CONTROVERSES ET ACTUALITÉS EN CHIRURGIE VASCULAIRE
CONTROVERSIES & UPDATES IN VASCULAR SURGERY
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Risk Stratification Methods for Asymptomatic Carotid Plaques

Méthodes de Stratification du Risque des Plaques Carotidiennes Asymptomatiques

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Randomised trials in asymptomatic carotid stenosis (ACS)

- ACAS 1995; ACST 2004

Carotid endarterectomy reduced annual stroke risk from 2% to 1%

Perioperative stroke and death: 2.3%

Small net benefit after carotid endarterectomy for asymptomatic stenosis

Table 1 Five year risks of the main outcomes from ACAS and ACST, including the operative risk

	ACAS			ACST		
	BMT	CEA	ARR	BMT	CEA	ARR
Any stroke	17.5%	12.4%	5.1%	11.8%	6.4%	5.4%
No of 'any strokes' prevented per 1000 CEAs at 5 years		51			54	
Any major stroke	9.1%	6.4%	2.7%	6.1%	3.5%	2.6%
No of 'major strokes' prevented per 1000 CEAs at 5 years		27			26	
Ipsilateral stroke	11.0%	5.1%	5.9%	5.1%*	4.4%*	1.1%
No of ipsilateral strokes prevented per 100		59				
Major ips						n/a

"Up to 94% of interventions might not benefit the patient"

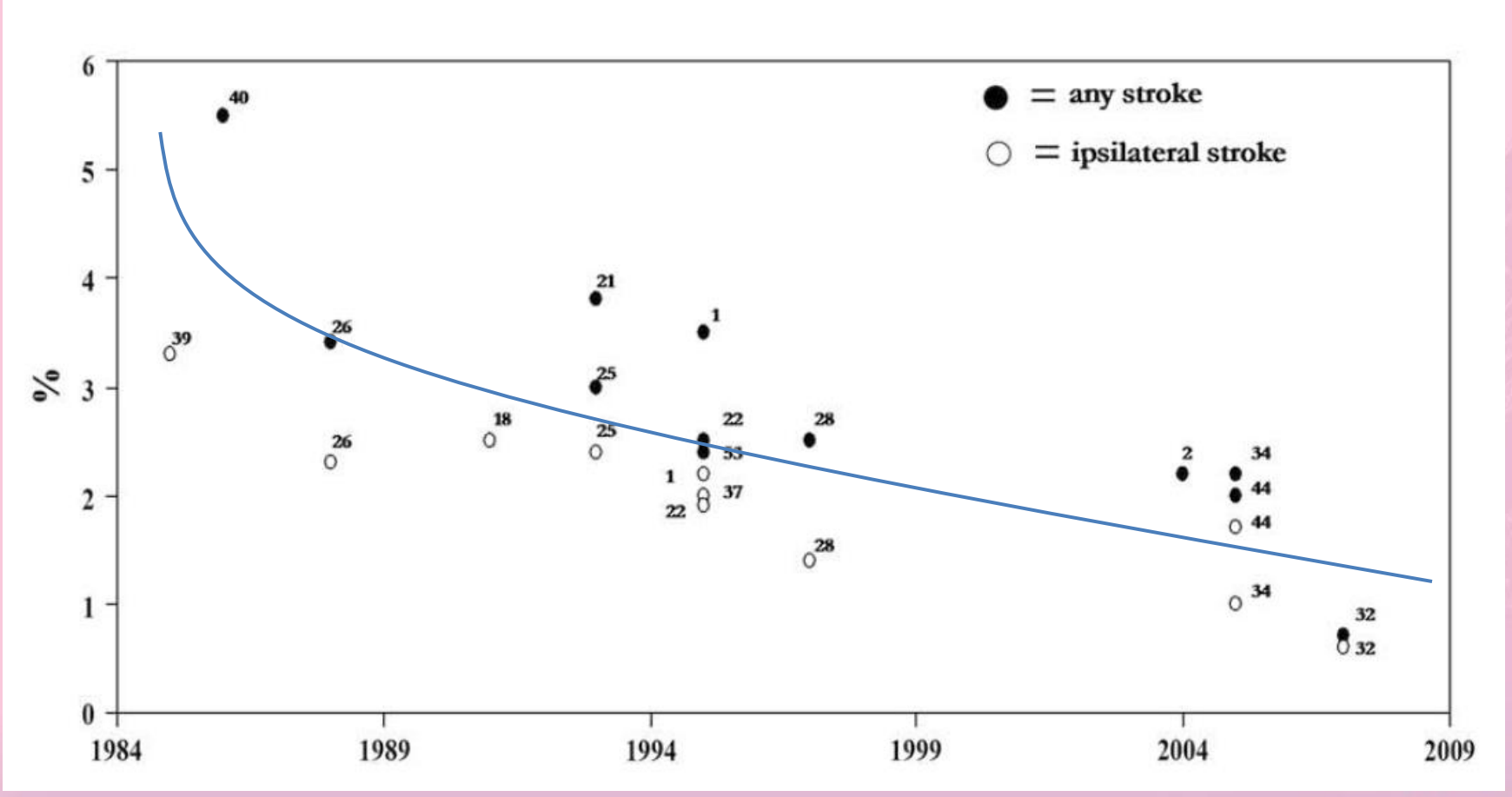
BMT = best medical therapy, CEA = carotid endarterectomy, * data derived from presentations about the 10 year ACST data. In the CEA group it includes a 2.8% operative risk, n/a = no data available, ARR = absolute risk reduction at 5 years.

Naylor 2009, EJVES

Therefore, a better risk stratification for ACS is urgently needed

Outcome improvement over time, as a result of medical therapy

Annual ipsilateral and "any" stroke (50-99% stenosis)
by year of publication



Modified from Naylor 2009 EJVES

Annual ipsilateral and "any" stroke (50-99% stenosis)
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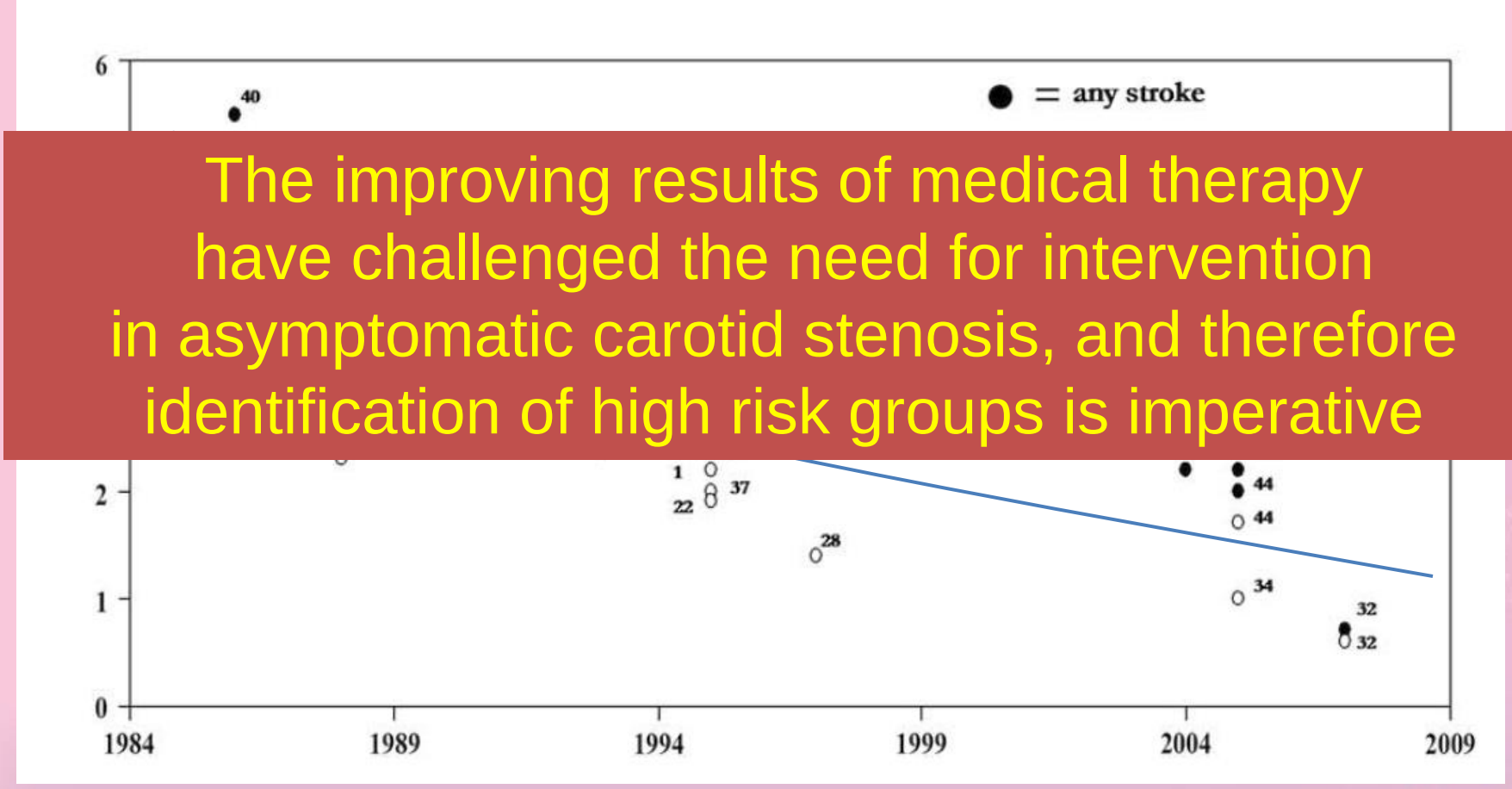


The improving results of medical therapy have challenged the need for intervention in asymptomatic carotid stenosis, and therefore identification of high risk groups is imperative

Modified from Naylor 2009 EJVES

Factors associated with a high risk of stroke in ACS

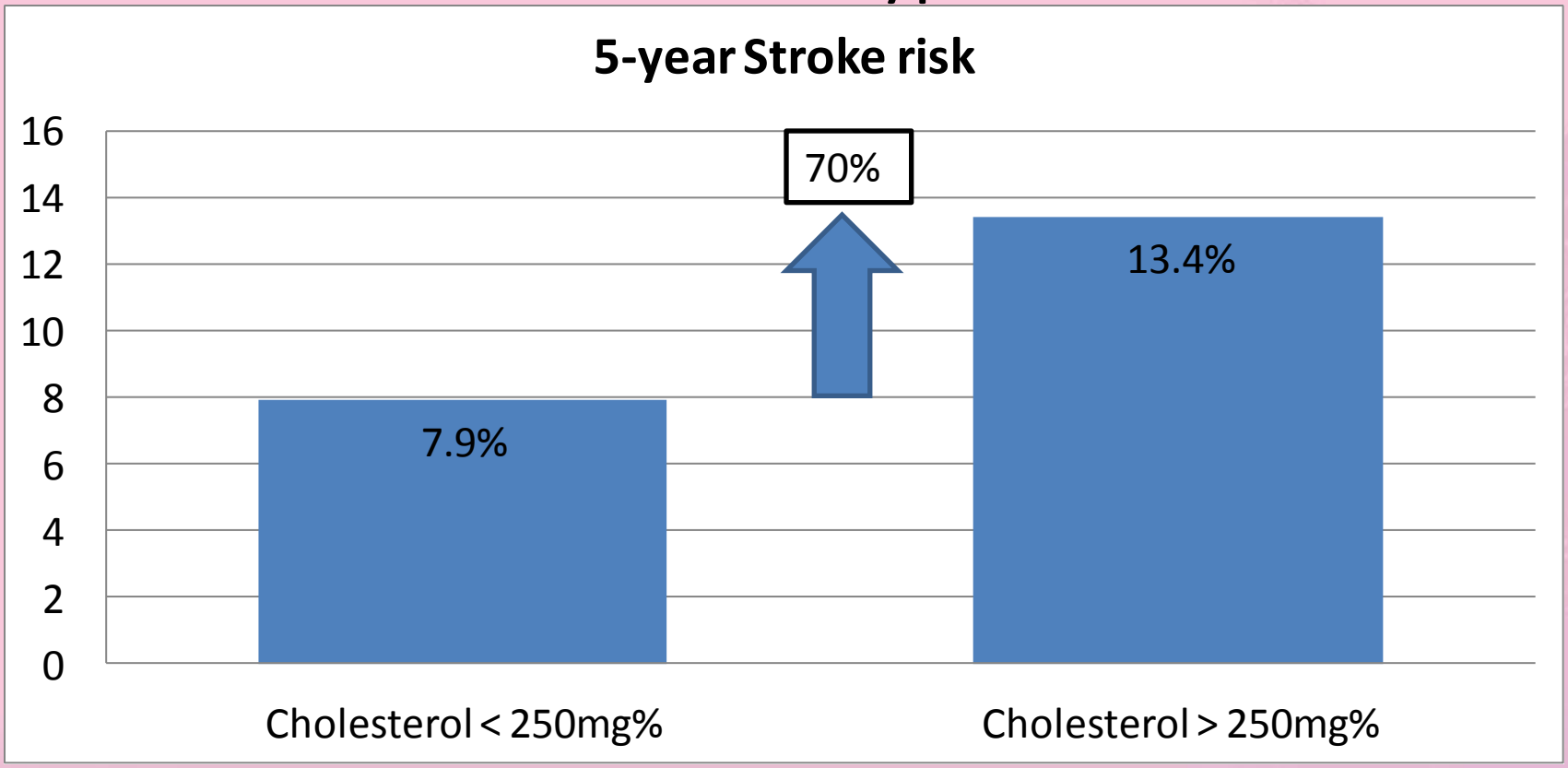
- Clinical characteristics
- Evidence of embolisation
  - Silent brain infarction
  - Embolic signals on TCD
- Lesion characteristics
  - Stenosis or Plaque characteristics

Factors associated with a high risk of stroke in ACS

- Clinical characteristics
  - Hypertension (Moore D, Ann Surg 1985)
  - Hypercholesterolaemia (ACST 2004)
  - Age (> 70 years) (Moore D, Ann Surg 1985)
  - History of contralateral neurological symptoms (ACST 2004, ACSRS 2005)

Factors associated with a high risk of stroke in ACS

- Clinical characteristics: Hypercholesterolaemia



ACST, Lancet, 2004

Factors associated with a high risk of stroke in ACS

- Clinical characteristics: History of contralateral neurological symptoms

Study	Risk estimate (95%CI)	p value	Method
ACST 2004	2.08 (1.35-3.18)*	0.001	Odds ratio
ACSRS 2013	2.2 (1.27-3.79)	0.005	Hazard ratio-Cox regression

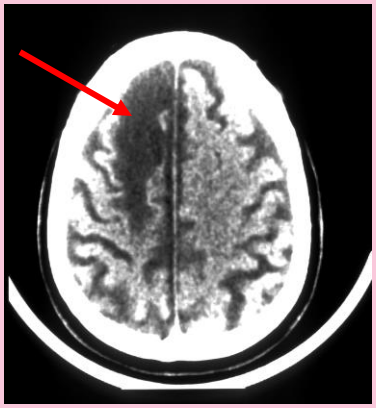
(Kakkos, JVS, 2013)

* calculated from the published data

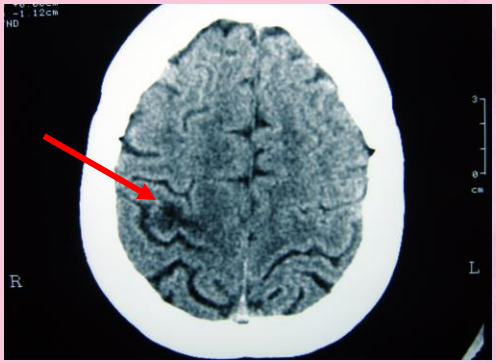
Factors associated with a high risk of stroke in ACS

"Embolic" infarction on CT brain scanning

Large cortical

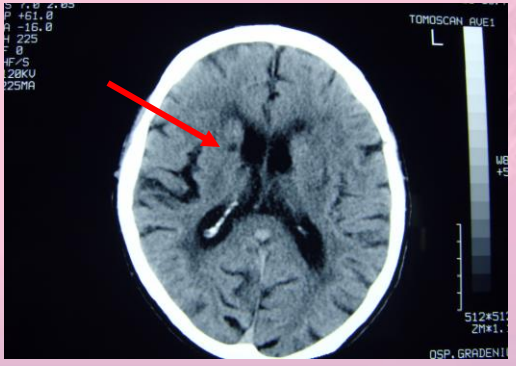


Small cortical

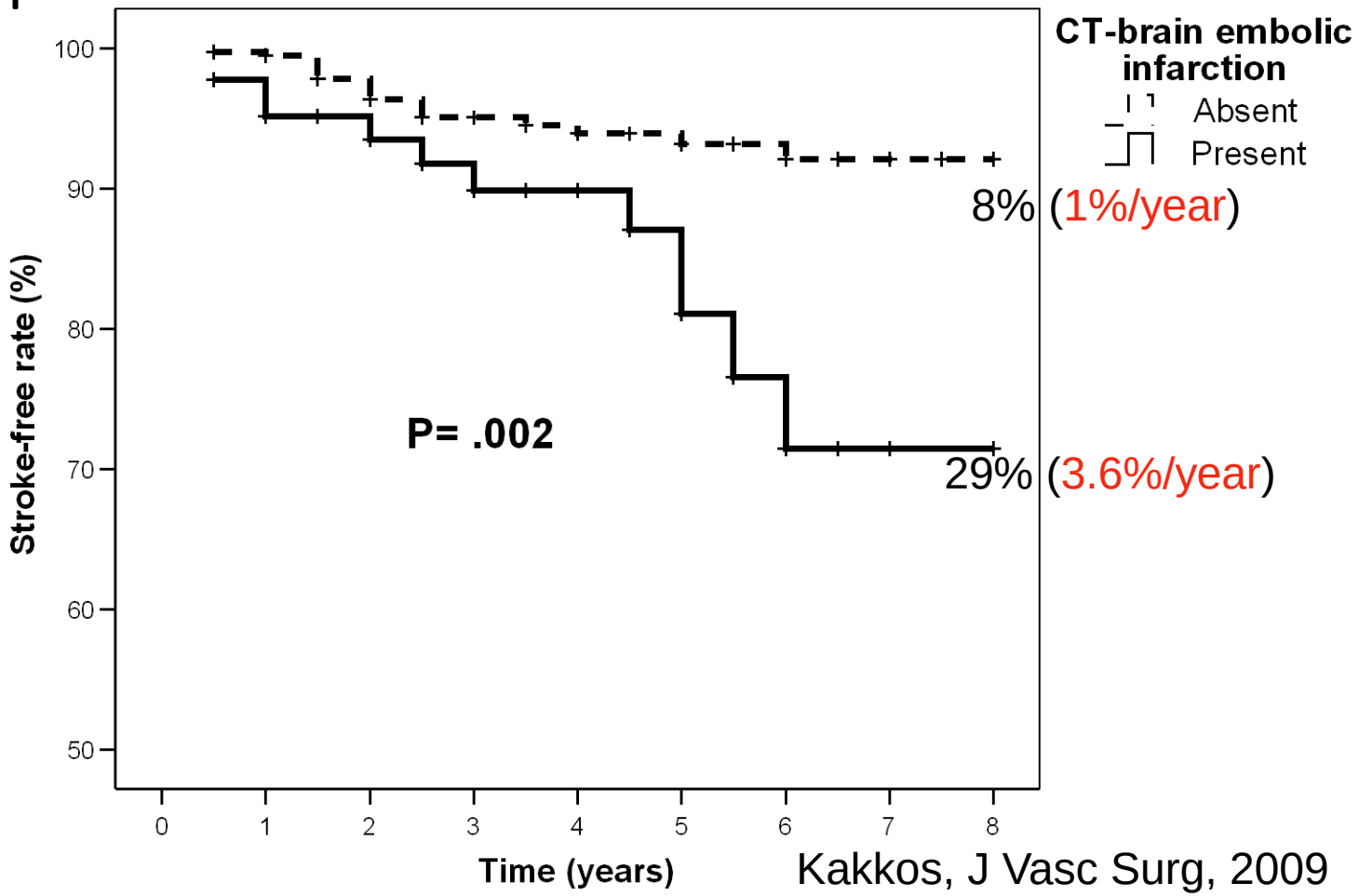


Discrete subcortical

Basal ganglia (non-lacunar) lesions



Ipsilateral stroke-free rate in patients with 60-99% (NASCET) ACS (n=462) in relation to "embolic" infarction: 70% of the plaques that will produce a stroke are missed



Kakkos, J Vasc Surg, 2009

Factors associated with a high risk of stroke in ACS

Embolic signals on TCD: 43% of the plaques that will produce a stroke are missed

	Embolic signals present	Embolic signals absent	Weight (%)	Odds ratio (95% CI)
Ipsilateral stroke				
Abbott[16]	2/60	4/171	20·2%	1·44 (0·26–8·07)
Molloy[21]	1/12	0/30	6·3%	7·96 (0·30–209·70)
Orlandi[22]	3/6	0/15	6·7%	31·00 (1·29–747·03)
Siebler[23]	1/8	1/56	8·1%	7·86 (0·44–140·14)
Spence[15]	5/32	3/287	25·8%	17·53 (3·97–77·38)
Subtotal	**12/118**	**8/559**	**67·0%**	**7·46 (2·24–24·89)**
Heterogeneity: τ^2=0·54; χ^2=6·62, df=4 (p=0·23); I^2=29%				
Test for overall effect: Z=3·27 (p=0·001)				
ACES	5/77	5/390	33·0%	5·35 (1·51–18·94)

Meta-analysis of ACES and Previous Studies

Marcus HS et al, Lancet Neurol. 2010;7: 663–671.

Factors associated with a high risk of stroke in ACS

- Stenosis characteristics
  - Increasing severity of carotid stenosis (ACSRS 2010)
  - Progression of carotid stenosis over time (Aburahma, J Vasc Surg 2002)
  - Occluded contralateral internal carotid artery (Aburahma, Ann Surg 2003)

Stenosis severity and risk of stroke ACSRS study

ECST stenosis (%)	*NASCET stenosis (%)*	*No.*	*CORI events*	*Strokes*
All patients		1121	130 (11.6%)	59 (5.3%)
50-69[a]	<50	198	16 (8.1%)	5 (2.5%)
70-89[a]	50-82	598	65 (10.9%)	29 (4.8%)
90-99[a]	83-99	325	49 (15.1%)	25 (7.7%)
			$P = .01$	$P = .008$

Nicolaides et al. J Vasc Surg 2010

Factors associated with a high risk of stroke in ACS

- Plaque characteristics
  - Plaque ulceration (Handa, Stroke 1995)
  - Unstable carotid plaque morphology on ultrasound

Subjective features:
  - plaque echolucency (Nicolaides, Kakkos, 2005)
  - discrete echogenic plaque components (Nicolaides ,2010)
  - plaque heterogeneity (Sterpetti, 1988)

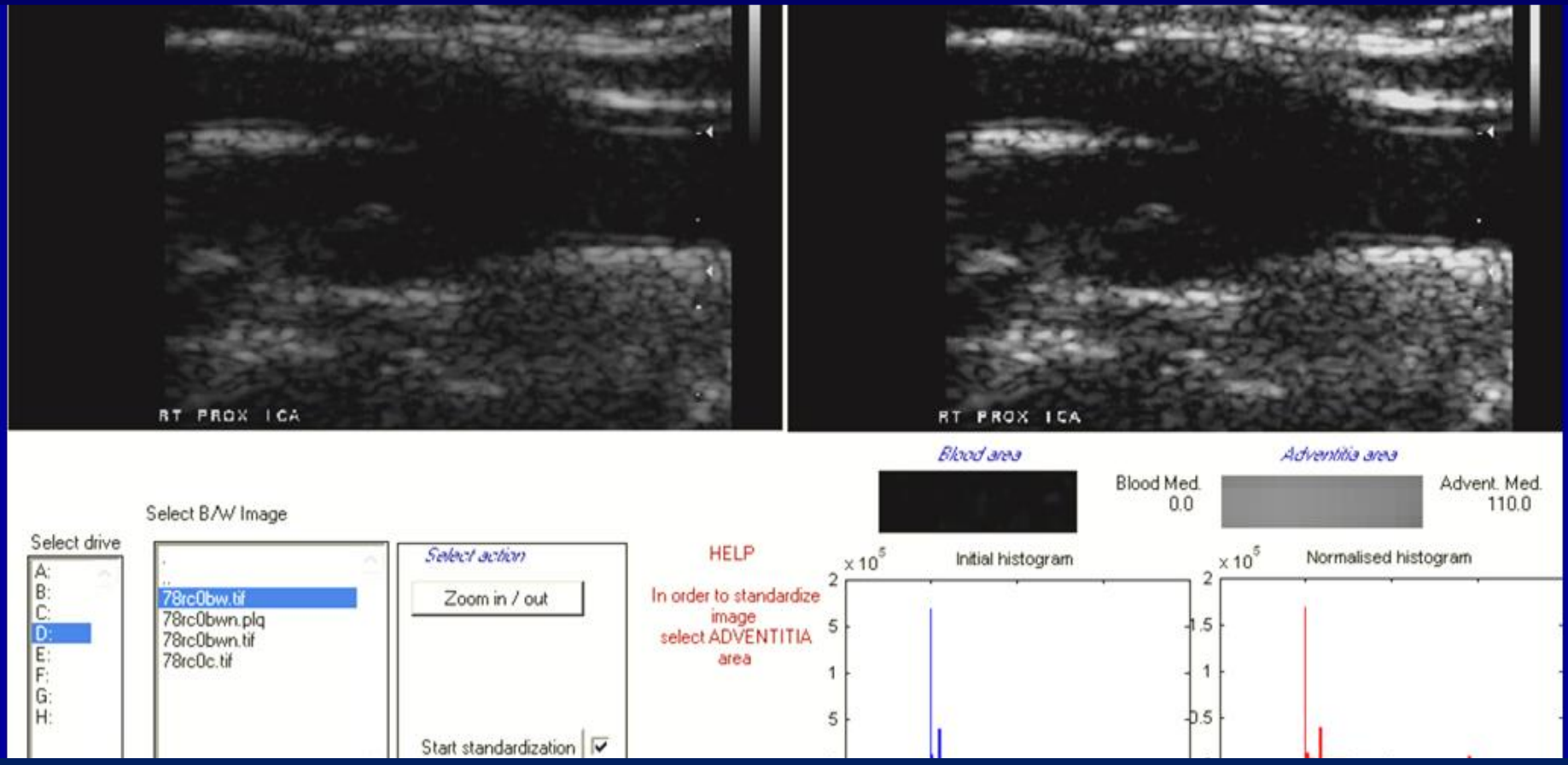
Objective features:
  - low gray scale median (GSM) (Nicolaides, 2010)
  - large plaque area (Nicolaides , 2010)
  - juxtaluminal black (echolucent) areas (JBA) (Kakkos, 2013)

Juxtaluminal Black Area (JBA): a U/S marker of plaque instability

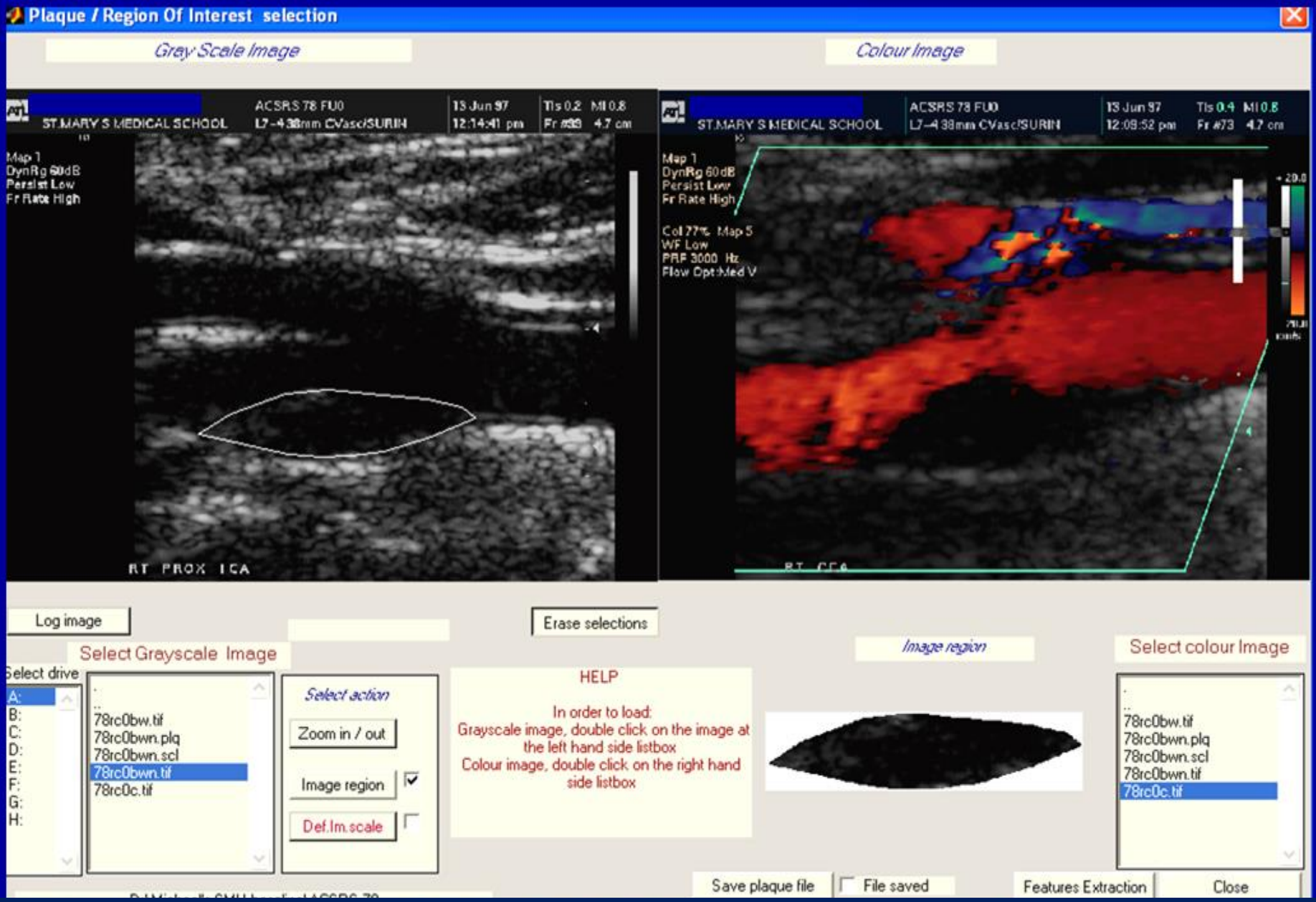
- ✓A juxtaluminal black (hypoechoic) area is observed more frequently in symptomatic compared to asymptomatic carotid plaques (Pedro, EJVES 2002)

Measurement of JBA

Images transferred to PC for processing



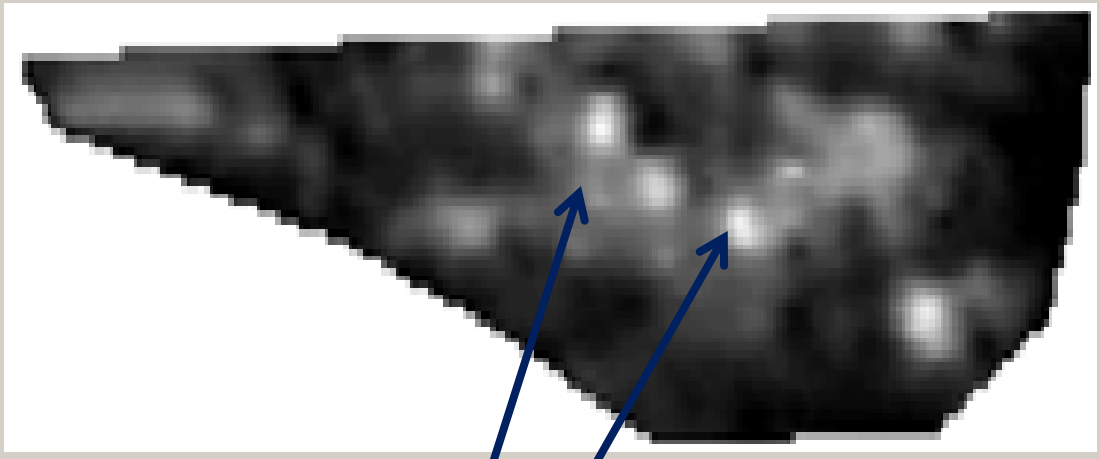
Images normalised for grey scale using two reference points: blood=0; adventitia=190



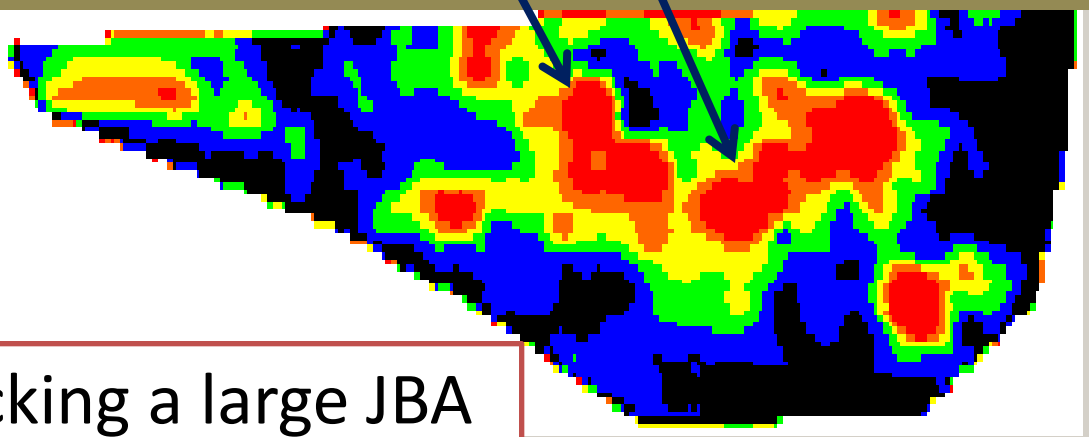
Plaque outlines were normalised to a pixel resolution of 20/mm

Image contouring

Grey scale	Colour
0-25	black
25-50	blue
50-75	green
75-100	yellow
100-125	orange
>125	red



Discrete plaque white areas (DWAs)



Example of a plaque lacking a large JBA

Example of a plaque with a large JBA

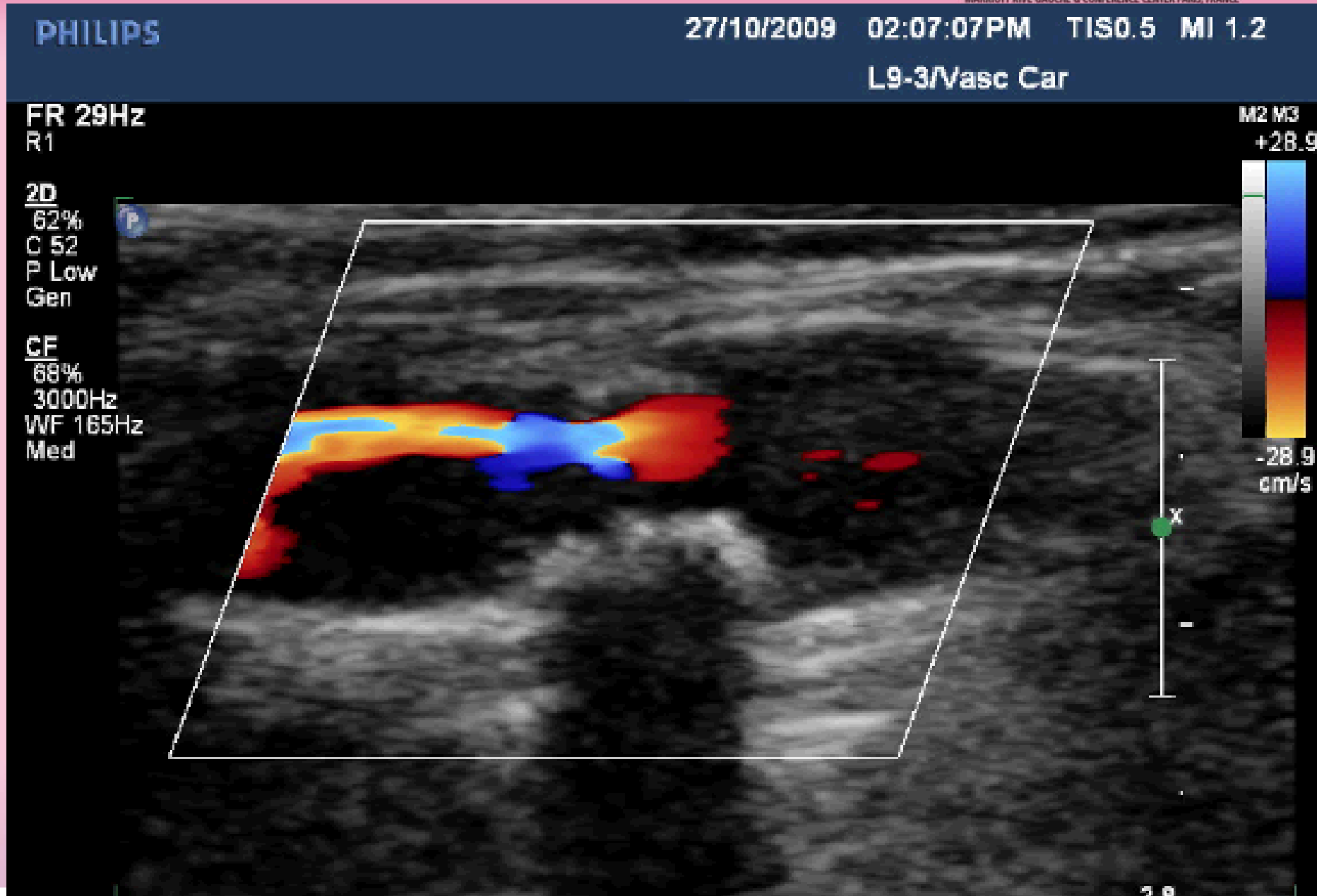


Image region

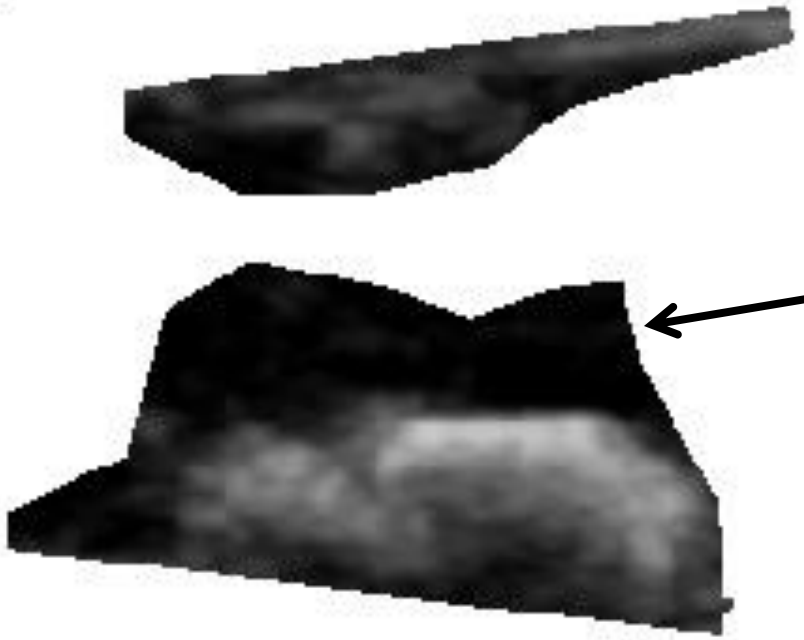
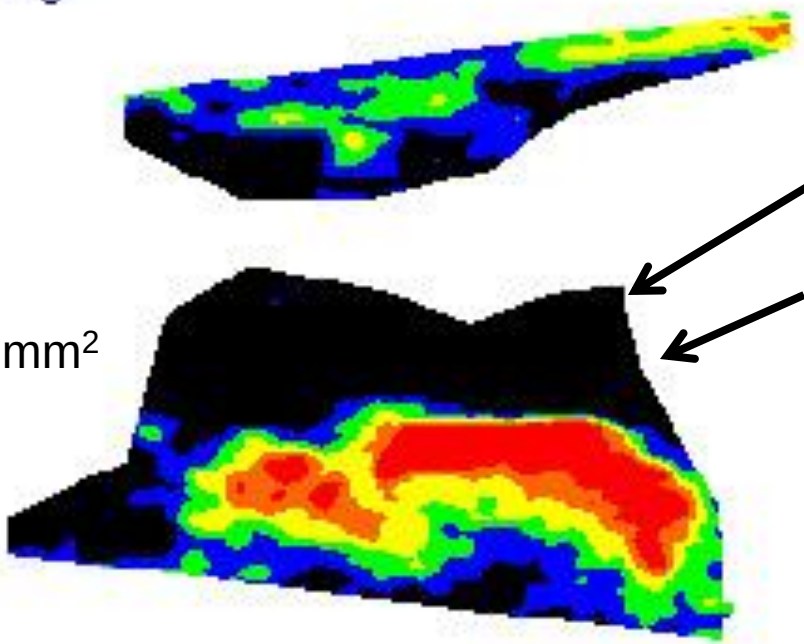


Image colouring



13.6 mm^2

DEFINITION

JBA is defined as an area of pixels adjacent to the lumen with gray scale value <25 and without a visible echogenic cap

JBA area is quantified in mm^2

Texture feature extraction

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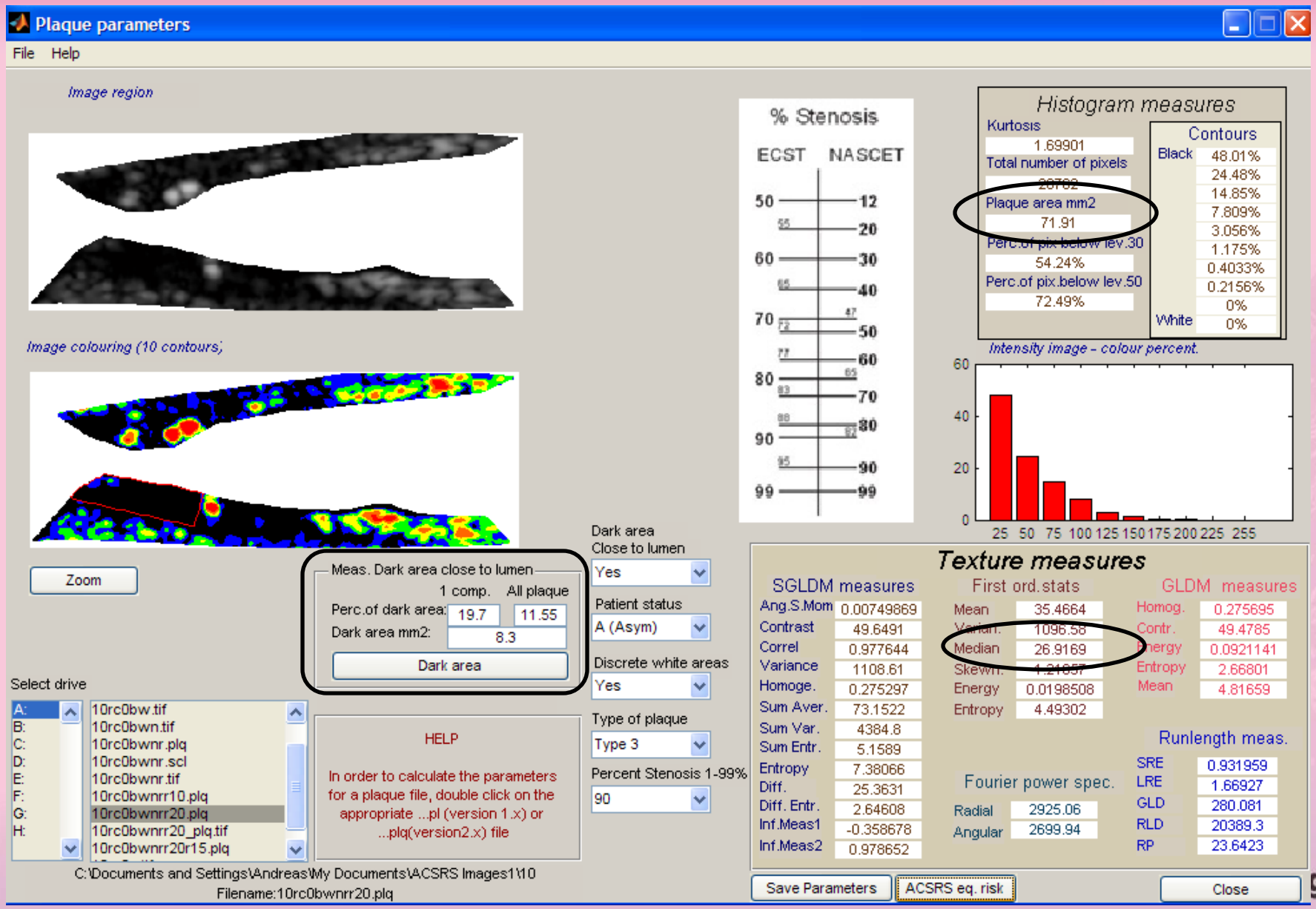
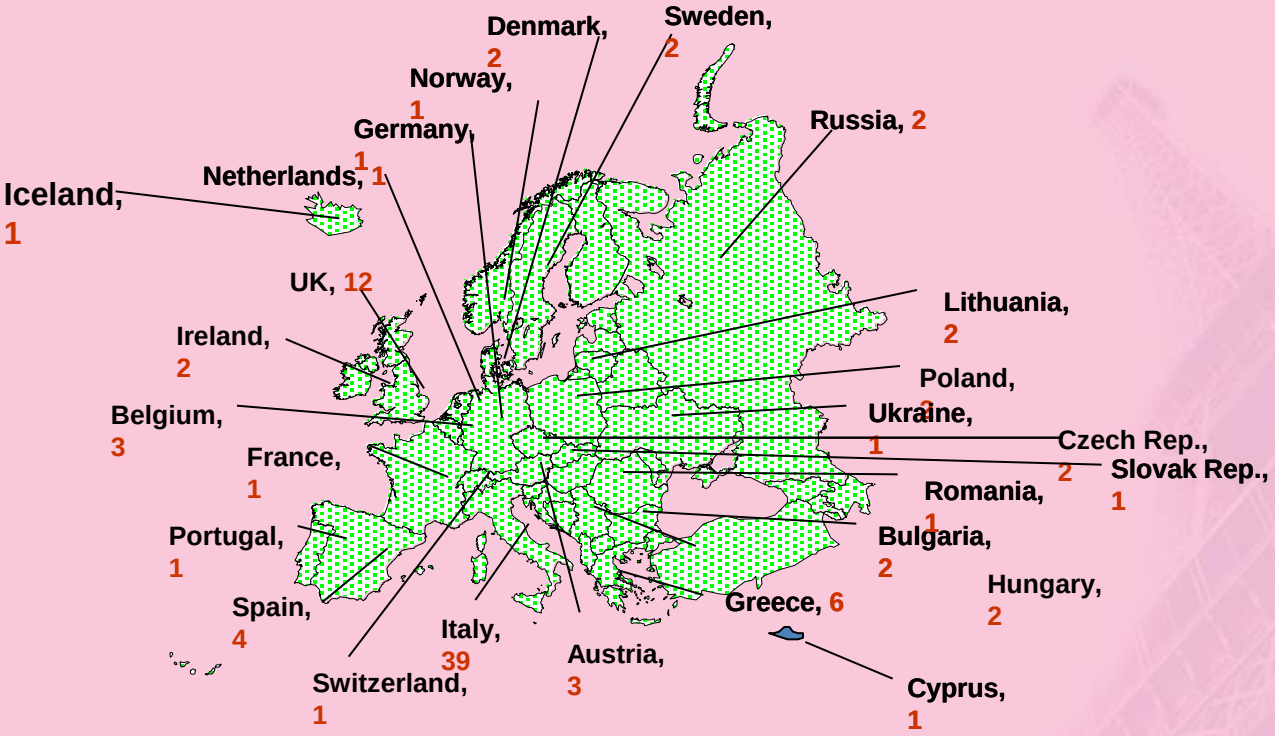


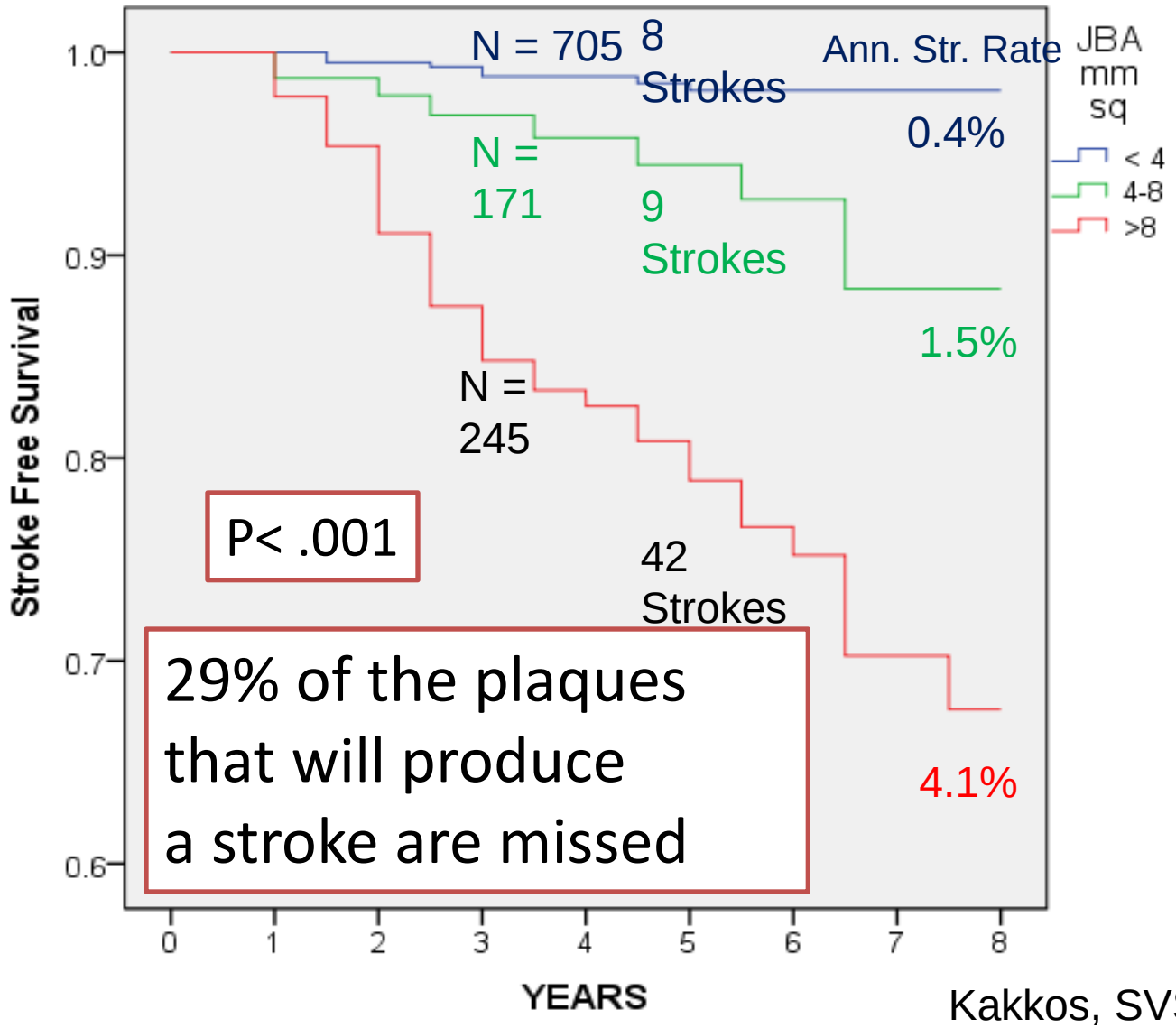
Europe

ACSRS Study: 1121 patients with > 50% ACS



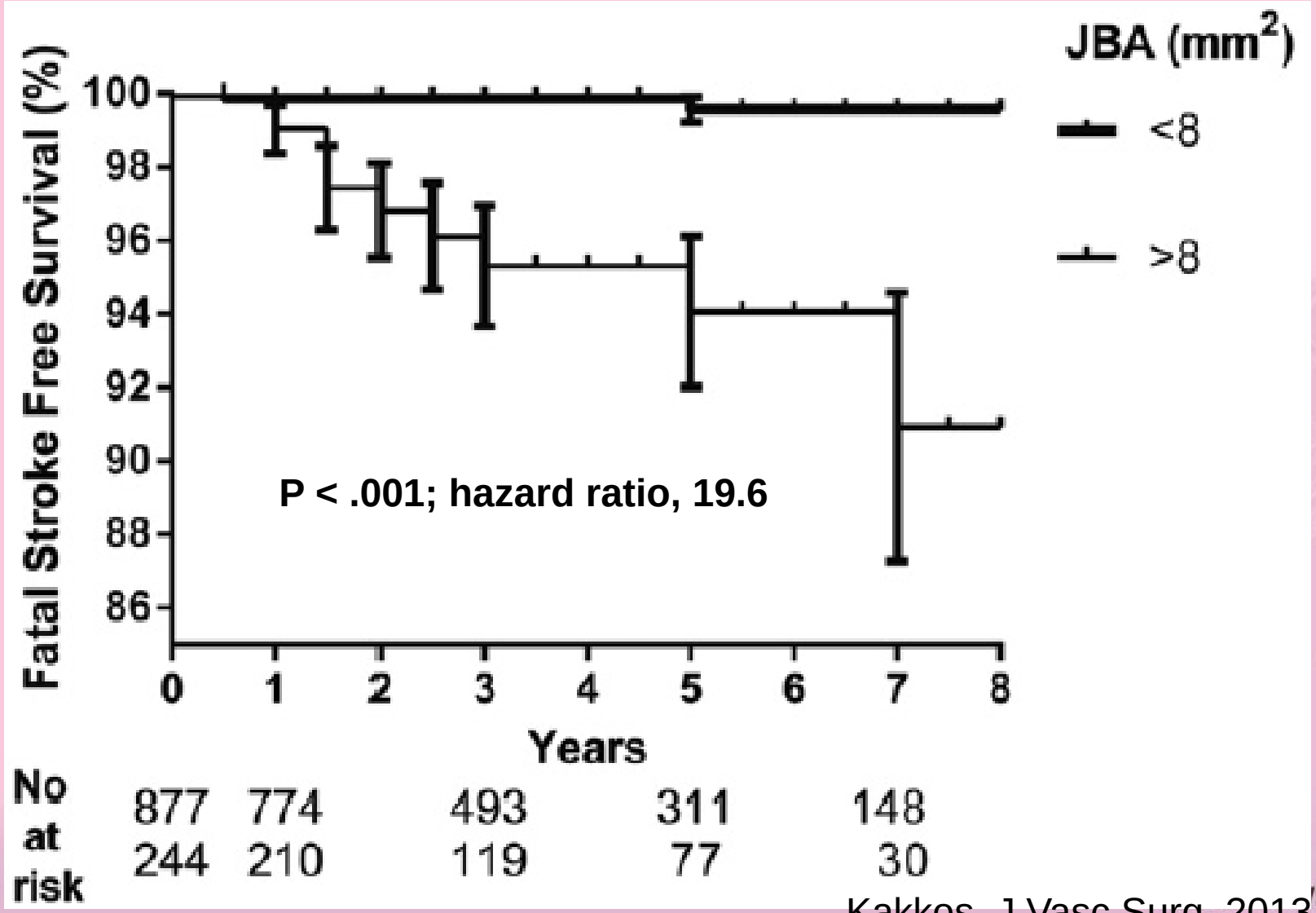
mean follow-up 4 years

Ipsilateral ischemic stroke in relation to JBA size in the ACSRS study



Kakkos, SVS 2012

Fatal ipsilateral ischemic stroke in relation to JBA in the ACSRS study



Kakkos, J Vasc Surg, 2013

Predictors of ipsilateral ischemic stroke on Cox Multivariate Analysis in ACSRS: risk stratification is possible

Independent predictors of risk	HR	95% CI	P value
JBA (4, 4-8, 8-10, >10) in mm^2	2.34	1.89-2.91	<0.001
Stenosis (50-69, 70-89, 90-99) (%)	1.59	1.06-2.37	0.023
DWA (present, absent)	1.90	0.98-3.27	0.059
History of contr. TIA or stroke (present, absent)	2.20	1.27-3.79	0.005

GSM and plaque area: Non significant

Kakkos S et al, JVS, 2013

Stenosis 70-89% ECST (50-82% NASCET) (n=598) and predicted annual stroke risk

		History of Contralateral TIAs or Stroke Absent						History of Contralateral TIAs or Stroke Present			
DWA	Present n =	0.6% 220	1.4% 50	2.8% 20	4.4% 44			0.8% 25	2.6% 7	5.8% 2	8.4% 15
	Absent n =	0.4% 129	0.9% 19	1.4% 3	2.6% 40			0.5% 12	1.6% 1	3.4% 2	5.4% 8
		< 4	4-8	8-10	≥ 10			< 4	4-8	8-10	≥ 10
			JBA mm^2						JBA mm^2		

Annual Stroke Rate %
≥ 6
4.0-5.9
2.0-3.9
1.0-1.9
< 1.0

Kakkos S et al, JVS, 2013

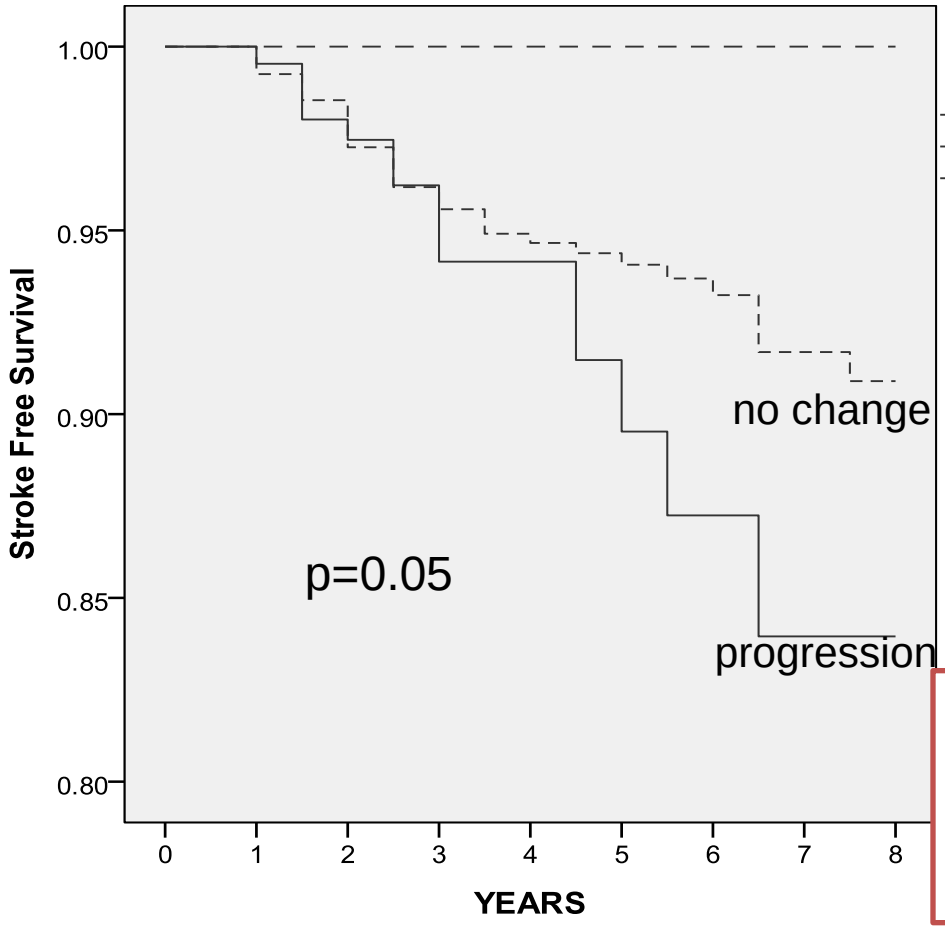
Stenosis 90-99% ECST (83-99% NASCET) (n=325) and predicted annual stroke risk

		History of Contralateral TIAs or Stroke Absent						History of Contralateral TIAs or Stroke Present			
DWA	Present n =	0.8% 101	2.0% 39	4.1% 8	6.2% 30			1.0% 19	3.6% 9	7.6% 4	10.0% 8
	Absent n =	0.6% 44	1.2% 16	3.0% 2	3.8% 24			0.7% 14	2.6% 2	5.2% 4	7.4% 0
		< 4	4-8	8-10	≥ 10			< 4	4-8	8-10	≥ 10
			JBA mm^2						JBA mm^2		

Annual Stroke Rate %
≥ 6
4.0-5.9
2.0-3.9
1.0-1.9
< 1.0

Kakkos S et al, JVS, 2013

Effect of changes in stenosis on ipsilateral ischemic stroke in the ACSRS study



	Average annual stroke rate over 8 years
40 strokes	1.1%
19 strokes	2.0%

68% of the plaques that will produce a stroke are missed

Numbers at risk				
Regression	38	28	19	5
No change	740	455	282	134
Progression	205	129	87	39

Kakkos S et al, JVS, in press

Progression of stenosis added as covariate in a proportional hazards model previously published* that could predict the risk of future events (ACSRS study)

Variable	β	HR	95% CI	p value
Ipsilateral stenosis (10% increase)	0.017	1.017	1.002-1.032	0.023
Log (GSM+40)	-2.464	0.085	0.042-0.171	< 0.001
Plaque area $^{1/3}$ (mm^2)	0.630	1.878	1.463-2.413	< 0.001
DWA	0.725	2.065	1.292-3.302	0.002
History of contr. TIAs or stroke	0.661	1.938	1.321-2.842	0.001
Progression	0.353	1.424	0.980-2.067	0.064

*Nicolaides et al, J Vasc Surg 2010

Kakkos S et al, JVS, in press

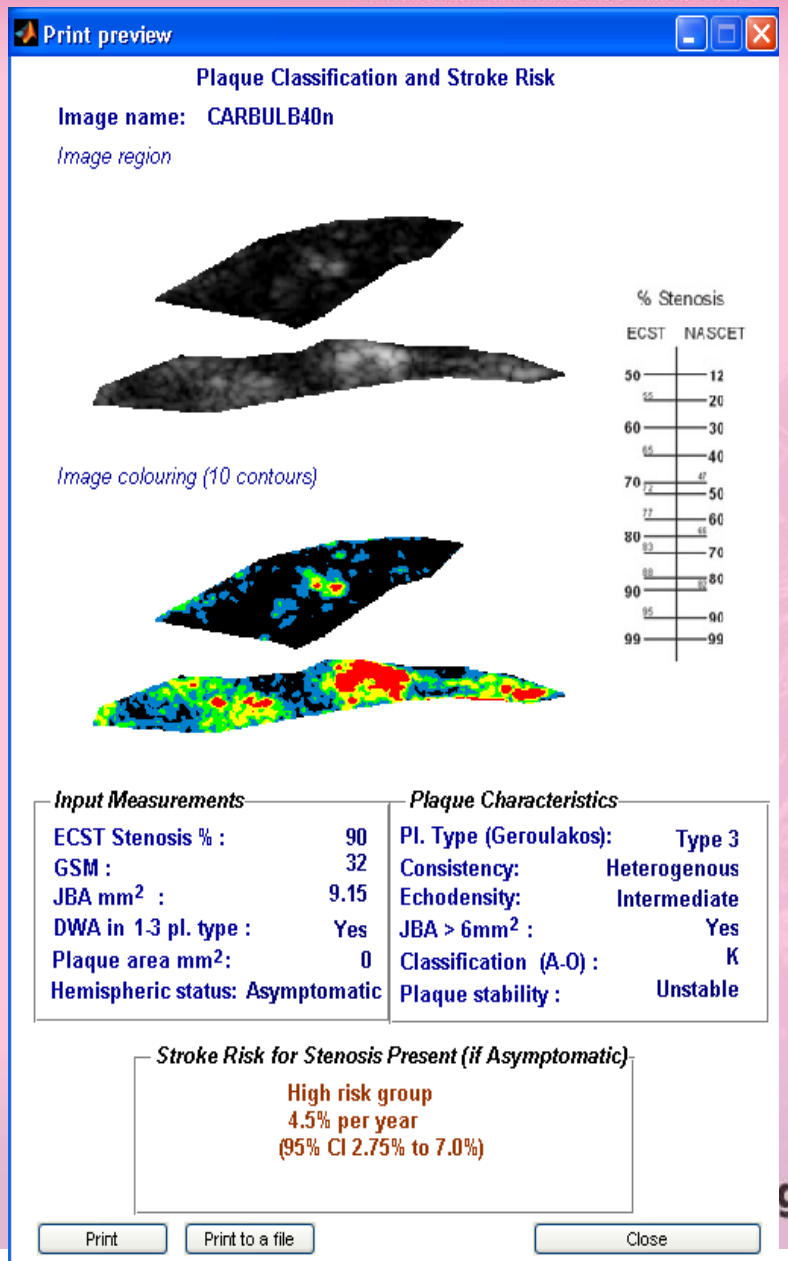
Conclusions

- Effective risk stratification methods in asymptomatic carotid artery stenosis has been reported in recent years, and this has improved the selection of patients in need of a carotid intervention.
- Not only the severity of stenosis, but also history of contralateral neurological symptoms, plaque features like JBA and DWA, and CT brain infarcts have all emerged as powerful predictors of stroke occurrence.

Where we go from here?

1. User friendly software
   for image analysis
   is now available
   for vascular labs

2. Doctors who like a
   number
   They should ask for
   (a) % Stenosis
   (b) Annual stroke risk



Thanks!