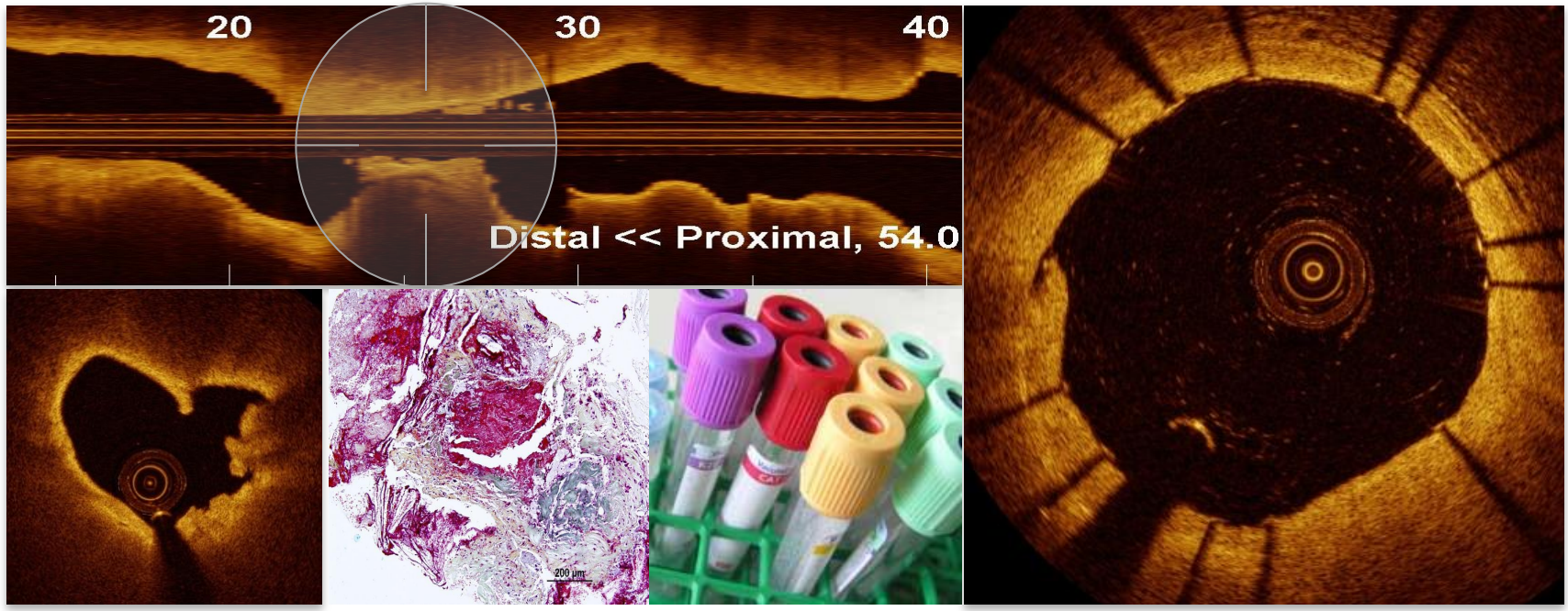
euro PCR 2014

The **OCTAVIA** Study

Optical **C**oherence **T**omography **A**ssessment of Gender Di**V**ersity **I**n Primary **A**ngioplasty

Mechanisms of Atherothrombosis and Vascular Response to Primary Percutaneous Coronary Intervention in Women versus Men with Acute Myocardial infarction



ClinicalTrials.gov Identifier: NCT01377207

OCTAVIA

RIGHT TO THE HEART

Funding Sources and disclosure statement

The study was promoted and supported by the Italian Society of Invasive Cardiology with unrestricted grant support provided by Abbott Vascular (Santa Clara, CA, USA)

OCT catheters for the study were donated by St. Jude Medical (St. Paul, MN, USA)

Giulio Guagliumi PI and chair

Research Grants: Abbott Vascular, Boston Scientific, St. Jude Medical

Consultant: Boston Scientific, St. Jude Medical

Background

Facts on STEMI in Women

- At time of presentation women are ≅10 yrs older than men
- More clustering of risk factors with different clinical impact
- Smaller coronary and peripheral arteries (access, treatment)

A gender difference in pathophysiology of STEMI is suggested by autopsy series, but never systematically investigated *in vivo* in the context of primary PCI

Objective: to determine if gender-related differences in the pathophysiology of STEMI and vascular response to primary PCI can be observed *in vivo* after accounting for the confounding effect of age.

Study Population and Age Matching

- Prospective, multicenter, controlled trial.
- 140 age-matched men and women with STEMI < 6hr undergoing primary PCI with everolimus-eluting stent (Xience Prime™) were investigated with serial OCT, histopathology-immunohistochemistry of thrombus aspirates, and serum biomarkers.
- Enrolment in a 1:1 ratio according to gender and age ensured by a computer-assisted interactive matching algorithm (diagnostic phase).

Study Endpoints

1. **Percentage of plaque rupture at the infarct-related lesion (superiority)**
2. **Percentage of stent strut coverage at 9 months after EES implantation (powered non-inferiority scope)**

ClinicalTrials.gov Identifier: NCT01377207

Study Organization

Promoter

- Italian Society of Invasive Ca

Executive Committee

- G. Guagliumi
- G. Musumeci
- D. Capodanno
- F. Saia
- M. Valgimigli
- C. Trani

Site Management and Data M

- MediTrial s.r.l., Rome, Italy

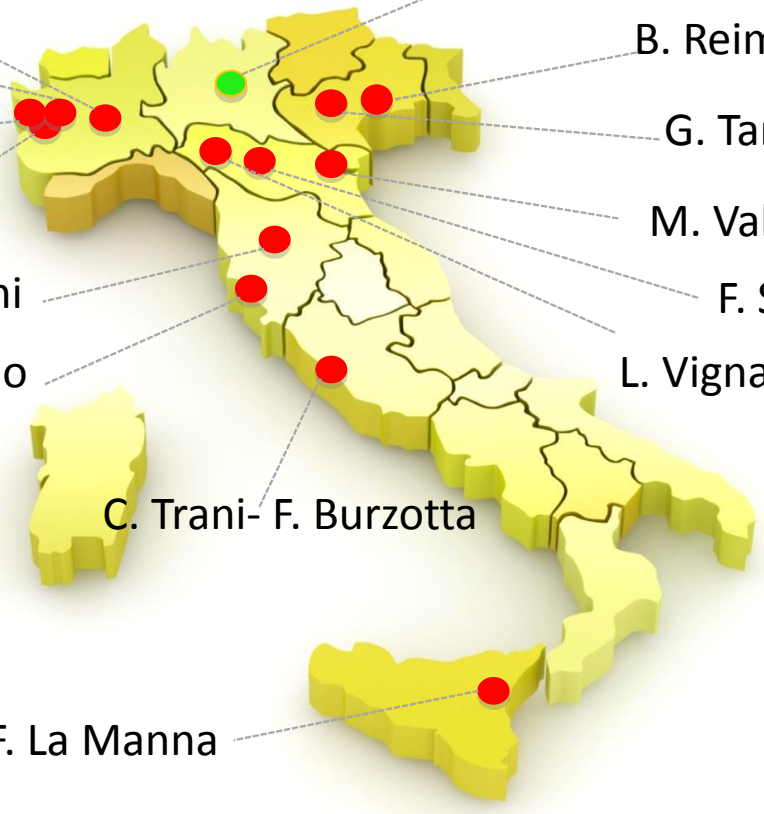
Data Management

- CatchTrial, Rome, Italy

Statistical Analysis

- Sapienza University of Rome, Italy
  G. Biondi Zoccai

Participating Sites



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Study Design

STEMI<6hours

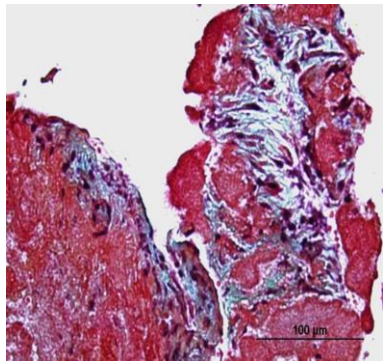
Serum biomarkers

Cath Lab

Angiography

Check clinical inclusion/exclusion criteria

Check angiographic inclusion/exclusion criteria



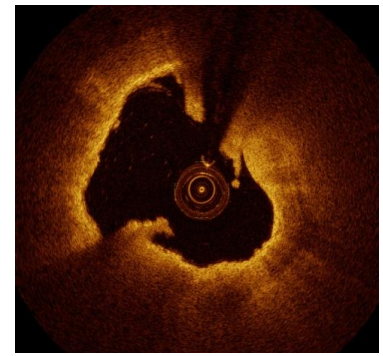
TIMI 0-1 or Filling defect

TIMI 2-3, No filling defect

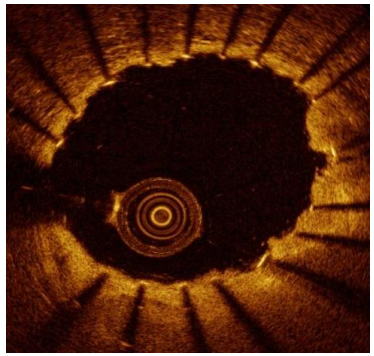
Thrombus aspiration

TIMI 2-3

Index OCT *



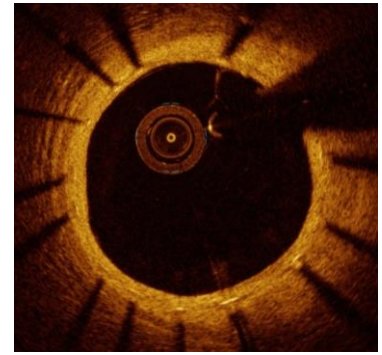
**no balloon dilation allowed*



Everolimus Eluted Stent

Size 2.5-4,0 mm, length<32 mm

Post-procedure OCT



OMT ≠

9 Months OCT FUP

Main Exclusion Criteria

Clinical

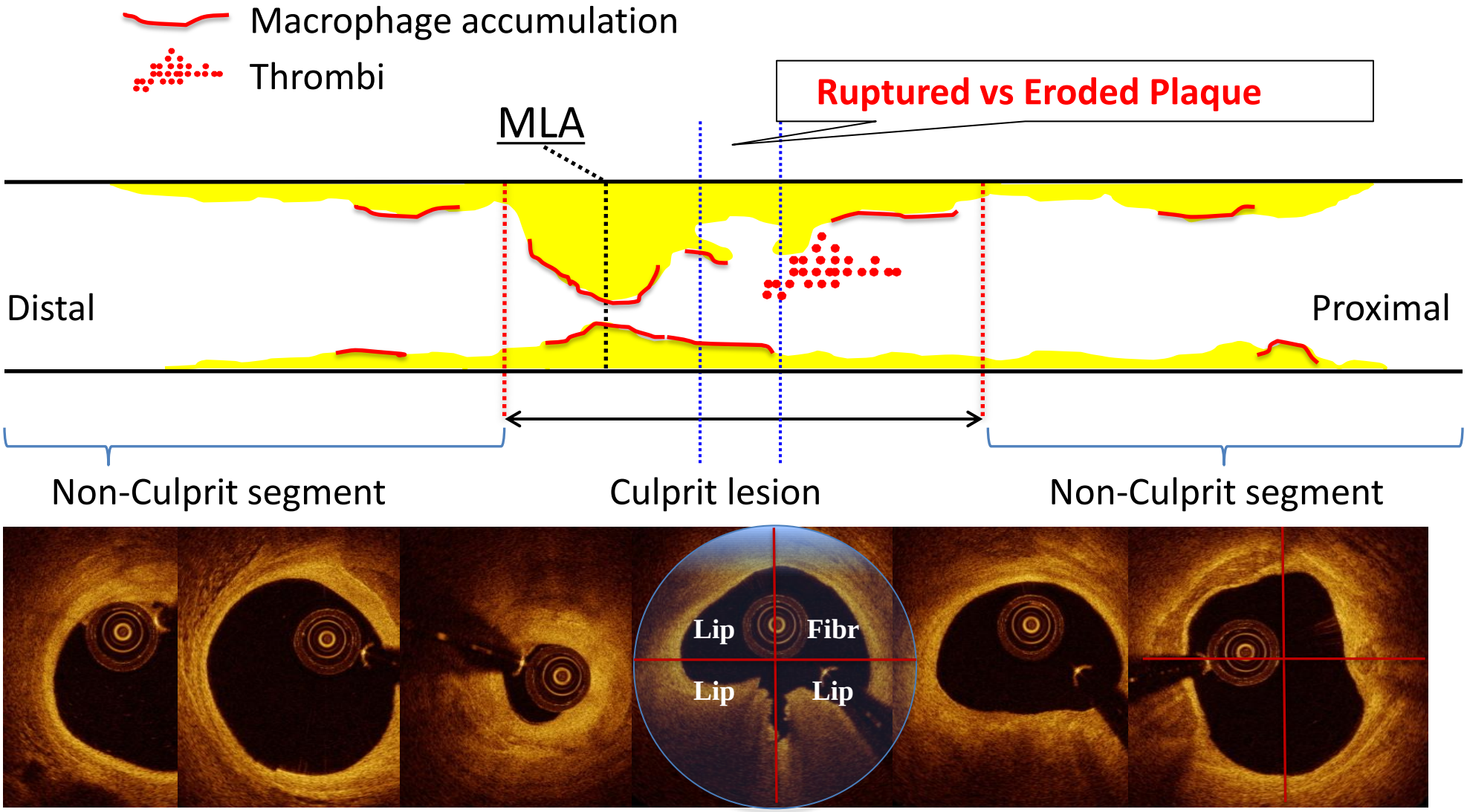
- Cardiogenic shock
- Cerebrovascular accident within the past 6 months
- History of renal insufficiency
- Pregnant or subjects who plan pregnancy in the period of follow-up.

Angiographic

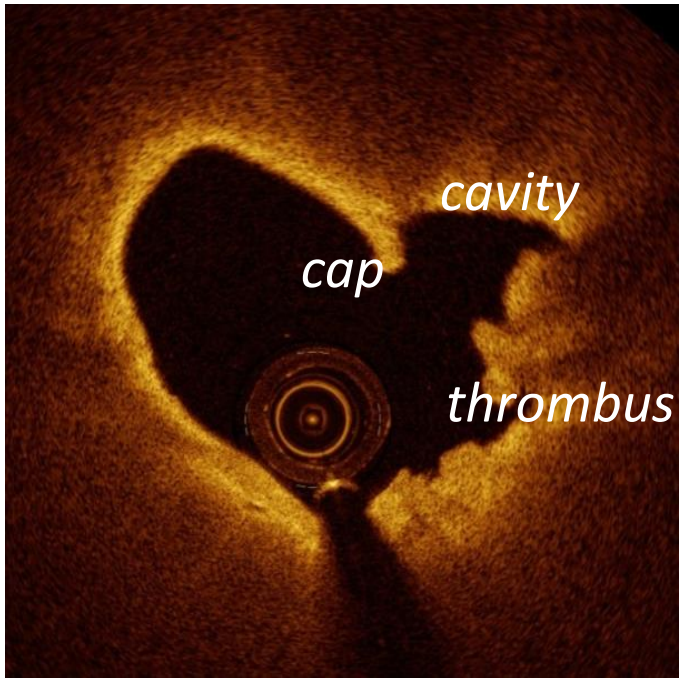
- Unprotected left main coronary artery disease with ≥ 50% stenosis
- Normal coronary arteries
- Infarction due to stent thrombosis
- Infarction in a bypass graft
- Thrombus aspiration catheter unable to cross the culprit lesion
- TIMI 0-1 flow grade after thrombus aspiration

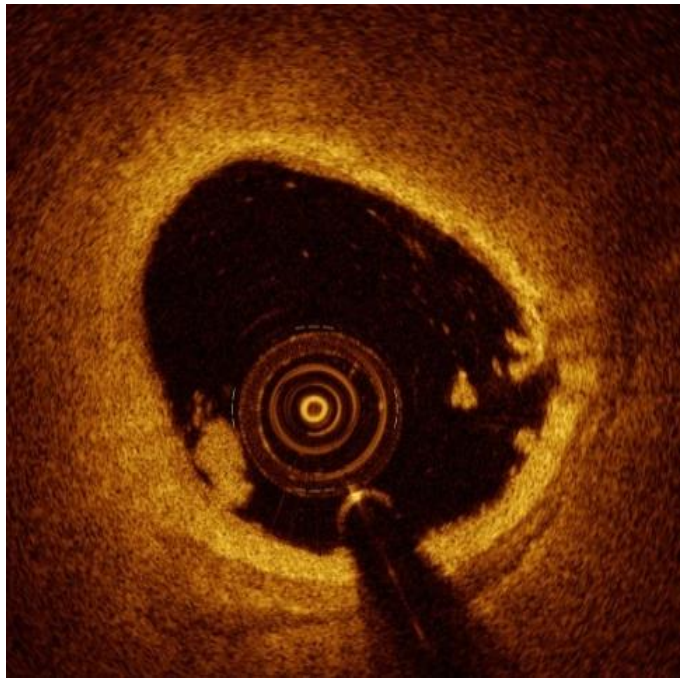
OCT Analysis in Culprit Vessel

every 0.2-0.6 mm analysis (Qualitative - Quantitative)



Culprit Plaque Morphology





Plaque rupture: presence of fibrous cap discontinuity and a cavity formation in the underlying plaque beginning at the luminal-intimal border.

Plaque non-rupture/erosion: lack of evidence of a fibrous cap rupture at the culprit site, evaluated in multiple adjacent frames, with evidence of an irregular luminal surface

Consensus Standards for acquisition, measurement and reporting of OCT ***JACC 2012; 20: 1058***

Study Flow

pPCI

140-age-matched patients with STEMI <6 hours

118/140 pts (84.3%) manual thrombus aspiration

79/104 (76.0%) aspirated thrombi analyzed

140/140 pts (100%) with OCT pullback of the culprit vessel before stent implantation

128/140 pts (91.4%) suitable for culprit lesion evaluation

PRIMARY EP

140/140 pts (100%) with OCT pullback post EES implantation

139/140 pts (99.3%) OCT post stent evaluation

9M FUP

120/134 pts (89.6%) elective coronary angiography and OCT

117/134 pts (87.3%) OCT of stented vessel analyzed

PRIMARY EP

12M FUP

134/140 pts (95.7%) 1-year follow-up

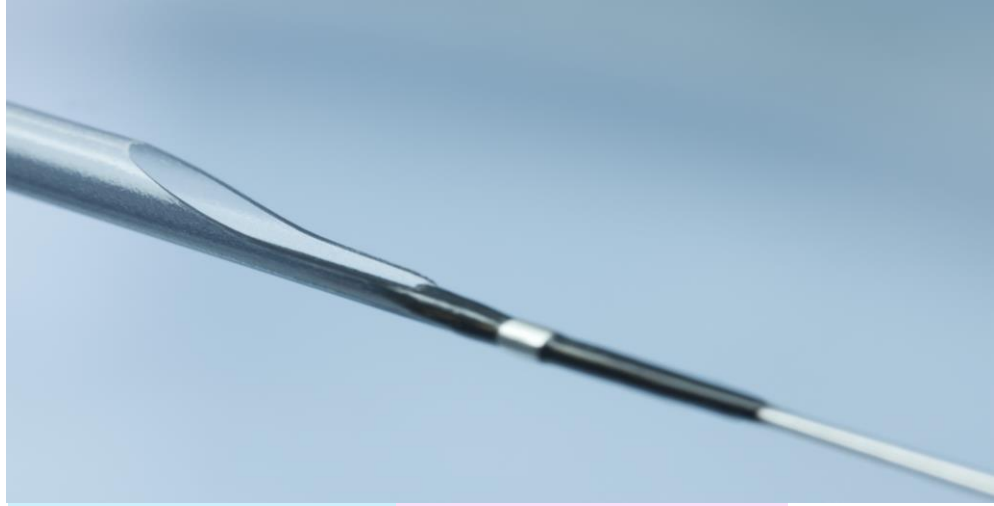
Baseline Demographic and Clinical Characteristics

Variable	Overall N=140	Men N=70	Women N=70	P value
Age, years	66.6±11.1	65.3±11.8	67.8±10.4	0.19
*Age group n. (%) **				1.00
<60 years	40/140 (28.5)	20/70 (28.5)	20/70 (28.5)	
61-80 years	82/140 (58.6)	41/70 (58.6)	41/70 (58.6)	
>80 years	18/140 (12.9)	9/70 (12.9)	9/70 (12.9)	
Body Surface Area, m^2	1.8±0.2	2.0±0.2	1.7±0.2	<0.001
Hypertension, no. (%)	80/140 (57.1)	41/70 (58.6)	39/70 (55.7)	0.73
Hyperlipidemia, no. (%)	40/140 (28.6)	21/70 (30.0)	19/70 (27.1)	0.71
Current Smoker, no. (%)	75/140 (53.6)	39/70 (55.7)	36/70 (51.4)	0.61
Diabetes, no. (%)	17/140 (12.1)	6/70 (8.6)	11/70 (15.7)	0.20
Time symptom to cath lab, hrs	2.4 (1.7-3.5)	2.3 (1.6- 3.1)	2.5 (1.8- 4.0)	0.05

** Only 3 women in pre-menopausal status*

Angiographic Characteristics

	Overall N=140	Men N=70	Women N=70	P value
Reference vessel diameter, mm	2.63±0.52	2.78±0.49	2.48±0.49	0.001
Baseline TIMI flow grade, no. (%)				0.45
0/1	83/140 (59.3)	43/70 (61.5)	40/70 (57.2)	
2	44/140 (31.4)	19/70 (27.1)	25/70 (35.7)	
3	13/140 (9.3)	8/70 (11.4)	5/70 (7.1)	
Final TIMI flow grade, no. (%)				0.47
0/1	0/140 (0)	0/70 (0)	0/70 (0)	
2	8/140 (5.7)	5/70 (7.1)	3/70 (4.3)	
3	132/140 (94.3)	65/70 (92.9)	67/70 (95.7)	



Procedural Characteristics

Variable	Overall N=140	Men N=70	Women N=70	P value
Radial access, no. (%)	82/140 (58.6)	47/70 (67.1)	35/70 (50.0)	0.04
Use of GP IIb/IIIa inhibitor, no. (%)	51/140 (36.4)	31/70 (44.3)	20/70 (28.6)	0.05
Pre-procedural thrombus, no. (%)	120/140 (85.7)	62/70 (88.6)	58/70 (82.9)	0.33
Use of aspiration catheter, no. (%)	118/140 (84.3)	61/70 (87.1)	57/70 (81.4)	0.35
Stents implanted per patient, no.	1.4±0.6	1.3±0.5	1.4±0.7	0.15
Total stent length per patient, mm	23.0 (18.8-33.0)	23.0 (21.8-33.0)	23.0 (18.0-35.3)	0.38

Serum biomarkers

SECONDARY ENDPOINT

Variable	Overall N=129	Men N=65	Women N=64	P value
CRP, mg/L	2.08 (1.00-4.11)	1.64 (0.88-4.77)	2.21 (1.01-4.02)	0.49
MPO, ng/mL	604.2 (290.5-1496.9)	512.7 (271.4-1308.7)	956.7 (303.7-1658.7)	0.09
ECP, µg/L	5.0 (2.8-9.1)	5.1 (2.5-10.5)	4.5 (2.9-7.9)	0.65
TBX2, pg/mL	117.2 (60.6-256.1)	117.2 (58.5-189.1)	117.3 (62.9-261.6)	0.63

CRP refers to C-reactive protein, MPO to myeloperoxidase, ECP to eosinophil cationic protein, TBX2 to thromboxane-B2.

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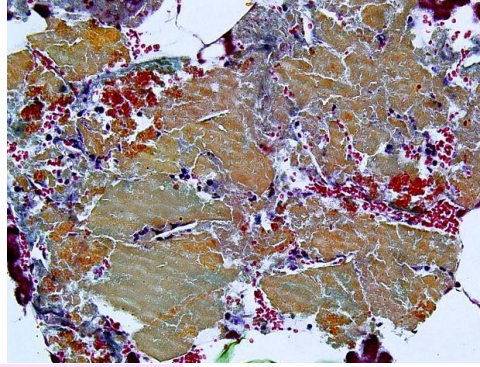
Histopathology of Thrombus



SECONDARY ENDPOINT

Aspirated thrombus	Overall N=79	Men N=40	Women N=39	P value
Thrombus volume, mm^3	6 (3-15)	6 (3-18)	6 (2-15)	0.70
Platelets presence, no. (%)	79/79 (100)	40/40 (100)	39/39 (100)	1.00
Average WBCs, no.	75 (50-150)	75 (50-200)	75 (50-150)	0.22
Plaque material, no (%)	40/79 (50.6)	20/40 (50.0)	20/39 (51.2)	0.91
Immunohistochemistry				
Myeloperoxidase, cells /5HPF	39 (26-90)	38 (24-86)	41 (26-91)	0.93
CD68, cells/5HPF	20 (10-40)	20 (10-50)	20 (10-30)	0.73
Interleukin-5, cells/5HPF	0 (0-1)	0 (0-1)	0 (0-1)	0.93
CD42b, score	2 (2-3)	2 (2-3)	2 (2-3)	0.18

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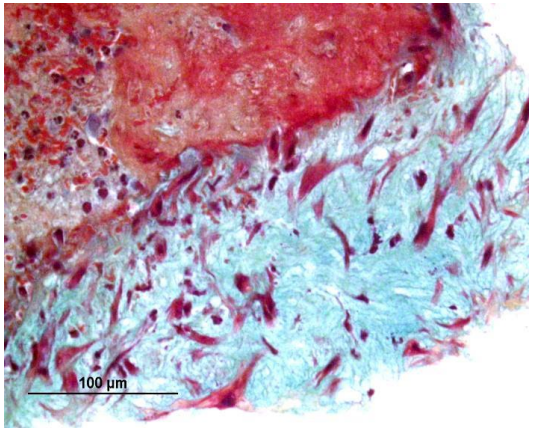
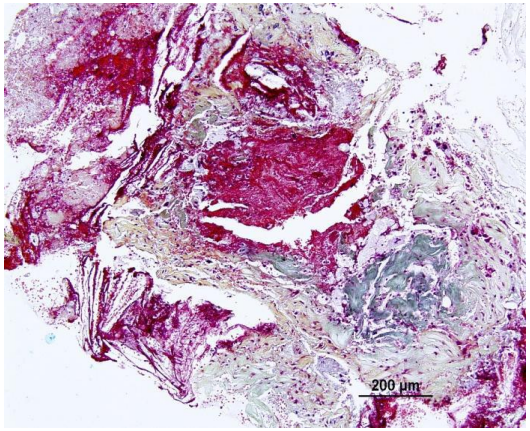
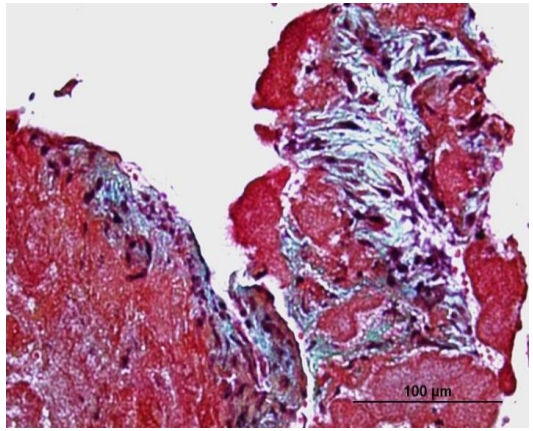
Age of the Thrombus







	Total n=79	Men n=40	Women n=39	P value
Thrombus Age				1.00
Early Thrombus	56 (70.9)	28 (70.0)	28 (69.8)	
Organized Thrombus	23 (29.1)	12 (30.0)	11 (28.2)	

- Early thrombus 0 to 3 days - alternating layers of platelets mixed with fibrin and acute inflammatory cells without organization
- Organized thrombus > 4 days presence of SMCs with or without proteoglycan matrix

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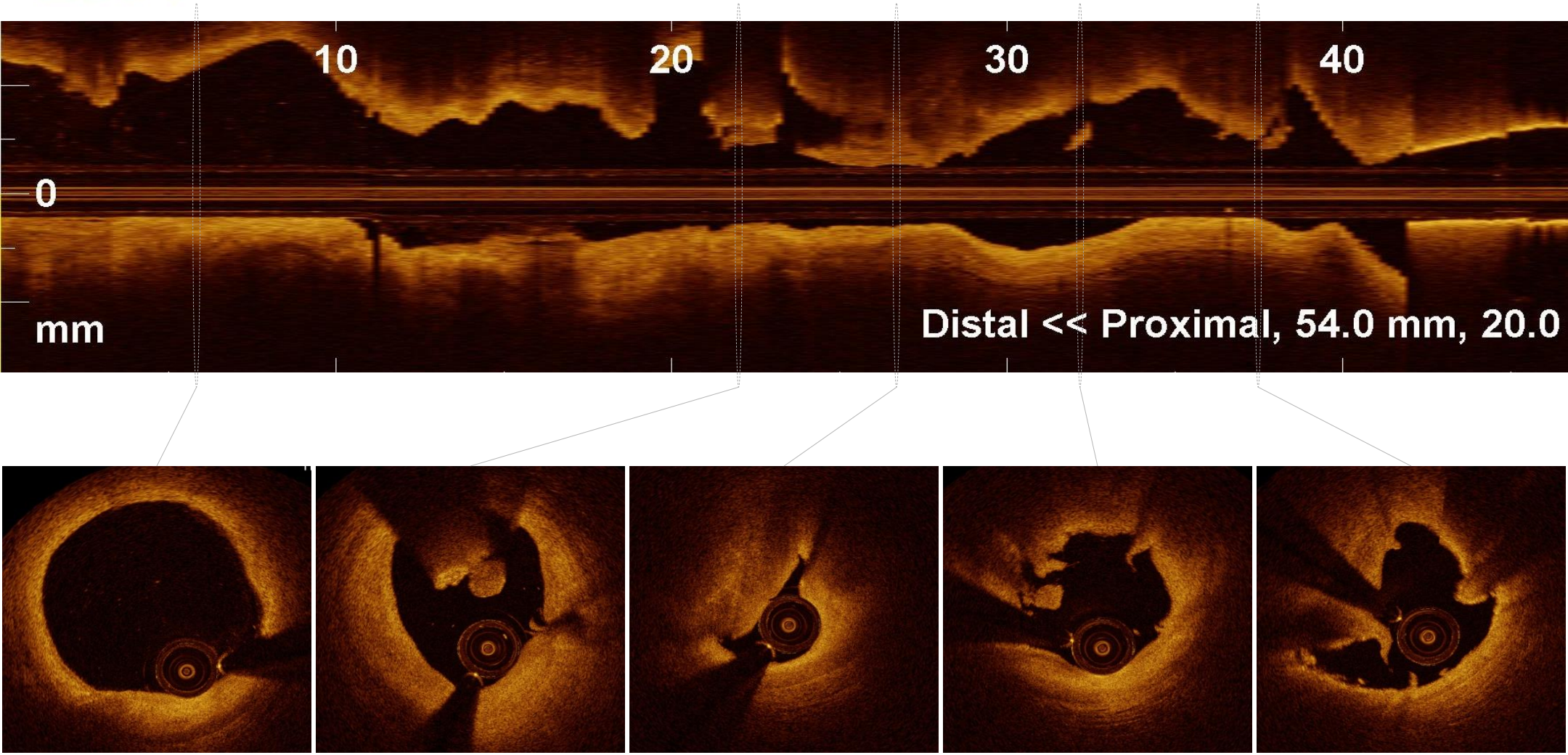
Remaining Thrombus After Aspiration*

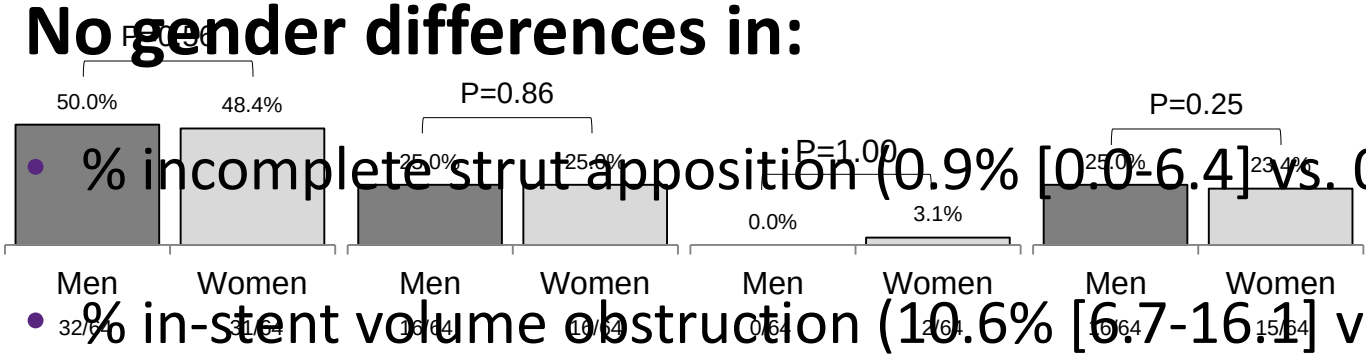


* *Regardless of device used for manual thrombectomy*

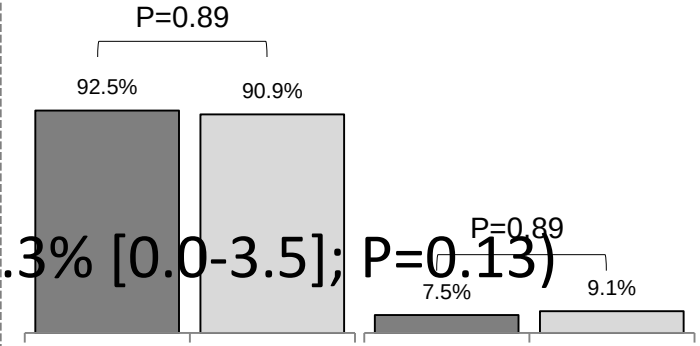
Primary Endpoints 9M Follow-up

SECONDARY ENDPOINT

Index Procedure: Culprit Plaque Morphology



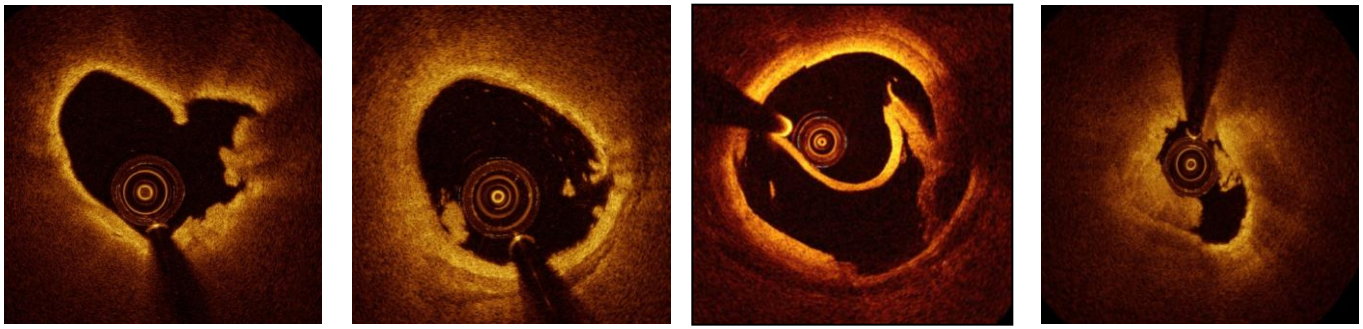
9M Follow-Up: struts coverage



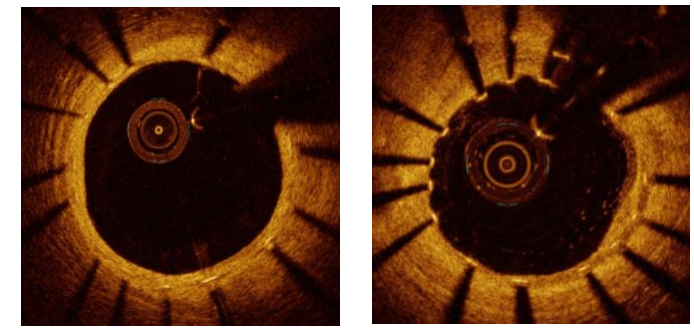
No gender differences in:

- % incomplete strut apposition (0.9% [0.0-6.4] vs. 0.3% [0.0-3.5]; P=0.13)
- % in-stent volume obstruction (10.6% [6.7-16.1] vs.10.3% [5.9-13.7]; P=0.76)

Ruptured plaques | **Non ruptured /Erosion** | **Spontaneous Dissection** | **Unclassifiable**



Covered struts | **Uncovered struts**



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Clinical Outcomes at 1 year

Variable	Overall N=140	Men N=70	Women N=70	P value
MACCE	9/140 (6.4)	5/70(7.1)	4/70 (5.7)	0.69
Death, no. (%)	6/140 (4.3)	3/70 (4.3)	3/70 (4.3)	1.00
Cardiac, no. (%)	3/140 (1.4)	1/70 (1.4)	2/70 (2.9)	0.57
Non cardiac, no. (%)	3/140 (2.9)	2/70 (2.9)	1/70 (1.4)	0.56
Reinfarction, no. (%)	2/140 (1.4)	2*/70 (2.9)	0/70 (0)	0.16
Stroke, no. (%)	1/140 (0.7)	1/70 (1.4)	0/70 (0)	0.31
Stent thrombosis, no. (%)	3/140 (2.1)	2*/70 (2.9)	1/70 (1.4)	0.55
Ischemia drivenTVR, no. (%)	5/140 (3.6)	3/70 (4.3)	2/70 (2.9)	0.69

* Cumulative events in the same patients

Study Limitations

- The entry criteria limited the enrolment to a low-intermediate risk population.
- The core laboratory was unable to classify the culprit plaque in 25% of the cases, due to the excessive remaining thrombus.
- While OCT criteria for plaque rupture are largely accepted, less explicit criteria apply for non-ruptured/eroded plaques.
- The study was not powered for clinical endpoints

Study Conclusions

OCTAVIA is the first prospective, multicenter study designed to assess, in age-matched men and women, the *in-vivo* mechanisms of STEMI and vascular response to primary PCI with current generation EES.

- In patients presenting with STEMI undergoing primary PCI, no differences in culprit plaque morphology and factors associated with coronary thrombosis were observed between age-matched men and women.
- *in-vivo* nonruptured/eroded plaques comprised 25% of all cases, with similar distribution in men and women
- Women, despite smaller vessels, also showed similar vascular healing response to EES compared with men, with high rate of complete strut coverage and low in-stent volume obstruction.

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Patients with classified vs unclassified plaques

Variable	Overall N=128	Classified N=97	Unclassified N=31	P value
Female gender, no. (%)	64/128 (50.0)	49/97 (50.5)	15/31 (48.4)	0.84
Age, years	66.3±10.8	66.7±11.1	65.1±9.8	0.48
Age group, no. (%)				0.67
≤60 years	36/128 (28.1)	26/97 (26.8)	10/31 (32.3)	
61-80 years	79/128 (61.7)	60/97 (61.9)	19/31 (61.3)	
>80 years	13/128 (10.2)	11/97 (11.3)	2/31 (6.5)	
Body Surface Area, m^2	1.8±0.2	1.8±0.2	1.9±0.2	0.32
Hypertension, no. (%)	74/128 (57.8)	53/97 (54.6)	21/31 (67.7)	0.20
Hyperlipidemia, no. (%)	37/128 (28.9)	26/97 (26.8)	11/31 (35.5)	0.35
Diabetes, no. (%)	16/128 (12.5)	10/97 (10.3)	6/31 (19.4)	0.22
Time symptom onset to cath lab, hrs	2.4 (1.7-3.4)	2.4 (1.7-3.4)	2.6 (1.6-3.8)	0.83
Pre-procedural thrombus, no. (%)	109/128 (85.2)	79/97 (81.4)	30/31 (96.8)	0.04
Use of aspiration catheter, no. (%)	107/128 (83.6)	83/97 (85.6)	24/31 (77.4)	0.29
TIMI pre 0/1, no. (%)	73/128 (57.0)	55/97 (56.7)	18/31 (58.1)	0.99

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Two Powered Co-Primary Endpoints

1. **Designed to evaluate whether culprit lesions in men with STEMI have a different probability of having a ruptured plaque morphology compared with women.**
   - Assuming a plaque rupture rate of 82% in males and 60% in females, with 1:1 assignment of 140 patients to the two groups, and 94% of the patients available for the analysis, the study would have 80% power, with 0.05 alpha (two-sided) and a superiority scope.
2. **Powered to show the non-inferiority of EES strut coverage at 9 months in women compared to men.**
   - Assuming a non-inferiority margin of 2% and a standard deviation of uncovered strut percentage of 4%, a similar 94.3% per-segment prevalence of uncovered struts in men and women, and 80% of the patients available for the analysis at 9 months, a total sample size of 140 patients would achieve 85% power and 0.05 alpha (one-sided), with a non-inferiority scope.

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