# Lessons learned from COBIS

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# COBIS studies

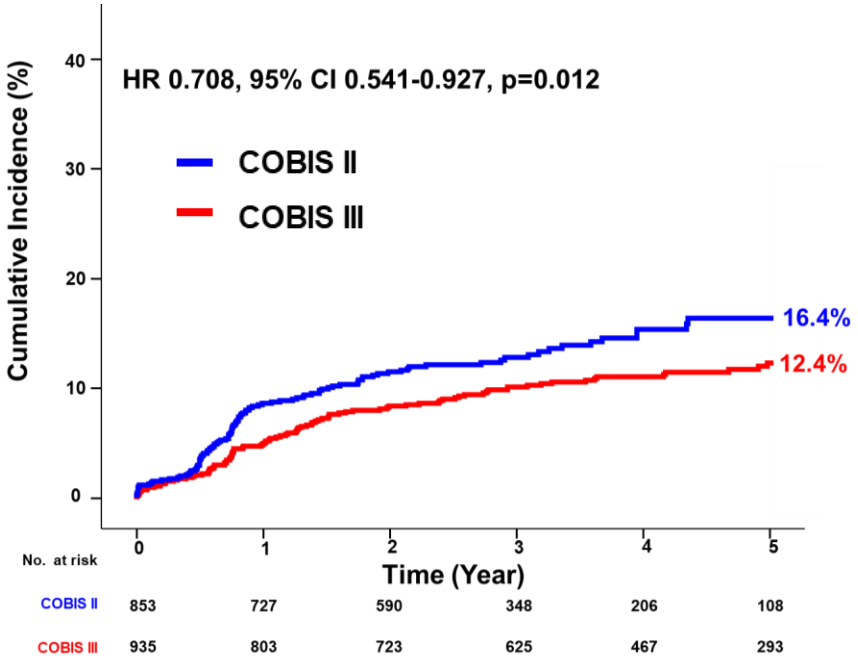
- Investigator-initiated nation wide multicenter registry studies for **CO**ronary **BI**furcation **S**tenting
- Endorsed by Korean Society of Interventional Cardiology
- Sponsored and managed by Korean Bifurcation Club (COBIS III)

| | COBIS I | COBIS II | COBIS III |
|---|---|---|---|
| **Patients No.** | **1691** | **2897** | **2648** |
| **Enrollment period** | **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** |
| Left main bifurcation | **X** | **O** | **O** |
| **DES generation** | **1st** | **1st + 2nd** | **2nd only** |
| **Median Follow-up Duration** | **25 months** | **38 months** | **53 months** |

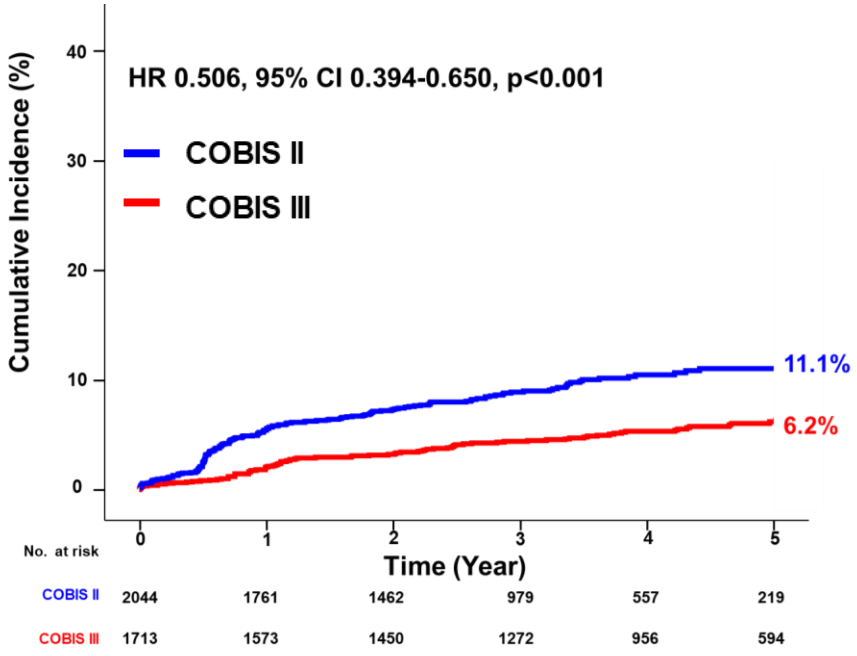
# What makes the difference?

## Device? Concept? Technique?

### TLF in LM bifurcation




### TLF in non-LM bifurcation



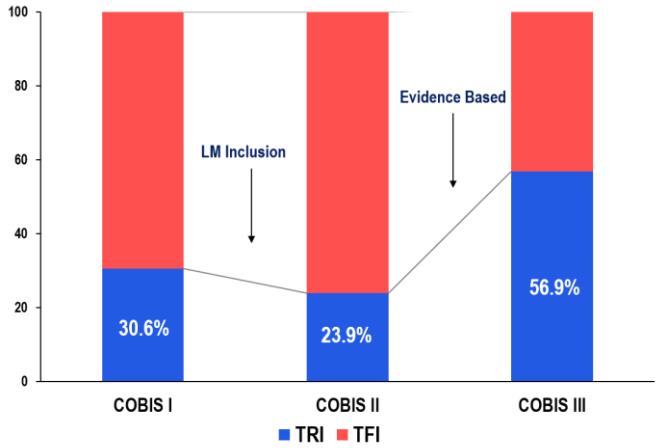
# What makes the difference?

## Device? Concept? Technique?

- Safer access: More trans-radial approach
- Better stents and better stenting technique
- Better PCI technique: Better kissing, NC balloon, POT
- Better concept: imaging guidance, SB relevance
- Better risk stratification: SB occlusion, risk stratification

COBIS Registry

# Transradial vs. Transfemoral for Bifurcation PCI



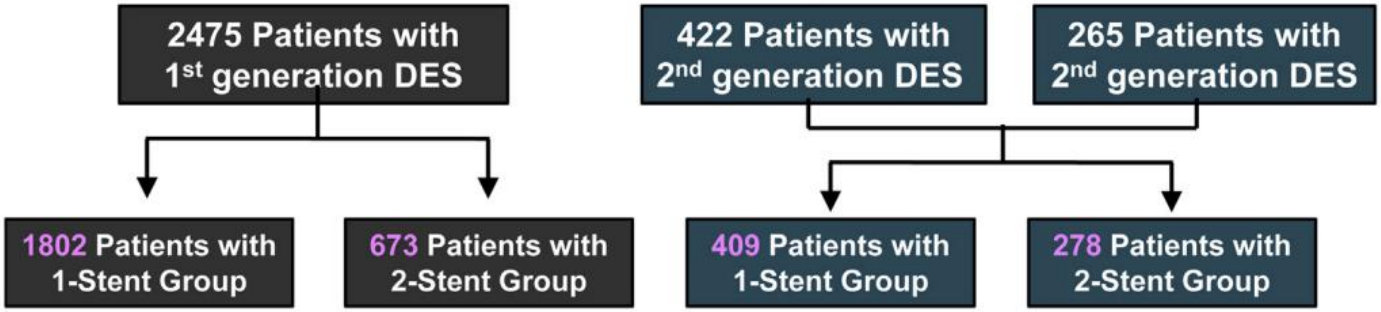

- LM bifurcation lesions from COBIS II (N=853)
- Transradial (N=212, 24.9%) vs. Transfemoral (N=641)
- Propensity score-matched analysis (1:2 ratio, 161 pairs)

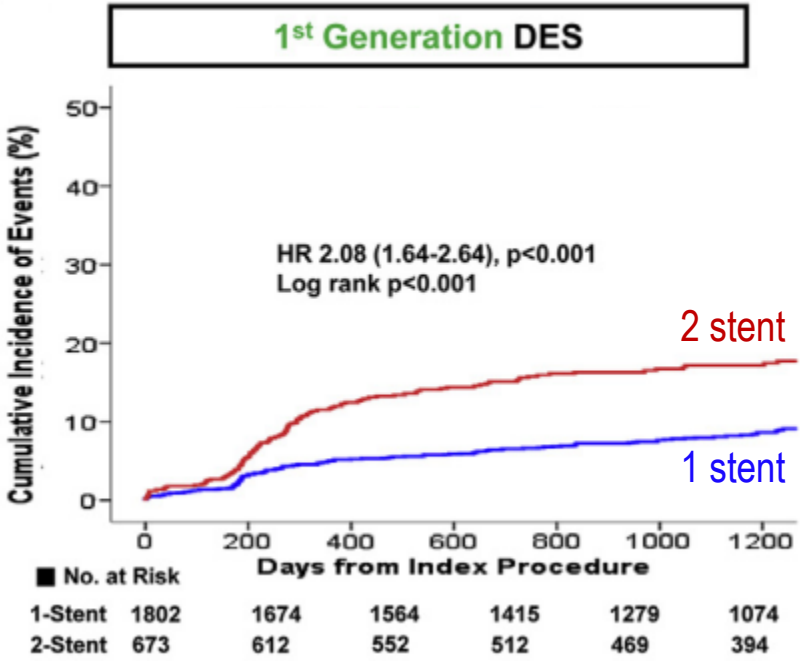
| | **Transradial** (N=161) | **Transfemoral** (N=322) | **Adjusted HR** (95% CI) | **p** |
|---|---|---|---|---|
| **MACE** | 14 (8.7) | 37 (11.5) | 0.48 (0.22-1.03) | 0.06 |
| Cardiac death | 4 (2.5) | 5 (1.6) | 0.33 (0.02-4.97) | 0.42 |
| Cardiac death or MI | 7 (4.3) | 8 (2.5) | 1.42 (0.35-5.69) | 0.62 |
| **TLR** | 7 (4.3) | 32 (9.9) | 0.30 (0.11-0.81) | 0.02 |
| | | | | |
| TIMI major or minor bleeding | 4 (2.5) | 27 (8.4) | | 0.01 |

Chung SM, et al., J Invasive Cardiol 2015

# Korean Bifurcation Pooled Cohort

# 1st vs. 2nd generation DES

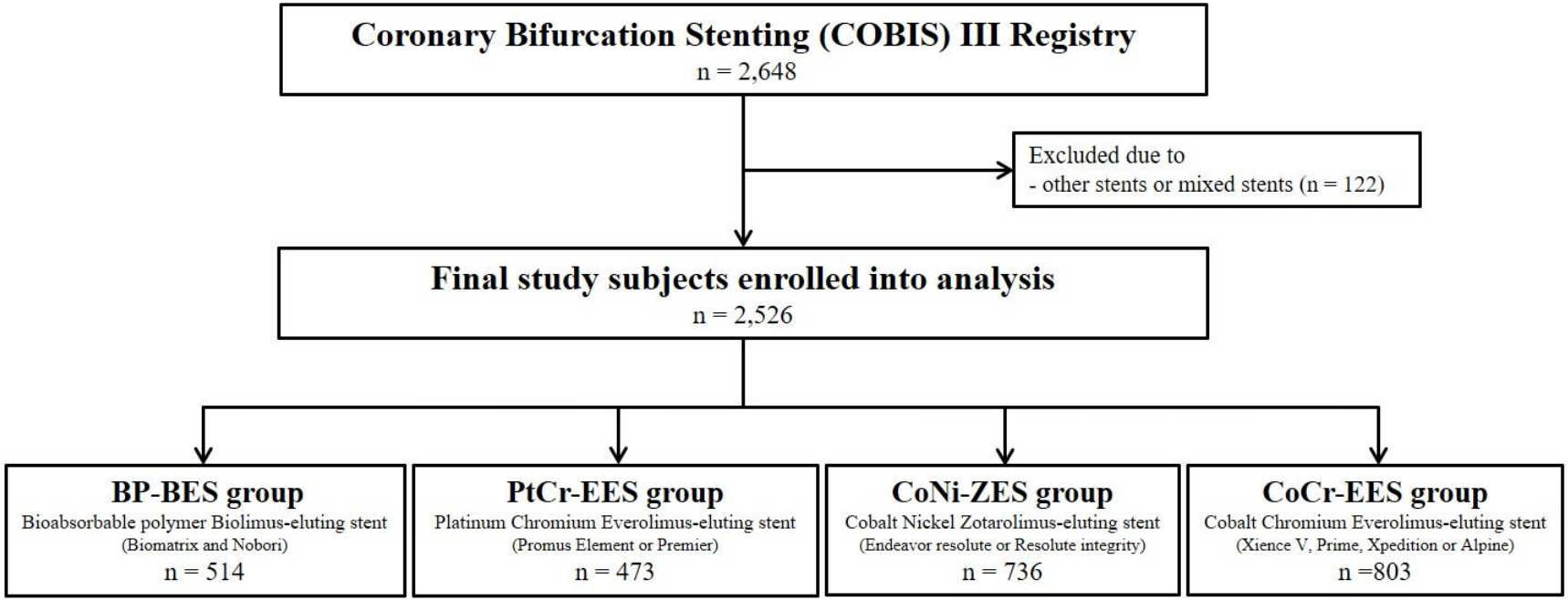



Lee JM, et al, JACC Interv 2015

COBIS III registry

# Clinical outcomes among 2nd generation DES

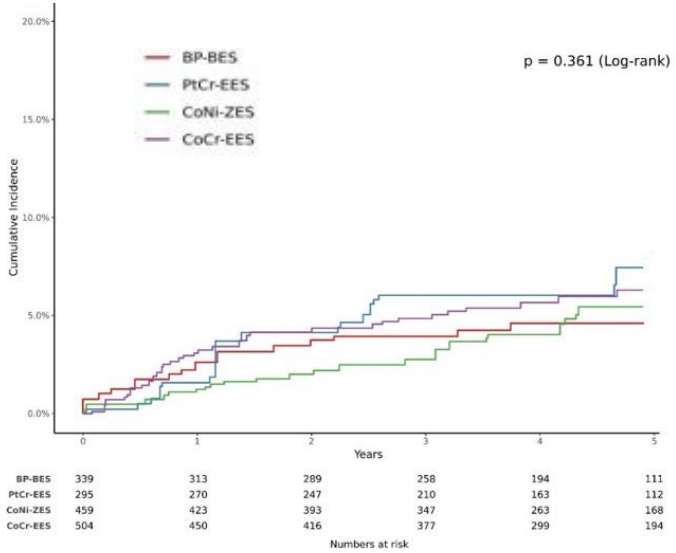


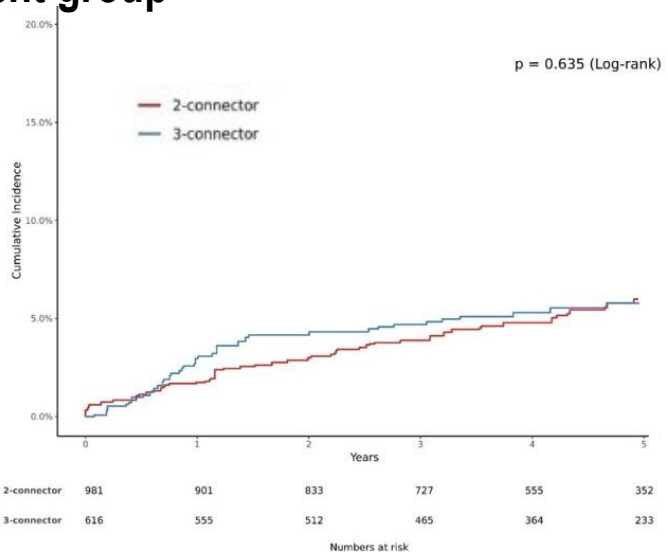

Jang WJ, et al. Under review

COBIS III registry

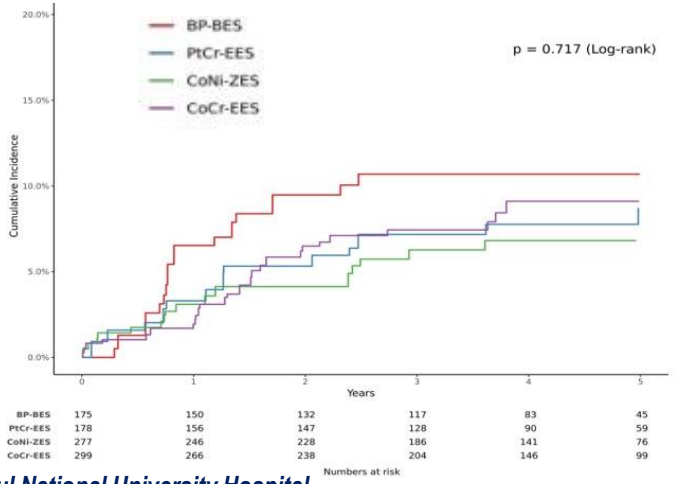
# Clinical outcome among 2nd generation DES

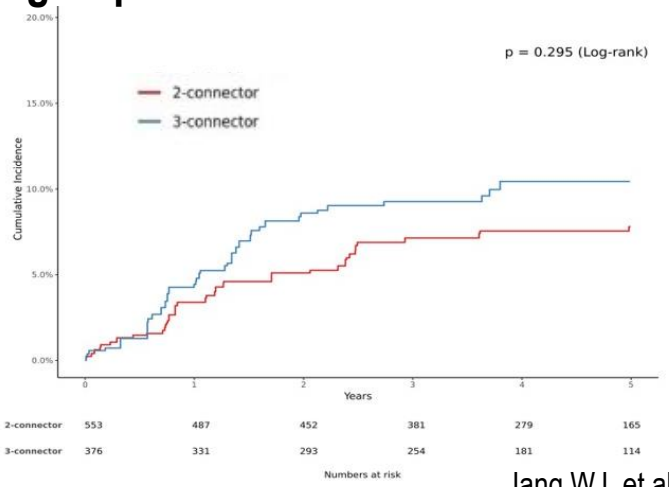
## SB No treatment group




## SB Treatment group

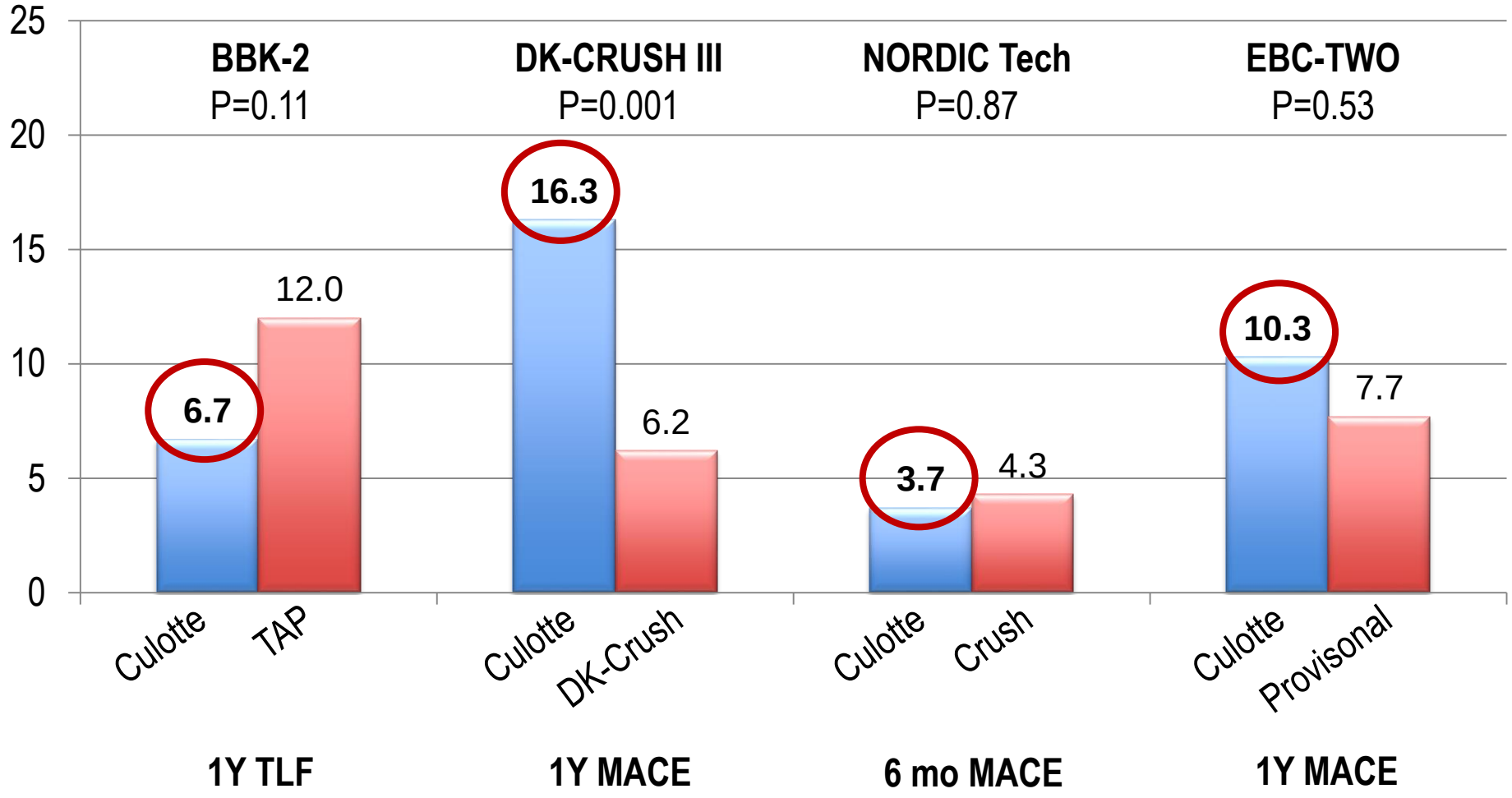



Jang WJ, et al. Under review

# What is the best 2-stent technique?

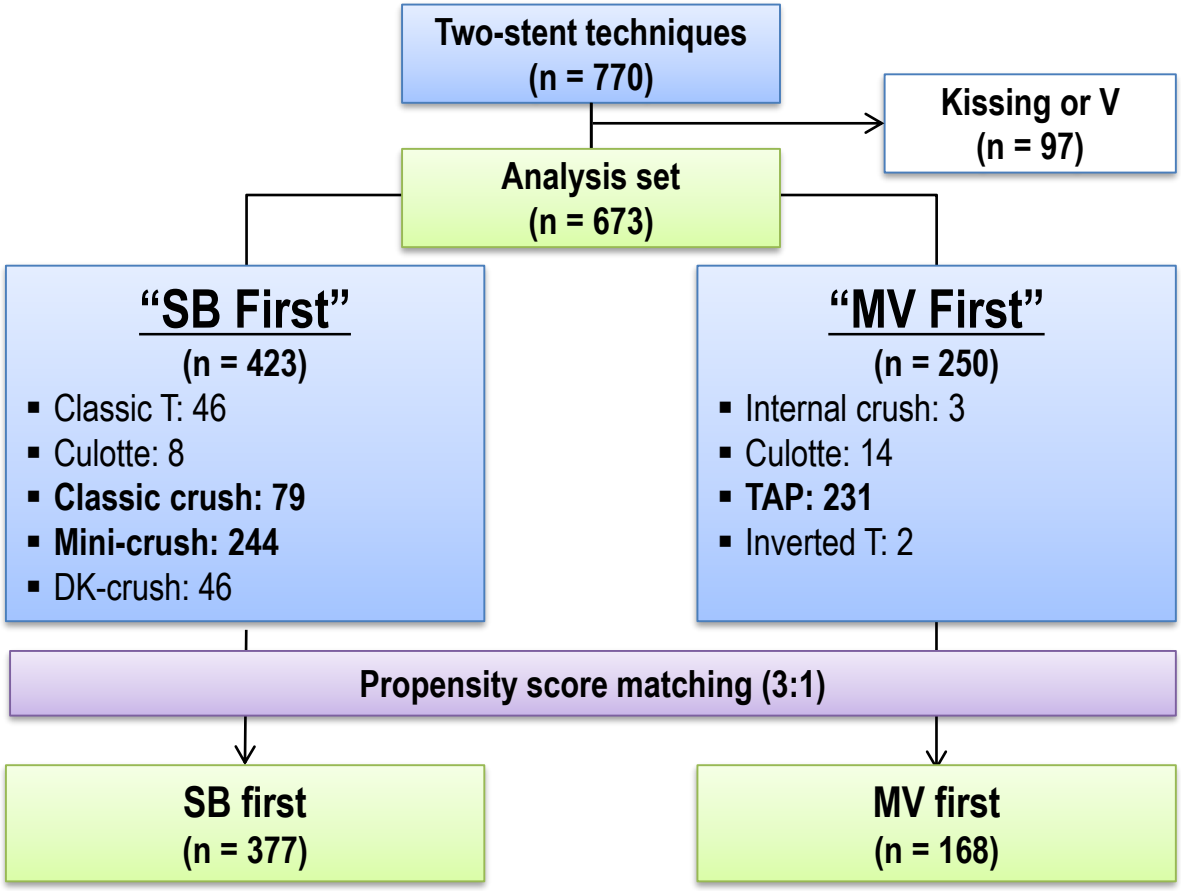
TAP technique? Culotte technique? DK crush technique?



COBIS II registry

# What is the best 2-stent technique?

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




Park TK, et al., Eurointervention 2017

COBIS II registry

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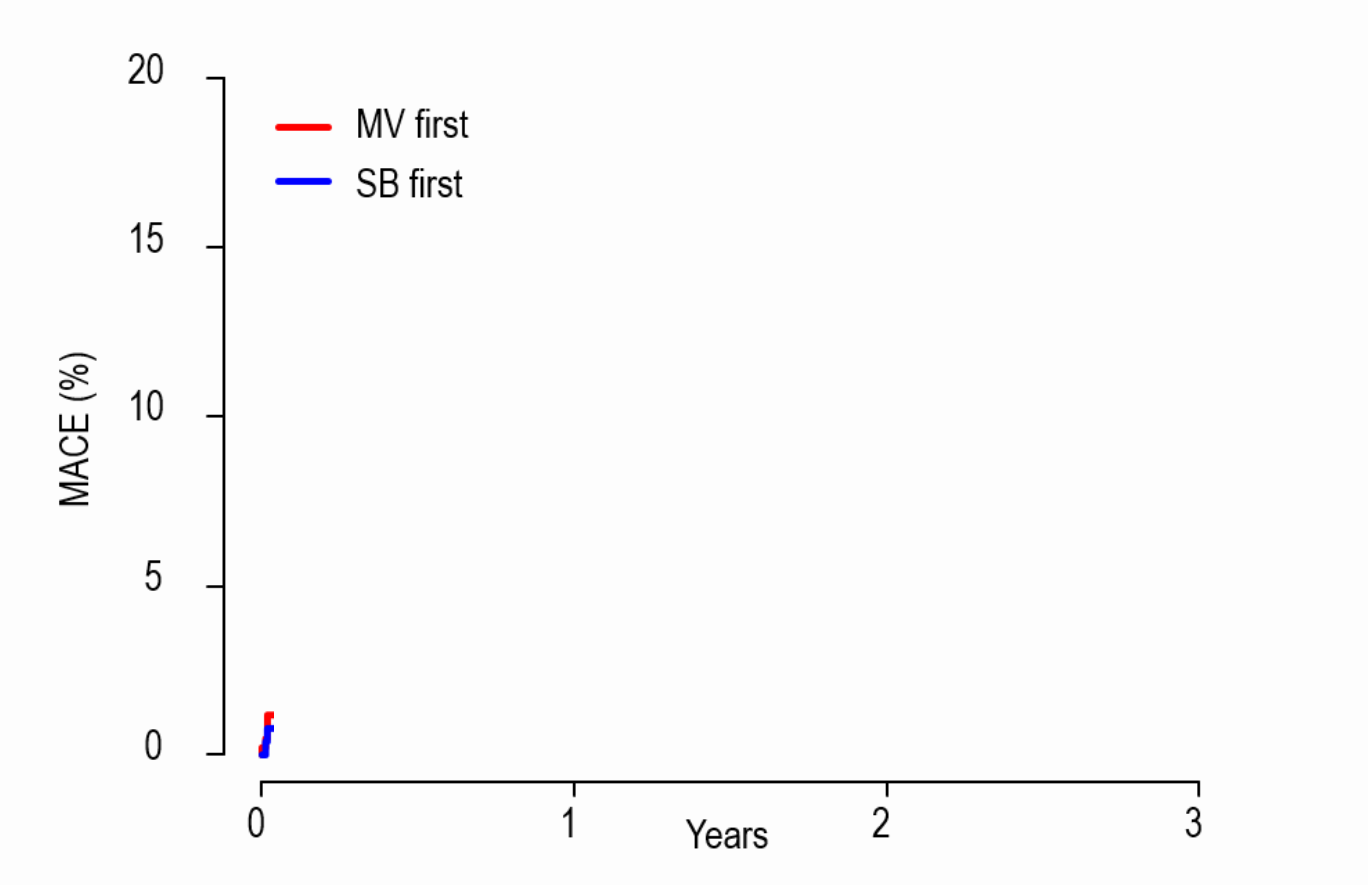


Park TK, et al., Eurointervention 2017

# COBIS III registry

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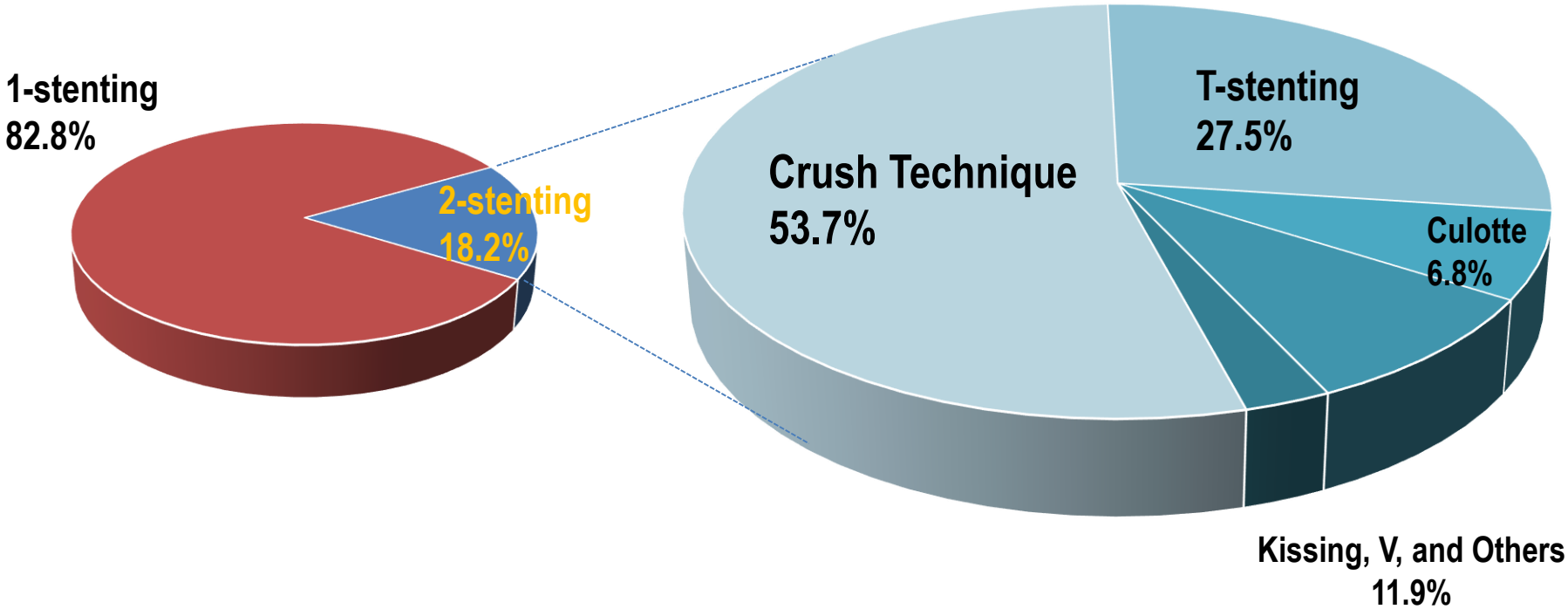


Kang JH, et al., KBC workshop 2019

# COBIS III registry

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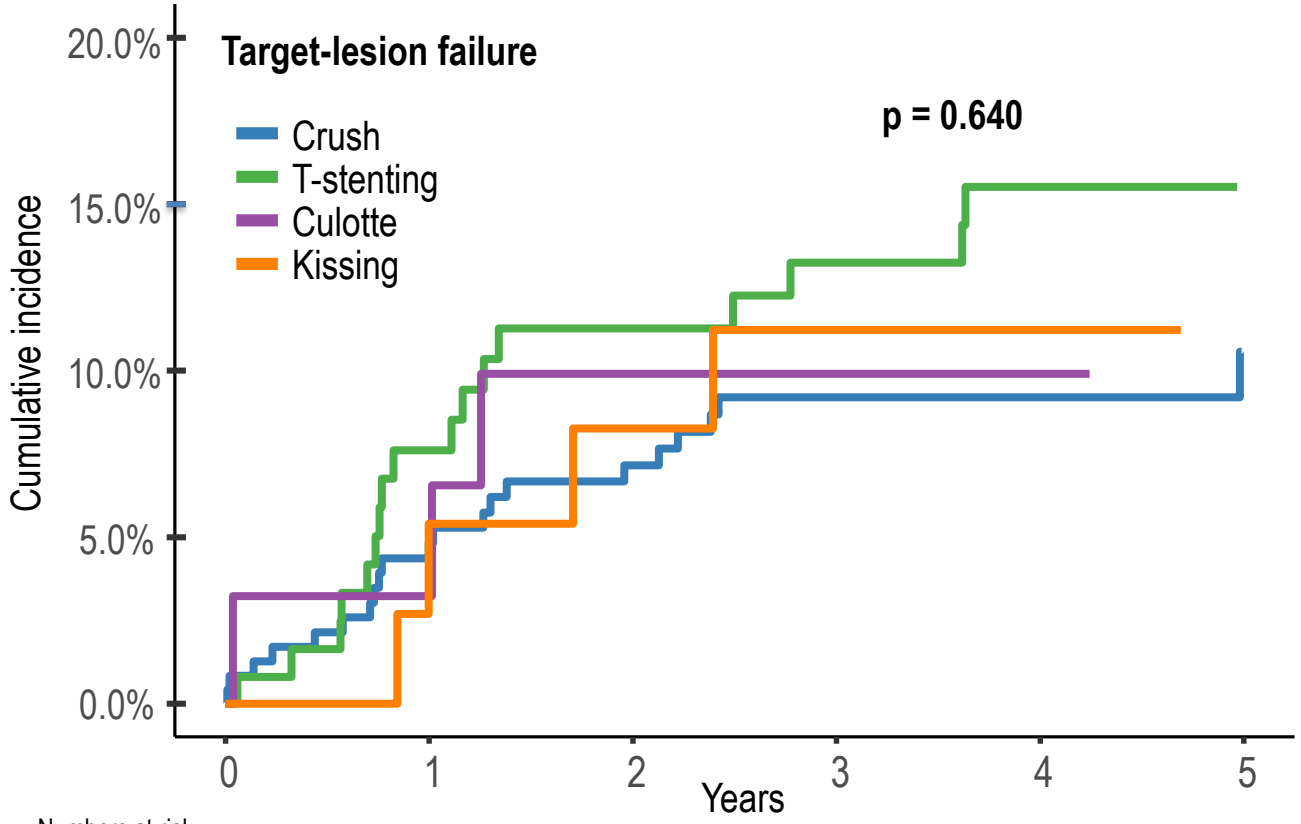



Numbers at risk

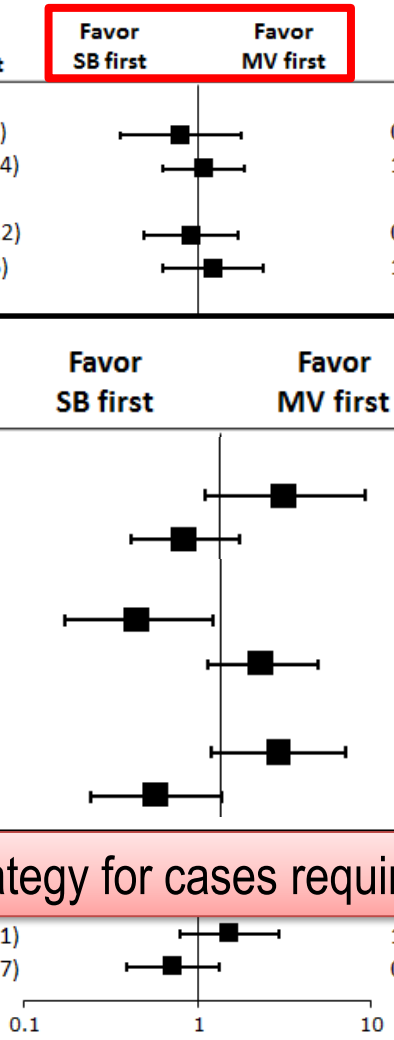
| | | | | | | |
|---|---|---|---|---|---|---|
| Crush | 244 | 210 | 187 | 152 | 108 | 64 |
| T-stenting | 125 | 104 | 94 | 85 | 66 | 39 |
| Culotte | 31 | 29 | 26 | 23 | 13 | 10 |
| Kissing | 41 | 35 | 32 | 27 | 17 | 11 |

Kang JH. KBC workshop 2019

# Insight from COBIS II registry

# What is the best 2-stent technique?

| Subgroup | Patients | TLR (%) SB first | TLR (%) MV first | Hazard ratio (95% CI) | p value | p for Interaction |
|---|---|---|---|---|---|---|
| MV RD | | | | | | 0.52 |
| ≥3.25 mm | 217 | 12/120 (10.0) | 12/97 (12.4) | 0.80 (0.36-1.78) | 0.59 | |
| <3.25 mm | 456 | 40/303 (13.2) | 19/153 (12.4) | 1.09 (0.63-1.88) | 0.77 | |
| SB RD | | | | | | 0.54 |
| ≥2.5 mm | 276 | 20/151 (13.2) | 19/125 (15.2) | 0.92 (0.49-1.72) | 0.79 | |
| <2.5 mm | 397 | 32/272 (11.8) | 12/125 (9.6) | 1.23 (0.63-2.38) | 0.55 | |
| SB RD > MV RD | | | | | | 0.78 |
| MV DS | | | | | | 0.04 |
| ≥70% | 257 | 22/156 (14.1) | 8/101 (7.9) | 1.94 (0.86-4.36) | 0.11 | |
| <70% | 416 | 30/267 (11.2) | 23/149 (15.4) | 0.71 (0.41-1.22) | 0.22 | |
| SB DS > MV DS | | | | | | 0.008 |
| Yes | 252 | 17/189 (9.0) | 12/63 (19.0) | 0.44 (0.21-0.92) | 0.03 | |
| No | 420 | 35/234 (15.0) | 19/186 (10.2) | 1.54 (0.88-2.68) | 0.13 | |
| MV Lesion Length | | | | | | 0.01 |
| ≥18 mm | 329 | 36/215 (16.7) | 11/114 (9.7) | 1.79 (0.91-3.53) | 0.09 | |
| <18 mm | 344 | 16/208 (7.7) | 20/136 (14.7) | 0.53 (0.27-1.01) | 0.05 | |
| ≥65° | 293 | 27/167 (16.2) | 14/126 (11.1) | 1.53 (0.80-2.92) | 0.20 | |
| <65° | 380 | 25/256 (9.8) | 17/124 (13.7) | 0.72 (0.39-1.33) | 0.29 | |




"MORE severe lesion FIRST" strategy for cases requiring systematic 2 stenting.

Park TK, et al., Eurointervention 2017

# What makes the difference?

## Device? Concept? Technique?

- Safer access: More trans-radial approach
- Better stents and better stenting technique
- Better PCI technique: Better kissing, NC balloon….
- Better concept: Imaging guidance, SB relevance
- Better risk stratification: SB occlusion, risk stratification

# "KISS" for 1-stent technique: Good or Bad?

| | Number Design | Primary endpoint | Outcomes | Results | Memo |
|---|---|---|---|---|---|
| Niemela M (NORDIC III) Circulation 2011 | N=477 RCT | 6-mo MACE | FKB 2.9%, non-FKB 2.9% P=NS | **Neutral** | |
| Gwon HC (COBIS I) Heart 2012 | N=1,065 Registry | 2-year MACE | FKB 9.5%, non-FKB 4.5% p=0.02 | **Bad** | Higher MV TLR in FKB group |
| Yamawaki M Circ J 2014 | N=253 Registry | 3-year MACE | FKB 14.6% vs. non-FKB 6.9% p=0.07 | **Bad** | Higher MV restenosis in FKB-group |
| Kim TH Int J Cardiol 2014 | N=251 Registry | 3-year MACE | FKB HR=0.40 (95% CI 0.19–0.84), p=0.015 | **Good** | ACS patients |
| Biondi-Zoccai G Heart Vessels 2014 | N=2,813 Registry | 2-year MACE | HR=1.01 (0.80–1.23) p=0.91 | **Neutral** | |
| Gao Z Chin Med J 2015 | N=790 Registry | 4-year MACE | FKB: 7.8%, non-FKB 10.0% p=0.33 | **Neutral** | Left main bifurcation |
| Kim YH (CROSS) JACC CVI 2015 | N=306 RCT | 1-year MACE | FKB 14.0%, non-FKB 11.6% p=0.57 | **Bad** | Higher MV restenosis in FKB group |
| Yu CW (COBIS II) JACC CVI 2015 | N=1,901 Registry | 3-year MACE | HR=0.50 (95% CI: 0.30- 0.85),p = 0.01 | **Good** | Lower MV TLR in FKB group |

COBIS II Registry

# "KISS" for 1-stent techniques

- Treated with 1-stent technique: N=1,901
- Final kissing ballooning (FKB): N=620 → PSM matched analysis: N=545 pairs

| | Propensity-Matched Population | | | |
|---|---|---|---|---|
| | FKB (n = 545) | Non-FKB (n = 545) | p Value | Standardized Difference |
| After MV stenting | | | | |
| Main vessel | | | | |
| Proximal MLD | 3.07 ± 0.55 | 3.02 ± 0.58 | 0.85 | 9.2 |
| Middle MLD | 2.76 ± 0.54 | 2.71 ± 0.56 | 0.72 | 9.6 |
| Distal MLD | 2.76 ± 0.49 | 2.72 ± 0.54 | 0.85 | 8.6 |
| Side branch | | | | |
| Ostial MLD | 1.26 ± 0.73 | 1.25 ± 0.69 | 0.71 | 1.3 |
| Distal MLD | 2.02 ± 0.69 | 1.96 ± 0.68 | 0.67 | 7.8 |
| Final | | | | |
| Main vessel | | | | |
| Proximal MI | | | | |
| Middle MLD | 2.86 ± 0.50 | 2.72 ± 0.56 | 0.001 | |
| Distal MLD | 2.83 ± 0.48 | 2.73 ± 0.55 | 0.04 | |
| Side branch | | | | |
| Ostial MLD | 1.85 ± 0.62 | 1.36 ± 0.69 | <0.001 | |
| Distal MLD | 2.15 ± 0.59 | 1.99 ± 0.68 | 0.04 | |

FKB reduces main vessel TLR, not side branch TLR.

**"Gentle KISS for MB and SB"**

| | Adjusted HR (95% CI) | p |
|---|---|---|
| **MACE** | **0.50** (0.30-0.85) | 0.01 |
| Cardiac death | 0.50 (0.11-2.29) | 0.37 |
| MI | 0.18 (0.01-20.4) | 0.48 |
| Stent thrombosis, | 0.77 (0.17-3.45) | 0.73 |
| | 1) | 0.02 |
| **Main vessel** | **0.51** (0.28-0.93) | **0.03** |
| Side branch | 0.57 (0.24-1.37) | 0.21 |

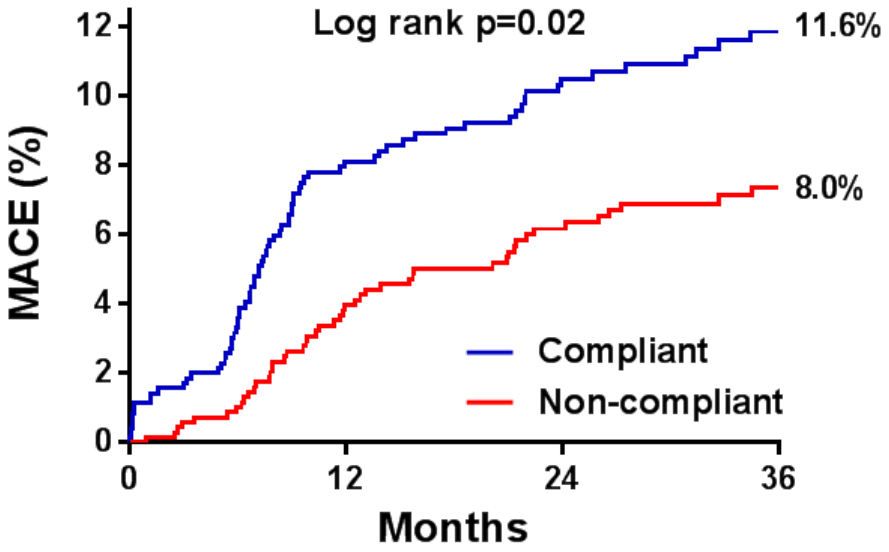
Yu CW and Yang JH, et al. JACC Interv 2015

COBIS II Registry

# Clinical impact of NC balloon

- Use of non-compliant balloon: N=752, 26.0%
- Propensity score-matched analysis: N=710 pairs

| | CB | NCB | p |
|---|---|---|---|
| Dissection >type B | 1.1% | 0.1% | 0.046 |
| Angiographic success | | | |
| Main vessel | 99.0% | 98.7% | 0.80 |
| Side branch | 75.4% | 79.7% | 0.03 |
| In-hospital MI | 0.8% | 0% | 0.04 |




Park TK, et al., EuroIntervention 2016

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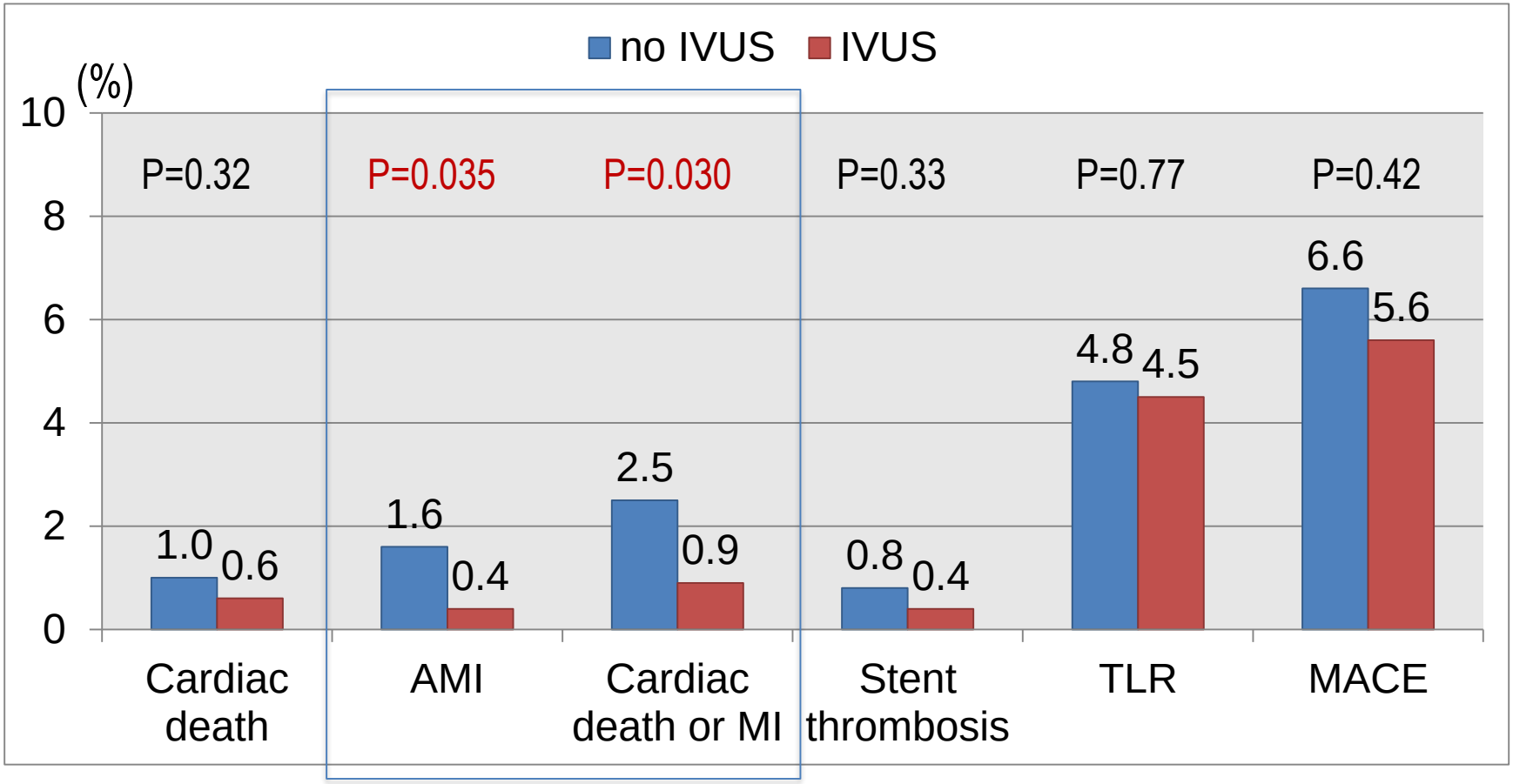
# COBIS Registry
# IVUS guidance improves outcomes



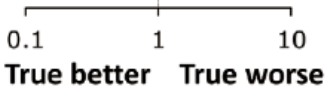

Kim JS, Am Heart J 2011

# COBIS II Registry

## True vs. Non-true bifurcation lesions: Clinical relevance of SB

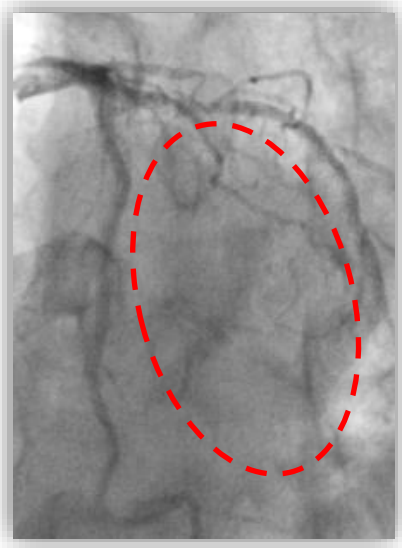
| Subgroup | Patients | MACE (%) True | MACE (%) NonTrue | Adjusted HR (95% CI) | P value | P for Interaction |
|---|---|---|---|---|---|---|
| **DM** | | | | | | |
| Yes | 840 | 69 (15.8) | 35 (8.7) | 1.95 (1.24-3.07) | 0.004 | **0.10** |
| No | 2057 | 112 (10.5) | 80 (8.1) | 1.18 (0.86-1.61) | 0.31 | |
| **Presentation** | | | | | | |
| ACS | 1798 | 117 (12.2) | 71 (8.5) | 1.35 (0.98-1.86) | 0.06 | **0.69** |
| Non-ACS | 1099 | 64 (11.8) | 44 (7.9) | 1.56 (1.01-2.42) | 0.05 | |
| **Left main** | | | | | | |
| Yes | 853 | 66 (18.4) | 48 (9.7) | 1.22 (0.78-1.90) | 0.38 | **0.43** |
| No | 2044 | 115 (10.1) | 67 (7.4) | 1.42 (1.04-1.95) | 0.03 | |
| **Two stent** | | | | | | |
| Yes | 770 | 102 (17.8) | 23 (11.7) | 1.54 (0.97-2.43) | 0.07 | **0.49** |
| No | 2127 | 79 (8.5) | 92 (7.7) | 1.20 (0.87-1.65) | 0.28 | |
| **FKB** | | | | | | |
| Yes | 1349 | 109 (12.8) | 39 (7.9) | 1.56 (1.06-2.30) | 0.03 | **0.74** |
| No | 1548 | 72 (11.1) | 76 (8.5) | 1.23 (0.87-1.76) | 0.25 | |
| **Type** | | | | | | |
| 1st | | | | | | **0.53** |
| 2nd | | | | | | |
| **SB reference diameter** | | | | | | |
| >2.5 mm | 1154 | 72 (14.0) | 43 (6.7) | 2.16 (1.48-3.15) | <0.001 | **0.02** |
| ≤2.5 mm | 1741 | 109 (11.0) | 72 (9.6) | 1.20 (0.89-1.62) | 0.23 | |

**Focus on true bifurcation with large SB.**

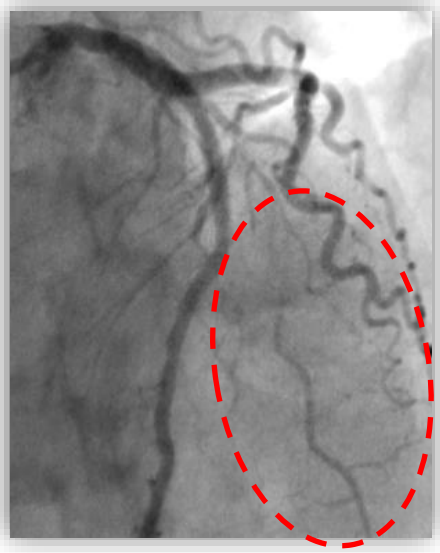



Park TK, et al., Circ J 2015

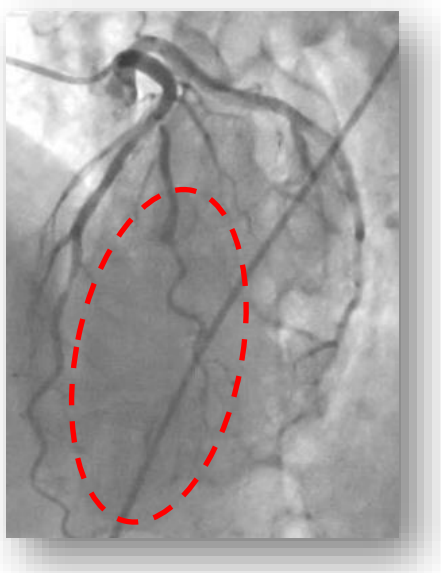
# How large is large enough?



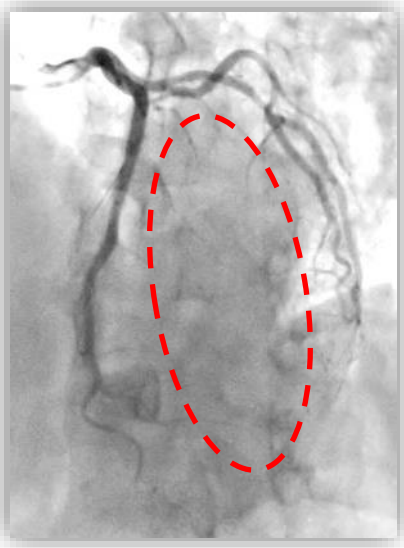
% ischemia: 15%



% ischemia: 11%



% ischemia: 10%



% ischemia: 12%


DECISION TREE LEARNING IS THE PROCESS OF CREATING/LEARNING A DECISION TREE FROM TRAINING DATA

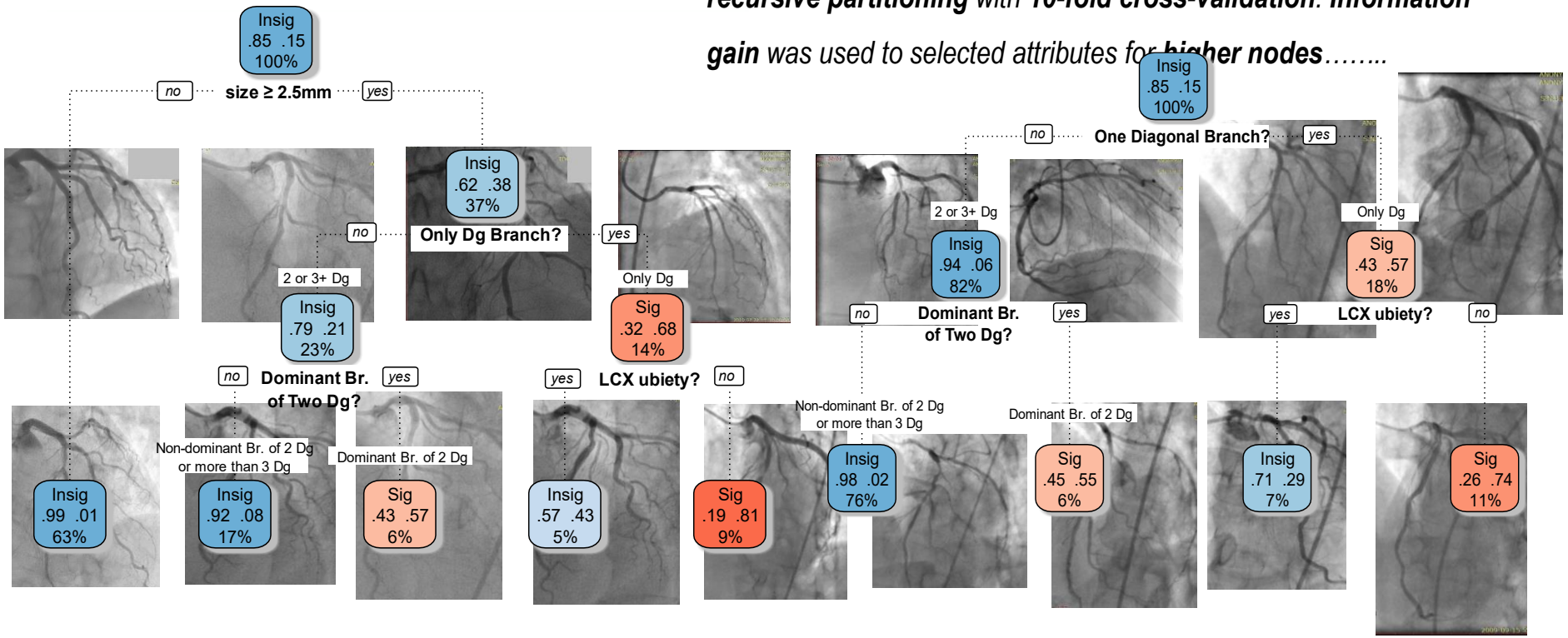
RECURSIVE PARTITIONING IS THE MOST COMMON STRATEGY FOR DECISION TREE LEARNING

ID3 C4.5 CART CHAID

DECISION TREE LEARNING ALGORITHMS BASED ON RECURSIVE PARTITIONING

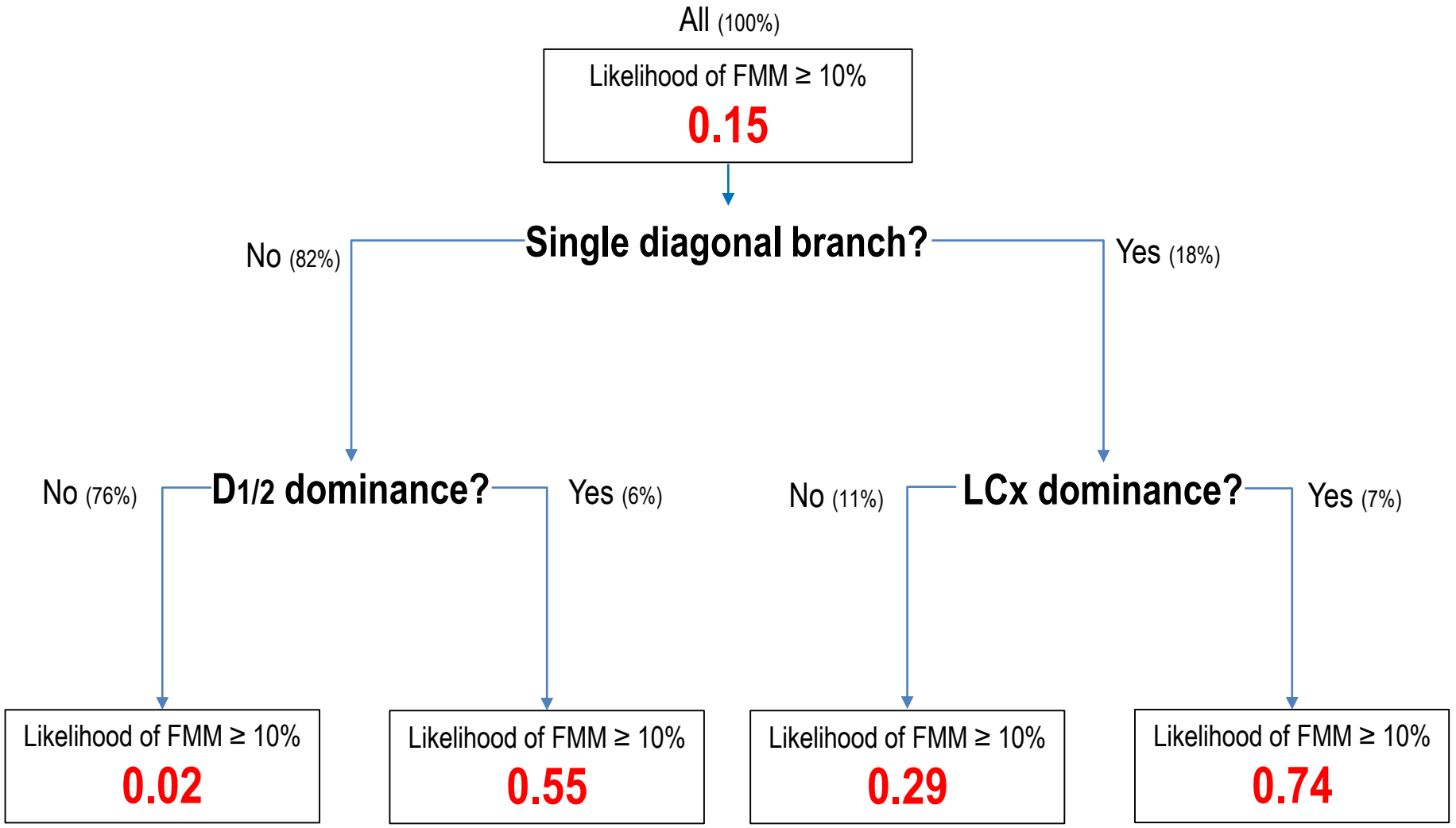
One branch? 2 branch? 3 branch? 2.8mm? 2.3mm? LCx dominance? D1/2 dominance? Non-dominant? ……..

*…..To train and validate models to predict % FMM ≥ 10%, the entire CCTA dataset was split into training and validation sets (4:1). To build a decision tree model, the training and validation sets were used for* ***recursive partitioning*** *with* ***10-fold cross-validation****.* ***Information gain*** *was used to selected attributes for* ***higher nodes****……..*



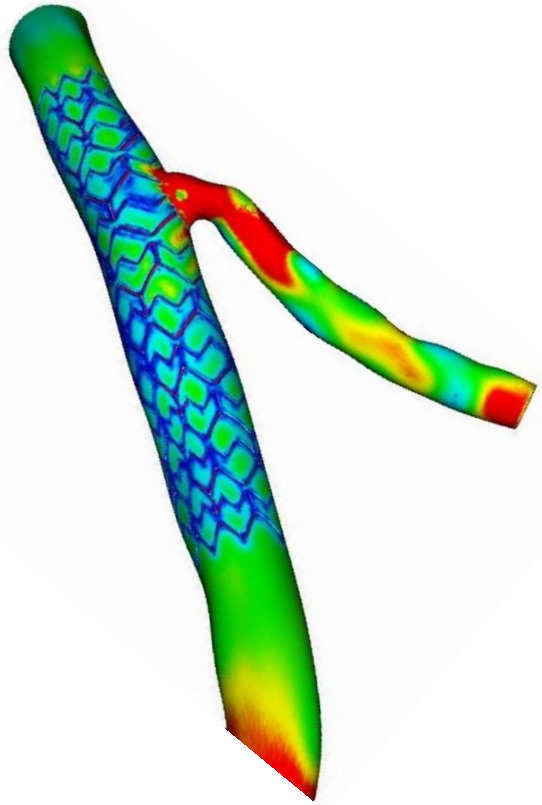

Jeon WK, Koo BK, et al. Eurointervention, In press

# Decision Tree for % FMM ≥ 10%




Jeon WK, Koo BK, et al. Eurointervention, In press

# Are you (un)happy with this?

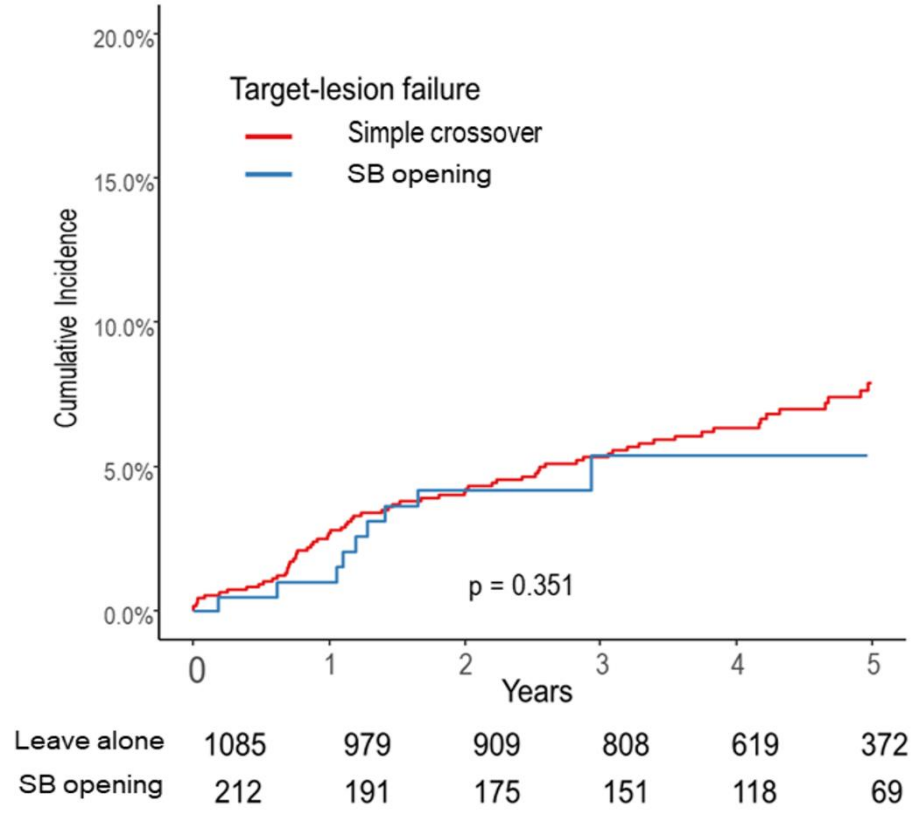

**OCT: 18 mo after Cypher**

Koo BK, LaDisa J, 2009

# COBIS III Registry

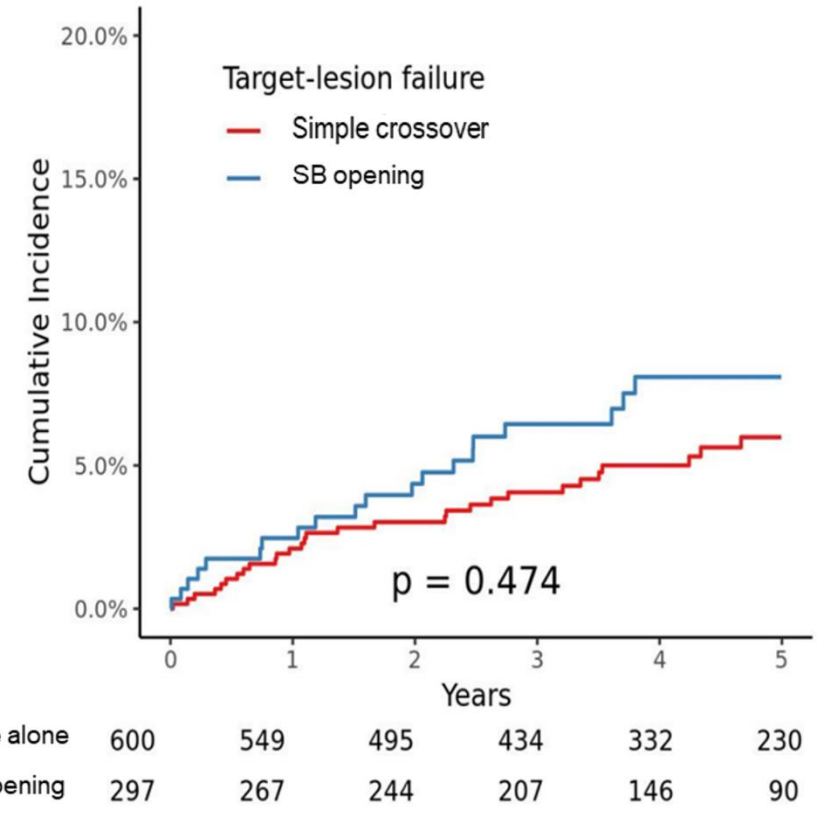
## Clinical relevance of SB opening

### Non-True Bifurcation




| | | | | | | |
|---|---|---|---|---|---|---|
| Leave alone | 1085 | 979 | 909 | 808 | 619 | 372 |
| SB opening | 212 | 191 | 175 | 151 | 118 | 69 |

### True Bifurcation




| | | | | | | |
|---|---|---|---|---|---|---|
| Leave alone | 600 | 549 | 495 | 434 | 332 | 230 |
| SB opening | 297 | 267 | 244 | 207 | 146 | 90 |



Nam CW, et al. Preliminary data from COBIS 3 registry

# What makes the difference?

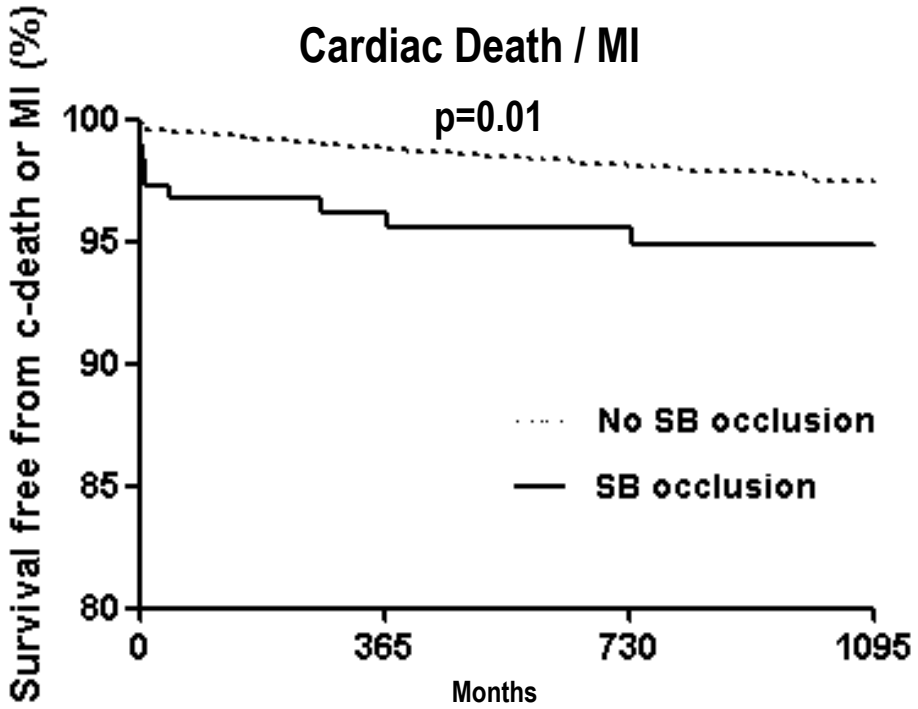
## Device? Concept? Technique?

- Safer access: More trans-radial approach
- Better stents and better stenting technique
- Better PCI technique: Better kissing, NC balloon, POT
- Better concept: imaging guidance, SB relevance
- Better risk stratification: SB occlusion, risk stratification

COBIS II Registry

# Clinical impact of SB occlusion

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




| | | | | |
|---|---|---|---|---|
| SB occlusion | 187 | 163 | 128 | 83 |
| No SB occlusion | 2040 | 1851 | 1542 | 991 |

Hahn JY, et al. JACC 2013

# How to avoid SB compromise after MV stenting?

- **How to protect SB?**
  - Jailed wire technique
  - SB predilation
  - Optimal stent sizing, ……

## Predictors of SB occlusion from COBIS II

| Variables | OR [95% CI] | p Value |
|---|---|---|
| SB DS ≥50% | 2.3 [1.59-3.43] | <0.001 |
| SB lesion length (by 1 mm) | 1.0[1.003-1.06] | <0.001 |
| Proximal MV DS ≥50% | 2.3 [1.57-3.50] | 0.03 |
| Acute coronary syndrome | 1.5 [1.06-2.19] | 0.02 |
| Left main lesions | 0.3 [0.16-0.72] | 0.005 |

Hahn JY, et al. JACC 2013

COBIS II Registry

# Predictor of SB recovery after occlusion

- SB flow recovery: 129 out of 187 occluded patients (69%).

| | SB recovery (n=129) | No SB recovery (n=58) | p Value |
|---|---|---|---|
| **Bifurcation location** | | | 0.65 |
| **Left main bifurcation** | 9 (7.0) | 5 (8.6) | |
| **LAD/diagonal** | 84 (65.1) | 40 (69.0) | |
| **LCX/OM** | 25 (19.4) | 7 (12.1) | |
| **RCA bifurcation** | 11 (8.5) | 6 (10.3) | |
| **True bifurcation** | 94 (72.9) | 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 intravascular ultrasound** | 39 (30.2) | 13 (22.4) | 0.27 |
| **MV stent diameter (mm)** | 3.0 (3.0-3.5) | 3.0 (2.9-3.5) | 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 |

Hahn JY, et al. JACC 2013

## 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).

Song PS, et al. JACC Interv 2016

# Conclusion

- COBIS registry started with bifurcation PCI patients since 2004 is still ongoing with dedicated QCA core laboratory/CRO, independent statistical analysis team and event adjudication committee.
- Results of COBIS studies expanded our knowledge on bifurcation treatment and improved the patients' clinical outcomes.
- Ongoing COBIS III study will provide more insights on coronary bifurcation lesions and their treatment.