Functional and morphological changes of significant non-culprit coronary artery stenosis by extensive LDL-C reduction with PCSK9 inhibitors

Results of the randomized, placebo-controlled FITTER trial

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Disclosure statement of financial interest

- I, Frans Mensink, 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.
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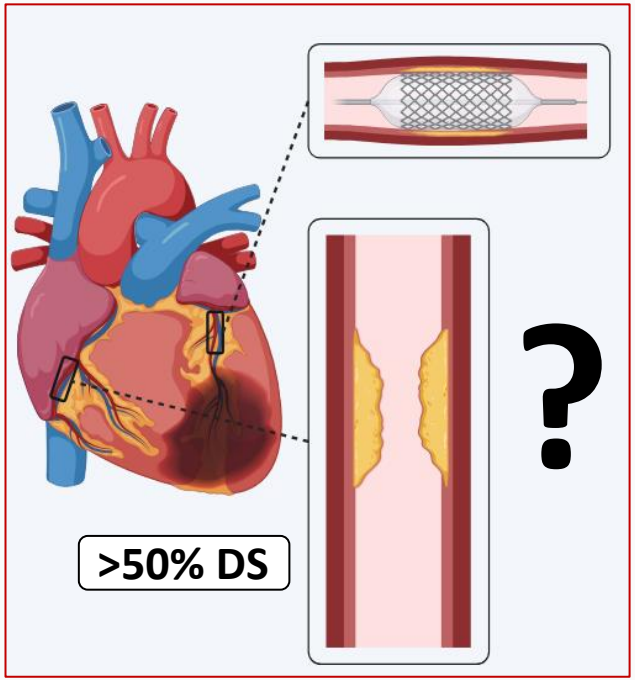
Background

- Approach of non-culprit lesions in ACS remains puzzling
- LDL-C lowering induces plaque regression and reduces MACE[1,2]
- PCSK9 inhibitors further reduce LDL-C post ACS[3]
- PCSK9 inhibitors for 52 weeks post-ACS improves plaque composition and lipid content[4,5]



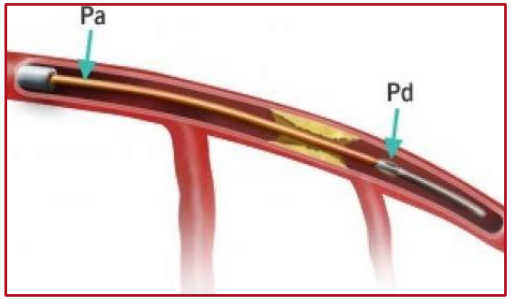
1. Nissen, ASTEROID, JAMA 2006
2. Schwartz, MIRACL, JAMA 2001
3. Koskinas, EVOPACS, JACC 2019
4. Räber, PACMAN-AMI, JAMA 2022
5. Nicholls, HUYGENS, JACC Img 2022

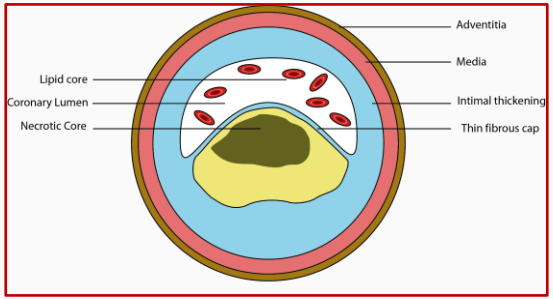
Questions

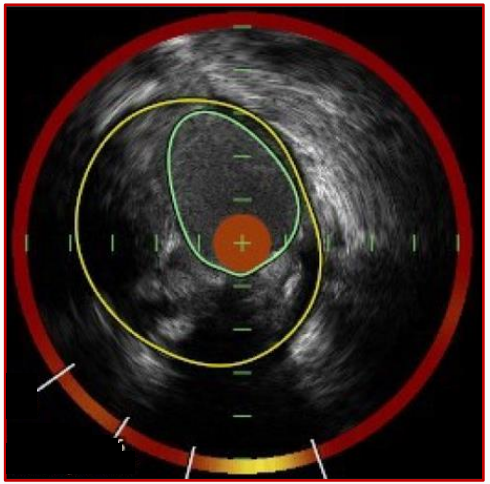
- **Is extensive LDL-C lowering with statins and PCSK9 inhibitors in patients with MVD-ACS and a staged procedure a viable treatment choice?**
  - Reduction of non-culprit plaque size or lipid content?
  - Improving non-culprit hemodynamics?
- **Is there a potential for reduction of additional stents?**

Objectives

- To determine the effects of evolocumab in addition to high-intensity statin therapy (HIST) on relevant coronary lesions using fractional flow reserve (FFR) measurements and multimodality intracoronary imaging (IVUS-NIRS).

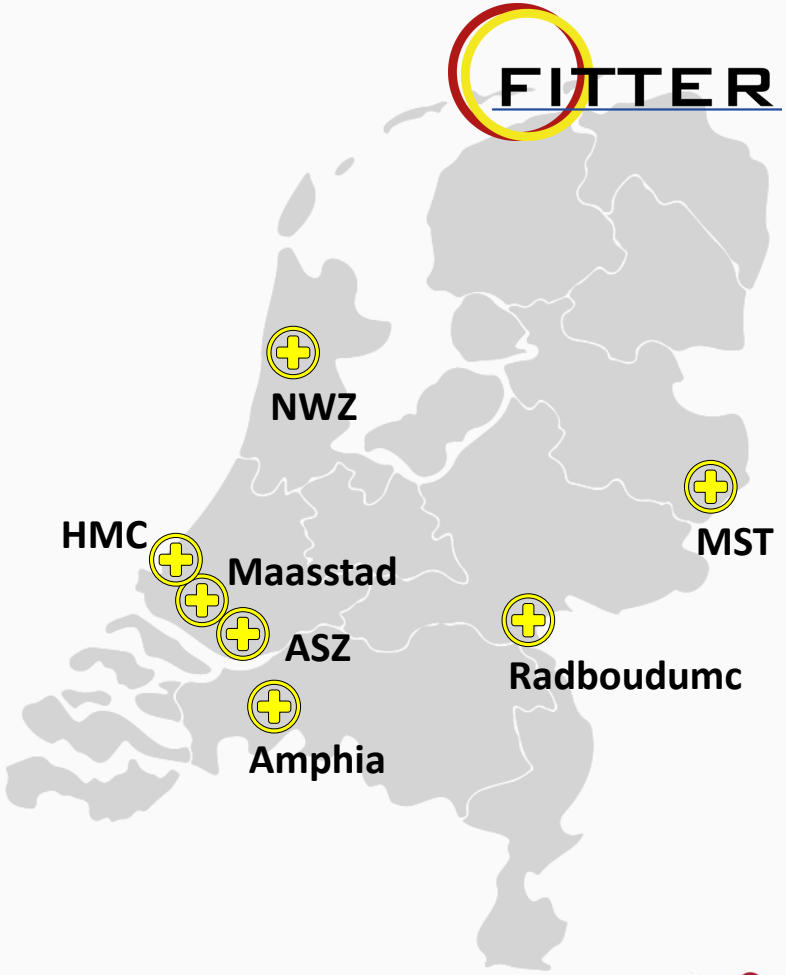






Trial design

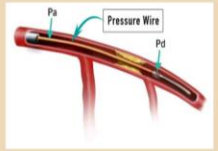
- Investigator initiated multicenter, double-blind, placebo-controlled, randomized clinical trial
- Blinding for lipid measurements throughout the study
- Independent datamonitoring
- Independent core-lab analysis for IVUS-NIRS (CVRI, Dublin, Ireland)



Trial design

FITTER

All ACS
MVD on angio
Succesful culprit PCI



non-culprit FFR
0.67 - 0.85

Non-culprit vessel IVUS-NIRS

1:1 R

Evolocumab
+
Statin

Placebo
+
Statin

12 WEEKS

12 WEEKS

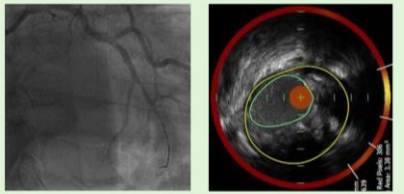
Monitoring treatment adherence

Clinical follow-up

Blood sampling

Follow-up procedure

- Repeat non-culprit FFR and IVUS-NIRS
- non-culprit PCI if applicable, operator's decision



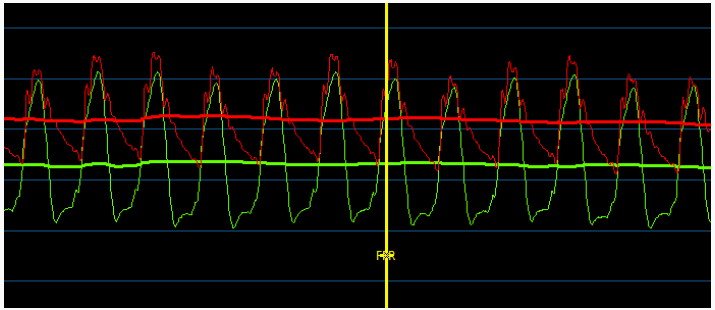
Key in- and exclusion criteria

- ACS with PCI of culprit stenosis
- Multivessel disease
- FFR of non-culprit stenosis:
  0.67 – 0.85
- Age ≥ 18 years at screening

- Complicated IRA treatment
  - Extravasation
  - Permanent no re-flow (TIMI flow 0-1)
  - Inability to implant a stent
- Non-IRA stenosis not amenable for PCI
- Prior CABG
- Untreated LM stenosis (FFR ≤ 0.80)
- Known LVEF < 30%
- Contra-indication for DAPT
- Known severe cardiac valve dysfunction
- Kidney disease (eGFR < 30 ml/min)
- Known severe liver disease
- Pregnancy or pregnancy wish

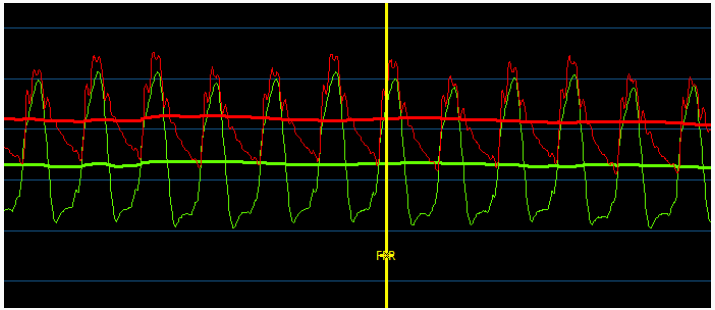
Study endpoints

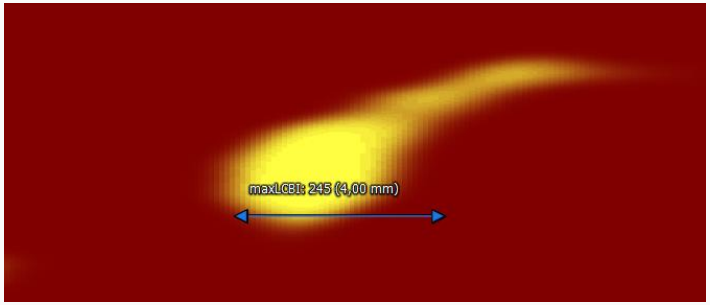
Primary endpoints	**1A. Physiological: Δ Fractional flow reserve (FFR)**



Study endpoints

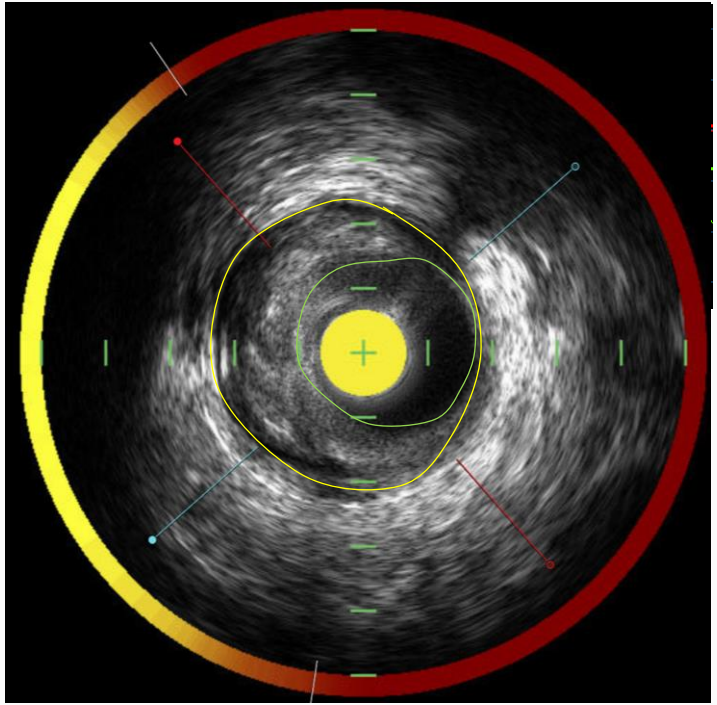
Primary endpoints	**1A. Physiological: Δ Fractional flow reserve (FFR)** **1B. Invasive imaging: Δ Lipid core burden index 4mm ($MaxLCBI_{4mm}$)**





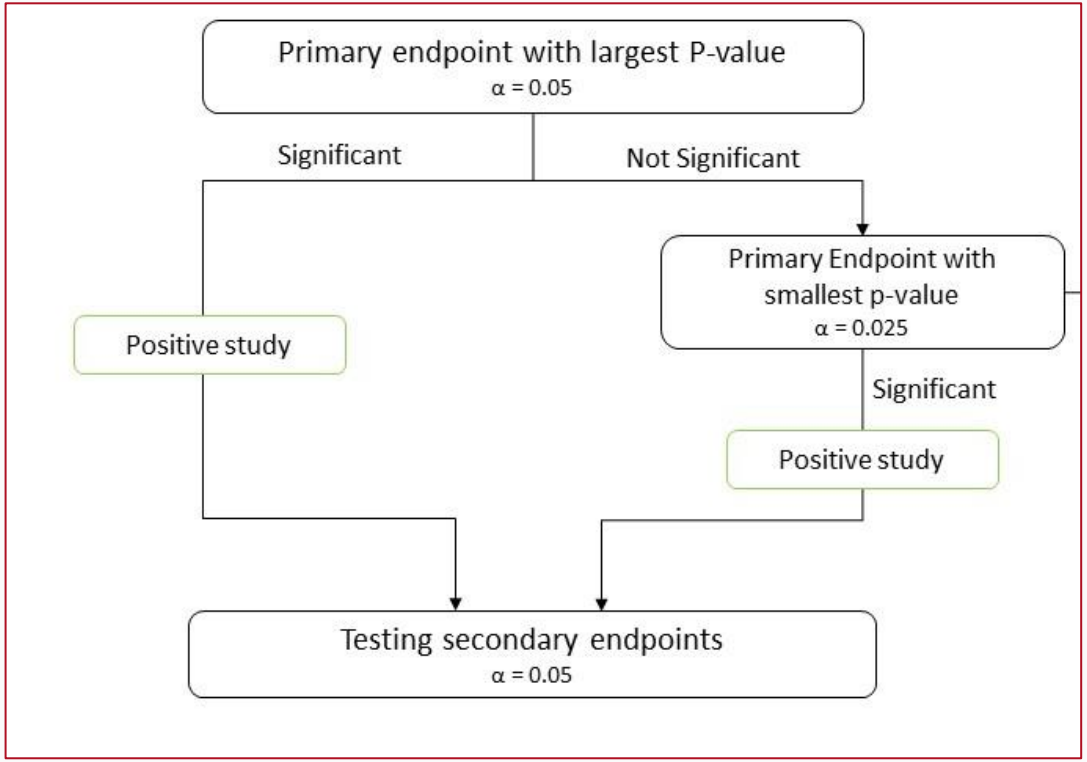
Study endpoints

Primary endpoints	**1A. Physiological: Δ Fractional flow reserve (FFR)** **1B. Invasive imaging: Δ Lipid core burden index 4mm ($MaxLCBI_{4mm}$)**
Secondary endpoints	**Δ Percent atheroma volume (PAV)** **Δ Normalized total atheroma volume (TAV)** **Δ Maximum plaque burden (PB)** **Δ Minimum lumen area (MLA)**

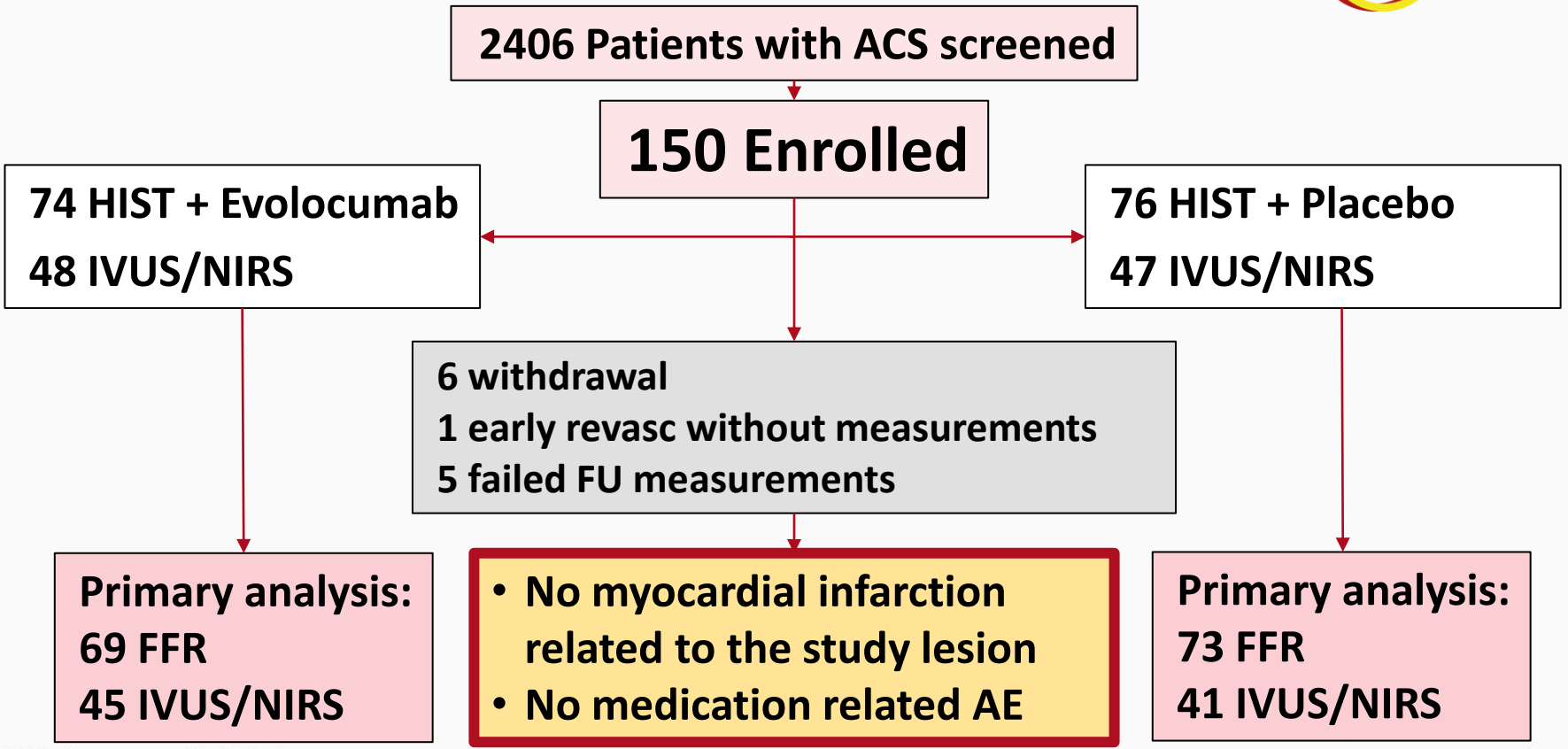


Statistical analysis and Power calculation

- **Hochberg method for multiple endpoints**
- **Physiological endpoint:**
  - **0.03 FFR points difference**
  - **80% power**
  - **127 patients**
- **Imaging endpoint:**
  - **14% difference in $MaxLCBI_{4mm}$**
  - **90% power**
  - **84 patients**



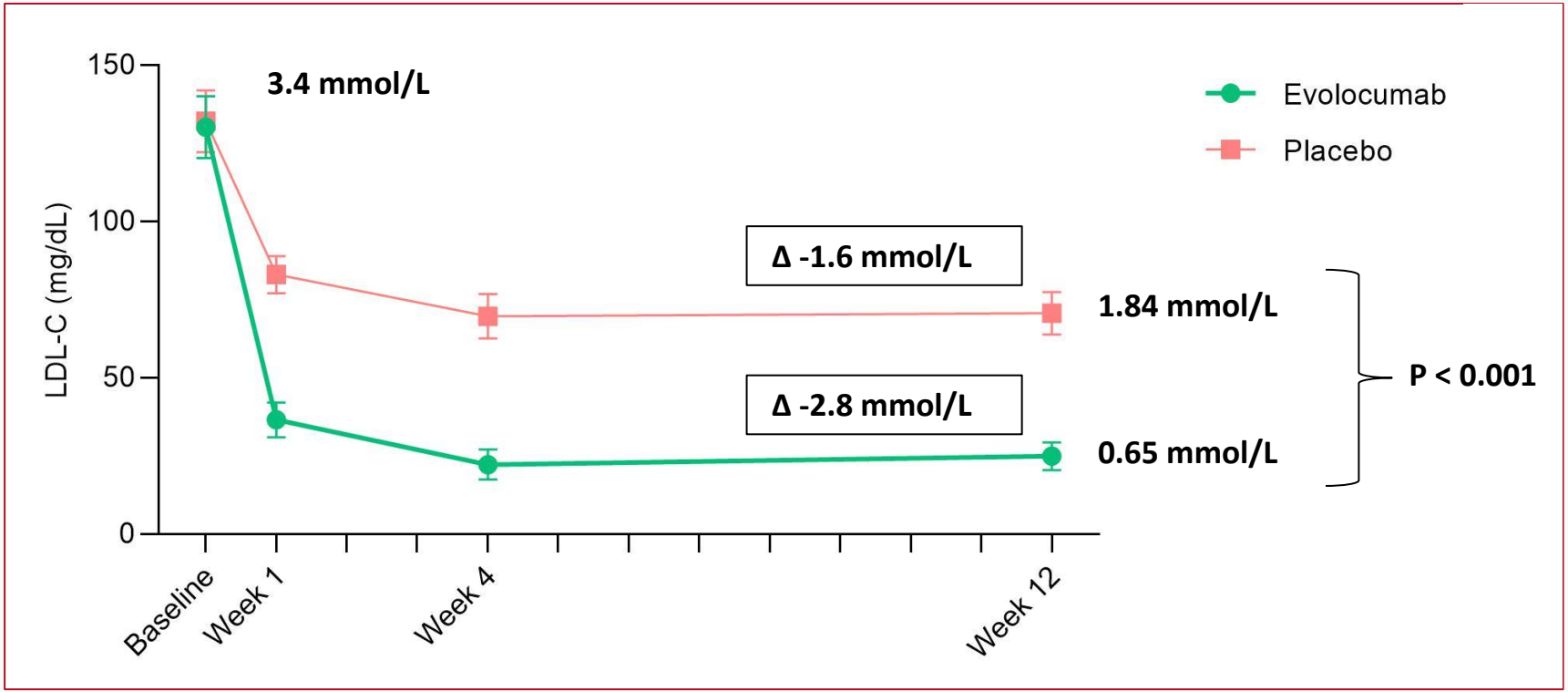
Trial flow diagram



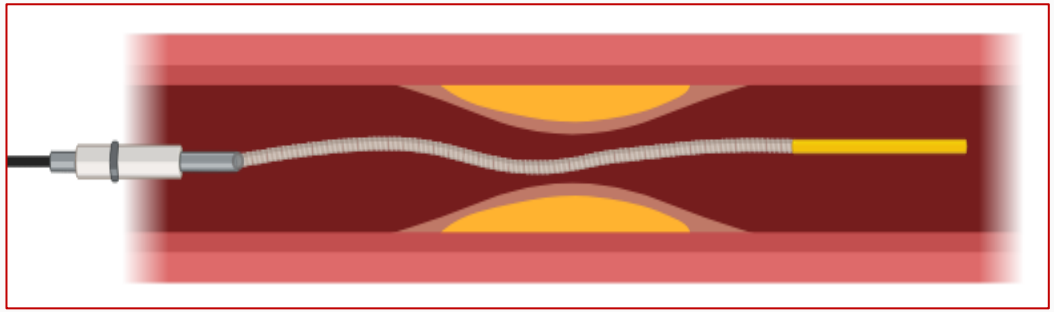
Baseline characteristics

	Overall (n = 150)	Evolocumab (n = 74)	Placebo (n = 76)
Age – years (±SD)	64.2 (8.5)	63.5 (8.3)	65.0 (8.8)
Sex, male – %	82.0%	78.4%	85.5%
Hypertension – %	39.3%	39.2%	39,5%
Dyslipidemia – %	42.0%	39.2%	44.7%
Family history of premature CAD – %	38.0%	34.7%	42.1%
Current Smoker – %	30.0%	32.4%	27.6%
Diabetes mellitus – %	10.0%	8.1%	11.8%
Stroke or TIA – %	4.7%	5.4%	3.9%
Prior MI – %	13.3%	9.5%	17.1%
Prior PCI – %	16.0%	14.9%	17.1%
Any statins – %	27.3%	24.3%	30.3%
High-intensity statin therapy – %	10.0%	10.8%	9.2%
STEMI – %	35.3%	35.1%	35.5%
NSTEMI – %	60.0%	60.8%	59.2%
UAP – %	4.7%	4.1%	5.3%

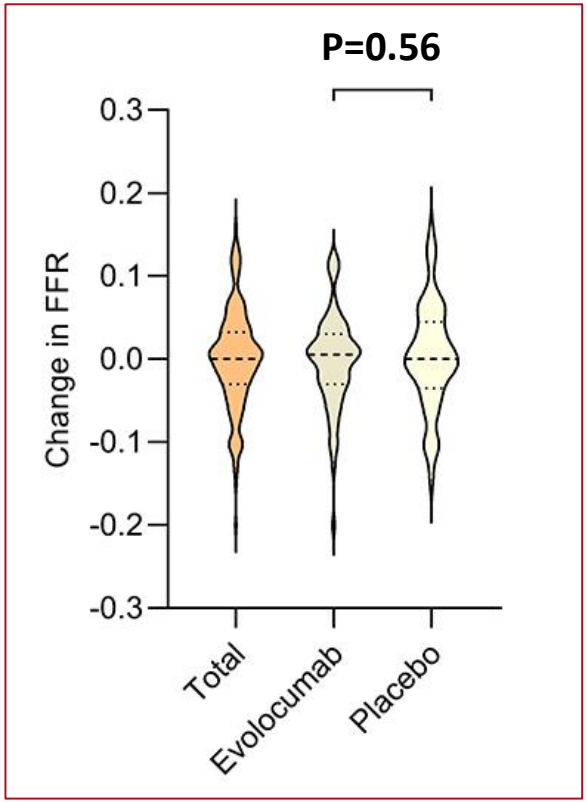
Results – Lipid levels



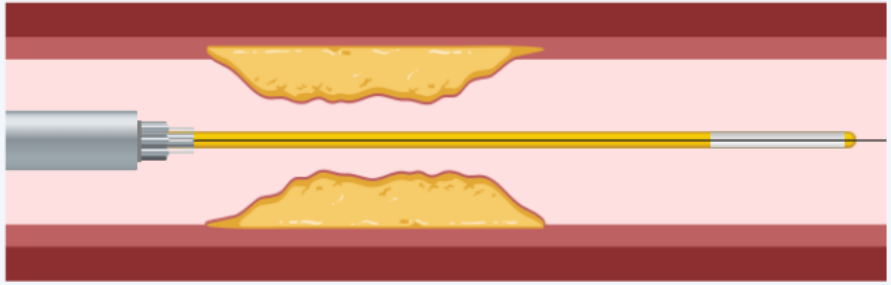
Results – Primary physiological endpoint (N= 142)



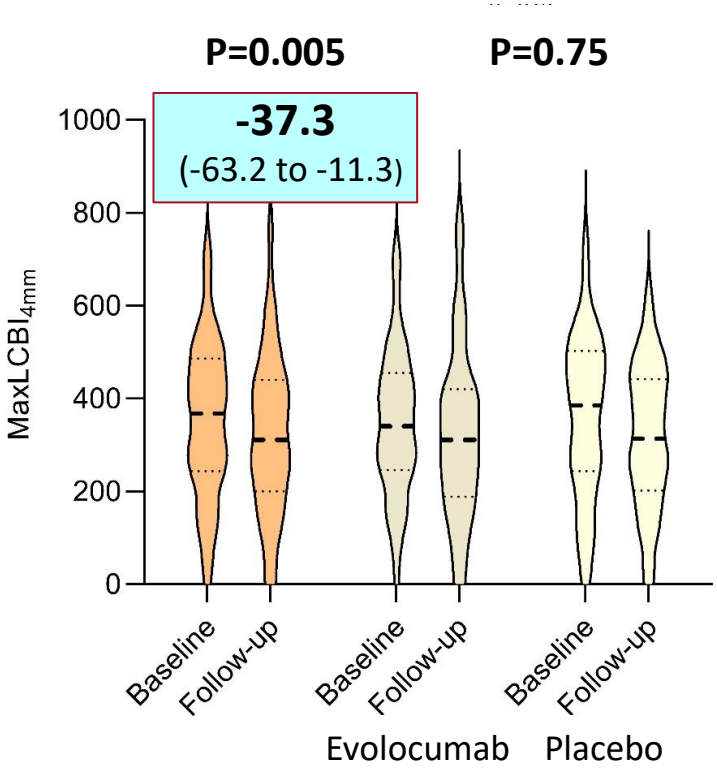
- Baseline FFR 0.78 (± 0.05)
- 12 weeks FFR 0.78 (± 0.07)
- No difference between groups



Results – Primary outcome LCBI (N=85)



- Baseline max$LCBI_{4mm}$ 358.5 (± 175.5)
- 12 weeks max$LCBI_{4mm}$ 321.3 (± 170.5)
- No difference between groups



Results – secondary outcome

Overall change between baseline and FU		P value
PAV, % – mean (95% CI)	-0.45 (-1.08 to 0.17)	0.15
nTAV, mm³ – mean (95% CI)	-9.00 (-18.09 to 0.09)	0.05
Max PB, % – mean (95% CI)	-0.81 (-1.64 to 0.02)	0.05
MLA, mm² – mean (95% CI)	-0.07 (-0.20 to 0.06)	0.39

Difference in change between evolocumab and placebo		P value
PAV, % – mean (95% CI)	-0.18 (-1.39 to 1.02)	0.76
nTAV, mm³ – mean (95% CI)	-3.63 (-21.11 to 13.86)	0.68
Max PB, % – mean (95% CI)	-0.33 (-1.94 to 1.29)	0.69
MLA, mm² – mean (95% CI)	0.07 (-0.19 to 0.32)	0.61

PAV: percent atheroma volume; nTAV: normalized total atheroma volume
PB: plaque burden; MLA: minimum lumen area

Conclusions

- No study lesion related events in 12 weeks in this high-risk population
- During intensive lipid-lowering directly post-ACS, non-culprit lipid content decreased in a very short timeframe of 12 weeks
- No difference in both primary endpoints of FFR and $maxLBCI_{4mm}$ after 12 weeks of treatment

Limitations

- Smaller study with wide confidence intervals
- High percentage of statin naive patients (75%) with already a large treatment effect on HIST only (LDL-C reduction of 50%)
- Short treatment period

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