

# Update on Carotid Disease

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# LN Hopkins, MD

I disclose the following financial relationship(s):

President, Gates Vascular Institute

CEO, Jacobs Institute

**Consultant/Honoraria** - Abbott, BARD, Boston Scientific, Cordis, Toshiba, Gore, Medtronic

**Financial Interest** - Boston Scientific, Claret, Ostial, Vascular Dynamics, Silk Road

**Director** - Access Closure, Claret, Ostial

**University Grants/Research Support** - Boston Scientific, Cordis, Micrus Toshiba

# Personal Experience

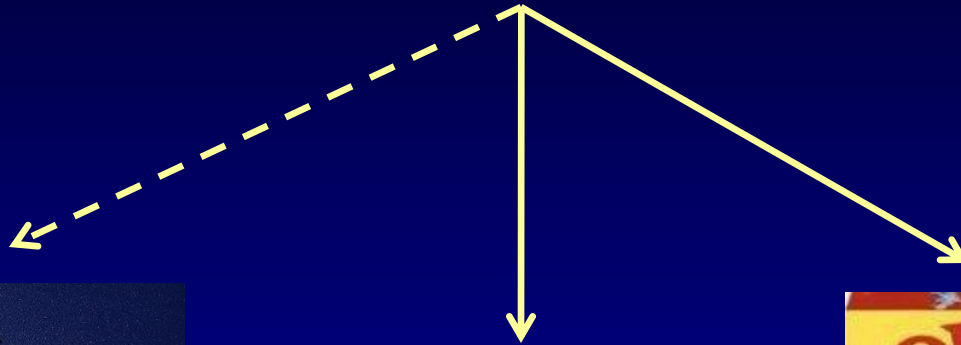
- CEA > 2000 (1979 - present)
- CAS > 2000 (1994 - present)
- UBNS > 3500 (1994-present)
- CREST: Neurosurgery PI, Executive Comm, National Endo Training Center
- Trial Experience as PI / Co PI / Steering Committee:

CREST  
SAPPHIRE  
VIVA  
ACT I  
EMPIRE  
ARMOUR

CABERNET  
CARESS  
CABANNA  
BEACH  
CAPTURE  
ARCHeR

# Carotid Stenosis...Therapeutic Options

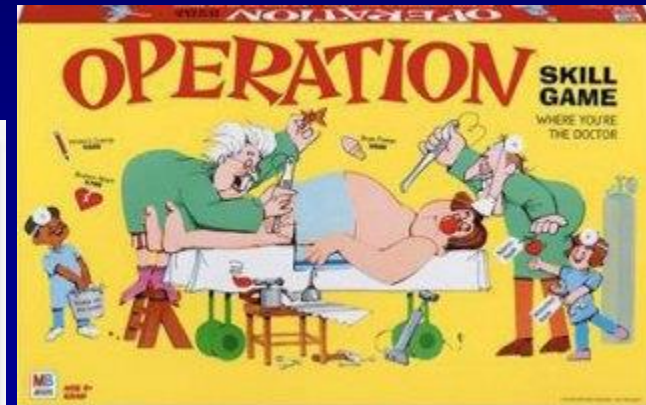
*Two Are Reimbursed*



**Stent**  
**>50% Sx**  
**>75% Asx**



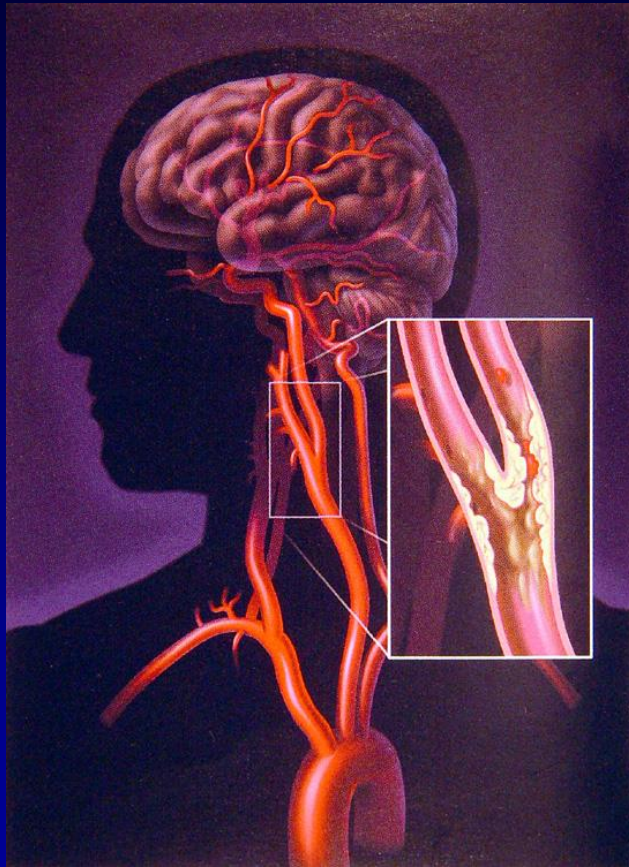
Best Medical Rx



**CEA**  
**>50% Sx**  
**>75% Asx**

## Carotid Endarterectomy...

- *Most studied operation in neuro*
- **WE KNOW WHO IS HIGH RISK**
- *What is it's role today?*



## Carotid Stenting...

*Why has it stagnated?  
Is there definitive data?  
What is it's role...today&future?*

# Symptomatic Carotid Stenosis: *What Do We Know?*

- Carotid stenosis is an emergency
- CEA works well (Nascet, Naylor)
- Less minor strokes than CAS
- Best medical therapy is helpful

*Arch Intern Med.* 2007 Dec 10;167(22):2417-22.

**Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis.**

Wu CM, McLaughlin K, Lorenzetti DL, Hill MD, Manns BJ, Ghali WA.

Department of Medicine, University of Calgary, Calgary, AB, Canada.

- All studies - risk of stroke 3.5% at 2 days, 8% at 30 days
- If only including studies with face-to-face follow up data (excluding studies using “administrative” data): 10% at 2 days and 13% at 30 days

# Asymptomatic Carotid Stenosis: *What Do We Know?*

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CEA is better than medical Tx (ACAS & ACST)

- CEA prevents strokes in women (ACST)
- CEA prevents disabling strokes (ACST)
- CEA prevents fatal strokes (ACST)

## **Does CAS Do The Same ?**

# Risk Factors for CEA vs Risk Factors for CAS

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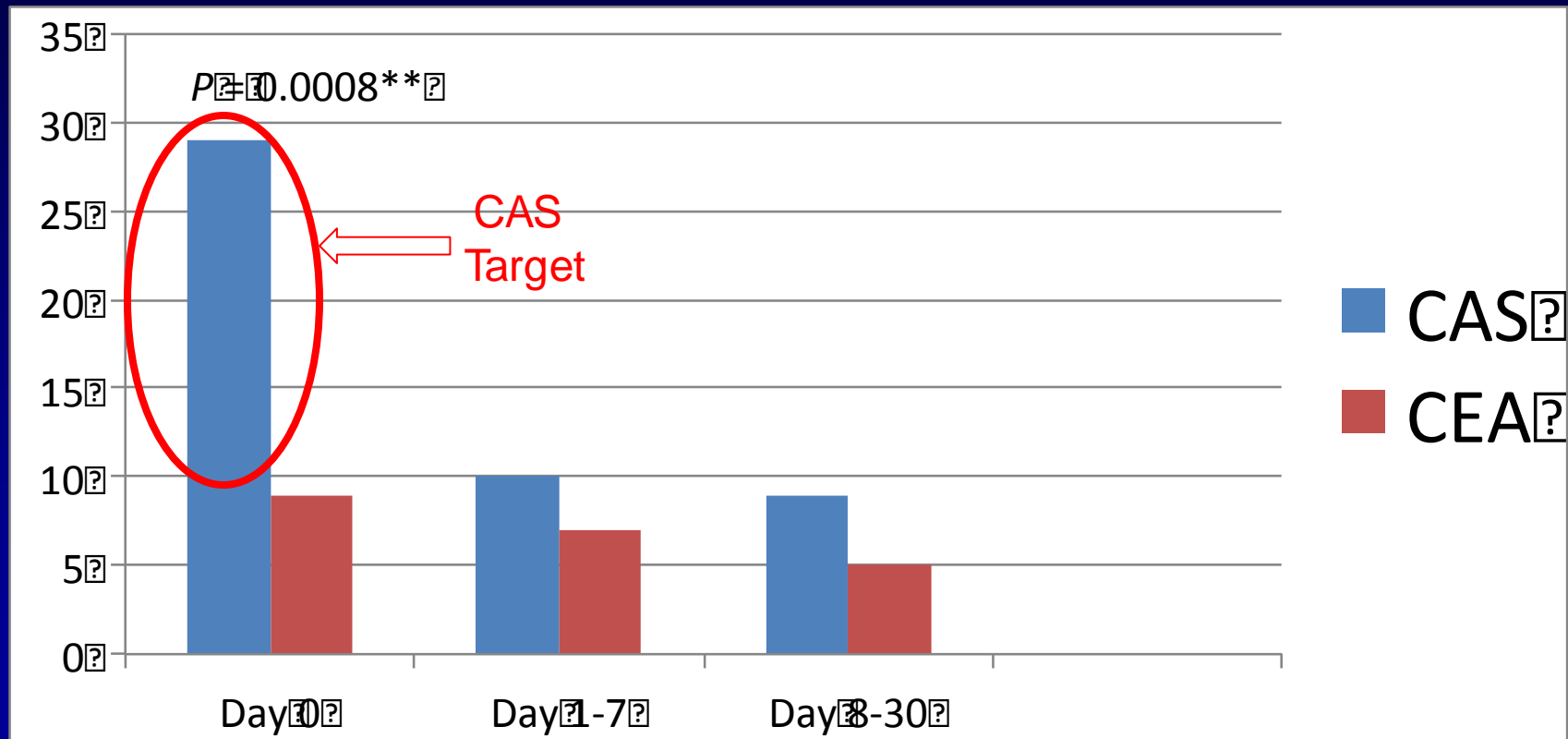
- Risk factors very different
- CEA risk factors well known
- CAS risk factors... we are still learning
- CREST design 1999 (5 yrs after 1<sup>st</sup> CAS)
- CREST trial 2000-2004 vs 2004-2008...  
learning curve... experience counts



## CEA vs. CAS

- CREST: established clinical equipoise of CEA and CAS
  - More MI's with CEA
  - More MINOR strokes with CAS
- Analysis of CREST data: stroke rate with CAS was significantly higher only **on day 0 of procedure**

# Timing of Stroke After Carotid Revascularization: CAS vs. CEA



# Evolution of CAS

## *Overcoming the Barriers*

- Elderly pts (high need/increased Tx risk)
- Symptomatic pts (high need/increased Tx risk)
- Access issues (femoral – arch - carotid)
- Perioperative stroke
- Experience and judgment in current reimbursement climate
  - **Today No choice for most patients!!**

# CEA and CAS: High Risk Profiles

## For CEA:

- Recurrent stenosis post CEA
- Previous neck surgery or radiation
- Tandem lesion
- Lesion above C2 or below clavicle
- Poor cardiac or pulmonary status

## For CAS:

- Tortuous and diseased arch or common carotid artery access
- Elderly and symptomatic patients(??)
- High risk for bleeding with dual antiplatelet therapy
- Severe dye allergy

# Unanswered Questions

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- Can we further reduce Risk for CAS ?
- Should we treat elderly pts with CAS ?
- Should we treat sx pts with CAS? If so, How??
- Are CEA and CAS complimentary?
- What is the future of CEA?

# What About Elderly Patients(75-79)

## *NASCET Analysis*

- Absolute risk reduction(ARR) overall = 17%
- **ARR in pts 75-79 = 30%**

**Elderly pts are at higher risk for stroke  
At higher risk for CEA and CAS and...**

**Are the patients who most need treatment**

# Decision Making for CAS

*It's Mostly About Anatomy and Pharmacology!*

- Anatomical factors
  - Arch disease, tortuosity
  - Tortuosity of the Common Carotid
  - Contralateral carotid occlusion
  - High bifurcation
  - Ostial and tandem lesion
  - Hostile neck
- Clinical factors
  - Intolerance to anti platelet meds
  - Associated medical conditions(CHF etc)

# European RPCT...CEA Looks Better??

- **EVA 3S**                      **9.6%**                      **vs**                      **3.9\***
- **SPACE**                      **6.8%**                      **vs**                      **6.3**
- **ICSS**                      **8.5%**                      **vs**                      **5.2\***

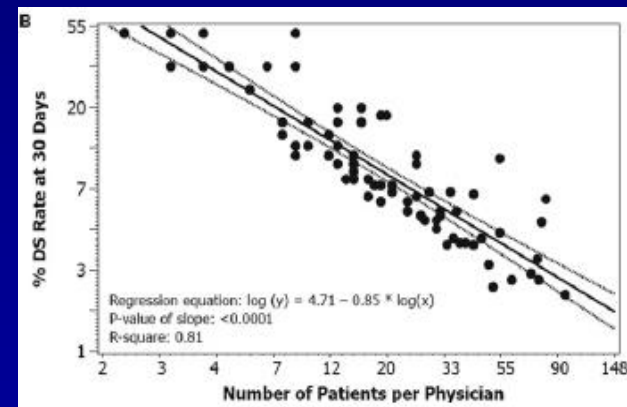
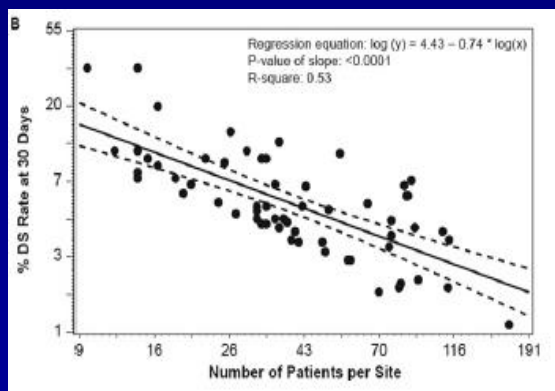
## What Have We Learned?

- More minor strokes with CAS
- Experience counts
- Embolic Protection Helps
- MI not searched for...does it matter?



## Facility and Physician Experience Positively Correlated with Favorable Outcomes\*

- 3,388 asymptomatic, non-octogenarian patients from 180 hospitals and 459 operators. 30-day DS rates were 2.7%. 82% of physicians had no DS events. The remaining 18% had at least 1 DS event; 92% of these operators had DS rates exceeding 3%.
- An inverse relationship between event rates and operator volume was observed. A **threshold of 72 cases** was found to be necessary for consistently achieving a D/S rate below 3%



\*Gray WM, Rosenfield KA, Jaff MR, Chaturvedi S, Peng L, Verta P. Influence of Site and Operator Characteristics on Carotid Artery Stent Outcomes Analysis of the CAPTURE2 Clinical Study. *JACC: Cardiol Intv* 2011;4:235-46.

*The* **NEW ENGLAND**  
**JOURNAL of MEDICINE**

Stenting versus Endarterectomy for Treatment  
of Carotid-Artery Stenosis

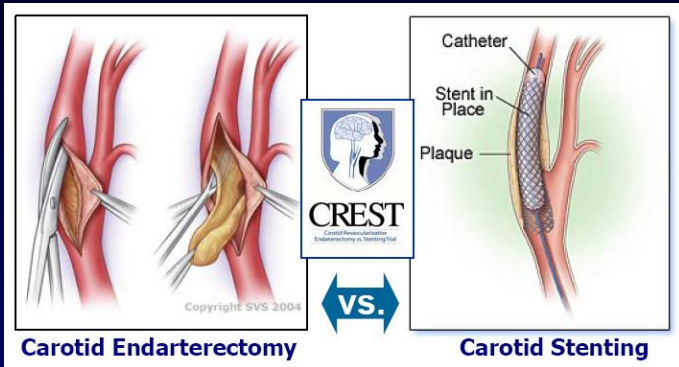
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JULY 1, 2010

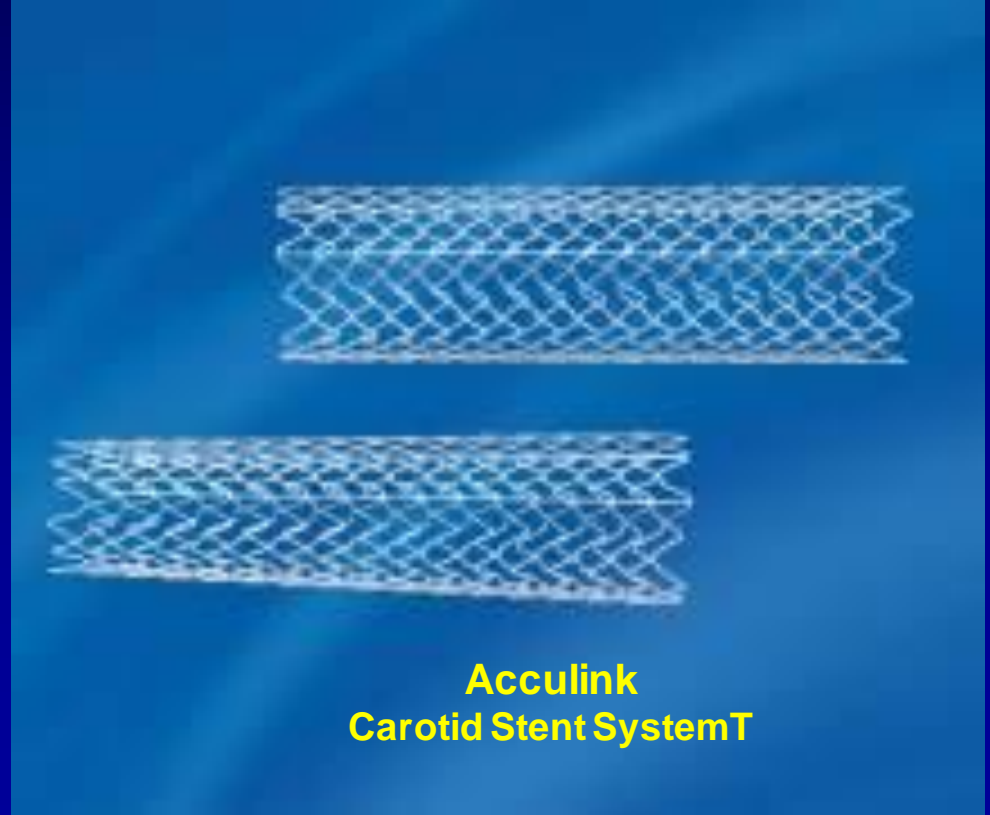
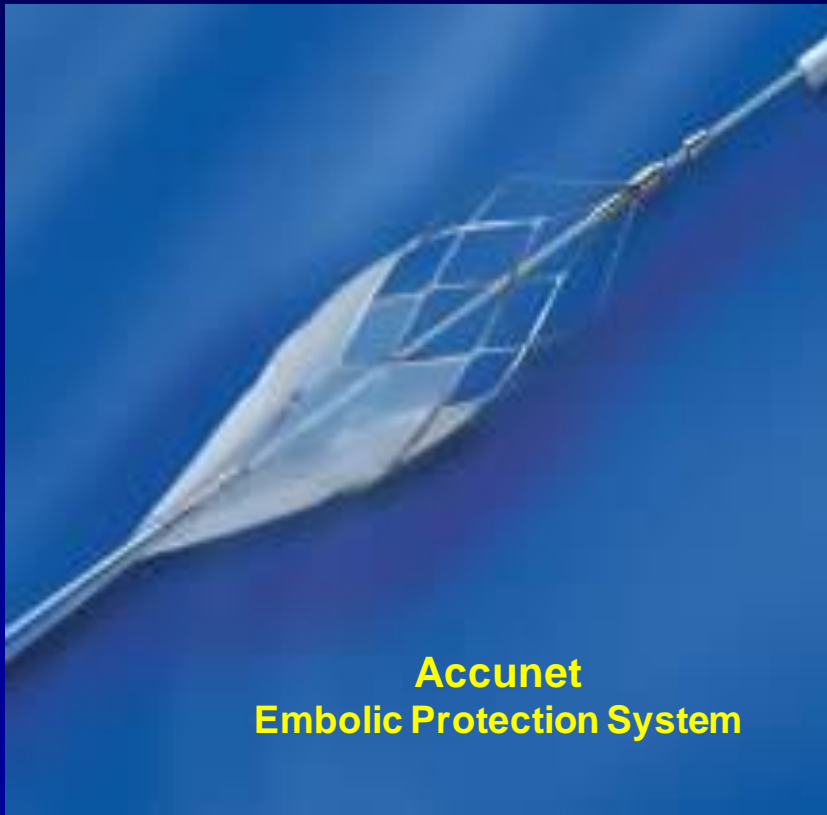
VOL. 363 NO. 1

**Carotid Revascularization  
Endarterectomy vs.  
Stenting Trial (CREST)**





# CREST Trial 2000-2008 First Gen Technology



# Primary Endpoint $\leq 4$ years

(any **stroke, MI, or death** within peri-procedural period plus ipsilateral stroke thereafter)

<b>CAS vs. CEA</b>	<b>Hazard Ratio, 95% CI</b>	<b>P-Value</b>
<b>7.2 vs. 6.8%</b>	<b>HR = 1.11; 95% CI: 0.81-1.51</b>	<b>0.51</b>

# Crest Take Home Points

## **1. Best ever results for CEA and CAS !!**

Overall Mortality 0.6%, Major Stroke 0.85 %

2. CEA results outstanding... 60 year evolution  
CAS results outstanding... 15 year history

**CAS early on learning and technology curve**

# The Major Issue = Minor Strokes Not Major Strokes

- **CREST in Context:**
  - Analysis of CREST compared to ICSS, EVA-3S, SPACE.

	Sx/Asx**	30d Stroke/Death		30d Stroke		30d Major Stroke†		30d MI		EPDs Used	
		CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA		
<b>EVA-3S</b>	527/0	9.6 %	3.9%	8.8 %	2.7 %	2.7 %	0.4 %	0.4 %	0.8 %	92 %	
<b>SPACE</b>	1196/0	6.9 %	6.5 %	7.5 %	6.2 %	4.1 %	2.9 %	NK	NK	27 %	
<b>ICSS*</b>	1713/0	7.4 %	3.4 %	7.0 %	3.3 %	1.7 %	1.7 %	0.4 %	0.6 %	72 %	
<b>CREST#</b>	1321/1181	Sx	6.0 %	3.2 %	5.5 %	3.2 %	0.9 %	0.6 %	1.0 %	2.3 %	96 %
		Asx	2.5 %	1.4%	2.5 %	1.4 %			1.2 %	2.2 %	

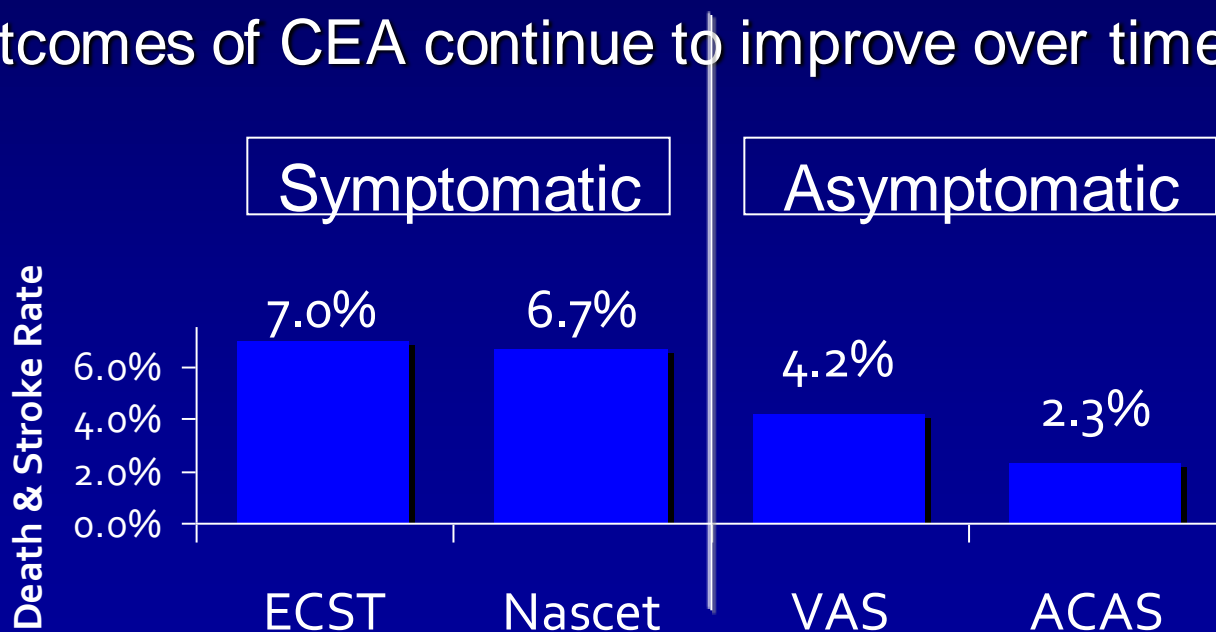
Message About Filters???

# History of Carotid Artery Stenting (CAS) Treatment

- **1994:** First CAS
- **1998-2000:** CREST planning - inclusion/ exclusion
  - 4 years after first CAS
- **2004:** First FDA approval of CAS for patients at high risk of CEA (Acculink stent system)
- **2011:** FDA Approval...low risk patients

# Outcomes of CEA Over Time

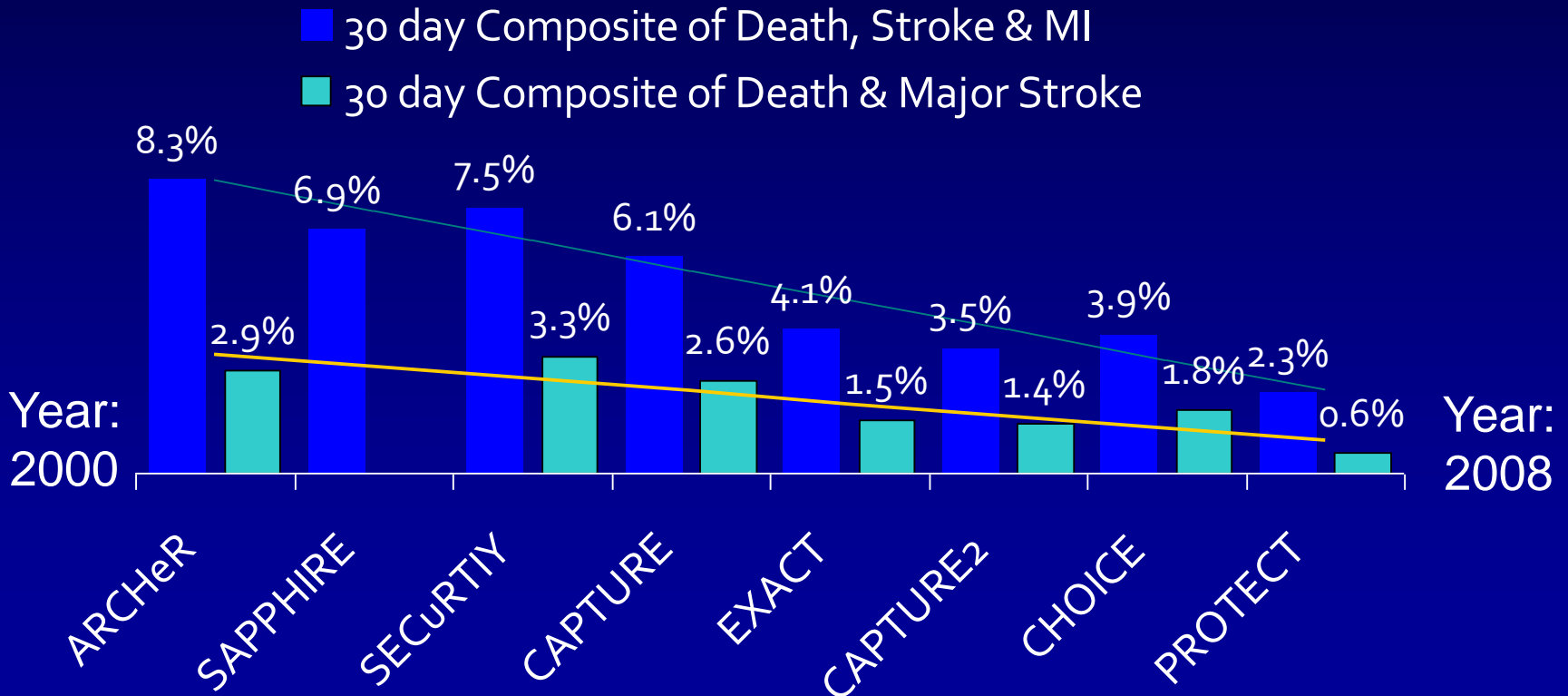
- In the 1970's: CEA risk up to 21% in some reports
  - Easton and Sherman
- In the 1990s: death and stroke rates were 6%-7% for symptomatic patients and 3%-4% for asymptomatic patients
- Outcomes of CEA continue to improve over time





# Outcomes of CAS Trials Over Time

- CAS results have vastly improved over time due to:
  - (1) more experienced operators; (2) better patient selection
  - (3) a wider spectrum of technology
- CAS outcomes have evolved over time similarly to CEA



(Enrollment: 2000-2004) CREST – 5.7%

(Enrollment: 2005-2008) CREST – 1.1%

# Why are Recent CAS Results Better ?

## CREST CAS Specific Exclusion Criteria Asx Patients Randomization Often Based on Ultrasound Alone

- 1. Severe vascular tortuosity or anatomy that would preclude the safe introduction of a guiding catheter, guiding sheath or stent placement.
- 2. Presence of extensive or diffuse atherosclerotic disease involving the aortic arch and proximal common carotid artery that would preclude the safe introduction of a guiding catheter or guiding sheath.
- Criteria based on operator discretion

**CREST CEA Specific Exclusions = 22**

## Today We Have a Better Understanding...

### Stenting Exclusion Criteria Proposed for CREST II

- Occlusive or critical ilio-femoral disease that precludes safe femoral access to the aortic arch.
- Angiographic, C.T., M.R. or ultrasound evidence of severe atherosclerosis of the aortic arch or origin of the innominate or common carotid arteries.
- Type III, calcified aortic arch anatomy in patients > 75 years that may preclude safe and expeditious sheath access to the common carotid arteries.
- Angulation or tortuosity (>90 degree) of the innominate, right common carotid artery or left common carotid artery that precludes safe, expeditious sheath placement or will transmit a severe loop to the internal carotid after sheath placement.
- Severe angulation or tortuosity of the internal carotid artery (including calyceal origin from the carotid bifurcation) that precludes safe embolic protection device or stent placement. Severe tortuosity is defined as 2 or more >90 degree bend points within 3cm of the target Stenosis.
- Excessive circumferential calcification of the stenotic lesion defined as > 3mm of calcification seen in orthogonal views on fluoroscopy.
- Elderly subjects (>75 years) with any 2 or more of the following (including advanced age)
- Unfavorable arch anatomy or tortuosity as defined in exclusions 3, 4 & 5.
- Excessive calcification.
- Decreased Cerebral Reserve. Defined as prior (remote) large stroke, multiple lacunar infarcts, or dementia. Prior large stroke was defined by > 1/3 middle cerebral artery territory infarction on CT brain; multiple lacunar infarcts was defined by diffuse lacunes associated with encephalomalacia and/or cerebral atrophy on CT brain; dementia was assessed by a mini-mental state examination if indicated by clinical suspicion.
- Stenosis of the carotid bifurcation (common carotid) and/or ipsilateral external carotid artery in combination with a hostile arch-type III, heavily calcified or atherosclerotic that precludes safe sheath placement in to the common carotid artery.
- Stenosis that contain visible thrombus.
- Occlusion (TIMI0 flow) or "string sign of the ipsilateral common or internal carotid artery.
- Stenotic lesions (normal appearing vessel to normal appearing vessel) greater than 25mm in length.



# **PMA Analysis of the CREST Trial**

## *FDA Analysis of the RX Acculink Carotid Stent System for Revascularization of Carotid Artery Stenosis in Standard Surgical Risk Patients*

**PMA Analysis = Per Protocol**



**TOSHIBA**  
**STROKE**  
**RESEARCH**  
**CENTER**



**KALEIDA**  
H E A L T H



**University at Buffalo**  
*State University of New York*

# PMA Primary Endpoint

Composite of all death, any stroke, or MI to 30 days

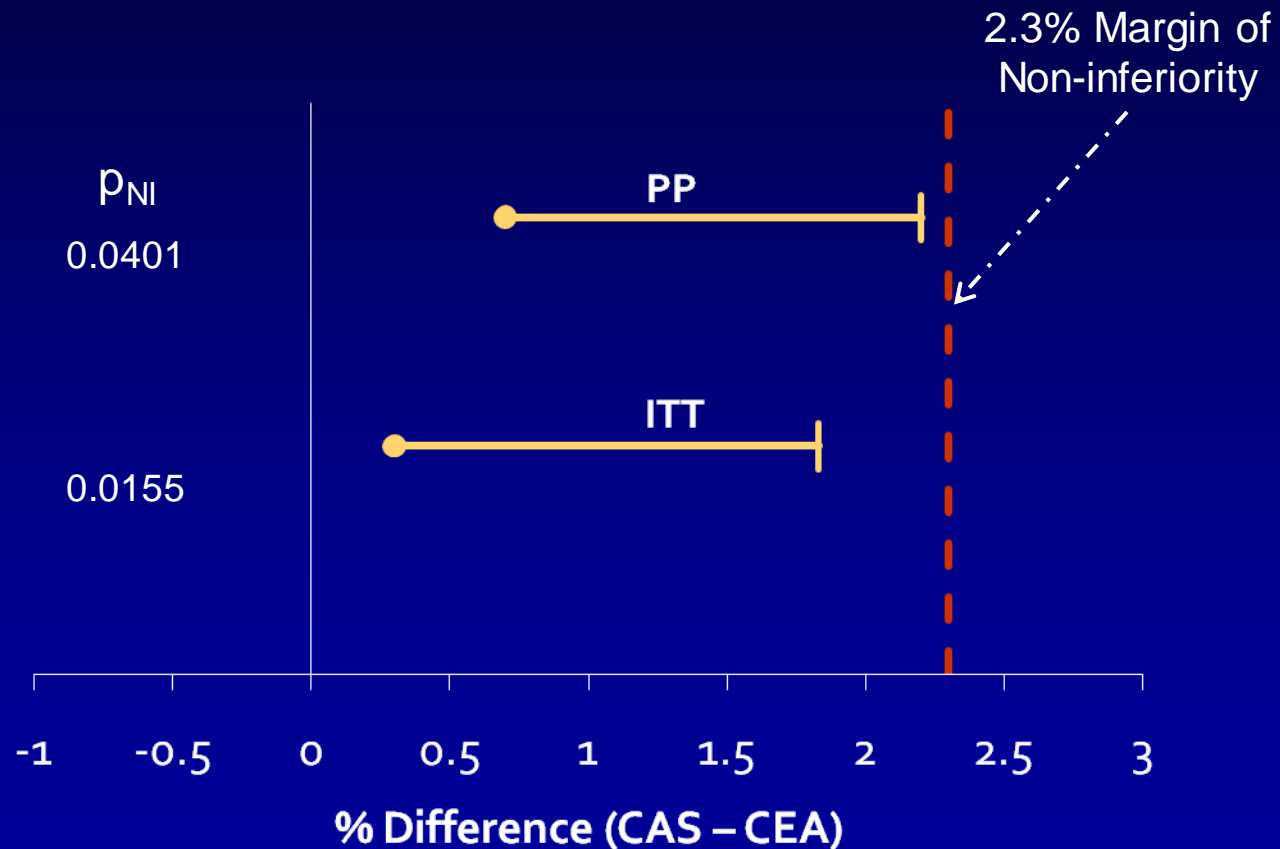
Plus

Ipsilateral stroke from 31 to 365 days



# CAS is Non-inferior to CEA for Peri-Procedural DSMI

	CAS	CEA	95% CL	$p_{NI}$
PP	5.8%	5.1%	2.20%	0.0401
ITT	5.8%	5.5%	1.83%	0.0155



## Key Differences...

### *Death, Stroke and MI within 30 Days*

Per protocol	CAS N = 1,131	CEA N = 1,176	Difference	Unadjusted p-value*
All Death, Stroke, or MI	5.8% (65)	5.1% (60)	0.7%	0.5200
Death	0.53% (6)	0.26% (3)	0.27%	0.3335
Any Stroke	4.1% (46)	1.9% (22)	2.2%	<b>0.0019</b>
Major Stroke	0.9% (10)	0.4% (5)	0.5%	0.2005
Minor Stroke	3.2% (36)	1.5% (18)	1.7%	<b>0.0088</b>
MI	2.0% (22)	3.4% (40)	-1.5%	<b>0.0387</b>

\* Fisher's exact p-values were not adjusted for multiple comparisons; p-values for descriptive purposes only

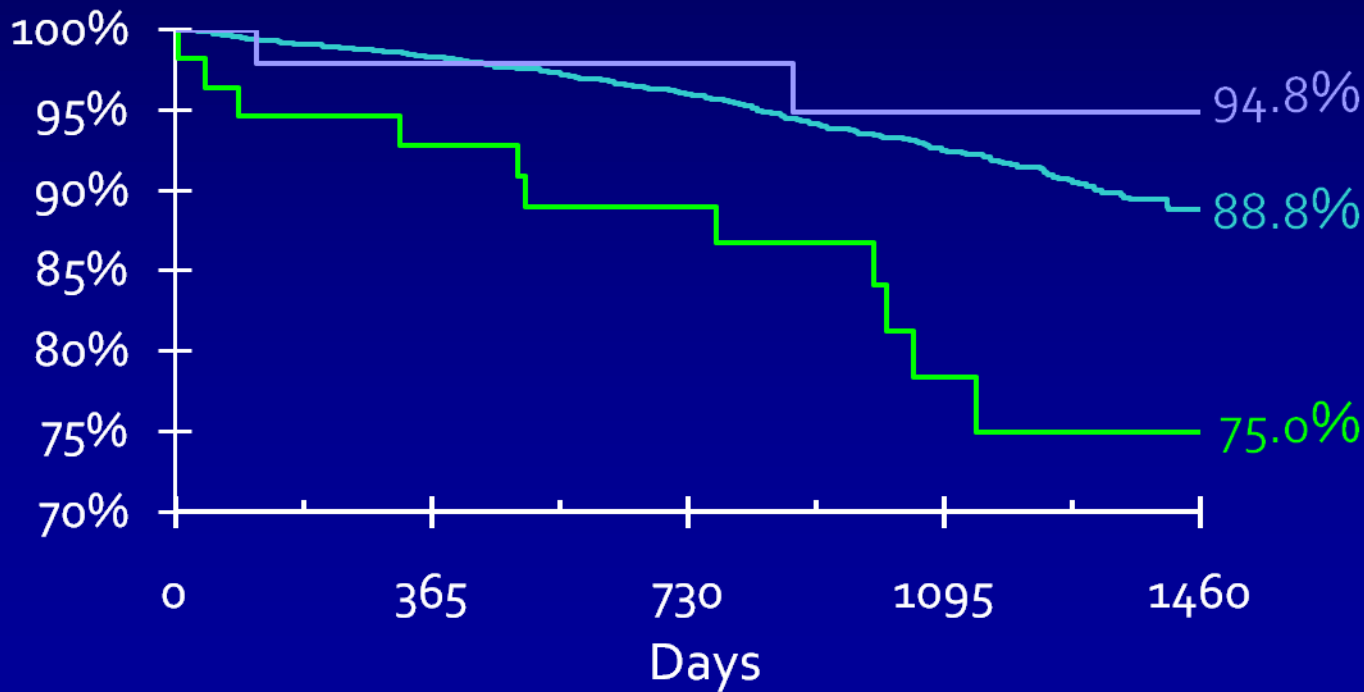


# Why MI as a Primary Endpoint ?

## Long Term Mortality- Minor Stroke vs MI

Comparison	HR	HR Confidence Interval	Log Rank P-value
MI vs. Control	2.81	[1.53 - 5.17]	0.0005
Minor Stroke vs. Control	0.52	[0.13 - 2.09]	0.34
MI vs. Minor Stroke	5.18	[1.15 - 23.4]	0.02

Freedom From All Cause Mortality





# Outcomes Balance for CAS and CEA

- Death or Major Stroke
  - Low rates for both CAS and CEA
  - Decreasing MAE rates for CAS over time
  - Similar rates for CAS and CEA in the second half of the study
- Minor stroke
  - More frequent with CAS at 30 days (absolute difference 1.7%)
  - Decreasing rates for CAS over time
  - By 6 months, CAS and CEA show similar low rates of residual neurological disability (0.80% vs 0.50% for overall population)
- Peri-procedural MI
  - More frequent with CEA at 30 days (absolute difference 1.5%)
  - Shows a significant relationship to mortality

# What Have We Really Learned From CREST ?

Politics have killed expanded reimbursement

More data needed

# What is Clear From CAS Trials...

## **CAS Compliments CEA**

- Medical Co morbidities... esp cardiac
- Surgical high risk... esp recurrent stenosis
- Poor collateral circulation/tandem lesions
- Neurologic instability
- Anatomical considerations



~~CEA or CAS~~

**CEA AND CAS**



# Barriers to CAS

- Reimbursement: <10% covered by CMS
  - Experience factor
  - Industry turn off thwarting new technology
- Competing specialties
  - VS leadership against CAS
  - Neurology against all Carotid surgery
  - Cardiology vested interest
- Higher incidence of preoperative stroke



**CREST**  
Carotid Revascularization  
Endarterectomy vs. Stenting Trial

# Factors Adverse for CAS and Favoring CEA

- Age greater than 80...?? anatomy
- Female gender
- Compromised arterial access
- Tortuous aortic arch or severe atherosclerosis
- Carotid artery tortuosity
- Elongated plaque of the internal carotid artery
- Carotid plaque ulceration
- Severe carotid plaque calcification

# Important Risk Factors for CAS

## Remaining Obstacles ...

*From All the Trial Data*



- Symptomatic Patients  
“Hot Lesions”
  - Octogenarians
  - Tortuosity



*Current State of Affairs*  
**More Minor Strokes with CAS**  
*Elderly and Sx Patients*

**The Issues:**

**Anatomy & Case selection**

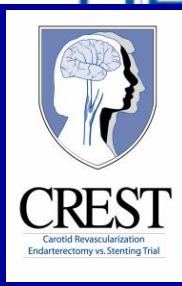
**Experience**

**Which type EP to use?**

**3 main types**

- distal occlusion balloons
- distal filters
- proximal protection devices





# Factors Adverse for CEA and Favoring CAS

- History of congestive heart failure
- Unstable angina pectoris
- Un-reconstructable triple vessel coronary disease
- Need for combined coronary and carotid revascularization
- Severe pulmonary dysfunction
- Dialysis dependent renal failure
- Hostile neck anatomy
- Prior cervical radiation with skin damage
- Lesion of internal carotid artery extending above C-2
- Recurrent carotid stenosis after prior CEA
- Contra-lateral carotid occlusion

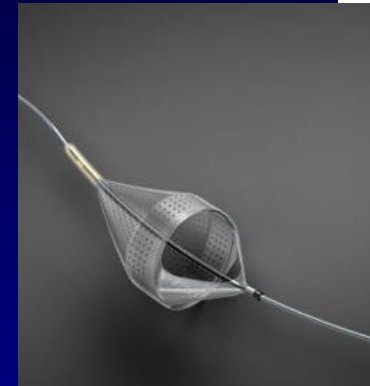
# DWI and TCD Studies Post CEA & CAS

- More hits post CAS
- More hits with filters vs proximal EP
- No definite clinical correlation
- Significance of concern

## Solving CAS Problems

### *Proximal Versus Distal Protection*

- Distal protection – filters
- Proximal protection – flow arrest or reversal
- Outstanding FDA trial results with proximal EP (Gore, Invatec)
- Direct Carotid Approach (ROADSTER)



# Solving CAS Problems

- **Proximal protection devices**
  - **Complete flow arrest/reversal**
  - **Advantages**
    - Protection before traversing the lesion
    - Valuable with tight irregular stenosis
    - Allows capture of all size particles
    - **Trial results are excellent**
      - EMPIRE, ARMOUR
- **Better results with symptomatic patients**

# Elderly Patients??

Solving CAS Problems

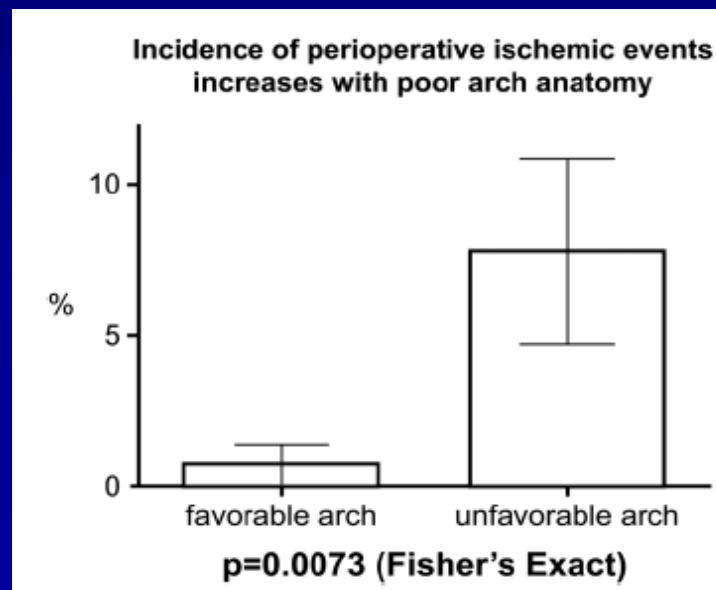
Journal of

NEUROINTERVENTIONAL SURGERY

Understanding risk factors for perioperative ischemic events with carotid stenting: is patient age over 80 years or is unfavorable arch anatomy to blame?

Travis M Dumont,<sup>1,2</sup> Maxim Mokin,<sup>1,2</sup> Michael M Wach,<sup>1,2</sup> Patrick S Drummond,<sup>1,2</sup>  
Adnan H Siddiqui,<sup>1,2,3,4</sup> Elad I Levy,<sup>1,2,3,4</sup> L Nelson Hopkins<sup>1,2,3,4,5</sup>

- Increased incidence of perioperative complications in patients with unfavorable aortic arch anatomy
- Excellent results in elderly pts with favorable anatomy



**Understanding risk factors for perioperative ischemic events with carotid stenting: is it patient age over 80 years or is it unfavorable arch anatomy to blame?**

Consecutive series, mean age 71.6, N=240

**Difficult arch: 7.9% M&M** (TIA or minor stroke)  
52% age > 80, female, < CAD, L side lesions

**Normal arch: 0.7% M&M** (TIA or minor stroke)  
29% > age 80

**It's NOT the age, It's the Anatomy!**

# Access Obstacles for CAS

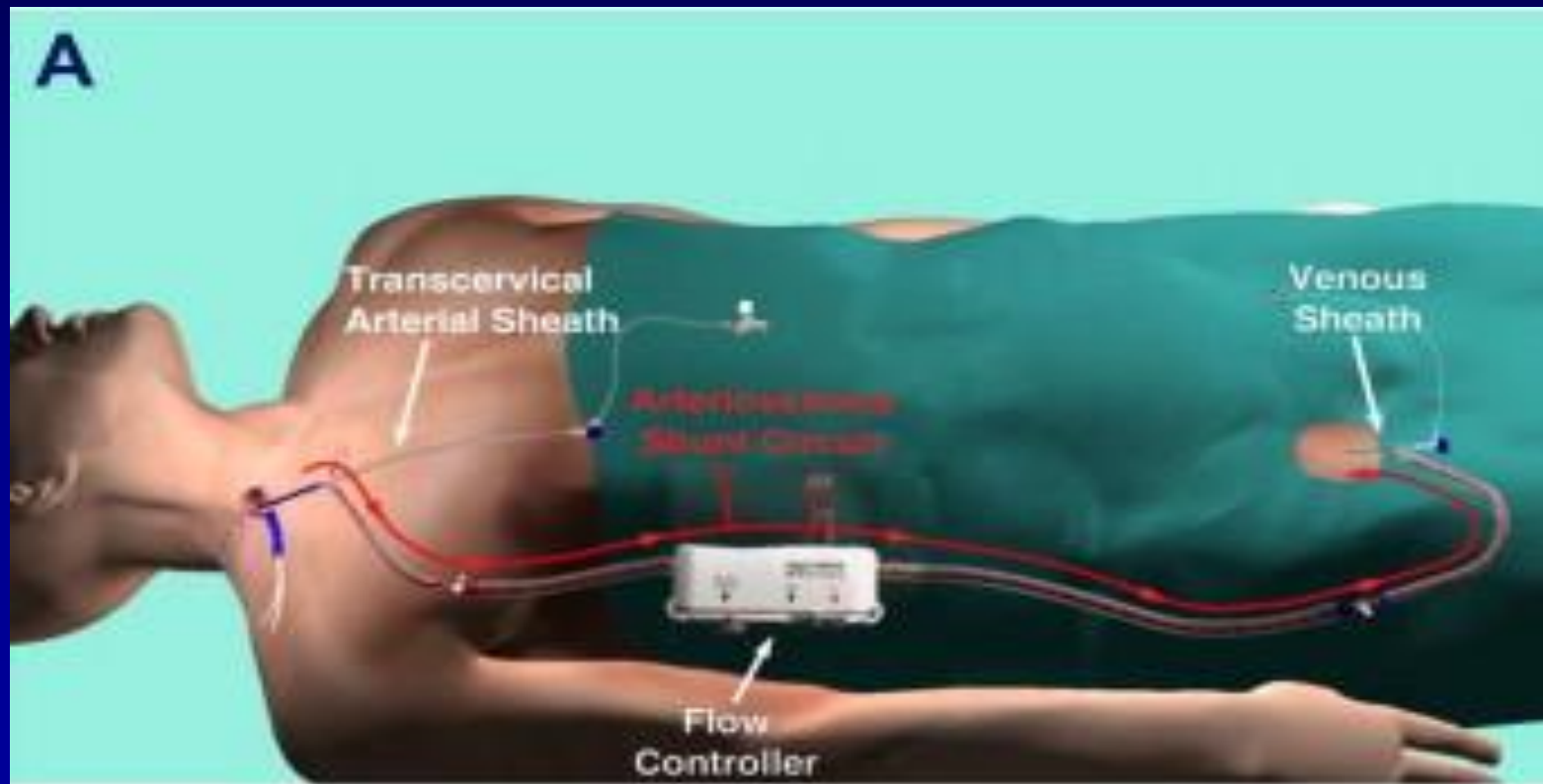
*Arch Issues ...Especially in Elderly Patients*



- Arch Anatomy
- Arch Tortuosity
- Arch disease
- Ostial disease
- Prox CCA kinks

# Prevention

## *Direct Carotid Access and CAS*

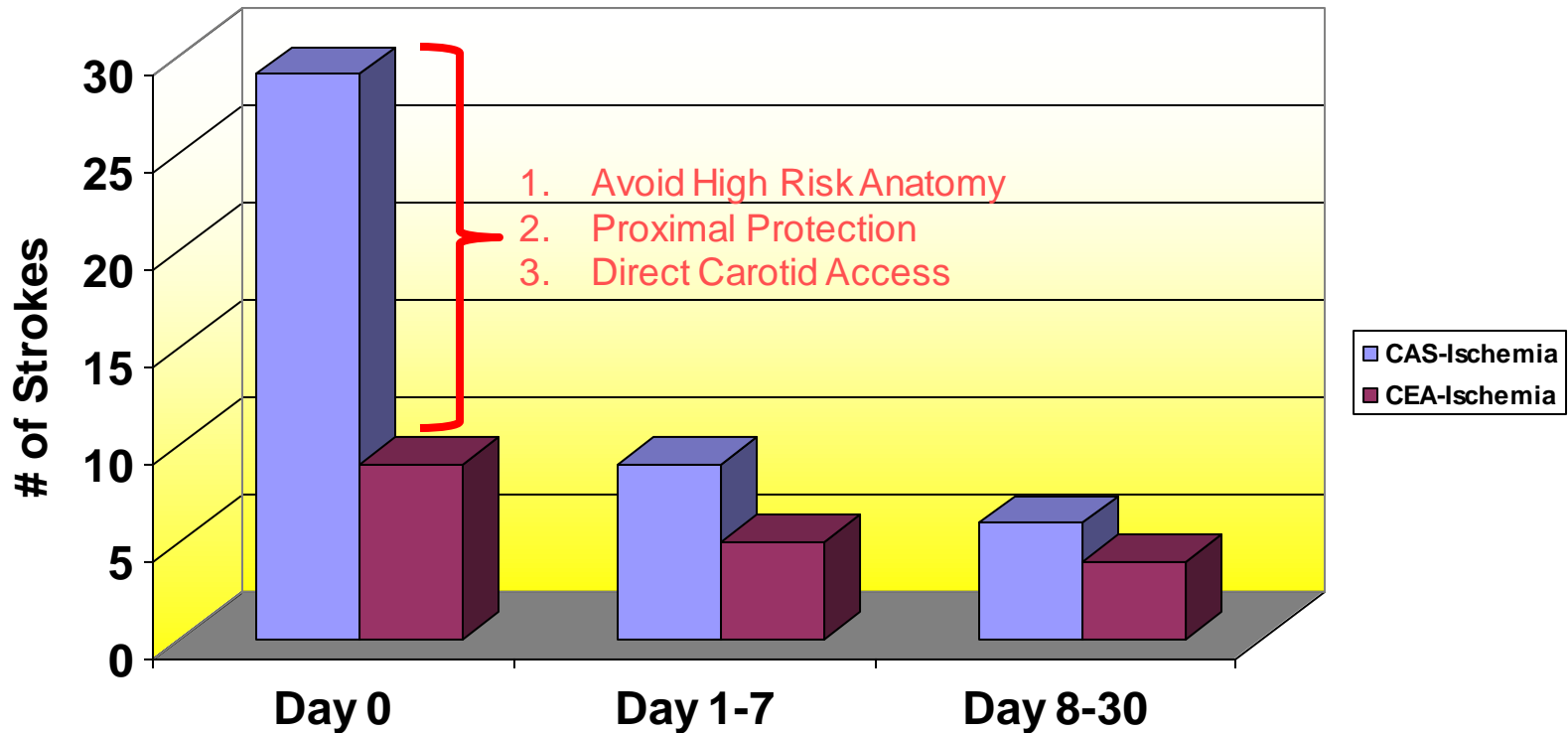




# Procedural Stroke

## New Tools

Timing from Procedure for Ischemic Stroke



# Delayed Stroke

- 78-year old WM
- Visual difficulties ?TMB Right
- PMH:Cardiac stents x5
- Carotid dopplers: Rt 80-99% stenosis
- Dx Angio : Right ICA stenosis 81% left< 50%

# Pre-stent angioplasty followed by exact stent deployment



# IVUS detected thrombus

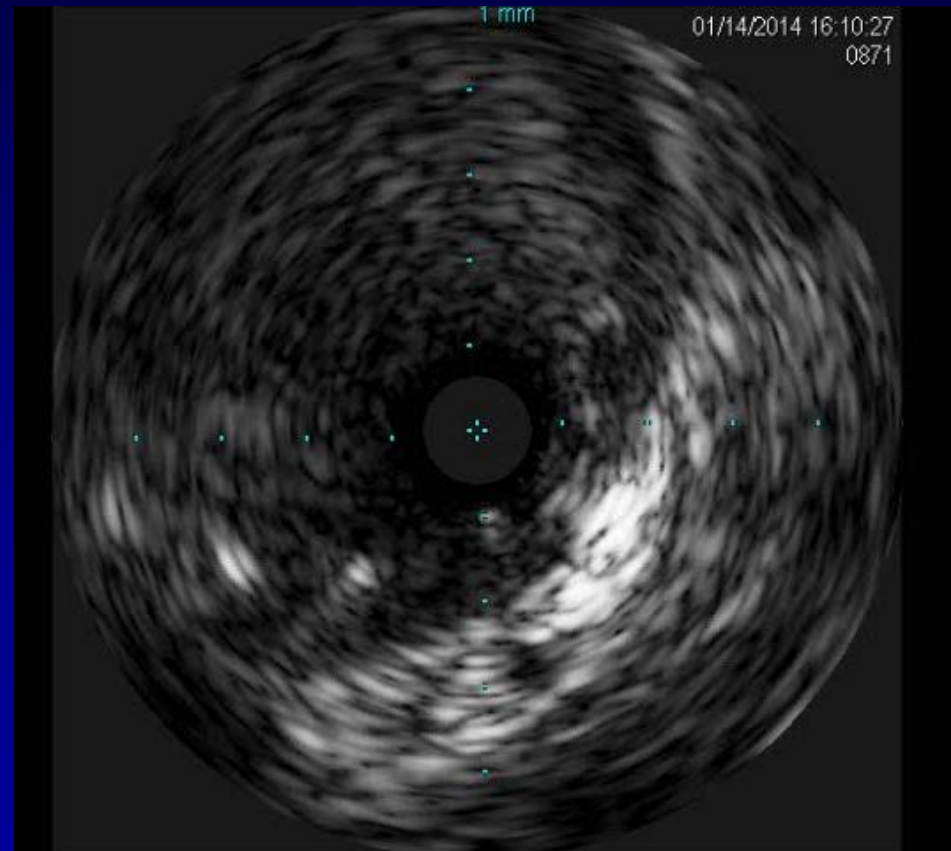
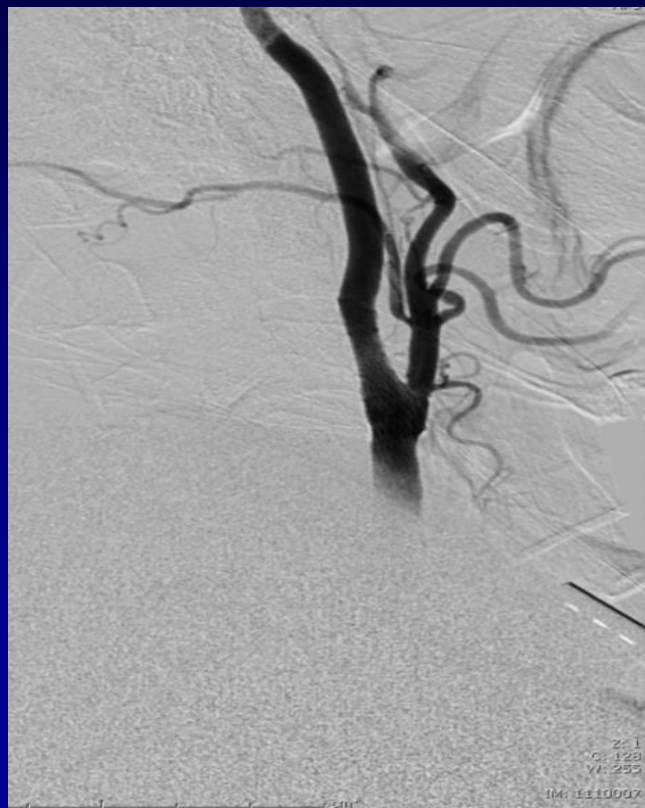
Repeated aspiration  
and flow reversal did  
not dislodge the clot



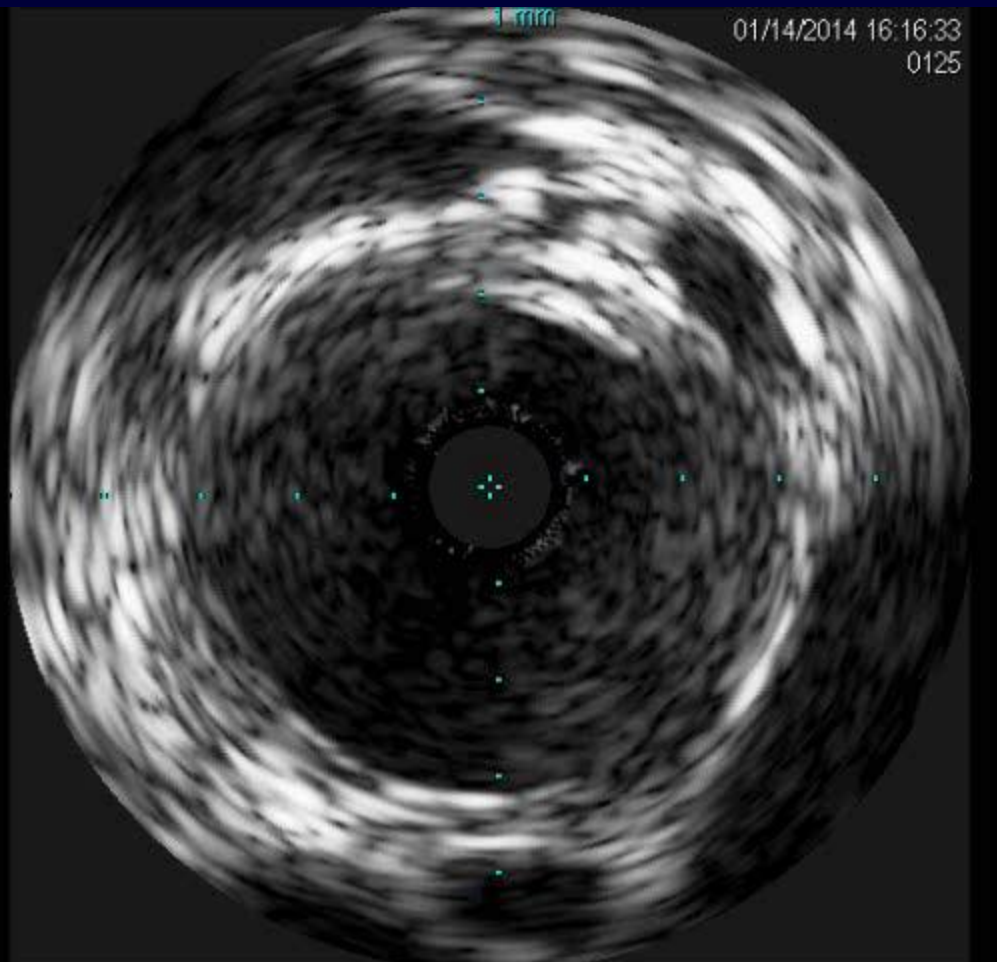


# Second Stent placed

IVUS still showed thrombus



# In stent Angioplasty

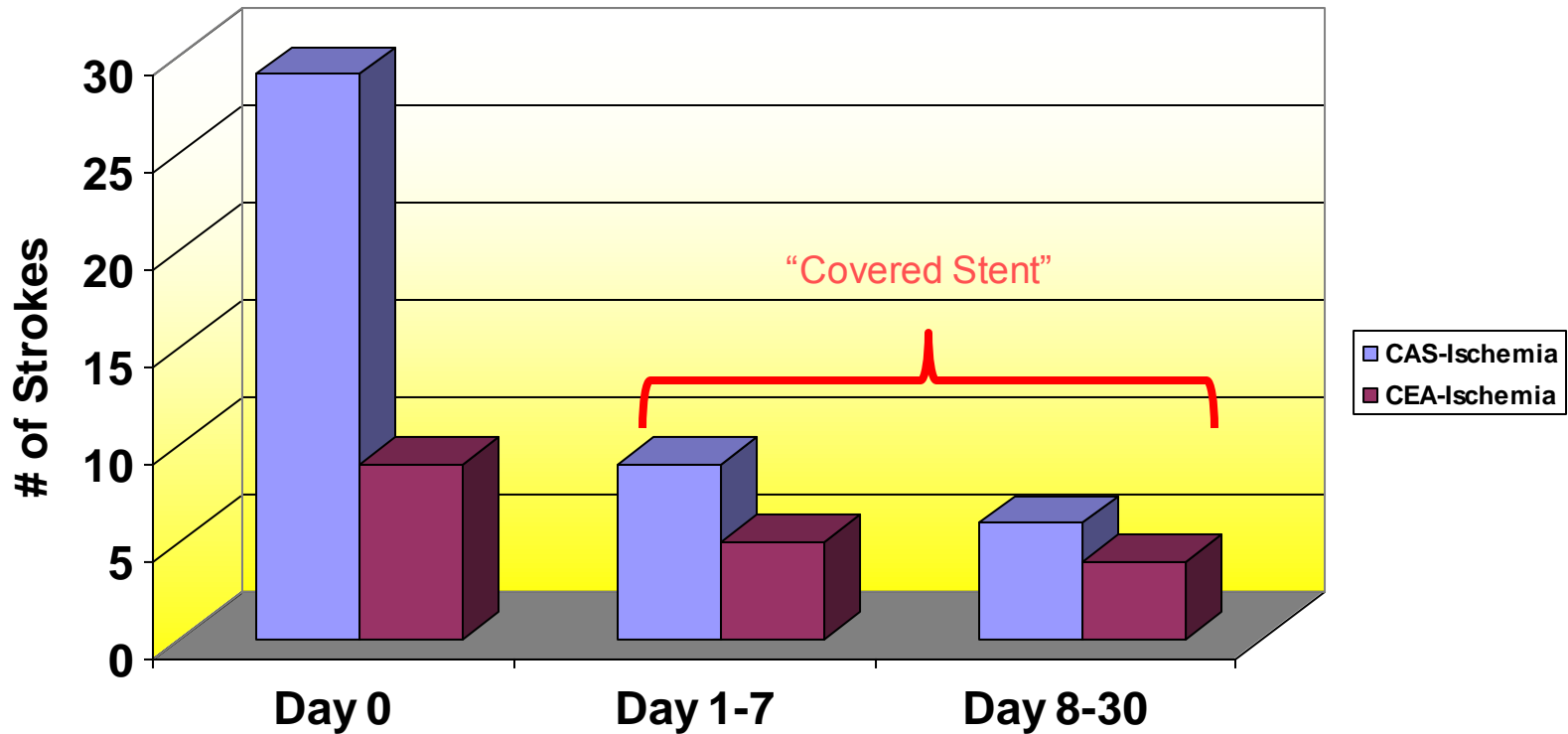


- Intraluminal thrombus disappeared

# Procedural Stroke

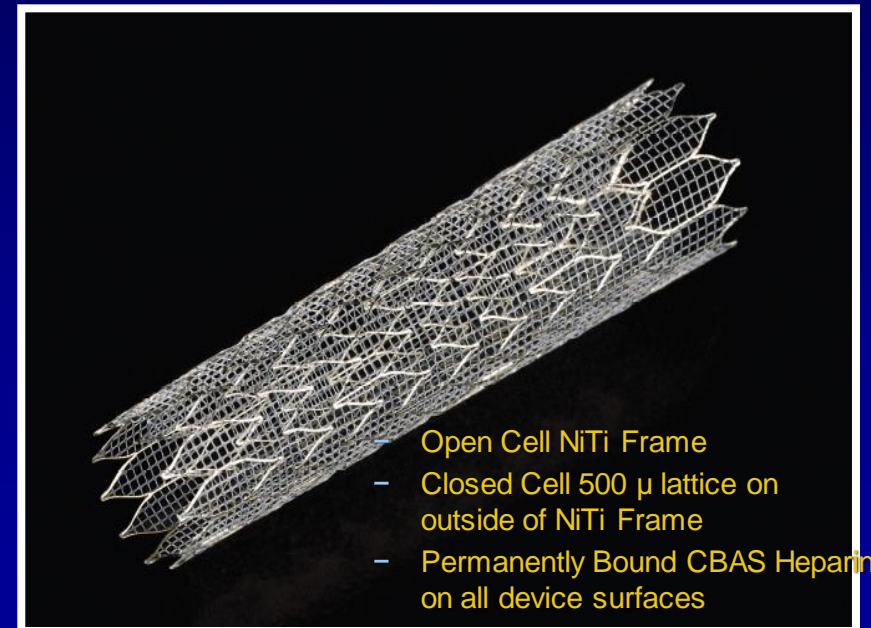
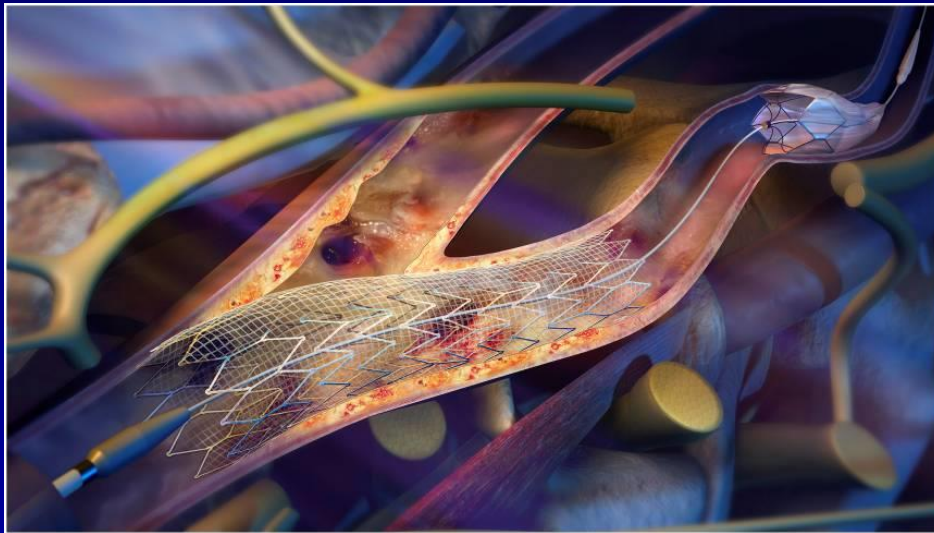
## New Tools

Timing from Procedure for Ischemic Stroke



# Delayed Stroke

- Peri Procedural Strokes Post Procedure
  - The Next CAS Frontier ?
  - Gore Scaffold



- Open Cell NiTi Frame
- Closed Cell 500  $\mu$  lattice on outside of NiTi Frame
- Permanently Bound CBAS Heparin on all device surfaces



# Future

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- Patient individualization
- Plaque interrogation for Asx patients
  - TCD, MRI, CTA
- Vascular inflammation markers (Lp-Pla2)
- Optimal medical management
- **Peri Procedural Strokes Post Procedure**
  - The Next CAS Frontier ?**

# Conclusions

## *CAS and CEA are Complimentary*

- CAS is NOT going away
- **More minor strokes with CAS... Must be fixed !**
- **More MI's after CEA... MI is BAD !**
- **CAS improving with experience + technology**
- **Patient selection and technology are KEY!**
- **We must prove Asx pts will benefit from CAS**

Come Innovate With Us

