Experience and Opportunities for Asia-PAC in Global Device Studies

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Global device study

- Reasons for the need of global device study
  - Outcomes from a device study could be influenced by backgrounds such as race, diseases, drugs, etc.
    - The data from one country/region may not be applicable for the other.
    - Possibility of different outcome makes Regulators cautious in the countries with tight regulatory system such as USA(FDA) or Japan. (PMDA).
  - Rapid data collection through global study may help for shortening device lag.
- What we did?
  - Two global device studies were completed under the "Harmonization By Doing"* program.

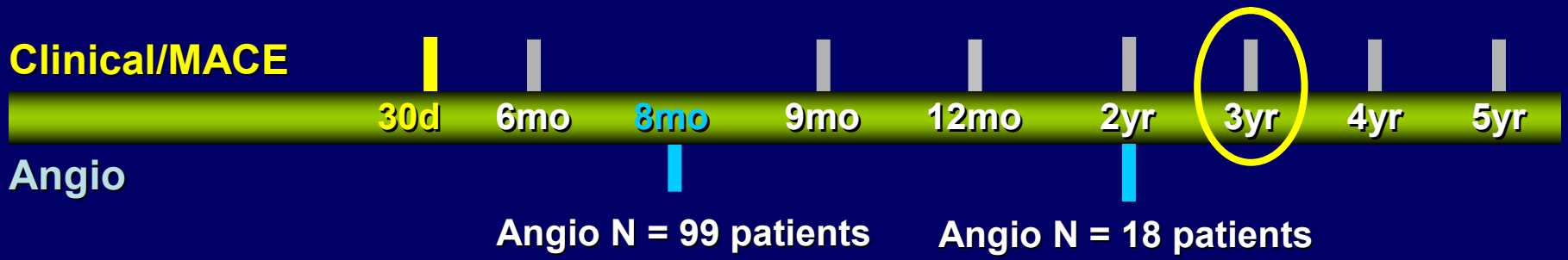
*Cooperative work between USA & Japan with Industry, Regulators, and Academia to solve problems such as device access or device approval.

ENDEAVOR Japan

Prospective, Multicenter, Single-Arm Study
Assessing Safety and Efficacy in a Japanese Population
As a Part of Global ENDEAVOR Studies

Single *De Novo* Native
Coronary Artery Lesions (Type A-B2)
Stent Diameter: 2.25-3.5 mm
Stent Lengths: 18-30 mm (8/9 mm bailout)
Lesion Length: 14-27 mm
Pre-dilatation required

N = 99 patients (includes 20 PK Sub-Study Patients)
11 sites in Japan



Primary Endpoint: TVF (cardiac death, MI, TVR) at 9 months
Drug Therapy: ASA and Ticlid ≥3 months
Zotarolimus Dose: 10 μg per mm stent length

Differences in Dual Anti-Platelet Therapy

Between Other ENDEAVOR Trials AND ENDEAVOR Japan

ENDEAVOR II	ENDEAVOR Japan
Pre Procedure	**Pre Procedure**
Clopidogrel 300 mg loading	Ticlopidine 200 mg/day for 2 weeks prior to the procedure
Intra Procedural	**Intra Procedural**
Heparin as needed	Heparin as needed
Nitroglycerin intra coronary	Nitroglycerin intra coronary
IIb/IIIa Inhibitors optional	N/A
Discharge	**Discharge**
ASA 75 mg/day indefinitely	ASA 200 mg/day 12 weeks then 100 mg/day indefinitely
Clopidogrel 75 mg/day minimum of 12 weeks	Ticlopidine 200 mg/day minimum of 12 weeks

More contemporary anti-thrombotic agents such as GpIIbIIIa antagonists and bivalirudin are not available in Japan.

ENDEAVOR Japan

Patient Demographics

	Japan n = 99	EII n = 598	*P* value
Male Gender (%)	67.7	77.2	0.043
Age (years)	67.7 ± 10.3	61.6 ± 10.5	<0.001
Prior MI (%)	24.2	39.7	0.003
Prior PCI (%)	31.3	21.7	0.040
Diabetes Mellitus (%)	38.4	18.2	<0.001
Insulin-dependent	10.1	4.5	0.030
Unstable Angina (%)	4.0	30.3	<0.001
Hyperlipidemia (%)	76.8	80.5	0.415
Current Smoker (%) (within 30 days)	27.3	25.9	0.805

ENDEAVOR Japan

Pre-Procedural Characteristics

	Japan n = 99	EII n = 598	*P* value
LAD (%)	39.4	43.2	0.511
B2/C Lesions (%)	88.9	78.5	0.015
RVD (mm)	2.78 ± 0.52	2.73 ± 0.48	0.395
Lesion Length (mm)	13.90 ± 6.05	14.04 ± 5.56	0.828
Stent Length (mm)	21.87 ± 5.10	23.38 ± 6.69	0.010
Pre-procedure MLD (mm)	0.84 ± 0.38	0.83 ± 0.34	0.655

ENDEAVOR Japan

Post-Procedural Characteristics

	Japan n = 99	EII n = 598	*P* value
In-Stent MLD (mm)	2.68 ± 0.46	2.59 ± 0.43	0.061
In-Stent Acute Gain (mm)	1.83 ± 0.40	1.76 ± 0.44	0.124
In-Stent DS (%)	3.05 ± 11.37	6.04 ± 10.43	0.009
In-Segment MLD (mm)	2.23 ± 0.51	2.21 ± 0.49	0.709
In-Segment DS (%)	20.15 ± 9.37	20.39 ± 10.26	0.825
Stent Length/Lesion Length	1.75 ± 0.62	1.84 ± 0.74	0.232
Stents per Lesion	1.07 ± 0.26	1.13 ± 0.38	0.058

ENDEAVOR Japan

Angiographic Results at 8 months

	Japan n = 98	EII n = 264	*P* value
QCA			
RVD (mm)	2.80 ± 0.51	2.75 ± 0.43	0.391
In-stent			
DS (%)	23.7 ± 17.9	27.9 ± 17.3	0.041
LL (mm)	0.53 ± 0.43	0.62 ± 0.46	0.089
ABR (%)	8.2	9.5	0.838
In-segment			
DS (%)	29.2 ± 15.3	32.7 ± 16.3	0.067
LL (mm)	0.23 ± 0.42	0.36 ± 0.46	0.018
ABR (%)	8.2	13.3	0.205

ENDEAVOR Japan

Clinical Results at 36 months vs EII

	Japan 36 months N = 94	EII 36 months N = 585	*P* value
Composite MACE	10.6% (10/94)	12.1% (71/585)	0.864
Death	3.2% (3/94)	3.6% (21/585)	1.000
Q-Wave MI	0.0% (0/94)	0.3% (2/585)	1.000
Non Q-Wave MI	2.1% (2/94)	2.9% (17/585)	1.000
TLR	5.3% (5/94)	7.2% (42/585)	0.663
TL-CABG	0.0% (0/94)	0.5% (3/585)	1.000
TL-PCI	5.3% (5/94)	6.8% (40/585)	0.823
TVR (non-TL)	1.1% (1/94)	2.9% (17/585)	0.492
TVF	9.6% (9/94)	12.6% (74/585)	0.498
Stent Thrombosis (ARC Def/Prob)	0.0% (0/94)	0.9% (5/585)	1.000
Early (<30 days)	0.0% (0/94)	0.5% (3/585)	1.000
Late (≥30 days)	0.0% (0/94)	0.2% (1/585)	1.000
Very Late (≥365 days)	0.0% (0/94)	0.2% (1/585)	1.000

Numbers are based on E Japan 3 year, and E II 5 year locked databases.

ENDEAVOR Japan

Conclusions

- The 8-, 12- and 36-month outcomes in a Japanese population are consistent with those from the international ENDEAVOR II trial
- No stent thrombosis was found in the Japan study

SPIRIT III Japan

- US – Japan Single Protocol Study
  - Under Harmonization By Doing (HBD)
  - Identical Eligibility Criteria and Study Procedure
  - CEC, Angiographic Corelab, IVUS Corelab, and DSMB are responsible for review/analyze/adjudicate both US and Japan data
  - Difference in Antiplatelet Medication (ticlopidine vs. clopidogrel)

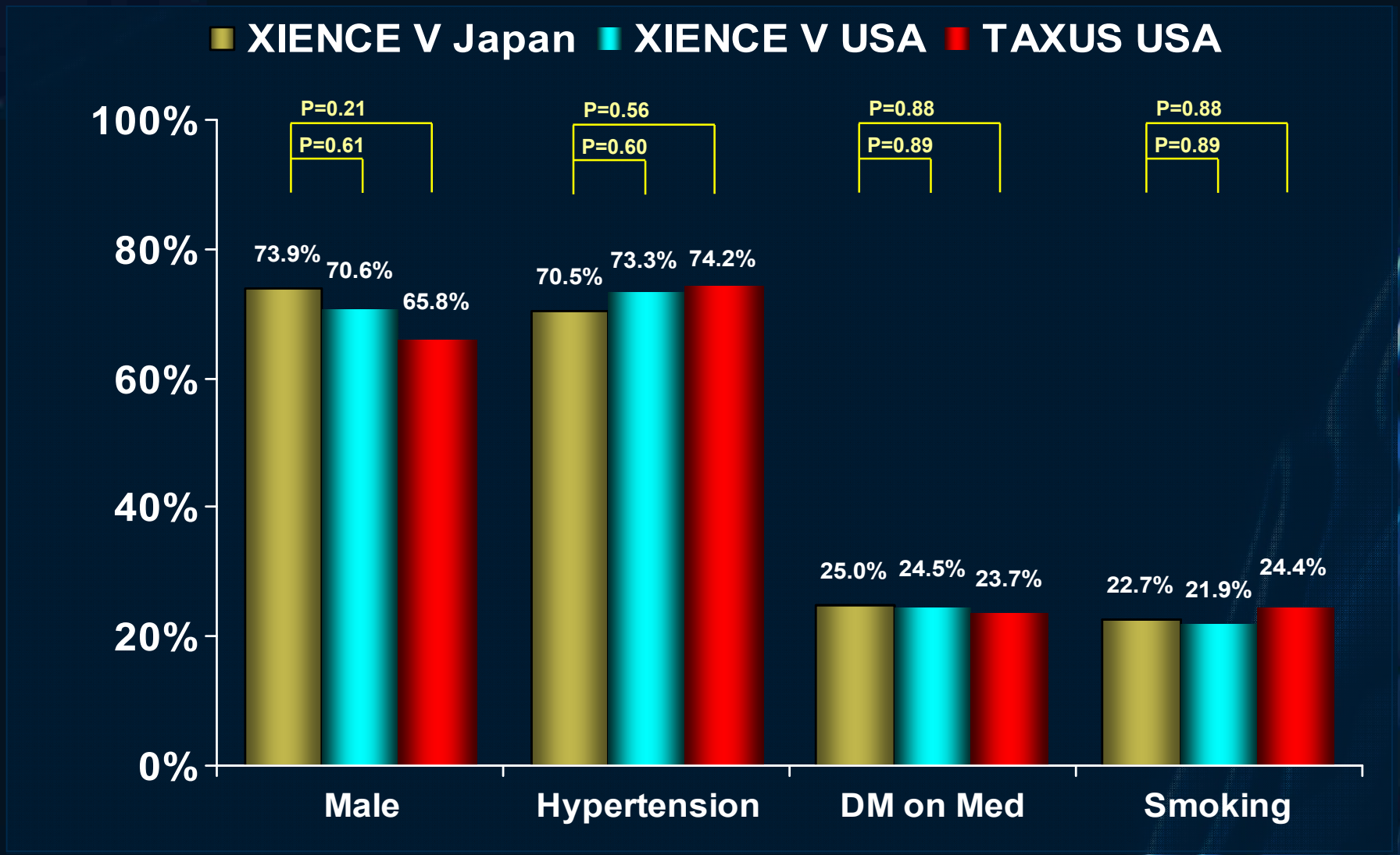
Spirit III

Patients Enrolled

XIENCE V Japan	XIENCE V US Angio Cohort	TAXUS US Angio Cohort
88 patients	445 patients	188 patients
102 lesions	496 lesions	220 lesions
(102 IVUS lesions)	(181 IVUS lesions)	(93 IVUS lesions)

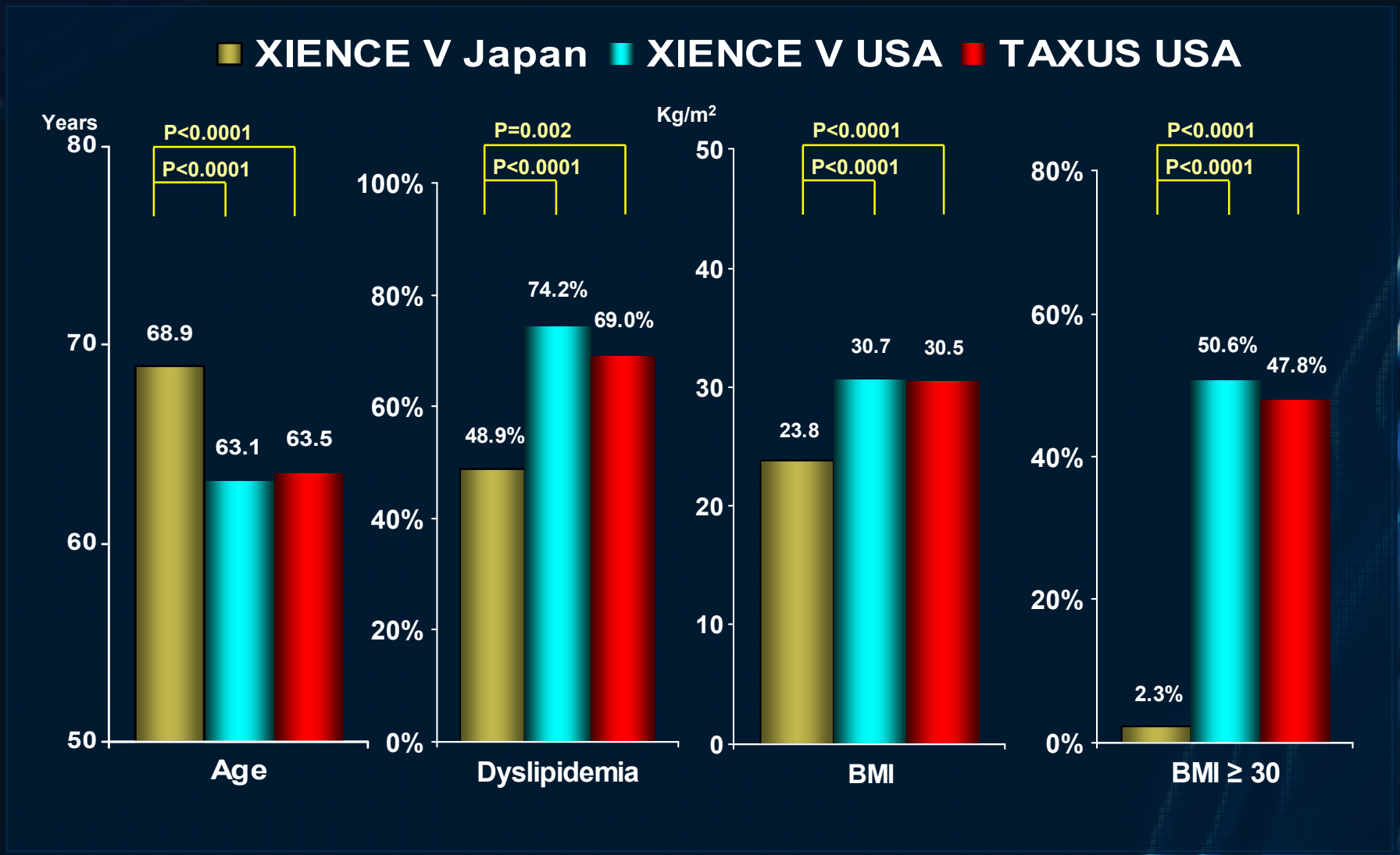
SPIRIT Trials

Patient Background - Similar Characteristics



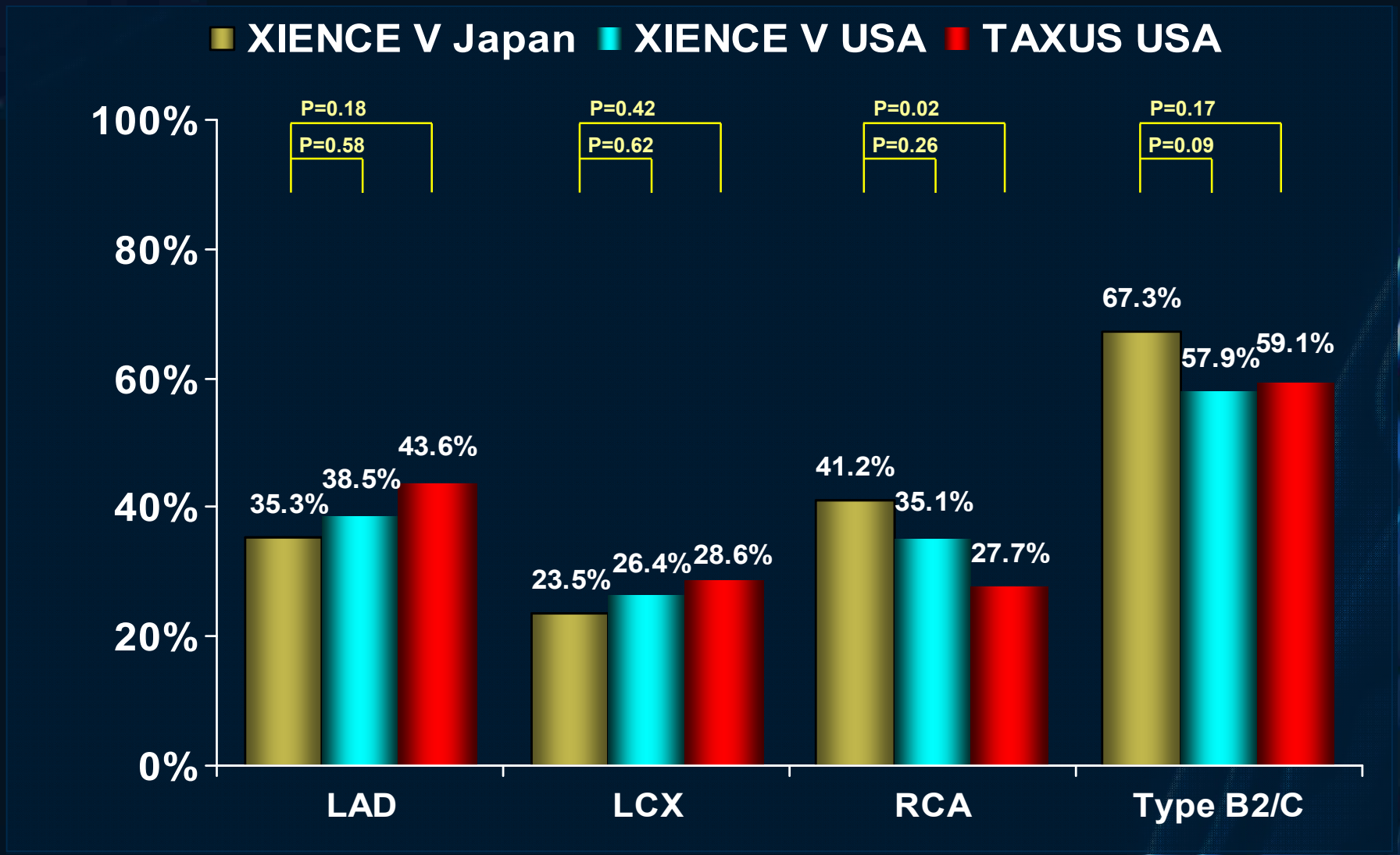
SPIRIT Trials

Patient Background
- Different Characteristics



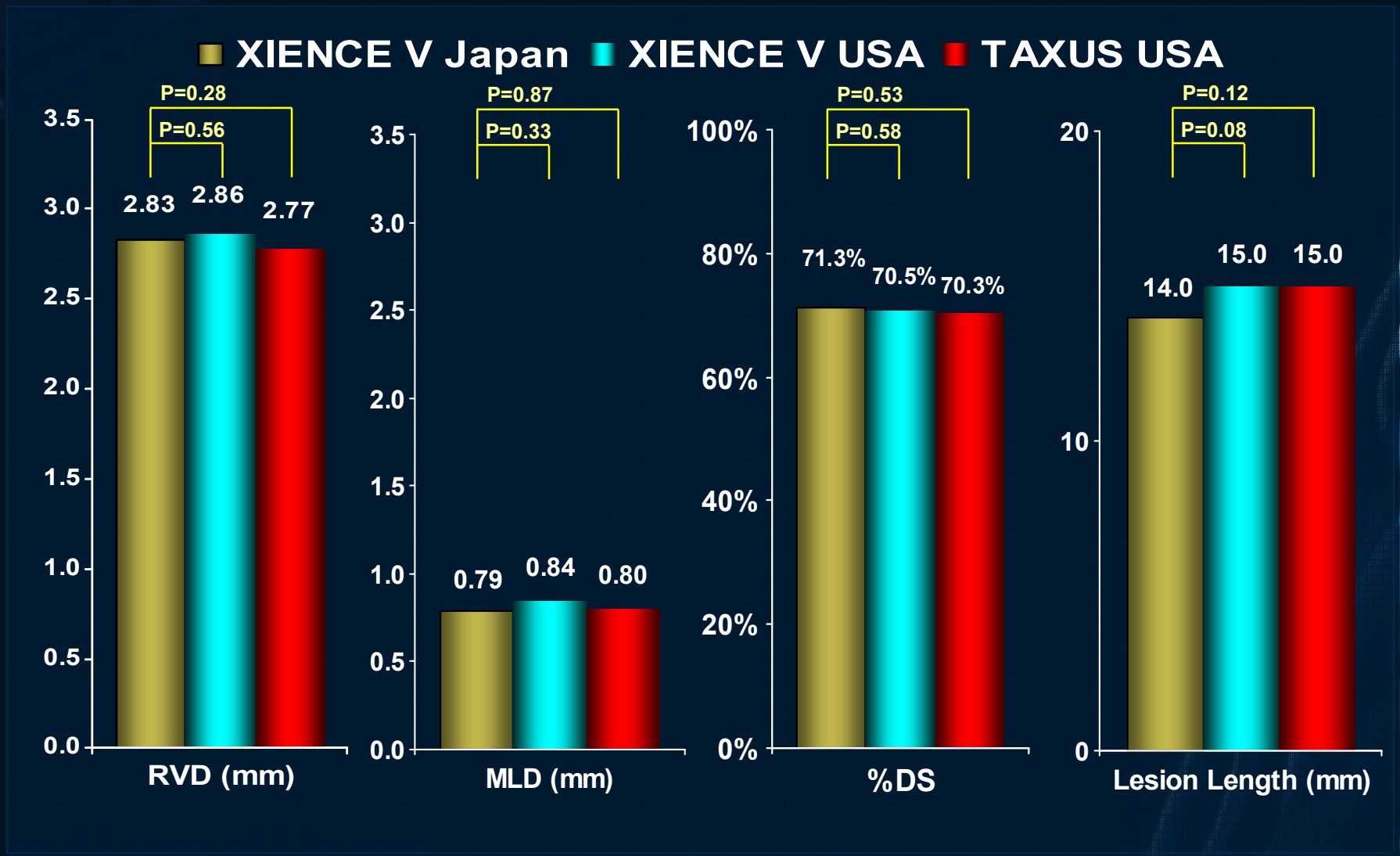
SPIRIT Trials

Lesion Characteristics

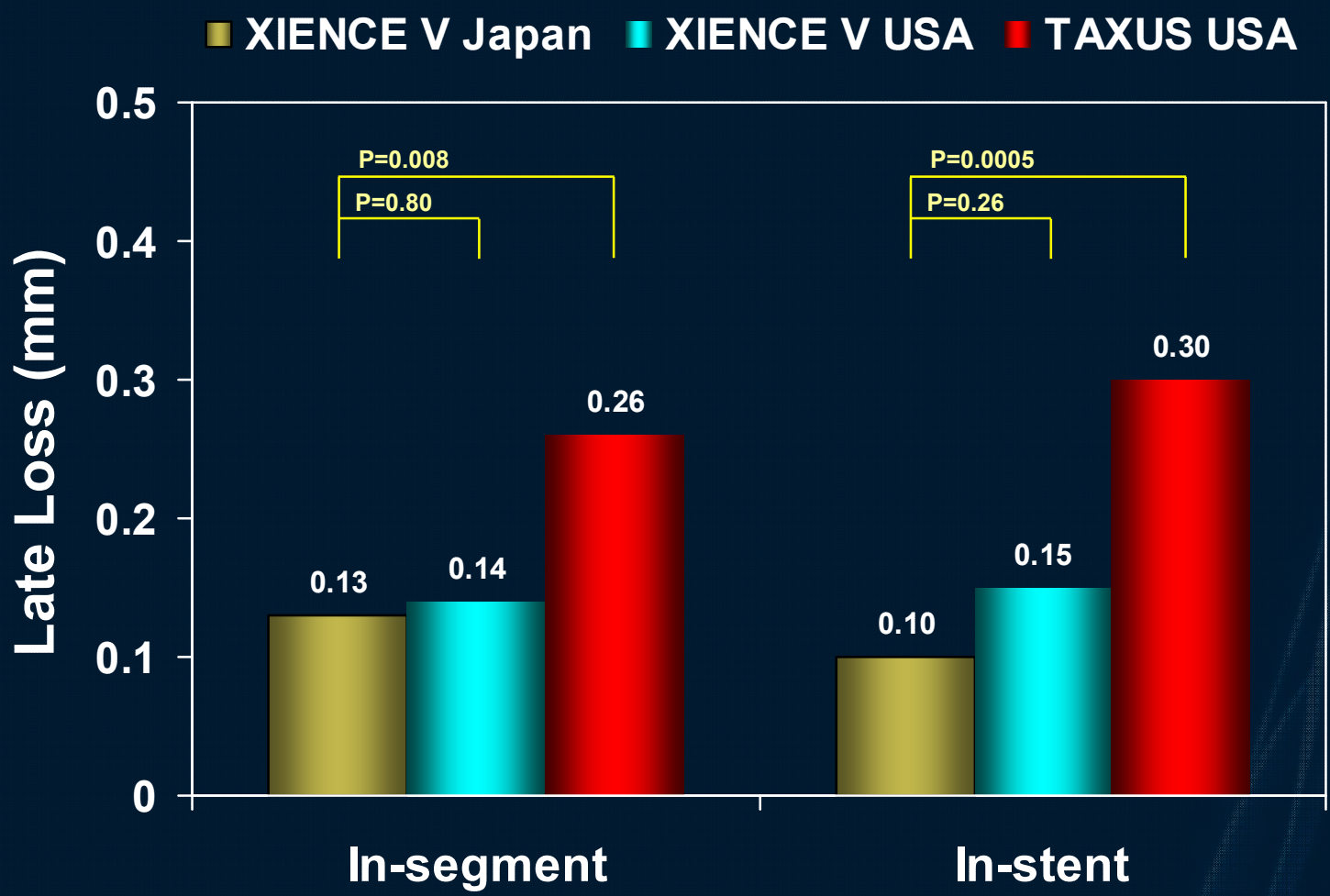


SPIRIT Trials

Baseline QCA

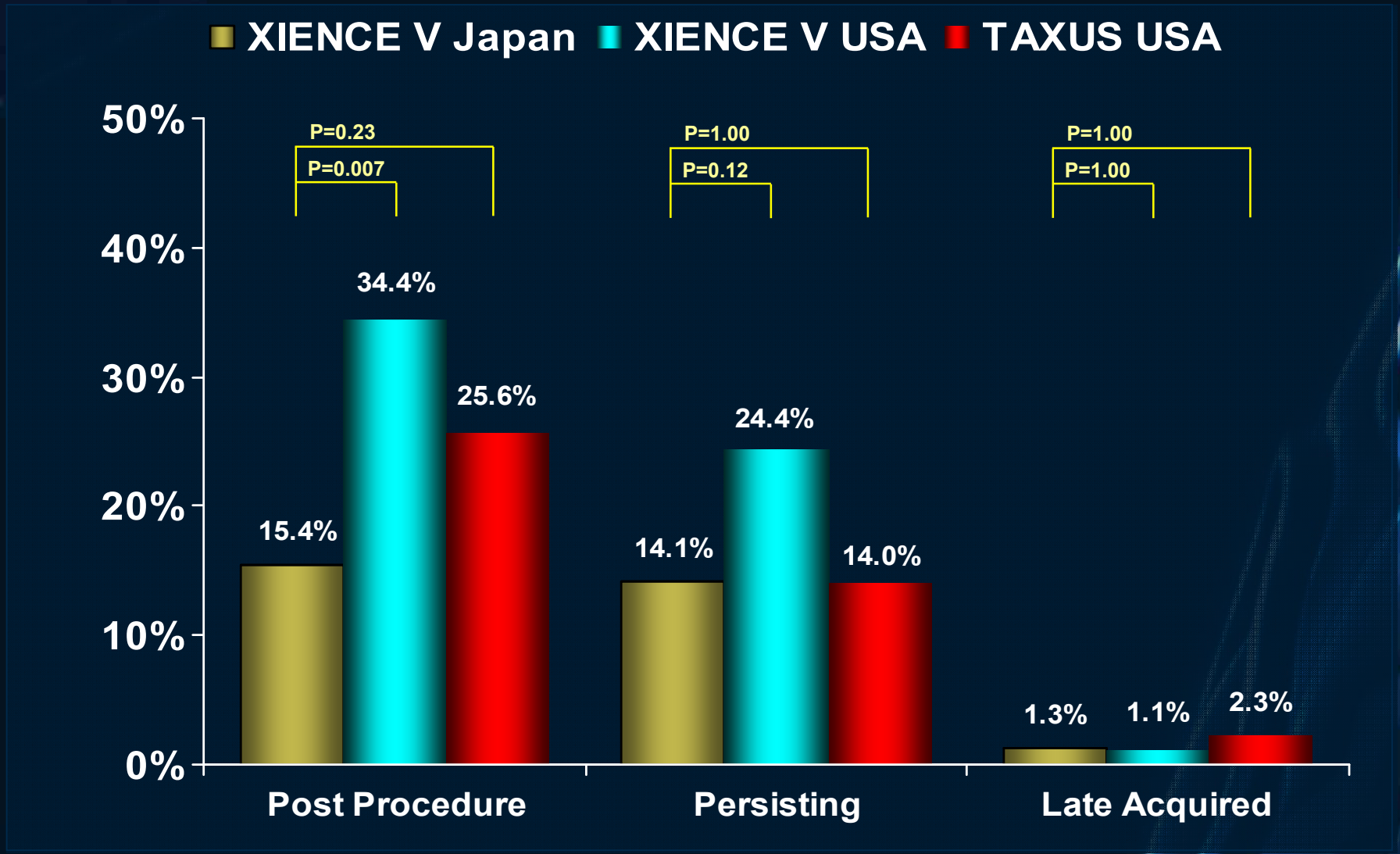


Late Loss at 8 Month (All Target Lesions)



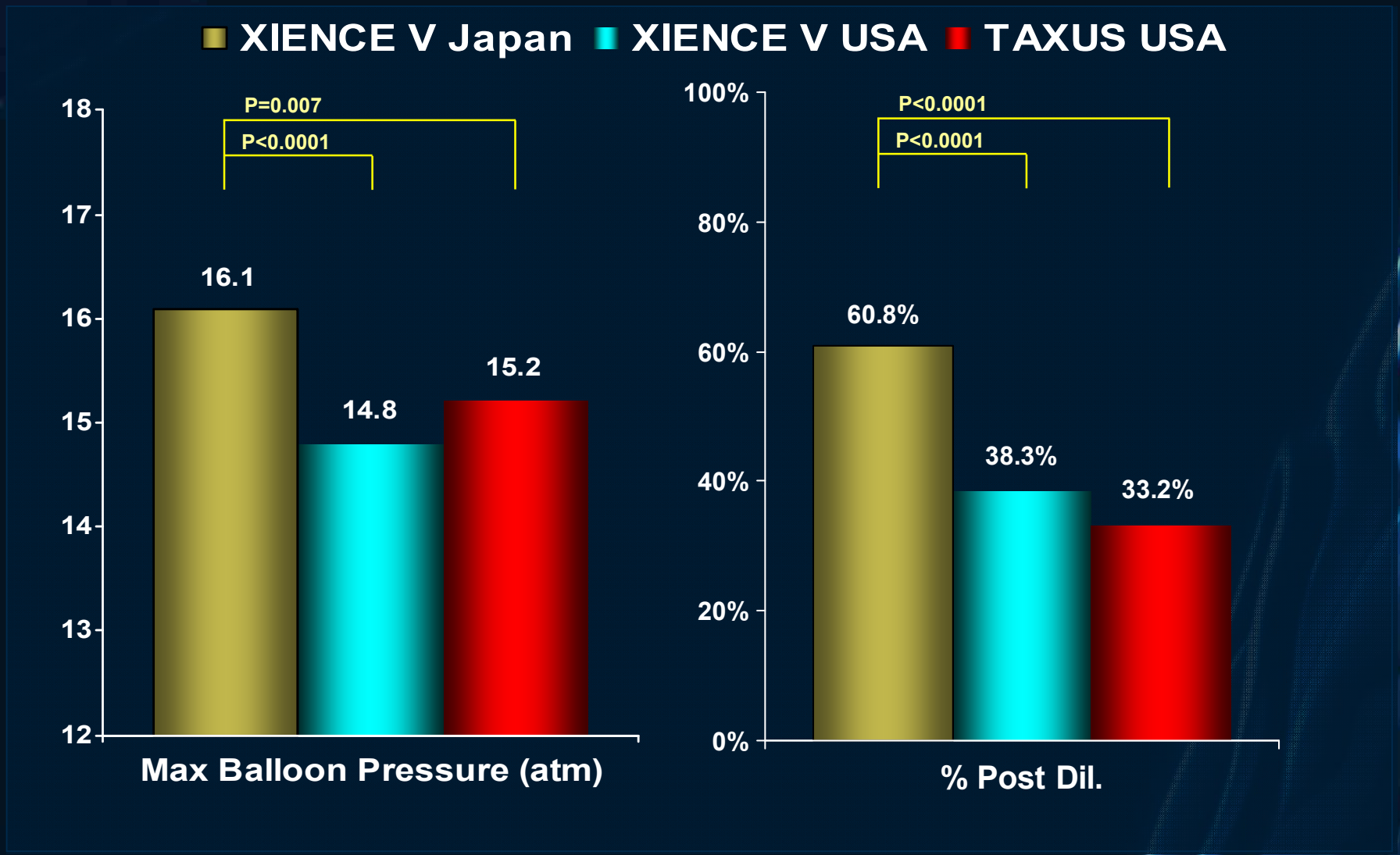
SPIRIT Trials

Incomplete Stent Apposition



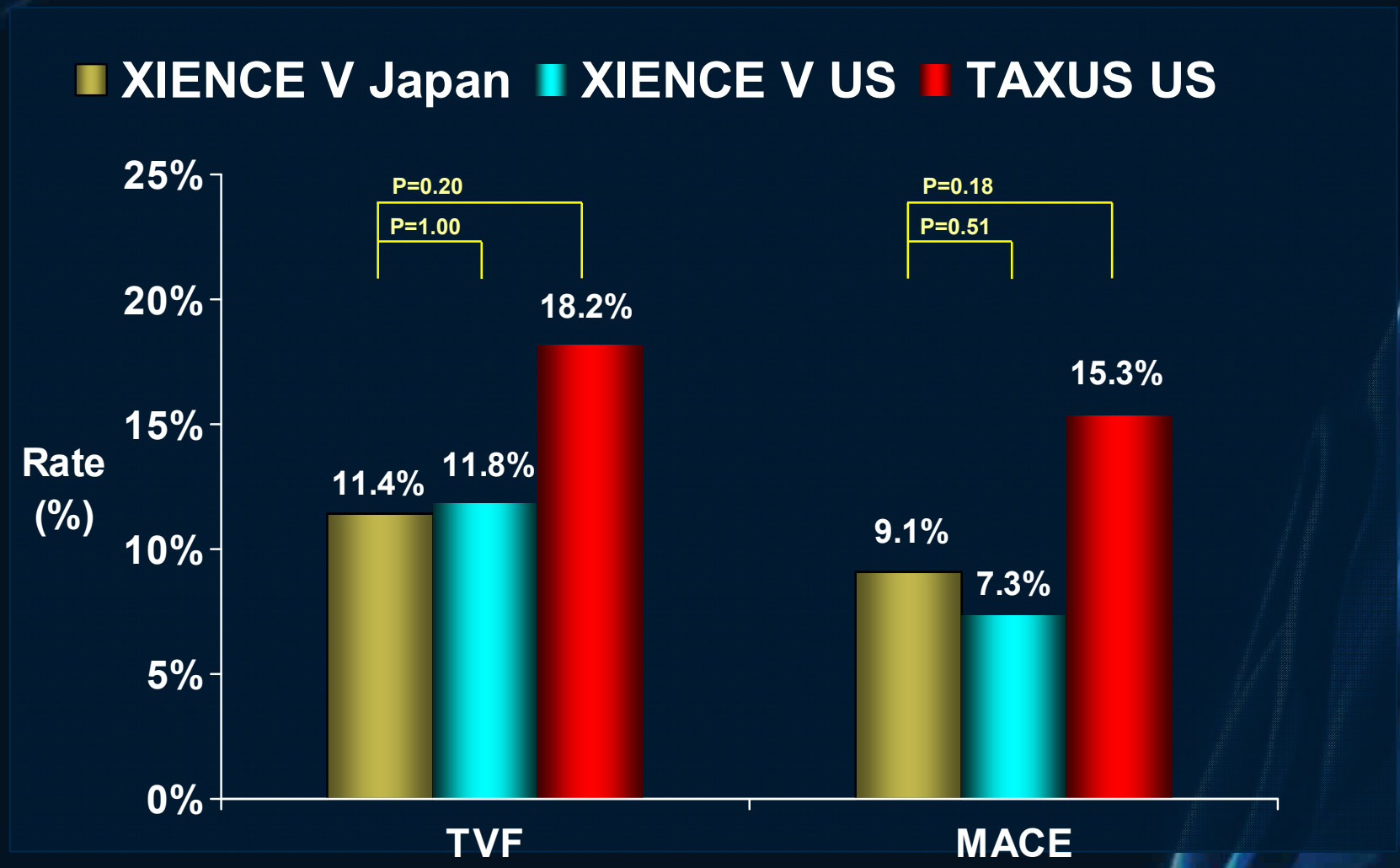
SPIRIT Trials

Max Pressure and Post Dilatation



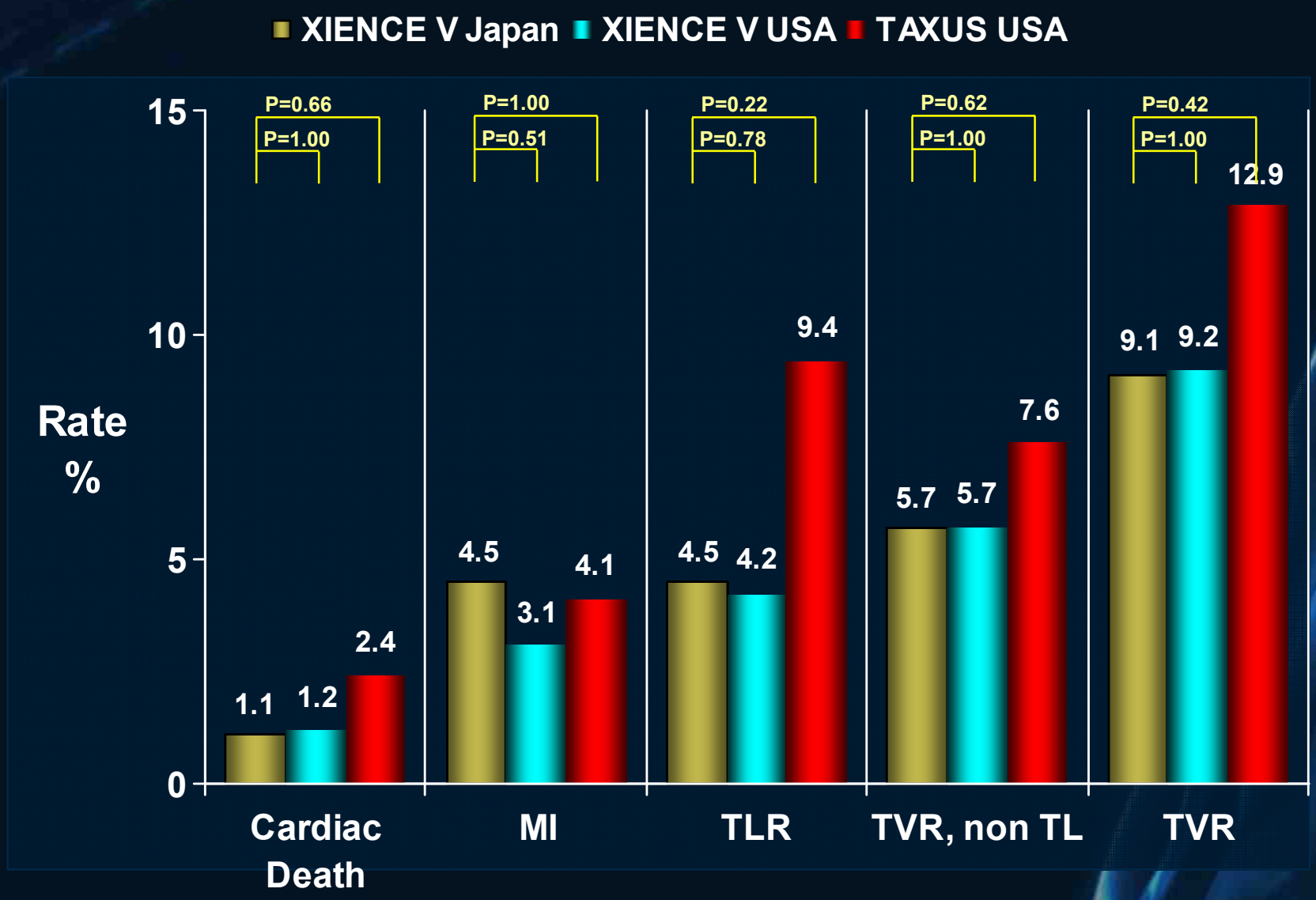
SPIRIT Trials

TVF and MACE through 2 Years



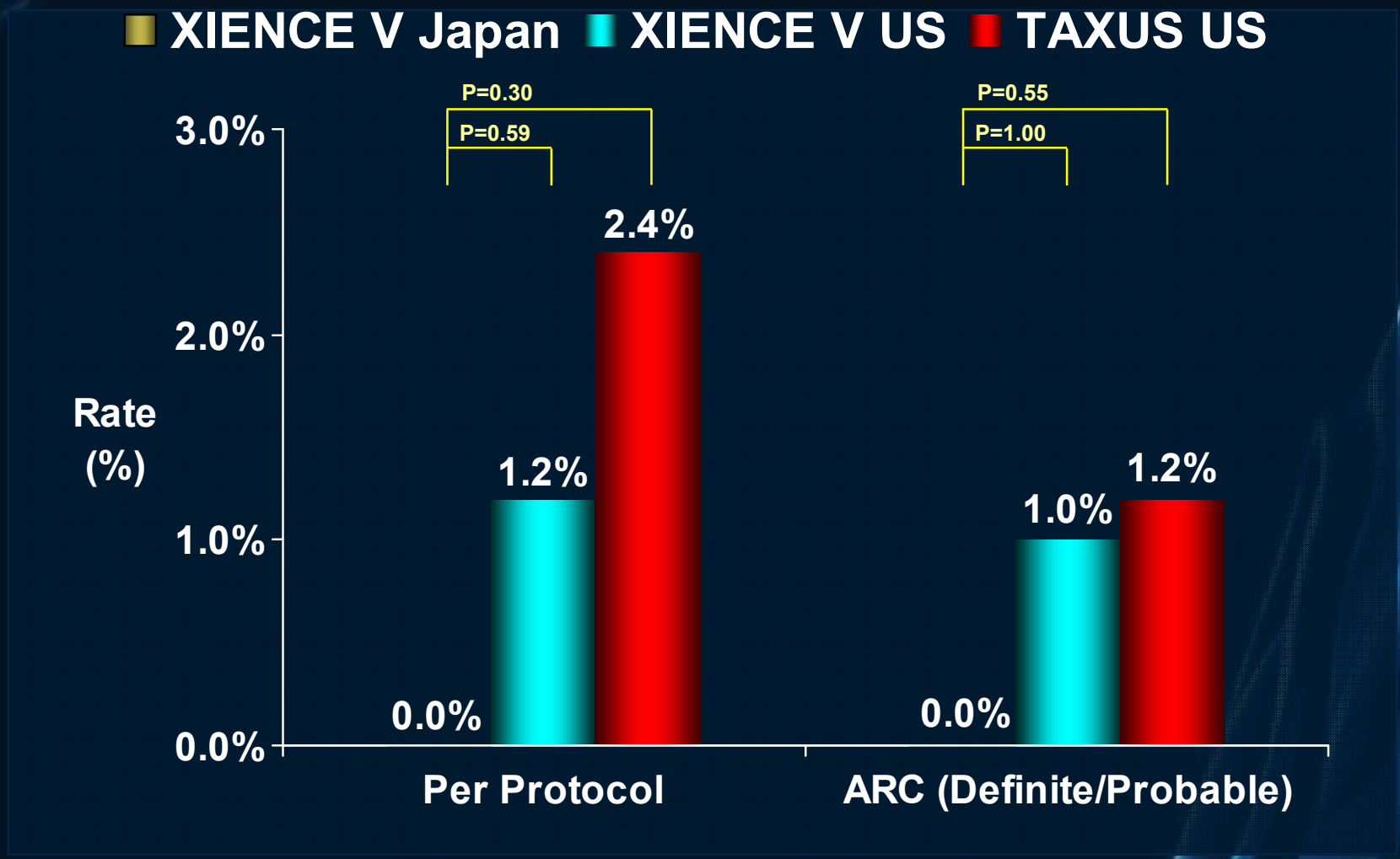
SPIRIT Trials

TVF Components Through 2 Years



SPIRIT Trials

STENT Thrombosis to Two years



SPIRIT Trials

Conclusions

- Angiographic endpoints were similar between the Japan and US XIENCE V cohort.
- Less post-procedure incomplete stent apposition was observed in the Japan study
- XIENCE V showed consistent safety and effectiveness up to 2 years in Japan, comparable to US patients
- No stent thrombosis was reported in Japan study

Summary

- Global device studies of 2 new generation DES
  - showed similar clinical outcomes despite the differences in patient/lesion backgrounds, PCI strategy or anti-platelet drugs.
  - revealed no stent thrombosis in Japanese patients.

Messages from our experiences

- Global device studies try to evaluate outcomes in patients with different backgrounds.
- The results of global device studies may affect PCI related strategies such as angiographic f/u or IVUS usage, etc.
- Even with HBD, it seems not easy to increase device access to Japan with shortening device lag.