

# ***CAS: Results and Current Limitation to Widespread Application***

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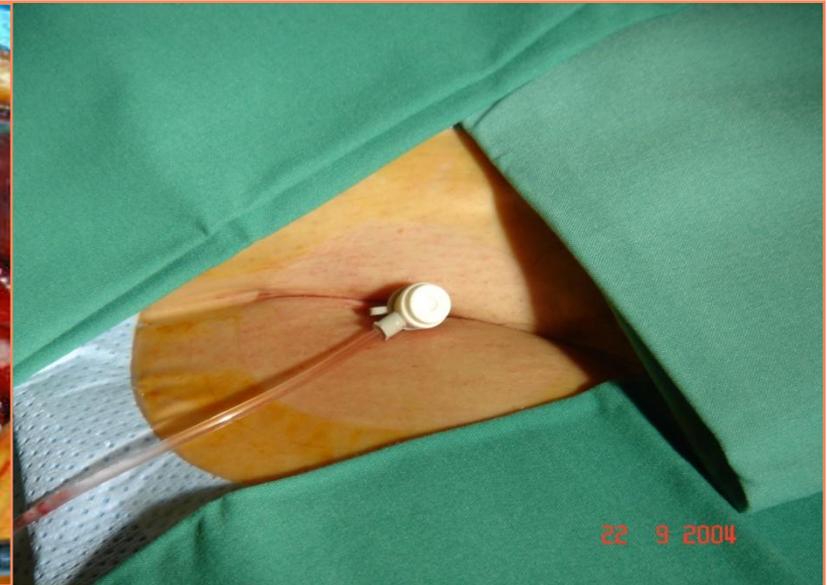
Molecular Imaging - Nuclear Medicine

Klinikum Dortmund / Germany

I have nothing to disclose

# Why CAS?

because...



all of us - patient and physician - want a less traumatic tx

## What are limitations for CAS?

- evidence of benefit
- patient's age and anatomy
- dedicated devices
- experience of interventionalists

## Do results limit CAS?

Yes, as long as we have not proven  
equivalence of outcome:

- stroke
- MI
- death
- recurrent stenosis

- The benchmark for CAS:**
- CEA**
  - best medical tx**

## CEA

What are the preceudural stroke rates?

ECST	7.5%	1991	}	symptomatic stenosis
NASCET	5.8%	1991		
ACAS	2.3%	1995	}	asymptomatic stenosis
ACST	3.1%	2004		

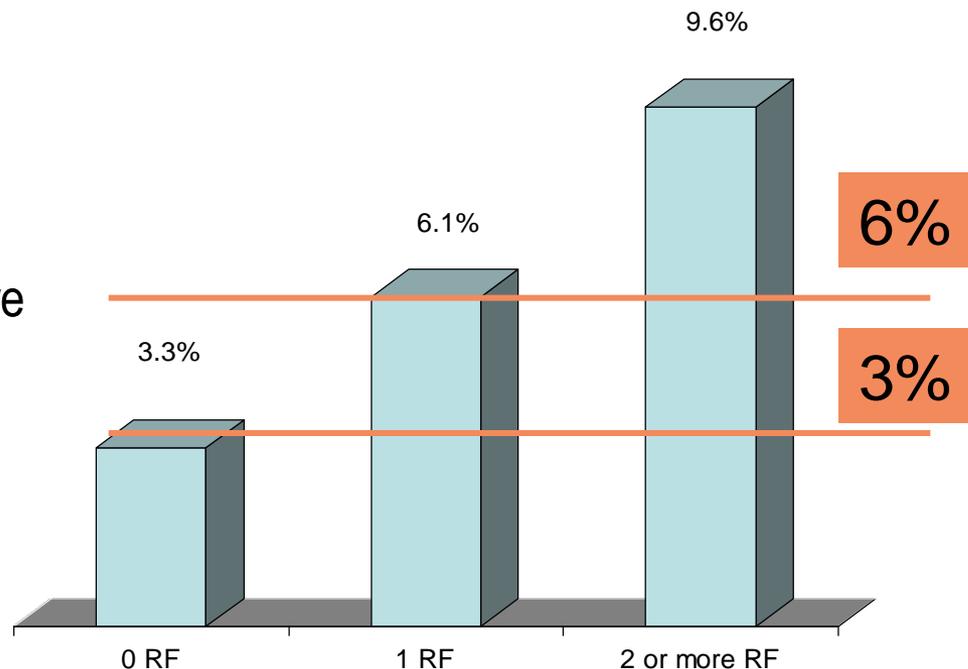
# CEA - What are the risks?

# Risk Factors for Death/Stroke after CEA Ontario CEA Registry

6,038 patients, 1994-1997; 30-day death/stroke rate 6.0%

5 independent predictors (RF) of 30-day death/stroke

- symptomatic carotid stenosis
- contralateral carotid occlusion
- history of atrial fibrillation
- history of congestive heart failure
- diabetes



# Impact of Cardiovascular Risk Factors on Outcomes Following CEA

1002 CEA in 852 patients, prospective data collection  
 Prospective assessment, University of Brussels  
 Clinical evaluation by the surgeon

	<u>30-Day death/stroke</u>	<u>OR</u>
Overall	2.7%	
Diabetes	5.7%	3.3
DM + HTN + Hyperlip	9.4%	4.2

Are these also th Risk Factors  
of CAS?

**NO!**

We have different RFs for CAS

- age >80                      10%    stroke rate
- aortic arch atherosclerosis
- arterial tortuosity
- severe CCA/ICA calcifications
- freely floating thrombus

# Why Does Vascular Surgery Have Such a High Cardiac Complication Rate?

## Asymptomatic Coronary Disease in Patients with Carotid Stenosis

Systematic coronary angiography in 200 patients with carotid disease and no symptoms of CAD

40% severe CAD (>70% stenosis of  $\geq 1$  vessel)

46% mild-moderate CAD

14% normal coronary arteries

## AHA Scientific Statement On Coronary Risk Evaluation in Patients With Ischemic Stroke/TIA

Overall, evidence suggests that 25% to 60% of patients with carotid stenosis and no symptoms of CAD have abnormal provocative tests results for myocardial ischemia or angiographic evidence of severe CAD.

# Cardiovascular Impact of CEA

Prospective single center randomized study on CEA  
in general anesthesia (GA) versus  
loco-regional anesthesia (LA)

n=107, continuous 12-lead ECG during surgery and for 24 hours  
postoperatively

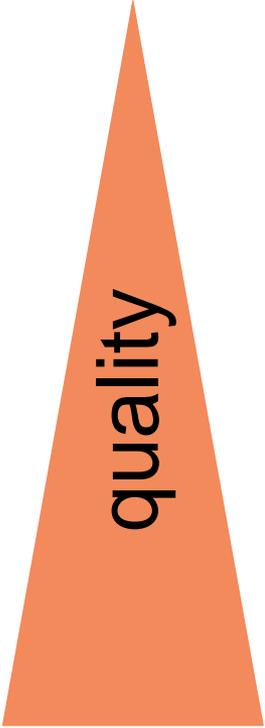
Myocardial ischemia in 22 patients (20.5%)

No difference between general or local anesthesia

**CAS ...**

## CAS - What we have to-day

- registries
  - self-reporting
  - independent control
- one-arm prospective trials  
*market- or post-market trials*
- prospective randomized trials  
*CAS vs CEA*



quality

## Clinical Trials

Study	Study Design	Sample Size	Status
ARCHER 1-3	high-risk registry	581	completed
BEACH	high-risk registry	480	completed
CABERNET	high-risk registry	488	completed
CASES	high-risk registry		enrolling
CREATE I			completed
CAPTURE			enrolling
MAVERIC			completed
MOMA	EU registry	157	completed
PASCAL	high-risk registry	113	completed
PRIAMUS	Italian MoMa registry	416	completed
ProCAS	German all-CAS registry	>8,000	enrolling
RULE	EU registry	60	completed
SECURITY	high-risk registry	398	completed
VIVA	high-risk registry	400	starting

**>20,000 tx**

## What is the purpose of these trials?

- establishing evidence
- approval of CAS by health systems and governments
- getting reimbursement
- getting approval of devices
- offering patients a less invasive tx

## Why High Risk Patients?

CEA for higher-risk patients does not produce the standard 6% (symptomatic) and 3% (asymptomatic) complication rates that the medical community expects

## The High Risk Dilemma

Patients excluded from NASCET and ECST  
= medical high risk

Patients after surgery and/or radiotherapy of  
the neck  
= surgical high risk

High proportion of asymptomatic patients (72-86%)  
= interventional high risk (5-8%) - no benefit for the patient

## High Risk Patients

- ACT I
  - ARCHER I-III
  - CASES
  - CABERNET
  - CREATE
  - CHRS
  - EXACT
  - MAVERIC
  - PASCAL
  - SECURITY
  - SAPPHIRE
- registries
- randomized trial
- 
- The diagram shows a list of ten clinical trials. A large right-facing curly bracket groups the first nine trials (ACT I, ARCHER I-III, CASES, CABERNET, CREATE, CHRS, EXACT, MAVERIC, and PASCAL) under the label 'registries'. A horizontal line points from the tenth trial, 'SAPPHIRE', to the label 'randomized trial'.

# US Carotid Stent Registries

30-day composite endpoint  
(stroke, MI, death)

CABERNET	3.8%
BEACH	5.4%
SECURITY	7.2%
ARCHER 2	7.8%
SAPPHIRE	7.8%

no benefit  
with such a  
complication  
rate!!!

# Current CAS Approvals

## FDA:

High-risk for CEA with stenosis

- symptomatic >50%
- asymptomatic >80%

# Prospective Randomized Trials

- CAVATAS
  - SPACE
  - EVA-3S
  - ICSS
  - CREST
  - SAPPHERE
- } symptomatic patients
- } sympt. + asympt. patients
- } sympt. + asympt. high risk patients

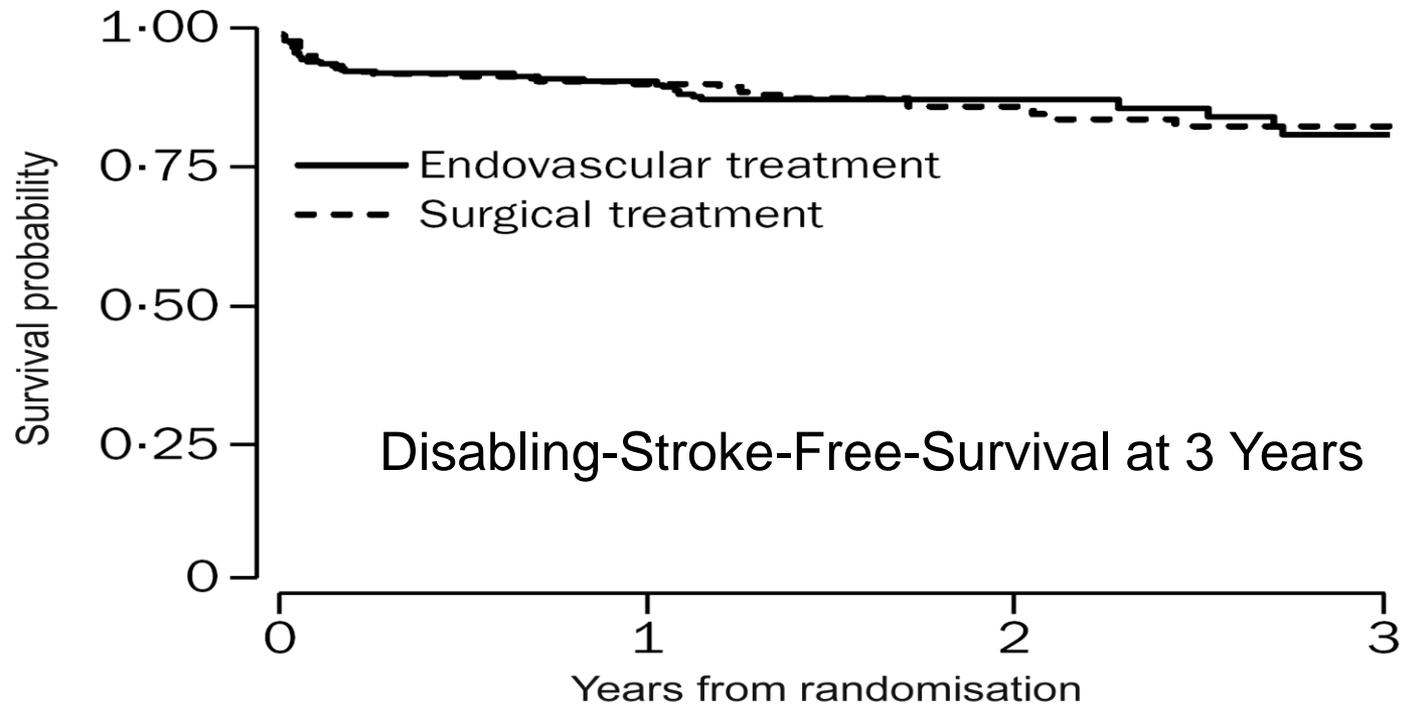
**CAVATAS ...**

# CAVATAS

Type of Procedure	Technical Success	Neurological Deficits	Stroke & Death	3-Year Patency
CAS	>95%	8%	10.0%	no significant difference
CEA	>95%	8%	10.0%	

Brown et al. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. Lancet 2001;357:1729-37

# CAVATAS



Brown et al. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* 2001;357:1729-37

# SPACE

**Stent-protected *P*ercutaneous *A*ngioplasty of the  
*C*arotid Artery vs. *E*ndarterectomy**

## Primary Endpoints

- **ipsilateral stroke**  
ischemic stroke and/or intracerebral bleeding with symptoms lasting more than 24 hours **or**
- **death**  
of every cause between randomisation and day 30
- **MI not included**

## Secondary Endpoints

- ipsilateral stroke or vascular death within 24 months after treatment
- ipsilateral stroke with an impairment  $\geq 3$  on the modified Rankin scale or death of every cause between randomization and day  $30 \pm 3$  after tx
- strokes of every localisation and severity within 24 months after the intervention
- re-stenosis more than 70% measured with US
- procedural failure

# Study Population

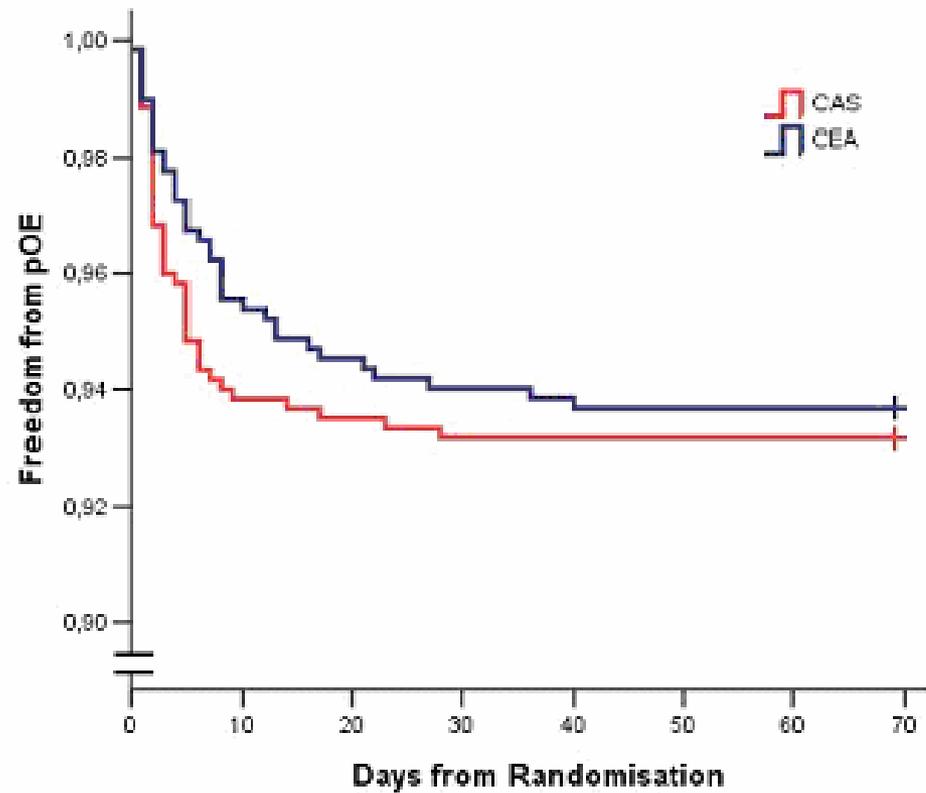
randomised 1200		
	<b>CAS</b>	<b>CEA</b>
consent withdrawn	6	11
ITT-pop	599	584
not treated	1	1
switched tx	13	6
PP-pop	585	577
EPD	yes 172	no 413

## Primary Endpoint Results

any ipsilateral stroke and death between randomization and day 30

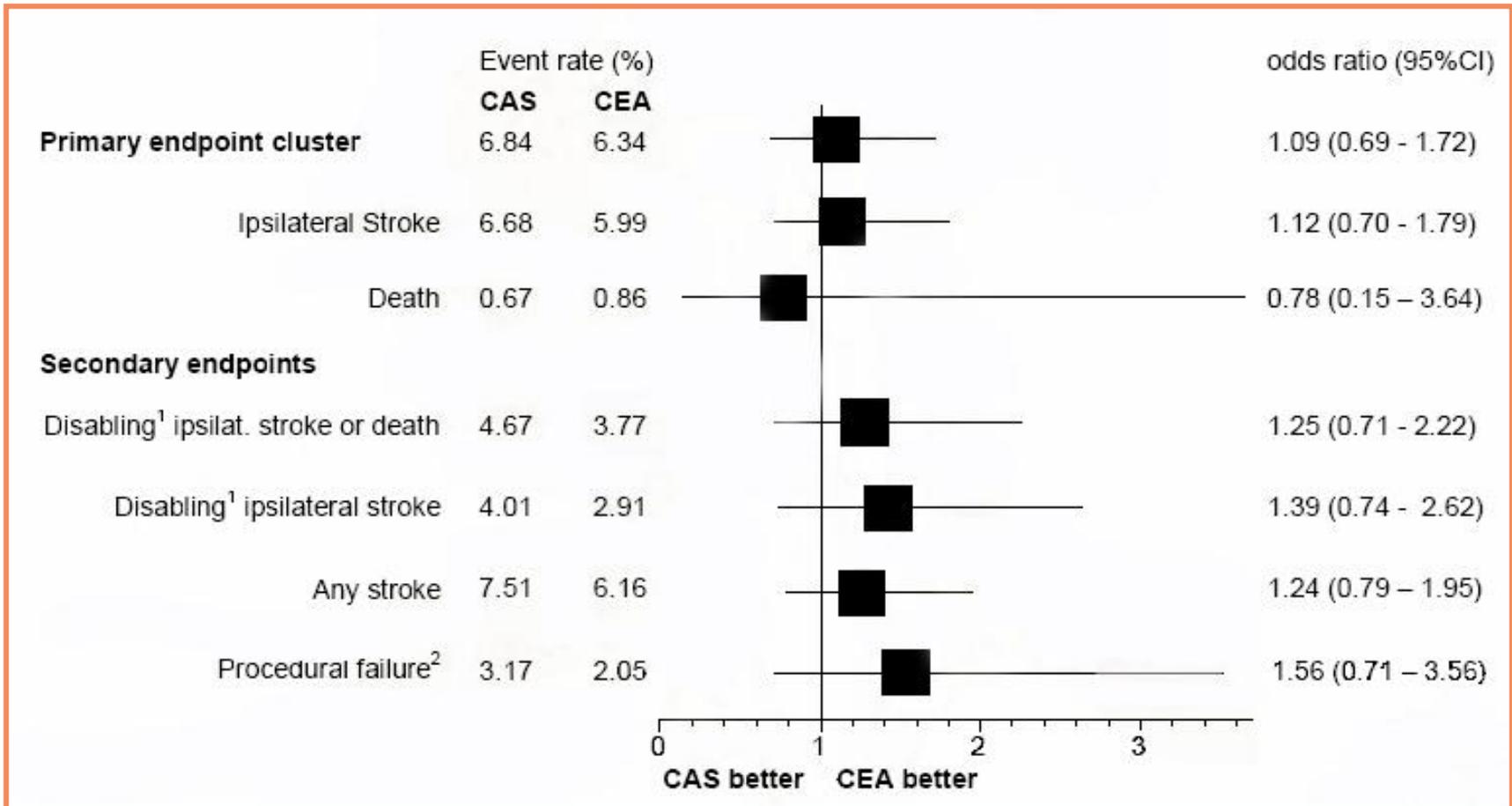
	CAS (n=599)	CEA (n=584)
primary endpoints	41 6.84%	37 6.34%
absolute difference (95% CI)	0.51% (-2.37 to 3.39%)	
odd ratio (95% CI)	1.09 (0.69 to 1.72)	
		p = 0.09

# Primary Endpoint Results



CAS	599	562	560	558	558	558	558	558
CEA	584	558	552	549	548	547	547	547

# Primary Endpoint Results



## SPACE 2-Y FU Data

- Periprocedural stroke or death, plus ipsilateral ischemic stroke
 

– CEA 8.8%	+1.9%	}	1% strokes/y
– CAS 9.5%	+2.2%		
- the rate of recurrent ipsilateral ischemic strokes is similar for both treatment groups after 2 years

# EVA-3S

French prospective randomized trial

# EVA-3S

## Inclusion criteria

- retinal or hemispheric TIA
- non-disabling stroke
- 60-99% stenosis
- plaque morphology irrelevant

## Exclusion criteria

- m-Rankin scale  $\geq 3$
- non-atherosclerotic disease
- tandem stenosis
- bleeding disorder
- previous revascularization
- uncontrolled hypertension, DM, unstable angina
- contraindication to heparin, ticlopidine, clopidogrel
- life expectancy  $< 2$  years

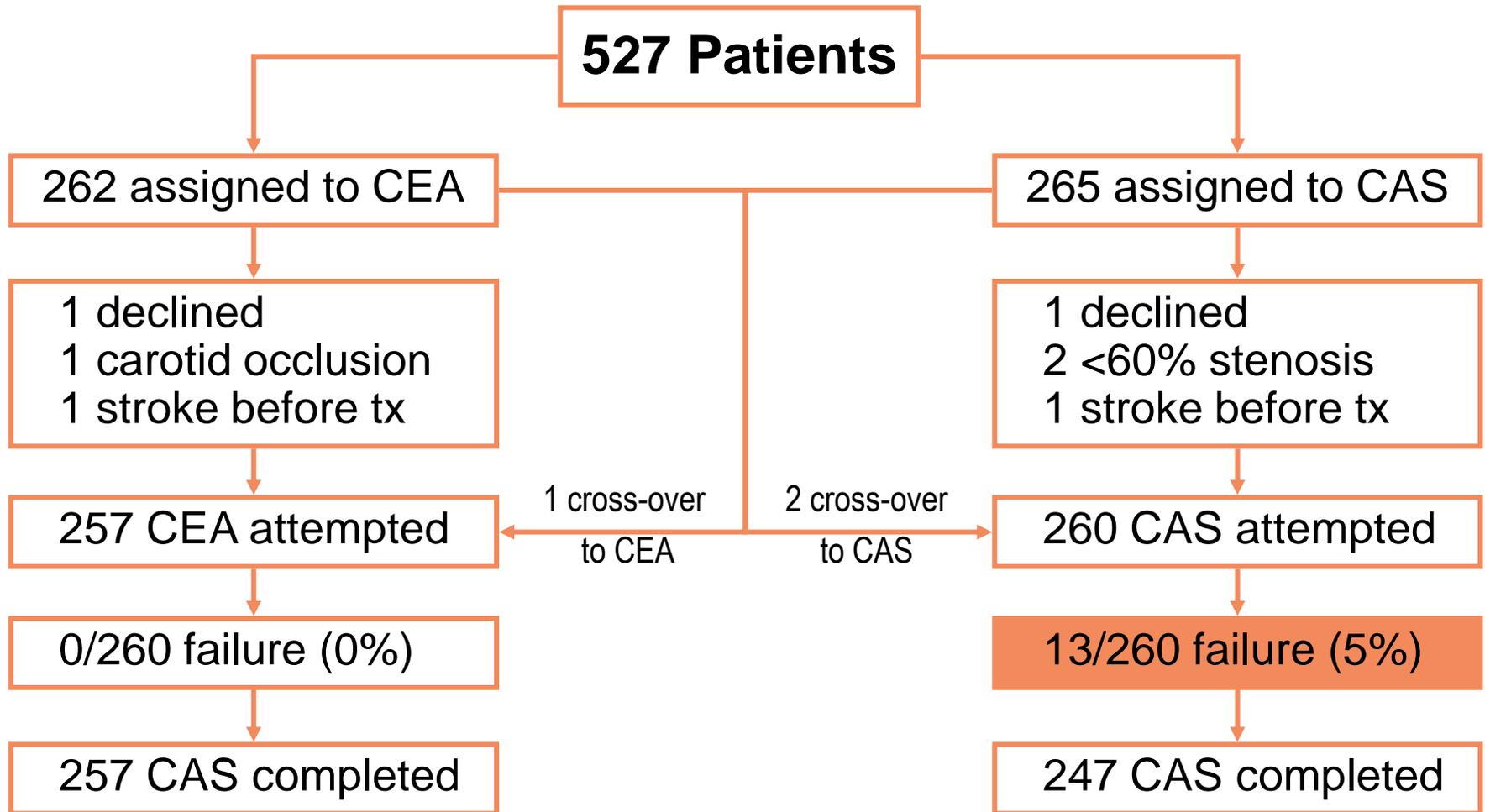
# EVA-3S

*Trial enrolled patients from*

Nov-2000 to Sep 2005

527 patients randomized

stopped due to  
recommendation of  
the safety committee

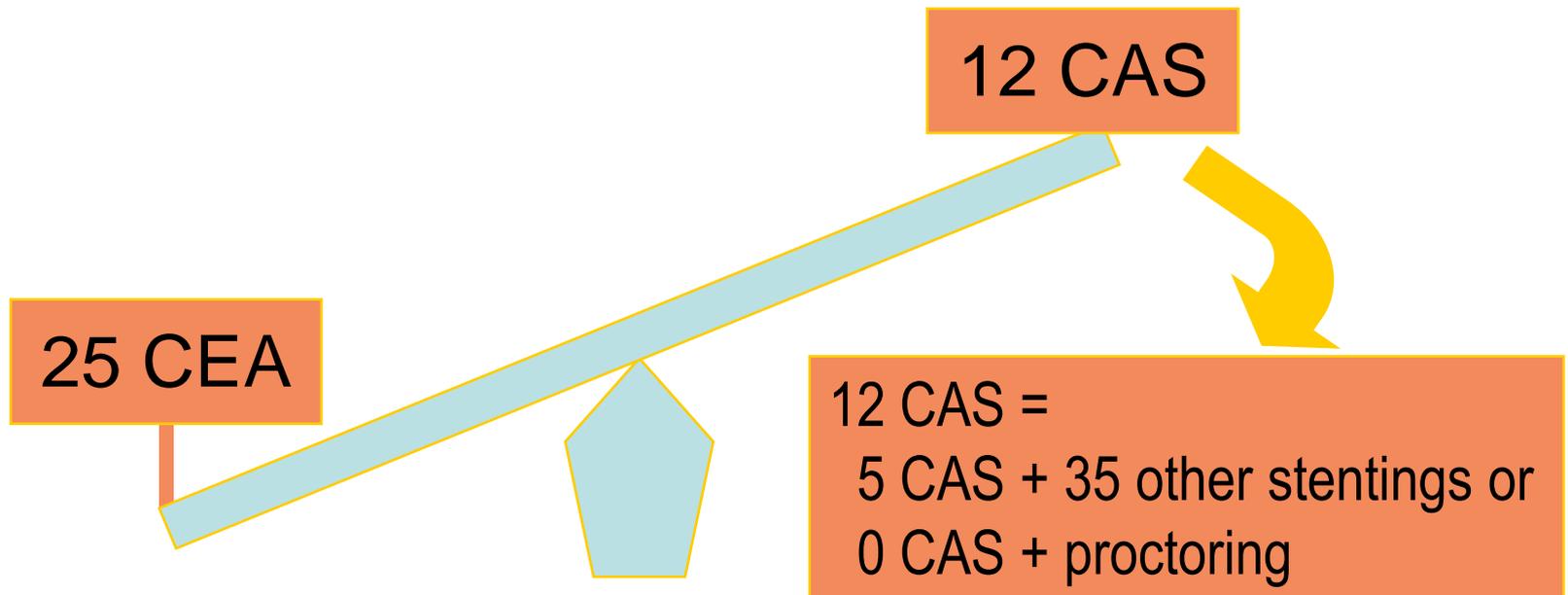


# EVA-3S

Outcome Event	CEA	CAS	unadjusted RR	p-value
nonfatal stroke	7 (2.7%)	23 (8.8%)	3.3 (1.4-7.5)	0.004
- sympt. > 7d	6 (2.3%)	20 (7.7%)		
- nondisabling	6 (2.3%)	16 (6.1%)		
- disabling	1 (0.4%)	7 (2.7%)		
death	3 (1.2%)	2 (0.8%)	0.7 (0.1-3.9)	0.68
- fatal stroke	2 (0.8%)	1 (0.4%)		
- other cause	1 (0.4%)	1 (0.4%)		
any stroke or death	10 (3.9%)	25 (9.6%)	2.5 (1.2-5.1)	0.01
any disabling stroke or death	4 (1.5%)	9 (3.4%)	2.2 (0.7-7.2)	0.26
TIA	2 (0.8%)	6 (2.3%)	3.0 (0.6-14.6)	0.28
MI	2 (0.8%)	1 (0.4%)	0.5 (0.04-5.4)	0.62

# EVA-3S

## Unbalanced Preconditions



## EVA-3S

*How to interpret this trial?*

### Recruitment of Operators

16% of pts. tx by interventionalist with >50 CAS

45% of pts. tx by interventionalists with < 50 CAS

39% of pts. tx by physicians in training

# EVA-3S

*How to interpret this trial?*

## Severe Complications

- fatal stroke      CAS 50% lower than CEA
- MI                    CAS 50% lower than CEA
- death                CAS 20% lower than CEA

Even CAS beginners have a better outcome with  
severe complications !!!

## EVA-3S 4-Y FU Data

Periprocedural and non-periprocedural ipsilateral stroke or death

CEA	6.2%	3.9%	+2.3%
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CAS	11.1%	9.6%	+1.5%
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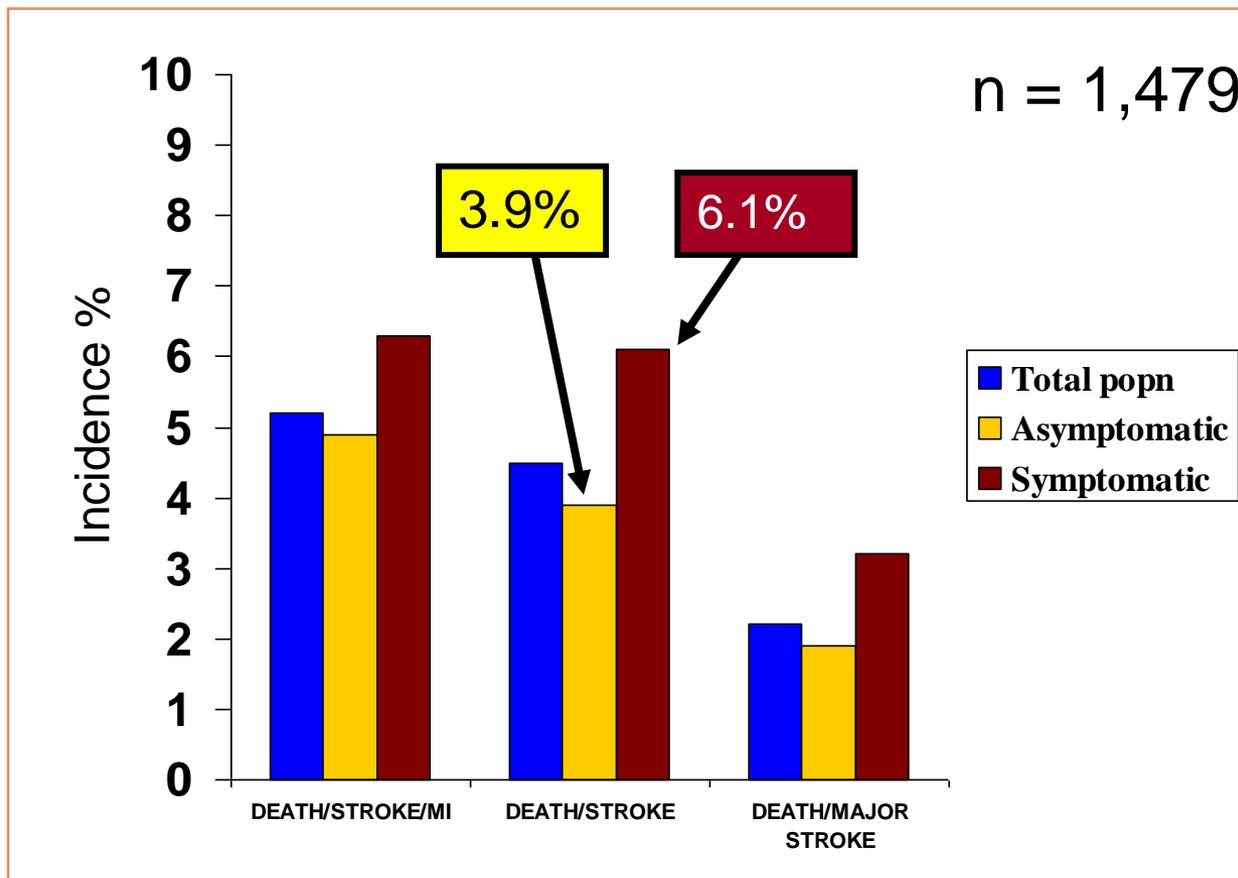
Mas: “Carotid stenting is as effective as carotid endarterectomy for middle-term prevention of ipsilateral stroke, but the safety of carotid stenting needs to be improved before it can be used as an alternative to carotid endarterectomy in patients with symptomatic carotid stenosis,”

JL Mas et al, Lancet Neurology, published online September 6, 2008.  
European Stroke Conference 2008, May 14.

**CREST ...**

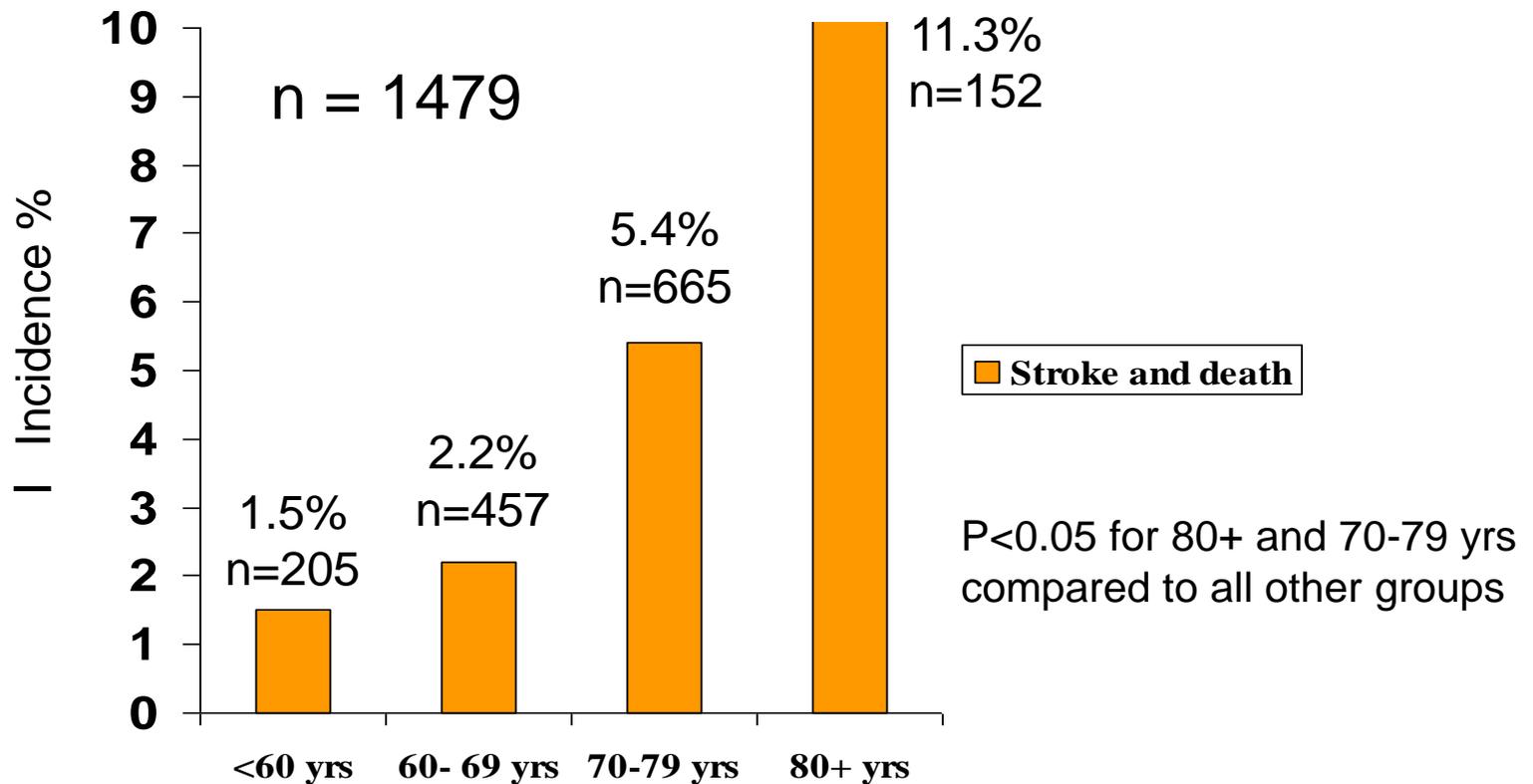
# CREST

## Total Population - 30 day Events



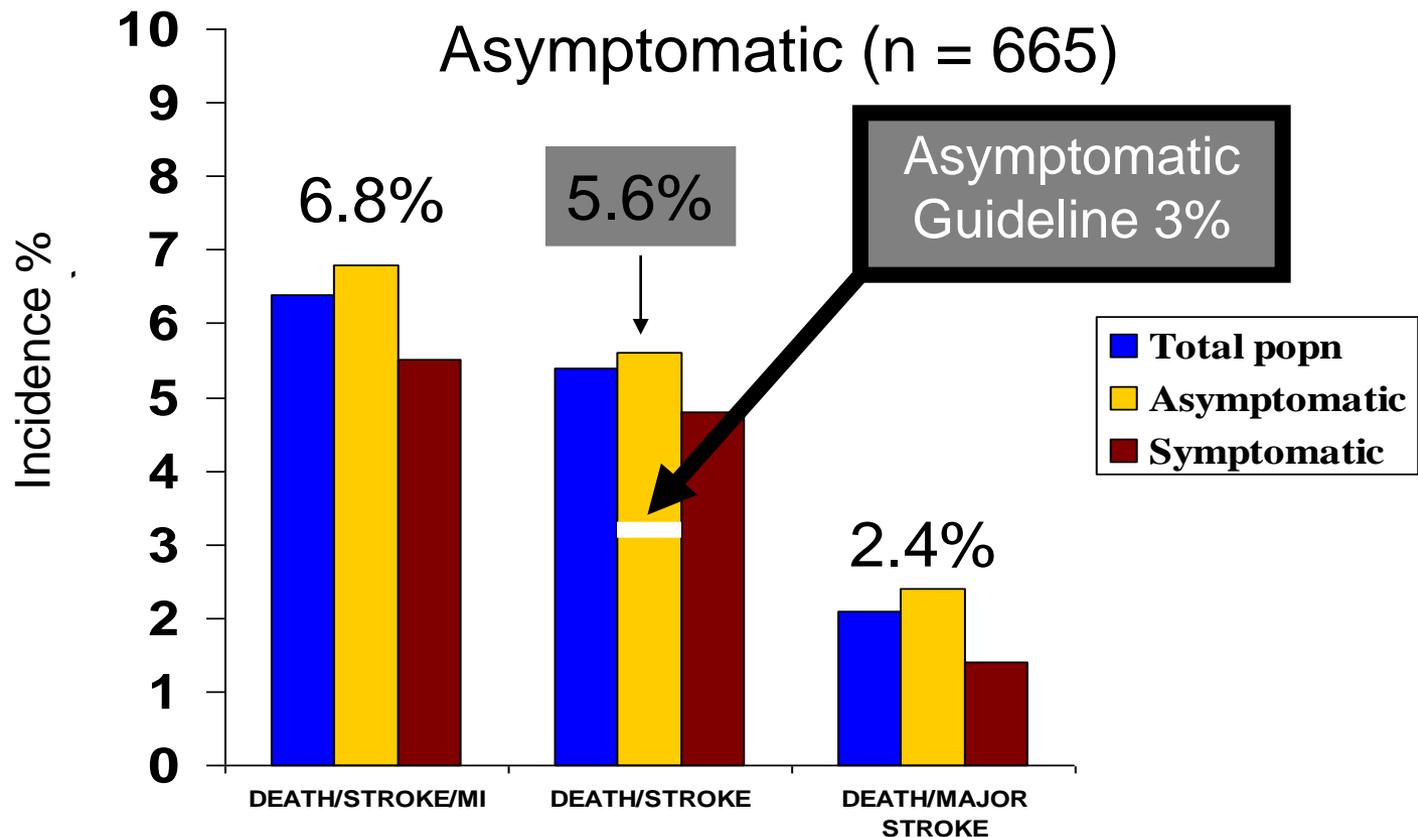
# CREST

## Total Population Outcomes vs Age



# CREST

## 70-79 yrs Age Group 30 day Events



**SAPPHIRE ...**

# SAPPHIRE

Medical and surgical high risk patients  
symptomatic and asymptomatic

## Primary Endpoints

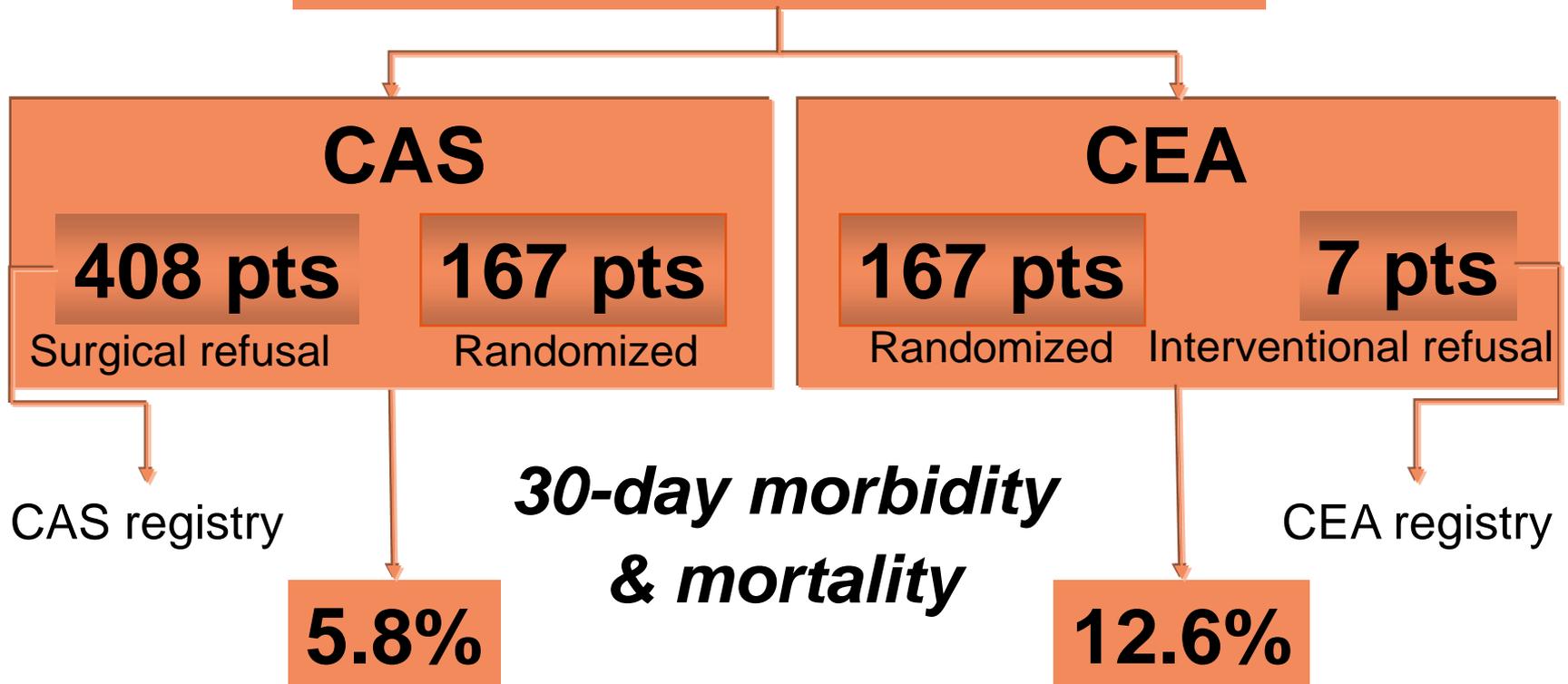
- Death, any Stroke, and **MI** at 30-days post-procedure

MI rate higher with CEA vs CAS

- Death and Ipsilateral Stroke between 31-days and 12-months post-procedure

# SAPPHIRE

723 pts with ICA stenosis



# SAPPHIRE

## 1 year data randomized patients

<u>Events</u>	<u>Stent (159 pts)</u>	<u>CEA (151 pts)</u>	<u>p Value</u>
Death:	11 (6.9%)	19 (12.6%)	0.12
Stroke:	9 (5.7%)	11 (7.3%)	0.65
Major Ipsilateral:	0 (0.0%)	5 (3.3%)	0.03*
Major Non-Ipsilateral:	1 (0.6%)	1 (0.7%)	>0.99
Minor Ipsilateral:	6 (3.8%)	3 (2.0%)	0.50
Minor Non-Ipsilateral:	3 (1.9%)	3 (2.0%)	>0.99
MI (Q or NQ)	4 (2.5%)	12 (7.9%)	0.04*
Q- Wave MI	0 (0.0%)	2 (1.3%)	0.24
Non-Q-Wave MI	4 (2.5%)	10 (6.6%)	0.10
MAE:	19 (11.9%)	30 (19.9%)	0.06

\* Significant Difference

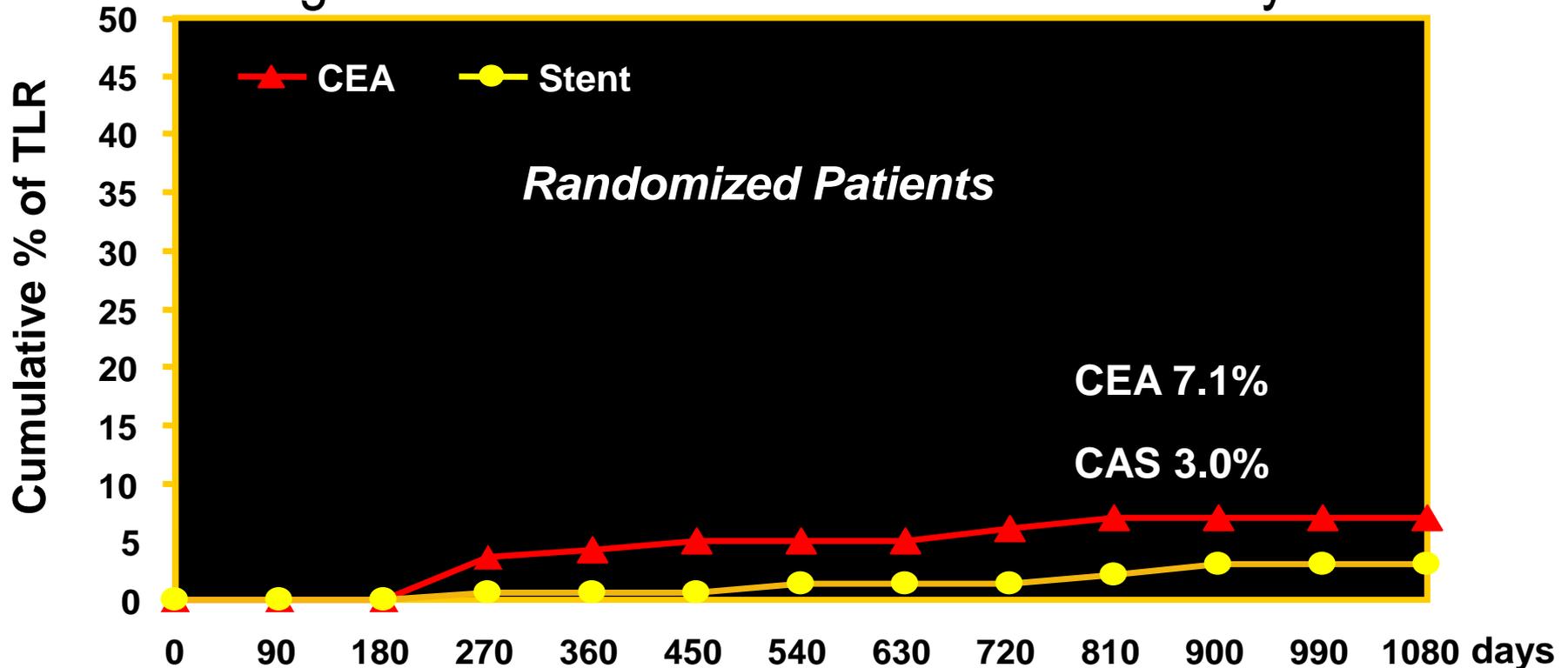
# SAPPHIRE

1 year data randomized patients

Events	Stent (159 pts)	CEA (151 pts)	p Value
MAE without non neuro deaths >30 days	9 (5.7%)	19 (12.6%)	<0.05*
MAE without MI or non-neuro deaths >30 days	8 (5.0%)	11 (7.3%)	0.48

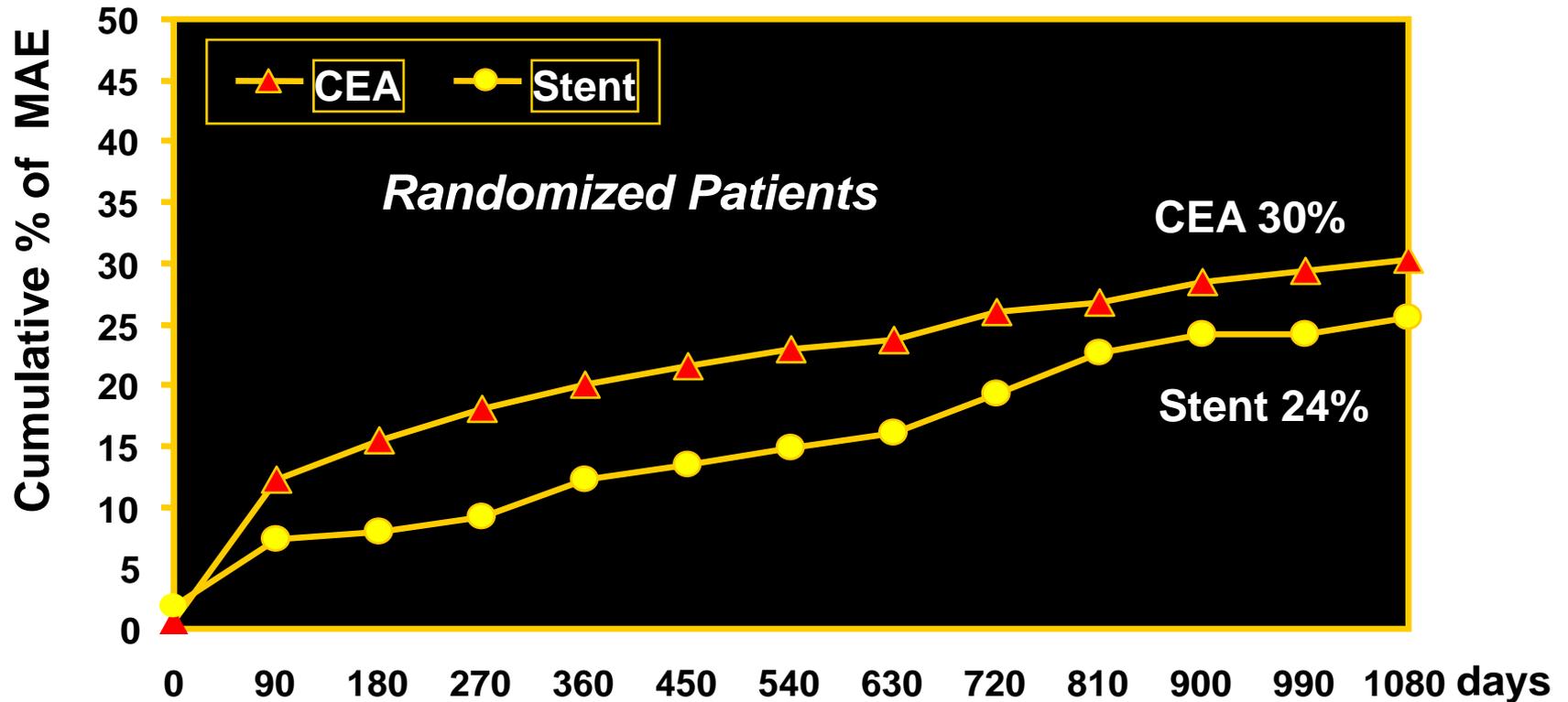
\* Significant Difference

## SAPPHIRE: Cumulative Percentage of Target Lesion Revascularization at 1080 Days



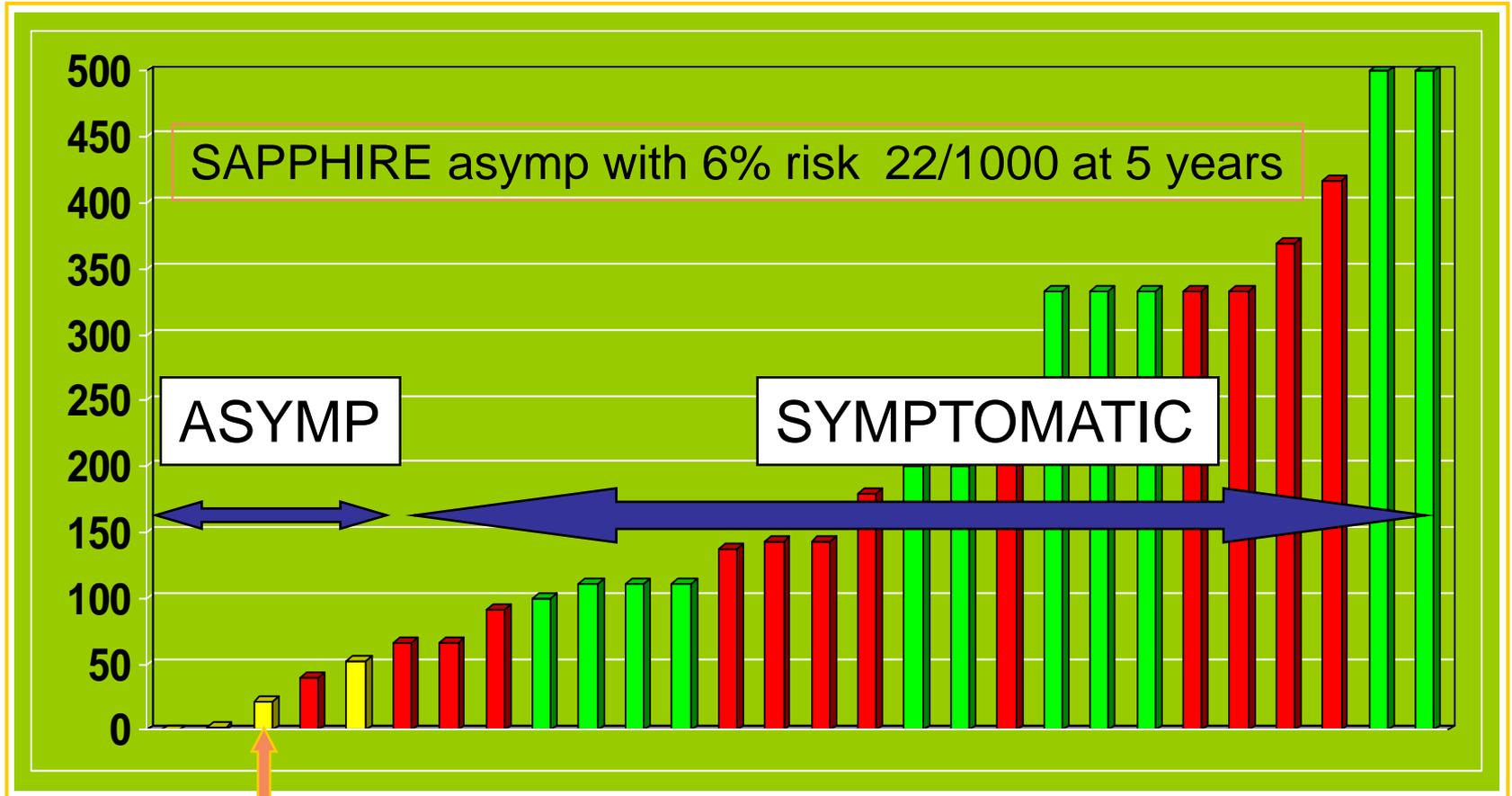
Days:	0	360	720	1080
CEA:	167	150 (90%)	134 (80%)	112 (67%)
Stent:	167	161 (96%)	154 (92%)	139 (83%)

# SAPPHIRE: Cumulative Percentage of MAE at 1080 Days



Days	0	360	720	1080
CEA	167	150 (90%)	139 (83%)	117 (70%)
Stent	167	161 (96%)	154 (92%)	139 (76%)

# Strokes Prevented per 1000 CEA/CAS



SAPHIRE

source: ACAS, ACST, ECST & NASCET

„Contrary to what is generally assumed, no systematic evidence exists to support the preferential use of CEA over CAS or vice versa“

Naylor, AR. Vascular surgeon, SPACE editorial, Lancet, September 2006

# Anatomy



## Problems:

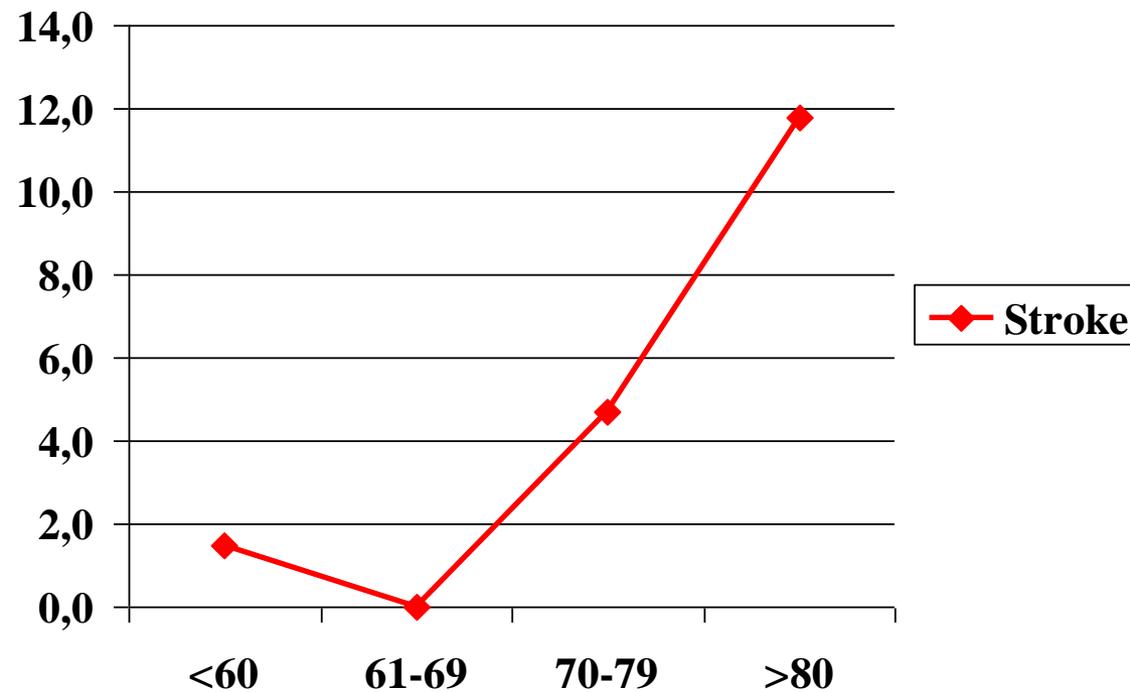
Access: diffuse atherosclerosis, stenosis, occlusion, tortuosity

Lesion characteristic: calcification, fresh thrombus, string sign

Cerebral protection: placement, ischemic reactions, retrieval ...

# Age

## CREST



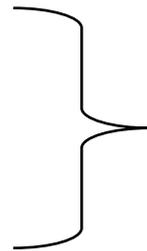
# Experience

Learning Curve often underestimated!

US registries

EVA-3S

SPACE



Not within the AHA limits of  
3% asymptomatic stenosis  
6% symptomatic stenosis

Complication rate is decreasing with more than  
100 to 150 CAS cases!

# Conclusions

## CAS Limitations - What we can improve

- evidence of benefit
- dedicated devices
- experience of interventionalists

## CAS Limitations - What we must respect

- patient's age and anatomy



Velocity of earth 108,000 km/h  
Our journey during this talk 36,000 Km  
Thank you for flying with me!