Brott TG, Howard G, Lal BK, et al. Medical Management and Revascularization for Asymptomatic Carotid Stenosis. *N Engl J Med*.

Images & graphics created with Google Gemini
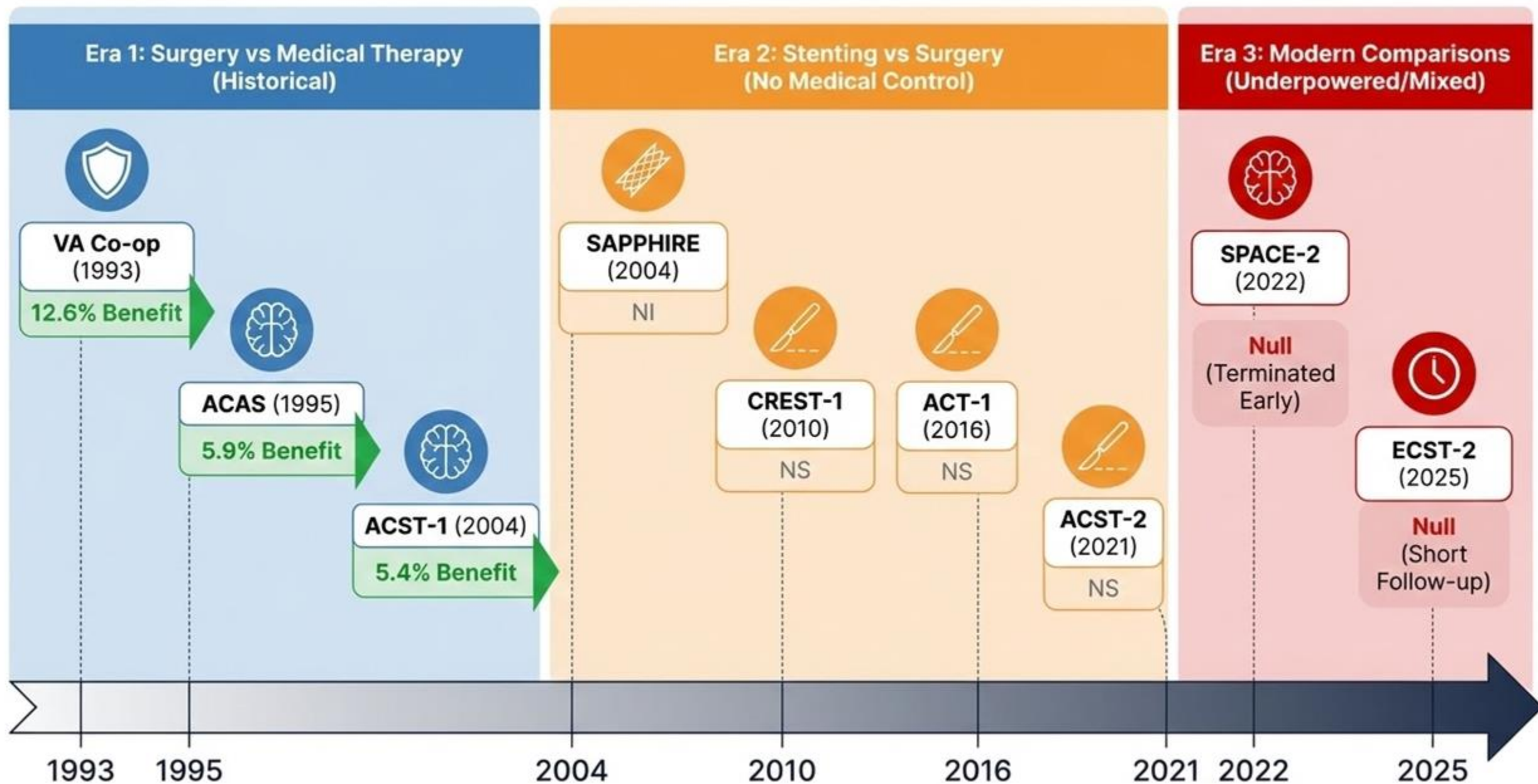
Trial (Year)	Population & Stenosis	Comparison	Primary Outcome (ARD)	Safety (30d S/D)	
Era 1: Surgery vs Medical Therapy (Historical)					
VA Co-op (1993)	Asympt Men >50%	CEA vs Med	**Ipsilateral TIA/Stroke** 8.0% vs 20.6% **(12.6% Benefit)**	4.7% (CEA)	Men only; TIA outcome included
ACAS (1995)	Asympt >60%	CEA vs Med	**5y Ipsi Stroke/Death** 5.1% vs 11.0% **(5.9% Benefit)**	2.3% (CEA)	Aspirin only control; Minor stroke driven
ACST-1 (2004)	Asympt >60%	Immediate vs Deferred CEA	**5y Any Stroke/Death** 6.4% vs 11.8% **(5.4% Benefit)**	3.1% (CEA)	Variable statin use
Era 2: Stenting vs Surgery (No Medical Control)					
SAPPHIRE (2004)	Mixed (High Risk) Asym>80%	CAS vs CEA	**1y D/S/MI** 12.2% vs 20.1% (NI)	4.8% vs 5.4%	High risk cohort only; MI drove the difference
CREST-1 (2010)	Mixed Asymp >70%	CAS vs CEA	**4y D/S/MI** 7.2% vs 6.8% (NS)	2.5% vs 1.4%	Mixed (53% Symptomatic)
ACT-1 (2016)	Asympt >70%	CAS vs CEA	**1y D/S/MI** 3.8% vs 3.4% (NS)	2.9% vs 1.7%	CAS perioperative-stroke ~2x CEA
ACST-2 (2021)	Asympt >60%	CAS vs CEA	**5y Proc + Non-Proc S** 5.3% vs 4.5% (NS)	3.6% vs 2.4%	Supports procedural equivalence
Era 3: Modern Comparisons (Underpowered/Mixed)					
SPACE-2 (2022)	Asympt >70%	Revasc vs Med	**5y Stroke/Death** 2.5% (CEA) vs 4.4% (CAS) vs 3.1% (Med) (Null)	~2.5%	Terminated early (n=513); Underpowered
ECST-2 (2025)	Mixed >50%	Revasc vs Med	**2y Interim** 10.5% vs 10.2% (Null)	1.2%	Mixed population; Short follow-up

Trends in Carotid Revascularization: United States

Volumes (2006-2022, 17y)
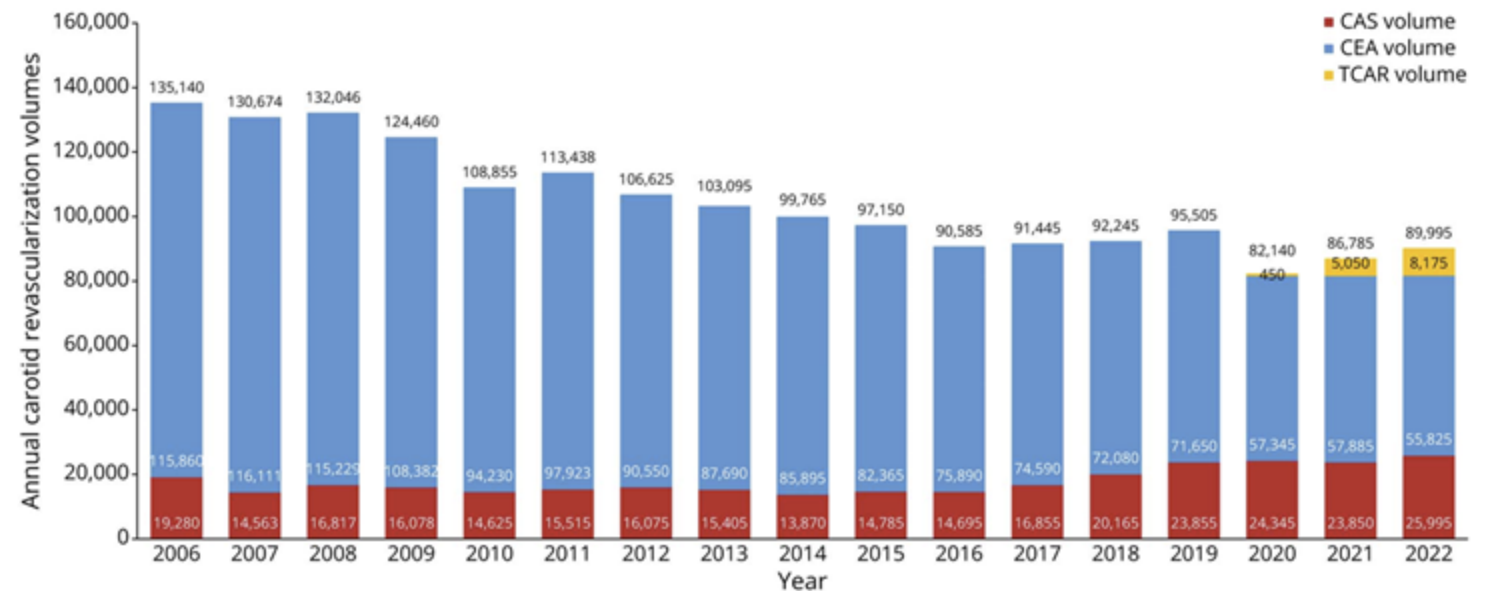
- *Overall*: ↓ -3.9%/yr until 2015
- *CEA*: ↓ -5.5%/yr
- *CAS*: ↑ +12.0%/yr since 2016
- *TCAR*

Asymptomatic **74.3%**
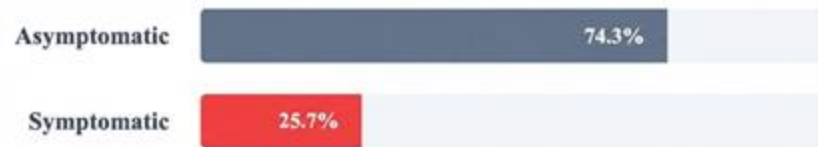
Symptomatic **25.7%**

≈ 75%
PROCEDURES ARE FOR ASYMPTOMATIC DISEASE

Figure 1 Annual Volumes of Carotid Revascularizations in the United States From 2006 to 2022 According to Revascularization Type
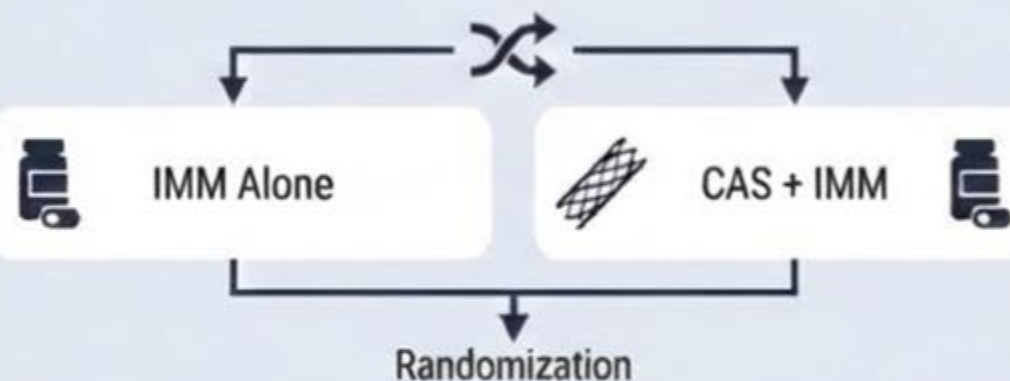

TCAR estimates are for the period October 2020–December 2023. CAS = carotid artery stenting; CEA = carotid endarterectomy; TCAR = transcarotid artery revascularization.
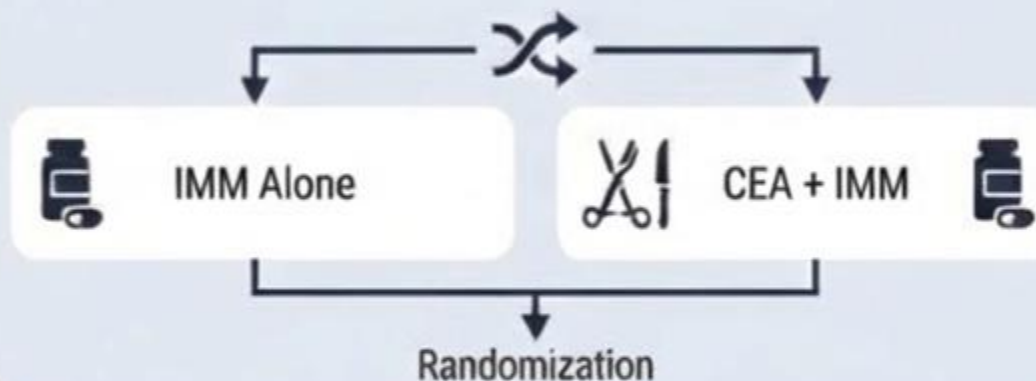
CREST-2

Treatment Procedures: Intensive Medical Management and Revascularization

Intensive Medical Management (IMM)

- **Protocol:** Identical across all arms (except periprocedural antiplatelets)
- **Primary Targets:** SBP < 130 mmHg, LDL < 70 mg/dL
- **Management:** Glucose, HbA1c, lifestyle factors (smoking, weight, activity)
- **Telephone health coaching**

Procedure	Pre-procedure Antiplatelets (≥48h before)	Post-procedure Antiplatelets
Procedure: Local anesthesia, embolic protection required	Aspirin (325 mg/d) + Clopidogrel (75 mg bid)	Clopidogrel (75 mg/d) + Aspirin (75-325 mg/d) for 30d, then Aspirin (70-325 mg/d)
Carotid Endarterectomy (CEA)	Aspirin (325 mg/d)	Aspirin (70-325 mg/d)

Follow–up Assessments and Outcomes

Follow-up Assessments

12-36h 44d 4m 8m 12m then every 6m to 48m

Scheduled Visits
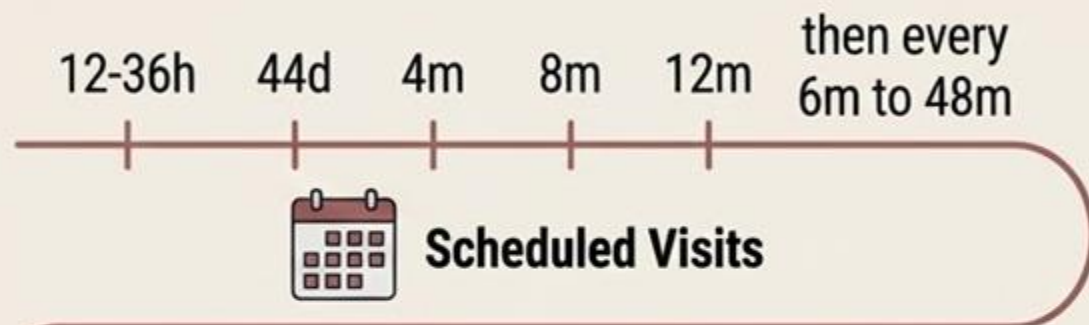
Triggered Imaging: MRI/CT if NIHSS ≥2 increase or suspected stroke/TIA.

Primary and Secondary Outcomes

Primary Outcome (4-Year Composite, ITT)
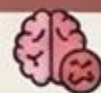
Periprocedural (≤44d): Any Stroke or Death

Postprocedural (>44d - 4y): Ipsilateral Ischemic Stroke

Stroke Definition & Adjudication

Blinded Committee, WHO criteria

Classification: Major (NIHSS ≥6), Disabling (mRS ≥3 @ 30d), Ischemic/Hemorrhagic.
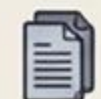
Secondary Outcomes: Primary Outcome + Postprocedural Contralateral Stroke, Tissue-Based Infarction / ICH / SAH.

Analysis

- 1° analysis (4-year ITT): Kaplan-Meier & CIF (accounting for competing risk of death)
- Power: 85%, 3.6% 4-year event rate in CAS/CEA groups, $\alpha = 0.05$ → detect medical tx rates <0.8% or >8.4%
  - 5% crossover & 2.5% annual withdrawal
- Estimation: 95% CIs via bootstrap methods (100K reps)
- No correction for multiplicity (2° outcomes) or imputation (missing data)

Patient at Start of Trial

Path A (Outcome of Interest) → **Stroke**

Path B (Competing Risk) → **Non-Stroke Death** (e.g., Cancer, Heart Attack)

These paths are mutually exclusive; death from a competing risk prevents the outcome of interest (stroke) from occurring

Example Cumulative Incidence Function (CIF) Curves

— Stroke (Outcome of Interest)

— Non-Stroke Death (Competing Risk)
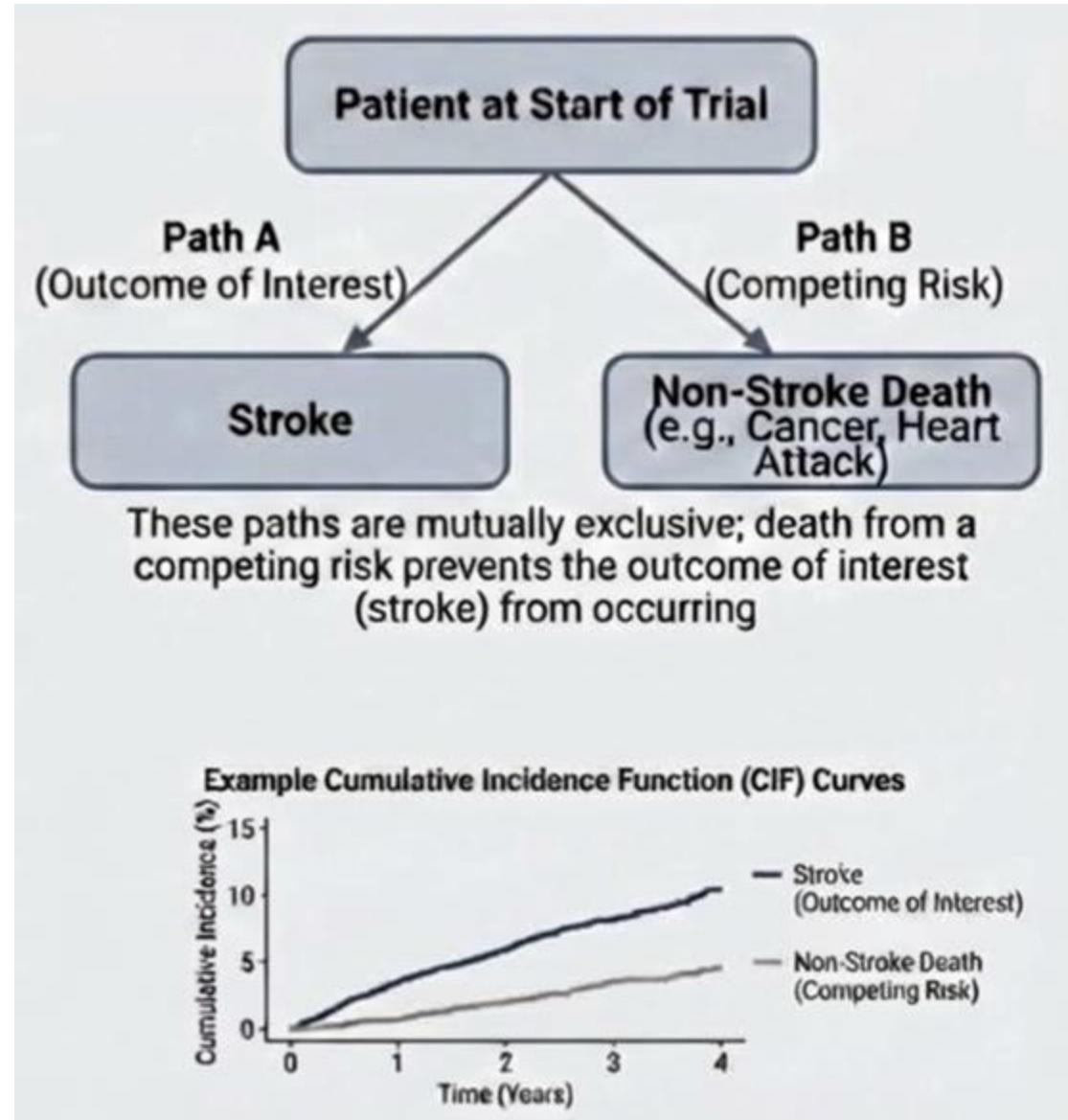
Results

- mean age ~70 yr
- ~⅔ men
- ~90% White
- ↑ vascular RF burden
- ~90% mRS=0

Table 1. Demographic and Clinical Characteristics of the Patients in the Two Trials, According to Treatment Assignment.*

| Characteristic	Stenting Trial (N=1245)		Endarterectomy Trial (N=1240)	
	Medical Therapy Alone (N=629)	Stenting (N=616)	Medical Therapy Alone (N=623)	Endarterectomy (N=617)
Age — yr	69.7±7.7	69.3±8.1	70.4±7.6	70.7±7.8
Female sex — %	38.2	36.9	39.0	35.3
Race — %†				
White	90.1	92.9	88.3	90.0
Black	6.2	5.7	6.9	6.0
Other, not reported, or missing data	3.7	1.5	4.8	4.1
Hispanic ethnic group — %†	4.7	4.8	3.9	4.4
Previous stroke or TIA on target lesion >180 days before randomization — %	4.9	8.0	8.4	8.9
Risk factors — %				
Hypertension	87.4	88.0	84.9	85.1
Diabetes	37.8	40.7	38.0	34.4
Dyslipidemia	93.3	92.0	90.0	91.5
Current smoking	21.0	18.8	21.2	21.1
Previous cardiovascular disease or CABG	54.5	53.7	43.3	44.3
Blood pressure — mm Hg				
Systolic	138.8±20.2	138.2±20.2	137.9±19.8	139.3±20.2
Diastolic	73.2±10.8	73.1±11.2	72.6±10.2	73.1±10.7
LDL cholesterol — mg/dl‡	76.7±34.6	77.1±36.5	81.3±33.9	80.3±33.6
Body-mass index§	28.7±5.6	29.3±5.5	28.5±5.4	28.7±5.3
Stenosis at randomization — %				
Index artery				
≥70% stenosis	97.6	97.7	97.1	97.4
Peak systolic velocity ≥389 cm/sec¶	33.5	31.1	32.9	37.2
Nonindex artery: ≥50% stenosis	34.4	37.0	37.2	35.7
Modified Rankin scale score of 0 — %‖	87.8	88.8	87.9	87.0
CHA_2DS_2-VASc score of ≥4 — %**	56.9	60.1	53.8	55.9

Medical Mgmt.

- ~70% achieved SBP & LDL-C targets
- No performance bias from medical "co-interventions"

Figure 1. Proportion of Patients with Risk-Factor Values in Target Range over Time.
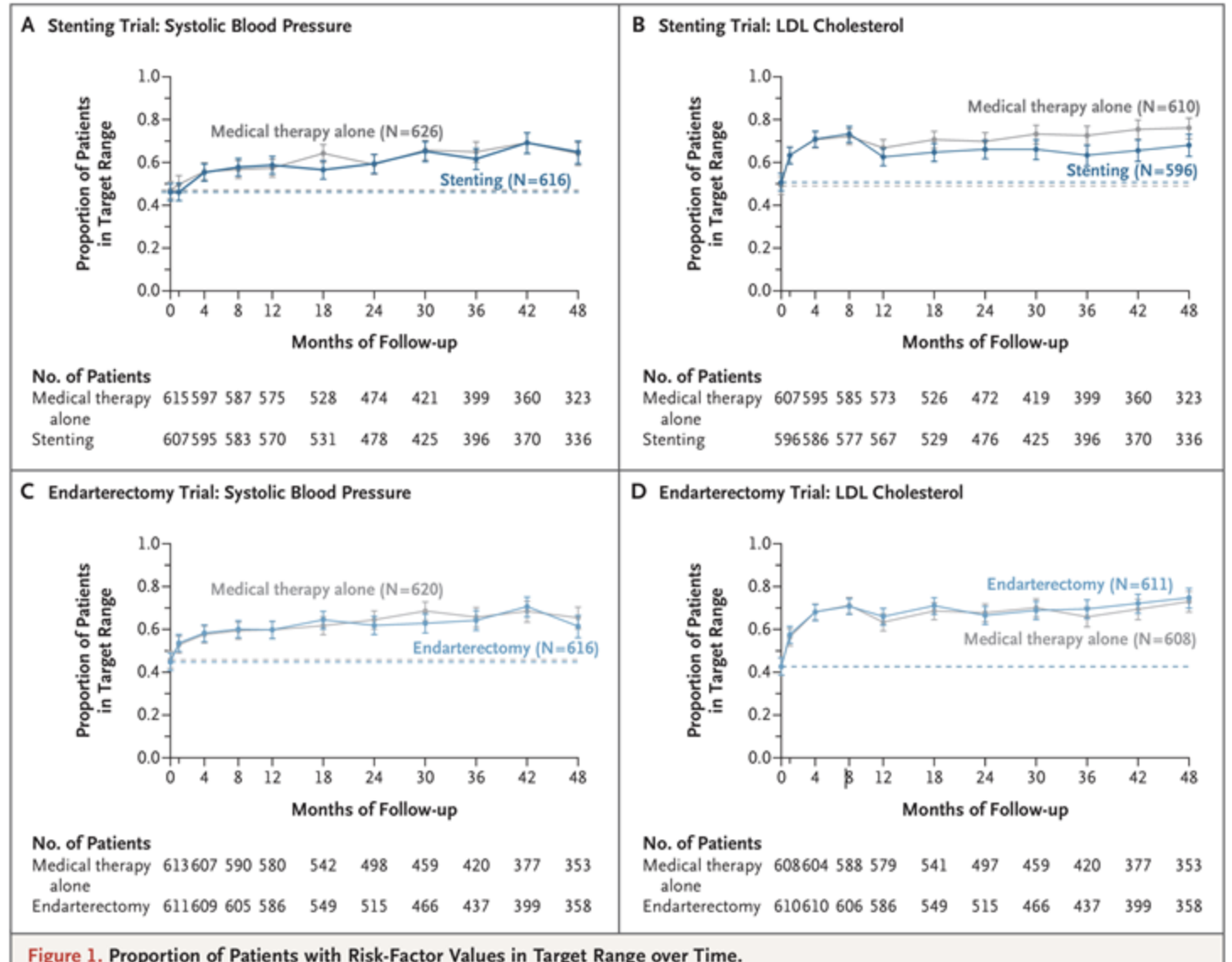
CAS:
- NNT ≅31
- periprocedural risk <
long-term risk reduction

CEA:
- ARD 1.6%
- underpowered for
small effect size

Table 2. Analysis of Primary Outcome and Components.

Variable	Stenting Trial		Endarterectomy Trial	
	Medical Therapy Alone	Stenting	Medical Therapy Alone	Endarterectomy
Primary 4-yr composite outcome*				
Event rate (95% CI) — %	6.0 (3.8 to 8.3)	2.8 (1.5 to 4.3)	5.3 (3.3 to 7.4)	3.7 (2.1 to 5.5)
Absolute difference (95% CI) — percentage points†	3.2 (0.6 to 5.9)		1.6 (–1.1 to 4.3)	
P value for difference	0.02		0.24	
Relative risk (95% CI)†	2.13 (1.15 to 4.39)		1.43 (0.78 to 2.72)	
Components of primary outcome				
Periprocedural period: stroke or death				
No. of events/no. of patients	0/629	8/616	3/623	9/617
Percent of patients with event (95% CI)	0.0 (0.0 to 0.6)	1.3 (0.6 to 2.5)	0.5 (0.1 to 1.4)	1.5 (0.7 to 2.8)
Difference (95% CI) — percentage points	–1.3 (–2.2 to 0.4)		–1.0 (–2.1 to 0.1)	
Postprocedural period: ipsilateral ischemic stroke				
No. of person-yr	1686	1714	1761	1823
No. of events/no. of patients	28/600	7/582	23/600	10/596
Annual event rate per person-yr (95% CI) — %	1.7 (1.1 to 2.4)	0.4 (0.2 to 0.9)	1.3 (0.9 to 2.0)	0.5 (0.3 to 1.0)
Relative risk (95% CI)	4.07 (1.78 to 9.31)		2.38 (1.13 to 5.00)	

A Primary-Outcome Analysis
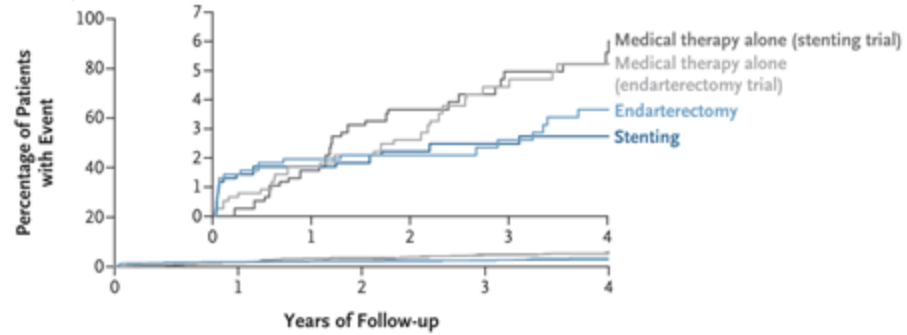
No. of Patients

Stenting trial					
Medical therapy alone	629	537	428	360	276
Stenting	616	543	431	375	289
Endarterectomy trial					
Medical therapy alone	623	550	461	381	304
Endarterectomy	617	561	482	411	319

B Periprocedural Component of Primary-Outcome Analysis (days 0 to 44)
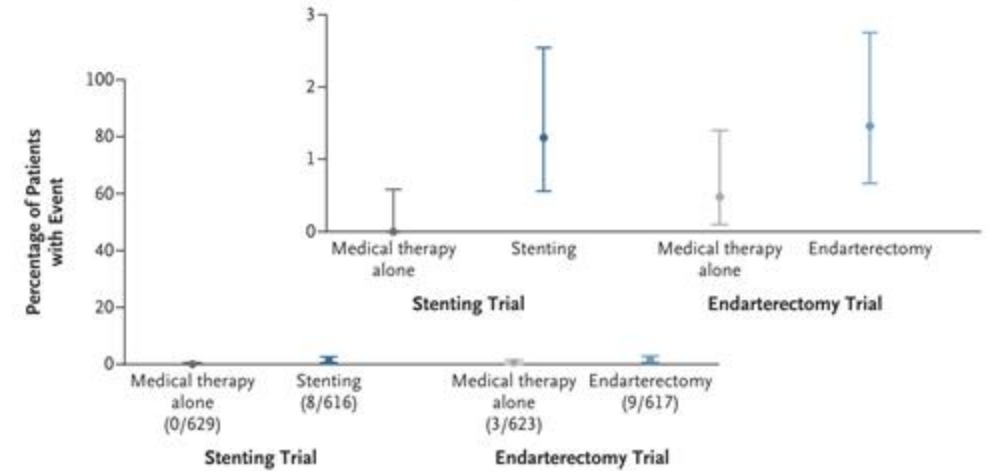
C Postprocedural Component of Primary-Outcome Analysis (after 44 days)
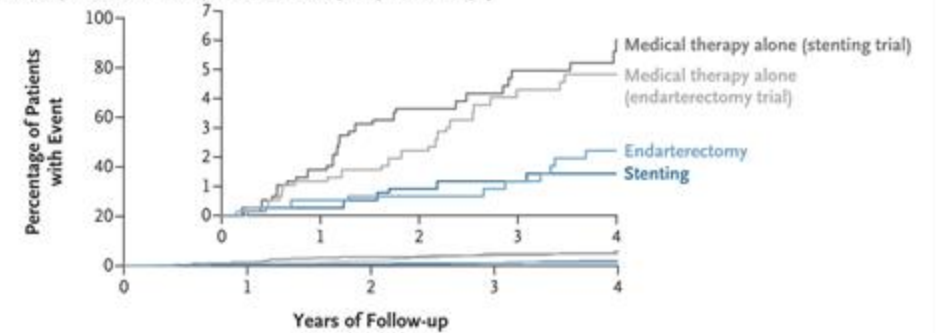
No. of Patients

Stenting trial					
Medical therapy alone	600	537	428	360	276
Stenting	582	543	431	375	289
Endarterectomy trial					
Medical therapy alone	600	550	461	381	304
Endarterectomy	596	559	480	409	317

Metric	CAS Trial (Sig)	CEA Trial (NS)
Periprocedural Events (0-44d)	1.3% (7 strokes, 1 death)	1.5% (9 strokes)
IMM Arm Risk (0-44d)	0%	0.5%
Post-procedural Annual Stroke Rate	0.4% vs 1.7%	0.5% vs 1.3%
Safety Threshold (<3%)	Met (1.3%)	Met (1.5%)

Secondary Outcomes

OUTCOME	CAS (VS MED)	CEA (VS MED)
Primary (WHO) Clinical sx >24h	**2.8% vs 6.0%** SIG (P=0.02)	**3.7% vs 5.3%** NS (P=0.24)
Any Tissue-Based MRI Infarction (S4I)	**6.8% vs 8.8%**	**7.8% vs 11.4%**
Disabling Stroke mRS ≥ 3	**1.6% vs 1.2%**	**1.5% vs 0.5%**
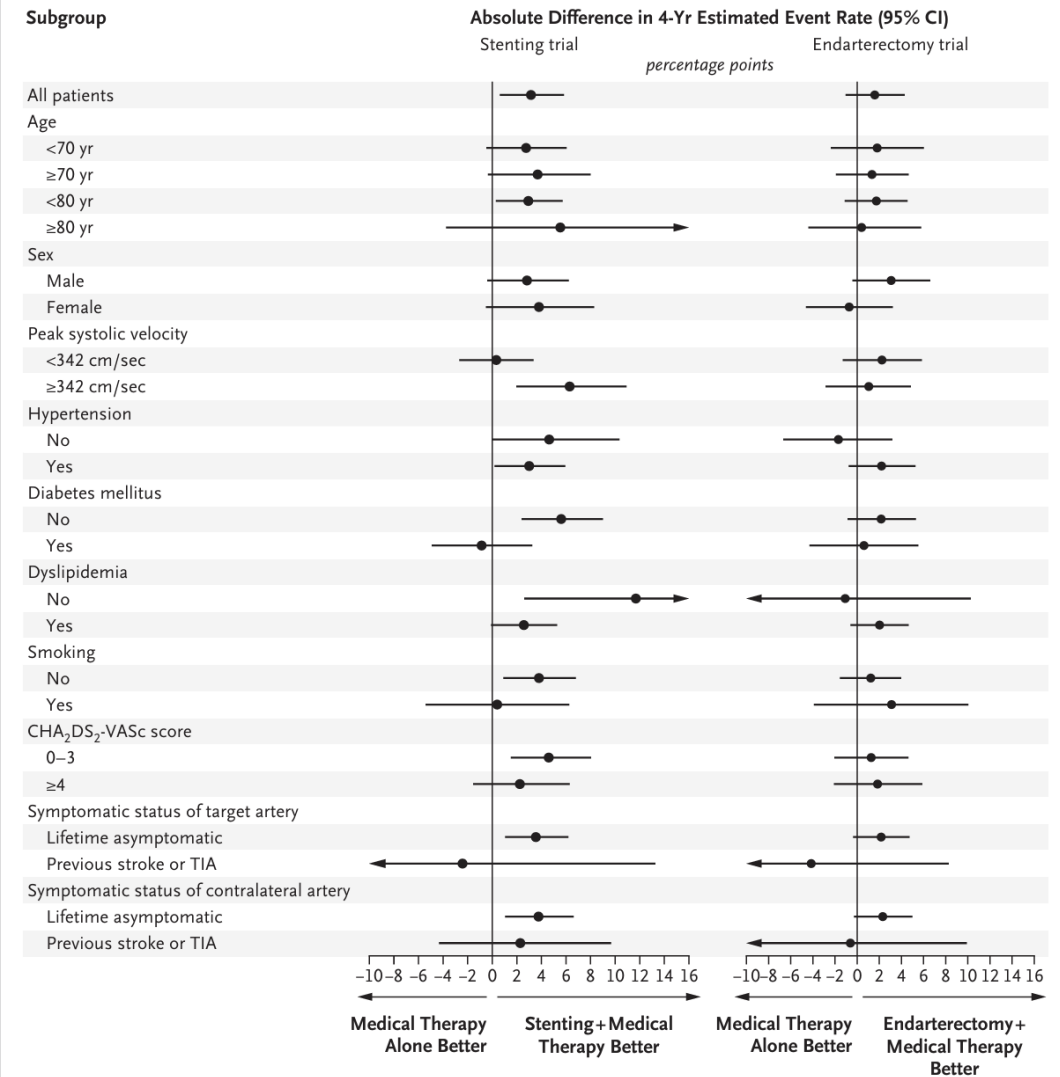
Figure 3. Absolute Between-Group Differences in the 4-Year Estimated Event Rate in the Stenting and Endarterectomy Trials, According to Risk-Factor Subgroups.

Tipping Point Analysis

CAS Trial

Events required to lose significance (P > 0.05):

Remove events from Medical Arm	**≥ 4 Events**
Add events to Stenting Arm	**≥ 3 Events**

Interpretation: Fragility index of ≈ 3 events, minor real-world increase in procedural risk would likely nullify observed benefit.

CEA Trial

Events required to gain significance (P < 0.05):

Add events to Medical Arm	**≥ 6 Events**
Remove events from CEA Arm	**≥ 5 Events**

Interpretation: Likely underpowered for small effect size, 5-6 event change required to reverse conclusion.

Conclusions

Temporal Trends

Reduction in revascularization benefit
Natural history → lower event rates → modest CAS benefit

Parallel trends
CAS risks ↓ & improved natural history of asymptomatic high-grade carotid stenosis

Medical treatment could have been better
Potentially eliminating benefit of CAS

Stroke severity
Disabling strokes uncommon in CREST-2

Implications

Risk balance
Does long-term benefit > periprocedural risk?

The operator factor
Outcomes dependent on operator volume & complication rates

Intensive medical management

> *We can conclude that there is no longer a role for routine carotid endarterectomy in persons with asymptomatic stenosis.*
>
> — BROWN & BONATTI, NEJM EDITORIAL

Limitations

- Open-label
- Medical tx
  - PCSK9i
  - GLP-1RA, SGLT2i
  - BP
- Limited generalizability to low-volume centers
  - real-world complication rates ↑
- Longer-term Δ in events, subclinical injury, cognition, & stent complications
- TCAR
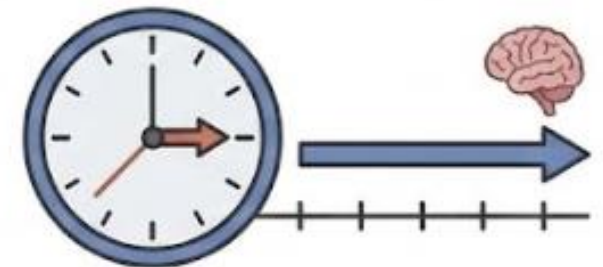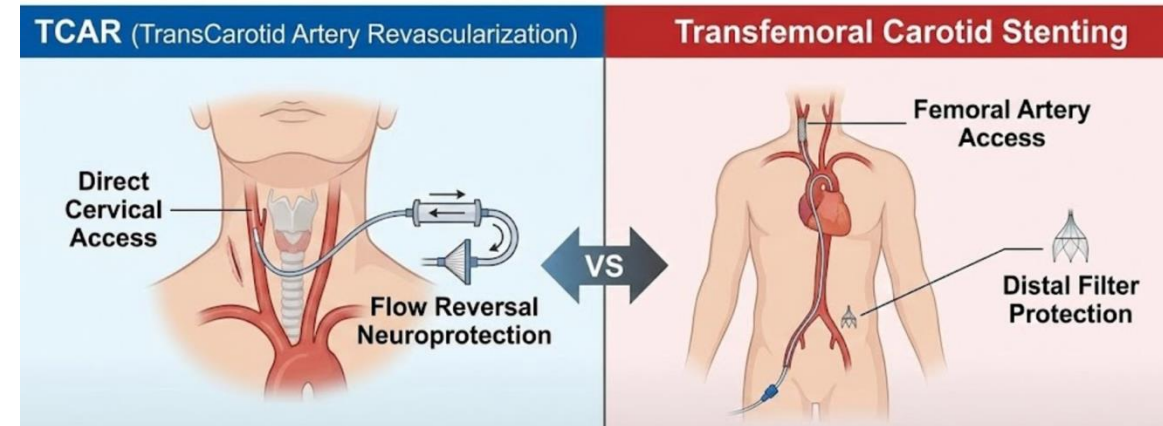
Implementation

- Shared-decision making
  - 1.3% immediate risk to prevent ~1 stroke per 31 patients over 4 years
- High-risk plaque imaging features, progression of stenosis despite medical tx
- Skilled operator w/ <3% complication rate
- Medical mgmt., follow-up, serial CUS/imaging

Figure 2. Risk of Ipsilateral Ischemic Cerebrovascular Events in Patients With Asymptomatic Carotid Stenosis With High-risk Features.

Study by specific feature	Sample	HR event+	HR event−	LR event+	LR event−	Odds ratio (95% CI)	Weight, %
Lipid-rich necrotic core							
Takaya et al,[36] 2006	154	11	100	3	40	1.5 (0.4-5.5)	5.26
Echolucency							
Polak et al,[37] 1998	4886	30	826	73	3957	2.0 (1.3-3.0)	13.39
Mathiesen et al,[38] 2001	223	18	112	4	89	3.6 (1.2-10.9)	6.56
Nicolaides et al,[43] 2005	1092	61	348	55	628	2.0 (1.4-2.9)	13.88
Huibers et al,[47] 2016	814	27	376	19	392	1.5 (0.8-2.7)	11.40
Ulceration							
Madani et al,[41] 2011	253	4	113	2	134	2.4 (0.4-13.2)	3.62
Impaired CVR							
Gur et al,[46] 1996	44	7	14	0	23	24.3 (1.3-458.3)	1.45
Silvestrini et al,[51] 2000	94	11	29	5	49	3.7 (1.2-11.8)	6.32
King et al,[48] 2011	106	1	31	1	73	2.4 (0.1-38.9)	1.57
Liu et al,[49] 2017	45	7	6	6	26	5.1 (1.2-20.6)	4.86
Microembolic signals							
Siebler et al,[50] 1995	64	3	5	2	54	16.2 (2.2-120.9)	2.81
Molloy and Markus,[42] 1999	42	2	10	0	30	14.5 (0.6-327.7)	1.30
Abbott et al,[39] 2005	202	6	54	12	130	1.2 (0.4-3.4)	7.21
Zhang et al,[45] 2009	62	3	7	1	51	21.9 (2.0-240.2)	2.08
Markus et al,[35] 2010	467	10	67	22	368	2.5 (1.1-5.5)	9.36
Spence et al,[44] 2010	468	8	29	10	421	11.6 (4.3-31.7)	7.43
AHA type 4, 5, or 6							
Esposito-Bauer et al,[40] 2013	77	9	27	0	41	28.7 (1.6-513.0)	1.49
Overall: $P = .01$; $I^2 = 48.8\%$						3.0 (2.1-4.3)	100.0

Favors lower risk of events — Favors higher risk of events

0.2 — 1 — 5
Odds ratio (95% CI)