20 YEARS OF INNOVATION
TCT2008

The Interventional Perspective: Long Term Data on Carotid Stenting Supports Its Efficacy In Stroke Prevention

Emerging And Novel Insights From CaRESS, SAPPHIRE. ARCHeR And Others

Subbarao Myla MD, FACC, FSCAI
Hoag Memorial Hospital Presbyterian
Newport Beach, CA, USA

CARDIOVASCULAR RESEARCH FOUNDATION

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- **Stockholder**
  - Boston Scientific, Lumen Bio

Objectives

- Is CAS Durable?
  - In Stroke Prevention?
    - Compared to what? CEA or Medical RX
    - In which patient groups?
  - In Maintaining Patency?
    - Restenosis
    - Role in stroke
    - Issues With Carotid Duplex

Proposed mechanism of stroke prevention in CAS

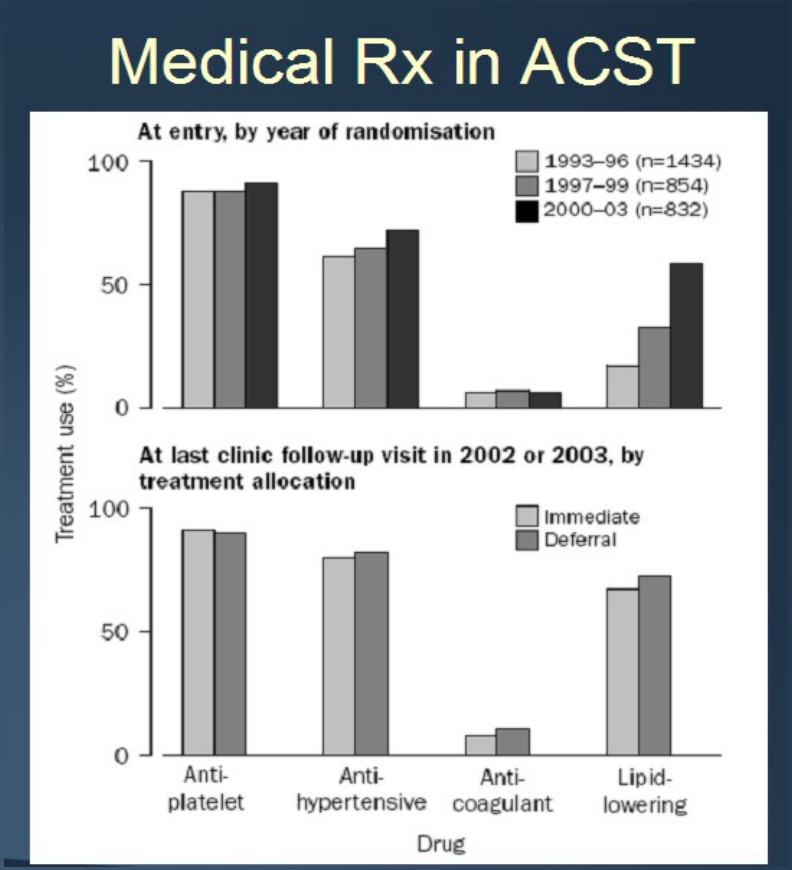
- Most stroke is related to non-hemodynamic effects of extra-cranial bifurcation disease
  - Plaque rupture with thrombo-/athero- emboli in >90% symptomatic disease

- "Passivating" the plaque, then, is the presumed mechanism of stroke prevention in CAS
  - Trapping plaque behind stent
  - Neo-intimal formation "seals" the plaque thereafter
  - May reduce long-term (5-10 year) atherosclerosis recurrence

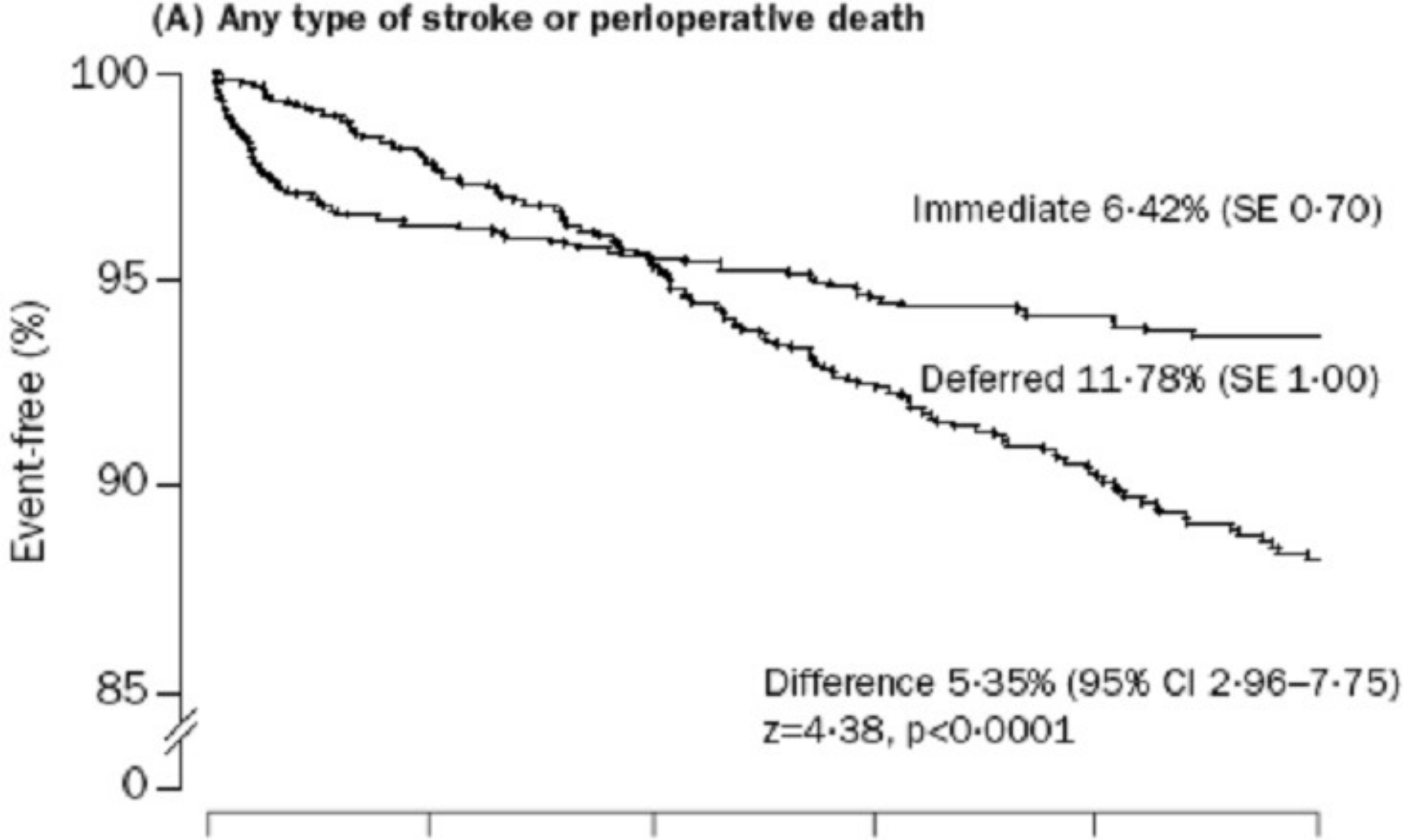
Historical, Randomized And Registry Trials

- Medical Therapy
- NASCET. ACAS.
- ECST. ACST
- CAVATAS
- SAPPHIRE, ARCHER. CaRESS
- SPACE, EVA 3S
- CREST lead In

No Comparator For Medical Therapy In High Risk Patients



ACST


(A) Any type of stroke or perioperative death
100
95
90
85
0
Event-free (%)
Immediate 6·42% (SE 0·70)
Deferred 11·78% (SE 1·00)
Difference 5·35% (95% CI 2·96–7·75)
z=4·38, p<0·0001

Stroke prevention: natural history comparators

- Symptomatic patients:
  - NASCET: ~13%/year
    - 26% recurrent stroke at 2 years
    - Worse with worse stenosis
    - Worse with hemispheric symptoms
    - Not on “modern” medical Rx
  - SPARCL: 2.5%/year
    - 13% recurrent stroke at 5 years
    - Modern medical Rx except statins
- Asymptomatic patients:
  - ACST, ACAS: 2.0%-2.5%/year
  - 11%-12% stroke at 5 years
    - Not uniform modern medical therapy
  - ACSRS: ~6% stroke at 1 year in severe stenosis, renal failure, contralateral TIA

Stroke prevention: surgical comparators

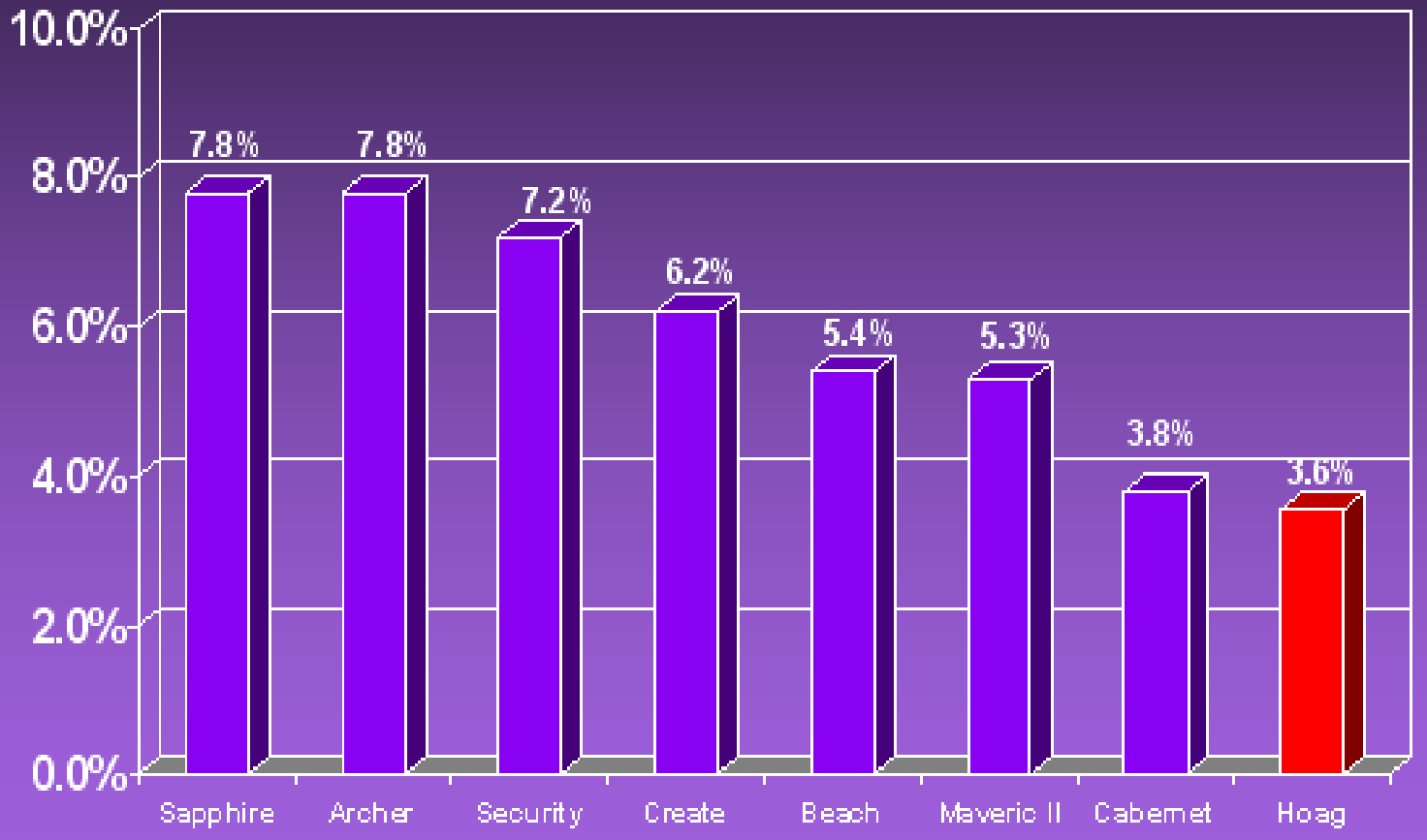
- Symptomatic patients
  - NASCET: ~4%/year
    - 9% recurrent stroke at 2 years includes initial surgical morbidity
- Asymptomatic patients
  - ACST, ACAS: 1%/year
    - 5%-6% recurrent stroke at 5 years includes initial surgical morbidity

Ipsilateral Stroke Risk Reduction: Medical vs. Surgical

	Normal Risk Revascularization		Medical Therapy	
	ACAS (5 years)	**ACST (5 years)**	**SPARCL (5 years)**	**Heart Protection (5 years)**
Stroke/Endpoint Definition	*Ipsilateral stroke or any perioperative stroke or death*	*Perioperative and Non-perioperative stroke*	*All fatal and non fatal stroke*	*All stroke*
Cumulative Absolute Risk	5.1% CEA 11.0% Med Tx	6.4% Immed. CEA 11.8% Def. CEA	11.2% Med Tx 13.1% Placebo	4.3% Med Tx 5.7% Placebo
Absolute Risk Reduction	**5.9%**	**5.4%**	**2.2%**	**1.4%**
Relative Risk Reduction	**53%**	**46%**	**15%**	**25%**

Source: ACAS, JAMA 1995; ACST, Lancet 2004; SPARCL, NEJM 2006; Heart Protection, Lancet 2003

30 Day Composite Endpoints in Carotid Artery Stenting (Stroke/Heart Attack/Death)



Successful Technology Transfer with improving Learning Curve

HOAG HEART & VASCULAR INSTITUTE
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Impact of peri-procedural minor strokes

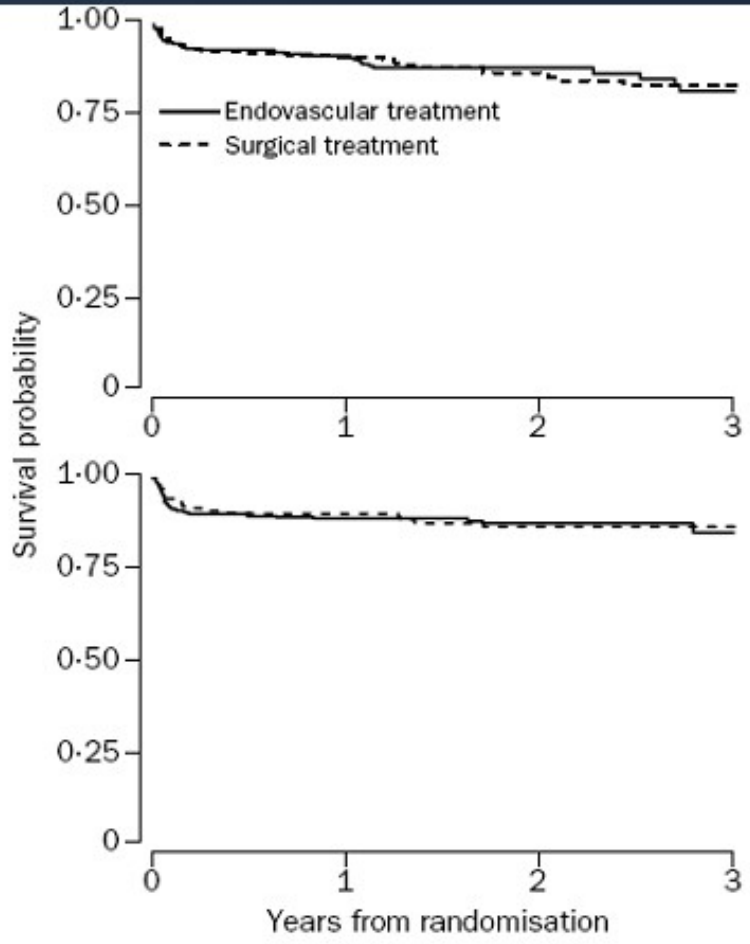
1 year neurological status in patients with minor stroke

	NIHSS=0 or 1	NIHSS>1
ARCHeR 1 and 2	100%	0%

Negligible clinical impact at 1 year

Direct comparison of CEA vs. CAS in standard risk: CAVATAS

- CAVATAS (n=504)
  - Suboptimal CAS
    - No embolic protection
    - Only ~25% actually received stents
  - No difference between CEA and CAS at 3 years
    - Not in stroke
    - Not in stroke and death



Total number at risk				
Death or disabling stroke	504	378	193	93
Ipsilateral stroke > 7 days	504	363	178	80

Figure 4: **Death or disabling stroke in any vascular terrritory (upper) or ipsilateral stroke lasting more than 7 days (lower)**

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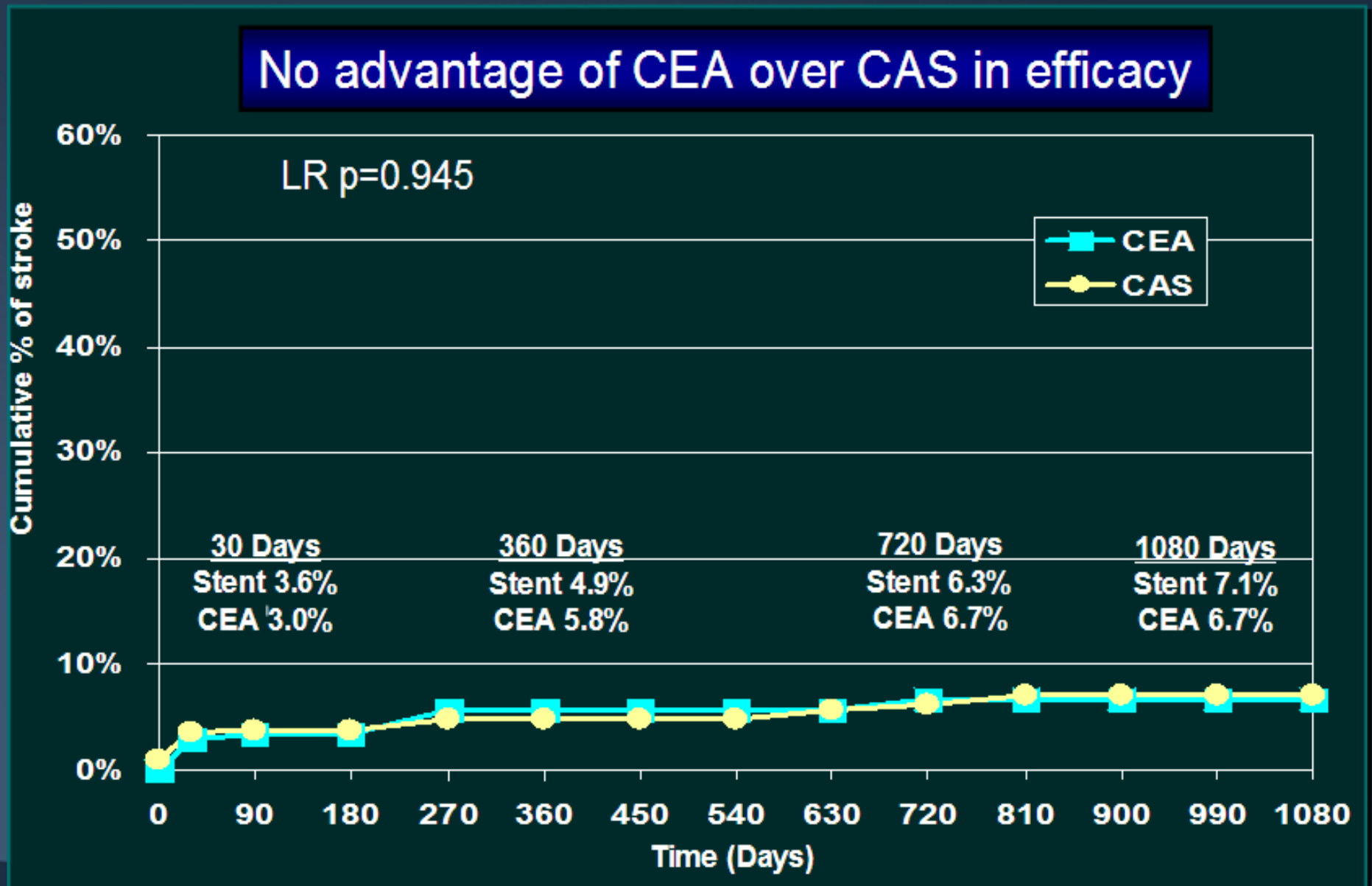
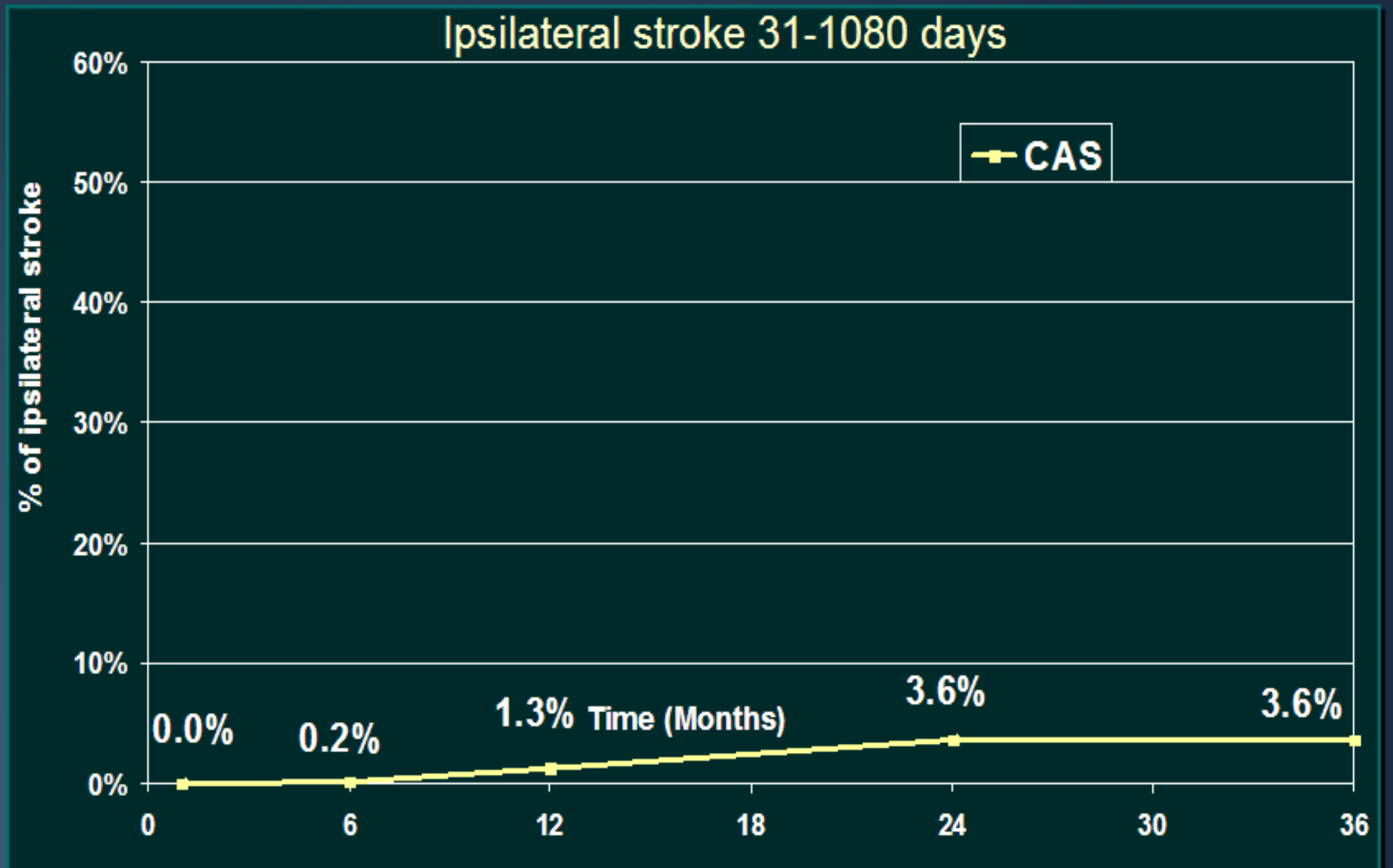
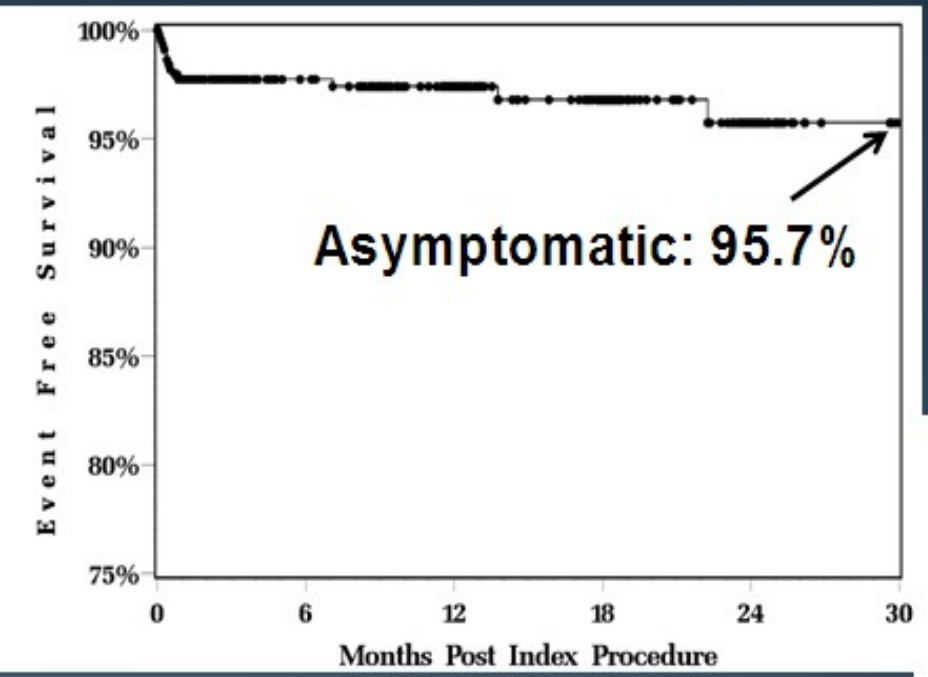
Direct comparison of CEA vs. CAS in high risk: SAPPHIRE

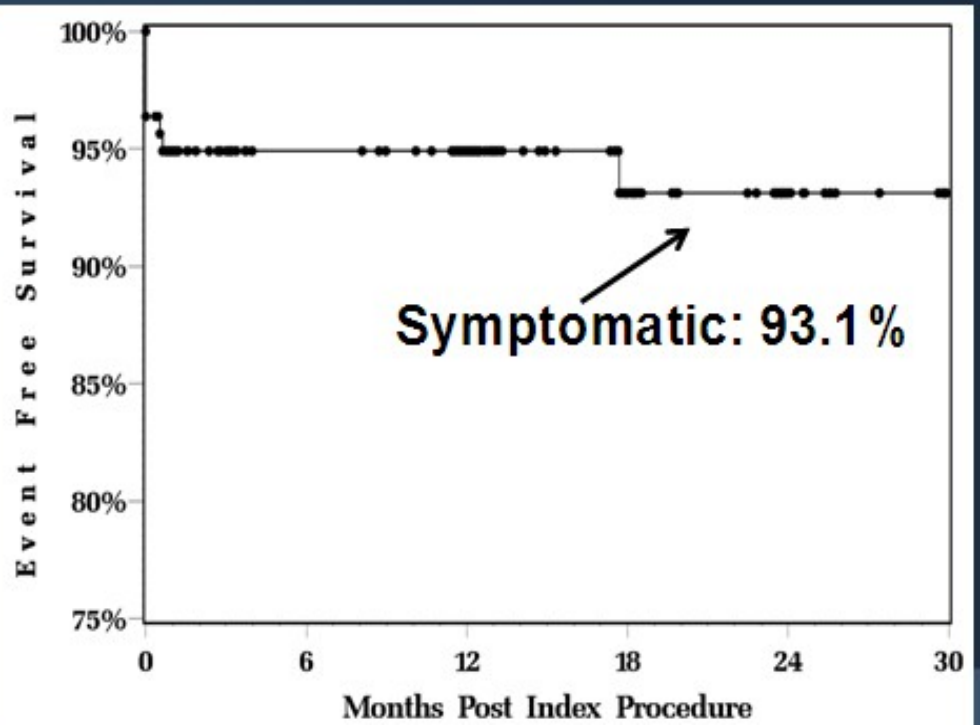


Indirect comparison of CEA vs. CAS in high risk: ARCHeR registry patients: CAS only



ARCHeR: Freedom from periprocedural death/major stroke/major ipsilateral stroke 1 month to 2.5 years





Long Term Stroke Risk

	Normal Risk			High Risk		
	NASCET (2 years)	ACAS (5 years)	ACST (5 years)	SAPPHIRE* (3 Years)		ARCHeR* (3 Years)
Procedure Type	CEA	CEA	CEA	CEA	CAS	CAS
Patient Population	Symptomatic	Asymptomatic	Asymptomatic	Symptomatic & Asymptomatic	Symptomatic & Asymptomatic	Symptomatic & Asymptomatic
Ipsilateral stroke including perioperative stroke or death	9.0%	5.1%	6.4%	6.7% (stroke only)	7.1% rand. 10.3% non-rand. *(stroke only)*	10.4%
Annualized non-periprocedural ipsilateral stroke (estimate)	**1.8%**	**0.6%**	**0.7%**	**1.2%**	**1.2% rand. 1.8% non-rand.**	**1.2%**

Ipsilateral strokes 1 month to 2.5 years*

Number of Events

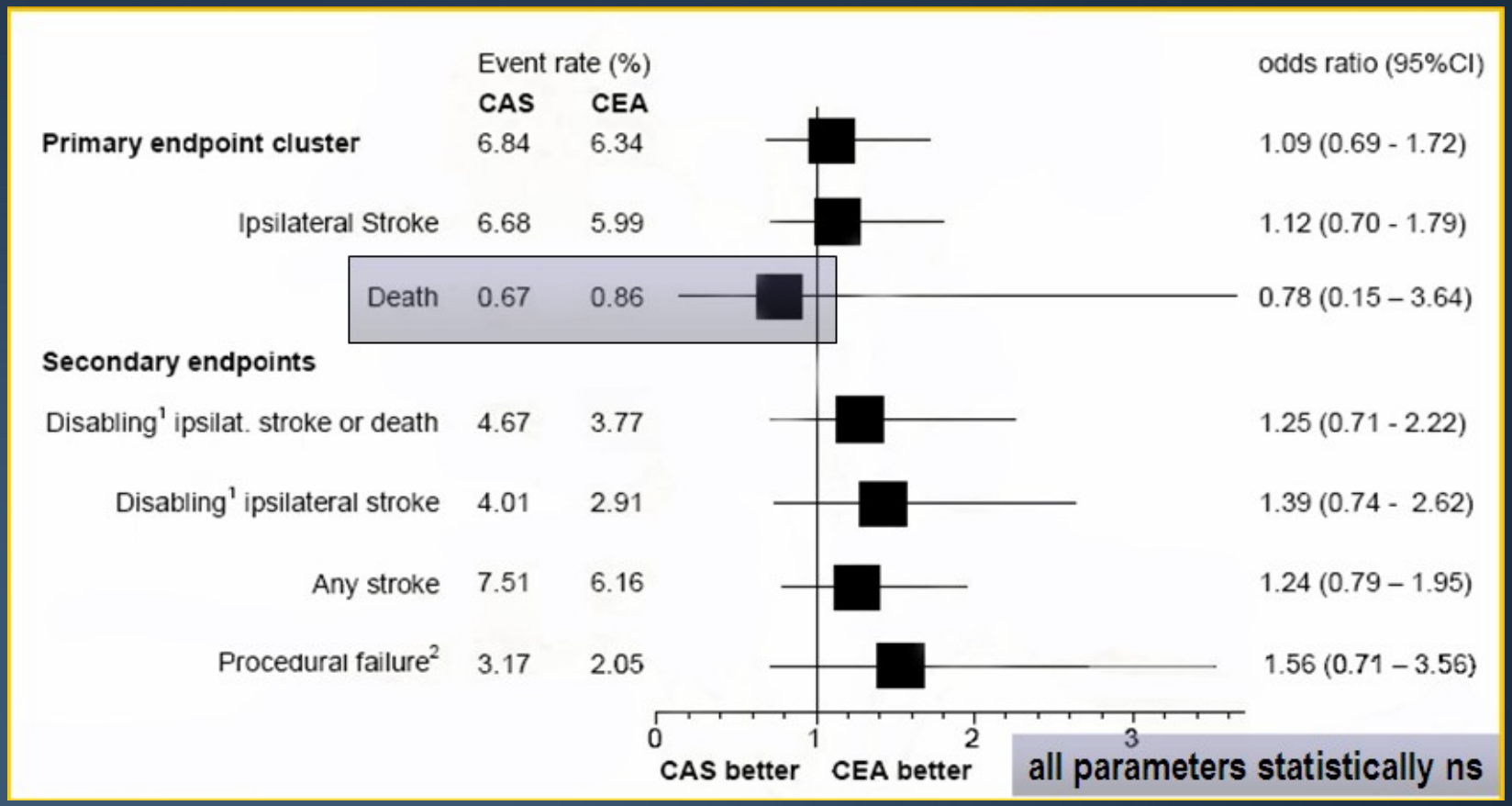
		ARCHeR 1 and 2 N = 436
Fatal strokes		0
	Ischemic	*0*
	Hemorrhagic	*0*
Non-fatal major strokes		4
	Ischemic	*2*
	Hemorrhagic	*2#*
Minor strokes		8
	Ischemic	*8*
	Hemorrhagic	*0*

Average stroke rate/year following CAS: ~0.9%

 # 2 of the major ipsilateral strokes were hemorrhagicsuggesting a non-carotid origin.

*** from Kaplan-Meier estimate at 2.5 years**
Mean follow-up of 502 days
Max follow-up of 1180 days

SPACE


Event rate (%)
CAS
CEA
odds ratio (95%CI)
Primary endpoint cluster
6.84
6.34
1.09 (0.69 - 1.72)
Ipsilateral Stroke
6.68
5.99
1.12 (0.70 - 1.79)
Death
0.67
0.86
0.78 (0.15 – 3.64)
Secondary endpoints
Disabling[1] ipsilat. stroke or death
4.67
3.77
1.25 (0.71 - 2.22)
Disabling[1] ipsilateral stroke
4.01
2.91
1.39 (0.74 - 2.62)
Any stroke
7.51
6.16
1.24 (0.79 – 1.95)
Procedural failure[2]
3.17
2.05
1.56 (0.71 – 3.56)
0
1
2
3
CAS better
CEA better
all parameters statistically ns

SPACE

2-Jahresergebnis

Ipsilateraler Schlaganfall

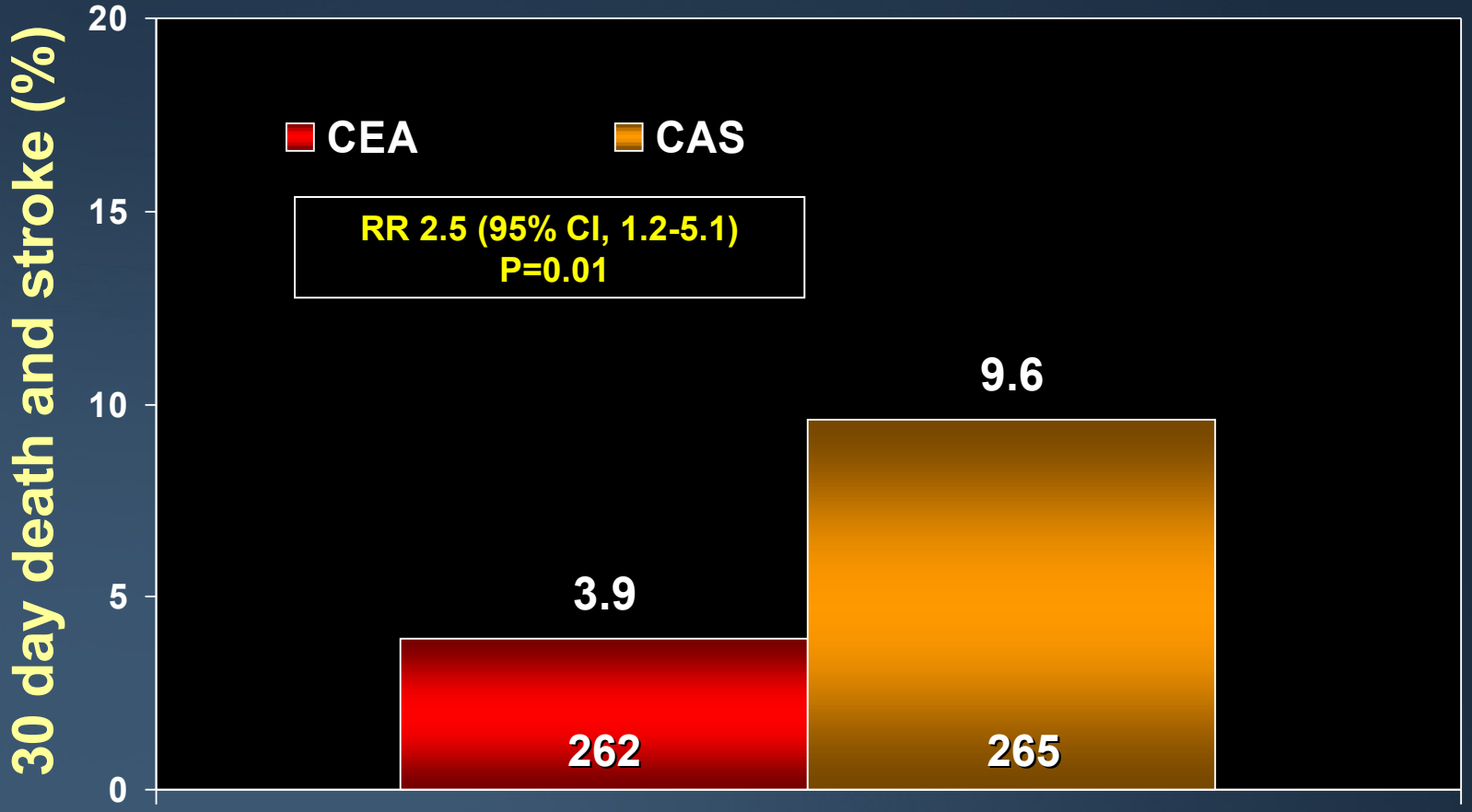
CAS	9,2%	
CEA	8,5%	n.s.

Neue ipsilaterale Schlaganfälle

CAS	12	2,0%	
CEA	10	1,8%	n.s.

P. Ringleb, European Stroke Conference 2008

EVA-3S: Randomized CEA vs. CAS



Mas JL et al. New Engl J Med 2006;355:1661-71

EVA 3S Study

EVA-3S: Stroke or Death at 4 Years by Carotid Treatment

End Point	CAS (%)	CEA (%)	Hazard Ratio (95% CI)	*P*
Periprocedural stroke or death and nonprocedural ipsilateral stroke	11.1	6.2	1.97 (1.06 – 3.67)	.03

EVA-3S: Risk for Stroke or Death at 4 Years for Stenting vs Endarterectomy

End Point	Hazard Ratio	95% CI	*P*
Any stroke or periprocedural death	1.77	1.03 – 3.02	.04
Any stroke or death	1.39	0.96 – 2.00	.08

Mas JL et al, Lancet September 2008

CARESS STUDY

- No difference in Any Stroke between Surgery or stent at 30 days or 4 yrs.

Interval	CEA	Stent	P
30 days	2.2%	2.0%	NS
4 yrs	9.6%	8.6%	NS

JVS2005, C.Zarins TCT 2009 Oct 11th 2008

One-year target lesion revascularization

SAPPHIRE Randomized	
• Stent Arm:	
▪ Clinically Driven TLR:	0.6% (1/159)
• CEA Arm:	
▪ Clinically Driven TLR:	4.0% (6/151) *(p value = 0.06)*

ARCHeR	2.5 year TLR
	3.4%

CREST RESTENOSIS

Results: Overall Restenosis Rates n=643

Restenosis ≥50% in 182 patients:	28%
• Moderate (50-69%) in 134 patients:	21%
• Severe (70-99%) in 45 patients:	7%
• Occlusion in 2 patients:	0.3%

Helmut Lutsup for CREST Investigators 2007

CREST RESTENOSIS

Results: Vessel Characteristics by Angiography

	Restenosed (n=182)	Not restenosed (n=461)	p-value
Lesion length, mm (mean ± SD)	18.7 ± 8.1	17.6 ± 10.1	0.21
Baseline % diameter (mean ± SD)	79.2 ± 9.7	78.8 ± 10.9	0.63
Post % diameter (mean ± SD)	10.8 ± 13.2	7.5 ± 9.7	<0.01

Helmut Lutsup for CREST Investigators 2007

CREST RESTENOSIS

ICA restenosis of 50% or more seen in 28%

- Only 7% had severe stenosis
- No apparent association with new stroke by 1 yr

Possible role for certain clinical risks or vessel characteristics

- Diabetes, dyslipidemia, eccentric lesion and residual stenosis post-procedure tended to be more frequent in restenosis group

Helmut Lutsup for CREST Investigators 2007

CARESS RESTENOSIS

- Baseline characteristics Impacting Restenosis.
- Restenosis as Inclusion Criteria
  - CEA 11%
  - CAS 36% P < 0.001

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CARESS RESTENOSIS

- 4 yr Restenosis by Duplex/ Angiography
- Procedure

Procedure	CEA	CAS	P
Restenosis	5.9%	14.7%	0.01
Repeat Angio	5.1%	11.2%	0.05
TVR	2.18%	5.6%	0.26

- Hawthorne Effect
- More angiography triggers more TVR
- Duplex Criteria?

JVS2005, C. Zarins TCT 2009 Oct 11th 2008

CARESS RESTENOSIS

- Restenosis by Duplex/ Angiography
- Procedure I yr 4 yr
  - CEA 3.6% 5.9%
  - CAS 6.3% 14.7%
  - P < 0.001

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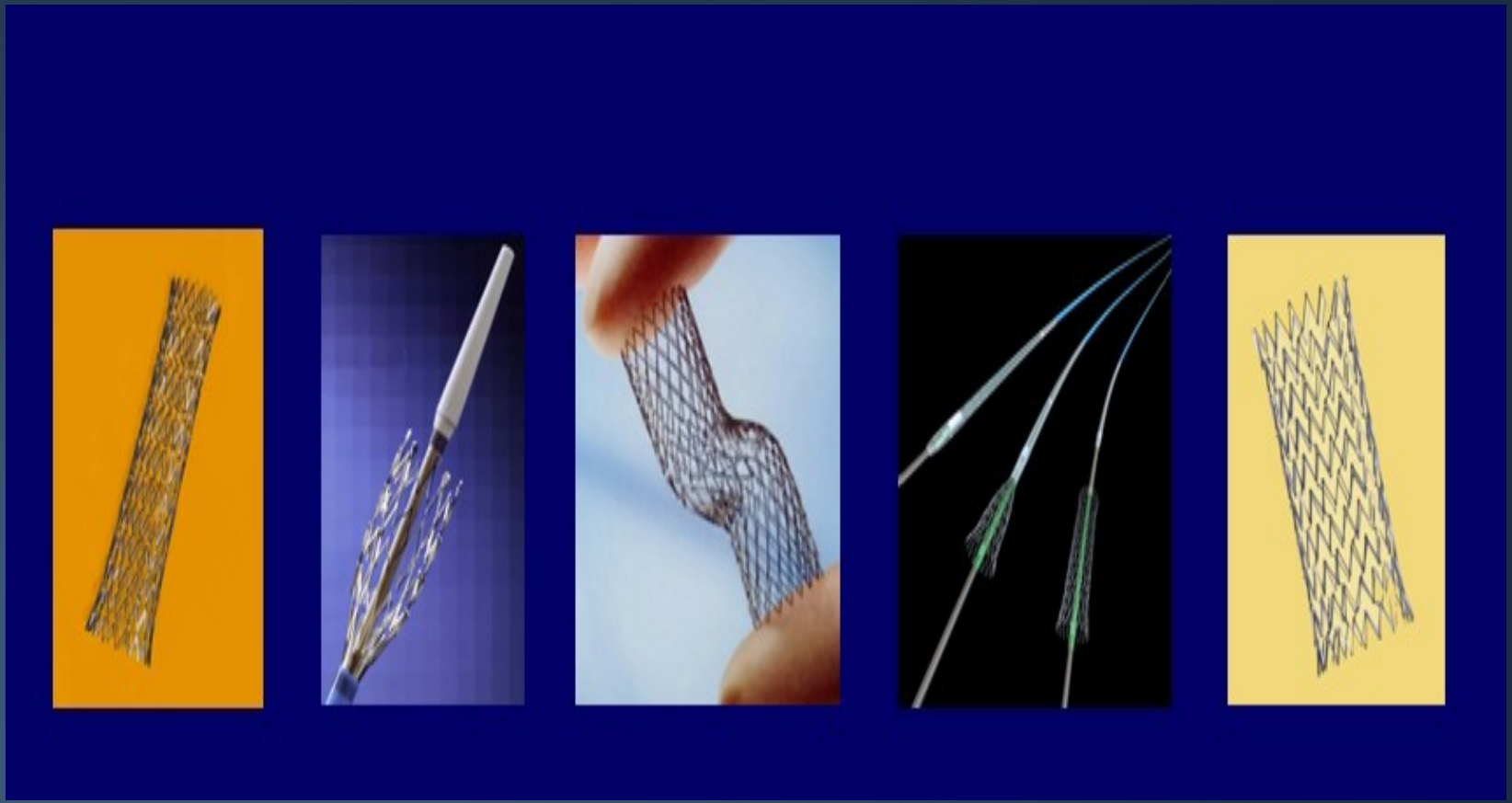
Is Restenosis Stent Dependent?



Carotid Duplex Velocity Criteria Revisited For The Diagnosis Of Carotid In-Stent Restenosis

Ali F. AbuRahma, Damian Maxwell, MD, Kris Eads, MD, Sarah K. Flaherty and Tabitha Stutler, RN
Robert C. Byrd Health Sciences Center of W. Va. Univ., Charleston, WV

Conclusions:

The currently utilized carotid DUS velocity criteria over-estimated the incidence of in-stent restenosis. We propose new velocity criteria of the ICA PSV of >155 c/s to define ≥30% in-stent resteno

Predictive Ability Of Carotid Duplex For Carotid Stent Stenosis

Sam A Zakhary[1,2], Satish Muluk[2]
[1]Baylor University Medical Center, Dallas, TX;[2]Allegheny General Hospital, Pittsburgh, PA

CONCLUSIONS: Currently accepted US velocity criteria for nonstented carotid arteries falsely classified several non-stenotic stented ICAs as having residual in-stent stenosis 50% or greater. We propose new criteria of PSV > 217 cm/s or ICA/CCA ratio > 2.98 as better predictors of >50% stenosis in the stented ICA. Our results suggest that placement of a stent in the carotid artery alters its biomechanical properties, which may cause an increase in US velocity measurements in the absence of a true in-stent stenosis.

New Criteria PSV >217cm/s or ICA/CCA Ratio >2.98 Predicts >50% Stenosis

Conclusions

- CAS is a durable procedure in Stroke Prevention and maintaining Patency
- CAS Restenosis is a benign uncommon event.
- Carotid Duplex Criteria for CAS follow up need validation