Stop ISR: How to Treat DES ISR Summary

Alan C. Yeung, MD
Li Ka Shing Professor of Medicine
Interventional Cardiology
Stanford University School of Medicine

Mechanisms of In-Stent Restenosis

	BMS	DES
• Biological factors		
Drug resistance		X
Hypersensitivity	X	X
Hyperproliferative status (e.g. diabetes)	X	X
• Mechanical factors		
Non uniform stent strut distribution	X	X
Stent fractures	?	X
Polymer peeling		X
Non uniform drug deposition		X
• Technical factors		
Stent underexpansion	X	X
Uncovered edge lesions	X	X
Barotrauma to unstented segments	X	X

Adapted from Dangas 2010

RESOLUTE Global Clinical Program

2 All-comer Trials with Data on ISR Lesions

Enrollment Complete - In Follow Up

RESOLUTE[1]	Non-RCT First-in-Human (R=139)		5 yr
RESOLUTE AC[2,3]	1:1 RCT vs. Xience V (R=1140; X=1152)		3 yr
RESOLUTE Int[4]	Non-RCT Observational (R=2349)		2 yr
RESOLUTE US[5]	2.25 – 4.0 mm Non-RCT vs. Hx Control (R=1402)		2 yr
RESOLUTE Japan	2.5 – 3.5 mm Non-RCT (R=100) vs. Hx Control		2 yr
R Japan SVS	2.25 Non-RCT vs. PG (R=65)		< 1yr
RESOLUTE US	38 mm sub-study Non-RCT vs. PG (R=114)		< 1yr
R-China RCT	1:1 RCT vs. Taxus (R=200; T=200)		< 1yr
RESOLUTE Asia	Non-RCT Observational (R=312)		< 1yr
R-China Registry	Non-RCT Observational (R=1800)		< 1yr

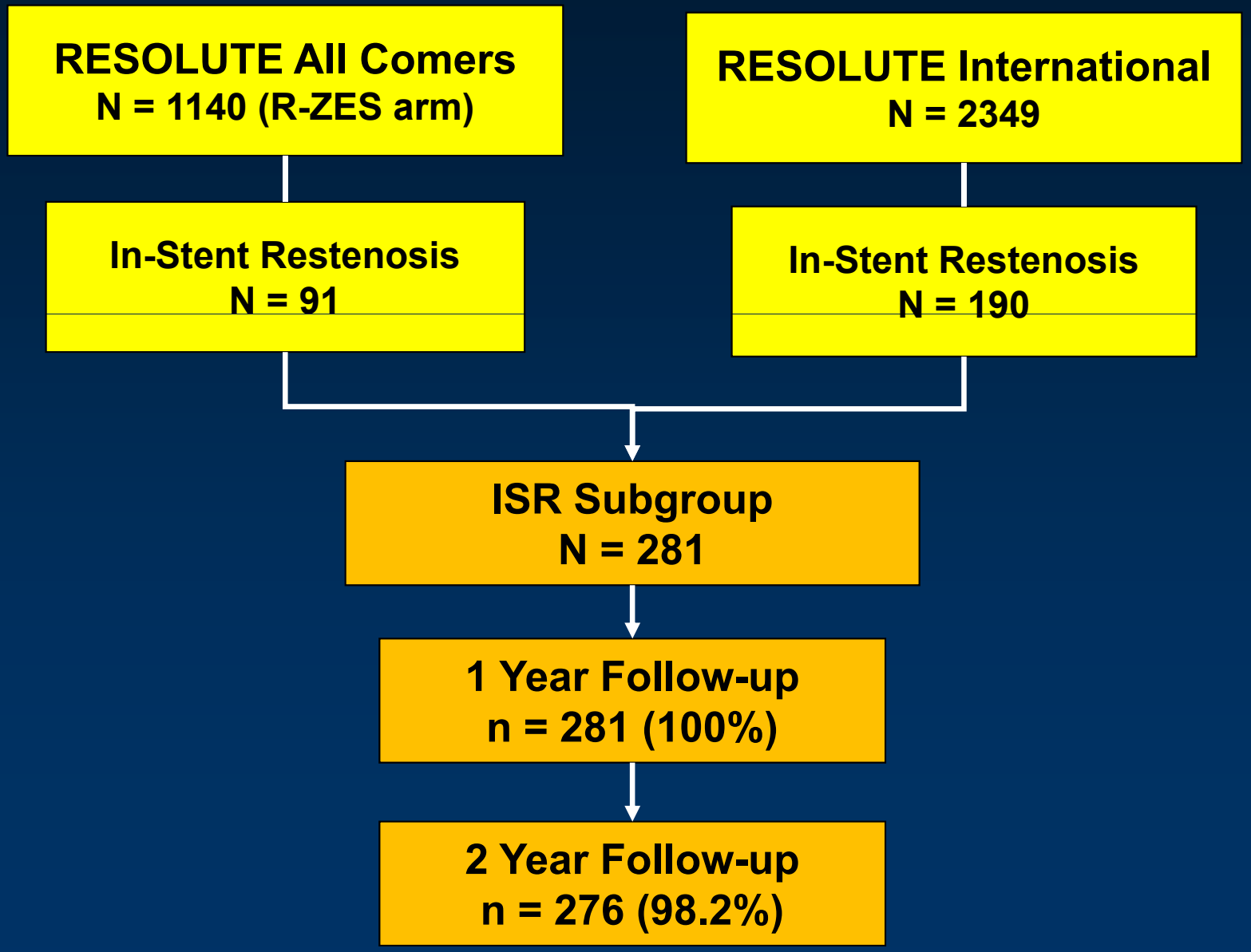
Enrolling / Planning

RI-US Registry	Post-approval study (R=230)		plan

[1] Meredith IT, et al. *EuroIntervention.* 2010;5:692-7. [2] Serruys PW, et al. *N Engl J Med.* 2010;363:136-46. [3] Silber S, et al. *Lancet.* 2011;377:1241-47. [4] Neumann FJ, et al. *EuroIntervention*. 2012;7(10):1181-8. [5] Yeung AC, et al. *JACC*. 2011;57:1778-83.

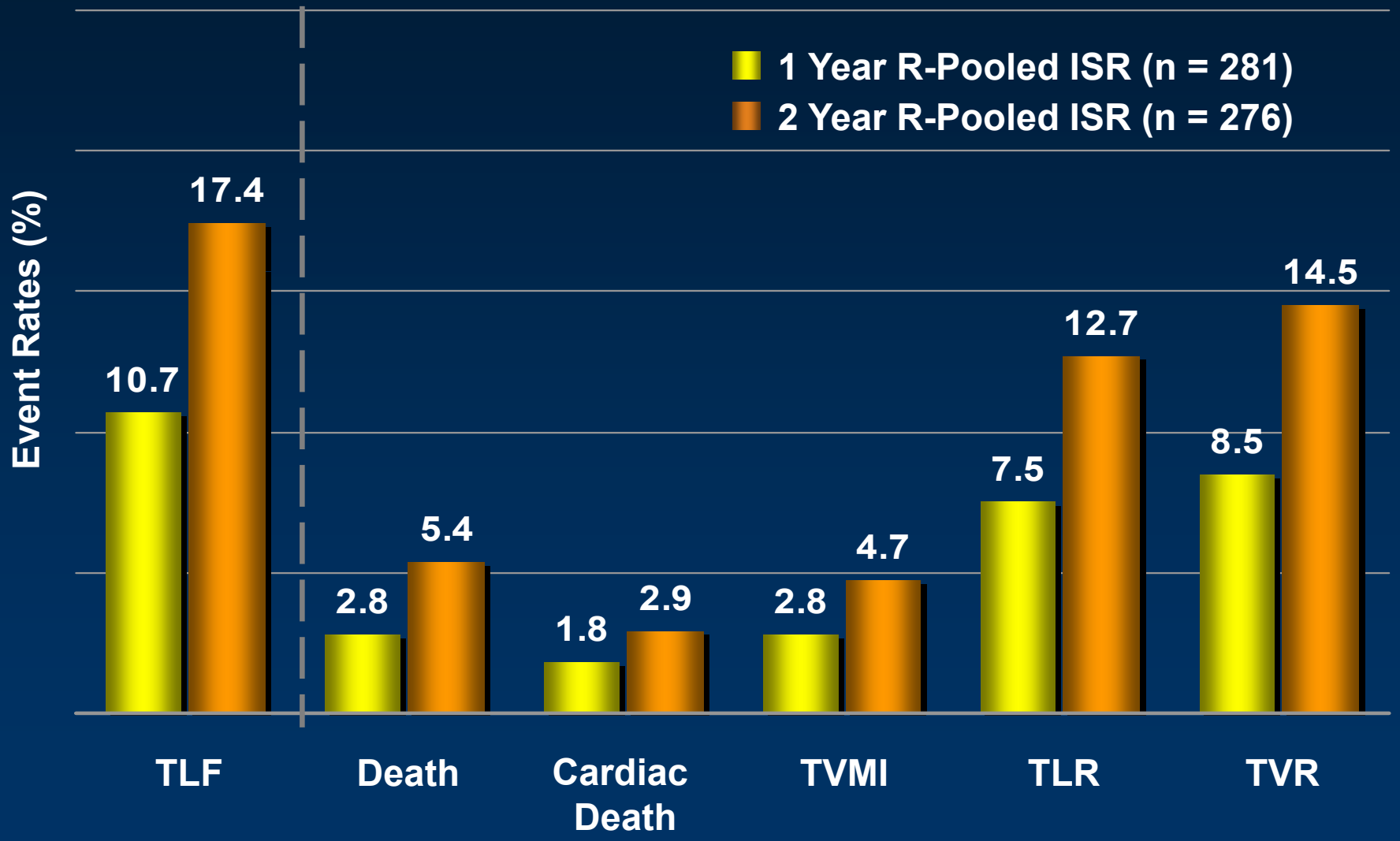
RESOLUTE Pooled – ISR Subgroup

Patient Flowchart



RESOLUTE Pooled – ISR Subgroup

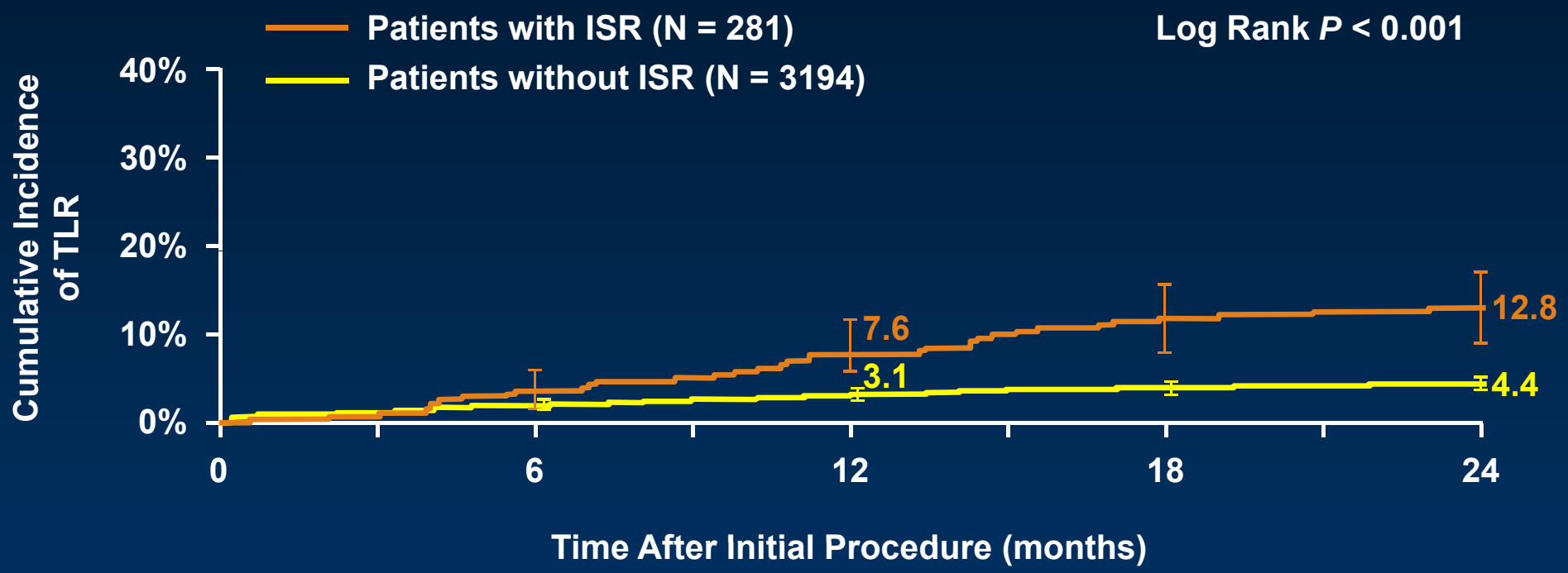
Clinical Outcomes at 1 & 2 Years



TLF (Target Lesion Failure) is defined as cardiac death, TVMI, or clinically indicated TLR.
Note previous reported data on patients with ISR: TAXUS V-ISR TVR at 9 months: 10.5%, ISAR-DESIRE TVR at 1 year: SES 8%, PES 19%, PEP-CAD II trial TLR at 1 year for PES:15.4%.

RESOLUTE Pooled – ISR Subgroup

Target Lesion Revascularization to 2 Years

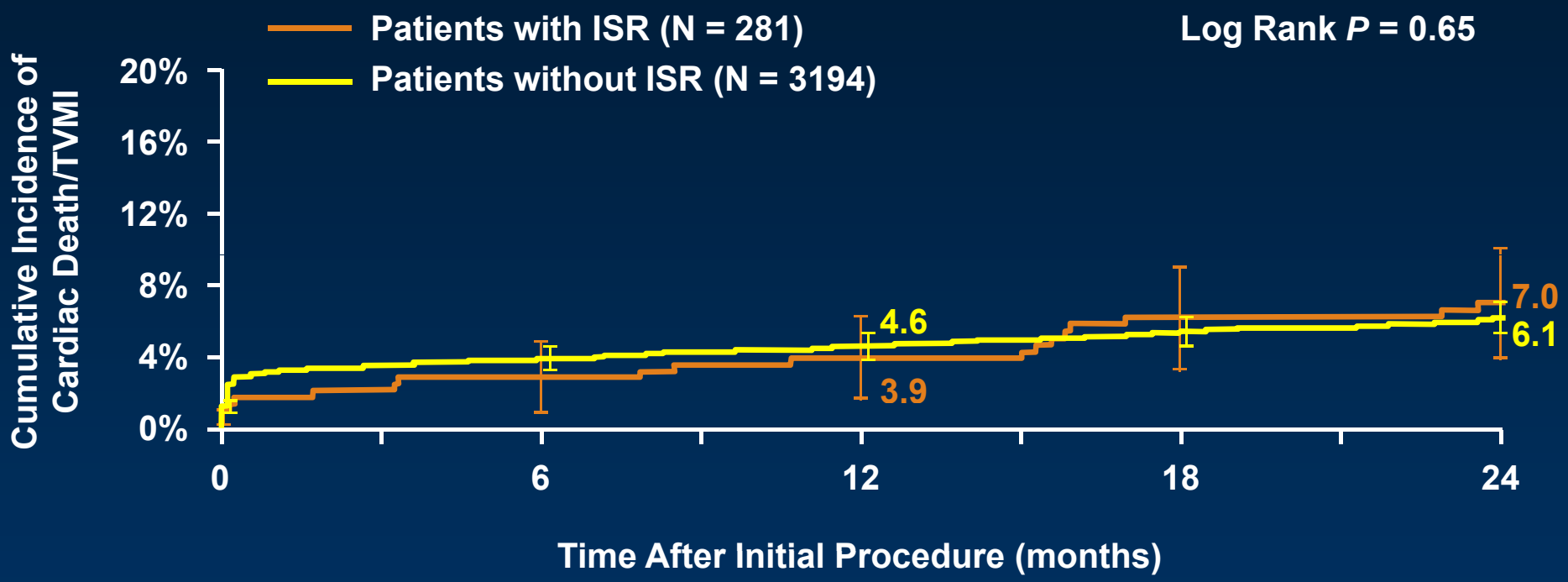


Pts at risk					
ISR	281	281	267	253	237
% CI	0.0	3.6	7.6	11.7	12.8
No-ISR	3194	3188	3072	2994	2903
% CI	0.1	1.9	3.1	3.9	4.4

TLR is clinically driven.
Note previous reported data on patients with ISR: PEP-CAD II trial TLR at 1 year for PES:15.4%.

RESOLUTE Pooled – ISR Subgroup

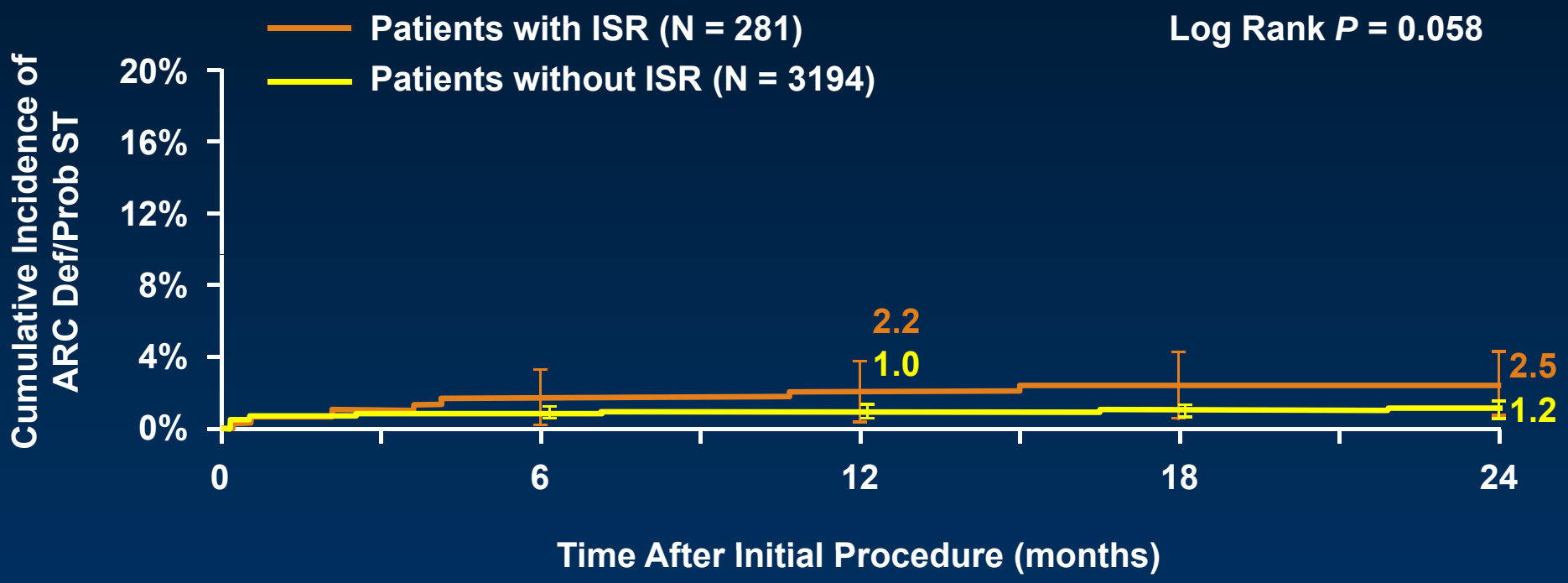
Cardiac Death & Target Vessel MI to 2 Years



Pts at risk					
ISR	281	280	271	267	257
% CI	0.4	2.9	3.9	6.1	7.0
No-ISR	3194	3150	3034	2984	2912
% CI	1.3	3.9	4.6	5.4	6.1

RESOLUTE Pooled – ISR Subgroup

ARC Def/Prob Stent Thrombosis to 2 Years



Pts at risk					
ISR	281	281	274	270	264
% CI	0.0	1.8	2.2	2.5	2.5
No-ISR	3194	3186	3109	3065	2995
% CI	0.2	0.9	1.0	1.1	1.2

RESOLUTE Pooled – ISR Subgroup

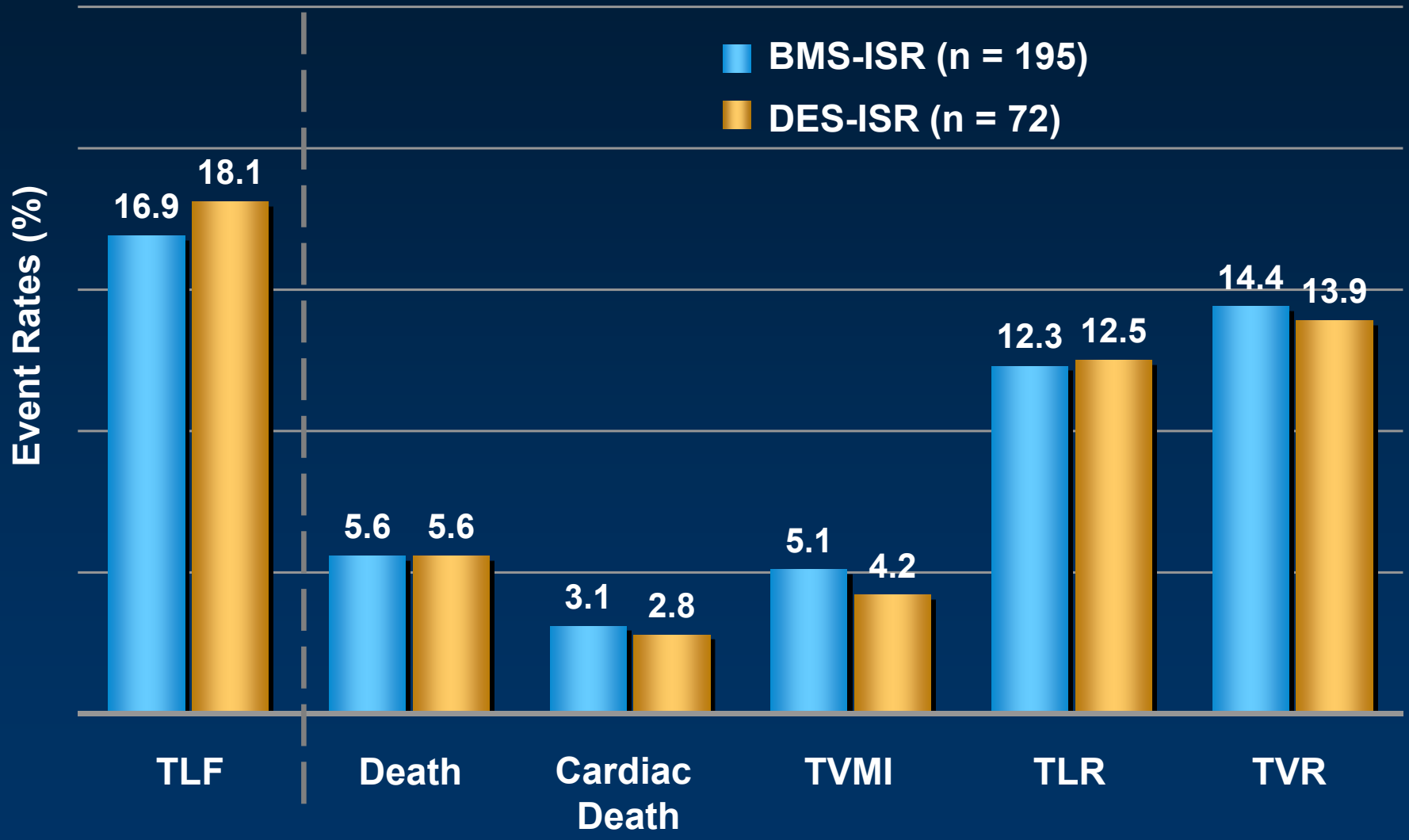
Multivariate Analysis: Predictors of TLF to 2 Years

Total Population	*Odds Ratio*	*P-Value*
ISR	1.853	<0.001
Prior CABG	1.757	<0.001
Bend ≥45 °	1.380	0.010
Previous MI	1.293	0.040
Unstable Angina	1.272	0.041
Pre-procedure RVD (mm)	0.801	0.049

ISR Population	*Odds Ratio*	*P-Value*
Prior CABG	4.195	<0.001
Unstable Angina	2.516	0.009
Age (yrs)	0.963	0.021

RESOLUTE Pooled – ISR of BMS vs. DES

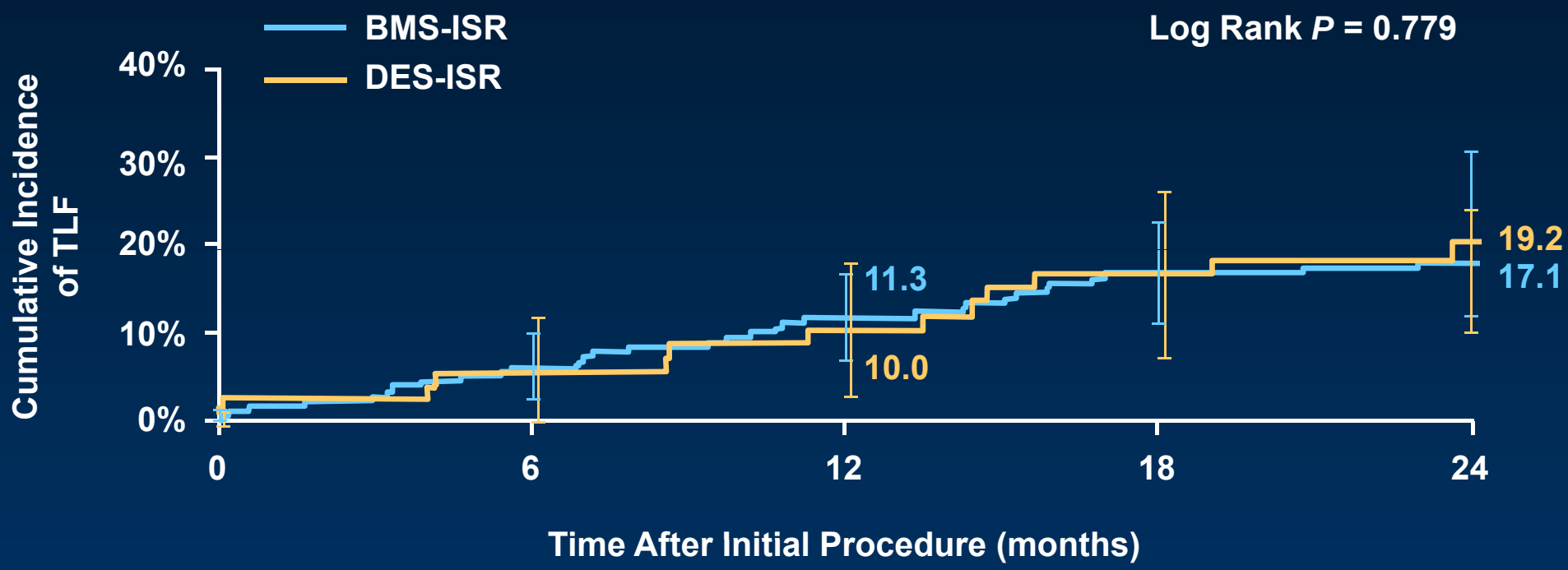
Clinical Outcomes at 2 Years



TLF (Target Lesion Failure) is defined as cardiac death, TVMI, or clinically driven TLR.
Note, previously reported data on BMS-ISR: TAXUS V-ISR TVR at 9 months was 10.5% and on DES-ISR: ISAR-DESIRE II TLR at 1 year was SES 16.6%, PES 14.6%.

RESOLUTE Pooled – ISR of BMS vs. DES

Target Lesion Failure (TLF) to 2 Years



Pts at risk					
BMS-ISR	196	195	182	172	160
% CI	0.5	6.2	11.3	16.0	17.1
DES-ISR	70	70	66	62	57
% CI	0.0	5.7	10.0	15.9	19.2

TLF (Target Lesion Failure) is defined as cardiac death, TVMI, or clinically driven TLR.
Note, previously reported data on BMS-ISR: TAXUS V-ISR TVR at 9 months was 10.5% and on DES-ISR: ISAR-DESIRE II TLR at 1 year was SES 16.6%, PES 14.6%.

RESOLUTE Pooled – ISR of BMS vs. DES

Data in Perspective at 12 Months

Trial	*Type of ISR*	*N*	*Device*	*TLR*	*TVR*
RESOLUTE Pooled	BMS-ISR	195	R-ZES	8.0%	9.0%
ISAR DESIRE[1]	BMS-ISR	100 100	SES PES		8% 19%
PEPCAD II[2]	BMS-ISR	66 65	DEB PES	6.3% 15.4%	
TAXUS V-ISR[3]	BMS-ISR	195	PES		10.5% (9M)
Steinberg et al.[4]	BMS-ISR	119	DES		10.3%
RESOLUTE Pooled	DES-ISR	73	R-ZES	5.5%	6.8%
ISAR DESIRE II[5]	DES-ISR	225 225	SES PES	16.6% 14.6%	
PEPCAD-DES[6]	DES-ISR	72	DEB	15.3% (6M)	
Steinberg et al.[4]	DES-ISR	119	DES		22.2%

[1] Kastrati A, et al. *JAMA*. 2005;293:165-71.
[2] Unverdorben M, et al. *Circulation*. 2009;119:2986-94.
[3] Koizumi T, et al. *Cardiovasc Revasc Med*. 2010;11:140-8.
[4] Steinberg D, et al. *Am J Cardiol* .2009;103:491-5.
[5] Mehilli J, et al. *J Am Coll Cardiol* . 2010;55:2710-6.
[6] Rittger H, et al. *J Am Coll Cardiol* .2012;59: 1377-82.

Treatment Options According to the Mechanism of Restenosis

Type of restenosis	Mechanism of Restenosis	Treatment Option
- Focal	- Underexpansion - Fracture - Heterogenous Drug Distribution	DEB DEB? Different DES? Different DES
- Focal at stent edge	- Geographical miss - Plaque progression	DES DES
- Diffuse in-stent	- Vessel biology/Drug resistance	Different DES/CABG
- Proliferative	- Vessel biology/Drug resistance	Another DES/ CABG