I-LOVE-IT 2:

A Prospective, Randomized Trial of a Biodegradable Polymer, Cobalt Chromium, Sirolimus-Eluting Stent Versus a Durable Polymer, Cobalt Chromium, Sirolimus-Eluting Stent in Patients with Coronary Artery Disease

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On behalf of the I-LOVE-IT 2 Trial Investigators

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Financial Disclosures

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- All of the authors have no relevant personal conflicts of interest to disclose

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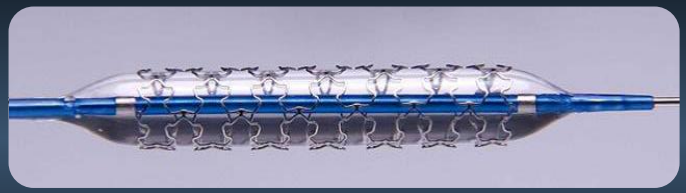
Background

- No randomized trials have compared safety and efficacy of biodegradable polymer-coated sirolimus-eluting stent (BP-SES) versus durable polymer-coated sirolimus-eluting stent (DP-SES) on similar cobalt-chromium platforms, thereby isolating the effect of the polymer type

- Moreover, optimal duration of dual antiplatelet therapy (DAPT) after BP-SES implantation remains underdetermined

Stefanini GG, et al, *Eur Heart J* 2012
Christiansen EH, et al, *Lancet* 2013

Comparison of Specifications between BP-SES and DP-SES



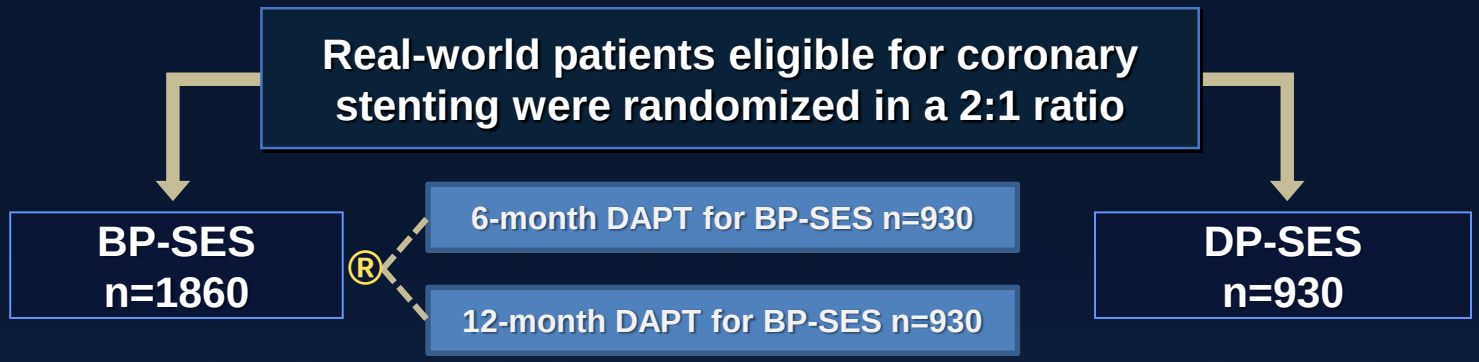
	Tivoli®	Firebird 2™
Manufactory	Essen Technology, Beijing, China	MicroPort, Shanghai, China
Stent Platform Material	Cobalt-Chromium (L605)	Cobalt-Chromium (L605)
Strut Thickness	0.080 mm	0.086 mm
Stent Profile	< 1.10 mm	< 1.12 mm
Diameter	2.50, 2.75, 3.00, 3.50, 4.00 mm	2.50, 2.75, 3.00, 3.50, 4.00 mm
Length	10, 15, 18, 21, 25, 30, 35 mm	13, 18, 23, 29, 33 mm
Drug	Sirolimus	Sirolimus
Drug Dose	8 µg/mm	9 µg/mm
Polymer	PLGA (biodegradable)	SBS (durable)
Polymer Thickness	5.5 µm	6.0 µm
Drug Release	75% at 28 days	> 80% at 30 days

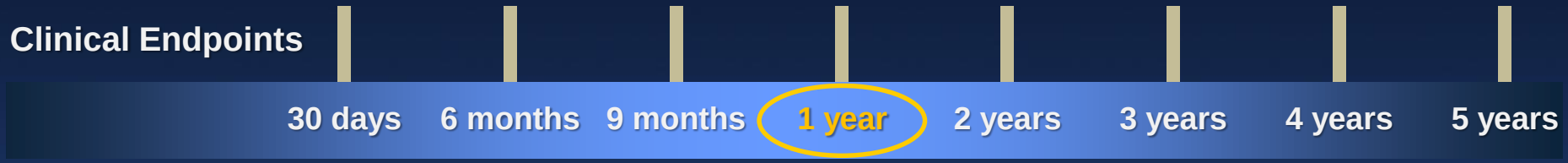
Objectives

- To investigate the hypothesis that a novel BP-SES (Tivoli, Essen Tech, Beijing, China) is noninferior in safety and efficacy outcomes to a DP-SES (Firebird 2, MicroPort, Shanghai, China)

- To investigate whether the safety and efficacy of 6-month DAPT are comparable with 12-month DAPT in patients receiving BP-SES implantations

Study Design





Primary Endpoint: 1-year TLF (composite of cardiac death, TVMI, and CI-TLR)

Major Secondary Endpoints: 1-year TLF and NACCE (composite of death, MI, stroke, major bleeding (BARC >= II)) between 6- and 12-month DAPT groups after BP-SES implantations

Secondary Endpoints: individual TLF components, definite/probable stent thrombosis, device/lesion/procedure success rates, and PoCE (composite of all cause death, all MI, and any revascularization)

**TLF = target lesion failure; TVMI = target vessel myocardial infarction; CI-TLR = clinically indicated target lesion revascularization; NACCE = net adverse clinical and cerebral events; PoCE = patient-oriented composite endpoint*

Inclusion Criteria

Major Inclusion:

- Age ≥18 years
- Chronic, stable coronary artery disease or acute coronary syndromes, including MI with or without ST-segment elevation
- Acceptable candidate for CABG
- At least one *de novo* coronary lesion with diameter stenosis ≥ 70% in a vessel with reference diameter ≥ 2.5 mm and ≤ 4.0 mm
- Patients with multivessel disease must receive complete revascularization within 30 days using same study stents if needed

Exclusion Criteria

Major Exclusion:

- Intolerance to a study drug, metal alloys, or contrast media
- Life expectancy less than one year
- Restenotic lesions
- Stent implantation within one year
- Left ventricular ejection fraction < 40%
- Severe renal or hepatic dysfunction, hemodynamic instability
- Planned surgery within 6 months after index procedure
- Childbearing potential within one year
- Clinical indications of inability to tolerate DAPT for 12 months
- Inability to provide written informed consent
- Participation in another trial before reaching the primary endpoint

Statistical Assumption

Primary Endpoint: **Target Lesion Failure at 1 year**

- **Expected TLF at 1 year in both groups = 8.3%**
- **Noninferiority margin = 3.7%**
- **One-sided type I error = 0.025**

- **2631 patients (1754 patients in BP-SES group and 877 patients in DP-SES group) randomized in a 2:1 ratio would yield at least 90% power to detect noninferiority of BP-SES**
- **Considering anticipated loss to follow-up of 5%, a total of 2790 subjects would need to be enrolled**

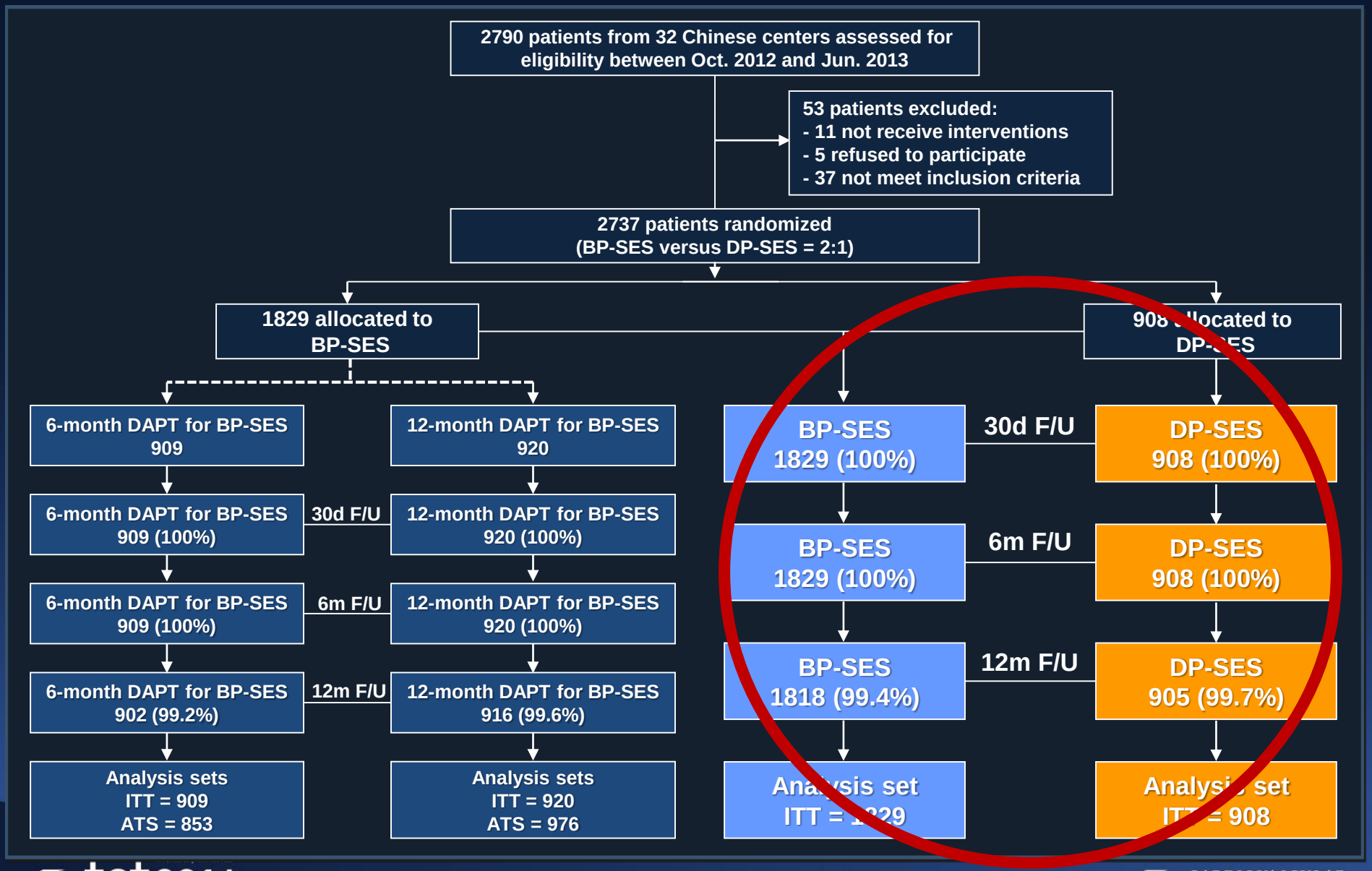
Study Organization

Principle Investigator	Yaling Han, MD
Honorary Chairman	Runlin Gao, MD
Co-Principle Investigators	Yuejin Yang, MD; Shuzheng Lu, MD
Executive Committee Directors	Bo Xu, MD; Quanmin Jing, MD
Clinical Events Committee	Zhujun Shen, MD (Chair); Lefeng Wang, MD; Jingxuan Guo, MD
Angiographic Core Lab	CCRF, Beijing, China
Data Management	
Data Monitoring	
Statistical Analysis	
Sponsor	Essen Technology, Beijing, China

I-LOVE-IT 2 Enrollers

Site PI	Hospital, City	Patients Enrolled	Site PI	Hospital, City	Patients Enrolled
Yaling Han	General Hospital of Shenyang Military Region, Shenyang	690	*Zhe Jin*	Affiliated Zhongshan Hospital of Dalian University, Dalian	45
Yuejin Yang	Fu Wai Hospital, National Center for Cardiovascular Diseases, Beijing	424	*Zishan Hou*	Linyi People's Hospital, Linyi	31
Lixia Yang	General Hospital of Chengdu Military Region, Kunming	325	*Likun Ma*	Anhui Provincial Hospital, Hefei	26
Shuzheng Lu	Affiliated Anzhen Hospital of Capital Medical University, Beijing	114	*Zhi Zhang*	Third Affiliated Hospital of Liaoning Medical College, Jinzhou	24
Qiangsun Zheng	Affiliated Tangdu Hospital of the Fourth Military Medical University, Xi'an	112	*Lianmin Wang*	Mudanjiang Cardiovascular Hospital, Mudanjiang	22
Xueqi Li	Fourth Affiliated Hospital of Haerbin Medical University, Haerbin	111	*Pitian Zhao*	Yidu Central Hospital of Weifang City, Weifang	21
Xianxian Zhao	Affiliated Changhai Hospital of the Second Military Medical University, Shanghai	104	*Xin Huang*	Benxi Central Hospital, Benxi	20
Haichang Wang	Affiliated Xijing Hospital of the Fourth Military Medical University, Xi'an	99	*Chunjiang Li*	Chinese PLA 202 Hospital, Shenyang	18
Xuezhong Zhao	Jilin University First Hospital, Changchun	89	*Yongwei Zhao*	Mishan People's Hospital, Mishan	17
Xiaoyan Li	General Hospital of Jinan Military Region, Jinan	71	*Jianqiu Liang*	Second People's Hospital of Foshan City, Foshan	11
Pengfei Yu	Pingdu People's Hospital, Pingdu	65	*Yingxian Sun*	Affiliated First Hospital of China Medical University, Shenyang	10
Hongyun Zang	Chinese PLA 463 Hospital, Shenyang	56	*Hong Yu*	Panjin Central Hospital, Panjin	9
Xuebin Cao	Chinese PLA 252 Hospital, Baoding	52	*Shaohong Dong*	Shenzhen People’s Hospital, Shenzhen	8
Jun Zhang	Cangzhou Central Hospital, Cangzhou	52	*Guizhou Tao*	First Affiliated Hospital of Liaoning Medical College, Jinzhou	7
Wenyue Pan	Affiliated Shengjing Hospital of China Medical University, Shenyang	50	*Zhenshun Xiu*	Jimo People's Hospital, Jimo	5
Zhifang Wang	Xinxiang Central Hospital, Xinxiang	48	*Chuanyu Gao*	Henan Provincial People's Hospital, Zhengzhou	1

Patient Flow



Baseline Patient Characteristics

	BP-SES (n=1829)	DP-SES (n=908)	*P*
Age, years	60.2 ± 10.1	60.2 ± 10.0	0.89
Male	68.0 (1243)	70.0 (636)	0.27
Body Mass Index, kg/m^2	25.2 ± 3.0	25.1 ± 3.0	0.64
Diabetes Mellitus	22.6 (414)	21.3 (193)	0.41
Insulin-requiring Diabetes	8.4 (154)	8.0 (73)	0.73
Hypertension	62.9 (1150)	61.6 (559)	0.50
Hyperlipidemia	24.3 (445)	204 (22.5)	0.28
Family History of CAD	5.7 (104)	5.8 (53)	0.87
Smoking History			0.85
Current Smoker	37.5 (685)	36.9 (335)	
Ex-smoker	11.7 (213)	11.1 (101)	
None	50.9 (931)	52.0 (472)	
Prior Myocardial Infarction	16.5 (301)	16.6 (151)	0.91
Prior Stroke	9.4 (171)	10.1 (92)	0.51
Peripheral Arterial Disease	1.3 (23)	0.4 (4)	*0.04*
Prior PCI	7.5 (137)	7.1 (64)	0.68
Prior CABG	0.4 (8)	0.7 (6)	0.57
Stable Angina	14.7 (269)	13.9 (126)	0.56
Unstable Angina	72.7 (1330)	76.1 (691)	0.06
AMI within 24 Hours	4.7 (86)	5.6 (51)	0.30
LVEF (%)	60.5 ± 8.3	61.0 ± 8.0	0.18

Baseline Lesion Characteristics (1)

	BP-SES (Patient, n=1829; Lesion, n=2495)	DP-SES (Patient, n=908; Lesion, n=1235)	*P*
Target Vessel Disease Extent			0.28
1-vessel Disease	74.1 (1356)	72.2 (656)	
2-vessel Disease	21.7 (396)	21.9 (199)	
3-vessel Disease	1.8 (33)	2.3 (21)	
Left main Disease	2.4 (44)	3.5 (32)	
Baseline SYNTAX Score	11.7 ± 8.2	11.7 ± 8.5	0.99
Number of Target Lesions			0.88
1	68.7 (1257)	68.6 (623)	
2	27.6 (504)	27.1 (246)	
3	3.4 (63)	4.0 (36)	
4	0.3 (5)	0.3 (3)	
Number of Target Lesion per Patient	1.35 ± 0.56	1.36 ± 0.57	0.88
Target Vessel Location			0.39
Left Main Artery	1.8 (44)	2.6 (32)	
Left Anterior Descending Artery	45.6 (1138)	44.5 (550)	
Left Circumflex Artery	22.6 (563)	22.8 (281)	
Right Coronary Artery	30.1 (750)	30.1 (372)	

Baseline Lesion Characteristics (2)

	BP-SES (Patient, n=1829; Lesion, n=2495)	DP-SES (Patient, n=908; Lesion, n=1235)	*P*
ACC/AHA Lesion Classification B2+C	83.5 (2083)	85.1 (1051)	0.21
Complex Lesions	44.4 (1109)	46.2 (571)	0.30
Bifurcation Lesion	31.9 (797)	33.1 (409)	0.48
Ostial Lesion	1.0 (25)	0.7 (9)	0.41
Total Occlusion	12.3 (306)	12.2 (150)	0.92
Severely Tortuous or Angulated Lesion	2.3 (57)	2.4 (30)	0.78
Moderate to Heavy Calcification	2.7 (66)	3.3 (41)	0.25
Preprocedural TIMI Flow			0.37
0	12.3 (307)	12.2 (151)	
1	1.8 (44)	1.5 (18)	
2	5.3 (133)	4.1 (51)	
3	80.6 (2011)	82.2 (1015)	
Preprocedural QCA			
Reference Vessel Diameter, mm	2.79 ± 0.47	2.79 ± 0.44	0.85
Lesion Length, mm	20.6 ± 12.3	21.2 ± 12.9	0.25
Minimal Lumen Diameter, mm	0.80 ± 0.51	0.81 ± 0.51	0.78
Diameter Stenosis, %	71.6 ± 16.9	71.6 ± 16.6	0.96

*Complex lesions were defined by presence of at least one of the following lesion characteristics: unprotected left main coronary artery, bifurcation, ostial lesion, total occlusion, severely tortuous or angulated lesion, and moderate to heavy calcification.

Procedural Characteristics and Results

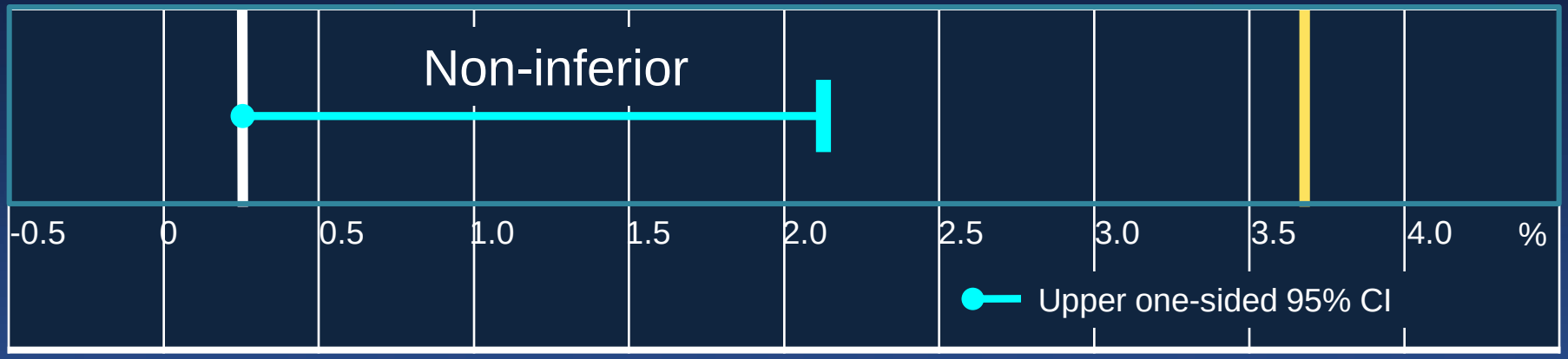
	BP-SES (Patient, n=1829; Lesion, n=2495)	DP-SES (Patient, n=908; Lesion, n=1235)	*P*
Transradial Approach	92.7 (1696)	93.5 (849)	0.46
Use of IVUS and/or OCT	3.3 (60)	3.1 (28)	*0.78*
Balloon Predilation	79.3 (1979)	82.2 (1015)	*0.04*
Stents per Patient	1.70 ± 0.86	1.75 ± 0.89	0.19
Stents per Lesion	1.26 ± 0.50	1.29 ± 0.52	0.12
≥ 3 Stents Implanted per Patient	15.7 (287)	17.8 (162)	0.15
Stent Diameter, mm	3.05 ± 0.44	3.04 ± 0.40	0.35
Total Stent Length per Patient, mm	41.1 ± 24.4	42.7 ± 24.8	0.11
Total Stent Length per Lesion, mm	30.4 ± 15.8	31.4 ± 16.5	0.07
Postdilation	51.4 (1282)	46.2 (571)	*0.003*
Postprocedural TIMI 3 Flow	99.5 (2482)	99.4 (1228)	0.86
Postprocedural QCA			
Minimal Lumen Diameter, mm			
In-stent	2.54 ± 0.42	2.57 ± 0.40	0.07
In-segment	2.38 ± 0.46	2.39 ± 0.44	0.36
Diameter Stenosis, %			
In-stent	8.4 ± 5.2	8.4 ± 5.5	0.94
In-segment	11.7 ± 7.2	12.0 ± 7.7	0.17
Residual SYNTAX Score	3.3 ± 5.1	3.2 ± 5.6	0.74
Device Success	99.5 (3116)	99.6 (1589)	0.62
Lesion Success	99.3 (2478)	99.4 (1228)	0.67
Procedure Success	95.8 (1752)	95.6 (868)	0.81

Primary Endpoint: TLF at 1 Year

(Cardiac Death, TVMI, and CI-TLR)

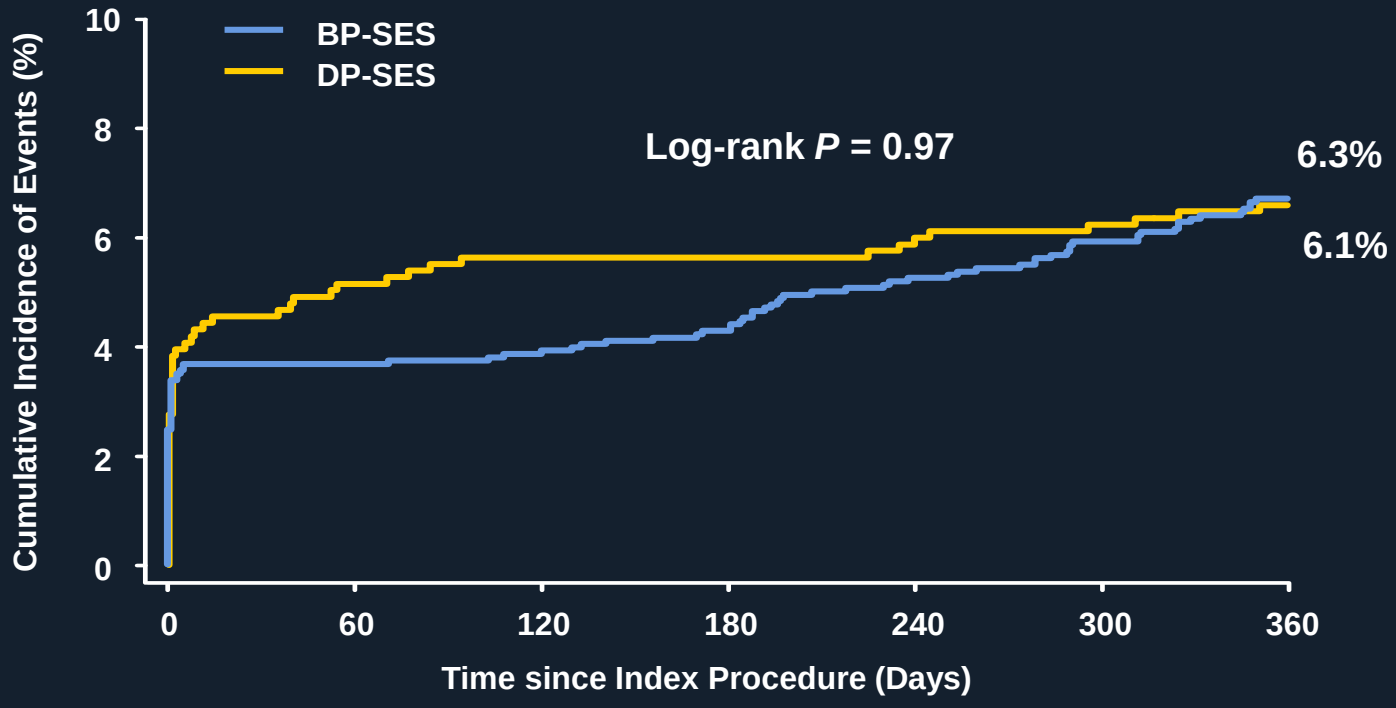
BP-SES (n = 1818) 6.3%	DP-SES (n = 905) 6.1%	Difference : 0.25% Upper 1-sided 95% CI: 2.17%	Noninferiority *P* value = 0.0002

Zone of noninferiority
Pre-specified margin = 3.7%



Primary Noninferiority Endpoint Met

Target Lesion Failure Through 1 Year



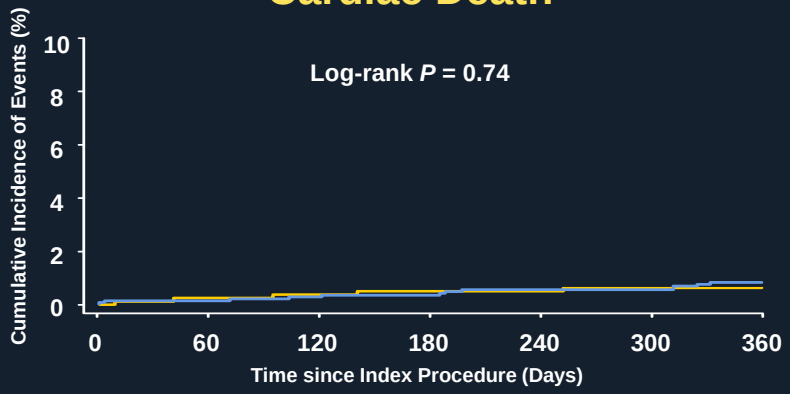
Patients at Risk:

Days	0	60	120	180	240	300	360
BP-SES	1829	1766	1760	1754	1735	1724	1708
DP-SES	908	864	860	859	856	854	849

TLF Components and PoCE Through 1 Year

BP-SES — DP-SES

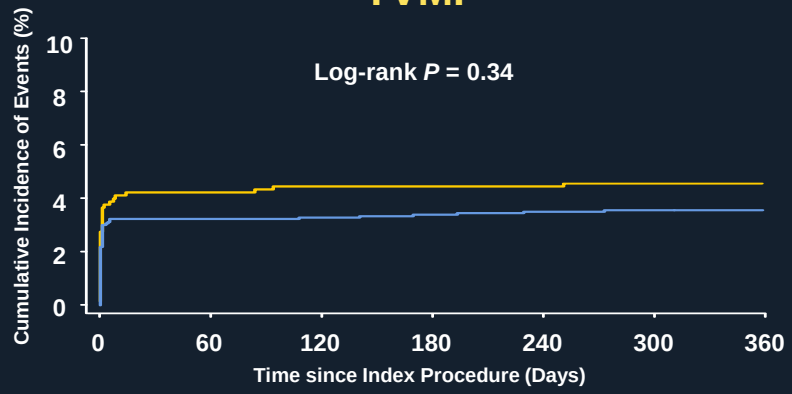
Cardiac Death



Patients at Risk:

Days	0	60	120	180	240	300	360
BP-SES	1829	1824	1820	1819	1813	1813	1806
DP-SES	908	904	903	901	901	900	898

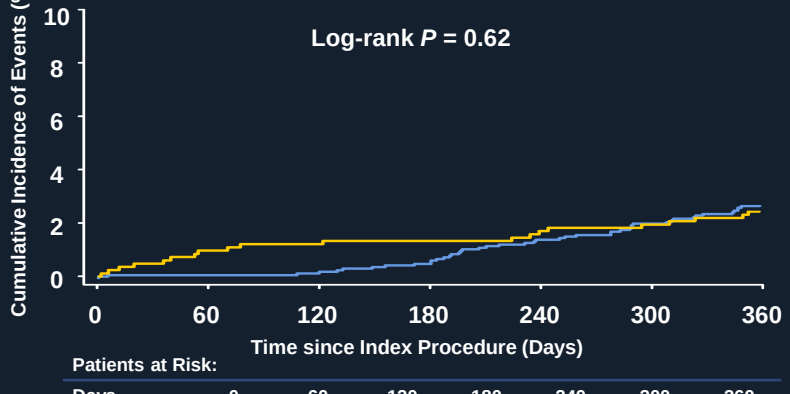
TVMI



Patients at Risk:

Days	0	60	120	180	240	300	360
BP-SES	1829	1766	1761	1759	1751	1750	1743
DP-SES	908	869	867	866	866	865	863

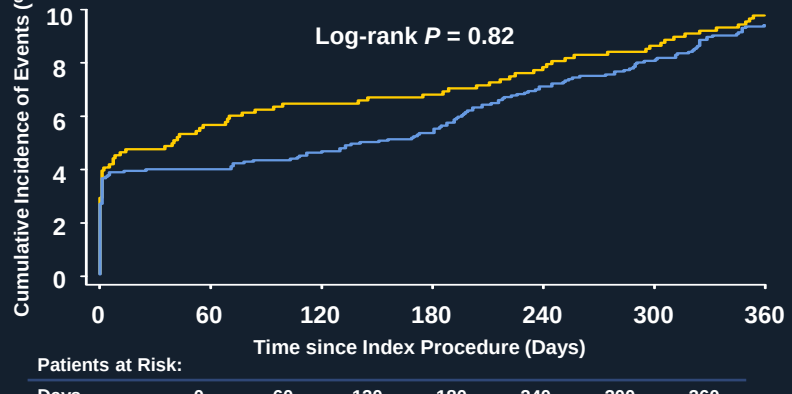
CI-TLR



Patients at Risk:

Days	0	60	120	180	240	300	360
BP-SES	1829	1822	1816	1810	1789	1779	1762
DP-SES	908	897	894	892	889	887	881

PoCE

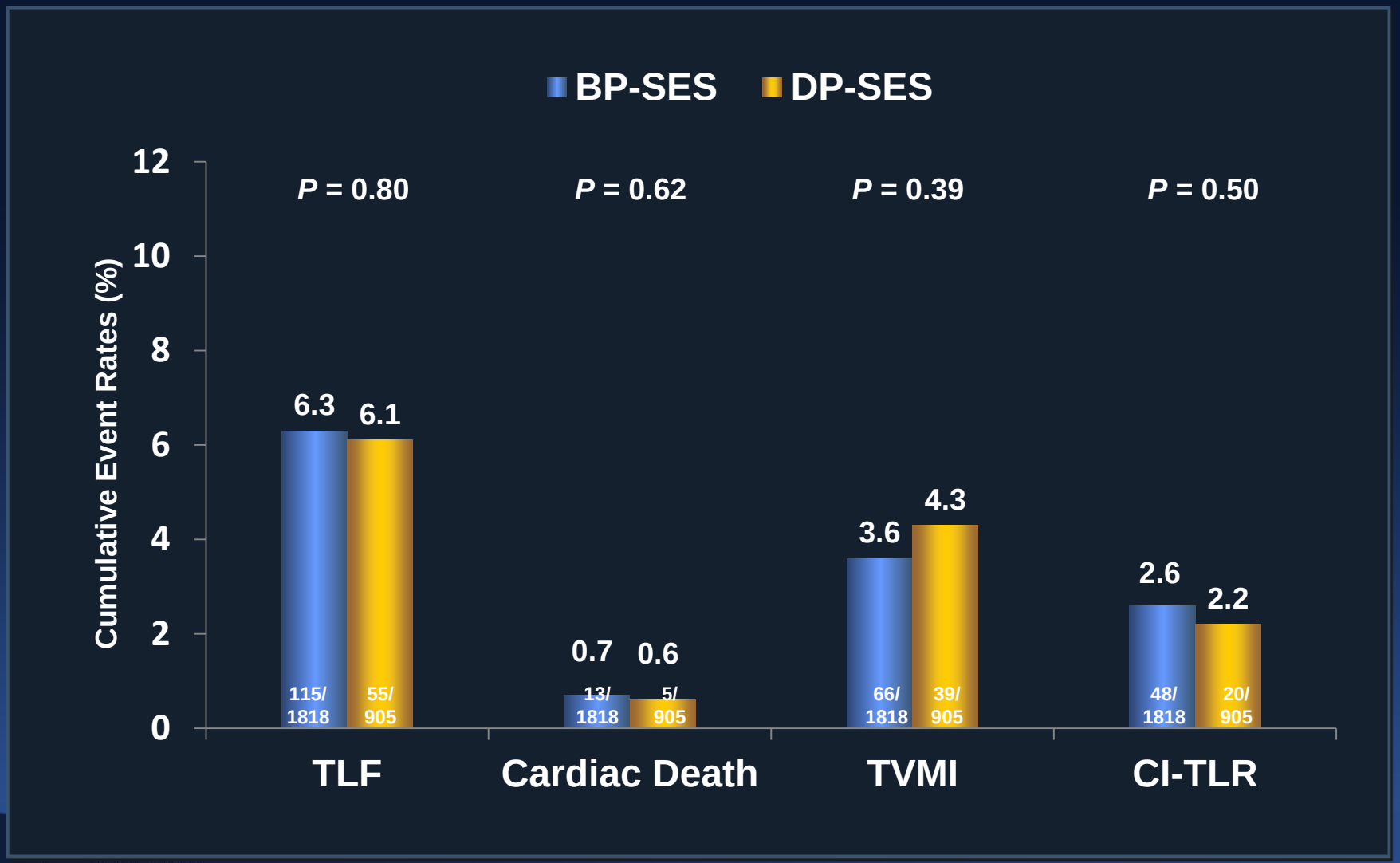


Patients at Risk:

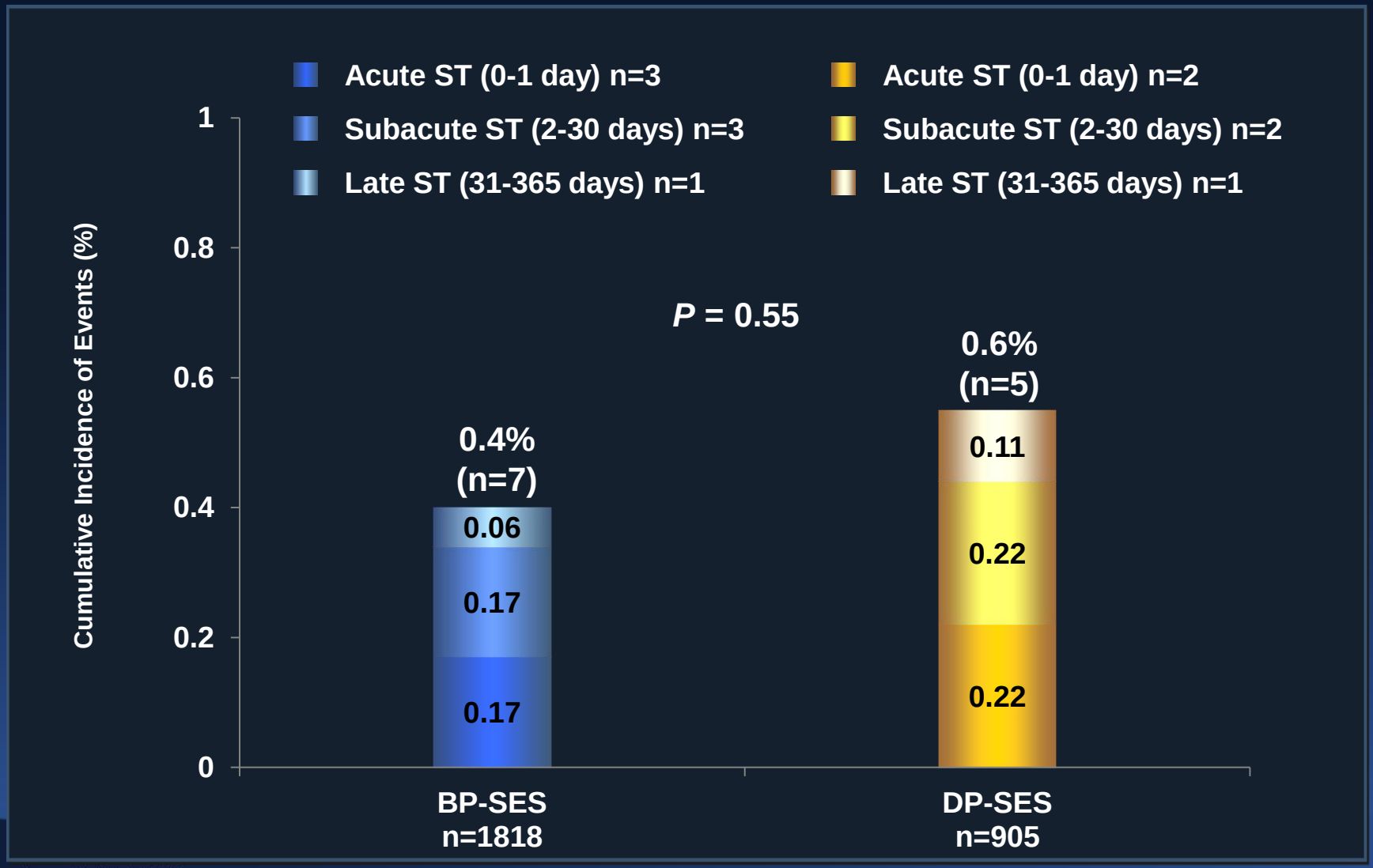
Days	0	60	120	180	240	300	360
BP-SES	1829	1759	1747	1735	1704	1687	1663
DP-SES	908	859	852	849	840	833	823

PoCE = All Cause Death + All MI + Any Revascularization

TLF and Components at 1 Year



Def/Prob Stent Thrombosis at 1 Year

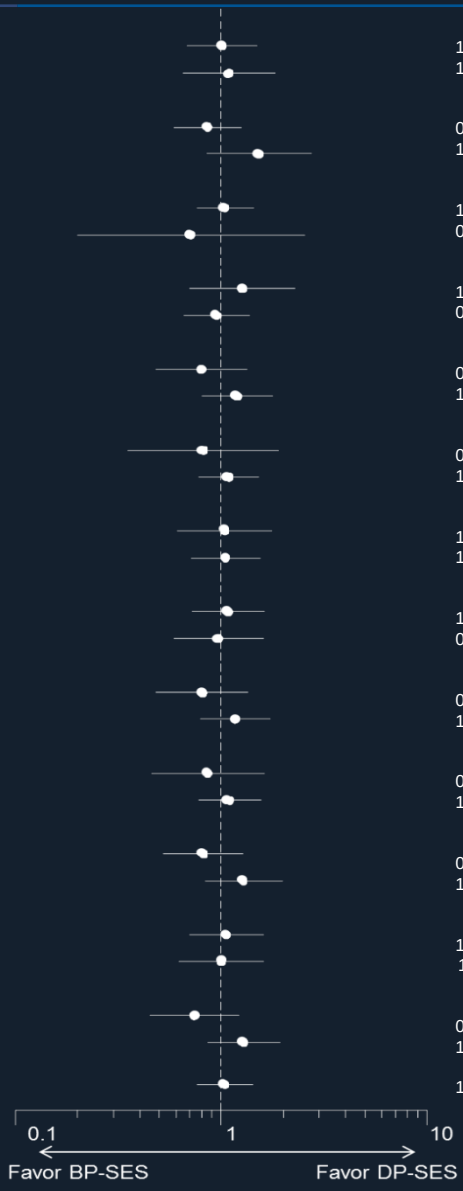


Independent Predictors of 1-Year TLF by Multivariable Cox Regression Analysis

Variables	Hazard Ratio [95% CI]	*P*
Emergent PCI for AMI	2.455 [1.435, 4.198]	0.001
Baseline SYNTAX Score	1.029 [1.010, 1.047]	0.002
Total Stent Length per Patient	1.009 [1.003, 1.015]	0.003
Lesion Unsuccessful	4.324 [1.876, 9.967]	0.0006

TLF Among Subgroups at 1 Year

	Target Lesion Failure - *Events/Total (%)*			Relative Risk (95% CI)	p Value for Interaction
	BP-SES	DP-SES	p Value		
Age					
<65 years	73/1242 (5.9)	36/618 (5.8)	0.96	1.01 (0.68-1.49)	0.81
≥65 years	42/587 (7.2)	19/290 (6.6)	0.74	1.09 (0.65-1.84)	
Gender					
Male	69/1243 (5.6)	41/636 (6.4)	0.43	0.86 (0.59-1.25)	0.10
Female	46/586 (7.8)	14/272 (5.1)	0.15	1.53 (0.85-2.73)	
Body mass index					
<30	108/1682 (6.4)	51/828 (6.2)	0.80	1.04 (0.76-1.44)	0.57
≥30	5/114 (4.4)	4/65 (6.2)	0.73	0.71 (0.20-2.56)	
Diabetes mellitus					
Yes	38/414 (9.2)	14/193 (7.3)	0.43	1.27 (0.70-2.28)	0.42
No	77/1415 (5.4)	41/715 (5.7)	0.78	0.95 (0.66-1.37)	
Current smoker					
Yes	36/685 (5.3)	22/335 (6.6)	0.40	0.80 (0.48-1.34)	0.22
No	79/1144 (6.9)	33/573 (5.8)	0.36	1.20 (0.81-1.78)	
Emergent PCI for AMI					
Yes	11/86 (12.8)	8/51 (15.7)	0.64	0.82 (0.35-1.89)	0.53
No	104/1743 (6.0)	47/857 (5.5)	0.62	1.09 (0.78-1.52)	
Multivessel PCI					
Yes	37/473 (7.8)	19/252 (7.5)	0.89	1.04 (0.61-1.77)	0.98
No	78/1356 (5.8)	36/656 (5.5)	0.82	1.05 (0.71-1.54)	
Number of treated lesion					
1	72/1257 (5.7)	33/623 (5.3)	0.70	1.08 (0.72-1.61)	0.75
≥2	43/572 (7.5)	22/285 (7.7)	0.92	0.97 (0.59-1.60)	
Preprocedural TIMI flow					
0-2	36/452 (8.0)	21/213 (9.9)	0.42	0.81 (0.48-1.35)	0.53
3	79/1377 (5.7)	34/694 (4.9)	0.43	1.17 (0.79-1.73)	
Chronic total occlusion					
Yes	24/294 (8.2)	14/148 (9.5)	0.65	0.86 (0.46-1.62)	0.98
No	91/1535 (5.9)	41/759 (5.4)	0.61	1.10 (0.77-1.57)	
Bifurcation					
Yes	47/717 (6.6)	29/362 (8.0)	0.38	0.82 (0.52-1.28)	0.75
No	45/765 (5.9)	26/545 (4.8)	0.27	1.28 (0.83-1.99)	
Reference vessel diameter					
≤2.75 mm	70/1064 (6.6)	30/483 (6.2)	0.79	1.06 (0.70-1.60)	0.85
>2.75 mm	45/765 (5.9)	25/424 (5.9)	0.99	1.00 (0.62-1.60	
Lesion length					
≤20 mm	38/939 (4.0)	25/459 (5.4)	0.24	0.74 (0.45-1.22)	0.09
>20 mm	77/890 (8.7)	30/448 (6.7)	0.21	1.29 (0.86-1.94)	
Overall	115/1829 (6.3)	55/908 (6.1)	0.81	1.04 (0.76-1.42)	



Limitations

- We enrolled only part of the total PCI population at enrolling centers, rather than consecutive patients, and we cannot rule out some selection bias.
- The study was not powered enough to evaluate the safety endpoints at 12 months, especially stent thrombosis, warranting longer follow-up or larger trials.
- We used the old universal definition of periprocedural MI, which may overestimate the occurrence of TVMI.
- Although baseline characteristics bias has been well controlled in this randomized trial, there are some differences in procedural characteristics, e.g. rates of balloon predilation and postdilation, which might reflect minor difference between two stent platforms.

Conclusions

- The present I-LOVE-IT 2 trial has demonstrated that the BP-SES is noninferior in terms of efficacy to DP-SES in clinical practice

- Whether BP-SES improves safety with respect to lowering stent thrombosis incidence compared with DP-SES, remains to be shown in longer-term follow-up of this trial or in future studies

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