



Management of Carotid Atherosclerosis:

An Academic Neurologists's Perspective
in January 2012

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Carotid Stenosis (50-99%)

Aims of Routine Practice Management

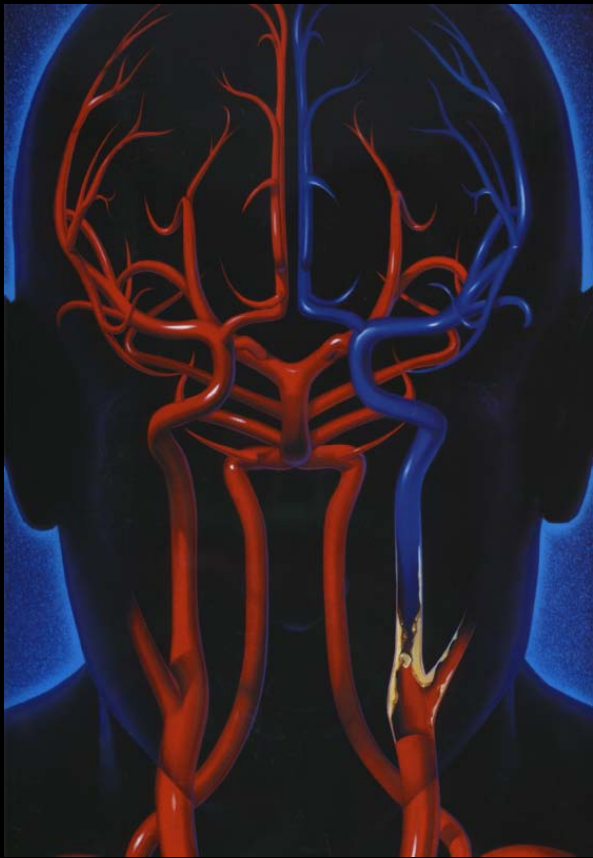


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Brain Foundation

To give patients the
best chance
of preventing

1. stroke &
2. other complications

Management Options



Courtesy of A/Prof C. Levi
John Hunter Hospital

1. Surgery
(CEA)
2. Angioplasty/stent
(CAS)
3. Medical
(non-invasive)



Courtesy of A/Prof B. Yan
Royal Melbourne Hospital

What is Best & Why?





















































































50-99% carotid stenosis

1. Asymptomatic – Medical alone
2. Symptomatic – Medical + surgery for selective cases

Asymptomatic Carotid Stenosis

Inefficiency of Surgical Stroke Prevention

NNT in ACAS = 83 to be *ahead* by 1 ipsilateral stroke/yr

Caused (2)	No Effect (78)	Prevented (3)
 	                                                                              	  

2.3% peri-operative stroke/death rate in ACAS.

ARR calculated from 5 yr KM rate estimate stroke/death/ipsilateral stroke (5.1% for CEA vs 11.0% for medical only).

NNT to be **ahead** by one ipsilateral stroke over 12 months = $100/1.2 = 83$.

Benefit began by 10 months and significant by 3 years. No long term benefit established.

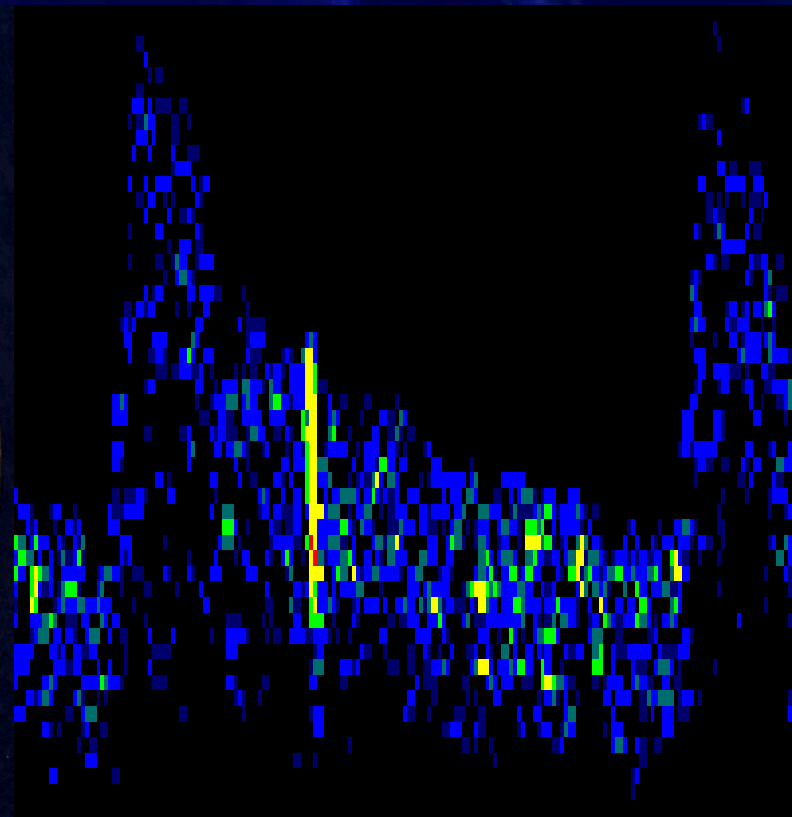
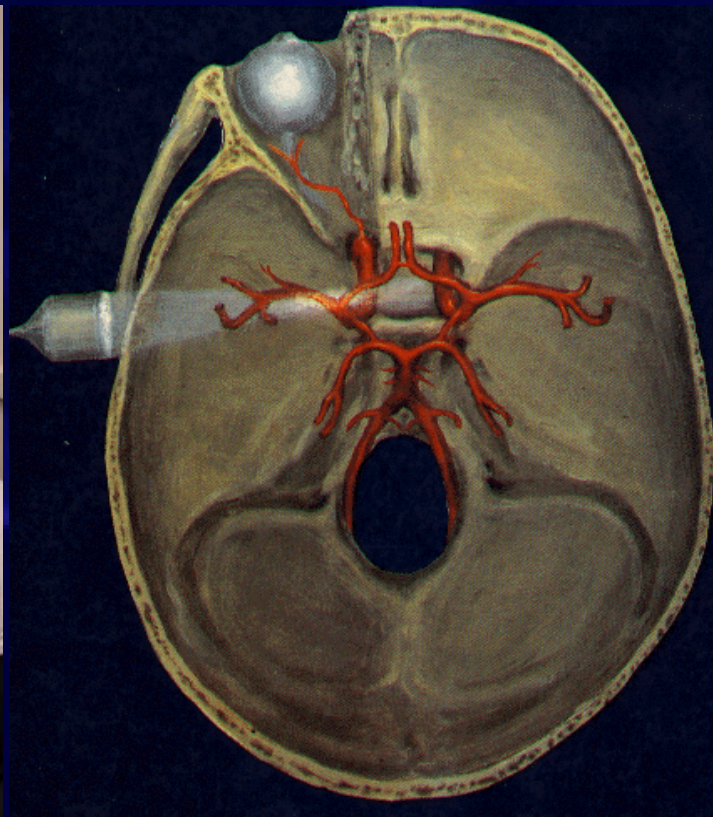
All patients exposed to other complications of CEA- hyperperfusion, heart attack, heart failure, cranial nerve damage, recurrent stenosis etc

Randomization: 1987-1993

Asymptomatic Carotid Stenosis (50-99%)

My PhD (1998-2004)

Embolic Signals Predict Stroke/TIA?



Main PhD Results

(Abbott et al, Stroke 2005)

- 202 patients: 68% male, mean age 74yrs
- Mean follow-up: 2.8 yrs
- Average annual rate of first
 - ipsilateral stroke: 1%
 - ipsilateral stroke/TIA: 3%
- Low ES rates: about 1 / 6 hrs
- Trend in ES & risk of ipsilateral stroke/TIA:
(OR, 1.47; 95% CI, 0.43, 4.48; $P=0.624$ vs OR, 2.17; 95% CI, 0.36, 22.90; $P=0.59$)

My Post-doc Studies

A Systematic Review & Analysis

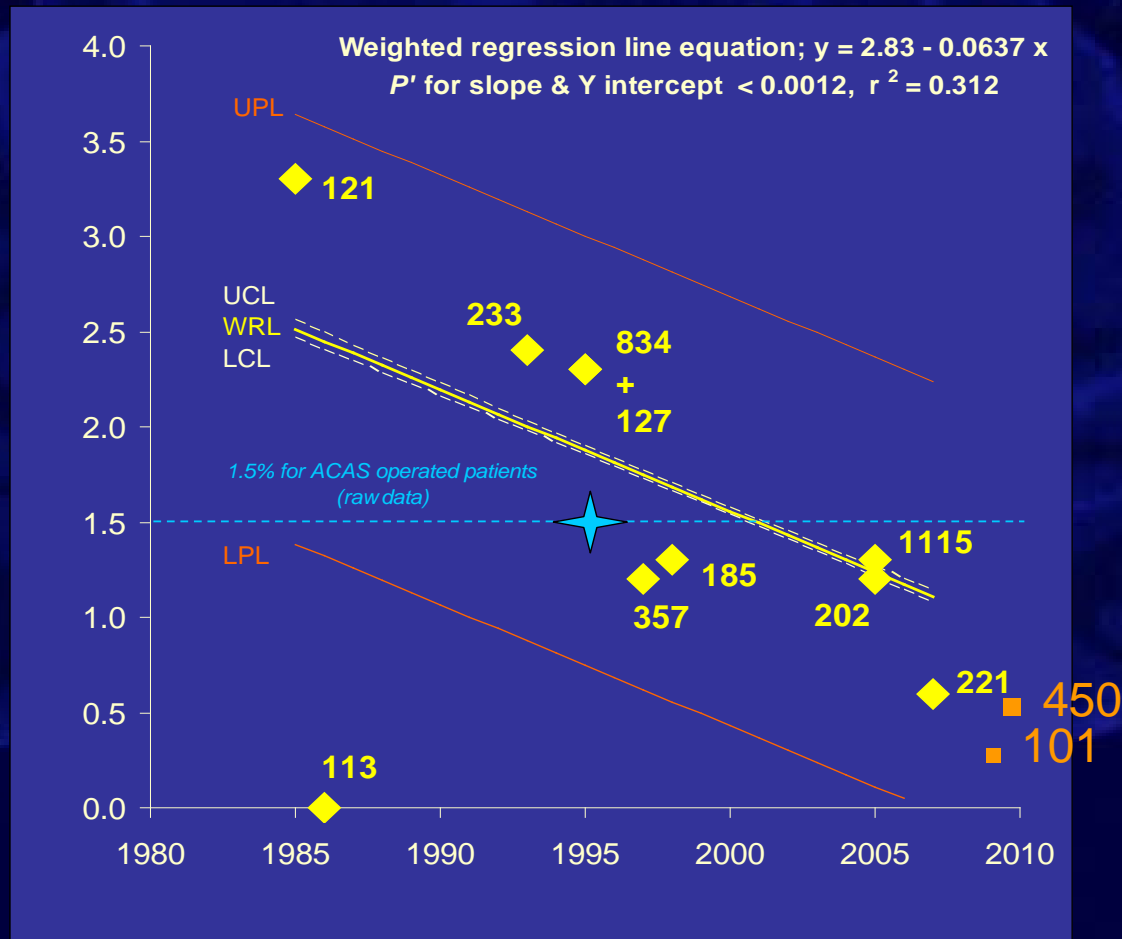
- Medline & bibliography search
- Prospective, >100 patients, 50-99% asymptomatic stenosis
- Average, annual patient rate of stroke (+/- TIA)
- First event of interest per patient
- Separate rates from raw data & KM risk estimates
- Weighted linear regression analysis
- Ryan-Holm stepdown Bonferroni correction for multiple comparisons, converting P to P'
- 95% confidence & prediction limits

Results

Study Type		Name	Year	n
Hospital	Observational	Johnson	1985	121
		Toronto	1986	113
		ACBS	1997	357
		ACSRS	2005	1115
		ASED	2005	202
		SMART	2007	221
	RT asymptomatic carotid stenosis	VACS	1993	233
		ACAS	1995	834
	RT contralateral symptomatic carotid stenosis	ECST	1995	127
		NASCET	2000	216
Community	Observational	CHS	1998	185

Ipsilateral Stroke Rates 50-99% Asymptomatic Carotid Stenosis

Average
Annual
Rate
(Raw data,%)

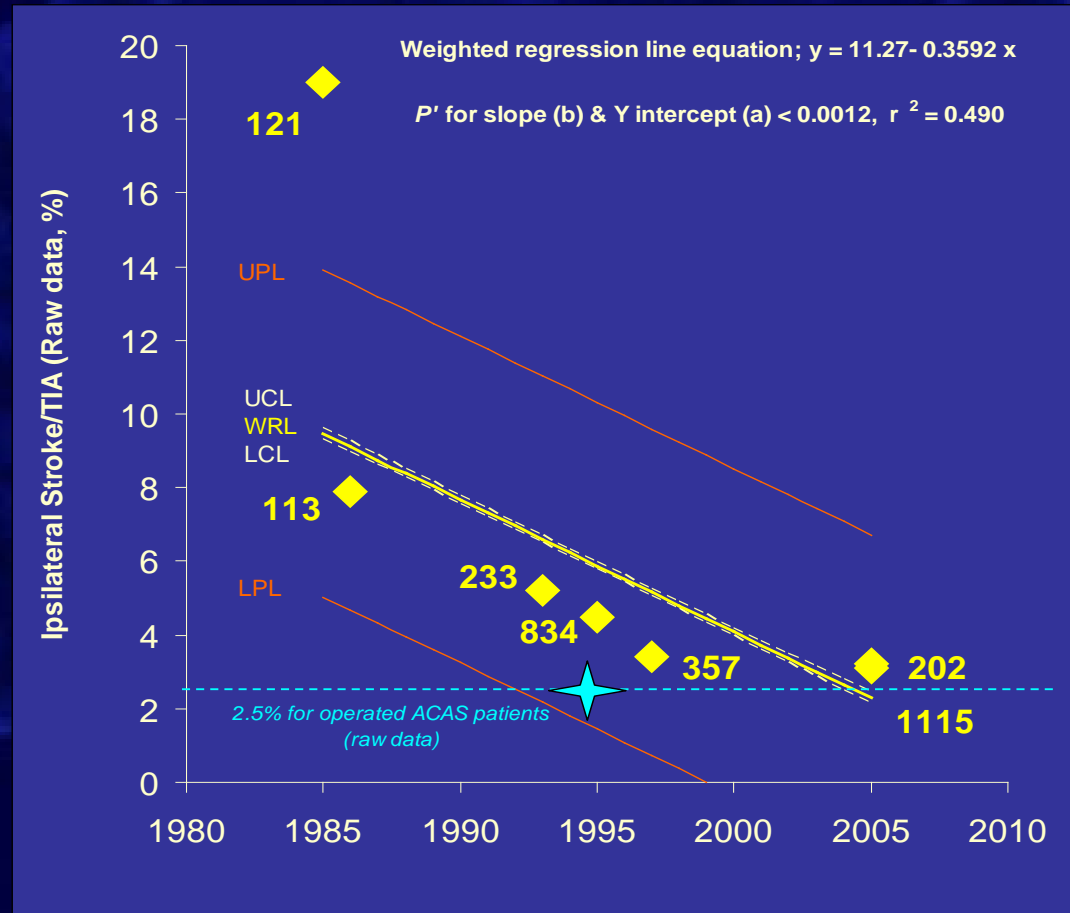


Abbott. Stroke.2009

Publication Year

Ipsilateral Stroke/TIA Rates 50-99% Asymptomatic Carotid Stenosis

Average
Annual
Rate
(Raw data,%)

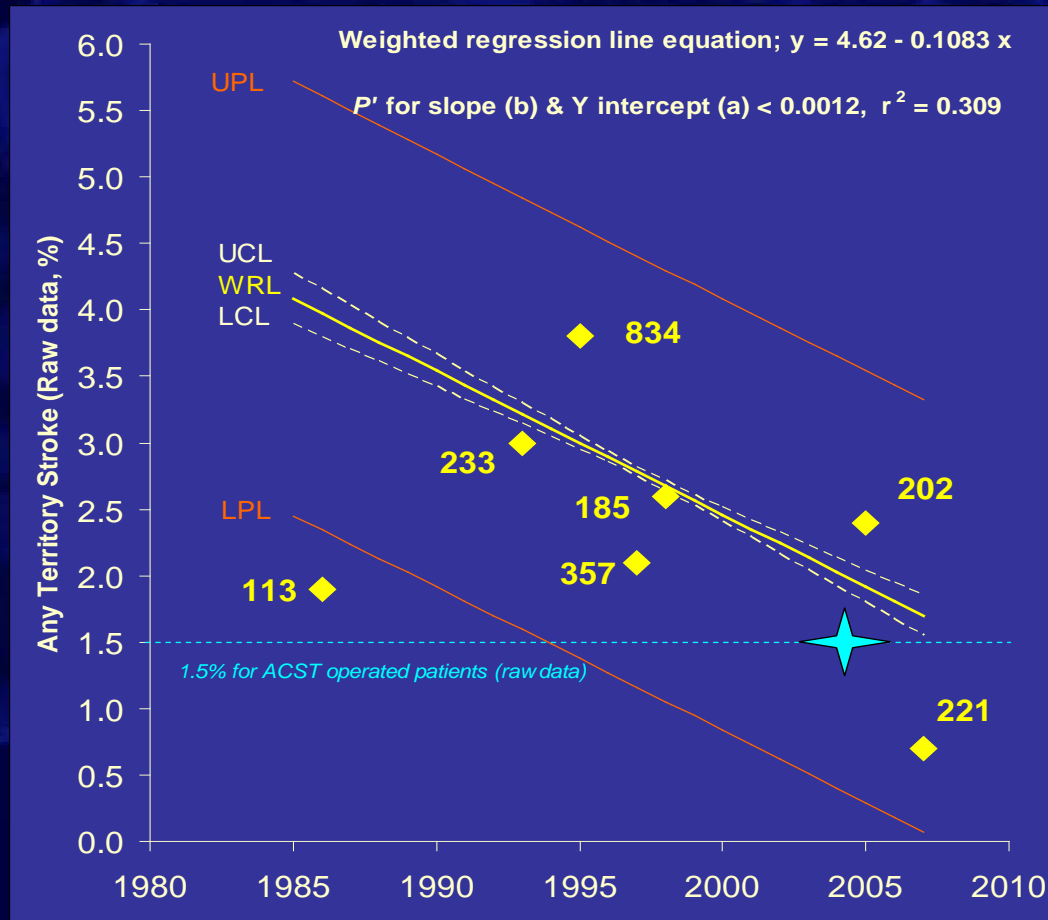


Abbott. Stroke.2009

Publication Year

Any Territory Stroke Rates 50-99% Asymptomatic Carotid Stenosis

Average
Annual
Rate
(Raw data,%)

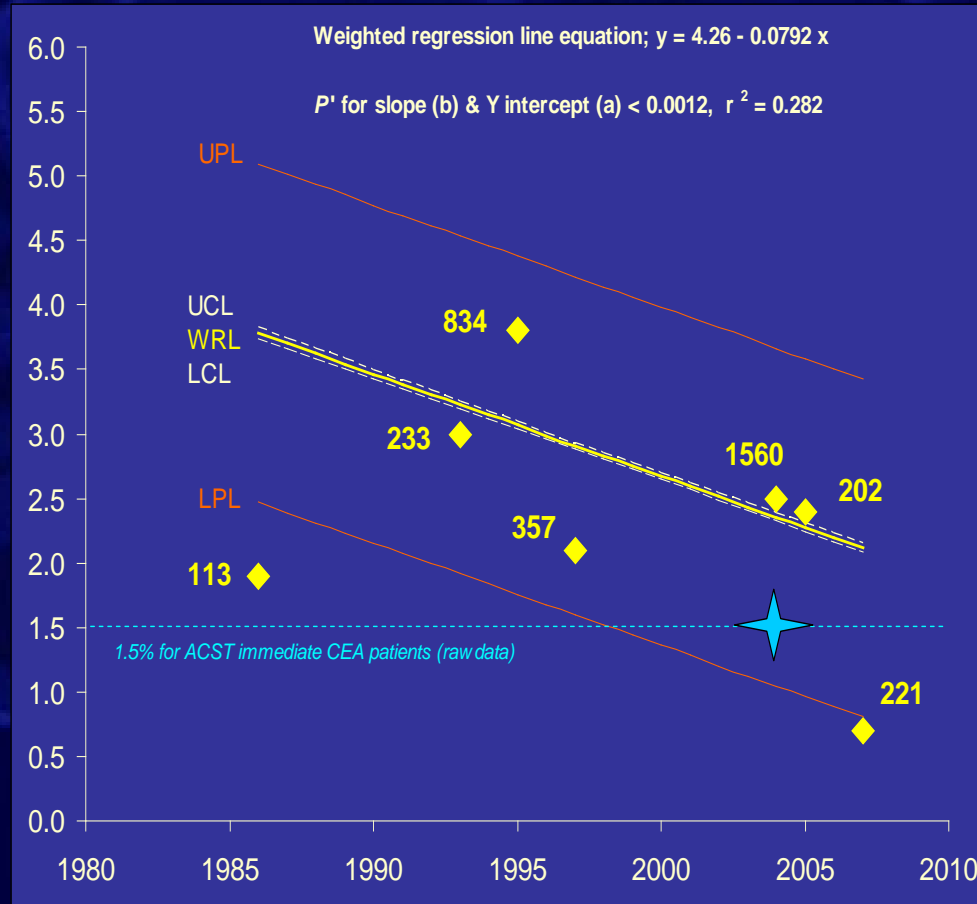


Abbott. Stroke.2009

Publication Year

Any Territory Stroke Rates (Adding deferred ACST-CEA)

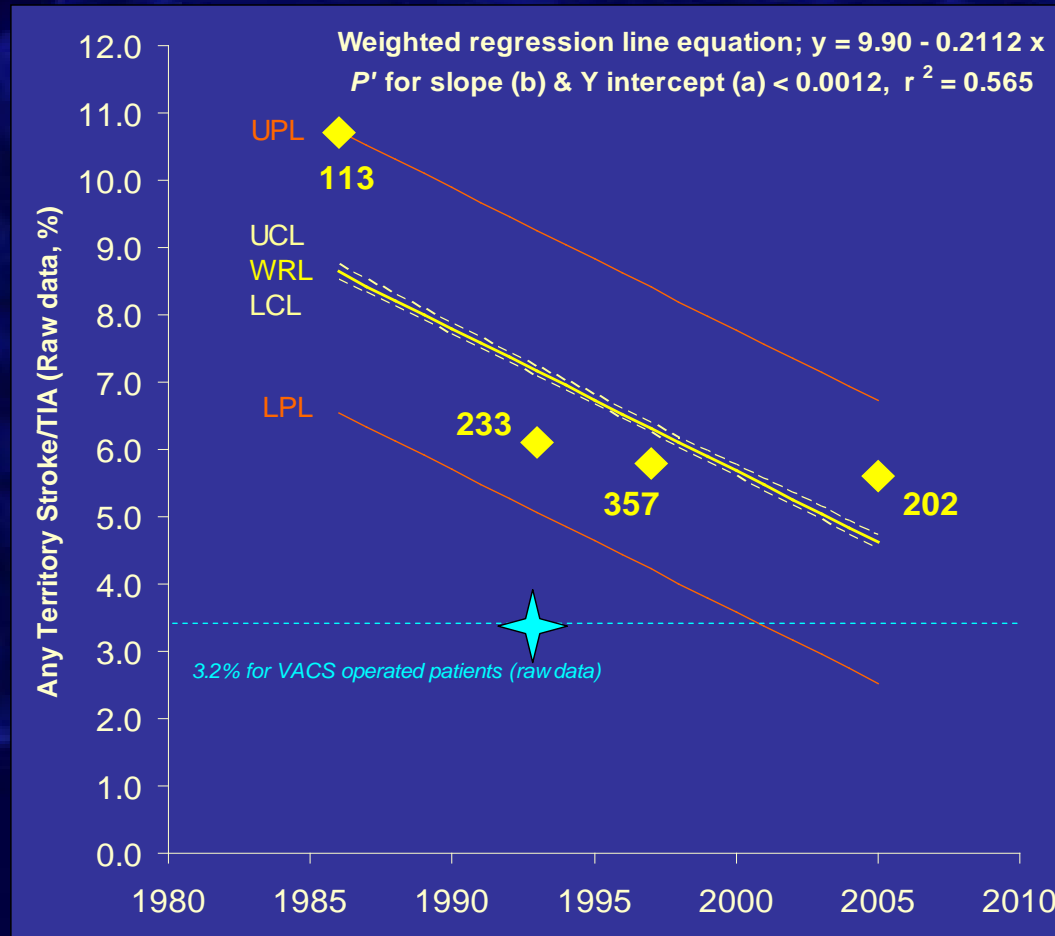
Average
Annual
Rate
(Raw data,%)



Abbott. Stroke.2009

Any Territory Stroke/TIA Rates 50-99% Asymptomatic Carotid Stenosis

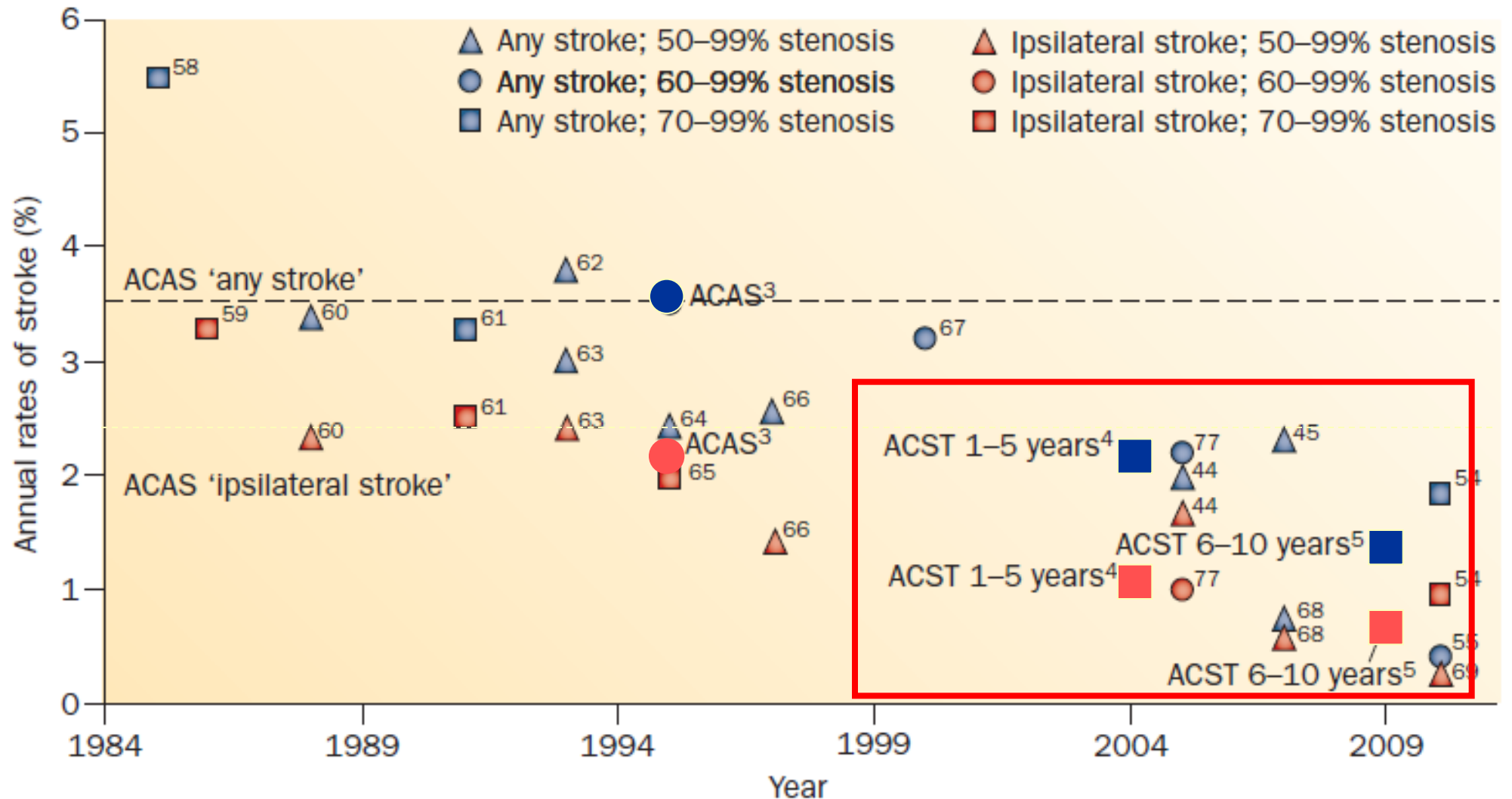
Average
Annual
Rate
(Raw data,%)



Abbott. Stroke.2009

2011 update

AR Naylor *Nature: Cardiology Reviews* (in press)



Asymptomatic Carotid Stenosis (50-99%)

Summary of Research Results

1. The average annual risk of ipsilateral stroke:
 - Has fallen 1.5 - 2.5 % with medical therapy alone
 - A 60 - 80% relative risk reduction
 - Is now about 0.5%
2. Medical therapy prevents other complications
3. Medical therapy is > 4 - 8 times cheaper for stroke prevention

Comparison of Intervention Strategies

Strategy	Annual Ipsilateral Stroke Rate (Average, Raw)	Ipsilateral Strokes / 2000 Patients/yr	Excess Number of Strokes Above Current Medical Alone	Extra Rx Cost Over Current Medical (\$US)
1980-1995 Medical (ACAS, R=1987-1993)	2.5%	50	40	-
Current Medical	0.5%	10	0	N/A
ACAS CEA+ ACAS Medical (30-D: 2.3%)	1.5%	30	20	40 million (\$20,000- NIS median CEA cost ACS, 2007)
CREST CEA + CREST Medical (30-D: 1.4%)	0.9%	18	8	
CREST CAS + CREST Medical (30-D: 2.5%)	1.6%	32	22	66 million (\$33,000- NIS median CAS cost ACS, 2007)

Asymptomatic Carotid Stenosis


What is Now Best for Routine Practice/Research

1. Medical therapy alone for all.
2. Update best practice guidelines.
3. Define/measure impact of current optimal medical therapy.
4. Measure risk of all vascular disease complications.
5. Risk stratification studies to improve medical intervention rather than select for CEA or CAS. Now $< 5\%$ will benefit from CAS/CEA if procedural risk is 0% .
6. Find out if screening is useful for patients / cost-effective.

Symptomatic Carotid Stenosis

Inefficiency of Surgical Stroke Prevention

Pooled data NNT = 53 to be *ahead* by 1 ipsilateral stroke/yr

Caused (6)	No Effect (40)	Prevented (7)
	       	
	       	
	       	
	       	
	       	
	       	
		

6.2% peri-operative stroke/death rate for 70-99% stenosis (excluding near occlusion, pooled individual data NASCET, ECST, VACS).
ARR calculated from 5 yr KM rate estimate peri-operative stroke/death or later ipsilateral stroke (11.2% for CEA vs 20.8% for medical only).
NNT to be **ahead** by one ipsilateral stroke over 12 months = $100/1.9 = 53$.
All patients exposed to other complications of CEA- hyperperfusion, heart attack, heart failure, cranial nerve damage, recurrent stenosis etc
Randomization: 1981 - 1994

Symptomatic Carotid Stenosis

(70-99%)

Current guidelines:

CEA / CAS as long as the patient is reasonably fit & 30-day stroke/death is $\leq 6\%$

For CEA: these guidelines are out-dated & too liberal:

- i. Medical intervention has improved
- ii. Surgical technique may have improved
- iii. CEA (CAS) 30-day stroke/death rates falling in trials
- iv. Subgroups shown to benefit not emphasised
- v. Not enough accountability in routine practice

Symptomatic Carotid Stenosis

(70-99%)

For CAS, such guidelines are scientifically flawed:

- i. Assume a 30-day stroke/death rate of $\leq 6\%$ is still OK.
- ii. CAS is associated with about double the procedural & long term risk of stroke compared to CEA.
 - Randomised trials
 - Meta-analyses
 - Registries
- iii. A higher rate of peri-procedural myocardial infarction with CEA in CREST doesn't justify routine practice CAS.
 - Mortality up to 4 years: MI = stroke
 - Stroke more common than MI
 - Quality of life worse with stroke

Symptomatic Carotid Stenosis

What is Now Best for Routine Practice/Research

- i. Correct errors in current best-practice guidelines.
- ii. Organize routine practice to replicate trial methods.
- iii. Measure 30-day stroke/death rates.
- iv. Recognise CEA/CAS are increasingly specialised.
- v. Re-define 30-day stroke/death rate now likely to confer a stroke prevention benefit over medical therapy.
- vi. Risk stratification studies to identify the culprit carotid plaque in patients with recent stroke/TIA.

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Key References

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Summary of Event Rate Falls

(Medical Therapy Alone. Hospital Based Studies Only)

Outcome	Raw Data Rates	
	Interval / (n, n)	% Change
Ipsilateral stroke	1985-2007 (9, 3323)	1.5
Ipsilateral stroke/TIA	1985-2005 (7, 2975)	7.0
Any stroke	1986-2007 (6, 1960)	3.2
Any stroke/TIA	1986-2005 (4, 913)	4.2

Changes in Baseline Risk factors

Increasing prevalence

Characteristic	No. of Studies	WRL equation	Date Interval	* Rate Change	P' for slope	r ²
High total cholesterol	5	y=17.7+1.669x	1986-2005	32% ↑	<0.01	0.589
Age	10	y= 62.9+0.259x	1986-2007	5.5 yr ↑	<0.01	0.256
Hypertension	9	y= 58.2+0.197x	1986-2005	4% ↑	<0.01	0.025
Diabetes	10	y=20.8+0.008x	1986-2007	<1% ↑	>0.999	0.0002

* For hospital based studies only, respectively; no change, 6yr ↑, 5% ↑, no change

Changes in Baseline Risk factors

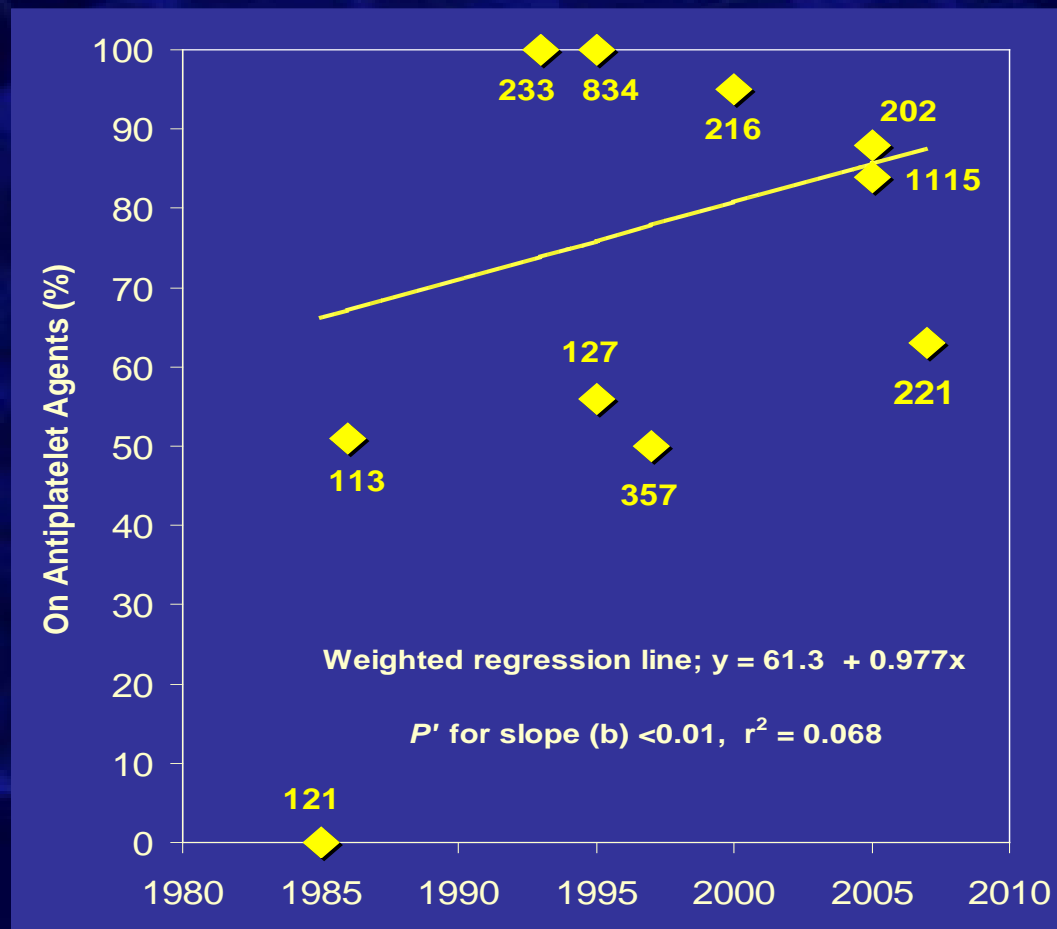
Decreasing prevalence

Characteristic	No. of Studies	WRL equation	Date Interval	* Rate change	P' for slope	r ²
Ischaemic heart disease	10	y=82.3-1.736x	1986-2007	36% ↓	<0.01	0.377
Atrial fibrillation	6	y=12.6-0.437x	1993-2005	5.5% ↓	<0.01	0.233
Current smoker	9	y=46.7-1.001x	1993-2007	14% ↓	<0.01	0.205
Ever smoker	6	y=83.0-0.364x	1986-2007	8% ↓	<0.01	0.055
Male sex	10	y=69.7-0.305x	1986-2007	7% ↓	<0.01	0.016
Peripheral vascular disease	9	y=42.2-0.311x	1986-2007	6.0% ↓	<0.01	0.013
Other stroke/TIA	11	y=24.9-0.0339x	1985-2007	1% ↓	>0.999	0.0001

* For hospital based studies only, respectively; 37%↓, no change, 15%↓, 12%↓, 8%↓, 11%↓, no change

Baseline Antiplatelet Agents

% of
patients



Publication Year

What medical intervention was given?

Study Type		Name	Year	n
Hospital	Observational	Johnson	1985	121
		Toronto	1986	113
		ACBS	1997	357
		ACSRS	2005	1115
		ASED	2005	202
		SMART	2007	221
	RST asymptomatic carotid stenosis	VACS	1993	233
		ACAS	1995	834
	RST contralateral symptomatic carotid stenosis	ECST	1995	127
		NASCET	2000	216
Community	Observational	CHS	1998	185

Vascular disease medical intervention in the ASED Study

Class	Subtype & % usage
Antiplatelet	Aspirin-86%, Persantin-9%, Ticlid-6%, Plavix+/- Ticlid-10%
Lipids	Statin-64%, fibrate-5%, bile acid sequestrant-9%
Blood pressure	Ca blocker- 45%, ACEI 40%, B Blocker-26%, low threshold diuretic-20%, ARB-15%
Blood Sugar	Sulphonamides-9%, Biguanides-8%, insulin-5%
Antiarrhythmic	Amiodarone/sotalol-5%, flecanide-0.5%
Other CV drugs	Angina-14-24%, high threshold diuretics-20%, digoxin-6%, thyroxine-6%

Vascular disease medical intervention in the ASED Study

Intervention	Usage (%)	Annual Cost \$AUS <small>(Per 100 patients, maximal usage/dosage, 2009 costs)</small>
Biannual medical review	100	25 000*
Antiplatelet agents	93	22 750
Blood pressure lowering	75	88 100
Lipid lowering	66	88 100
Blood sugar lowering	15	32 700
Anti-dysrhythmic	5	4 000
Other cardiovascular drugs <small>(angina, heart failure, digoxin, thyroxine)</small>	42	26 900
		TOTAL: 287 550*

Comparison of Cost/Event Saved (\$AUS)

Current Common-place Vascular Disease Medical Intervention VS CEA

Event	Medical intervention Cost / Event Saved (Max. Costs)	CEA in Randomised Trials Cost / Event Ahead (Operations alone)
Ipsilateral stroke	191 700	600 000 (ACAS) *3.1
Any territory stroke	89 860	650 000 (ACST) *7.2
Ipsilateral stroke/TIA	41 100	320 000 (ACAS) *7.8
Any stroke/TIA	68 470	242 000 (VACS) *3.5

Historical Landmark Trials

Asymptomatic Stenosis (>50/60%)

- VACS, ACAS, ACST (n=5226)
- Randomisation; 1983 - 2003
- Overall **1%↓** in average, annual stroke rate
- Bench marks for surgical benefit: **stroke/death rate <3%**

Symptomatic Stenosis (70-99%, NASCET)

- VACS, ECST, NASCET (n= 6092)
- Randomisation; 1981 - 1994
- Overall **2%↓** in average annual stroke rate
- Bench marks for surgical benefits: **stroke/death rate <6%**



Randomised Trial CEA Immediate stroke/death risk

Asymptomatic Carotid Stenosis

	VACS	ACAS	ACST
30-day stroke/death (%)	4.3*	2.3	3.1

What about Carotid Stenting?

Asymptomatic stenosis (>50-80% in RTs)

30-day Stroke/Death

- | | |
|---|------|
| 1. CREST, 2010 (USA/Canada, n= 593): | 2.5% |
| 2. SAPHIRE, 2004 (USA, n=237) | 4.6% |
| 3. Lexington, 2004 (USA, n= 43) | 0% |
| 4. SVS Vascular Registry (USA, n= 805): | 4.1% |

In-Hospital Stroke/Death

- | | |
|-----------------------------------|-------|
| 4. NIS, 2004+2005 (USA, n= 2733): | 2.4% |
| 5. NIS, 2004+2005: | 1.9%* |



Courtesy of A/Prof B. Yan

Royal Melbourne Hospital

Cost: more than CEA



Robert
21/12/10

No Smoking
Safety First!

