Predictors of restenosis and stent thrombosis in bifurcation PCI

Bon-Kwon Koo, MD, PhD, FACC

Seoul National University Hospital, Seoul, Korea
Predictors of restenosis and stent thrombosis in bifurcation PCI

• In-stent restenosis: How frequent and Why?

• In-stent restenosis: Stenosis vs. Clinical relevance

• Stent thrombosis in bifurcation PCI

• Stent thrombosis: Lumen vs. Flow
Does restenosis matter in bifurcation lesions?

<table>
<thead>
<tr>
<th></th>
<th>One stent Restenosis rate, %</th>
<th>Two stents Restenosis rate, %</th>
<th>One stent TVR rate, %</th>
<th>Two stents TVR rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS</td>
<td>27</td>
<td>54</td>
<td>17.5</td>
<td>38.9</td>
</tr>
</tbody>
</table>

Niccoli, AHA 2005

**SIRIUS Bifurcation study**

<table>
<thead>
<tr>
<th></th>
<th>In-Hospital</th>
<th>6 Months</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stent/Stent (63 Patients)</td>
<td>Stent/PTCA (22 Patients)</td>
<td>Stent/Stent (63 Patients)</td>
<td>Stent/PTCA (22 Patients)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>0</td>
<td>1 (4.5)</td>
<td>1 (1.6)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Non-Q-wave MI</td>
<td>6 (9.5)</td>
<td>1 (4.5)</td>
<td>6 (9.5)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td><strong>MB restenosis</strong>*</td>
<td>...</td>
<td>...</td>
<td>3/53 (5.7)</td>
<td>1/21 (4.8)</td>
</tr>
<tr>
<td><strong>SB restenosis</strong>*</td>
<td>...</td>
<td>...</td>
<td>12/55 (21.8)</td>
<td>3/21 (14.2)</td>
</tr>
<tr>
<td>Re-PTCA, TLR</td>
<td>1 (1.6)</td>
<td>0</td>
<td>6 (9.5)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Bypass</td>
<td>0</td>
<td>0</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Re-PTCA, TVR</td>
<td>0</td>
<td>1 (4.3)</td>
<td>7 (11.1)</td>
<td>2 (9.0)</td>
</tr>
<tr>
<td>TVF</td>
<td>6 (9.5)</td>
<td>2 (9.1)</td>
<td>12 (19.0)</td>
<td>3 (13.6)</td>
</tr>
</tbody>
</table>

Does restenosis matter in bifurcation lesions?

Complex disease, complex intervention and high restenosis

Total 403 patients treated with LM PCI
All had post-stenting IVUS and 9-month FU angiography

Single-stent (n=289)
- Non-bifurcation (n=67)
  - Restenosis 4.5% (3/67) 
    - LM ostium: 3 (4.5%)

Bifurcation with single-stent cross-over (n=222)
  - Restenosis 6.3% (14/222)
    - LM (above POC): 2 (1.0%)
    - POC: 1 (0.5%)
    - LAD ostium: 3 (1.4%)
    - non-stented LCX os: 9 (4.1%)

Two-stent (n=114)
- Bifurcation with two-stent (including 99 crushing and 15 T-stent)
  - Restenosis 25.4% (29/114)
    - LM (above POC): 5 (4.4%)
    - POC: 6 (5.3%)
    - LAD ostium: 8 (7.0%)
    - LCX ostium: 27 (23.7%)

Why more restenosis in side branch ostium?

Unique plaque location, remodeling pattern

- Eccentric plaque
- Disease free wall at carina
- Negative remodeling

- Difficult to achieve enough lumen area
- Easy dissection
- More injury → More tissue reaction
Determinants of restenosis

Serial IVUS study after T stenting

Location of post-procedural minimal stent area

Neointimal hyperplasia at follow-up

Hahn JY, et al. JACC 2009
Larger post-procedural MSA for larger MLA during follow-up after T-stenting

Small IVUS stent area and under-expansion are the determinants of ISR

Minimal stent area cutoff for ISR

Frequency of under-expansion in 2 stent group

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• In-stent restenosis: Stenosis vs. Clinical relevance

• Stent thrombosis in bifurcation PCI

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### Main vessel restenosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Simple strategy (n/N)</th>
<th>Complex strategy (n/N)</th>
<th>Relative ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan, et al.</td>
<td>1/41 2.4%</td>
<td>4/39 10.3%</td>
<td>0.24 (0.03, 2.04)</td>
</tr>
<tr>
<td>NORDIC</td>
<td>7/151 4.6%</td>
<td>8/156 5.1%</td>
<td>0.90 (0.34, 2.43)</td>
</tr>
<tr>
<td>BBK</td>
<td>7/96 7.3%</td>
<td>3/96 3.1%</td>
<td>2.33 (0.62, 8.75)</td>
</tr>
<tr>
<td>CACTUS</td>
<td>10/150 6.7%</td>
<td>7/152 4.6%</td>
<td>1.45 (0.57, 3.70)</td>
</tr>
<tr>
<td>Overall</td>
<td>25/438 5.7%</td>
<td>22/443 5.0%</td>
<td>1.15 (0.66, 2.00)</td>
</tr>
</tbody>
</table>

(Fixed Effects)

Higher number, higher event?

### Side branch restenosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Simple strategy (n/N)</th>
<th>Complex strategy (n/N)</th>
<th>Relative ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan, et al.</td>
<td>2/41 4.9%</td>
<td>6/39 66.7%</td>
<td>0.32 (0.07, 1.48)</td>
</tr>
<tr>
<td>NORDIC</td>
<td>29/151 19.2%</td>
<td>18/156 11.5%</td>
<td>1.66 (0.67, 2.87)</td>
</tr>
<tr>
<td>BBK</td>
<td>9/96 9.4%</td>
<td>12/96 12.5%</td>
<td>0.75 (0.33, 1.70)</td>
</tr>
<tr>
<td>CACTUS</td>
<td>22/150 14.7%</td>
<td>20/152 13.2%</td>
<td>1.11 (0.64, 1.96)</td>
</tr>
<tr>
<td>Overall</td>
<td>62/438 14.2%</td>
<td>56/443 12.6%</td>
<td>1.12 (0.80, 1.57)</td>
</tr>
</tbody>
</table>

(Fixed Effects)

Test for heterogeneity: chi-squared = 5.54 (d.f. = 3) $P = 0.14$

Test for overall effect: z = 0.66 P = 0.50

Zhang, et al. Heart 2009
What is significant restenosis?

TABLE 5. Rate of Significant Stenosis at 8-Month Follow-Up in Bifurcation Segments

<table>
<thead>
<tr>
<th>Variable</th>
<th>Proximal MV Segment</th>
<th>Distal MV Segment</th>
<th>Side Branch</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MV</td>
<td>MV + SB</td>
<td>P</td>
</tr>
<tr>
<td>In-stent stenosis, n (%)*</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Edge stenosis, n (%)</td>
<td>3 (2.0)</td>
<td>4 (2.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>SB stenosis/occlusion, n (%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Does restenosis (residual stenosis) of a side branch matter?

Angiographic inaccuracy to predict the presence of myocardial ischemia

**FFR vs. % diameter stenosis in jailed side branches**

![Graph showing FFR vs. Angiographic % diameter stenosis](image)


Ahn JM, et al. JACC intv 2012
Does restenosis (residual stenosis) of a side branch matter?

Amount of ischemia is more important than the presence of ischemia

### 2010 ESC guidelines for revascularization

<table>
<thead>
<tr>
<th>For prognosis</th>
<th>Subset of CAD by anatomy</th>
<th>Class*</th>
<th>Levela</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left main &gt;50%d</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Any proximal LAD &gt;50%d</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>2VD or 3VD with impaired LV functiond</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Proven large area of ischaemia (&gt;10% LV)</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Single remaining patent vessel &gt;50% stenosisd</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>IVD without proximal LAD and without &gt;10% ischaemia</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>

| For symptoms  | Any stenosis >50% with limiting angina or angina equivalent, unresponsive to OMT | I      | A      |
|               | Dyspnoea/CHF and >10% LV ischaemia/viability supplied by >50% stenotic artery | IIa    | B      |
|               | No limiting symptoms with OMT | III    | C      |

### Comparison of clinical and electrocardiographic relevance between LAD and diagonal branches

<table>
<thead>
<tr>
<th></th>
<th>LAD</th>
<th>Diagonal</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 min occlusion of flow</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain score</td>
<td>4.1±3.5</td>
<td>2.3±2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ST elevation +</td>
<td>60 (92%)</td>
<td>24 (37%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTc segment, msec</td>
<td>413±34</td>
<td>406±30</td>
<td>0.05</td>
</tr>
<tr>
<td>QTc dispersion, msec</td>
<td>100±35</td>
<td>84±27</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Koo BK, et al JACC intv, in revision
Predictors of restenosis and stent thrombosis in bifurcation PCI

• In-stent restenosis: How frequent and Why?

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• Stent thrombosis: Lumen vs. Flow
Is bifurcation lesion a predictor of stent thrombosis?

Incidence and predictors of coronary stent thrombosis: Evidence from an international collaborative meta-analysis including 30 studies, 221,066 patients, and 4276 thromboses.

Most powerful predictors of definite or probable stent thrombosis:

- ATD <30 days: Relative risk 36.50
- Residual dissection: Relative risk 17.80
- ATD 30-180 days: Relative risk 13.74
- Stent undersizing: Relative risk 13.40
- Prior brachytherapy: Relative risk 7.20
- Left ventricular systolic dysfunction: Relative risk 6.00
- Smoking status: Relative risk 5.90
- Bifurcation/ostial: Relative risk 5.80
- ACS (including STEMI): Relative risk 5.5
- Small vessel CAD: Relative risk 5.4

D'Ascenzo F, et al IJCA, in press
Is two stenting a predictor of stent thrombosis?

Stent Thrombosis
- 1 stent vs. 2 stent -

Pathologic/IVUS mechanisms of DES ST

- Chronic inflammation
- Stenting along major side branches
- Stenting over major branching points
- Late incomplete apposition
- Post-procedural incomplete apposition with stent underexpansion
- In-stent restenosis
- Strut penetration of necrotic core

Joner, et al. JACC 2006
Fujii, et al. JACC 2005
Okabe, et al. AJC 2007
Excellent results?
Angiographically excellent, but....

Figure 4. (A) Intravascular ultrasound image showing complete crush (apposition) of the side branch (SB) stent; arrows indicate the three layers of stent struts. (B, C) Intravascular ultrasound images showing incomplete crush (apposition) of the SB stent struts (arrows).
IVUS-guided PCI for bifurcation lesion may improve outcomes

Long-Term Outcomes of Intravascular Ultrasound-Guided Stenting in Coronary Bifurcation Lesions

Sang-Hwan Kim, MD, PhD, Young-Hak Kim, MD, PhD, Soon-Jin Kang, MD, PhD, Duk-Woo Park, MD, PhD, Seung-Whan Lee, MD, PhD, Cheol Whan Lee, MD, PhD, Myeong-Ki Hong, MD, PhD, Sang-Sig Cheong, MD, PhD, Jae-Joon Kim, MD, PhD, Soon-Wook Park, MD, PhD, and Seung-Jung Park, MD, PhD

In conclusion, IVUS-guided stenting for bifurcation lesions significantly reduced the 4-year mortality compared to conventional angiographically guided stenting.

Impact of intravascular ultrasound guidance on long-term clinical outcomes in patients treated with drug-eluting stent for bifurcation lesions: Data from a Korean multicenter bifurcation registry

Jung-Sun Kim, MD, PhD, a Myeong-Ki Hong, MD, PhD, b Young-Guk Ko, MD, PhD, c Donghoon Choi, MD, PhD, b Jung-Hoon Youn, MD, PhD, d Seung-Hyeok Choi, MD, PhD, e Jeong-Hwan Han, MD, PhD, f Myeong-Chul Kim, MD, PhD, a Hye-Soo Kim, MD, PhD, a In-Woo Seong, MD, PhD, a Je-Yoong Yang, MD, PhD, d Seung-Won Rha, MD, PhD, e Seung-Jae Tahl, MD, PhD, e Ki Baek Seong, MD, PhD, f Seung-Jung Park, MD, PhD, a and Yongsoo Jung, MD, PhD, a b c d e f

Background Although intravascular ultrasound (IVUS) has been widely used for complex lesions during coronary intervention, IVUS for stenting at bifurcation lesions has not been sufficiently assessed. The aim of this study was to investigate the impact of IVUS guidance on long-term clinical outcomes during drug-eluting stent (DES) implantation for bifurcation lesions.

Methods The Korean multicenter bifurcation registry studied 1,609 patients with non-left main de novo bifurcation lesions who underwent DES implantation between January 2004 and June 2016. Using propensity score matching with clinical and angiographic characteristics, 847 patients with IVUS guidance and 847 patients with angiography guidance were selected. The long-term clinical outcomes were compared between the 2 groups.

Results Baseline clinical and angiographic characteristics were well matched and showed no significant differences between the 2 groups. Two-tailed Student’s t test and Fisher’s exact test were more frequently performed in the IVUS-guided group. Maximal stent diameter at the side branch was larger in the IVUS-guided group. Periprocedural creatine kinase-MB elevation (>3 times upper normal limit) was frequently observed in the angiography-guided group. The incidence of death or myocardial infarction was significantly lower in the IVUS-guided group compared to the angiography-guided group (3.5% vs 7.0%, log rank P = .03, hazard ratio 0.44, 95% CI 0.26 to 0.73). Cox model P = .04).

Conclusions Intravascular ultrasound guidance during DES implantation at bifurcation lesions may be helpful to improve long-term clinical outcomes by reducing the occurrence of death or myocardial infarction. (Am Heart J 2011;161:180-7)

CONCLUSIONS:
IVUS guidance during DES implantation at bifurcation lesions may be helpful to improve long-term clinical outcomes by reducing the occurrence of death or myocardial infarction.
IVUS-guided PCI for bifurcation lesion may improve outcomes

Impact of Intravascular Ultrasound Guidance on Long-Term Mortality in Stenting for Unprotected Left Main Coronary Artery Stenosis

Seung-Jung Park, MD, PhD; Young-Hak Kim, MD, PhD; Duk-Woo Park, MD, PhD; Seung-Whan Lee, MD, PhD; Won-Jang Kim, MD, PhD; Jun Suh, MD; Sung-Cheol Yun, PhD; Cheol Whan Lee, MD, PhD; Myeong-Ki Hong, MD, PhD; Jae-Hwan Lee, MD, PhD; Seong-Wook Park, MD, PhD; for the MAIN-COMPARE Investigators

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• Stent thrombosis in bifurcation PCI
• Stent thrombosis: Lumen vs. Flow
Cardiology Is Flow

Yoram Richter, PhD; Elazer R. Edelman, MD, PhD

Panta rhei. *(Everything flows).*¹

Cardiology is about flow. The primary purpose of the

therosclerosis. Flow disturbances are therefore ubiquitous; they are a

fundamental feature of the vascular system. An entire field of

study arose correlating disease with its overlying flow pat-

**Abnormal Flow**

**Pro-thrombotic**

MCP-1

VCAM-1

**Pro-migration**

**Pro-apoptosis**

**Pro-growth**

Ang II

PDGF

Endothelin-1

Atherosclerotic lesion

**Recirculating zone and/or abnormal shear stress → Inflammation, Proliferation, Thrombosis**

*Circulation* 2006

Courtesy of Dr. Finet
Keeping the natural laws to minimize the flow disturbance

**Murray’s law**
\[ D_m^3 = Dd_1^3 + Dd_2^3 \]

**Kassab’s**
\[ D_m^{2.2} = Dd_1^{2.2} + Dd_2^{2.2} \]

**Finet’s law**
\[ D_m = 0.678 (Dd_1 + Dd_2) \]

**Area conservation**
\[ D_m^2 = Dd_1^2 + Dd_2^2 \]
**Under-expansion**

Average Diameter: 3.2mm

Estimated ideal diameter by Finet’s law = 4.4mm

**Over-expansion**

Average Diameter: 3.2mm

Estimated ideal diameter by Finet’s law = 3.7mm

Reference segment
- Average diameter: 3.7mm
- Eccentricity: 3.5/3.75 = 0.93

Proximal stent
- Average diameter: 4.2mm
- Eccentricity: 3.6/5.0 = 0.71
Optimized vs. Non-optimized

Side branch = 2.2 mm

Proximal MB = 3.5 mm

Distal MB = 2.8 mm

D_1 = 3.5 mm

Distal MB = 3.5 mm

Mean wall shear stress (dynes/cm^2)

Koo BK and Taylor C. European Bifurcation Club 2010
Restenosis and Stent thrombosis in bifurcations

- Restenosis and stent thrombosis are more frequent in bifurcation lesions.

- Inadequate lumen area, complex procedures and un-natural bifurcation geometry are the main predictors of restenosis and stent thrombosis.

- Understanding the clinical relevance of a stenosis and keeping the “natural bifurcation laws” after PCI may be the key to improve the patients’ outcomes.