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CONTROVERSIES & UPDATES IN VASCULAR SURGERY
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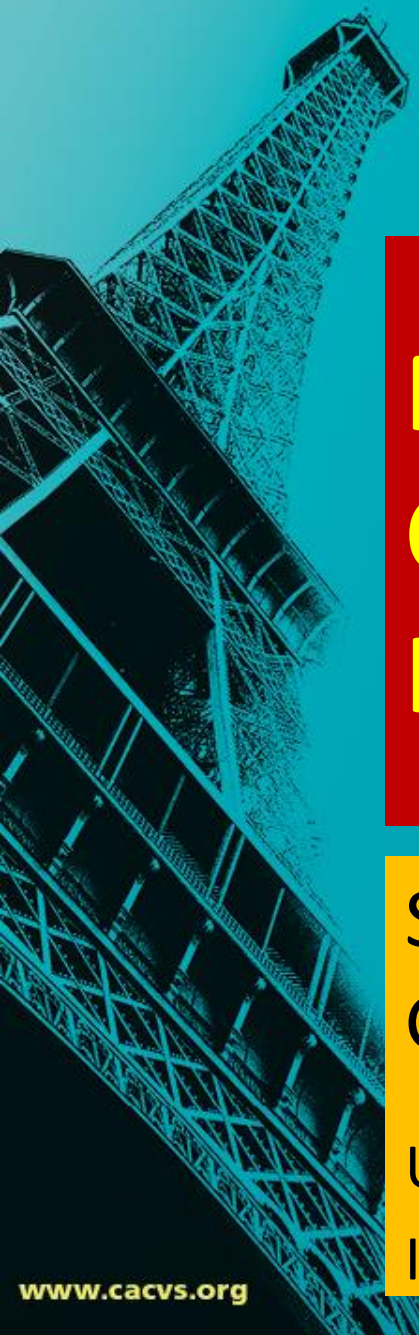

Progression of Asymptomatic Carotid Stenosis: Is it a Risk Factor of Stroke?

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Disclosure

Speaker name:

..Stavros Kakkos.....

☐ I have the following potential conflicts of interest to report:

☐ Consulting

☐ Employment in industry

☐ Shareholder in a healthcare company

☐ Owner of a healthcare company

☐ Other(s)

☒ I do not have any potential conflict of interest

Background

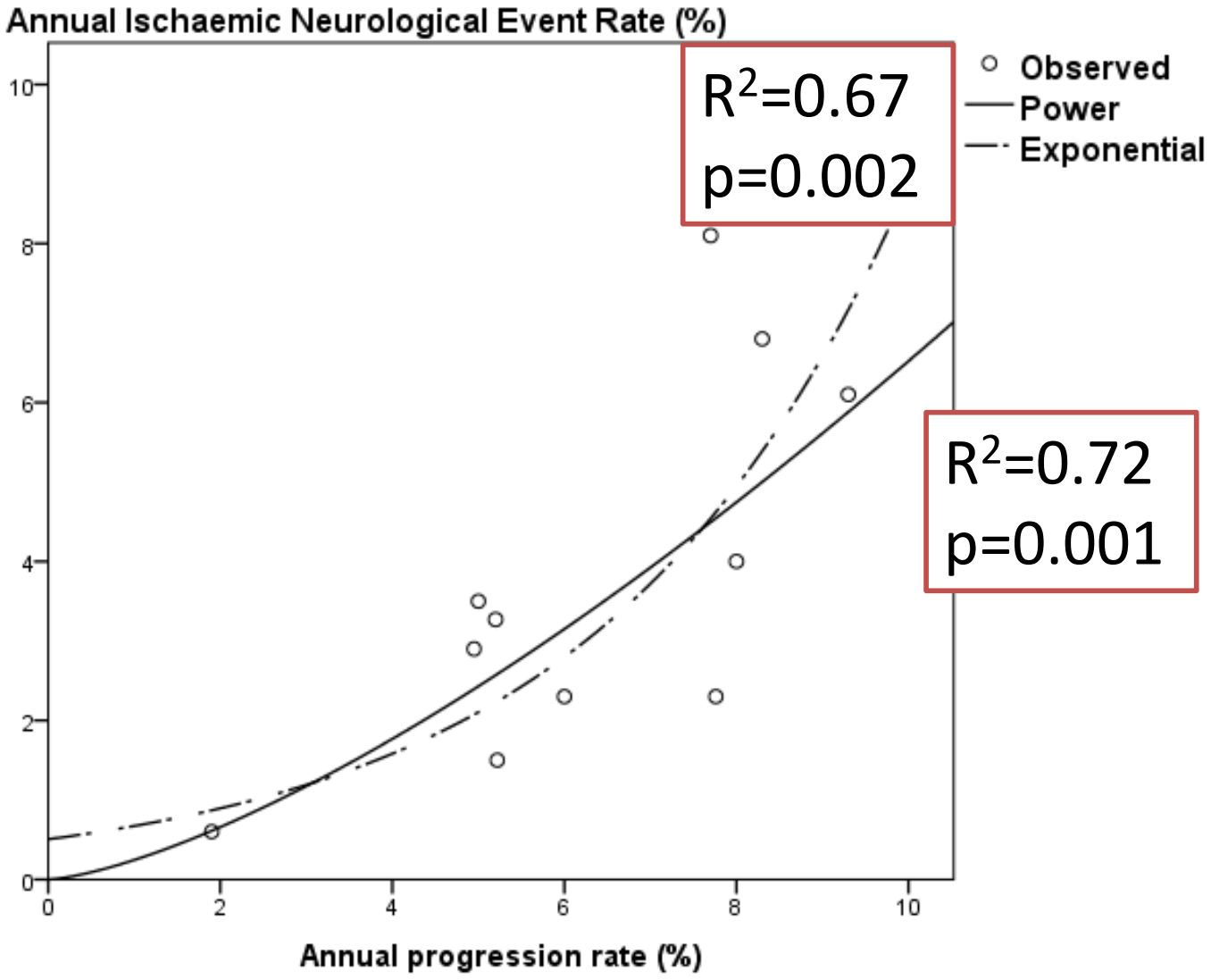
- Several natural history studies in patients with asymptomatic carotid stenosis have investigated the association between stenosis progression and risk of subsequent ipsilateral cerebrovascular events.

Background: Summary of 13 studies on 8,330 pts

Study	No of pts	Annual progression rate	Annual event rate	Follow-up period (y)	Association between progression and Sx
Roederer, 1984	167	8%	4%	3 (max)	Yes
Mackey, 1997	715	8.3%	6.8%	3.6 (mean)	Yes
Olin, 1998	465	6%	2.3%	2 (mean)	Yes
Mansour, 1999	344	7.7%	8.1%	2.1 (mean)	Yes
Muluk, 1999	1004	9.3%	6.1%*	2.3 (mean)	No for Blsten>50%*
Liapis, 2000	332	5%	3.5%	3.7 (mean)	Yes
Raman, 2004	279	4.3% (ipsi)	-	2.3 (mean)	-
Sabeti, 2007	1065	14%	-	0.63 (median)	Yes
Fluri, 2008	361	1.9%	1.6% vs 0.6%	7.4 (mean)	Yes
Conrad, 2013	794	7.76%	2.3%	3.6 (mean)	Yes
Hirt, 2014	1469	5.2%	3.27	5.2 (mean)	Yes
ACSRS, 2014	1121	4.95%	2.90	4.0 (mean)	Yes
Singh, 2015	214	5.22%	1.5%	13 (median)	No

Stenosis progression is associated with an increased risk of cerebrovascular events

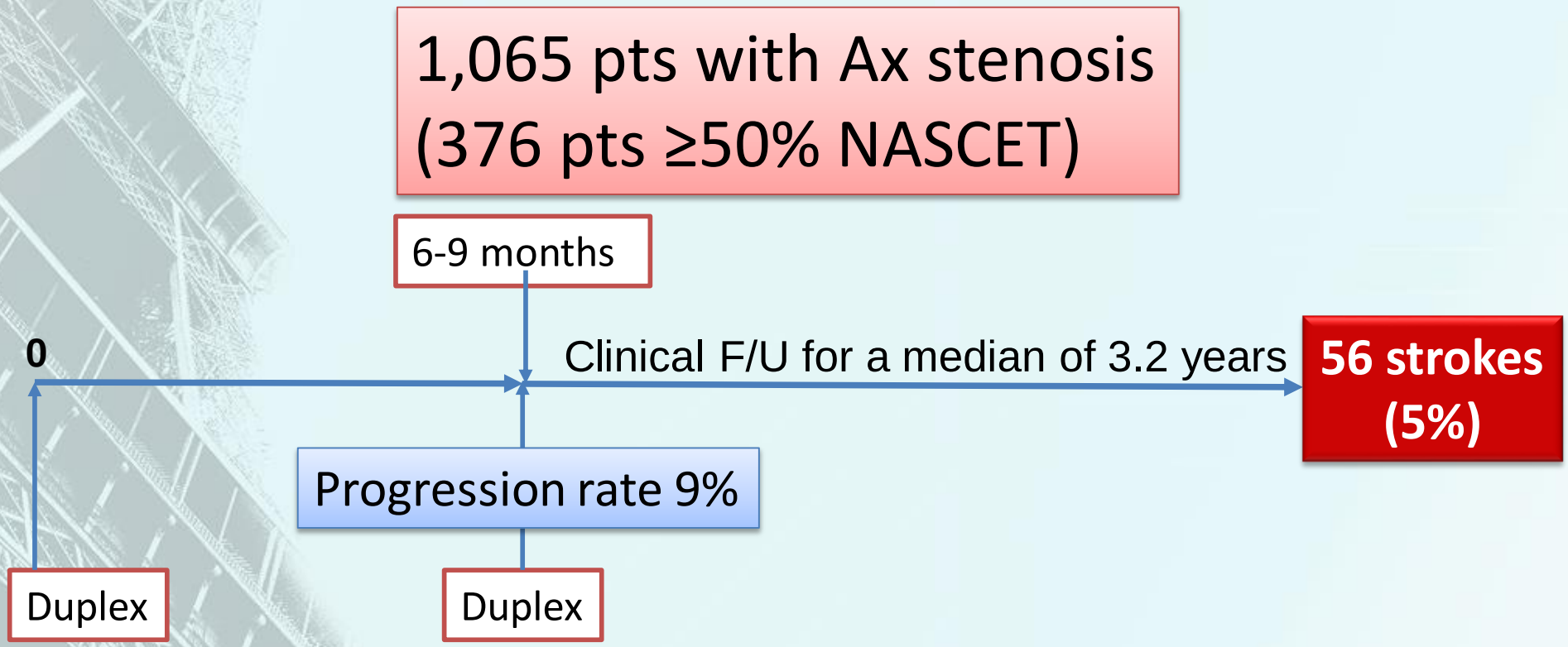
Association between annual neuro-event and progression rates in 11 studies on 6,990 pts



Background

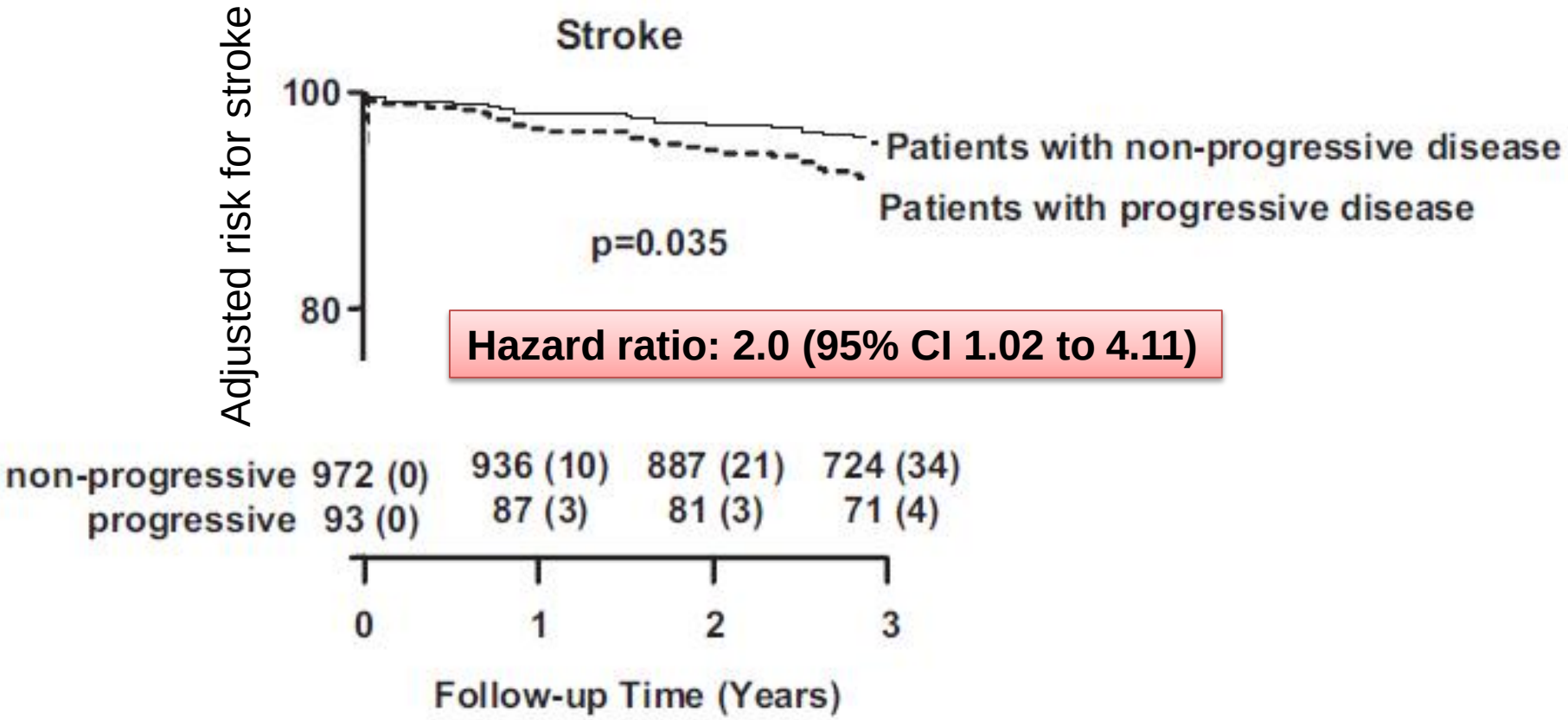
- However, most of these studies had limitations such as
  - the small number of cerebrovascular events and short duration of follow up
  - lack of reporting TIAs and stroke as separate outcome events
  - multivariate analysis was not performed to adjust for stenosis severity
- Most studies concluded that the value of repeat US scanning to predict cerebrovascular events was limited by a low incidence of outcome events and low rates of progression.

Progression of Carotid Stenosis Detected by Duplex Ultrasonography Predicts Adverse Outcomes in Cardiovascular High-Risk Patients



Sabeti, Stroke, 2007

Progression of Carotid Stenosis Detected by Duplex Ultrasonography Predicts Adverse Outcomes in Cardiovascular High-Risk Patients



Modified from Sabeti, Stroke, 2007

Progression of Carotid Stenosis Detected by Duplex Ultrasonography Predicts Adverse Outcomes in Cardiovascular High-Risk Patients

- Of 56 strokes, 53 were ischemic and 3 were hemorrhagic.
- Half of all strokes occurred in stenoses <50% (NASCET).
- Only 9 of 56 strokes occurred in patients with progressive carotid disease.
- Only 7 (13%) of these strokes were ipsilateral to the progressive stenosis.

Sabeti, Stroke, 2007

Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study

(The IUA international multicentre natural history study)

Primary aim

To determine the cerebrovascular risk stratification potential of baseline

- degree of stenosis
- clinical features and
- ultrasonic plaque characteristics

in patients with asymptomatic carotid stenosis 50% -99% ECST.

Nicolaides et al, J Vasc Surg 2010,

Kakkos et al, J Vasc Surg 2013

Secondary objective of the ACSRS study

To assess the value of stenosis progression or regression using repeated (six monthly) duplex scanning and to determine

(a) the incidence of progression and regression

(b) the association of baseline clinical, biochemical and plaque characteristics with progression or regression

Secondary objective of the ACSRS study

(c) the association between progression or regression and ipsilateral cerebral or retinal ischemic (CORI) events, including stroke

(d) whether progression is a predictor of cerebrovascular events, independent of stenosis and

(e) the contribution of progression (or regression) in stroke risk stratification when used in combination with established risk factors.

Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis

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Objective: To determine baseline clinical and ultrasonographic plaque factors predictive of progression or regression of asymptomatic carotid stenosis and the predictive value of changes in stenosis severity on risk of first ipsilateral cerebral or retinal ischemic events (including stroke).

Methods: A total of 1121 patients with asymptomatic carotid stenosis of 50% to 99% in relation to the bulb diameter (European Carotid Surgery Trial [ECST] method) underwent six monthly clinical assessments and carotid duplexes for up to 8 years (mean follow-up, 4 years). Progression or regression was considered present if there was a change of at least one grade higher or lower, respectively, persisting for at least two consecutive examinations.

Results: Regression occurred in 43 (3.8%), no change in 856 (76.4%), and progression in 222 (19.8%) patients. Younger age, high grades of stenosis, absence of discrete white areas in the plaque, and taking lipid lowering therapy were independent baseline predictors of increased incidence of regression. High serum creatinine, male gender, not taking lipid lowering therapy, low grades of stenosis, and increased plaque area were independent baseline predictors of progression.

One hundred and thirty first ipsilateral cerebral or retinal ischemic events, including 59 strokes, occurred. Forty (67.8%) of the strokes occurred in patients whose stenosis was unchanged, 19 (32.2%) in those with progression, and zero in those with regression. For the entire cohort, the 8-year cumulative ipsilateral cerebral ischemic stroke rate was zero in patients with regression, 9% if the stenosis was unchanged, and 16% if there was progression (average annual stroke rates of 0%, 1.1%, and 2.0%, respectively; log-rank, $P = .05$; relative risk in patients with progression, 1.92; 95% confidence interval, 1.14-3.25).

For patients with baseline stenosis 70% to 99% in relation to the distal internal carotid (North American Symptomatic Carotid Endarterectomy Trial [NASCET] method), in the absence of progression (n = 349), the 8-year cumulative ipsilateral cerebral ischemic stroke rate was 12%. In the presence of progression (n = 77), it was 21% (average annual stroke rates of 1.5% and 2.6%, respectively; log-rank, $P = .34$). Only nine (30%) of the 30 strokes occurred in the progression group.

Conclusions: Progressive asymptomatic carotid stenosis identified a subgroup with about twice the risk of ipsilateral stroke compared with those without progression. However, the clinical value of screening for progression simply for selecting patients for carotid procedures is limited because of the low frequency of progression and its relatively low associated stroke rate. The cost effectiveness of screening for change in stenosis severity to better direct current optimal medical treatment needs testing. (J Vasc Surg 2014;59:956-67.)

Participating centres in ACSRS

EUROPE

1,121 patients

Information Collected

- Clinical

  Age, gender, ht and wt, clinic of origin, medical history, c.v. risk factors, medications, family history.

- Biochemical

  Creatinine, fibrinogen, hematocrit, total cholesterol, LDL, HDL, triglycerides.

Information Collected

- Duplex examination

  To grade the degree of stenosis (ECST and NASCET) and to assess carotid plaques. Recorded on video. Training provided at coordinating centre.

- **Six monthly follow up**

  For progression of stenosis and development of symptoms.

- Video tapes reported centrally -- Quality control.

Medical Therapy

Medical therapy was left to the discretion of the physician in charge

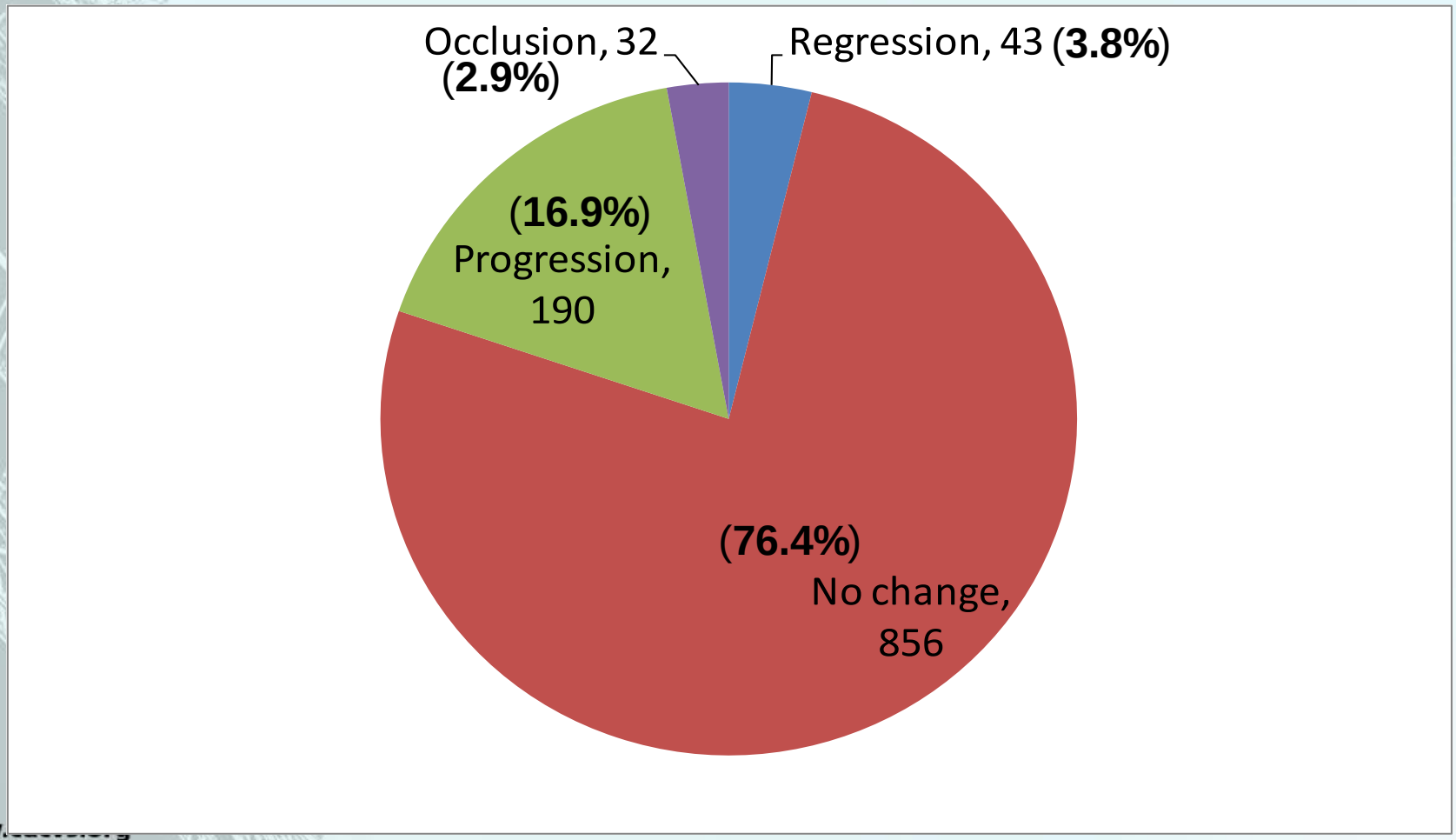
- 20% of patients were on lipid lowering therapy
- 80% of patients were on antiplatelet therapy

Methodology

- Stenosis was graded using a combination of velocities and velocity ratios, including PSVic/EDVcc, into six groups: 50-59%, 60-69%, 70-79%, 80-89%, 90-95% or 96-99% (**ECST**)

- Progression or regression was considered present if there was a change to adjacent groups that persisted for at least two consecutive visits

Change in degree of stenosis during follow-up (mean 4 years)



Relationship between the incidence of regression, progression and occlusion and baseline stenosis

Stenosis Class	Regression	No change	Progression	Occlusion
50-59%	0	61 (66%)	30 (33%)	1 (1.1%)
60-69%	3 (3.1%)	59 (61%)	34 (35%)	1 (1.0%)
70-79%	9 (2.8%)	262 (81%)	50 (15%)	1 (0.3%)
80-89%	16 (4.7%)	252 (78%)	45 (14%)	8 (2.5%)
90-95%	15 (5.4%)	214 (76%)	31 (11%)	20 (7.1%)
95-99%	0	8 (89%)	0	1 (11%)
Total	43 (3.8%)	856 (76%)	190 (17%)	32 (2.9%)
Chi sq: P =	0.031	------	< 0.001	< 0.001

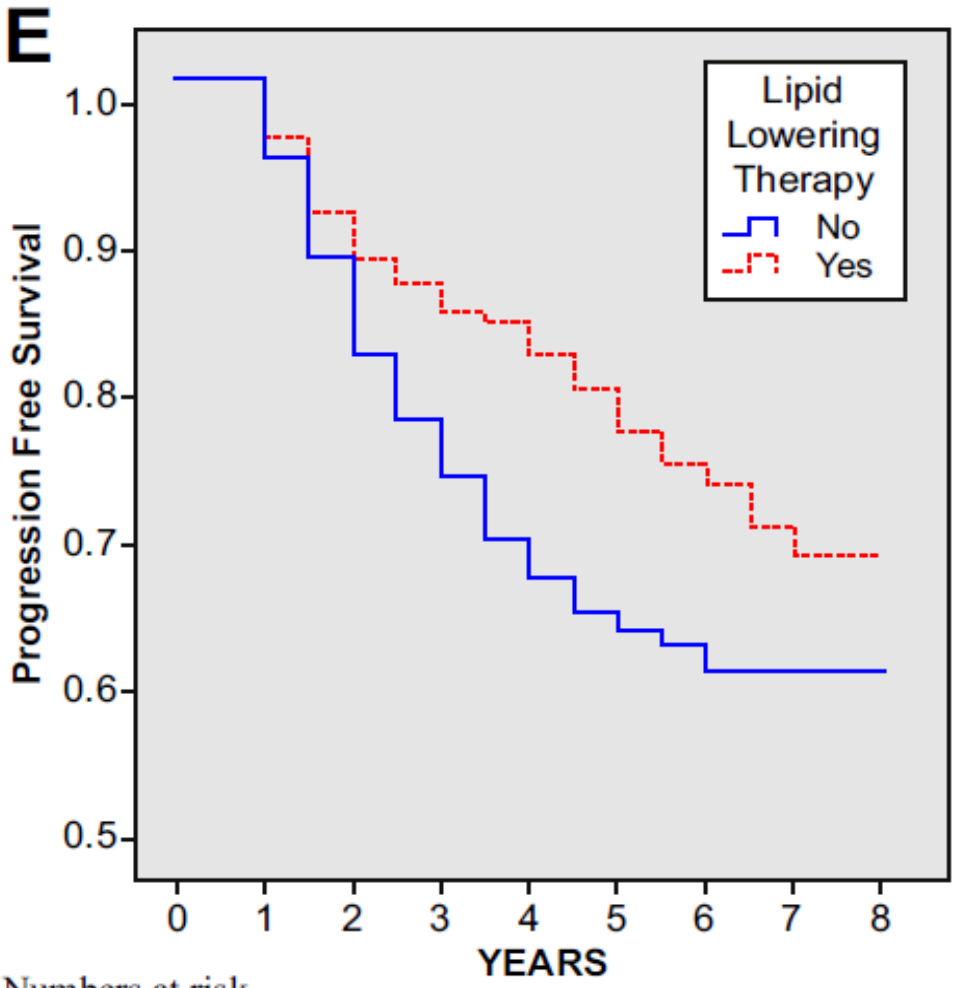
Chi sq: chi square for trend in comparison to the "No change" group.

Unadjusted hazard ratios of risk factors for ipsilateral stenosis progression

Risk Factor	Hazard Ratio	95% CI	p
Age (10 year increase)	1.19	1.01-1.41	0.044
Male	1.71	1.28-2.28	0.001*
Coronary artery disease	1.36	1.04-1.78	0.023
Creatinine (20% increase)	1.22	1.13-1.32	<0.001*
Plaque area $^{1/3}$ (mm^2)	1.37	1.14-1.65	0.001*
Lipid lowering therapy	**0.66**	0.48-0.91	0.011*
Degree of stenosis (10% increase)	**0.84**	0.76-0.93	0.001*

* Significant in multivariate analysis

Significant predictors of progression



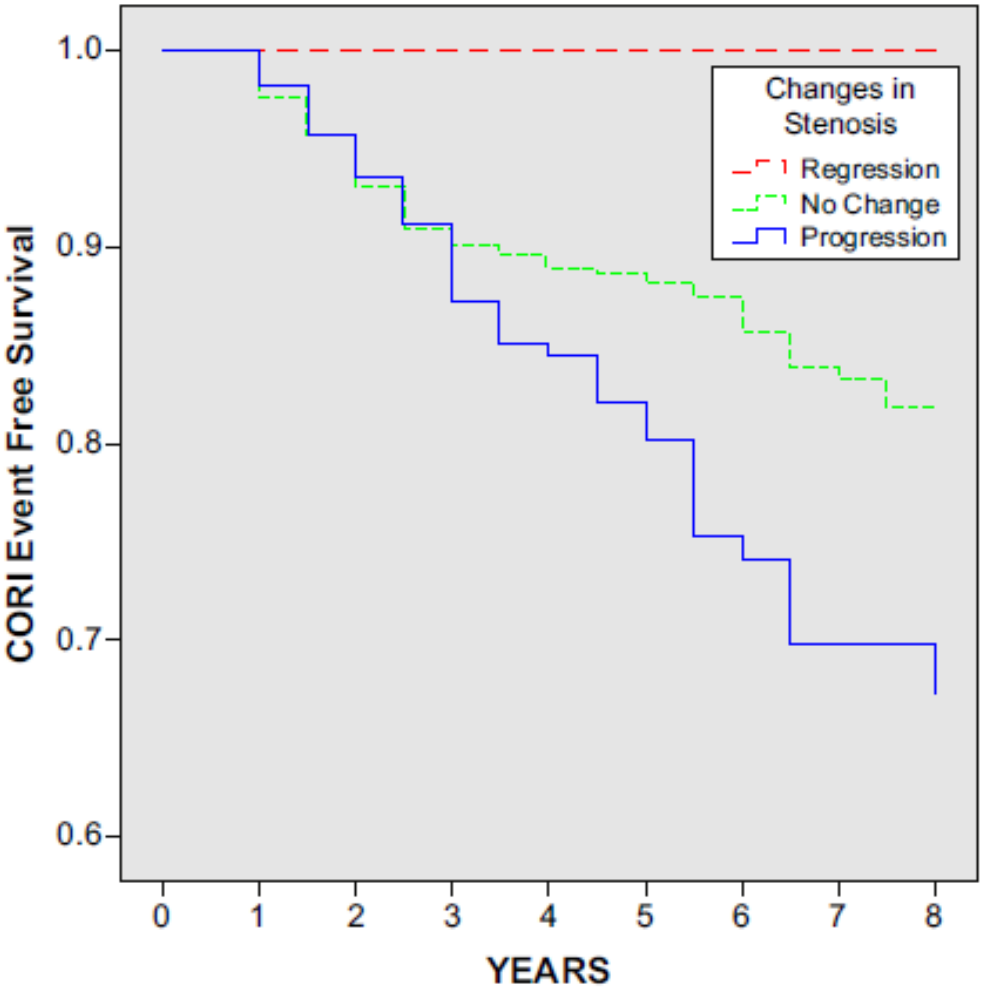
Numbers at risk

Lipid lowering therapy				
No	236	167	104	44
Yes	686	370	208	67

Protective

Lipid-lowering therapy
log-rank P = 0.009

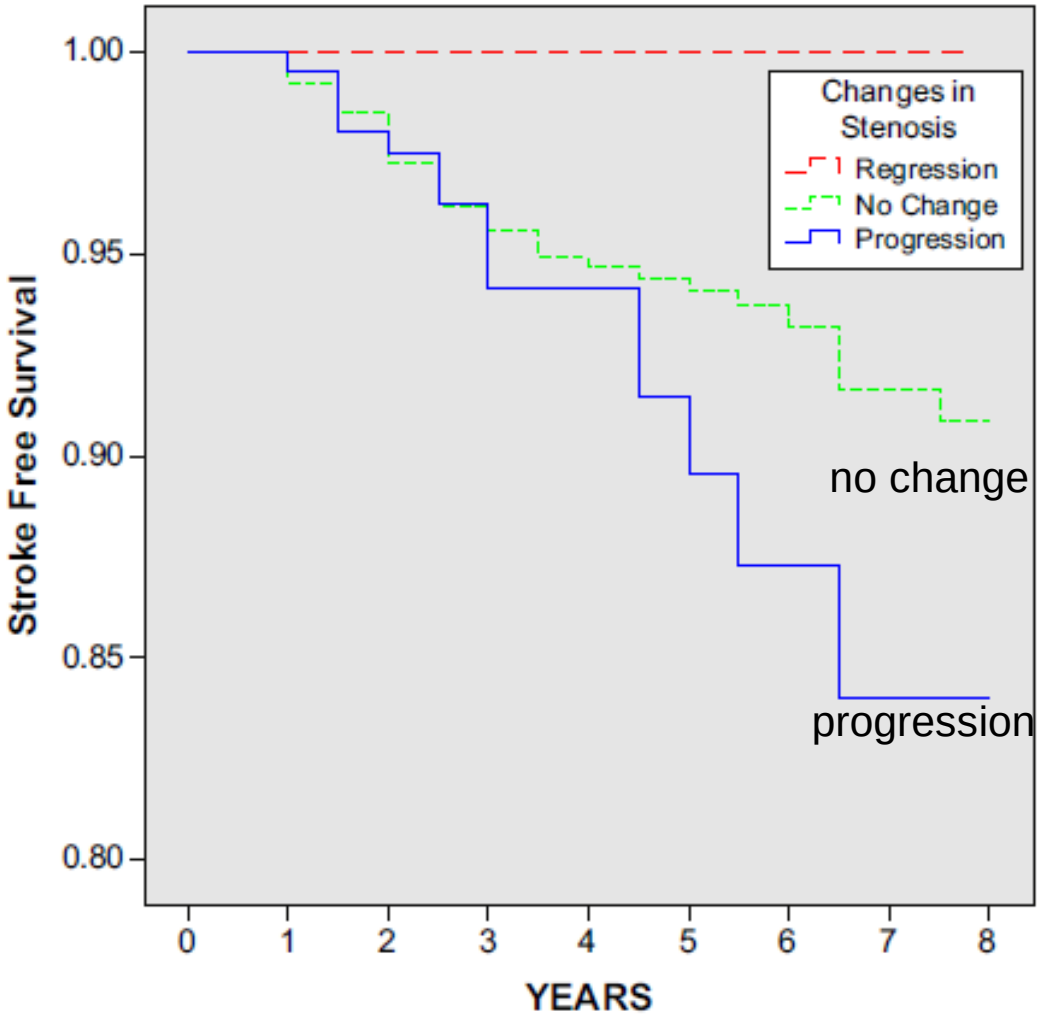
Effect of changes in stenosis on ipsilateral cerebrovascular or retinal ischemic (CORI) events



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

log-rank P <0.001

Effect of changes in stenosis on ipsilateral ischemic stroke



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

log-rank P = 0.05

Average annual stroke rate over 8 years

40 strokes **1.1%**

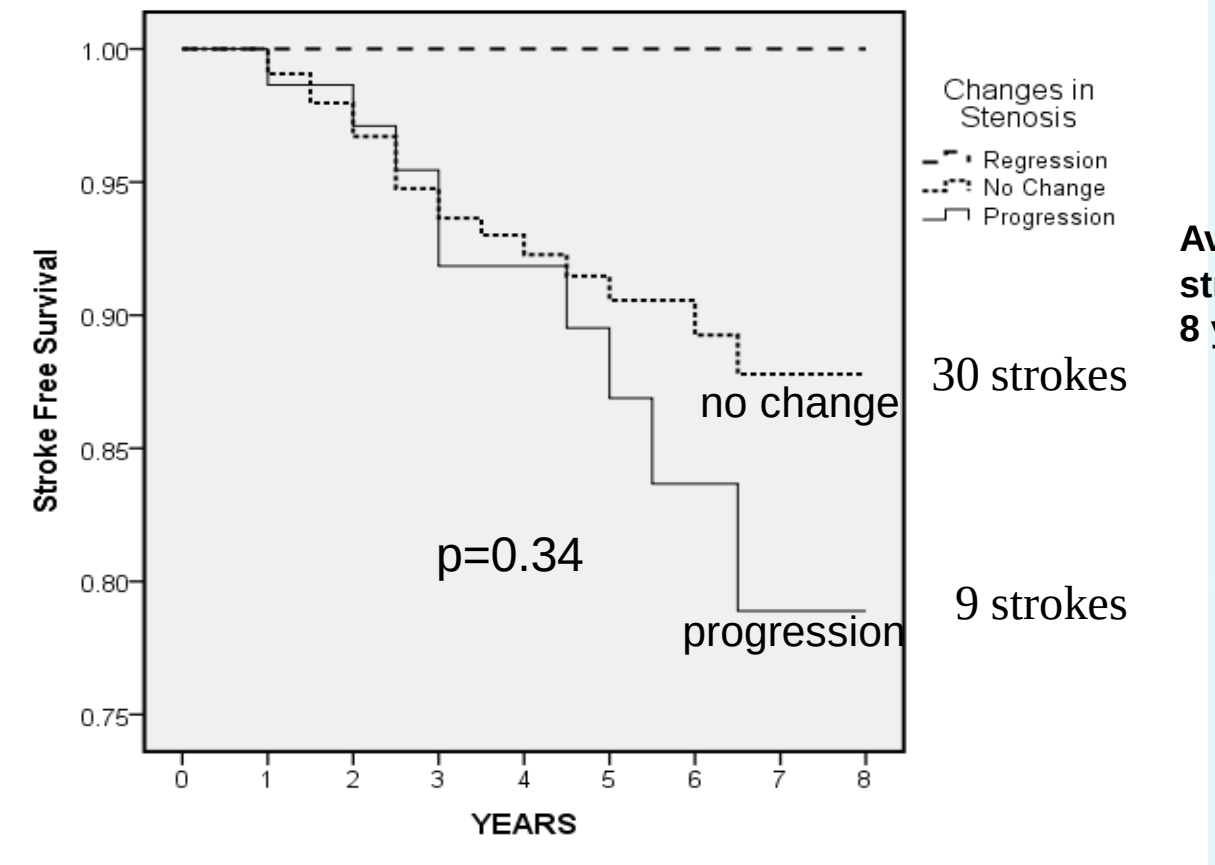
RR 1.9

19 strokes **2.0%**

40/59 strokes occurred in the group of patients <u>without</u> progression

Similar pattern for stenosis subgroups

Effect of changes in stenosis on ipsilateral ischemic stroke in patients with > 70% NASCET stenosis (N = 449)



30 strokes

9 strokes

Average annual stroke rate over 8 years

1.5%

2.6%

Numbers at risk				
Regression	21	13	9	2
No change	292	159	91	45
Progression	77	49	31	11

Multivariate (Cox) model with stenosis and progression as covariates and stroke as the dependent variable

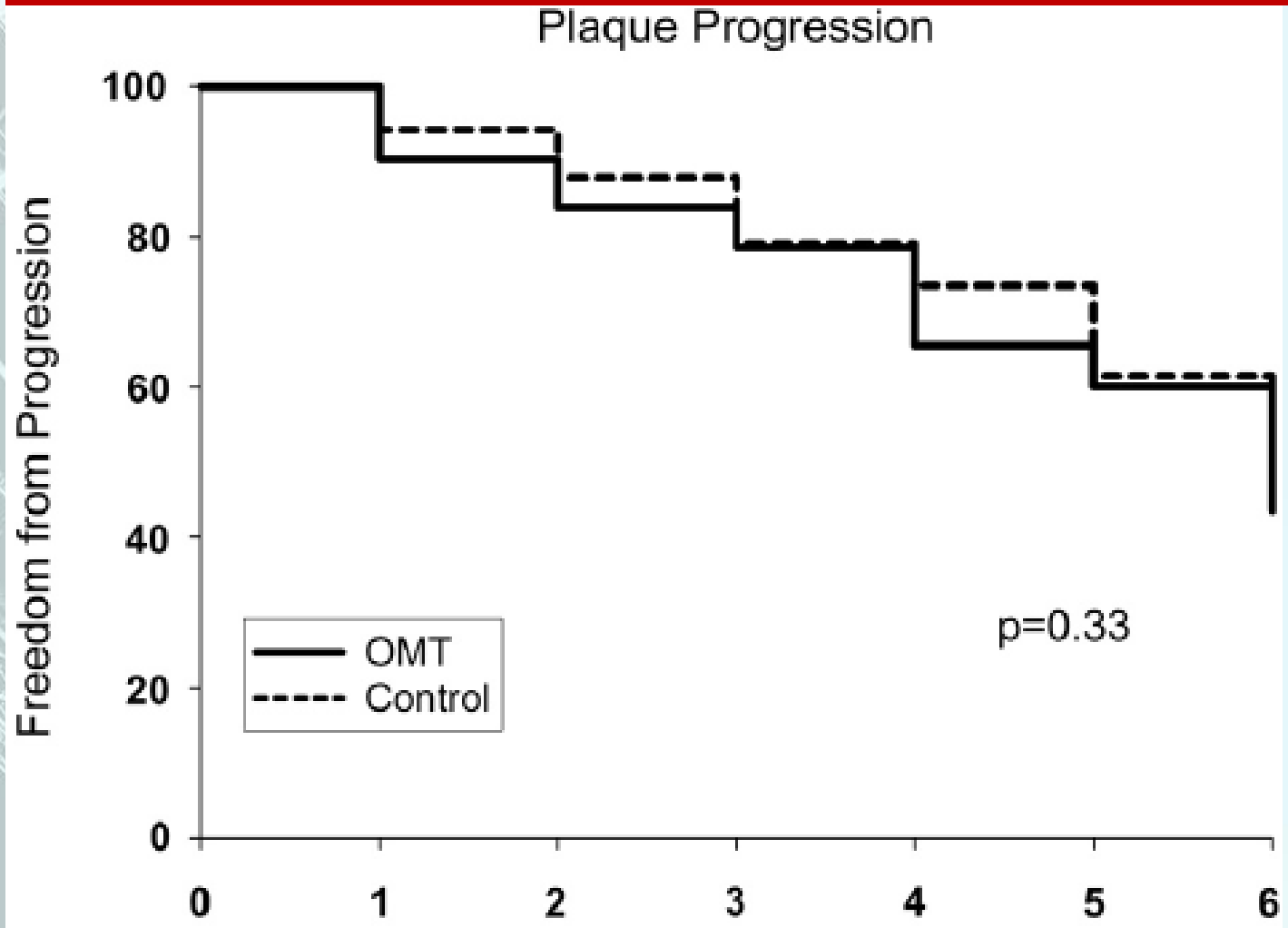
Variable	β	HR	95% CI	p value
Ipsilateral stenosis (10% increase)	0.295	1.343	1.068-1.687	0.011
Progression	0.616	1.852	1.072-3.202	0.027

Progression of stenosis added as covariate in a Cox model previously published* that could predict the risk of future events

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

Urgent need for studies using modern best medical treatment



Progression of asymptomatic carotid stenosis despite optimal medical therapy (2005-6). Conrad, J Vasc Surg, 2013

Conclusions (I)

- Progression is very common in stenosis 50-69% ECST.
- One in three patients in this subgroup will develop progression and approach or reach a “surgical threshold”.
- About 24 Duplex tests (1,200-2,400 €) have to be performed to detect one clinically significant progression in this subgroup.

Conclusions (II)

- The severity of stenosis and progression are both associated with the occurrence of ischemic events and stroke in patients with asymptomatic carotid stenosis.

Conclusions (III)

- Progression identifies a group at increased risk of stroke, but it is of relatively limited value compared with stenosis combined with plaque image analysis.

- Further studies using current medical therapy may be suggested.


Thank You