Resolute update
comparison with EES (Xience/Promus)

**Lessons from Korean Multicenter Registries
(HOST-EXCELLENT & -RESOLUTE)
&
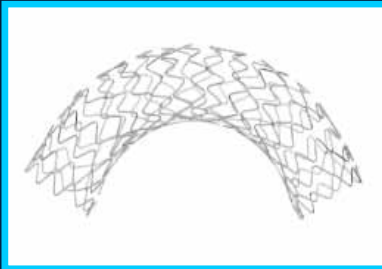Two RCT's (Resolute AC & TWENTE)**

Hyo-Soo Kim, MD/PhD/FAHA
Cardiovascular Center
Seoul National University Hospital (SNUH)

Evolution from Endeavor™ to Resolute™
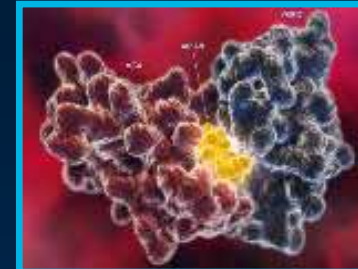
SIMILAR

Cobalt Alloy Stent (Driver™ / Integrity™)

Stent Delivery System (Sprint™ / MicroTrac™)

IDENTICAL

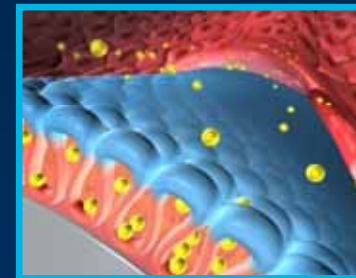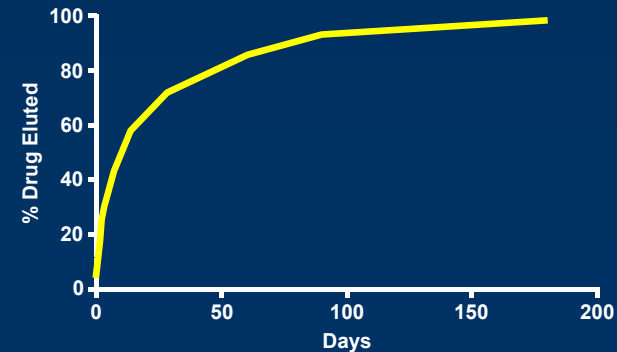**Zotarolimus Drug**

DIFFERENT

POLYMER

Endeavor DES: PC Polymer

Resolute DES: BioLinx™ Polymer

DRUG ELUTION

% Drug Eluted — Time (Days): 0, 50, 100, 150, 200

% Drug Eluted: 0, 20, 40, 60, 80, 100 — Days: 0, 50, 100, 150, 200
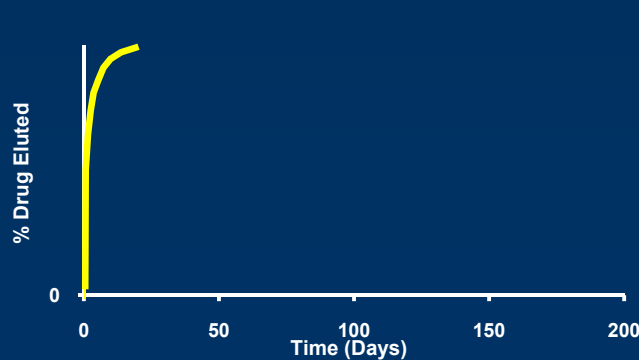
Contemporary Newest DES
Resolute (ZES) vs Xience/Promus (EES)

	Resolute™	Xience V™/Promus™
Strut Design	Modular, Round, Edgeless	Laser Cut, Rectangular
Stent Material	Cobalt Alloy	Cobalt Alloy
Strut Thickness	91 µm	81 µm
Cell Area (3.5 x 18 mm)	1.0mm²	3.7mm²
Nominal pressure	All diameters: 9 atm	2.5 – 2.75 mm: 8 atm / 3.0 – 4.0 mm: 9 atm
Polymer	BioLinx™ Polymer *Hydrophilic*	Fluoropolymer *Hydrophobic*
Polymer Thickness	5.6 µm	7.8 µm
Drug	Zotarolimus *Complete elution by 180 days*	Everolimus *Complete elution by 120 days*
Drug Density	1.6 µg/mm²	1.0 µg/mm²
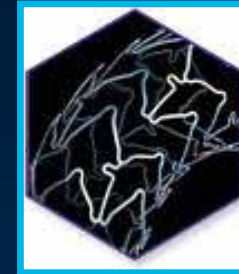
Comparison of ZES & EES

- **Two Randomized Trials**
  - **(Resolute AC & TWENTE)**

- **Korean Multicenter Registries**
  - **(HOST-EXCELLENT & -RESOLUTE)**

RESOLUTE All Comers
Patient Flow Chart

Patients Enrolled
N = 2292

Resolute™ ZES	Randomized 1:1	Xience V™ EES
N = 1140		**N = 1152**
n = 1130 **99.1%**	**1 Yr Follow-up**	**n =1141** **99.0%**
n =1126 **98.8%**	**2 Yr Follow-up**	**n = 1135** **98.5%**
n =1120 **98.2%**	**3 Yr Follow-up**	**n = 1130** **98.1%**
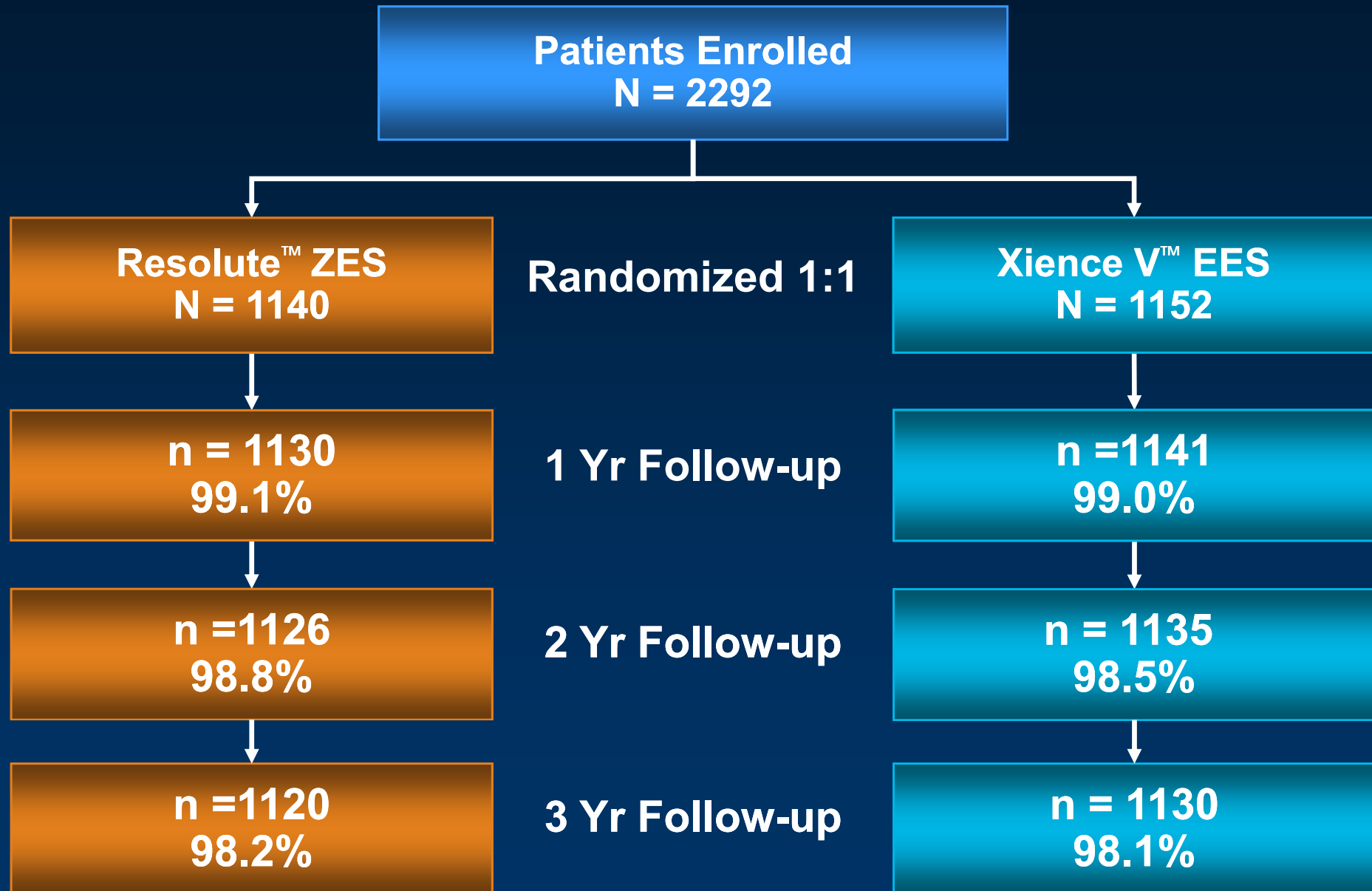
Windecker S. PCR 2012

RESOLUTE All Comers
Patient Eligibility

Inclusion Criteria

Coronary artery disease

- **Stable angina**
- **Silent ischemia**
- **Acute coronary syndrome including UA, NSTEMI and STEMI**

Lesion characteristics

- **Number of lesions** : no limitation
- **Number of vessels** : no limitation
- **Lesion length** : no limitation

Written informed consent

Exclusion Criteria

Known intolerance to

Aspirin, clopidogrel, heparin, cobalt alloy, everolimus, zotarolimus, contrast material, polymer coating

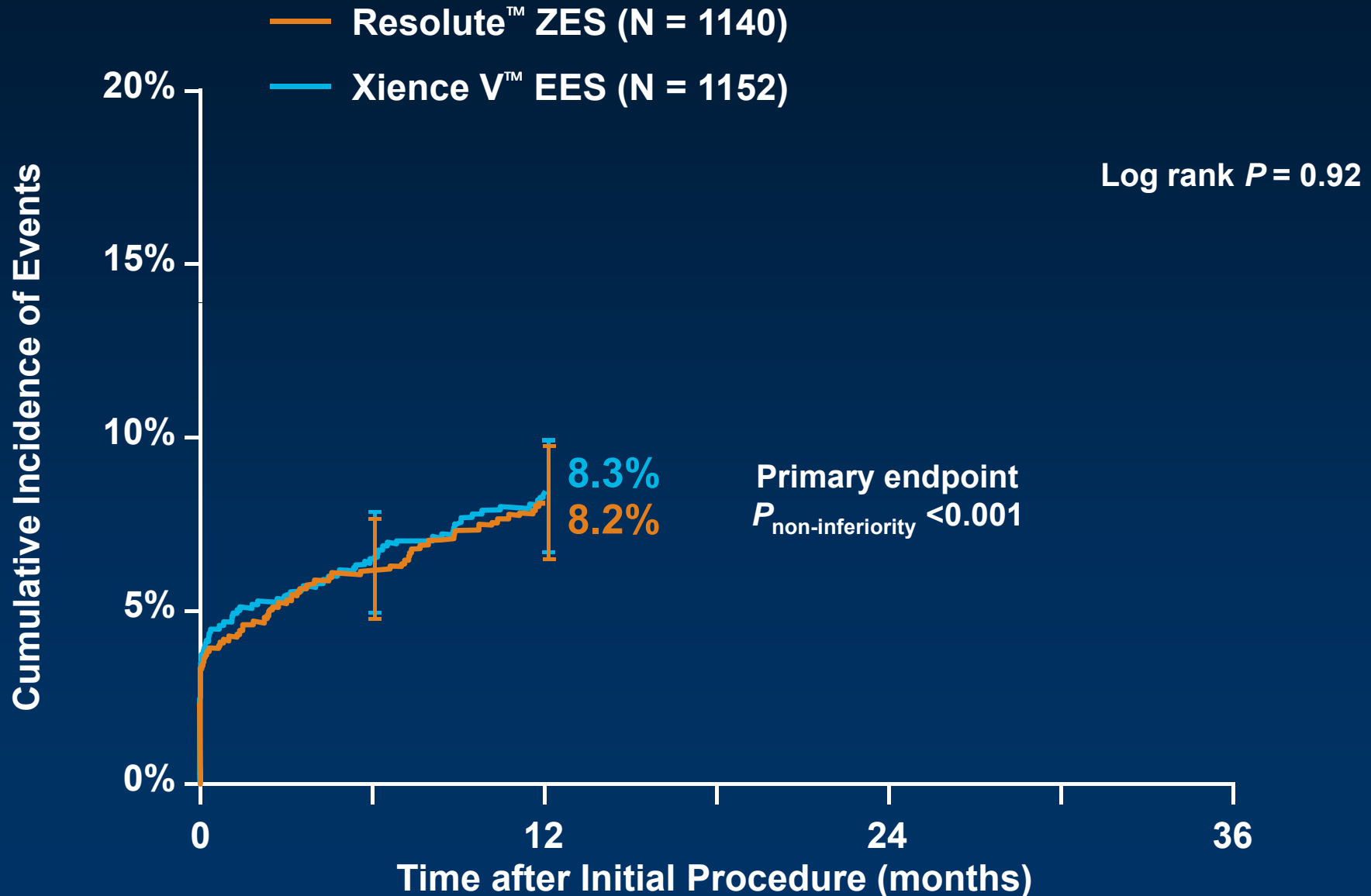**Planned, elective surgery within 6 months of PCI**

Unless dual anti-platelet therapy could be maintained

Pregnancy

Participation in another trial

RESOLUTE All Comers
Target Lesion Failure – Primary Endpoint

Resolute™ ZES (N = 1140)
Xience V™ EES (N = 1152)

Cumulative Incidence of Events

20%
15%
10%
5%
0%

Log rank *P* = 0.92

8.3%
8.2%

Primary endpoint
$P_{non-inferiority}$ <0.001

0   12   24   36

Time after Initial Procedure (months)

Serruys PW, et al., N Engl J Med. 2010;363(2):136-46.
Target Lesion Failure (TLF) is defined as cardiac death, TVMI, or clinically driven TLR.

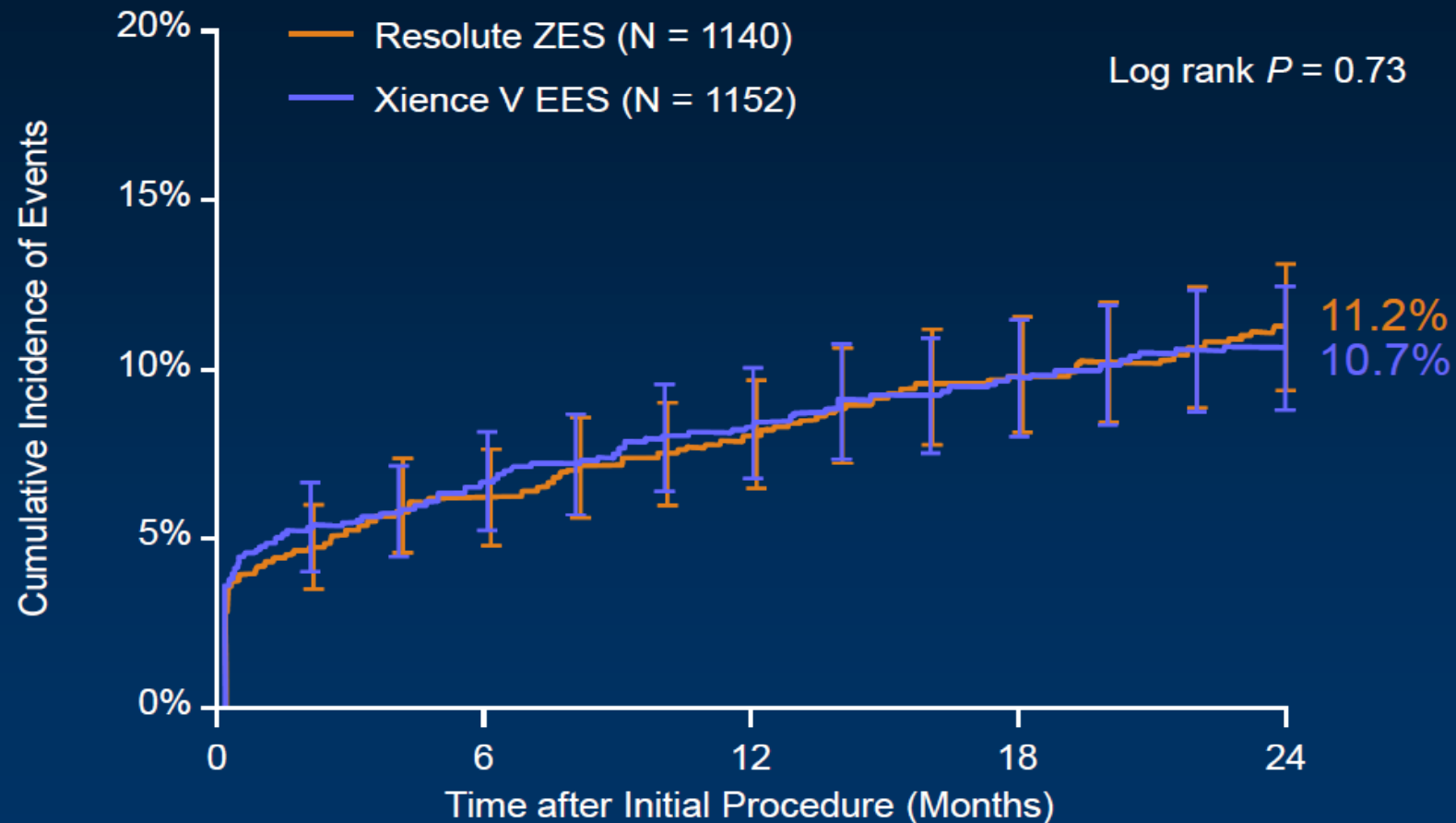# RESOLUTE ALL Comers Trial

Patient: 2292 All comers (Minimum exclusion criteria)
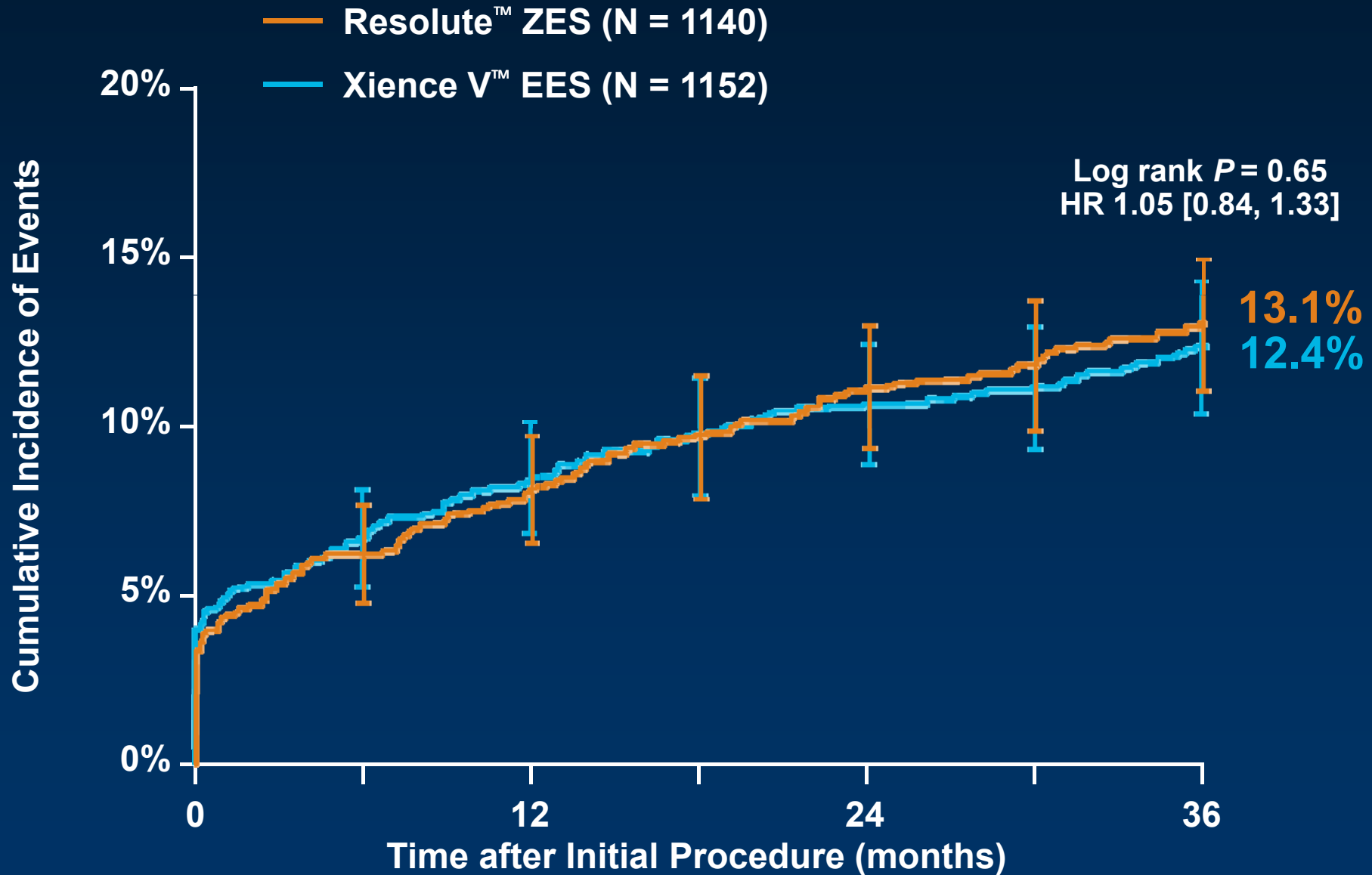**Intervention:** Resolute ZES
Comparison: Xience V EES
Outcomes: Target Lesion Failure up to 2Y

Target Lesion Failure to 2 Years (Cardiac Death, TV-MI, CD-TLR)

RESOLUTE All Comers
Target Lesion Failure to 3 Years

Resolute™ ZES (N = 1140)
Xience V™ EES (N = 1152)

Log rank *P* = 0.65
HR 1.05 [0.84, 1.33]

20%
15%
10%
5%
0%

Cumulative Incidence of Events

13.1%
12.4%

0   12   24   36

Time after Initial Procedure (months)

TLF (Target Lesion Failure) is defined as cardiac death, TVMI, or clinically driven TLR.

Windecker S. PCR 2012

TWENTE Trial

Patient: 1391 All comers (excluded STEMI patients)
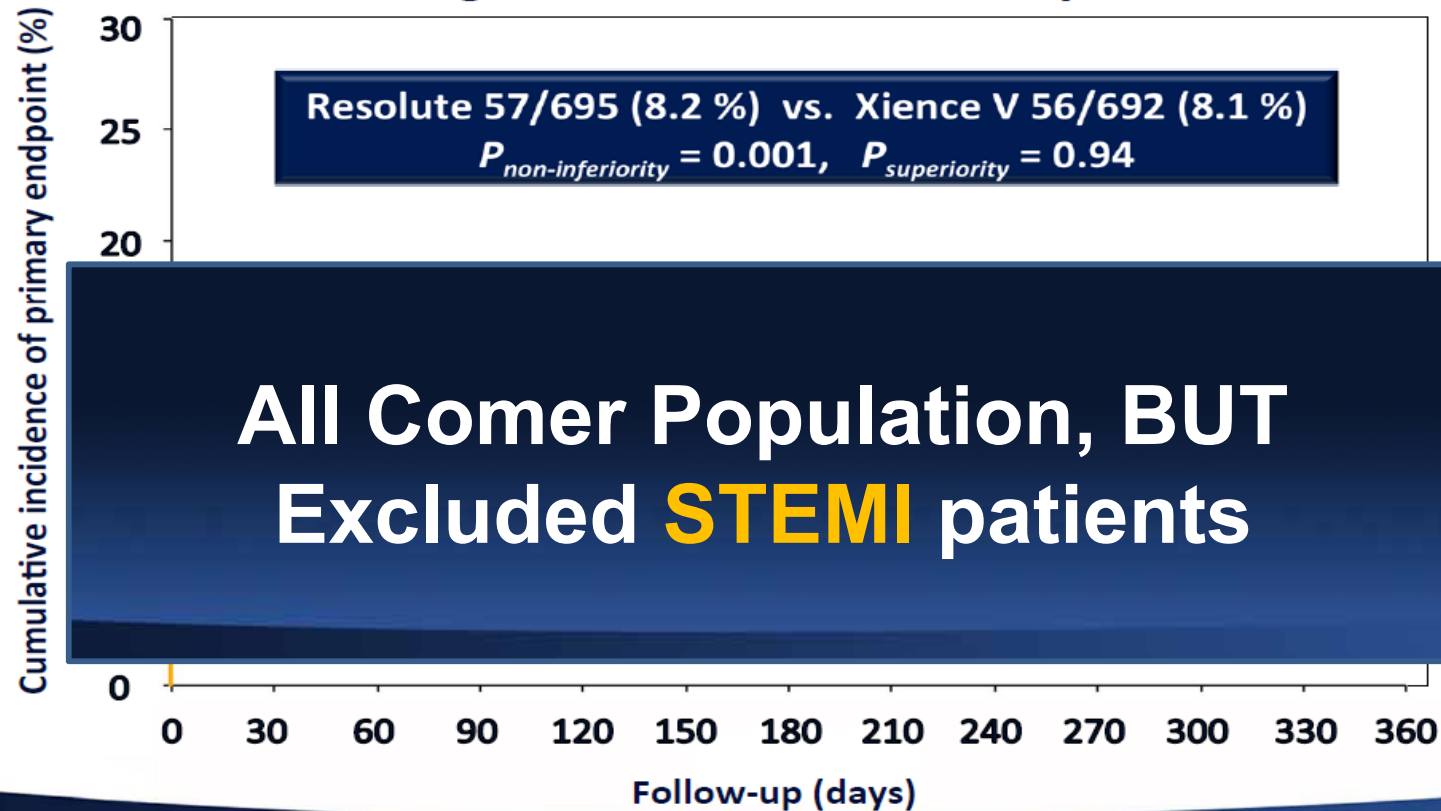**Intervention:** Resolute ZES
Comparison: Xience V EES
Outcomes: Target Vessel Failure at 1Y

Primary Endpoint (n=1,391)
Target Vessel Failure at 1 year

Resolute 57/695 (8.2 %) vs. Xience V 56/692 (8.1 %)
$P_{non-inferiority} = 0.001$, $P_{superiority} = 0.94$

All Comer Population, BUT Excluded STEMI patients

Cumulative incidence of primary endpoint (%)

Follow-up (days)

TCT2011

All Comers RCTs = Real-world practice ?

Patient: 1242 consecutive patients in Erasmus Medical Center
Trials: LEADERS, RESOLUTE ALL Comers trial
Comparison: AC-RCTs Participants vs. Non-Participants
Outcomes: All-cause mortality at 1Y

P=0.002
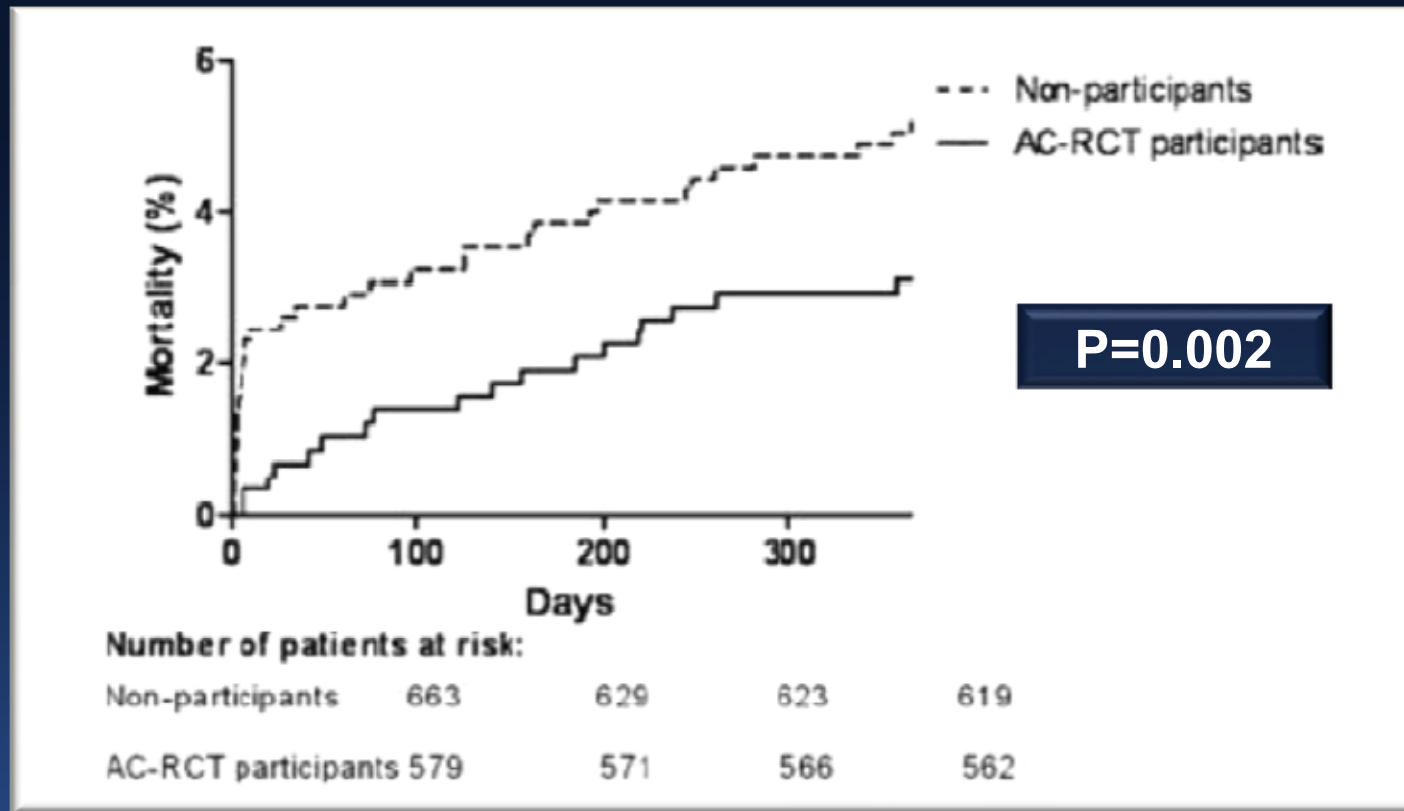
Evenif they are "all-comers" in AC-RCT, the actually-enrolled patients were only 48% of consecutive patients and their prognosis was significantly better than non-participants to AC-RCT.

de Boer SP, et al. Eur Heart J 2011;32:2161-7

Objective of Korean Registries

To assess clinical outcomes of
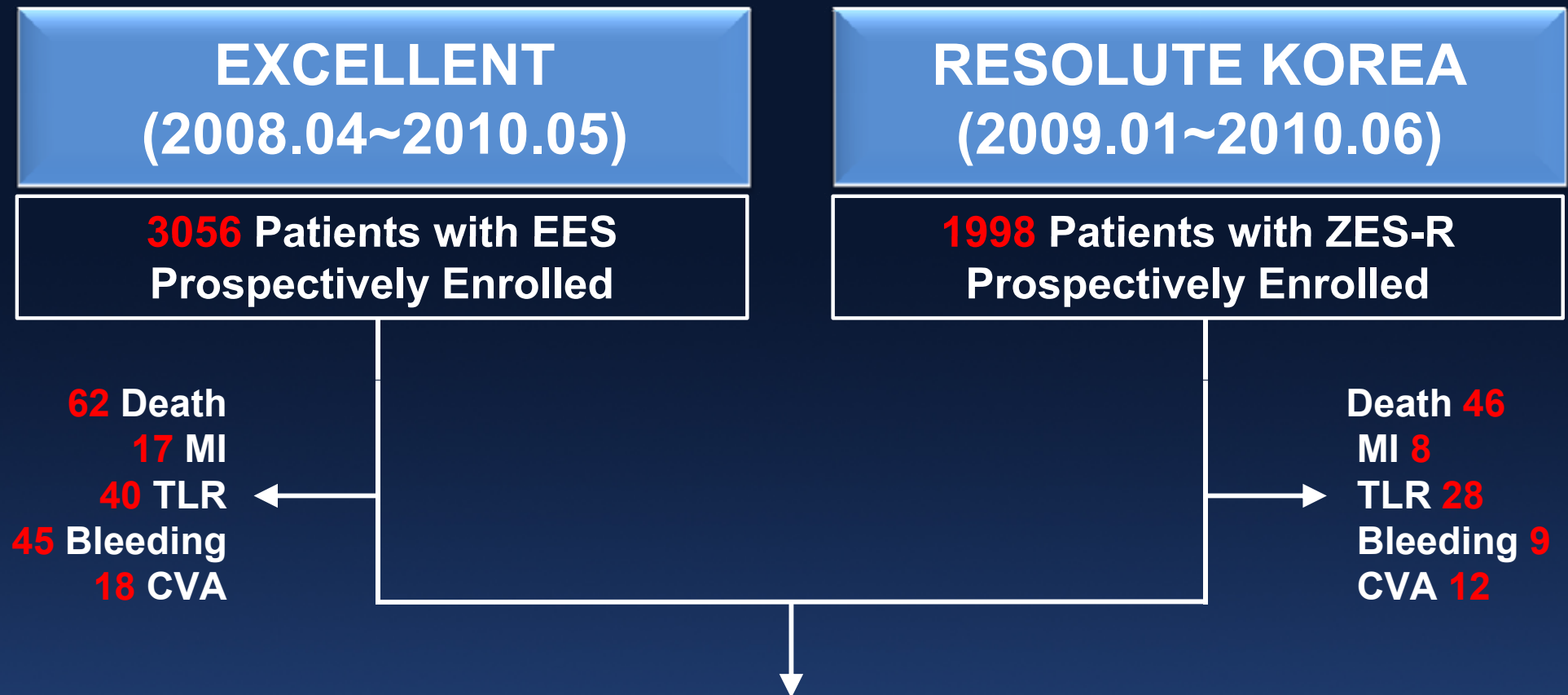Resolute ZES versus XienceV/Promus EES
in the real world all-comers

– Primary Endpoint: Target Lesion Failure
(Cardiac death, Target vessel MI, TLR)

– Secondary Endpoint: Patient-oriented
composite outcome (All death, Any MI, Any
Revascularization)

HOST-registries in Korea

	EXCELLENT	RESOLUTE-Korea
Devices	**Xience V/Promus**	**Endeavor Resolute**
Enrollment Periods	**2008.04~2010.05**	**2009.01~2010.06**
Inclusion	**All-Comers who were treated with at least 1 EES or ZES-R**	
Participating Centers	**29 Centers**	**25 Centers**
Exclusion	Only exclusion criterion was rejection of patient	
Complete Follow-up	98.2% †	98.4% †

† The vital status of 100% of the patients were cross-checked with the national system (mandatory national health insurance). Therefore, even in those lost to follow-up, the occurrence of death was confirmed.

Safety and Efficacy of Second-Generation Everolimus-Eluting Xience V Stents Versus Zotarolimus-Eluting Resolute Stents in Real-World Practice

Patient-Related and Stent-Related Outcomes from the Multicenter Prospective EXCELLENT and RESOLUTE-Korea Registries

Kyung Woo Park, MD, PhD,* Joo Myung Lee, MD,* Si-Hyuck Kang, MD,* Hyo-Suk Ahn, MD,*
Han-Mo Yang, MD, PhD,* Hae-Young Lee, MD, PhD,* Hyun-Jae Kang, MD, PhD,*
Bon-Kwon Koo, MD, PhD,* Janghyun Cho, MD, PhD,† Hyeon-Cheol Gwon, MD, PhD,‡
Sung Yoon Lee, MD, PhD,§ In-Ho Chae, MD, PhD,‖ Tae-Jin Youn, MD, PhD,‖
Jei Keon Chae, MD, PhD,¶ Kyoo-Rok Han, MD, PhD,# Cheol Woong Yu, MD, PhD,**
Hyo-Soo Kim, MD, PhD*

Seoul, Suncheon, Koyang, Seongnam, Jeonju, and Bucheon, Korea

Primary Outcome Analysis
Target Lesion Failure at 1 year

Major Secondary Outcome Analysis
Patient-Oriented Composite Outcome at 1 year

Log rank p = 0.717

ZES-R : 153 (7.7%)

EES : 225 (7.4%)

No. at Risk				
EES	3056	2951	2908	2787
ZES-R	1998	1929	1907	1836

SNUH

KW Park,, HS Kim. J Am Coll Cardiol 2013

Propensity Score Matching

Percentage Standardized Difference of Variables
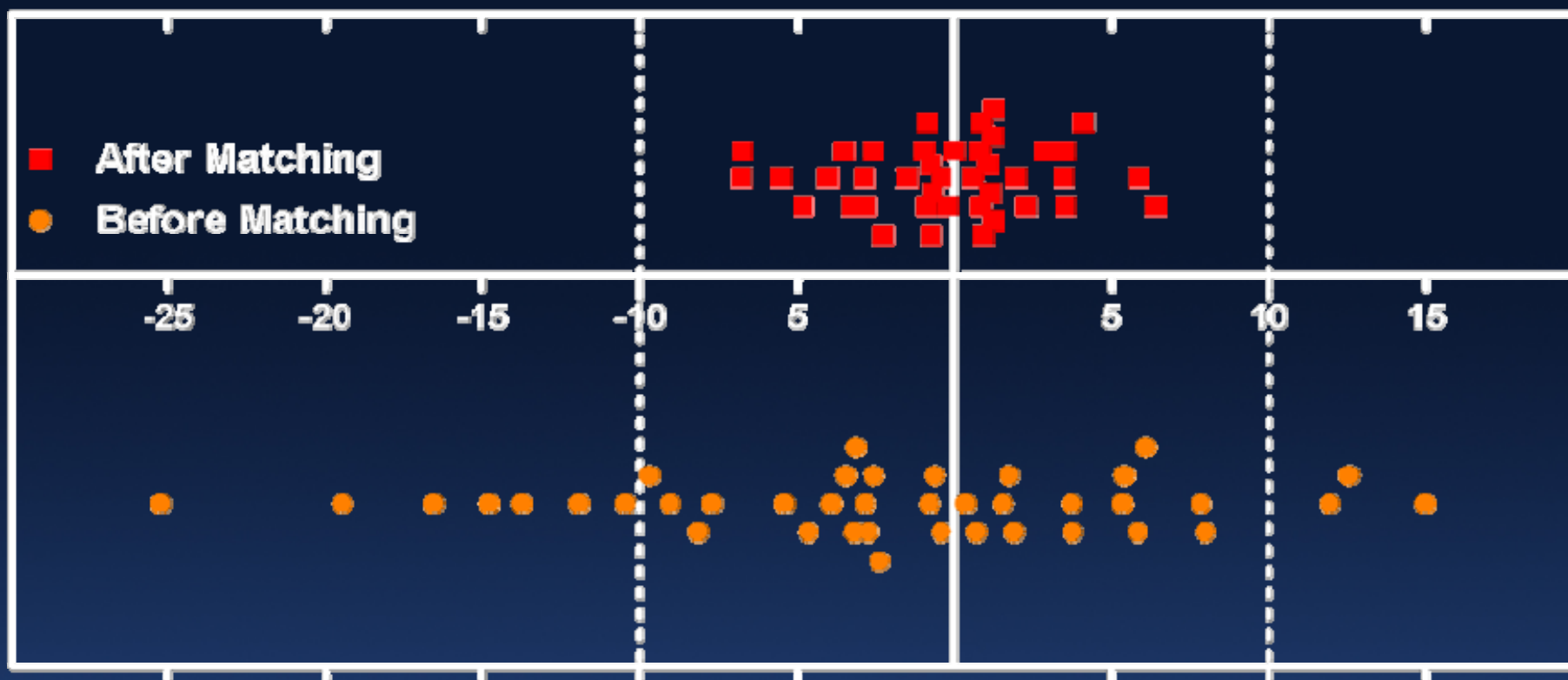
Included variables (38 variables) : Age, Sex, Hypertension, Diabetes mellitus, Current smoking, Dyslipidemia, Chronic renal failure, Peripheral vascular disease, Family history of cardiovascular disease, LVEF, Serum Creatinine, Previous PCI, Previous coronary bypass surgery, Previous MI, Previous congestive heart failure, Previous cerebrovascular accident, Angiographic extent of disease (1 vessel disease [VD], 2VD, 3VD), Clinical indication of PCI (stable angina, unstable angina, non ST segment elevation MI [NSTEMI], ST segment elevation MI [STEMI], silent ischemia), Left main coronary artery stenting, Bypass graft PCI, In-stent restenosis lesion, Bifurcation, The presence of thrombus which was induced thrombosuction, Long lesion (lesion length ≥ 28 mm), Small vessel treatment(reference diameter ≤ 2.75 mm), Off label indication, Baseline medications including insulin, and Multivessel procedure (2 or more vessel stenting) or not.

Primary Outcome Analysis
Target Lesion Failure at 1 year

Propensity Score Matched Group Analysis
EES 1014 vs. ZES-R 1014 patients

Log rank p = 0.675

EES : 28 (2.8%)

ZES-R : 25 (2.5%)
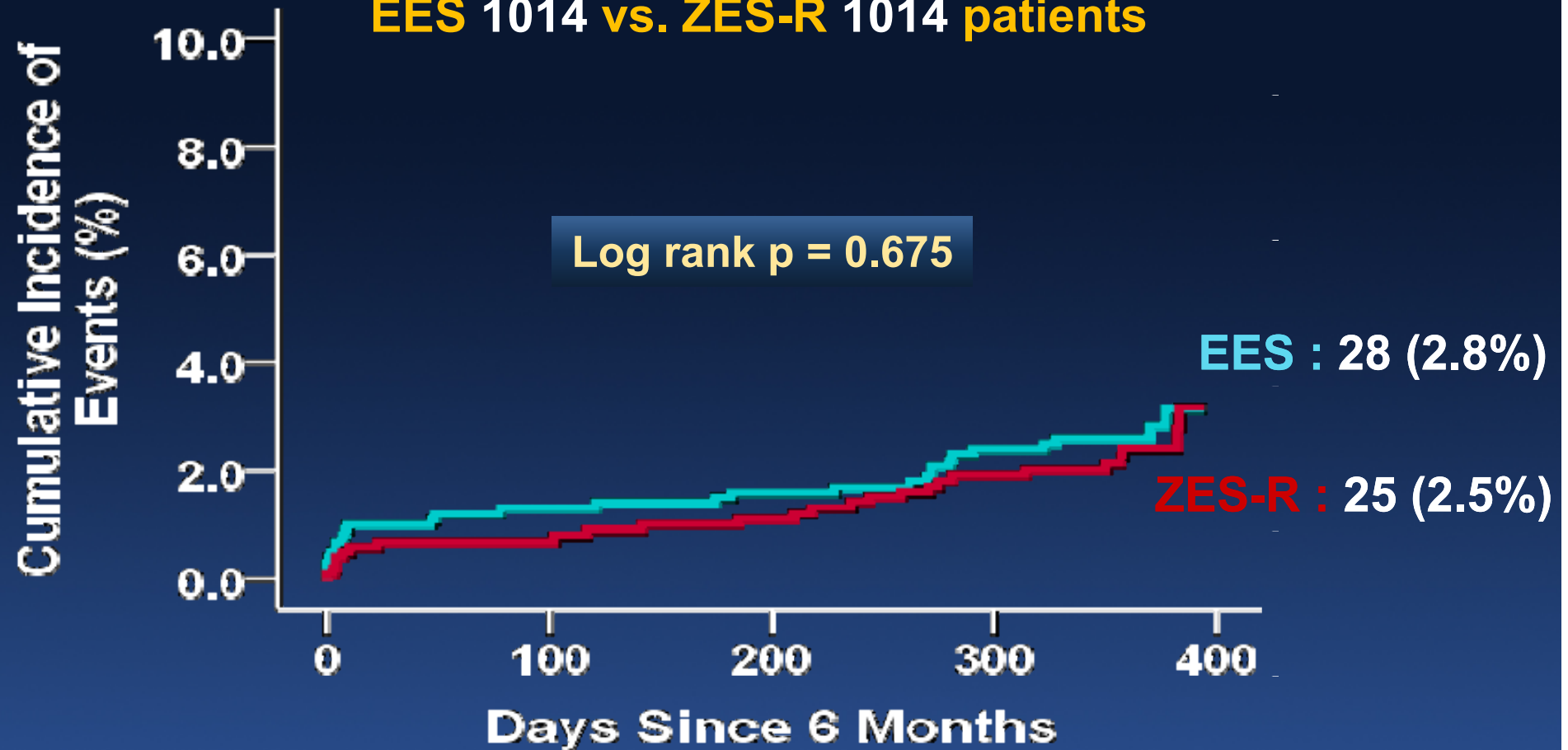
No. at Risk				
EES	1014	989	986	963
ZES-R	1014	989	982	961

Major Secondary Outcome Analysis
Patient-Oriented Composite Outcome at 1 year

Propensity Score Matched Group Analysis
EES 1014 vs. ZES-R 1014 patients

Log rank p = 0.708

EES 71 (7.0%)

ZES-R 67 (6.6%)

Cumulative Incidence of Events (%)

Days Since 6 Months

No. at Risk

EES	1014	986	973	933
ZES-R	1014	984	974	936

Stent Thrombosis at 1 year
ARC defined Stent Thrombosis

■ **EES (N=3056)** ■ **ZES-R (N=1998)**

P=0.306 **P=0.751** **P=0.464**

0.6%
(18)

0.4%
(7)

* Number of events in parenthesis

0.2%
(6)

0.2%
(3)

0.4%
(12)

0.3%
(5)

Definite/Probable ST **Definite ST** **Probable ST**
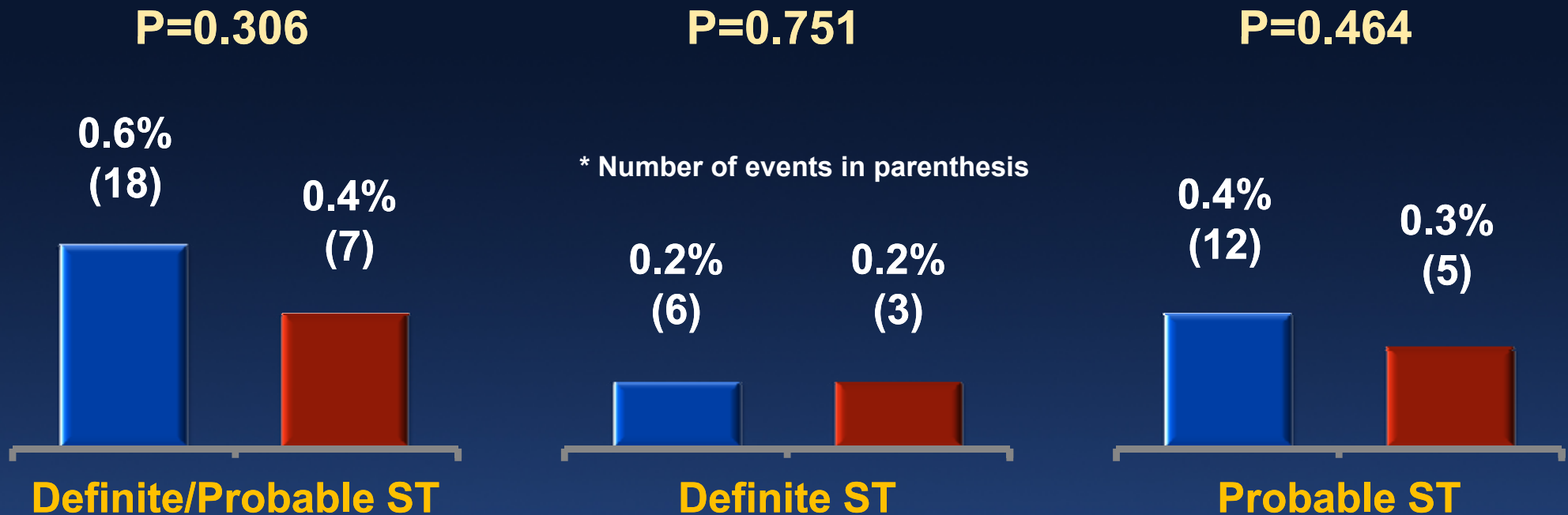
Dual Anti-platelet Therapy	EES	ZES-R	P value
At 6 months	96.8%	96.8%	0.930
At 1 year	84.8%	84.7%	0.898
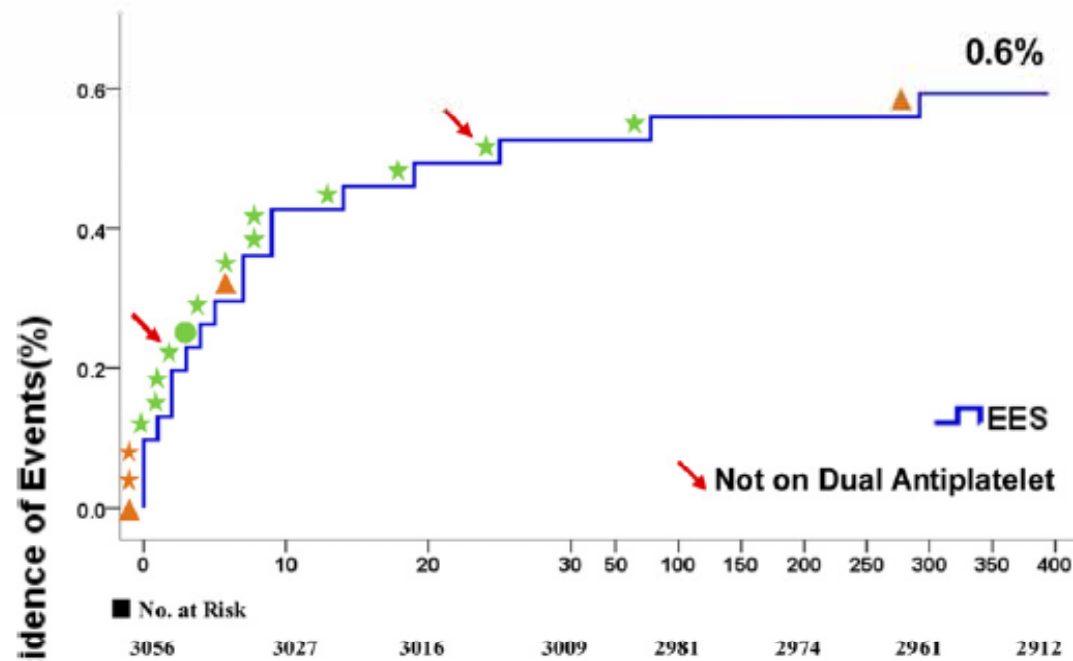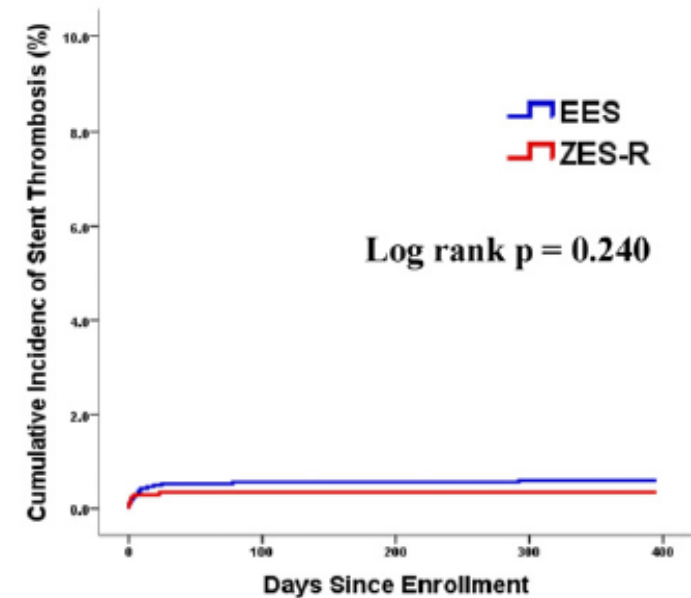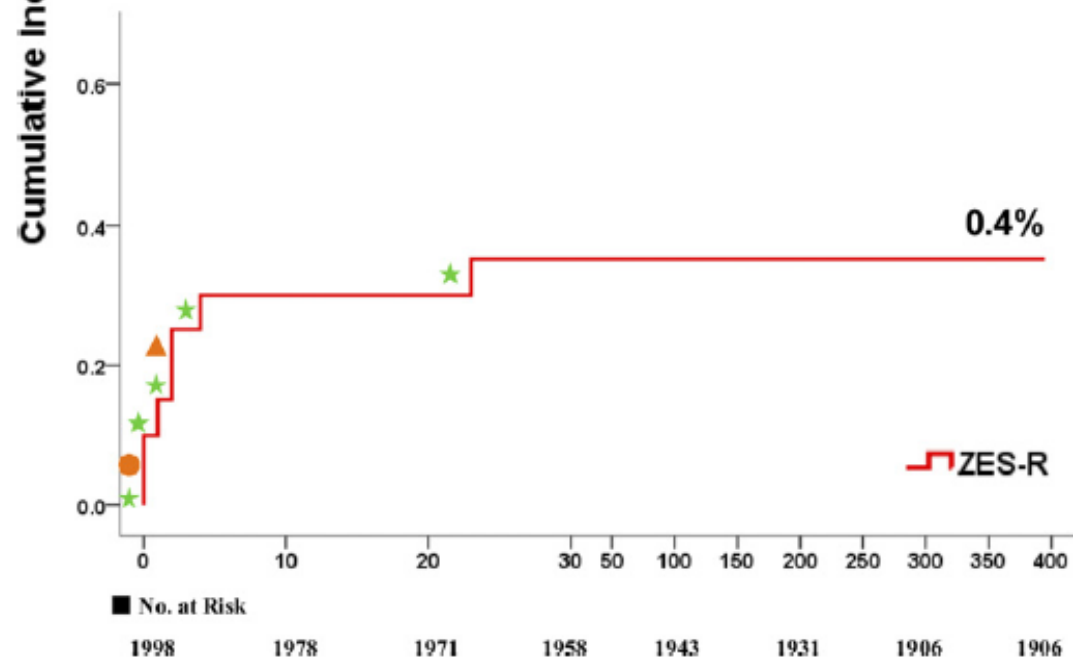
Figure 2 Survival Analysis: Definite or Probable ST

Arrow indicates the patients not taking dual-antiplatelet therapy at time of ST. EES = everolimus-eluting stent; ZES-R = Resolute zotarolimus-eluting stent.

RESOLUTE All Comers vs. TWENTE
Stent Thrombosis (Definite/Probable) to 1 Year

RESOLUTE All Comers
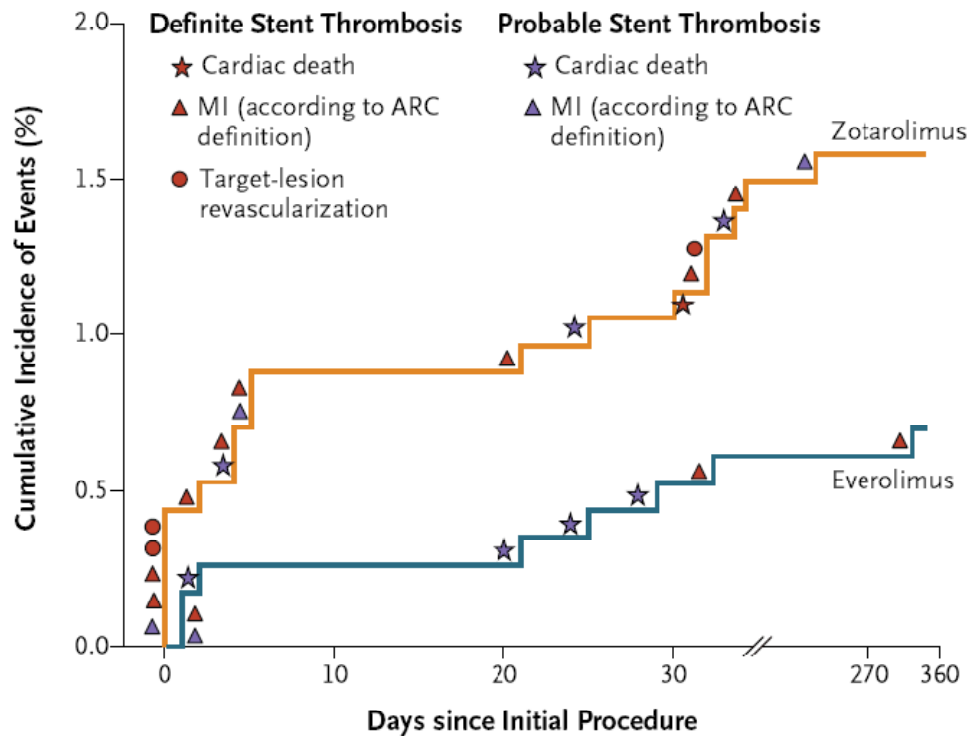
TWENTE
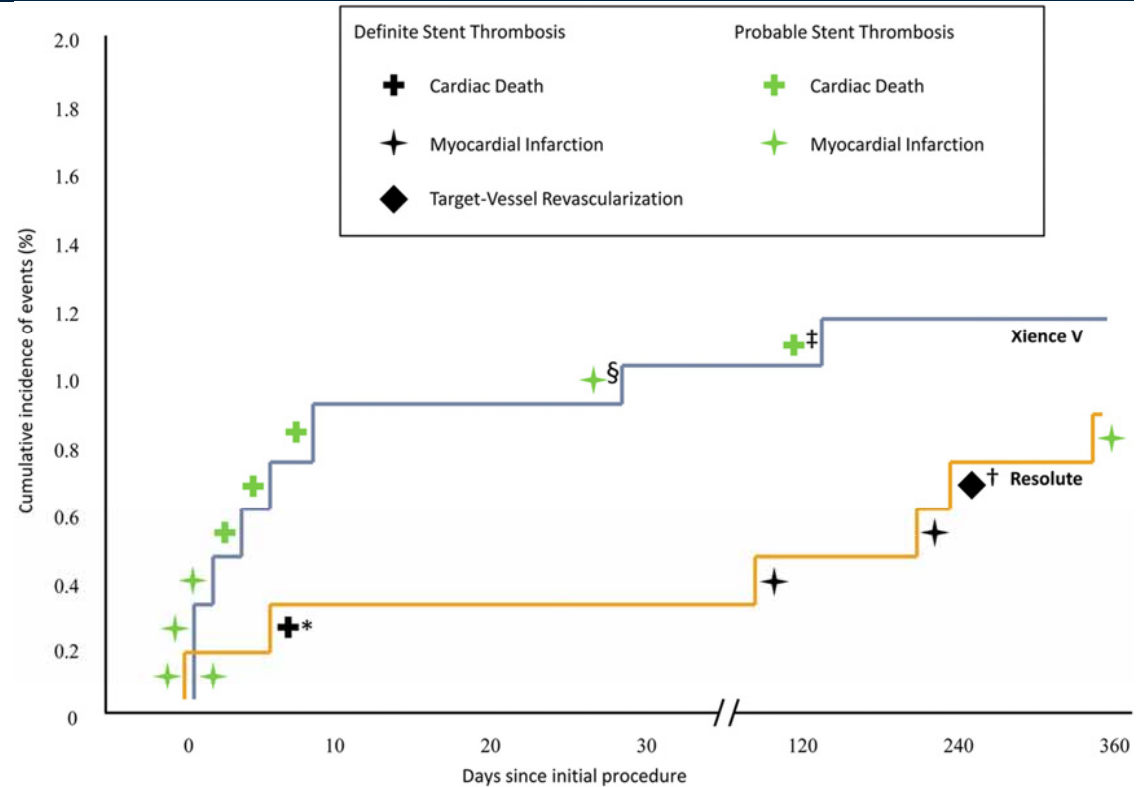
Serruys PW, et al. *N Engl J Med.* 2010;363(2):136-46

Von Birgelen C, et al. *J Am Coll Cardiol*. 2012;59:1350–61

Stent Thrombosis – Pooled Analysis
with RESOLUTE ALL Comers, TWENTE trials

Study or Subgroup	EES Events	EES Total	ZES-R Events	ZES-R Total	Weight	Odds Ratio M-H, Random, 95% CI
EXCELLENT vs RESOLUTE	18	3056	7	1998	33.6%	1.69 [0.70, 4.04]
RESOLUTE ALL COMER 2YR	11	1128	21	1121	38.4%	0.52 [0.25, 1.07]
TWENTE	8	692	6	695	28.0%	1.34 [0.46, 3.89]
Total (95% CI)		4876		3814	100.0%	1.00 [0.46, 2.19]
Total events	37		34			

Heterogeneity: Tau² = 0.27; Chi² = 4.71, df = 2 (P = 0.10); I² = 58%
Test for overall effect: Z = 0.01 (P = 0.99)

Favours EES   Favours ZES-R

Pooled OR for definite/probable ST : 1.00 (95% CI 0.46-2.19), p=0.99

ST in Real World Trials
Studies not powered for this low frequency ST event

ARC Definite/Probable ST at 12 Months

Xience V™ DES | Resolute™ DES

Bar chart values (Percentage %):

Xience V™ DES:
- RESOLUTE All Comers[1] N = 1152: 0.7
- COMPARE[2] N = 897: 0.7
- XIENCE V USA[3] N = 5054: 0.84
- TWENTE[4] N = 694: 1.16
- ISAR TEST 4[5] N = 652: 1.4
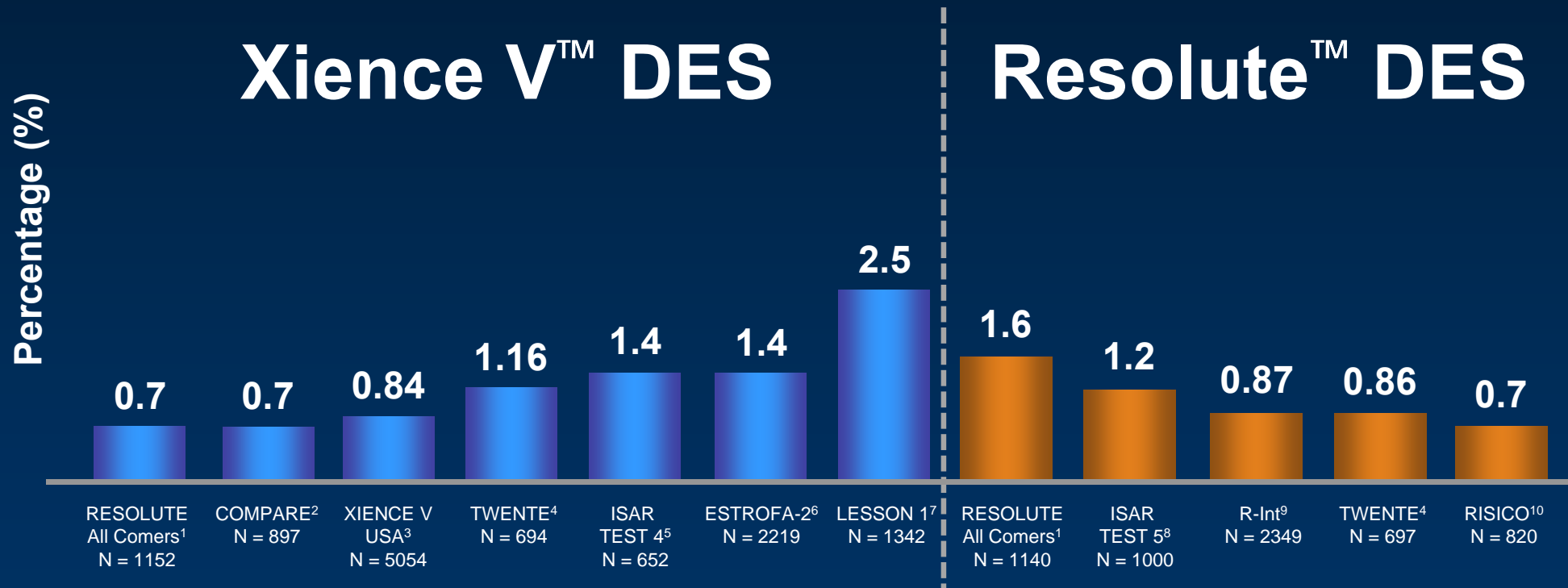- ESTROFA-2[6] N = 2219: 1.4
- LESSON 1[7] N = 1342: 2.5

Resolute™ DES:
- RESOLUTE All Comers[1] N = 1140: 1.6
- ISAR TEST 5[8] N = 1000: 1.2
- R-Int[9] N = 2349: 0.87
- TWENTE[4] N = 697: 0.86
- RISICO[10] N = 820: 0.7

Results from clinical trials are not directly comparable. Real world data not yet available for Promus Element DES.

[1] Serruys PW, et al. *N Engl J Med*. 2010;363:136-46. [2] Kedhi E, et al, *Lancet*. 2010;375:201-9. [3] Krucoff MW, et al. *J Am Coll Cardiol Intv*. 2011;4:1298–309. [4] Von Birgelen C, et al. *J Am Coll Cardiol*. 2012;59:1350–61. [5] Kastrati A, TCT 2009. [6] De la Torre Hernàndez JM, et al. *J Am Coll Cardiol Intv*. 2010;3:911–9. [7] Räber L, et al. *J Am Coll Cardiol*. 2011;57:2143–51. [8] Massberg S, et al. *Circulation*. 2011;124:624-32. [9] Neumann FJ, et al. *EuroIntervention*. 2012;7(10):1181-8. [10] Romagnoli G, et al. *Catheter Cardiovasc Interv*. 2012;79:567–74.

Stent Thrombosis depends on risk profiles

ARC Def/Prob Stent Thrombosis at 1 y

Real-World Patients | **Standard Risk Patients**

Percentage (%)

1.6	0.87	1.2	0.86	0.7	0.1	0.0	0.0
RESOLUTE All-Comers[1] N = 1140	RESOLUTE International[2] N = 2349	ISAR TEST 5[3] N = 1000	TWENTE[4] N = 697	RISICO[5] N = 820	RESOLUTE US*[6] N = 1402	RESOLUTE Japan*[7] N = 100	RESOLUTE FIM[8] N = 139
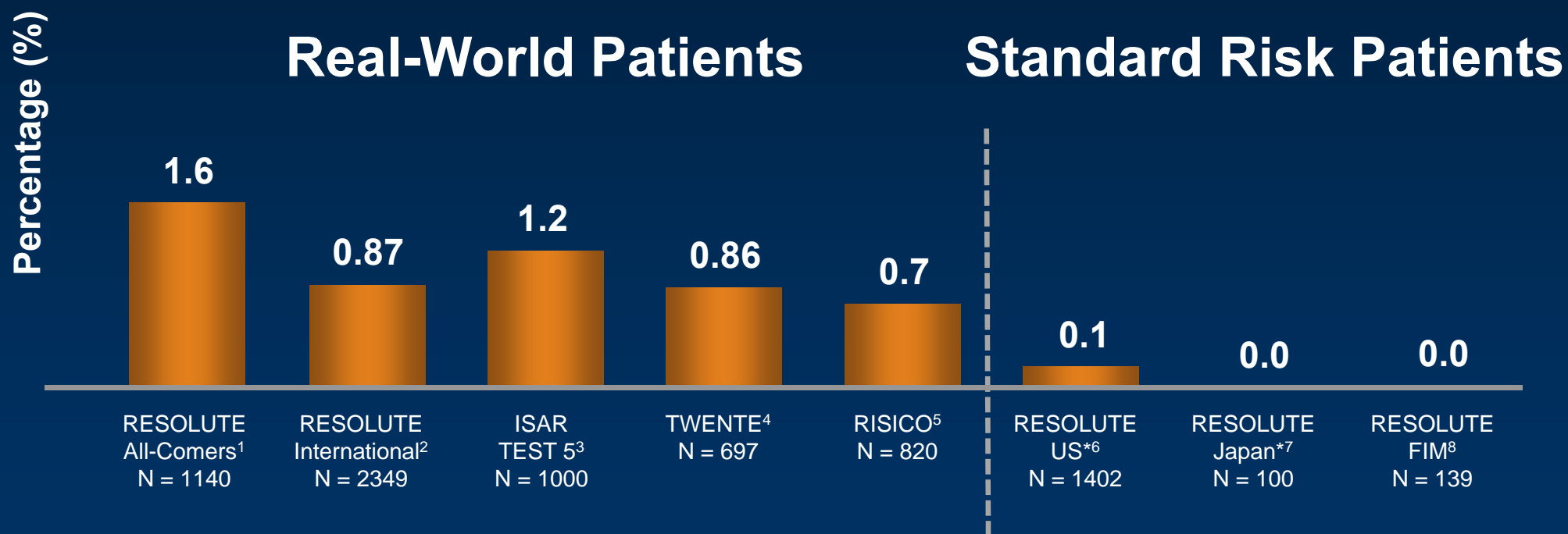
Results from clinical trials are not directly comparable.
* Included dual vessel patients.

[1] Serruys PW, et al. *N Engl J Med*. 2010;363:136-46. [2] Neumann FJ, et al. *EuroIntervention*. 2012;7(10):1181-8. [3] Massberg S, et al. *Circulation*. 2011;124:624-32. [4] Von Birgelen C, et al. *J Am Coll Cardiol*. 2012;59:1350–61. [5] Romagnoli G, et al. *Catheter Cardiovasc Interv*. 2012;79:567–74. [6] Yeung AC, et al. *J Am Coll Cardiol*. 2011;57:1778–83. [7] Saito S, CVIT 2011. [8] Meredith IT, et al. *J Am Coll Cardiol Intv*. 2009;2:977– 85.

Resolute vs XienceV/Promus

- After unrestricted use of 2nd generation DES in all-comers receiving PCI, **both stents showed comparable safety and efficacy at 1 year follow-up,** with very low event rates

- **Overall incidences** of target lesion failure and definite stent thrombosis were **low**, **even in** the patients with **off label indication**

- **This is suggesting excellent safety and efficacy of both types of second generation drug-eluting stents.**
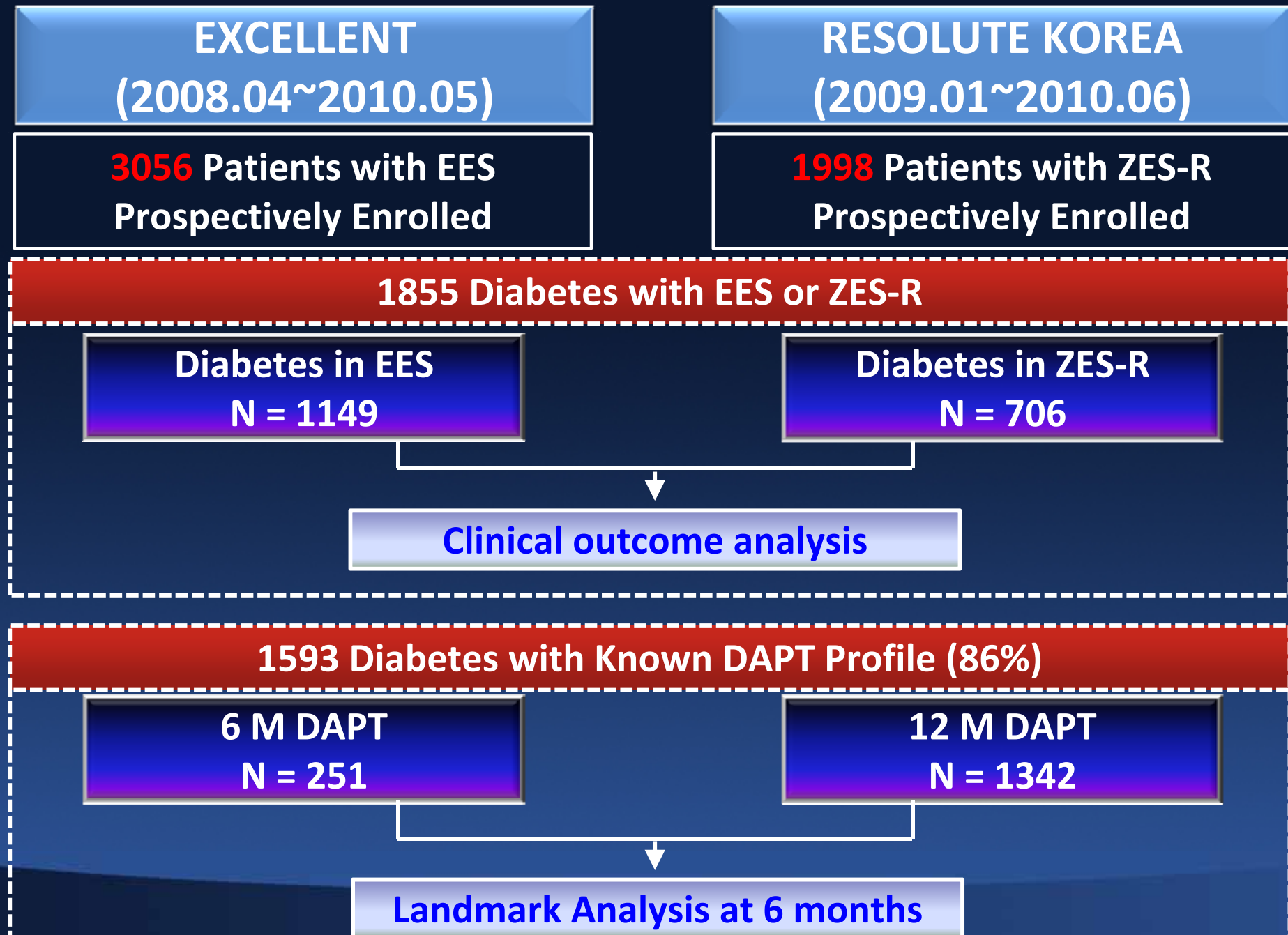
Baseline Characteristics in DM

Metabolic status

Characteristic	EES (n = 1149)		ZES-R (n = 706)		p-value
Diabetes Treatment					
No DM treatment	140	12.2%	69	9.8%	0.113
Life style modification only	50	4.4%	32	4.5%	0.907
Oral hypoglycemic agent	850	74.0%	500	70.8%	0.147
Insulin	**140**	**12.2%**	**115**	**16.3%**	**0.015**
HBA1C (%)	**7.5 ± 1.5**		**7.6 ± 1.4**		**0.031**
HBA1C < 7%	**396**	**44.6%**	**192**	**38.2%**	**0.021**
Total cholesterol (mg/dL)	166.3 ± 44.3		163.0 ± 43.1		0.125
LDL cholesterol	98.9 ± 34.9		95.6 ± 33.8		0.066
LDL < 100 mg/dL	571	54.6%	339	59.1%	0.094
HDL cholesterol	41.5 ± 11.6		40.8 ± 10.8		0.212
Creatinine (mg/dL)	1.3 ± 1.6		1.4 ± 1.7		0.350

Baseline Characteristics in DM

Angiographic & Procedural Characteristics

Characteristic	EES (n = 1149)		ZES-R (n = 706)		p-value
Angiographic disease extent					0.263
1-vessel disease	442	38.6%	245	34.9%	
2-vessel disease	360	31.5%	235	33.4%	
3-vessel disease	342	29.9%	223	31.7%	
No. of lesions treated/patient	1.53 ± 0.77		1.56 ± 0.85		0.436
No. of stents/patient	1.74 ± 1.00		1.74 ± 0.99		0.977
Total stent length/patient (mm)	39.80 ± 26.51		43.16 ± 26.80		0.008
In-stent restenosis	100	8.7%	50	7.1%	0.221
Bifurcation	158	13.8%	161	22.8%	<.001
Length ≥ 28 mm	501	43.6%	371	52.5%	<.001
Vessel diameter ≤ 2.75 mm	299	26.0%	172	24.4%	0.442
Left main PCI	66	5.7%	28	4.0%	0.090
GP IIb/IIIa inhibitor use	27	2.6%	24	3.4%	0.385
Use of IVUS or OCT	621	37.8%	367	37.8%	0.364
Off label indication	851	74.1%	581	82.3%	<.001

Diabetes versus Non-diabetes
Clinical outcomes at 1 year

Whole Patients of
EXCELLENT (3056 patients) vs. RESOLUTE-Korea (1998 patients)

Target Lesion Failure	Patient-Oriented Composite Outcome

Left panel — Target Lesion Failure:
Log rank p = 0.004
DM : 4.4%
Non-DM : 2.7%

Right panel — Patient-Oriented Composite Outcome:
Log rank p < 0.001
DM : 11.7%
Non-DM : 7.7%

No. at Risk
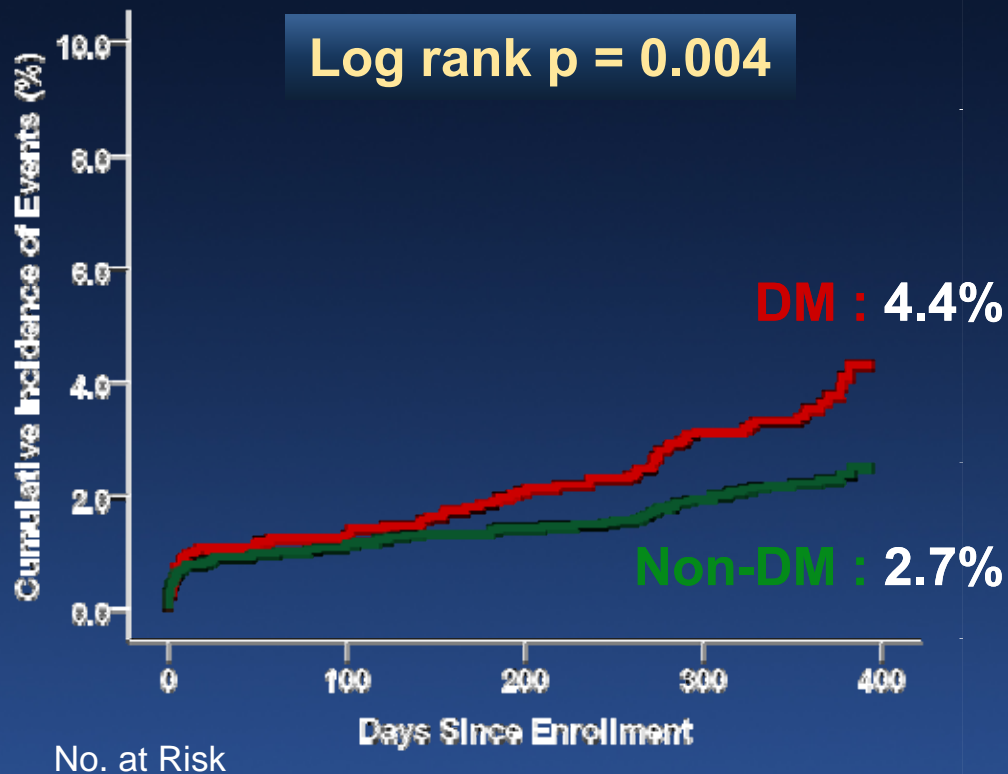
DM	1855	1793	1774	1730	1719
Non-DM	3174	3091	3076	3019	3008
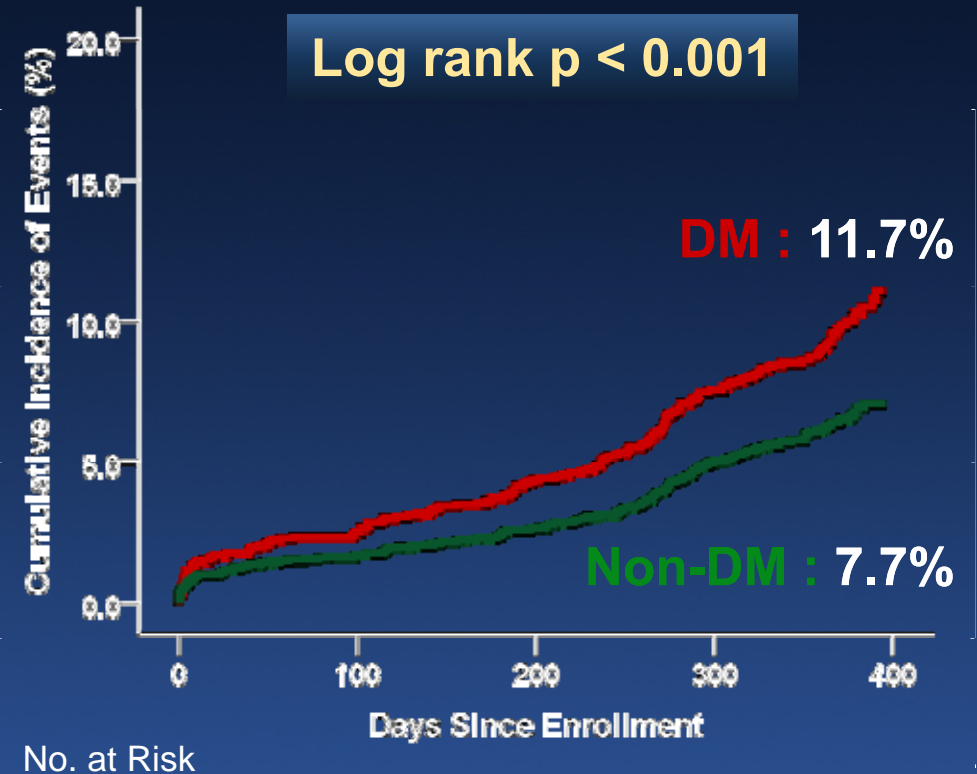
DM	1855	1780	1745	1665	1627
Non-DM	3174	3081	3051	2942	2899

Stent Comparison in Diabetics

EES vs. ZES-R

Primary Outcome in DM
Target Lesion Failure at 1 year

Log rank p = 0.832

EES : 4.5%

ZES-R : 4.2%

No. at Risk					
EES	1149	1105	1095	1066	1059
ZES-R	706	688	679	664	660

Major Secondary Outcome in DM
Patient-Oriented Composite Outcome at 1 year

Log rank p = 0.432

ZES-R : 13.2%
EES : 10.7%

Cumulative Incidence of Events (%)

Days Since Enrollment

No. at Risk
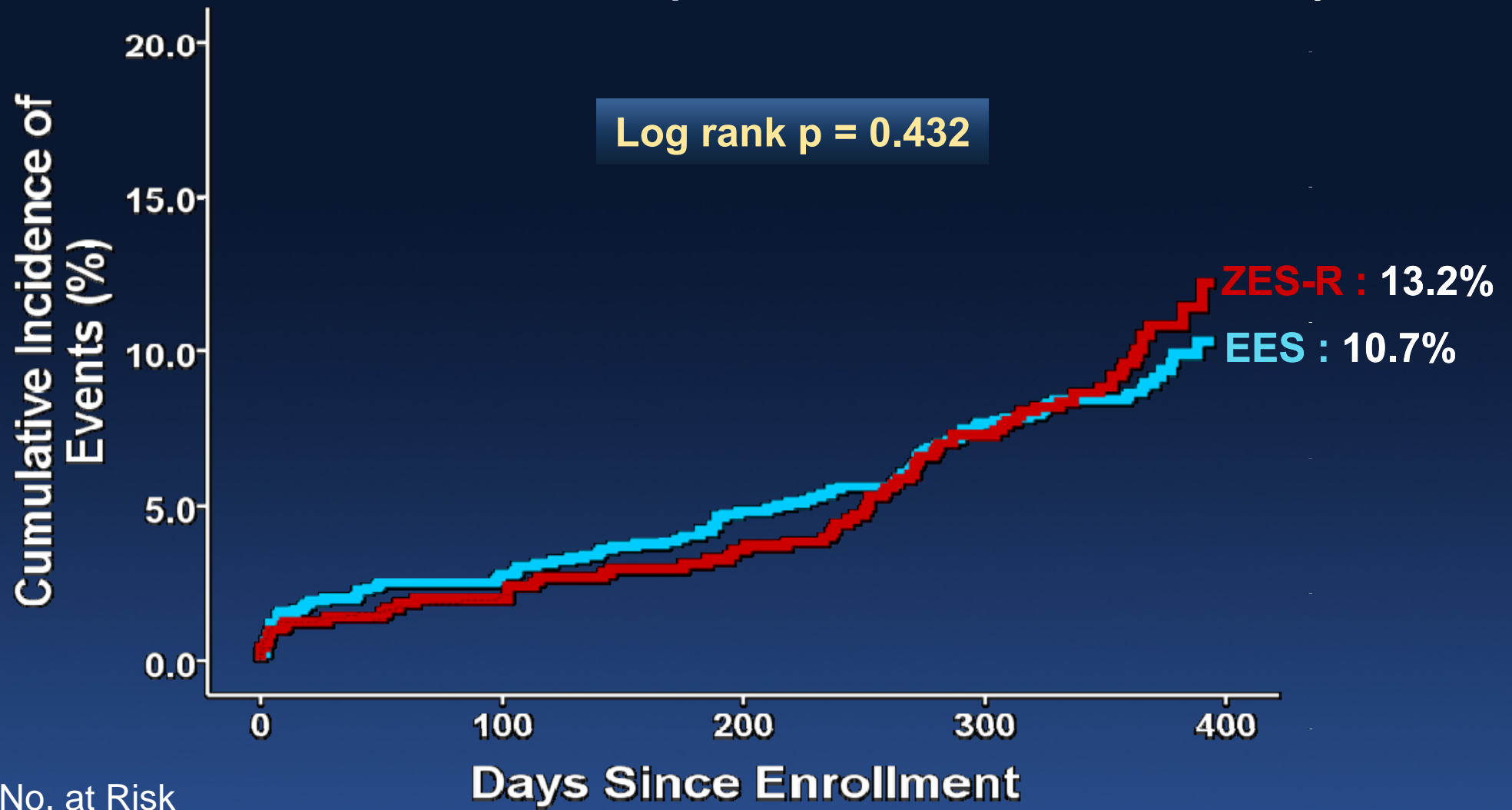
	0	100	200	300	400
EES	1149	1098	1075	1027	1010
ZES-R	706	682	670	638	617

SNUH

Propensity Score Matching in DM

## Percentage Standardized Difference of Variables
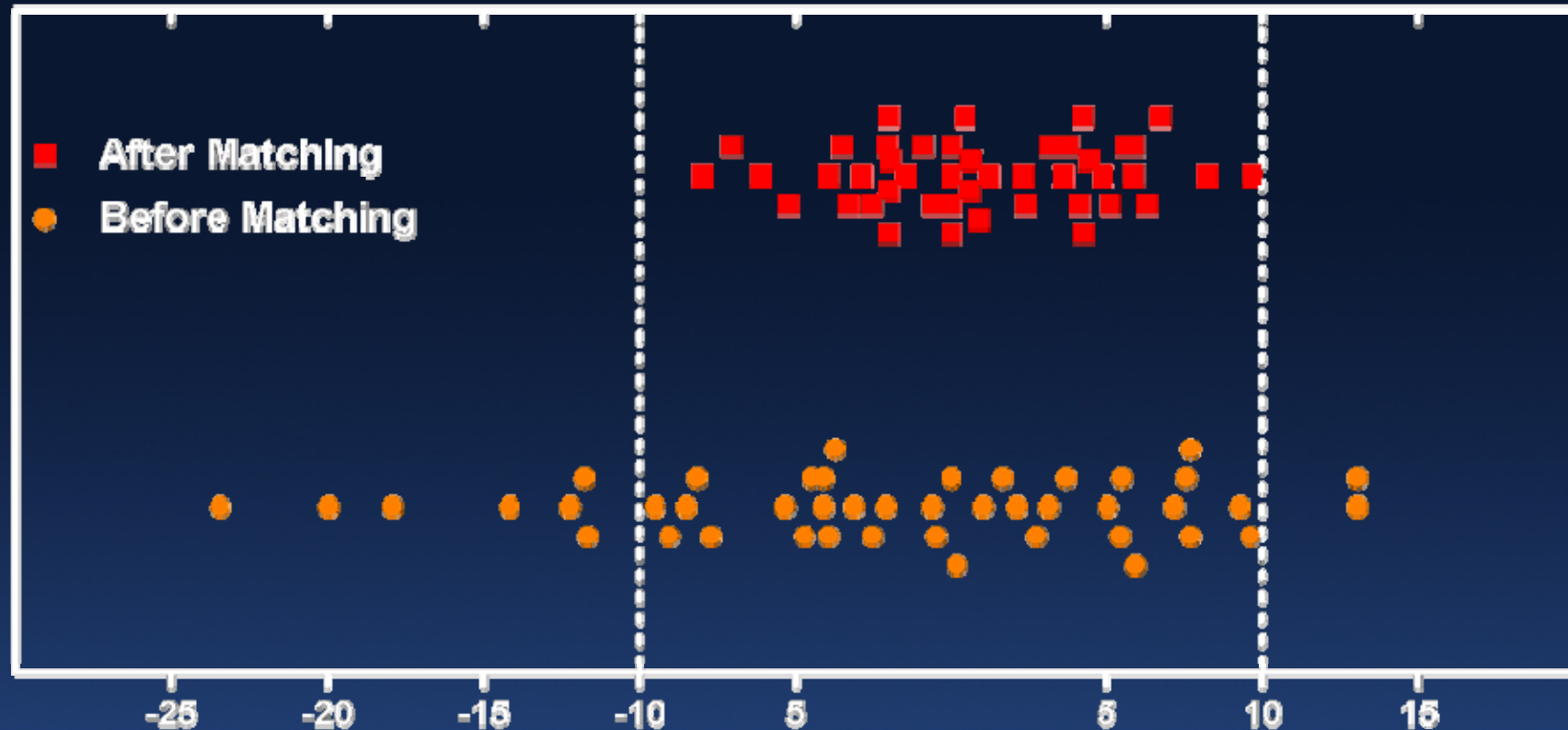
Included variables (44 variables) : Age, BMI, EF, Creatinine, eGFR, Total treated lesion number, HBA1C, Total cholesterol, LDL, Male, Previous PCI, Previous CABG, Previous MI, Previous CHF, CRF, Previous CVA, HTN, Peripheral vascular disease, Current Smoking, Dyslipidemia, Family history of CAD, GPI Use, 1VD, 2VD, 3VD, In-stent restenosis, Bifurcation, Thrombotic total occlusion, Long lesion (≥ 28 mm), Small vessel (≤ 2.75 mm), Stable angina, Unstable Angina, NSTEMI, STEMI, Silent Ischemia, AMI, Off label indication, HBA1C < 7%, No treated DM, Therapeutic life style modification-DM, Oral hypoglycemic agent-DM, Insulin treated DM, LV dysfunction (LVEF < 30%), Multivessel PCI

Primary Outcome in the Matched DM
Target Lesion Failure at 1 year

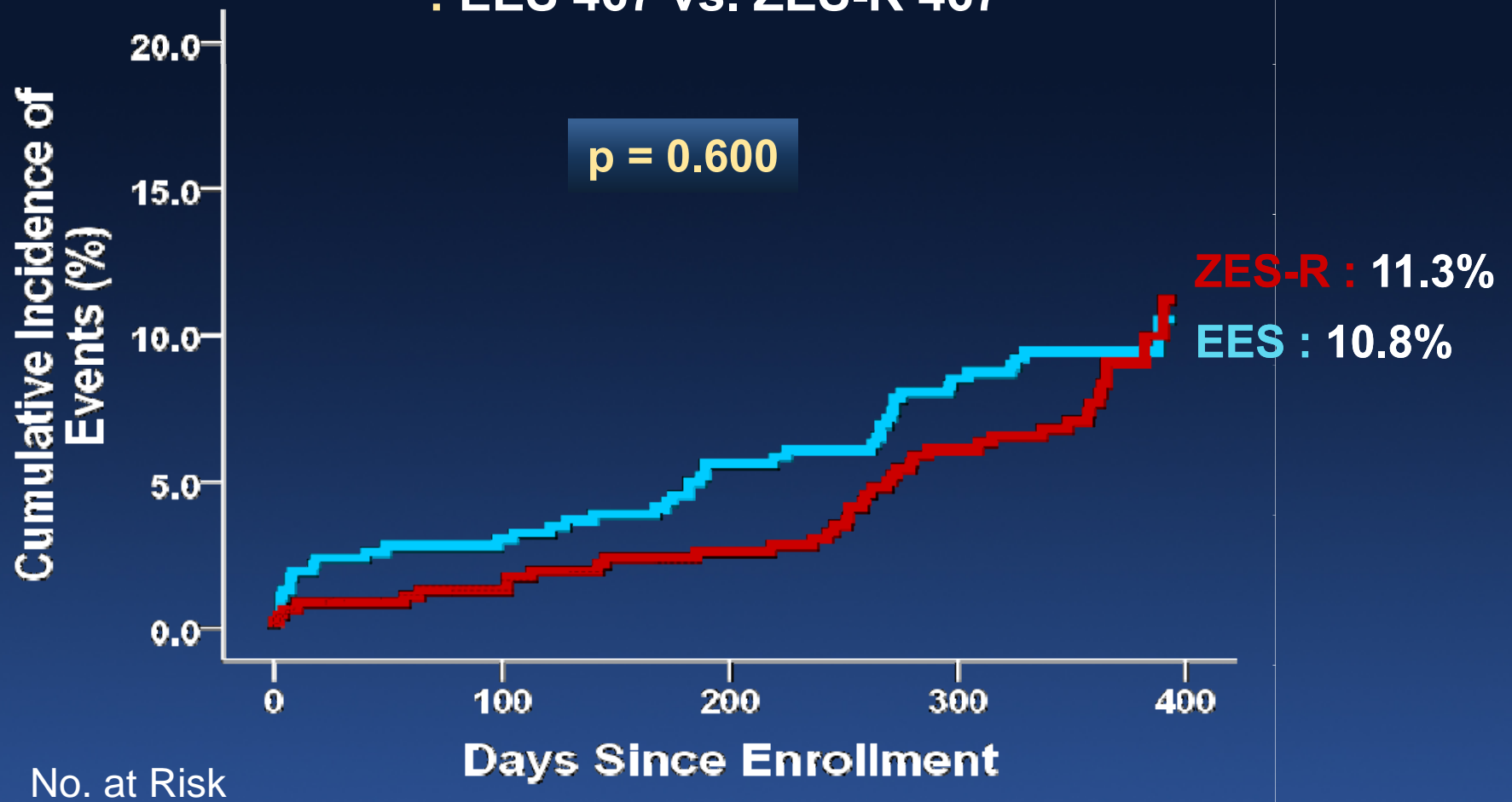**Propensity Score Matched Group Analysis : EES 467 vs. ZES-R 467**

p = 0.700

ZES-R : 4.4%
EES : 4.2%

Cumulative Incidence of Events (%)

Days Since Enrollment
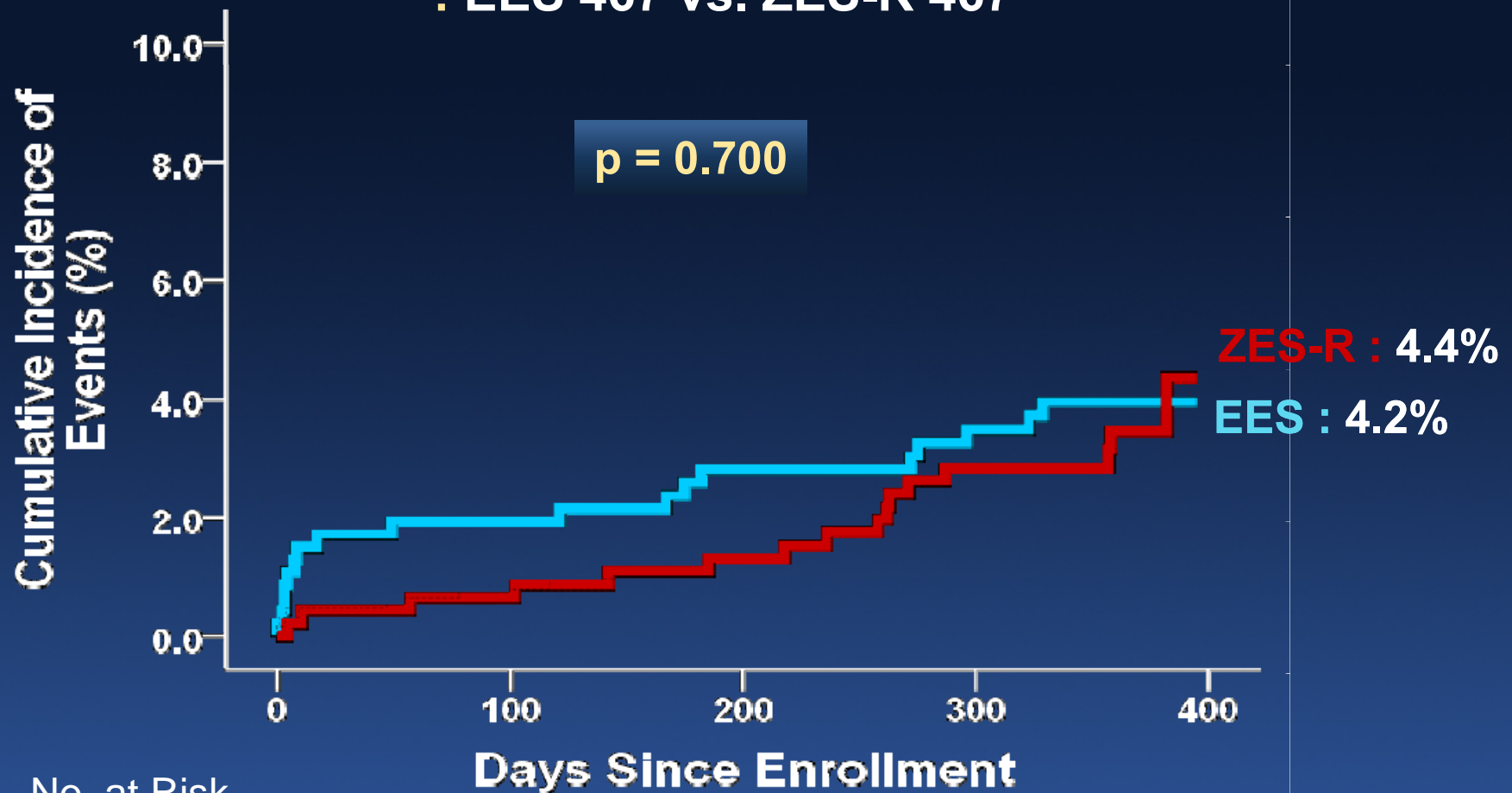
No. at Risk

EES	467	446	441	424	422
ZES-R	467	455	450	439	436

Major Secondary Outcome in the Matched DM
Patient-Oriented Composite Outcome at 1 year

Propensity Score Matched Group Analysis
: EES 467 vs. ZES-R 467

p = 0.600

ZES-R : 11.3%
EES : 10.8%

Cumulative Incidence of Events (%)

20.0

15.0

10.0

5.0

0.0

0   100   200   300   400

Days Since Enrollment

No. at Risk

EES	467	446	441	424	422
ZES-R	467	455	450	439	436

6M vs. 12M DAPT in Diabetics

6 Mo vs. 12 Mo

SNUH

Baseline Characteristics

6M DAPT vs. 12M DAPT in Diabetics

Characteristic	12M DAPT (n = 1342)		6M DAPT (n = 251)		p-value
Actual Duration of DAPT	**369.6 ± 17.1**		**298.3 ± 40.4**		**<.001**
Used Drug-eluting stent					0.887
Xience V/Promus EES	836	62.3%	155	61.8%	
Resolute ZES	506	37.7%	96	38.2%	
Insulin treated Diabetes	174	13.0%	39	15.5%	0.312
LDL cholesterol (mg/dL)	98.65 ± 34.72		95.54 ± 34.22		0.223
eGFR (ml/min/1.73m²)	66.66 ± 28.02		67.88 ± 30.24		0.550
LV Ejection fraction	58.9 ± 11.5		57.6 ± 12.4		0.108
3-vessel disease	395	29.5%	79	31.7%	0.498
STEMI	154	11.5%	31	12.4%	0.747
In-stent restenosis	108	8.0%	17	6.8%	0.526
Bifurcation	236	17.6%	34	13.5%	0.120
Length ≥ 28 mm	629	46.9%	113	45.0%	0.630
Vessel diameter ≤ 2.75 mm	356	26.5%	55	21.9%	0.136
Off label indication	1028	76.6%	189	75.3%	0.686

Landmark Analysis of
Target Lesion Failure at 6 Months
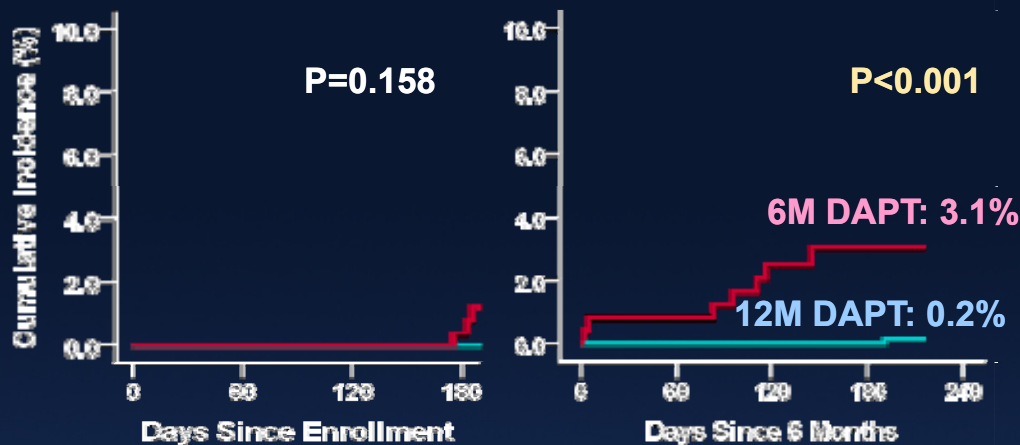
Composite of Cardiac death, Target vessel MI, TLR

Left panel: Log rank p = 0.293

Right panel: Log rank p = 0.001

6M DAPT: 5.0%
12M DAPT: 2.4%

y-axis: Cumulative Incidence of Events (%), 0.0, 2.0, 4.0, 6.0, 8.0, 10.0

Left x-axis: Days Since Enrollment, 0, 60, 120, 180

Right x-axis: Days Since 6 Months, 0, 60, 120, 180, 240
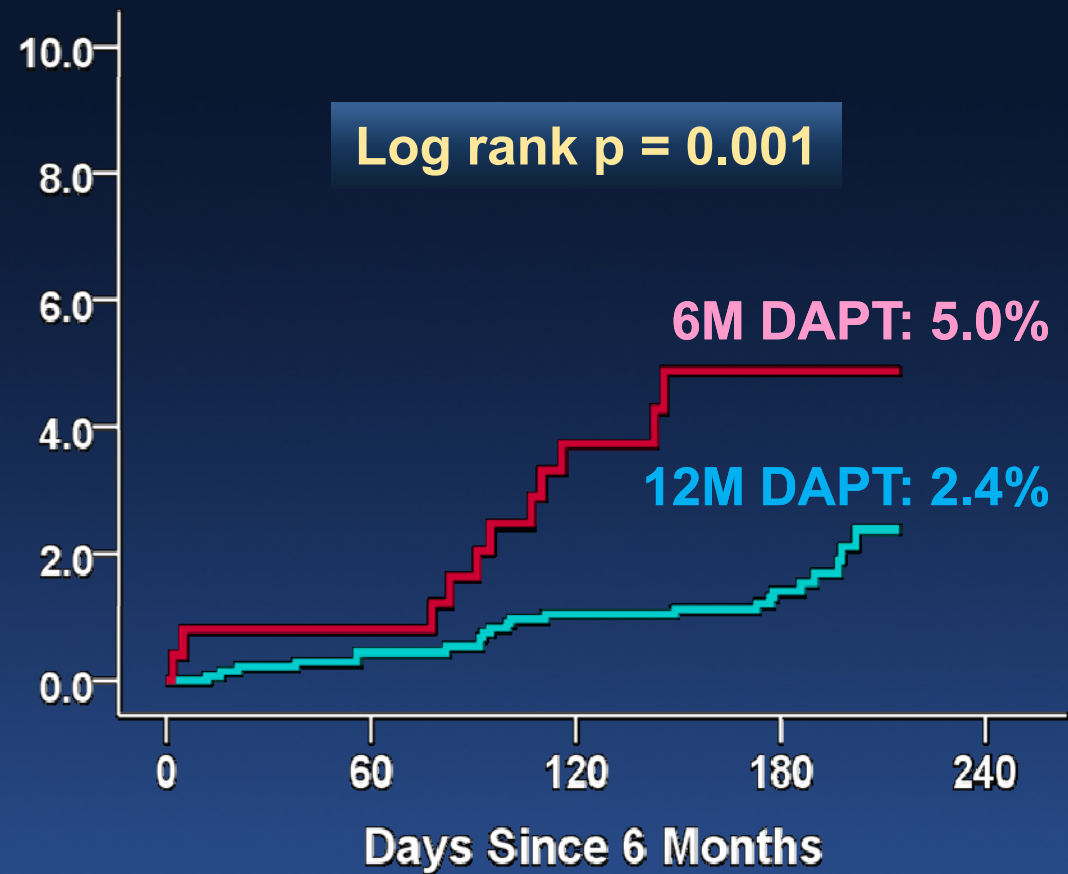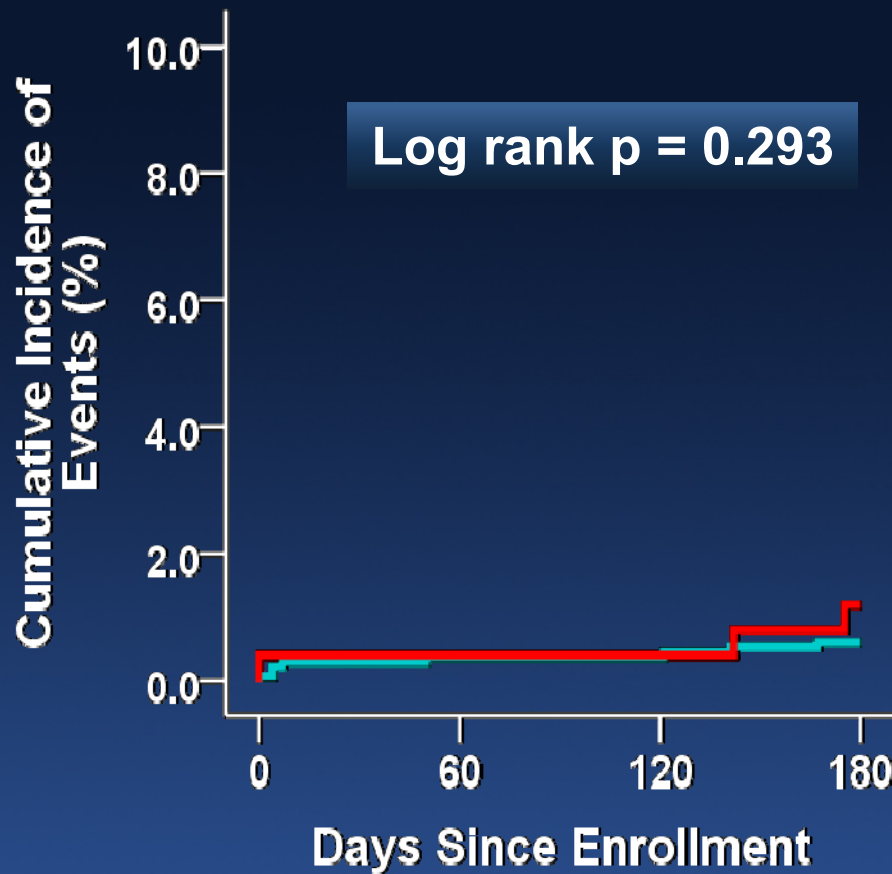
No. at Risk									
12M DAPT	1342	1337	1337	1334	1342	1336	1328	968	963
6M DAPT	251	250	250	247	249	244	222	82	82

Landmark Analysis of Individual Components of Target Lesion Failure at 6 Months

Interaction between DM vs. duration of DAPT

Subgroup	6M DAPT		12M DAPT		HR	p-value
	Events/Patient	%	Events/Patient	%		
Diabetes Mellitus	14/251	5.6%	31/1342	2.3%	4.459 (2.221-8.952)	<.001
No Diabetes Mellitus	5/337	1.5%	34/2382	1.4%	1.557 (0.589-4.117)	0.372

Diabetes Mellitus

No Diabetes Mellitus

P Interaction = 0.044

0.1 Favors 6M 1 Favors 12M 10
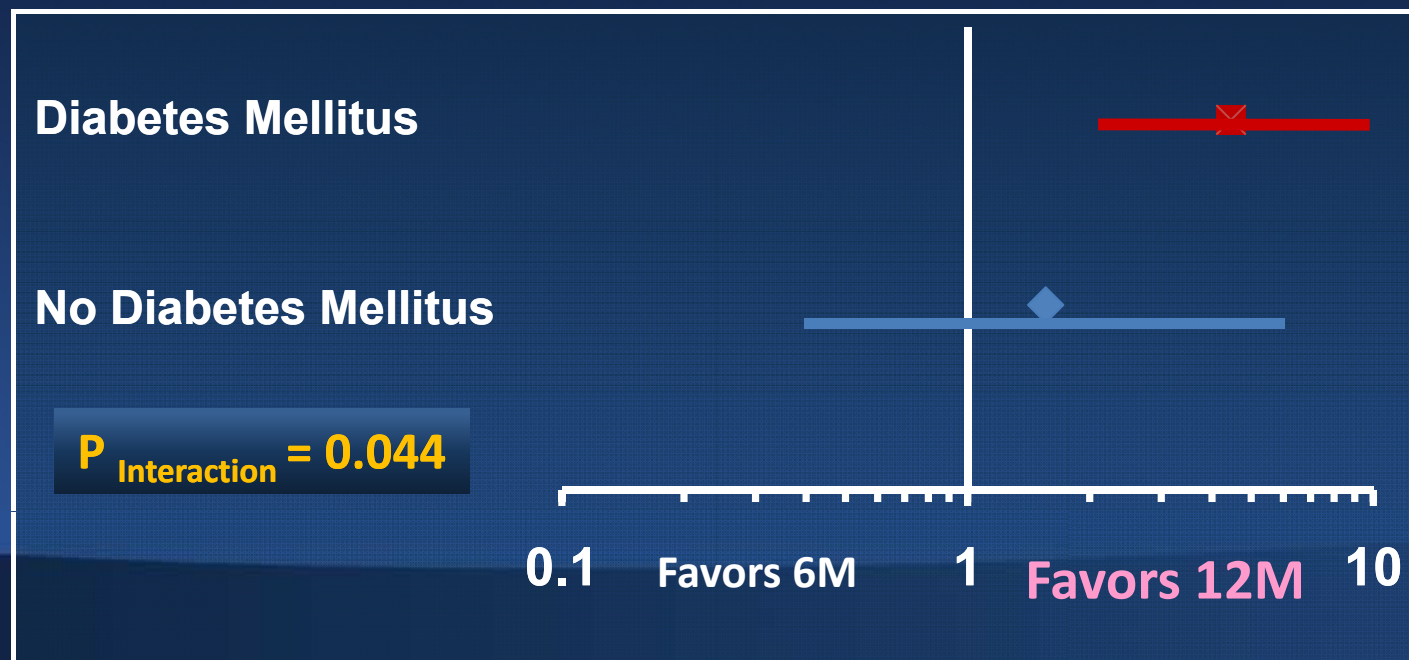
Independent Predictors of TLF in DM

Adjusted Hazard Ratio in Whole DM Population

Factors	Hazard Ratio	95% C.I.	p-value
SAPT after 6 months	4.459	2.221 - 8.952	<.001
Chronic Renal Failure	4.393	1.913 – 10.087	<.001
In-stent restenosis	4.226	1.843 – 9.690	0.001
Left main PCI	4.082	1.561 – 10.674	0.004
Vessel diameter ≤ 2.75 mm	2.690	1.325 – 5.463	0.006
EES versus ZES-R ¶	0.922	0.475 – 1.788	0.810

¶ In Propensity Score Matched Group of Diabetes

EES versus ZES-R	1.237	0.595 – 2.571	0.570

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Resolute vs Xience : DM & DAPT duration

- **After unrestricted use of 2nd generation DES in all-comers receiving PCI, <u>diabetics had significantly worse clinical outcomes than</u> non-diabetics.**

- **Within 2nd generation DES for DM,**

  → EES and ZES-R showed <u>similar outcomes</u> up to 1 year follow-up.

- **In Diabetics → <u>shorter duration of DAPT</u> resulted in <u>significantly worse outcome</u> than prolonged duration of DAPT even with the use of 2nd generation DES.**

- **Our data support <u>longer-term DAPT</u> even with the use of 2nd generation DES <u>in diabetics</u>**