Clinical impact of IVUS-guided CTO intervention on the clinical outcomes after new generation DES implantation;

**Randomized CTO-IVUS study**

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On behalf of CTO-IVUS investigator

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Yonsei University College of Medicine, Seoul, Korea
Disclosure Statement of Financial Interest

I, (Yangsoo Jang) DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
Background

- **PCI for chronic total occlusion (CTO)** is still challenging and there are unmet needs even with the availability of DESs.

- Despite the development of novel techniques and technologies for CTO intervention, the increased clinical and angiographic risk factors accompanying complex procedures have been associated with worse clinical outcomes.


- The **use of intravascular ultrasound (IVUS)** has been recommended as one way to improve PCI clinical outcomes.

Role of IVUS for CTO intervention

For CTO wire crossing
- Detecting the proximal entry point in stumpless or ostial CTO lesions
- Repositioning a guidewire after subintimal passage
- Ensuring of the distal guidewire in the true lumen

For stenting
- Determination of lesion coverage
- Stent optimization (expansion and apposition)
- Detecting procedure-related complications (dissection, hematoma, rupture)

However, few data exists regarding the relationship between PCI by IVUS guidance after successful wire crossing and clinical outcomes after stent implantation.
To test the hypothesis ...

“IVUS-guided CTO intervention is superior to conventional angiography-guided CTO intervention”

we sought to conduct multi-center prospective randomized trial using new generation DES.
Methods

Prospective, randomized trial conducted at 20 centers in Korea

1. Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Korea
2. Kyungpook National University Hospital, Daegu, Korea
3. Korea University Guro Hospital, Seoul, Korea
4. Sejong General Hospital, Bucheon, Korea
5. SoonChunHyang University Hospital, Cheonan, Korea
6. The Catholic University of Korea Bucheon St. Mary's Hospital, Bucheon, Korea
7. Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
8. Gil Hospital, Gachon University College of Medicine, Incheon, Korea
9. Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
10. Kyung Hee University Hospital, Seoul, Korea
11. Kangwon National University Hospital, Chuncheon, Korea
12. Kangnam Sacred Heart Hospital, Seoul, Korea
13. Chonnam National University Hospital, Gwangju, Korea
14. Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, Wonju, Korea
15. Myong Ji Hospital, Koyang-si, Korea
16. Kwangju Christian Hospital, Kwangju, Korea
17. St. Carollo Hospital, Sooncheon, Korea
18. Yeungnam University Hospital, Daegu, Korea
19. The Catholic university of Korea Daejeon St. Mary`s Hospital, Daejeon, Korea
20. The Catholic university of Korea Uijengbu St. Mary`s Hospital, Uijengbu, Korea

Principal investigator; Yangsoo Jang, MD, Ph D,
**Major inclusion criteria;**
- 20–80 years old with CTO and typical symptomatic angina or positive stress test
- Reference vessel diameter of 2.5–4.0 mm by operator assessment
- Total CTO lesion length ≤80 mm and number of stents implanted ≤4

# CTO, defined as TIMI flow grade 0 with estimated occlusion duration ≥3 months

**Major Exclusion criteria;**
- Unprotected left main disease
- Lesions with in-stent restenosis or graft vessel occlusion
- History of PCI for the same CTO lesion within 2 weeks
- Initial clinical presentation as acute MI
- Cardiogenic shock or left ventricle ejection fraction <30%
- Serum creatinine level ≥2.0 mg/dL or end-stage renal disease
Endpoints

- **Primary endpoint**
  - Composite of cardiac death, MI, and target-vessel revascularization at 12 months

- **Secondary endpoints**
  - Composite of cardiac death and MI
  - Individual components of the primary endpoint
Statistical analyses; Power calculation for sample size

**Background; Randomized TULIP study** (BMS for the diffuse long lesions)

- IVUS Guidance (n=73) vs. Angio Guidance (n=71)
- Composite rate of cardiac death, MI, and TLR at 12 months
  
  $= 12\% \text{ vs. } 27\% \ (p=0.026)$

**Two assumptions**

1) Event rate of CTO would be similar to that of diffuse long lesions
2) The current DESs could reduce the TVR rate more than 50%.

Hypothesis ... “IVUS-guided CTO intervention is superior to conventional angiography guidance”

; Difference of the primary endpoint $\cong 9\%$.

$\rightarrow$ A total of 400 patients would be sufficient.

(10% dropout rate, 90% power to detect a difference and an alpha error rate of 0.05)

✓ Compared by Kaplan–Meier method and log-rank test (hazard ratio, 95% CI)
Total 467 patients with CTO were initially screened. Of these, 402 patients were finally enrolled after successful guidewire-crossing.

- Exclusion: Wiring failure (61 patients) and refusal of study enrollment (4 patients).

A total of 402 patients were then randomized into two groups:

1. IVUS-guided group (n=201)
2. Angiography-guided group (n=201)

Each group was further randomized into two subgroups:

1. 1:1 randomization: R-ZES vs. N-BES

Clinical follow-up was performed for 12 months.

Primary endpoint: Composite of Cardiac death, MI, & TVR at 12 months.
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>IVUS-guided group (n=201)</th>
<th>Angiography-guided group (n=201)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61.0 ± 11.1</td>
<td>61.4 ± 10.1</td>
<td>0.739</td>
</tr>
<tr>
<td>Male gender</td>
<td>162 (80.6%)</td>
<td>162 (80.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>126 (62.7%)</td>
<td>128 (63.7%)</td>
<td>0.836</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>70 (34.8%)</td>
<td>68 (33.8%)</td>
<td>0.834</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>12 (6.0%)</td>
<td>10 (5.0%)</td>
<td>0.661</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>56.9 ± 13.1</td>
<td>56.7 ± 11.4</td>
<td>0.808</td>
</tr>
<tr>
<td>Prior MI</td>
<td>16 (8.0%)</td>
<td>16 (8.0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>31 (15.4%)</td>
<td>32 (15.9%)</td>
<td>0.891</td>
</tr>
<tr>
<td>Stable angina presentation</td>
<td>147 (73.1%)</td>
<td>147 (73.1%)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>CTO lesion characteristics</strong></td>
<td></td>
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</tr>
<tr>
<td>LAD</td>
<td>84 (41.8%)</td>
<td>94 (46.8%)</td>
<td>0.478</td>
</tr>
<tr>
<td>Stumpless CTO</td>
<td>23 (11.4%)</td>
<td>22 (10.9%)</td>
<td>0.874</td>
</tr>
<tr>
<td>Bridging collaterals</td>
<td>24 (11.9%)</td>
<td>29 (14.4%)</td>
<td>0.461</td>
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</tbody>
</table>
## Procedural summary for CTO intervention

<table>
<thead>
<tr>
<th>Category</th>
<th>IVUS-guided (n=201)</th>
<th>Angiography-guided (n=201)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure success</td>
<td>199 (99.0%)</td>
<td>197 (98.0%)</td>
<td>0.411</td>
</tr>
<tr>
<td>Femoral artery access</td>
<td>149 (74.1%)</td>
<td>145 (72.1%)</td>
<td>0.653</td>
</tr>
<tr>
<td>Contralateral angiogram</td>
<td>101 (50.2%)</td>
<td>92 (45.8%)</td>
<td>0.369</td>
</tr>
<tr>
<td>Retrograde approach</td>
<td>14 (7.0%)</td>
<td>19 (9.5%)</td>
<td>0.364</td>
</tr>
<tr>
<td>Total number of stents, n</td>
<td>1.7 ± 0.8</td>
<td>1.6 ± 0.7</td>
<td>0.198</td>
</tr>
<tr>
<td>Mean stent diameter, mm</td>
<td>2.91 ± 0.52</td>
<td>2.85 ± 0.41</td>
<td>0.228</td>
</tr>
<tr>
<td>Total stented length, mm</td>
<td>43.6 ± 18.7</td>
<td>41.5 ± 17.6</td>
<td>0.245</td>
</tr>
<tr>
<td>High-pressure post-stent dilation</td>
<td>103 (51.2%)</td>
<td>83 (41.3%)</td>
<td>0.045</td>
</tr>
<tr>
<td>Maximum post-stent balloon pressure, atm</td>
<td>14.6 ± 3.7</td>
<td>13.8 ± 3.8</td>
<td>0.040</td>
</tr>
<tr>
<td>Total procedure time, min</td>
<td>95 ± 50</td>
<td>88 ± 47</td>
<td>0.167</td>
</tr>
<tr>
<td>Total fluoroscopic time, min</td>
<td>41 ± 26</td>
<td>37 ± 24</td>
<td>0.155</td>
</tr>
<tr>
<td>Total contrast volume used, mL</td>
<td>299 ± 128</td>
<td>295 ± 123</td>
<td>0.728</td>
</tr>
<tr>
<td>Balloon angioplasty without stent</td>
<td>2 (1.0%)</td>
<td>1 (0.5%)</td>
<td>0.562</td>
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</tbody>
</table>
### Quantitative & qualitative angiographic analyses

<table>
<thead>
<tr>
<th></th>
<th>IVUS-guided (n=201)</th>
<th>Angiography-guided (n=201)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of CTO, mm</strong></td>
<td>26.8 ± 17.3</td>
<td>26.4 ± 17.6</td>
<td>0.860</td>
</tr>
<tr>
<td><strong>Total lesion length, mm</strong></td>
<td>36.3 ± 17.1</td>
<td>35.5 ± 17.0</td>
<td>0.615</td>
</tr>
<tr>
<td><strong>Pre-procedural Reference vessel diameter, mm</strong></td>
<td>2.69 ± 0.44</td>
<td>2.64 ± 0.55</td>
<td>0.346</td>
</tr>
<tr>
<td><strong>Post-procedure</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Reference vessel diameter, mm</strong></td>
<td>2.92 ± 0.39</td>
<td>2.86 ± 0.45</td>
<td>0.144</td>
</tr>
<tr>
<td><strong>Minimum luminal diameter, mm</strong></td>
<td>2.64 ± 0.35</td>
<td>2.56 ± 0.41</td>
<td>0.025</td>
</tr>
<tr>
<td><strong>Percent diameter stenosis, %</strong></td>
<td>9.0 ± 9.8</td>
<td>10.2 ± 10.9</td>
<td>0.272</td>
</tr>
<tr>
<td><strong>Stent edge dissection</strong></td>
<td>18 (9.0%)</td>
<td>27 (13.4%)</td>
<td>0.155</td>
</tr>
</tbody>
</table>
Primary endpoint (Cardiac death, MI, TVR)

Follow-up duration (months)

Cumulative incidence (%)

Angiography-guided group

IVUS-guided group

HR=0.35, 95% CI = 0.13 – 0.97

p = 0.035

Number at risk

Angiography-guided 201

IVUS-guided 201

Angiography-guided group

IVUS-guided group

(No. of events)

12-month

10

9

8

7

6

5

4

3

2

1

0

0

3

6

9

12

7.1% (14)

2.6% (5)

SEVERANCE CARDIOVASCULAR HOSPITAL

YONSEI UNIVERSITY COLLEGE OF MEDICINE
Cardiac death or MI

Follow-up duration (months)

Cumulative incidence (%)

- Angiography-guided group
- IVUS-guided group

* \( p = 0.045 \)

Number at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography-guided</td>
<td>201</td>
<td>198</td>
<td>187</td>
<td>187</td>
<td>180</td>
</tr>
<tr>
<td>IVUS-guided</td>
<td>201</td>
<td>199</td>
<td>190</td>
<td>190</td>
<td>186</td>
</tr>
</tbody>
</table>

TVR

Follow-up duration (months)

Cumulative incidence (%)

- Angiography-guided group
- IVUS-guided group

HR = 0.48, 95% CI = 0.17–1.42

* \( p = 0.186 \)

*Not calculable HR or CI because of no occurrence of the event
Cross-over

IVUS-guided group (n=201)

☑ Cross-over; 5 patients (2.5%)

# Reason for cross-over
• Failure of IVUS catheter passage; 5

Angiography-guided group (n=201)

☑ Cross-over; 35 patients (17.4%)

# Reason for cross-over
• Estimation of vessel size; 19
• Evaluation of stent and stent edge; 11
• Confirmation of wire location; 5

Intention-to-treat analysis

Per-protocol analysis

p < 0.001

IVUS-guided group (n=231)

IVUS-guided group (n=171)
Primary endpoint (Cardiac death, MI, TVR)

Per-protocol Analysis

Cumulative incidence (%)

12-month

Follow-up duration (months)

Angiography-guided group

IVUS-guided group

HR=0.26, 95% CI = 0.09–0.71

P = 0.005

(No. of events)

8.4% (14)

2.2% (5)

Number at risk

Angiography-guide  171

IVUS-guide  231

167

229

151

214
Per-protocol Analysis

Cardiac death or MI

Cumulative incidence (%)

Follow-up duration (months)

- Angiography-guided group
- IVUS-guided group

$P = 0.019$

P = 0.019

Number at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>12-month</th>
<th>6-month</th>
<th>3-month</th>
<th>0-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography-guide</td>
<td>171</td>
<td>167</td>
<td>159</td>
<td>159</td>
</tr>
<tr>
<td>IVUS-guide</td>
<td>231</td>
<td>230</td>
<td>218</td>
<td>218</td>
</tr>
</tbody>
</table>

TVR

Follow-up duration (months)

$P = 0.049$

P = 0.049

Number at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>12-month</th>
<th>6-month</th>
<th>3-month</th>
<th>0-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography-guide</td>
<td>171</td>
<td>168</td>
<td>152</td>
<td>152</td>
</tr>
<tr>
<td>IVUS-guide</td>
<td>231</td>
<td>229</td>
<td>214</td>
<td>214</td>
</tr>
</tbody>
</table>
# Subgroup analysis of the primary endpoint (Cardiac death, MI, TVR)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
<th>p-for-interaction</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
<th>p-for-interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt; 65 (n=233)</td>
<td>0.38</td>
<td>0.10~1.43</td>
<td>0.154</td>
<td></td>
<td>0.857</td>
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<tr>
<td>≥ 65 (n=169)</td>
<td>0.31</td>
<td>0.06~1.56</td>
<td>0.156</td>
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<tr>
<td><strong>Gender</strong></td>
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<tr>
<td>Male (n=324)</td>
<td>0.44</td>
<td>0.15~1.28</td>
<td>0.131</td>
<td></td>
<td>0.956</td>
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<tr>
<td>Female (n=78)</td>
<td>0.02</td>
<td>0.00~164.9</td>
<td>0.378</td>
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<tr>
<td><strong>Diabetes mellitus</strong></td>
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<tr>
<td>Yes (n=138)</td>
<td>0.60</td>
<td>0.10~3.72</td>
<td>0.601</td>
<td></td>
<td>0.465</td>
<td></td>
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<tr>
<td>No (n=264)</td>
<td>0.28</td>
<td>0.08~0.99</td>
<td>0.045</td>
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<tr>
<td><strong>Hypertension</strong></td>
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<tr>
<td>Yes (n=254)</td>
<td>0.25</td>
<td>0.05~1.18</td>
<td>0.080</td>
<td></td>
<td>0.547</td>
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<tr>
<td>No (n=148)</td>
<td>0.48</td>
<td>0.12~1.9</td>
<td>0.293</td>
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<tr>
<td><strong>Three-vessel disease</strong></td>
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</tr>
<tr>
<td>Yes (n=140)</td>
<td>0.13</td>
<td>0.02~1.04</td>
<td>0.054</td>
<td></td>
<td>0.225</td>
<td></td>
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</tr>
<tr>
<td>No (n=262)</td>
<td>0.56</td>
<td>0.17~1.87</td>
<td>0.350</td>
<td></td>
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<tr>
<td><strong>Heart failure</strong></td>
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</tr>
<tr>
<td>Yes (n=22)</td>
<td>0.39</td>
<td>0.04~4.27</td>
<td>0.438</td>
<td></td>
<td>0.978</td>
<td></td>
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<tr>
<td>No (n=380)</td>
<td>0.33</td>
<td>0.11~1.03</td>
<td>0.057</td>
<td></td>
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<tr>
<td><strong>Type of drug-eluting stents</strong></td>
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<td></td>
</tr>
<tr>
<td>R-ZES (n=201)</td>
<td>0.02</td>
<td>0.00~4.43</td>
<td>0.148</td>
<td></td>
<td>0.834</td>
<td></td>
<td></td>
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<tr>
<td>N-BES (n=201)</td>
<td>0.83</td>
<td>0.25~2.71</td>
<td>0.754</td>
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<tr>
<td><strong>Total number of stents implanted</strong></td>
<td></td>
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<tr>
<td>≤1 (n=175)</td>
<td>0.26</td>
<td>0.03~2.36</td>
<td>0.233</td>
<td></td>
<td>0.778</td>
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</tr>
<tr>
<td>≥2 (n=227)</td>
<td>0.37</td>
<td>0.12~1.19</td>
<td>0.097</td>
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<tr>
<td><strong>CTO length</strong></td>
<td></td>
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<tr>
<td>≤28 (n=160)</td>
<td>0.20</td>
<td>0.02~1.69</td>
<td>0.139</td>
<td></td>
<td>0.533</td>
<td></td>
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<tr>
<td>&gt;28 (n=242)</td>
<td>0.43</td>
<td>0.13~1.41</td>
<td>0.163</td>
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<tr>
<td><strong>Reference vessel diameter</strong></td>
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<td></td>
</tr>
<tr>
<td>&lt;3.0 mm (n=244)</td>
<td>0.31</td>
<td>0.08~1.13</td>
<td>0.077</td>
<td></td>
<td>0.745</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3.0 mm (n=158)</td>
<td>0.44</td>
<td>0.09~2.26</td>
<td>0.324</td>
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<td><strong>LAD intervention</strong></td>
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<tr>
<td>LAD (n=178)</td>
<td>0.22</td>
<td>0.03~1.91</td>
<td>0.172</td>
<td></td>
<td>0.653</td>
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<tr>
<td>Non-LAD (n=224)</td>
<td>0.39</td>
<td>0.12~1.28</td>
<td>0.120</td>
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<td><strong>Overall</strong></td>
<td>0.35</td>
<td>0.13~0.97</td>
<td>0.035</td>
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Summary of CTO-IVUS study

This CTO-IVUS study is the first randomized trial investigating the clinical benefits of IVUS guidance for CTO intervention after successful guidewire crossing in the era of new generation DES.

This study demonstrated that ...

- As compared to conventional angiography-guided CTO intervention, IVUS-guided CTO intervention
  - caused a more frequent use of high-pressure post-dilation and a larger post-procedural MLD
  - finally, significantly improved clinical outcomes after DES implantation
Limitation

- Some assumptions for power calculation were arbitrary.
- For the comparison of acute procedure results, only QCA analysis was available.
- Follow-up duration of this study was only 12 months.
Conclusion

Compared to conventional angiography-guided CTO intervention, **IVUS-guided CTO intervention** significantly **improved clinical outcomes during the 12 months** following new generation DES implantation.
Thank you for your attention