# Medical management of extra-cranial cerebral artery stenosis

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# Talk plan

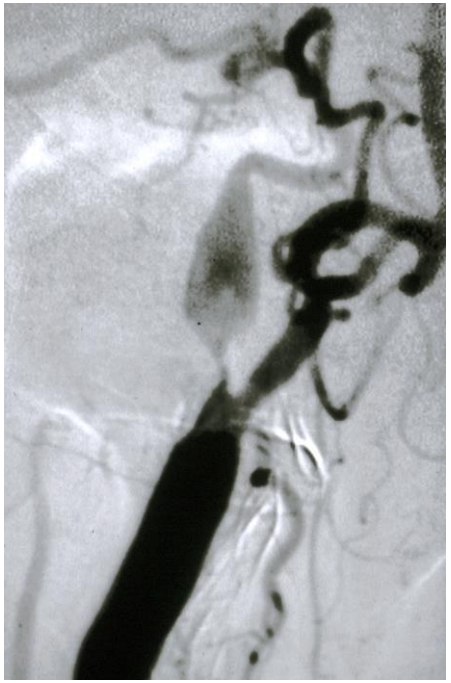
Symptomatic disease

- Atherosclerotic carotid artery stenosis
- Carotid dissection

Asymptomatic carotid stenosis

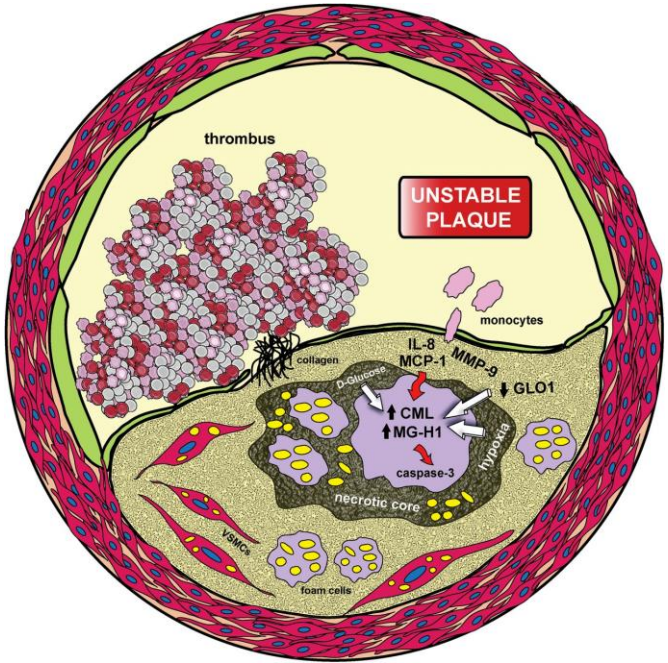
# Large artery stenosis

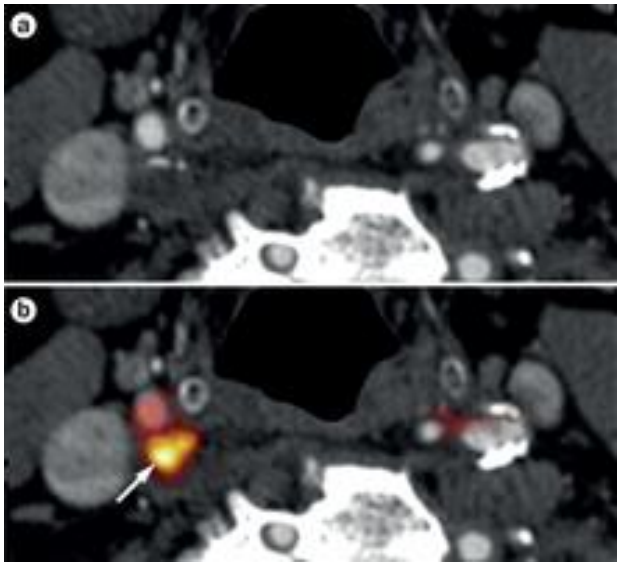
- Approximately 20% of ischaemic stroke
- Mainly extracranial in UK
- BUT different pattern- more intracranial- in other regions eg Far East Asia



# Large artery stenosis
## *Pathogenesis of stroke*

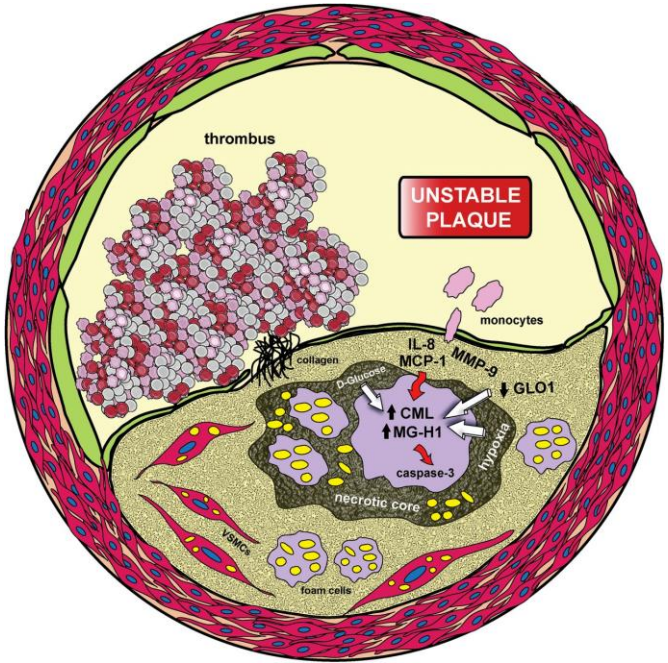
- Asymptomatic stenosis associated with low stroke risk
- Symptomatic status followed by period of markedly increased stroke risk

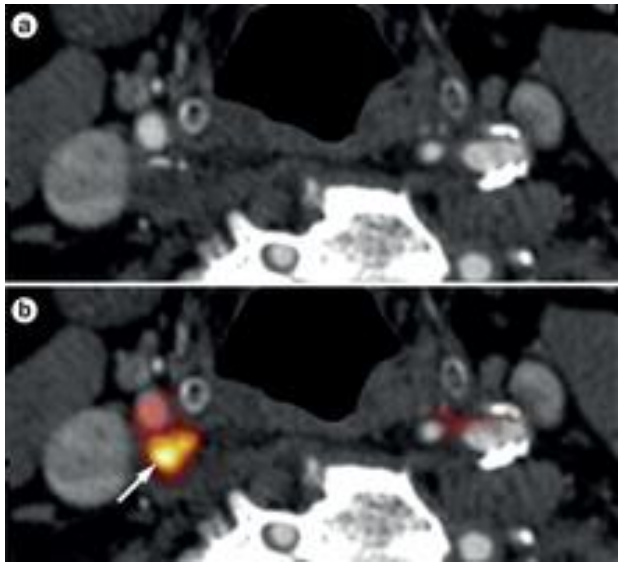


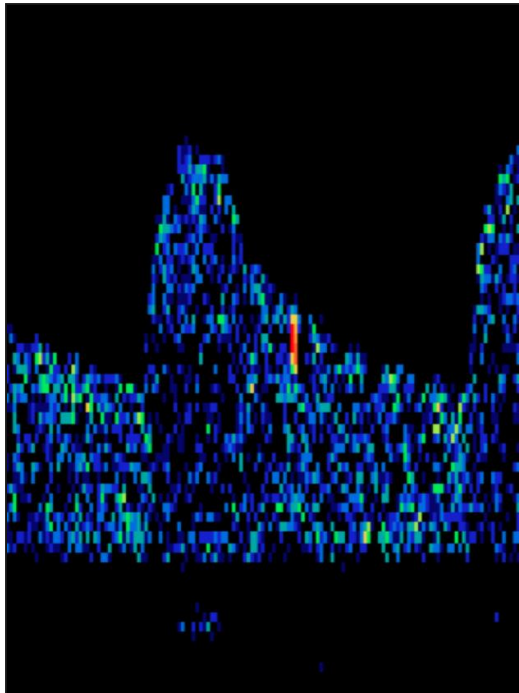



# Large artery stenosis
## *Pathogenesis of stroke*

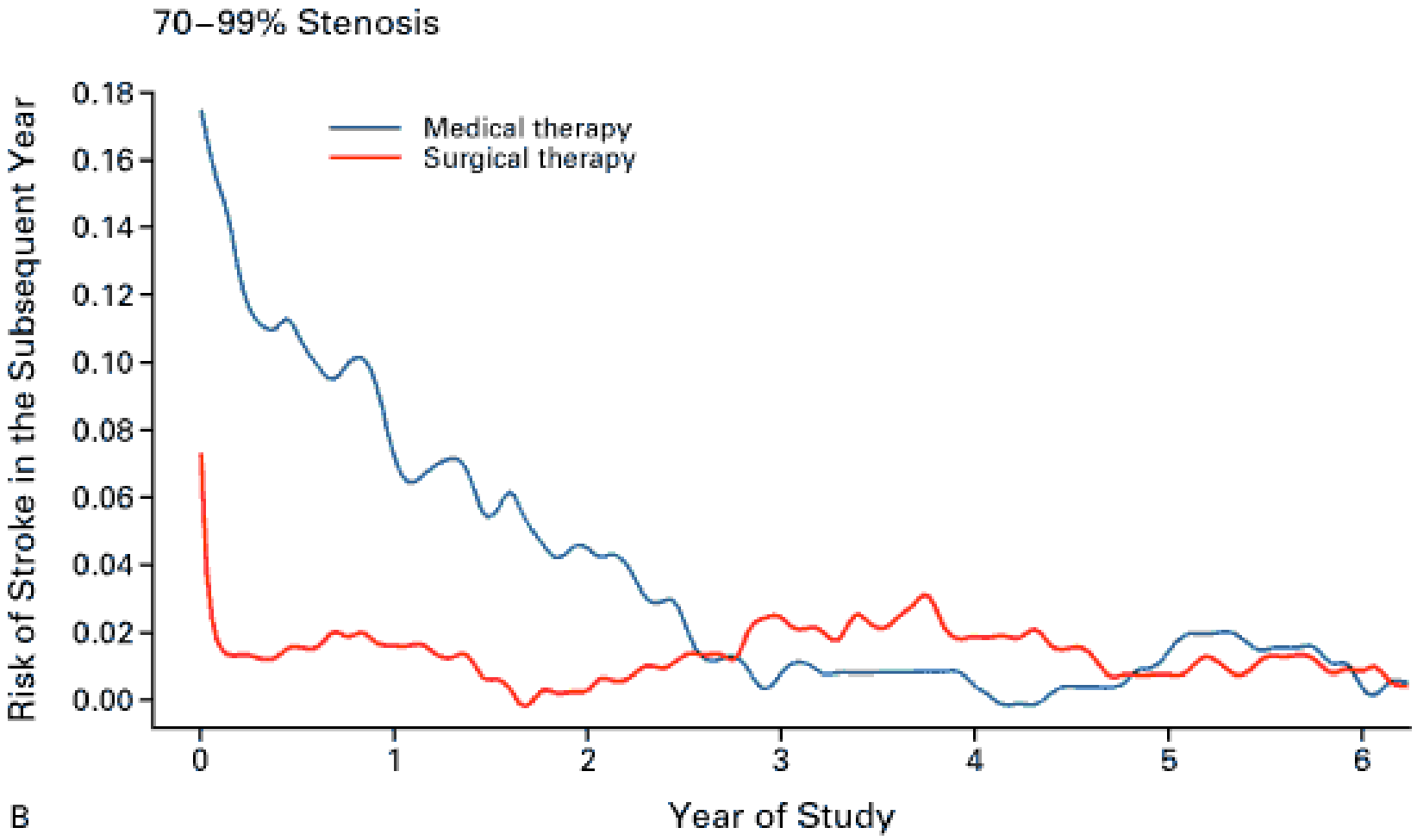
- Asymptomatic stenosis associated with low stroke risk
- Symptomatic status followed by period of markedly increased stroke risk
- Pathogenesis of stroke primarily embolic



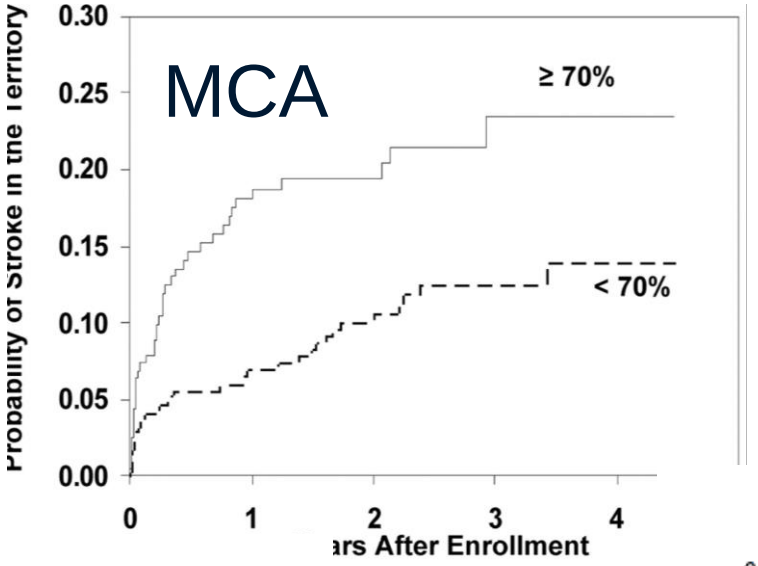



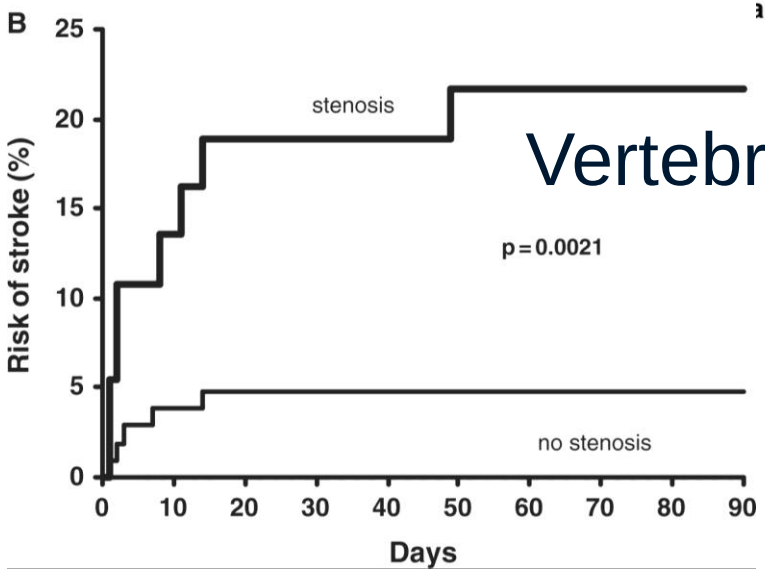



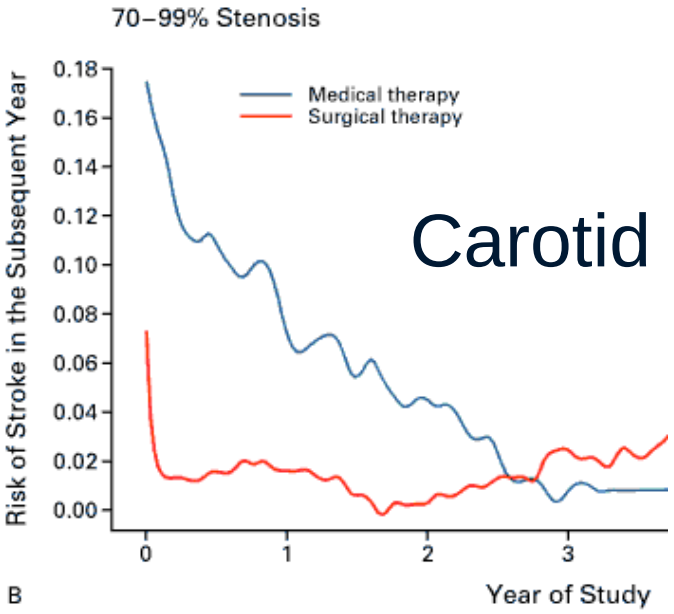
# Symptomatic carotid stenosis


70–99% Stenosis
Medical therapy
Surgical therapy
Risk of Stroke in the Subsequent Year
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0
1
2
3
4
5
6
Year of Study
B

# Transient high risk after a stroke or TIA
# Very similar risk profile across cerebrovascular beds



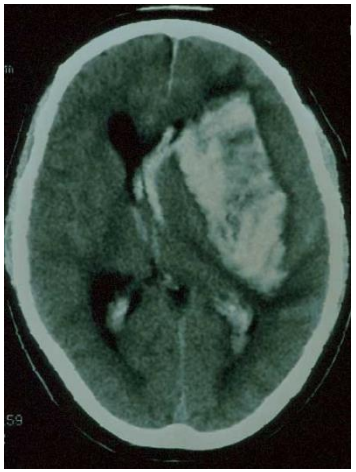



# Standard therapy for all stroke /TIA

- Anti-hyperintensives - PROGRESS Trial
- Statins- SPARCL
- Diabetes
- Life Style
  - Smoking cessation
  - Weight loss
  - Exercise
  - Alcohol reduction
- Anti-thrombotic
  - Anticoagulants – cardioembolic stroke / A Fib
  - Antiplatelets – the rest

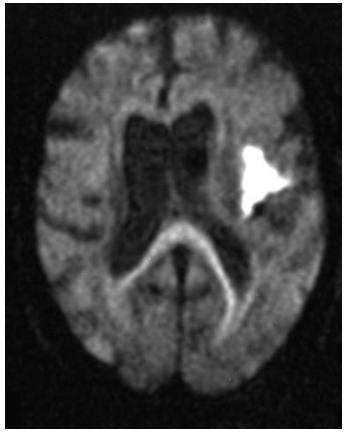
# Stroke is a syndrome of different pathologies, not a single disease



**STROKE**

Haemorrhagic

Ischaemic

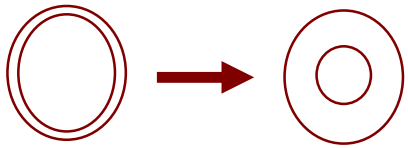


Intracerebral

SAH

Large vessel disease

Lacunar stroke



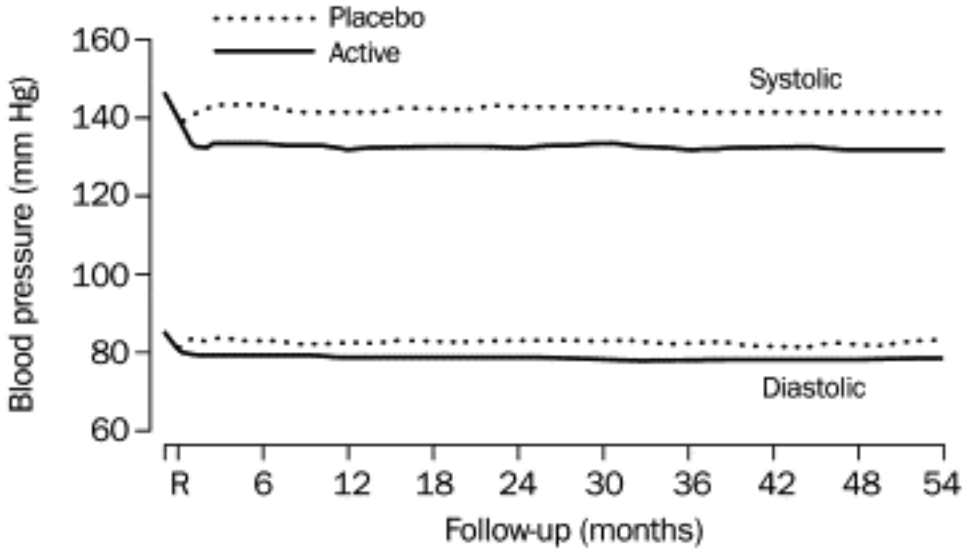
Cardioembolic

Unknown and rare causes

**What about data on symptomatic large artery disease, as opposed to all stroke?**

# Blood pressure

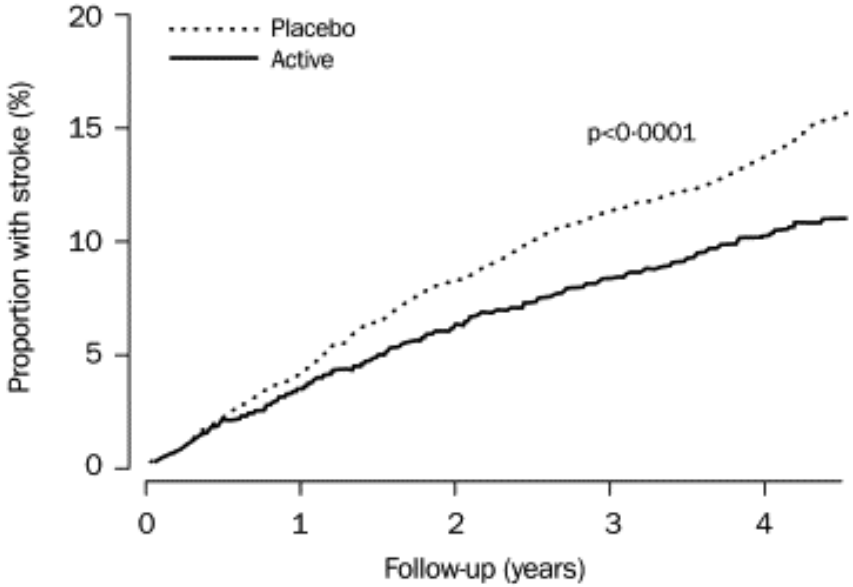
- As important as for other stroke subtypes




# Antihypertensive Treatment

**PROGRESS Trial**
**N= 6105**
**previous stroke or TIA**

Perindopril +/- Indapamide v placebo

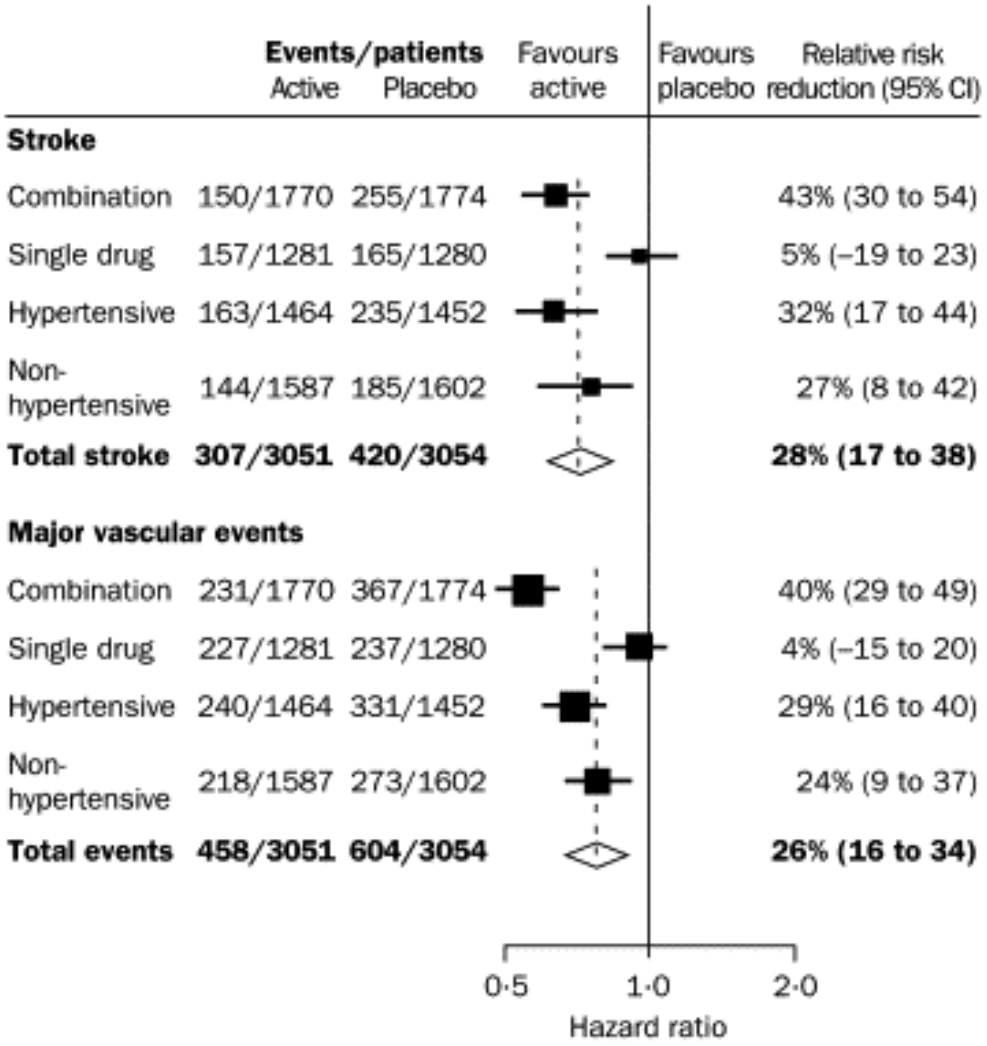



**Numbers at risk**

| | | | | | |
|---|---|---|---|---|---|
| Active | 3051 | 2902 | 2765 | 2634 | 1595 |
| Placebo | 3054 | 2880 | 2707 | 2551 | 1533 |

Lancet 2001; 358, 1033–1041

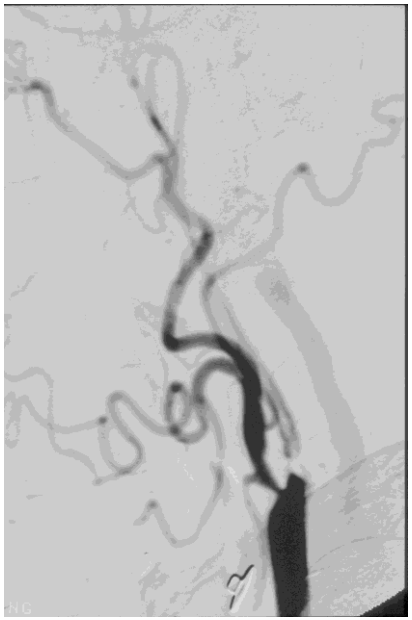
# PROGRESS Trial




Lancet 2001; 358, 1033–1041

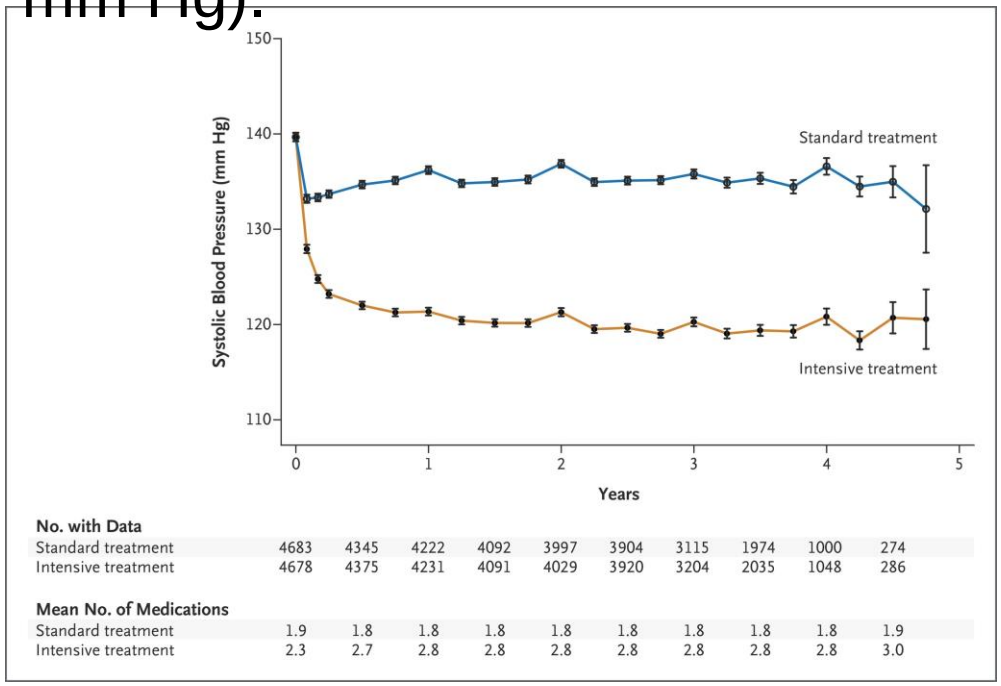
# Blood pressure

- As important as for other stroke subtypes
- EXCEPT- ? tight stenosis with poor collateral supply



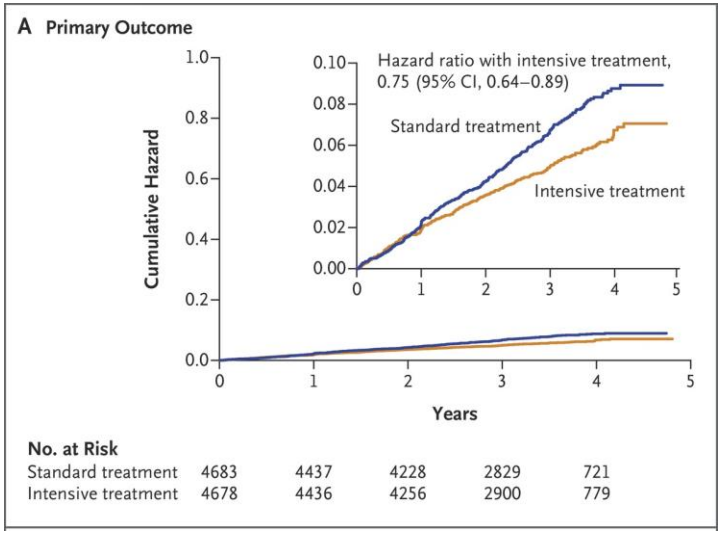
# SPRINT TRIAL

Patients at increased cardiovascular risk but without diabetes were assigned to intensive treatment of systolic BP (target, <120 mm Hg) or standard treatment (target, <140 mm Hg).




| No. with Data | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Standard treatment | 4683 | 4345 | 4222 | 4092 | 3997 | 3904 | 3115 | 1974 | 1000 | 274 |
| Intensive treatment | 4678 | 4375 | 4231 | 4091 | 4029 | 3920 | 3204 | 2035 | 1048 | 286 |

| Mean No. of Medications | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Standard treatment | 1.9 | 1.8 | 1.8 | 1.8 | 1.8 | 1.8 | 1.8 | 1.8 | 1.8 | 1.9 |
| Intensive treatment | 2.3 | 2.7 | 2.8 | 2.8 | 2.8 | 2.8 | 2.8 | 2.8 | 2.8 | 3.0 |




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Standard treatment | 4683 | 4437 | 4228 | 2829 | 721 |
| Intensive treatment | 4678 | 4436 | 4256 | 2900 | 779 |

NEJM 2016; 373:2103-2116

# Statins

# Patients benefit even with normal cholesterol

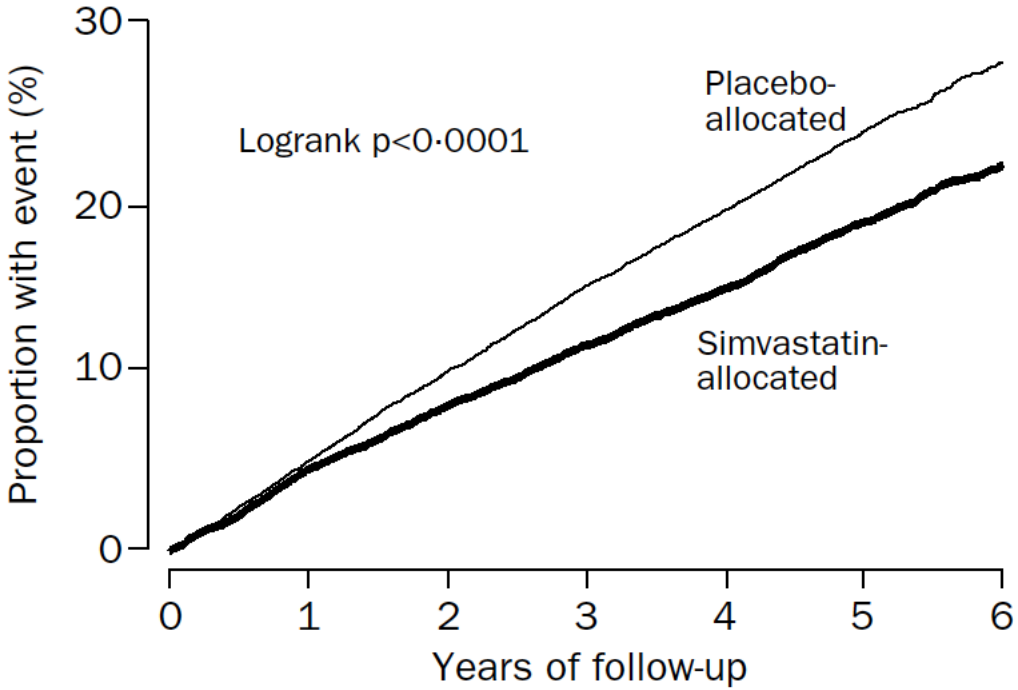


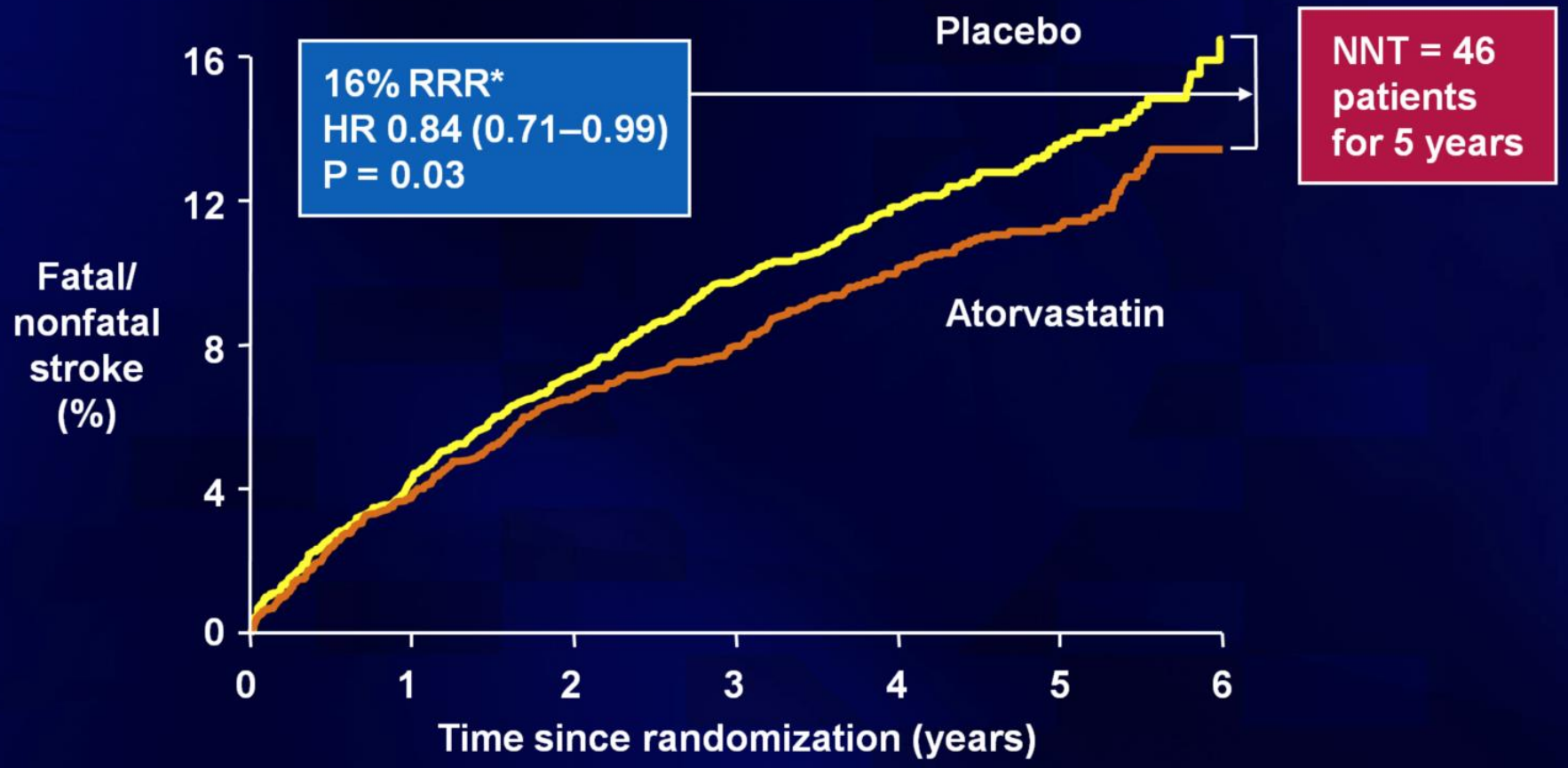

Figure 6: **Life-table plot of effects of simvastatin allocation on percentages having major vascular events**

See figure 5 for numbers of participants having a first event during each year of follow-up.

Heart protection study. Lancet 2012

# SPARCL: High-dose statin treatment reduces fatal/nonfatal stroke

## Primary outcome




*Adjusted

SPARCL Investigators. *N Engl J Med.* 2006;355:549-59.

# Patients benefit even with normal cholesterol

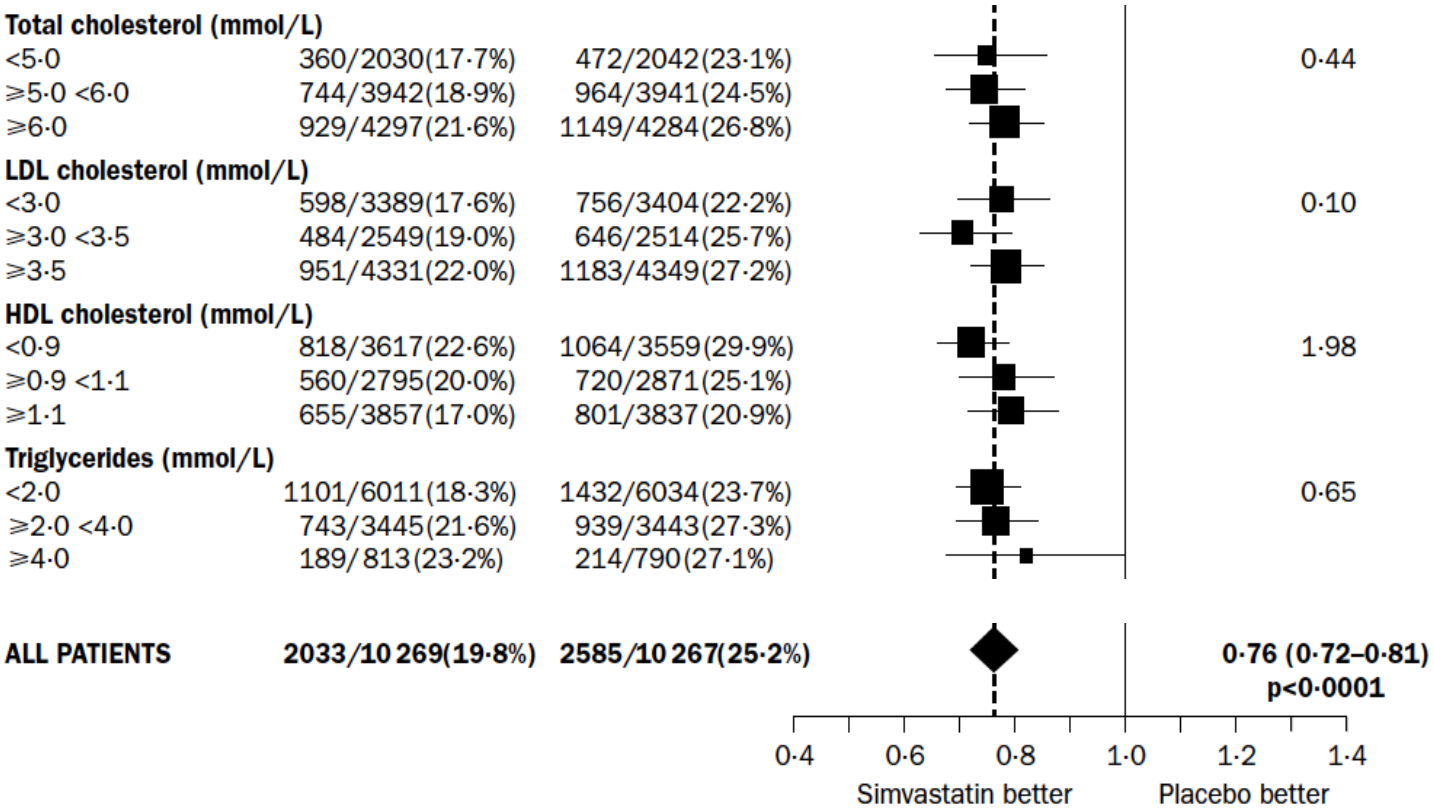



Figure 8: **Effects of simvastatin allocation on first major vascular event in different categories of participant**

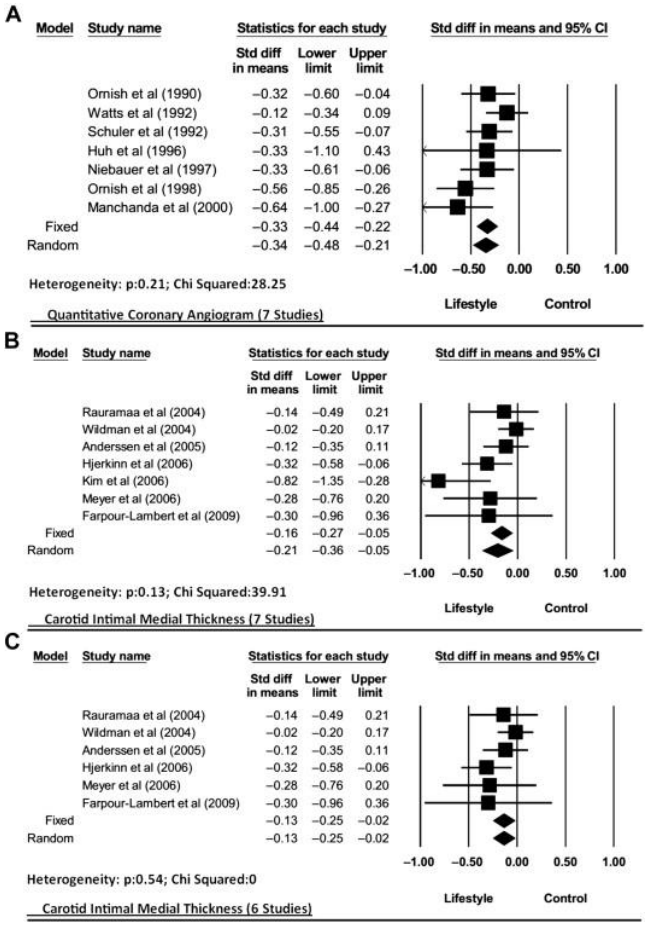
Heart protection study. Lancet 2012

# The importance of life style modifications

## Meta-Analysis of the Effects of Lifestyle Modifications on Coronary and Carotid Atherosclerotic Burden

Sunny Jhamnani, MD[a,b,*], Dhavalkumar Patel, MD[a,c], Layla Heimlich, MSILS[a], Fred King, MSLS[a], Brian Walitt, MD[a], and Joseph Lindsay, MD[a]

Lifestyle modifications are the crux of atherosclerotic disease management. The goal of this study was to determine the effectiveness of diet and exercise in decreasing coronary and carotid atherosclerotic burden. Randomized controlled trials examining the effects of intensive lifestyle measures on atherosclerotic progression in coronary and carotid arteries as measured by baseline and follow-up quantitative coronary angiogram and ultrasonographic carotid intimal-medial thickness (CIMT), respectively, were included. Studies were excluded if the intervention additionally included a medication. MEDLINE, EMBASE, CINAHL, Cochrane Controlled Trials Registers, reports, and abstracts from major cardiology meetings were searched by 2 researchers independently and verified by the primary investigator. Standardized mean difference (SMD) with 95% confidence intervals (CIs) was calculated using random-effects model. Publication bias and heterogeneity were assessed. Fourteen trials were included. Seven used quantitative coronary angiogram, and 7 used CIMT; 1,343 lesions in 340 patients in the coronary group and 919 patients in the carotid group were analyzed. Overall, lifestyle modifications were associated with a decrease in coronary atherosclerotic burden in percent stenosis by −0.34 (95% CI −0.48 to −0.21) SMD, with no significant publication bias and heterogeneity ($p = 0.21$, $I^2 = 28.25$). Similarly, in the carotids, there was a decrease in the CIMT, in millimeter, by −0.21 (95% CI −0.36 to −0.05) SMD and by −0.13 (95% CI −0.25 to −0.02) SMD, before and after accounting for publication bias and heterogeneity ($p = 0.13$, $I^2 = 39.91$; $p = 0.54$, $I^2 = 0$), respectively. In conclusion, these results suggest that intensive lifestyle modifications are associated with a decrease in coronary and carotid atherosclerotic burden.  (Am J Cardiol 2015;115:268−275)



# Should we give more intensive antiplatelet therapy?

Current secondary prevention options in stroke / TIA

- Aspirin and dipyridamole
- Clopidogrel

- Clopidogrel > Aspirin – CAPRIE
- Aspirin and Dipyridamole > Aspirin ESPRIT
- Clopidogrel = Aspirin + Dipyridamole (PROFESS)

NICE recommends A + D or Clop for long term secondary prevention

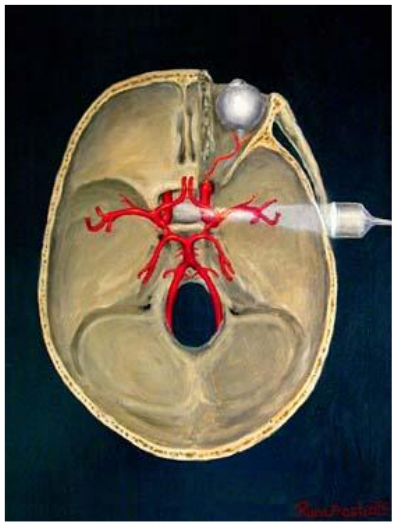
# Should we give more intensive antiplatelet therapy?

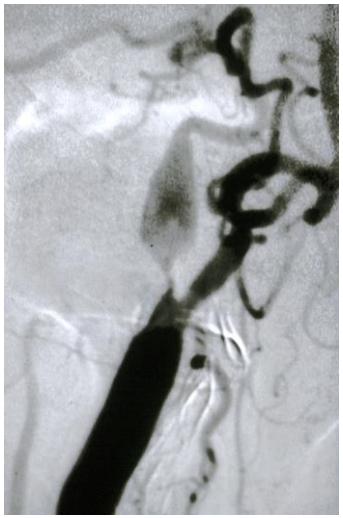
BUT

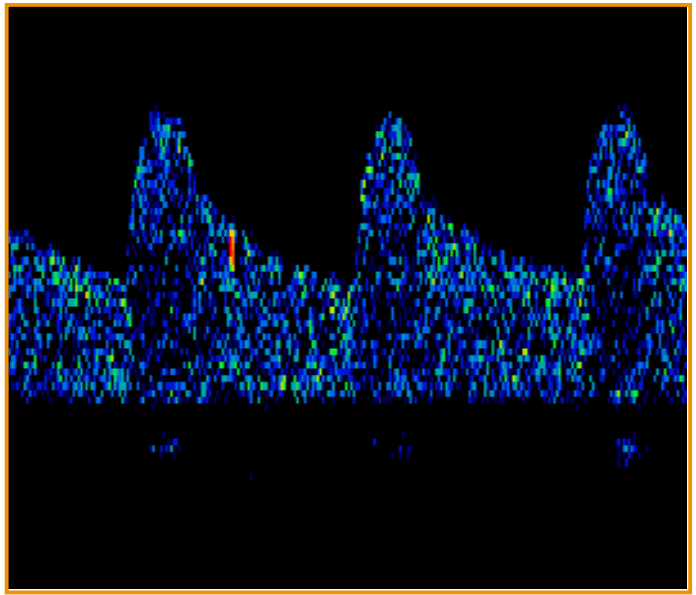
Secondary prevention trials have all focused on long term prevention and had few acutely treated patients

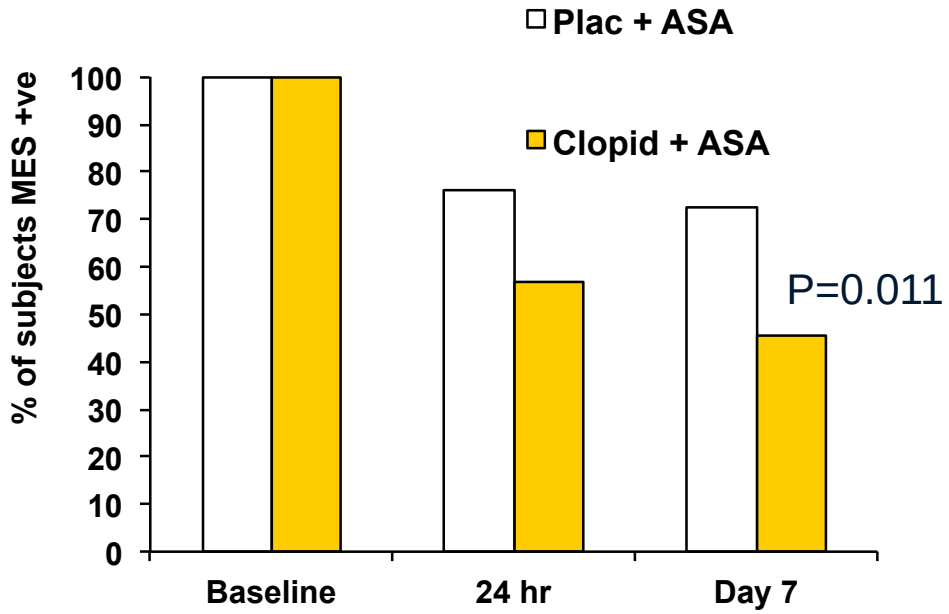
Risk benefit profile will differ for acute period- higher risk and shorter duration of treatment

# Dual anti-platelet treatment prevents embolisation in acute carotid stenosis










CARESS Trial
Markus et al. Circulation. 2005; 111: 2233-2240

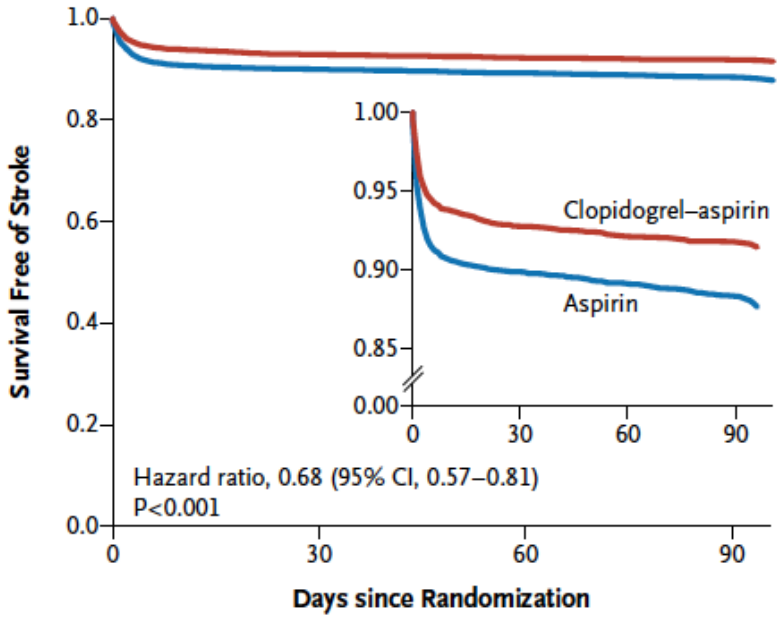
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# CHANCE Trial

## Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

ENGL J MED 369;1 NEJM.ORG JULY 4, 2013




**No. at Risk**

| | | | | |
|---|---|---|---|---|
| Aspirin | 2586 | 2307 | 2287 | 1906 |
| Clopidogrel–aspirin | 2584 | 2376 | 2361 | 1989 |

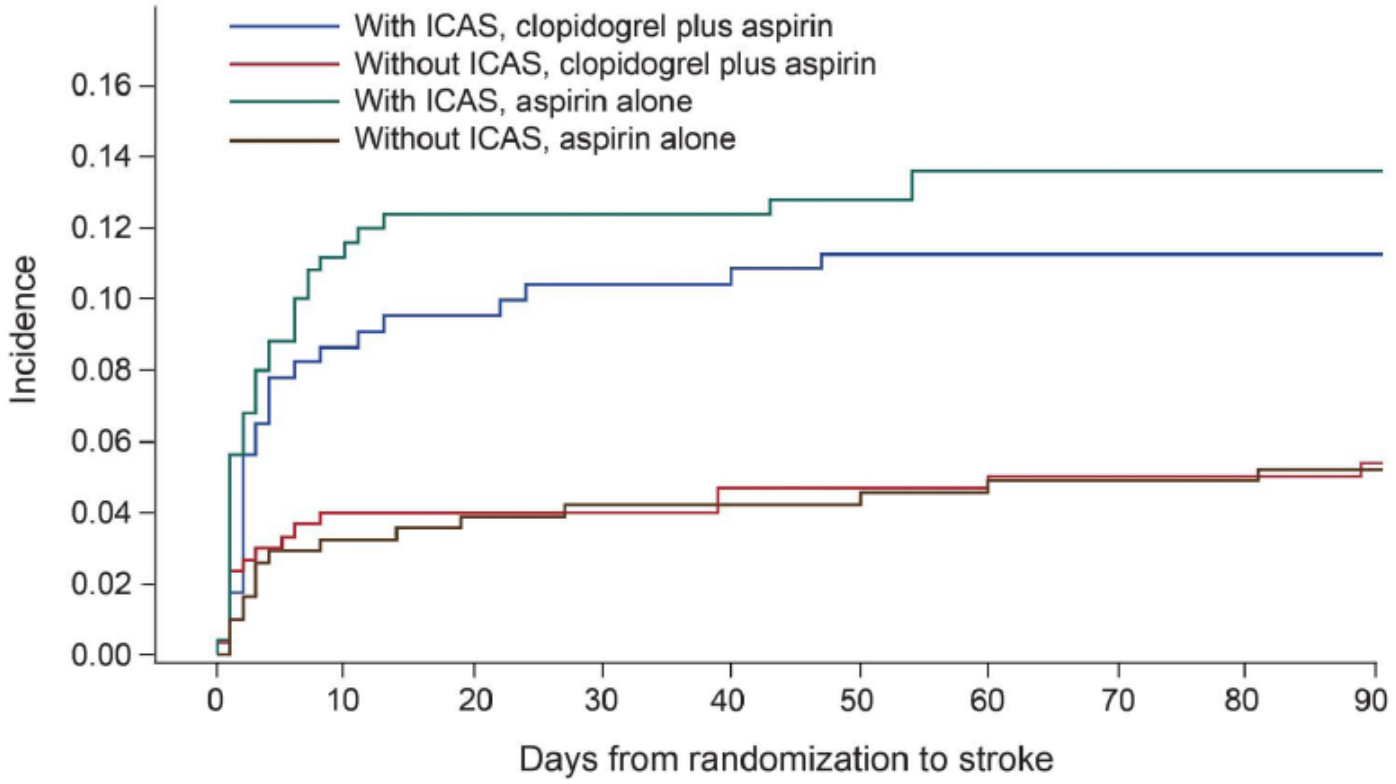
**Figure 1. Probability of Survival Free of Stroke.**

The primary outcome was ischemic or hemorrhagic stroke. The inset shows the same data on an enlarged segment of the y axis.

- 114 centers in China
- 5170 patients
- Within 24 hours of minor ischemic stroke or high-risk TIA
- Clopidogrel (300 mg loading then 75mg od for 90 days) plus aspirin 75 mg od
- OR placebo plus aspirin 75 mg od.

Liu et al
Neurology
2015
85: 1154

**Figure 1** Kaplan-Meier curves for the primary efficacy outcome of any stroke




| Number at risk | | | | |
|---|---|---|---|---|
| With ICAS, aspirin alone | 250 | 219 | 216 | 179 |
| With ICAS, clopidogrel plus aspirin | 231 | 204 | 202 | 164 |
| Without ICAS, aspirin alone | 308 | 294 | 293 | 236 |
| Without ICAS, clopidogrel plus aspirin | 300 | 285 | 283 | 231 |

Kaplan-Meier curves showing the time to the primary efficacy outcome event (any stroke) in patients with and without ICAS, treated with clopidogrel plus aspirin, or placebo plus aspirin. ICAS = intracranial arterial stenosis.

# My Medical Treatment
## *For all recently symptomatic extra- and intracranial large artery disease*

- Aspirin 300mg loading then 75 mg a day

AND

- Clopidogrel 300 mg loading , then 75 mg a day

THEN AFTER 3-6 months

- Clopidogrel 75 mg od alone

# Medical Treatment
## *For recently symptomatic extracranial large artery disease*

- All evidence points to the need or intensive therapy
  - High dose statin
  - BP reduction
  - Dual anti-platelets
  - Life style measures

# The importance of intensive therapy

ORIGINAL ARTICLE

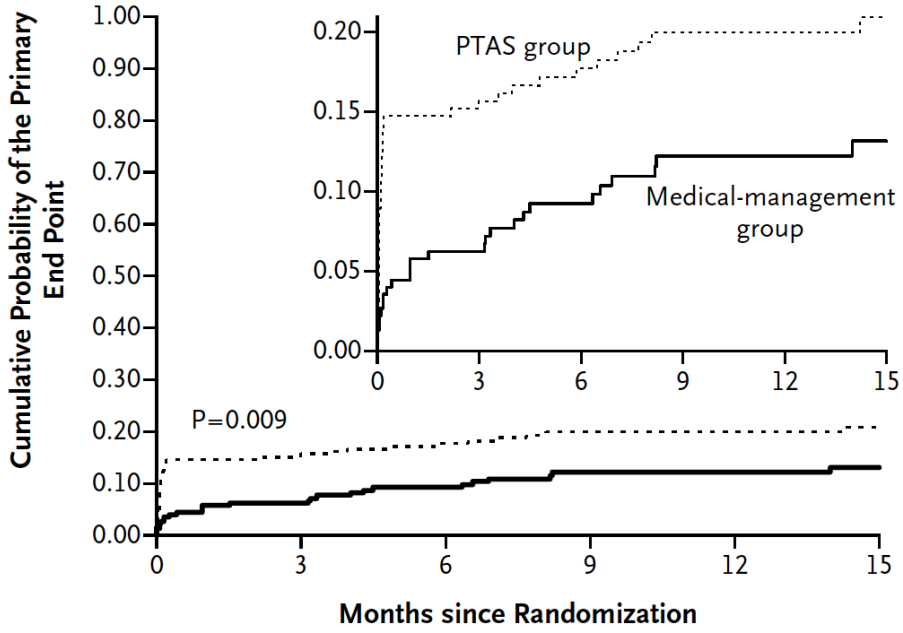
The NEW ENGLAND JOURNAL of MEDICINE

## Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis

**TABLE 4** Elements of Intensive Medical Therapy in SAMMPRIS Study

| Treatment | Comments |
|---|---|
| Aspirin + clopidogrel | For initial 90 days |
| Aspirin alone | Beyond 90 days |
| Rosuvastatin | Target LDL <70 mg/dl |
| Systolic BP lowering | Target <140 mm Hg for nondiabetic patients |
| Systolic BP lowering | Target <130 mm Hg for diabetic patients |
| INTERVENT program | Lifestyle modification assistance (smoking cessation, exercise, diet) |

BP = blood pressure; LDL = low-density lipoprotein; SAMMPRIS = Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis.




**No. at Risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| Medical management group | 227 | 196 | 164 | 132 | 115 | 92 |
| PTAS group | 224 | 182 | 153 | 125 | 98 | 83 |

**Figure 1. Kaplan–Meier Curves for the Cumulative Probability of the Primary End Point, According to Treatment Assignment.**

The primary end point was stroke or death within 30 days after enrollment or after a revascularization procedure for the qualifying lesion during the follow-up period or stroke in the territory of the qualifying artery beyond 30 days. The curves were truncated at 15 months because relatively few patients have been followed beyond this time and there have only been two primary end-point events beyond 15 months, both in the group receiving percutaneous transluminal angioplasty and stenting (PTAS) (one at 26.1 months and one at 26.2 months). The maximum duration of follow-up is 28.9 months for the group receiving medical management only and 28.1 months for the PTAS group. The inset shows the same data on an enlarged segment of the y axis.

# Urgent Best Medical Therapy May Obviate the Need for Urgent Surgery in Patients With Symptomatic Carotid Stenosis

Saeid Shahidi, MD; Alan Owen-Falkenberg, MD; Ulrik Hjerpsted, MD; Amrit Rai, MD, PhD; Karsten Ellemann, MD

***Background and Purpose***—The purpose of this study was to analyze the 30-day outcome after introduction of a rapid carotid endarterectomy (CEA) program. Reasons for delay in CEA and the incidence of early recurrence neurological symptoms were recorded.

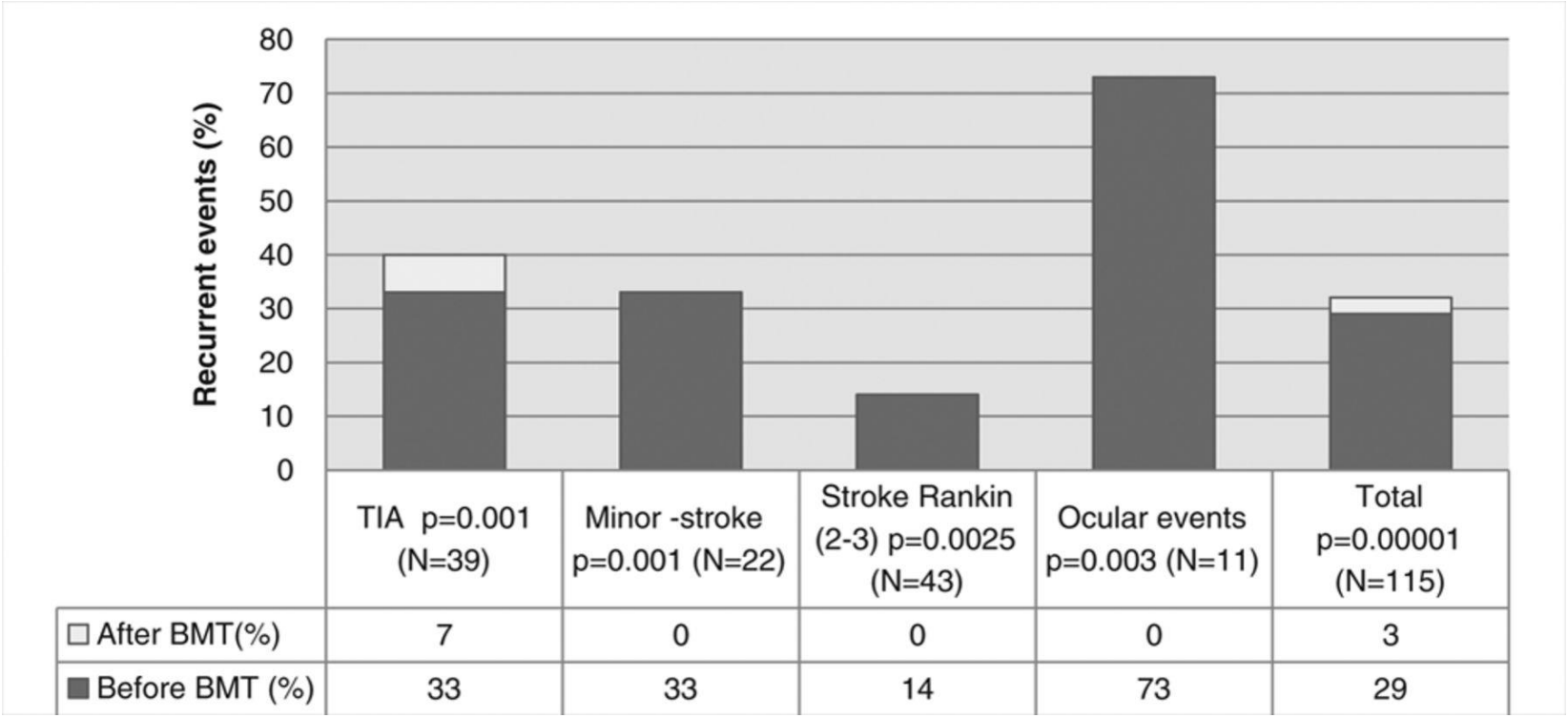
***Methods***—This is a prospective population-based study of delays to CEA and 30-day outcome in patients with symptomatic carotid stenosis. Neurological recurrence (NR) rate was determined after initiation of urgent best medical treatment (loading dose aspirin/clopidogrel and duel therapy with aspirin plus clopidogrel with a statin) until CEA and compared with NR ≤90 days prior index event.

***Results***—Of a total of 4905 (transient ischemic attack/ischemic stroke, and ocular events) patients, 115 symptomatic patients underwent CEA, 42% within 14 days of the index event and 99% within 14 days of surgical referral. The overall NR from index event to CEA in symptomatic carotid stenosis patients was significantly lower (2.5% [95% confidence interval, 1%–6%]) after best medical treatment when compared with NR ≤90 days in those before referral to a stroke clinic (29% [95% confidence interval, 22%–37%]; $P<0.00001$). There were no significant differences in outcomes among 48 early (<14 days), 46 intermediate (14–30 days), and 21 delayed (>30 days) CEAs.

***Conclusions***—CEA can be performed in the subacute period without significantly increasing the operative risk. The urgent best medical treatment was associated with significant reduction in the risk of early NR in CEA patients. It seems that urgent aggressive best medical treatment may obviate the need for urgent CEA. **(*Stroke*. 2013;44:2220-2225.)**

**Key Words:** carotid stenosis ■ emergency medical services ■ emergency medicine ■ endarterectomy, carotid

**Incidence of recurrent events in our cohort in carotid endarterectomy (CEA) patients.**




| | TIA p=0.001 (N=39) | Minor -stroke p=0.001 (N=22) | Stroke Rankin (2-3) p=0.0025 (N=43) | Ocular events p=0.003 (N=11) | Total p=0.00001 (N=115) |
|---|---|---|---|---|---|
| After BMT(%) | 7 | 0 | 0 | 0 | 3 |
| Before BMT (%) | 33 | 33 | 14 | 73 | 29 |

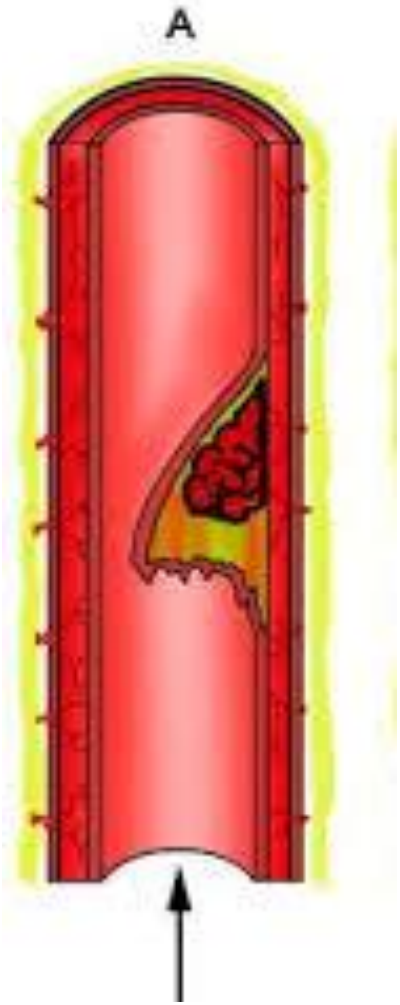
**Saeid Shahidi et al. Stroke. 2013;44:2220-2225**

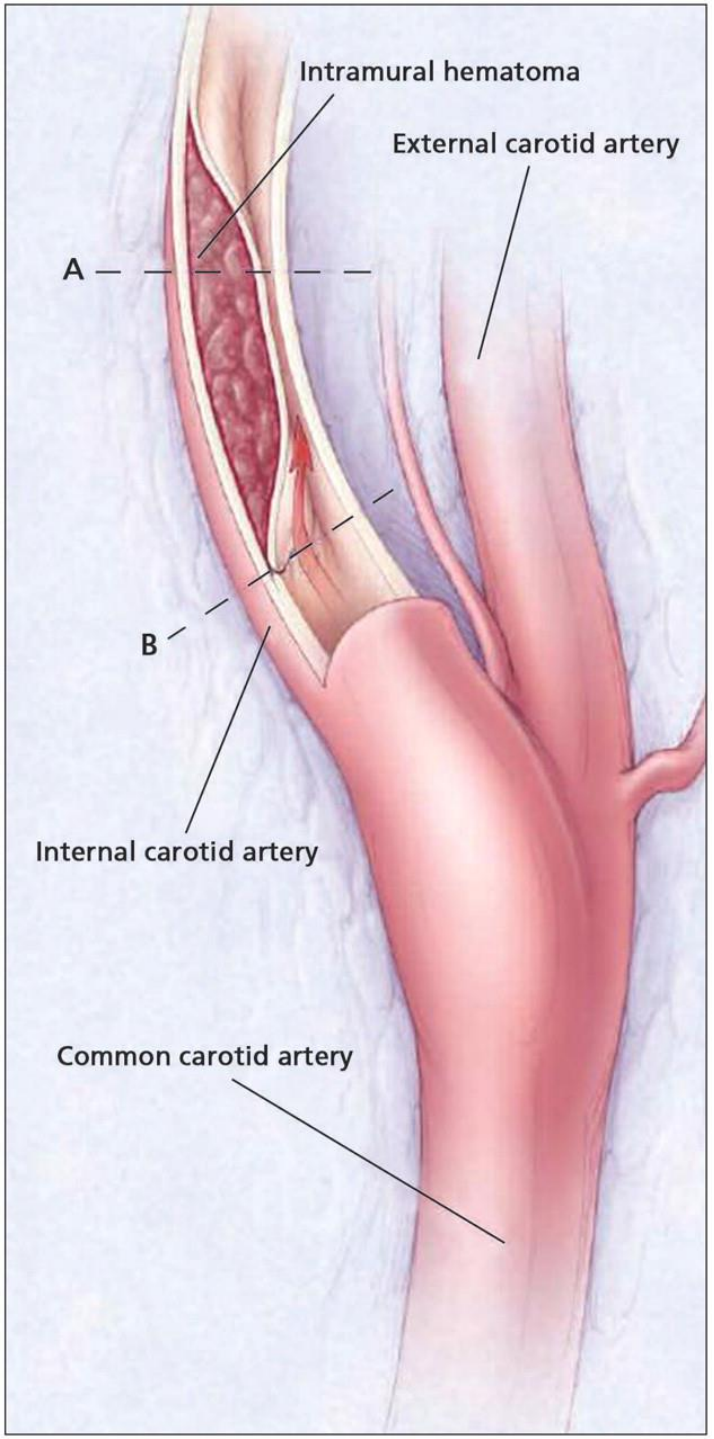
# Current status for symptomatic stenosis

- **Intensive** medical therapies can reduce the stroke risk in unoperated symptomatic carotid stenosis
- Treating hypertension and cholesterol in the normal range also reduces risk
- Magnitude of benefit compared with carotid endarterectomy unknown
- Difficult to do direct comparison trials in unselected group in view of major benefit of CEA in the trials

# Carotid artery dissection

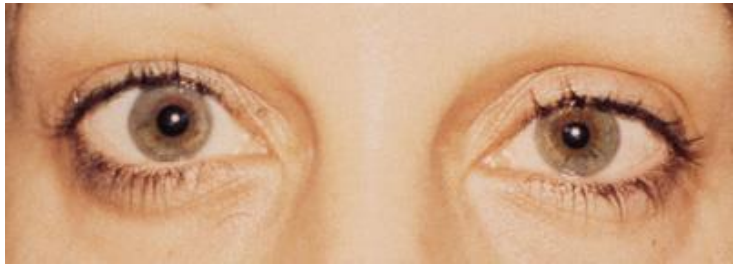
- Major cause of ischemic stroke in young and middle-aged adults ~= 25% young ischaemic stroke
- Annual incidence of 2.5 -3 per 100000 for carotid artery dissection
- Internal carotid artery 60% v vertebral artery 40%
- Mean age = 40s years
- Men: 53-57%


A

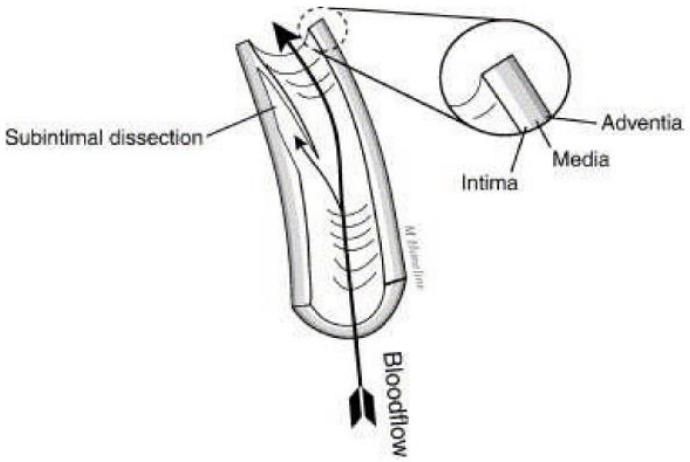

Intramural hematoma
External carotid artery
A
B
Internal carotid artery
Common carotid artery

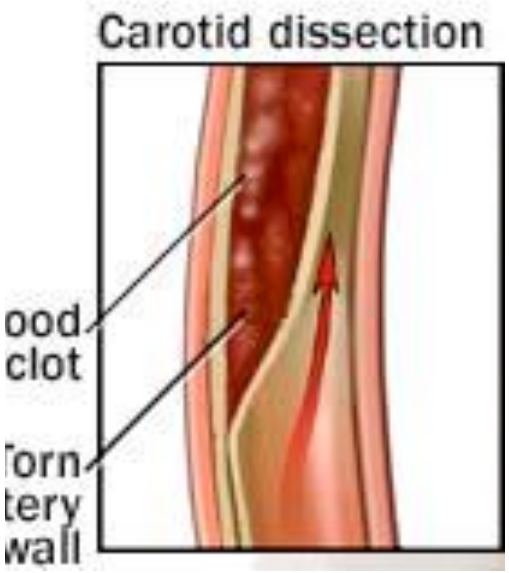
# Clinical Presentation

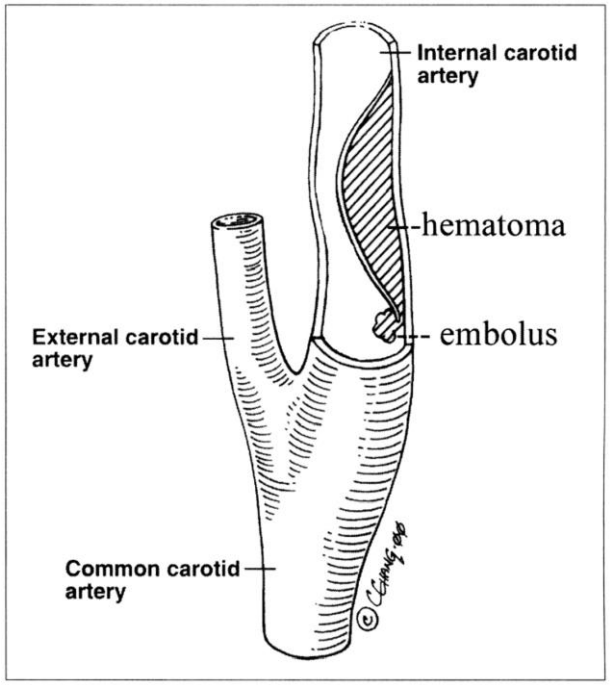
- Local  symptoms and signs:
  - Headache, cervical pain
  - Horner syndrome
  - Cranial nerve palsy (XII, IX, X)
- Cerebral ischemia:
  - Transient Ischemic Attack
  - Brain Infarct
- Other
  - Retinal ischemia
  - Spinal cord ischemia
  - Subarachnoid hemorrhage



# Carotid and vertebral dissection




## Possible stroke mechanisms

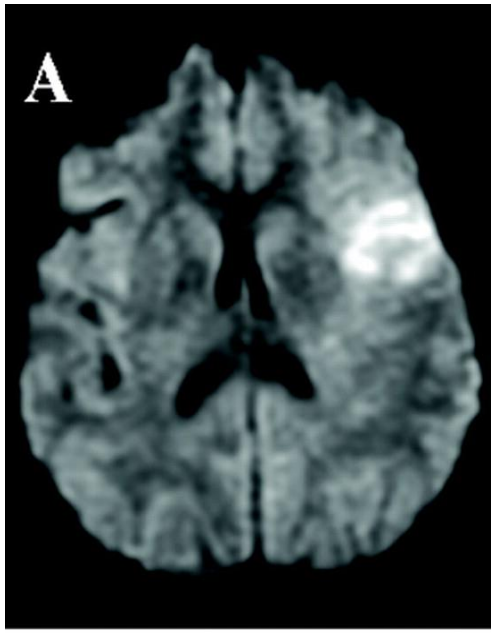
- Vessel occlusion and haemodynamic compromise
- Embolism from clot at the site of the tear

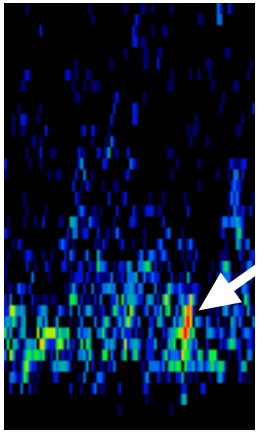
# Carotid and vertebral dissection
## *Support for a role of embolism*

1. Pattern of infarcts – fits with emboli

2. Stroke occurs even if no tight stenosis/occlusion

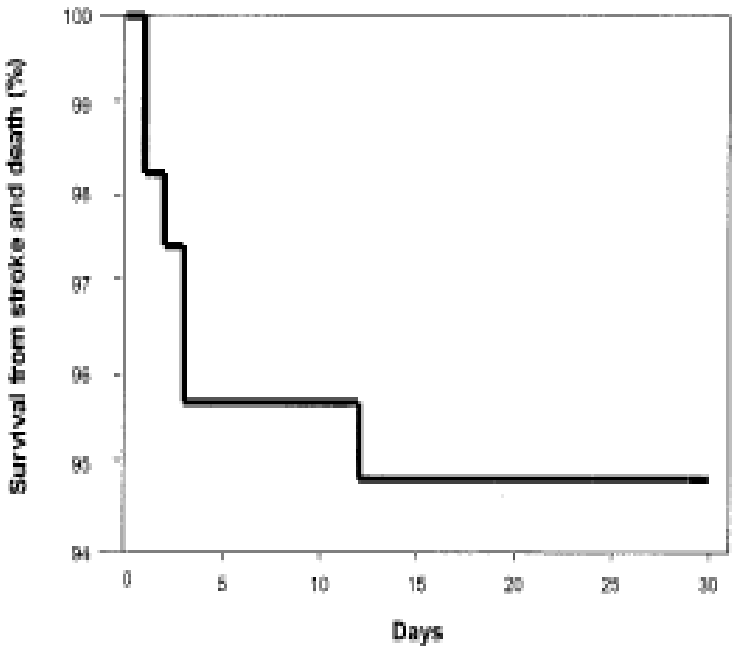
3. Transcranial Doppler (TCD) can detect circulating embolic signals distal to the dissection



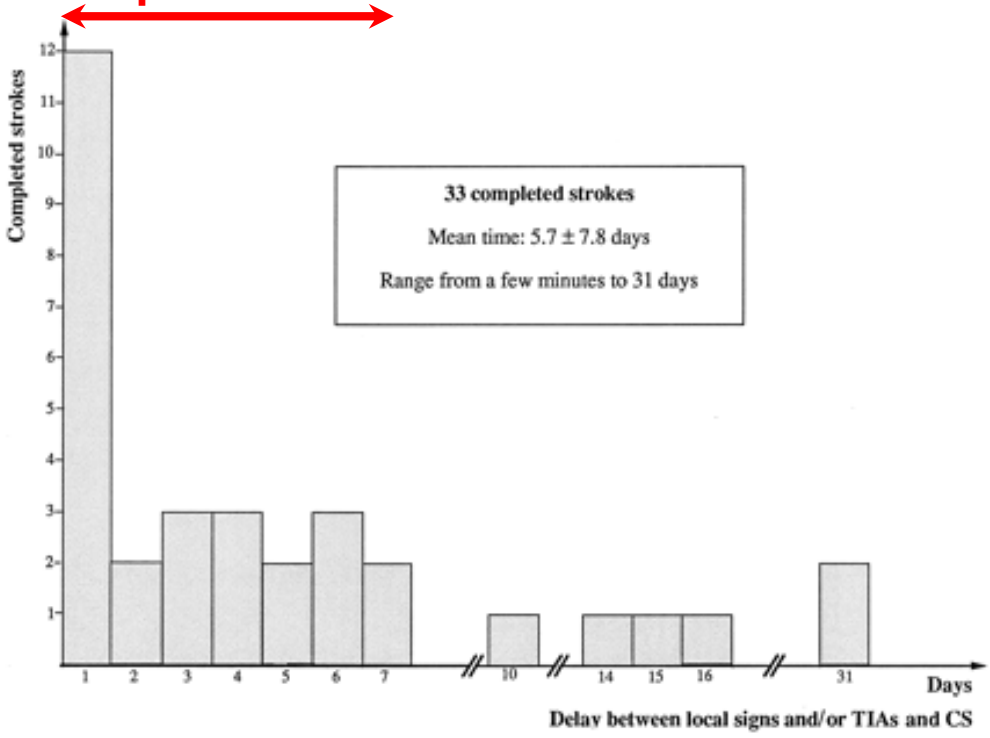
# Early Recurrent Risk

**2 weeks post-dissection**




Beletsky *et al.,* 2003 Stroke

**1 week post-dissection**




Biousse *et al*., 1995 Stroke

**High risk period - 1st month**

# CADISS

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## Antiplatelet treatment compared with anticoagulation treatment for cervical artery dissection (CADISS): a randomised trial

*The CADISS trial investigators**

Aim: To determine whether antiplatelet agents or anticoagulation are more effective at preventing stroke in acute (<1 week) cervical dissection

# Endpoints

| Recurrent stroke rate | 3 months | 12 months |
|---|---|---|
| | 1.6% | 2.4% |

1 major bleed – SAH (vertebral dissection)

CADISS Investigators. Lancet Neurology 2015
CADISS Investigators. JAMA Neurology 2019

# Endpoints – Intention to treat
## *3 and 12 month follow-up*

| | | Intention to Treat analysis | | | |
|---|---|---|---|---|---|
| | | Antiplatelets, n=126 | | Anticoagulants, n=124 | |
| | | 0-3 months | 3-12 months | 0-3 months | 3-12 months |
| | | n | n | n | n |
| Ischemic stroke | | | | | |
| | Ipsilateral | 3 | 1 | 1 | 1 |
| | Other | 0 | 0 | 0 | 0 |
| TIA | | | | | |
| | Ipsilateral | 1 | 0 | 4 | 0 |
| | Other | 1 | 0 | 0 | 1 |
| Major bleeding | | 0 | 0 | 1 | 0 |
| Death | | 0 | 1* | 0 | 0 |
| **Stroke, death, major bleeding** | | **3** | **4** | **2** | **3** |

* death due to a fatal recurrent stroke in a patient who had had a first recurrent stroke within the first 3 month follow-up period

# CADISS : Recanalisation rates

*In 181 with confirmed dissection and follow-up imaging at 3/12*

| Residual narrowing or occlusion | AP (N=92) | AC (N=89) |
|---|---|---|
| Yes | 56 (60.9%) | 53 (59.6%) |
| No | 36 (39.1%) | 36 (40.4%) |

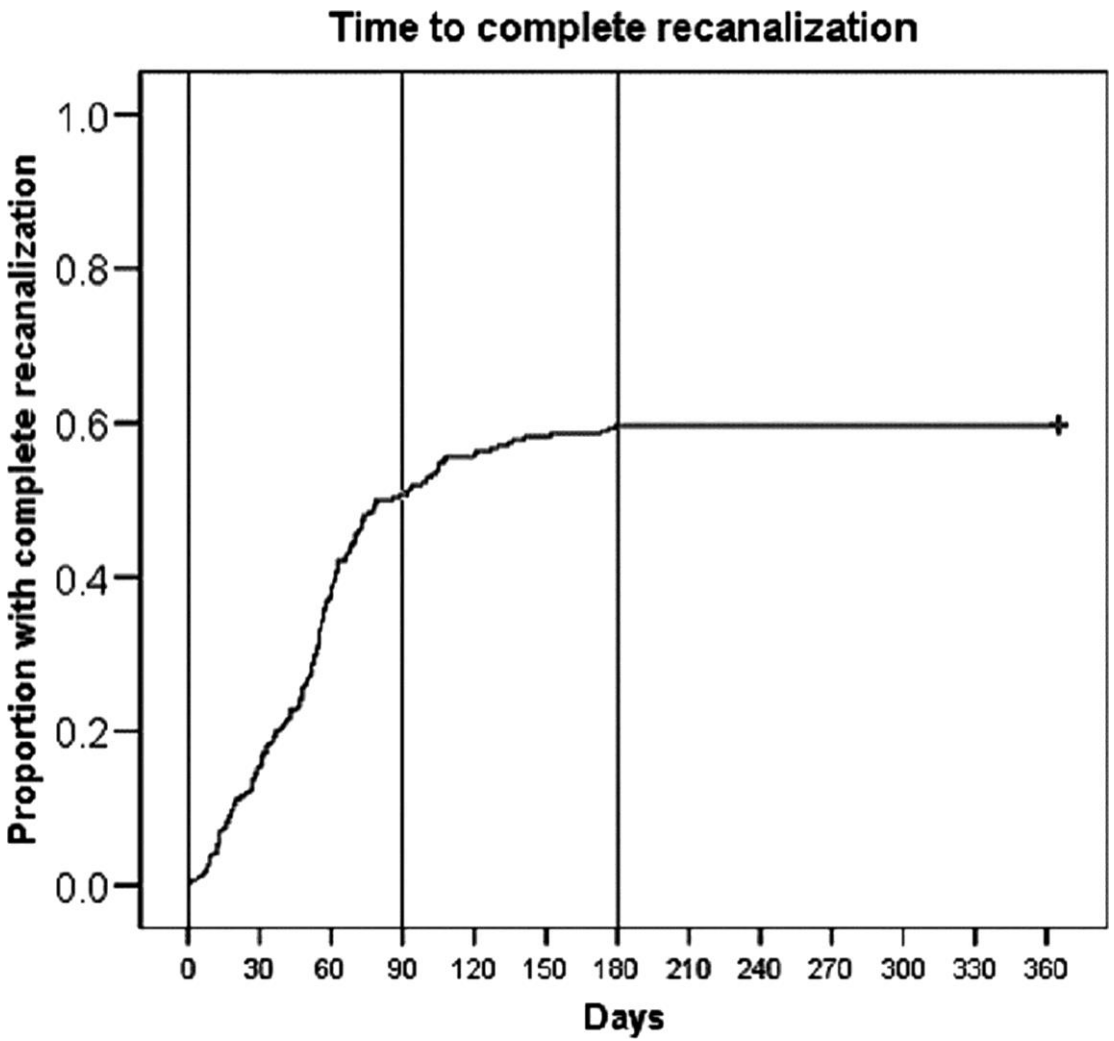
CADISS Investigators. JAMA Neurology 2019 76:657-664

# Management of stroke in dissection

## Should you remove the stenosis?

- Stenting has been performed acutely with good technical results
- BUT operative stroke risk 5% ; recurrent stroke risk may be no more
- AND most arteries recannalise :

**Figure. Time to complete recanalization.**




Krassen Nedeltchev et al. Stroke. 2009;40:499-504

# Follow-up imaging in CADISS

Angiographic imaging with either CTA or MRA at baseline and at 3 months was available for 181 of the 198 cases with radiologically confirmed dissection.

At Baseline

Narrowing or occlusion: 163 (90%)

At 3 months

- Normal 61 (33.7%)
- Residual irregularity or narrowing 64 (35.3%)
- Occlusion 45 (24.9%)

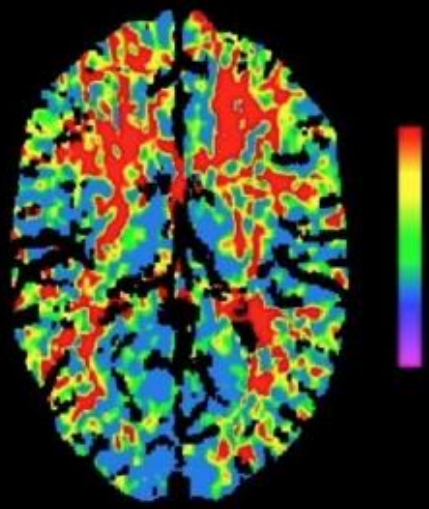
CADISS Investigators. JAMA Neurology 2019 76:657-664

# Endovascular therapy

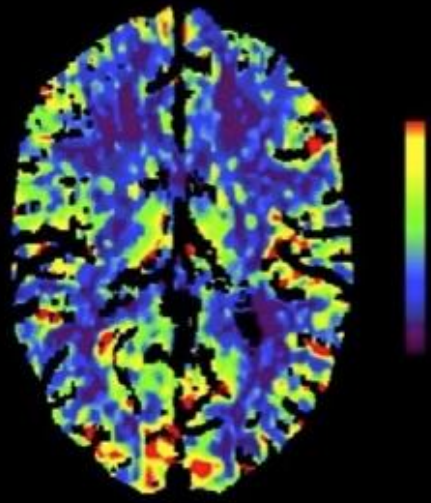
- Not indicated acutely as most stenoses spontaneously recanalise in first few weeks

- BUT very occasionally : consider in :
  - Acute haemodynamic compromise due to stenosis due to  dissection

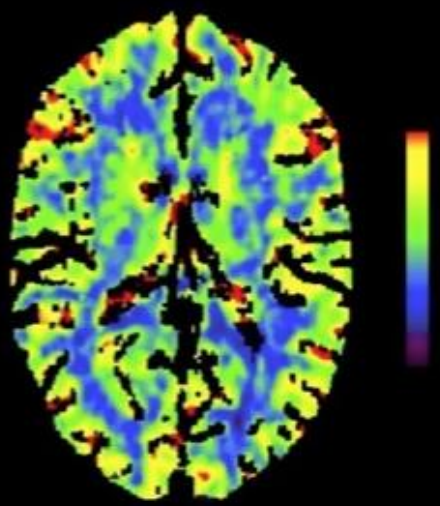
PRE STENT INSERTION - BILATERAL CAD



MEAN TRANSIT TIME
MTT

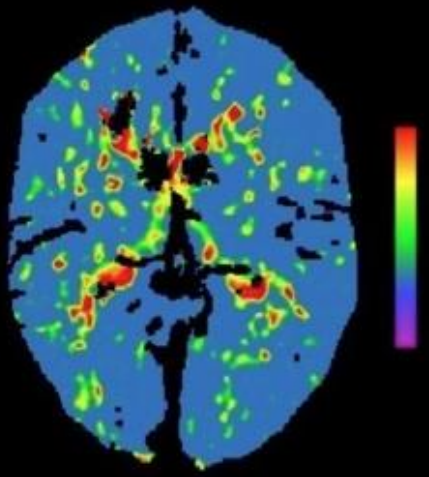


CEREBRAL BLOOD FLOW
CBF

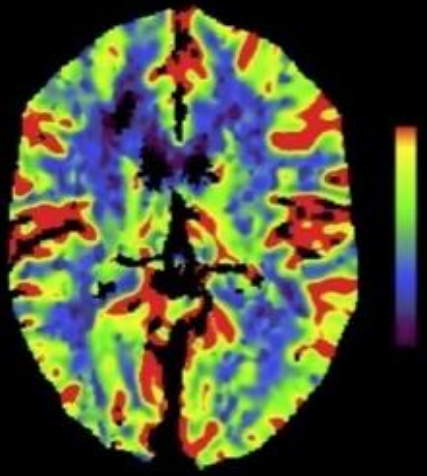


CEREBRAL BLOOD VOLUME
CBV

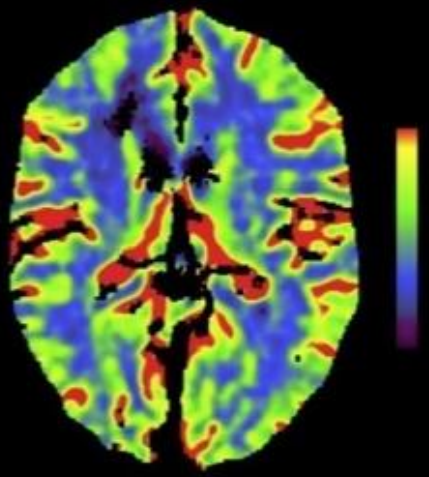
POST STENT INSERTION



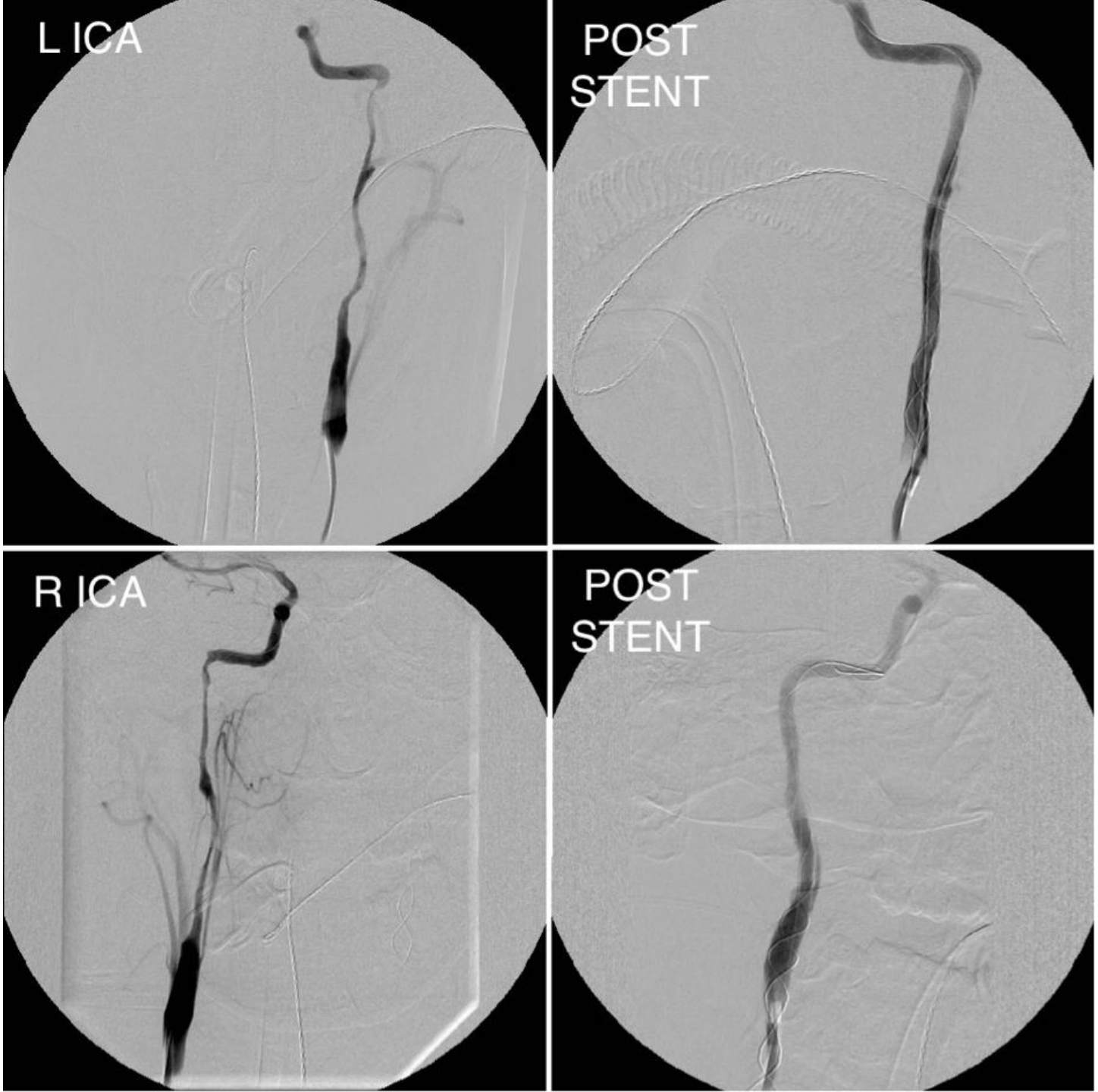
MEAN TRANSIT TIME
MTT



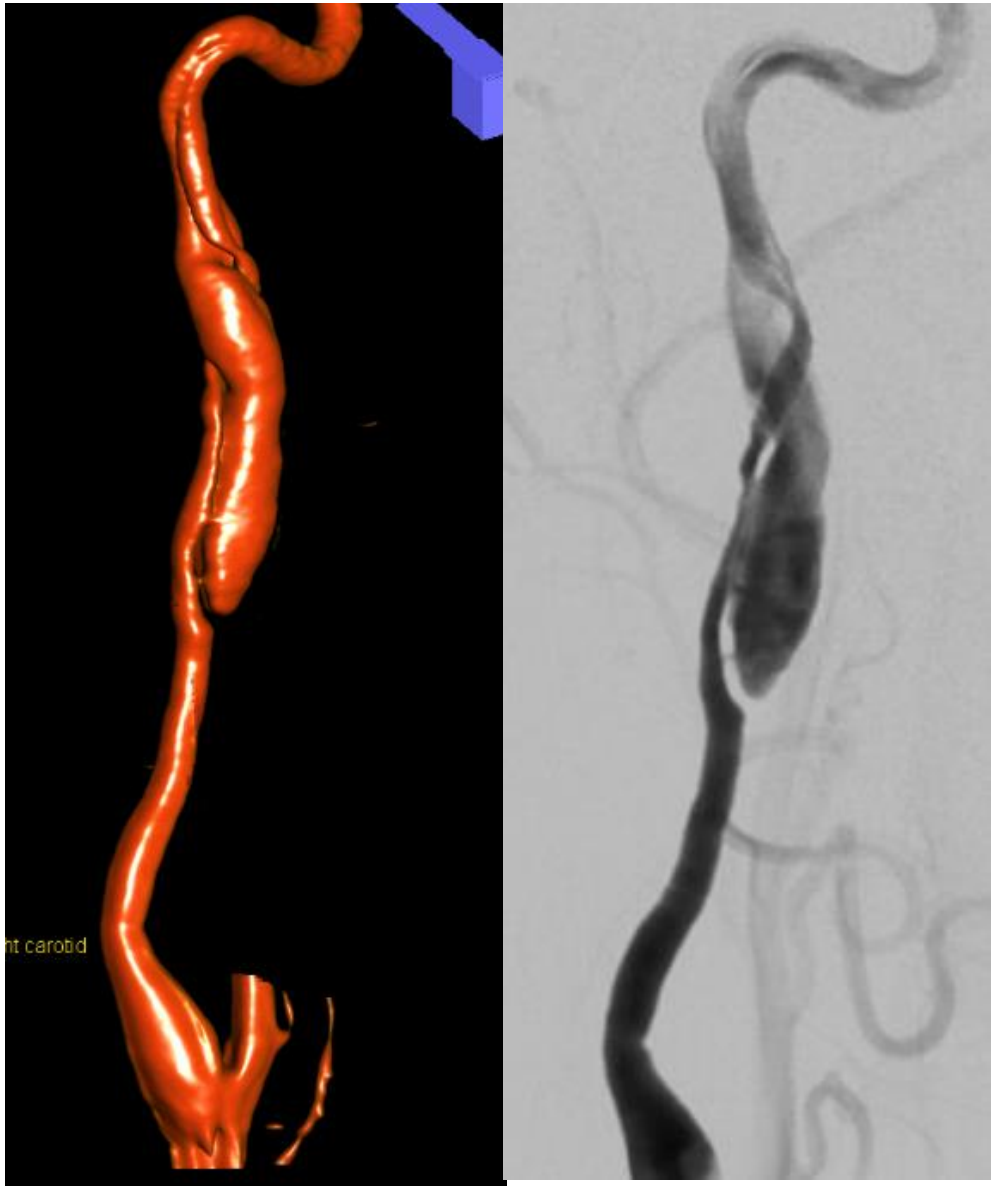
CEREBRAL BLOOD FLOW
CBF



CEREBRAL BLOOD VOLUME
CBV


L ICA
POST
STENT
R ICA
POST
STENT

# Dissecting aneurysms post carotid dissection




# Dissecting aneurysms in CADISS

- Analysis of CADISS and CADISS-non-randomised in cases with confirmed dissection
- DA were present in 24 of 264 patients with imaging confirmed CAD at baseline.
- In 36 of 248 patients with follow-up neuroimaging at 3 months, 12 of the 24 baseline DAs persisted, and 24 new DA had developed.

Larsson et al Neurology 2017

# Dissecting aneurysm resolution or new formation was not affected by treatment allocation

| Outcome | Antiplatelet therapy (n=139) | Anticoagulant therapy (n=109) | Unadjusted OR (95% CI) | Adjusted OR (95% CI)[a] | *p* value[a] |
|---|---|---|---|---|---|
| Persistent DA | 8/14 (57%)[b] | 4/10 (40%)[b] | 0.50 (0.10-2.60) | 0.57 (0.09-3.51) | 0.54 |
| New DA | 12/125 (10%)[b,c] | 12/99 (12%)[b,c] | 1.33 (0.66-2.70) | 1.34 (0.66-2.71) | 0.42 |

Larsson et al Neurology 2017

# Dissecting aneurysms did not predict increased stroke risk

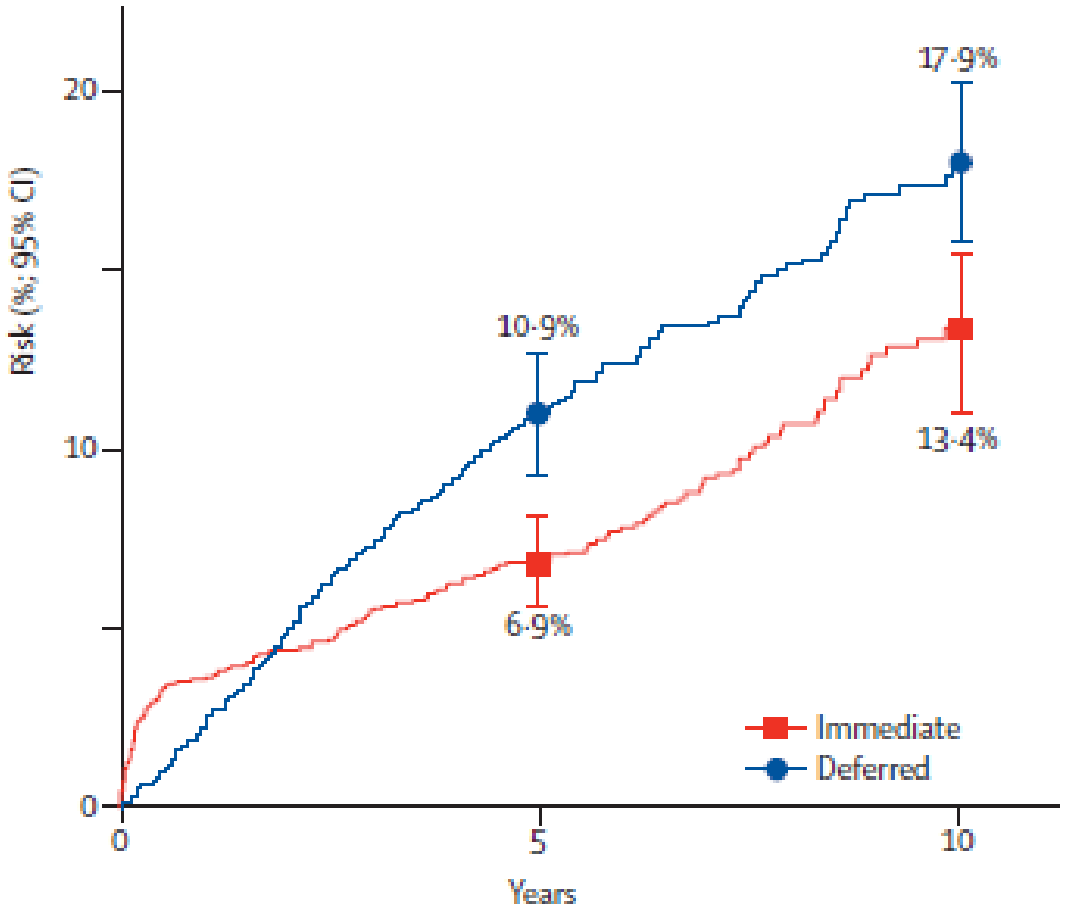
- During 12 months of follow-up, stroke occurred in:
  - one of 48 patients with DA
  - 7 of 216 patients without DA
  - age- and sex-adjusted odds ratio, 0.84; 95% confidence interval, 0.10–7.31; *P* = 0.88.

- Results consistent with meta-analysis on (limited) existing data

Larsson et al Neurology 2017

# Asymptomatic carotid stenosis

# Asymptomatic Carotid Surgery Trial (ACST)
# n=3120, recruited 1993-2003
# 10-year results: Any stroke or perioperative death




Halliday A et al. *Lancet* 2010; 376: 1074–1084

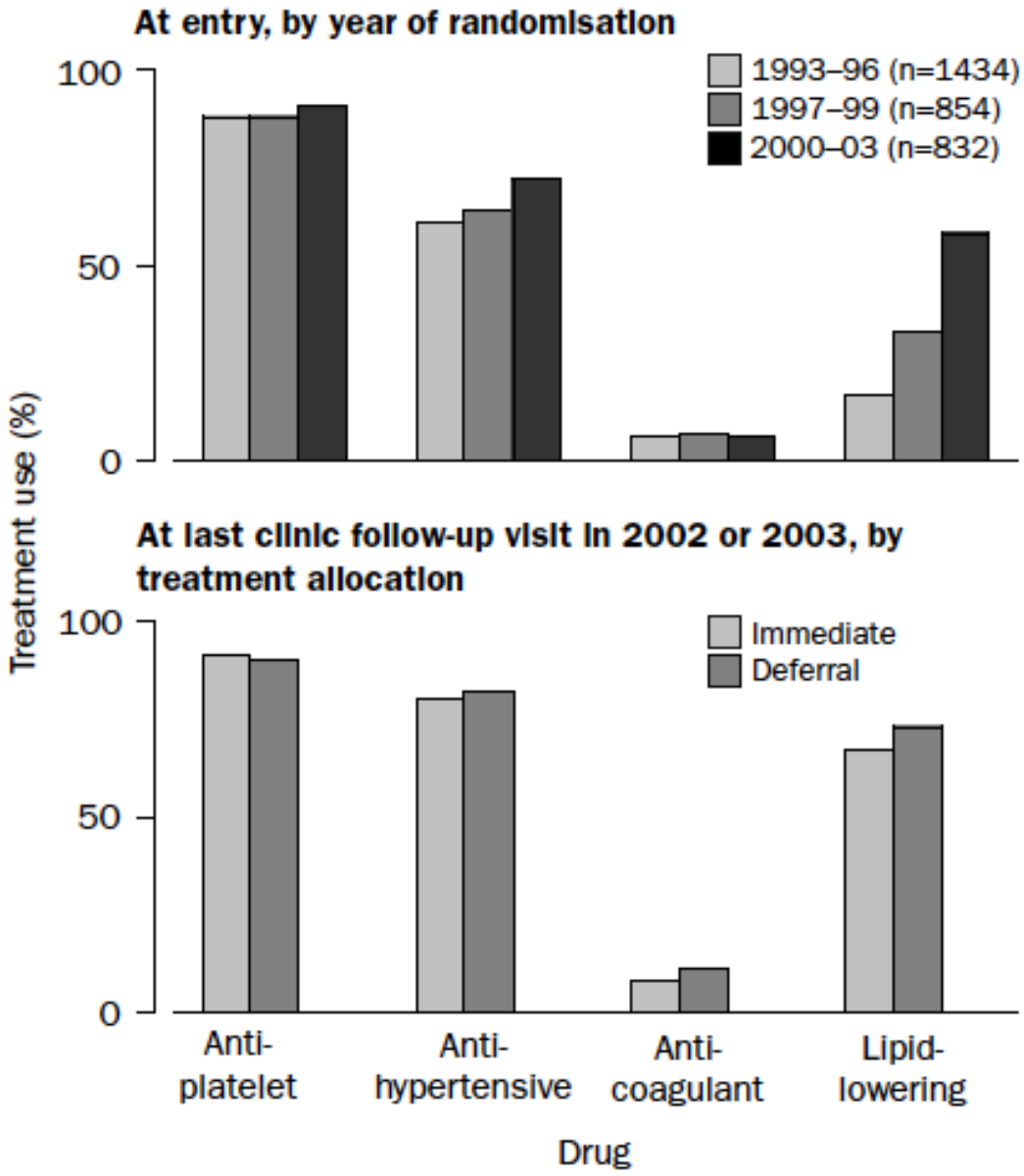
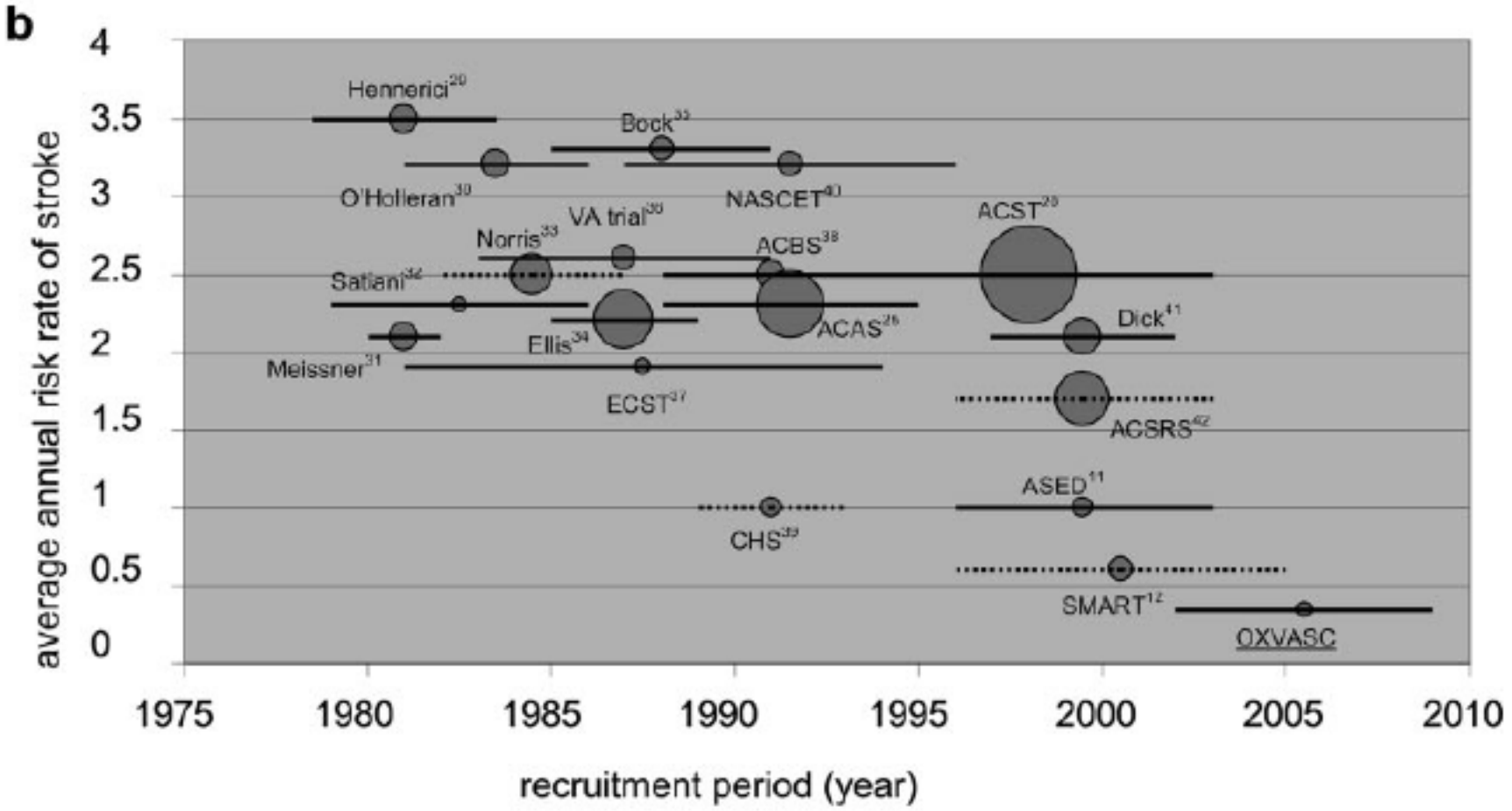



Figure 6: **Use of medical treatments**
At follow-up in 2002 or 2003, mean blood pressure was 148/79 in both groups.


b
average annual risk rate of stroke
4
3.5
3
2.5
2
1.5
1
0.5
0
Hennerici[29]
Bock[33]
O'Holleran[30]
NASCET[40]
VA trial[36]
ACST[28]
Norris[33]
ACBS[38]
Satiani[32]
Dick[41]
ACAS[26]
Ellis[34]
Meissner[31]
ECST[27]
AGSRS[42]
ASED[11]
CHS[39]
SMART[12]
OXVASC
1975
1980
1985
1990
1995
2000
2005
2010
recruitment period (year)

# Medical treatment in asymptomatic stenosis in any cerebrovascular bed

- More important than surgical / NR intervention
- Needs to be ongoing
- Risk factors
  - Statins
  - Blood pressure
  - Diabetes
- Lifestyle modification including smoking
- Antiplatelets- clopidogrel (or aspirin)

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**Treats other CVS outcomes as well as carotid disease**

# Conclusions

- **Symptomatic stenosis**
  - Intensive medical therapy markedly reduces risk, even in patients with “low” risk factor profile,  and should be started as soon as possible after TIA/stroke
- **Dissection**
  - Either antiplatelets or anticoagulation are Ok
  - Dissecting aneurysms can be left
  - Stenosis do not usually need opening up
- **Asymptomatic stenosis**
  - Stroke risk in untreated patients appears to have reduced to <=1% per annum - This raises the question as to whether ii could be more effective than CEA or stenting
  - Medical therapy is important