# Medical therapies for stroke prevention 2008

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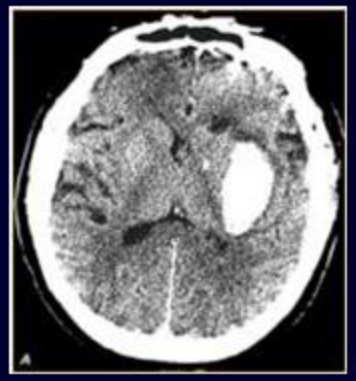
# Disclosure Statement of Financial Interest

*Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.*

| | *Company* |
|---|---|
| *Grant/Research Support* | *Boehringer-Ingelheim, Schering, J&J* |
| *Consulting Fees/Honoraria* | *Boehringer-Ingelheim, BMS/Sanofi, Pfizer, Abbott Vascular* |

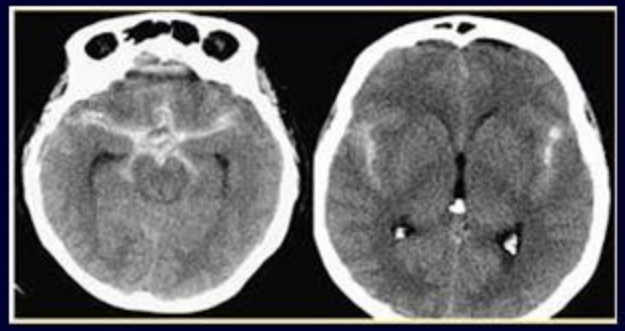
# Cerebrovascular Disease: Pathogenesis

**Hemorrhagic stroke (12%)**



Intracerebral hemorrhage (59%)

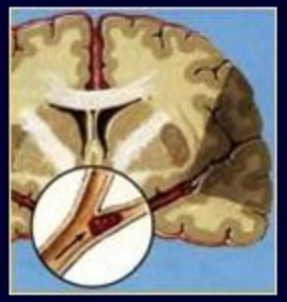
Subarachnoid hemorrhage (41%)



**Ischemic stroke (88%)**

Atherosclerotic cerebrovascular disease (20%)

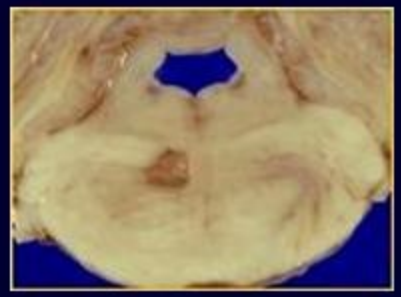
Embolism (20%)



Cryptogenic (30%)

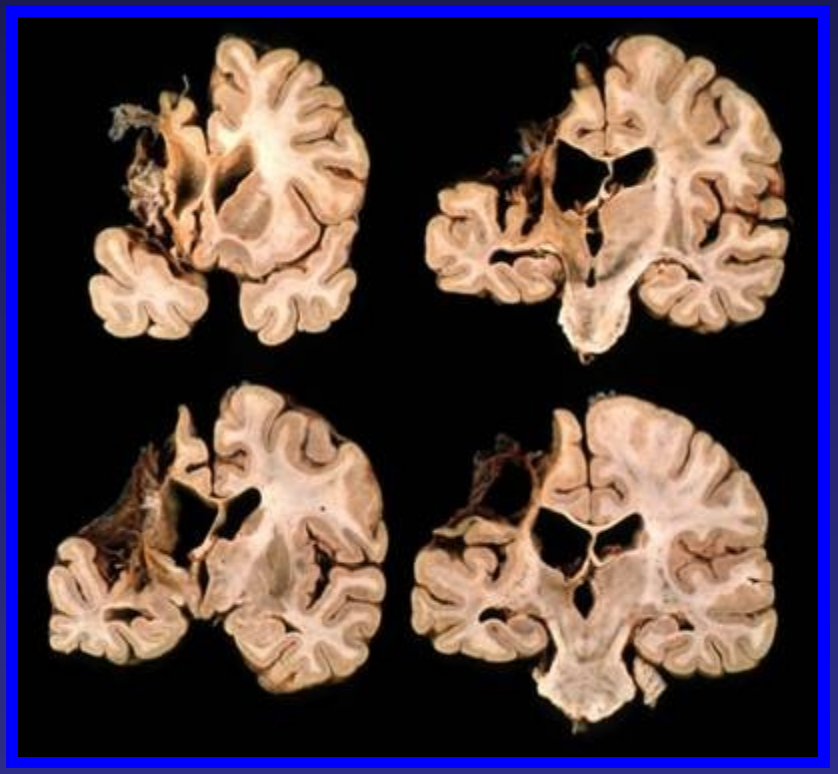
?

Lacunar (25%)



Albers GW et al. *Chest*. 1998;114(5 suppl):683S-698S.
Rosamond WD et al. *Stroke*. 1999;30:736-743.

# Stroke
## Incidence and Cost in United States



- 750,000 cases annually

  -70% first strokes
- # 3 cause of death
- $ 55 billion annual health cost
- 4 million stroke survivors at risk for recurrence

***Most strokes can be prevented***

# Transient Ischemic Attacks

EDITED BY
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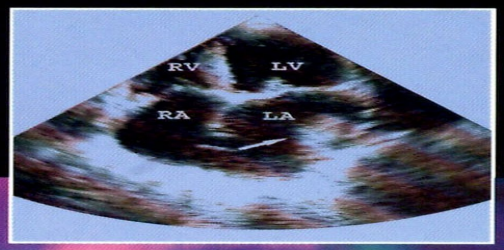
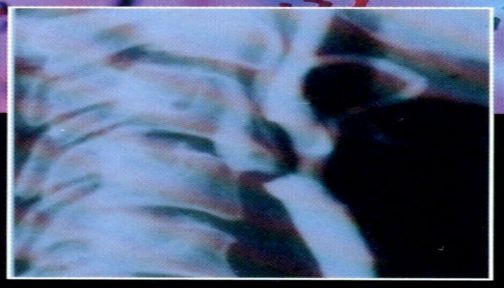
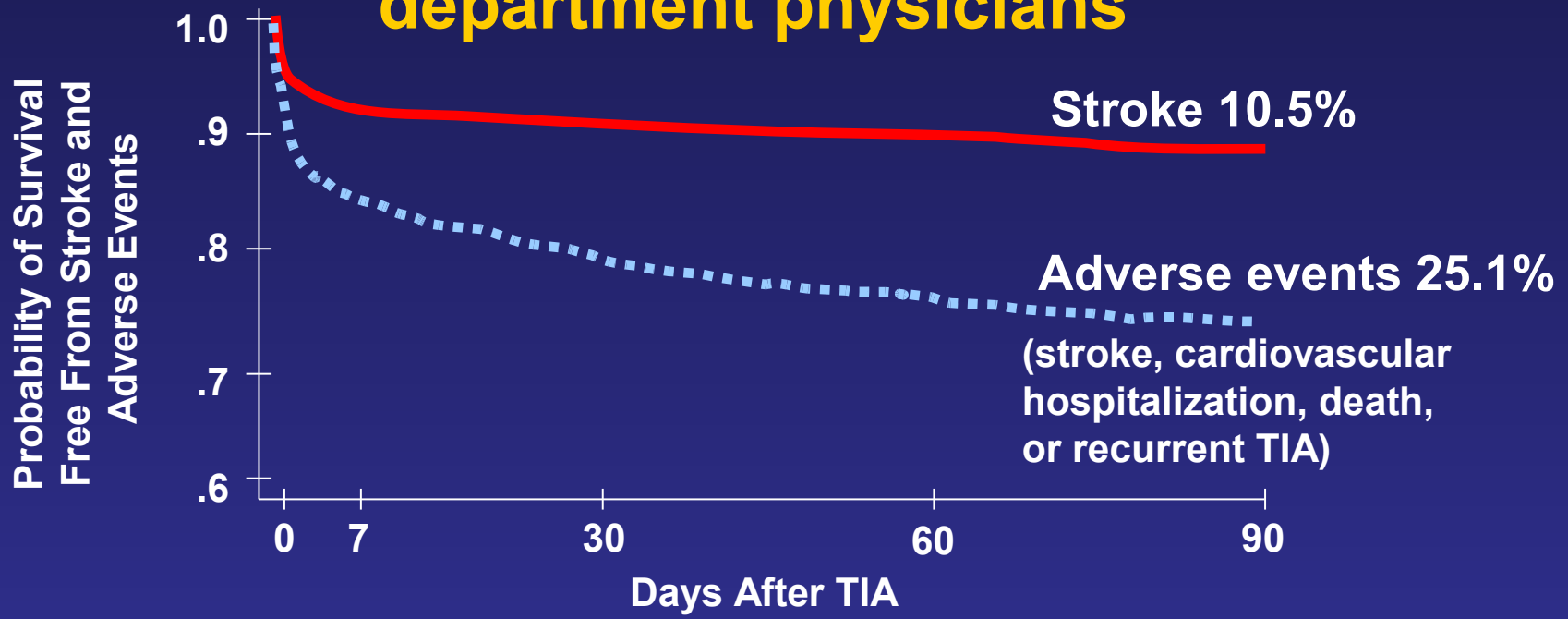


Blackwell
Futura

# Prognosis After Transient Ischemic Attack (TIA)

**1707 patients with TIA identified by emergency department physicians**




Johnston SC et al. *JAMA*. 2000;284:2901-2906.

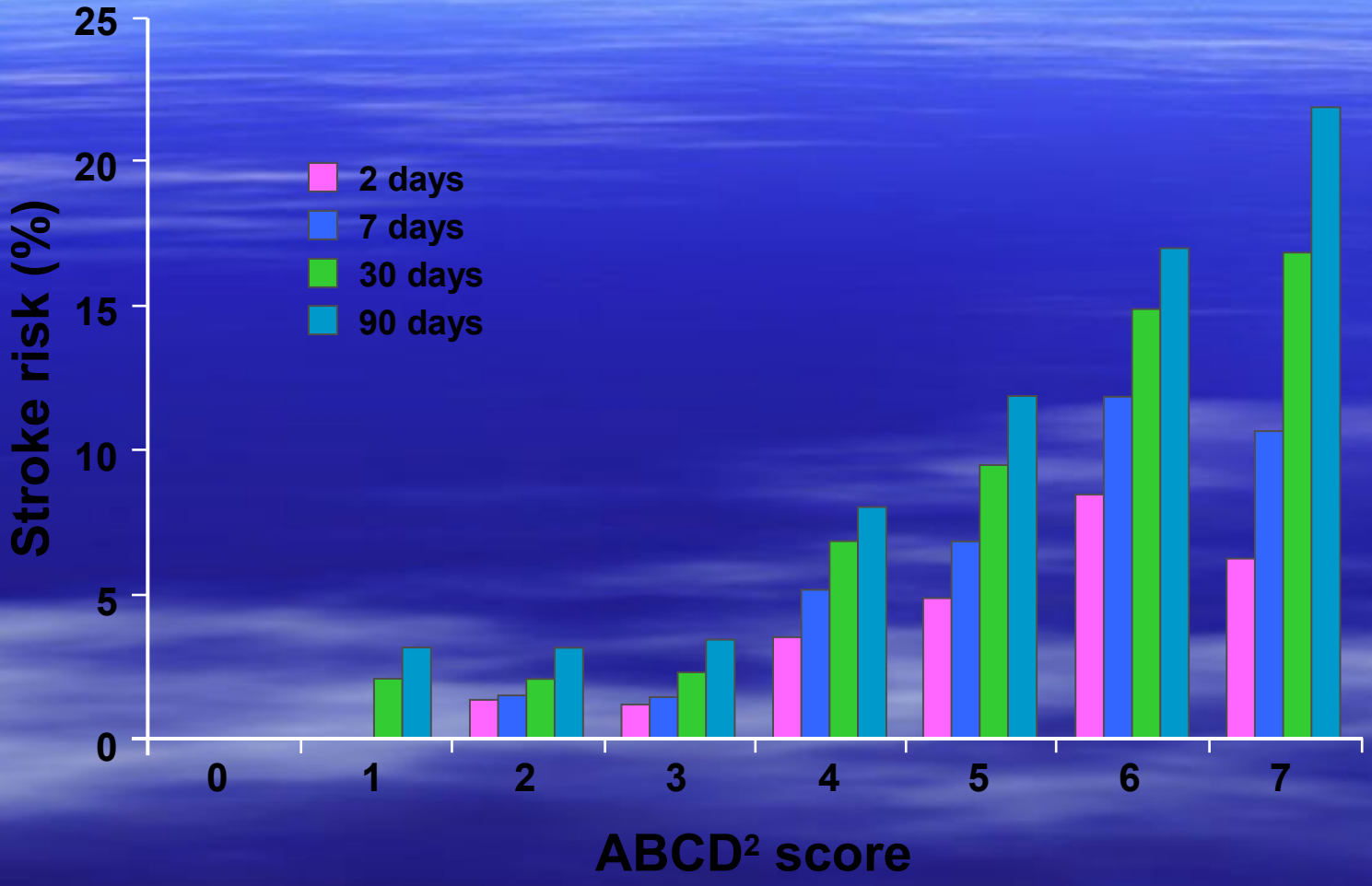
# ABCD$^2$ Score

| Symptom | Score |
|---|---|
| **A**ge ≥60 years | **1 point** |
| **B**lood pressure ≥140/90 mm Hg | **1 point** |
| **C**linical features [of TIA] | **2 points** for unilateral weakness<br>**1 point** for speech impairment without weakness |
| **D**uration [of TIA] | **2 points** for ≥60 minutes<br>**1 point** for 10-59 minutes |
| **D**iabetes | **1 point** |

Maximum score is 7. Score 6 or 7 = high risk.

Johnston SC, et al. *Lancet.* 2007;369:283-292.

# Stroke Risk by ABCD$^2$ Score




N=4799.

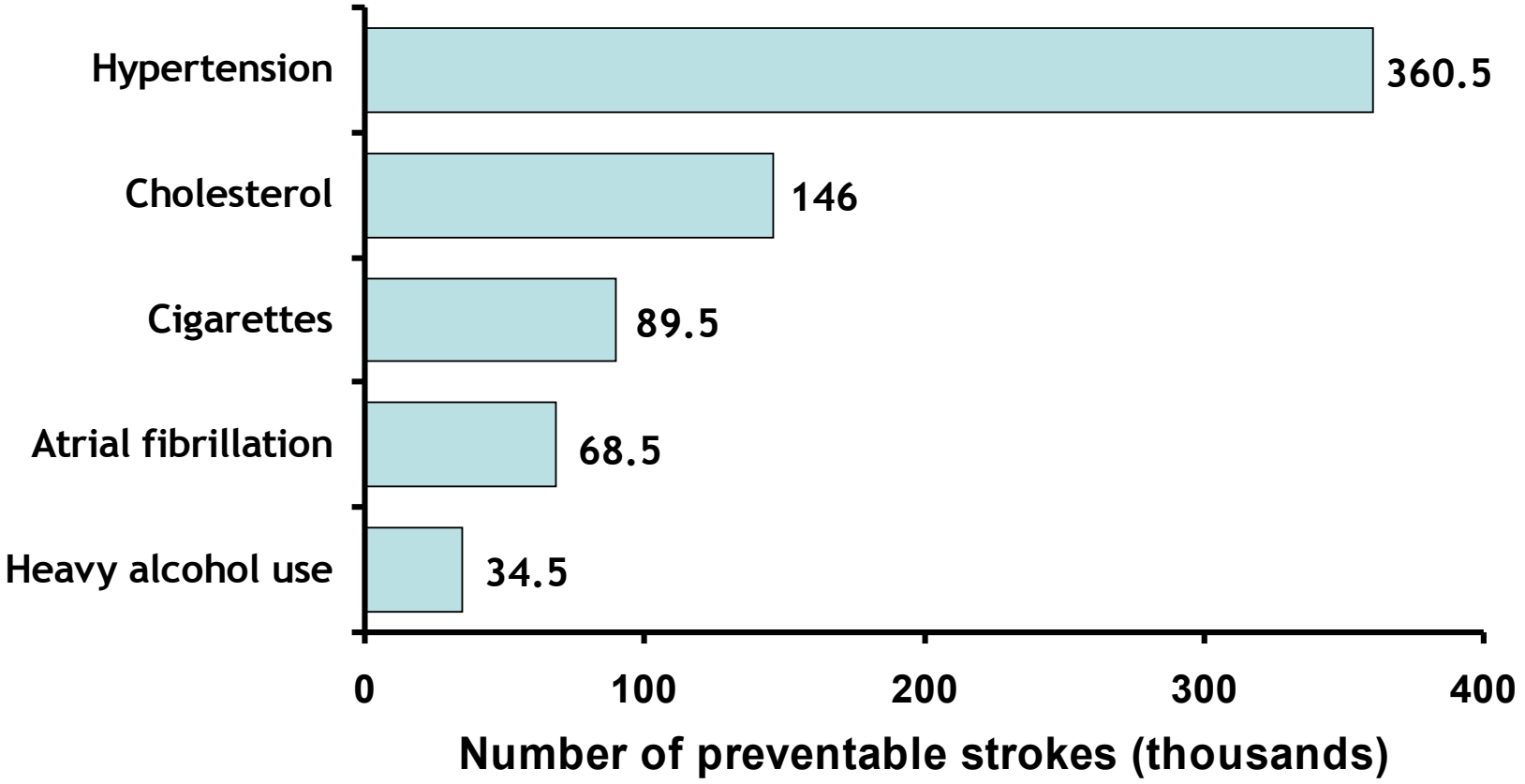
Reproduced with permission from Johnston SC, et al. *Lancet.* 2007;369:283-292.

# Ischemic Stroke Risk Reduction With Treatment

- Hypertension
  - 36%-42%
- Smoking
  - Risk reduces to that of nonsmokers 3 to 5 years after quitting
- Diabetes mellitus
  - 44% with hypertension control
- Hyperlipidemia
  - 20%-30% with statins

Madhavan R, Chaturvedi S. *CNS Drugs.* 2003;17:293-305.

# How Many Strokes Can Be Prevented by Risk-factor Control?

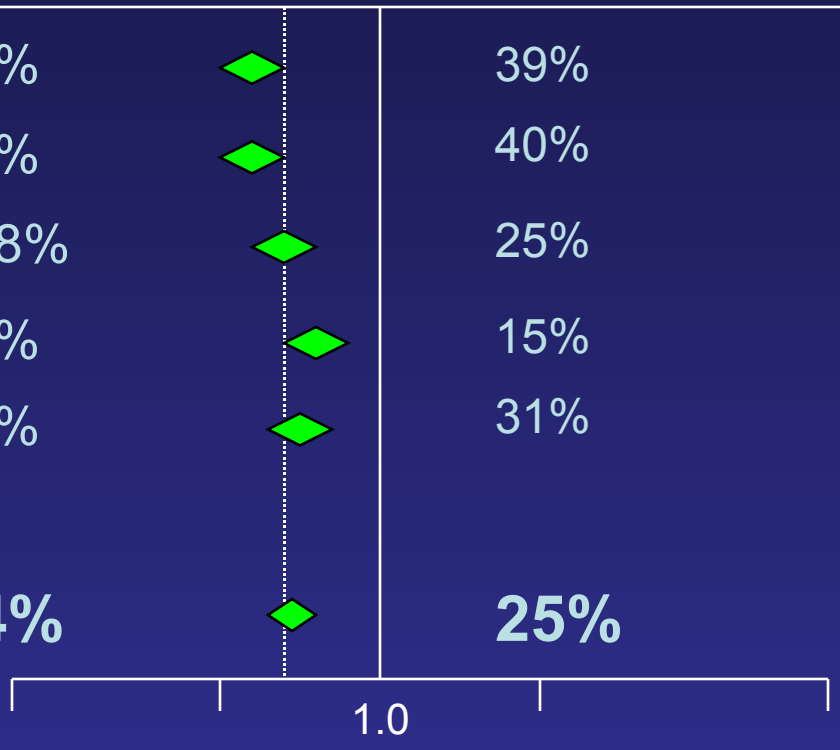



*Based on estimated 700,000 annual strokes in the US.

Gorelick PB. *Arch Neurol*. 1995;52:347-355.
Gorelick PB. *Stroke*. 2002;33:862-875.

# Effect of Antiplatelet Therapy on Non-Fatal Stroke

| Category | APT | Control | Reduction |
|---|---|---|---|
| Prior MI | 0.9% | 1.4% | 39% |
| Acute MI | 0.3% | 0.6% | 40% |
| Prior stroke/TIA | 8.3% | 10.8% | 25% |
| Acute stroke | 2.1% | 2.5% | 15% |
| Other HR | 1.5% | 2.1% | 31% |
| **All Trials** | **2.6%** | **3.4%** | **25%** |




**287 randomized trials with >200,000 patients**

**Antithrombotic Trialists Collaboration BMJ 2002; 324: 71-86**

# Aspirin and Secondary Stroke Prevention

- Aspirin reduces recurrent stroke risk by 20%
- Dosages as low as 50 mg/day reduce stroke
- Recommended dosage is 50-325 mg/day
- Combined antiplatelet therapy may have additive benefit in stroke prevention
  - May increase risk of bleeding

Weisman SM, Graham DY. *Arch Intern Med*. 2002;162:2197-2202.

# Prevention Regimen for Effectively Avoiding Second Strokes Trial (PRoFESS)

**Objectives**

- PRoFESS was designed to compare Aggrenox® (extended-release dipyridamole [ER-DP] plus ASA) vs clopidogrel, and to compare telmisartan vs placebo

**Design**

- The comparison between ASA + DP and clopidogrel was to be based on an initial assessment of noninferiority,* followed by evaluation of superiority
- Randomized, double-blind, 2 × 2 factorial design clinical trial

**Primary Outcome**

- Recurrent stroke (ischemic, hemorrhagic, or cause unknown)

* The power to detect noninferiority (one-sided, $\alpha = 0.025$) was determined to be 90% assuming that the relative hazard reduction of DP + ASA compared to clopidogrel could be as low as 6.5% which is half of the hypothesized hazard reduction. Diener HC, Sacco R, Yusuf S. *Cerebrovasc Dis.* 2007;23:368-380.

# PRoFESS: Primary Efficacy Outcome

| | Aggrenox (ER-DP + ASA) | Plavix® (clopidogrel bisulfate) | Hazard Ratio (95% Confidence Interval) | *P* Value |
|---|---|---|---|---|
| **First recurrent stroke** | 9.0% | 8.8% | 1.01 (0.92-1.11) | 0.783 |
| Recurrent ischemic stroke | 7.7% | 7.9% | | |
| Hemorrhagic stroke | 0.8% | 0.4% | | |

Sacco R. European Stroke Conference Webcast. Available at http://eurostroke.org. Accessed May 15, 2008.

# PRoFESS: Safety

- **Major hemorrhagic events and intracranial bleeds occurred more frequently in the ER-DP plus ASA group compared with clopidogrel**

| | Aggrenox (ER-DP + ASA) | PLAVIX | Hazard Ratio (95% Confidence Interval) | *P* Value |
|---|---|---|---|---|
| **Major hemorrhagic events** | 4.1% | 3.6% | 1.15 (1.00-1.32) | 0.06 |
| **Intracranial hemorrhage*** | 1.4% | 1.0% | 1.42(1.11-1.83) | 0.006 |

* All intracranial hemorrhages, which includes 128 of the 250 repeated ICH events, which were also reported in the primary outcome
Sacco R. European Stroke Conference Webcast. Available at http://eurostroke.org/. Accessed May 15, 2008.

# Adverse Events

- Dropouts due to headache occurred more frequently with ER-DP plus ASA than with clopidogrel

| | Aggrenox (ER-DP + ASA) | PLAVIX |
|---|---|---|
| Number of randomized patients | 10,181 | 10,151 |
| Headache with permanent discontinuation | 600 (5.9%) | 88 (0.9%) |
| Dizziness or lightheadedness | 1,365 (13.6%) | 908 (9.1%) |
| Fainting | 149 (1.5%) | 76 (0.8%) |
| Migraine during first 6 months of study | 562 (5.9%) | 314 (3.3%) |

Sacco R. European Stroke Conference webcast. Available at http://eurostroke.org. Accessed May 15, 2008.

# Recommendations for Therapy in Patients With Noncardioembolic Stroke or TIA

For patients with noncardioembolic ischemic stroke or TIA:


- Antiplatelet agents rather than oral anticoagulation are recommended to reduce the risk of recurrent stroke and other cardiovascular events ***(Class I, Level of Evidence A)***


- Aspirin (50 to 325 mg/d), the combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable options for initial therapy ***(Class IIa, Level of Evidence A)***

Sacco RL et al. *Stroke*. 2006;37:577-617.

# Hypertension in the very elderly (HYVET study)

- Enrolled patients age 80 years or more
- Sustained systolic HTN
- Treated with extended release indapamide +- perindopril
- Target BP 150/80

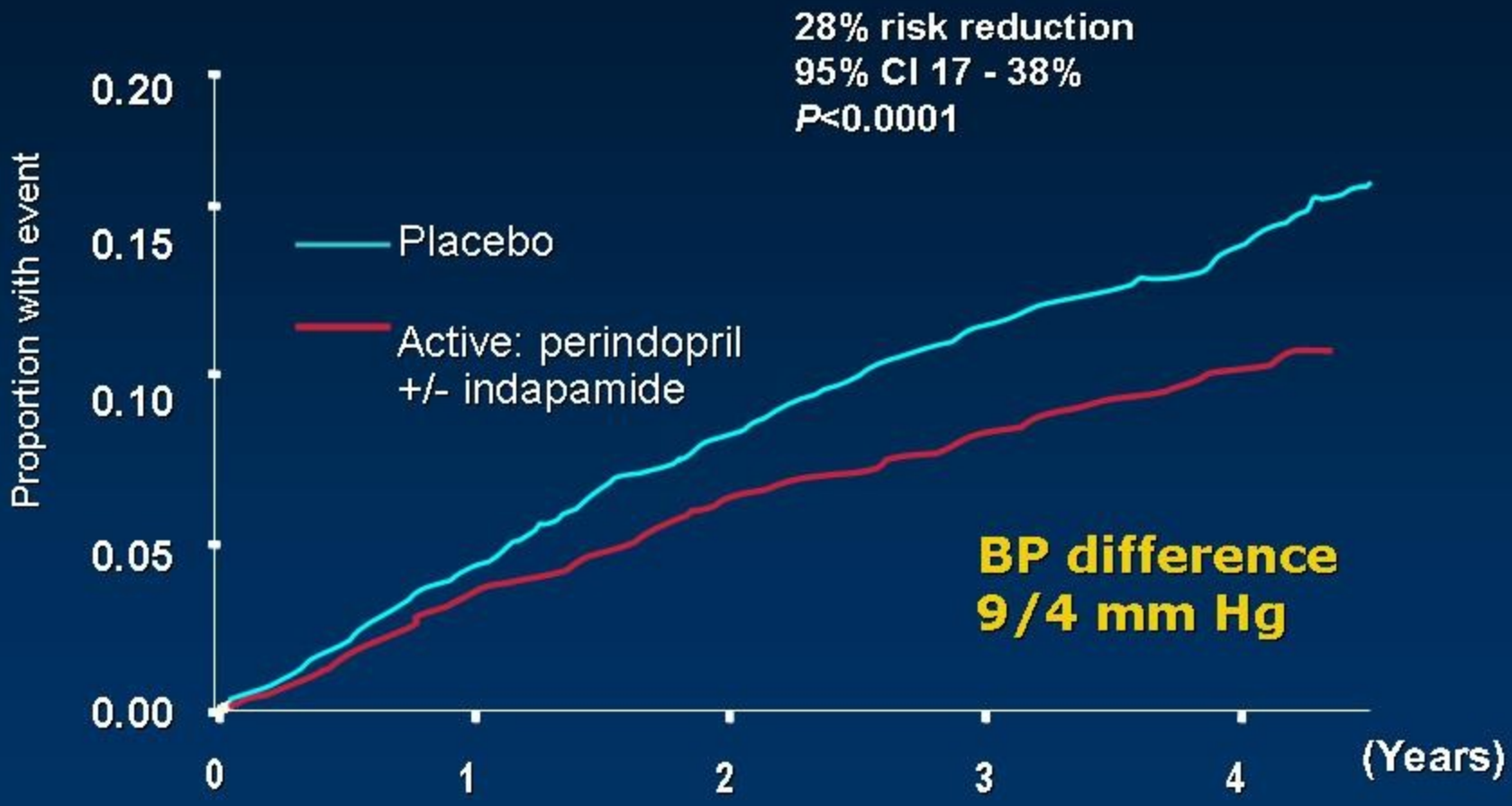
# HYVET study endpoints

**Table 2. Main Fatal and Nonfatal End Points in the Intention-to-Treat Population.**

| End Point | Rate per 1000 Patient-Yr (No. of Events) | | Unadjusted Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | Active | Placebo | | |
| | *no. (%)* | | | |
| Stroke | | | | |
| Fatal or nonfatal | 12.4 (51) | 17.7 (69) | 0.70 (0.49–1.01) | 0.06 |
| Death from stroke | 6.5 (27) | 10.7 (42) | 0.61 (0.38–0.99) | 0.046 |
| Death | | | | |
| From any cause | 47.2 (196) | 59.6 (235) | 0.79 (0.65–0.95) | 0.02 |
| From noncardiovascular or unknown causes | 23.4 (97) | 28.9 (114) | 0.81 (0.62–1.06) | 0.12 |
| From cardiovascular cause | 23.9 (99) | 30.7 (121) | 0.77 (0.60–1.01) | 0.06 |
| From cardiac cause* | 6.0 (25) | 8.4 (33) | 0.71 (0.42–1.19) | 0.19 |
| From heart failure | 1.5 (6) | 3.0 (12) | 0.48 (0.18–1.28) | 0.14 |
| Fatal or nonfatal | | | | |
| Any myocardial infarction | 2.2 (9) | 3.1 (12) | 0.72 (0.30–1.70) | 0.45 |
| Any heart failure | 5.3 (22) | 14.8 (57) | 0.36 (0.22–0.58) | <0.001 |
| Any cardiovascular event† | 33.7 (138) | 50.6 (193) | 0.66 (0.53–0.82) | <0.001 |

* Death from cardiac causes was defined as fatal myocardial infarction, fatal heart failure, and sudden death.
† Any cardiovascular event was defined as death from cardiovascular causes or stroke, myocardial infarction, or heart failure.

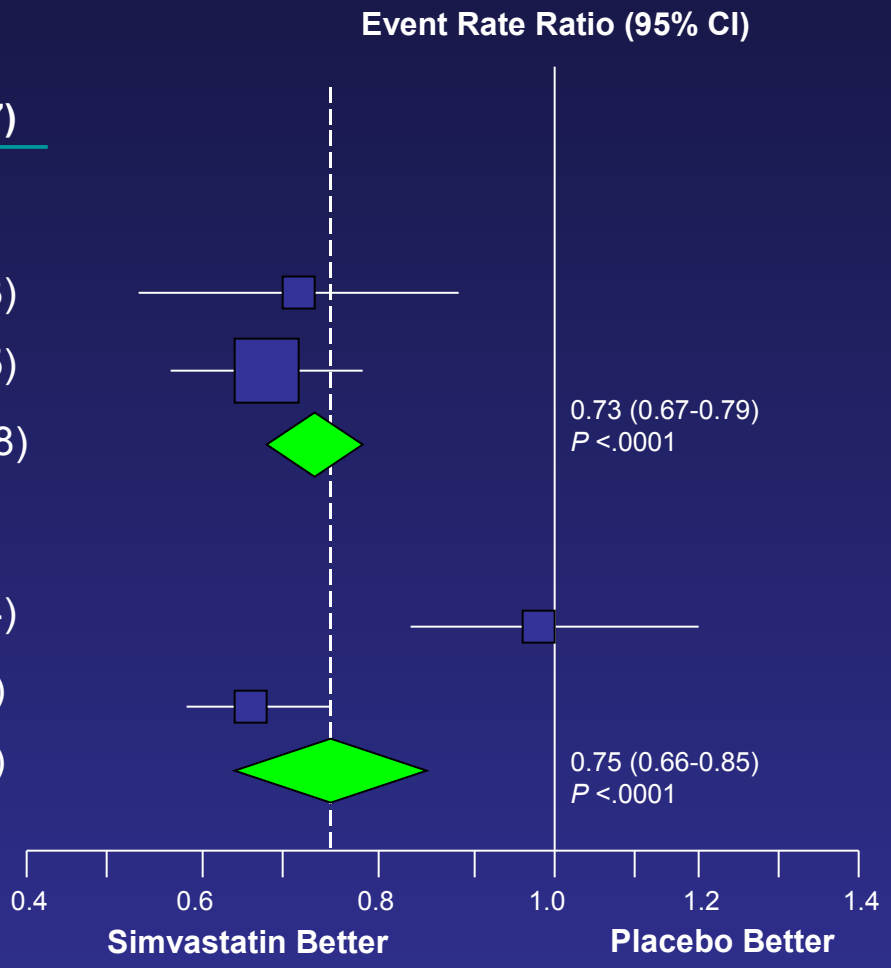
# Stroke Risk Reduction in PROGRESS
## All participants




PROGRESS Collaborative Group. *Lancet* 2001;358:1033-41

# Effects of Simvastatin on First Major Coronary Event or Stroke

| Major Event & Prior Disease | Simvastatin (n=10,269) | Placebo (n=10,267) |
|---|---|---|
| **Major Coronary Events (%)** | | |
| Prior CVD | 171 (10.4) | 218 (13.3) |
| No prior CVD | 727 (8.4) | 994 (11.5) |
| Subtotal coronary | 898 (8.7) | 1212 (11.8) |
| **Strokes (%)** | | |
| Prior CVD | 169 (10.3) | 170 (10.4) |
| No prior CVD | 275 (3.2) | 415 (4.8) |
| Subtotal strokes | 444 (4.3) | 585 (5.7) |

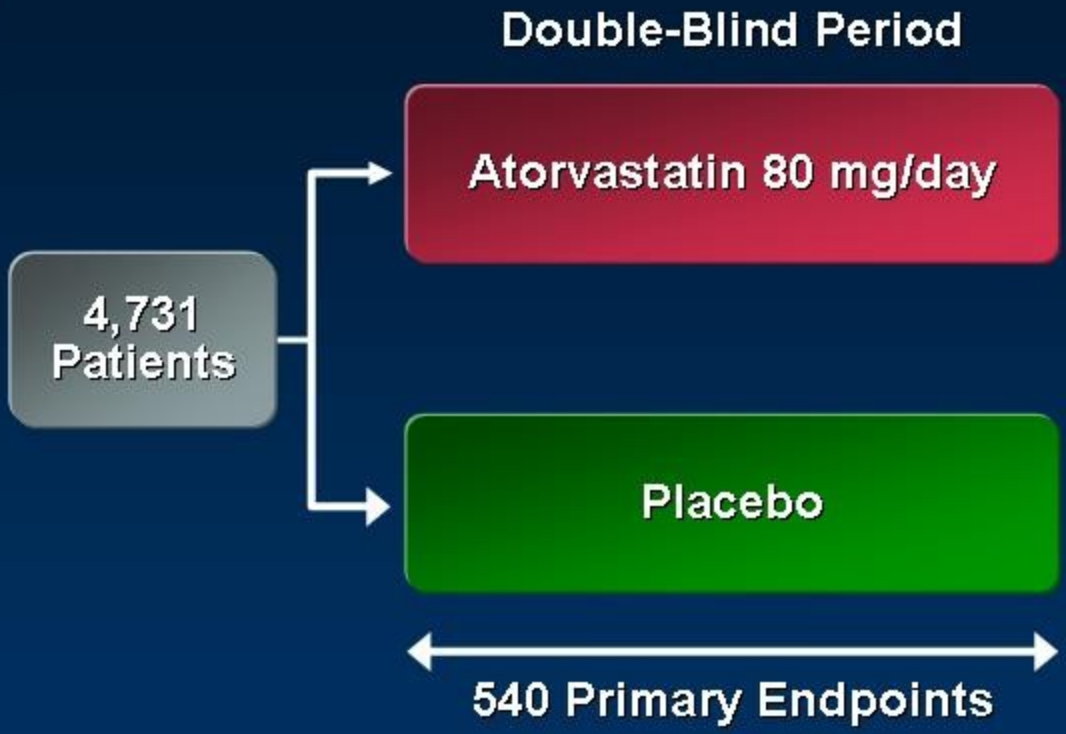



Adapted from the Heart Protection Study Collaborative Group. *Lancet.* 2004;363;757-767.
Heart Protection Study Collaborative Group. *Lancet.* 2002;360;7-22.

# SPARCL: Study Design

## Patient Population

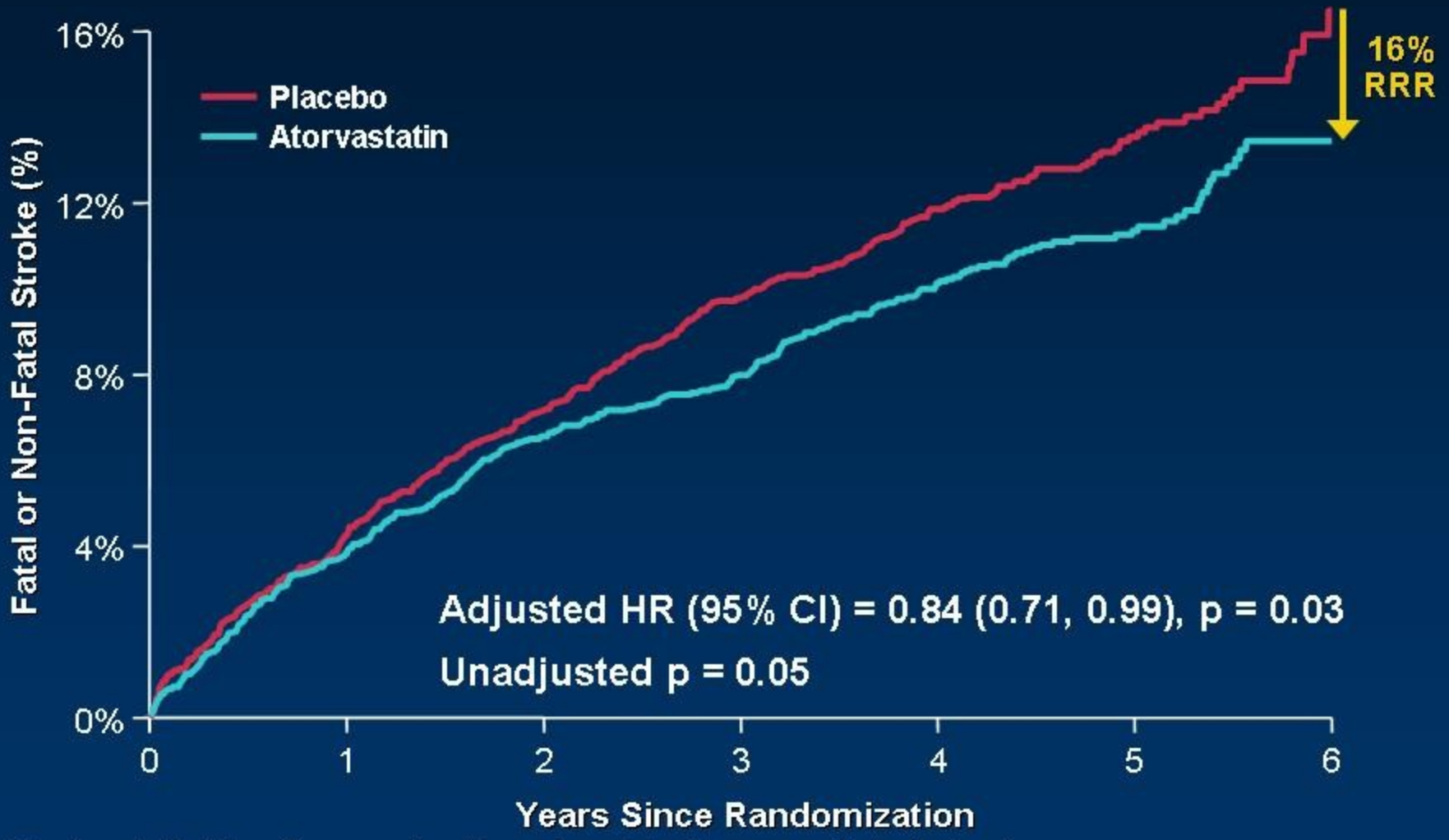
- 205 sites worldwide
- Previously documented stroke or TIA within 6 months
- No history of CHD
- LDL-C levels ≥100 mg/dL and ≤190 mg/dL
- Modified Rankin ≤ 3




## Primary End Point
**Time to the First Occurrence of a Fatal or Nonfatal Stroke**

Source: The SPARCL Investigators. *Cerebrovasc Dis.* 2003;16:389-395

# SPARCL Primary Endpoint: Time to Fatal or Non-Fatal Stroke




*Treatment effect from Cox proportional hazards models with pre-specified adjustment for geographical region, entry event, time since entry event, gender, and baseline age.

# SPARCL: Prespecified and Post-Hoc Analyses

| Prespecified Analysis | Atorvastatin (n=2365) n (%) | Placebo (n=2366) n (%) | HR (95% CI)* | *P*-value |
|---|---|---|---|---|
| **Primary Endpoint** | **265** (11.2) | **311** (13.1) | **0.84** (0.71, 0.99) | **.03** |
| Fatal Stroke | **24** (1.0) | **41** (1.7) | **0.57** (0.35, 0.95) | **.03** |
| Non-fatal Stroke | **247** (10.4) | **280** (11.8) | **0.87** (0.73, 1.03) | **.11** |
| **Post-Hoc Analysis** | | | | |
| Ischemic | **218** (9.2) | **274** (11.6) | **0.78** (0.66, 0.94) | |
| Hemorrhagic | **55** (2.3) | **33** (1.4) | **1.66** (1.08, 2.55) | |

* Treatment effect from Cox proportional hazards models with pre-specified adjustment for geographical region, entry event, time since entry event, gender, and baseline age.
HR, hazard ratio; CI, confidence interval.

The SPARCL Investigators. *N Engl J Med*. 2006;355:549-559.

# Discontinuation Rates of Cardiovascular Pharmacological Agents in the Study Population Who Discontinued Statin Therapy

| | | 12-Month Discontinuation Rate | | | |
|---|---|---|---|---|---|
| | Prescription Rate at Discharge | Overall | Survivors | Nonsurvivors | *P* Value* |
| **Antiplatelet agents, patients (%)** | 618 (97.9) | 108 (17.4) | 47 (9.3) | 61 (53.5) | 0.0001 |
| **Statins, patients (%)** | 631 (100.0) | 246 (38.9) | 154 (29.9) | 92 (79.3) | 0.0001 |
| **ACE inhibitors, patients (%)** | 221 (35.0) | 24 (10.8) | 19 (10.6) | 5 (11.9) | 0.808 |
| **Calcium channel blockers, patients (%)** | 271 (43.1) | 32 (11.8) | 24 (10.9) | 8 (15.6) | 0.340 |
| **Angiotensin receptor blockers, patients (%)** | 123 (19.4) | 10 (8.1) | 8 (7.8) | 2 (9.5) | 0.679 |
| **B-Blockers, patients (%)** | 48 (7.6) | 9 (18.7) | 7 (19.4) | 2 (16.6) | 1.0 |
| **Diuretics, patients (%)** | 262 (41.5) | 67 (25.5) | 51 (24.1) | 16 (31.3) | 0.290 |

*Comparison between survivors and nonsurvivors.

# AHA/ASA 2008 Stroke Guideline Update

- **New Recommendation**

**B**

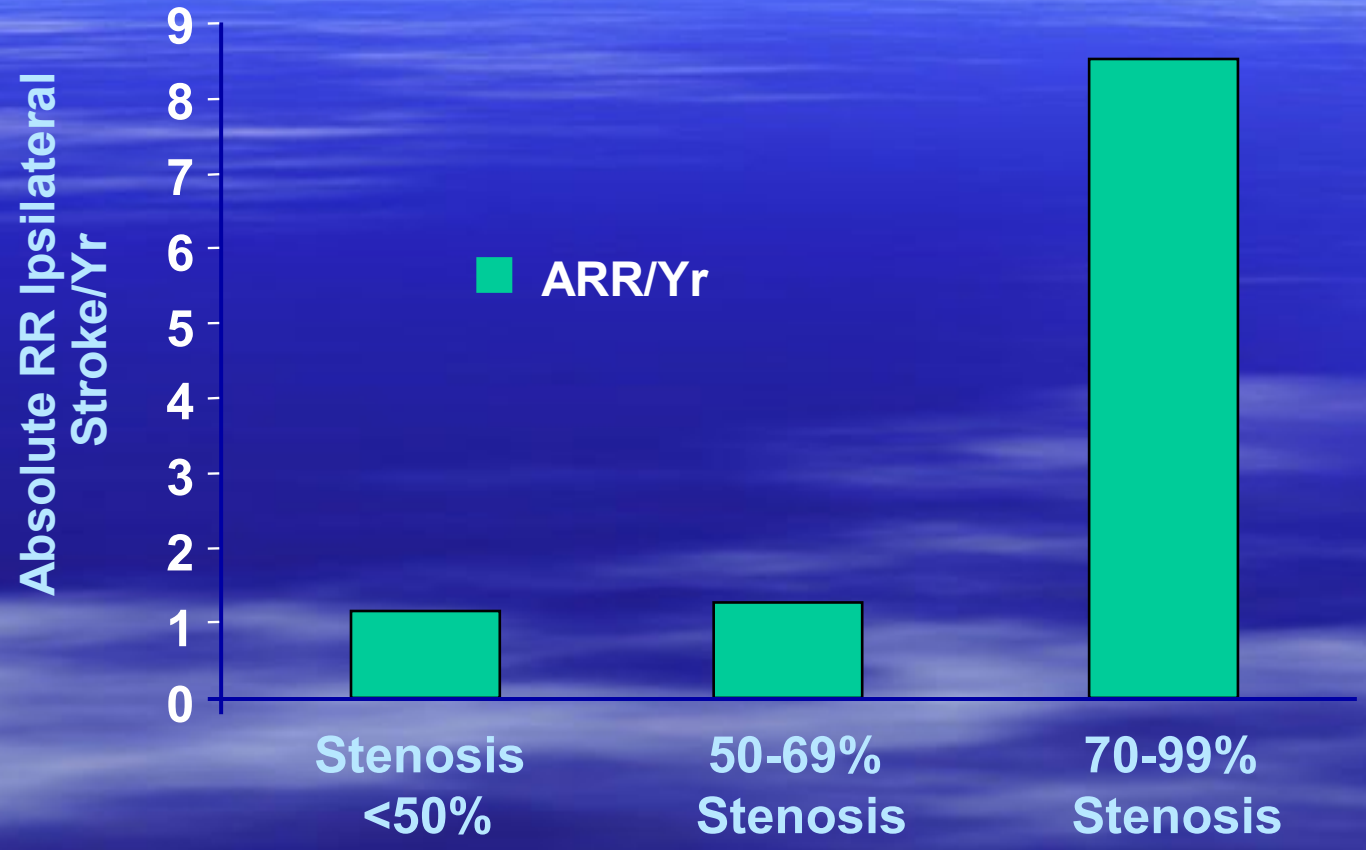
- On the basis of the SPARCL trial, administration of statin therapy with intensive lipid-lowering effects is recommended for patients with atherosclerotic *ischemic* stroke or TIA and without known CHD to reduce the risk of stroke and cardiovascular events

**B**

- Ischemic stroke or TIA patients with low HDL cholesterol may be considered for treatment with niacin or gemfibrozil

Adams RJ, et al. *Stroke.* 2008;39. doi:10.1161/STROKEAHA.107.189063.

# Absolute Benefits of Carotid Endarterectomy (CEA)




CEA showed only marginal benefits on annual rates of ipsilateral stroke for patients with asymptomatic or moderate lesions. Dramatic benefit was seen for high-grade symptomatic stenoses.

Barnett HJ, et al. *N Engl J Med*. 1998;339:1415-1425.

# Annual absolute risk reductions

| | |
|---|---|
| • Statins | • 0.4% |
| • Antiplatelets | • 0.2-1.5% |
| • BP Lowering | • 0.9% |
| • CEA primary prevention | • 1.2% (based on ACAS) |
| • CEA secondary prevention | • 1.3% (50-69% stenosis) |
| • CEA secondary prevention | • 8.5% (70-99% stenosis) |