Combined Optical Coherence Tomography and Fractional Flow Reserve Assessment to Better Predict Adverse Event Outcomes in DM Patients

COMBINE (OCT–FFR) Trial

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On behalf of COMBINE investigators
Background

• Fractional Flow Reserve (FFR) is widely used (Class A recommendation) to guide the revascularization strategy in the catheterization lab

• Previous studies have shown that FFR-negative lesions (> 0.80) can be safely treated medically, while FFR-positive lesions (≤ 0.80) benefit from revascularisation (FAME I & II trials)

• However, recent evidence has shown that in some patient subgroups such DM and/or ACS, FFR-negative lesions have worse outcomes than in patients without DM or ACS, probably due to faster atherosclerosis progression in these populations
DM patients undergoing angiography for any indication with $\geq 1$ lesion (non-culprit if ACS) that has %DS $\geq 40\%$ and $\leq 80\%$, defined as target lesion, that underwent FFR.

**COMBINE (FFR-OCT) Design**

*Prospective Natural History Study*

- **Primary Endpoint**
  - **Group A**
    - TCFA negative
    - OMT
  - **Group B**
    - TCFA positive
    - OMT

- **Secondary Endpoint**
  - **Group C**
    - Revascularization + OMT

- **FFR > 0.80** Corelab OCT lesion assessment
- **FFR \leq 0.80**
Study Endpoints

• **Primary endpoint:** The incidence of target lesion related MACE defined as: *Cardiac death*, *target vessel myocardial infarction (MI)*, *clinically-driven target lesion revascularisation (TLR)*, or *hospitalisation due to unstable or progressive angina* at 18 months in the **FFR-negative TCFA patients (Group B)** vs. **FFR-negative No-TCFA patients (Group A)**

• **Key secondary endpoint:** Incidence of MACE (Cardiac Death, TV-MI, CD-TLR, or hospitalisation for unstable angina) between **FFR-negative TCFA-positive (Group B)** vs. **Revascularized FFR-positive lesions (Group C)**

* Not directly related to non-target lesion events  ** Any Unstable Angina not related to non-target lesions events
550 patients enrolled

3 violation of exclusion criteria
2 malignancies
1 failure to revascularize the culprit lesion

2 malignancies
1 failure to revascularize the culprit lesion

6 had no eligible target lesion
(restenosis)
6 had no FFR performed

547 entered study procedure

19 had no revascularization in FFR (+) lesions

423 had FFR > 0.80

3 had PCI in FFR (-)
30 had no OCT or not analyzable OCT

390 had valid OCT

112 FFR ≤ 0.80

6 had no FFR performed

19 had no revascularization in FFR (+) lesions

292 No-TCFA

1 lost to FU

291 18M FU

98 TCFA

1 lost to FU

97 18M FU

93 had revascularizations

1 lost to FU

92 18M FU
Primary Endpoint
(CD, TVMI, CD-TLR, or Hospitalization UAP)

**Cumulative Incidence %**

- **HR 4.7 95%CI (2.0-10.9) p = 0.0004**
- **Log-rank test p < 0.0001**

**Nr. at Risk**

<table>
<thead>
<tr>
<th>TCFA</th>
<th>98</th>
<th>88</th>
<th>86</th>
<th>44</th>
</tr>
</thead>
<tbody>
<tr>
<td>No TCFA</td>
<td>292</td>
<td>286</td>
<td>281</td>
<td>144</td>
</tr>
</tbody>
</table>

**Days since enrollment**
Primary Endpoint Composites

Log rank p = 0.57
Log rank p < 0.001
Log rank p = <0.0001
Log rank p = 0.002

Cumulative Incidence %

Cardiac Death
TVMI
CD-TLR
Hospitalisation
UAP

0 0.34
0 4.1
11.2
6.2

TCFA  NoTCFA
**Secondary Endpoint**

**HR** 1.25, 95% CI (0.28-5.59) $p = 0.77$

*Log-rank test $p = 0.42$*

**Nr. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>TCFA</th>
<th>FFR + Revascularization</th>
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<tbody>
<tr>
<td><strong>30</strong></td>
<td>98</td>
<td>93</td>
</tr>
<tr>
<td><strong>182</strong></td>
<td>88</td>
<td>87</td>
</tr>
<tr>
<td><strong>365</strong></td>
<td>86</td>
<td>84</td>
</tr>
<tr>
<td><strong>546</strong></td>
<td>44</td>
<td>47</td>
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Secondary Endpoint: Composites

- Cardiac Death: Log rank p = 0.31
- TVMI: Log rank p = 0.77
- CD-TLR: Log rank p = 0.01
- Hosp UAP: Log rank p = 0.55

Cumulative Incidence %

- TCFA
- FFR(+) Revascularized
Multivariable COX Regression Analyses

<table>
<thead>
<tr>
<th>Multivariable Cox Regression</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Group (TCFA)</td>
<td>4.60</td>
<td>1.95 - 10.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.95 - 1.03</td>
<td>0.66</td>
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<tr>
<td>MI at presentation</td>
<td>2.48</td>
<td>0.94 - 6.53</td>
<td>0.07</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>2.21</td>
<td>0.94 - 5.21</td>
<td>0.07</td>
</tr>
<tr>
<td>MLA (decrease 1mm²)</td>
<td>1.57</td>
<td>1.02 - 2.41</td>
<td>0.04</td>
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</table>

*Insulin treated DM was not significant in univariable regression analysis and was not included in multivariable analysis*
Conclusions

• **COMBINE** showed for the first time that in **DM patients**
  
  - **Prevalence:** More than 25% of all FFR (-) lesions represent high-risk plaques (OCT-assessed TCFA)
  
  - **Impact:** Presence of a high-risk plaque *(TCFA)* is a strong predictor of future MACE, despite lack of ischemia
  
  - **Amplitude:** Patients with high-risk plaques *(TCFAs)* have a significant (HR 4.7) increase in target-lesion related MACE *(and MI)* as compared to patients without TCFA, already at 18 months
  
  - **New insights:** *Ischemia* and future adverse events represent, to a large extent, two separate concepts

• **COMBINED FFR & OCT** can improve the accuracy of high-risk lesion/patient identification and should therefore be embraced