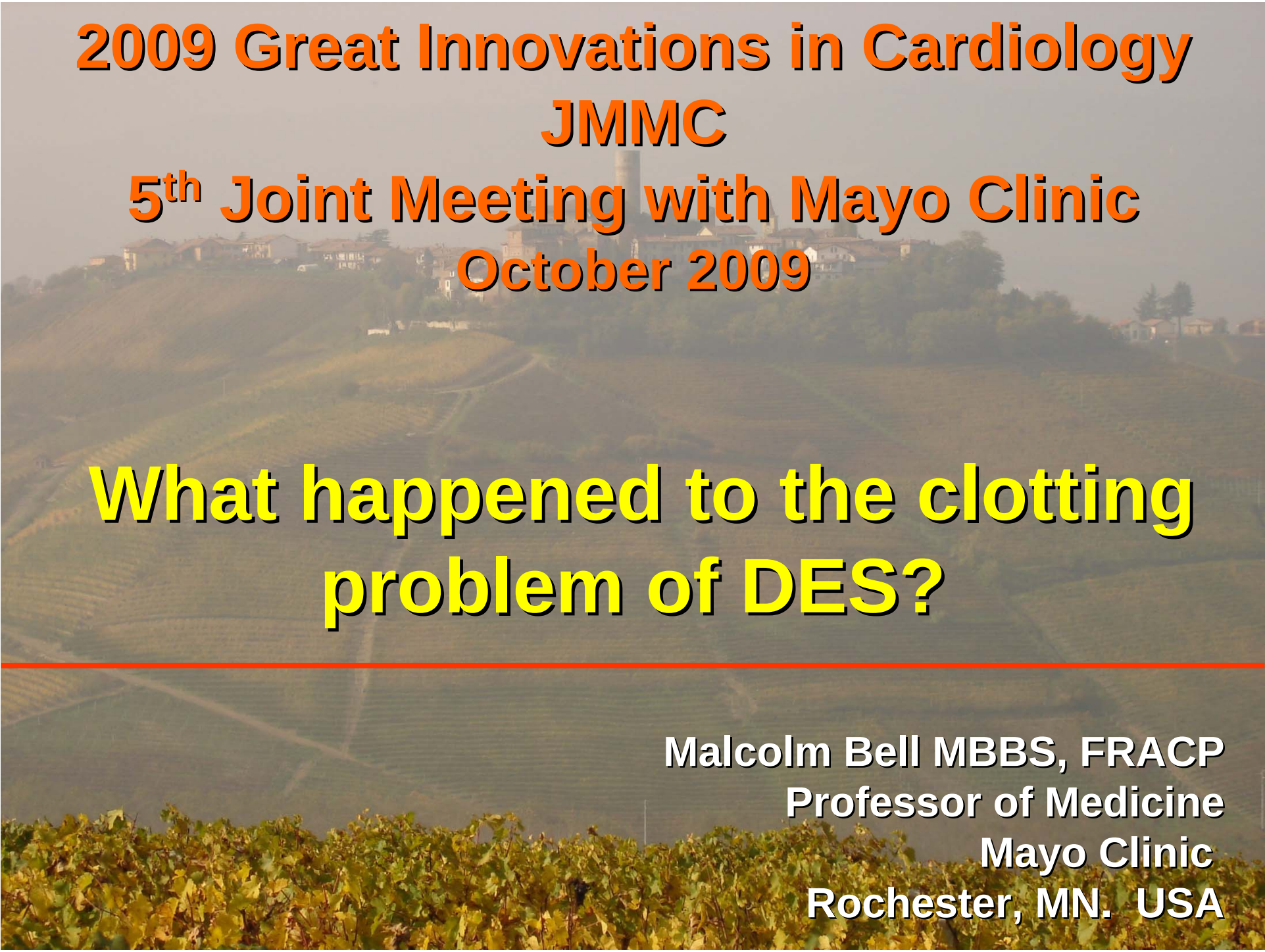




2009 Great Innovations in Cardiology JMMC

**5th Joint Meeting with Mayo Clinic
October 2009**

What happened to the clotting problem of DES?

**Malcolm Bell MBBS, FRACP
Professor of Medicine
Mayo Clinic
Rochester, MN. USA**

DISCLOSURE

Relevant Financial Relationship(s)

None

Off Label Usage

Clopidogrel for use with stents

DES in AMI

ESC 2006

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 XVII World Congress of Cardiology

Do drug-eluting stents increase deaths?

TWO SEPARATE, independent meta-analyses, presented in Hot Line session 1, suggest drug-eluting stents (DES) may increase death, Q-wave myocardial infarction (clinical surrogate 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'm a fan of the data we're seeing today is only the tip of the iceberg. We need to encourage more public access to the data."

Professor, Esports Cancerized (Luzern, Switzerland), said recent case reports had flagged up the problem of in-stent thrombosis resulting from DES. The BASKET-LATE data



shows the data from the manufacturers," said Hoffmann. 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 arrival of PCI is an incisive change in the culture of cardiology that needs to be reversed," he said. The use of PCI has 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 preventing short-term relief of chest pain. It's not re-creating that life but the thousands of lives you don't see. Stable angina can be controlled with full medical management," Yusuf said. Yusuf stressed that included pharmaceutical companies, who have

2006

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2007-08 Analyses of DES vs. BMS

- Significantly less repeat revascularization

- About 60% reduction in high risk patients

- Diabetes, small vessels, long lesions

- No difference in either mortality or MI

- Bern Meta-analysis: Stettler C, Lancet 2007

- Ontario Stent Study: Tu JV, NEJM 2007

- SCAAR: TCT 2007

- NHLBI: Marroquin OC, NEJM 2008

Stent Thrombosis

- NOT a new phenomenon
 - Seen with BMS before arrival of DES
- Frequency about 0.5 - 2%
- Classification based on timing:

– Acute	<24 hours	<i>BMS = DES</i>
– Subacute	1-30 days	<i>BMS = DES</i>
– Late	30-365 days	<i>BMS > DES</i>
– Very late	>365 days	<i>DES > BMS</i>

Clinical Presentation and Outcomes

- Acute MI, sudden death, silent
- Clinical practice: ST is not subtle event
 - Usually a STEMI
 - Clear MI 60-80%
- 30-d mortality is 20-50%
- Treatment is PCI
 - With Gp IIb/IIIa inhibitor



Contributing Factors

- Diabetes mellitus
- Renal insufficiency
- Stent placed for AMI
 - particularly <12 months
- Long stents
- Bifurcation lesions
- Premature cessation of antiplatelet Rx
- Malignancy

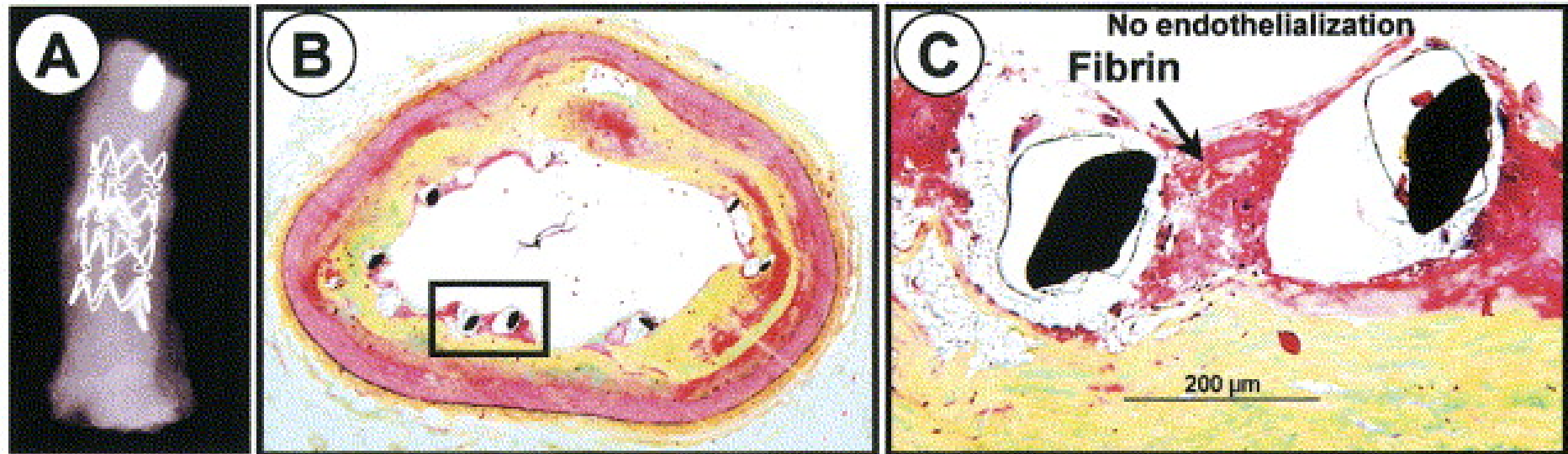
High risk

Late and Very Late Stent Thrombosis after DES

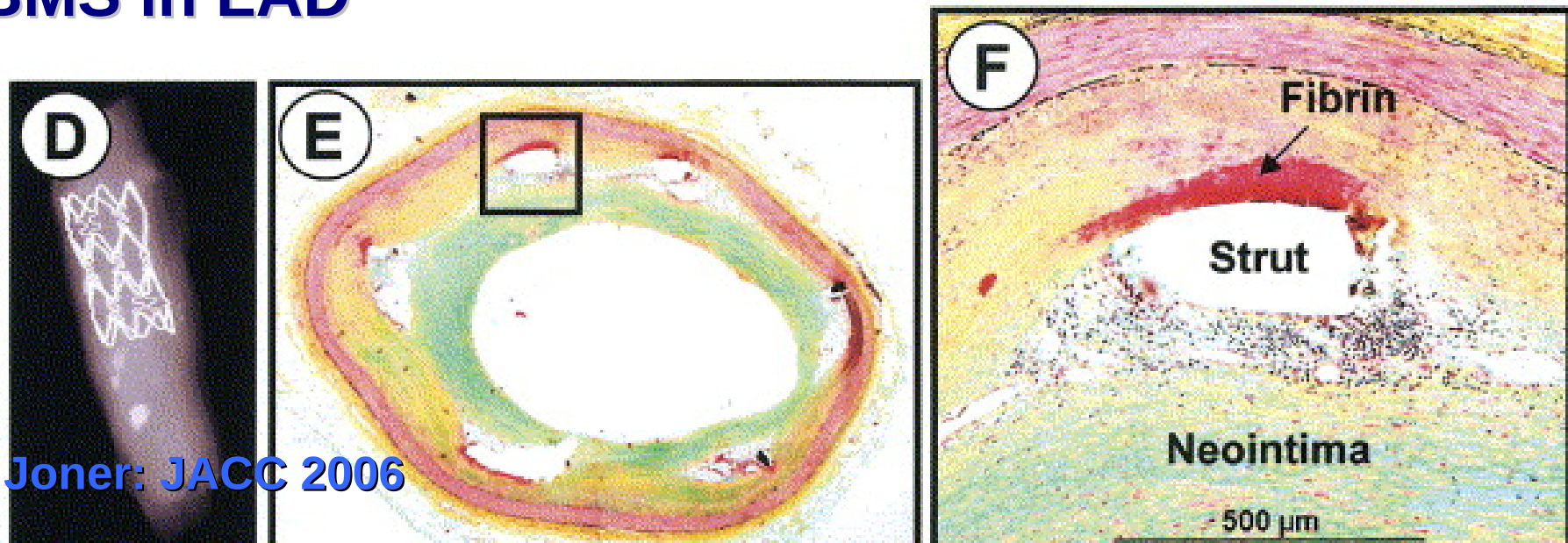
Possible stent factors:

- Late incomplete stent apposition
 - 10-20% of all DES
- Delayed or absence of healing
- Hypersensitivity and inflammation
- Restenosis

DES in LAD



BMS in LAD

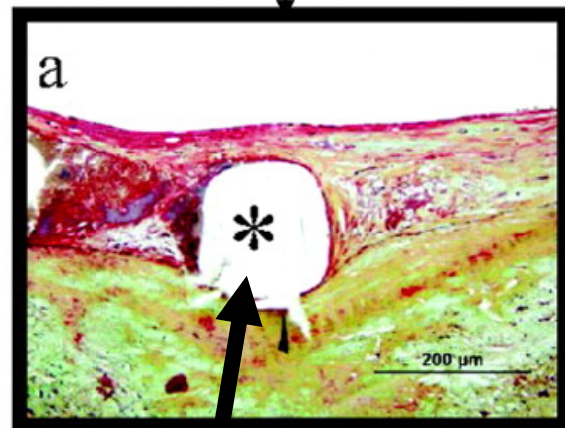
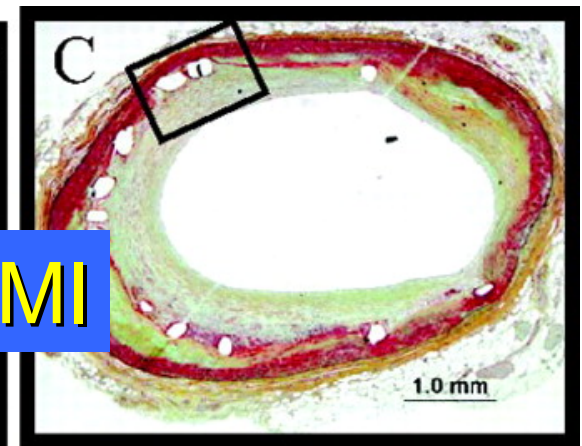
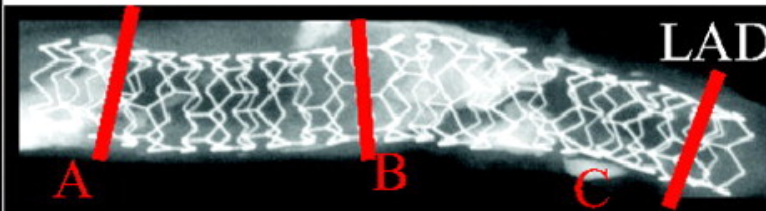
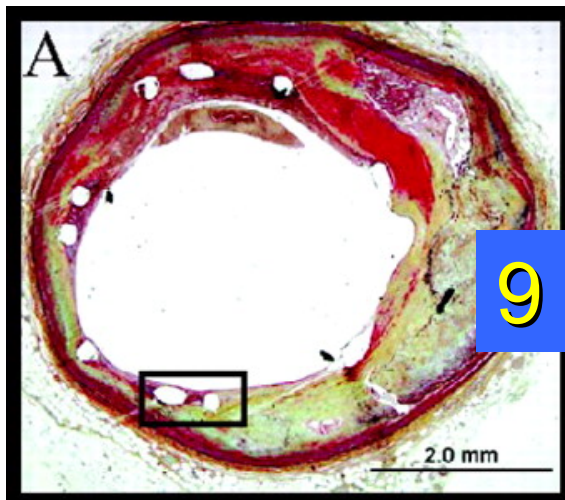


Joner: JACC 2006

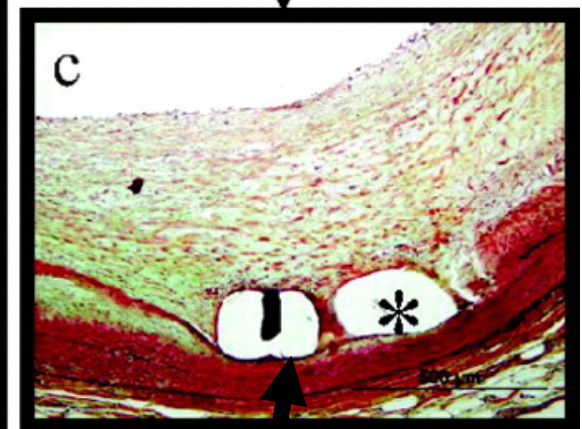
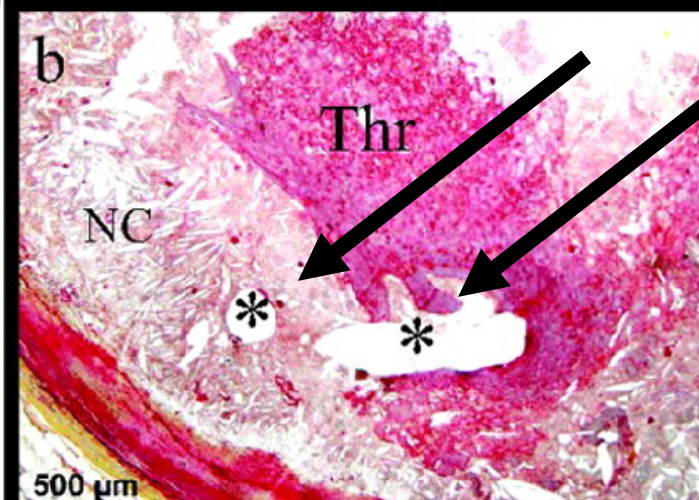
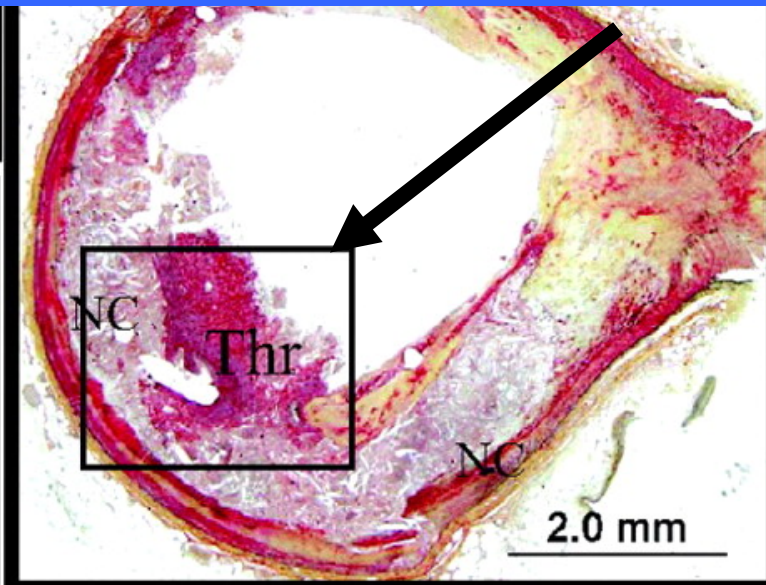
Acute MI

- Strong predictor of stent thrombosis
- “Middle of the night” challenge
 - Selecting DES or BMS
 - rapidly assess future compliance with long-term dual antiplatelet therapy

9 m after TAXUS for AMI



Proximal



Distal

DES vs BMS in STEMI

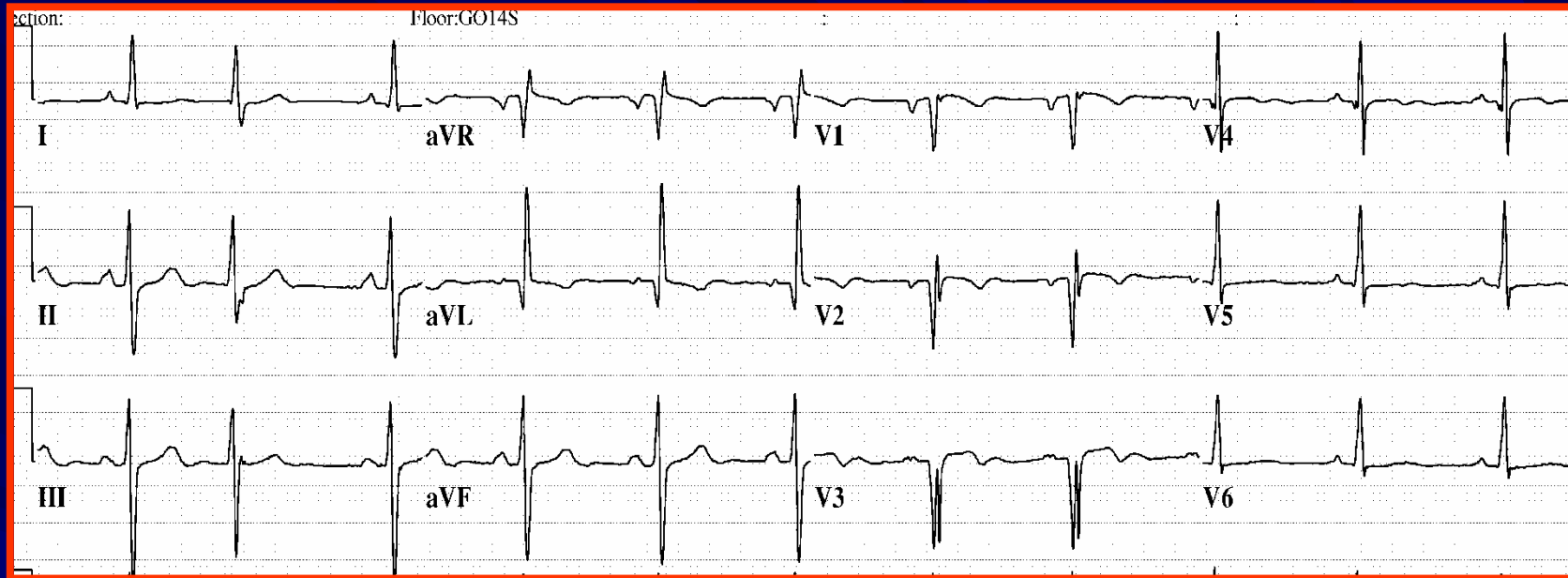
2008 Meta-analysis

	DES vs BMS	
	Hazard ratio	<i>P</i> value
Reintervention (TLR)	0.36 (0.28-0.47)	<0.0001
Stent thrombosis	0.76 (0.47-1.23)	NS
Death	0.91 (0.66-1.08)	NS
Recurrent MI	0.85 (0.58-1.23)	NS

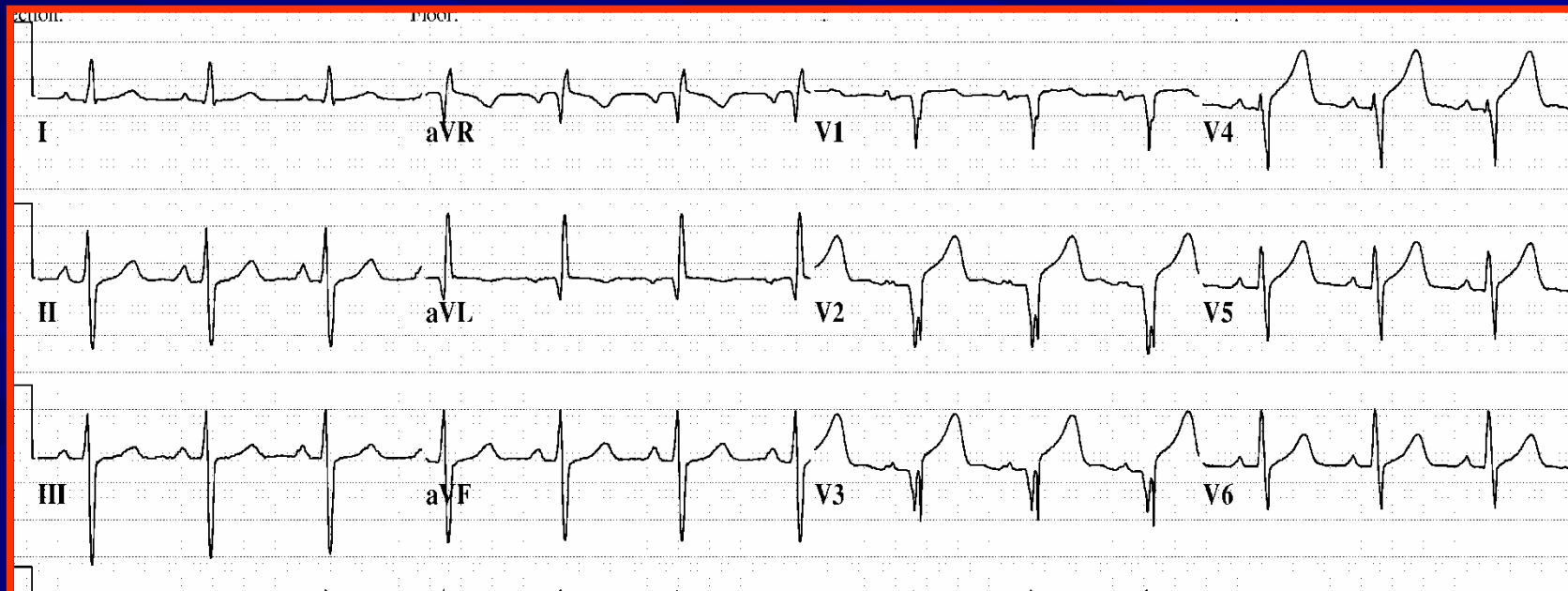
Favors DES (NNT = 13)

Clinical case – Sept 2008

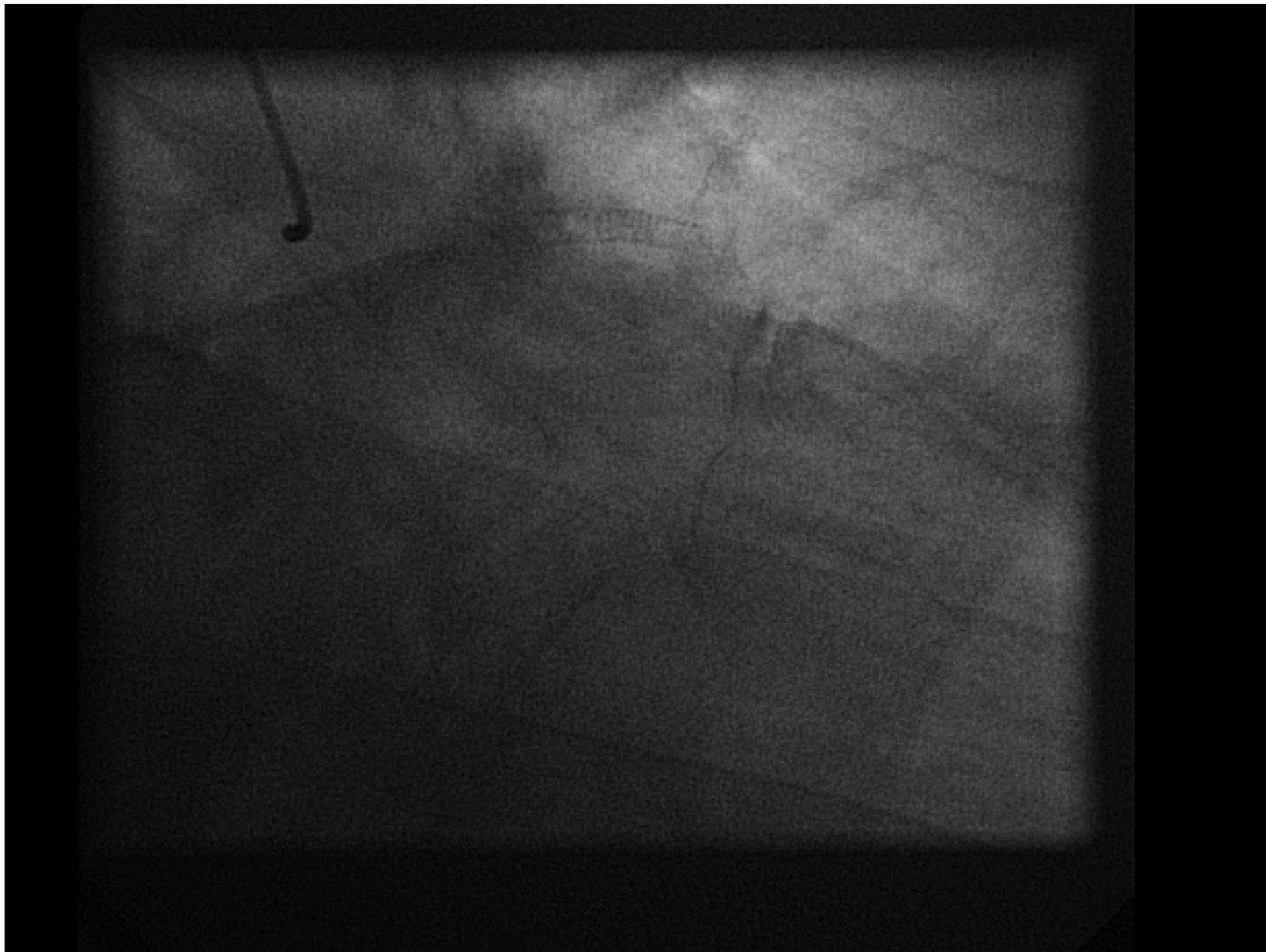
- 74 yr - man needed revision of R total hip
- CAD history:
 - DES to LAD 2005
 - AMI secondary to stent thrombosis Jan 2008
 - Repeat stenting
- Plavix stopped for surgery
- Chest pain in recovery room immediately post-op



Baseline



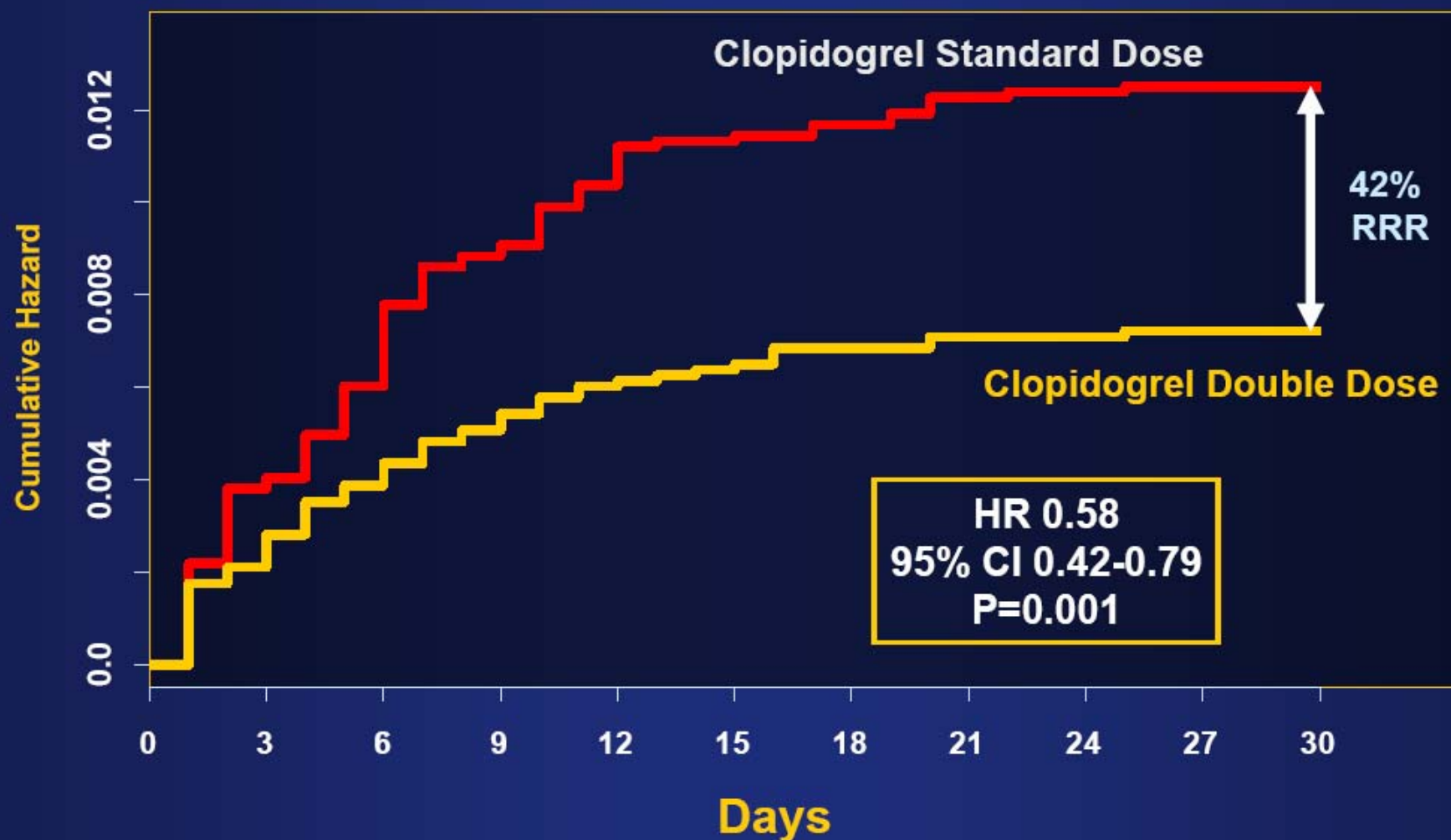
Post-op



Clopidogrel Resistance or “hypo responders”

- Prevalence 5-40% - definitions vary
- Many factors, including clinical features
 - e.g. increased platelet reactivity in diabetes not suppressed by usual doses of clopidogrel
- Probably clinically relevant
- Often coexists with ASA resistance
- No consensus on testing

Clopidogrel: Double vs Standard Dose Definite Stent Thrombosis (Angio confirmed)





Clopidogrel Double vs Standard Dose Bleeding PCI Population

	Clopidogrel		Hazard Ratio	95% CI	P
	Standard N= 8684	Double N=8548			
TIMI Major ¹	0.5	0.5	1.06	0.70-1.61	0.79
CURRENT Major ²	1.1	1.6	1.44	1.11-1.86	0.006
CURRENT Severe ³	0.8	1.1	1.39	1.02-1.90	0.034
Fatal	0.15	0.07	0.47	0.18-1.23	0.125
ICH	0.035	0.046	1.35	0.30-6.04	0.69
RBC transfusion $\geq$ 2U	0.91	1.35	1.49	1.11-1.98	0.007
CABG-related Major	0.1	0.1	1.69	0.61-4.7	0.31

¹ICH, Hb drop $\geq$ 5 g/dL (each unit of RBC transfusion counts as 1 g/dL drop) or fatal

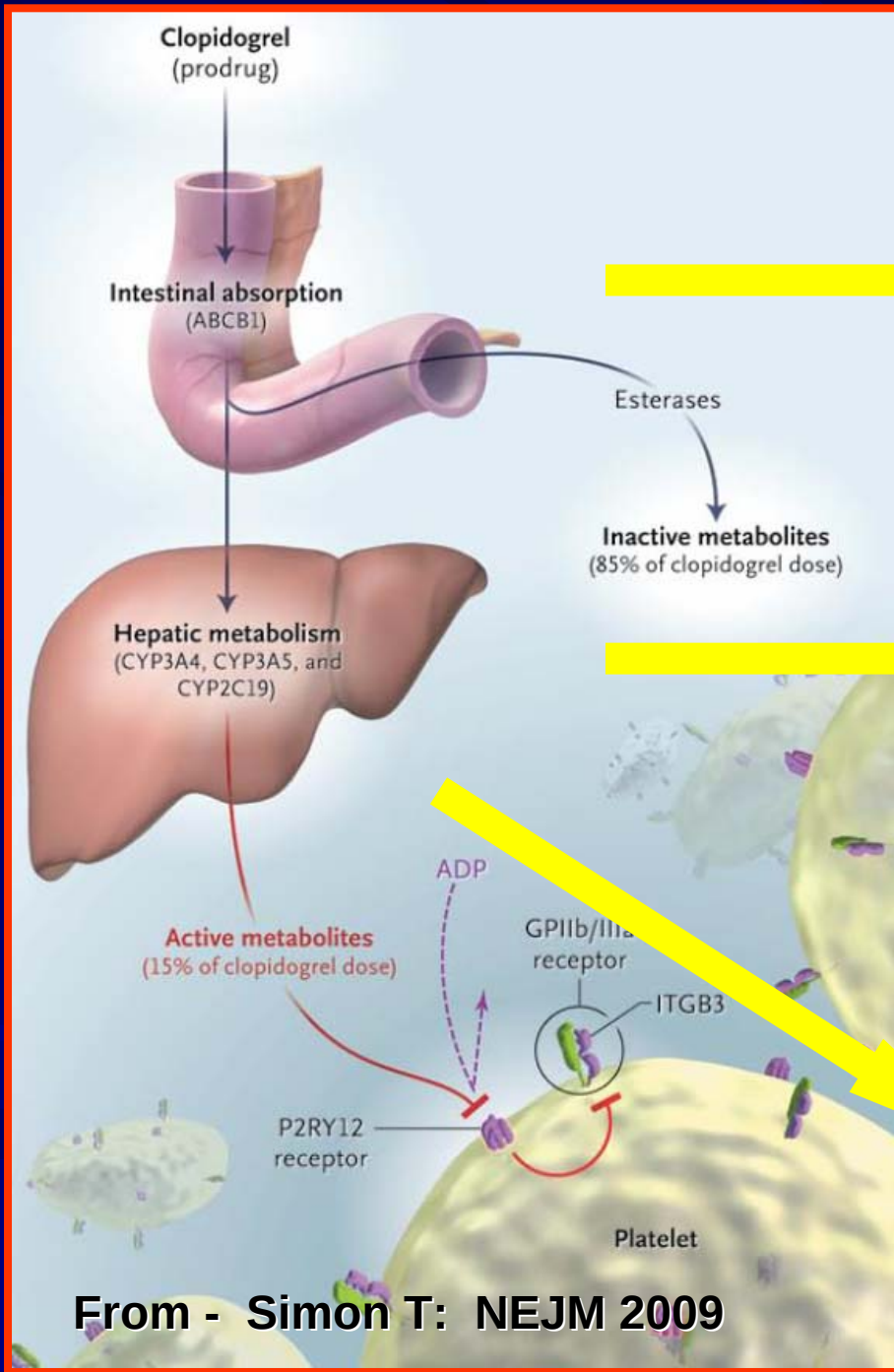
²Severe bleed + disabling or intraocular or requiring transfusion of 2-3 units

³Fatal or $\downarrow$ Hb $\geq$ 5 g/dL, sig hypotension + inotropes/surgery, ICH or txn of $\geq$ 4 units

Clopidogrel and Proton Pump Inhibitors

- Confusing!! – lack randomized controlled trial
- 45% of patients on PPI in PLATO*
- Risk of GI event high in patients on NSAIDs**
 - 2-5% per year
 - 1 in 7 of elderly patients
- No clinical effect in analysis of PRINCIPLE and TRITON trials***
- Reassess need for PPI but caution with stopping!

*Wallentin L: NEJM 2009; **Bhatt D: JACC 2009; ***O'Donoghue ML: Lancet 2009



ABCB1 gene

2 variable alleles:

↓ absorption

↑ CV event rates

CYP2C19 gene

Many variable alleles:

↓ biotransformation to active metabolite

Drug inhibition

e.g. omeprazole

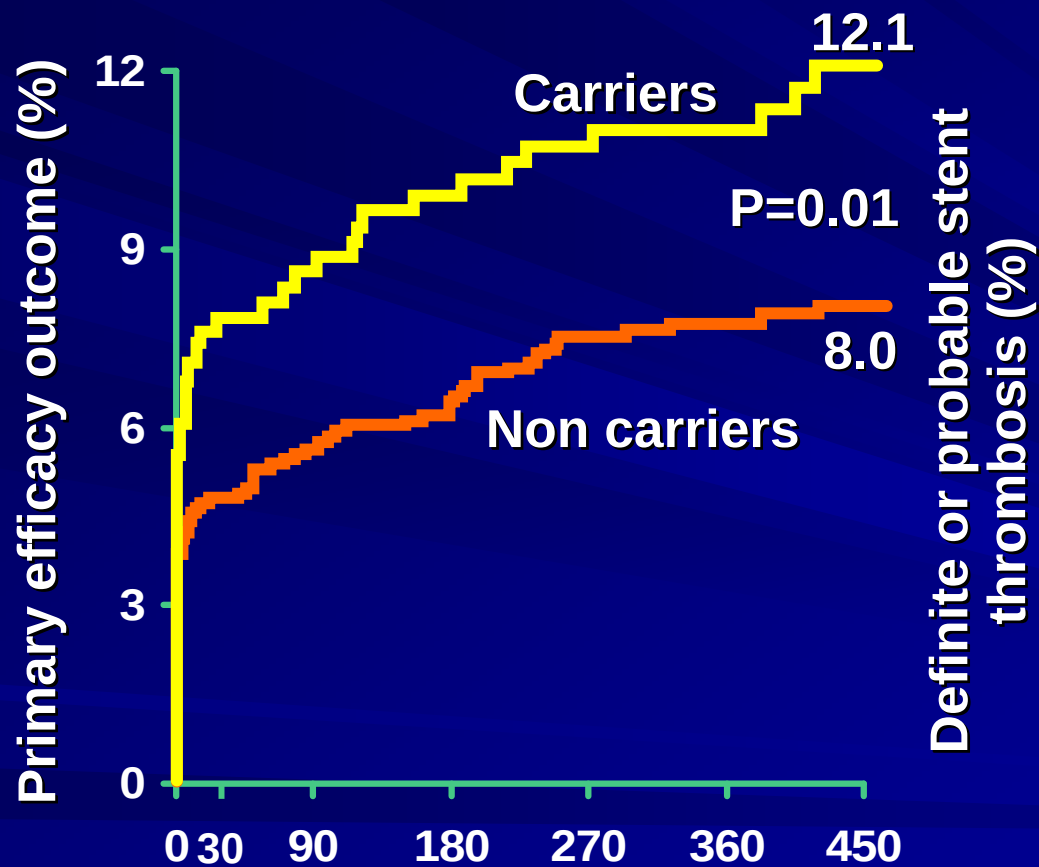
CYP3A gene

Blocked by CCBs

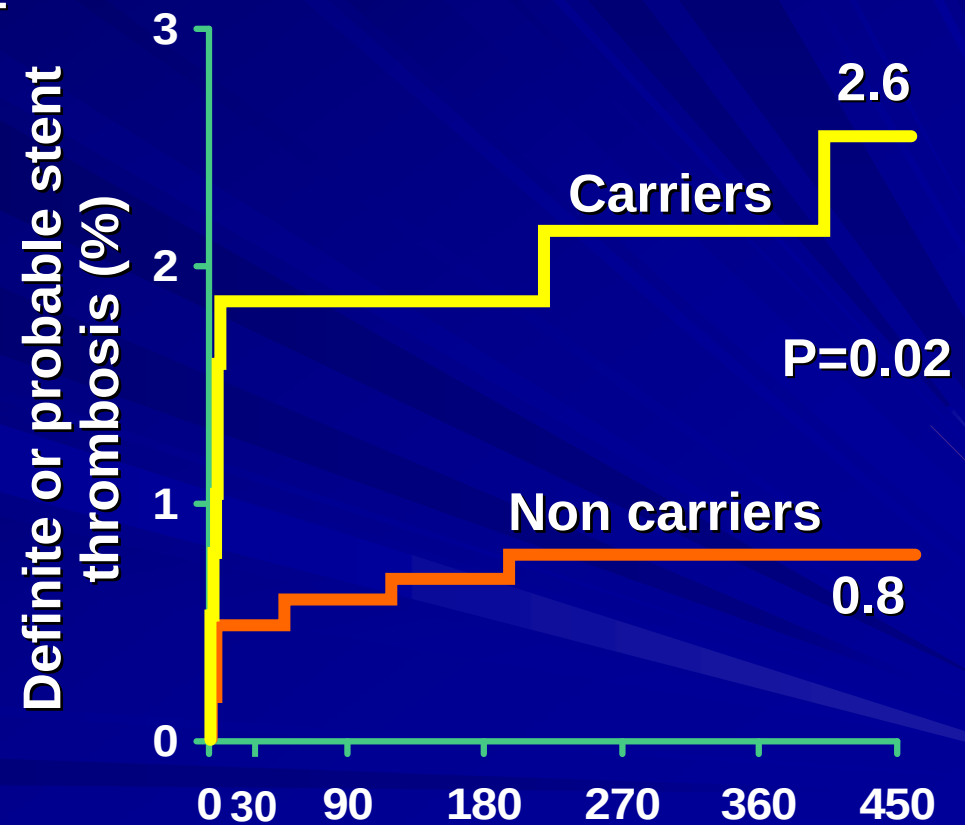
Genetic Polymorphisms and Clopidogrel (Observations from TRITON)

CYP2C19 reduced-function allele

Primary Efficacy Outcome



Stent Thrombosis



Days after randomization

Genetic Polymorphisms

CYP2C19*1

Cytochrome P-450 encoded by polymorphic genes

“Loss of function” variant alleles
CYP2C19*2 (or *3, *4, *5, *17)

↓Active
metabolite
↓Platelet
inhibition

30% Whites
40% Blacks
55% East Asians

Hazard Ratio:
CV event = 1.53
ST = 3.0

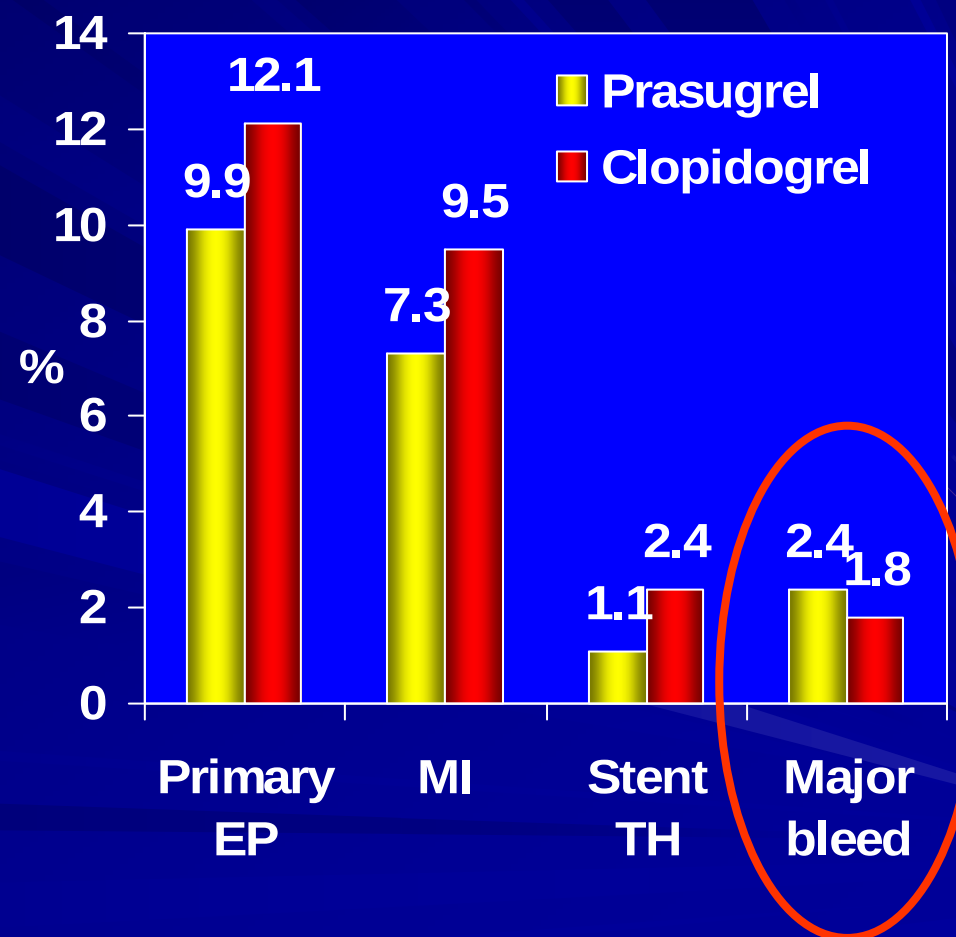
*Mega JL: NEJM 2009; **Desta Z: Clin Pharmacokinet 2002

TRITON - TIMI 38

Prasugrel vs Clopidogrel in High-risk ACS

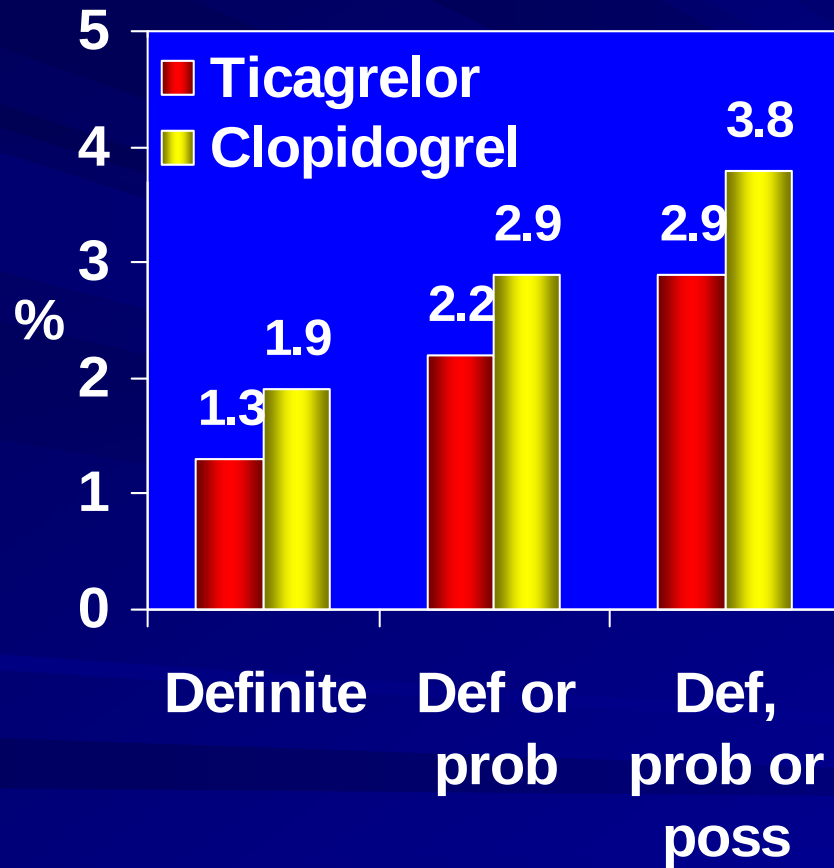
- Prasugrel
 - Thienopyridine (pro-drug)
 - Faster onset
 - More consistent and potent
- ACS Trial - planned PCI

- Concern over life-threatening bleeds
 - Elderly
 - Low BMI
 - Prior TIA/CVA

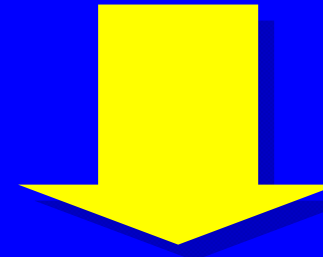


Is Ticagrelor the Answer?

Stent thrombosis in PLATO



But...



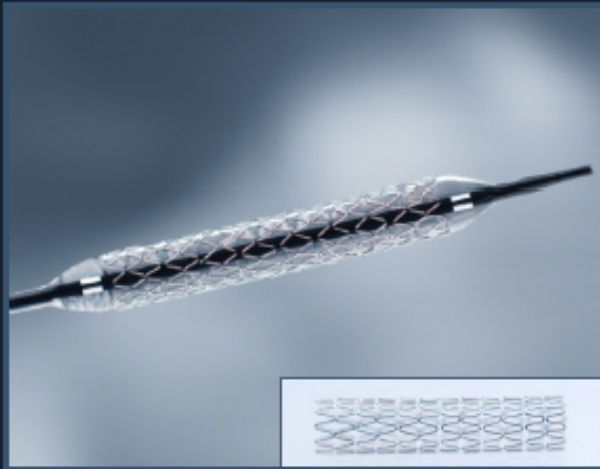
More major bleeding:

- Non-CABG related
- Intracranial bleeds



Resolute DES System

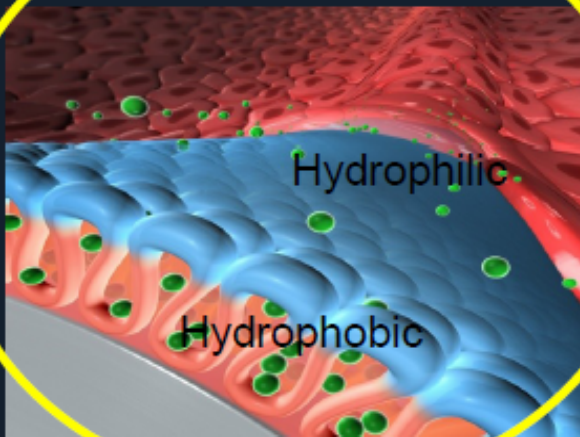
Driver Cobalt Alloy Stent



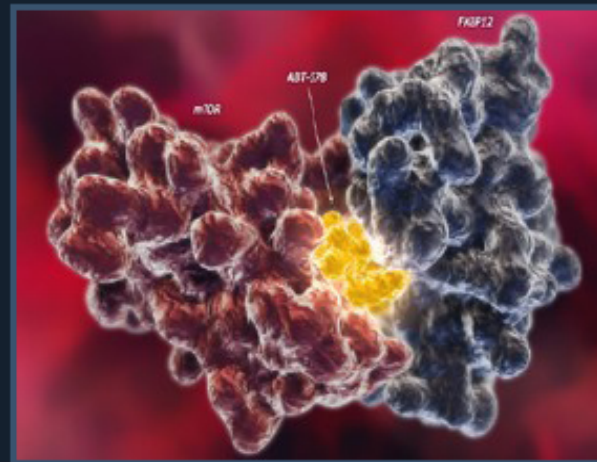
Stent Delivery System



BioLinx Polymer



Drug: Zotarolimus



14 Day Endothelialization: Rabbit Iliac Model

XIENCE™ V

Everolimus



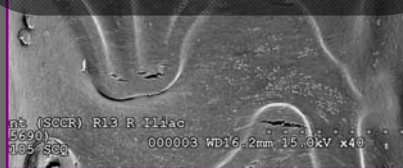
Stent thrombosis

Zero at 5-yr

SPIRIT I

0.3% 1 thru 3-yr

SPIRIT III



CYPHER®

Sirolimus

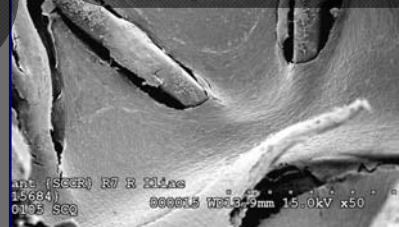


Stent thrombosis

Zero at 3-yr

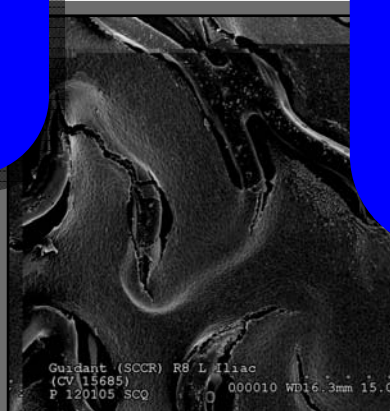
ENDEAVOR

I, II, III



TAXUS®

Paclitaxel



ENDEAVOR™

Zotarolimus



Stent thrombosis

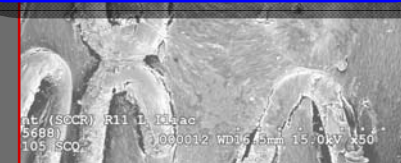
ENDEAVOR pooled

0.8% at 5-yr

0.2% >1-yr

ENDEAVOR IV

0.1% >1-yr



courtesy R. Virmani; TCT2009 (SPIRIT - Stone G; ENDEAVOR - Leon MB)

DES Pooled Programs

ARC Def/Prob ST Landmark to 5 Years



1. Mauri et al. PCR 2009.

2. 5 year Outcomes in the Sirius Trial, Weisz et al. JACC Vol. 53, No. 17, 2009

3. Mauri L et al. N Engl J Med. 2007;356:1020-1029.

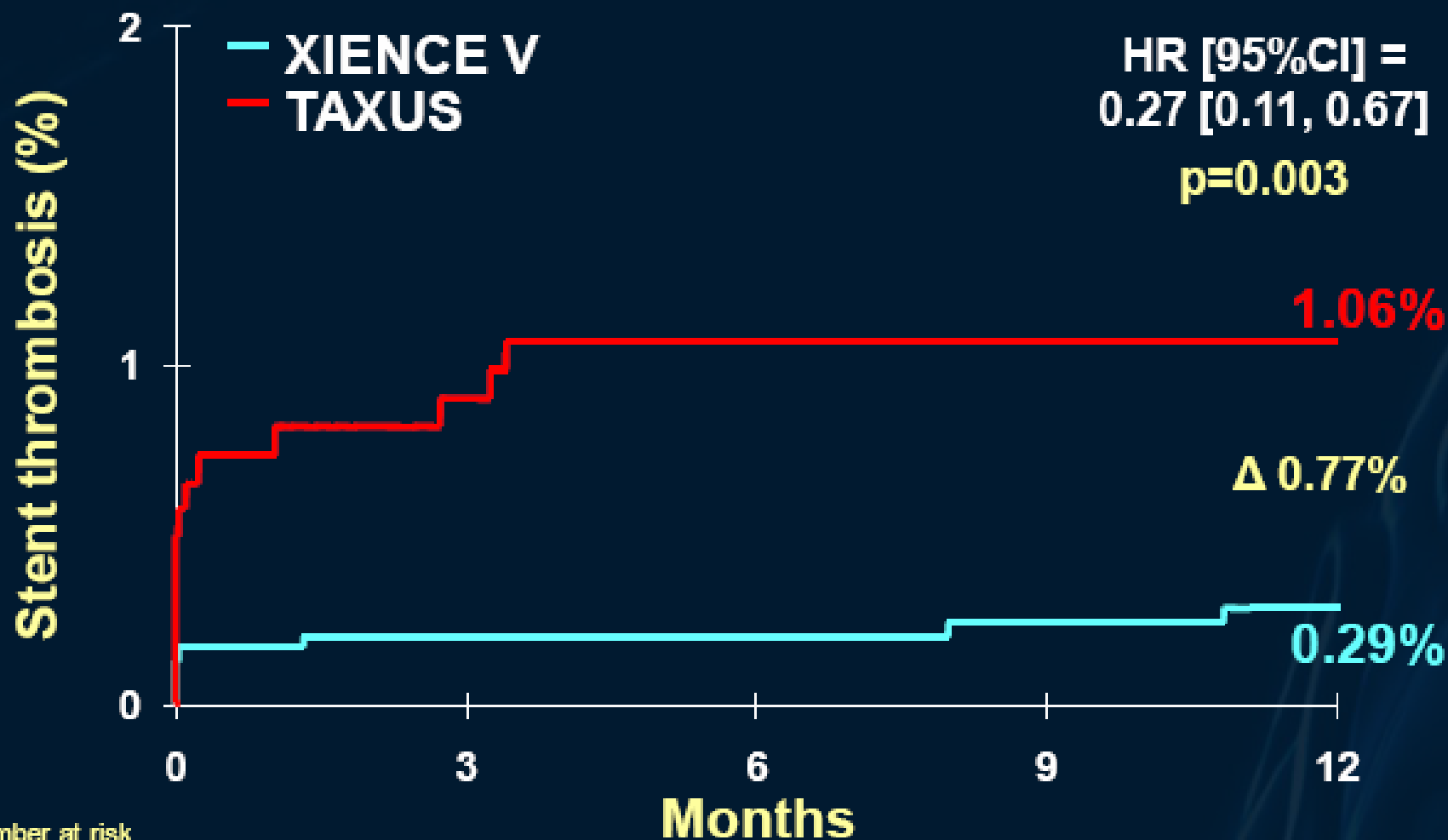
4. Stone, G et al., New SPIRIT Clinical Data, ACC. 09.

The Future: New Stents and Drugs, New Paradigms

- New drug targets – not cytotoxic
- Promote proper healing
 - EPCs to promote endothelial cell deposition
 - Need “normal” endothelium
- Biodegradable stents
- Customize stents
 - e.g. abciximab-coated stent for AMI*

*Kim W: JACC 2006 (Chonnam National University)

Stent Thrombosis (ARC Def or Prob)

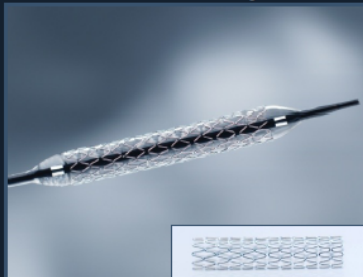


Number at risk

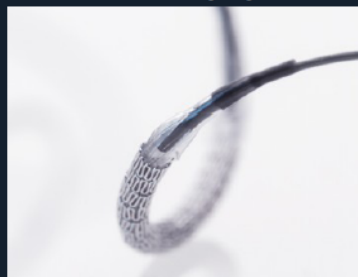
XIENCE V	2458	2426	2412	2388	2376
TAXUS	1229	1195	1184	1174	1166

Endeavor DES System

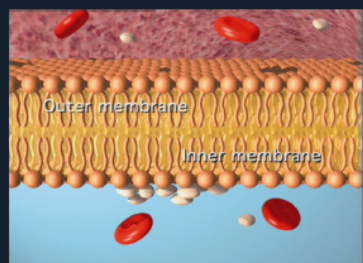
Driver Cobalt Alloy Stent



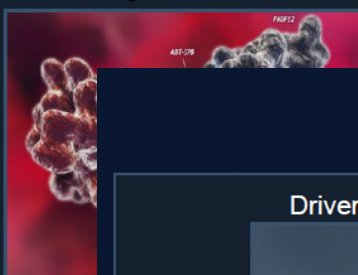
Stent Delivery System



PC Technology



Drug: Zotarolimus

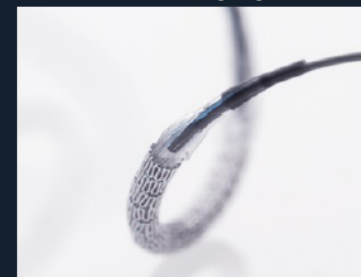


Resolute DES System

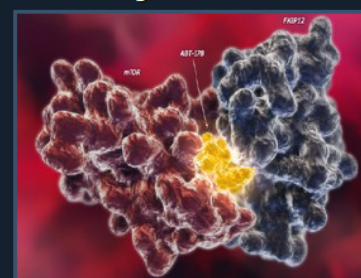
Driver Cobalt Alloy Stent



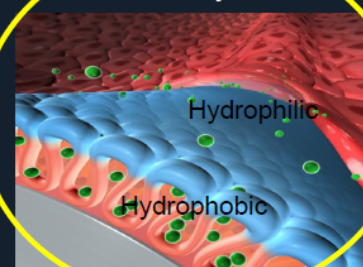
Stent Delivery System



Drug: Zotarolimus



BioLinx Polymer

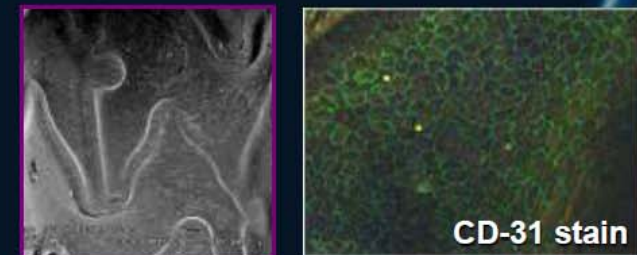


XIENCE V Design Parameters and Pre-clinical Results

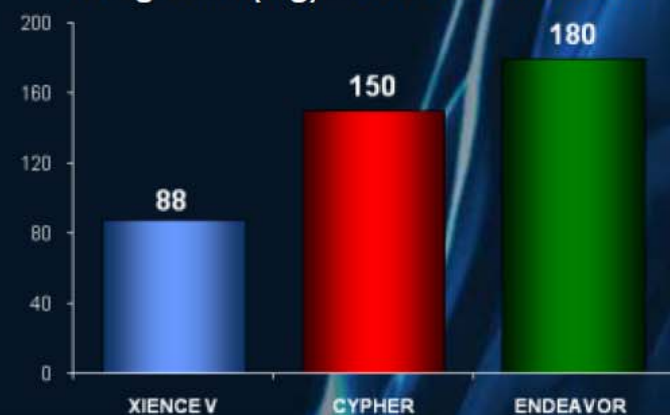
- **Low profile, flexible, deliverable stent**
 - 0.0032" cobalt chromium
- **Highly resistant to strut fracture**
- **Thin, adhesive, inert durable polymer**
 - promotes endothelialization
 - minimal bonding and webbing
 - minimal inflammation, without hypersensitivity reactions
- **Lowest dose of a “limus” on any DES**



14 day endothelialization: Rabbit Iliac



Drug Load (mg) - 3.0 x 18 mm stents



Good News with New Stents?

Stent thrombosis (ARC definition):

Zotarolimus-eluting stent (Endeavour)

- ENDEAVOUR III – Zero at 9 m*
- ENDEAVOR IV (Leonn MB DES SUMMIT 2009)
 - 0.9 E v 0.1 T <360, 0.1 1.5 >360
- ENDEAVOUR I, II and III trials**
 - 0.5% after 3 years
 - Zero in Cypher comparison arm

Everolimus-eluting stent (Xience V)**

- Zero in SPIRIT I after two years
- Zero in SPIRIT III after one year
- SPIRIT IV 3 yr Stone GW TCT 2009 – ARC 0.3%
Xinece, 1.0% TAXUS

*Kandzari DE: JACC 2006; **Zeicher A: Euro PCR 2007; **ACC 2007

The **New** Drugs

■ Prasugrel

- Irreversible inhibitor of ADP P2Y₁₂ receptor
- Maximal concentration by median of 30 min
 - Rapid absorption and metabolism
- Greater platelet inhibition vs. clopidogrel up to 28 days

■ Ticagrelor (tested in PLATO trial)

- Reversible oral P2Y₁₂ receptor inhibitor
- Peak plasma level 2 hours