

Lessons Learned from COBIS Studies

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On the behalf of COBIS Registry Investigators

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Coronary Bifurcation Stent (COBIS) Registries

- Multi-center retrospective real-world registry of drug-eluting stenting in coronary bifurcation lesions in Korea

	COBIS I	COBIS II	COBIS III
Enrolled Patients	1691	2897	2648
Term	2004.1~2006.6	2003.1 ~ 2009.12	2010.1 ~ 2014.12
Inclusion			
Main vessel Diameter (mm)	≥ 2.5	≥ 2.5	≥ 2.5
Side branch Diameter (mm)	≥ 2.0	≥ 2.3	≥ 2.3
LM Bifurcation	X	O (29%)	O
DES generation	1 st	1 st + 2 nd (14%)	2 nd only
Sponsor	Korean Society of Interventional Cardiology	ENCORE SEOUL Internal fund	Korean Bifurcation Club

First papers in COBIS I



Long-Term Clinical Results and Predictors of Adverse Outcomes After Drug-Eluting Stent Implantation for Bifurcation Lesions in a Real-World Practice

– The COBIS (Coronary Bifurcation Stenting) Registry –

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Background: Limited data exists regarding long-term clinical results and predictors of adverse outcomes after drug-eluting stents (DES) implantation for coronary bifurcation lesions in a real-world practice.

Methods and Results: A total of 1,691 non-left main bifurcation lesions with side branches ≥ 2.0 mm in 1,668 patients undergoing DES implantation between January 2004 and June 2006 from 16 centers in Korea were evaluated. True bifurcation was found in 69.2% of lesions and 82.7% of lesions were treated with 1-stent technique. During follow-up (median 22 months), cardiac death occurred in 0.9%, myocardial infarction (MI) in 1.2%, target lesion revascularization (TLR) in 4.7% and stent thrombosis in 0.7% of patients. There was no significant difference in major adverse cardiac events (MACE: composite of cardiac death, MI and TLR) between the 1-stent and the 2-stent groups (6.1% vs 7.5%, $P=0.36$). Stent length in the main vessel (hazard ratio (HR) 1.02, 95% confidence interval (CI) 1.001–1.03, $P=0.03$), paclitaxel-eluting stent (HR 1.98, 95%CI 1.34–2.92, $P=0.001$) and kissing ballooning (HR 2.01, 95%CI 1.29–3.13, $P=0.002$) were independent predictors of MACE. Kissing ballooning increased the risk of MACE especially in the 1-stent group, but not in the 2-stent group.

Conclusions: In this large real-world registry, overall outcomes after DES implantation in bifurcation lesions were favorable and similar between the 1-stent and 2-stent groups. (*Circ J* 2010; **74**: 2322–2328)

Key Words: Bifurcation; Drug-eluting stents; Percutaneous coronary intervention

Coronary bifurcation lesions are one of the most challenging lesion subsets and known to have a lower angiographic success rate and a higher risk of procedural complications with a greater restenosis rate than non-bifurcation lesions.^{1–3} Therefore, coronary bifurcation lesions have been the subject of many studies; however, real-world practice patterns and long-term clinical outcomes have not been adequately addressed by previous studies. Most previous studies focused on either treatment strategies or techniques and were of a small to medium sample size with a

follow-up period of 6–12 months in a randomized setting.^{1,4,5} Although a few of these previous studies used real-world data sets, these studies were not based on registries dedicated to bifurcation lesions and had only a medium sample size that was inadequate to identify prognostic factors by multivariate analysis.^{6,7} Therefore, we investigated long-term clinical results and predictors of adverse outcomes after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) for coronary bifurcation lesions using data from a dedicated, large, multicenter real-world registry.

EXPEDITED PUBLICATION

Sirolimus- Versus Paclitaxel-Eluting Stents for the Treatment of Coronary Bifurcations

Results From the COBIS (Coronary Bifurcation Stenting) Registry

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Objectives	We aimed to compare the long-term clinical outcomes of patients treated with sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES) for coronary bifurcation lesions.
Background	There are limited data regarding comparisons of SES and PES for the treatment of bifurcation lesions.
Methods	Patients who received percutaneous coronary intervention for non-left main bifurcation lesions were enrolled from 16 centers in Korea between January 2004 and June 2006. We compared major adverse cardiac events (MACE [cardiac death, myocardial infarction, or target lesion revascularization]) between the SES and PES groups in patients overall and in 407 patient pairs generated by propensity-score matching.
Results	We evaluated 1,033 patients with bifurcation lesions treated with SES and 562 patients treated with PES. The median follow-up duration was 22 months. Treatment with SES was associated with a lower incidence of MACE (hazard ratio [HR]: 0.53, 95% confidence interval [CI]: 0.32 to 0.89, $p < 0.01$) and target lesion revascularization (HR: 0.55, 95% CI: 0.31 to 0.97, $p = 0.02$), but not of cardiac death (HR: 2.77, 95% CI: 0.40 to 18.99, $p = 0.62$) and cardiac death or myocardial infarction (HR: 0.97, 95% CI: 0.38 to 2.49, $p = 0.94$). After propensity-score matching, patients with SES still had fewer MACE and target lesion revascularization incidences than did patients with PES (HR: 0.52, 95% CI: 0.30 to 0.91, $p = 0.02$, and HR: 0.48, 95% CI: 0.25 to 0.91, $p = 0.02$, respectively). There was no significant difference in the occurrences of stent thrombosis between the groups (0.7% vs 0.7%, $p = 0.94$).
Conclusions	In patients with bifurcation lesions, the use of SES resulted in better long-term outcomes than did the use of PES, primarily by decreasing the rate of repeat revascularization. (Coronary Bifurcation Stenting Registry in South Korea [COBIS]; NCT00851526) (<i>J Am Coll Cardiol</i> 2010;55:1743–50) © 2010 by the American College of Cardiology Foundation

Sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) have been shown to markedly improve angiographic and clinical outcomes after percutaneous coronary intervention (PCI) when compared to bare-metal stents (1,2). A number of studies comparing the efficacy and safety of SES and PES have been performed in a variety of lesion subsets

and clinical settings (3–7), but there are limited data comparing these 2 stents in the treatment of bifurcation lesions. Although 3 previous studies compared the clinical outcomes of patients treated with SES or PES for bifurcation lesions, these studies were small and underpowered, and the data from these studies are conflicting

COBIS I & II Registries: 31 papers so far



COBIS I	Year	Journal	COBIS II	Year	Journal
Predictors of outcomes	2010	Circ J	Predictors of SB occlusion	2013	J Am Coll Cardiol
SES vs. PES	2010	J Am Coll Cardiol	Medina 001	2014	CCI
IVUS guidance	2011	Am Heart J	Left main bifurcation	2014	JACC CVI
SES vs. PES in left main	2011	Clin Cardiol	Antiplatelet therapy	2015	Heart Vessel
Bifurcation angle	2012	Cardiology	EES vs. SES	2015	Circ J
Final kissing ballooning	2012	Heart	Transradial vs. transfemoral	2015	J Invasiv Cardiol
Acute coronary syndrome	2012	Clin cardiol	2nd generation DES	2015	JACC CVI
1-stent vs. 2-stent	2013	Int J Cardiol	True bifurcation	2015	Circ J
2-stent techniques	2013	Int J Cardiol	Final kissing ballooning	2015	JACC CVI
Peri-procedural MI	2013	Int J Cardiol	SB stenosis	2016	Int J Cardiol
Predilation	2014	Rev Cardiol Esp	NC balloon	2016	Eurointervention
Predictors of SB failure	2016	Am J Cardiol	Predictors of outcomes	2016	JACC CVI
			2-stent strategy	2016	Eurointervention
			Calcification	2017	Eurointervention
			Predilation	2018	Circ J
			Acute coronary syndrome	2018	CCI
			Prolonged DAPT	2018	CCI
			ST elevation MI	2018	Rev Cardiol Esp
			POT	2019	KCJ

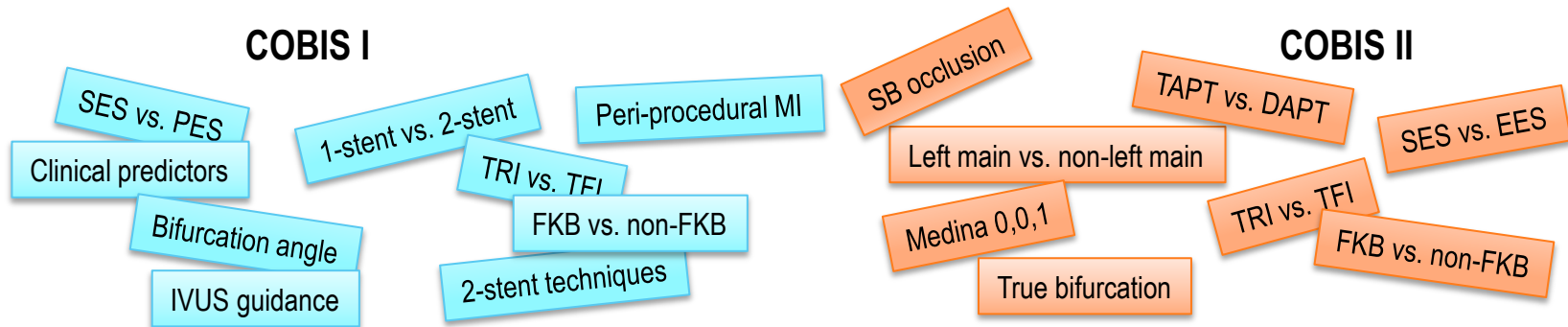
COBIS III registry



- Background
 - 2nd generation DES only in 14% of patients in COBIS II
- Design and inclusion criteria
 - Same as COBIS II registry
- Steered and sponsored by **Korean Bifurcation Club**
- Included patients receiving 2nd generation DES in 2010.1 ~ 2014.12

COBIS I & II Registries

	COBIS I	COBIS II
N	1,668	2,897
Procedure period	2004.1~2006.6	2003.1~2009.12
Side branch RD	≥ 2.0 mm	≥ 2.3 mm (by QCA)
Left main bifurcation	None	29%
2nd generation DES	None	15%
2-stent technique	18%	27%



Preprocedure-related issues

COBIS I

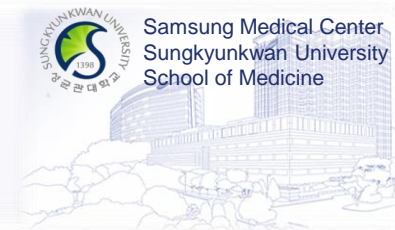
1. Song PS, et al. Impact of **Acute Coronary Syndrome** Classification and Procedural Technique on Clinical Outcomes in Patients With Coronary Bifurcation Lesions Treated With Drug-Eluting Stents. Clin Cardiol 2012
2. Yang JH, et al. Impact of Coronary **Bifurcation Angle** on Clinical Outcomes after Percutaneous Coronary Intervention in Real-World Practice: Results from the COBIS Registry. Cardiology 2012
3. Chung SM, et al. **Trans-Radial versus Trans-Femoral Intervention** for the Treatment of Coronary Bifurcations: Results from Coronary Bifurcation Stenting Registry. JKMS 2013

COBIS II

1. Jang WJ, et al. Impact of bifurcation stent technique on clinical outcomes in patients with a **Medina 0,0,1** coronary bifurcation lesion: Results from the COBIS (COronary BIfurcation Stenting) II registry. Catheter Cardiovasc Interv 2014
2. Chung SM, et al. **Transradial versus transfemoral intervention** for the treatment of left main coronary bifurcations: results from the COBIS (COronary BIfurcation Stenting) II Registry. J Invasive Cardiol 2015
3. Park TK, et al. Long-Term Clinical Outcomes of **True and Non-True Bifurcation Lesions** According to Medina Classification- Results From the COBIS (COronary BIfurcation Stent) II Registry. Circ J 2015

True vs. Non-true bifurcation lesions

COBIS II Registry



• True (N=1,502, 51.8%)

1.1.1



0.1.1



1.0.1



vs. Non-true (N=1,395, 48.2%)

vs. 1.1.0



0.1.0



1.0.0



0.0.1

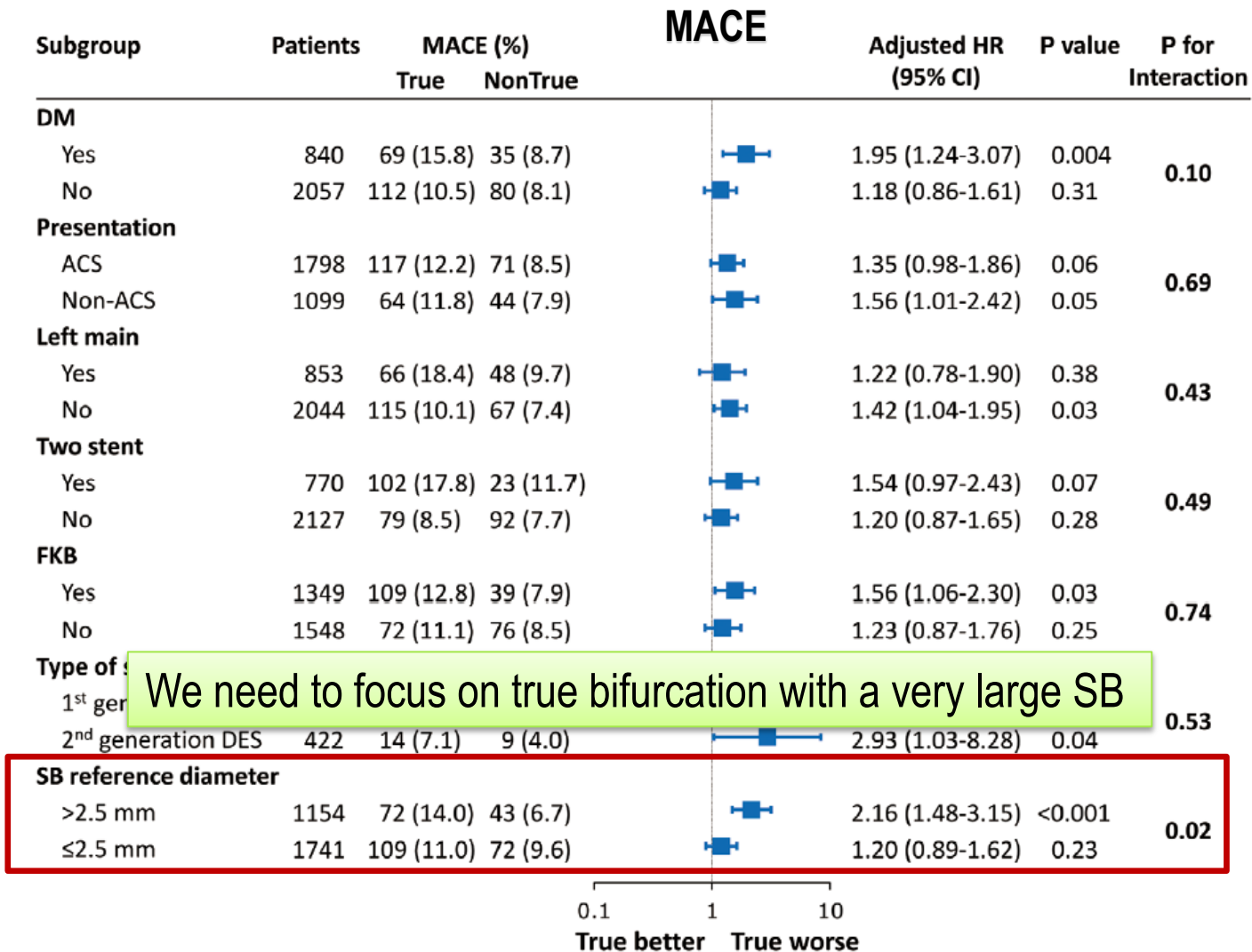


	Adjusted HR (95% CI)	p Value	Post-PCI QCA data	True	Non- true	p Value
MACE	1.39 (1.08-1.80)	0.01	Main vessel			
Cardiac death or MI	1.66 (1.03-2.67)	0.04	RD, mm	3.0	3.1	0.001
Death	1.56 (1.03-2.36)	0.04	MLD, mm	2.6	2.7	<0.001
Cardiac death	2.08 (0.98-4.39)	0.06	DS, %	13.8	12.7	0.04
MI	1.26 (0.69-2.32)	0.46	Side branch			
Stent thrombosis, definite or probable	2.82 (1.03-7.67)	0.04	RD, mm	2.4	2.5	<0.001
TLR						<0.001

True bifurcation lesions were associated with higher risks of cardiovascular events, possibly due to inferior procedural results.

True vs. Non-true bifurcation lesions

COBIS II Registry



We need to focus on true bifurcation with a very large SB

SB reference diameter

>2.5 mm 1154 72 (14.0) 43 (6.7) Adjusted HR 2.16 (1.48-3.15) <0.001

≤2.5 mm 1741 109 (11.0) 72 (9.6) Adjusted HR 1.20 (0.89-1.62) 0.23

Procedure-related issues

Stent itself



COBIS I

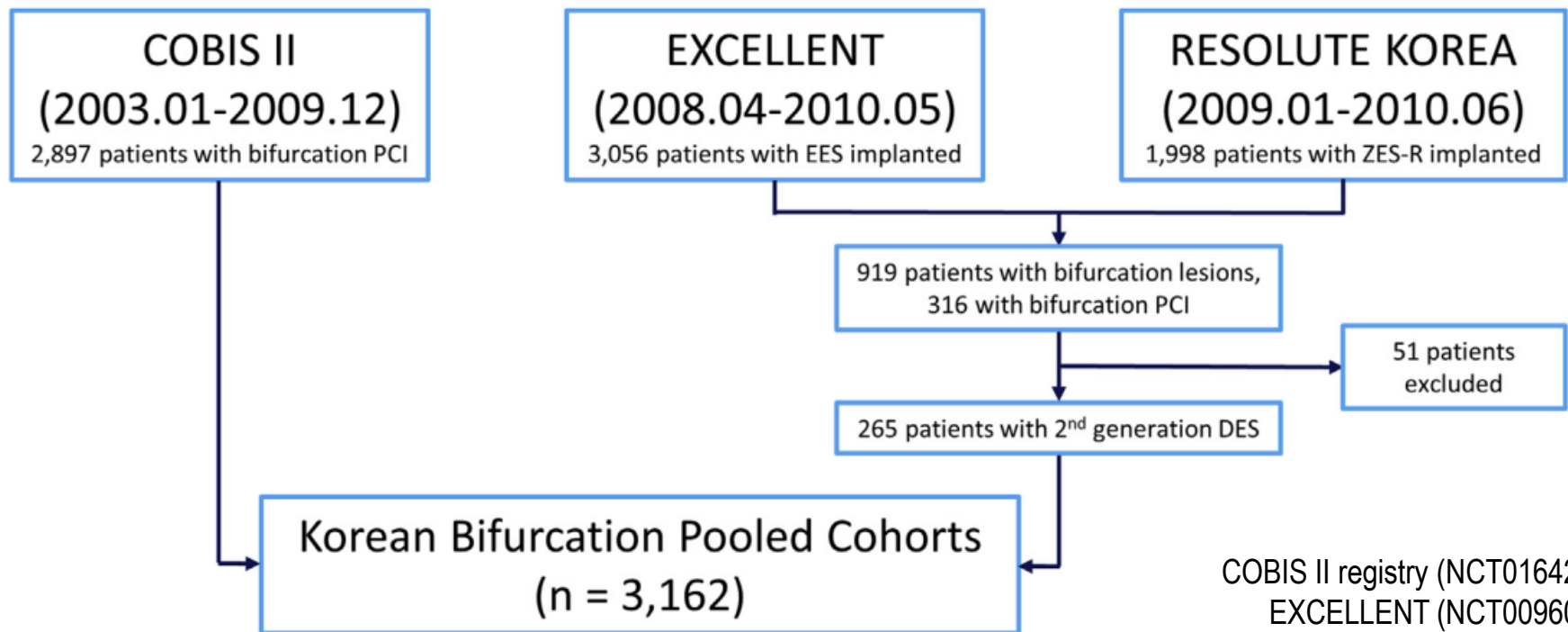
1. Song YB, et al. Sirolimus- Versus Paclitaxel-Eluting Stents for the Treatment of Coronary Bifurcations: Results From the COBIS (Coronary Bifurcation Stenting) Registry. JACC 2010

COBIS II

1. Cho Y, et al. Comparison of the first- and second-generation limus-eluting stents for bifurcation lesions from a korean multicenter registry. Circ J 2015
2. Lee JM, et al. Differential Prognostic Effect Between First- and Second-Generation Drug-Eluting Stents in Coronary Bifurcation Lesions: Patient-Level Analysis of the Korean Bifurcation Pooled Cohorts. JACC CVI 2015

Korean Bifurcation Pooled Cohorts

- From the EXCELLENT and RESOLUTE-Korea registries, 265 patients met the inclusion and exclusion criteria, and were analyzed by the same bifurcation QCA system as the COBIS II registry.
- 2nd generation DES: N=422 (14.6%) → N=687 (21.7%)



COBIS II registry (NCT01642992)
EXCELLENT (NCT00960648)
RESOLUTE-Korea (NCT00960908)

Korean Bifurcation Pooled Cohorts

1-stent vs. 2-stent in 1st- vs. 2nd DES



2475 Patients with 1st generation DES

1802 Patients with 1-Stent Group

673 Patients with 2-Stent Group

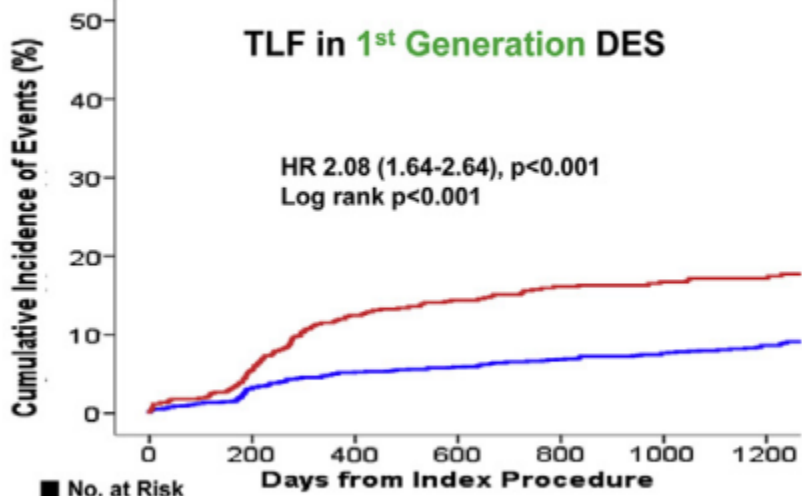
422 Patients with 2nd generation DES

265 Patients with 2nd generation DES

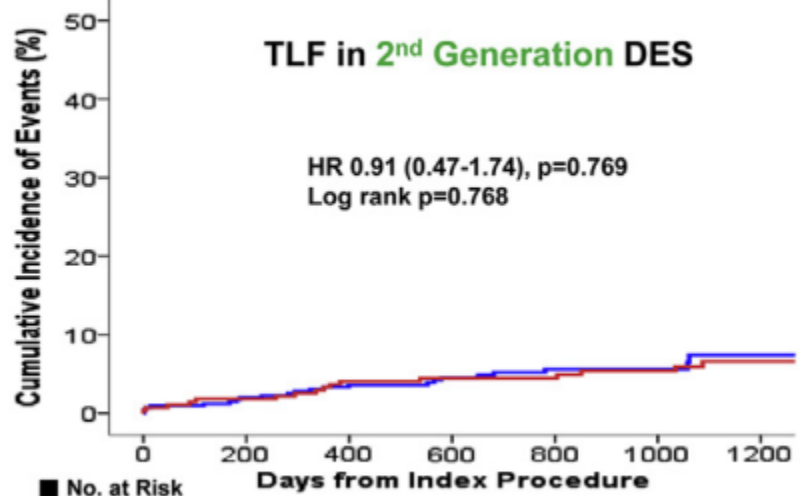
409 Patients with 1-Stent Group

278 Patients with 2-Stent Group

1st Generation DES



2nd Generation DES



Procedure-related issues

Techniques used



COBIS I

1. Shin DH, et al. Comparing **Two-Stent Strategies** for Bifurcation Coronary Lesions: Which Vessel Should be Stented First, the Main Vessel or the Side Branch? JKMS 2011
2. Gwon HC, et al. **Final kissing ballooning** and long-term clinical outcomes in coronary bifurcation lesions treated with 1-stent technique: results from the COBIS registry. Heart 2012
3. Koh YS, et al. Long-Term Clinical Outcomes of the **One-Stent Technique versus the Two-Stent Technique** for Non-Left Main True Coronary Bifurcation Disease in the Era of Drug-Eluting Stents. JIC 2013.
4. Song PS, et al. The Impact of **Side Branch Predilatation** on Procedural and Long-term Clinical Outcomes in Coronary Bifurcation Lesions Treated by the Provisional Approach. REC 2014

COBIS II

1. Song YB, et al. Differential prognostic impact of **treatment strategy among patients with left main versus non-left main bifurcation lesions** undergoing percutaneous coronary intervention: results from the COBIS (Coronary Bifurcation Stenting) Registry II. JACC CVI 2014
2. Yu CW, et al. Long-Term Clinical Outcomes of **Final Kissing Ballooning** in Coronary Bifurcation Lesions Treated With the 1-Stent Technique: Results From the COBIS II Registry (Korean Coronary Bifurcation Stenting Registry). JACC CVI 2015
3. Jang WJ, et al. Differential effect of **side branch intervention** on long-term clinical outcomes according to side branch stenosis after main vessel stenting: Results from the COBIS (Coronary Bifurcation Stenting) Registry II. IJC 2016

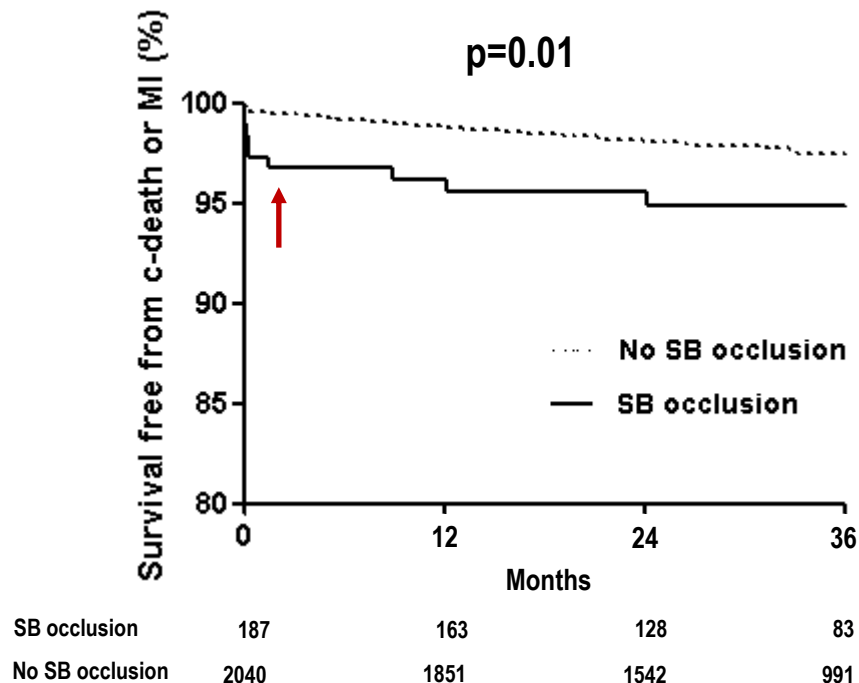
Clinical impact of SB occlusion

COBIS II Registry



- Main vessel first stenting strategy: N=2,227
- SB occlusion after MV stenting (TIMI flow <3): N=187, 8.4%

Cardiac Death / MI



How to avoid SB compromise after MV stenting

COBIS II Registry



- How to protect SB
 - Jailed wire technique
 - SB predilation
 - Optimal stent sizing

COBIS II : Predictors of SB occlusion

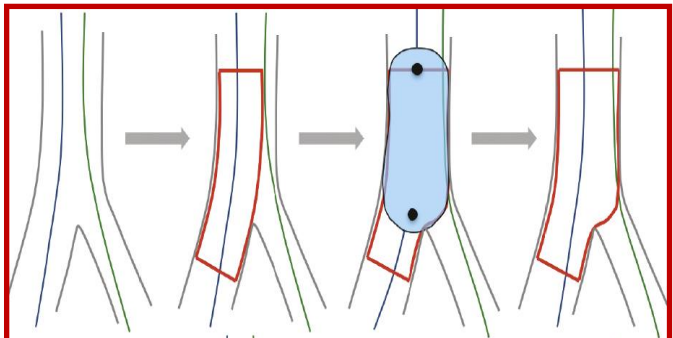
Variables	OR [95% CI]	p Value
SB DS \geq 50%	2.34 [1.59-3.43]	<0.001
SB lesion length (by 1 mm)	1.03 [1.003-1.06]	<0.001
Proximal MV DS \geq 50%	2.34 [1.57-3.50]	0.03
Acute coronary syndrome	1.53 [1.06-2.19]	0.02
Left main lesions	0.34 [0.16-0.72]	0.005

ACS = acute coronary syndrome, DS = diameter stenosis,
SB = side branch, MV = main vessel

**Important non-predictors:
jailed wire technique, SB pre-dilation, IVUS guidance**

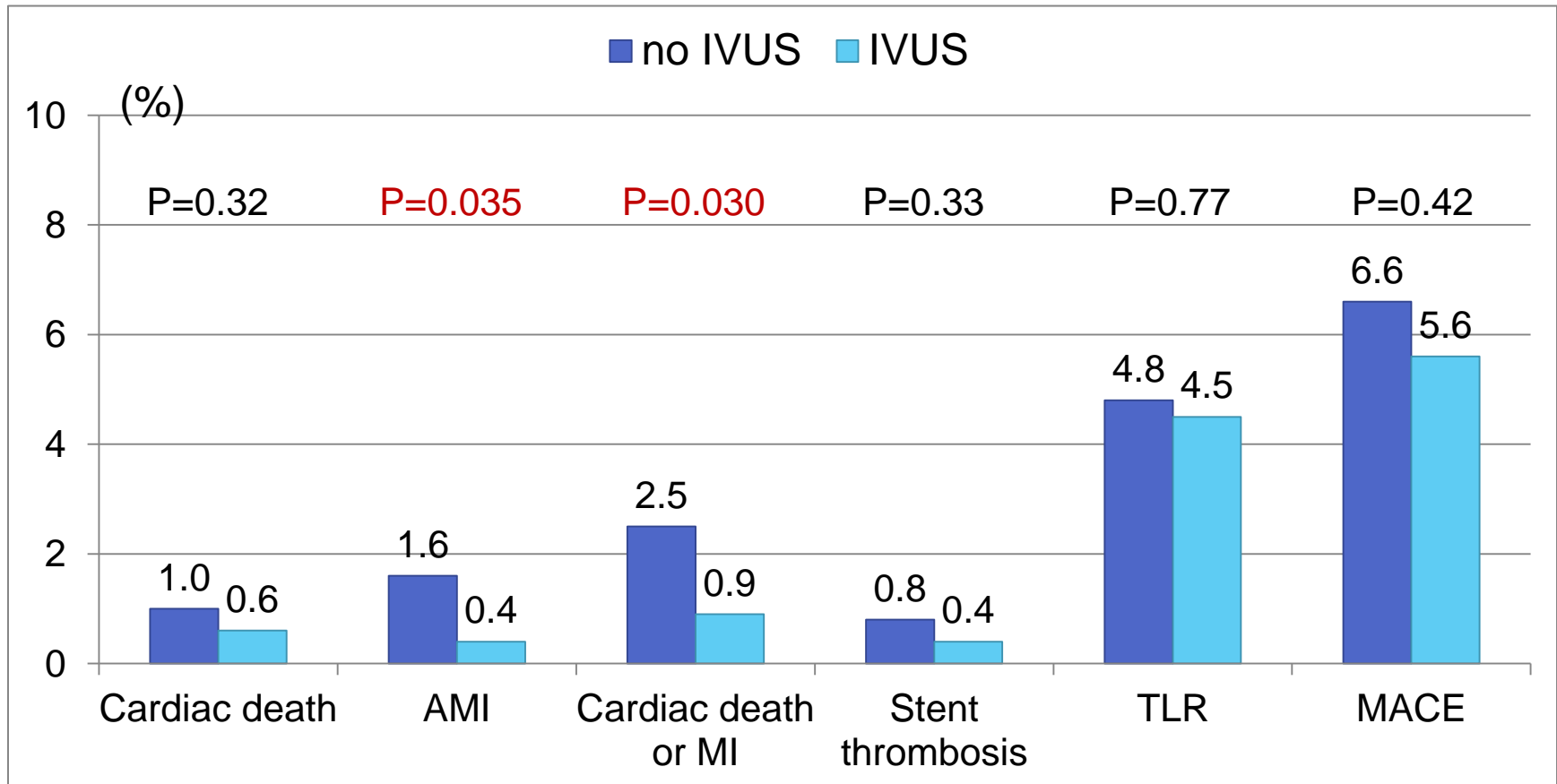
Jailed wire was not a predictor of SB compromise but a predictor of SB recovery in COBIS II registry

SB occlusion in 187 patients (8.4%), and SB flow was recovered in 129 patients (69%) among them.

	SB recovery (n=129)	No SB recovery (n=58)	p Value
Bifurcation location			0.65
Left main bifurcation			5 (8.6)
LAD/diagonal			40 (69.0)
LCX/OM			7 (12.1)
RCA bifurcation	6 (10.3)		
True bifurcation	45 (77.6)		0.49
Jailed wire in the SB	92 (71.3)	31 (53.4)	0.02
SB predilation before MV stenting	45 (34.9)	16 (27.6)	0.33
Guidance of	<div style="border: 1px solid blue; padding: 5px;"> Jailed wire technique is a preferred technique, as long as it is simple to place wires in the branches. </div>		0.27
MV stent diameter			0.62
MV stent length (mm)	24.0 (20.0-30.0)	24.0 (20.0-32.0)	0.91
MV stent maximal pressure (atm)	12.0 (10.0-15.5)	12.0 (10.0-14.0)	0.57
MV stent to artery ratio	1.2 (1.1-1.3)	1.2 (1.1-1.4)	0.25

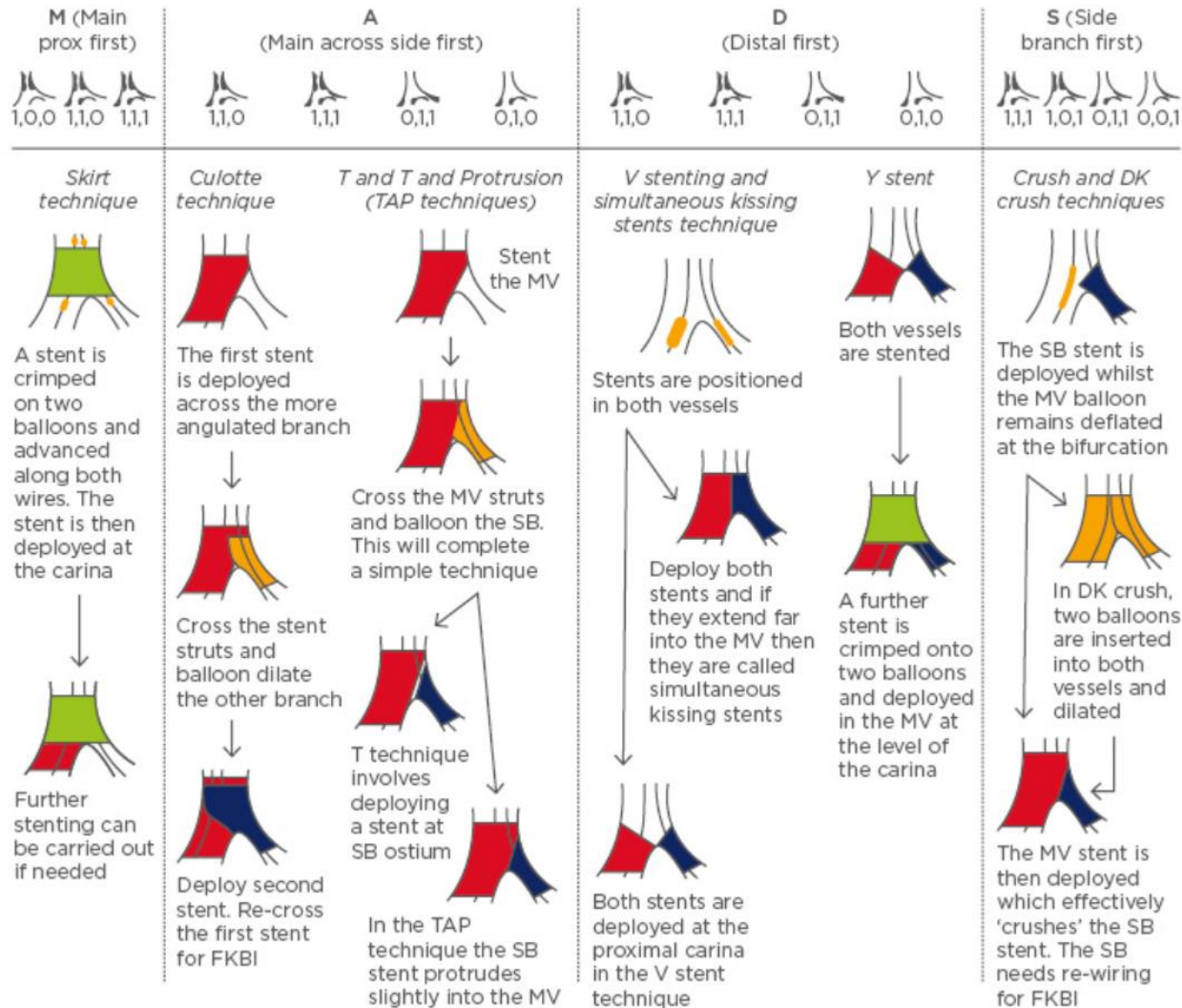
IVUS guidance may improve safety

COBIS I Registry



IVUS guidance improves the safety of bifurcation stenting, most likely by better stent apposition and expansion

How many options for bifurcation lesions?

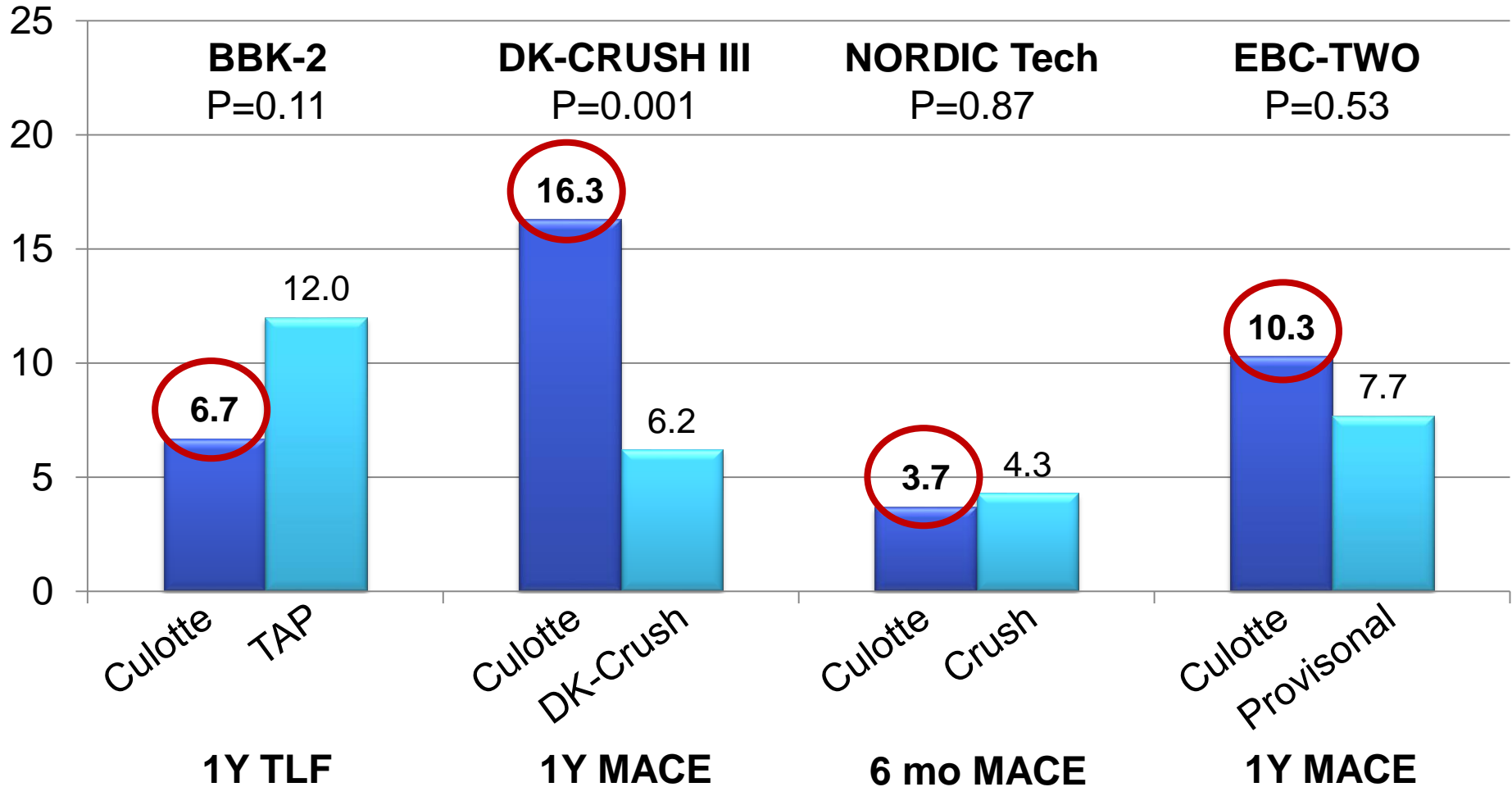


What is the best 2-stent technique?

TAP technique? Culotte technique? DK crush technique?



Outcomes were highly variable

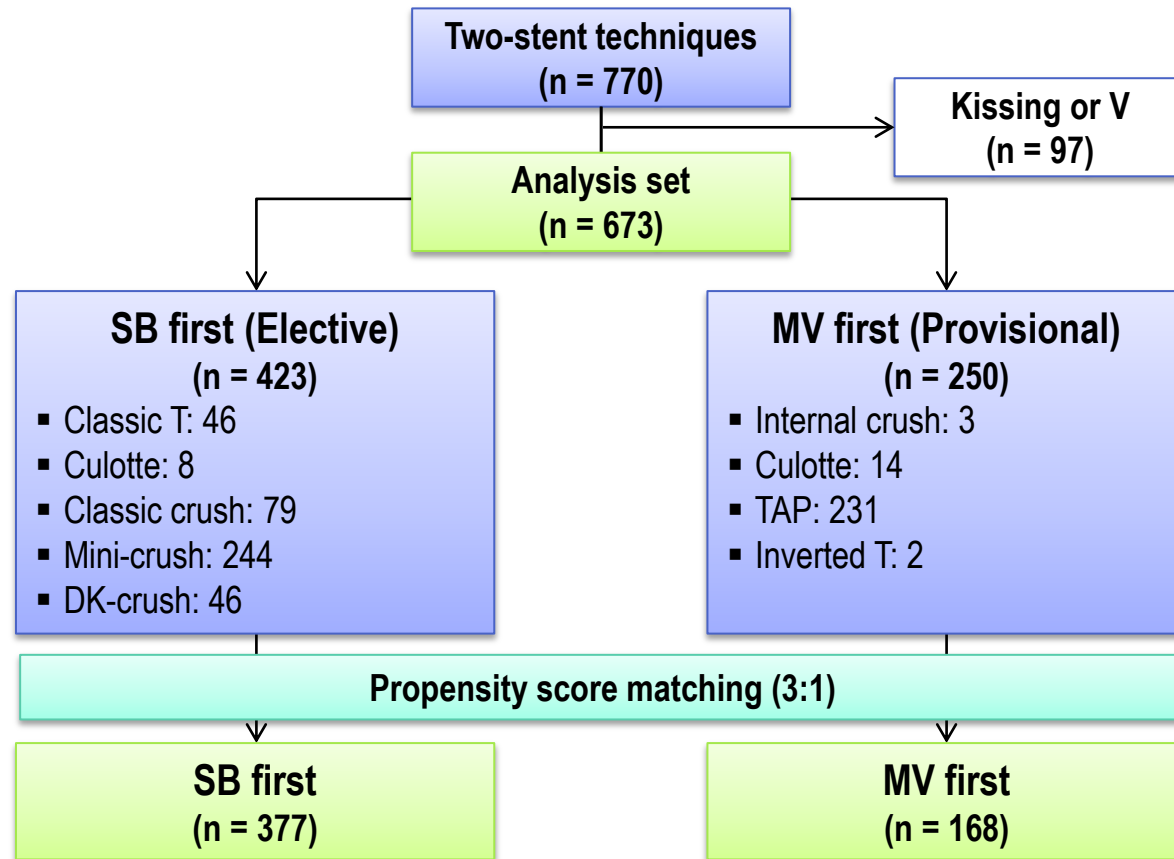


What is the best 2-stent technique?

COBIS II registry



- N=673, treated with 2-stent technique (except kissing or V-stenting)

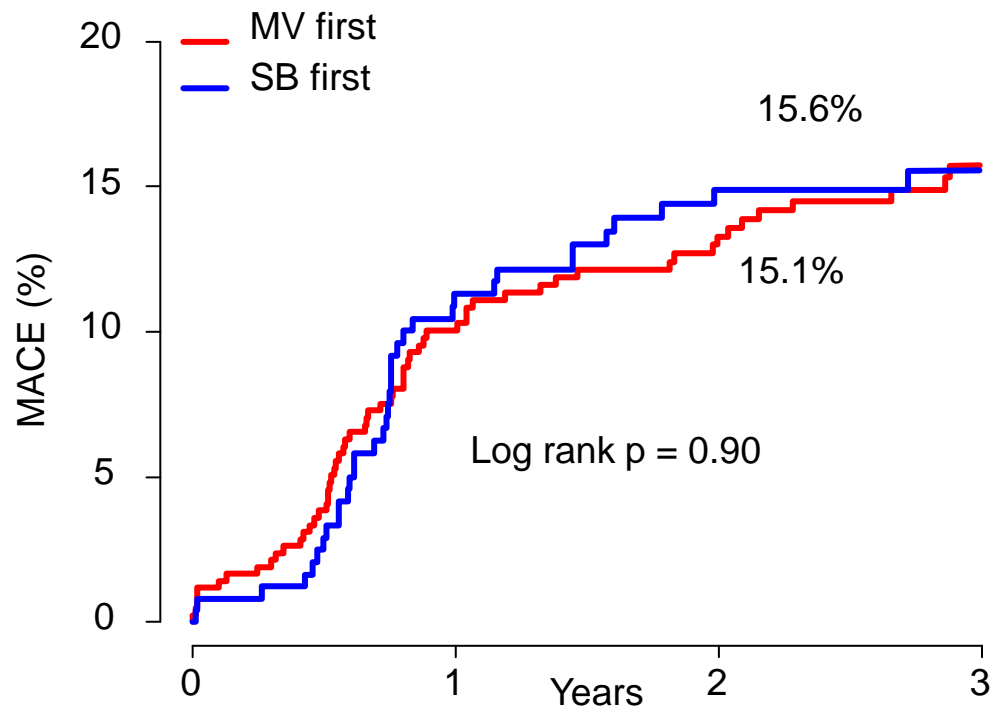


What is the best 2-stent technique?

COBIS II registry



- N=673, treated with 2-stent technique (except kissing or V-stenting)



Postprocedure-related issues

COBIS I

1. Gwon HC, et al. **Long-term clinical results and predictors of adverse outcomes** after drug-eluting stent implantation for bifurcation lesions in a real-world practice: the COBIS (Coronary Bifurcation Stenting) registry. Circ J 2010
2. Song PS, et al. **Periprocedural myocardial infarction** is not associated with an increased risk of long-term cardiac mortality after coronary bifurcation stenting. IJC 2012

COBIS II

1. Song PS, et al. **Triple versus dual antiplatelet therapy** after percutaneous coronary intervention for coronary bifurcation lesions: results from the COBIS (COronary BIfurcation Stent) II Registry. Heart Vessels 2014
2. Song PS, et al. **Major Predictors of Long-Term Clinical Outcomes** After Percutaneous Coronary Intervention for Coronary Bifurcation Lesions With 2-Stent Strategy: Patient-Level Analysis of the Korean Bifurcation Pooled Cohorts. JACC CVI 2016

Korean Bifurcation Pooled Cohorts

Predictors of TVF in 2-stent strategy



- Treated with 2-stent strategy: N=951

	Adjusted HR*	95% CI	p Value
Treated bifurcation in LM	2.09	1.43 – 3.03	<0.001
High SYNTAX score >32	2.00	1.28 – 3.14	0.002
Diabetes mellitus	1.41	1.00 – 1.99	0.05
Second-generation DES	0.26	0.12 – 0.57	0.001
Non-compliant balloon	0.53	0.36 – 0.79	0.002
Final kissing ballooning	0.44	0.29 – 0.68	<0.001

*Adjusted for age (continuous), acute coronary syndrome as presentation, preprocedural hemoglobin level, pre-procedural creatinine level, bifurcation angle (continuous), multi-vessel coronary disease, transradial approach, intravascular ultrasound, provisional approach, stenting techniques, total stent length in side branch (continuous).

Conclusions



- **COBIS I & II registries have contributed much to answering questions regarding bifurcation treatment. However, these results do not reflect the current practice.**
- **COBIS III will provide more update insight on the treatment of bifurcation lesion.**

Thank You For Your Attention !

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