Why I do not believe the EVA-3S Trial…

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Potential Conflicts

Consultant & research support:
Boston Scientific, Cordis, Medtronic, Guidant

Financial interests:
Boston Scientific EPI, Cordis, J&J, Micrus, Endotex, Access Closure Inc

EVA-3S

Results Must Not Dictate Treatment

- Just another trial..
- Results not congruent with other trials
- Results not congruent with our experience
- Lots of issues with the trial…
- All trials have flaws… accumulation of data over many years will help us to decide which operation for which patient

Problems with EVA-3S

- Enrollment Bias…?
  - Estimated 15% or less of all patients randomized
    - Thirty hospitals
    - Assuming only 1 vascular surgeon per hospital with the enrollment criteria minimum 25 cases/yr
    - 4.75 years of enrollment = 3562.5 patients

Problems with EVA-3S

- Limited investigator experience
- Experienced operators defined by 12 *lifetime* CAS procedures or 5 CAS procedure if 35 supra-aortic procedure
  - These operators were deemed experienced and allowed to tutor the non-experienced
  - No centralized training qualification process (local proctors pronounced the operators qualified)
  - Approximately 2/3 of sites were under tutelage at the beginning of their *randomized* participation.
  - Although analysis among the tertiles of MD experience showing no difference, it is underpowered

Problems with EVA-3S

- Early and/or non-standard technique resulted in unnecessary morbidity
  - Use of EPD not widespread or familiar
    - Lack of use in the early phase of the trial likely responsible for 4-5 excess strokes (~20% of all CAS strokes)
  - *5%* stent procedure failure requiring emergency surgery in this trial resulting in 2 strokes in the CAS group
    - Major pivotal trials in this country (e.g., SAPPHIRE, ARCHeR) have not reported *any* emergent surgical conversions
  - Significant (beyond local) anesthesia was employed in ~30% of procedures (estimated <5% in US).

Problems with EVA-3S

- Important adjunctive CAS anti-platelet therapy missing
  - Recommended, but not required, therapy resulted in ~15% of CAS patients not receiving medication before or after procedure

Problems with EVA-3S

- No standardized stent or EPD introduces confounding feature
  - Many different systems especially early on the learning curve

Our Own Results Don’t Agree

CAS: Personal Experience
SUNY Buffalo

30 Day M&M	CAS	CEA
Death	1.7%	1.1%
Stroke	0.8%	0.0%
Myocardial infarction	0.8%	3.2%
MAE	3.3%	3.2%

Ecker at al JNS 07

CAS Risk Factors From Other Trials

1. *Sx (hot) lesion…*
2. *Elderly pts…*
3. *Low GSM…*
4. *Multiple stents…*
5. *Duration Filter…*
6. *Pre dil without EP…*
7. *Tortuousity- severe…*
8. *Concentric calcium…*
9. *Aortic Arch disease…*
10. *Renal Failure...*

Randomized Controlled Trials Comparing CEA and CAS

CAVATAS	Kentucky A	Kentucky B	Leicester	WALLSTENT	SAPPHIRE
2001	2001	2004	1998	2001	2004
Multicenter	Single center	Single center	Single center	Multicenter	Multicenter
N=504	N=104	N=85	N=23	N=219	N=334
Symptomatic / Asymptomatic					
488/16	104/0	0/85	23/0	219/0	96/238
Randomized to Endovascular Treatment					
251	53	43	11	107	167
Stent = 55 PTA = 158	All stents	All stents	All stents	All stents	All stents
Randomized to Surgery					
253	51	42	12	112	167

Coward L.J., et al., *Stroke* 2005, 36:905-11.

Outcomes in the Individual Trials

CAVATAS	Kentucky A	Kentucky B	Leicester	WALLSTENT	SAPPHIRE
30-day Death or Stroke (Endovascular / Surgery)					
25 (10.0%) / 25 (9.9%)	0 / 1 (2.0%)	0 / 0	5 (45.5%) / 0	13 (12.1%) / 5 (4.5%)	8 (4.8%) / 9 (5.4%)
30-day Death or Disabling Stroke (Endovascular / Surgery)					
16 (6.4%) / 15 (5.9%)	0 / 1 (2.0%)	0 / 0	3 (27.3%) / 0	Not known	Not known
1-year Death or Stroke (Endovascular / Surgery)					
36 (14.3%) / 34(13.4%)	Not known	Not known	Not known	13 (12.1%) / 4 (3.6%)	22 (13.2%) / 33 (19.8%)
30-day Cranial Nerve Injury (Endovascular / Surgery)					
0 / 22 (8.7%)	0 / 4 (7.8%)	0 / 0	0 / 0	Not known	0 / 8 (4.8%)
30-day Death, Stroke or MI (Endovascular / Surgery)					
25 (10.0%) / 28 (11.1%)	0 / 1 (2.0%)	0 / 0	5 (45.5%) / 0	13 (12.1%) / 5 (4.5%)	8 (4.8%) / 16 (9.6%)

Coward L.J., et al., *Stroke* 2005, 36:905-11.

SPACE: the latest

Subsequent analysis of SPACE data demonstrates age-related outcomes differences between CAS and CEA

Stingele et al

CREST 6/08

Randomized Patients

2,470

What will CREST teach us?

- CREST: Randomized CAS vs. CEA
- Started in 2000, 94 centers
- Plans to enroll 2500 patients

- 2461 randomized (as of 12/07)
- 1387 lead-in cases
  - 789 carotid stents reported in November 2004
  - 30 day stroke and death = **4.6%**
  - 30 day MI = 1.1%

Compare to 9.6% in EVA-3S

CREST

- Differences from EVA-3S
  - Distal Embolic Protection
  - MI rates are monitored
  - Dual antiplatelet therapy in all patients
  - More rigorous interventionalist credentialing

30-day and 1-year Outcome*
All Age Groups (n=1541)

Event	30-day			1-year		
	Total	**Asympt (n=1131)**	**Sympt (n=409)**	**Total**	**Asympt (n=1131)**	**Sympt (n=409)**
Death or major stroke (%)	**2.2 ± 0.4**	**1.8 ± 0.4**	**3.2 ± 0.9**	**2.3 ± 0.4**	**1.9 ± 0.4**	**3.2 ± 0.9**

Values are mean ± SEM

30-day and 1-year Outcome* By Age (n=1541)

Event	30-day				1-year			
	< 60 (n=231)	60-69 (n=498)	70-79 (n=680)	> 80 (n=131)	< 60 (n=231)	60-69 (n=498)	70-79 (n=680)	> 80 (n=131)
Stroke or death (%)	1.8 ± 0.9	2.1 ± 0.6	5.4 ± 0.9	12.4 ± 2.9	2.4 ± 1.1	2.8 ± 0.9	5.8 ± 0.9	13.3 ± 3.0

Values are mean ± SEM

Problems with CREST

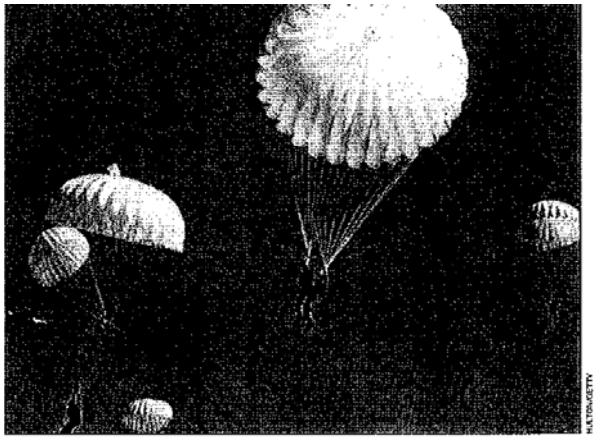
- Inexperience… learning curve
- Early start (first CAS 5 yrs earlier)
- First generation technology
- Stent and filter now rarely used
- Judgment and patient selection evolution

Worshiping at the Shrine of the RPCT…

- “Equipoise”
- New & evolving technology

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell



Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

A call to (broken) arms

Only two options exist. The first is that we accept that, under exceptional circumstances, common sense might be applied when considering the potential risks and benefits of interventions. The second is that we continue our quest for the holy grail of exclusively evidence based interventions and preclude parachute use outside the context of a properly conducted trial.

Lessons from CAS Trials

- We will learn from all trials, CREST will teach us much, but…
- Randomizes Prospective Controlled Trials May NOT Be The Answer for future study of these **complementary** procedures where equipoise is not established

CARESS

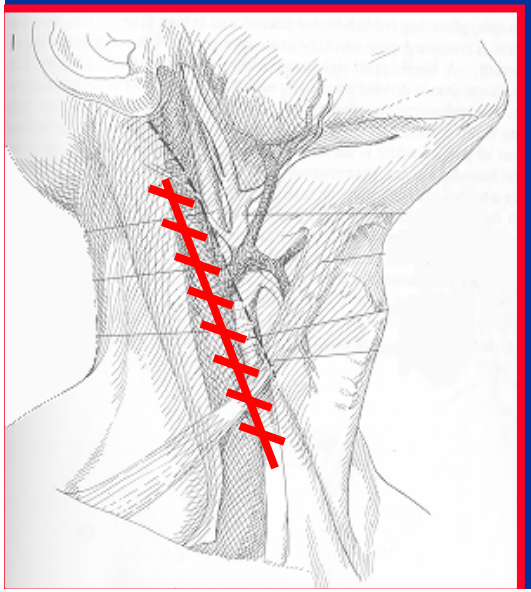
CAROTID REVASCULARIZATION

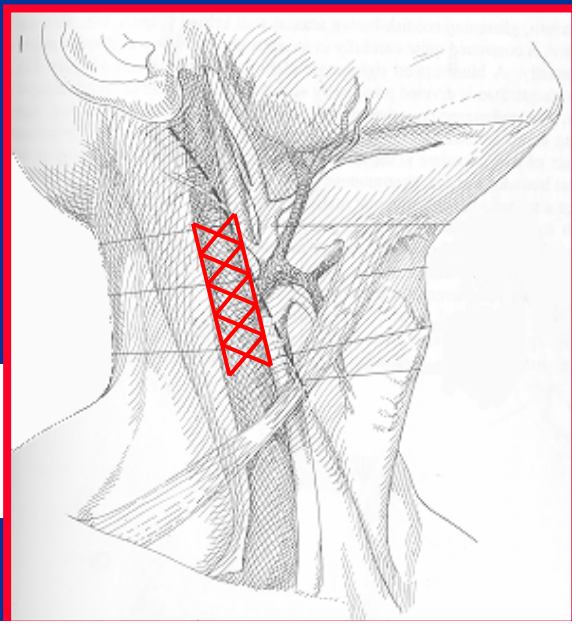
ENDARTERECTOMY vs. STENTING SYSTEM

PHASE ONE

PROSPECTIVE, MULTICENTER

COHORT STUDY





INTERNATIONAL SOCIETY OF ENDOVASCULAR SPECIALISTS

CARESS

FEASIBILITY STUDY

- Low risk patients NOT CREST CANDIDATES
- Design: Non-randomized concurrent controls
- 20 sites
- 450 patients, 300 CEA, 150 Stent
- Purpose is to determine CEA event rates for pivotal study design
- BSC Wallstent / PercuSurge protection device

CARESS
30-DAY OUTCOMES

	CEA	STENT
STROKE / DEATH `	2%	2%
STROKE / DEATH / MI	3%	2%

AHA 2003 WHITE et al


Thank You!