ACC.25

# Comparison of angiography-derived fractional flow reserve-guided and intravascular ultrasound-guided PCI strategies (FLAVOUR II)

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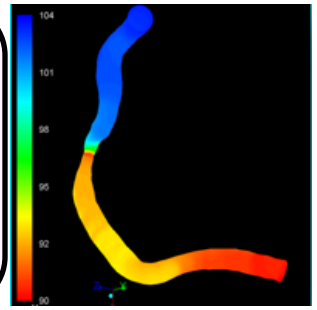
# Background

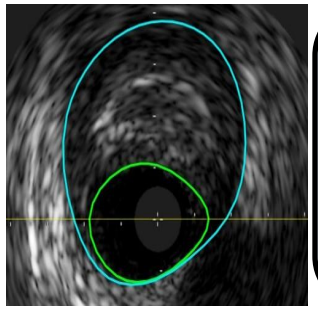
- In the cath-lab, a comprehensive strategy is essential for patients with CAD, which includes **decision-making for PCI** and **optimizing the PCI procedure**.
- Physiological assessment is effective in guiding PCI decision-making. However, despite strong recommendations and robust evidence, the global adoption of the conventional wire-based physiological assessment in clinical practice remains limited.
- AngioFFR is a simplified physiological assessment obtained directly from angiography without additional invasive procedures and carries a Class IB recommendation in current guidelines.
- In addition to the role of decision-making, AngioFFR could be used for optimizing procedures.
- Intravascular imaging plays a key role in optimizing PCI procedure and is superior than the angiography-only-guided PCI.

**Angiography-Derived Fractional Flow Reserve (AngioFFR)**

A next-generation non-invasive physiological assessment, excels in determining the need for PCI




VS



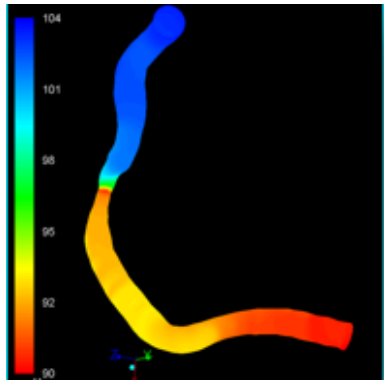
**Intravascular Ultrasound (IVUS)**

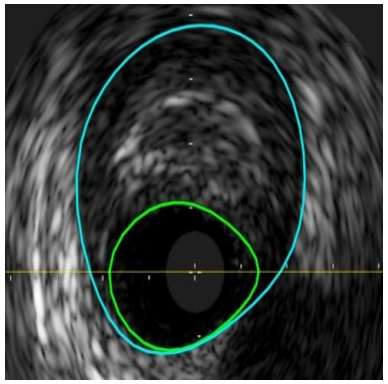
The most commonly used intravascular imaging tool, excels in optimizing PCI procedure

**Differences in outcomes when a single modality is used for both purposes remain unclear.**

# Objective and Hypthesis

When employed as a comprehensive strategy, encompassing both **PCI decision-making** and **procedure optimization**, whether **a novel computational physiologic technique** can perform as effectively as **the most commonly used conventional intravascular imaging technique** ?



**Objective: To compare the efficacy of AngioFFR- and IVUS-guided PCI strategies in patients with angiographically significant stenosis.**

**Hypothesis: The AngioFFR-guided PCI strategy will be non-inferior to the IVUS-guided PCI strategy in terms of clinical outcomes at 12 months.**

# Clinical Outcomes and Sample Size

- **Primary outcome**
  - A composite of death, MI, or revascularization at 12 months
- **Key Secondary Outcomes**
  - Death, MI or revascularization at 24 and 60 months
  - Target vessel failure (a composite of cardiac death, target-vessel MI, or target lesion revascularization)
  - All-cause and cardiac death
  - Target-vessel and all-cause nonfatal MI with/without peri-procedural MI
  - Any revascularization (ischemia-driven or all)
- **Sample size calculation**
  - Assumed 12-month event rate in the AngioFFR-guided PCI group: 7.0%
  - Assumed 12-month event rate in the IVUS-guided PCI group: 8.0%
  - Type I error: one-side 0.025, Power: 80%
  - Non-inferiority margin: 2.5%

A total of 1,872 cases

# Randomization and Data Collection

- **Randomization**
  - Eligible patients were randomized via a web-based randomization sequence.
  - Stratification methods were applied by participating centers and by the presence of diabetes mellitus.

- **Data collection and management**
  - Data collected by a web-based electronic case report form (eCRF)
  - An independent data and safety monitoring board monitored the trial.
  - All clinical events were adjudicated by an independent clinical event adjudication committee.

# Study Organization

- **Principal Investigators**
  Jian'an Wang
  Bon-Kwon Koo

- **Steering Committee**
  Jian'an Wang
  Bon-Kwon Koo
  Xinyang Hu
  Chang-Wook Nam
  William F Fearon

- **Clinical Event Adjudication Committee**
  Jin-Sin Koh (Chair)
  Keehwan Lee
  So Dam Jung

- **Data Safety Monitoring Board**
  Xin Du (Chair)
  Rongchong Huang
  Hyun-Kuk Kim
  Hyun Jong Lee
  Woojoo Lee (Statistician)

- **Data Coordination and Management**
  Xiaoyuan Qu (Beijing Yjheal Medical Research Center)

# Investigators

## FLAVOUR II is an investigator-initiated, multicenter, randomized trial


Linjun Guo / Peking University Third Hospital

Bon-Kown Koo / Seoul National University Hospital

Jian An / Shanxi Cardiovascular Hospital

Bin Yang / Second hospital of Shanxi Medical University

Eun-Seok Shin / Ulsan Medical Center

Jianliang Ma/ The Affiliated Hospital of Shandong University of TCM

Qian Liu / The Fourth People's Hospitala of Jinan

Daqing Song / Jining No.1 People's Hospital

Jun Bu / Renji Hospital Shanghai Jiaotong University School of Medicine

Yongzhen Fan/ Zhongnan Hospital of Wuhan University

Jian'an Wang / Second Affiliated Hospital of Zhejiang University School of Medicine

Jinyu Huang / Affiliated Hangzhou First People's Hospital

Peng Chen / The first affiliated hospital of Wenzhou Medical University

Fan Jiang / The Affiliated Hospital of Hangzhou Normal University

Hao Zhou / The second affiliated hospital of Wenzhou Medical University

Dongsheng Lu / Changxing People's Hospital

Wenming He / The Affiliated Hospital of Medical School of Ningbo University

Zhenfeng Cheng / Huzhou Central Hospital

Xiaoping Peng / The First Affiliated Hospital of Nanchang University

Yibin Pan / Jinhua Central Hospital

Hongping Si / Dongyang People's Hospital

Zhaohui Meng / First Affiliated Hospital of Kunming Medical Univsrsity

Shiqiang Li / Zhejiang Greentwon Cardiovascular Hospital

Lijiang Tang / Zhejiang Hospital

Jilin Li/ The Second Affiliated Hospital of Shantou University Medical College

# Study Design and Patient Population

## 1,872 patients from 22 centers in China

### *Key Inclusion criteria*

a) Subject must be ≥ 18 years

b) Patients with ≥ 50% stenosis by angiography-based visual estimation.

c) Target vessel size ≥ 2.5mm in visual estimation

d) Target vessels are limited to LAD, LCX, and RCA

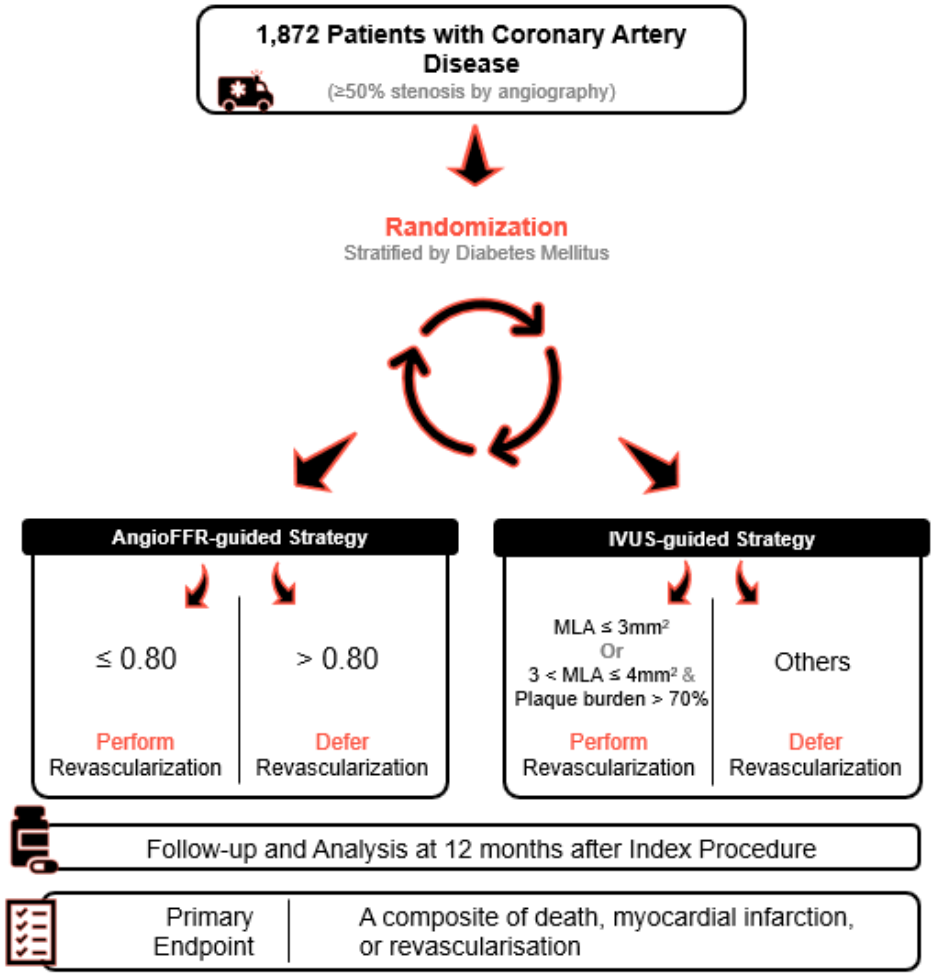
### *Exclusion criteria*

a) Target vessel total occlusion

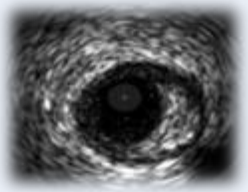
b) Target lesion located in coronary arterial bypass graft

c) Target lesion located in the left main coronary artery

d) Not eligible for AngioFFR (myocardial bridging, severe tortuosity, severe overlap, poor image quality)



# Indications and Optimization Criteria for PCI

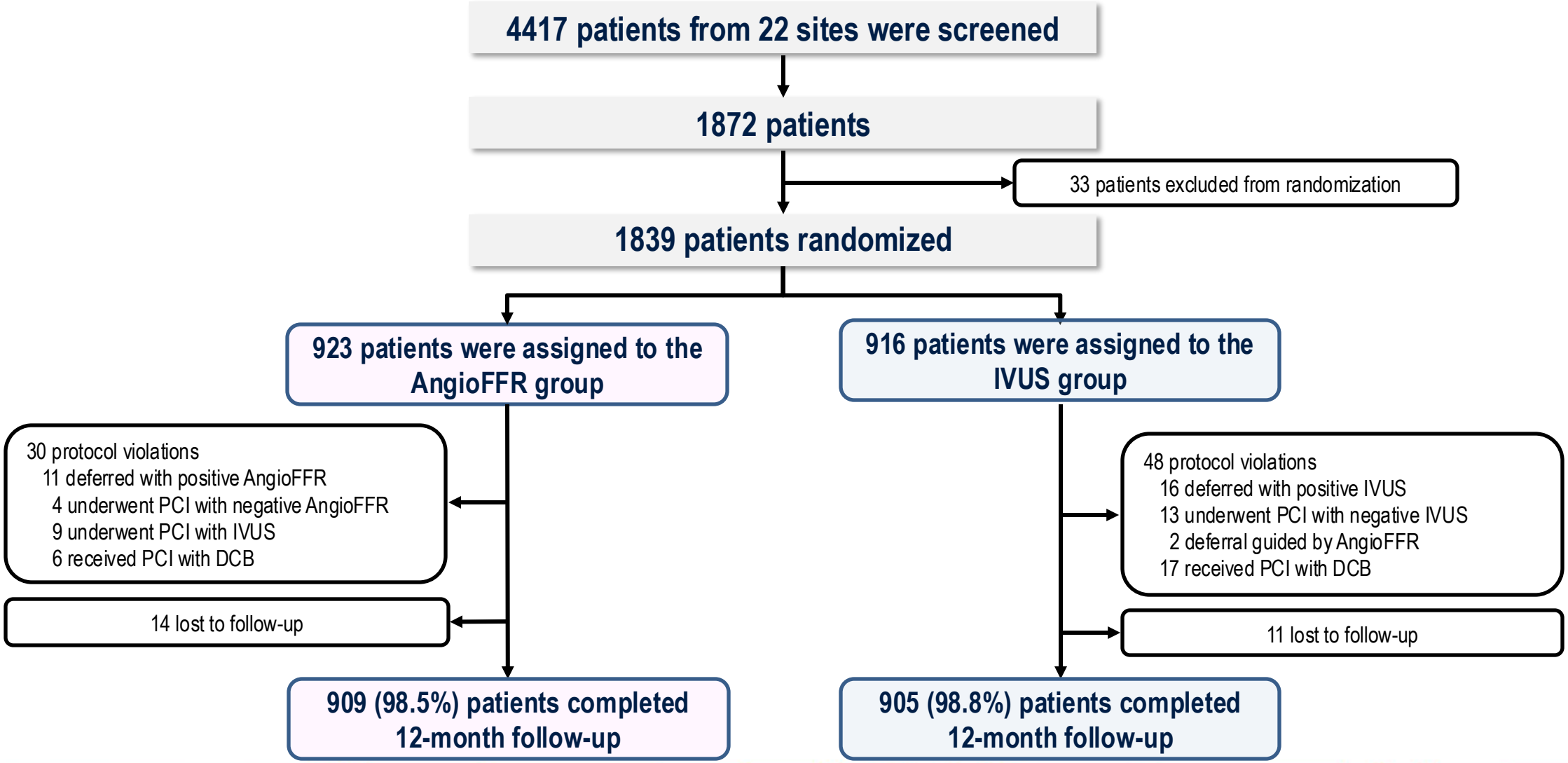
| AngioFFR-guided PCI group | | IVUS-guided PCI group | |
|---|---|---|---|
|  | AngioFFR ≤ 0.80 |  | Minimum lumen area (MLA) ≤ 3mm$^2$<br>or<br>3< MLA ≤ 4mm$^2$ & Plaque burden > 70% |

**PCI**

Post PCI AngioFFR ≥ 0.88
or
Post PCI ΔAngioFFR (across the stent) < 0.05

Plaque burden at stent edge ≤ 55%
Minimal stent area ≥ 5.5mm$^2$
or
Plaque burden at stent edge ≤ 55%
Minimal stent area ≥ distal reference lumen area

# Trial Flow


4417 patients from 22 sites were screened
1872 patients
33 patients excluded from randomization
1839 patients randomized
923 patients were assigned to the AngioFFR group
916 patients were assigned to the IVUS group
30 protocol violations
11 deferred with positive AngioFFR
4 underwent PCI with negative AngioFFR
9 underwent PCI with IVUS
6 received PCI with DCB
14 lost to follow-up
48 protocol violations
16 deferred with positive IVUS
13 underwent PCI with negative IVUS
2 deferral guided by AngioFFR
17 received PCI with DCB
11 lost to follow-up
909 (98.5%) patients completed 12-month follow-up
905 (98.8%) patients completed 12-month follow-up

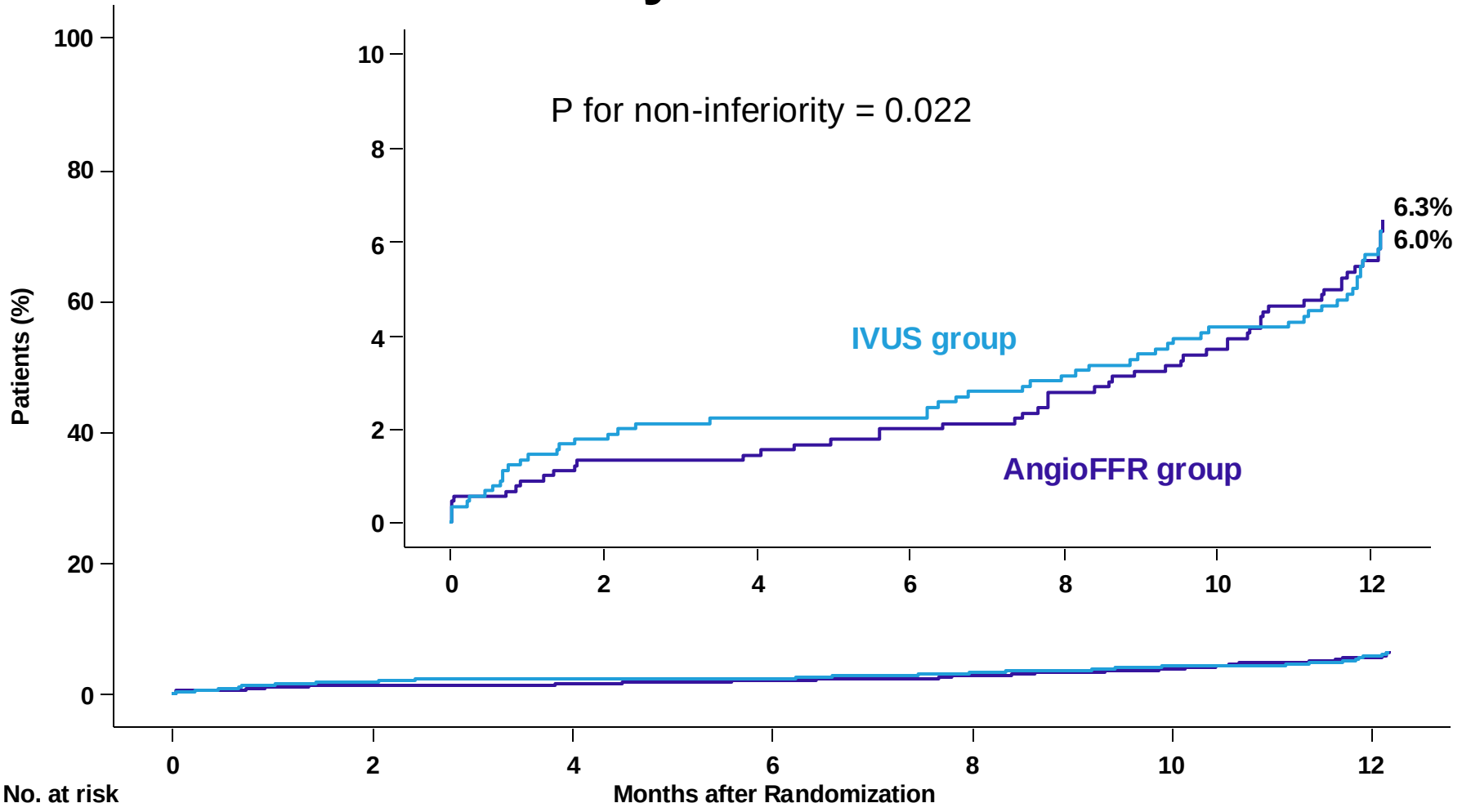
# Clinical Characteristics

| | AngioFFR (n=923) | IVUS (n=916) |
|---|---|---|
| **Age, years** | 66.0 (58.0-72.0) | 66.0 (58.0-72.0) |
| **Sex** | | |
| Male | 624 (67.6%) | 624 (68.1%) |
| Female | 299 (32.4%) | 292 (31.9%) |
| **Diagnosis, n (%)** | | |
| Chronic coronary disease | 371 (40.2) | 365 (39.8) |
| Acute coronary syndrome | 545 (59.0) | 542 (59.2) |
| **Diabetes mellitus, n (%)** | 279 (30.2) | 290 (31.7) |
| **Hypertension, n (%)** | 615 (66.6) | 628 (68.6) |
| **Current smoking, n (%)** | 242 (26.2) | 235 (25.7) |
| **Prior MI, n (%)** | 129 (14.0) | 126 (13.8) |
| ***Discharge medication*** | | |
| **Aspirin, n (%)** | 816 (88.4) | 826 (90.2) |
| **$P2Y_{12}$ inhibitor, n (%)** | 792 (85.8) | 830 (90.6) |
| **Dual antiplatelet therapy, n (%)** | 711 (77.0) | 755 (82.4) |
| **Statin, n (%)** | 888 (96.2) | 885 (96.6) |
| **Beta blocker, n (%)** | 509 (55.1) | 513 (56.0) |

# Procedural Characteristics

| | AngioFFR | IVUS | p value |
|---|---|---|---|
| ***Angiographic findings*** | n=923 | n=916 | |
| Patients who received PCI, n (%) | 682 (73.9) | 761 (83.1) | <0.0001 |
| Total stent number per patient | 1.06±0.90 | 1.21±0.92 | <0.0001 |
| SYNTAX score | 10 (5-15) | 9 (5-15) | 0.66 |
| Additional procedures due to suboptimal conditions | 126 (18.5) | 165 (21.7) | 0.15 |
| PCI achieved optimization criteria | 606 (88.9) | 430 (56.5) | <0.0001 |
| ***Target vessel*** | n=985 | n=984 | |
| Lesion length, mm | 19.0 (12.5-29.8) | 20.3 (13.2-30.5) | 0.083 |
| Reference vessel diameter, mm | 2.93 (2.61-3.30) | 2.96 (2.65-3.35) | 0.16 |
| Diameter stenosis, % | 62.3 (53.8-70.9) | 62.2 (54.7-70.0) | 0.94 |
| Target vessel PCI, n (%) | 688 (69.5) | 797 (81.0) | <0.0001 |
| ***IVUS findings*** | | | |
| Minimal luminal area, $mm^2$ | | 2.68 (2.19-3.35) | |
| Plaque burden, % | | 76.0 (70.0-81.0) | |
| Post-PCI minimal stent area, $mm^2$ | | 6.76 (5.49-8.57) | |
| ***AngioFFR findings*** | | | |
| AngioFFR | 0.73 (0.56-0.84) | | |
| Post-PCI AngioFFR | 0.96 (0.93-0.98) | | |

# Primary Outcome



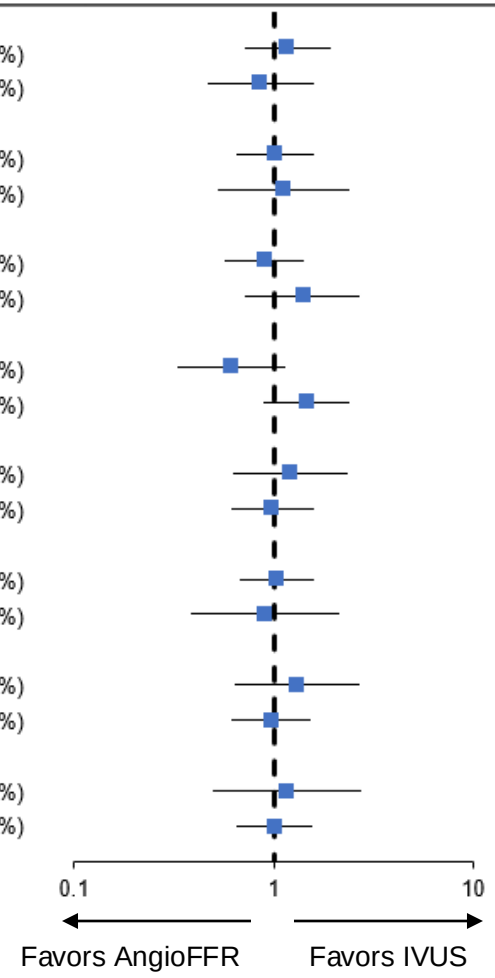

| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| AngioFFR group | 923 | 904 | 901 | 895 | 886 | 865 | 813 |
| IVUS group | 916 | 895 | 889 | 887 | 878 | 864 | 811 |

# Clinical Outcomes

| | Total (n=1839) | AngioFFR (n=923) | IVUS (n=916) | Difference 95%CI |
|---|---|---|---|---|
| **Death** | | | | |
| - Any | 28 (1.6) | 16 (1.8) | 12 (1.3) | 0.4% (-0.7 to 1.6) |
| - From cardiac cause | 10 (0.6) | 6 (0.7) | 4 (0.4) | 0.2% (-0.5 to 0.9) |
| **Myocardial infarction** | | | | |
| - Any | 10 (0.6) | 6 (0.7) | 4 (0.4) | 0.2% (-0.5 to 0.9) |
| - Target vessel | 1 (0.05) | 0 | 1 (0.1) | -0.1% (-0.3 to 0.1) |
| **Revascularization** | | | | |
| - Any | 77 (4.4) | 36 (4.1) | 41 (4.7) | -0.6% (-2.5 to 1.4) |
| - Ischemia driven | 54 (3.0) | 25 (2.8) | 29 (3.3) | -0.4% (-2.0 to 1.2) |
| - Target vessel | 29 (1.7) | 15 (1.7) | 14 (1.6) | 0.1% (-1.1 to 1.3) |
| **Stroke** | 15 (0.8) | 6 (0.7) | 9 (1.0) | -0.3% (-1.2 to 0.5) |

# Subgroup Analysis

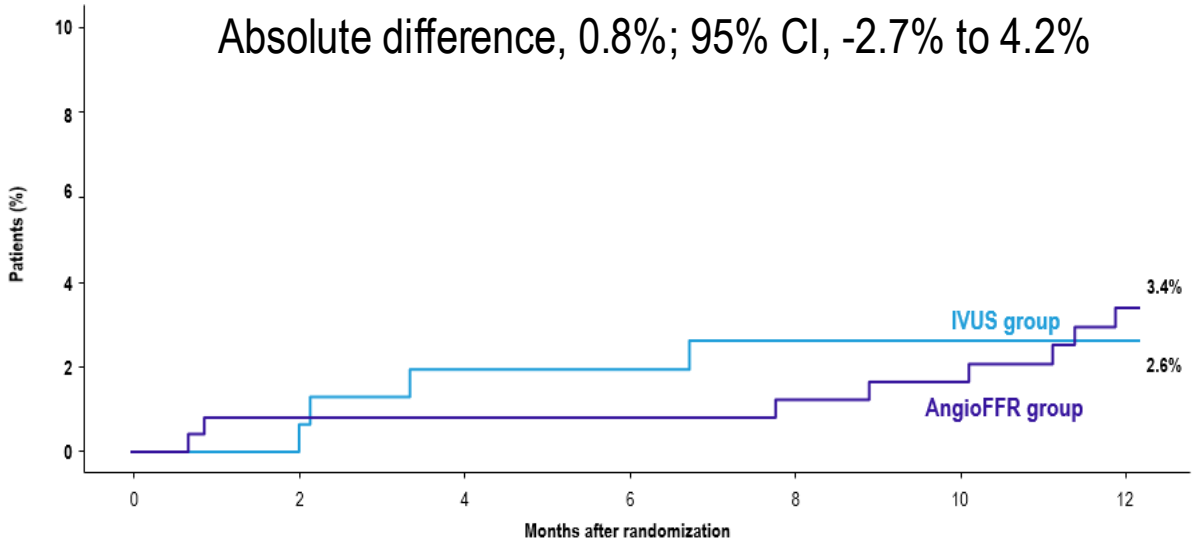
| Subgroup | AngioFFR (events/patients) | IVUS (events/patients) | Hazard Ratio (95% CI) |
|---|---|---|---|
| Age | | | |
| ≥ 65 years | 36/511 (7.3%) | 31/511 (6.2%) | 1.17 (0.72-1.89) |
| < 65 years | 20/412 (5.0%) | 23/405 (5.8%) | 0.86 (0.47-1.57) |
| Sex | | | |
| Male | 41/624 (6.8%) | 41/624 (6.8%) | 1.01 (0.66-1.56) |
| Female | 15/299 (5.1%) | 13/292 (4.5%) | 1.12 (0.53-2.36) |
| Acute coronary syndrome | | | |
| Yes | 35/545 (6.7%) | 39/542 (7.4%) | 0.90 (0.57-1.41) |
| No | 21/378 (5.6%) | 15/374 (4.1%) | 1.40 (0.72-2.72) |
| Diabetes mellitus | | | |
| Yes | 16/279 (5.9%) | 27/290 (9.6%) | 0.61 (0.33-1.13) |
| No | 40/644 (6.4%) | 27/625 (4.4%) | 1.46 (0.89-2.38) |
| Chronic kidney disease | | | |
| Yes | 19/210 (9.3%) | 18/237 (7.8%) | 1.21 (0.63-2.30) |
| No | 37/713 (5.4%) | 36/679 (5.4%) | 0.98 (0.62-1.56) |
| Mutivessel disease | | | |
| Yes | 46/622 (7.7%) | 42/590 (7.3%) | 1.03 (0.68-1.56) |
| No | 10/301 (3.4%) | 12/326 (3.8%) | 0.91 (0.39-2.12) |
| Prior PCI | | | |
| Yes | 19/300 (6.6%) | 13/259 (5.2%) | 1.30 (0.64-2.64) |
| No | 37/623 (6.1%) | 41/657 (6.4%) | 0.97 (0.62-1.51) |
| Type of AgioFFR | | | |
| QFR | 12/175 (6.9%) | 10/169 (5.9%) | 1.17 (0.50-2.71) |
| μQFR | 44/748 (6.1%) | 44/747 (6.1%) | 1.01 (0.66-1.53) |



# Primary Outcome According to Treatment

## Medical treatment

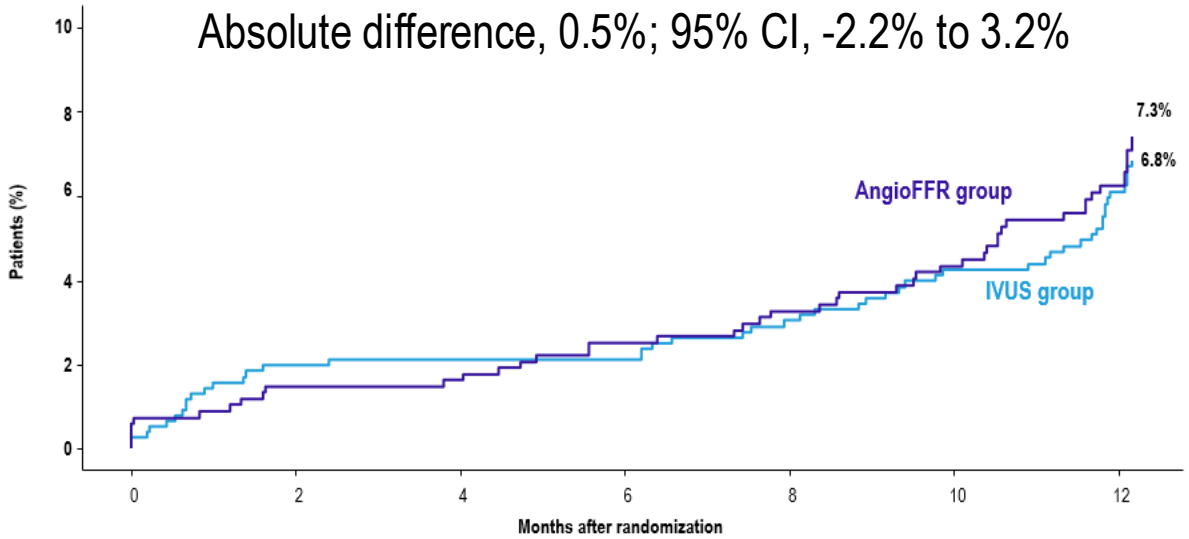
Absolute difference, 0.8%; 95% CI, -2.7% to 4.2%




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| AngioFFR group | 241 | 239 | 239 | 239 | 237 | 232 | 216 |
| IVUS group | 155 | 152 | 149 | 148 | 149 | 148 | 144 |

## PCI

Absolute difference, 0.5%; 95% CI, -2.2% to 3.2%




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| AngioFFR group | 682 | 665 | 662 | 655 | 649 | 633 | 597 |
| IVUS group | 761 | 743 | 739 | 738 | 730 | 716 | 665 |

# Limitations

- The study population had relatively low anatomical complexity, with a median SYNTAX score of 9.
- The PCI criteria in the IVUS group may have contributed to the higher PCI rate, given the lack of a definitive standard for IVUS-guided revascularization.
- The higher PCI optimization rate was influenced by both the AngioFFR technique itself and the criteria used to define optimization, as no universally accepted standard for AngioFFR-based PCI optimization exists.

# Conclusions

In the patients with non-complex coronary artery disease

- The AngioFFR-guided comprehensive PCI strategy, encompassing PCI decision-making and stent optimization, was non-inferior to the IVUS-guided strategy with respect to the composite endpoint of death, myocardial infarction, or revascularization at 12 months.

- This finding might have implications for future guidelines on its role and application.

# Thank You !

It symbolizes the value treasured by SAHZU people till today: "***The Needs of Patients and Customers Come First***."

The photo was taken in early 20th century. The scene captures Dr. David Duncan Main, a British physician and the first hospital president of Guangji Hospital, greeted a pediatric patient with reciprocal humility and respect.