



In search for predictors of carotid plaque destabilization: Update from the ongoing CRACK-VH* study.

*Carotid arteRy plaque morphology And atherosClerosis biomarkers: Krakow – Virtual Histology study

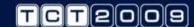
P. Musiałek, P. Pieniążek, A. Undas, Ł. Tekieli, A. Kabłak-Ziembicka, T. Przewłocki, E. Stepień, M. Pasowicz, K. Żmudka, W. Tracz

JAGIELLONIAN UNIVERSITY DEPT. OF CARDIAC & VASCULAR DISEASES, AND JOHN PAUL II HOSPITAL, KRAKÓW, POLAND



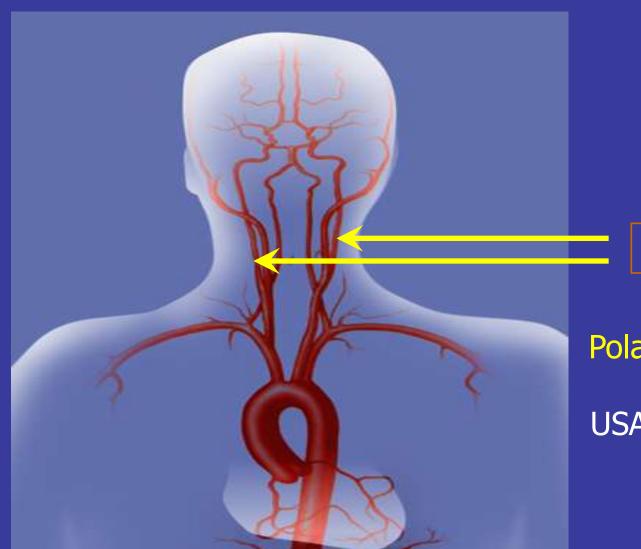
Disclosure Statement of Financial Interest

I, Piotr Musialek DO NOT have any 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.





Carotid artery stenosis and stroke



~20% strokes

Poland: (~ 12 000 / y

USA: $\sim 140\ 000\ /\ y$

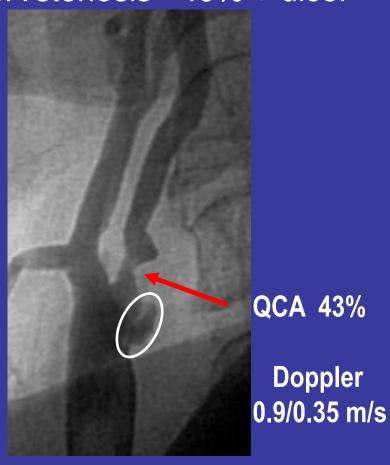


The Problem

MZ, 74y, asymptomatic LICA stenosis 85%



SŻ, 68y, *asymptomatic* LICA stenosis ~40% + ulcer



Whether –and which of the two– plaques should be treated by mechanical stabilization (CAS) or removal (CEA)?

Stroke 2006:37:577-617

Guidelines for Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Council on Stroke: Co-Sponsored by the Council on Cardiovascular Radiology and Intervention: The American Academy of Neurology affirms the value of this guideline. Ralph L. Sacco, Robert Adams, Greg Albers, Mark J. Alberts, Oscar Benavente, Karen Furie, Larry B. Goldstein, Philip Gorelick, Jonathan Halperin, Robert Harbaugh, S. Claiborne Johnston, Irene Katzan, Marguret Kelly-Hayes, Edgar J. Kenton, Michael Marks, Lee H. Schwamm and Thomas Tomsick



ped redukcją dr hab, med, Adams Witkowskiego ACCF/SCAL/SVMB/SIR/ASITN 2007 Clinical Expert

ACCF/SCAL/SVMB/SIR/ASITM CLINICAL EXPERT CONSENSUS DOCUMENT

Consensus Document on Carotid Stenting

A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (ACCF/SCAI/SVMB/SIR/ASITN Clinical Expert Consensus Document Committee on Carotid Stenting)

Carotid artery stenosis: Indications to CEA or CAS

stenosis ≤ 50%

no indications to CEA / CAS

(even if 'high risk' plaque) (even if symptoms: TIA/stroke!)

- asymptomatic stenosis < 80% —— no indications to CEA / CAS)
- symptomatic stenosis > 50% ----CEA (or CAS)
- asymptomatic stenosis > 80% --- one may perform CEA (or CAS)

Guidelines for Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Council on Stroke: Co-Sponsored by the Council on Cardiovascular Radiology and Intervention: The American Academy of Neurology affirms the value of this guideline. Ralph L. Sacco, Robert Adams, Greg Albers, Mark J. Alberts, Oscar Benavente, Karen Furie, Larry B. Goldstein, Philip Gorelick, Jonathan Halperin, Robert Harbaugh, S. Claiborne Johnston, Irene Katzan, Marguret Kelly-Hayes, Edgar J. Kenton, Michael Marks, Lee H. Schwamm and Thomas Tomsick



ACCF/SCAL/SVMB/SIR/ASITM CLINICAL EXPERT CONSENSUS DOCUMENT

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- symptomatic stenosis > 50%
 — CEA (or CAS)
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TCT2009 TRANSCATHETER Z, 74y, asymptomatic LICA stenosis 85%



indication to CEA / CAS

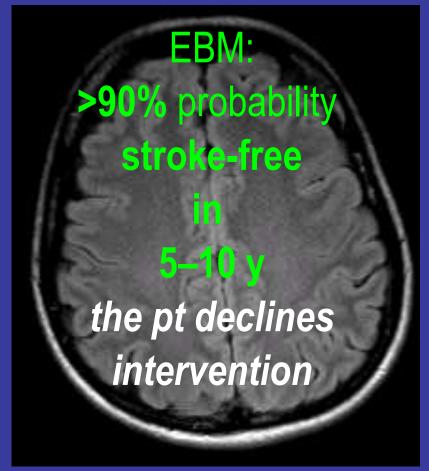
SŻ, 65y, asymptomatic LICA stenosis ~40%



no indication to CEA / CAS

(in both – 'full' pharmacotherapy incl. 'high-dose' statin, ASA, ACEI)

TCT2009 TRANSCATIFIED, 74y, asymptomatic LICA stenosis 85%



indication to CEA / CAS

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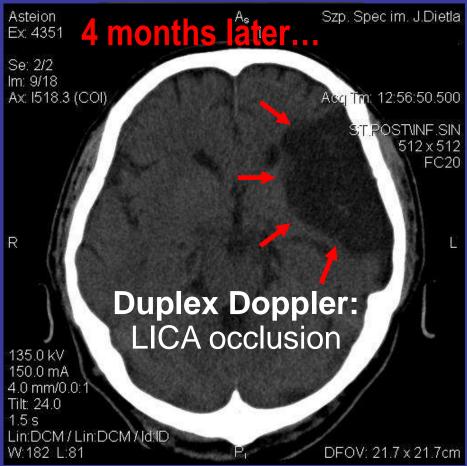
no indication to CEA / CAS (in both – 'full' pharmacotherapy incl. 'high-dose' statin, ASA, ACEI)

TCT2009 TRANSCATHETER 74y, asymptomatic LICA stenosis 85%

EBM: >90% probability stroke-free the pt declines intervention

> indication to CEA / CAS

SŻ, 65y, asymptomatic LICA stenosis ~40%



no indication NIH-SS 5 to CEA / CAS Rankin 3

motoric aphasia 4/5 right hemiparesis 3/5

74y, asymptomatic LICA stenosis 85%

> EBM: >90% probability stroke-free the pt declines intervention

SŻ, 65y, asymptomatic LICA stenosis ~40%



indication to CEA / CAS no indication NIH-SS to CEA / CAS Rankin

motoric aphasia 4/5 right hemiparesis 3/5

... still in 2009!

TREATMENT OF **CAROTID STENOSIS**

$$NNT = 6$$

$$VNT = 12$$
 (20-30)

NNT = 12 complications < 3%

... still in 2009!

TREATMENT OF **CAROTID STENOSIS**

$$NNT = 6$$

$$NNT = 12$$
 (20-30)

but 80% major strokes occur

w/o ANY prodromal signs (TIA)



'The tighter the lesion the higher the risk' ... not necessarily!

TABLE 2. Relationship Between Severity of Stenosis and Stroke Rate

		Patient Stroke Rate					
Stenosis Severity*	NASCET	NASCET (2-Year)11		ECST (3-Year)12		ACAS (3-Year) ¹³	
60%-69%	428†	13%	137	11%	131	6%	
70%-79%	43	21%	170	9%	94	5%	
80%-89%	33	27%	159	21%	NS		
90%-99%	24	35%	60	32%		NS	
80%-99%	57	31%	219	24%	88	3%	

Values given are the ipsilateral stroke rates at the time points stated. NS indicates not stated.

†For patients with 50%-69% stenosis.17

Golledge J, Stroke 2000

TABLE 2. Relationship Between Degree of Stenosis and Risk of Stroke With Medical Therapy (Pooled From ACAS and ACST)

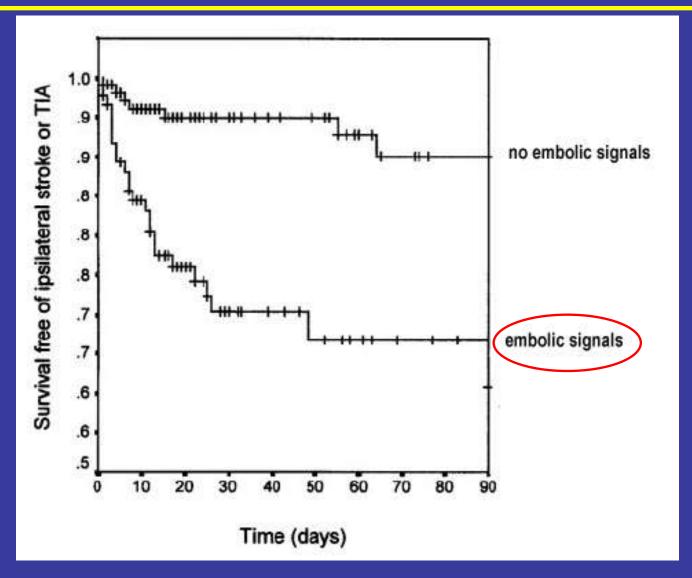
Stenosis 60%-69% 70%-79% $\geq 80\%$ No. with stroke/total No. 60/774 (7.8%) 40/541 (7.4%) 28/550 (5.1%)

Derdeyn CP, Stroke 2007

^{*}Definition of stenosis varied.

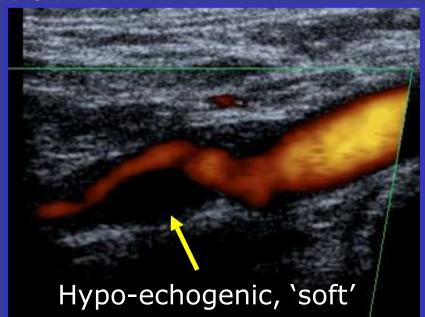


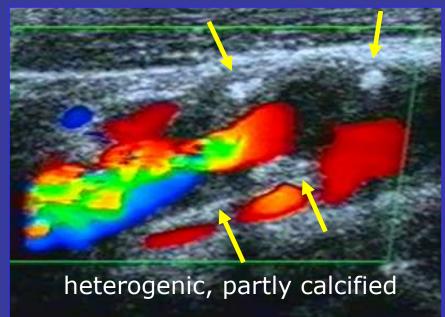
Asymptomatic embolization | from the carotid plaque vs. Stroke risk

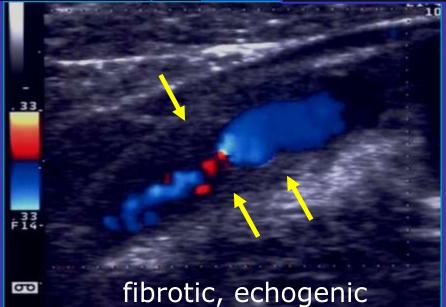


TCT2009 TRANSCATHETER CARDIOVASCULAR THERAPEUTICS

Can Duplex Doppler help?





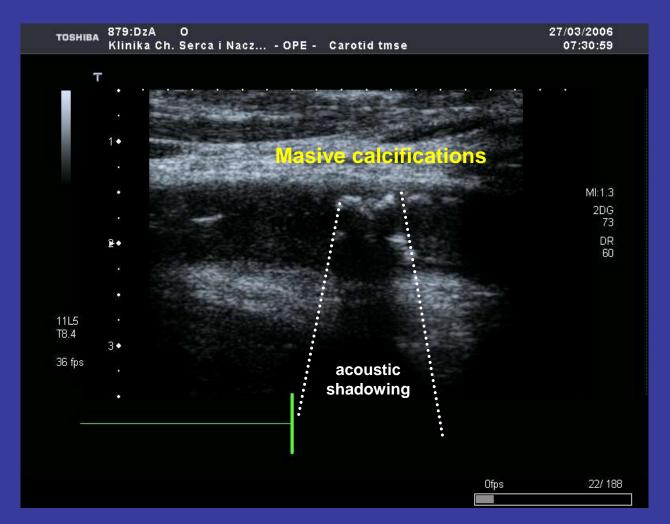


A. Kabłak-Ziembicka, Kraków



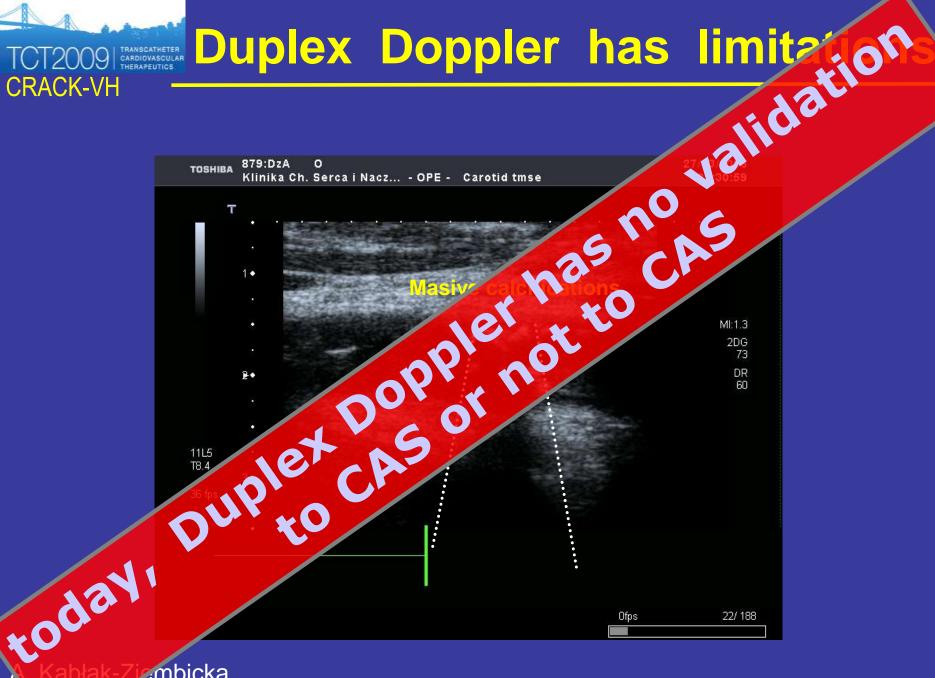


Duplex Doppler has limitations









embicka,



but Duplex Doppler can help in the selection of EPD and stent type!

J ENDOVASC THER 2008;15:249-262	2
◆ CLINICAL INVESTIGATION —	
Carotid Artery Stanting With Patient, and	

Carotid Artery Stenting With Patient- and Lesion-Tailored Selection of the Neuroprotection System and Stent Type: Early and 5-Year Results From a Prospective Academic Registry of 535 Consecutive Procedures (TARGET-CAS)

Piotr Pieniazek, MD, PhD¹; Piotr Musialek, MD, PhD¹; Anna Kablak-Ziembicka, MD, PhD¹; Lukasz Tekieli, MD¹; Rafal Motyl, MD, PhD²; Tadeusz Przewlocki,

Zbigniew Moczulski, MD³; Mieczyslaw Pasowicz, MD, PhD³; Andrzej Sokolowski, MD, PhD⁴; Agata Lesniak-Sobelga, MD, PhD Krzysztof Zmudka, MD, PhD⁵; and Wieslawa Tracz, MD, PhD¹

Departments of ¹Cardiac and Vascular Diseases and ⁵Hemodynar Angiocardiography, Jagiellonian University Institute of Cardiolog Centers of ²Clinical Neurology and ³Diagnostics and Rehabilitatic Pulmonary Diseases, John Paul II Hospital, Krakow, Poland. ⁴Dep Krakow University of Economics, Krakow, Poland.

Purpose: To develop and prospectively evaluate the safety and efficacy of an algorithm for tailoring neuroprotection devices (NPD) and stent types to the patient/lesion in carotid artery stenting (CAS).

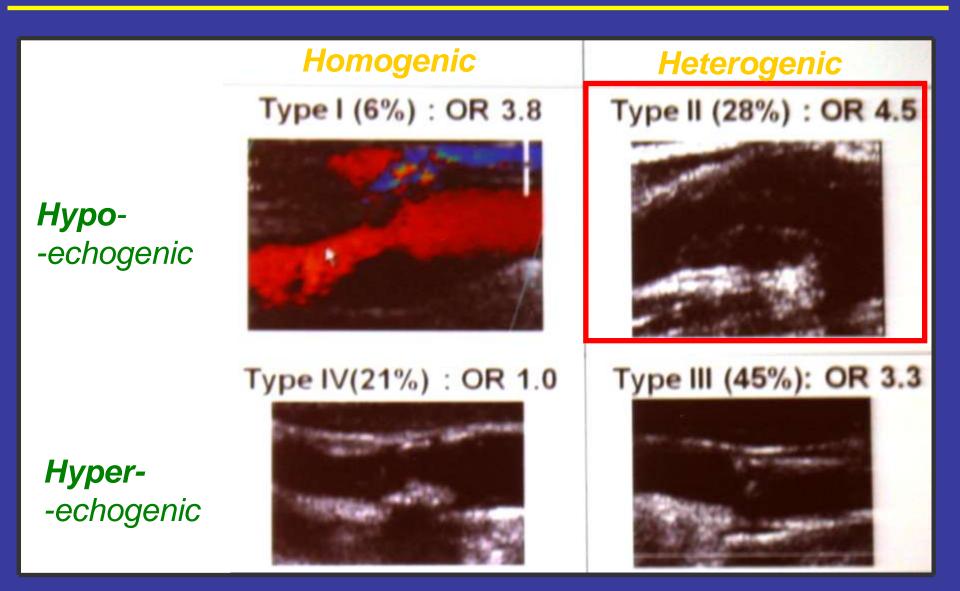
Methods: From November 2002 to October 2007, 499 patients (360 men; mean age 65.2±8.4 years, range 36–88) were prospectively enrolled in a safety and efficacy study of tailored CAS using proximal (flow blockade or reversal) or distal (filters or occlusion) NPDs and closed- or open-cell self-expanding stents. Of the 535 lesions treated in the study, 175 (32.7%) were "high risk" by morphology. Half (50.1%) the patients were symptomatic.

Results: A quarter (137, 25.6%) of the procedures were performed under proximal protection and the remainder (398, 74.4%) with distal NPDs; the direct stenting rate was 66.9%. High-risk lesions were treated predominantly with a proximal NPD and closed-cell stent (77.1% and 82.9%, respectively) and less frequently by direct stenting (37.1%, p<0.0001 versus non-high-risk lesions). The in-hospital death/stroke rate was 2.0% (95% CI 0.85% to 3.23%), and the death/major stroke rate was 0.7% (95% CI 0.02% to 1.48%). There were no myocardial infarctions, but there was 1 (0.2%) further death within 30 days. With the tailored approach, symptom status and high-risk lesion morphology were not risk factors for an adverse outcome after CAS; only age >75 years (p<0.001) was a predictor of short-term death. Long-term survival (95.4% at 1 and 88.3% at 5 years) was similar for symptomatic versus asymptomatic patients, direct stenting versus predilation, and closed-vs. open-cell stent design; only coronary artery disease adversely impacted survival (p=0.04). The rates of freedom from death/ipsilateral stroke were 94.9% at 1 year and 85.9% at 5 years.

Conclusion: Tailored CAS is associated with a low complication rate and high long-term efficacy. CAS operators should have a practical knowledge of different NPDs, including at least one proximal type.



TCT2009 TRANSCATHETER Carotid plaque on DD and symptom risk





Classic ('gray-scale') IVUS in border-line carotid lesions





V max 1.6 / 0.54 m/s indicates non-significant RICA stenosis (ca. 50%)

[in this patient – recent L hemisph stroke, LICA occluded]

P. Musiałek P. Pieniazek PCR06

MLA densitometry MLA circular

% area stenosis densitometry

% area stenosis circular

reduced contrast opacification
('brightening')

indicates that plaque burden might be higher...

COMPUTER DEFINED OBSTRUCTION ANALYSIS RICA 3.73 mm MLD 30 % % diameter stenosis 5.31 mm Reference diameter 10.20 mm Length stenotic segment 1.78 mm Position of proximal border 7.88 mm2 MLA densitometry 10.93 mm2 MLA circular 64 % % area stenosis densitometry 51 % % area stenosis circular Reference area 22.18 mm2 **RCCA** 4.04 mm MLD 32 % % diameter stenosis 5.98 mm Reference diameter 11.32 mm Length stenotic segment Position of proximal border 1.60 mm

Emboshield-protected CAS performed

cutting balloon predilatation

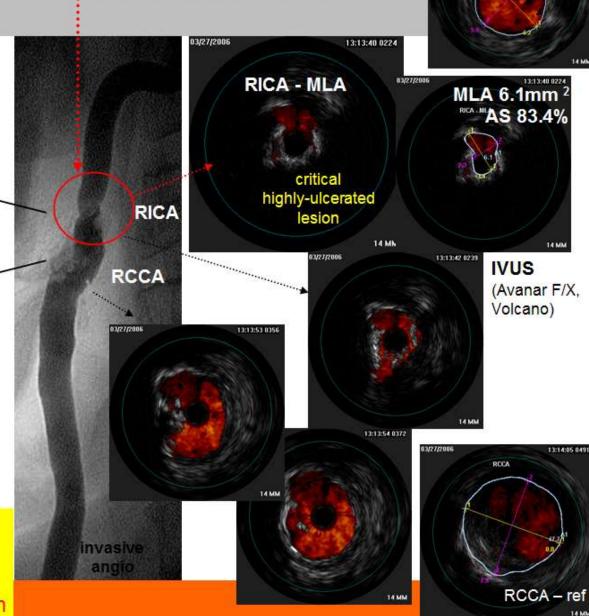
23.89 mm2

12.83 mm2 15 %

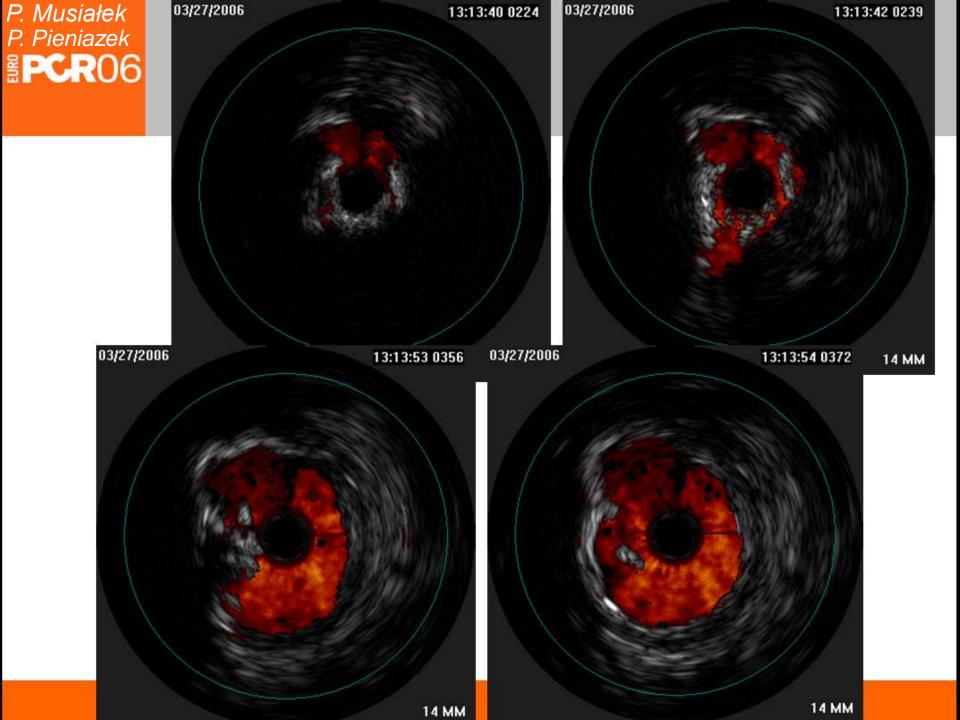
54 %

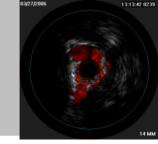
Carotid Wallstent 7.0 x 30mm

QCA

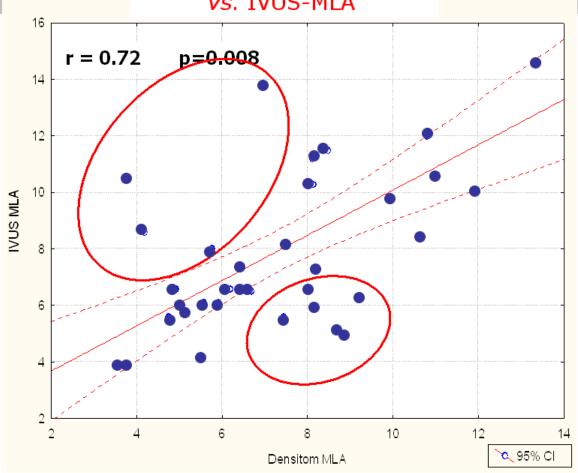


RICA – distal ref



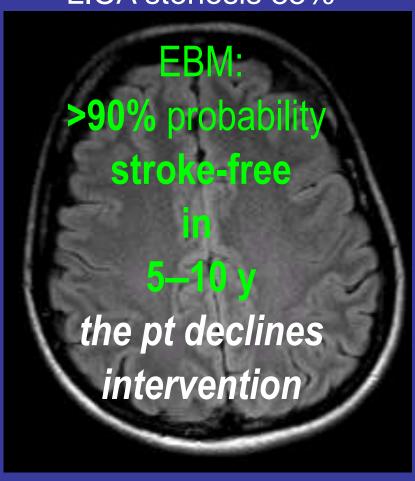






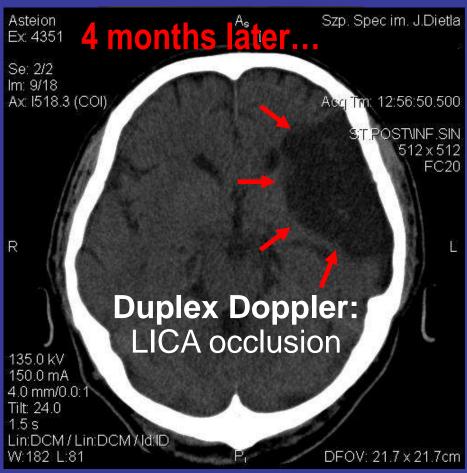
but densitometric MLA still not accurate enough to replace IVUS in decision-making

TCT2009 MZ, 74y, asymptomatic LICA stenosis 85%



indication to CEA / CAS

SŻ, 65y, asymptomatic LICA stenosis ~40%



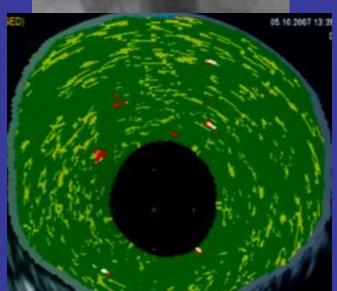
no indication NIH-SS 5 to CEA / CAS Rankin 3

motoric aphasia 4/5 right hemiparesis 3/5



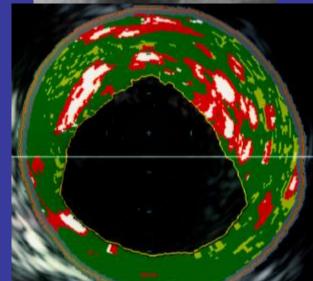
MZ, 74y, asymptomatic LICA stenosis 85%

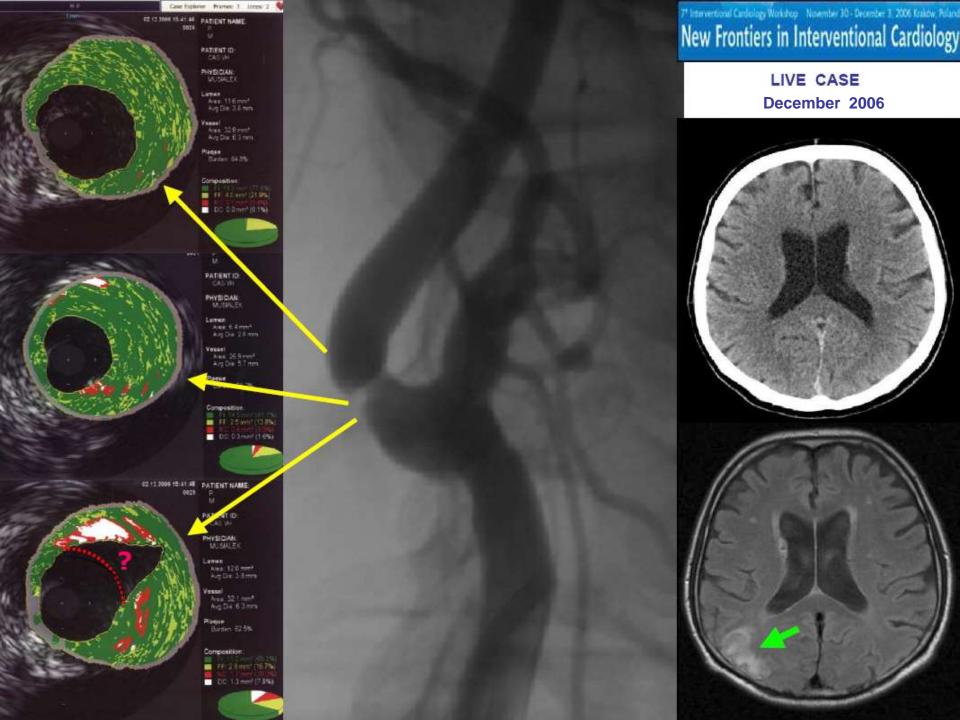




SŻ, 68y, asymptomatic LICA stenosis ~40%







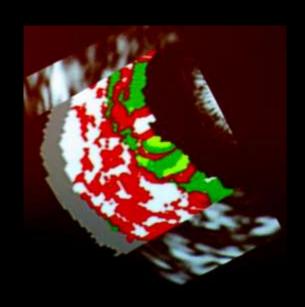


November 2006

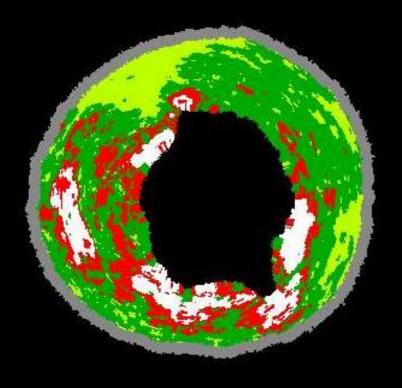


COMPUTER DEFINED OBSTRUCTION ANA	ALYSIS
MLD % diameter stenosis Reference diameter Length stenotic segment Position of proximal border	: 2.95 mm : 51 % : 5.98 mm : 7.37 mm : 2.97 mm
MLA densitometry MLA circular % area stenosis densitometry % area stenosis circular Reference area Volume stenotic segment Plaque area	: 66 % : 22.26 mm2 : 83.11 mm3 : 10.23 mm2
Plaque volume	: 56.24 mm3

IVUS – Virtual Histology (VH)



- Calcifications
- Fibrotic
- Fibro-fatty
- Necrotic core



Volcano Corp.

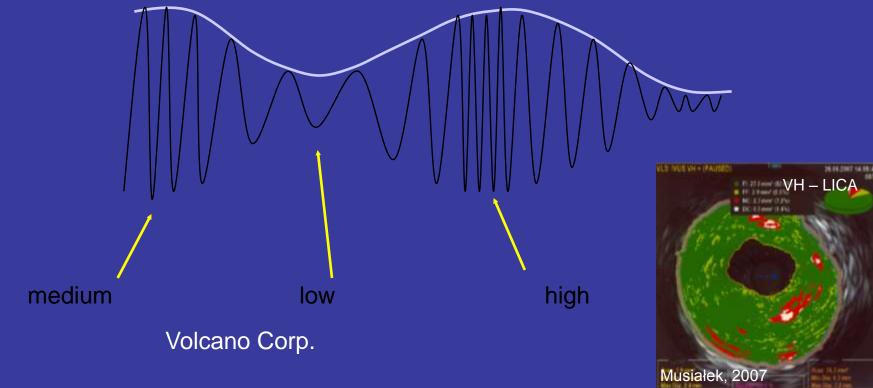
IVUS - VH



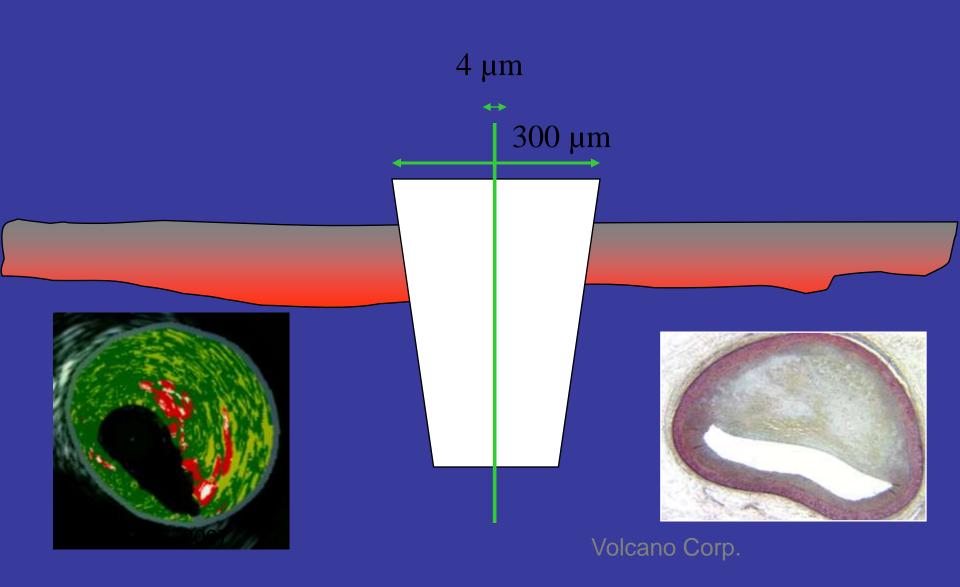
Combined analysis of

AMPLITUDE + FREQUENCY

of tissue-reflected ultrasound



VH 'slice' vs. histology slice



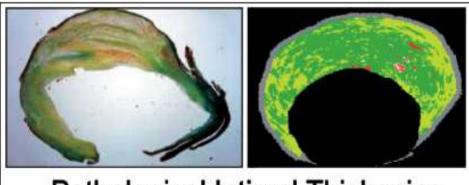
IVUS-VH: validated for the carotids

EB Diethrich et al.

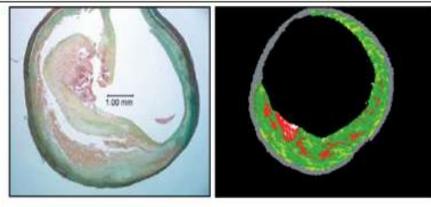
J ENDOVASC THER 2007;14:676-686

TABLE 3 VH IVUS Accuracy by Plaque Types

	Diagnostic Accuracy	Sensitivity	Specificity
Thin-cap fibroatheroma	99.4%	75.0%	100%
Calcified thin-cap fibroatheroma	96.1%	90.0%	97.1%
Fibroatheroma	85.9%	54.1%	96.9%
Fibrocalcific	85.5%	87.1%	84.5%
Pathological intimal thickening	83.4%	88.5%	82.0%
Calcified fibroatheroma	72.4%	32.5%	93.0%

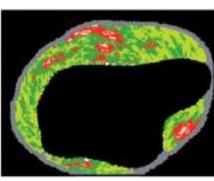


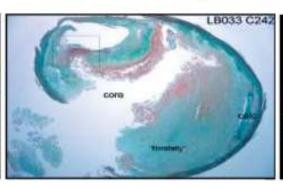
Pathological Intimal Thickening

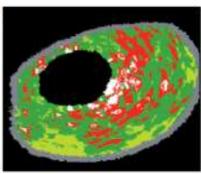


Thin-Cap Fibroatheroma



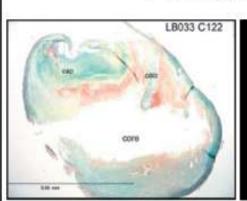


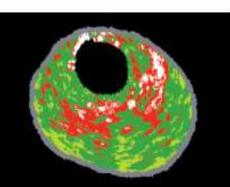




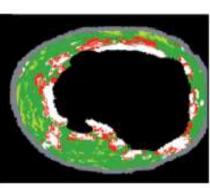
Fibroatheroma

Calcified Thin-Cap Fibroatheroma









Calcified Fibroatheroma

Fibrocalcific

EB Diethrich, R Virmani, 2007



CRACK-VH

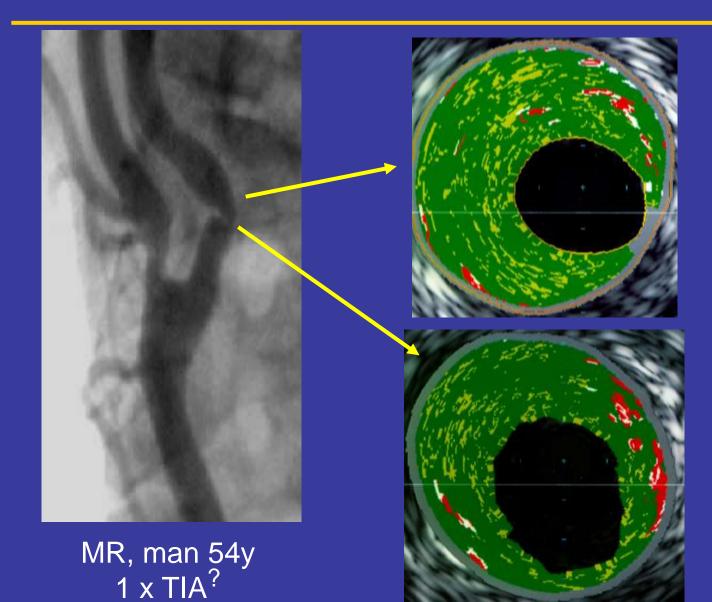


- a prospective academic study to establish the value of VH-carotid plaque characteristics combined with biomarkers in evaluating carotid atherosclerosis in relation to neurological symptoms/symptom risk
- study began in 2006, first CRACK-VH data submitted to NFIC (Nov 2007), ESC (Feb 2008) and TCT (April 2008)
- 206 patients recruited (102 symptomatic or previously symptomatic) (age 66±8 years, range 38-82y, 67% men)
 all referred for CAS after consultation by independent neurologist—
- 226 carotid arteries imaged with IVUS-VH

 64 IVUS imaging without EPD (28.3%)
 in 35 IVUS imaging under a proximal EPD (GoreFR or MoMa) (15.5%)
- 58 lesions (25.7%) not stented (i.e., left for f/u) { longitudinal, prosp.}
- Ethical Committe—approved, no industry funding/sponsorship



IVUS – VH: cross-section @ max stenosis site can be misleading!

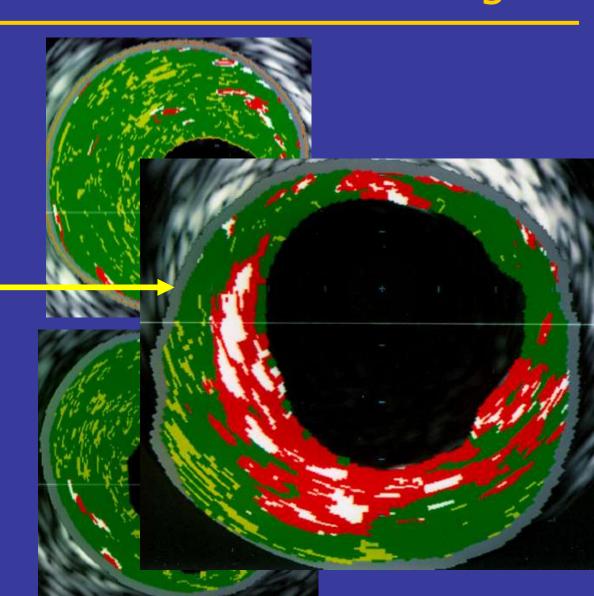




IVUS – VH: cross-section @ max stenosis site can be misleading!



MR, man 54y 1 x TIA?





IVUS-VH acquired under proximal EPD (ICA fow reversal, Gore NPS)



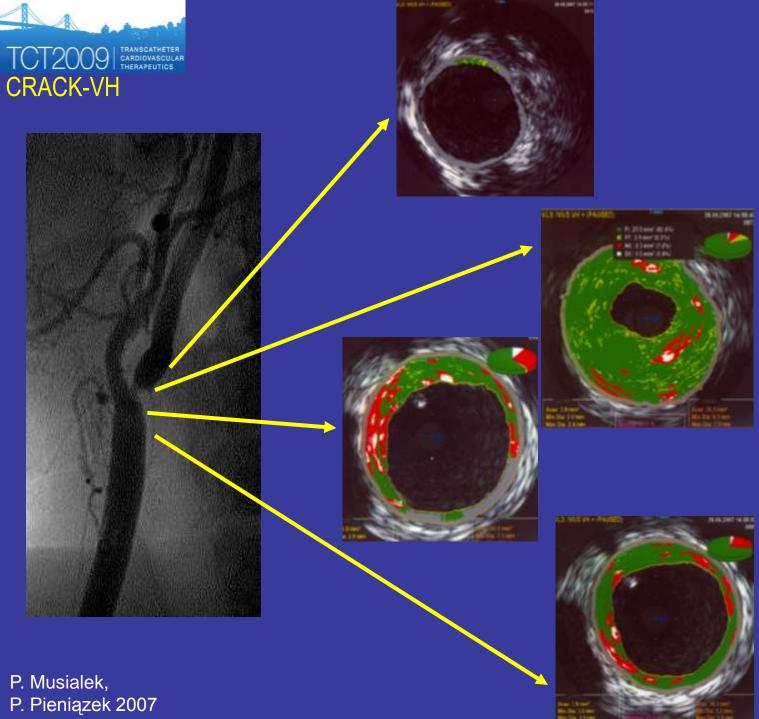
woman, 48y, asympt. LICA father – stroke 53 y.



lesion crossing with a guidewire



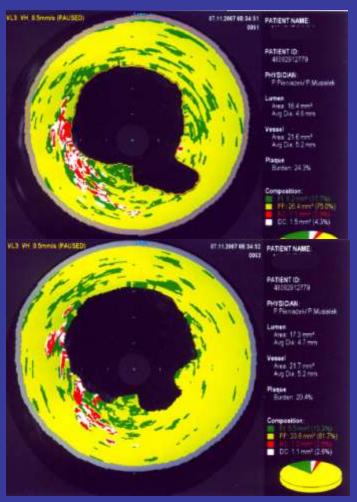
then IVUS-VH acquisition



RICA (95% stenosis)

LICA (TIAs – recurr. aphasia R hand numbness)

man 56y, bilateral carotid stenosis



LICA: highly lipidic, ulcerated plaque





How to assess carotid plaques with VH?

- 'worst' frame (NC, TCFA?)
 single?
 average from 3-5 consecutive?
- volumetric analysis ('out of field' problem)
- how to reconcile divergent findings from the same plaque at different 'levels' – those are 'natural'
- virgin asymptomatic vs. past-symptomatic (>6mo)
- clinical symptoms or eg. brain MRI



Results

IVUS-VH imaging was pefrormed w/o complications.

Pilot analysis indicated:

- No difference in angiographic stenosis severity between S and aS (52-84% vs. 49-88%, p=0.37).
- Plaque ulceration on IVUS more prevalent in S (63.2 vs. 29.0%, p<0.05).
- In aS, average MLA larger (7.1 vs. 5.8mm², p=0.02)
 and plaque burden lower (76.8% vs. 84.9%, p=0.01).



Results (pilot analysis, cont'd)

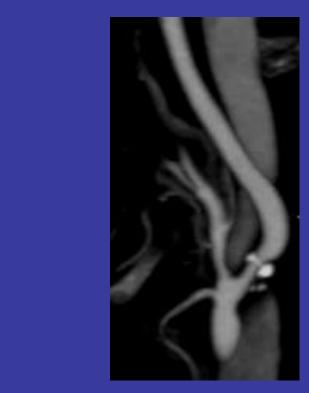
- Peak <u>DENSE CALCIUM (DC)</u> similar in both groups
 (S vs. aS): 3.3 (0.6–7.2) vs. 4.4 (0.3–18.2)%.
- Peak FIBRO-FATTY (FF) and Peak NECROTIC CORE (NC) tended to be higher in S 17.7 (4.3–81.7) vs. 15.1 (7.6–32.1)% and 10.2 (1.5–29.3) vs. 6.8 (2.0–17.3)% (but p>0.05)
- NECROTIC CORE in direct contact with the lumen (by VH), indicating fibrous cap <150µm, was more prevalent in S (89.5 vs. 52.9%, p<0.01).
- Macroscopic evidence of plaque debris captured by EPD was 57.9% in S and 35.3% aS (p=0.06).



WG, woman 62y, L hemisph. stroke May 2009

RICA 2.28/0.95 m/s 'AS'



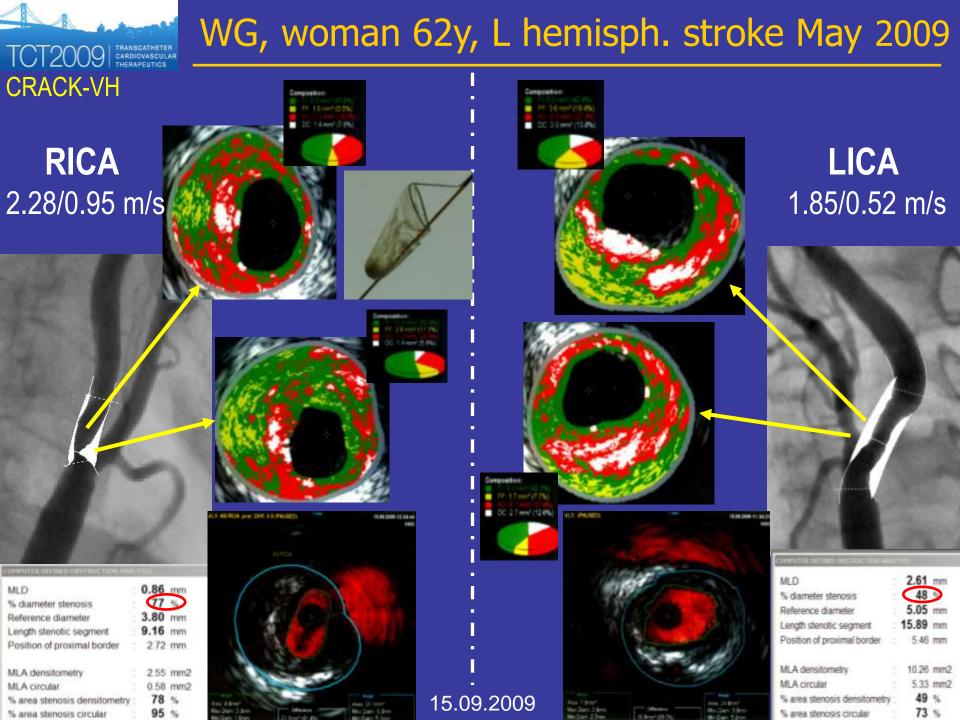


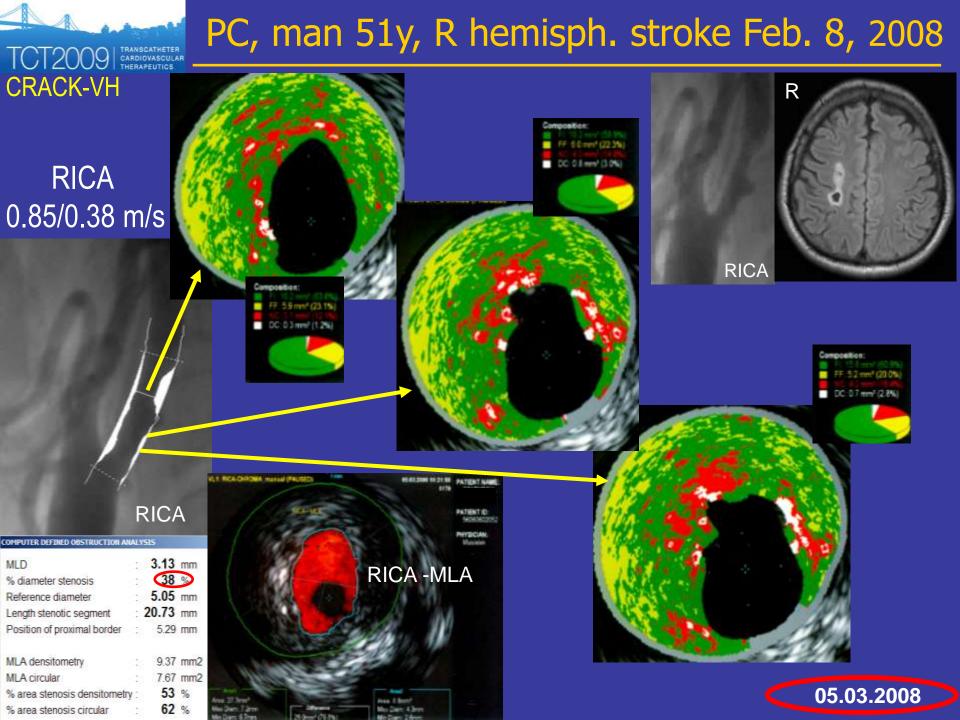
LICA1.85/0.52 m/s
'S'

Neuro consultation Sept. 14, 2009

- R upper limb weakness
- motoric aphasia
- NIH-SS 4

Conclusion: Symptomatic LICA, Asymptomatic RICA stenosis For LICA-CAS (RICA stenosis to be monitored)





PC, man 52y, R hemisph. stroke Feb. 8, 2008 **CRACK-VH** + 3 x TIA Aug. 2009 **RICA** Composition: FI: 14.2 mm² (49.1%) FF: 11.5 mm² (39.6%) 0.48 mm 91 % % diameter stenosis DC: 0.8 mm² (2.8%) 5.35 mm Reference diameter 25.25 mm Length stenotic segment Position of proximal border 1.82 mm MLA densitometry 0.78 mm2 08.2009 0.18 mm2 97 % area stenosis densitometry % area stenosis circular



Biomarkers (first n=75 pts)

• hsCRP (ng/mL)
$$5.01 \pm 8.19$$
 (0.50 – 74.20)

• IL-1B (pg/mL)
$$0.12 \pm 0.27$$
 (0.00 - 1.90)

•
$$L-6$$
 (pg/mL) 3.93 ± 7.83 (0.02 – 52.69)

•
$$L-8$$
 (pg/mL) 11.37 ± 1.50 (9.00 – 21.25)

• CD 40L (pg/mL)
$$321.13 \pm 252.8$$
 (42.5 – 1238.6)

• MMP-9 (ng/mL)
$$123.47 \pm 79.4$$
 (13.0 – 444.0)

• MMP-10 (pg/mL)
$$665.59 \pm 373.8$$
 (223.4 – 2156.3)

• Visfatin (ng/mL)
$$0.967 \pm 3.59$$
 (0.00 – 29.87)

• Lp-PLA₂ (ng/mL)
$$349.39 \pm 63.4$$
 (221.4 – 560.6)

•
$$sVCAM$$
 (ng/mL) 836.55 ± 112.9 (0.0 – 2101.0)

Pilot biomarker analysis

indicated significant correlations between:

• CD40L/IL-1ß

• IL-8/IL-1ß

• IL-8/CD40L

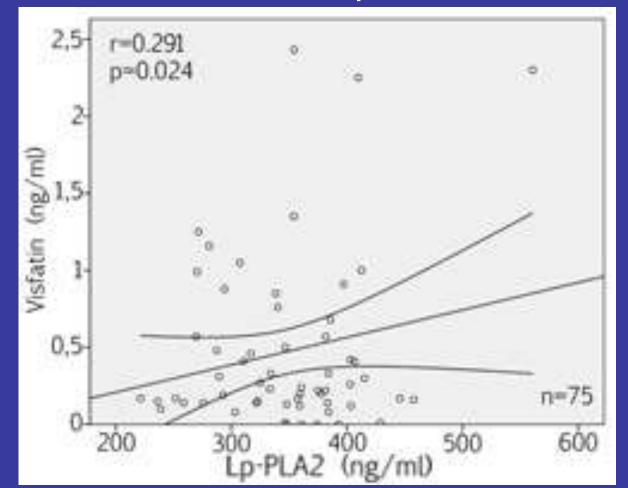
Visfatin/Lp-PLA2

r = 0.44

r = 0.46

r = 0.42

r=0.29 (p<0.05 for all)

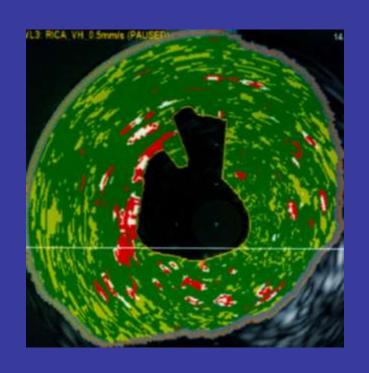


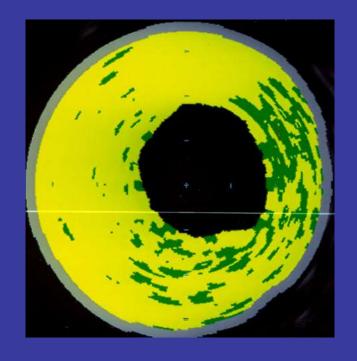
P. Musialek et al. 2009





EPD-captured embolic particles vs. VH









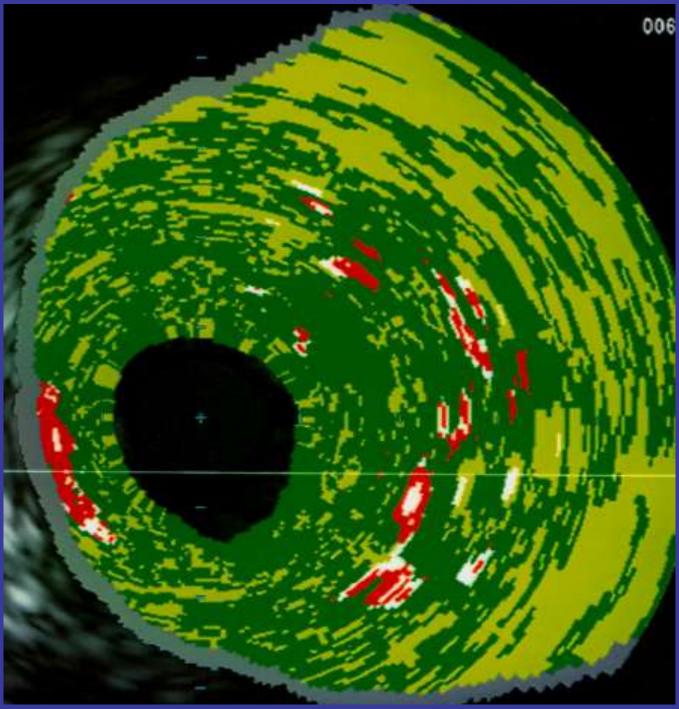


Carotid VH: current limitations

- thrombus imaging, stent imaging
- 'out of field' (10mm) problem
- no metabolic or vasa vasorum imaging
- need for manual contour adjustment (each frame) => v. laborious
- carotid media often difficult to define
- v. tight plaques should not be imaged (unless predilated) (risk of iatrogenic embolization!)
- fibrous cap of 150µm: thin enough or thick enough?
- massive calcifications are a problem









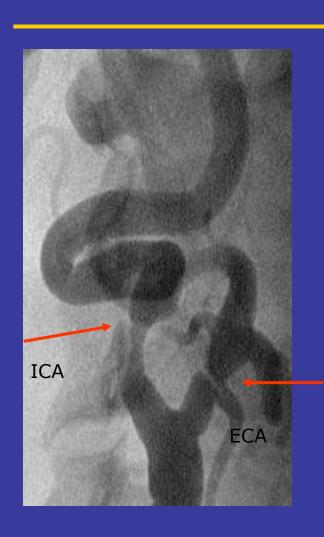
Conclusions



- Carotid plaque evaluation with IVUS-VH is safe.
- IVUS-VH can be acquired under proximal EPDs
- Plaque ulceration and the thin fibrous cap appeared more prevalent in the symptomatic carotid plaques.
- Initial findings seem consistent with the role of carotid plaque rupture and distal (brain) embolization as a mechanism of ischaemic stroke in a proportion of patients with non-critical carotid artery stenosis.



Woman, 68y, asymptomatic lesion

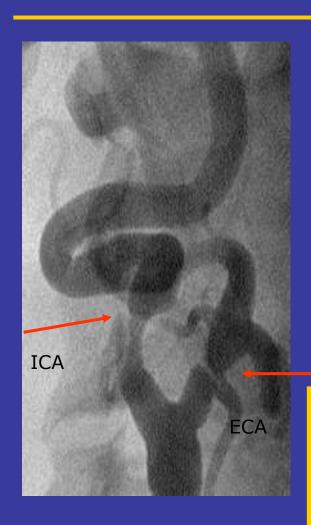


2009

- CAS (or CEA) ?
- Clinical & DD follow-up
 - + pharmacotherapy?



Woman, 68y, asymptomatic lesion



Within the next 5 years...

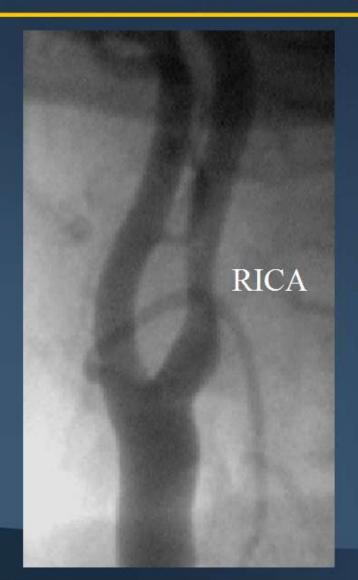
- CAS (or CEA) ?
- Clinical & DD follow-up+ pharmacotherapy ?
- RISK of symptoms?
 (MRI? CT? IVUS-VH?)
 ('biomarkers'?)
- IVUS-VH for decision-making?

Man, 63y, 'asymptomatic' RICA lesion CIPOOB (in 2001 CEA for a tight LICA stenosis + TIAs)

Duplex Doppler (July 2008): RICA 2.1 / 0.6 m/s



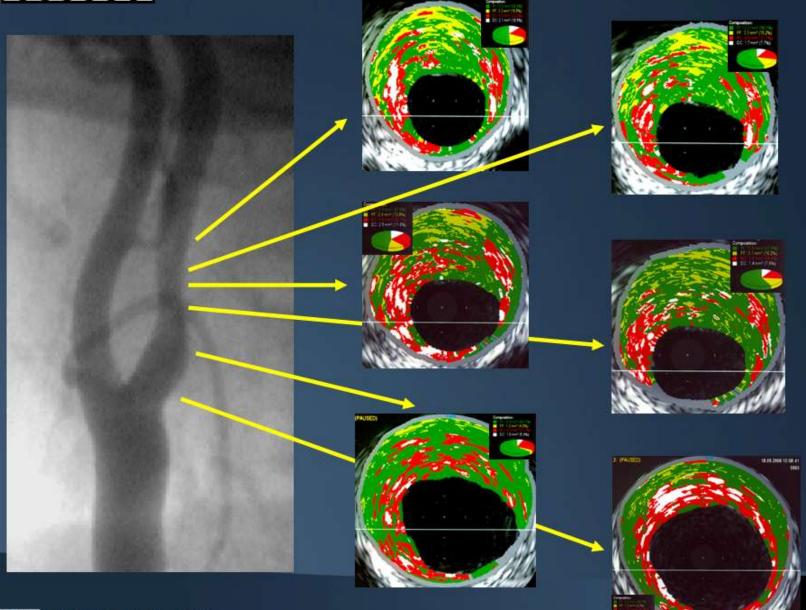
Duplex Doppler (July 2008): RICA 2.1 / 0.6 m/s





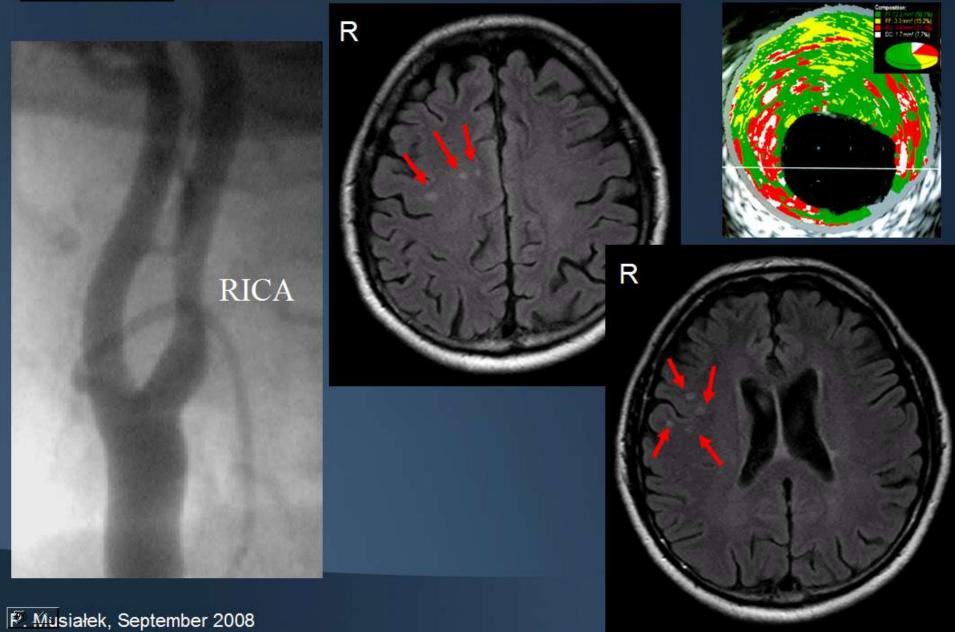


what would you do?





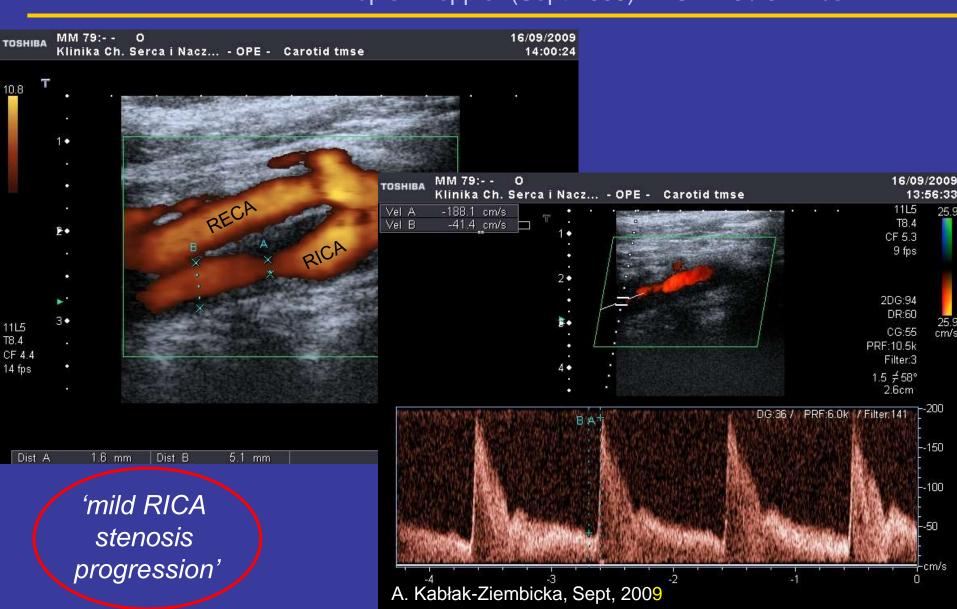
MZ, man 63y, lesion clinically asymptomatic

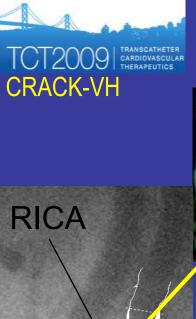




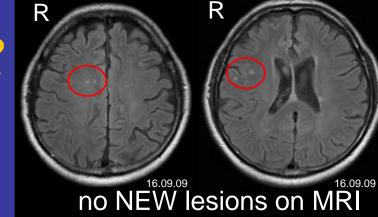
MM, man, 64y, RICA lesion still 'asymptomatic'

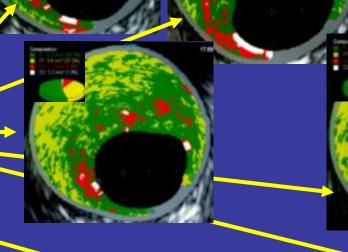
Duplex Doppler (Sept 2009): RICA 1.9 / 0.4 m/s



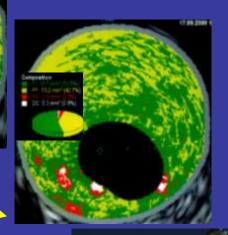


what would you do now (Sept 17, 2009)?





RICA -MLA



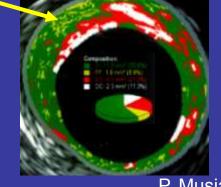


% area stenosis densitometry

% area stenosis circular

50

78 %



P. Musiałek, Sept 17, 2009