Update Clinical Trials for Management Carotid Stenosis

Gregory L. Moneta, MD

OHSU, Division of Vascular Surgery
Department of Surgery
Knight Cardiovascular Institute

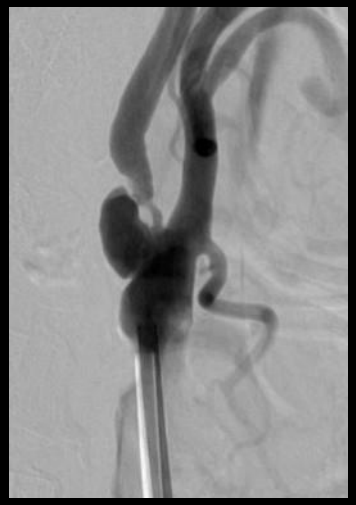
OREGON HEALTH & SCIENCE UNIVERSITY

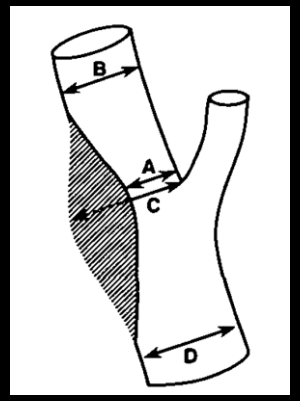
KNIGHT CARDIOVASCULAR Institute

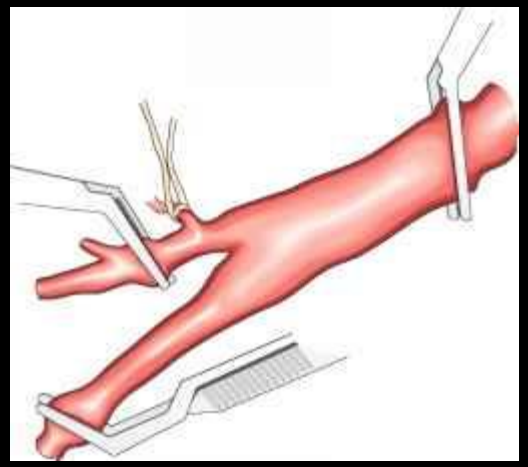
Nothing to Disclose

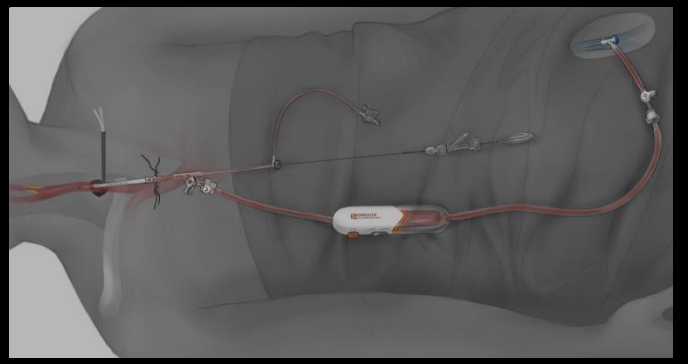
Carotid Clinical Trials Update: Methods

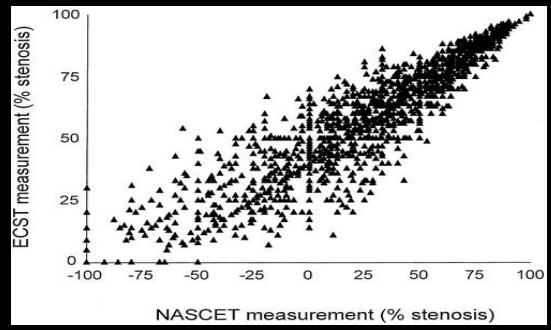
- Background/History Clinical trials for Carotid Stenosis
- Review ClinicalTrials.gov to identify recent Ongoing/Completed Clinical trials for Carotid Stenosis
- Summary Most Impactful Recent Ongoing/Completed Clinical trials for Carotid Stenosis



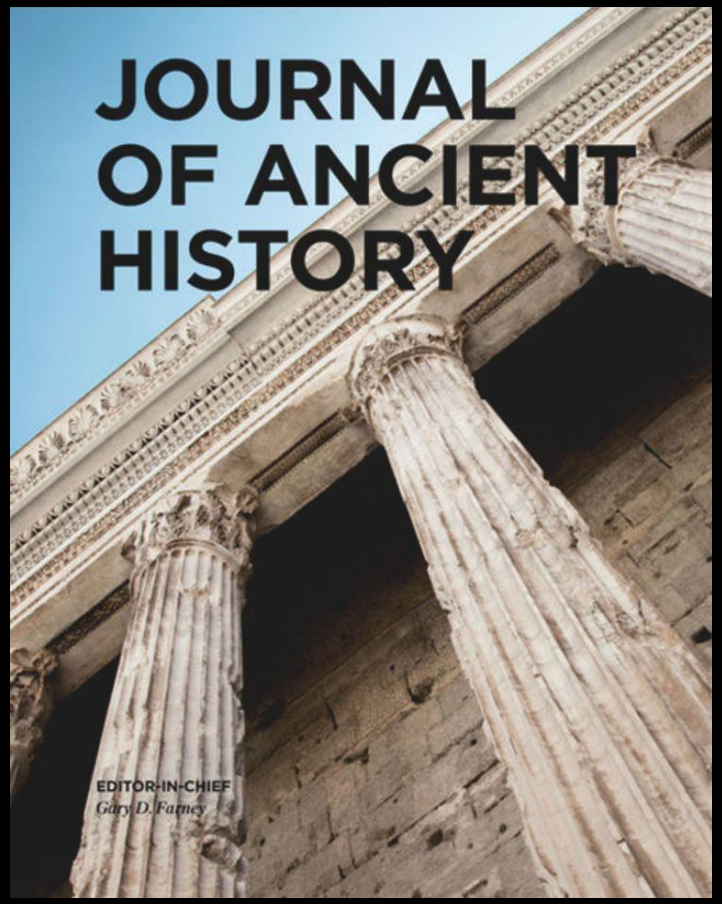








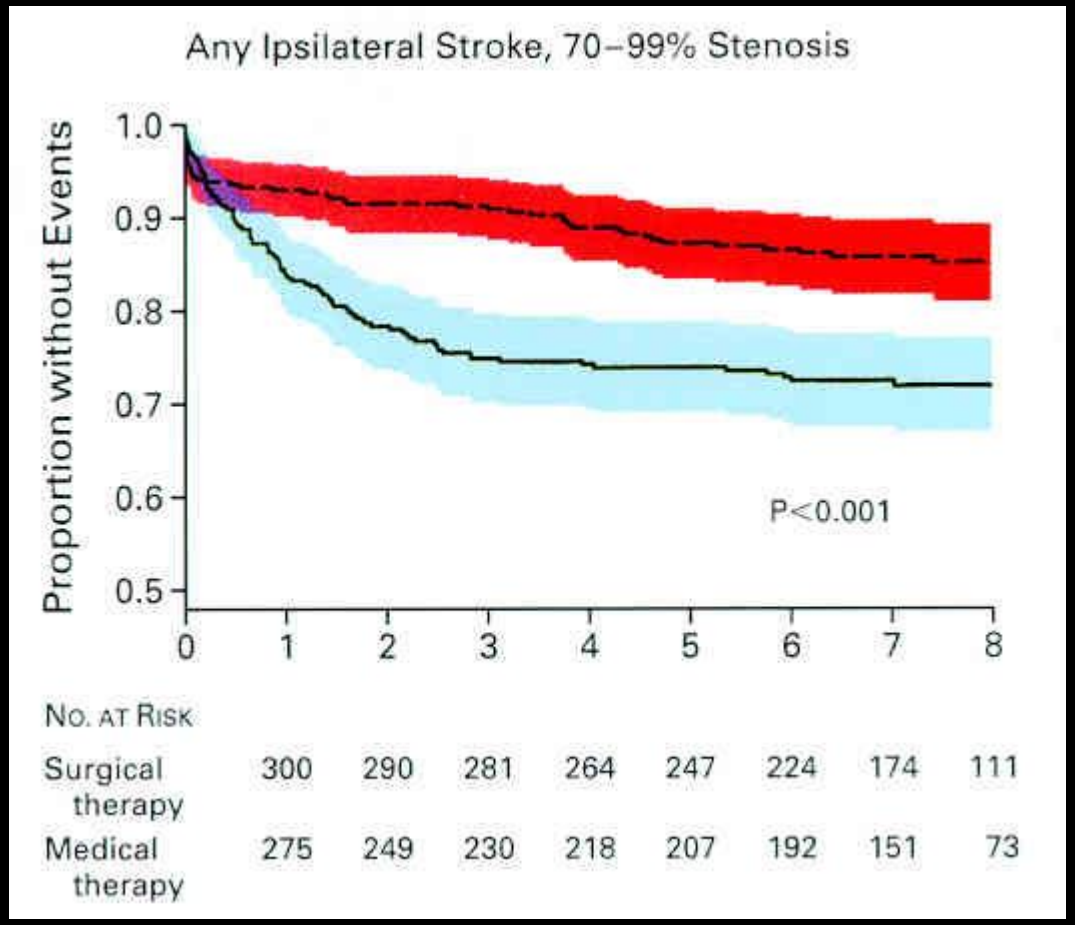
Carotid stenosis/Carotid endarterectomy

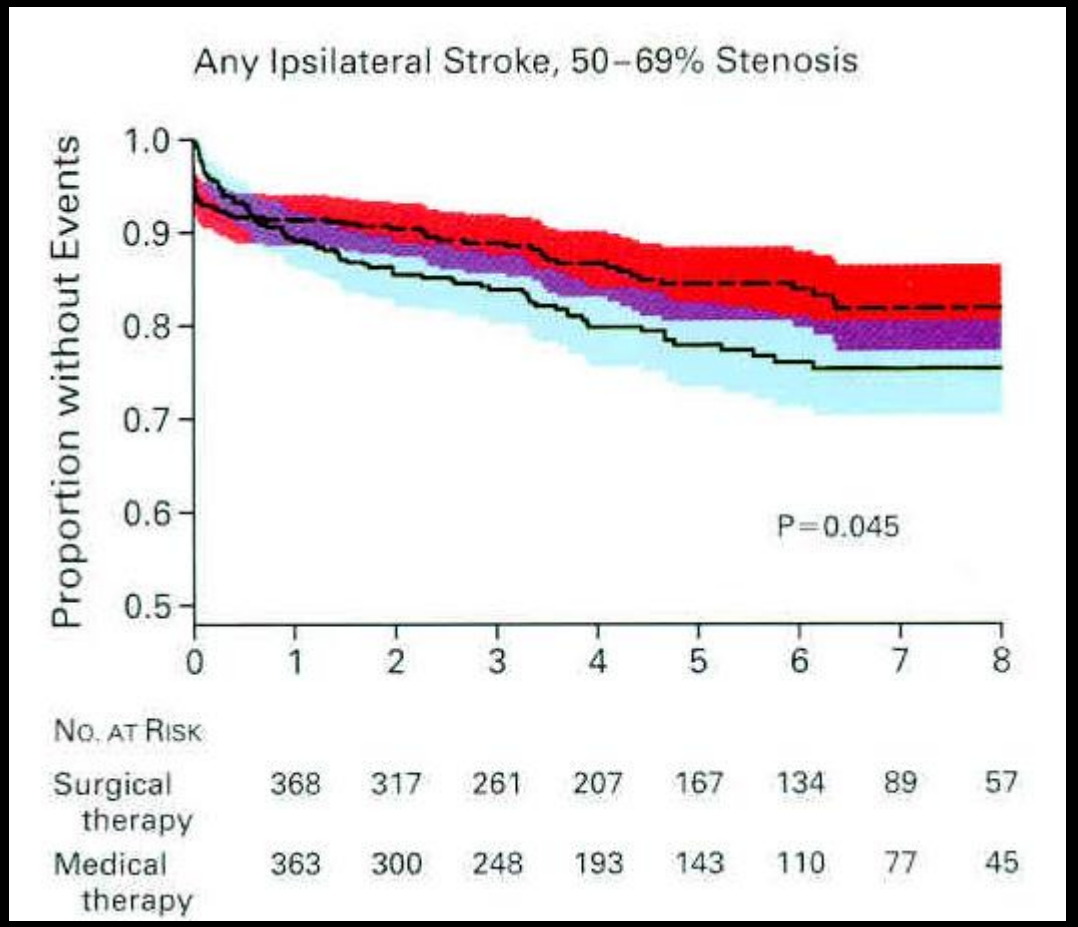


- NASCET, 1991
- ECST
- ACAS

NASCET

NASCET

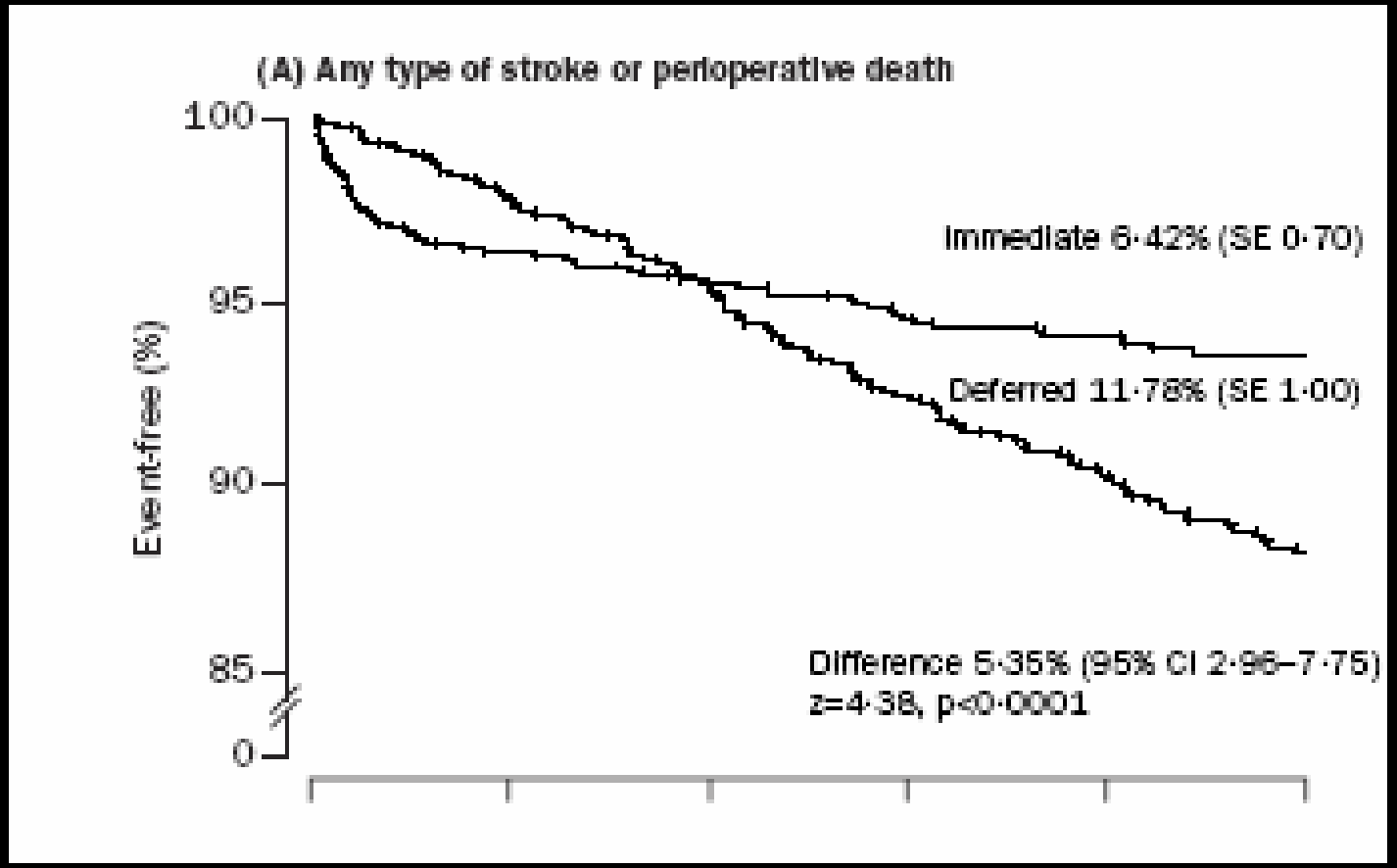




Simultaneous European Carotid Surgery Trial (ECST) produced similar results

Asymptomatic Carotid Surgery Trial

Event	Risk Reduction	p-value
Ipsilateral stroke/death	53%	0.004
Major ipsilateral stroke/death	43%	0.12



Stroke and Death at 5-Years

NASCET

ICA Stenosis	Medical Group	Surgical Group	NNT*
70% - 99%	26.1%	12.9%	8
50% - 69%	22.2%	15.7%	15
<50%	18.7%	14.9%	26

ACAS

	11%	5.1%	19

*NNT is the number of patients needed to treat to prevent one stroke.

ClinicalTrials.gov

- Registry and Results database of clinical trials developed and maintained by the National Library of Medicine in response to The Food and Drug Modernization Act (FDAMA), Section 113, passed by Congress in 1997.

- Each study record includes a summary of the study protocol, including the purpose, recruitment status, and eligibility criteria.

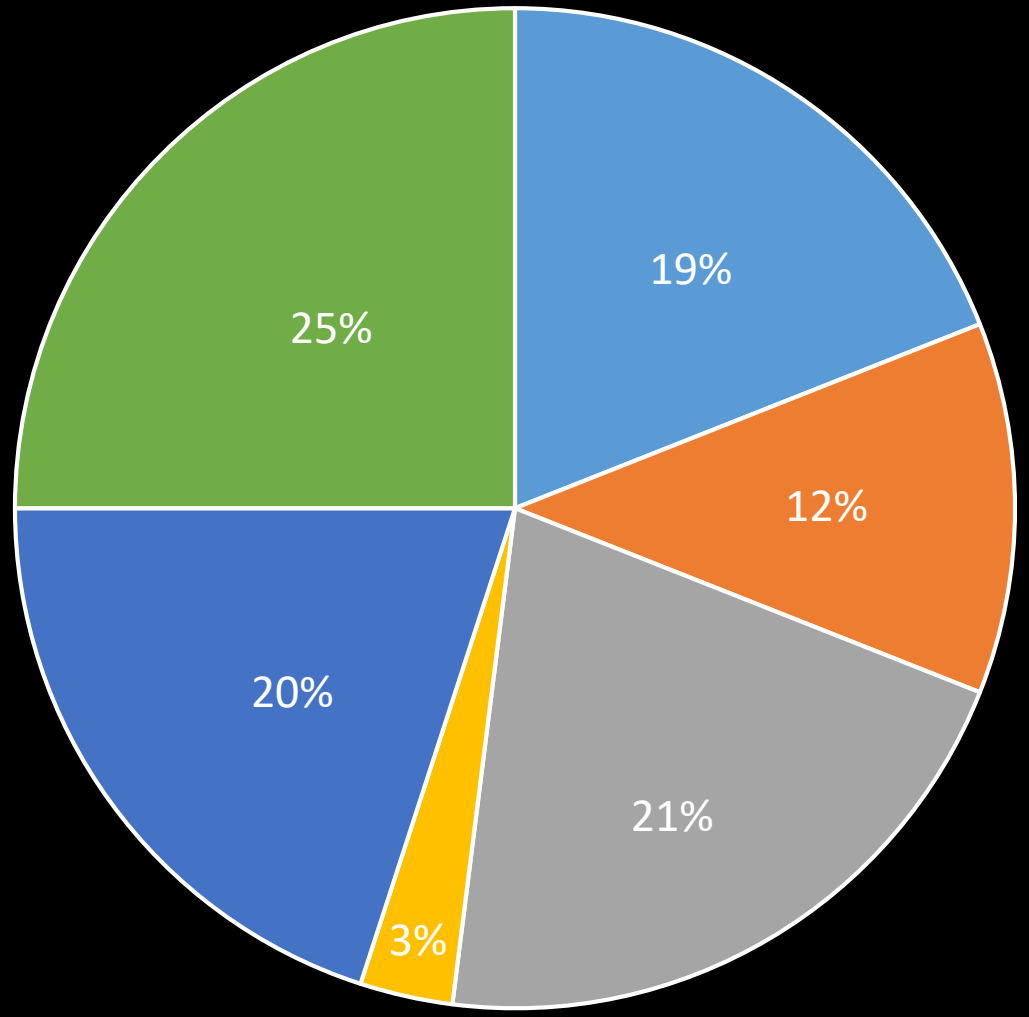
- Sponsors or investigators of certain clinical trials are required by U.S. law to register their trials on and submit summary results to ClinicalTrials.gov

- Other countries also require registration.

ClinicalTrials.gov

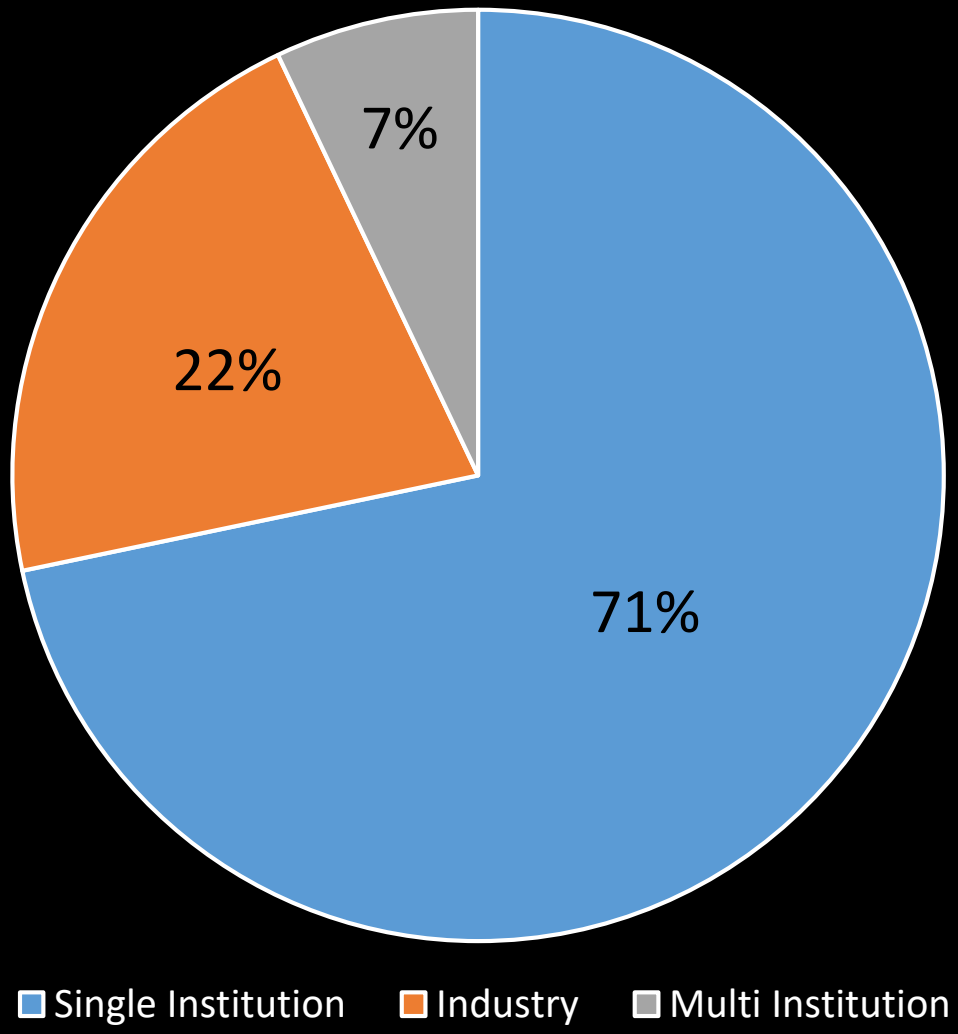
- Released by the National Institutes of Health in 2000 for use by researchers, industry and the public.
- 2005: International Committee of Medical Journal Editors issued a requirement for trial registration.
- As of December, 2021 there were 399,549 clinical trials from around the world indexed and searchable by key words.
- 261 for Carotid Stenosis

ClinicalTrials.gov: Type of Studies for Carotid Stenosis (n=261)*



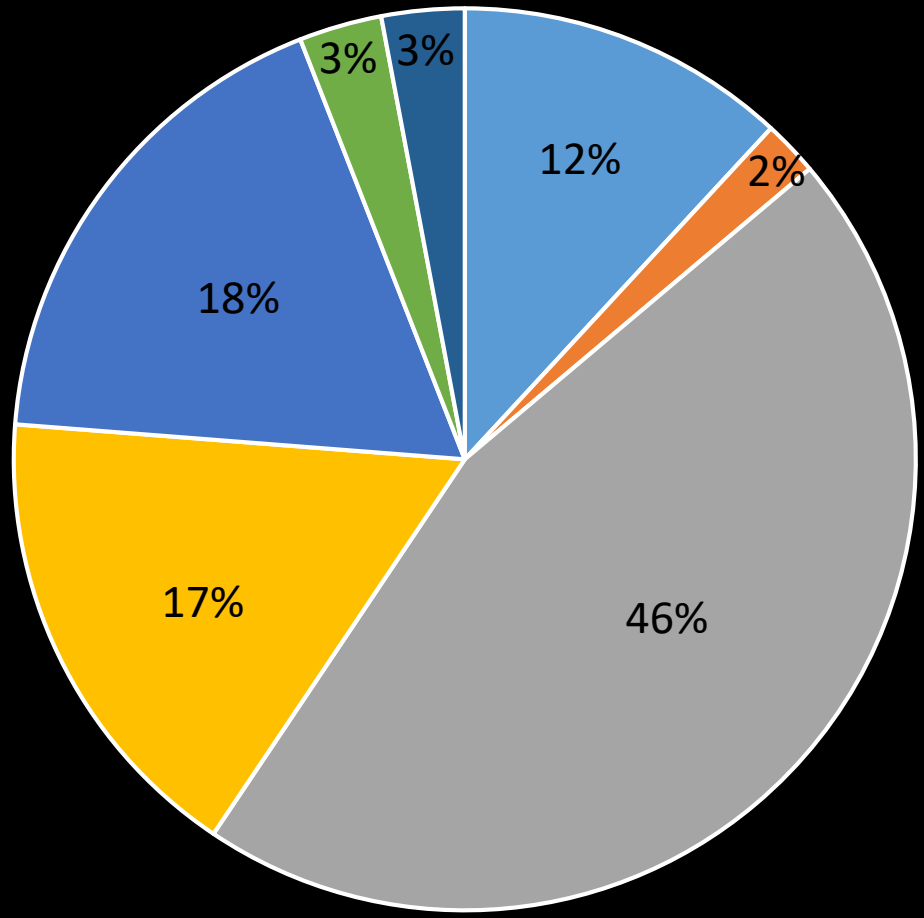
*Accessed Dec 28, 2021
Key word: Carotid Stenosis

ClinicalTrials.gov: Source of Studies for carotid Stenosis (n=261)*



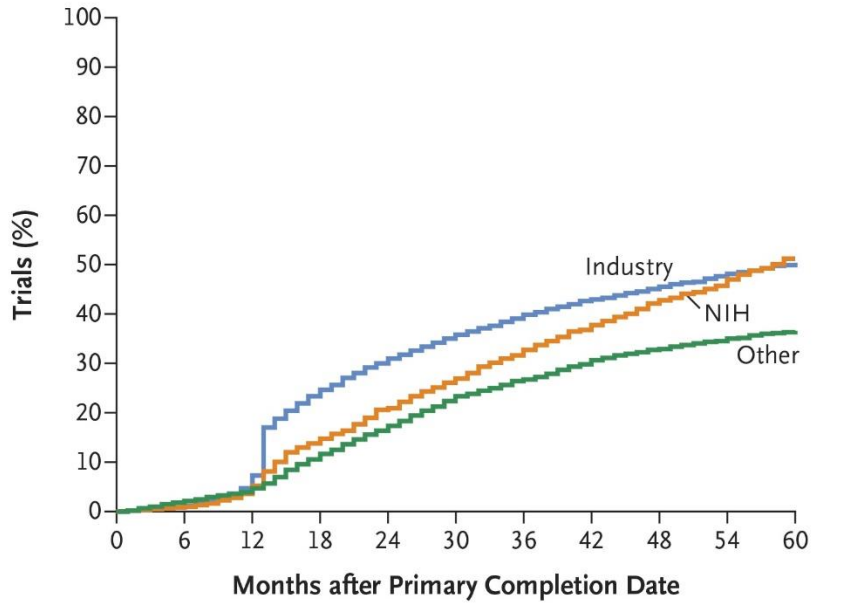
*Accessed Dec 28, 2021
Key word: Carotid Stenosis

ClinicalTrials.gov: Study Status for Studies of Carotid Stenosis (n=261)*



*Accessed Dec 28, 2021
Key word: Carotid Stenosis

Compliance ClinicalTrials.gov: Not good



No. of Trials	0 Mo	<12 Mo	<24 Mo	<36 Mo	<48 Mo	<60 Mo
Industry	8728	8321	5132	3408	2127	914
NIH	1895	1828	1323	925	544	212
Other	2691	2585	1872	1208	717	320

- Of 4209 clinical trials due to report results over a one-year period during 2018 and 2019; 1722 (40.9%) did so within the required 1-year deadline.
- Only 63·8% (2686) ever reported results
- Industry sponsors were more likely to be compliant than non-industry, non-US Government sponsors (OR 3·08 [95% CI 2·52–3·77])
- Sponsors running large numbers of trials were more likely to be compliant than smaller sponsors (OR 11·84 [9·36–14·99]).

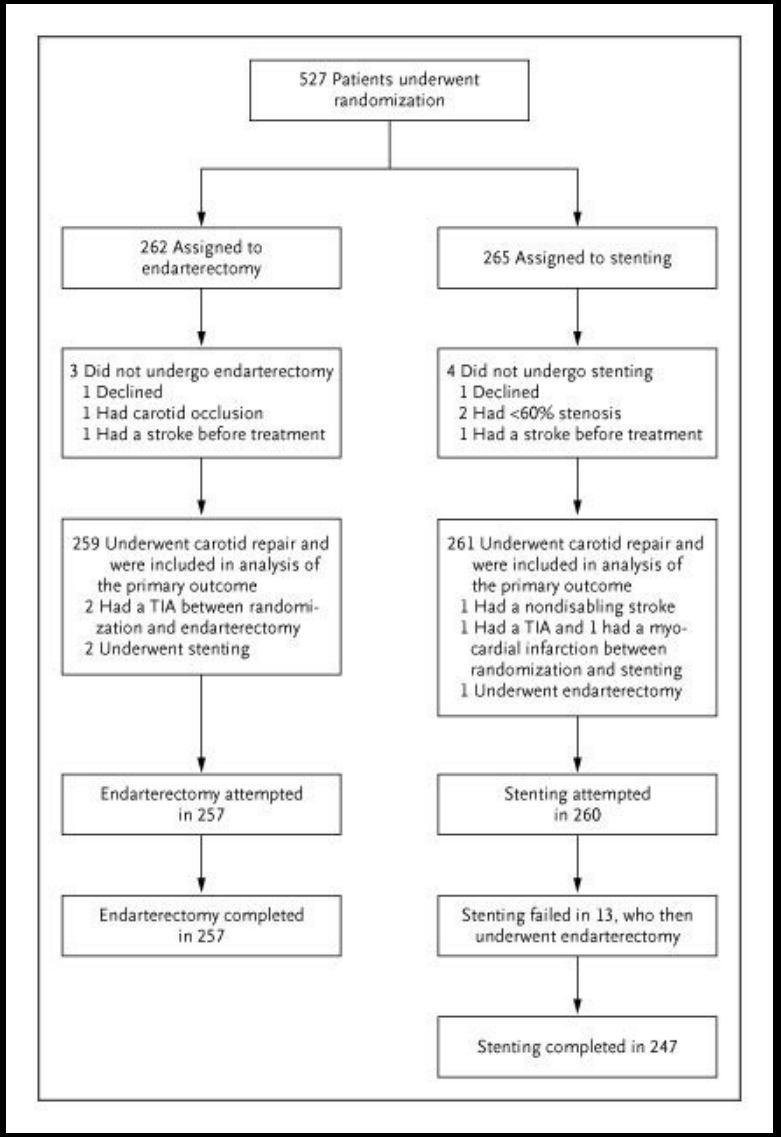
N Engl J Med 2015; 372:1031-1039

Lancet 2020; 395, 10224: 361-369

Endarterectomy vs stenting in patients with severe symptomatic carotid stenosis (EVA 3S)*

NCT00190398

- 30 French centers
- >60% symptomatic carotid stenosis
- Randomized, noninferiority design
- Stenting: transfemoral, ASA and clopidgrel or ticlopidine 3 days prior and 30 days post stent
- CEA: per surgical routine
- 1^0 endpoint: composite any stroke or death <30 days
- 2^0 endpoints: multiple composites of any stroke, ipsilateral stroke, MI, death <30 days and up to 4yrs
- Stopped for futility and safety after 527 patients randomized



*N Engl J Med 2006;355: 1493-1501

Results: Endarterectomy vs stenting in patients with severe symptomatic carotid stenosis (EVA 3S)*

Outcome Event	Endarterectomy (N=259)	Stenting (N=261)	Unadjusted Relative Risk (95% CI)	P Value
	no. of patients (%)			
Nonfatal stroke	7 (2.7)†	23 (8.8)‡	3.3 (1.4–7.5)	0.004
Symptoms lasting 7 days or more	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
Transient ischemic attack	2 (0.8)	6 (2.3)	3.0 (0.6–14.6)	0.28
Myocardial infarction**	2 (0.8)	1 (0.4)	0.5 (0.04–5.4)	0.62

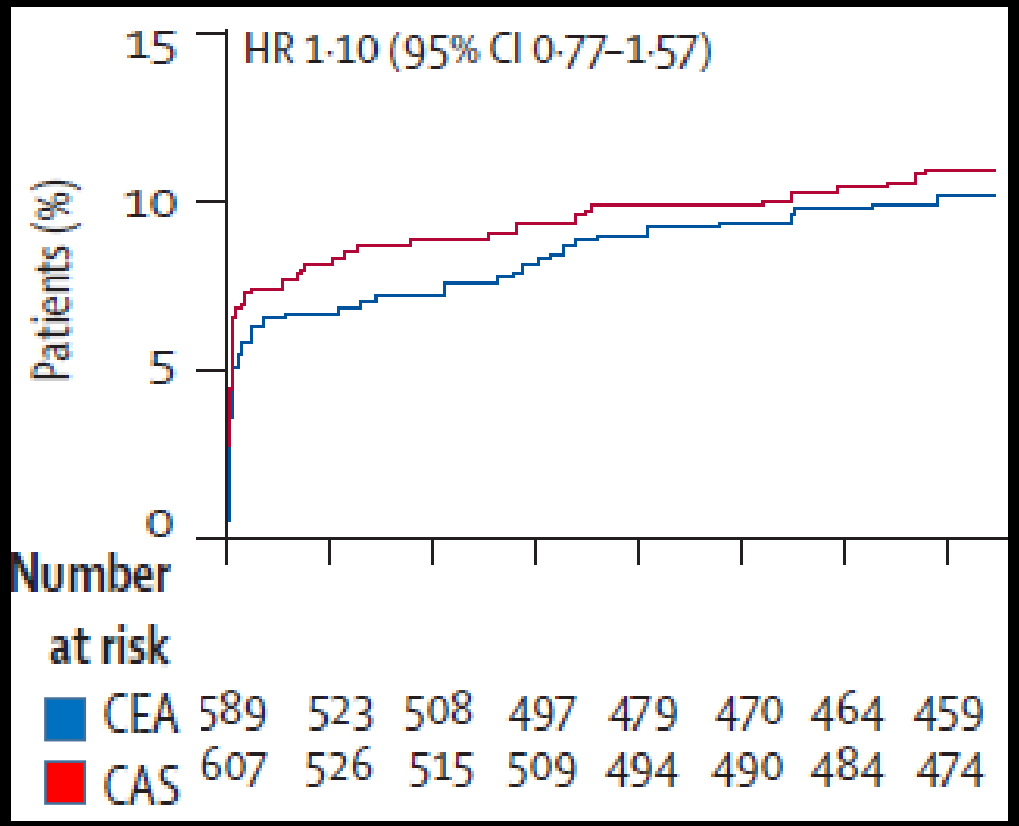
*N Engl J Med 2006;355: 1493-1501

Stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial (SPACE)*

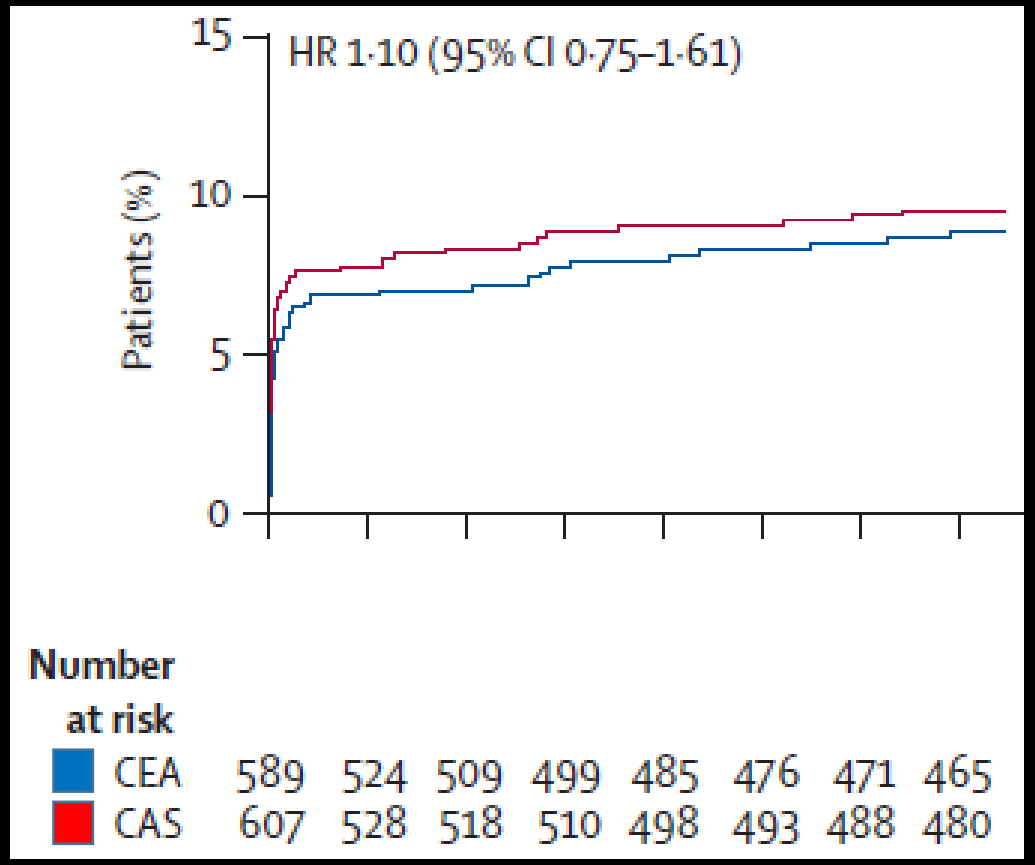
- Randomized, intention to treat, non inferiority study; symptomatic >70% stenosis
- International standard randomized controlled trial number ISRCTN57874028.
- German trial with 1200 randomized (605 CAS, 595 CEA)
- 1183 analyzed
- 1^{o} endpoint: ipsilateral stroke or death from randomization to 30 days post procedure
- 6.84% CAS vs 6.34 CEA; p value for non-inferiority: 0.09
- Author conclusion: “SPACE failed to prove non-inferiority of carotid-artery stenting compared with carotid endarterectomy for the periprocedural complication rate. The results of this trial do not justify the widespread use in the short-term of carotid-artery stenting for treatment of carotid-artery stenoses.”

*Lancet Neurology2006; 368:1239-1247

2-Year Results: Stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial (SPACE)*



Any stroke



Any stroke or death up to day 30 and ipsilateral ischemic stroke after day 30

*Lancet Neurology2008; 7:893-902

Sapphire (NCT00231270)

- Stent with embolic protection vs CEA
- Pts high risk for CEA (symptomatic >50% and asymptomatic >80% ICA stenosis
- Industry sponsored with Industry reps on steering committee
- 334 patients; non inferiority design
- Endpoints composite stroke, death, MI within 30 days and death, ipsilateral stroke at 3 years.
- Bottom line: No difference at 3 years

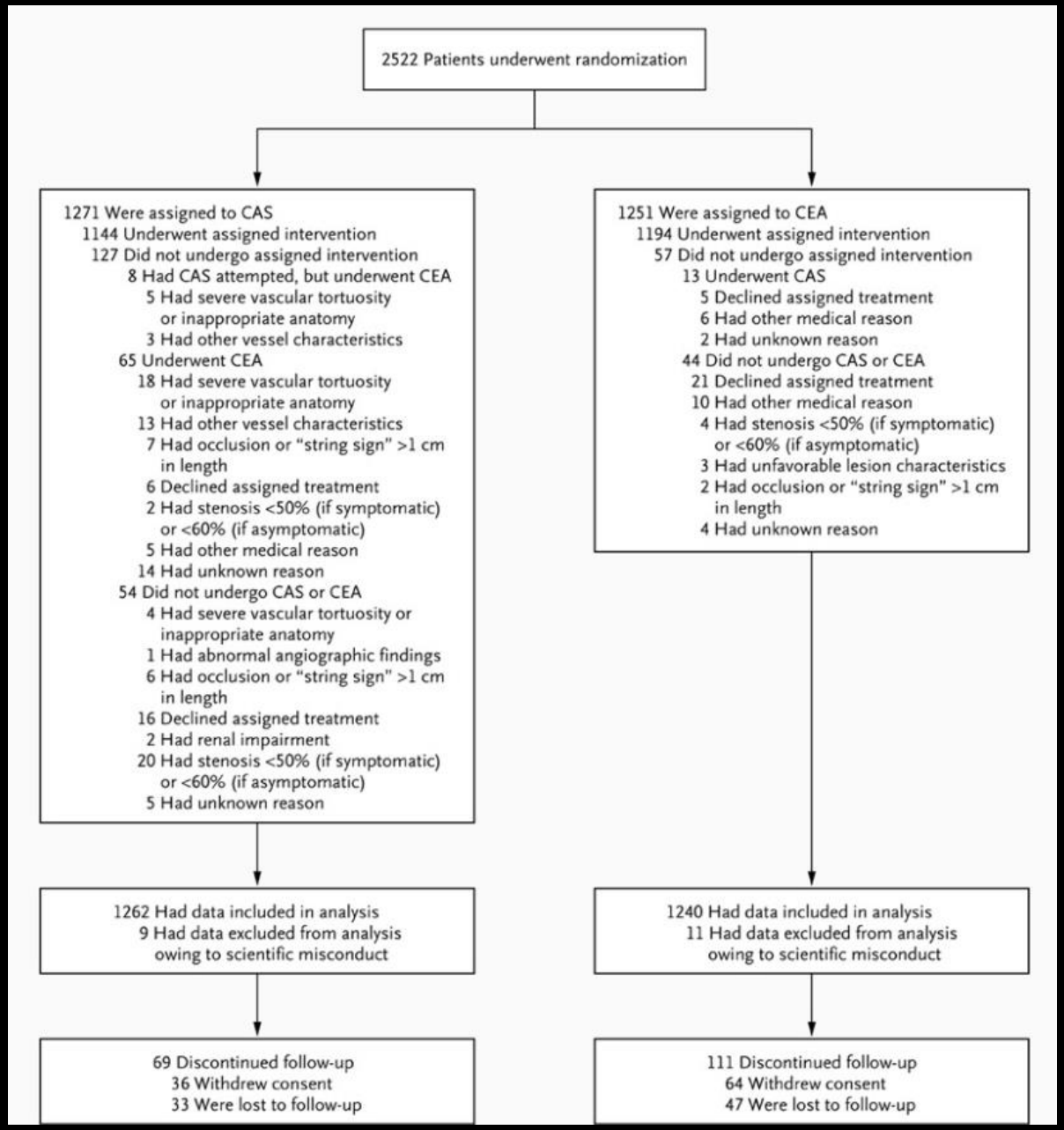
N Engl J Med 2008;358:1572-1579

Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)

(NCT00004732)

- Randomized, NIH funded, clinical trial
- CAS vs CEA
- Symptomatic (>50% stenosis)and asymptomatic (>60% stenosis) patients
- Primary endpoint: Any Periprocedural Stroke, Myocardial Infarction, or Death During a 30-day Peri-procedural Period, and Postprocedural Ipsilateral Stroke Thereafter, up to 4-years. [Time Frame: 30 days and 4 years]

CREST: Consort Diagram*



*N Engl J Med 2010; 363:11-23

CREST RESULTS*

End Point	Periprocedural Period				
	CAS (N=1262)	CEA (N=1240)	Absolute Treatment Effect of CAS vs. CEA (95% CI)	Hazard Ratio for CAS vs. CEA (95% CI)	P Value
	no. of patients (% ±SE)		*percentage points*		
Death	9 (0.7±0.2)	4 (0.3±0.2)	0.4 (−0.2 to 1.0)	2.25 (0.69 to 7.30)†	0.18†
Stroke					
Any	52 (4.1±0.6)	29 (2.3±0.4)	1.8 (0.4 to 3.2)	1.79 (1.14 to 2.82)	0.01
Major ipsilateral	11 (0.9±0.3)	4 (0.3±0.2)	0.5 (−0.1 to 1.2)	2.67 (0.85 to 8.40)	0.09
Major nonipsilateral‡	0	4 (0.3±0.2)	NA	NA	NA
Minor ipsilateral	37 (2.9±0.5)	17 (1.4±0.3)	1.6 (0.4 to 2.7)	2.16 (1.22 to 3.83)	0.009
Minor nonipsilateral	4 (0.3±0.2)	4 (0.3±0.2)	0.0 (−0.4 to 0.4)	1.02 (0.25 to 4.07)	0.98†
Myocardial infarction	14 (1.1±0.3)	28 (2.3±0.4)	−1.1 (−2.2 to −0.1)	0.50 (0.26 to 0.94)	0.03
Any periprocedural stroke or postprocedural ipsilateral stroke	52 (4.1±0.6)	29 (2.3±0.4)	1.8 (0.4 to 3.2)	1.79 (1.14 to 2.82)	0.01
Major stroke	11 (0.9±0.3)	8 (0.6±0.2)	0.2 (−0.5 to 0.9)	1.35 (0.54 to 3.36)	0.52
Minor stroke	41 (3.2±0.5)	21 (1.7±0.4)	1.6 (0.3 to 2.8)	1.95 (1.15 to 3.30)	0.01
Any periprocedural stroke or death or post-procedural ipsilateral stroke	55 (4.4±0.6)	29 (2.3±0.4)	2.0 (0.6 to 3.4)	1.90 (1.21 to 2.98)	0.005
Primary end point (any periprocedural stroke, myocardial infarction, or death or postprocedural ipsilateral stroke)	66 (5.2±0.6)	56 (4.5±0.6)	0.7 (−1.0 to 2.4)	1.18 (0.82 to 1.68)	0.38

*N Engl J Med 2010; 363:11-23

CREST: Slicing the Salami in search of the LPU*

CREST investigators prolific salami slicers

- >20 spin off publications:
  - Patients >80 years
  - Credentialing investigators
  - Quality of Life
  - Stroke
  - MI
  - Cost effectiveness
  - Men vs women
  - CAS by vascular surgeons
  - Symptom status

*LPU: Least publishable unit

Carotid Angioplasty and Stenting Versus Endarterectomy in Asymptomatic Subjects Who Are at Standard Risk for Carotid Endarterectomy With Significant Extracranial Carotid Stenotic Disease (ACT 1)

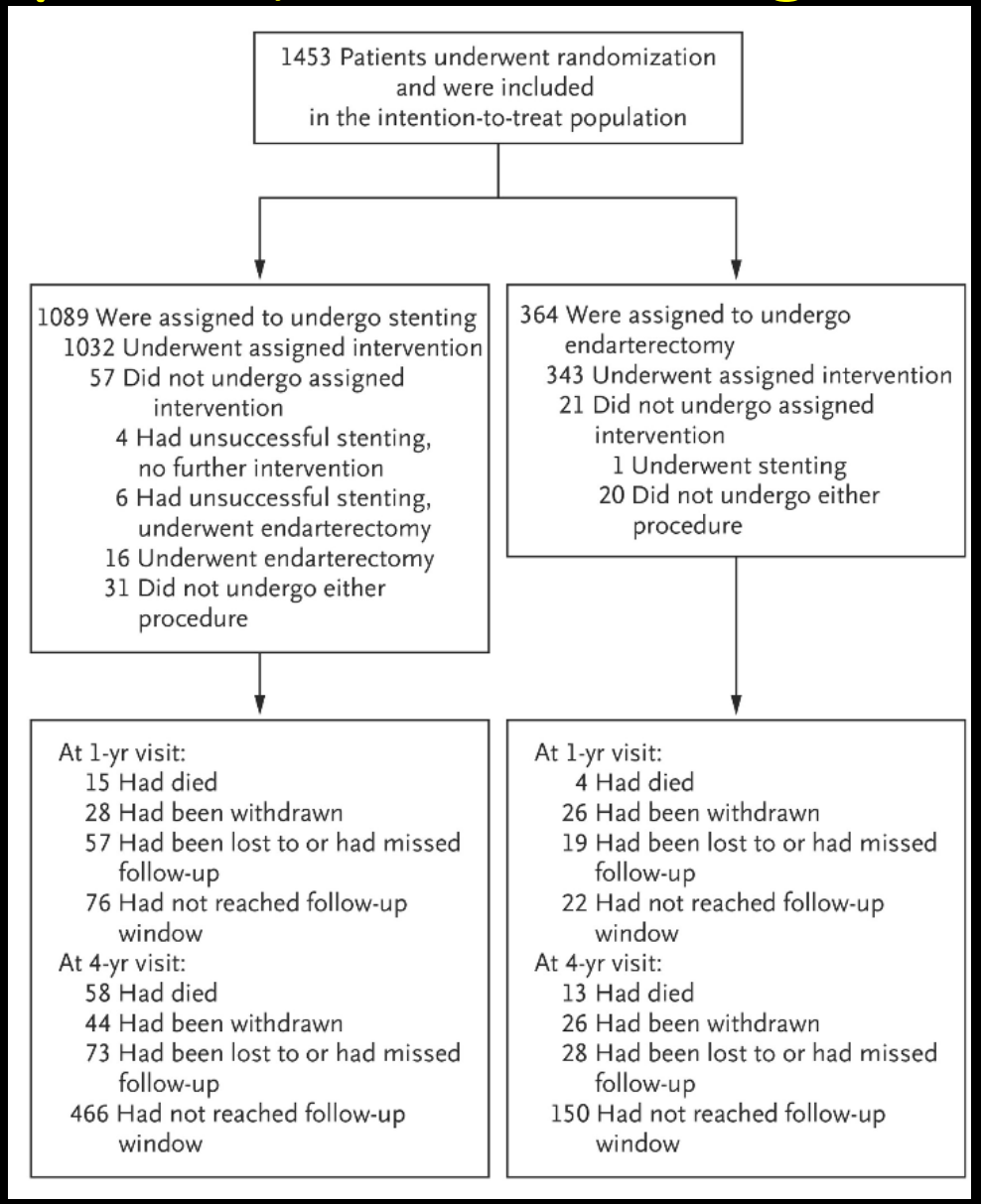
NCT00106938

- Primary Endpoint: Composite of Death, Stroke (Ipsilateral or Contralateral; Major or Minor) and Myocardial Infarction (DSMI) Through 30 Days Post-procedure, Plus Ipsilateral Stroke 31 to 365 Days. [Time Frame: 0 to 365 days]

- 32 secondary endpoints

- Terminated early “(Business decision and not a result of any patient or product safety issues.)”

Stent versus Surgery for Asymptomatic Carotid Stenosis (ACT 1) Consort Diagram*

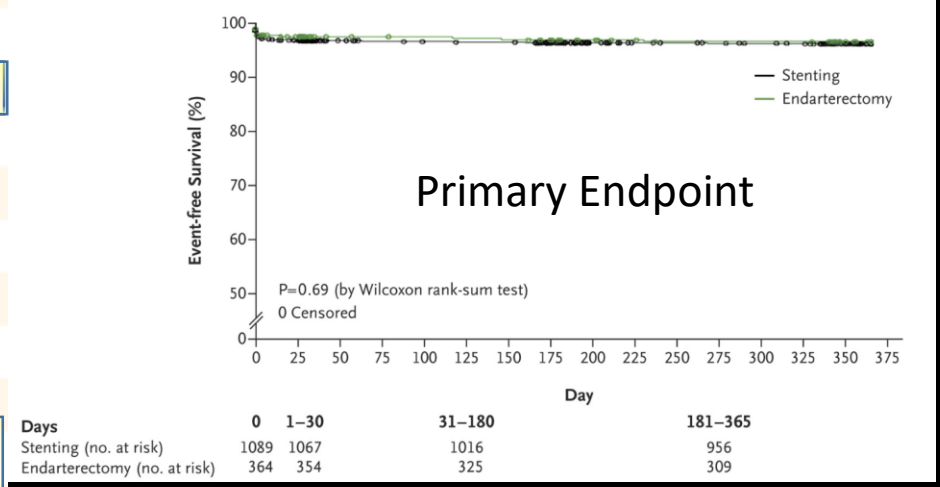


*N Engl J Med 2016; 374:1011-1020

ACT 1: Results*

Table 2. Death, Stroke, or Myocardial Infarction and Composite Measure of Complications within 30 Days after Index Procedure.*

Outcome	Stenting (N=1089)	Endarterectomy (N=364)	P Value†
	no. of patients/total no. (%)		
Death, stroke, or myocardial infarction	35/1072 (3.3)	9/348 (2.6)	0.60
Death or stroke	31/1072 (2.9)	6/348 (1.7)	0.33
Death or major stroke	6/1072 (0.6)	2/348 (0.6)	1.00
Death	1/1072 (0.1)	1/348 (0.3)	0.43
All stroke	30/1072 (2.8)	5/348 (1.4)	0.23
Major stroke	5/1072 (0.5)	1/348 (0.3)	1.00
Ipsilateral	4/1072 (0.4)	1/348 (0.3)	1.00
Nonipsilateral	1/1072 (0.1)	0/348	1.00
Minor stroke	26/1072 (2.4)	4/348 (1.1)	0.20
Ipsilateral	22/1072 (2.1)	4/348 (1.1)	0.36
Nonipsilateral	4/1072 (0.4)	0/348	0.58
Myocardial infarction	5/1072 (0.5)	3/348 (0.9)	0.41
Composite measure of complications	31/1089 (2.8)	17/364 (4.7)	0.13
Cranial-nerve injury	1/1089 (0.1)‡	4/364 (1.1)	0.02
Peripheral-nerve injury	0/1089	0/364	NA
Vascular injury	8/1089 (0.7)	3/364 (0.8)	1.00
Noncerebral bleeding	21/1089 (1.9)	6/364 (1.6)	0.83
Endarterectomy incision or puncture-site bleeding	3/1089 (0.3)	4/364 (1.1)	0.07
Other complications	0/1089	0/364	NA



*N Engl J Med 2016; 374:1011-1020

Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2)*

Estimated Enrollment :	**2480 participants**
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	CREST-2 is two parallel multi-center randomized, observer-blinded endpoint clinical trials.
Masking:	Single (Investigator)
Masking Description:	CREST-2 is two parallel multi-center randomized, observer-blinded endpoint clinical trials.
Primary Purpose:	Prevention
Official Title:	**Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial**
Study Start Date :	December 2014
Estimated Primary Completion Date :	December 2022
Estimated Study Completion Date :	December 2022

*NCT 02089217

Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2)*

- Primary Outcome Measures:
- Stroke and death: Composite of stroke plus death within 44 days after randomization and ipsilateral stroke up to 4 years.

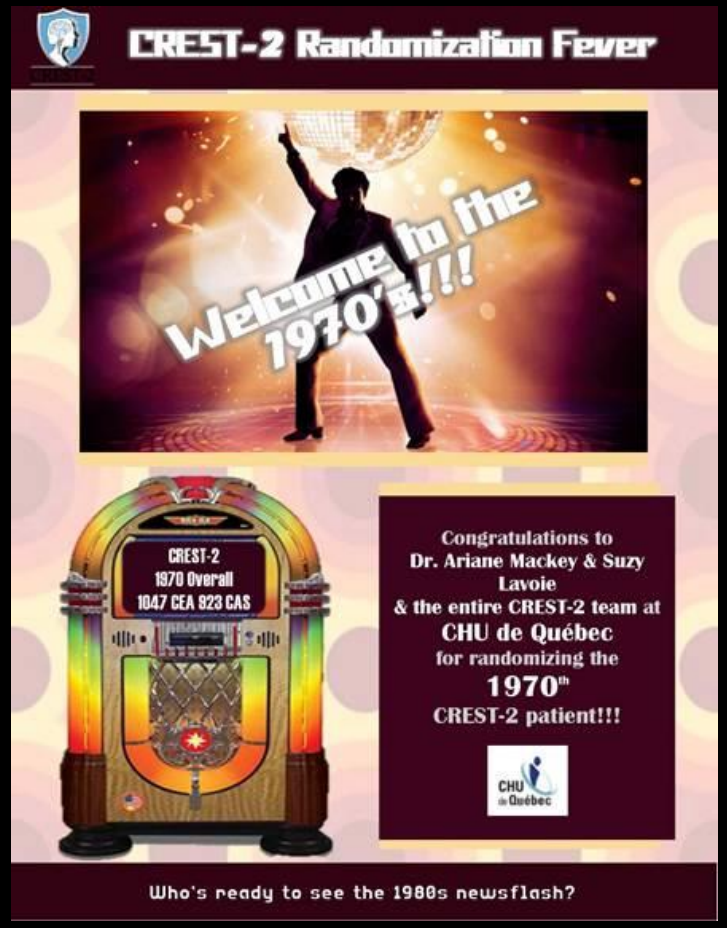
- Secondary Outcome Measures:

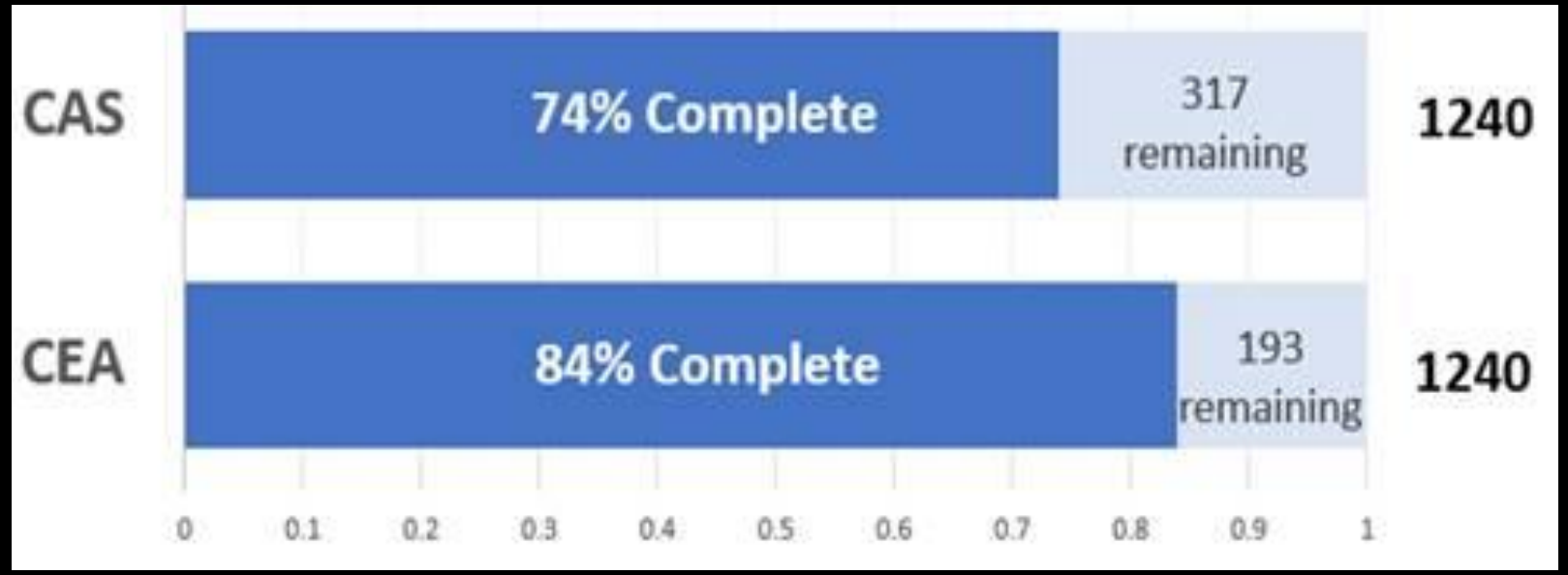
-Cognitive Function: Does MEDICAL management differ from CAS, and from CEA, to maintain cognitive function at 4-years?

-Major Stroke: Are there differences in the incidence of major stroke at 4-years among all arms of the study?

-Effect modification: Are there potential modifications of the effects of CEA or CAS based on patient age, sex, severity of carotid stenosis, restenosis, risk factor level, and duration of the asymptomatic period?

CREST-2 Enrollment Update, December 2021





TCAR:Roadster I*
NCT01685567

- 208 patients, 18 sites

-67 lead in cases

-141 cases for analysis (26% symptomatic)

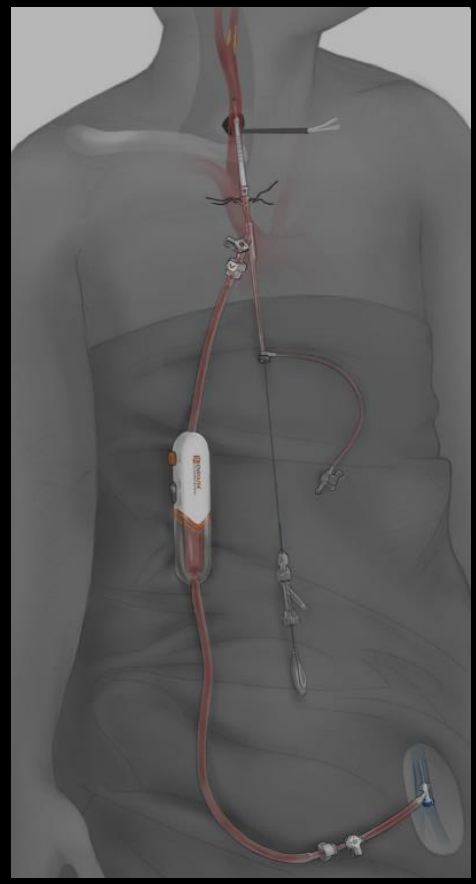
-Acute device and Technical success: 99%

-2 strokes (1.4%)

-2 deaths (1.4%)

-Stroke and death (2.8%)

-1 Cranial nerve injury resolved at 6 months



*J Vasc Surg 2015;62:1227-34

Roadster II (TCAR Post Market Registry) NCT02536378

- **Primary Outcome Measure :**

-Procedural Success @ 30 Days defined as acute device success (successful insertion of the ENROUTE NPS and establishment of flow reversal), technical success (deployment of interventional tools) and the absence of a major adverse events (hierarchical stroke/death/myocardial infarction) through 30 days.

- **Secondary Outcome Measures :**

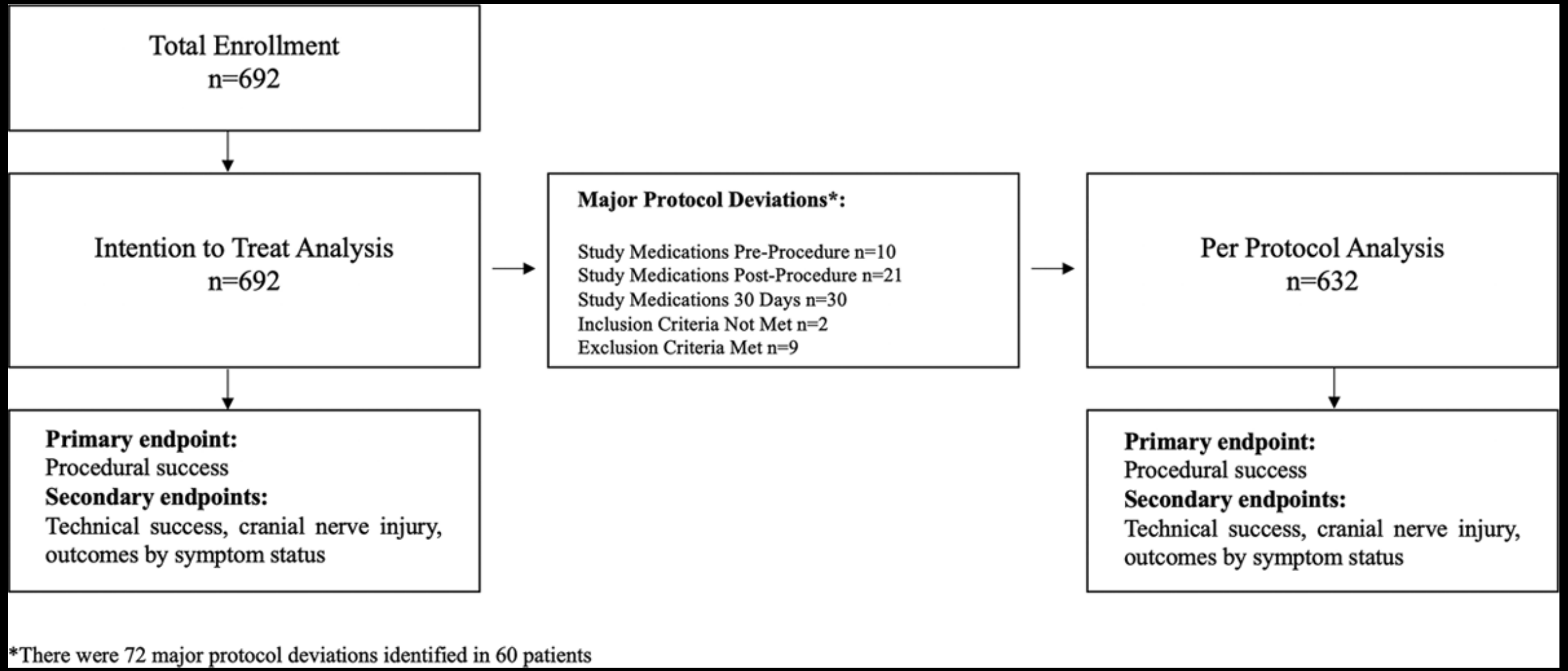
-Major Adverse Event @ 30 days (stroke, death or myocardial infarction) and rate stroke, stroke death or myocardial infarction, cardiac death by symptom status.

-Acute Device Success defined as the ability to insert the device, establish flow reversal, and remove the device within 2 hours.

-Number of Participants With Technical Success defined as acute device success plus the ability to deliver interventional tools

-Cranial Nerve Injury suspected to be caused by surgical procedure and adjudicated by CEC.

Roadster II (TCAR Post Market Registry)
NCT02536378



Roadster II (TCAR Post Market Registry)*
NCT02536378

- 43 sites, US and Europe
- 70% investigators new to TCAR (not involved Roadster 1)
- 692 analyzed ITT analysis
- Technical Success: 99.7%
- Procedural success: 96.5%

- 13 strokes (1.9%)
  -4.4 % symptomatic patients
  -1% asymptomatic patients
- 3 deaths (0.4%)
- Stroke/death: 2.3%
  -4.4 % symptomatic patients
  -1% asymptomatic patients
- Stroke/death/MI: 3.2%

*Stroke 2020;51: 2620-2629

Summary/Conclusions

- Carotid interventions are among the best studied invasive procedures.
- Little doubt of benefit of CEA or CAS for symptomatic patients with high grade ICA stenosis.
- Little doubt transfemoral stents have higher periprocedural stroke risk than CEA.
- Longer term outcomes of CAS and CEA may be about the same.
- Current efforts are focused on decreasing initial stroke risk with stents.
- Medical therapy has evolved and there is legitimate debate about intervention for asymptomatic stenosis with modern medical management.