VH Registry and Clinical Trial Data Review

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Introduction

- VH-IVUS is one of the most studied diagnostic tool in medicine.
- After only four years in the clinical arena there are more than 70 publications on VH-IVUS, and many more in preparation.
- This presentation will give only a brief overview of these studies with emphasis on the VH registry.†

Global VH Registry

Total enrollment of 3002 patients complete

First Interim Analysis of 990 patients

Registry Design

- Global, prospective, multi-center, non-randomized registry
- Duration of Registry
  - Spring 2004; Planned conclusion – December 2006
  - Focus in 2006 on re-enrolled patients
- Principle Investigators
  - Marty Leon, MD & Robert Schwartz, MD
  - Patrick Serruys, MD, PhD
  - O. Katoh, MD & T. Suzuki, MD
- IVUS & VH IVUS Core Laboratories
  - Cardiovascular Research Foundation (CRF)
  - Cardialysis-ErasmusMC Research Lab
  - Toyohashi Medical Center
- Database
  - Pacific Data Design, California
- Status
  - Enrollment closed at n=3002 at 42 centers

Materials / Methods

- Materials
  - IVG3 with VH™IVUS Software
  - Eagle Eye™ Catheter
  - TrakBack Pullback / R-100 Pullback Devices

- Methods
  - Standard IVUS Procedure performed
  - Motorized pullback speed 0.5mm/sec
  - VH IVUS data stored on DVD and sent to core lab (Cardialysis, Rotterdam, and Cardiovascular Research Foundation, CRF, New York, for analysis
  - Data Base: Pacific Data Design, California
  - Data was analyzed using the JMP® statistical software
  - Statistical Analysis: Roseann M. White, Statistical Fellow, Abbot Vascular and M Pauliina Margolis, MD, PhD, Medical Director of Volcano Corp.

Patient Population

- Inclusion Criteria
  - Patients indicated for IVUS examination of their coronary arteries.
  - Age ≥ than 18 years old.
- Exclusion Criteria
  - Contraindicated for IVUS examination.

Volcano Global Registry Centers

- US
  - Mid America Heart, Kansas City, MO
  - Mayo Clinic, MN
  - Mt. Sinai, Miami FL
  - Columbia Medical Center, New York
  - Pinnacle Health, Harrisburg PA
  - UC Davis, CA
  - Mt. Clemens, MI
  - Arizona Heart, Phoenix, AZ
  - Cleveland Clinic Foundation, Cleveland OH
  - Winchester Medical, VA
  - Forsyth Medical Center, NC
  - St. Louis University, MO
  - St. Francis, IN
  - Nebraska Heart, NE

- Japan
  - Toyohashi Hear Center, Aichi
  - Rinku General Medical Center, Osaka
  - Nihon University Itabashi Hospital, Tokyo

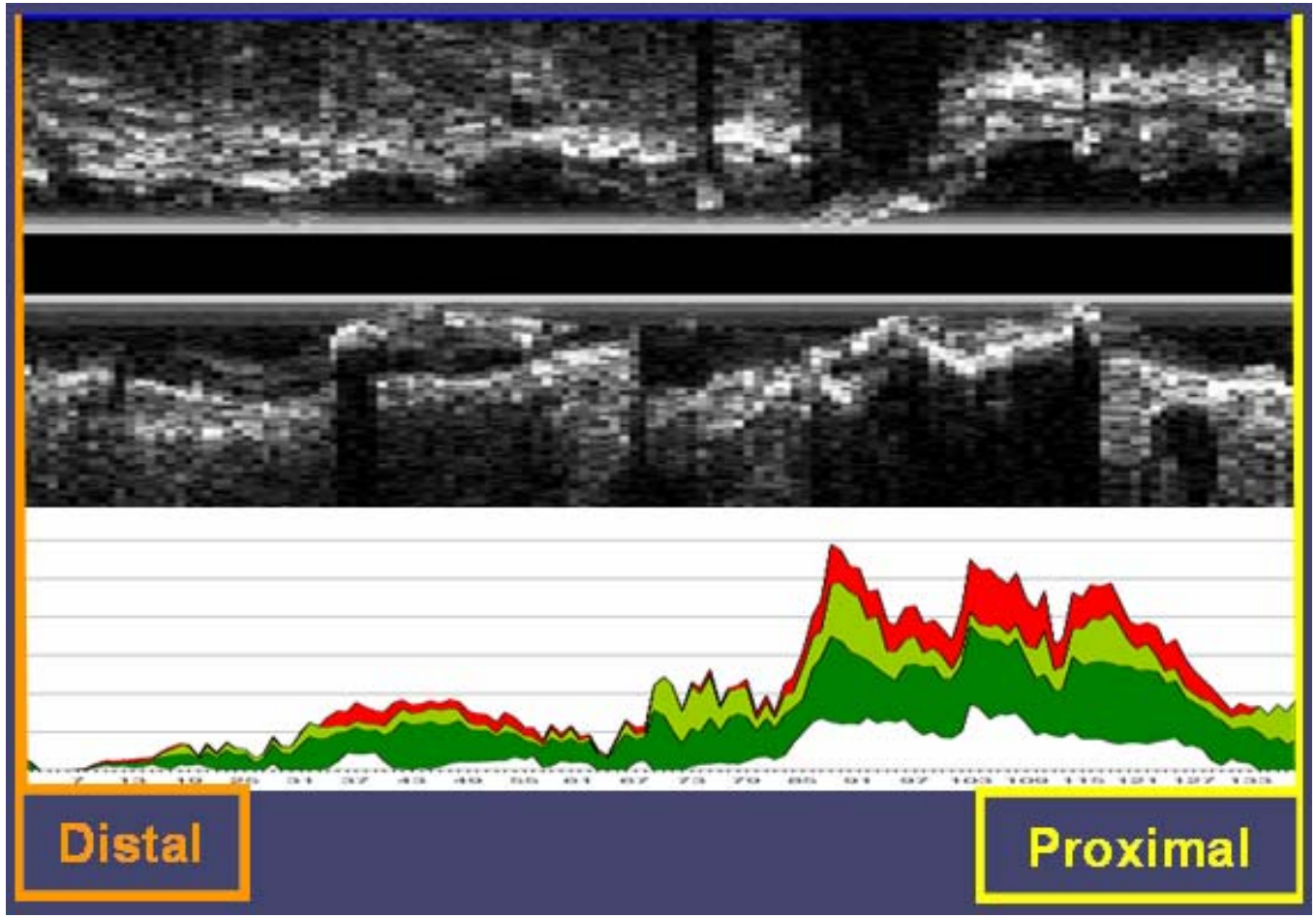
- Europe
  - Klinikum Innenstadt, Munich
  - Herz- und Neurozentrum Kreuzlingen
  - Haukeland University Hospital, Bergen
  - OLVZ, Aalst
  - University Hospital,Essen
  - Ichilov, Tel Aviv
  - Hospital Santa Marta, Lisabon
  - AKH, Vienna
  - Cliniche Gavazzeni, Bergamo
  - University Hospital Leiden, Leiden
  - Meixoeiro Hospital, Vigo
  - Valdecilla, Santander
  - Clinico San Carlos, Madrid
  - Jagiellonian University Hospital, Krakow
  - Clinica Humanitas, Rozzano
  - Centre Hospitalier Universitaire Jean-Minjoz, Besancon
  - Rabin Medical Center Golda, Petah Tiqwa
  - University Hospital, Lund
  - CHU Vaudois, Lausanne
  - Erasmus University Thoraxcenter, Rotterdam
  - San Giovanni Hospital, Roma

O b j e c t i v e
Evaluate Correlation Between:

- VH™IVUS data –
  - Whole vessel analysis (entire pullback, artery analysis)
  - Regional (lesion specific analysis)
- Patient data such as:
  - Demographics
  - Clinical presentation
  - Risk factors identified for coronary artery disease

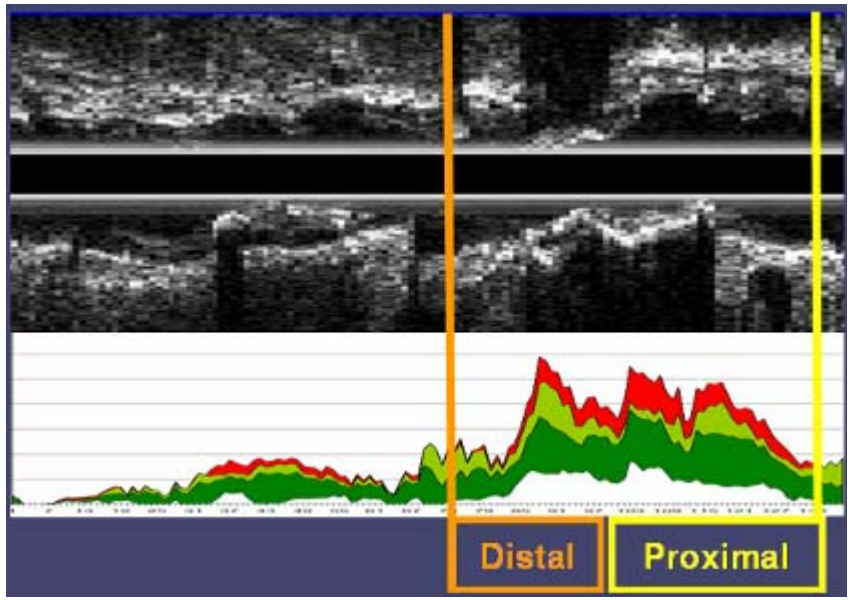
Whole Vessel Analysis - Entire Pullback

- ✓Average Cross Sectional Area (mm^2).
- ✓Total volume (mm^3) and % of total volume of different plaque components.
- ✓Plaque burden.
- ✓Vessel and lumen diameters of the ENTIRE PULLBACK.

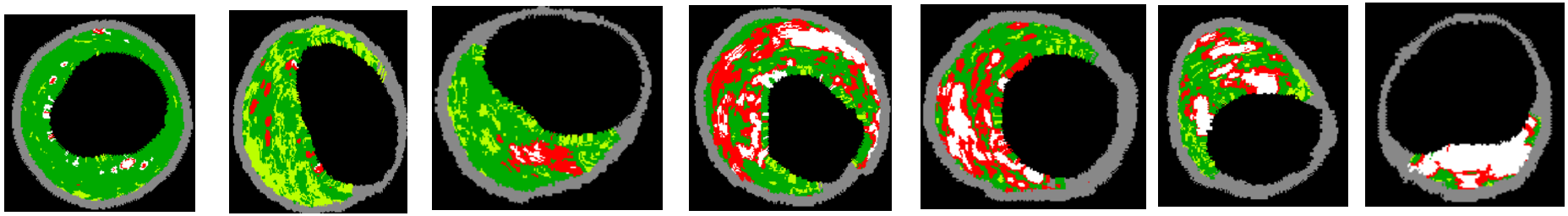


Lesion Analysis

- ✓Total volume (mm^3) and % of total volume of different plaque components.
- ✓Vessel and lumen diameters of the LESION.
- ✓Plaque burden.
- ✓Average Cross Sectional Area (mm^2).
- ✓Plaque classification.



Fibrotic | **Pathological Intimal Thickening** | **FibroAtheroma** | **FA Calcified** | **Thin Cap FA** | **TICFA with previous ruptures** | **Fibrocalcific**



Patient Demographics

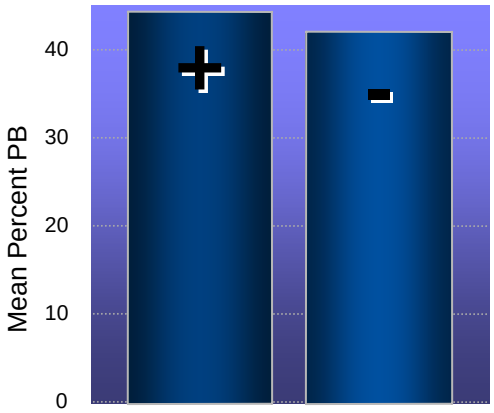
N	990
Age (mean ± SD)	62.2 ± 11.4
% Female (n)	24.5% (243)
% Diabetes (n)	24.5% (241)
% Insulin Dependent (n)	6.2% (61)
% Current Smoker (n)	26.4% (255)
% Hypertension (n)	63.9% (629)
% Prior MI (n)	28% (272)
% Congestive Heart Failure (n)	6.6% (65)
% Family History of CAD (n)	47.1% (427)
% Chr. Inflammatory Disease (n)	2.8% (24)
% Dyslipidemia (n)	66.2% (645)

Clinical Presentation

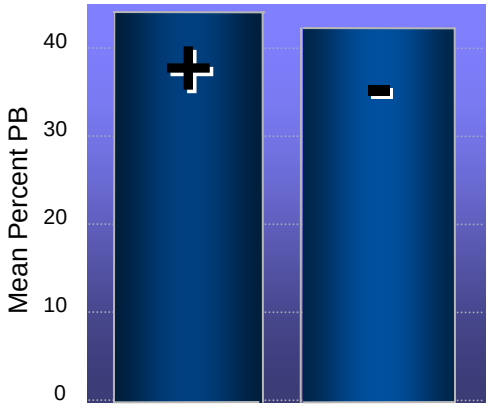
MI (Q-Wave/non Q-Wave)	18.0% (187)
Unstable Angina	21.7% (215)
Stable Angina	43.6% (431)
No Angina	15.8% (156)
Missing	1
Target Lesion Type	N=990
DeNovo	804
In-stent Restenosis[1]	67
Other restenosis	39
Unknown	80

[1]**Stented region excluded from the VH analysis**

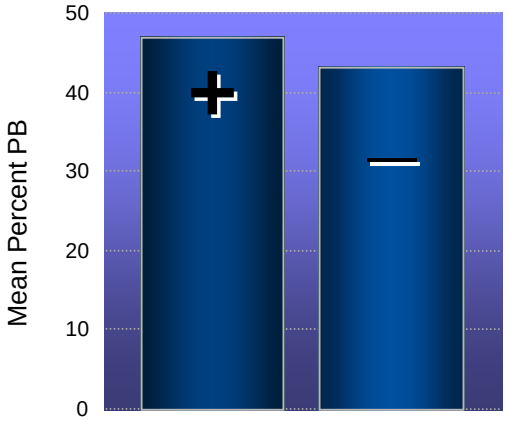
Grayscale IVUS shows that Mean % Plaque Burden and Mean Plaque Area (PA, mm^2) Correlate well with Known Risk Factors for CAD and Ischemia



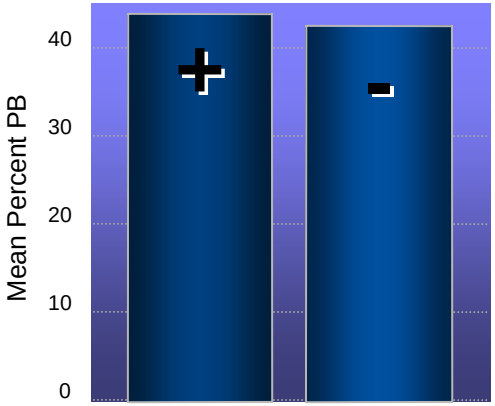
Prior Cardiac History
p < 0.001 (PA p < 0.01)



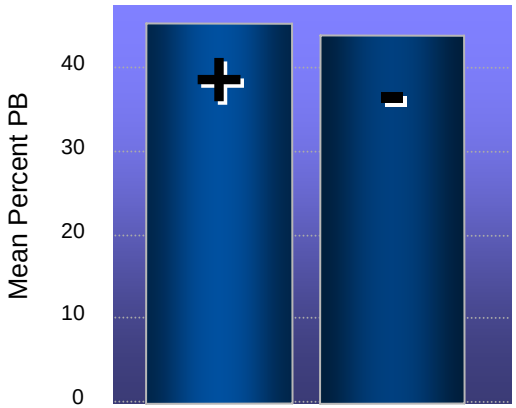
Hypertension
p = 0.001 (PA p< 0.05)



Insulin Dependent DM
p = 0.001 (PA p < 0.05)



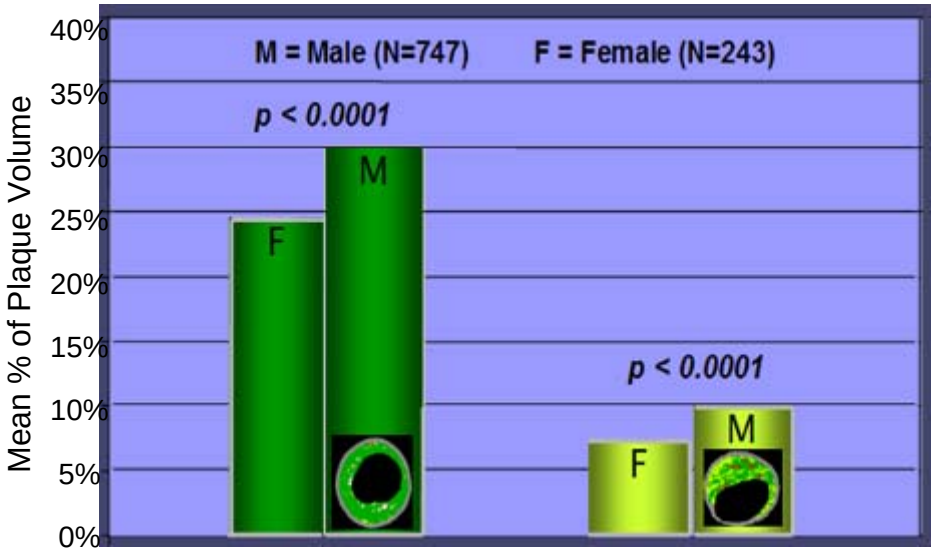
Lipid Disorder
p < 0.05 (PA ns)



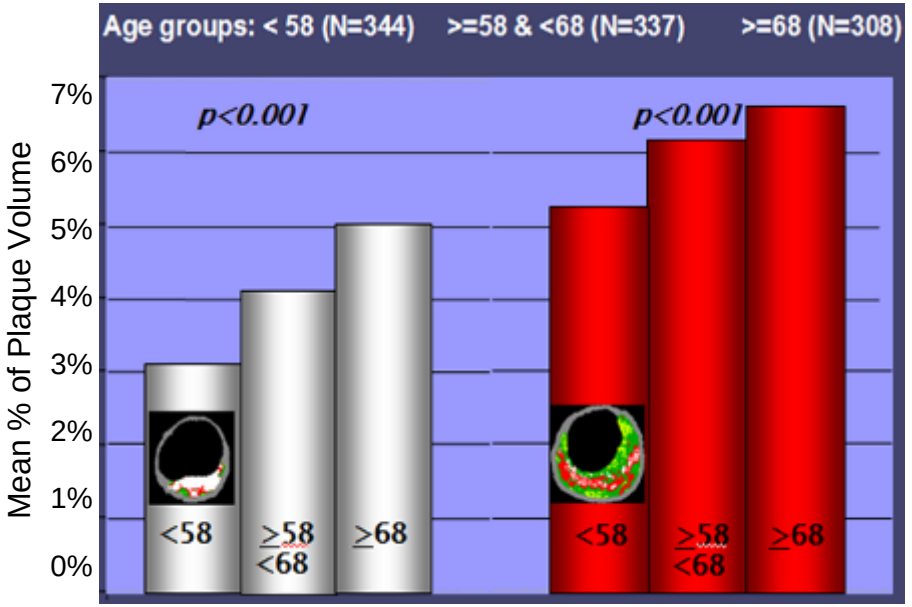
Ischemia on ECG
p < 0.05 (PA ns)

VH IVUS Demonstrates More Detailed and Significant Correlations with Previous Postmortem Data

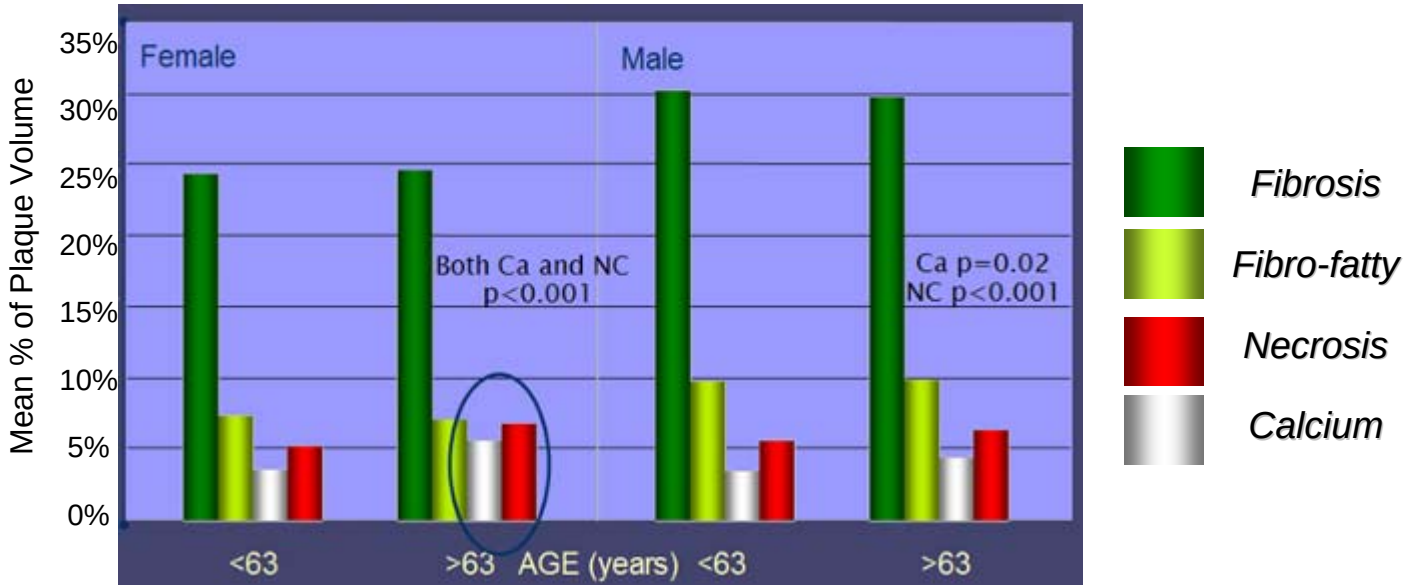
SEX



AGE

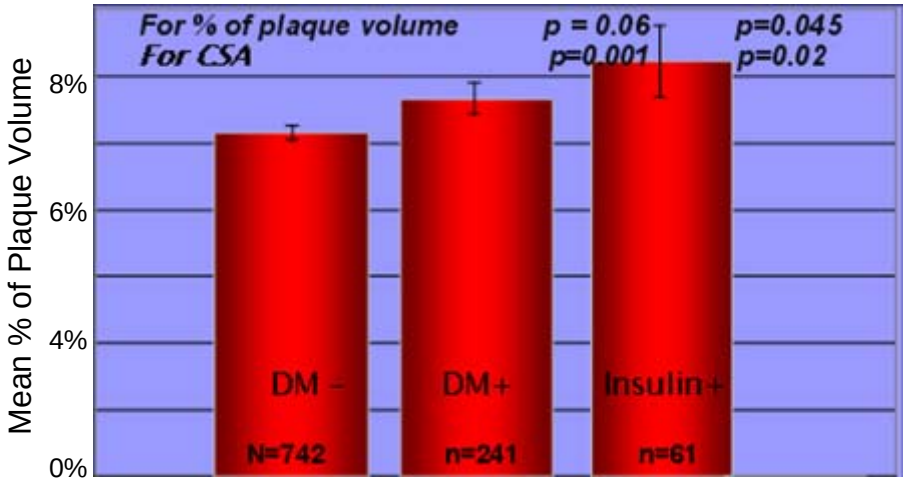


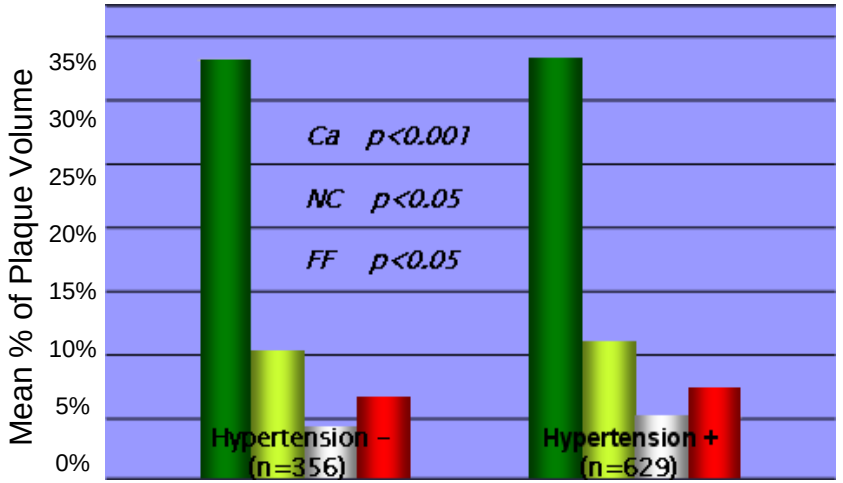
AGE + SEX

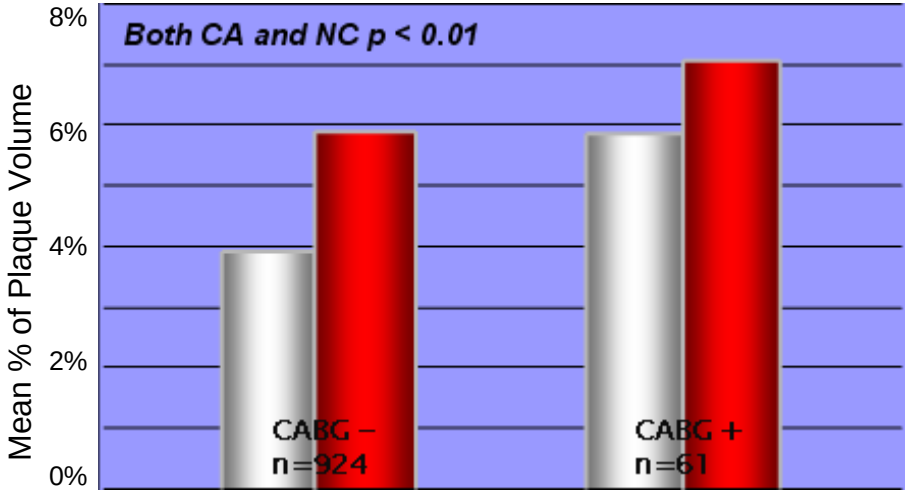


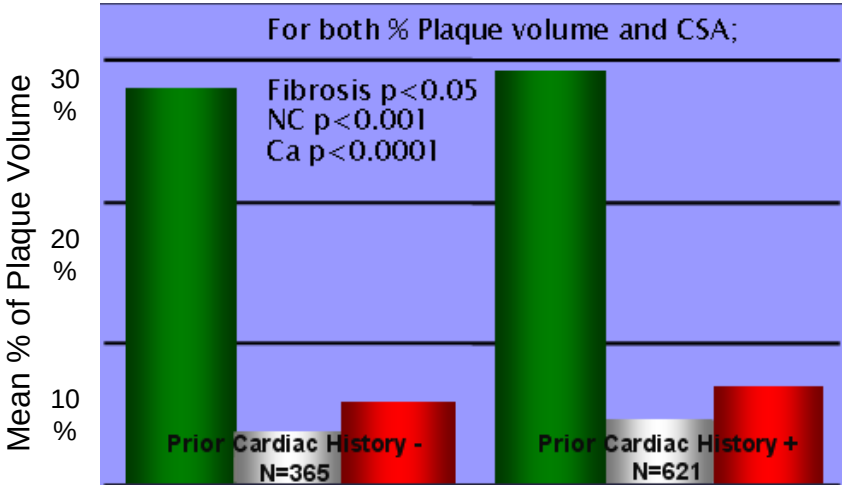
Fibrosis
Fibro-fatty
Necrosis
Calcium

Significant Correlations with Known Risk Factors for CAD

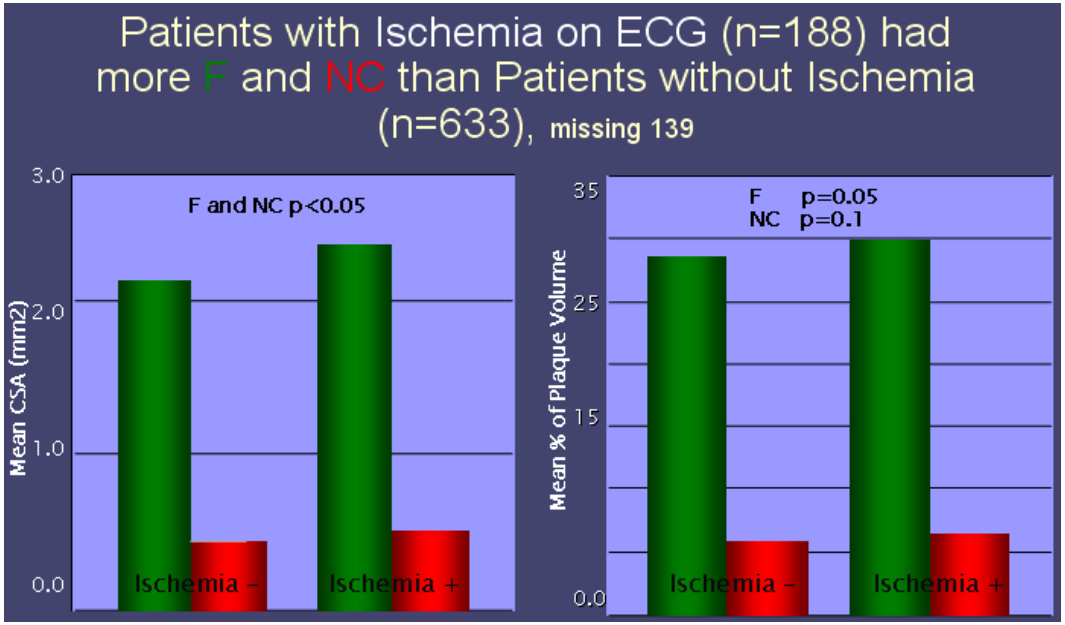


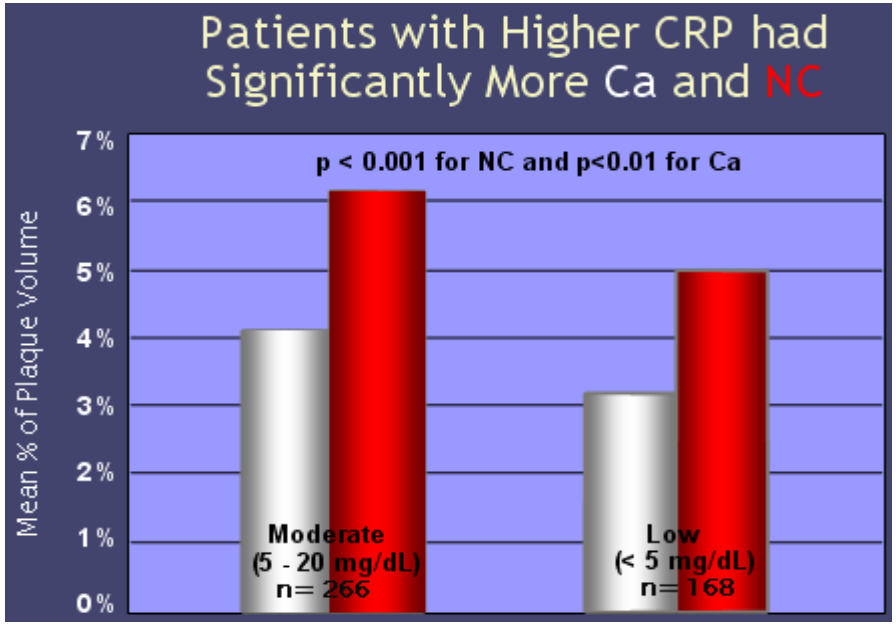


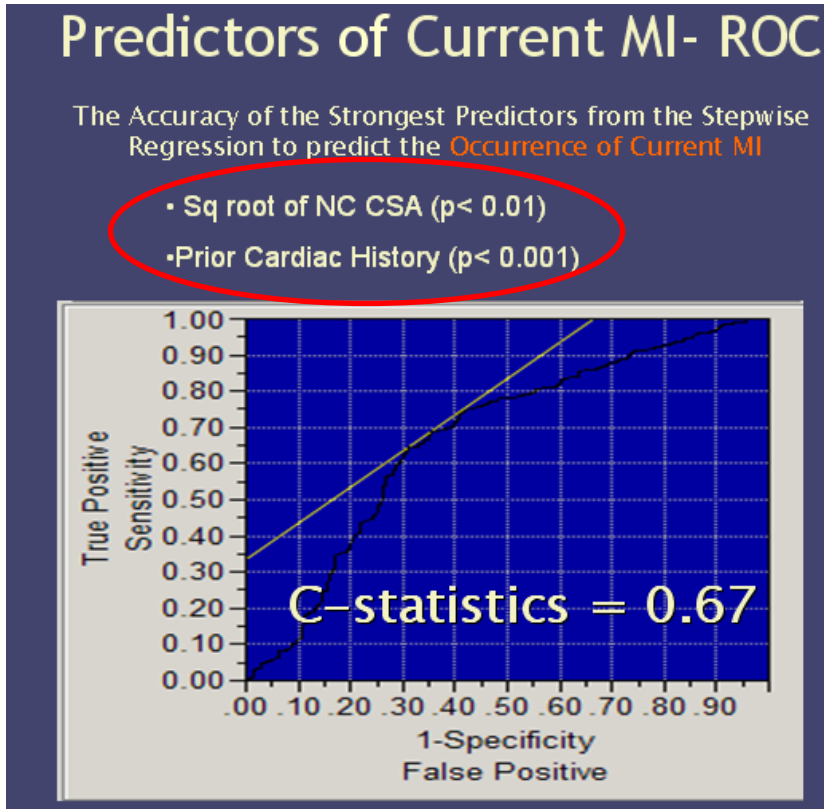




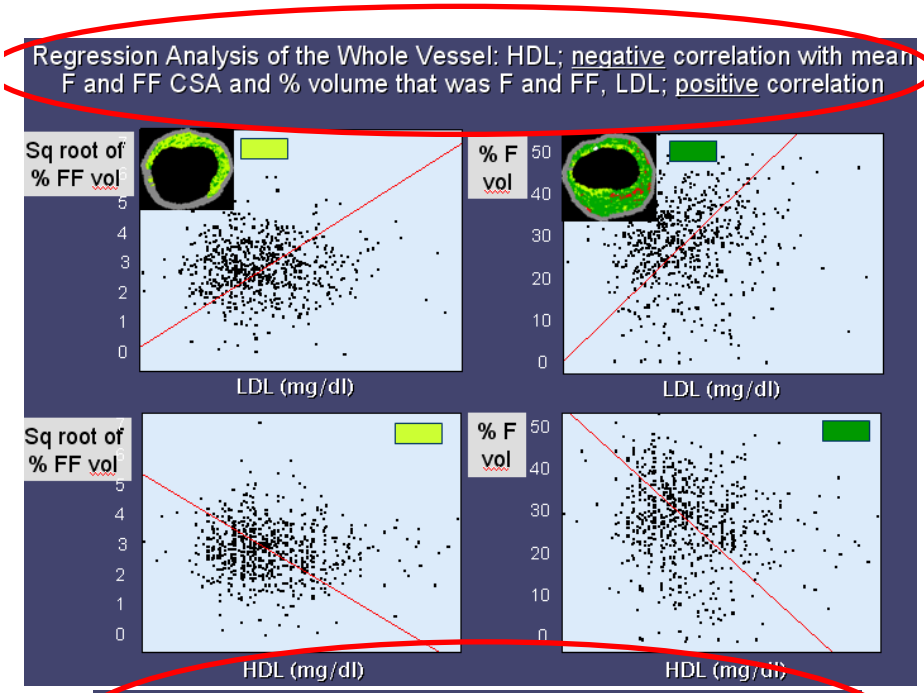
Significant Correlations with Myocardial Ischemia



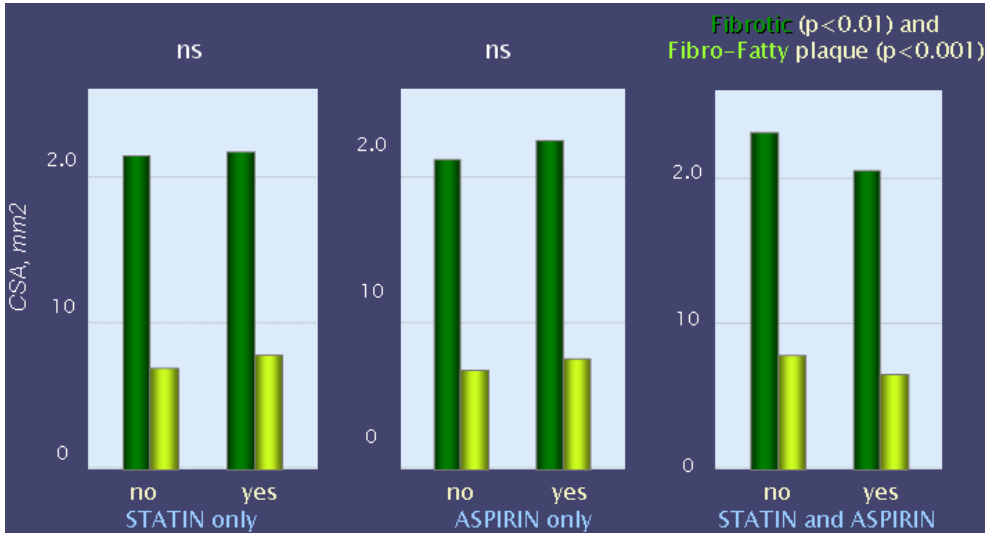


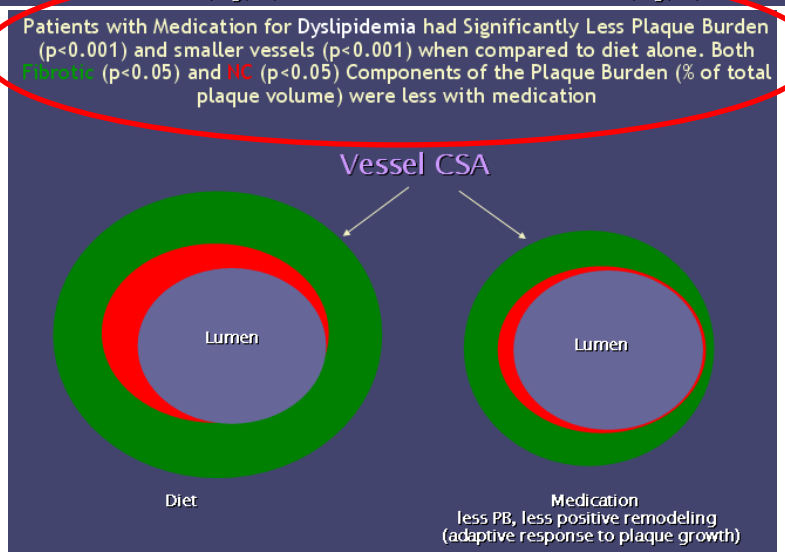


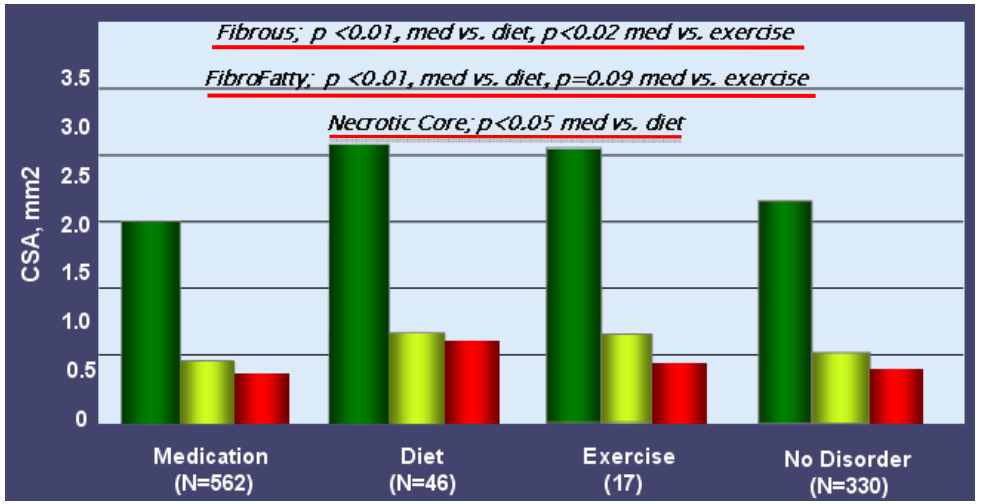
Significant Correlations with Dyslipidemia and Treatment for Dyslipidemia



Only the Combination of Statin and Aspirin was associated with Less Fibrofatty and Fibrotic Plaque, no Difference was seen in the Amount of NC and Ca







Correlation of Necrotic Core and Calcium

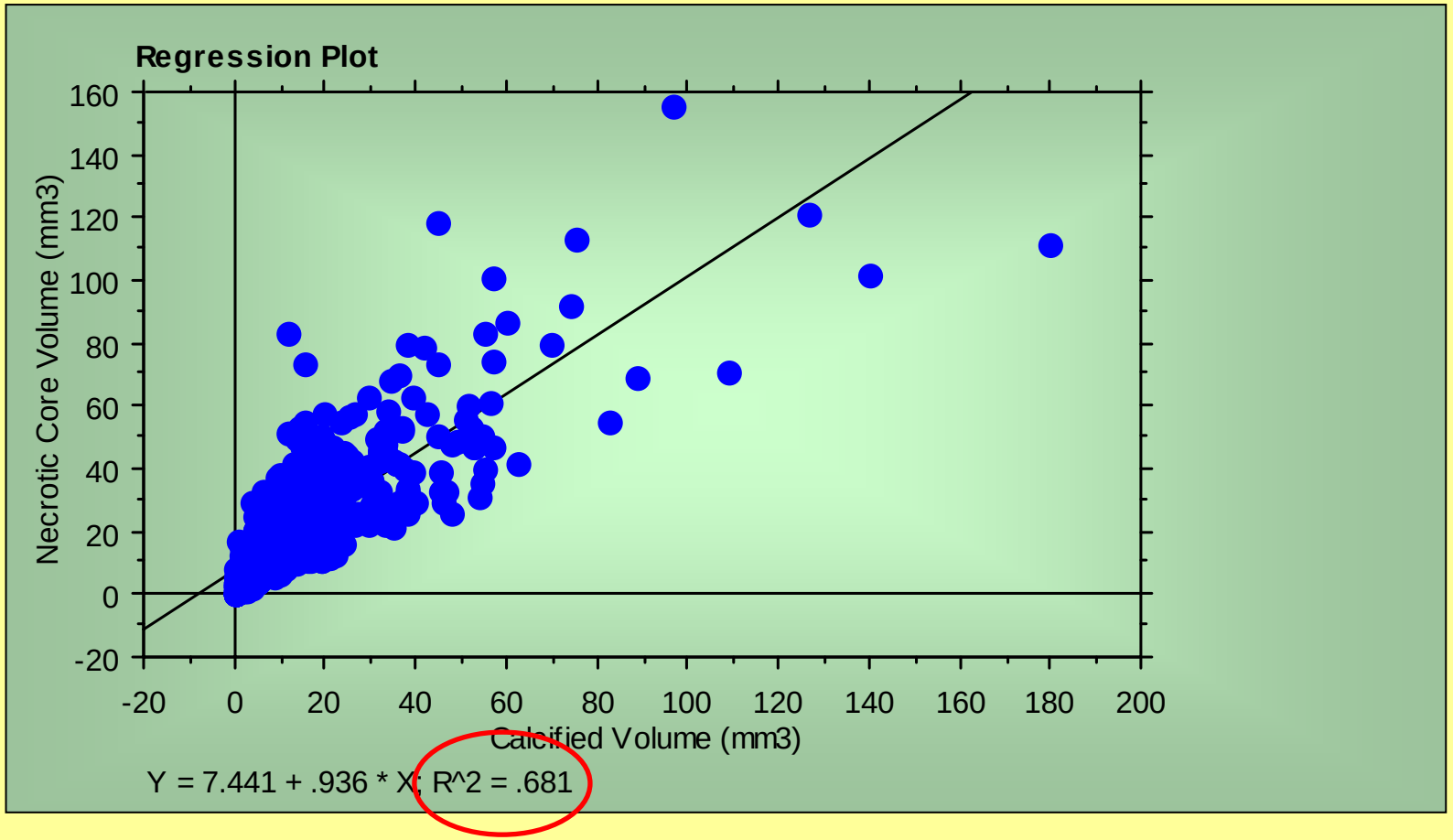
- European Society of Cardiology Congress 2007, Vienna – Austria
- AJC 2007 (in press)

Calcium is Strongly Correlated with Necrotic Core in Human Coronary Arteries: Insights from the Multicenter VH-IVUS Registry

Eduardo Missel, Gary S. Mintz, Stephane G. Carlier, Koichi Sano, Joanna Lui, Roxana Mehran, Jeffrey Moses, Gregg W. Stone, and Martin B. Leon

Cardiovascular Research Foundation
Columbia University Medical Center
New York – NY - USA

Relationship between NC and DC (n=625)



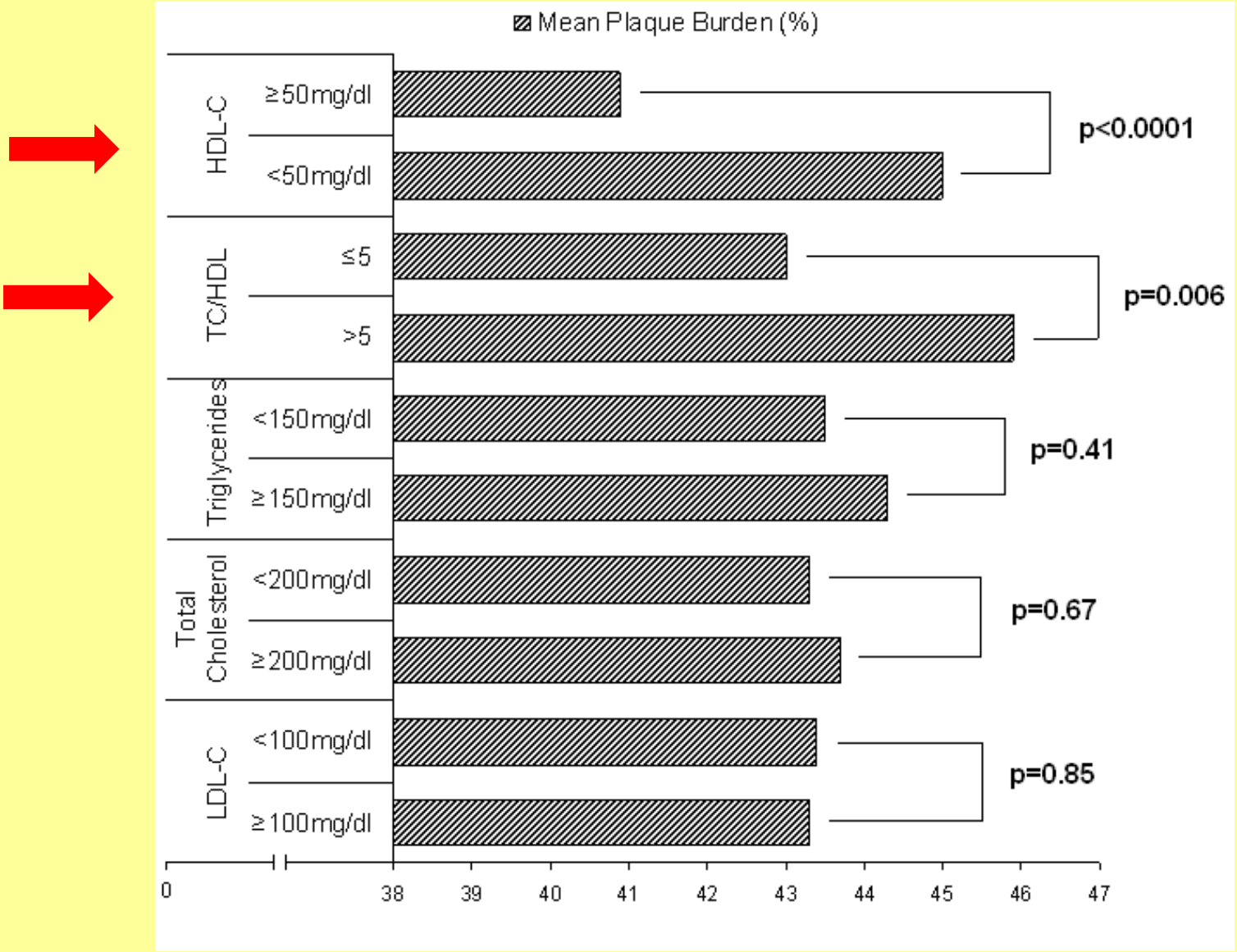
Conclusions

- Calcium has a strong correlation with necrotic core in human coronary arteries
- The NC/DC ratio has a significant positive association with an adverse lipid profile, and smoking.
- Even though calcium is not prominent within lesions of ACS patients, more calcium indicates larger and/or more numerous necrotic cores.
- These findings are consistent with the concept that an EBCT calcium score is a predictor for further coronary events.

Among Serum Lipid Profile Parameters High-Density Lipoprotein Cholesterol is the Major Determinant of Coronary Plaque Burden: A Volumetric Intravascular Ultrasound Analysis

Eduardo Missel, MD; Gary S Mintz, MD; Hector Garcia-Garcia, MD; Ryan K Kaple, BS; Sinan Biro, BS; Lokesh Dani, BS; Joanna Lui, BS; Gregg W Stone, MD and Martin B Leon, MD, TCT 2007

- **Background:** Although statins are highly effective in reducing future adverse cardiovascular events, the effect on plaque burden (PB) measured by intravascular ultrasound (IVUS) is, at best, modest. We assessed the relationship of lipid profile to IVUS parameters in order to explain this paradox.
  Methods: We performed volumetric IVUS analysis in a series of 625 patients and measured external elastic membrane (EEM), lumen, and plaque & media (P&M) areas and volumes and PB (EEM/P&M).
  Results: Patient age was 62.3±11.1yrs with 75% males and 23% diabetics. There was a negative association between HDL-C levels and mean PB (r= -0.18, p<0.0001), mean P&M CSA (r= -0.16, p=0.0008), and P&M volume (r=-0.11, p=0.02). Total cholesterol LDL-C and triglycerides were not related to any of these IVUS parameters. Multiple regression analysis revealed that among lipid profile parameters, HDL-C was the only independent predictor of PB (p<0.0001). Patients with HDL-C<50mg/dl had higher mean P&M area (7.1±2.6 vs. 6.2±2.5mm2), P&M volume (349.7±203.7 vs. 293.8±173.5 mm2, p=0.004), and mean PB (45.0±8.7 vs. 40.9±9.7%, p<0.0001) than pts with normal HDL levels. Patients with HDL-C levels in the 3rd tertile had significantly lower PB when compared to the 1st (p=0.002) or 2nd (p=0.006) tertiles.
- **Conclusion: Among lipid parameters, HDL-C is the major determinant of coronary plaque burden. The modest benefits of statins in terms of plaque regression more likely result from the slight effect on *increasing HDL-C levels* than in reducing LDL-C levels.**

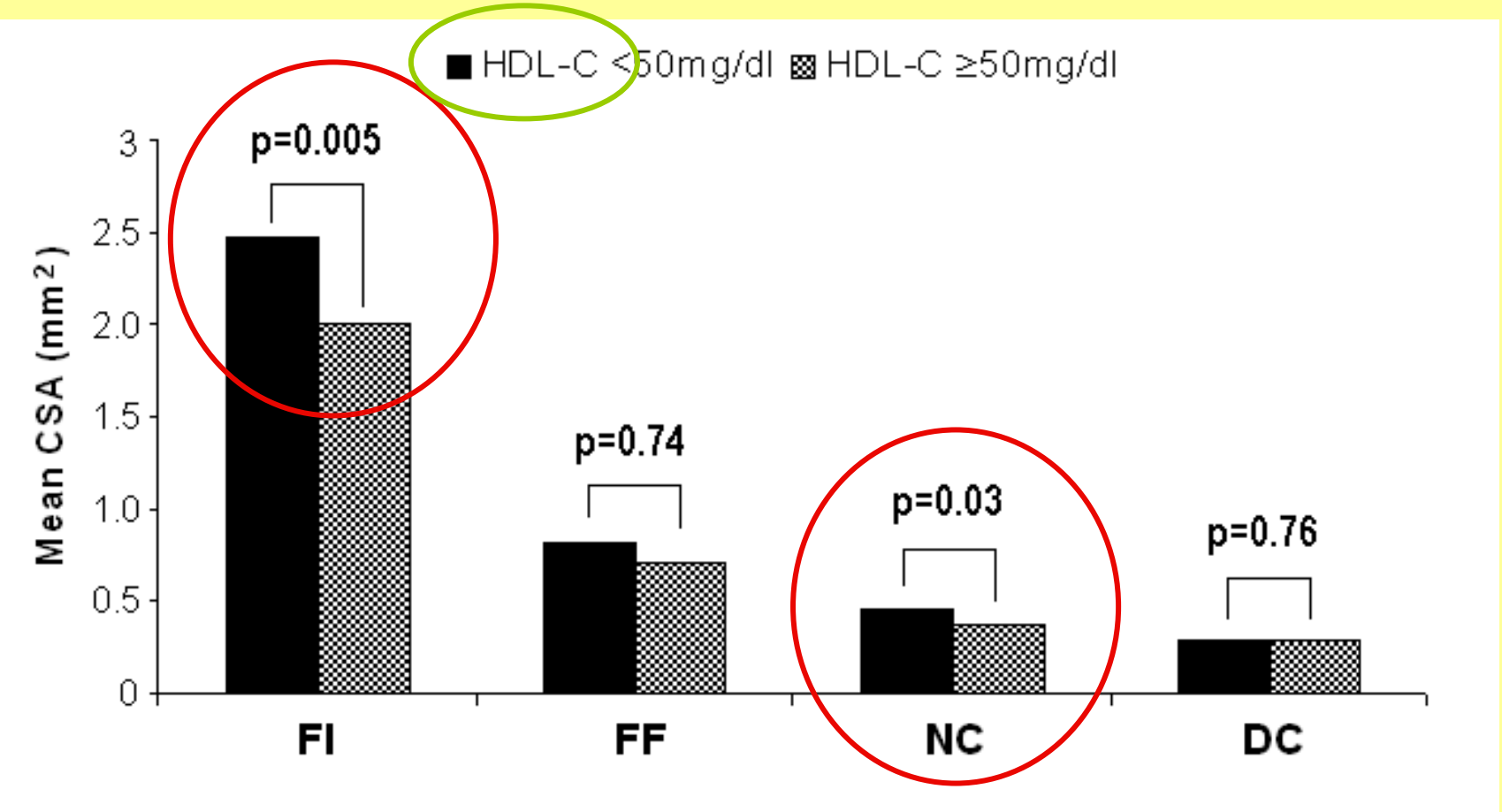

Mean Plaque Burden (%)
HDL-C
≥50mg/dl
<50mg/dl
p<0.0001
TC/HDL
≤5
>5
p=0.006
Triglycerides
<150mg/dl
≥150mg/dl
p=0.41
Total Cholesterol
<200mg/dl
≥200mg/dl
p=0.67
LDL-C
<100mg/dl
≥100mg/dl
p=0.85
0
38
39
40
41
42
43
44
45
46
47

In Vivo Virtual Histology Intravascular Ultrasound Correlates of Risk Factors for Sudden Coronary Death in Men: Results from the Prospective, Multi-center VH-IVUS Registry

Eduardo Missel, MD; Gary S Mintz, MD, FACC; Stephane G. Carlier, MD, PhD; Jie Qian, MD; Shoujie Shan, MD; Ryan Kaple, BSc; Sinan Biro, BSc; Jeffrey W. Moses, MD, FACC; Gregg W. Stone, MD, FACC and Martin B. Leon, MD, FACC, TCT 2007

- **Objectives:** We hypothesized a relationship between virtual histology intravascular ultrasound (VH-IVUS) findings and risk factors associated to sudden coronary death.
- **Background:** Histopathological data show that cigarette smoking and an increased total cholesterol to high-density lipoprotein ratio (TC/HDL>5) are associated to sudden coronary death (SCD) in men.
- **Methods:** We assessed volumetric VH-IVUS in a consecutive series of 473 male patients: fibrous (FI), fibro-fatty (FF), dense calcium (DC) and necrotic core (NC) as well as a calculated NC/DC ratio.
- **Results:** Patients' age was 61±11years with 27% current smokers and 69% having a lipid disorder. Among VH-IVUS parameters, the NC/DC ratio was the only parameter related to both TC/HDL ratio (r=0.18, p=0.0008) and LDL-C levels (r=0.17, p=0.002). The NC/DC ratio also had a negative correlation with HDL-C levels (r=0.11, p=0.03) and was significantly higher for smokers (median: 1.98 [1.35-3.18]) vs. non-smokers (median: 1.70 [1.23-2.53], p=0.006). Sensitivity and specificity curve analysis determined that a NC/DC value >3 was the threshold that best identified patients with a risk profile for sudden coronary death (smoking and/or TC/HDL>5) (odds ratio 3.0, p=0.0001). Receiver operator curves showed the superiority of the NC/DC ratio (AUC: 0.64, p<0.0001) over %DC (AUC: 0.58, p=0.006) or %DC (AUC: 0.51, p=0.43) as isolate parameters that identified male patients with a risk profile for SCD.
- **Conclusions: The ratio of necrotic core to calcification detected by VH-IVUS in diseased coronary segments is related to known risk factors for SCD and, thus, may be associated to a worse prognosis.**

Plaque composition of diseased coronary segments in patients with abnormal vs. normal HDL-C levels. CSA = cross sectional area, FI= fibrous, FF = Fibro-fatty, NC = necrotic core, DC = dense calcium



Necrotic Core and Its Ratio to Dense Calcium are Predictors of High-risk Non-ST-elevation Acute Coronary Syndromes

Eduardo Missel, M.D.; Gary S. Mintz, M.D.; Stephane G. Carlier, M.D., PhD; Koichi Sano,M.D., PhD; Jie Qian, M.D.; Ryan K Kaple, BS; Celia Castellanos, M.D.;

George Dangas, M.D., PhD; Roxana

Mehran, M.D., Jeffrey W Moses, M.D., Gregg W Stone, M.D.; Martin B Leon, M.D

Abstract

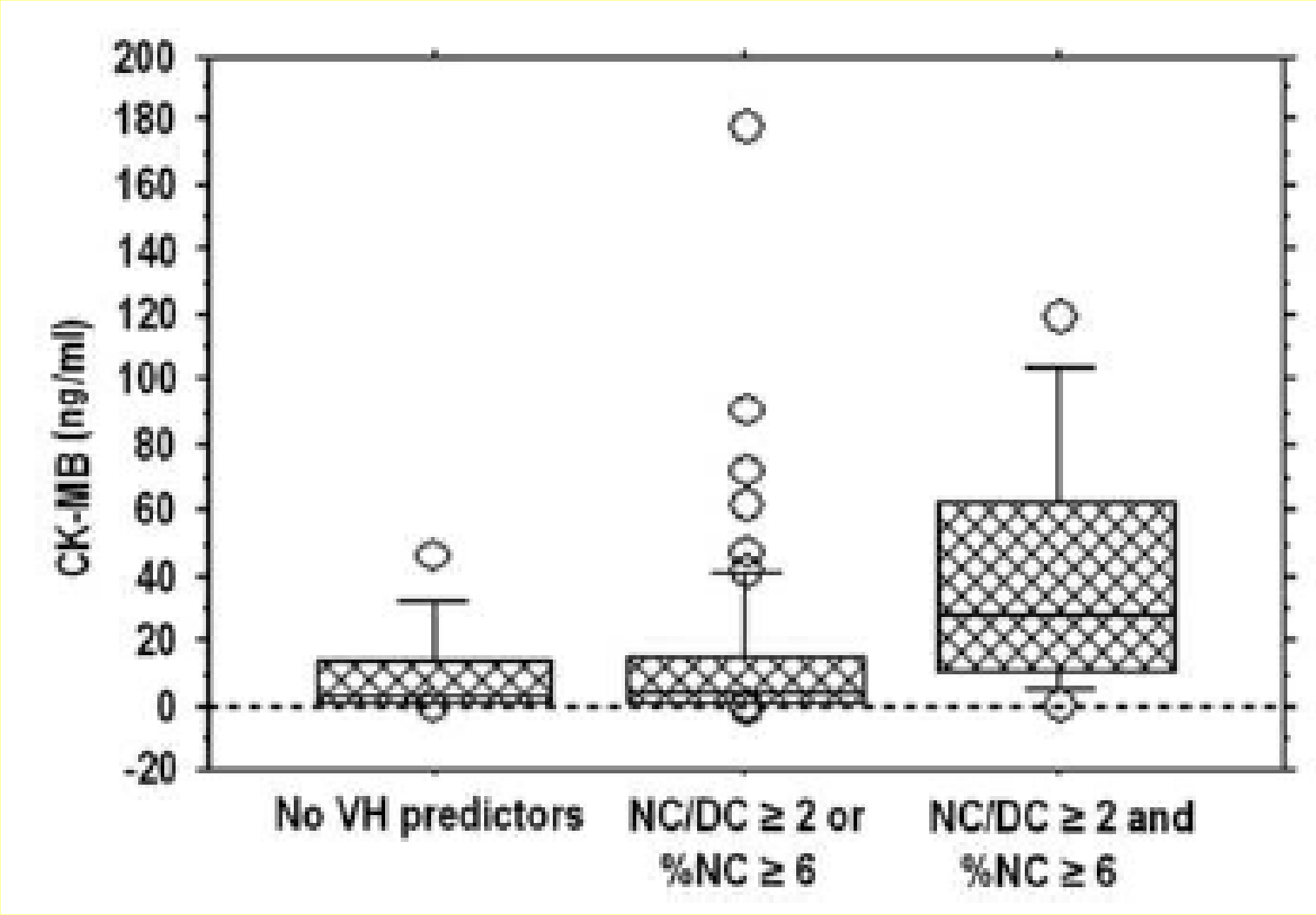
Increased creatine kinase-MB (CK-MB) levels and ST-segment depression are well known prognostic factors in the setting of non-ST elevation acute coronary syndromes (NSTE ACS).

We hypothesized a relation between virtual histology intravascular ultrasound (VH-IVUS) findings and these prognostic factors.

We performed "whole vessel" VH-IVUS analysis in culprit arteries of 225 patients presenting with ACS and measured the four basic VH-IVUS coronary plaque components - fibrous, fibrofatty, dense calcium (DC) and necrotic core (NC) - as well as calculated a NC/DC ratio. Patients' age was 62±11 years, with 72% males and 23% diabetics. Only the NC/DC ratio had a positive association to CK-MB levels (r=0.21, p=0.03) and was also significantly higher for ST-depression vs. non-ST-depression ACS patients (1.97±1.46 vs. 1.58±1.10, p=0.02). Sensitivity and specificity curves determined that a NC/DC value =2 (odds ratio 3.8, p=0.01) and %NC =6 (odds ratio 3.1, p=0.04) were thresholds that best separated high-risk NSTE ACS patients from those without abnormal CK-MB or ST-depression. Patients with both predictors had significantly higher total cholesterol (204.7±60.5 vs. 173.6±44.3, p=0.01), higher LDL-C (132.5±49.8 vs. 101.3±33.2, p=0.02) and more myocardial injury (CK-MB value of 42±38 vs. 12±21, p=0.01) than patients with no predictors.

In conclusion, VH-IVUS analysis showed that the percentage of necrotic core and its ratio to calcium in diseased coronary segments are positively associated to a high-risk ACS presentation.

Patients with both NC/DC ratio≥2 and NC≥6% had significantly higher creatine kinase-MB values when compared to patients with one (p=0.006) or none of these two predictors (p=0.002). DC, dense calcium; IVUS, intravascular ultrasound; NC, necrotic core; VH, virtual histology.



Conclusions

- The correlations seen in this registry provide confidence in the accuracy and reproducibility of VH.
- Further analysis will consider:
  - The entire enrolled population of over 3,000 patients.
  - Re-enrollers.
  - Regional characteristics of plaques (rather than whole vessel) – wherein we may gain a clearer understanding of stenotic lesions, intermediate lesions and diffuse disease.
- This work has started to uncover clues as to why events cluster in:
  - Proximal regions.
  - Certain patient populations with different risk factors.
  - It can eventually point us to possible early detection and treatment of vulnerable patients and/or vulnerable plaques.

Analysis of the Long-term Effects of Drug-eluting Stents on Coronary Arterial Healing by Virtual Histology Intravascular Ultrasound

Takashi Kubo, Akiko Maehara, Gray S. Mintz, Hiroshi Doi, Kenichi Tsujita, Junqing Yang, Jian Liu, Carlos Oviedo, Anthony Tam, Harpreet Bharaj, Joelson Guillaume, Richard Abendroth, Sinan Biro, Rasha Aaskar, Celia Castellanos, Lokesh Dani, Jeffrey W. Moses, Martin B. Leon, D.Geoffrey Vince, M. Pauliina Margolis, Gregg W. Stone, James R. Margolis, Cardiovascular Research Foundation, New York

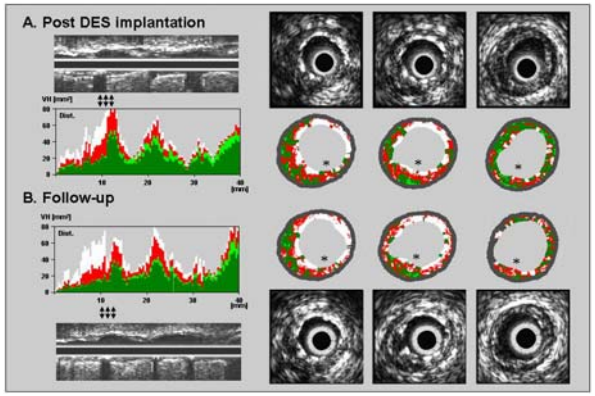
Background

Drug eluting stents (DES) have reduced rates of restenosis and target lesion revascularization compared with bare metal stents (BMS) and launched a revolution in the interventional treatment of symptomatic coronary artery disease. Some published studies of animal models with DES implanted in normal arteries show a substantial impairment of arterial healing relative to BMS. However, the long-term effects of DES on coronary arterial healing remain unclear in vivo. Spectral analysis of the radiofrequency backscatter signals of intravascular ultrasound (IVUS), known as Virtual Histology (VH), offers an in vivo opportunity to assess lesion morphology. We used VH-IVUS to assess long-term (mean=8 months) native artery vascular responses after DES implantation compared with BMS.

Methods

We enrolled 49 patients with acute coronary syndrome who received stenting (DES=36, BMS=13) for de novo coronary lesions. VH-IVUS examination was performed at post-stenting and follow-up using a 20-MHz, 3.2F, phased-array IVUS catheter (Eagle Eye, Volcano Therapeutics, Rancho Cordova, California, USA) and a motorized transducer pullback system (0.5 mm/s). VH-IVUS analysis classified and color-coded tissue as green (fibrotic), yellow-green (fibrofatty), white (dense calcium), and red (necrotic core: NC). Volumetric VH-IVUS analysis was performed at the stented lesion and the stent edge reference (5mm); calculations were made using Simpson's rule. VH-IVUS-derived thin-capped fibroatheroma (VH-TCFA) was defined as a lesion fulfilling the following criteria in at least 3 consecutive frames: 1) Confluent NC abutting the lumen. 2) NC >10% of total plaque volume.

Figure 1. Serial VH-IVUS images of stented lesion at post DES implantation (A) and follow-up (B).



VH-TCFA* was identified in the stented lesion at post DES implantation. Necrotic core still abutted the coronary lumen between the stent struts at follow-up.

Results

Baseline clinical characteristics were similar between DES and BMS. The stent profiles (diameter: 3.3 ± 0.3mm vs. 3.1 ± 0.4mm, p=0.8; length: 19.3 ± 7.6mm vs. 18.5 ± 7.0mm, p=0.8) were comparable between two groups. Mean follow-up period was 8.2 ± 0.9 months. Although NC volume was not significantly changed during the follow-up period in either group (Table 1 and Table 2), the frequency of NC abutting the lumen (Figure 1) at follow-up (42% vs. 14%, p=0.037) was significantly greater in DES than BMS (Table 3) because of the lack of an overlying, protective neointimal hyperplasia in DES-treated lesions. Furthermore, at the stent edge the frequency of thin-capped fibroatheromas (TCFAs) decreased in BMS-treated lesions (27% to 4%, p=0.015) but not in DES (25% to 22%, p=0.695).

Table 1. Postintervention and follow-up virtual histology intravascular ultrasound findings

	Drug-eluting stent			Bare metal stent		
	Post-stenting	Follow-up	p-value	Post-stenting	Follow-up	p-value
Stented lesion						
Vessel	331.6±151.3	329.1±151.4	0.753	246.6±116.1	255.2±106.1	0.537
Lumen	143.0±61.5	133.1±55.7	0.195	111.1±50.1	94.6±40.1	0.063
Plaque	188.7±100.2	196.0±106.6	0.613	135.5±72.0	160.7±76.0	0.018
FT	53.2±44.0	57.9±45.3	0.570	38.4±29.5	44.2±23.4	0.211
FF	11.6±14.6	10.2±8.9	0.592	6.9±6.8	9.1±6.3	0.115
DC	25.6±13.2	30.4±16.1	0.085	15.4±9.8	22.5±16.4	0.025
NC	25.8±18.9	27.6±19.4	0.328	22.5±17.1	25.8±18.7	0.237
Distal reference						
Vessel	67.5±37.9	64.7±36.3	0.128	61.4±28.3	57.6±28.6	0.015
Lumen	37.3±16.9	37.7±22.1	0.905	33.4±10.4	28.4±9.1	0.021
Plaque	30.3±23.5	27.9±18.8	0.348	27.7±22.3	29.2±25.5	0.419
FT	9.0±12.0	7.7±9.6	0.455	8.0±11.3	8.8±13.1	0.464
FF	2.8±4.2	1.7±2.0	0.136	1.1±1.1	2.2±3.7	0.234
DC	0.9±1.7	1.4±1.8	0.081	1.1±2.2	1.2±2.1	0.705
NC	2.1±3.6	2.2±2.8	0.863	2.6±5.1	2.7±4.4	0.810
Proximal reference						
Vessel	85.7±25.0	83.2±29.9	0.329	71.5±27.9	69.6±29.9	0.518
Lumen	47.5±18.7	44.0±20.1	0.026	35.5±13.3	30.2±7.7	0.041
Plaque	38.2±17.4	39.1±21.7	0.678	36.0±21.0	39.4±25.7	0.183
FT	11.1±10.2	12.3±13.0	0.327	12.4±11.5	13.4±12.2	0.534
FF	4.2±4.6	4.2±4.1	0.898	3.6±3.5	4.8±4.6	0.388
DC	1.3±1.4	1.6±1.6	0.122	1.6±1.8	1.6±2.1	0.733
NC	3.3±3.1	3.8±3.8	0.594	3.0±4.3	3.5±4.4	0.303

FT indicates fibrous tissue ACS; FF, fibro-fatty; DC, dense calcium; and NC, necrotic core. Values are given as mean ± SD.

Table 2. Postintervention and follow-up virtual histology intravascular ultrasound findings

	Drug-eluting stent	Bare metal stent	p-value
Stented lesion			
Δ Vessel	15.1±107.9	8.7±47.1	0.849
Δ Lumen	-9.9±30.1	-16.5±27.8	0.195
Δ Plaque	7.2± 57.9	25.2±31.4	0.338
Δ FT	4.6± 32.8	5.8±15.0	0.911
Δ FF	-1.3±10.0	2.2±4.5	0.264
Δ DC	4.9±10.9	7.2±9.6	0.560
Δ NC	2.2±13.8	2.3±13.7	0.081
Distal reference			
Δ Vessel	-2.9±6.6	-3.7±3.9	0.725
Δ Lumen	0.3±9.9	-5.0±5.7	0.141
Δ Plaque	-2.4±9.4	1.5±5.5	0.252
Δ FT	-1.3±6.5	0.8±3.2	0.356
Δ FF	2.8±4.2	1.7±2.0	0.057
Δ DC	-1.2±2.7	1.1±2.8	0.276
Δ NC	0.1±3.2	0.1±1.2	0.982
Proximal reference			
Δ Vessel	-2.6 ± 9.8	-1.8 ± 8.6	0.849
Δ Lumen	-3.5 ± 5.4	-5.2 ± 7.0	0.479
Δ Plaque	0.8 ± 8.0	3.4 ± 7.5	0.434
Δ FT	0.1 ± 1.9	1.2 ± 4.4	0.372
Δ FF	1.2 ± 4.6	0.9 ± 4.1	0.291
Δ DC	0.3 ± 0.8	0.1 ± 0.6	0.392
Δ NC	0.5 ± 3.7	0.5 ± 1.5	0.999

FT indicates fibrous tissue ACS; FF, fibro-fatty; DC, dense calcium; and NC, necrotic core. Values are given as mean ± SD.

Table 3. Change of the frequency of VH-TCFA during follow-up between drug-eruting stent and bare-metal stent.

	Drug-eluting stent	Bare-metal stent	p
Stented lesion			
Post-intervention	44	38	0.709
Follow-up	42	14	0.037
Stent-edge reference			
Post-intervention	25	27	0.847
Follow-up	22	4*	0.036

VH-TCFA indicates virtual histology intravascular ultrasound delivered thin-capped fibroatheroma. Values are given as %. *p<0.05, vs. post-intervention.

Summary

We used VH-IVUS to assess long-term (mean=8 months) native artery vascular responses after 36 DES implantation compared with 13 BMS. The frequency of NC abutting the lumen (i.e., vulnerable plaque) at follow-up (42% vs. 14%, p=0.037) was significantly greater in DES than BMS because of the lack of an overlying, protective neointimal hyperplasia in DES-treated lesions. Furthermore, at the stent edge the frequency of thin-capped fibroatheromas (TCFAs) decreased in BMS-treated lesions (27% to 4%, p=0.015) but not in DES (25% to 22%, p=0.695). The apparent mechanism is a suppression of the protective neointimal hyperplasia layer coupled with a lack of TCFA resolution at the stents.

Conclusions

Serial VH-IVUS analysis of DES-treated lesions show a greater frequency of unstable lesion morphometry (TCFAs or vulnerable plaques) at follow-up compared to BMS. The apparent mechanism is a suppression of the protective neointimal hyperplasia layer coupled with a lack of TCFA resolution at stent edges.

Disclosures

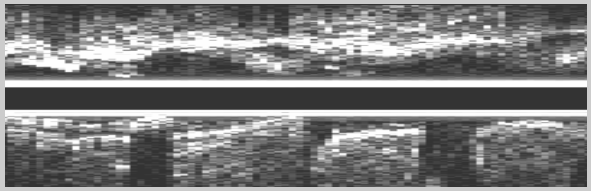
Dr. Gray S. Mintz and Dr. Gregg W. Stone are consultants for Volcano Company, and Dr. M. Pauliina Margolis is an employee for Volcano Company. Nil else to declare.

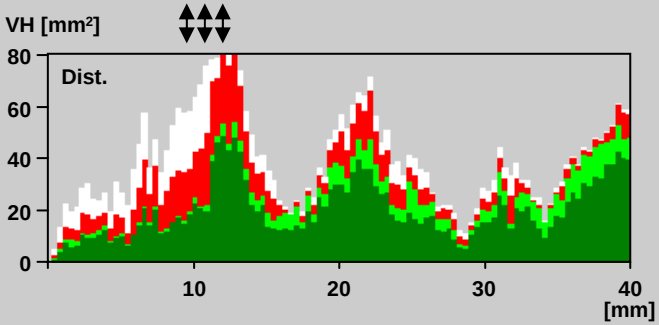
Table 3. Change of the frequency of VH-TCFA during follow-up between drug-eruting stent and bare-metal stent.

	Drug-eluting stent	Bare-metal stent	*p*
Stented lesion			
Post-intervention	44	38	0.709
Follow-up	42	14	0.037
Stent-edge reference			
Post-intervention	25	27	0.847
Follow-up	22	4*	0.036

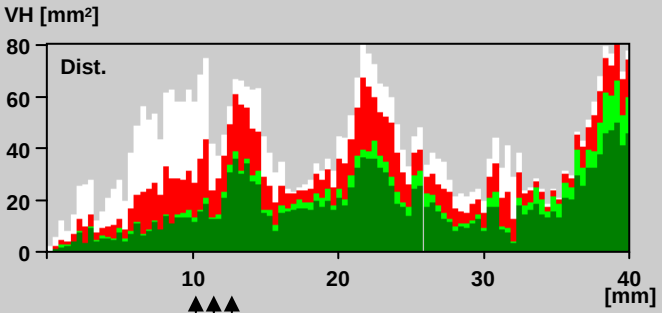
VH-TCFA indicates virtual histology intravascular ultrasound delivered thin-capped fibroatheroma. Values are given as %. *p<0.05, vs. post-intervention.

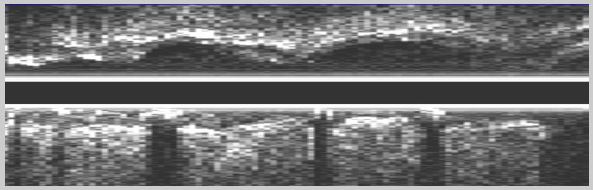
A. Post DES implantation

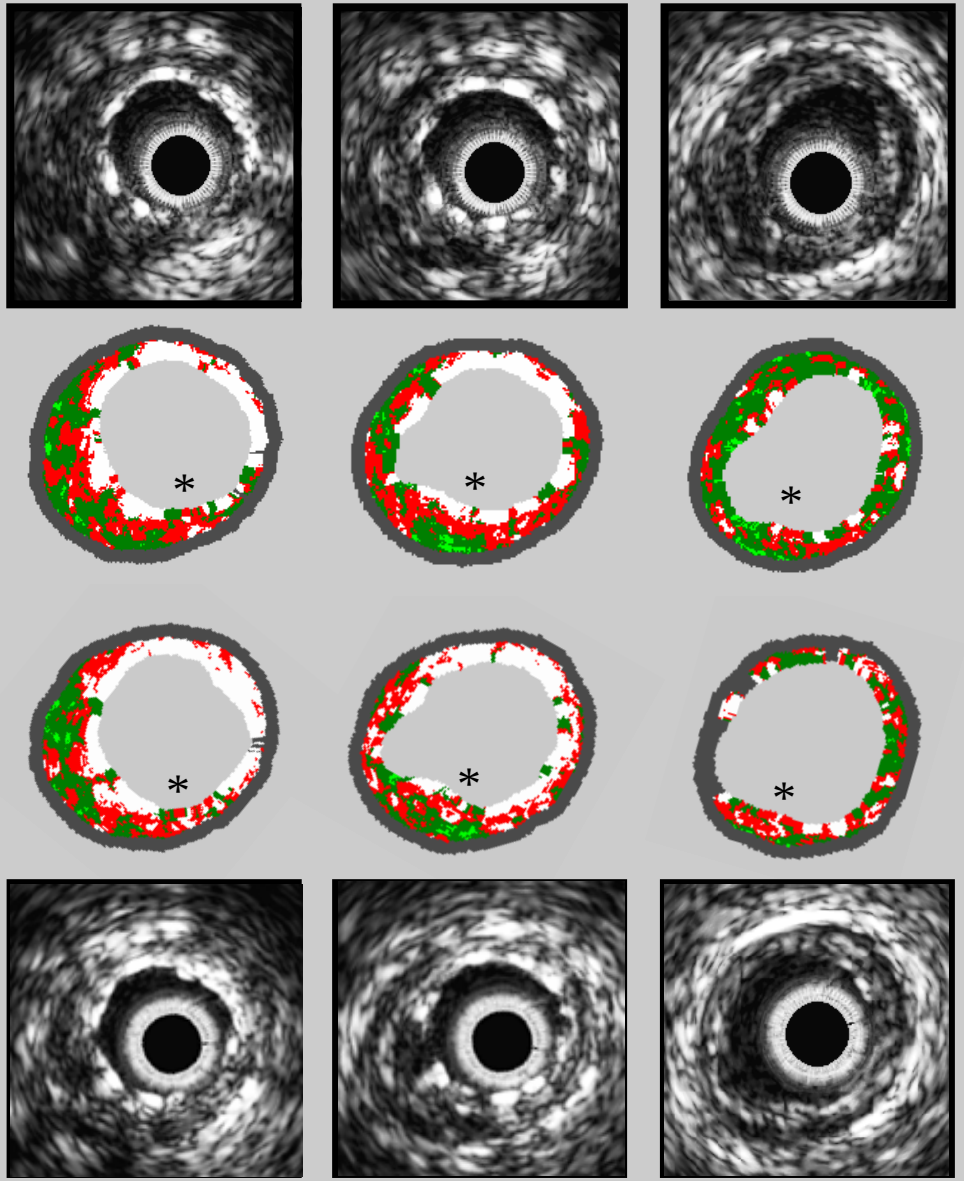




B. Follow-up





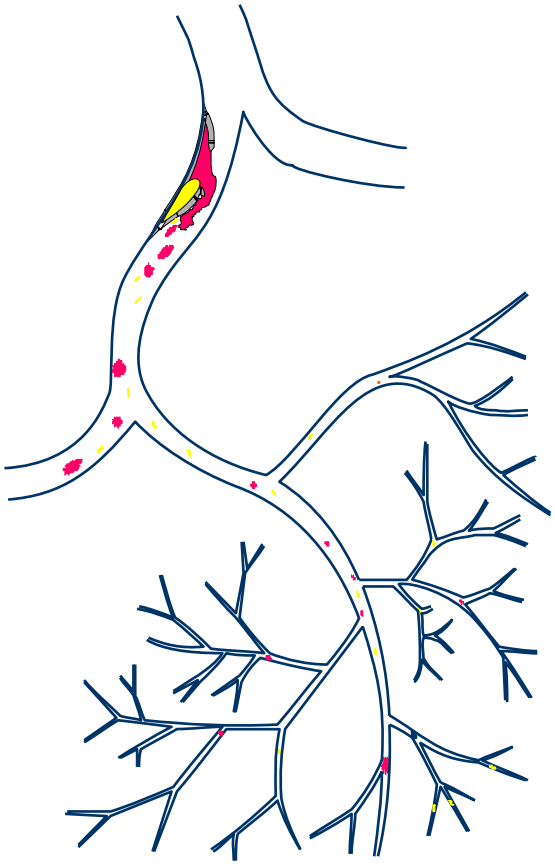


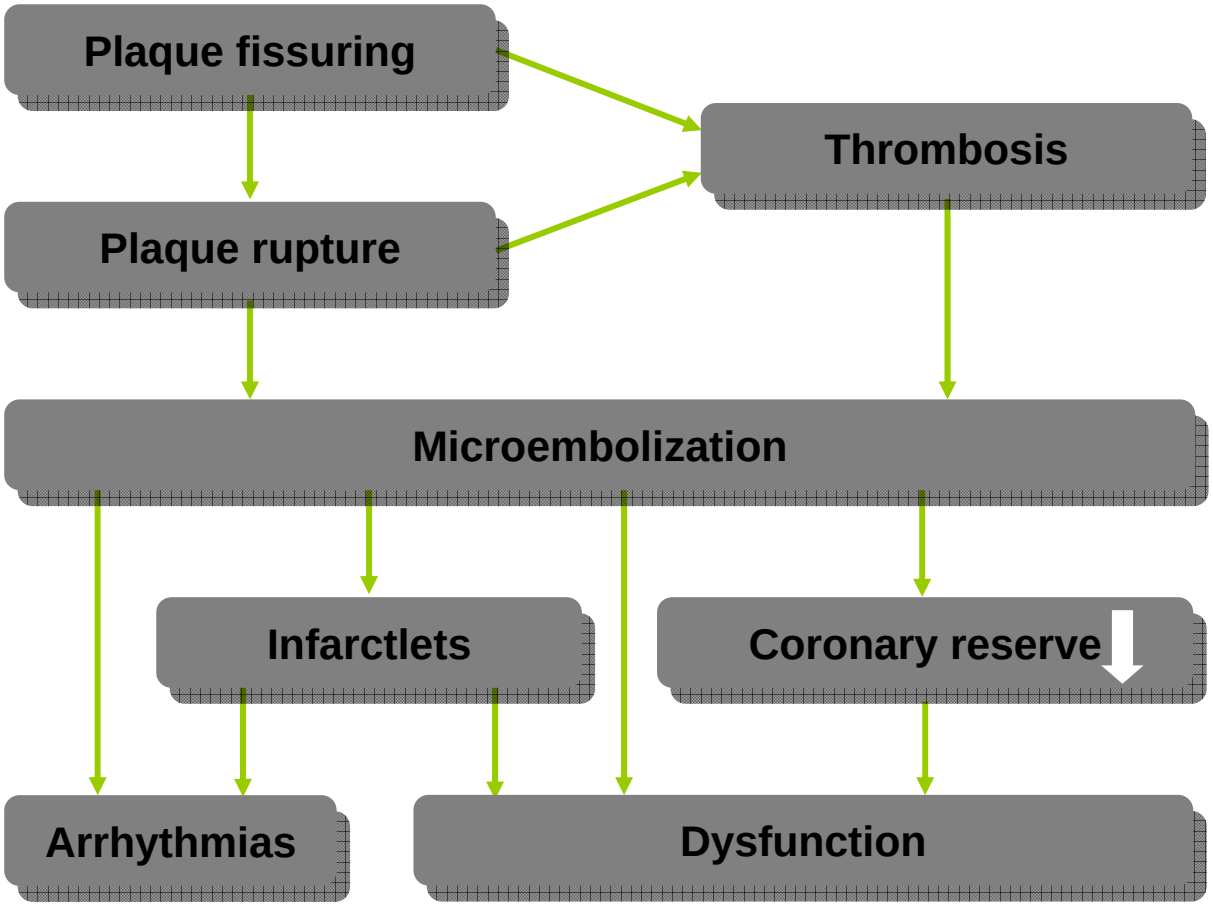
Other Studies

Correlation of Necrotic Core with Distal Embolization

Does Necrotic Core Embolize?

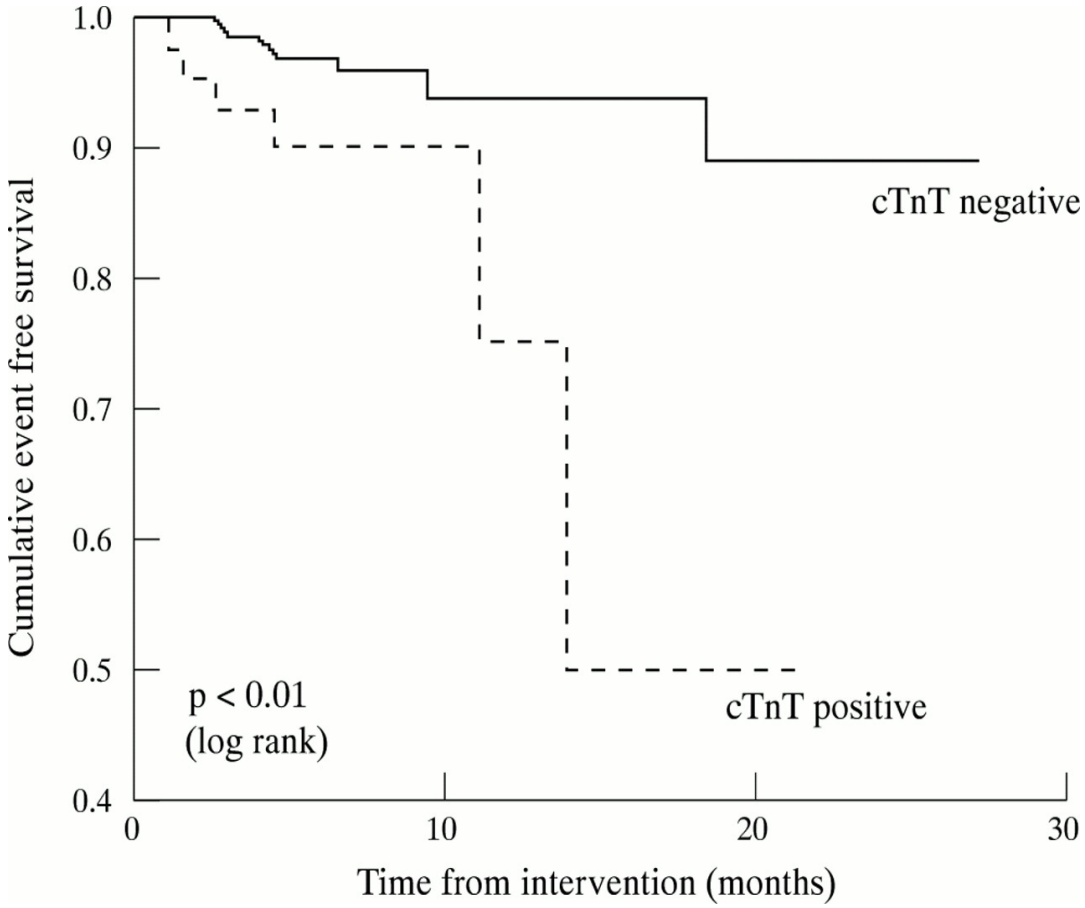
Coronary Microembolization



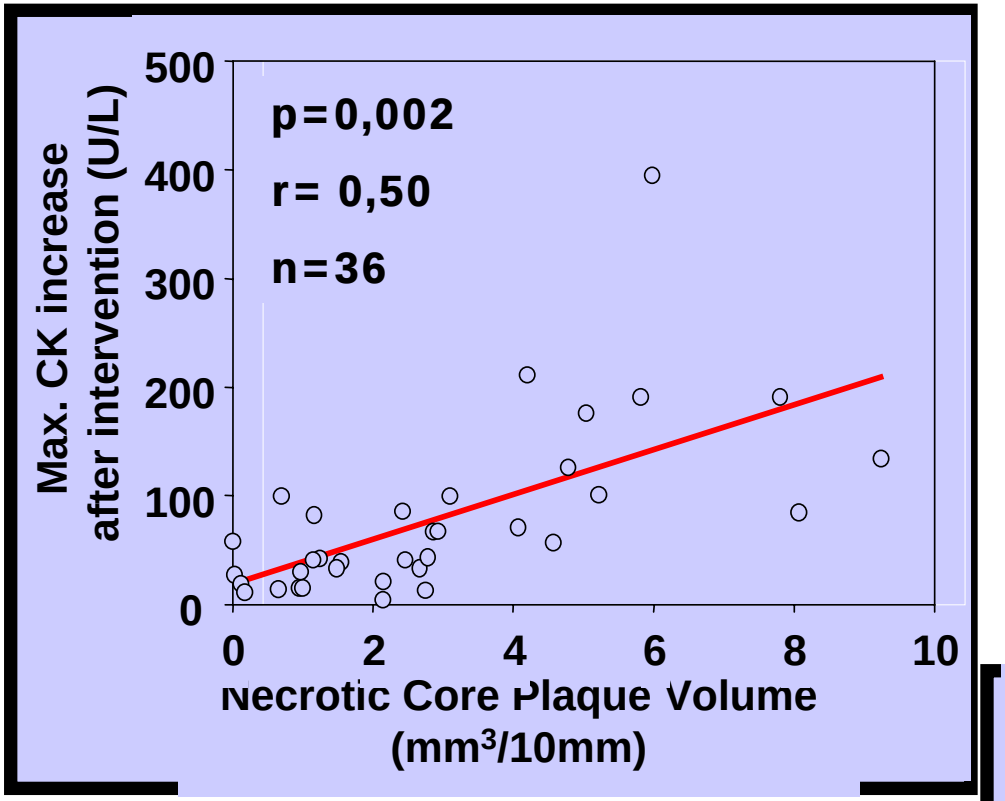


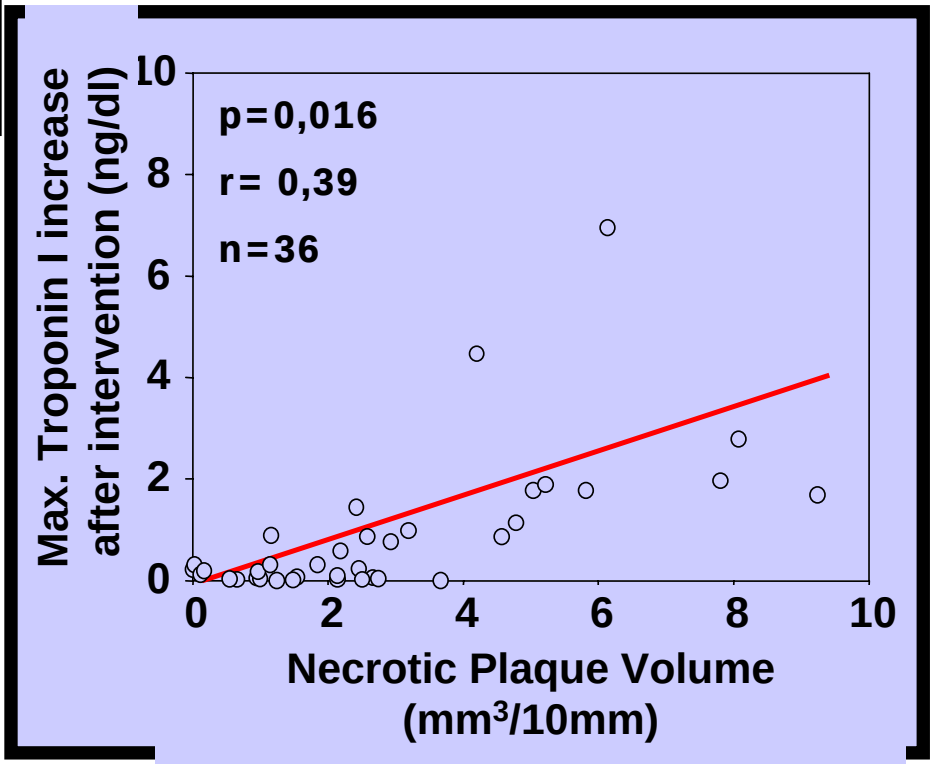
Erbel and Heusch, J Am Coll Cardiol 39:22-24 (2000)

Coronary Microembolization During PCI and Cardiac Events



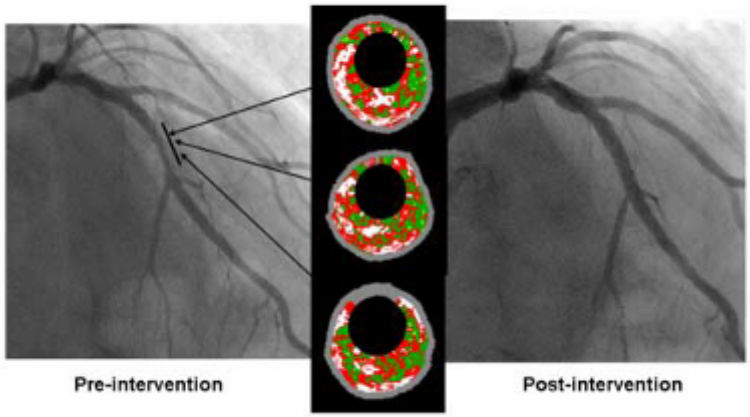
Coronary Microembolization during Standardized PCI Erbel, PCR 2006)

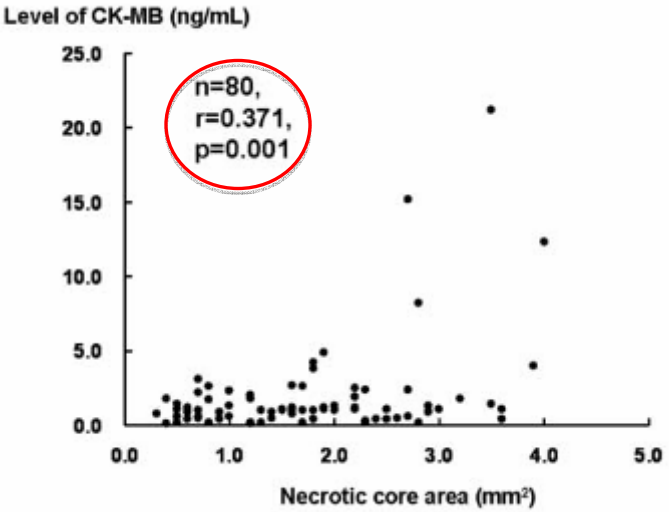




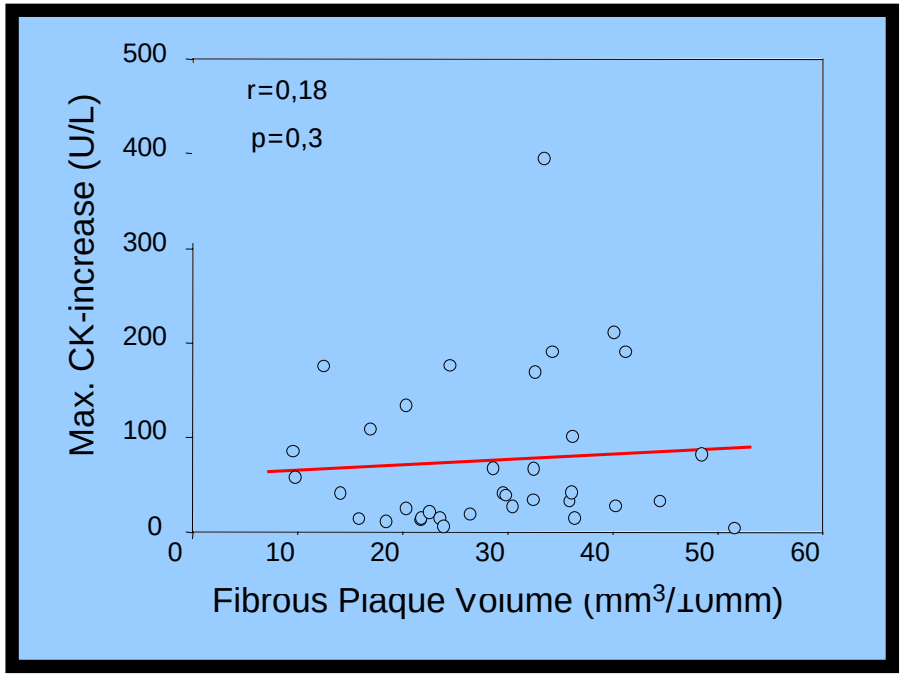
Coronary Plaque Composition and Its Effect on Creatine Kinase MB Enzyme Levels after Percutaneous Coronary Stenting: A Virtual Histology Intravascular Ultrasound Analysis; Myeong-Ki Hong; Gary S Mintz, MD; Cheol Whan Lee; Jeong-HoonKim; Jon Suh; Hyuk Ko; Duk-Woo Park; Seung-Whan Lee; Young-Hak Kim; Sang-SigCheong; Jae-Joong Kim; Seong-Wook Park; Seung-Jung Park, TCT 2006

Conclusion: post-PCI CKMB enzyme level correlated with a larger pre-PCI necrotic core area at the minimal lumen site as assessed by VH-IVUS analysis. More aggressive medical treatment (i.e. use of platelet glycoprotein IIb/IIIa inhibitors or a larger loading dose of clopidogrel or statin before PCI) and less aggressive procedures may be warranted to prevent higher CK-MB elevations in these lesion subsets

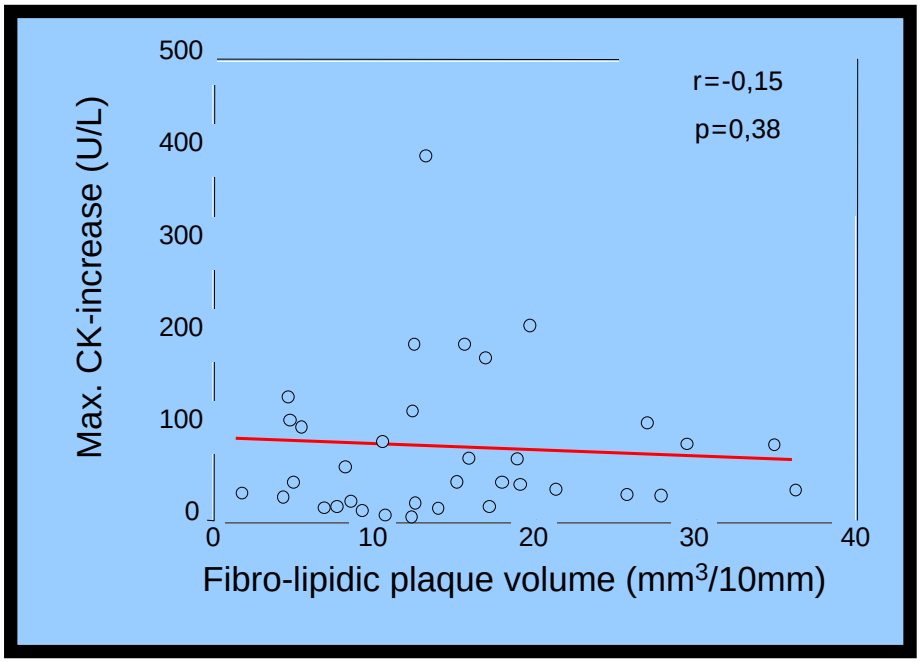


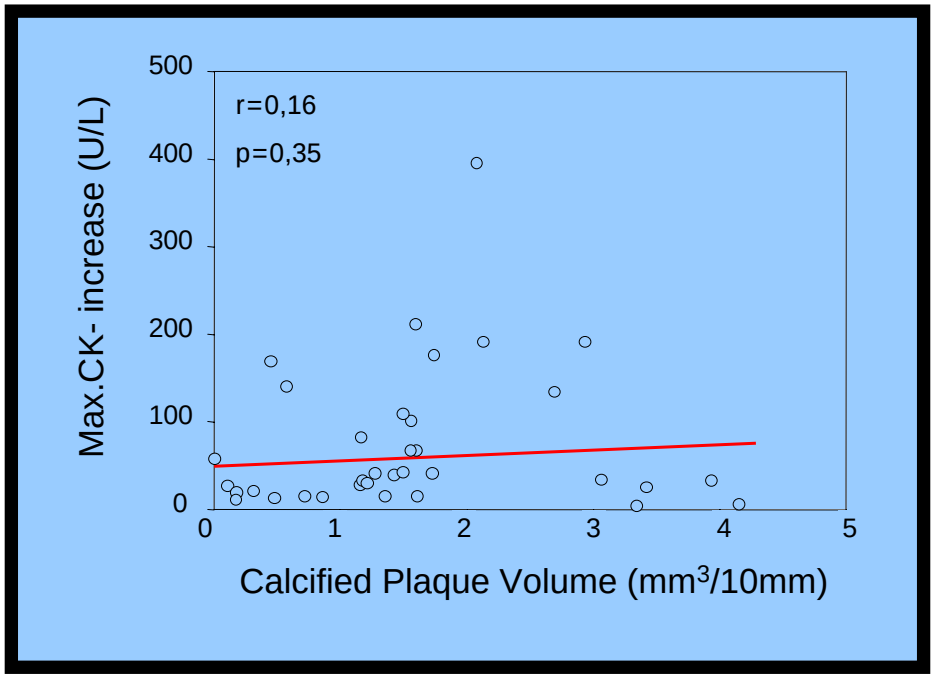


Coronary Microembolization during Standardized PCI Park AJC 2007



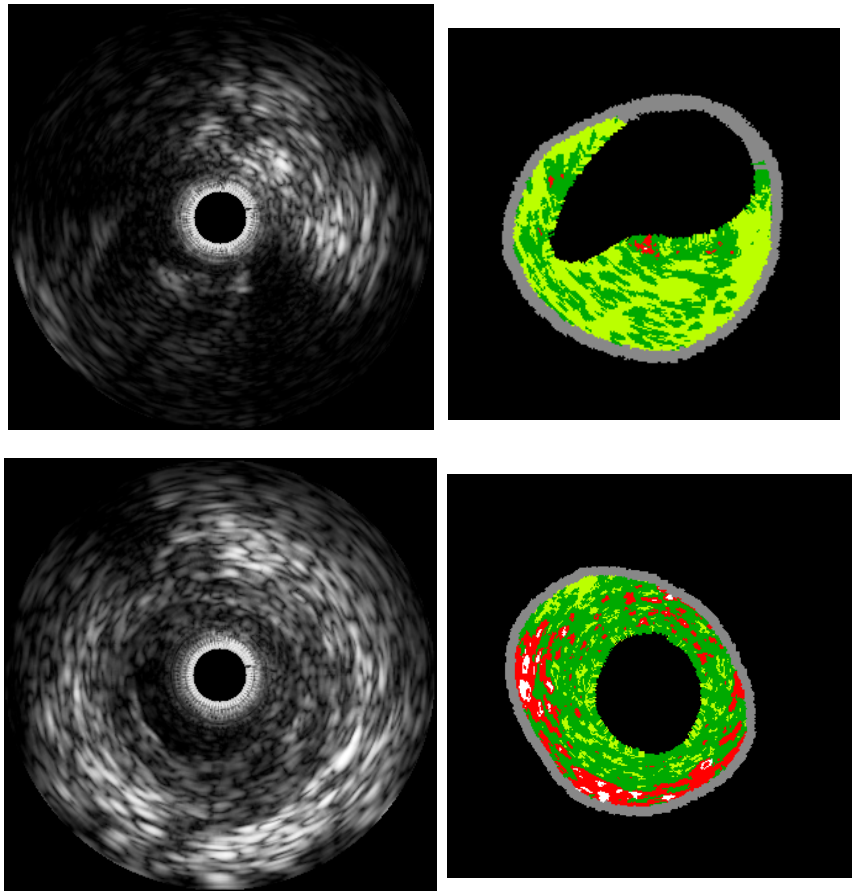
No correlation with plaque components other than necrotic core.





Fresh Thrombotic Lesions by VH IVUS

VH IVUS was **NOT** developed to identify fresh intra luminal thrombus or intramural hemorrhage. If fresh thrombus is included inside lumen contours it may appear as yellowish-green and more organized, already fibrotic thrombus as green



Examples of carotid lesions which caused material in the distal filter device during stenting. By histology (Dr. Virmani) the upper case was fresh thrombus the lower case was organized fibrotic lesion (T Diethrich; CAPITAL, JEVT 2007).

Angiographic no-reflow phenomenon and plaque characteristics by virtual histology intravascular ultrasound in patients with acute

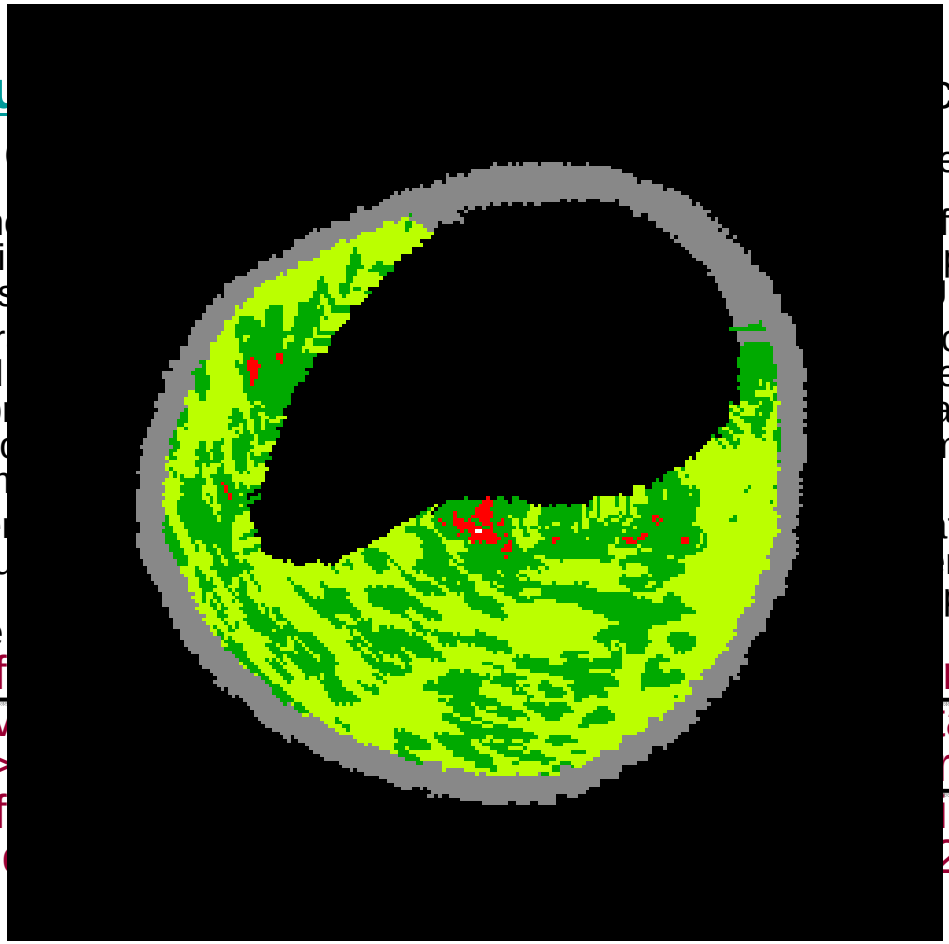
Nakamura T, Ku... cular Division, Jichi Medical University, (...

...ervCardiol 2007; 20:335-9

Objective: This study aim... f the angiographic no-reflow phenomenon i... preintervention plaque composition as asses... S).

Background: The angiogr... ctor in patients with AMI. Method: We enrolled... ed by primary stent implantation. All culpr... ation. The angiographic no-reflow phenomenc... mpared with TIMI flow grade before stent im...

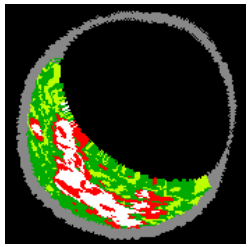
Results: Eight of 50 patie... tion. Gray-scale intravascular ultrasou... mbrane volume and plaque burden in the... percentage of fibro-fatty plaque volume in the... 17.0 +/- 1.1%, P = 0.05). The presence of... ro-fatty and fibrous plaque (plaque v... aining fibro-fatty plaque volume >... reflow (P = 0.02). Corrected TIMI f... image were significantly larg... 27.4 +/- 2.3, P = 0.01).



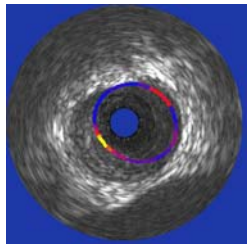
Conclusion: The culprit lesions with large plaque burden, or with "marble"-like image by VH-IVUS, are associated with the angiographic no-reflow phenomenon in patients with AMI.

PROSPECT & IBIS

Longitudinal Studies of Plaque Progression



The PROSPECT Trial



700 pts with ACS

UA (with ECG Δ) or NSTEMI or STEMI >24º

1-2 vessel CAD undergoing PCI

at up to 40 sites in U.S., Europe

Metabolic S.
- -Waist circum
- -Fast lipids
- -Fast glu
- -HgbA1C
- -Fast insulin
- -Creatinine

PCI of culprit lesion(s)

Successful and uncomplicated

Formally enrolled

Biomarkers
- -Hs CRP
- -IL-6
- -sCD40L
- -MPO
- -TNF α
- -MMP9
- -Lp-PLA2
- -others

PI: Gregg W. Stone
Sponsor: Abbott Vascular; Partner: Volcano

IBIS 2 (Europe)

(I**ntegrated** B**iomarkers and** I**maging Study**)

- European randomized controlled Study in ACS and non ACS patients.
- **Goal:** randomized systemic medication trial (LPPLA2 inhibition) to show plaque stabilization with palpography (primary end-point), with VH (secondary end-point).
- **Background**: IBIS 1 showed a significant correlation with the change in LPPLA2 level and the number of ROC level and the amount of NC.
- **N = 330 (in 23 EUR sites)**
- PI: P Serruys
- Sponsor: GSK
- **Status:** enrolment completed and fu complete. Data analysis on-going.

Other Studies

Relationship between cardiovascular risk as predicted by established risk scores and coronary artery plaque composition: a virtual histology intravascular ultrasound analysis

Ahmed Khattab et al, Bad Segeberg /Germany, TCT 2007

- For both algorithms, patients at low estimated risk of events showed significantly more fibrous tissue percentages than patients at high risk (p=0.002 and 0.004 for the SCORE and **Framingham algorithms**, respectively). Plaques of patients with higher risk showed a non-significantly higher necrotic core percentage. For the **SCORE risk prediction algorithm**, dense calcium percentage was significantly higher in patients with high risk compared to patients with low risk (13.9 ± 10.4% versus 4.9 ± 4.9%, p = 0.008). The prevalence of IVUS-derived thin cap fibroatheromas was significantly higher in patients at high risk, whereas patients at low risk had more stable plaque phenotypes (p=0.002 and 0.003 for the SCORE and Framingham algorithms, respectively).

- Conclusions: **In vivo plaque composition and morphology assessed by IVUS-VH were related to the cardiovascular risk predicted by established risk prediction algorithms in patients with non-obstructive coronary artery disease, supporting the role of plaque composition in the mechanisms of development of cardiovascular events.**

Relationship between high sensitive C-reactive protein and coronary plaque component in patients with acute coronary syndrome: Virtual Histology study

Sawada T, Shite J, Shinke T, Watanabe S, Otake H,Matsumoto D, Tanino Y, Ogasawara D, Paredes OL, Yokoyama M. Division of Cardiovascular and Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine.

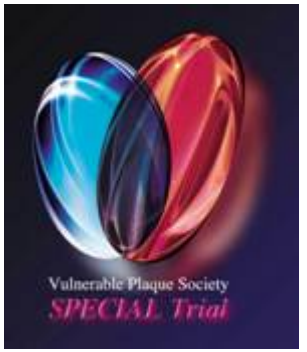
J Cardiol. 2006 Sep;48(3):141-50.

- OBJECTIVES: Elevated circulating C-reactive protein (CRP)is commonly observed in patients with acute coronary syndrome(ACS), suggesting enhanced inflammation in vulnerable plaques. However, few data are available on the relationship between the levels of CRP and the histological composition of coronary plaque. We investigated the relationship between plasma high sensitive CRP level and coronary plaque component with Virtual Histology intravascular ultrasound (VH-IVUS). METHODS: Twenty eight patients with ACS and 37 patients with non-ACS were enrolled in the study. Plasma high sensitve CRP levels were measured before catheterization. A total of 125 lesions (ACS; 24 culprit lesions, 30 non-culprit lesions, non-ACS; 34 culprit lesions, 37 non-culprit lesions)underwent IVUS volumetric investigation, and the volume of plaque and media were calculated. Spectral analysis of IVUS radiofrequency data was performed with VH software, and plaque and media were classified into fibrous, fibro-fatty, dense calcium, and necrotic core elements. RESULTS: Although the plasma high sensitive CRP level in patients with ACS was higher than that in those with non-ACS (0.26 +/- 0.2 vs 0.15 +/- 0.17 mg/dl, $p < 0.05$), necrotic core volume was not different between the two groups(11.7 +/- 7.3 vs 12.3 +/- 7.2mm3/cm, $p = 0.71$). There was a positive correlation between high sensitve CRP and necrotic core volume in patients with ACS, not only in culprit lesions ($p = 0.0004$, $r2 = 0.564$) but also in non-culprit lesions ($p = 0.0008$, $r2 = 0.473$), whereas patients with non-ACS showed no correlations.

- **CONCLUSIONS: IVUS spectral analysis revealed that elevated plasma high sensitve CRP level was correlated with necrotic core volume in patients with ACS, both in culprit and non-culprit lesions, suggesting enhanced vascular inflammation.**

SPECIAL

- **PIs: Dr Tadanori Aizawa and Dr Etsuo Tsuchikane**
- Multicenter study on the safety of 3-vessel IVUS interrogation, clinical event rate and silent plaque progression of angiographically intermediate lesions in ACS patients
- Angiographic and IVUS follow-up of all patients at 1 year
- All sites: Japan
- n=300
- Status: Enrolling



ATLANTA

Assessment of Tissue characteristics, Lesion morphology and hemodynamics by Angiography with fractional flow reserve, intravascular ultrasound and virtual histology and Non-invasive computed Tomography in Atherosclerotic plaques

- PI Dr S Voros
- Single center registry with one year clinical outcome (MACE) of intermediate lesions by angiogram and diagnostic correlation with further assessment by FFR, MSCT and grayscale and VH IVUS
- N=300
- Enrolling

Summary

- VH Registry has:
  - Demonstrated good correlation between plaque composition by histology and known risk factors for coronary atherosclerosis.
  - Highlighted the multi factorial nature of atherosclerosis and the pivotal role of necrotic core in adverse clinical outcome.
- Other recent studies have shown a significant correlation between plaque composition, clinical presentation, systemic risk factors, and blood born markers.
- Ongoing clinical registries are aimed to assess further, in a prospective manner, the role of plaque composition and type with:
  - PROSPECT; clinical events
  - SPECIAL: also clinically silent plaque progression
  - IBIS: correlation between systemic modification of known risk factors
  - ATLANTA: the correlation with VH IVUS and FFR with a non-invasive MSCT