The DEFINE-FLOW study
combined CFR and FFR assessment

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on behalf of the DEFINE-FLOW investigators

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Disclosure Statement of Financial Interest

Within the past 12+ months, Nils Johnson has had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- Grant/research support (to institution)
- Licensing and associated consulting (to institution)
- Support for educational meetings/training (honoraria/fees donated to institution)
- PET software 510(k) from FDA (application by Lance Gould, to institution)
- Patents filed (USPTO serial numbers 62/597,134 and 62/907,174)

Organizations (alphabetical)

- St Jude Medical (for CONTRAST study)
- Volcano/Philips (for DEFINE-FLOW study)
- Boston Scientific (for smart-minimum FFR algorithm)
- Various, including academic and industry
  - K113754 (cfrQuant, 2011)
  - K143664 (HeartSee, 2014)
  - K171303 (HeartSee update, 2017)
- SAVI and ΔP/Q methods
- Correction of fluid-filled catheter signal
How to treat CFR/FFR discordance?

57 year-old man with diabetes and CCS class I angina

Subject FLOW196 from DEFINE-FLOW (clinicaltrials.gov NCT02328820)
Vessels with
- abnormal $\text{FFR} \leq 0.8$ but intact $\text{CFR} \geq 2$
- will show non-inferior outcomes
- versus $\text{FFR} > 0.8$ and $\text{CFR} \geq 2$
- when treated medically.

Primary endpoint:
- composite of all-cause death, MI, PCI/CABG
- assessed after 2 years
- central adjudication by events committee
- non-inferiority margin of 10%
Treatment protocol

measure FFR and CFR

- FFR > 0.8: defer PCI
  (CFR adds value?)
- FFR ≤ 0.8:
  - CFR ≥ 2: defer PCI!
    (key difference)
  - CFR < 2: perform PCI
Study flow diagram

**Enrolled**
455 subjects
669 lesions
1729 measurements

**Excluded**
25 subjects
136 lesions
478 measurements

**Protocol-treated and followed**
430 subjects
533 lesions
1251 measurements

- **FFR > 0.8, CFR ≥ 2.0**
  - **Medical therapy**
  - 207 subjects
  - 236 lesions
  - FFR 0.88 (IQR 0.84-0.93)
  - CFR 2.5 (IQR 2.2-2.9)

- **FFR > 0.8, CFR < 2.0**
  - **Medical therapy**
  - 108 subjects
  - 123 lesions
  - FFR 0.89 (IQR 0.85-0.93)
  - CFR 1.7 (IQR 1.5-1.9)

- **FFR ≤ 0.8, CFR ≥ 2.0**
  - **Medical therapy**
  - 74 subjects
  - 74 lesions
  - FFR 0.75 (IQR 0.72-0.78)
  - CFR 2.6 (IQR 2.3-2.9)

- **FFR ≤ 0.8, CFR < 2.0**
  - **Revascularized by PCI**
  - 94 subjects
  - 100 lesions
  - FFR 0.70 (IQR 0.60-0.75)
  - CFR 1.4 (IQR 1.2-1.7)
### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>N = 430 subjects</th>
<th>N = 533 lesions</th>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>67 ± 10</td>
<td>LAD 59%</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>74%</td>
<td>LCx 23%</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>27%</td>
<td>RCA 18%</td>
</tr>
<tr>
<td><strong>Active tobacco</strong></td>
<td>22%</td>
<td>Prior PCI of vessel 14%</td>
</tr>
<tr>
<td><strong>Prior MI</strong></td>
<td>27%</td>
<td>FFR ≤0.80 33%</td>
</tr>
<tr>
<td><strong>Prior PCI</strong></td>
<td>40%</td>
<td>CFR &lt; 2.0 42%</td>
</tr>
<tr>
<td><strong>Stable presentation</strong></td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td><strong>Aspirin</strong></td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td><strong>Statin</strong></td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td><strong>≥2 anti-anginals</strong></td>
<td>50%</td>
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* = includes beta blockers, calcium blockers, nitrates, ranolazine, ivabradine, trimetazidine, and nicorandil.
CFR/FFR discordance

**Quadrants by binary FFR and CFR**
- FFR > 0.8, CFR ≥ 2.0 (44% of lesions)
- FFR > 0.8, CFR < 2.0 (23% of lesions)
- FFR ≤ 0.8, CFR ≥ 2.0 (14% of lesions)
- FFR ≤ 0.8, CFR < 2.0 (19% of lesions)
Primary endpoint

2-year MACE (death, MI, any PCI/CABG) (from Kaplan-Meier estimates, using site-reported FFR and CFR)

- FFR-/CFR- = 5.8%
- FFR+/CFR- = 10.8%
- FFR-/CFR+ = 12.4%
- FFR+/CFR+ = 14.4% (after PCI)

**FFR+/CFR- vs FFR-/CFR-**

- $\Delta = +5.0\%$ (95%CI -1.5% to +11.5%)
- p-value 0.065 for non-inferiority

natural history  NOT non-inferior for FFR+/CFR- and FFR-/CFR-
Secondary data: Target Vessel Failure

2-year TVF (MI or PCI/CABG of target) (from Kaplan-Meier estimates, using site-reported FFR and CFR)
- FFR-/CFR- = 3.0%
- FFR+/CFR- = 9.6%
- FFR-/CFR+ = 6.7%
- FFR+/CFR+ = 6.1% (after PCI)

Continuous predictors
- natural history (no FFR+/CFR+)
- 351 subjects, 433 lesions
- time-to-failure Cox mixed effects
- FFR hazard ratio <0.01, p=0.0067
- CFR hazard ratio 0.74, p=0.44
Secondary data: core lab

Measurements

- 69.8% of measurements accepted
- Δ FFR = 0.008 ± 0.026 (site<core lab)
- Δ CFR = 0.02 ± 0.23 (site>core lab)
  → core lab reduces sample size by 30%
  → but no change in FFR, CFR

TVF using continuous FFR, CFR

- natural history (no FFR+/CFR+)
- 286 subjects, 337 lesions
- time-to-failure Cox mixed effects
- FFR hazard ratio <0.01, p=0.038
- CFR hazard ratio 0.78, p=0.64
  → core lab analysis supports site analysis
Limitations

- Lack of randomization excludes causality
  (no comparison arm for FFR+/CFR- quadrant)
- Modest sample size with slow enrollment
  (took 3 years to enroll 455 subjects from 12 centers)
- Modest event rate with few “hard” endpoints
  (only 2 deaths [both non-cardiac], 5 infarcts)
- Unblinded subjects and physicians
  (might have biased the 32 TVR/TLR)
- Few lesions with severe FFR/CFR
  (FFR<0.75 in 20%, CFR≤1.7 in 27 %)
- Therefore, a hypothesis-generating study
Primary conclusion

Natural history of $\text{FFR} \leq 0.8 / \text{CFR} \geq 2$

is NOT non-inferior

to lesions with $\text{FFR} > 0.8 / \text{CFR} \geq 2$