Samsung Medical Center
Sungkyunkwan University
School of Medicine

15분

Dual Antiplatelet Therapy in the Era of 2nd Generation DES

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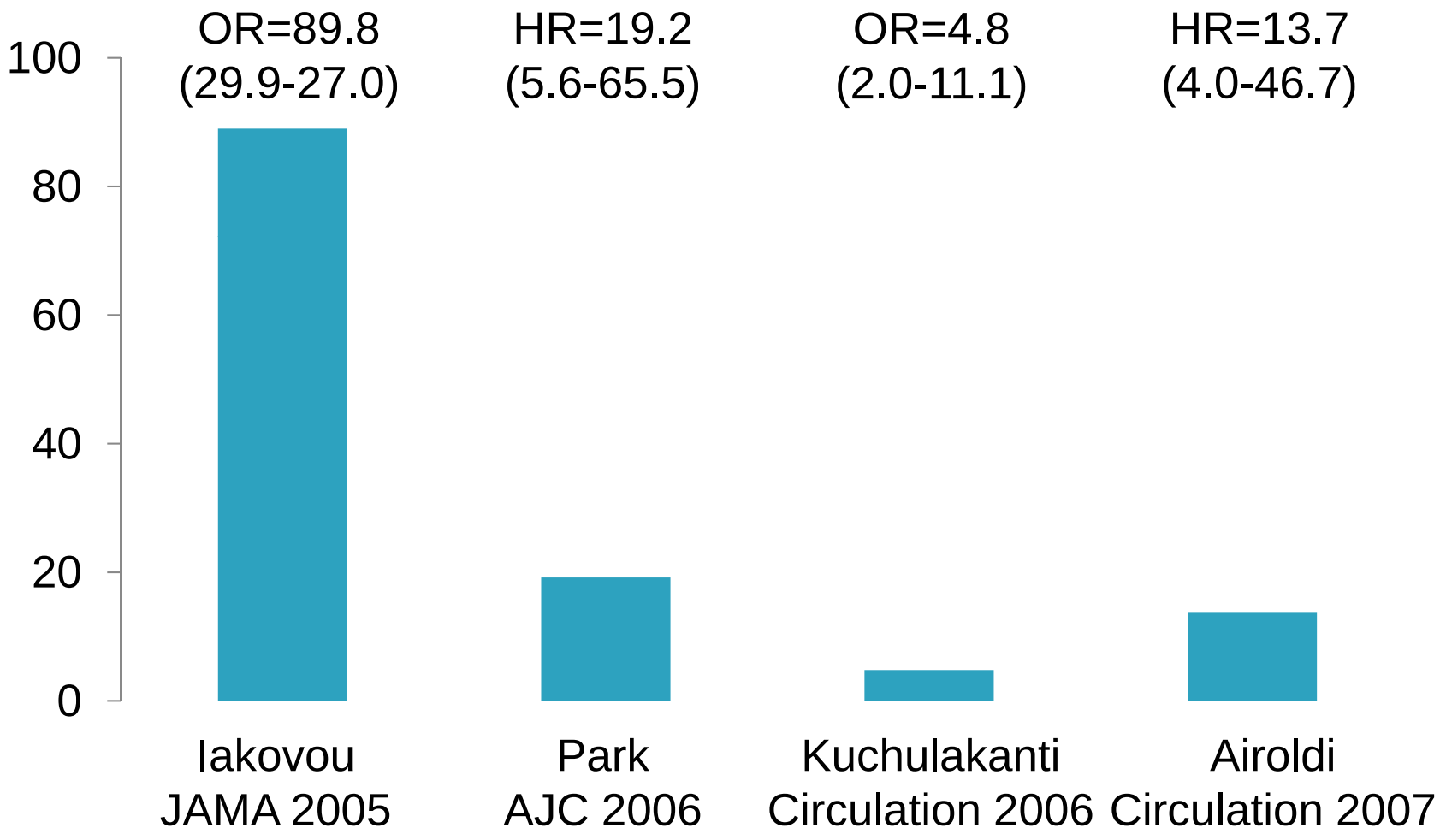
Premature Discontinuation of Antiplatelet Therapy: The most important predictor of stent thrombosis



ACC/AHA Guideline Focused Update 2011

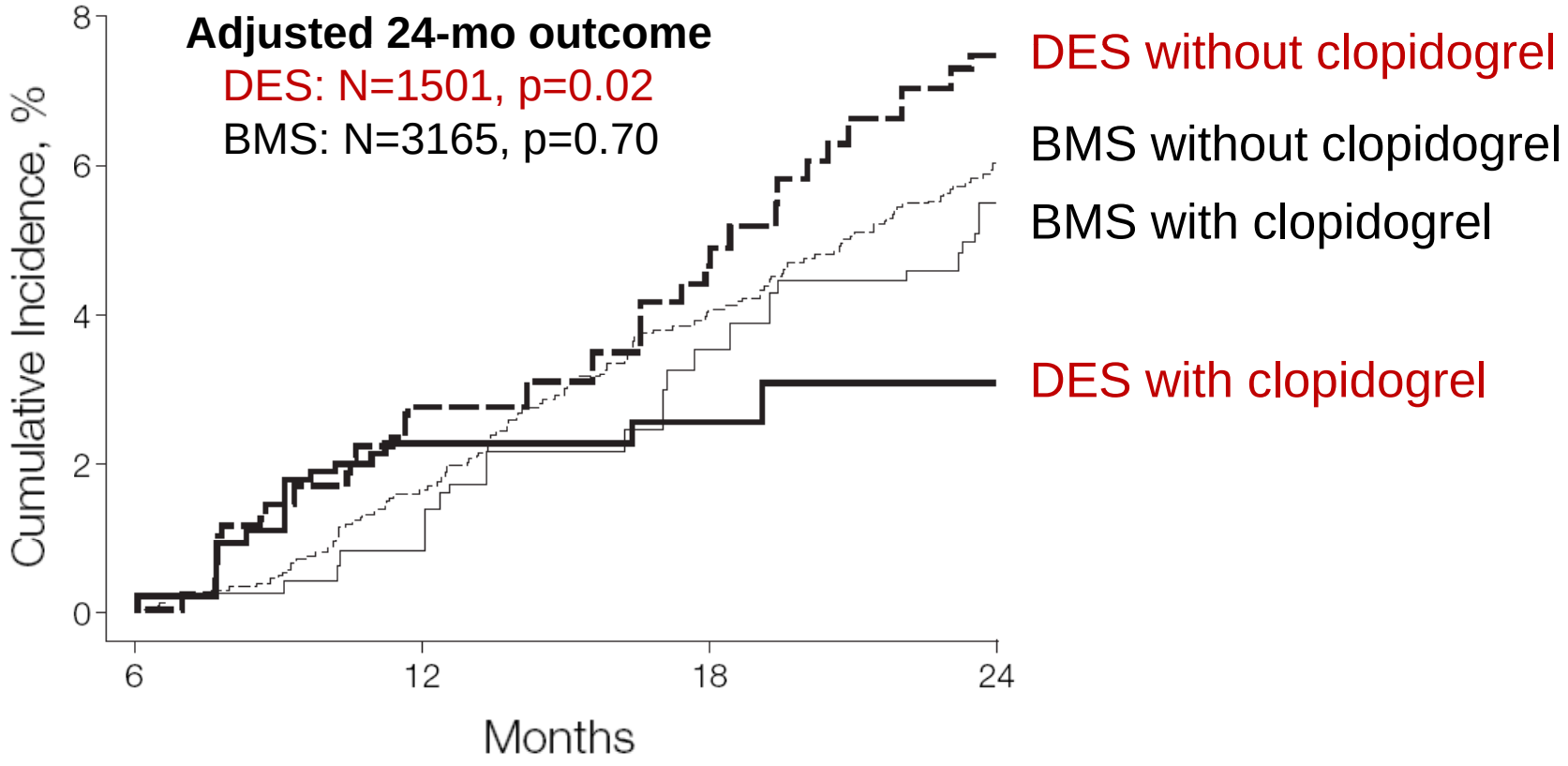
Duration of Dual Antiplatelet Therapy (DAPT) for DES

- **Class I**
  - In patients receiving a stent (BMS or DES) during **PCI for ACS**, $P2Y_{12}$ inhibitor therapy should be given **for at least 12 months**. (Level of Evidence: B)
  - In patients receiving **DES for a non-ACS indication**, clopidogrel 75 mg daily should be given for **at least 12 months if patients are not at high risk of bleeding**. (Level of Evidence: B)
- **Class IIa**
  - If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by a recommended duration of $P2Y_{12}$ inhibitor therapy after stent implantation, earlier discontinuation (e.g., 12 months) of $P2Y_{12}$ inhibitor therapy is reasonable. (Level of Evidence: C)
- **Class IIb**
  - Continuation of DAPT beyond 12 months may be considered in patients undergoing DES implantation. (Level of Evidence: C)

Class I for DES in non-ACS Patients
Ref. 212. Eisenstein EL, et al

- Single center registry (Duke database)

6-month landmark analysis for Death/MI

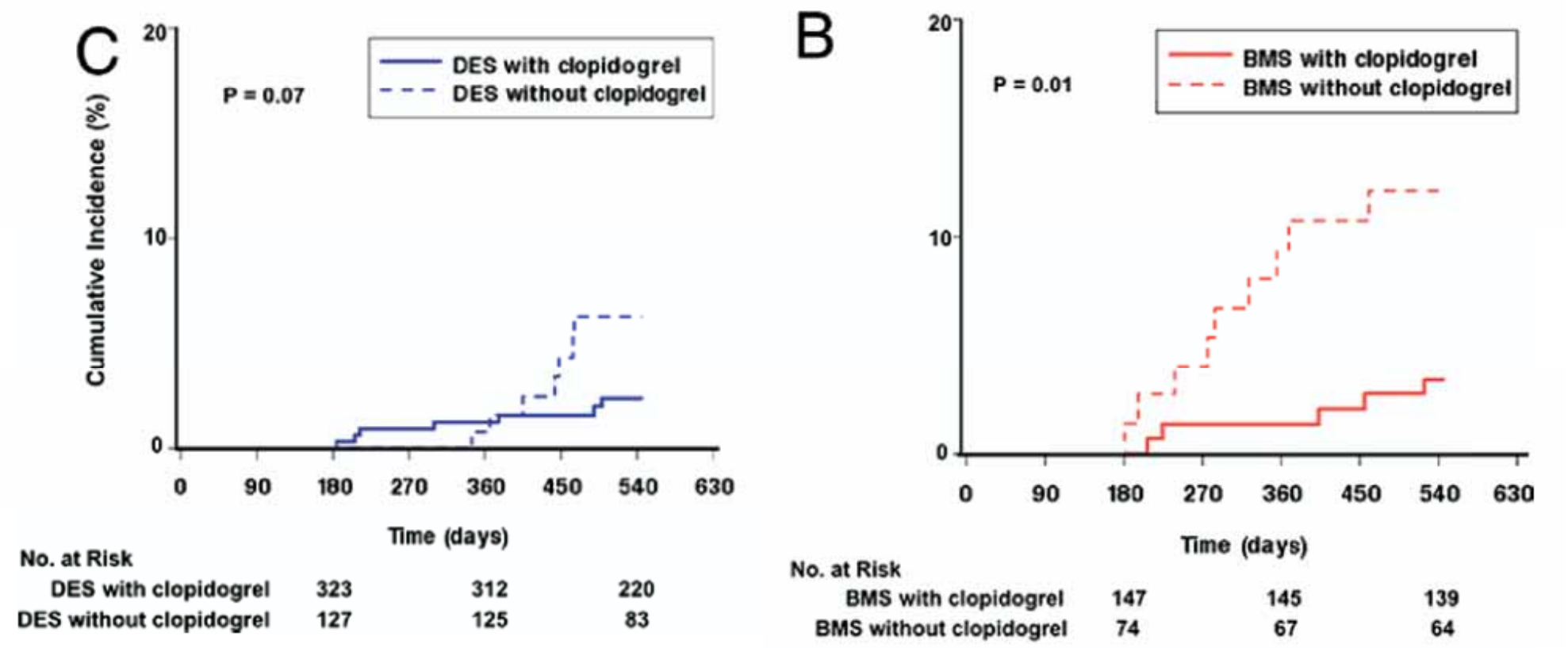


Eisenstein EL, JAMA 2007

Class I for non-ACS
Ref. 571. Brar SS, et al

- Single center registry of 749 diabetic patients

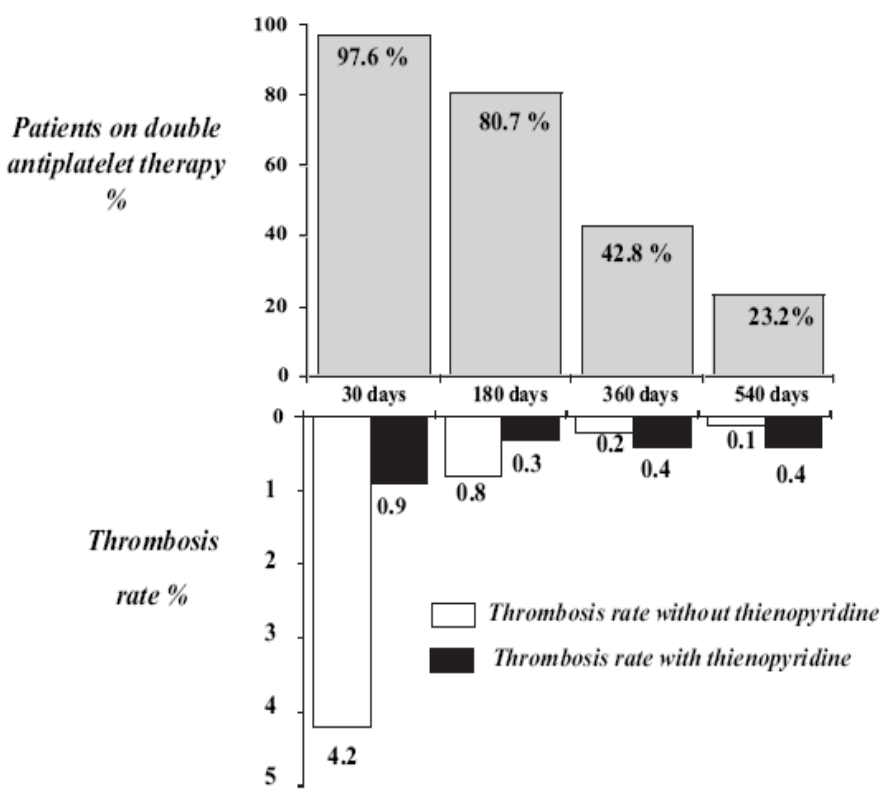
Death or Myocardial infarction

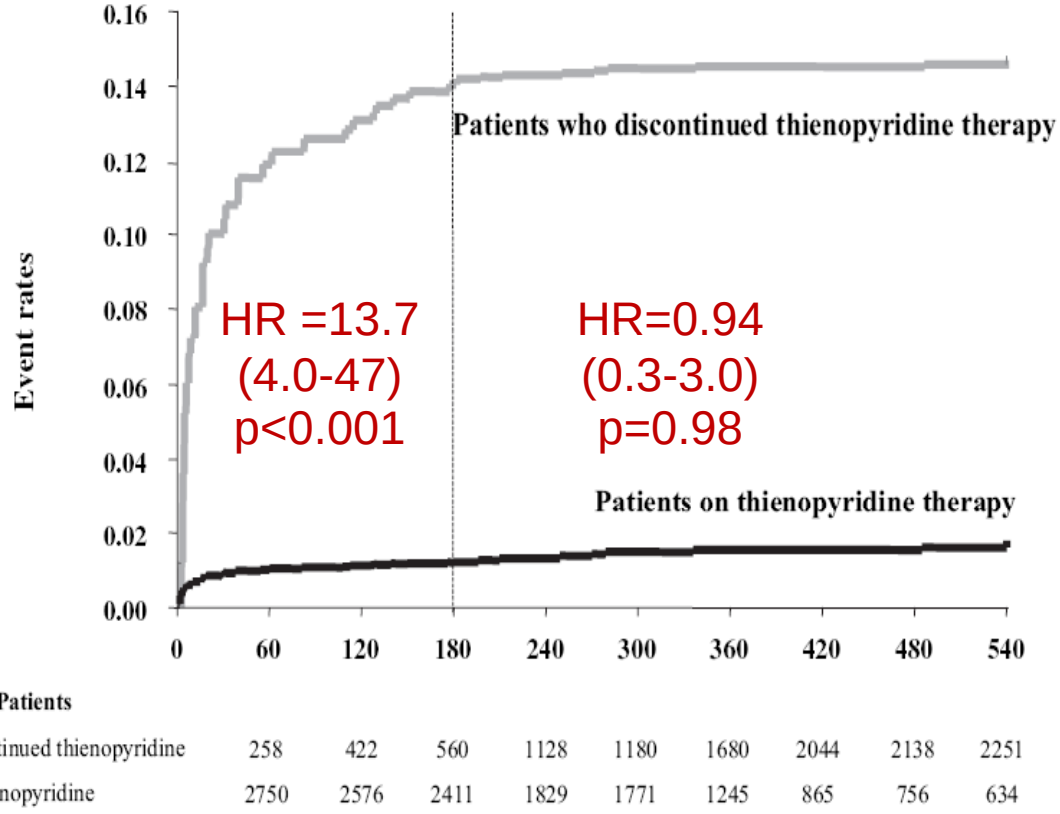


Brar SS, J Am Coll Cardiol 2008

No increase of risk by the discontinuation of clopidogrel after 6 months: Milan-Siegburg Study

- 3,021 patients treated with DES



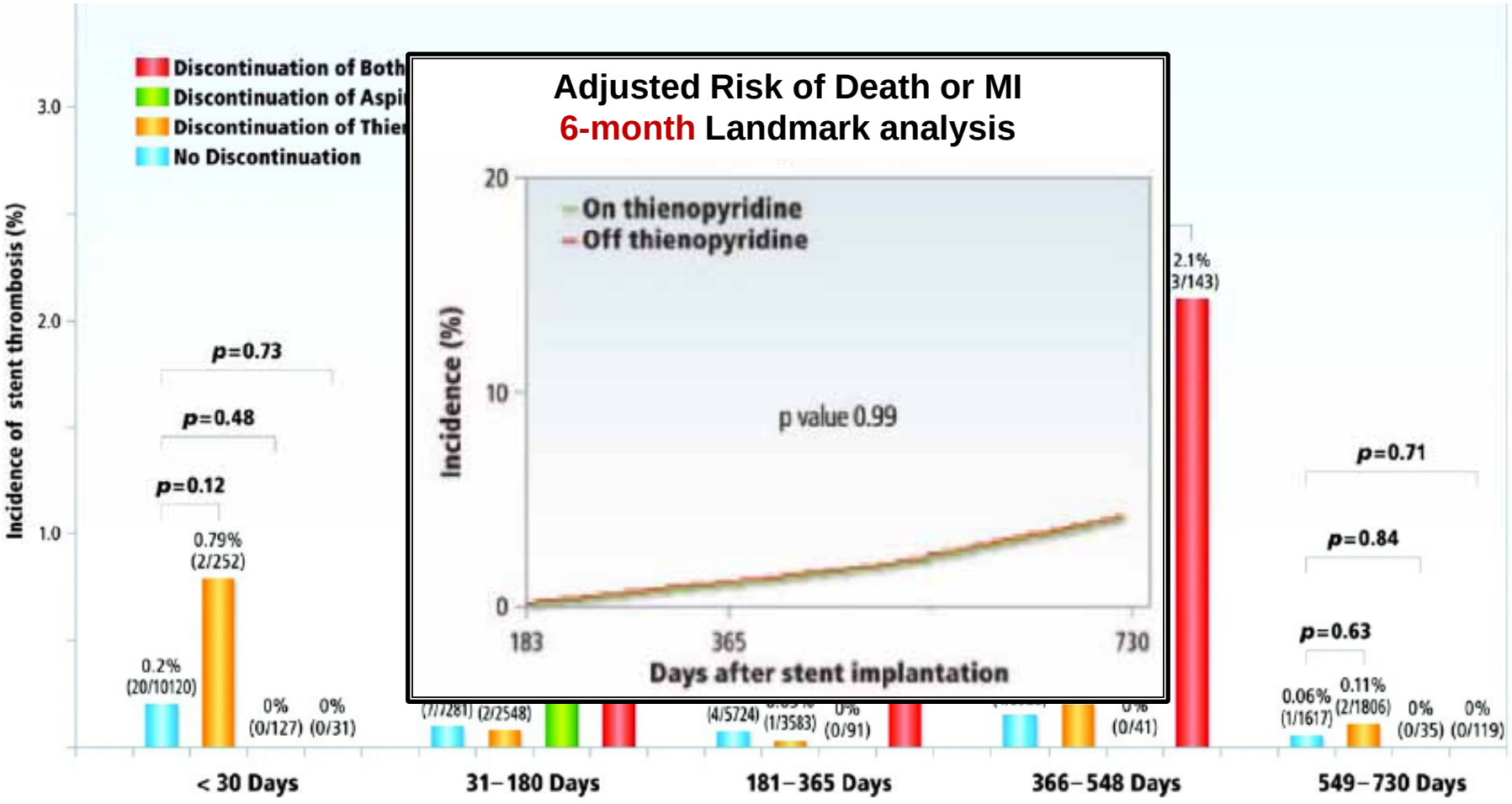


No. of Patients									
Discontinued thienopyridine	258	422	560	1128	1180	1680	2044	2138	2251
On thienopyridine	2750	2576	2411	1829	1771	1245	865	756	634

Airoldi F, Circulation 2007

No increase of risk by the discontinuation of clopidogrel after 6 months: J-Cypher Registry

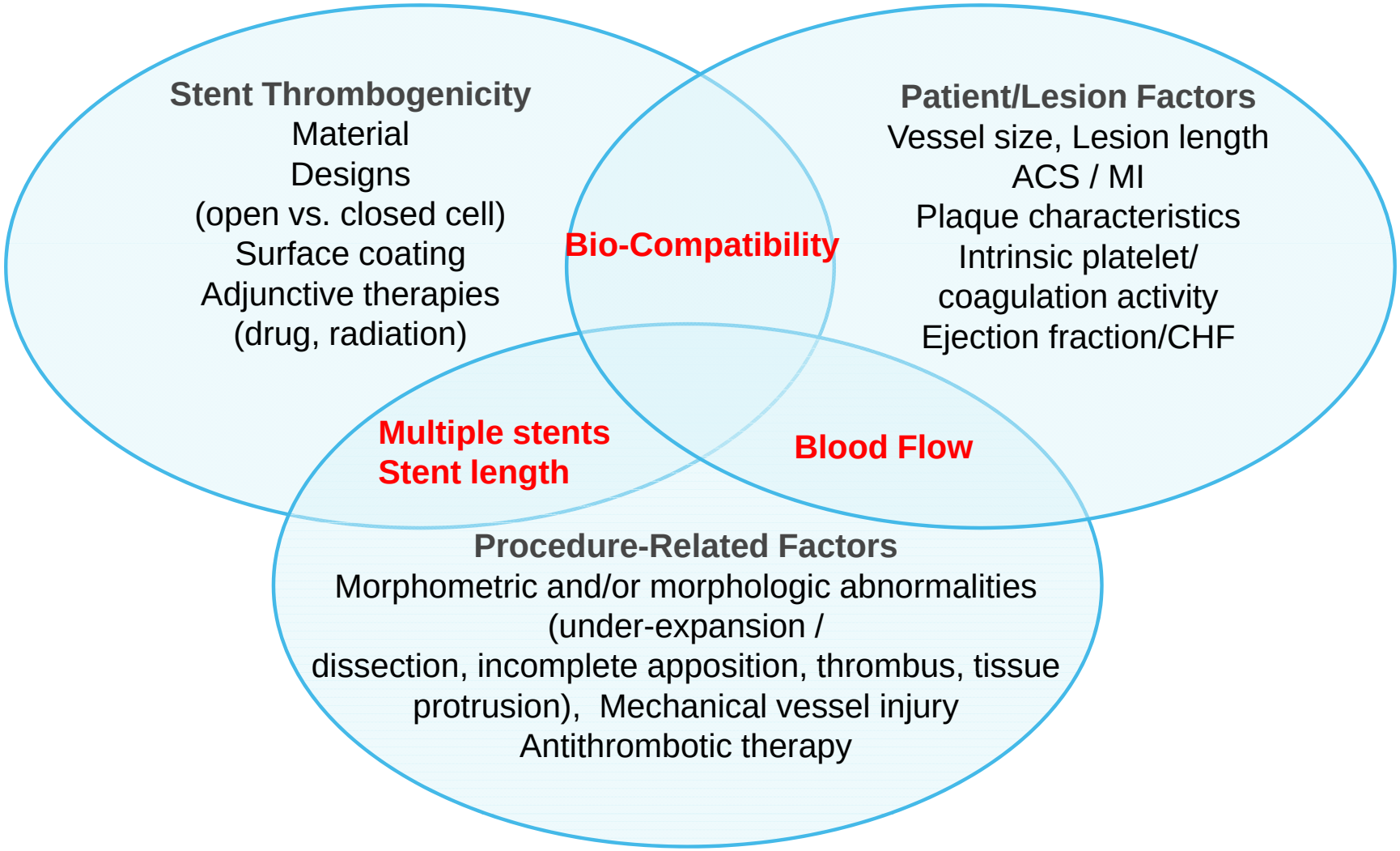
N=10,778 treated with sirolimus-eluting stent



Kimura T, Circulation 2009

Mechanisms of Stent Thrombosis

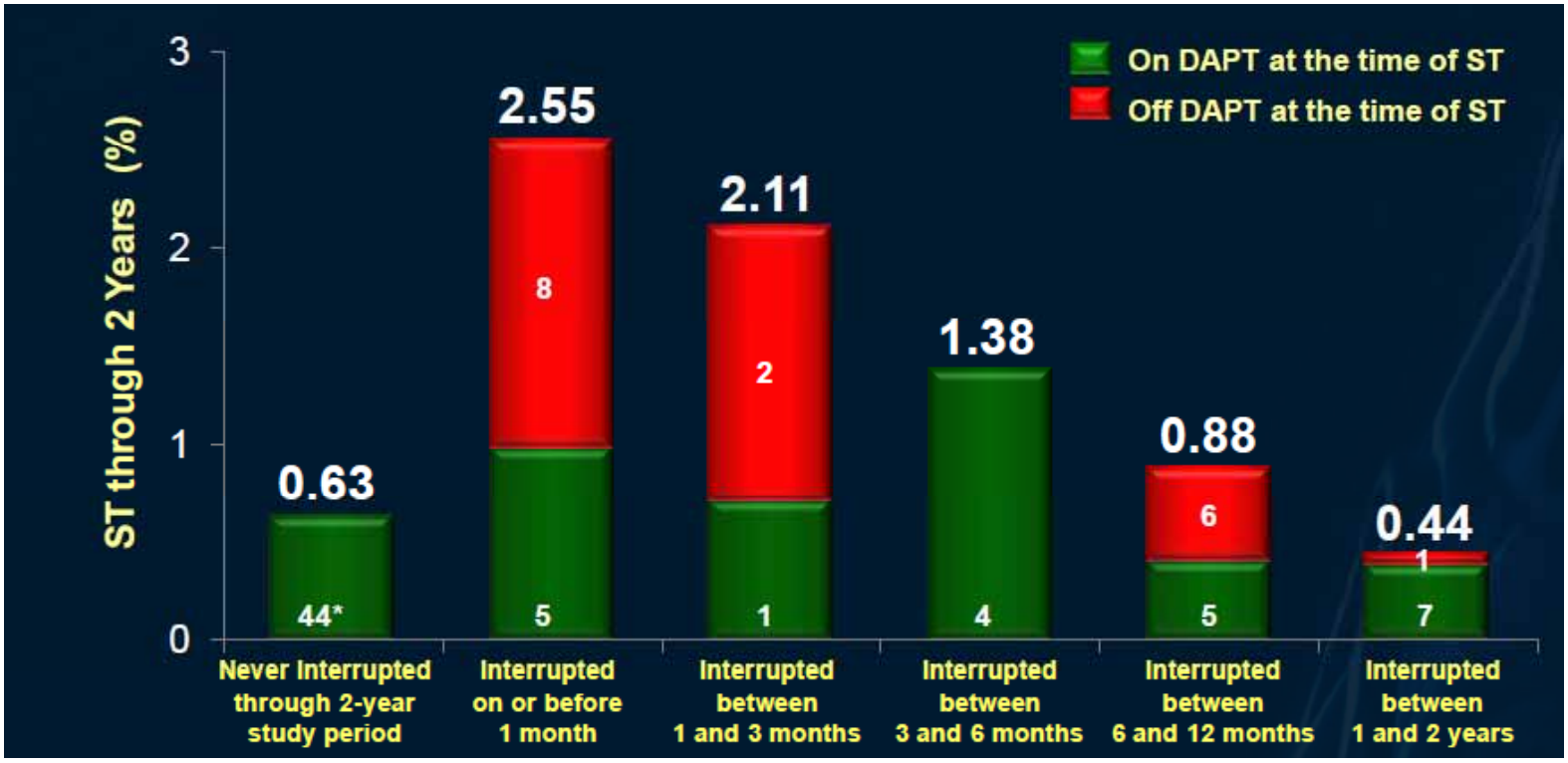
Discontinued antiplatelet therapy is not the sole risk factor for stent thrombosis



Kereiakes DK, Rev Cardiovasc Med 2004

Most of stent thrombosis occurs without prior DAPT discontinuation

- Pooled analysis of 7 EES trial (N=11,219)
- 70% of stent thrombosis episodes occur without prior DAPT discontinuation.
- DAPT interruption did not result in ST in 99.4% of patients.

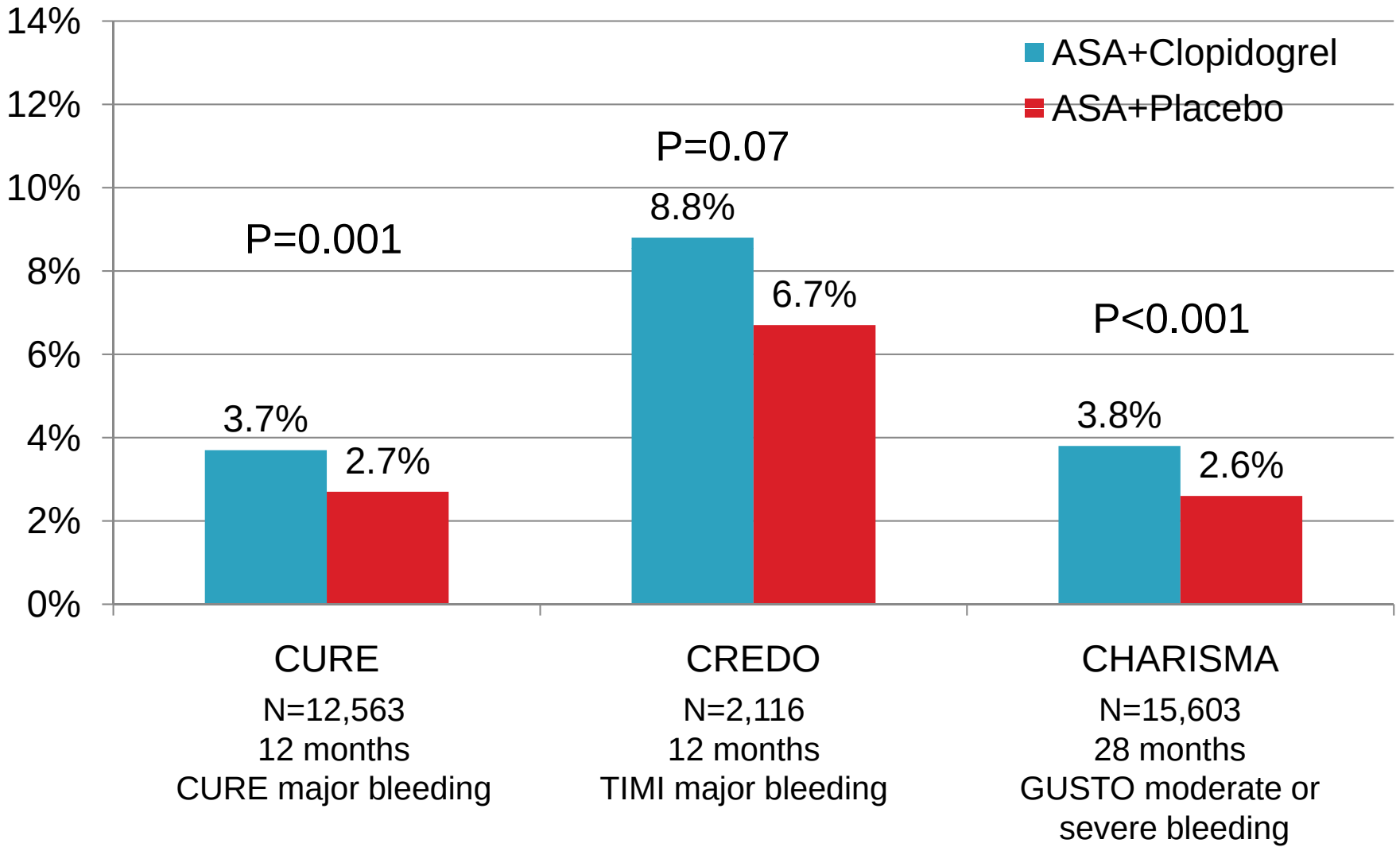


Stone G, TCT 2011

Cost, Inconvenience, and Bleeding

DAPT Increases major bleeding risk

* DAPT = dual antiplatelet therapy



Yusuf S, NEJM 2001, Steinhubl SR, JAMA 2002, Bhatt E, NEJM 2006

DAPT increases the risk of GI bleeding

Adjusted Odds Ratio of UGI Bleeding

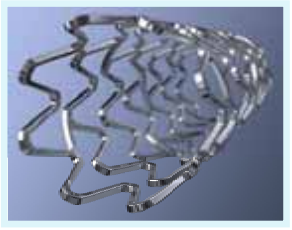
In 1443 UGIB vs. 57,720 control from Denmark

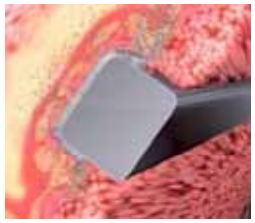
Low dose aspirin	1.8 (1.5-2.1)
Clopidogrel	1.1 (0.6-2.1)
Dipyridamole	1.9 (1.3-2.8)
Vitamin K antagonist	1.8 (1.3-2.4)
Aspirin and Clopidogrel	7.4 (3.5-15)
Aspirin and VKA	5.3 (2.9-9.5)
Aspirin and dipyridamole	2.3 (1.7-3.3)

Hallas J, BMJ 2006

Second Generation DES

	Promus Element	Xience Prime	Endeavor Resolute	Biomatrix
Company	Boston Sci	Abbott	Metronic	Biosensors
Drug	Everolimus	Everolimus	Zotarolimus	Biolimus A9
Polymer	Fluorinated	Fluorinated	BioLinx	Bioabsorbable
Strut material	PtCr	CoCr	CoNi	316L
Strut thickness	81 um	81 um	91 um	119 um
Stent design	Element	Multilink 8^2	Driver	S-stent



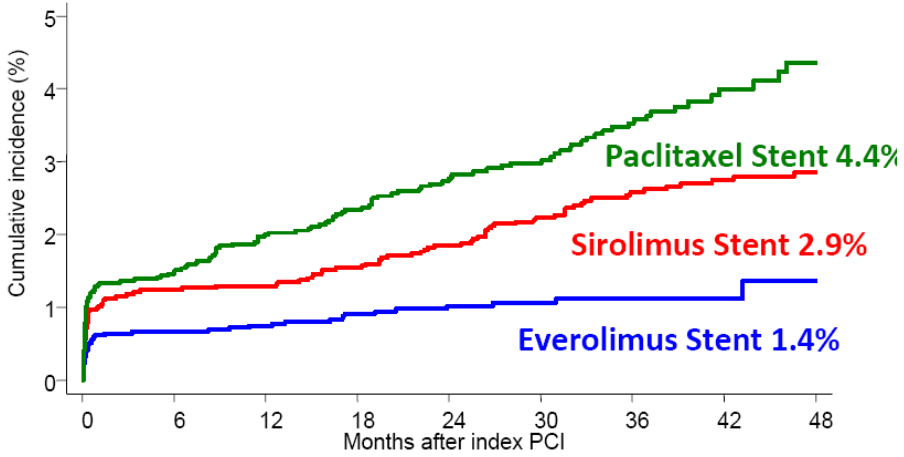



Registry: Lower ST risk in EES group

- Bern-Rotterdam Cohort Study
- Observation study in all consecutive patients
  - EES (n=4,212), SES (n=3,819), PES (n=4,308)

ARC Definite ST @ 4 Years

EES *vs.* SES *Hazard Ratio* = 0.41, 95% CI 0.27–0.62, P<0.0001*
EES *vs.* PES *Hazard Ratio* = 0.33, 95% CI 0.23-0.48, P <0.0001*

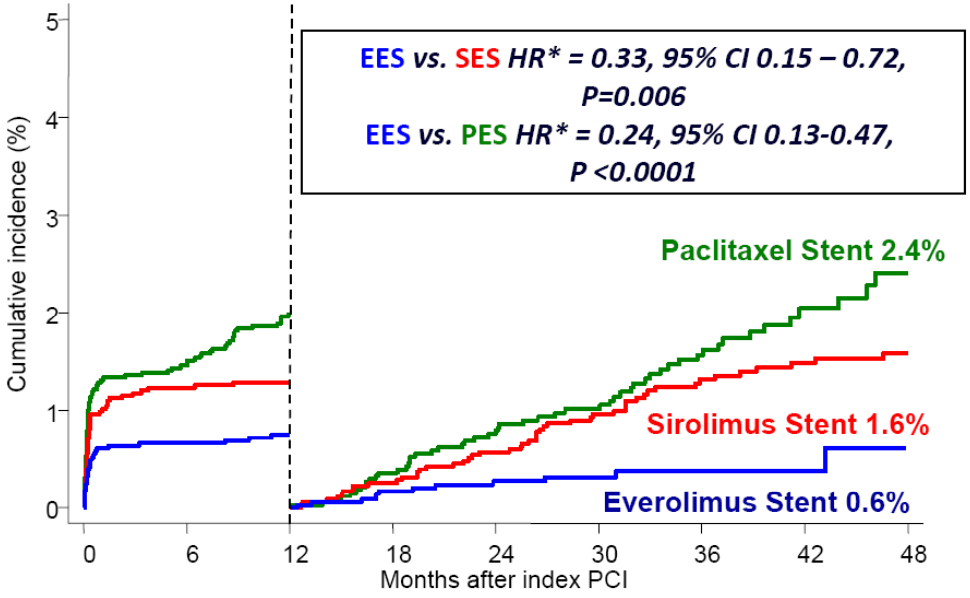


No. at risk

PES	4214	3916	3797	3176	2905	2344	1880	1077	686
SES	3784	3617	3569	3499	3404	3080	2521	2118	1734
EES	4135	3913	3793	3284	2604	1856	1041	514	208

*from Cox proportional hazards model

Very Late ST (1-4 yrs)

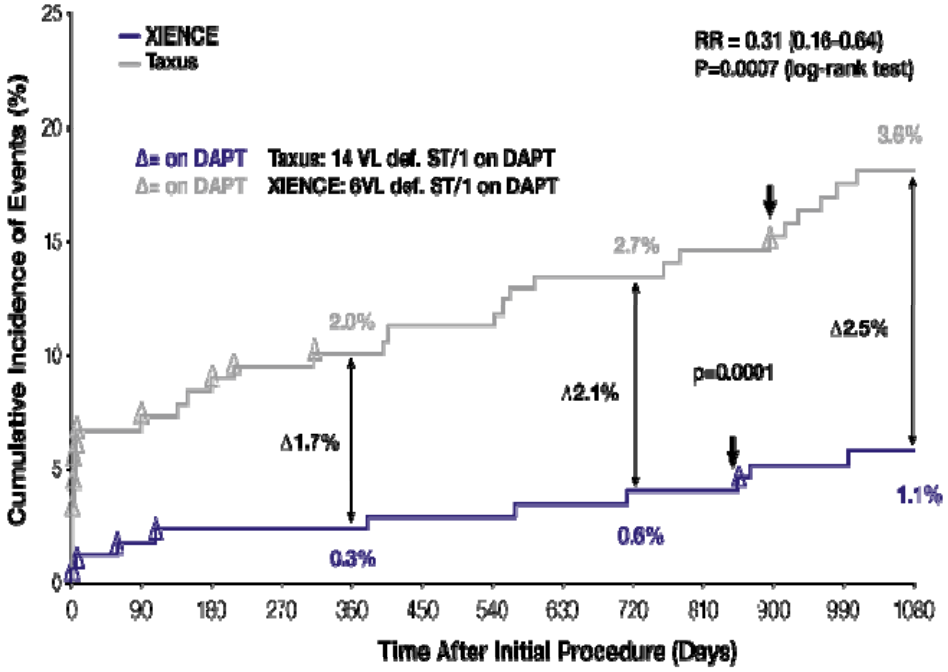


*from Cox proportional hazards model

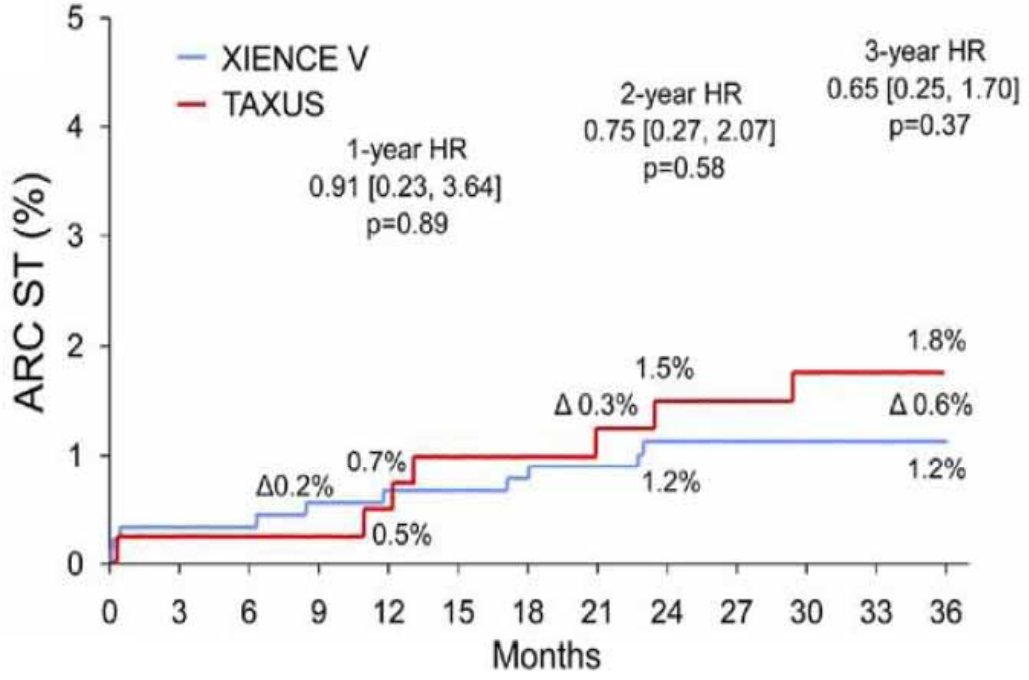
Räber L, European Society of Cardiology 2011

RCTs: Lower ST risk in EES group

COMPARE Trial 3Y FU
N=1,800



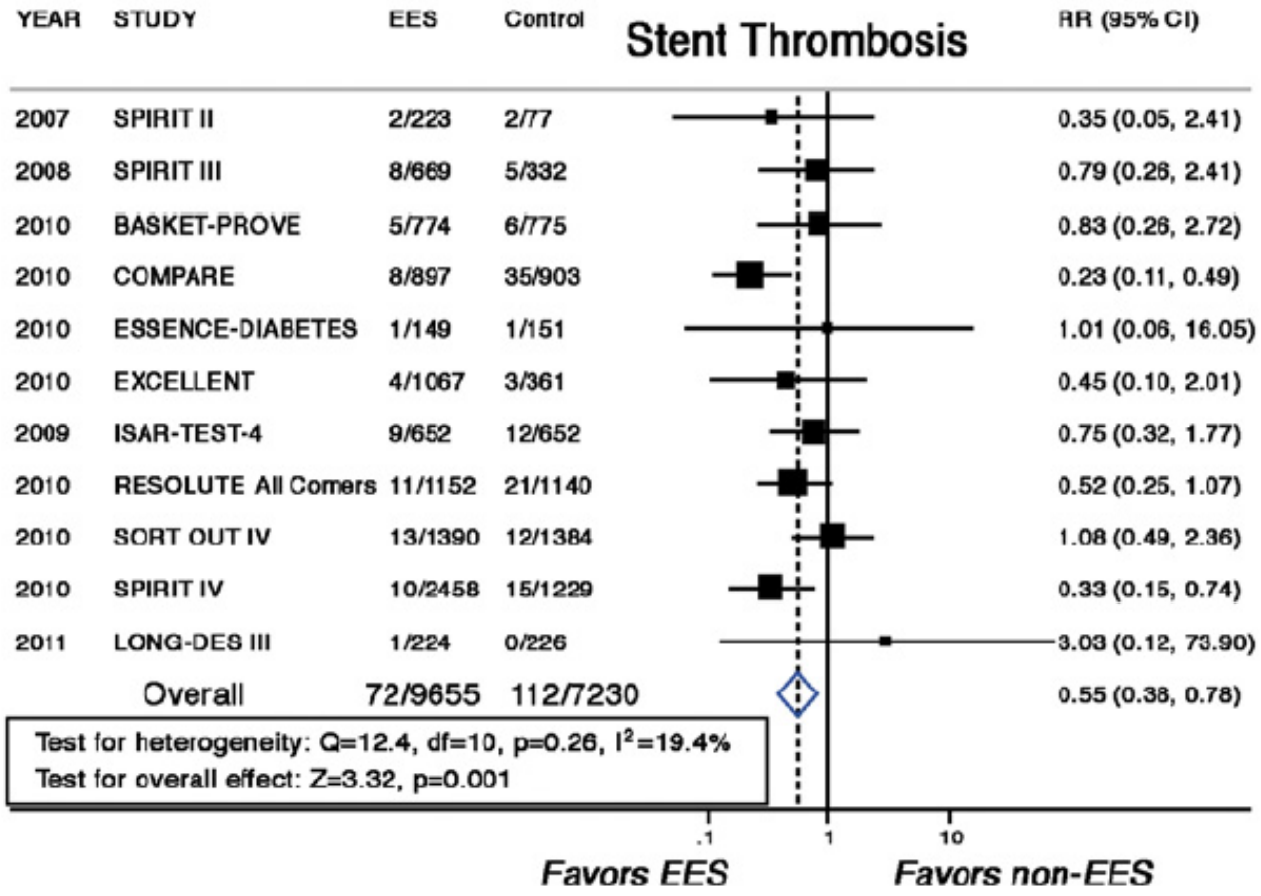
SPIRIT II/III Pooled Analysis
N=1,302



Smits P, TCT 2011, Caixeta, JACC CV Int 2010

Meta-analysis: Lower ST risk in EES group

- Meta-analysis of 17,101 patients from 13 RCTs

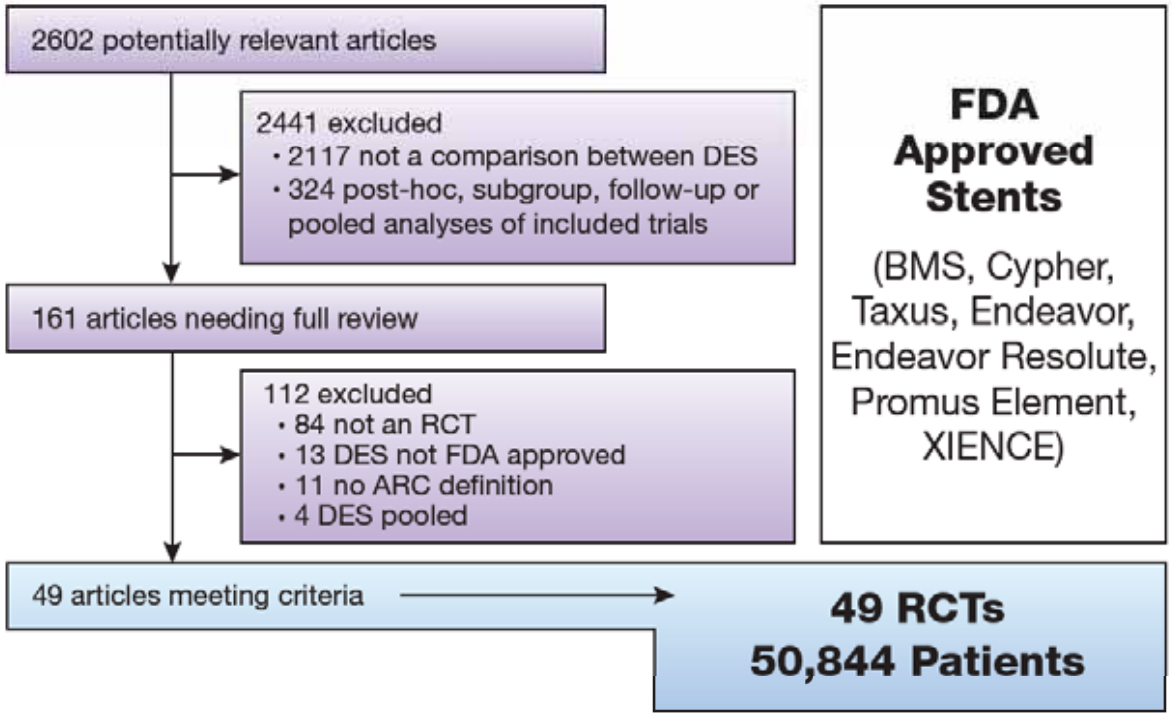


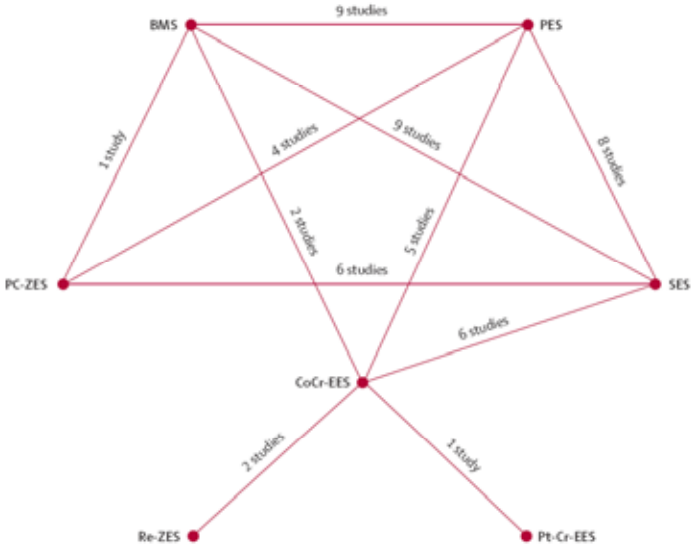
RR: 0.55 [0.38-0.78], p< 0.001

Barber U, Dangas GD, J Am Coll Cardiol 2012

Network Meta-analysis

Stent Thrombosis Network Meta-Analysis Protocol

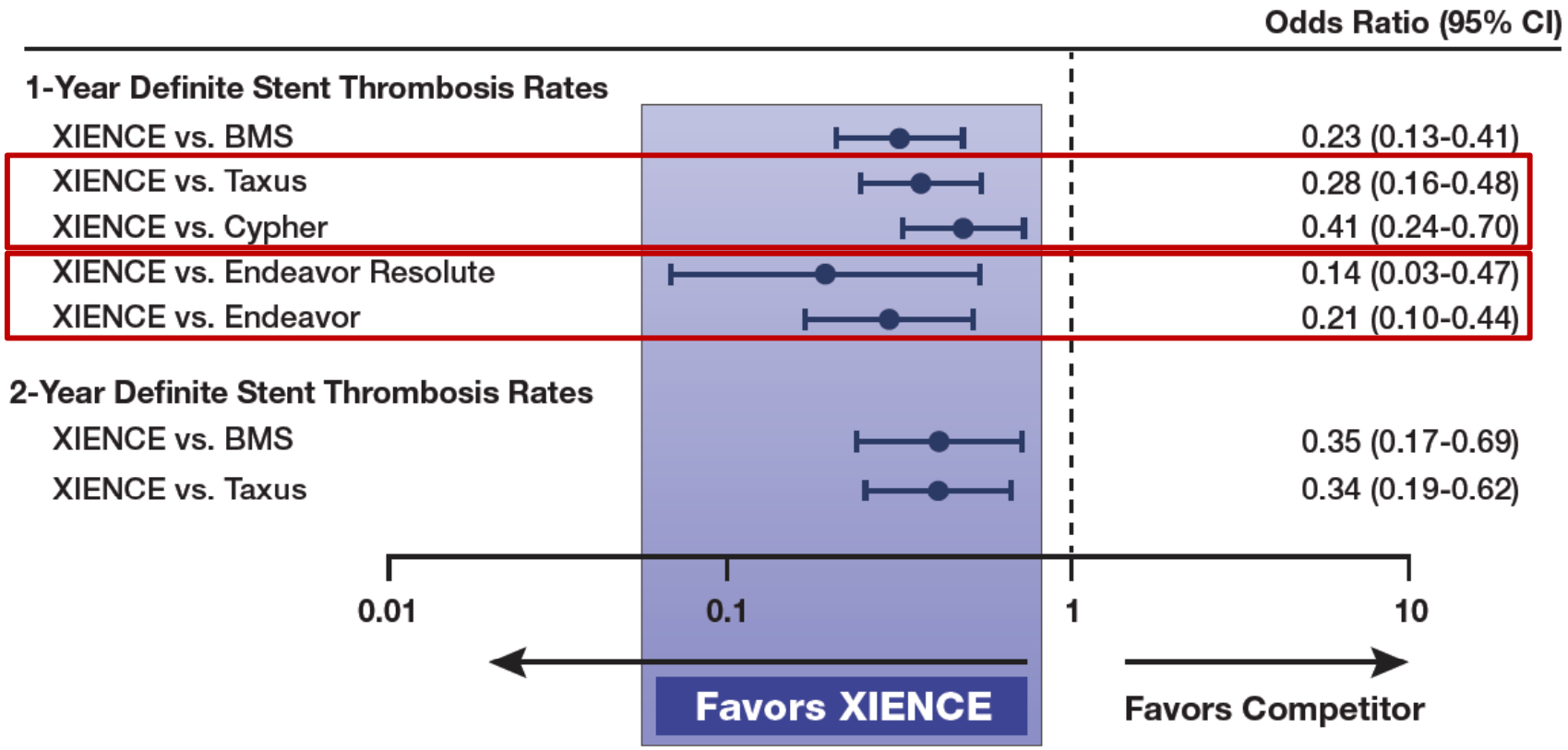




Palmerini T, Stone G, Lancet 2012;379:1393–402

Network Meta-analysis

- N=50,844, from 49 RCTs

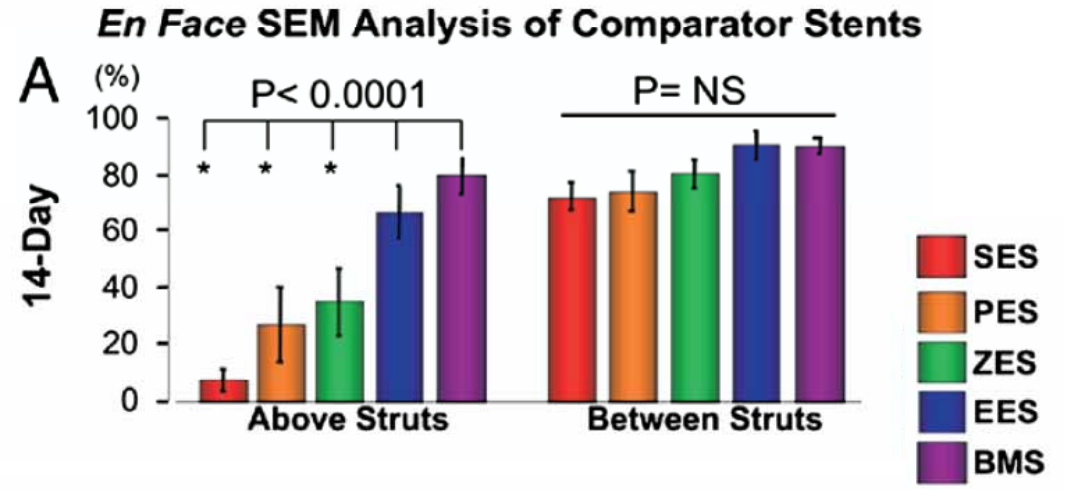


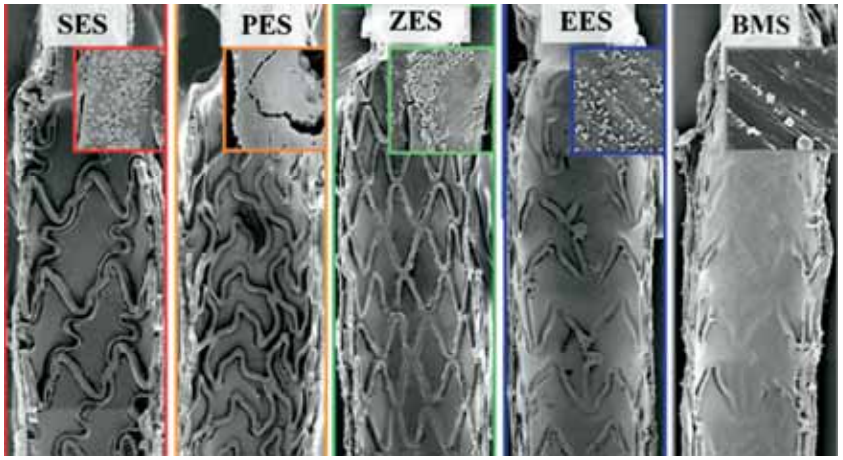
Palmerini T, Stone G, Lancet 2012;379:1393–402

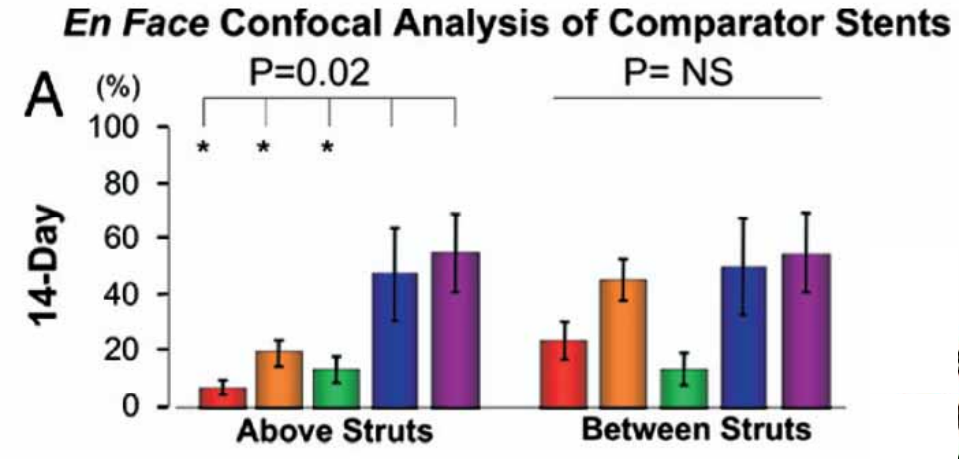
Endothelial Coverage of Stent Strut

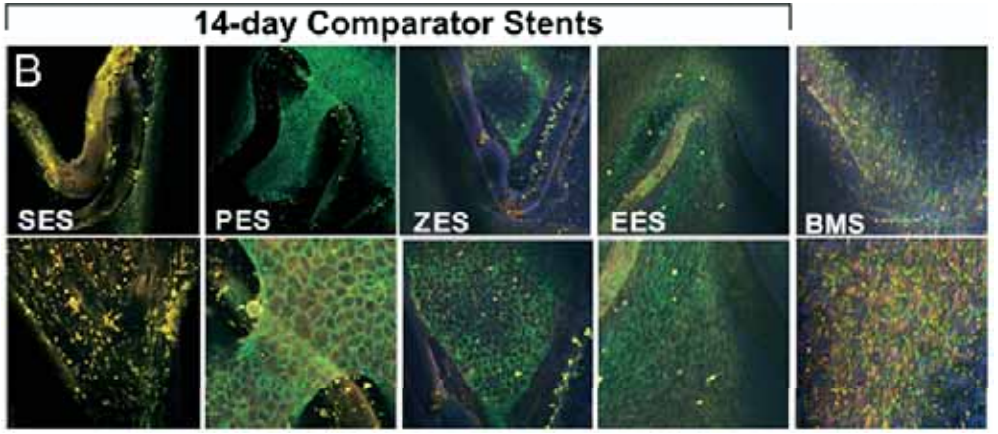
Atherosclerotic Rabbit Iliac Model

There is less endothelial cell surface coverage
in other DESs compared with EES and BMS.





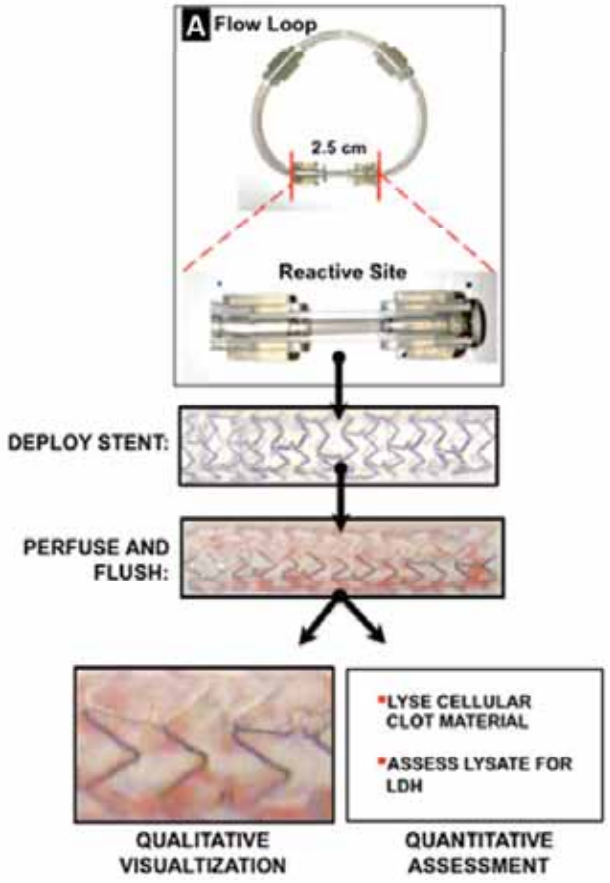


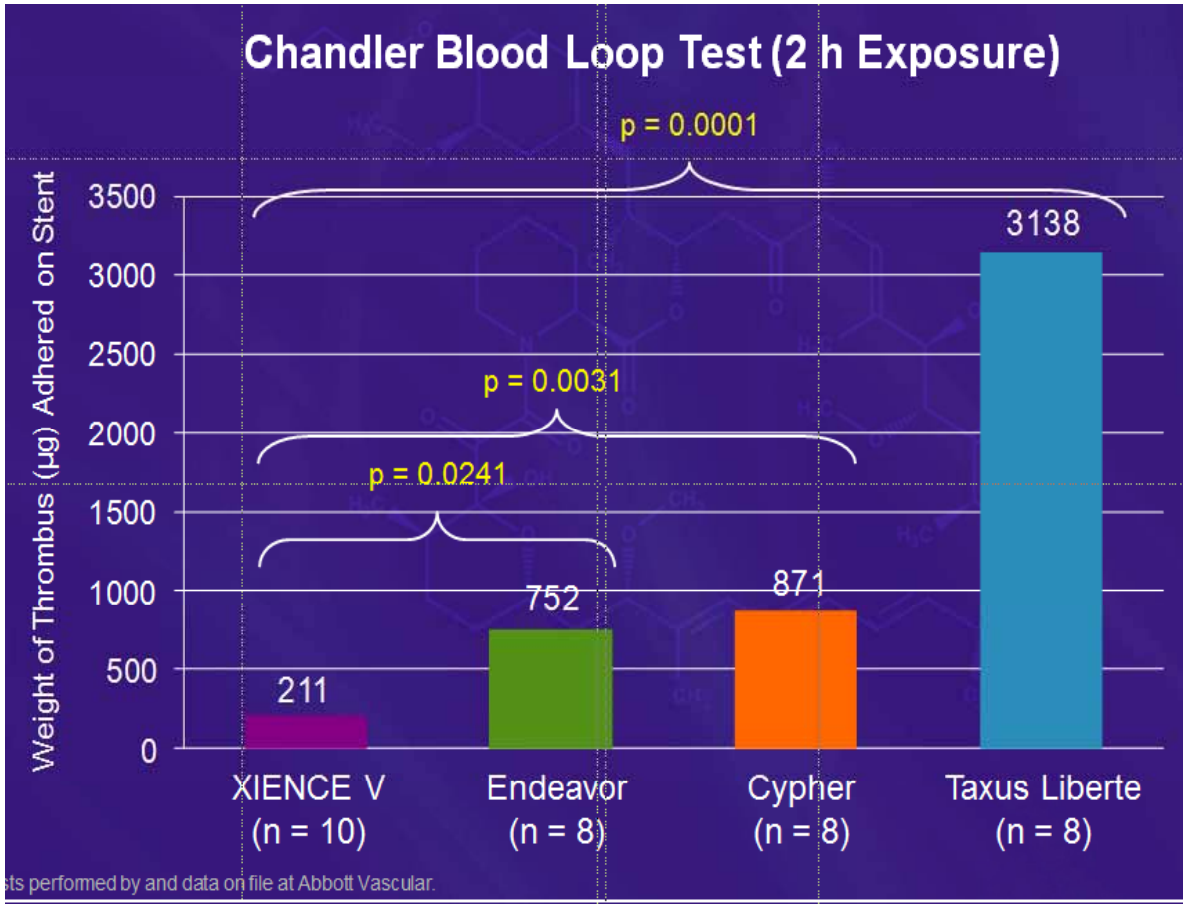


Joner M, Virmani R, JACC 2008

Why is EES better than other DESs?
Fluorinated Copolymer?

Unheparinized *Ex-Vivo* Shunt Study

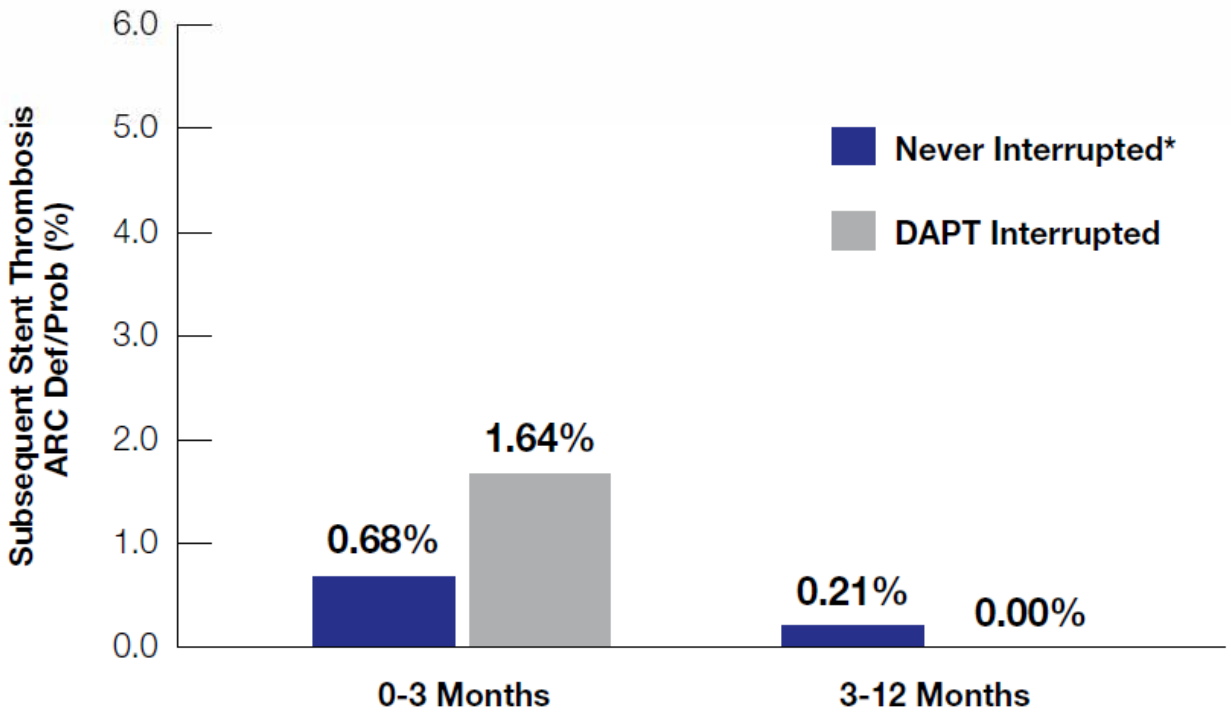




Data from Abbott Vascular

Xience Stents Receive CE Mark for 3-Month DAPT Duration?

Timing of First DAPT Interruption and Stent Thrombosis Through 12 Months



60# of pts at risk	60	11	18	0
# of events	8,996	700	8,996	919

- Pooled data of 10,615 patients from four real-world trials – XIENCE V USA (n=6,516), SPIRIT V (n=1,662), SPIRIT Women SAS (n=1,506) and XIENCE V India (n=931)
- 919 patients interrupted DAPT between 3 to 12 months
- "DAPT Interruption" includes patients who temporarily interrupted or permanently discontinued DAPT usage

From Abbott Vascular

Patient Flow and Stent Thrombosis Through 2 Years

Stone G, TCT 2011

Pooled analysis of SPIRIT II, III, IV, V, SPRIT Women, Xience V USA, XIENCE V India

13,259 total pts

2,040 pts (15.4%) without complete DAPT data (11 ST events, 0.54%)

Analysis population

11,219 pts (84.6%) with complete DAPT data through 2 years (follow-up rate 94.3%)

85 events in 83 pts (0.74%) through 2 years

45 ST events occurred in 44 pts with no DAPT interruption from day 1 through 2 yrs

45 events occurred "On" DAPT*

40 ST events occurred in 39 pts with some DAPT interruption from day 1 though 2 yrs

23 events occurred "On" DAPT

17 events occurred "Off" DAPT

►68/85 ST events (80.0%) occurred "On" DAPT

*One patient did not receive loading lose and was off DAPT at ST event (day 0) but started day 1 and never interrupted through 730 days.

SE2935904 Rev. B

Stent Thrombosis According to the Timing of First DAPT Interruption*

Stent thrombosis through the entire 2-year follow-up period:	**ST, %** No DAPT interruption in this interval except possibly after ST	**ST, %** DAPT interruption in this interval	HR [95% CI]	P Value
Between 0 and 1 mos	0.68% (N ST events = 71)	2.38% (N ST events = 12)	3.57 [1.96, 6.67]	<0.0001
Between 1 and 3 mos	0.58% (N ST events = 61)	1.85% (N ST events = 8)	3.23 [1.54, 6.67]	0.001
Between 3 and 6 mos	0.53% (N ST events = 54)	1.44% (N ST events = 9)	2.78 [1.37, 5.56]	0.003
Between 6 and 12 mos	0.50% (N ST events = 46)	0.83% (N ST events = 14)	1.64 [0.90, 3.03]	0.10
Between 12 and 24 mos	0.45% (N ST events = 32)	0.60% (N ST events = 21)	1.33 [0.76, 2.33]	0.31

Rates are Kaplan-Meier estimates

*Temporary or permanent

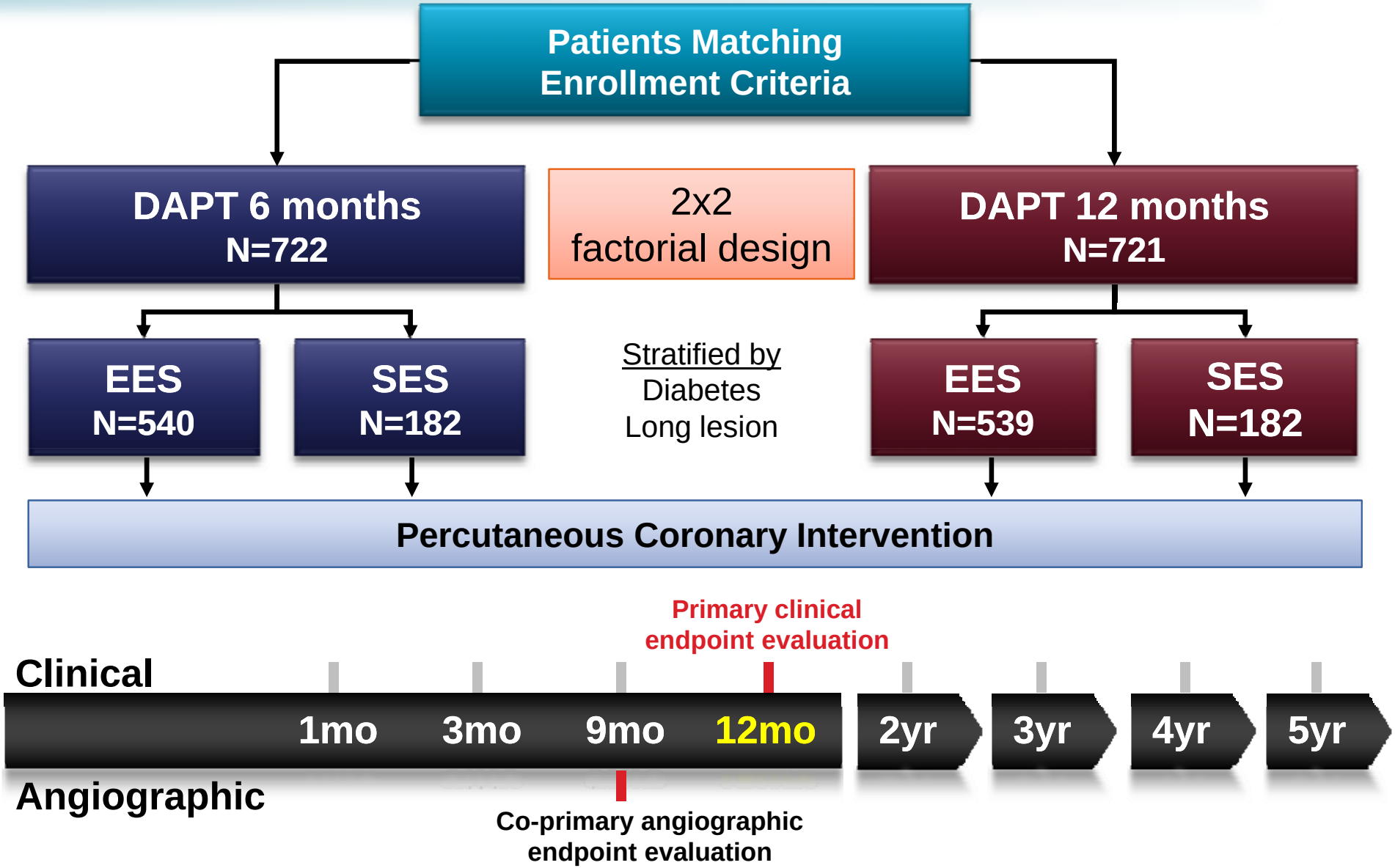
Stent Thrombosis According to the Timing of Permanent DAPT Interruption*

Stent thrombosis through the entire 2-year follow-up period:	ST, % No DAPT interruption except possibly after ST	ST, % Permanent DAPT discontinuation in this interval	HR [95% CI]	P Value
Between 0 and 1 mos	0.83% (32) (N at risk = 7,152)	4.95% (11) (N at risk = 229)	7.69 [4.00, 14.3]	<0.0001
Between 1 and 3 mos	0.83% (32) (N at risk = 7,152)	2.78% (2) (N at risk = 76)	5.00 [1.22, 20.0]	0.07
Between 3 and 6 mos	0.83% (32) (N at risk = 7,152)	0.78% (1) (N at risk = 146)	1.37 [0.19, 10.0]	0.87
Between 6 and 12 mos	0.83% (32) (N at risk = 7,152)	0.45% (4) (N at risk = 934)	0.86 [0.31, 2.38]	0.20
Between 12 and 24 mos	0.83% (32) (N at risk = 7,152)	0.16% (3) (N at risk = 1,925)	0.35 [0.11, 1.14]	0.002
Between 0 and 24 mos	0.83% (32) (N at risk = 7,152)	0.64% (21) (N at risk = 3,310)	0.77 [0.47, 1.27]	0.30

Rates are Kaplan-Meier estimates; excludes pts with temporary DAPT interruption

EXCELLENT Trial

Investigator-initiated, multi-center, open label, prospective randomized trial

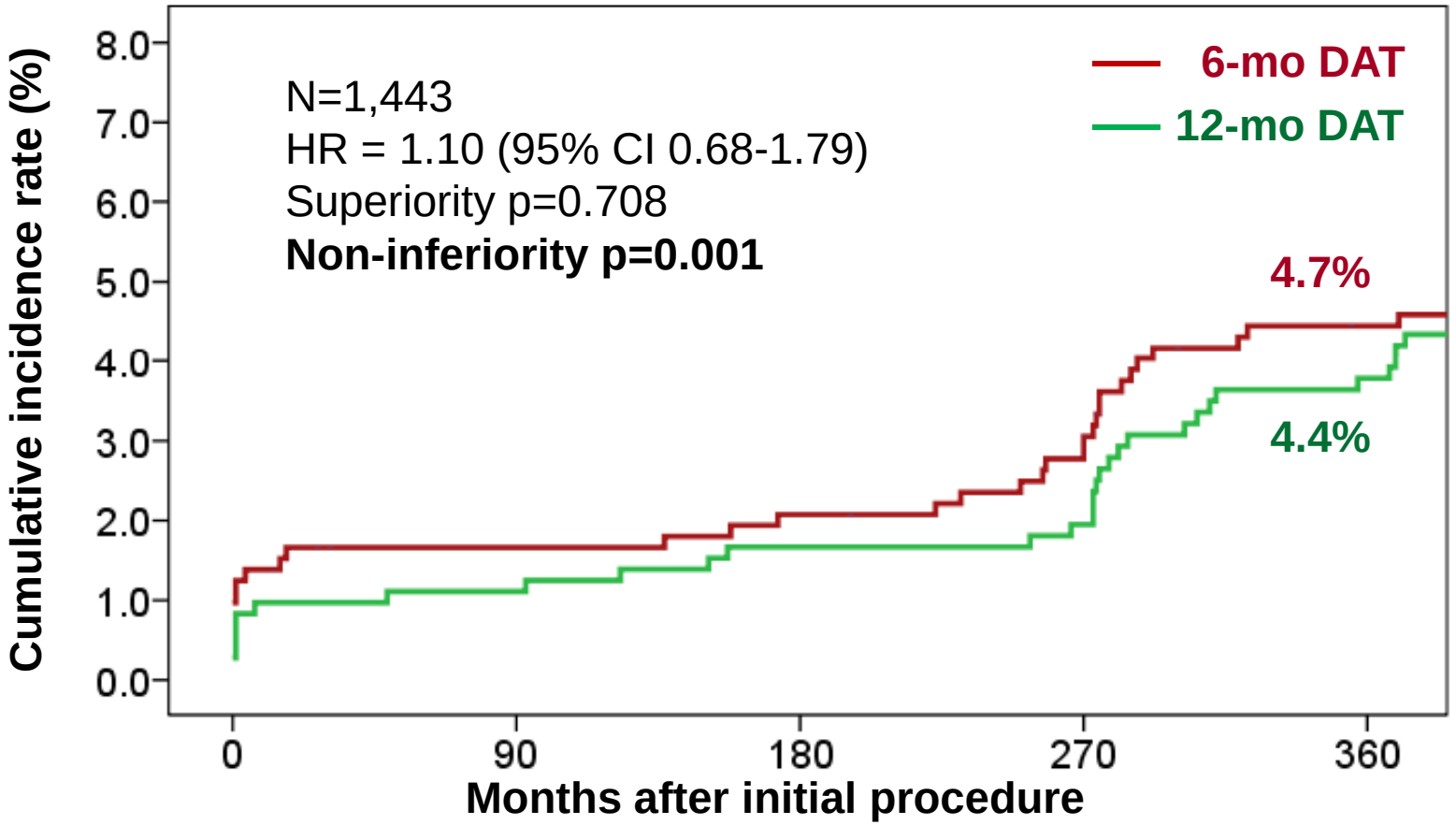


www.clinicaltrials.gov (NCT00698607).

Gwon HC, Kim HS, Circulation 2012

EXCELLENT Trial

1° EP: Target Vessel Failure (TVF)



Patient Number at Risks

6-month	722	707	704	698	682
12-month	721	710	703	698	682

* DAT = dual antiplatelet therapy

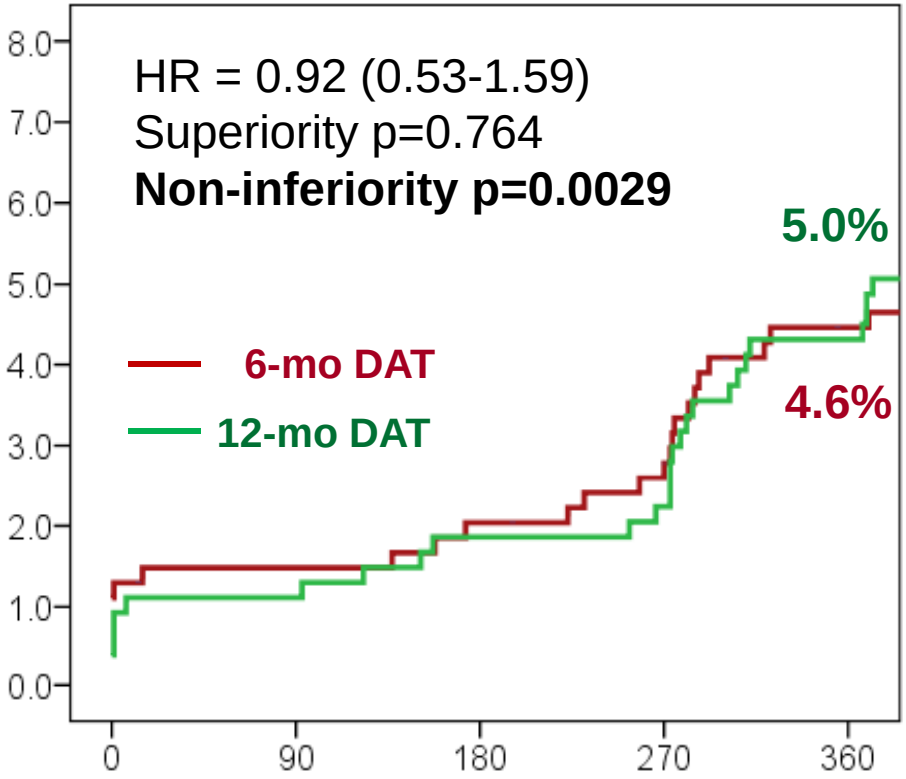
Gwon HC, Circulation 2012

EXCELLENT Trial

TVF in Stent Subgroups

(Randomized to EES vs. SES in 3:1 fashion)

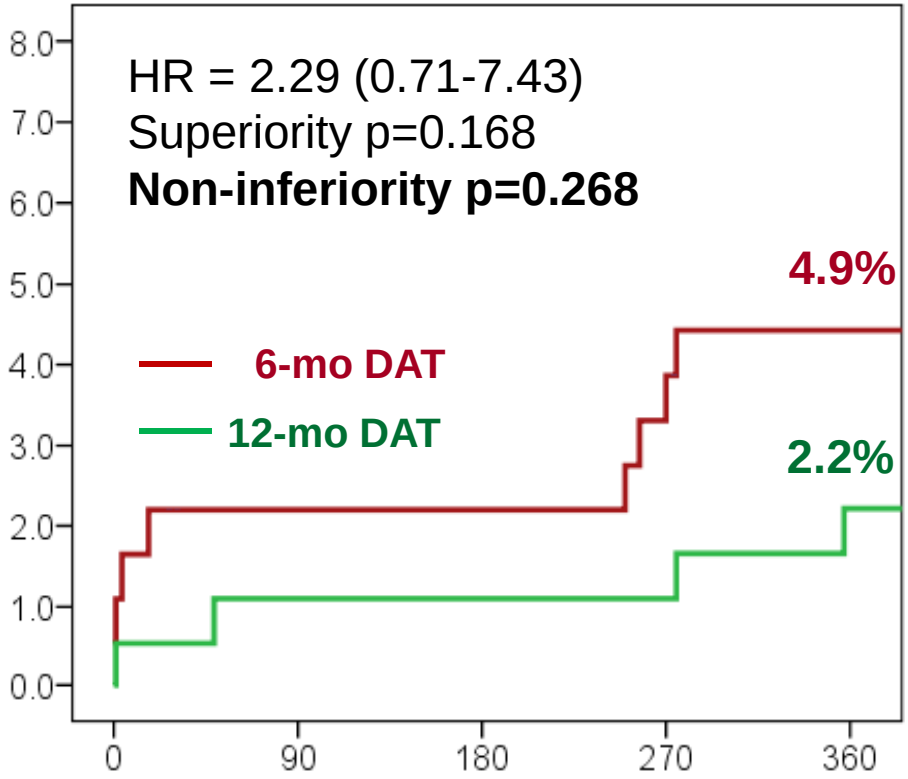
Everolimus-Eluting Stent



Patient Number at Risks

6-mo	540	531	528	524	511
12-mo	539	531	524	521	505

Sirolimus-Eluting Stent



Patient Number at Risks

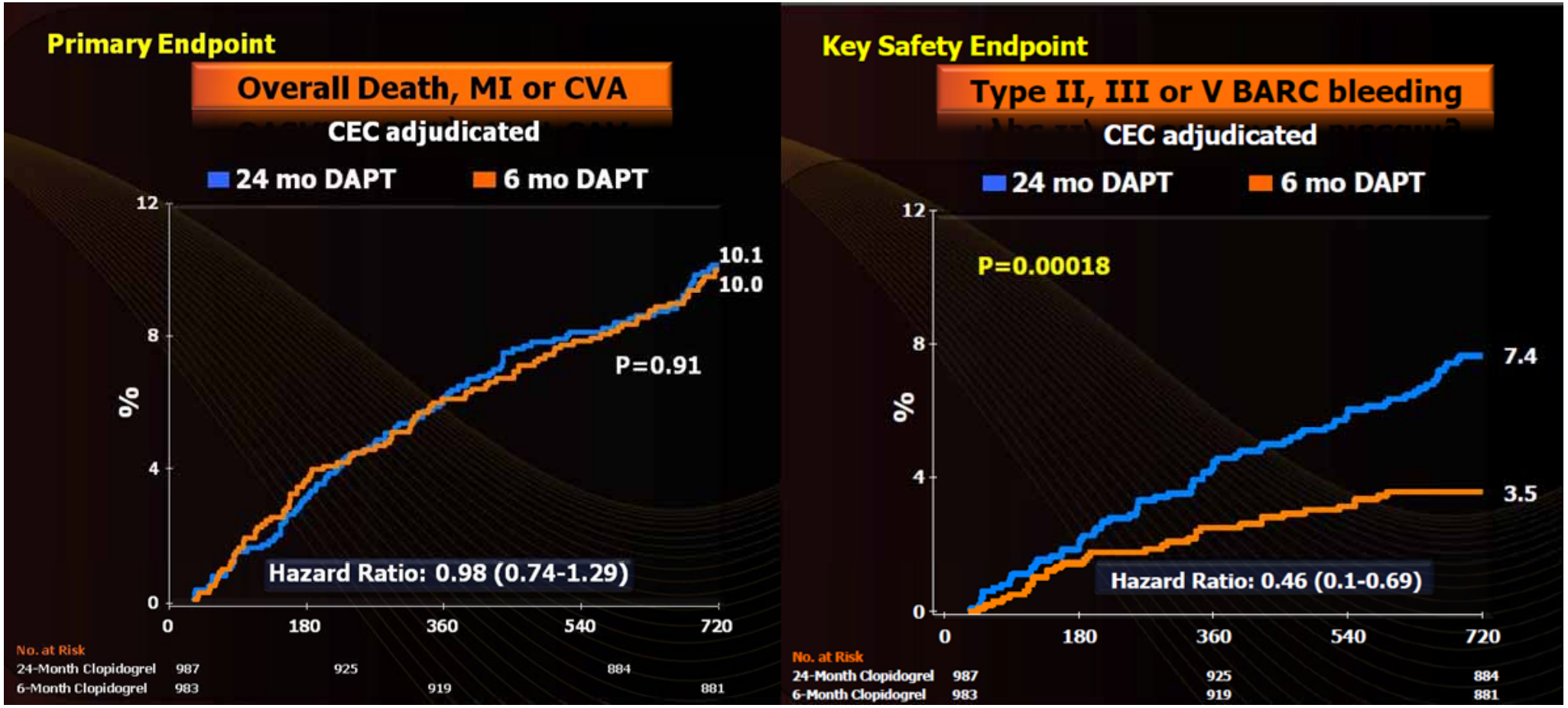
182	176	176	174	171	
182	179	179	178	176	

Gwon HC, Circulation 2012

PRODIGY Study

6-month vs. 24-month DAPT after stent implantation

- N=2,013, randomized to EES, ZES, PES, BMS



Valgimigli M, Circulation 2012

ACC/AHA Guideline Focused Update 2011

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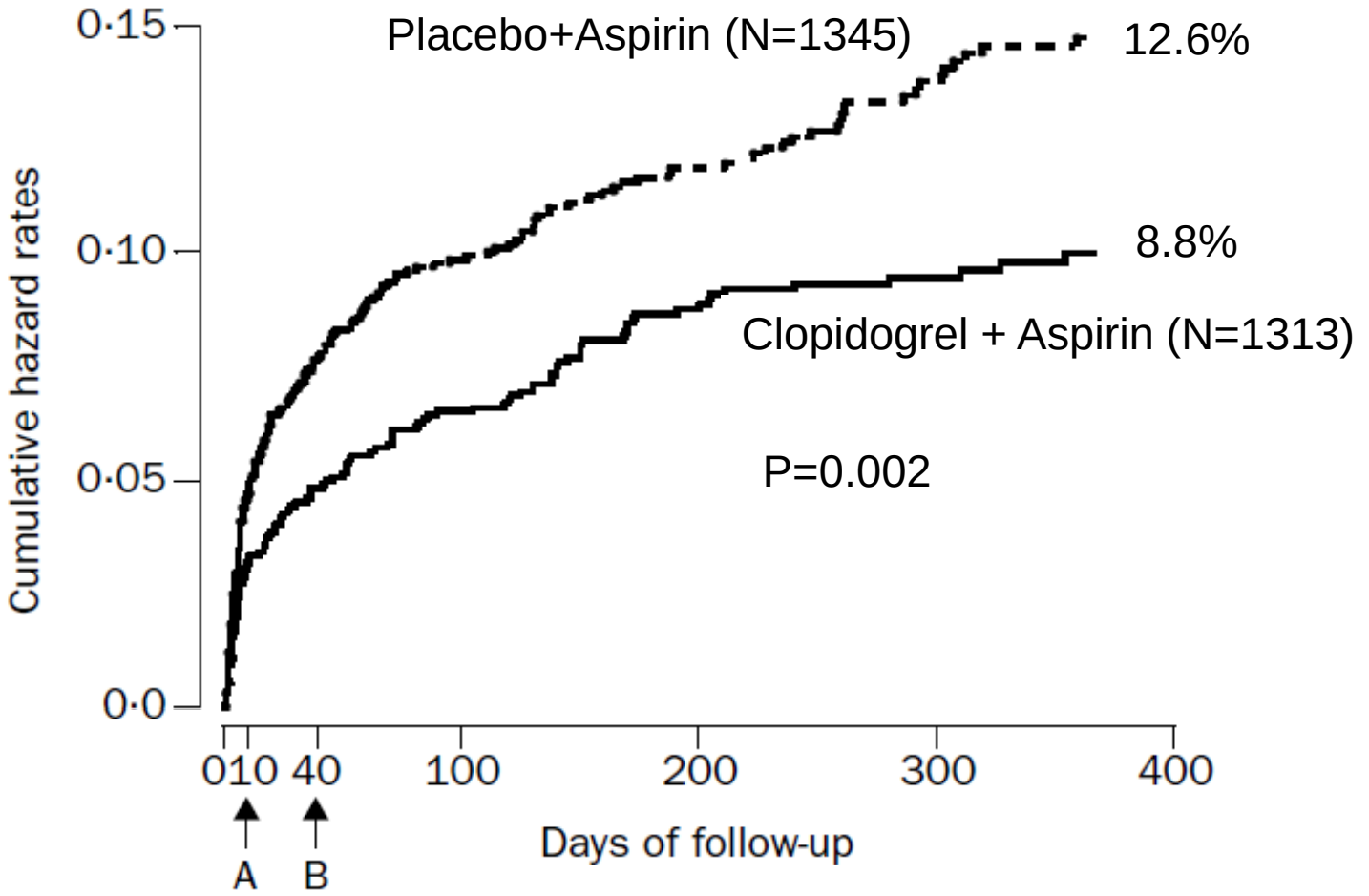
  - In patients receiving a stent (BMS or DES) during **PCI for ACS**, $P2Y_{12}$ inhibitor therapy should be given **for at least 12 months**. (Level of Evidence: B)
  - In patients receiving **DES for a non-ACS indication**, clopidogrel 75 mg daily should be given for **at least 12 months if patients are not at high risk of bleeding**. (Level of Evidence: B)
- **Class IIa**
  - If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by a recommended duration of $P2Y_{12}$ inhibitor therapy after stent implantation, earlier discontinuation (e.g., 12 months) of $P2Y_{12}$ inhibitor therapy is reasonable. (Level of Evidence: C)
- **Class IIb**
  - Continuation of DAPT beyond 12 months may be considered in patients undergoing DES implantation. (Level of Evidence: C)

Class I for ACS
Ref. 570. Mehta SR, et al.

PCI-CURE Study
CV Death or MI from Randomization



A=median time from randomization to percutaneous coronary intervention. B=30 days after median time of PCI

Mehta SR, Lancet 2001

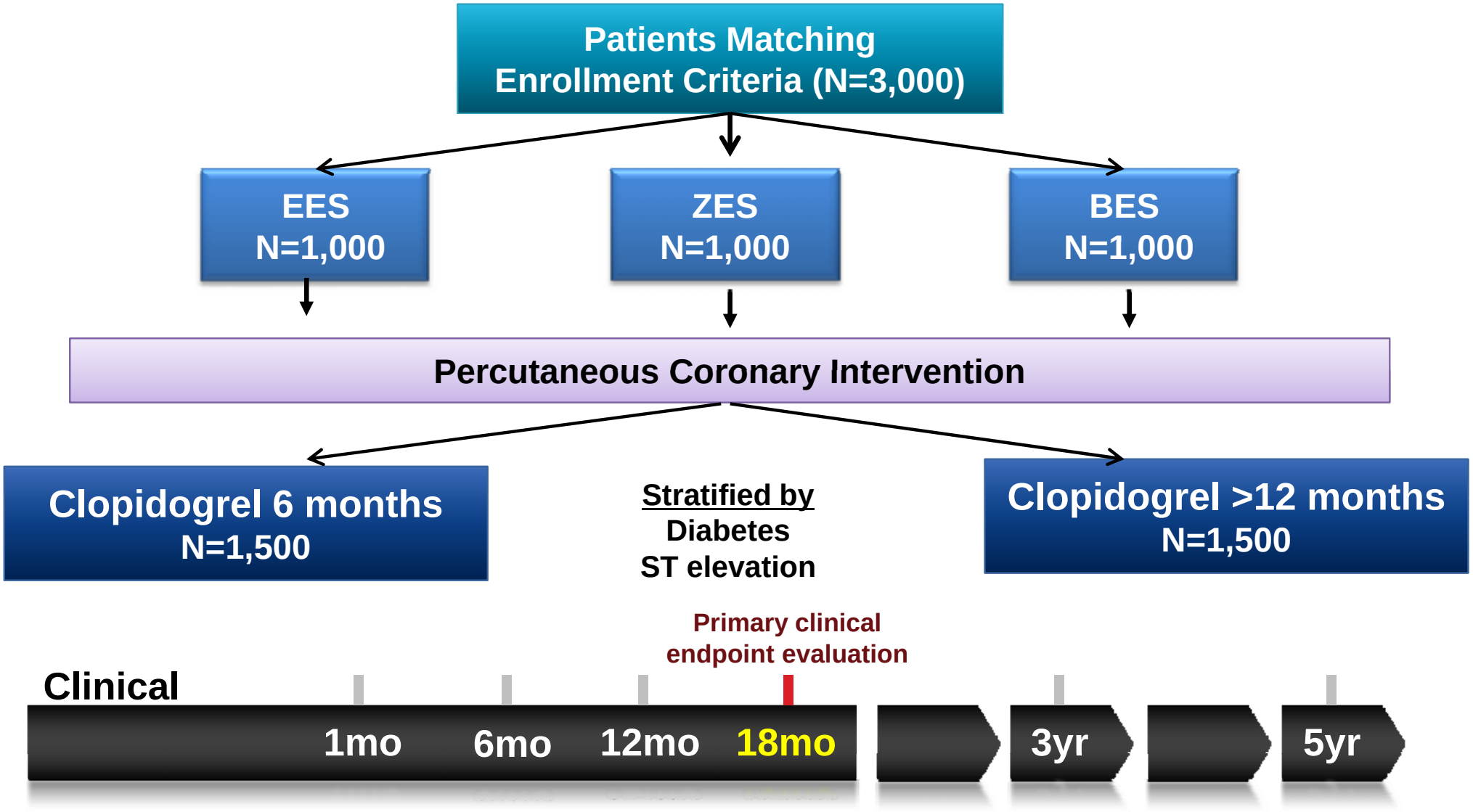
Understanding PCI-CURE Study

- A subgroup analysis of CURE study
- In clopidogrel group, 300 mg of clopidogrel was pre-loaded.
- Primary endpoint was cardiac death, MI, or urgent TVR for 30 days, not for 12 months.
- Mean follow-up duration was 8 months after randomization.
- No comparison between 6- vs. 12-month duration.
- Major benefit was observed in the first 30 days.

This was not a study for the optimal duration of clopidogrel, more likely a study for clopidogrel pre-loading.

SMART-DATE Trial

Smart Angioplasty Research Team - Safety of 6-month Duration of Dual Antiplatelet Therapy after Percutaneous Coronary Intervention in Patients with Acute Coronary Syndromes



Summary and Conclusions

- Current evidence showed that second generation DESs, particularly EES, seemed to be associated with the lower risk of stent thrombosis than first generation DESs.
- Recent data suggests that the shorter duration of DAPT might be safe, particularly after the implantation of 2nd generation DES.
- There are subgroups who are at a higher risk with a shorter duration of DAPT, which should be highlighted in the future studies.

Thank you for your attention