# Carotid Artery Stenting

## Current status and perspective

# Natural Incidence of CVA In Carotid Stenosis

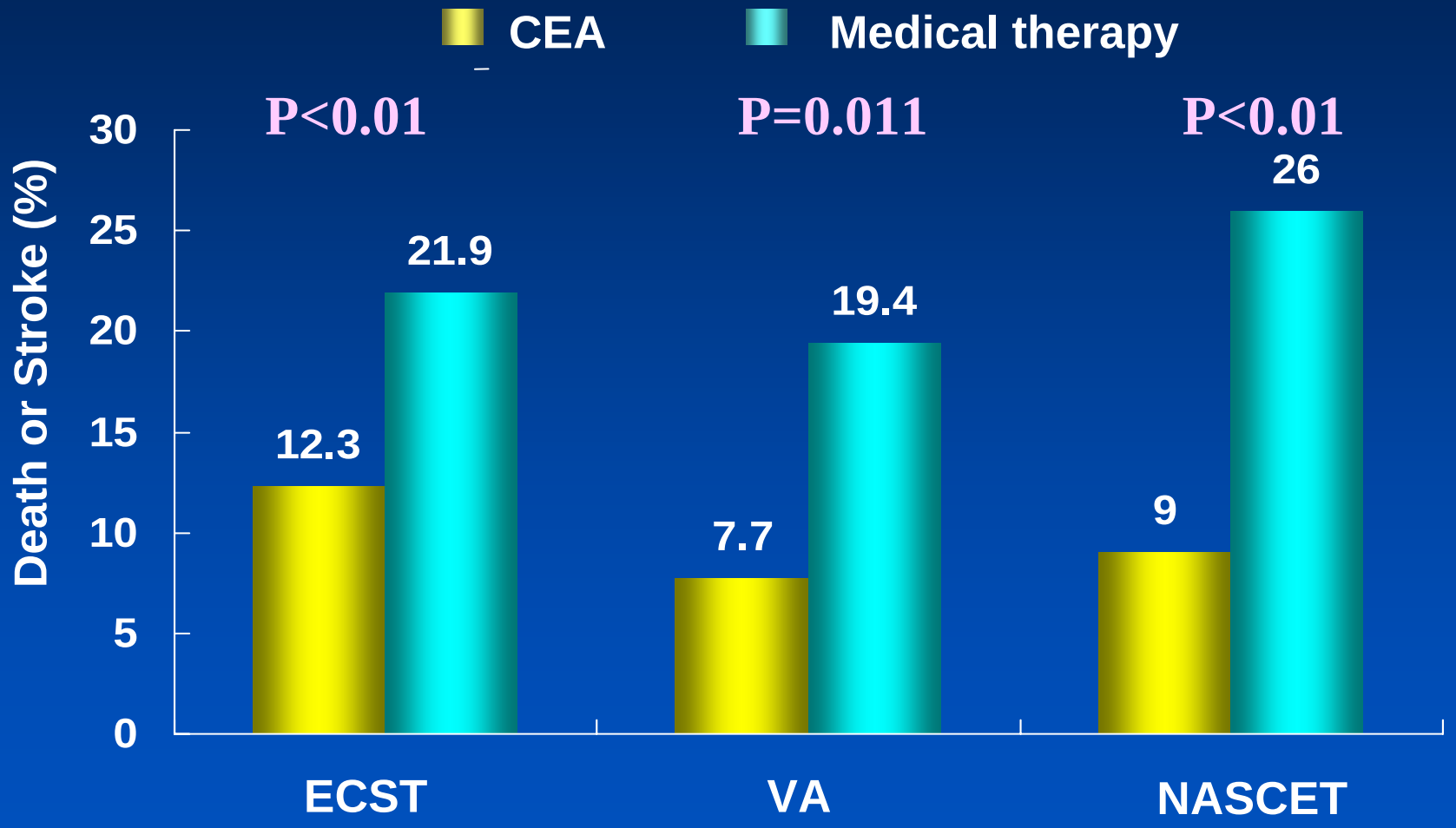
- Asymptomatic 80% carotid stenosis
  - 1.9%/ year (ESCT registry)
  - 12% / 5 year (ACAS, ACST)
- Symptomatic 50% carotid stenosis
  - 10% / year
  - 40% / 5 years

# Carotid Artery stenosis

## Current guidelines

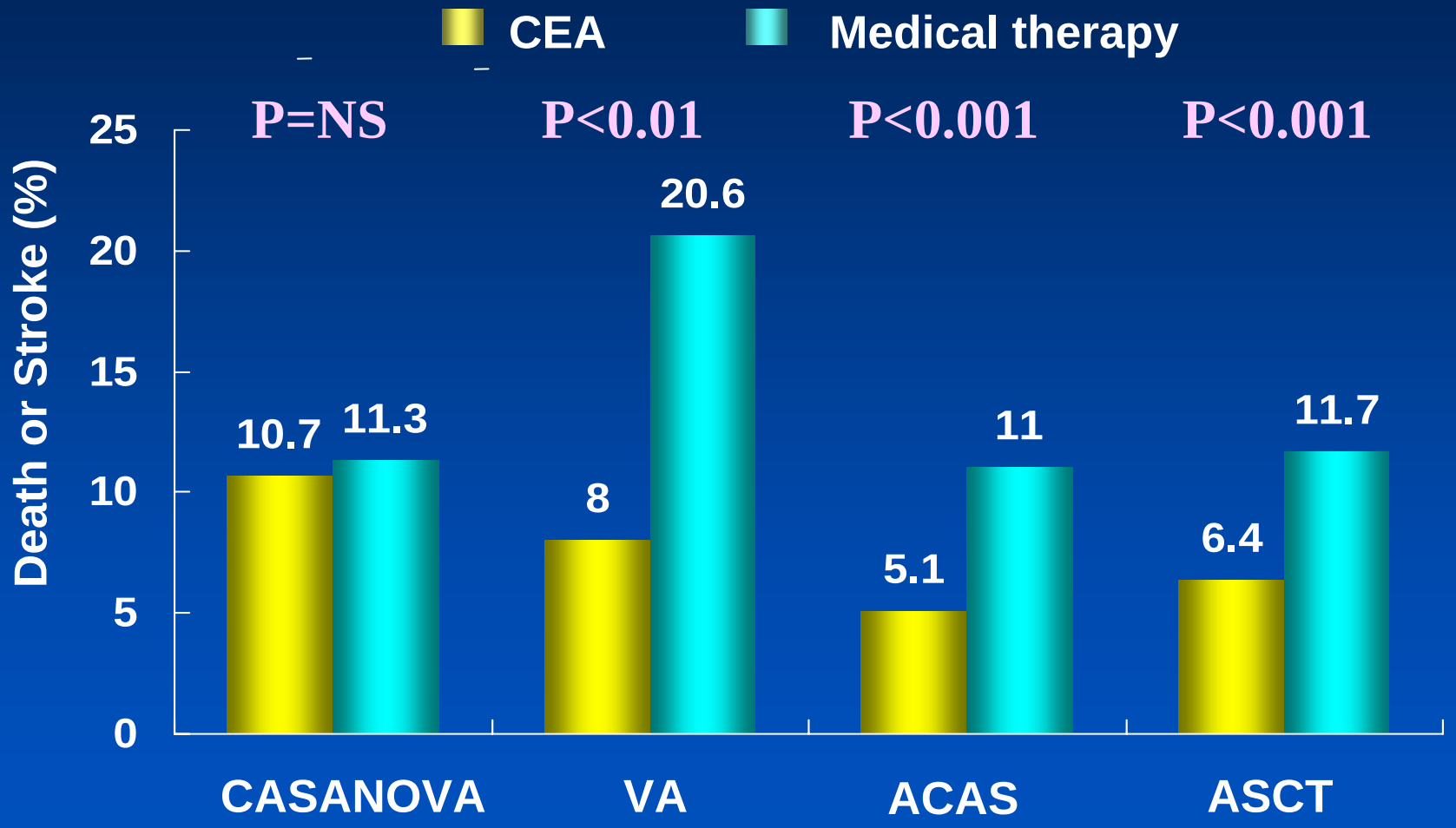
# CEA vs. Medical Rx

## Symptomatic Patients (DS≥ 70%)



# CEA vs. Medical Rx

## Asymptomatic Patients (DS > 60%)



# Indications for carotid artery revascularization

| Indication level | Symptomatic stenosis | Asymptomatic stenosis |
|---|---|---|
| **Proven** | • 70-99% stenosis<br>• Periprocedural complication risk <6% | • > 60% stenosis<br>• Periprocedural complication risk <3%<br>•Life expectancy > 5yrs |
| **Acceptable** | • 50-69% stenosis<br>• Periprocedural complication risk <6% | • > 60% stenosis<br>• Periprocedural complication risk <3%<br>• Planned CABG |
| **Unacceptable** | • <29% stenosis,<br>or<br>• Periprocedural complication risk > 6% | • < 60% stenosis<br>or<br>• Periprocedural complication risk >3%<br>• No indication for CABG |

*Circulation 2006;113:2021-2030*

# Carotid Stenting:

- NASCET-2 trial (2.226 pts, 50-69% stenosis) showed that a modest benefit in favor of surgery especially nondiabetics men with hemispheric, ischemic stroke in patients with ≥ 50%

**Current guideline of carotid revascularization**

**Symptomatic stenosis ≥ 70%**

**Asymptomatic stenosis ≥ 80%**

- ESCT group (2,295 pts) showed that different stroke risk of asymptomatic stenosis; < 2% of <80% stenosis, 9.8% of 80-89% stenosis, 14.4% of 90-99% at 3 years.

# Carotid Stenting:

- Currently, the only use of carotid stenting that has been approved by FDA is in **symptomatic patients with stenosis of the internal carotid artery exceeding 70%** who are at high risk for complications after surgery.

- The limited FDA approval of stenting is largely based on the results of SAPPHIRE trial, involving patients who had **symptomatic stenosis of the internal carotid artery exceeding 50% or asymptomatic stenosis exceeding 80%** and who were at high surgical risk mainly owing to severe coronary artery disease.

# Current Goal of Carotid stenting based on NASCET[1], ECST[2], ACAS[3], ACST[4]

**Morbidity and mortality after carotid intervention should be…**

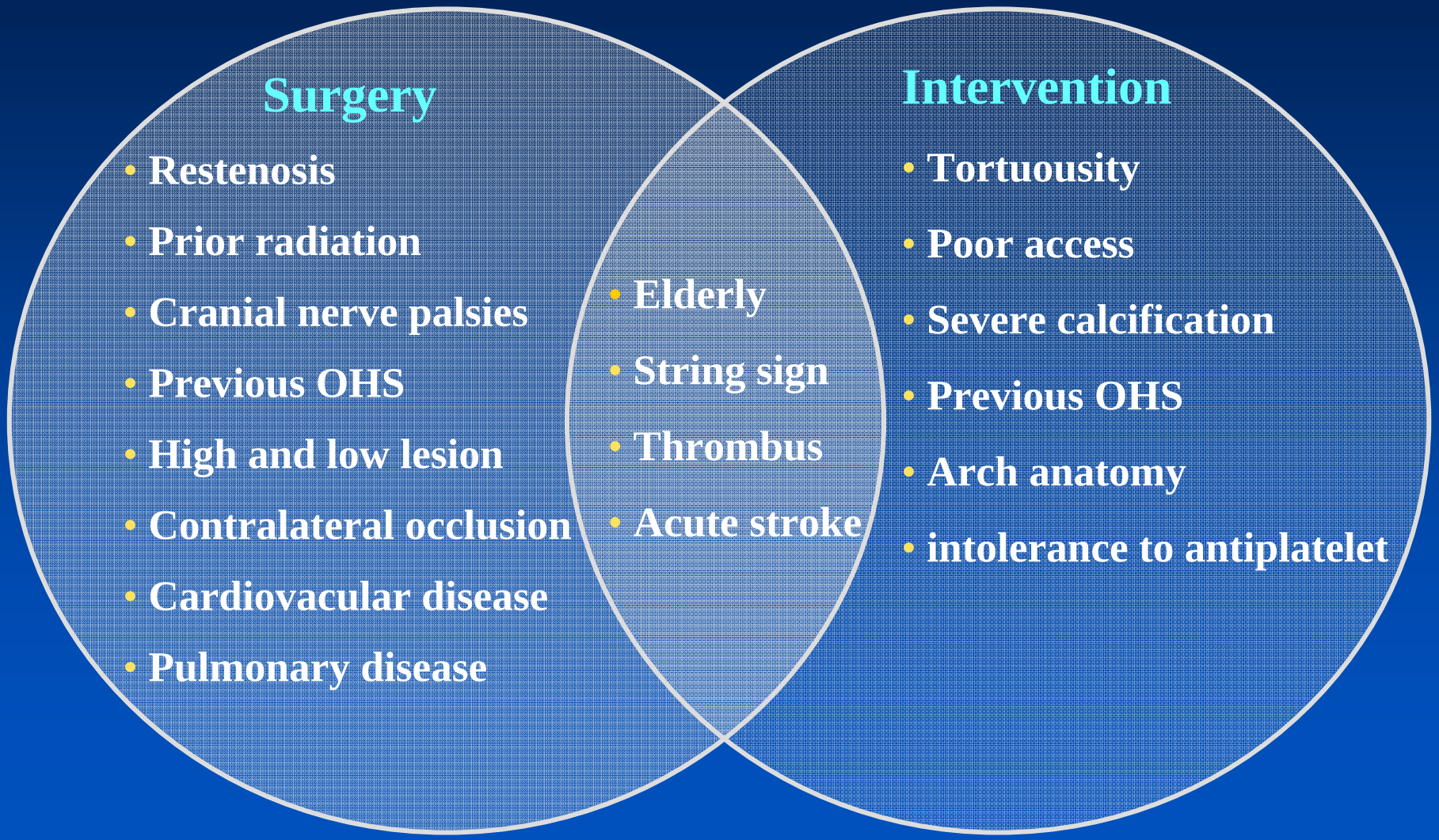
**Symptomatic < 6%[1,2]**
**Asymptomatic < 3%[3,4]**

# Carotid Artery stenosis

High risk group for surgery

High risk group for stenting

# High Risk Features of Surgery vs. Stenting for Carotid Stenosis



# Who is High Risk Patient?
## Clinical Criteria

- Age greater than 80
- Unstable angina CCS III-IV
- EF< 30%
- MI within past 6 wks
- Severe COPD (FEV1 < 30% predicted)
- Renarrowing after prior CEA (**80% Asx; 50% Sx)**
- Total occlusion of the contralateral ICA
- Two or more proximal or major coronary arteries with >70% stenosis

# Who is High Risk Patient?
## Anatomical Criteria

- Previous radiation treatment to neck
- Previous radical neck surgery
- Inability to extend neck
- Patient has a tracheostomy or tracheal stoma
- Laryngeal nerve palsy
- Lesion with difficult access

# Carotid End-Arterectomy

- 3,061 CEA during a 10-year period

| | Stroke | Death | Stroke, MI, Death |
|---|---|---|---|
| High Risk Patients | 3.5% | 4.4% | 7.4% |
| Low Risk Patients | 1.7% | 0.3% | 2.9% |

* **High risk patients**: severe coronary disease, COPD, renal insufficiency

Ouriel K, et al. J Vasc Surg 2001;33:728

# Features a/w increased procedural risks after carotid stenting

| | Risk factors | Features |
|---|---|---|
| Clinical | Advanced age | Age ≥ 80 yrs |
| | Decreased cerebral reserve | -Dementia<br>-Prior (remote) stroke<br>-Multiple lacunar infarcts<br>-Intracranial microangiopathy |
| Angiographic | Excessive tortuosity | ≥ 2 90˚ bends within 5 cm of the lesion |
| | Heavy calcification | -Concentric circumferential calcification<br>-Width ≥ 3mm |

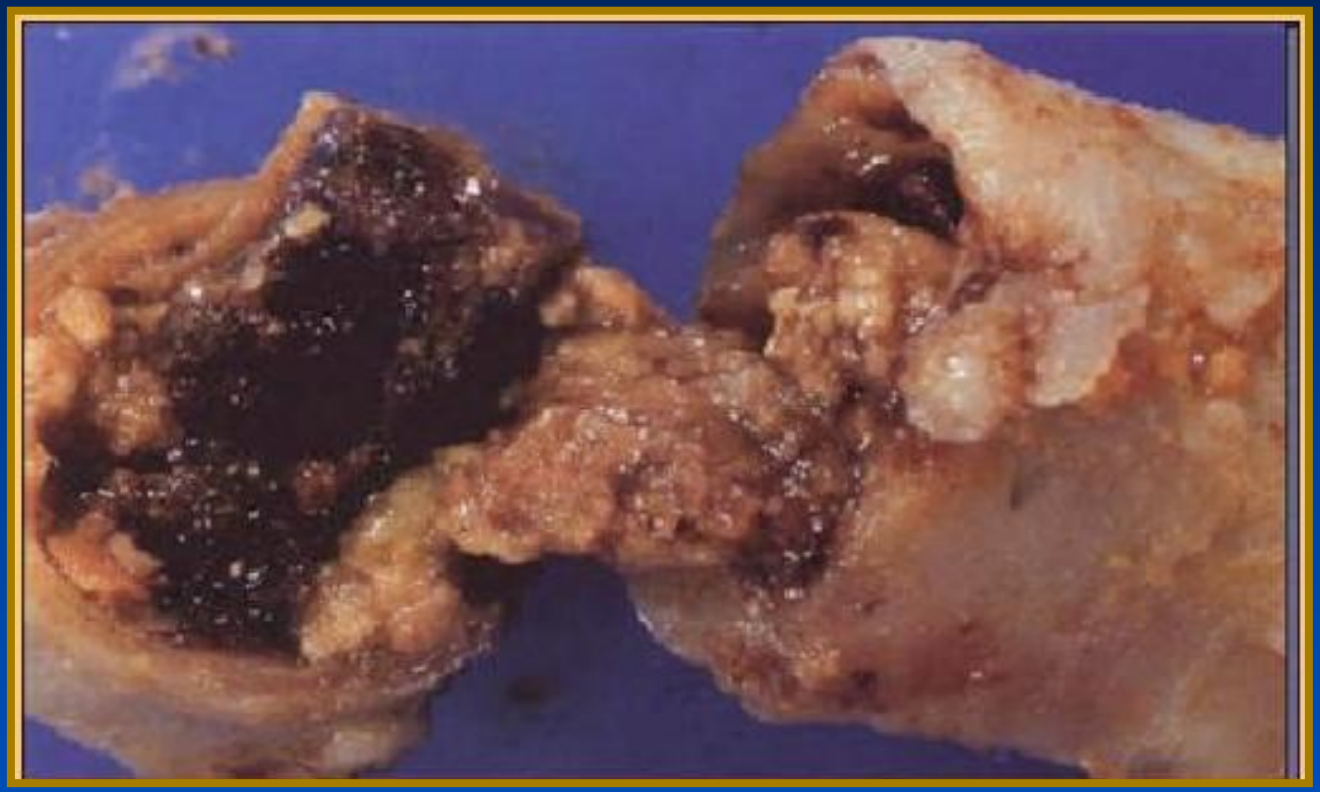
*Circulation 2006;113:2021-2030*

# Carotid Artery Stenting

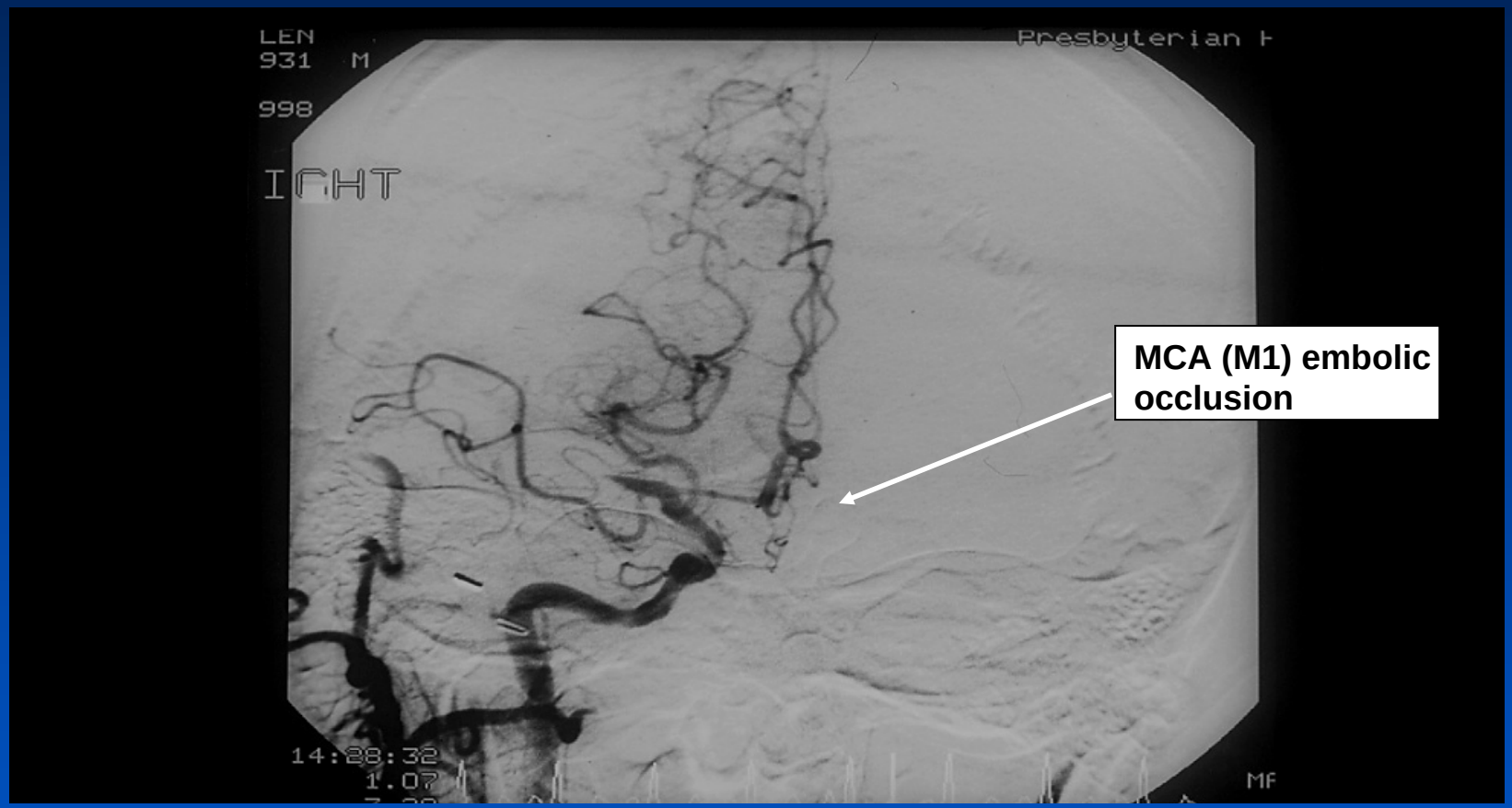
## Current status

**Embolic protection device (EPD) ??**

# Why Embolic Protection?

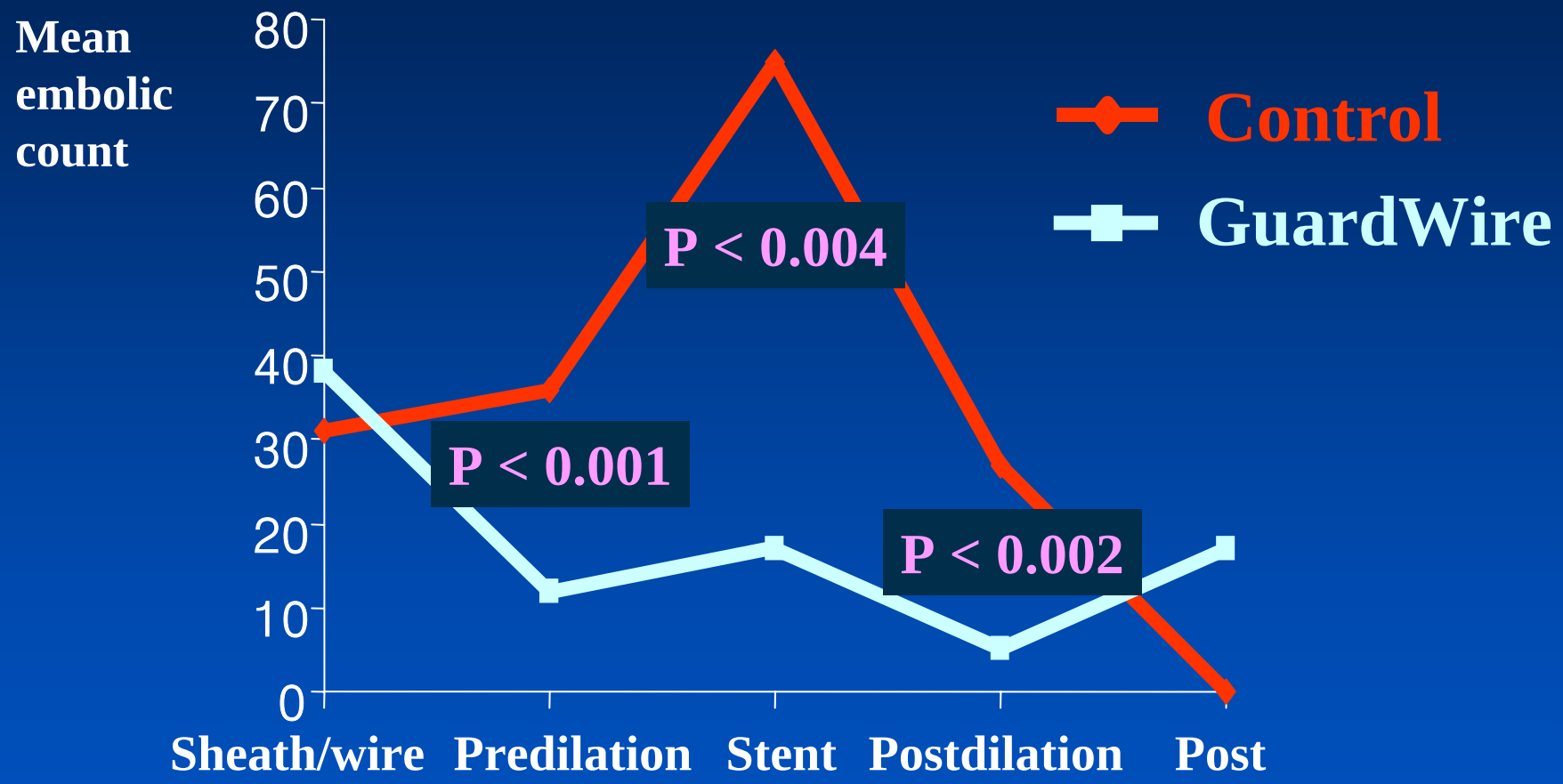


# Why Embolic Protection?



# Distal Occlusion Device

## PercuSurge GuardWire™



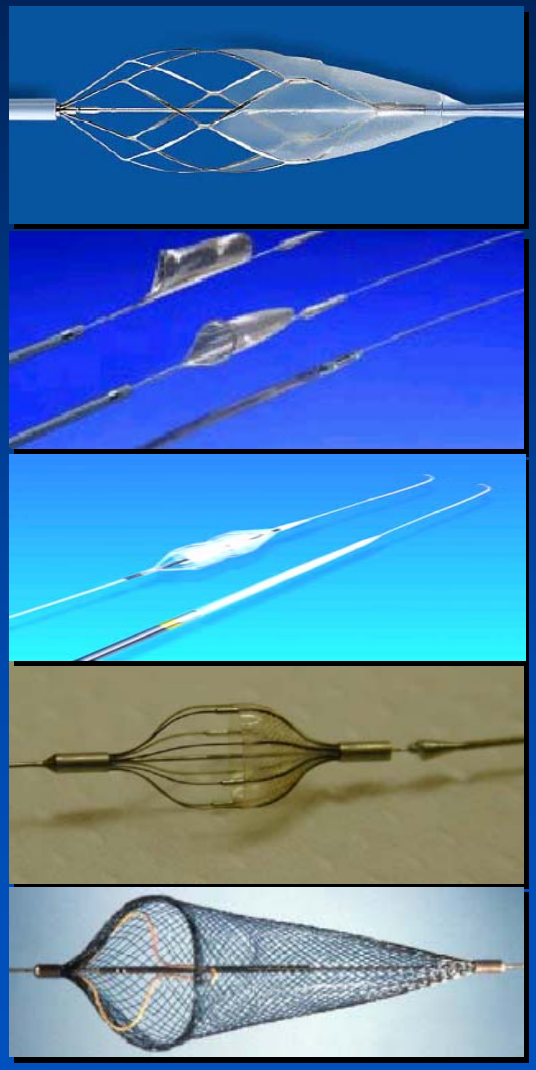

*Al-Mubarak et al, Circulation, 2001*

# Embolic Protection Device

## Distal Occlusion

*PercuSurge GUARDWIRE ™*

# Embolic Protection Devices (EPD)
## Filter



**Guidant - ACCUNET**

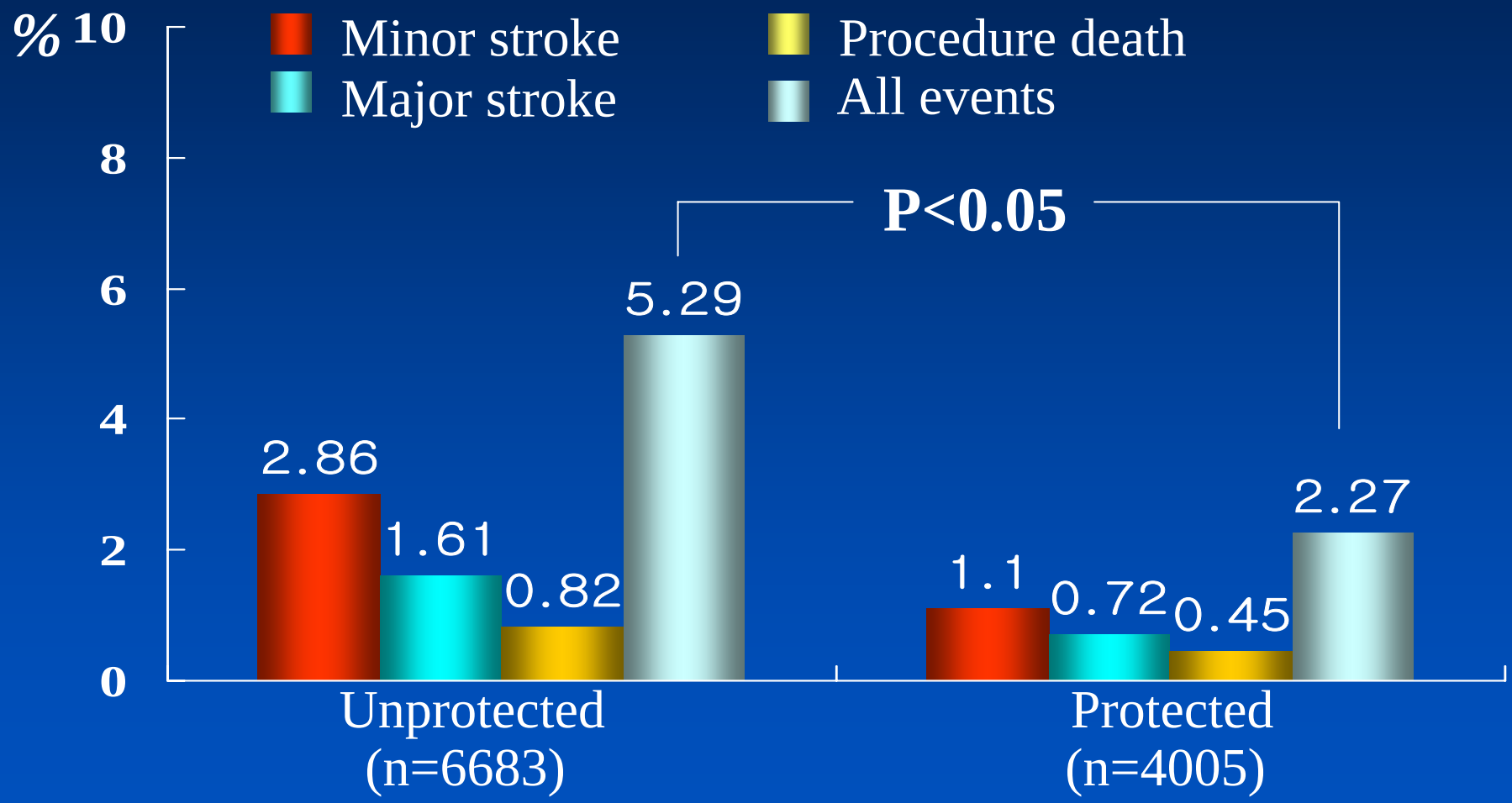
**BSC - FilterWire**

**ABBOTT - Emboshield**

**Cordis - Angioguard**

**EV3 - Spider**

# Benefit of Distal Protection
## Periprocedural Outcomes

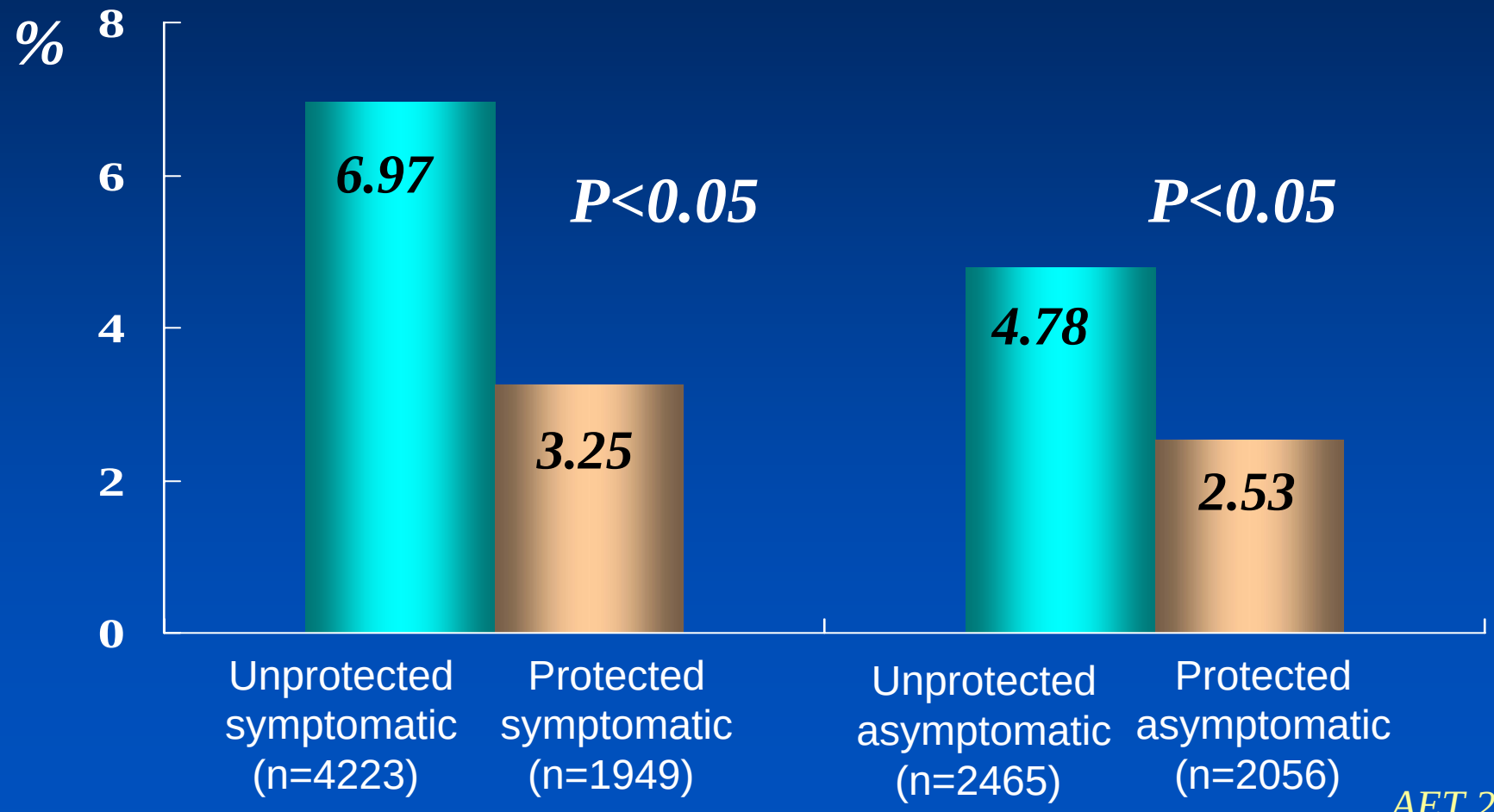



*AET 2003*

# Benefit of Distal Protection

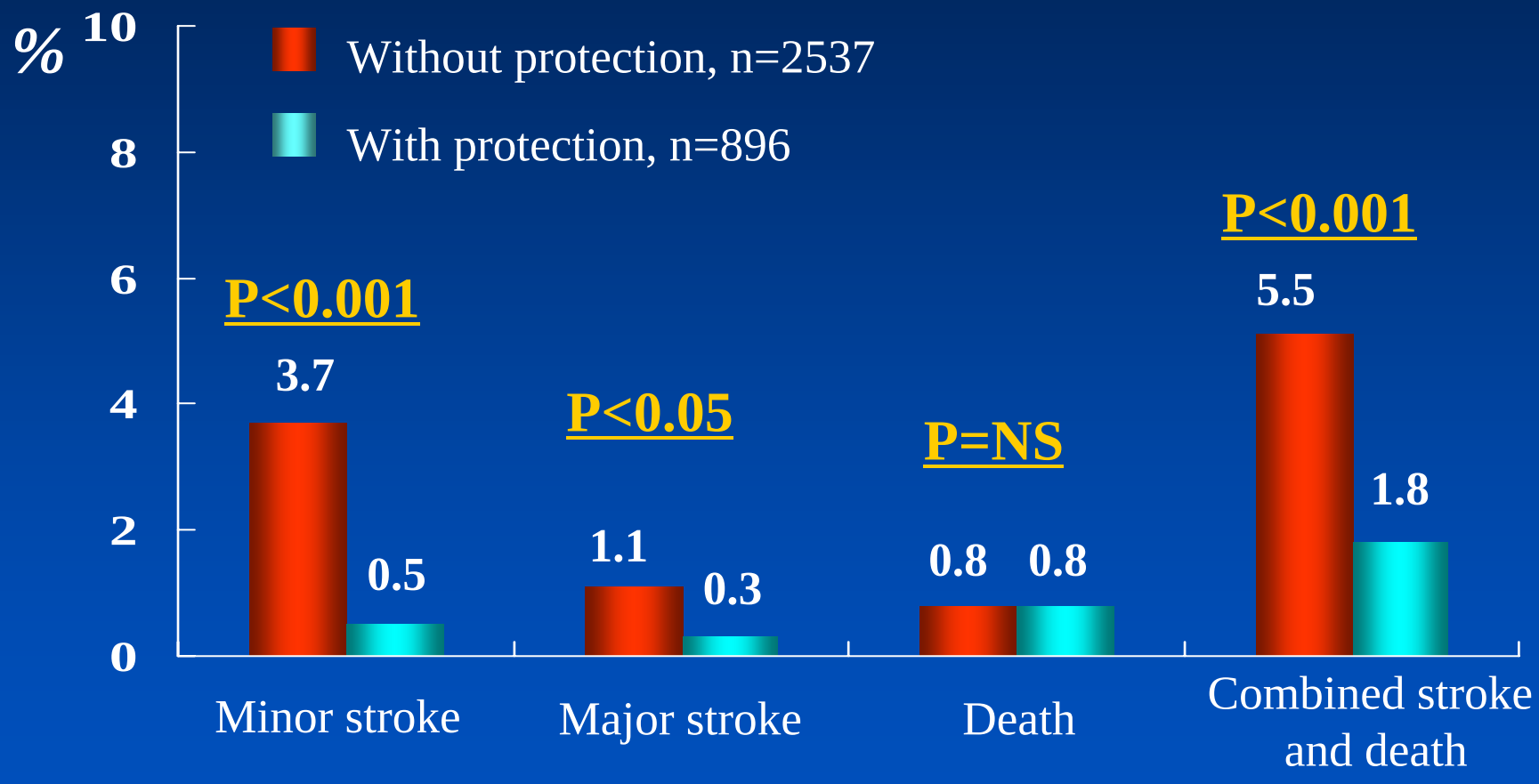
## Periprocedural Outcomes

### All cause death, major & minor stroke




*AET 2003*

# Benefit of Distal Protection
## 30-Day Outcomes




*Stroke 2003;34:813-819*

# Carotid Artery Stenting

## Current status

**Embolic protection device (EPD) is mandatory in CAS**

# Unended fight

# Carotid Endarterectomy

# vs.

# Carotid Stenting

# Carotid Stent Trial Data

## Pre-EPD

- Normal risk/randomized
  - WallStent trial-1999 (223)

## Post-EPD

- Normal risk/symptomatic and asymptomatic/randomized
  - CREST, ACT 1
- Normal risk/symptomatic/randomized
  - EVA-3S, SPACE, CAVATAS 2
- Normal risk/non-randomized
  - CARESS-2003 (143)
- High risk/randomized
  - SAPPHIRE-2002 (334)
- High risk/registry
  - SAPPHIRE-2002 (406)
  - ARCHeR-2003 (581)
  - SECuRITY-2003 (305)
  - BEACH-2004 (408)
  - CABERNET-2004 (454)
  - CREATE -2005 (413)

# US Carotid Stent Trials: pre-EPD

## Schneider Carotid Wallstent trial

- First randomized trial to compare stent (non-dedicated, tracheobronchial, no embolic protection) with CEA in ~200 patients
- A “normal risk” trial in symptomatic patients
- Stopped early as DSMB determined continued enrollment would not meet pre-specified endpoints

# Wallstent Trial Results (1997-1999)

| Event (1 year) | Stent (N=108) | Surgery (N=115) | Difference | P |
|---|---|---|---|---|
| Study-related death Or ipsilateral stroke | 12% (12/98) | 4% (4/91) | 7.8% | 0.067 |
| Study-related death | 6% (6/98) | 2% (2/91) | 3.9% | 0.28 |
| Ipsilateral stroke | 7% (6/92) | 3% (3/90) | 3.2% | 0.49 |
| Major | 2% (2/92) | 1% (1/89) | 1.1% | 1.00 |
| Minor | 2% (2/92) | 0% (0/89) | 2.2% | 0.49 |
| Undetermined | 2% (2/92) | 2% (2/90) | -0.0% | 1.00 |

# Schneider Carotid Wallstent Trial: Analysis

- No Phase I trial preceded this randomized effort
- Trial design flawed:
  - Power
  - Endpoints
- Operator training requirements were inadequate
- Non-dedicated equipment without embolic protection
- No PI or Executive Committee
  - As a result, after Schneider acquisition by BSC, continuity of trial conduct was disrupted
- Evolving technique and equipment represented a suboptimal environment for a randomized trial

# Symptomatic high surgical

# &

# Asymptomatic high surgical

# CAVATAS

## CEA vs. Angioplasty without protection in Low and High Surgical Risk group

| | Angioplasty N=251 | CEA N=253 |
|---|---|---|
| 30-day death & stroke | 6.4% | 5.9 % |
| Cranial neuropathy | 0 % | 8.7 % |
| 1-year restenosis (>70% DS)* | 14 % | 4 % |
| 3-year death or disabling stroke | 14.3 % | 14.2 % |

* Stenting = only in 26%

*Lancet 2001;357:1729-37*

# CES vs. CAS with Filter

From August 2000 to July 2002

**Carotid a stenosis with high risk (n=334)**

**Randomization (1:1)**

**Carotid Stenting with filter device (n=167)**

**Carotid endarterectomy (n=167)**

**Primary endpint: composite of death, stroke, or myocardial Infarction within 30 days or death or ipsilateral stroke btw 31days and 1 year**

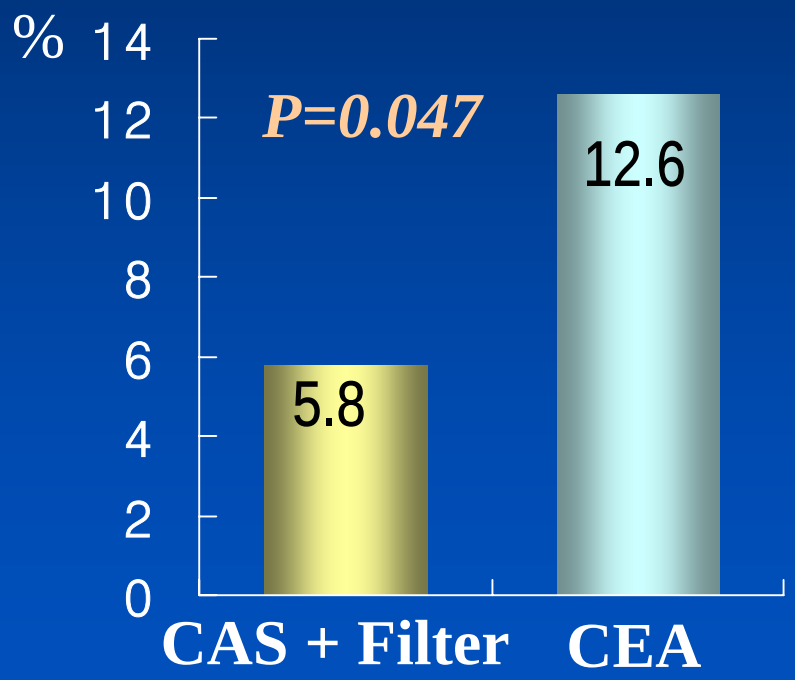
*Yadav JS, et al. NEJM 2004;351:1493*

SAPPHIRE

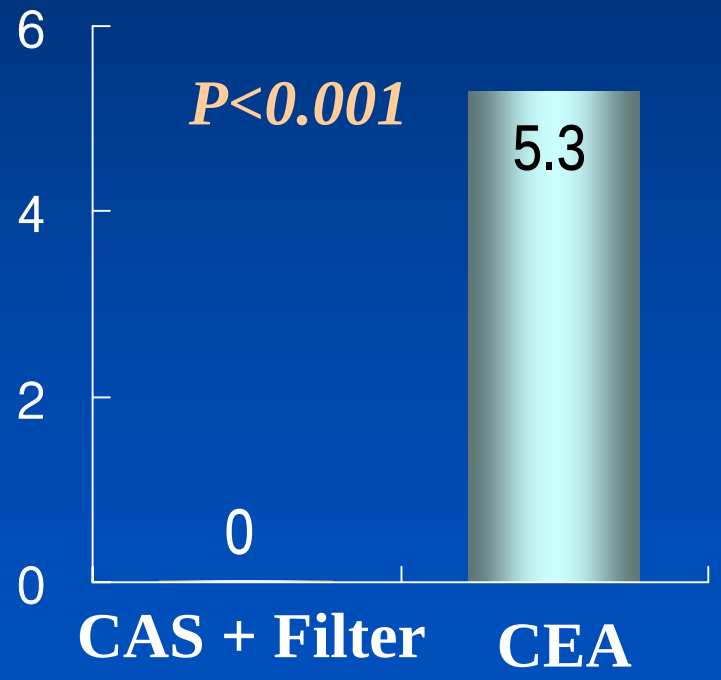
## CEA vs. CAS with Filter

# 30-Day Outcomes

### Death /MI /Stroke




### Cranial nerve palsy




*Yadav JS, et al. NEJM 2004;351:1493*

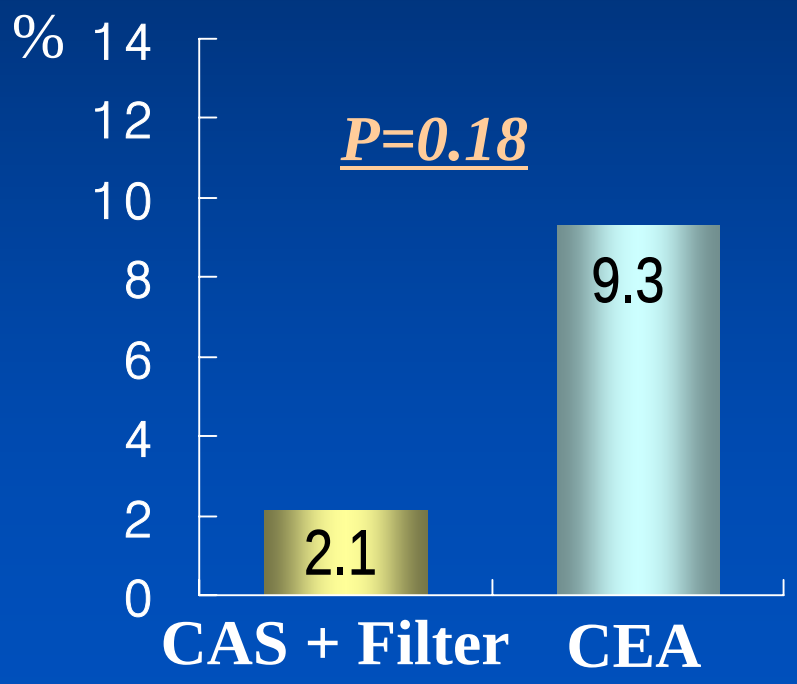
SAPPHIRE

## CEA vs. CAS with Filter

# 30-Day Outcomes

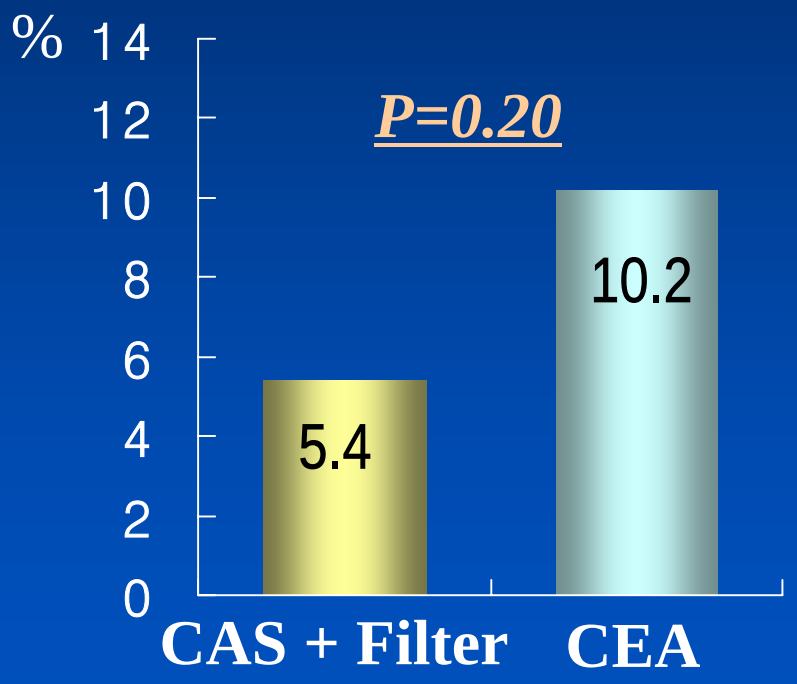
### Symptomatic patients

Death /MI /Stroke




### Asymptomatic patients

Death /MI /Stroke

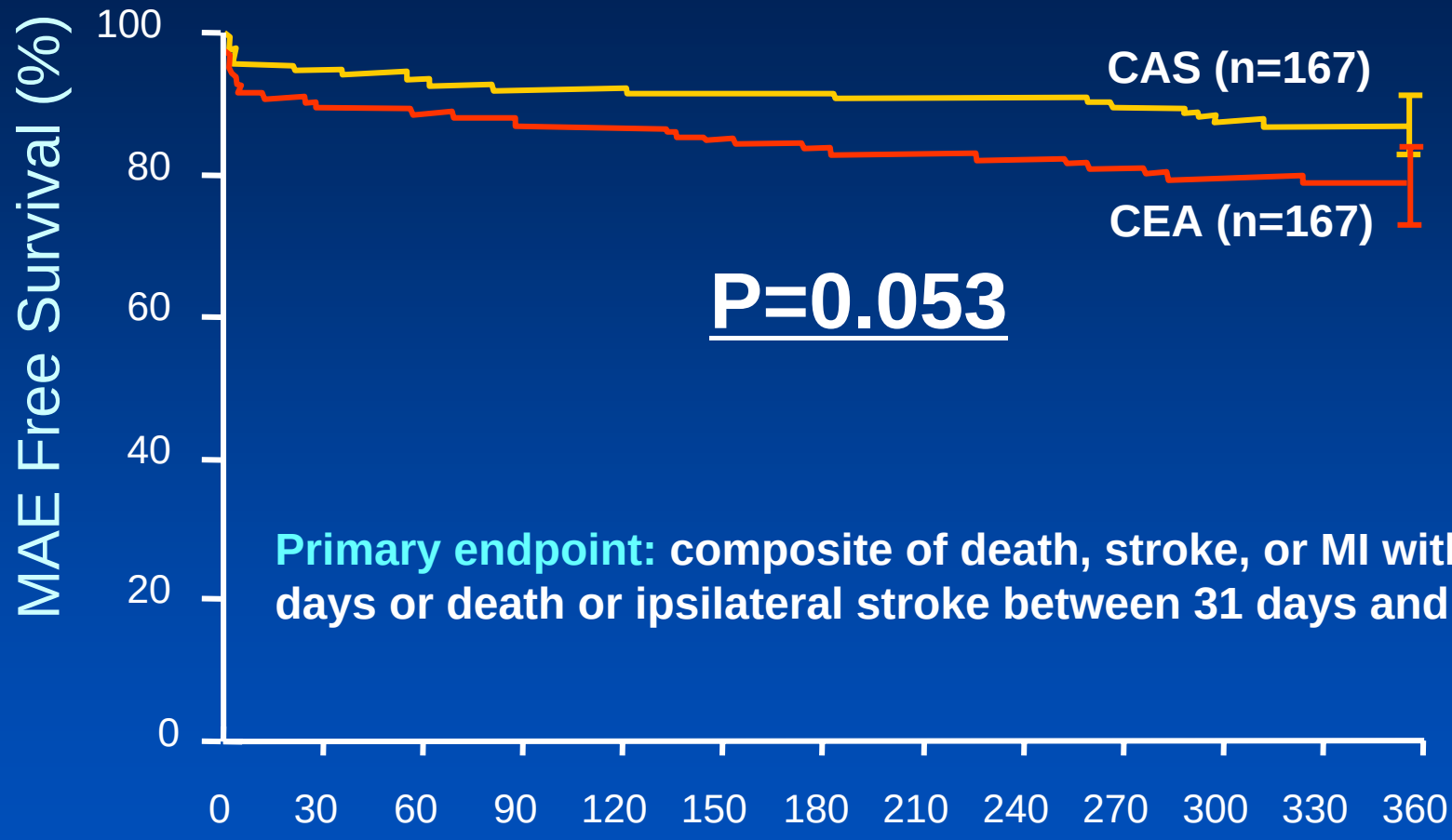



*Yadav JS, et al. NEJM 2004;351:1493*

CEA vs. CAS with Filter

SAPPHIRE

# 1-Year Clinical Outcomes




**Primary endpoint:** composite of death, stroke, or MI within 30 days or death or ipsilateral stroke between 31 days and 1 year

*Yadav JS, et al. NEJM 2004;351:1493*

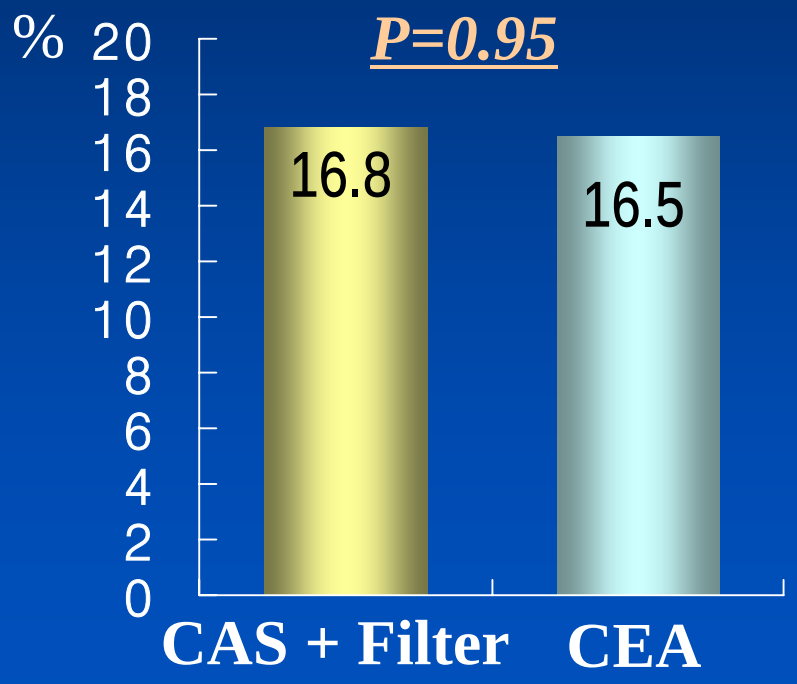
CEA vs. CAS with Filter

SAPPHIRE

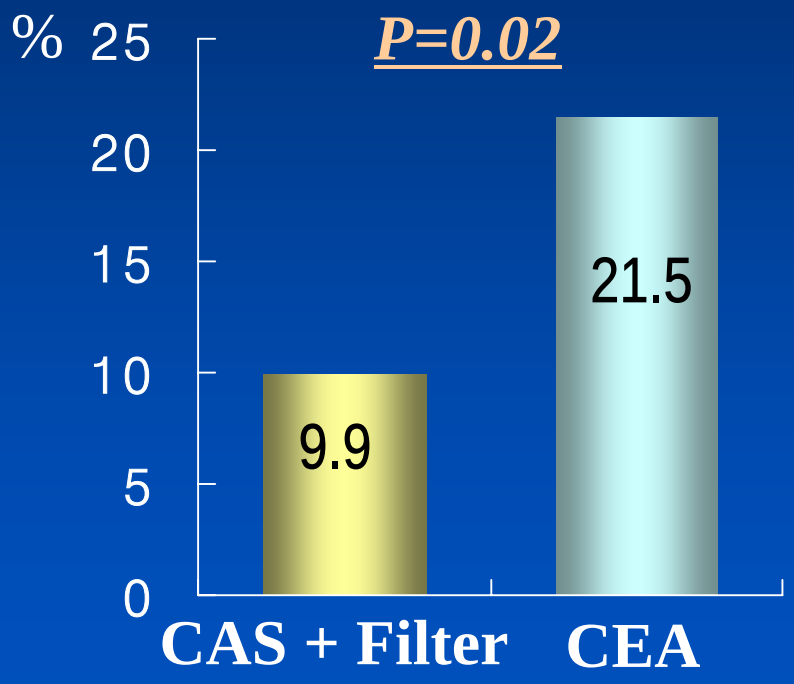
# 1-Year Clinical Outcomes

**Primary endpoint:** composite of death, stroke, or MI within 30 days or death or ipsilateral stroke between 31 days and 1 year

## Symptomatic patients



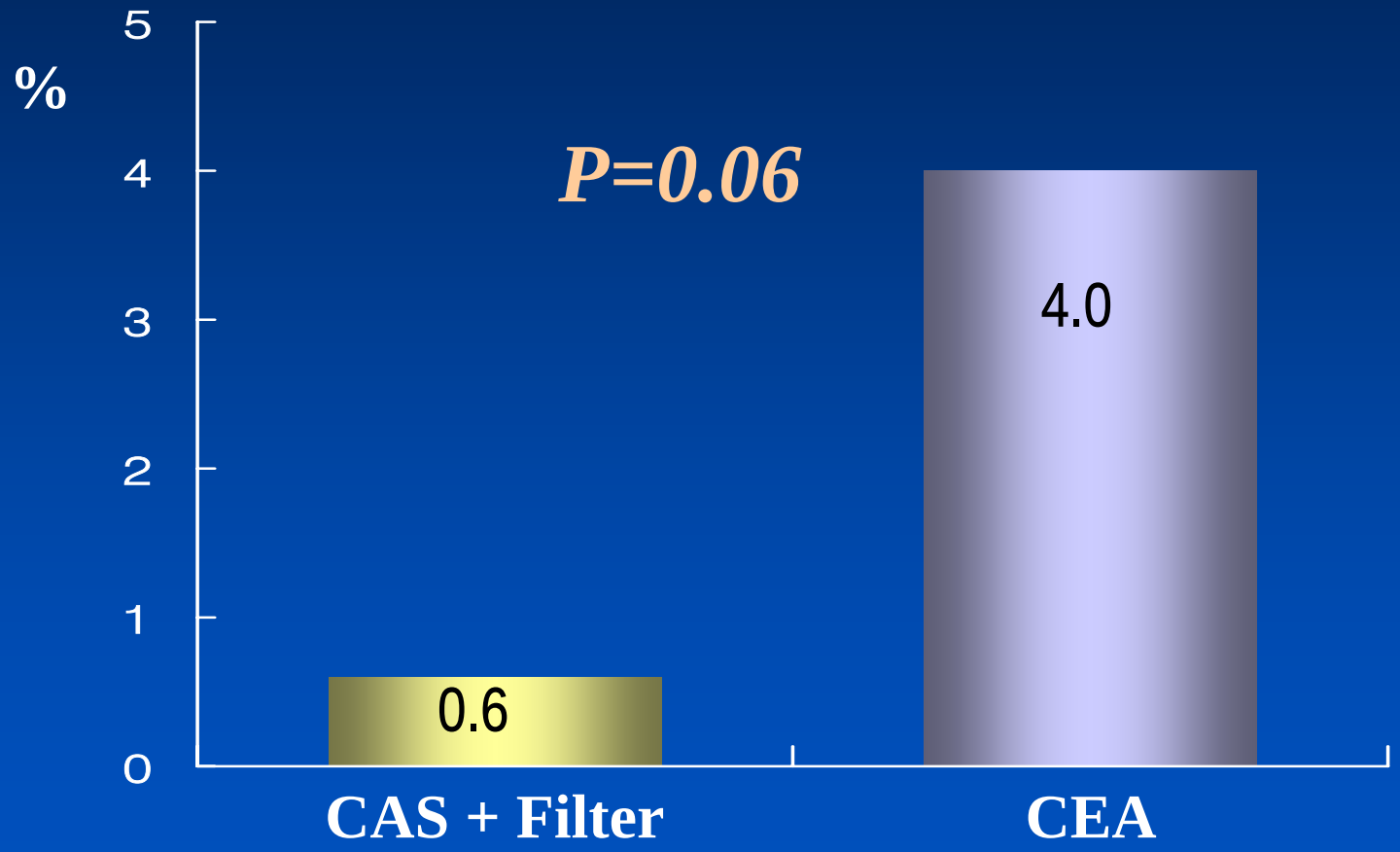

## Asymptomatic patients




*Yadav JS, et al. NEJM 2004;351:1493*

## CEA vs. CAS with Filter

# 1-Year TLR




*Yadav JS, et al. NEJM 2004;351:1493*

# Conclusion

- Among patients with severe carotid-artery stenosis and coexisting conditions, CAS with the use of an emboli-protection device is not inferior to CEA.

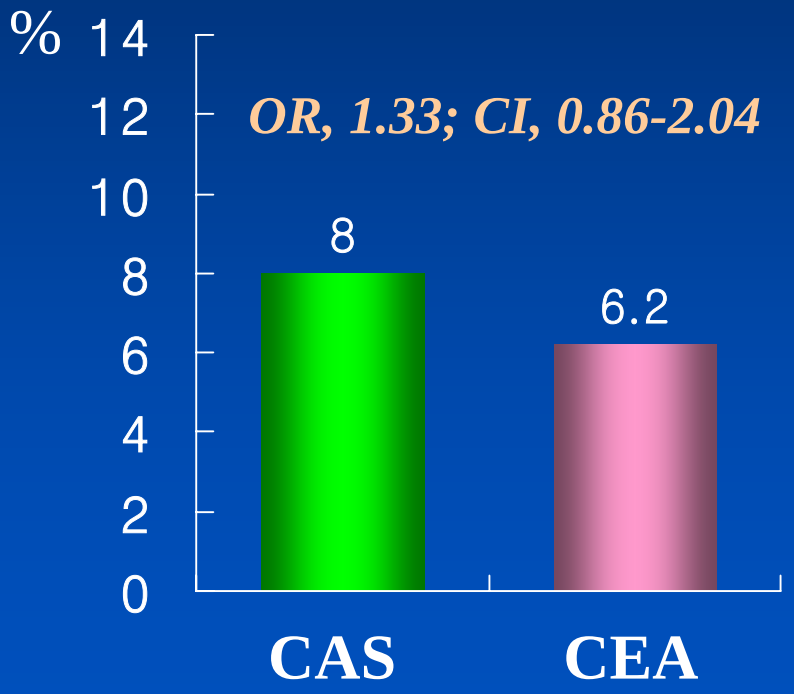
*Yadav JS, et al. NEJM 2004;351:1493*

# CEA vs. CAS with or without EPD

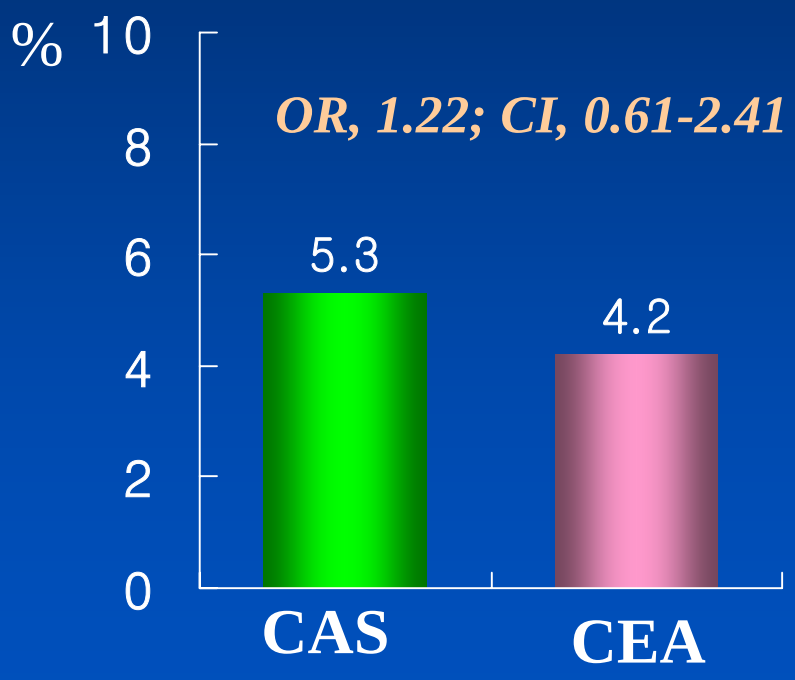
## 30 days outcomes from 5 RCT (n=1269)

**(CAVATAS, Kentucky A&B, Leicester, WALL STENT, SAPPHIRE)**

### Death / any stroke




### Death / disabling stroke



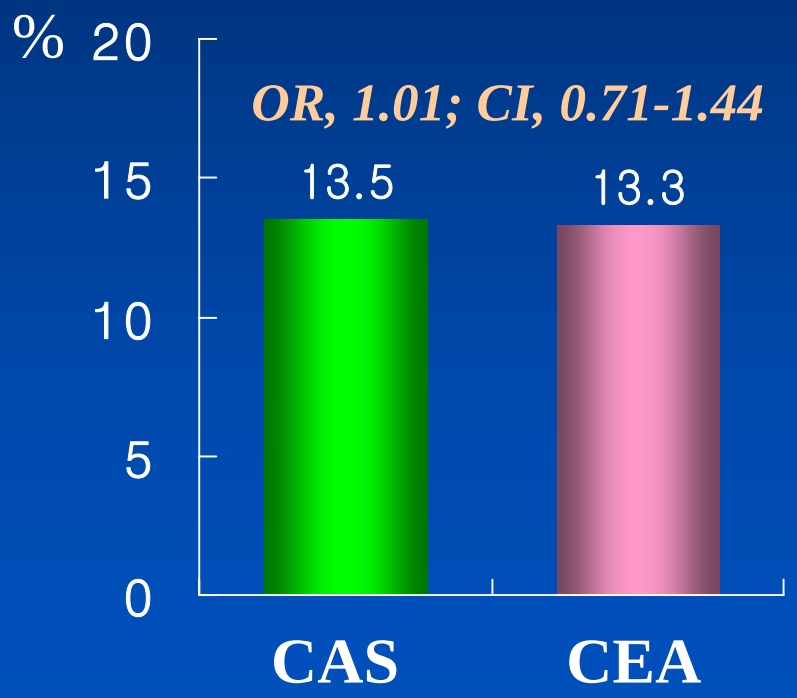

*Coward LJ, et al. Stroke 2005;36:905-911*

# CEA vs. CAS with or without EPD

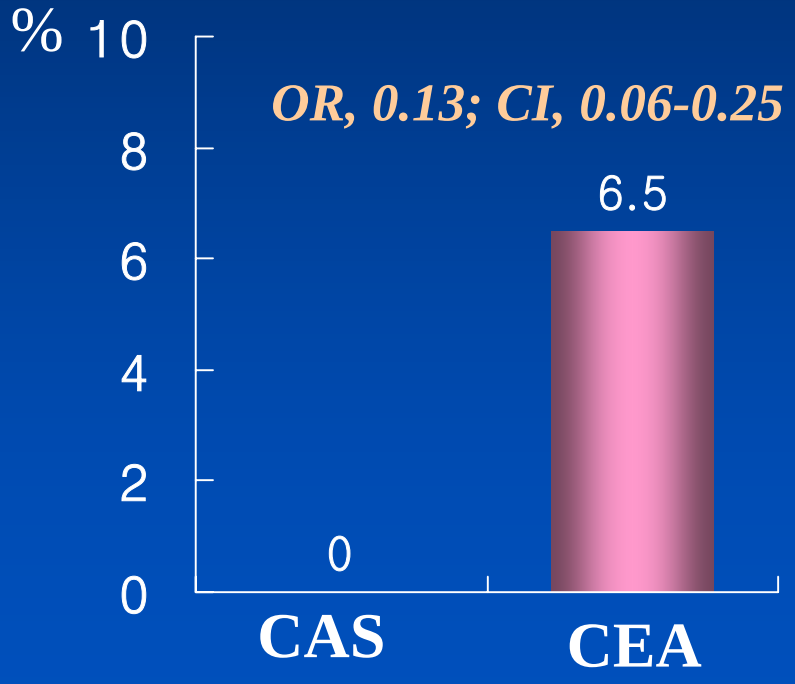
## Outcomes from 5 RCT (n=1269)

**(CAVATAS, Kentucky A&B, Leicester, WALL STENT, SAPPHIRE)**

### Death /any stroke @ 1 year




### Cranial nerve palsy




*Coward LJ, et al. Stroke 2005;36:905-911*

# CES vs. CAS with Accunet

**Multicenter, prospective, nonrandomized**

**Carotid a stenosis (n=581)**

**High-risk Sx & Asx patients**

**Carotid Stenting with Accunet (n=581)**

**Carotid endarterectomy (Historical control)**

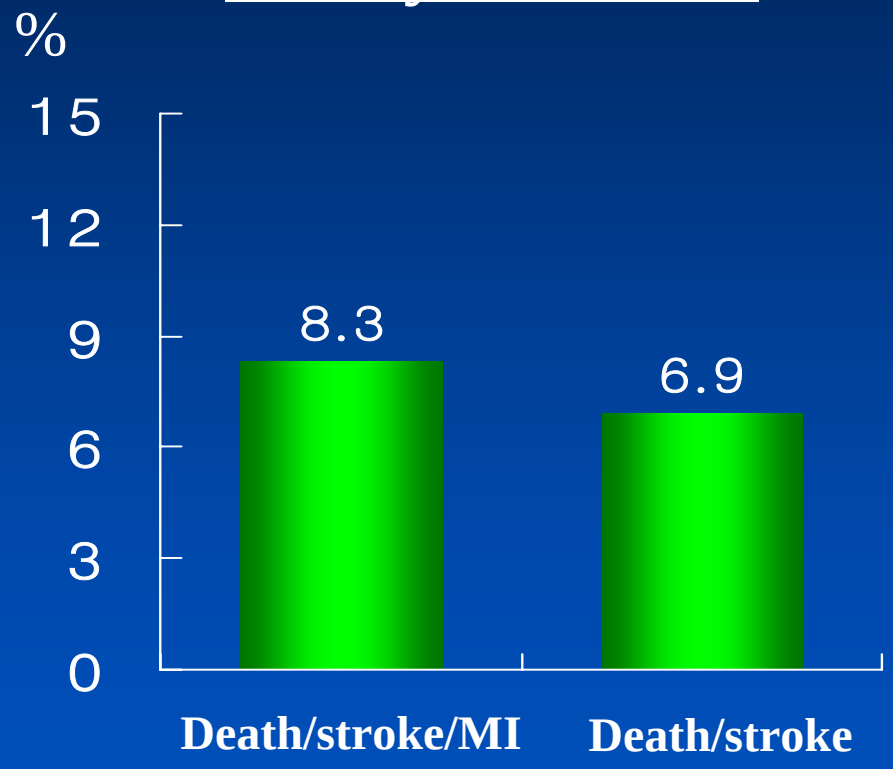
**Primary endpint:** composite of perprocedural death, stroke, or myocardial Infarction within 30 days, plus ipsilateral stroke btw 31days and 1 year

*Gray WA, et al. J Vasc Surg 2006;44:258-69*

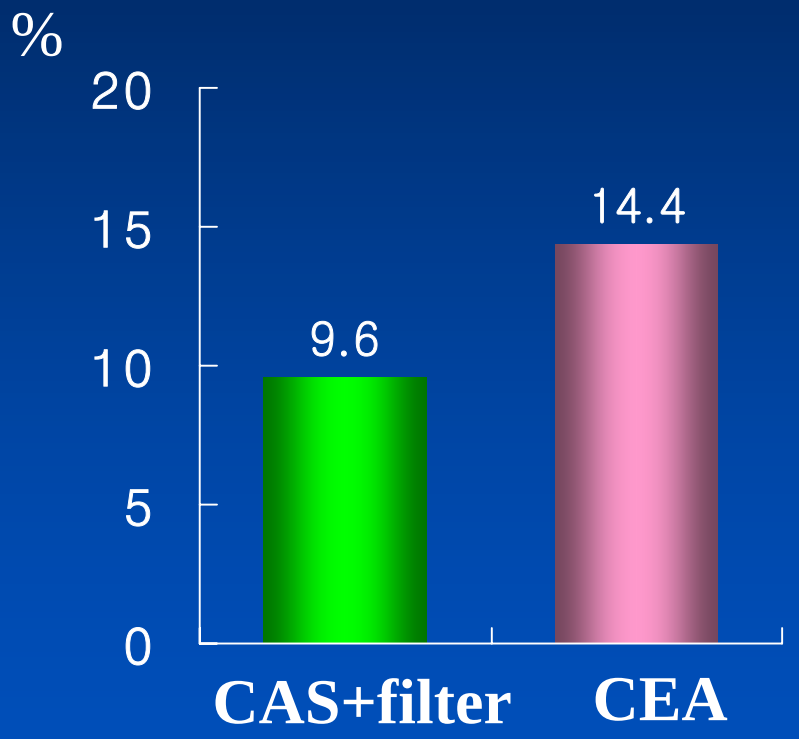
## CEA vs. CAS with Accunet

# 30-Day and 1-year Outcomes

### 30-day outcomes




### 1-year outcomes




**CAS + Filter**

*Gray WA, et al. J Vasc Surg 2006;44:258-69*

*Case-control study*

# CES vs. CAS with Filter

From 2001 to 2004

**Carotid a stenosis (n=602)**

**Concurrent-risk matched group**

**Carotid Stenting with filter device (n=301)**

**Carotid endarterectomy (n=301)**

**Perioperative and midterm results of CAS vs. CEA**

*Cao P, et al. Stroke 2006;37:1221-1226*

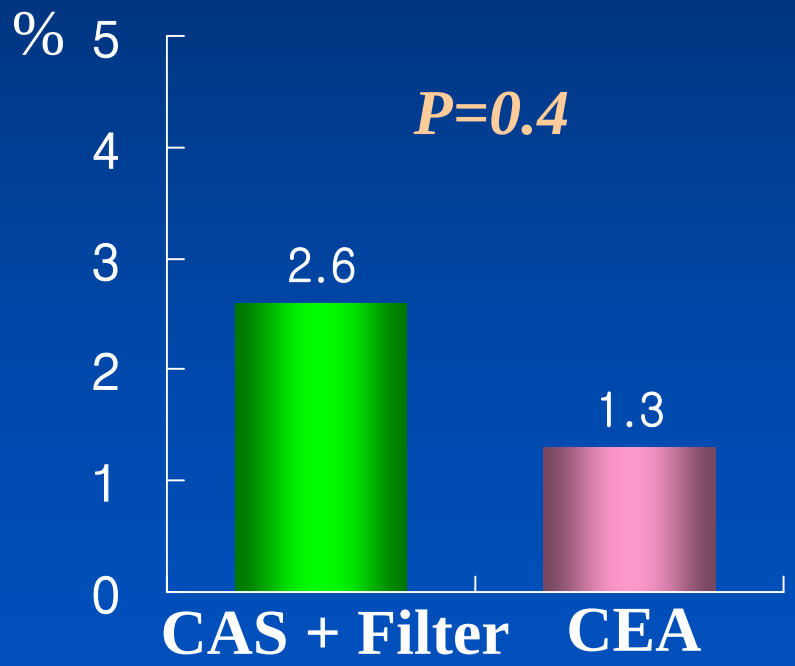
Case-control study

## CEA vs. CAS with Filter

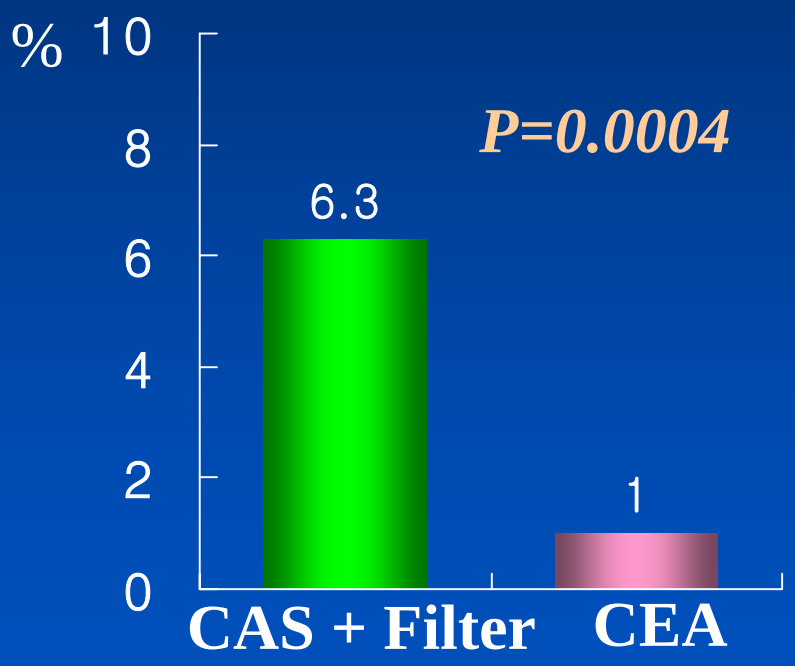
# 30-Day Outcomes

**50% of CAS disabling strokes occurred during cannulation of epiaortic vessel**

### Death / disabling stroke




### TIA




*Cao P, et al. Stroke 2006;37:1221-1226*

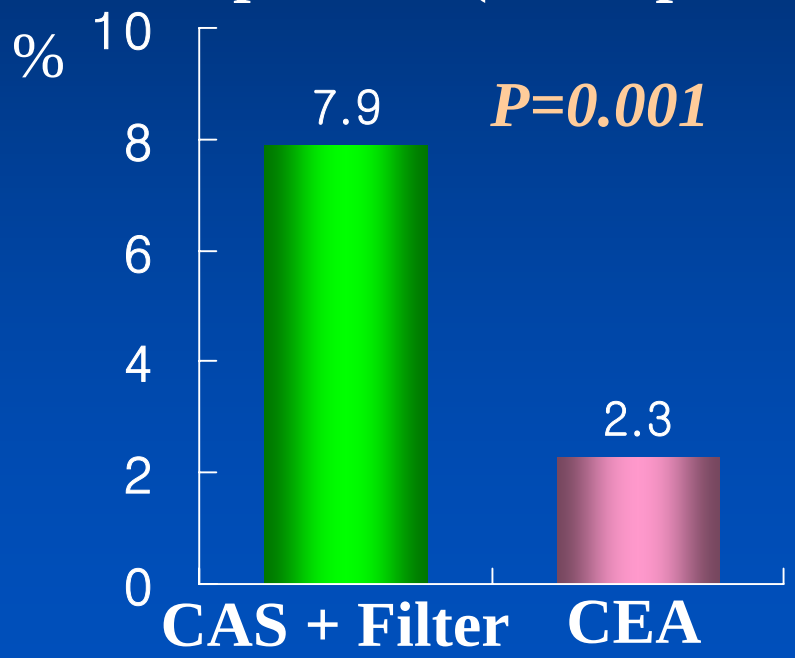
CEA vs. CAS with Filter

*Case-control study*

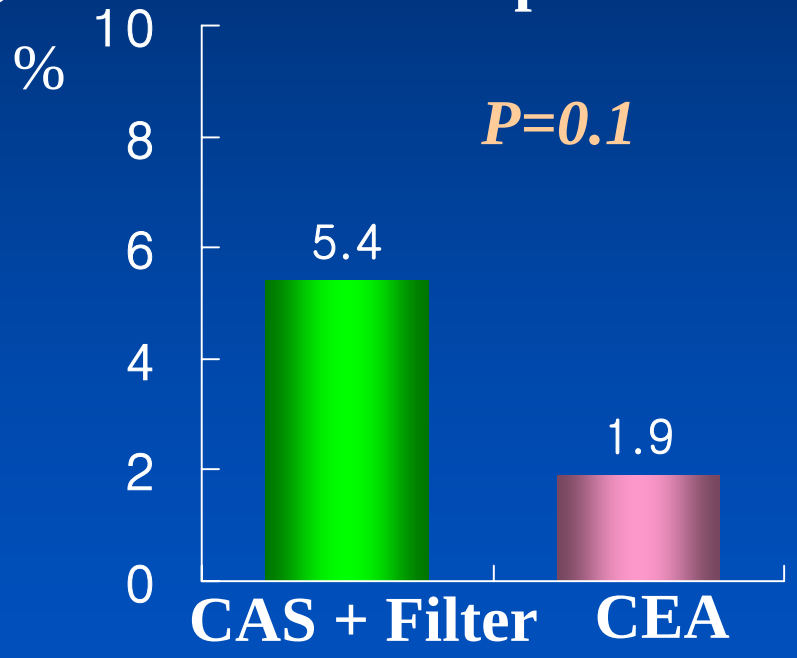
# 30-Day Outcomes

**A decreasing trend in 30-day stroke with expertise**

**Any stroke**
**All patients (n=301pts/arm)**




**Any stroke in**
**Last 201 pts/arm**

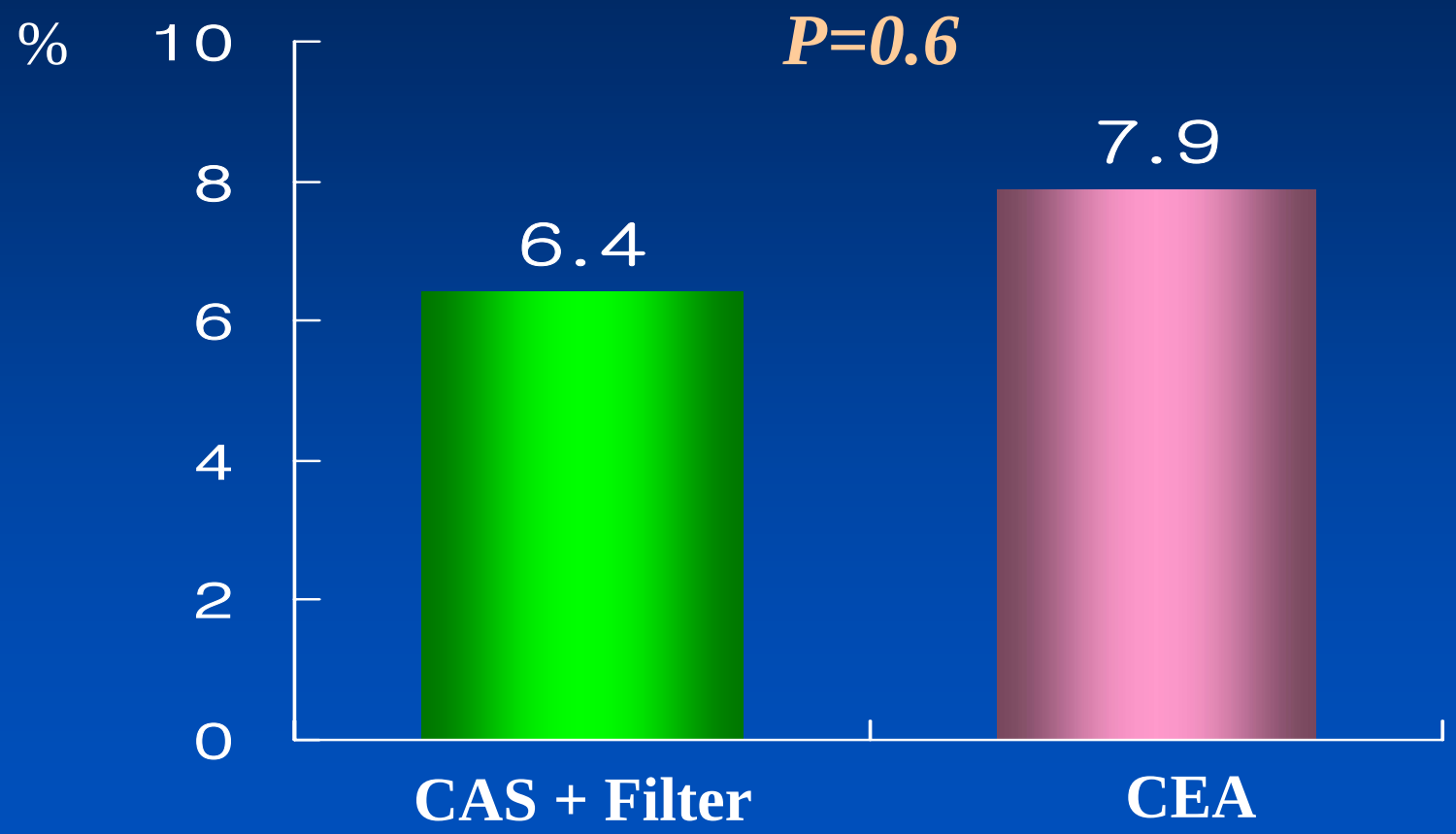



*Cao P, et al. Stroke 2006;37:1221-1226*

Case-control study

## CEA vs. CAS with Filter

# 36-Month restenosis




*Cao P, et al. Stroke 2006;37:1221-1226*

CEA vs. CAS with Filter

*Case-control study*

# Independent risk factors

| Predictors | Disabling stroke/death | Any stroke |
|---|---|---|
| CAS | HR 3.6 [0.93-13.9], p=0.06 | HR 3.9 [1.6-9.4], p=0.002 |
| Urgency | HR 8.9 [1.71-46.4], P=0.009 | HR 4.6 [1.2-18.6], P=0.03 |
| Diabetes | | HR 2.2 [1.01, 4.83], P=0.045 |
| Age | | HR 1.06 [1.01, 1.1], P=0.02 |

*Cao P, et al. Stroke 2006;37:1221-1226*

# AMC Experience

# Carotid Stenting in AMC

- From 04/2001’ to 04/2007’
- 103 consecutive patients (staged bilateral procedure in 5 patients)
- 108 lesions : bilateral stenting in 5 patients
- 103 severe (≥70% ) ICA stenosis
- 4 moderate (50-70%) ICA stenosis

# Baseline Characteristics

AMC

| Variables | N=103 |
|---|---|
| Age, years | 66.2±7.3 |
| Sex, men | 86 (79.6%) |
| Diabetes | 53 (49.1%) |
| Hypertension | 77 (71.3%) |
| Dyslipidemia | 32 (29.6%) |
| History of Smoking | 65 (60.2%) |
| History of IHD | 87 (80.6%) |
| Stable angina | 31 (28.7%) |
| Unstable angina | 48 (44.4%) |
| Recent or acute MI | 2 (1.9%) |
| Old MI | 9 (8.3%) |
| Congestive heart failure | 15 (13.9%) |
| Peripheral artery disease | 8 (7.4%) |
| Renal insufficiency | 12 (11.2%) |
| Chronic renal failure | 10 (9.3%) |
| End stage renal failure | 2 (1.9%) |
| Chronic obstructive pulmonary disease | 2 (1.9%) |

# Neurologic Status / Underlying Coronary & Carotid Disease

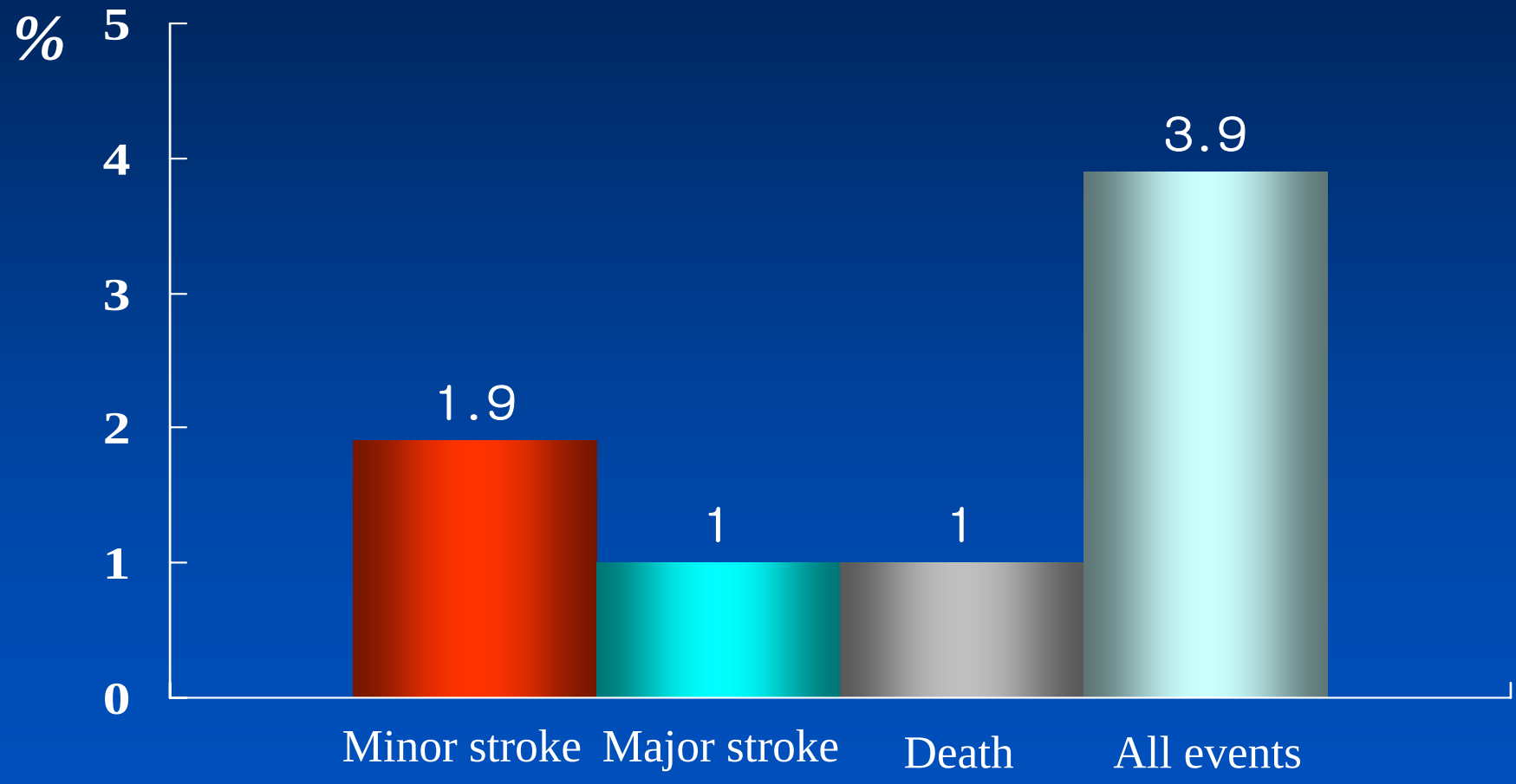
AMC

| Variables | N=103 |
|---|---|
| Prior history of CVA (>6months) | 27/103 (26%) |
| History of TIA | 6 |
| History of stroke | 21 |
| Symptomatic (<6months) | 34/103 (33%) |
| Amaurosis fugax | 3 |
| TIA | 11 |
| Minor stroke | 1 |
| Major stroke | 19 |
| Bilateral carotid stenosis (≥50%) | 34/103 (33%) |
| Target lesion | |
| Rt. ICA | 59 |
| Lt. ICA | 47 |
| Both ICA | 5 (4.9%) |
| Severe CAD requiring revascularization | 83/103 (81%) |

AMC

# 30-day outcomes

## Death/MI/Stroke

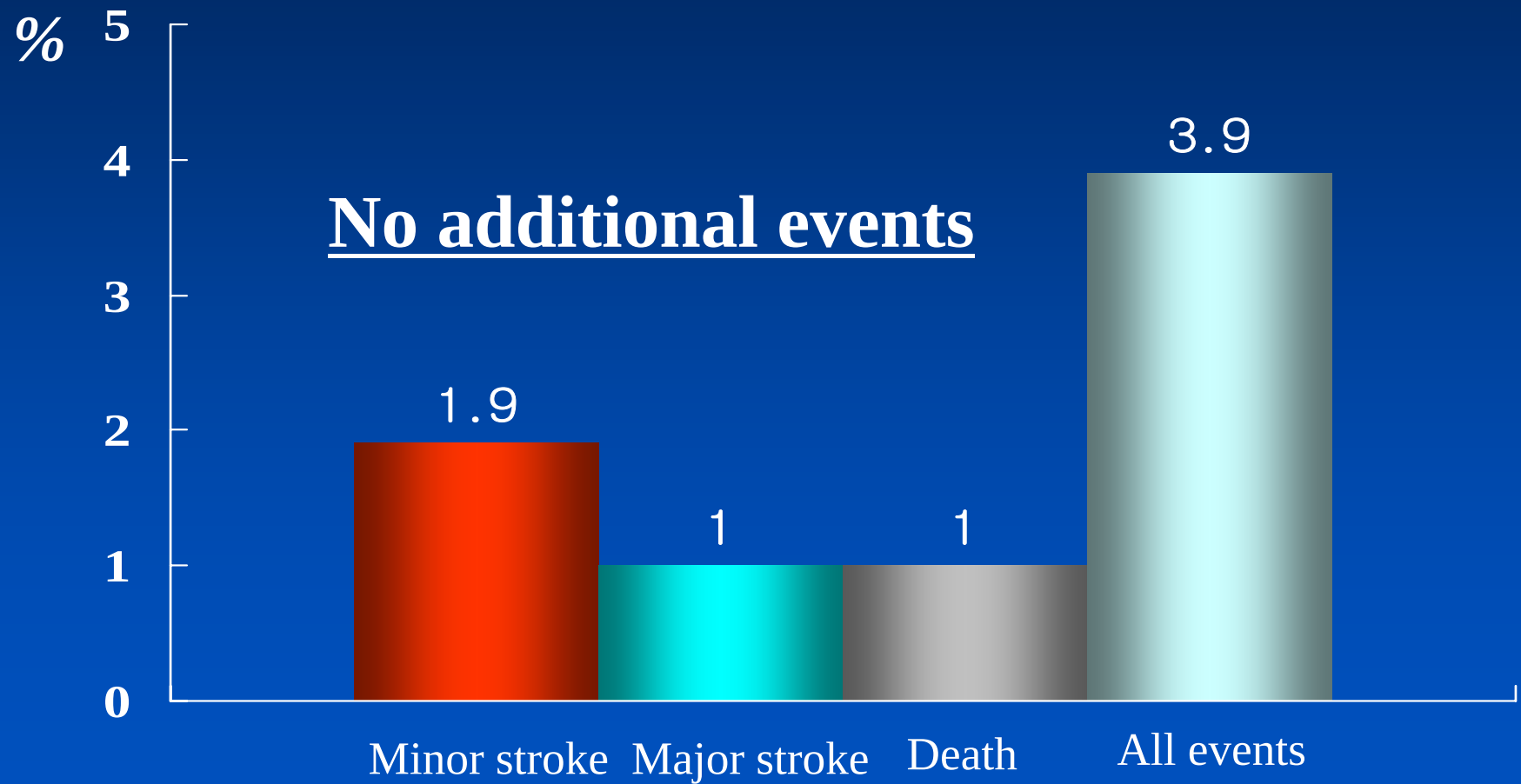


AMC

# Long-term outcomes

## Death/Stroke

**Follow-up duration : mean 14.5±13.7 months**

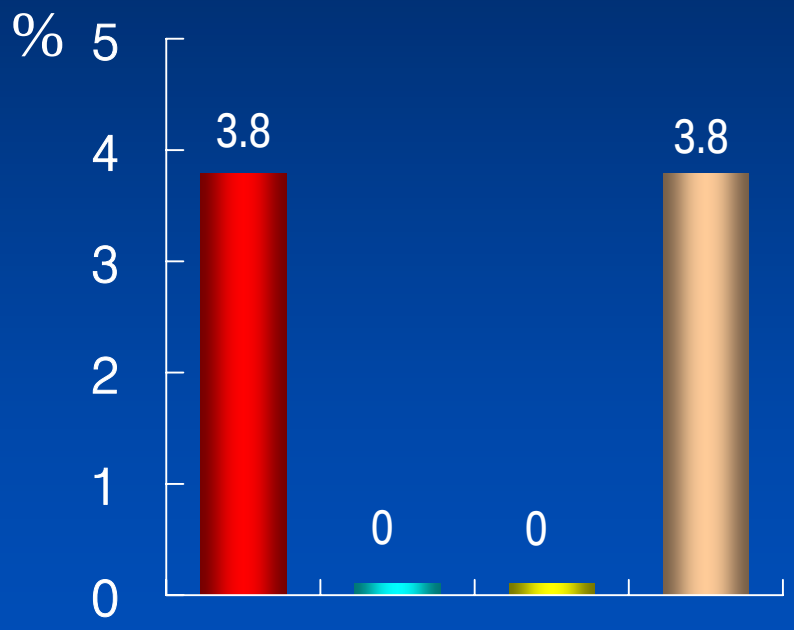


AMC

# 30-Day Outcomes

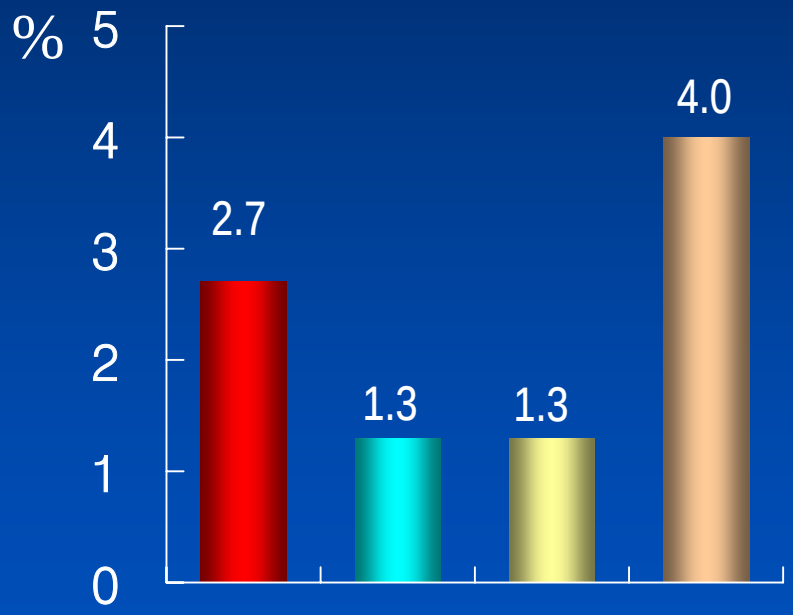
## Symptomatic (n=28)

### Death/Stroke




## Asymptomatic (n=75)

### Death/Stroke



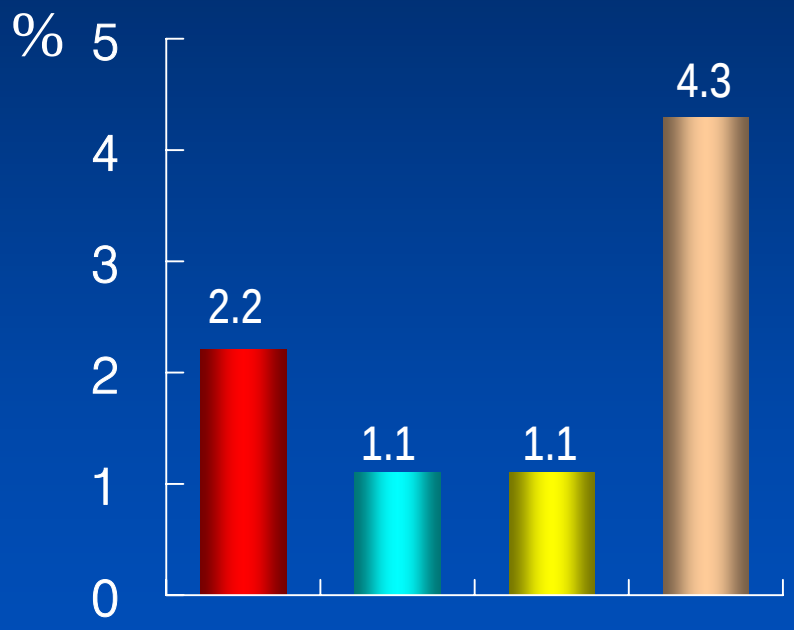

Minor stroke
Major stroke
Death
All events

AMC

# 30-Day Outcomes

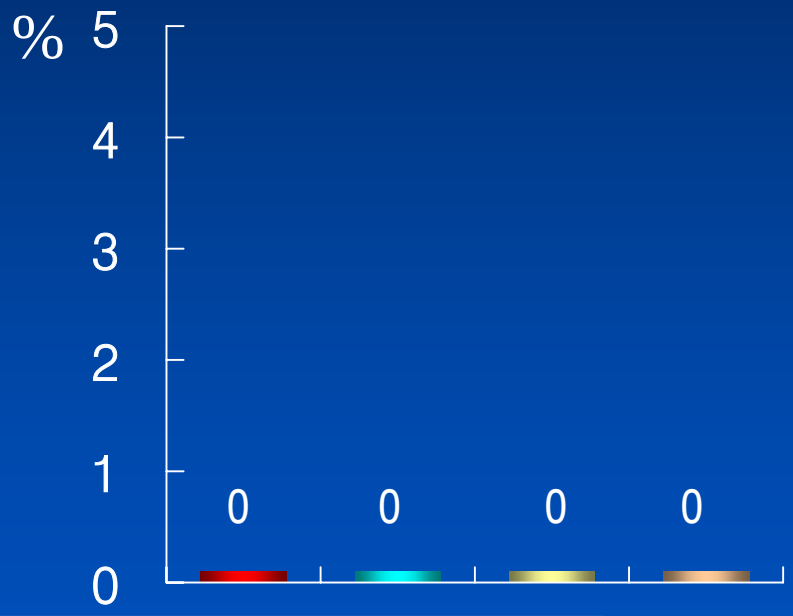
## High risk (n=93)

### Death/Stroke



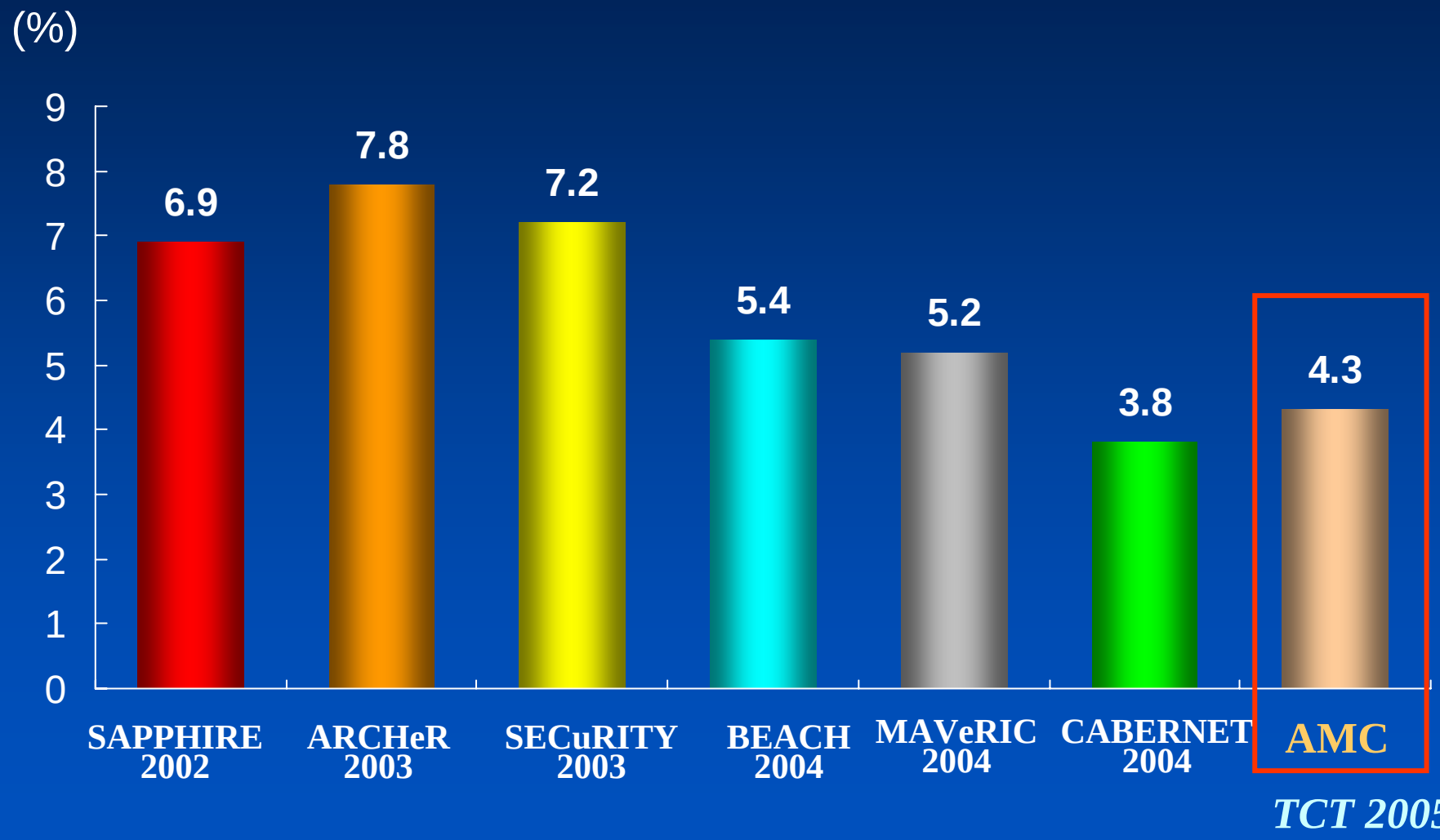

## Normal risk (n=10)

### Death/Stroke




Minor stroke
Major stroke
Death
All events

# 30 Day Stroke/Death/MI in high risk Registry




*TCT 2005*

# Symptomatic normal risk

# &

# Asymptomatic normal risk

CaRESS

# CES vs. CAS with GuardWire

**Multicenter, prospective, nonrandomized 1:2 ratio**

**Carotid a stenosis (n=397)**

**Normal-risk Sx & Asx patients**

**Carotid Stenting with GuardWire (n=143)**

**Carotid endarterectomy (n=254)**

**Primary endpint:** death and stroke at 30 days and a composite of death, stroke, or myocardial Infarction within 30 days and death or stroke btw 31days and 1 year

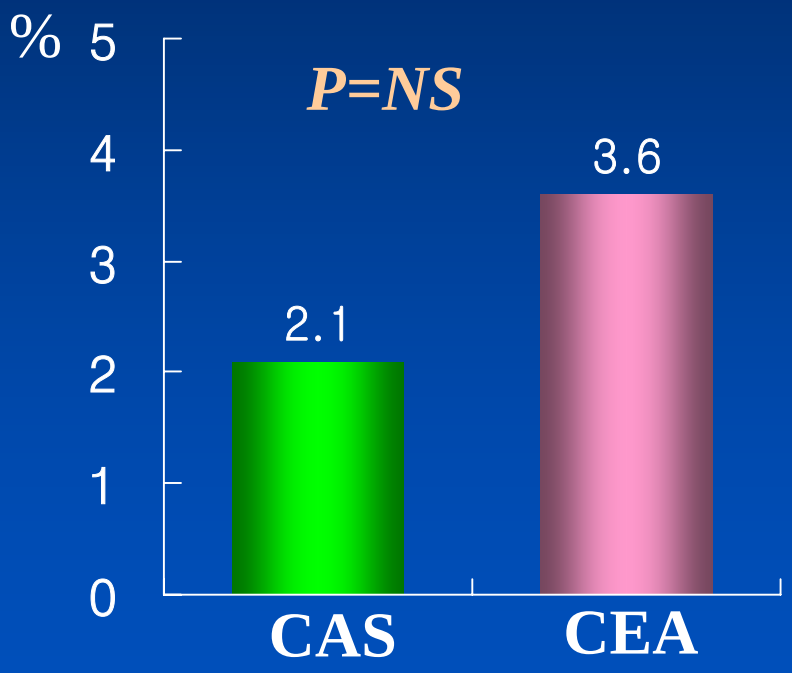
*J Vasc Surg 2005;42:213-9*

CaRESS

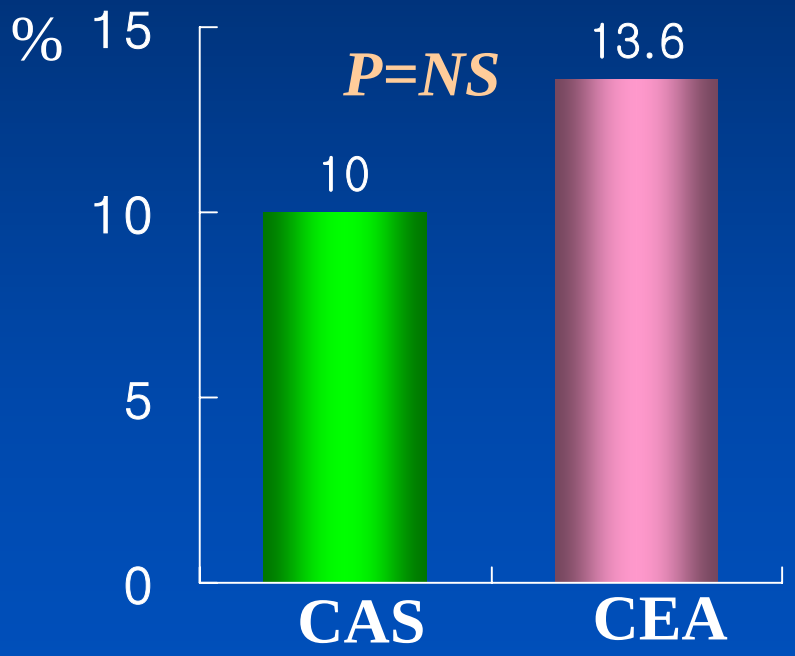
## CEA vs. CAS with GuardWire

# 30-Day and 1-year Outcomes

### Death / stroke at 30 days




### Death / stroke at 1 year




*J Vasc Surg 2005;42:213-9*

# CEA vs. CAS

From November 2000 to September 2005

**Symptomatic carotid stenosis of 60% or more**

**N=527**

**CEA (n=259)**

**CAS (n=261)**

**Primary end point: incidence of <u>any stroke or death</u> within 30 days after treatment**

*NEJM 2006;355:1660-71*

# Major eligibility Criteria

## Inclusion criteria

- Age ≥18yrs
- Hemispheric or retinal transient ischemic attack or nondisabling stroke (or retinal infarct) within 120 days before enrollment
- Stenosis ≥ 60%

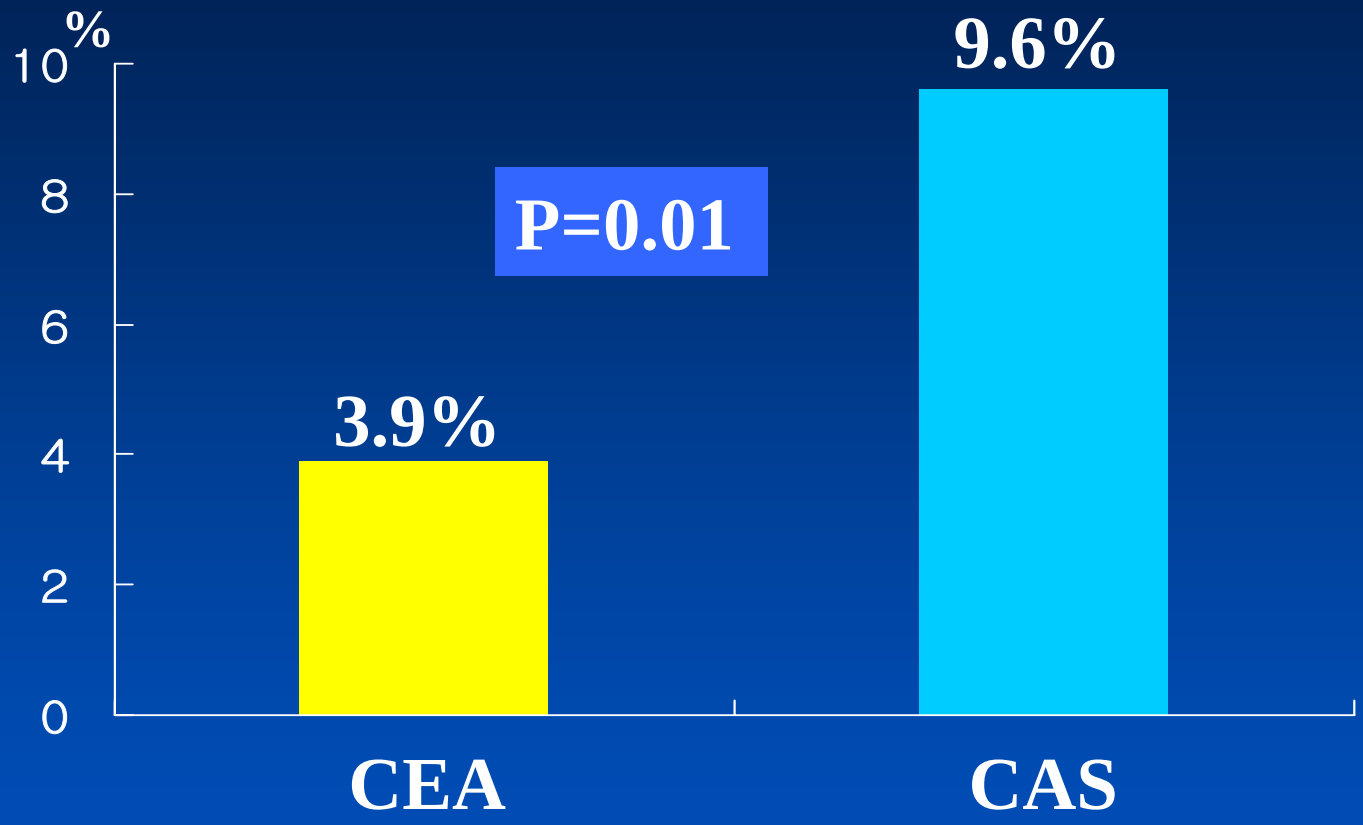
  in symptomatic carotid artery

## Exclusion criteria

- Modified Rankin S ≥ 3
- Severe tandem lesion
- Previous Hx. (CEA,CAS)
- Uncontrolled HT or DM
- Unstable angina
- Contra-Ix. of heparin, clopidogrel
- Hx. of bleeding disorder
- Life expectancy < 2yr

EVA-3S

# 30-Day Outcomes

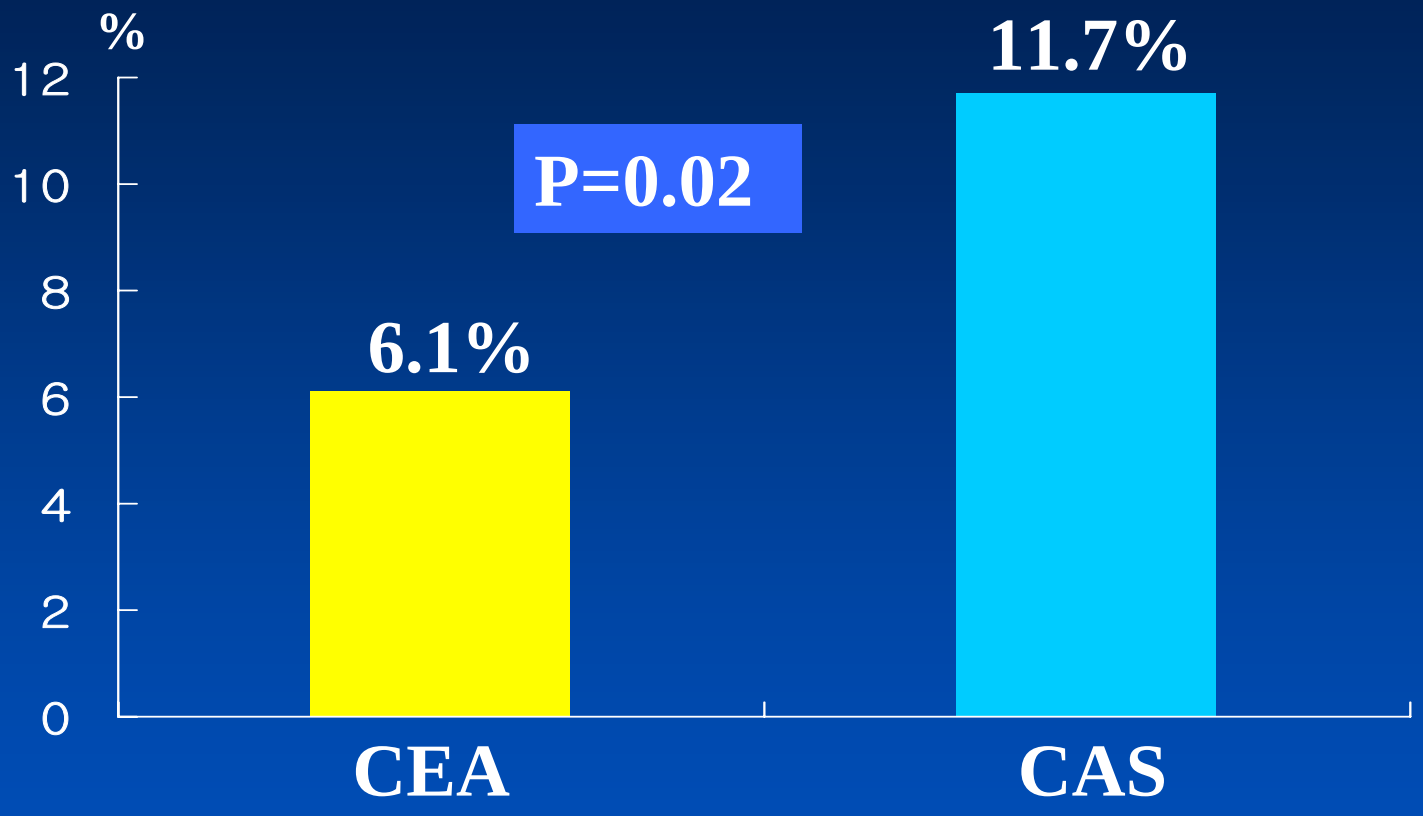



**Relative risk: 2.5 (95% CI, 1.2 to 5.1)**

*NEJM 2006;355:1660-71*

EVA-3S

# 6 Months Events




**Events: any stroke or death after treatment**

*NEJM 2006;355:1660-71*

# Conclusion

In patients with symptomatic carotid stenosis of 60% or more, the rates of death and stroke at 1 and 6 months were lower with endarterectomy than with stenting

*NEJM 2006;355:1660-71*

# Limitation

- Early in the EVA-3S trial, protection from embolism was not used among patients who underwent stenting, and the incidence of stroke was 25% (5 of 20).

  -Protection device was used in 91.9% of carotid stenting arm.

- Learning curve for carotid stenting; Involved center had a variable degree of experience in CAS.

  -Five different stents, seven different protection devices, and experience with two procedures was required for any new device used.

*NEJM 2006;355:1660-71*

# Limitation

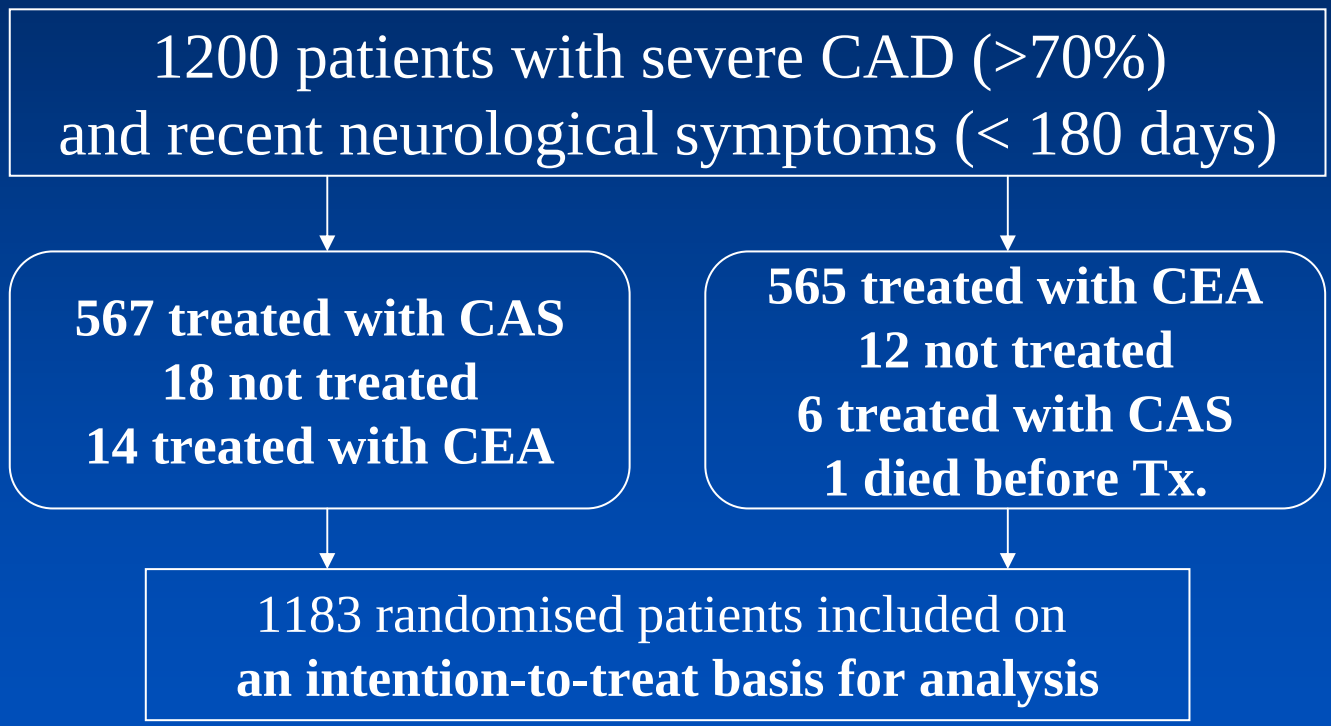
- Although the angiographic appearance of the lesion was not an eligibility criterion, plaque morphology (length, degree of ulceration, and presence or absence of thrombus) could be related to complication rates for stenting.

- 42 and 36 patients who underwent stenting in the EVA-3S trial received only single (unspecified) antiplatelet therapy before and after the procedure, respectively.

*NEJM 2006;355:1660-71*

# 30 days results from SPACE trial in symptomatic patients

## Randomized non-inferiority trial




*Lancet 2006;368;1239-47*

## Primary endpoint

Ipsilateral stroke (ischemic stroke or intracerebral bleeding or both , with symptoms lasting more than 24 hr) or death of any cause between randomization and 30 days after Treatment.

## Null hypothesis

The difference between the events rates in CAS and CEA group was 2.5% or more.

## Non-inferiority margin

defined as less than 2.5%

on the basis of an expected event rate 5%

*Lancet 2006;368;1239-47*

# Outcome events up to 30 days

| | Number (%) | | Absolute diff. | Odds ratio |
|---|---|---|---|---|
| | CAS (n=599) | CEA (n=584) | CAS-CEA (90% CI) | CAS/CEA (95% CI) |
| Primary endpoint | 41 (6.84%) | 37 (6.34%) | 0.51* (-1.89 to 2.91) | 1.09 (0.69 to 1.72) |
| Ipsilateral ischemic stroke | 39 (6.51%) | 30 (5.14%) | | 1.26 (0.77 to 2.18) |
| Ipsilateral intra-cerebral bleeding | 1 (0.71%) | 5 (0.86%) | | 0.19 (0.004 to 1.74) |
| Death | 4 (0.67%) | 5 (0.86%) | | 0.78 (0.15 to 3.64) |

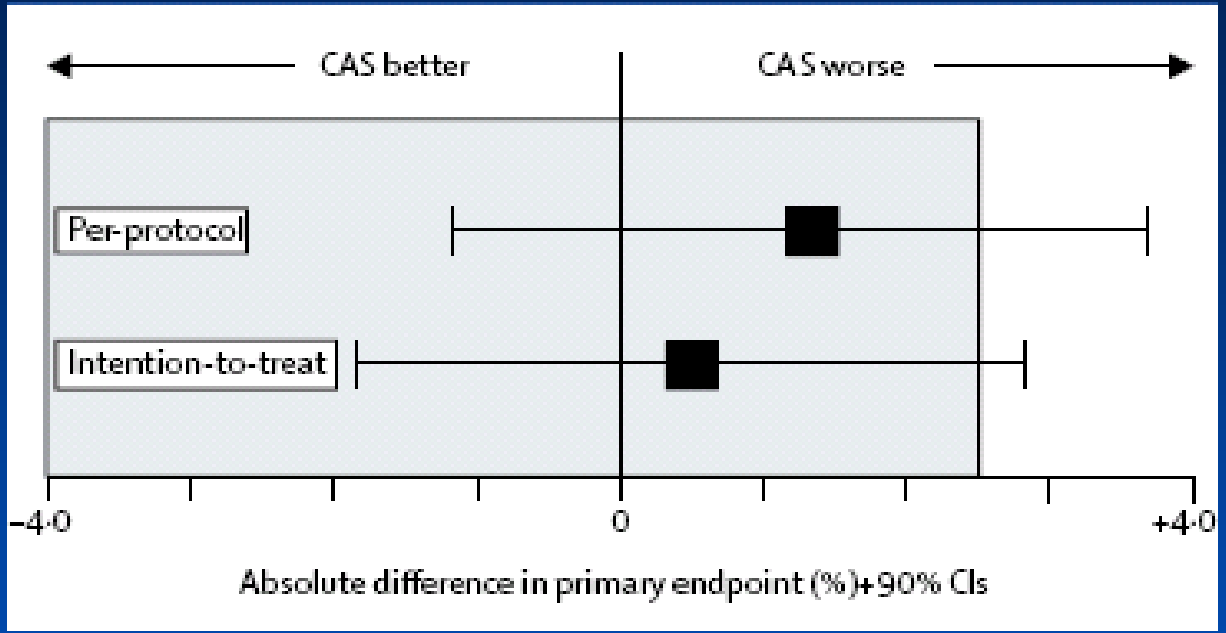
***One-sided p value for non-inferiority is 0.09**

# Conclusion

- SPACE failed to prove non-inferiority of CAS compared with CEA for the periprocedural complication rate.
- Results at 6-24 months are awaited

*Lancet 2006;368;1239-47*

# Limitation of SPACE trial




**Actual difference (90% CI) for primary endpoint in SPACE** Because upper CI is more than 2.5, study has failed to show non-inferiority for carotid angioplasty and stenting (CAS). However, because CIs cross zero, diff erence in primary outcome between carotid endarterectomy and carotid angioplasty and stenting was not statistically significant.

*Lancet 2006;368;1239-47*

# Limitation of SPACE trial

- Only 27% (n=151) of patients used embolic protection devices
- The difference between the two treatments is very small and many people might feel that a difference of only four events in almost 600 patients per group is negligible

*Lancet 2006;368;1239-47*

# Limitation of SPACE trial

- Despite SPACE being the biggest trial to date, one is left with the unavoidable conclusion that it was stopped prematurely.

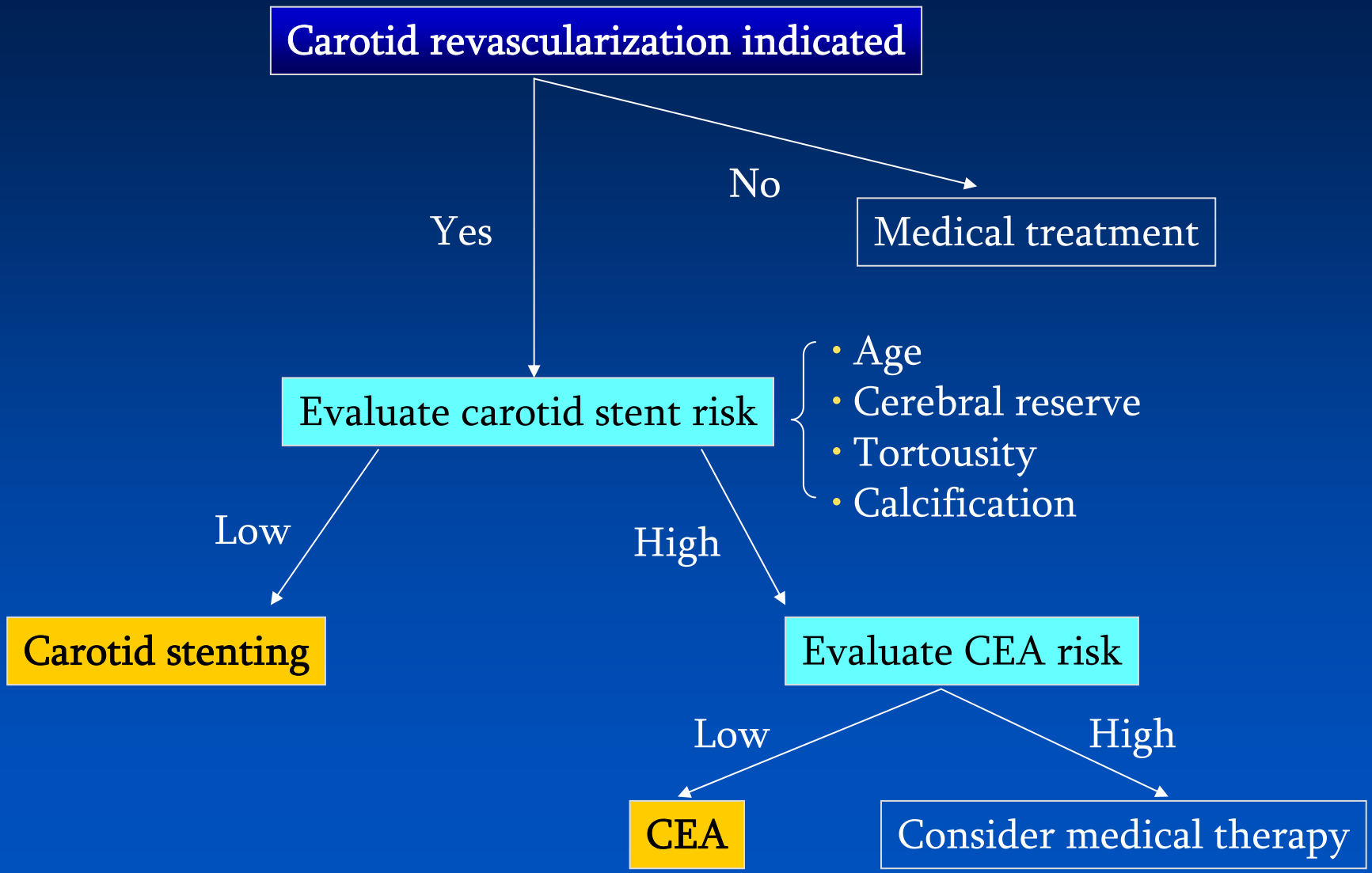
- Notwithstanding funding issues, the planned margin of non-inferiority (<2.5%) was based on a power calculation of 1900 patients and this larger sample might have provided much tighter CIs and more robust statistical data.

*Lancet 2006;368;1239-47*

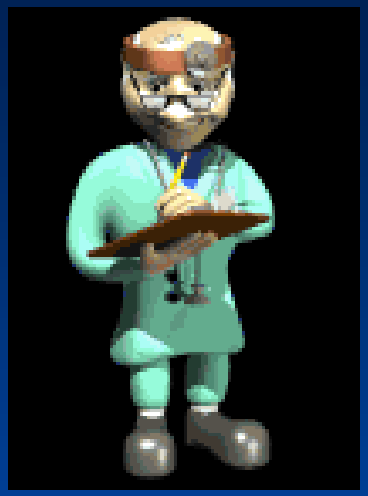
# Vascular Medicine Perspective: CEA versus Stent

- High risk symptomatic patient (>50%)
  – carotid stenting is preferred and reimbursed
- High risk asymptomatic patient (>80%)
  – carotid stenting is preferred and reimbursed
- Normal risk symptomatic patient (>50%)
  :CaRESS, SPACE, EVA-3S
  – More data are needed (CAVATAS-2, CREST)
- Normal risk asymptomatic patient (>80%)
  :CaRESS,
  – More data are needed (CREST, ACT1)

# Suggested Treatment algorythm



# Patient Preference



**Although all of us love our surgeons,**

**NOBODY loves surgery!**

# *Now.* Carotid Stenting

- Up to date, CS is at least equivalent results and a more preferred therapy to CEA with appropriate learning curve and the use of the protection device in *symptomatic and asymptomatic high surgical risk group*

- Technical progress, advance in technical expertise and *patients selection* are important to reduce the risk of CS

- CS may be extended to all patients subsets, such as symptomatic, asymptomatic, high risk, and low risk subgroups.