Stent-based Stabilization of Ruptured Carotid Plaques: Clinical Lessons and Biomarkers Patterns from the SUBMARINE Study, and Relevance to the Coronary Condition

Giuseppe Sangiorgi, FESC, FSCAI

San Raffaele Hospital and
Emo Centro Cuore Columbus
Milan- Italy

Interventional Vulnerable Plaque Strategies and Future Horizons
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Conflict of Interest Statement

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

❑**I have the following** potential conflicts of interest to report:

- ❑Consulting
- ❑Employment in industry
- ❑Stockholder of a healthcare company
- ❑Owner of a healthcare company
- ❑Other(s)

X **I do not have any potential conflict of interest**

Vulnerable Plaque: Investigation Plan

- Establish biological, pathological, and mechanical features of the vulnerable plaque: definition
- Look for the presence of vulnerable plaques elsewhere in the same patient
- Develop noninvasive and invasive tools to detect vulnerable plaque
- Test the performance of these tools to identify key features in plaques that have just caused ACS/Stroke/TIA
- Establish the natural history of these high-risk plaques
- Establish the potential impact of such finding on the procedural strategy and short-term outcome
- Test systemic and/or local therapies aiming at improving the natural history

Distribution of various plaque types in patients affected by CAD

* CS = coronary segments;

Plaque types	CS * of pts without SA who died for non-cardiac causes (CTRL group) (N=304)	CS * of pts with SA died for non-cardiac causes (SA group) (N=109)	CS * of pts died for AMI (AMI group) (N=544)
"Culprit plaques "with thromb.	0	0	16 (3.0%)
- associated to cap rupture	0	0	14 (2.6%)
- associated to cap erosion	0	0	2 (0.4%)
"Vulnerable plaques"	13 (4.3%)	4 (3.7%)	109 (20.0%)
- thin-fibrous cap atheromata	13 (1.0%)	0	31 (5.7%)
- superficial calcified nodule	8 (2.6%)	4 (3.7%)	31 (5.7%)
- plaques with stenosis >90%	2 (0.7%)	0	47 (8.6%)
- # vulnerable plaques/pts	1.4±0.3	0.8±0.3	6.8±0.5
"Stable plaques"	291 (95.7%)	105 (96.3%)	419 (77.0%)

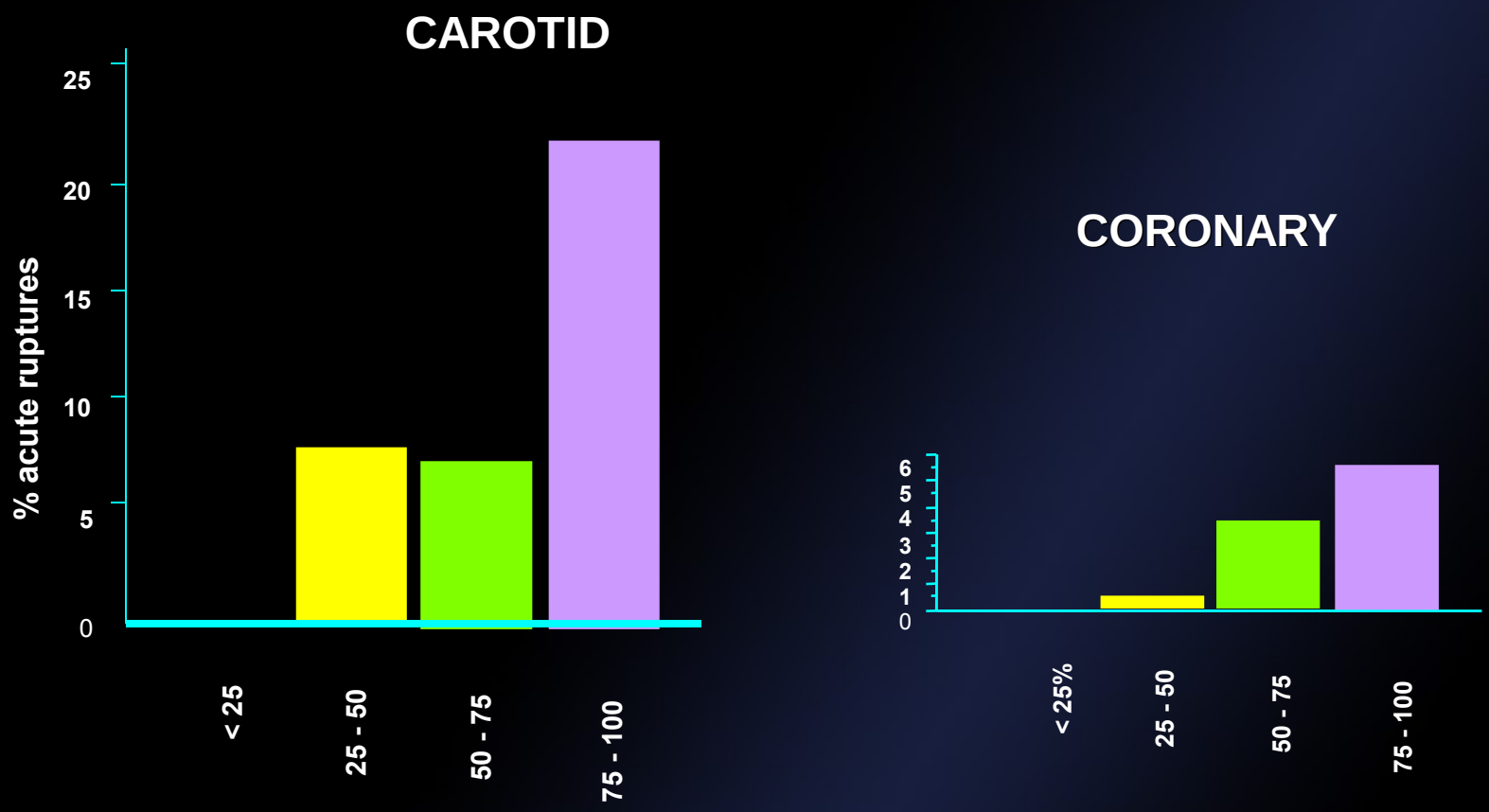
Mauriello A et al. JACC 2005; 45:1585-1593

Thrombotically Active Plaques, Cap Rupture and Cap Erosion by Disease State

	No. of Plaques			P value		
	Patients with Major Ipsilateral Stroke (N=96)	Patients with TIA (N=91)	Asymptomatic (N=82)	Stroke vs TIA	Stroke vs Asympt.	TIA vs Asympt.
Angiographic stenosis (%)						
Ipsilateral carotid	86.1	79.5	84.6	0.06	0.32	0.13
Controlateral Carotid	60.9	64.2	57.5	0.60	0.44	0.32
Thrombotically active plaque (n,%)	71 (74.0)	32 (35.2)	12 (14.6)	<0.001	<0.001	0.002
Cap Rupture	64 (66.7)	21 (23.1)	11 (13.4)	<0.001	<0.001	0.004
Cap Erosion	7 (7.3)	11 (12.1)	1 (1.2)	0.51	0.09	0.03

Spagnoli LG et al, JAMA 2004; 292:1845-1852

Frequency of acute ruptures by degree of luminal stenosis

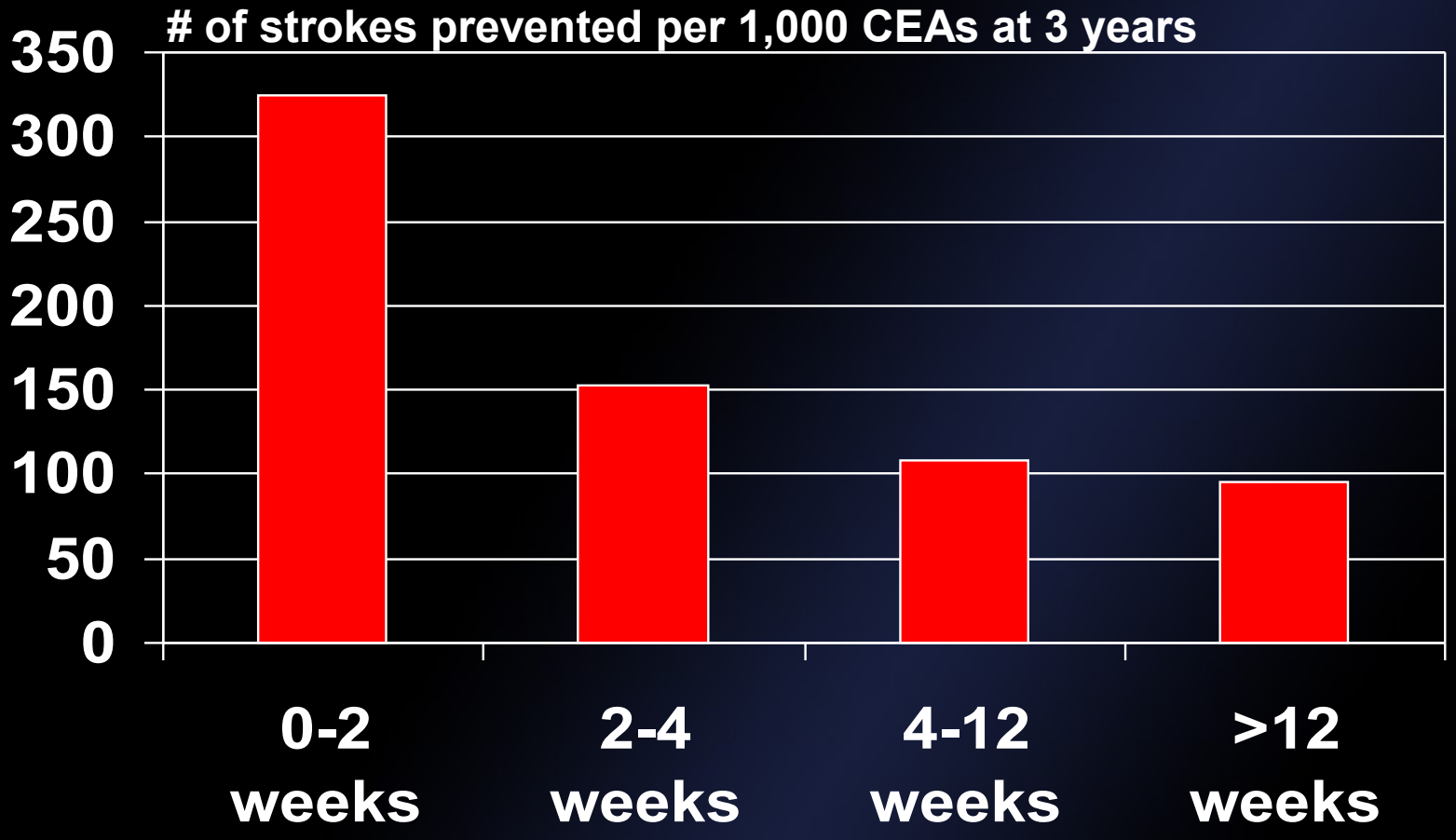


Thrombosis Related to Time Interval Between Symptom Onset and Surgery in pts with Stroke

	Time Interval between Acute Cerebrovascular Event and Endarterectomy, No %				
	0-2 mo (N=32)	3-6 mo (N=18)	7-12 mo (N=15)	13-24 mo (N=13)	25-30 mo (n=18)
Thrombotically active plaques (TAPs)	32 (100)	13 (72.2)	11 (73.3)	7 (53.8)	8 (44)
Organized thrombus	0	4 (22.2)	4 (26.7)	5 (38.5)	10 (55.6)
No thrombosis	0	1 (5.6)	0	1 (7.7)	0

Spagnoli LG et al, JAMA 2004; 292:1845-1852

Rapid Tx of Symptomatic Patients



Adapted from Rotwell 2004

JACC Vol. 32, No. 1
July 1998:283–5

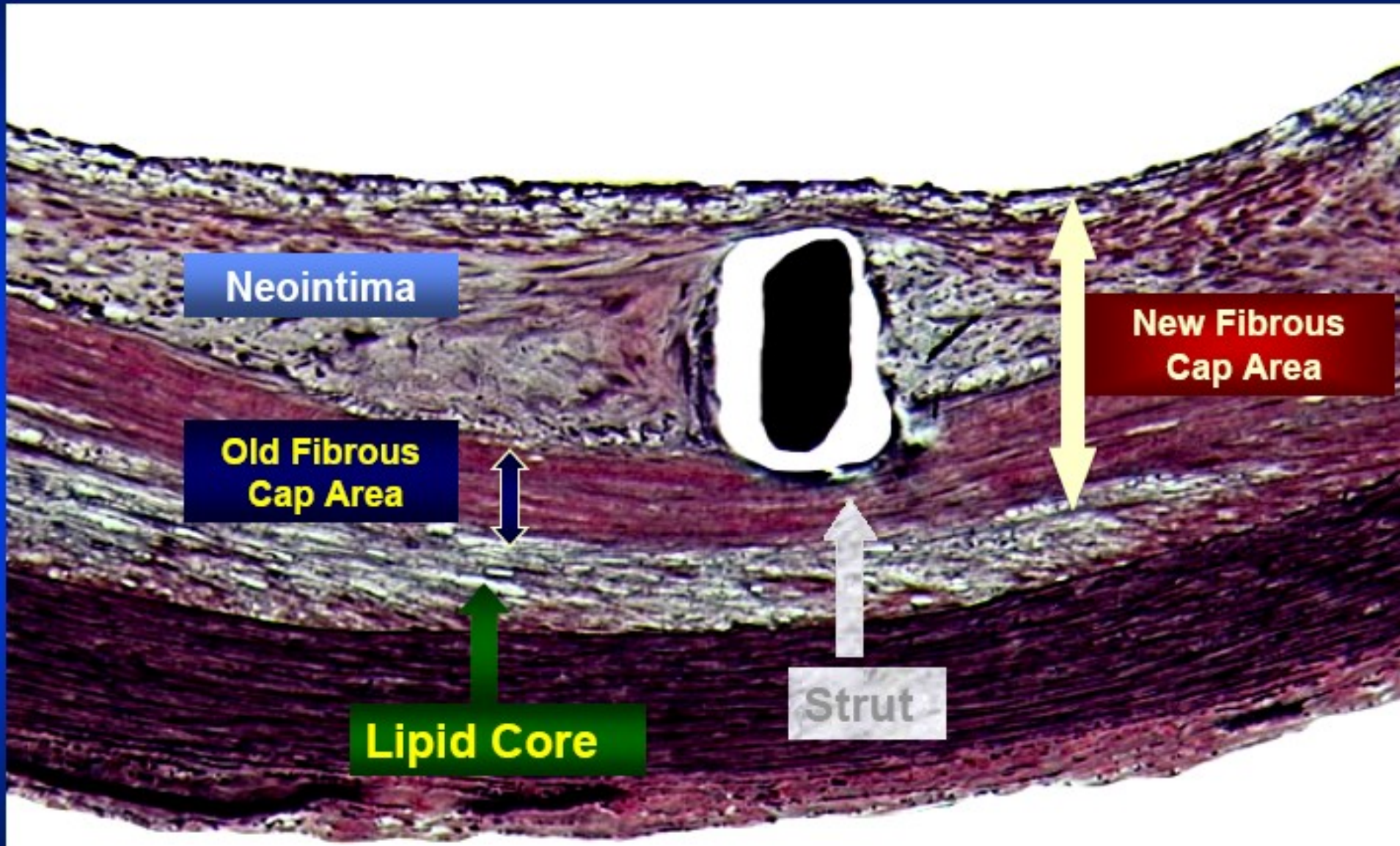
EDITORIAL

The Smooth Muscle Cell: Sinner or Saint in Restenosis and the Acute Coronary Syndromes?

ANTOINE LAFONT, MD, PETER LIBBY, MD, FACC*
Paris, France, and Boston, Massachusetts

If we could identify potentially unstable atheroma before they are evident, clinically, we might even contemplate angioplasty of nonsignificant stenoses to induce smooth muscle cell proliferation and reinforce the plaque's fibrous cap.

Strut Quantitative Measurements



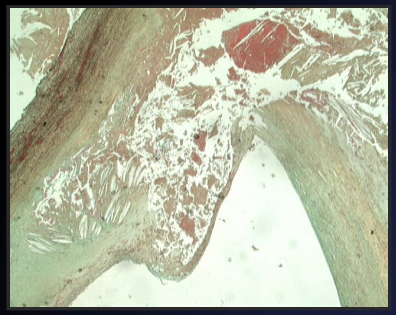
Clinical presentation, plaque types and PAPP-A levels observed in 65 carotid plaques submitted to histologic examination

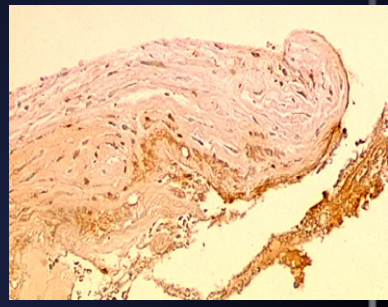
Histological Definition	Stroke (N=19)	TIA (N=24)	Asymptomatic (N=29)	PAPP-A Serum Levels (mIU/L)
Ruptured plaques (n=14)	7 (41.2%)	4 (20.0%)	3 (10.7%)	6.97±0.75
Vulnerable plaques (n=13)	5 (29.4%)	4 (20.0%)	4 (14.3%)	7.43±0.97
Stable plaques (N=38)	5 (29.4%)	12 (60.0%)	21 (75.0%)	4.02±0.18*

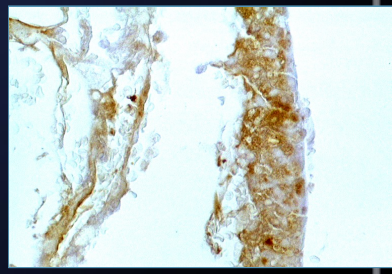
*p<0.02 Rupt/vuln vs. stable

Sangiorgi G et al, JACC 2006;47:2201-2211

Correlation PAPP-A / Cap Thickness







Correlation Coefficient = -0.6296 P<0.01

y = -53,177x + 219,96

R^2 = 0,3964

Cap Thickness (microns)

500
450
400
350
300
250
200
150
100
50
0

0
0,5
1
1,5
2
2,5
3
3,5

PAPP score

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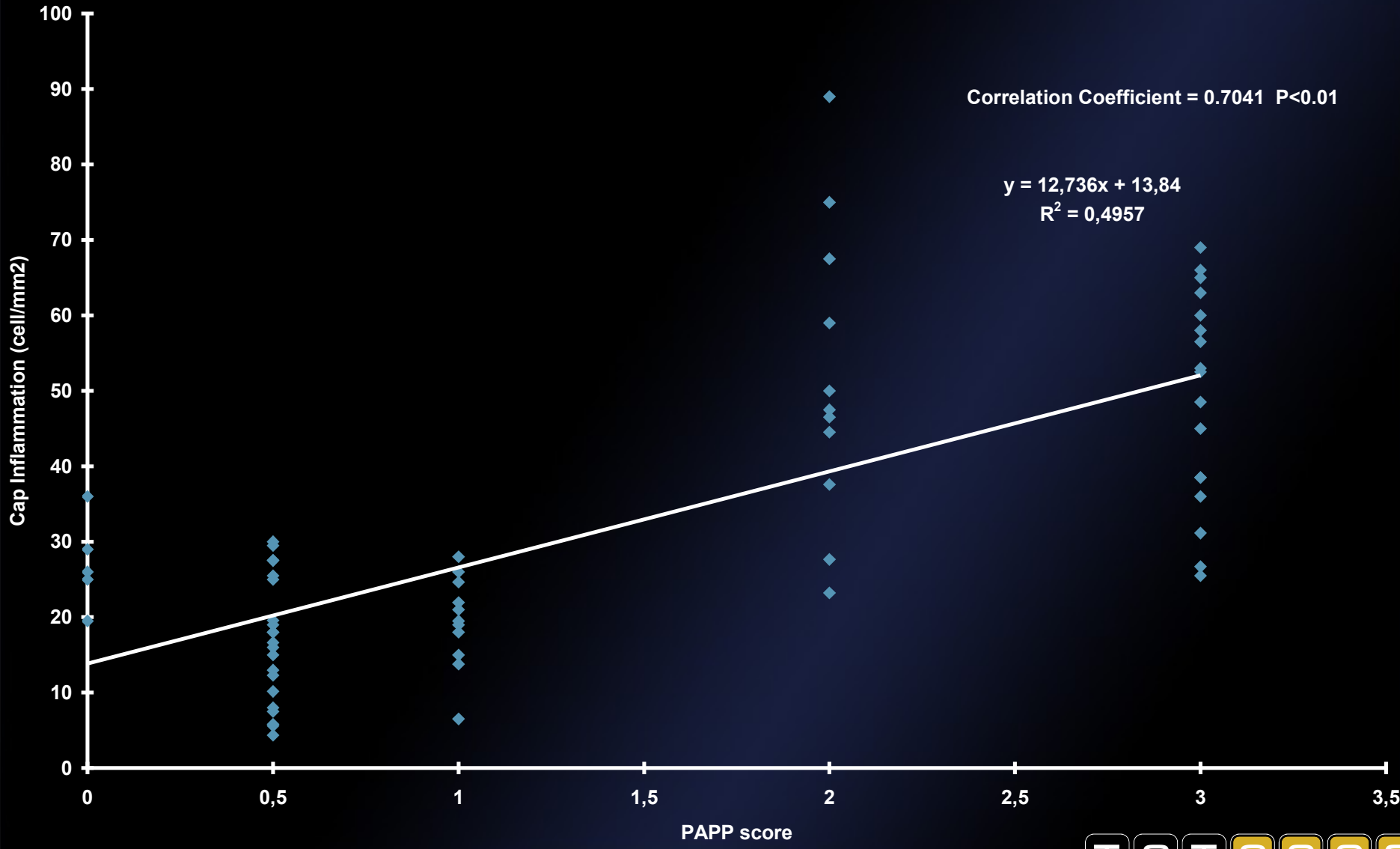
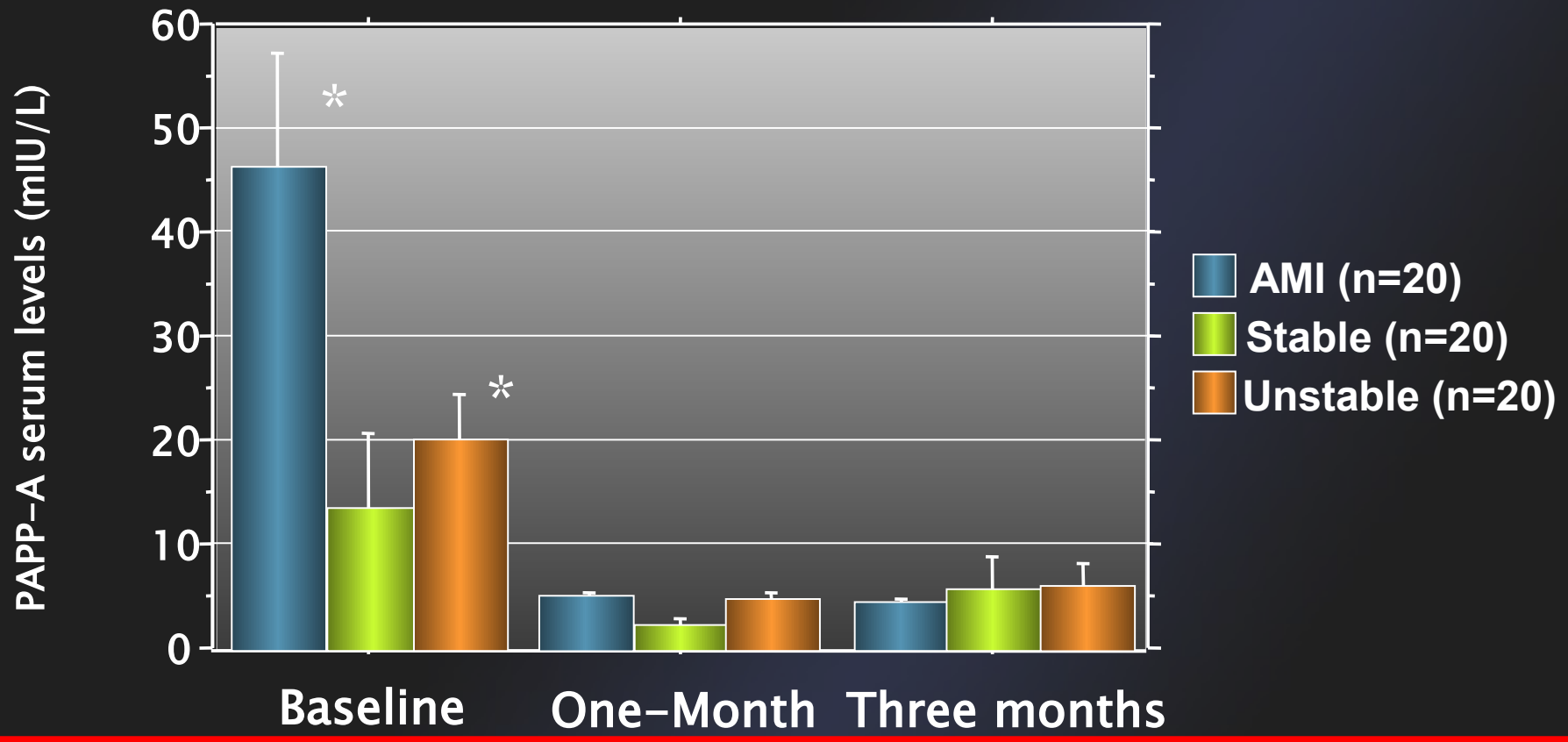
Correlation PAPP-A / Plaque Inflammation



PAPP-A Serologic Levels in Pts with Single Coronary Lesion after Stenting



P <.005 Baseline vs. 1 month vs. 3months

Sangiorgi G. et al. Eur Heart J 2002

SUBMARINE Study Design

SERUM AND URINARY PLAQUE VULNERABILITY BIOMARKERS DETECTION BEFORE AND AFTER CAROTID STENT IMPLANTATION

Minor Stroke

or First/Recurrent TIAs

Neurologic Assessment
Duplex Examination

Early CAS with NP Filter

SUBMARINE Study Design

SERUM AND URINARY PLAQUE VULNERABILITY BIOMARKERS DETECTION BEFORE AND AFTER CAROTID STENT IMPLANTATION

Minor Stroke
or First/Recurrent TIAs

Neurologic Assessment
Duplex Examination

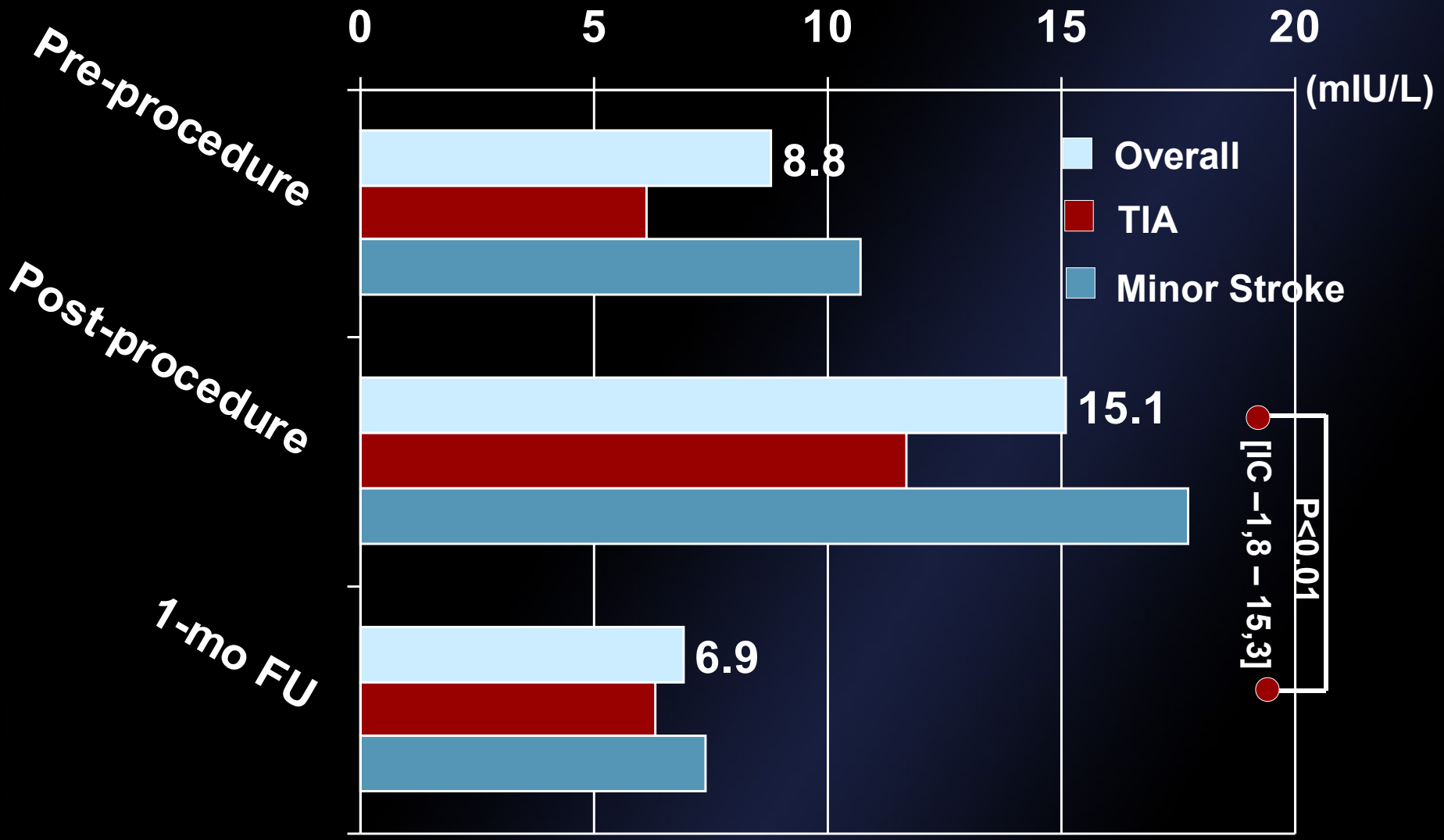
PAPP-A
hs-CRP
MMP-2/MMP-9
IL-6/IL-8
TNF alpha
CD40L

TIA
24/48 hrs
Minor Stroke
14-30 days

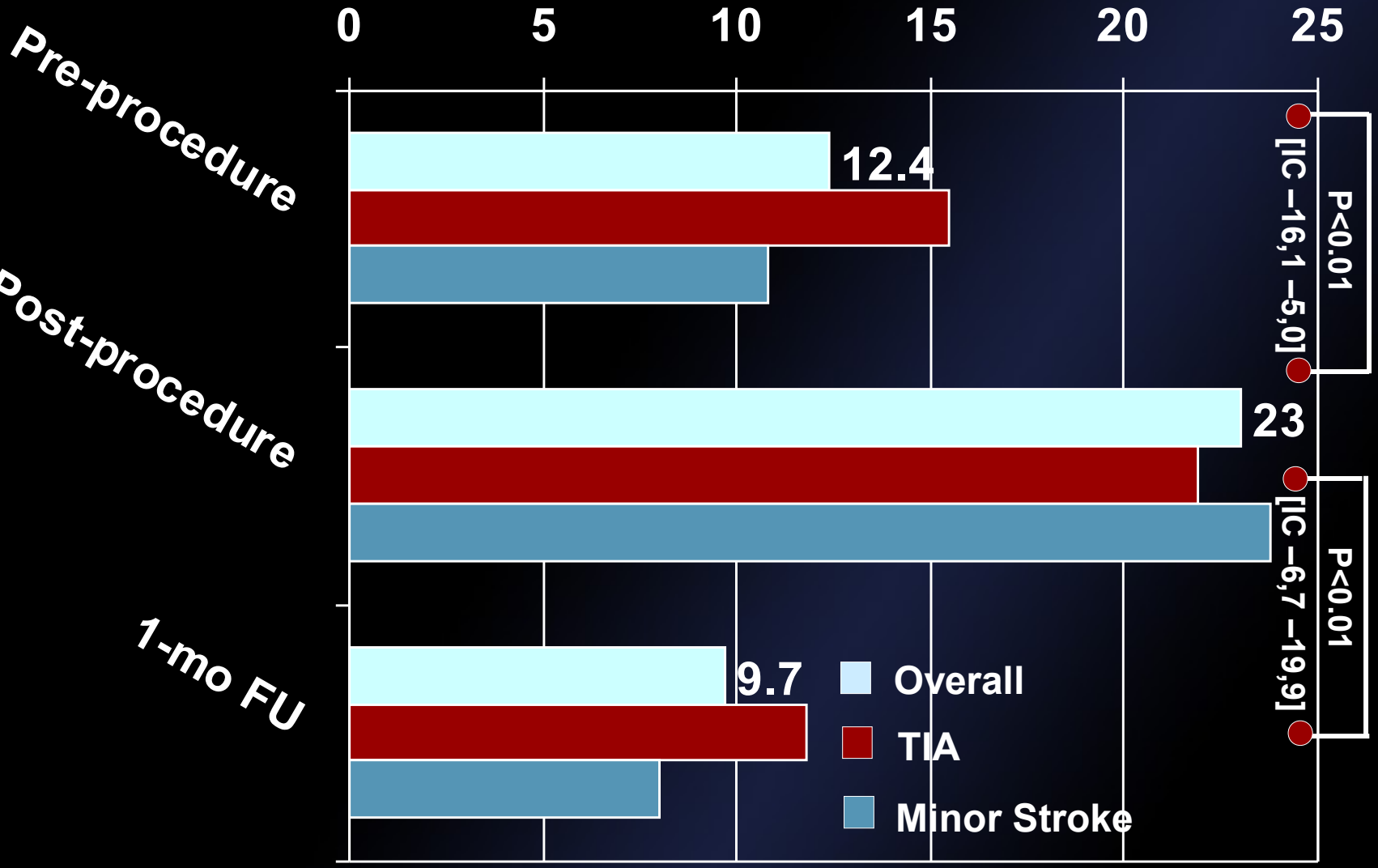
Histologic evaluation of plaque debris

Assessment of Vulnerability
Biomarkers at Pre-Post- and FU

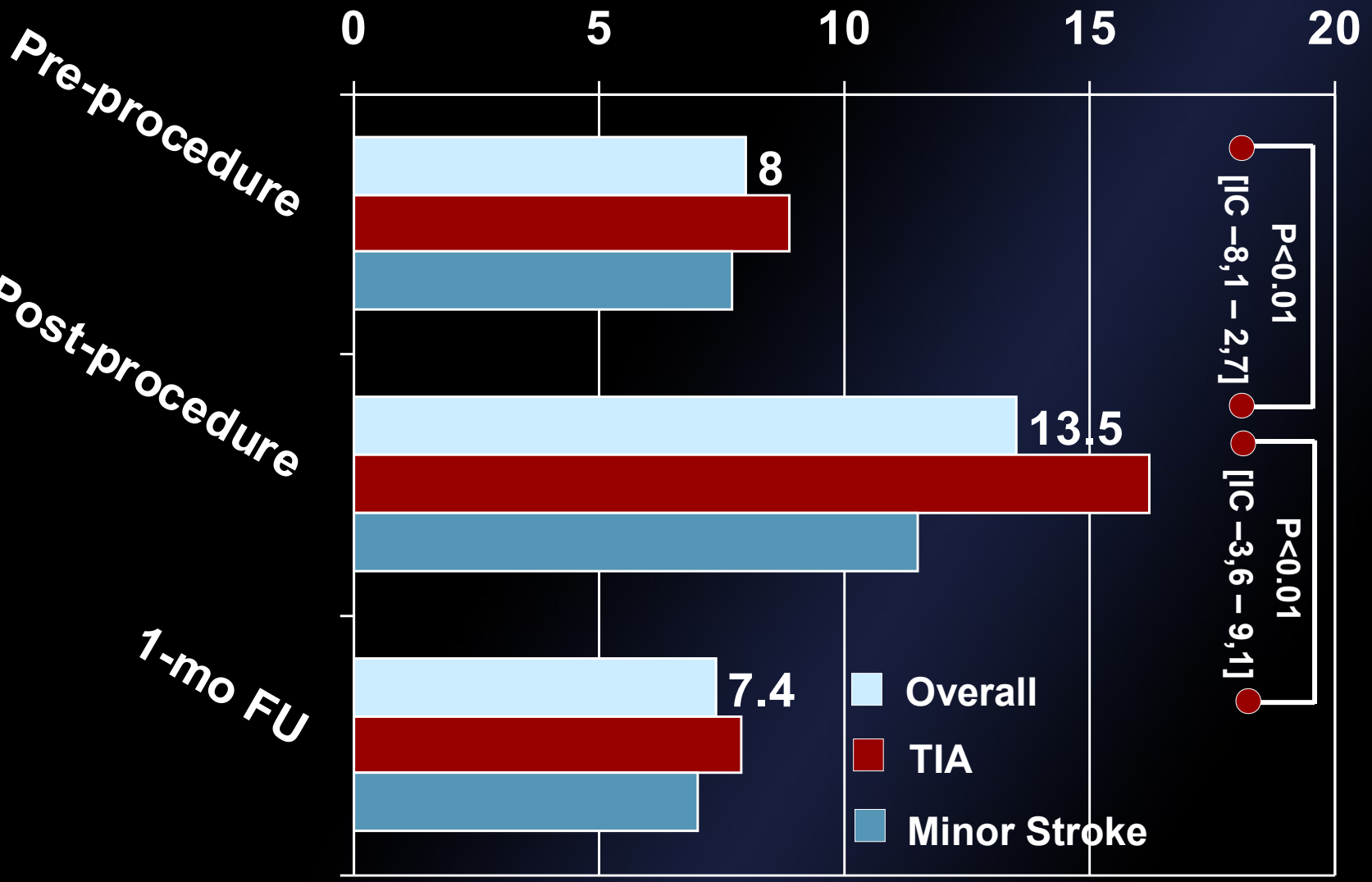
PAPP-A Serologic Levels at Different Time Intervals



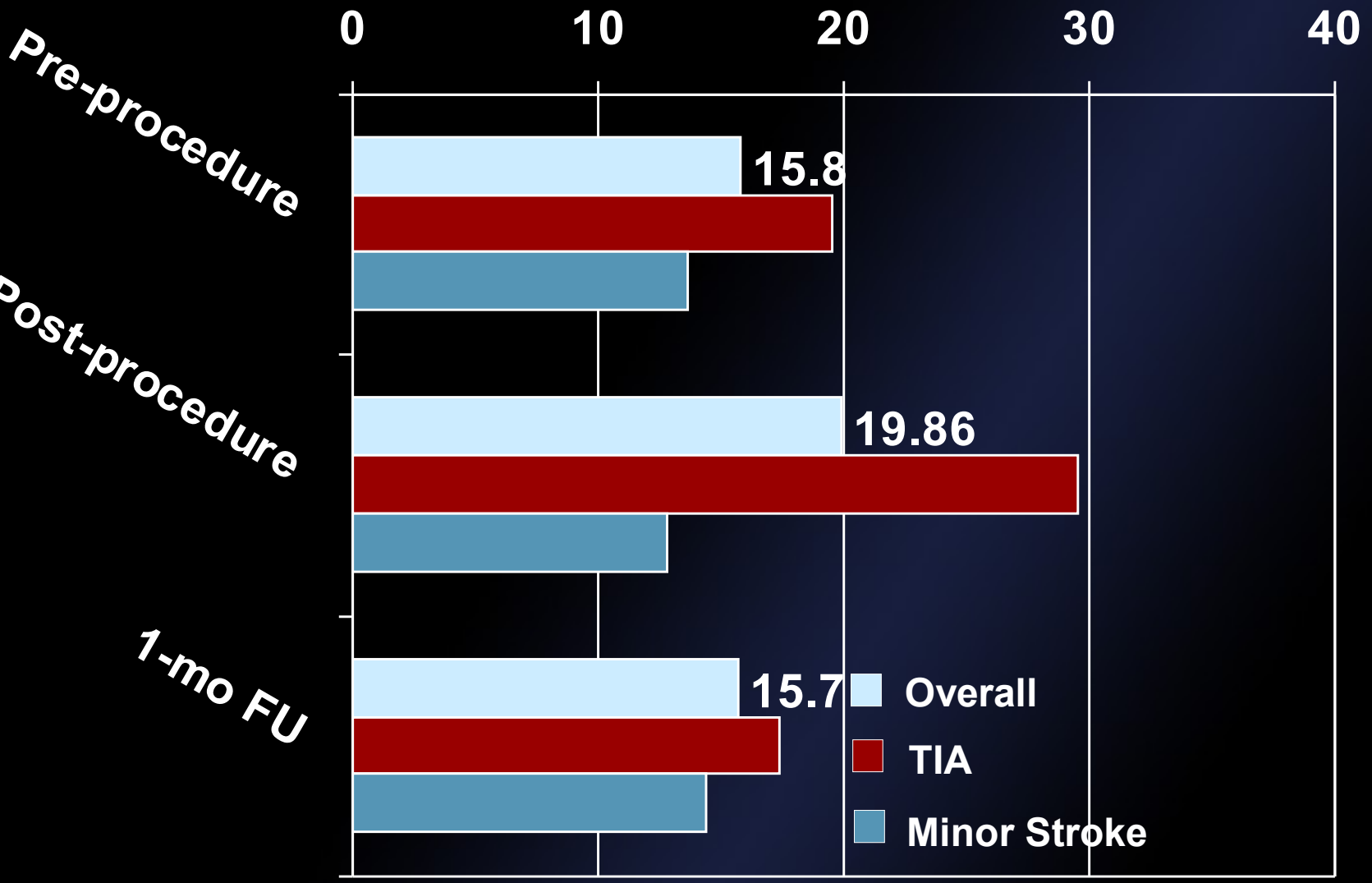
hs-CRP Serologic Levels at Different Time Intervals



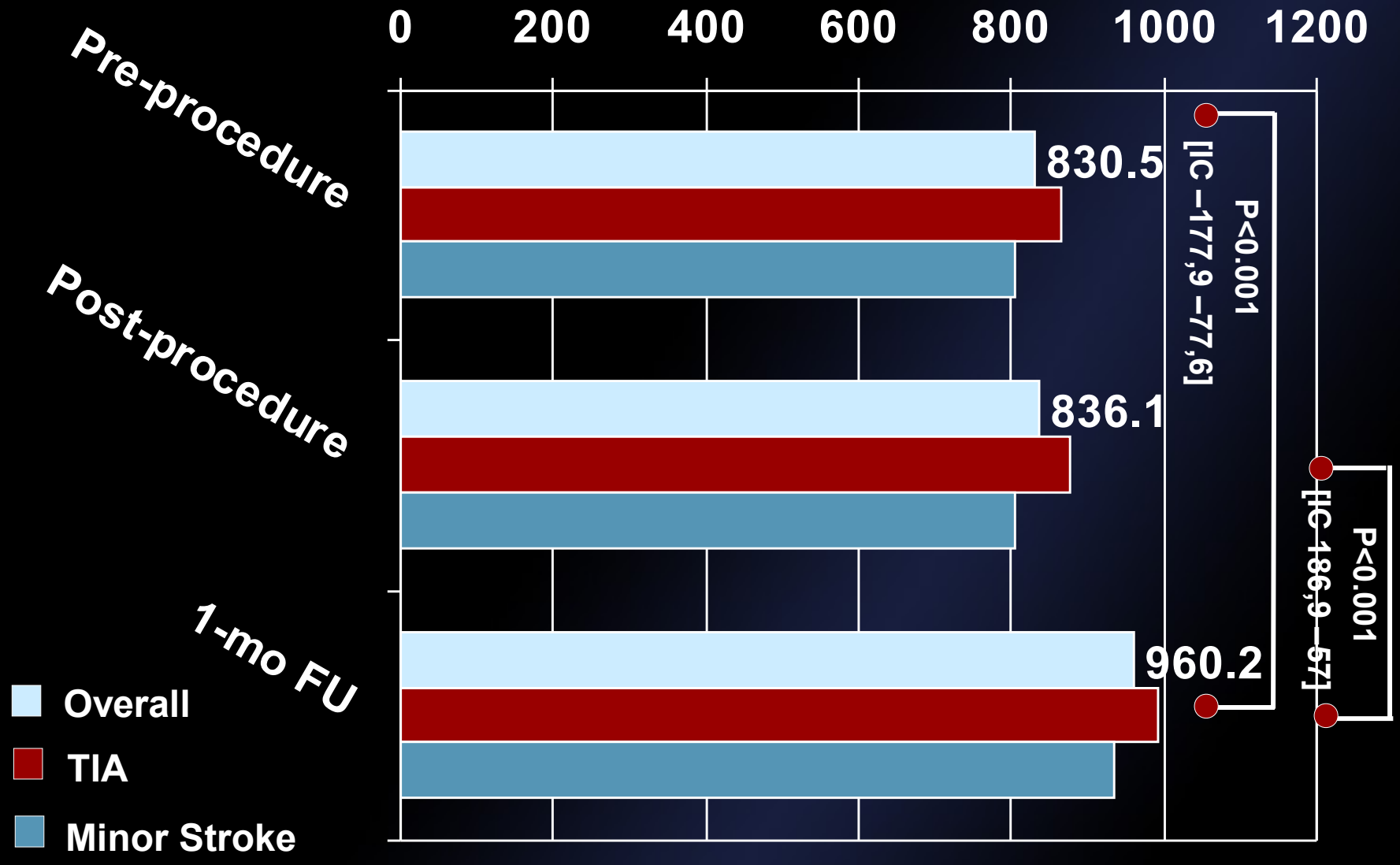
IL-6 Serologic Levels at Different Time Intervals



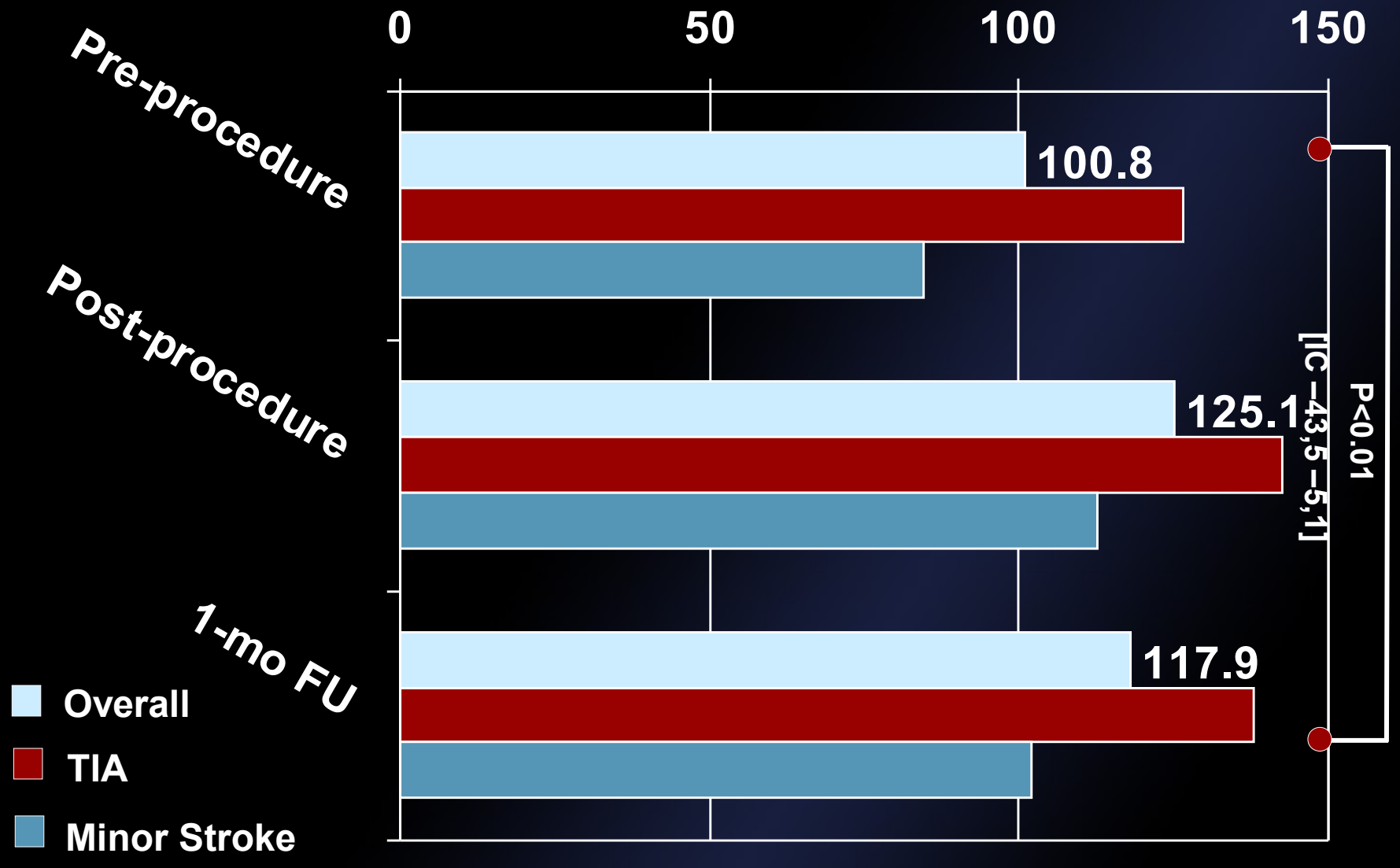
IL-8 Serologic Levels at Different Time Intervals



MMP-2 Serologic Levels at Different Time Intervals



MMP-9 Serologic Levels at Different Time Intervals



Conclusions

- Plaque vulnerability biomarkers are elevated at symptoms onset both in coronary and carotids plaques due to the related complex plaque characteristics
- Different biomarkers levels increase after stenting and at 1 month follow-up are significantly reduced to a level similar to the corresponding baseline time.
- Longer follow-up data are expected to demonstrate possible complete mechanical plaque stabilization