CAS is the Best Treatment for Young Healthy Patients with a High- Grade Asymptomatic Carotid Stenosis

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Disclosures

- ***Symposia Honoraria & Proctor Fees***:
  - Abbott, Endologix
- ***Symposia Honoraria***:
  - Boston Scientific, Medtronic, Penumbra, Shockwave
- ***VIVA Board Member***
- ***National PI/Co-PI***: C-GUARDIANS, CONFIDENCE, SAPPHIRE WW, CANOPY, PERFORMANCE 3, POWER PAD 2
- ***Stock Options:*** INSPIRE MD
- ***Research Grants, Stocks, Equity:*** None

For *YOUNG* Patients with *HIGH-GRADE* Carotid Stenosis, We Should Use Facts Rather than Opinions

Some Opinions/ Flawed "assumptions" too frequently proposed

- 1. Strokes are significantly less frequent in 2024, **AND**
  - "Stroke reduction " is **grossly misrepresented** in population Medline studies in patients with moderate stenosis and no neuro adjudication
  - Strokes are increasing and are a major source of morbidity/mortality- please check statistics, ask your stroke centers, check your hospital
- 2. This "great reduction" in strokes is "secondary to great improvements in optimized medical therapy"
  - We are not allowed to "declare" this opinion without evidence
  - "Advances" in medical therapy are modest at best

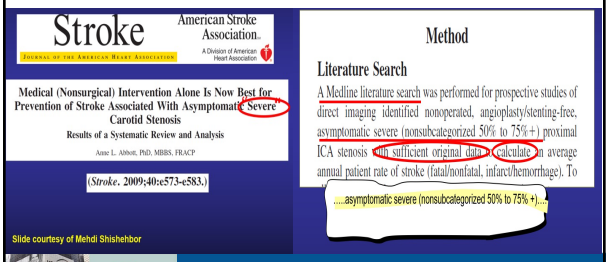
Stroke Incidence & Burden in the U.S.

$36.5 Billion
in Direct Medical Costs
from 2018-2019

- Stroke is the fifth leading cause of death
- Stroke deaths have increased 24% from 2010 to 2020
- In 2020, the following estimates were made:
  - Someone died from stroke every 3 minutes.
  - Stroke accounted for 1 of every 21 deaths in the U.S.
- In 2035, total direct medical stroke-related costs are projected to reach $94.3 billion.

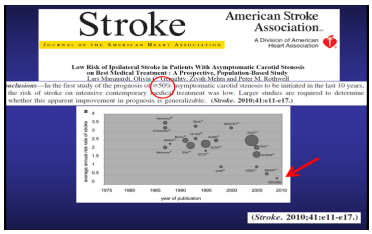
Tsao, C., et al. Heart Disease and Stroke Statistics—2023 Update: Report From the American Heart Association. Circulation. 2023.

Why the "Lower Stroke" Claims? *Flawed Methodology*



Slide courtesy of Mehdi Shishehbor

More "Lower Stroke" Claims? *Flawed Methodology*



Stroke
American Stroke Association
A Division of American Heart Association
JOURNAL OF THE AMERICAN HEART ASSOCIATION

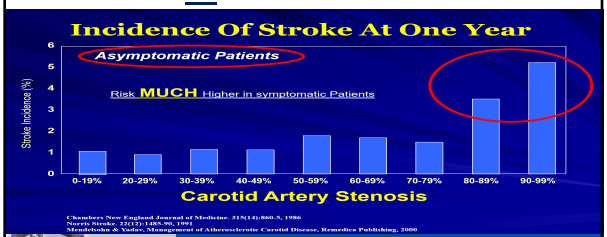
Low Risk of Ipsilateral Stroke in Patients With Asymptomatic Carotid Stenosis on Best Medical Treatment : A Prospective, Population-Based Study

Lars Marquardt, Olivia C. G... Rothwell

Of the 1153 imaged ... stenosis of at least 1 carotid b... had ≥50% symptomatic carotid ... 50% asymptomatic carotid steno... nts, 75 present- ..... the majority of p...nts had only 50% to 69% stenosis, with about a third of our patients having an asymptomatic carotid stenosis of 70% to 99%.

33 patients

Patients with TRUE "Severe" (≥80%) Carotid Disease *Do* Have HIGHER Stroke Risks



Chambers New England Journal of Medicine. 315(14):860-5, 1986
Norris Stroke. 22(15):1485-90, 1991
Mendelsohn & Yadav, Management of Atherosclerotic Carotid Disease, Remedica Publishing, 2000

OMT Patients with TRUE "Severe" (≥80%) Carotid Disease *Do* Have HIGHER Stroke Risks

Risk of stroke in relation to degree of asymptomatic carotid stenosis: a population-based cohort study, systematic review, and meta-analysis

Patients with 80-99% stenosis had significantly increased risk of 5-yr ipsilateral stroke than 50-79% stenosis patients

P<0.0001

5-year stroke risk 18.3%

The stroke risk … was *highly dependent* on degree of asymptomatic carotid stenosis, suggesting the benefit of CEA (CAS) might be underestimated in patients with severe stenosis

Oxford Study Group

Lancet Neurol 2021; 20: 193-202

Risk of stroke in relation to degree of asymptomatic carotid stenosis: a population-based cohort study, systematic review, and meta-analysis

Dominic P J Howard, Liam Gaziano, Peter M Rothwell, on behalf of the Oxford Vascular Study

More: OMT Patients with Severe Stenosis have Higher Annual Stroke Rates

1.

2.

Emerging evidence suggests that patients with high-grade asymptomatic carotid stenosis should be revascularized

3.

Stroke risk management in carotid atherosclerotic disease: a clinical consensus statement of the ESC Council on Stroke and the ESC Working Group on Aorta and Peripheral Vascular Diseases

10 yr CVA rate 12-25% in severe Carotid patients

1. Lancet Neurol 2021; 20: 193-202
2. Journal Vasc Surg January 2022 Supplement
3. Cardiovasc Research 2023- 0; 1-31

So, For Optimal Medical Therapy Alone….

- Strokes: still a MAJOR morbidity, mortality, & financial burden
- Strokes are ***unpredictable*** in asymptomatic patients
- Degree of stenosis and rate of progression of lesion severity are predictive of higher stroke rates (~ 3%/year for ≥ 80% CAS) even in patients on optimal medical therapy

Let's look at carotid revascularization and CAS in these (≥80%) patients looking at rigorous data

And If CAS/CEA can be done at low risk and results are durable, we win

CEA: 2-5 Year Ipsilateral CVA

Study	MED (%)	CEA (%)	RRR (%)
ACAS ASx	11.0	5.1	54*
NASCET Sx	26.0	9.0	65*

*p < 0.01

Surgery outcomes better than medical therapy; ~LOW risk pts; ↑volume operators

This difference was in patients w/ ≥ 60% lesions

"Contemporary" RCT's: CEA vs. CAS

White *et al*
Carotid Artery Stenting

JACC VOL. 80, NO. 2, 2022
JULY 12, 2022:155–170

TABLE 3 Randomized Trials of CAS Versus CEA in Asymptomatic Patients

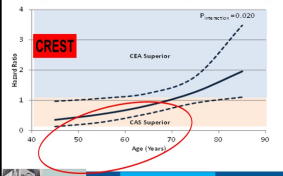
First Author/Study, Year (Ref. #)	N	EPD Use	30-Day Stroke/Death/MI	Comment
Brooks et al, 2004[25]	CAS = 43 CEA = 42	No	CAS = 0 CEA = 0	ASR, stenosis >80%, similar hospital costs.
SAPPHIRE, 2004[26]	CAS = 117 CEA = 119	Yes	CAS = 5.4% CEA = 3.2%	HSR, >80% stenosis, primary endpoint: CAS = 9.9%, CEA 21.5% (*P* = 0.02).[a]
CREST, 2010[3]	CAS = 594 CEA = 587	Yes	CAS = 3.5% CEA = 3.6%	ASR, >60% stenosis, primary endpoint[a]: CAS = 5.6%, CEA 4.9% (*P* = NS). Stroke/death at 4 y: CAS = 4.5%, CEA = 2.7% (*P* = 0.07). No difference between groups at 10 y.
ACT-1, 2016[5]	CAS = 1,089 CEA = 364	Yes	CAS = 3.3% CEA = 2.6%	ASR, stenosis >70%, primary endpoint: CAS = 3.8%, CEA = 3.4%[a] (*P* = NS).
SPACE-2, 2020[6]	CAS = 197 CEA = 203 MED = 113	Optional (36%)	CAS = 2.5% CEA = 2.5% MED = 0%	ASR, stenosis >70%, primary endpoint: CEA = 2.5%, CAS = 3.0%, MED = 0.9%; (*P* = NS)[a]. In all CAS patients with major secondary outcome events, no EPD was used.
ACST-2, 2021[7]	CAS = 1,811 CEA = 1,814	Yes (85%)	CAS = 3.9% CEA = 3.2%	ASR, stenosis >60%, nonprocedural stroke during follow-up CAS = 5.2%, CEA = 4.5%.

[a]Death, stroke, or MI within 30 days after the procedure or death or ipsilateral stroke between 31 days and 1 year. [b]The composite of any stroke, MI, or death during the periprocedural period or ipsilateral stroke within 4 years after randomization.
ACST-2 = Asymptomatic Carotid Surgery Trial-2; ACT-1 = Asymptomatic Carotid Trial; SPACE-2 = Stent Protected Angioplasty versus Carotid Endarterectomy-2; other abbreviations as in Tables 1 and 2.

And There is Level 1 Evidence Suggesting an Advantage for CAS in "Younger" Patients

CAS *May* be Better than CEA in Patients <70

Intuitive Arch and Carotid Anatomy CAS Advantages



SPACE

Outcomes related to age

DESPITE Low EPD utilization in SX Patients

"Best Fit" analysis

ACT 1 - Freedom from D/S/MI @ 30 Days and Ipsilateral Stroke to 5 Years

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 17, 2016 VOL. 374 NO. 11

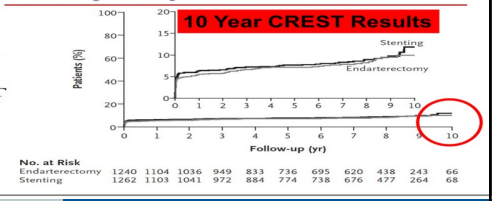
Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis

Kenneth Rosenfield, M.D., M.H.C.D.S., Jon S. Matsumura, M.D., Seemant Chaturvedi, M.D., Tom Riles, M.D., Gary M. Ansel, M.D., D. Chris Metzger, M.D., Lawrence Wechsler, M.D., Michael R. Jaff, D.O., and William Gray, M.D., for the ACT I Investigators*

CRF TCT

BOTH CEA and CAS are Durable at 10 Years

Primary Composite End Point



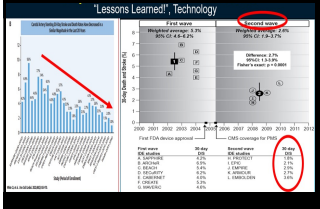
CREST

No. at Risk

Endarterectomy	1240	1104	1036	949	833	736	695	620	438	243	66
Stenting	1262	1103	1041	972	884	774	738	676	477	264	68

CAS/TCAR Results Continue to Improve

"Lessons Learned!", Technology



CREST 2 Registry (C2R) - Results

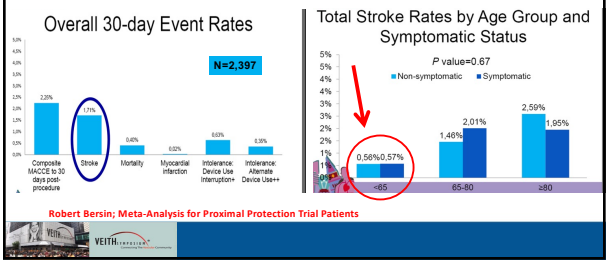
2141 Patients/ 2219 Procedures (Bilateral 78)

- 68 years old mean age; 65% Male
- Symptomatic 45%
- 30 Day Stroke and Death rate
  - Asymptomatic 1.4%
  - Symptomatic 2.8%
  - All patients 2.0%

1. JACC 2022;80: 155-170; 2. JACC; Vol 74, No. 25; 2019; 3. ROADSTER Pivotal Trial; 4. PERFORMANCE 2 IDE Trial; 5. C-GUARDIANS IDE Trial

Recent Pivotal ROADSTER, PERFORMANCE 2, C-GUARDIANS Trials
0.95-1.41 % Total Strokes with Neurologic Adjudication in High CEA- Risk patients !

Proximal Protection TF-CAS: Better results seen, was not included in RCT's

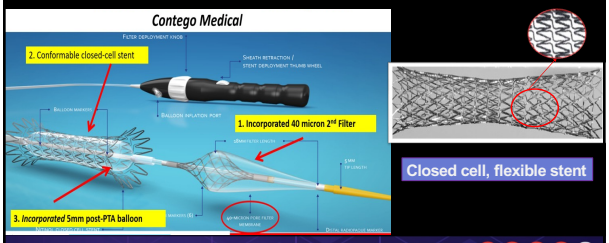


Robert Bersin; Meta-Analysis for Proximal Protection Trial Patients

- Newer technologies with EXTREMELY LOW Stroke rates in 621 High-CEA Risk Patients (Asymptomatic ≥ 80%, Symptomatic ≥50%) In Prospective scientifically rigorous IDE Trials with neurologic adjudication……

Neuroguard IEP® System

3-in-1 Carotid Stent Delivery System with Integrated Embolic Protection



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PERFORMANCE II Trial Design

Trial Objective	Evaluate the safety and effectiveness of the Neuroguard IEP Carotid Stent system in subjects for the treatment of carotid artery stenosis at elevated risk for adverse events following CEA		
Principal Investigators	William A. Gray, MD, FACC, FSCAI Global Principal Investigator Lankenau Heart Institute/Main Line Health, Wynnewood PA	Ralf Langhoff, MD European Principal Investigator Sankt Gertrauden Krankenhaus GmbH, Berlin Germany	
Sample Size and Patient Population	305 subjects	40 US and EU sites	Symptomatic with ≥ 50% stenosis or asymptomatic with ≥ 80% stenosis At least one anatomic or medical comorbidity considered to be high-risk for adverse events following CEA
Primary Endpoint	30-day rate of periprocedural death, stroke or myocardial infarction (MI) within 30 days of the index procedure ***plus*** ipsilateral stroke within 12 months (PG: 13.8%)		

Slide courtesy of Bill Gray, MD

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PERFORMANCE II: 30-Day Outcomes

N=305	Intention-to-Treat	Per-Protocol[1]
30-day Death Stroke/MI[3]	2.30% (7)	1.97% (6)
All stroke	1.31% (4)	0.98% (3)
Minor stroke	1.31% (4)	0.98% (3)
Major stroke	0.0% (0)	0.0% (0)
All Stroke - Asymptomatic Patients	0.81% (2)	0.81% (2)
All Stroke - Contralateral	0.0% (0)	0.0% (0)
Myocardial infarction	0.66% (2)	0.66% (2)
Death	0.33% (1)[2]	0.33% (1)

[1]One patient with hypercoagulable state who was on chronic anticoagulation (exclusion criteria)
[2]Patient with 3V CAD who died on day 30 due to cardiovascular causes after coming back for an uneventful follow up visit on day 25
[3]Hierarchical

All patients at baseline neurologically within 30 days

Slide courtesy of William A. Gray, MD

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PERFORMANCE II: 1 Year Outcomes

n=270	Intention-to-Treat	Per-Protocol
30 Day Death/Stroke/MI + Ipsilateral Stroke between Day 31 to 12 Months	2.67% (8)	2.33% (7)
Ipsilateral Stroke, day 31 to 12 months	0.37% (1)	0.37% (1)
Minor stroke	0.37% (1)	0.37% (1)[1]
Major stroke	0.0% (0)	0.0% (0)
30 Day All Stroke + Ipsilateral Stroke Day 31 to 12 months	1.68% (5)	1.34% (4)
Neurological Death	0.0% (0)	0.0% (0)
CD-TLR	0.0% (0)	0.0% (0)
Target Lesion Revascularization	1.47% (4)	1.47% (4)

CD-TLR: Any revascularization procedure of the original treatment site associated with narrowing of > 80% as determined by the angiographic core lab within 12 months of the index-procedure.

One Minor Stroke Between Day 31 and 12 Months
No Major Strokes at One Year
No Neurological Deaths at One Year

Slide courtesy of William A. Gray, MD

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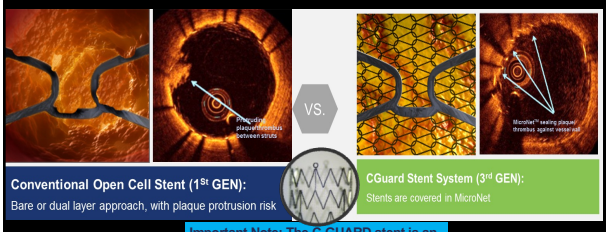
Next Stroke Prevention Strategy: MicroNet Technology



Conventional Open Cell Stent (1st GEN):
Bare or dual layer approach, with plaque protrusion risk

CGuard Stent System (3rd GEN):
Stents are covered in MicroNet

Important Note: The C-GUARD stent is an *investigational device ONLY* in the US

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C-GUARDIANS Trial Design

Design	Prospective, multicenter, international, single-arm clinical trial comparing the primary endpoint to a performance goal derived from literature
Trial Objective	Evaluate the safety and efficacy of the CGuard Prime™ Carotid Stent System in the treatment of carotid artery stenosis in symptomatic and asymptomatic patients at high risk for CEA (25% symptomatic) undergoing carotid artery stenting (CAS)
Principal Investigators	Dr. Chris Metzger, MD — OhioHealth Riverside Methodist Hospital, Columbus, Ohio, USA; Dr. Piotr Musialek, MD, PhD — Jagiellonian University, John Paul II Hospital, Kraków, Poland
Sample Size & Population	316 subjects; 24 US and EU sites; Symptomatic with ≥ 50% stenosis or asymptomatic with ≥ 80% stenosis; ≥ 80 years of age at high risk for CEA Pre-specified 25% symptomatic
Primary Endpoint	Incidence of death (all-cause mortality), all stroke, and myocardial infarction (DSMI) through 30-days post-index procedure or Ipsilateral stroke from 31 to 365 days

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C-GUARDIANS: 30-Day Major Adverse Events (LBCT VIVA 2023)

Event rate in % (n)	ITT (N=316)	Per Protocol*
Death, Stroke or MI*	0.95% (3)	0.63% (2)
Death#	0.32% (1)	0.00% (0)
Any stroke#	0.95% (3)	0.63% (2)
Major Stroke#	0.32% (1)	0.00% (0)
Minor Stroke#	0.63% (2)	0.32% (1)
MI#	0.00% (0)	0.00% (0)
Death or any stroke*	0.95% (3)	0.63% (2)
Death or major stroke*	0.63% (2)	0.32% (1)

30-day S/D/MI

*Hierarchical: patient count (each patient first occurrence of the most serious event). # Non hierarchical: event count (multiple events in each patient are counted individually).
** Per Protocol Analysis excludes 1 patient (did not take dual antiplatelet therapy; had a major stroke and died).

The CEC independently adjudicated all neurological, cardiac events:
- 1 major fatal stroke on post procedural day 10 after all DAPT stopped contrary to protocol requirements.
- 1 minor stroke. (NIHSS 2, post procedure). NIHSS 1, CDU patent 30 days, NIHSS 0 at 6 and 12 months
- 1 retinal infarct in a patient presenting with amaurosis fugax, adjudicated as a minor stroke. (NIHSS 1). NIHSS 0, CDU patent 30 days

CAUTION: The CGuard Stent System is Investigational Use Only and Not for Sale in the USA

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C-GUARDIANS Trial 1-Year Primary Endpoint Results

Event*	ITT	Per Protocol**
30-day DSMI + Ipsilateral stroke between 31 and 365 days	1.95 % (6)	1.70% (5)
30-day DSMI	0.95% (3)	
Ipsilateral stroke between 31 and 365 days	1.00% (3)	
TLR	0.98% (3)	1.01% (3)

1 year stroke rate for ASX 80% patients: 0.4%

* Kaplan-Meier estimate for all 1-year endpoints
** Per Protocol Analysis excludes 15 patients with Major Protocol Deviations

LINC 2024 LBCT

The CEC independently adjudicated all neurological, cardiac events:
- *1 minor stroke (retinal) on POD 189.*
- *1 major stroke on POD 280: Prostatectomy (Antiplatelet therapy stopped).*
- *1 major stroke on POD 307: Stent patent; A Fib discovered.*

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Conclusions

- The **cumulative** risk for **young** asymptomatic patients and **high- grade stenosis** is significant, and is **unpredictable**
- CAS in young asymptomatic patients **can predictably** be performed at low risk (< 1% minor stroke, <<1% major stroke)
- Once predictable low risk CAS is performed, the issue is "fixed", with durable long- term prevention of ipsilateral stroke and TLR
- Our treatment should be individualized to each patient with *their* involvement; and ALL patients should have optimized medical therapy and risk factor modification

Thank You for Your Attention!