



**Medical Therapy and
Revascularization for
Asymptomatic Carotid Artery
Disease: New Lessons from
the CREST-2 Trial**

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Yale SCHOOL OF MEDICINE

Disclosures

- **Christopher Regan, MD** - no relevant financial disclosures.

Learning Objectives

1. Review the pathophysiology, risk factors, and clinical presentation of carotid artery disease.
2. Compare contemporary management strategies for carotid artery stenosis, including optimal medical therapy, carotid endarterectomy, and carotid artery stenting
3. Evaluate the outcomes and clinical implications of the CREST-2 trial and apply its findings to evidence-based decision-making for patients with carotid artery disease

Practice Gap/ Educational Need

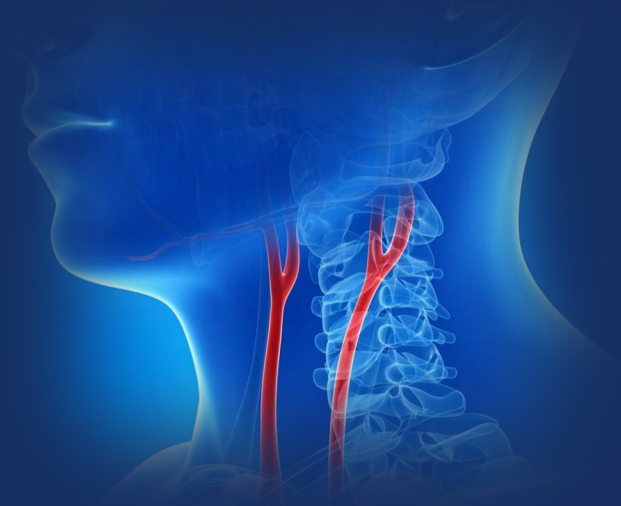
- Management of carotid artery stenosis, particularly asymptomatic disease, remains an area of clinical uncertainty.
- Clinician require updated education on the management of carotid artery disease, including the interpretation of the recent CREST-2 trial

Outcome

- The outcome of this presentation is to bring awareness of the CREST-2 trial and optimal patient outcomes for carotid artery disease

Overview

- 1 Review the background and historical context of **carotid artery stenosis (CAS)**.
- 2 Explore a **case-based discussion** highlighting contemporary management.
- 3 Summarize **the current state of the literature** and evolving guideline landscape.
- 4 Discuss **CREST-2 trial** results and implications for clinical practice.



Case Presentation

60-year-old man presenting for carotid artery evaluation

Past Medical History

- Hypertension
- Hyperlipidemia
- Diabetes
- Chronic Kidney Disease
- Prior neck radiation (Hodgkin's lymphoma)
- Coronary artery disease (+ PCI to LAD 2019)

Medications: Aspirin 81 mg, rosuvastatin 20mg, lisinopril 10 mg, carvedilol 25mg BID, dapagliflozin 25mg

- Underwent thyroid ultrasound as part of malignancy work up --> showed **carotid calcifications**
- Carotid ultrasound --> referred to peripheral vascular

History continued

Vitals/Labs

Blood pressure 120/68 mmHg

HR 70 bpm

Creatinine 1.5

LDL 26

HbA1c 7.6

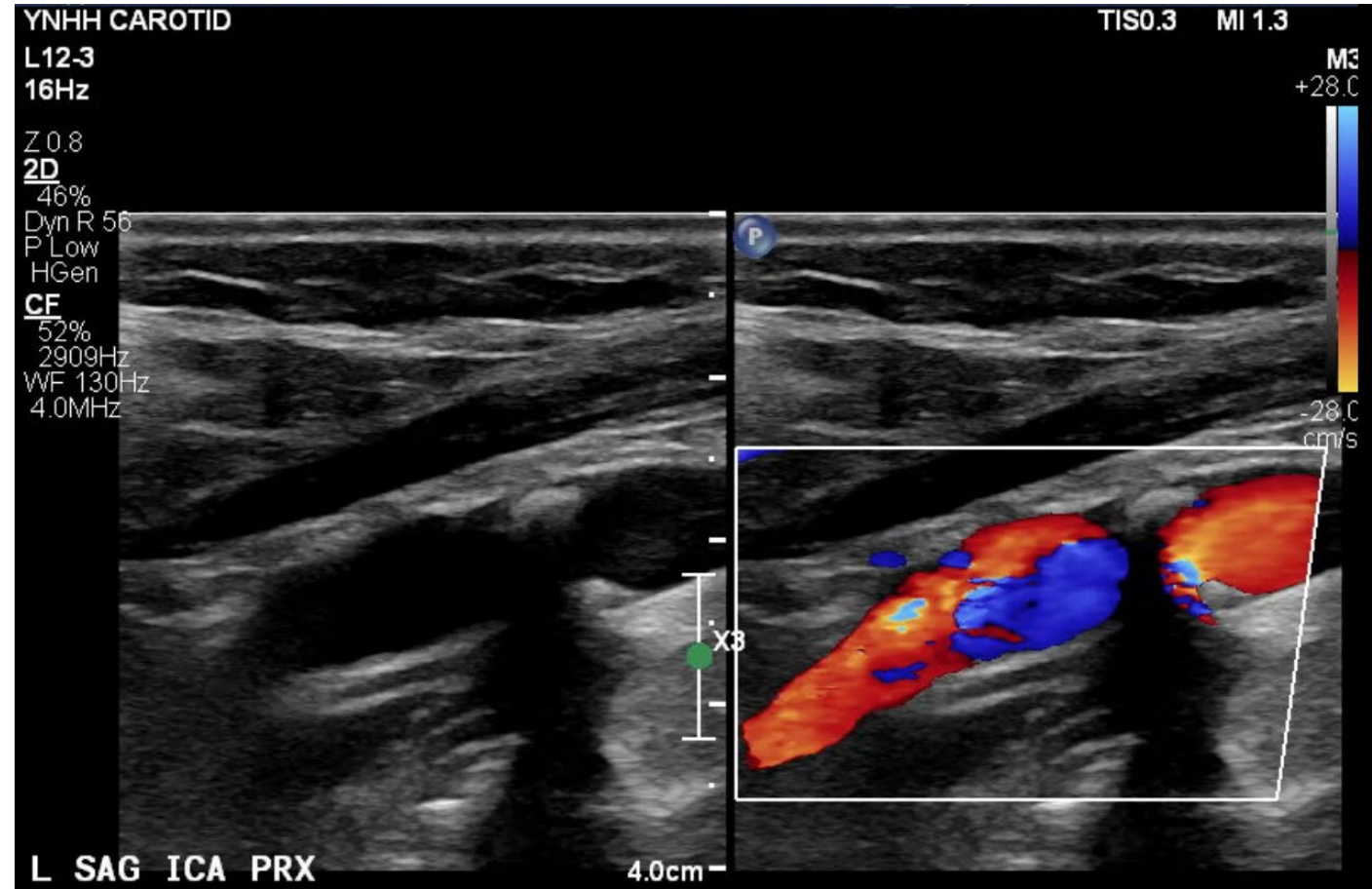
Exam/Additional History

- No significant bruits
- Non-focal neuro exam
- NIH SS 0, MRS 0

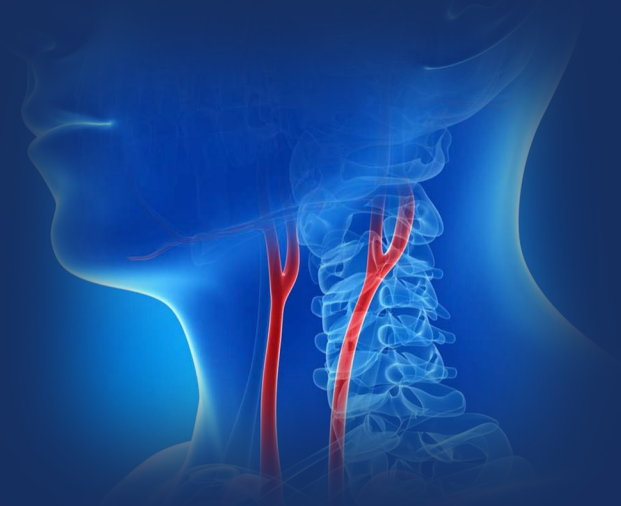
- **No prior stroke/TIA**
- No neurological symptoms
- Otherwise asymptomatic

Carotid Ultrasound

- Right: < 50% stenosis (PSV 87 cm/s)
- **Left: $\geq 70\%$ stenosis**
 - ICA PSV = 246 cm/s
 - EDV = 50 cm/s
 - ICA/CCA ratio = 3.28
- PSV increased from prior ultrasound



What is the optimal management for this patient?



Overview of Carotid Artery Stenosis

Carotid Artery Stenosis

Pathophysiology

- Atherosclerotic plaque development

Stroke Risk

- Cause of **10-20% of all ischemic strokes** from thromboembolism and hemodynamic compromise

Risk factors

- Age, hypertension, smoking, dyslipidemia, diabetes, prior radiation, male sex (2:1 predominance, narrows with age)

Prevalence

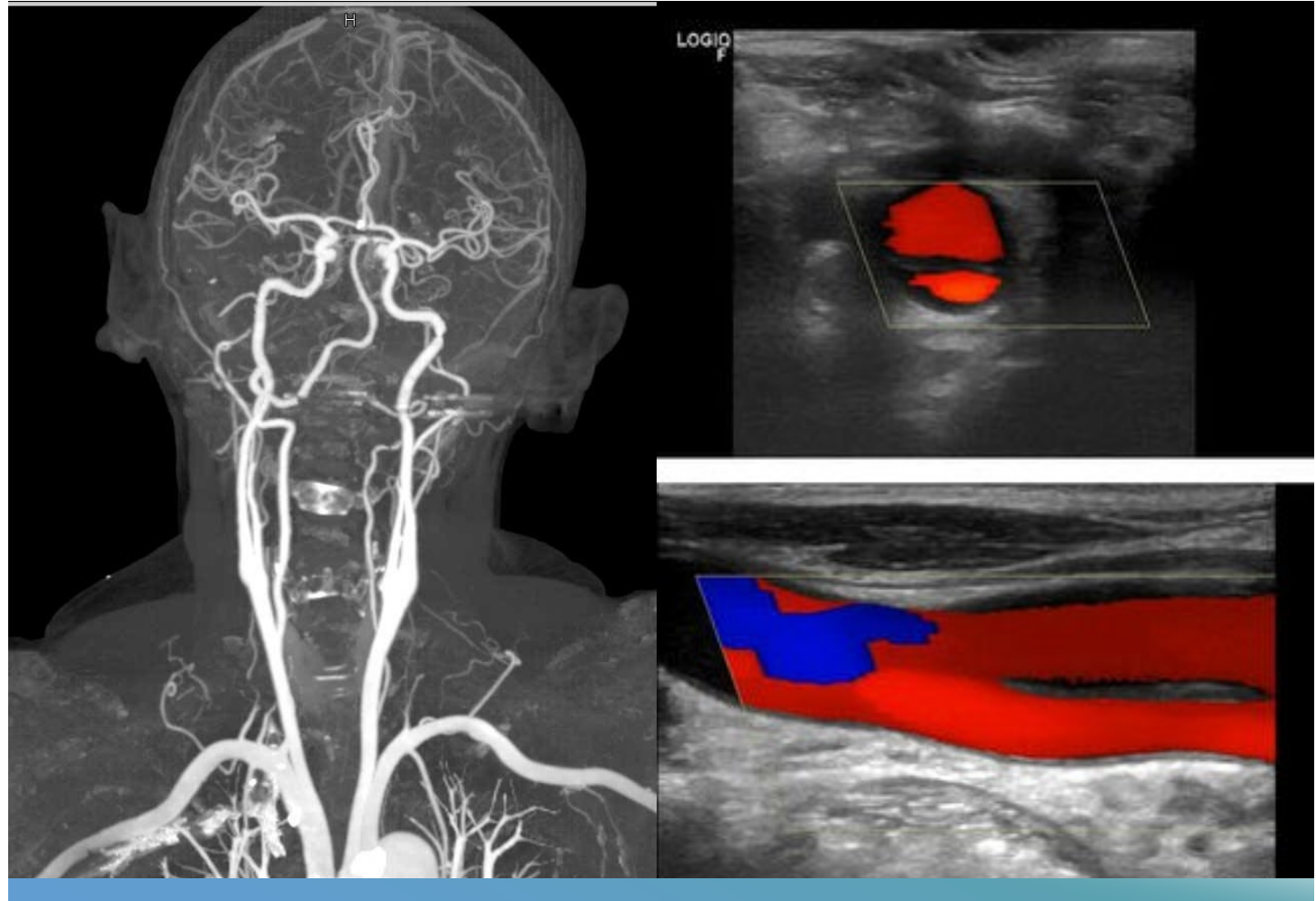
- ~1% of adults > age 65 years have $\geq 70\%$ stenosis

Outcomes

- Unknown the role plays in cognitive function, but may impair

Diagnosis of Carotid Artery Stenosis

- Carotid ultrasound or carotid CTA/MRA
- North American Symptomatic Carotid Endarterectomy Trial (**NASCET**) Criteria
 - Elevated peak systolic velocities/ratios
 - Plaque/narrowed lumen



Symptomatic (vs Asymptomatic) Carotid Artery Stenosis

- 1 Focal neurological deficit**
 - *Can be ipsilateral ischemic stroke, TIA, or retinal ischemia
 - ****Non-qualifying symptoms*** – *dizziness, syncope, headaches, mental status changes, cognitive decline, vertigo*
- 2 Attributable to the territory** supplied by the affected carotid artery
- 3 Occuring in the past 6 months**

Treatment Options



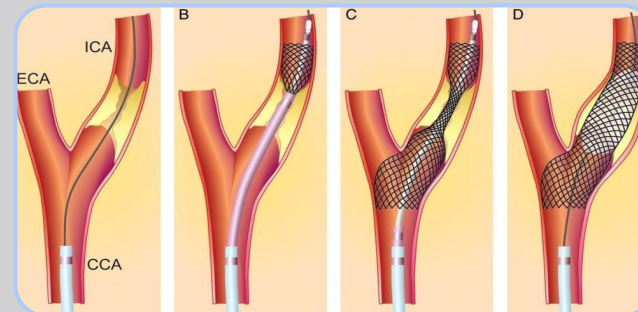
Optimal Medical Therapy

- Statin
- Antiplatelet
- Control of BP and DM
- Smoking cessation



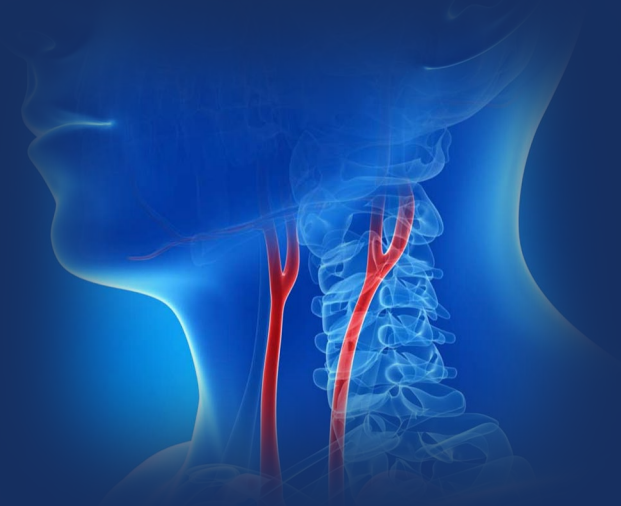
Carotid Endarterectomy

- Surgical approach



Carotid Stent

- Endovascular or surgical
- TCAR vs transfemoral/radial



Carotid Artery Stenosis - *State of the Literature*

Historical Treatment of Carotid Artery Stenosis

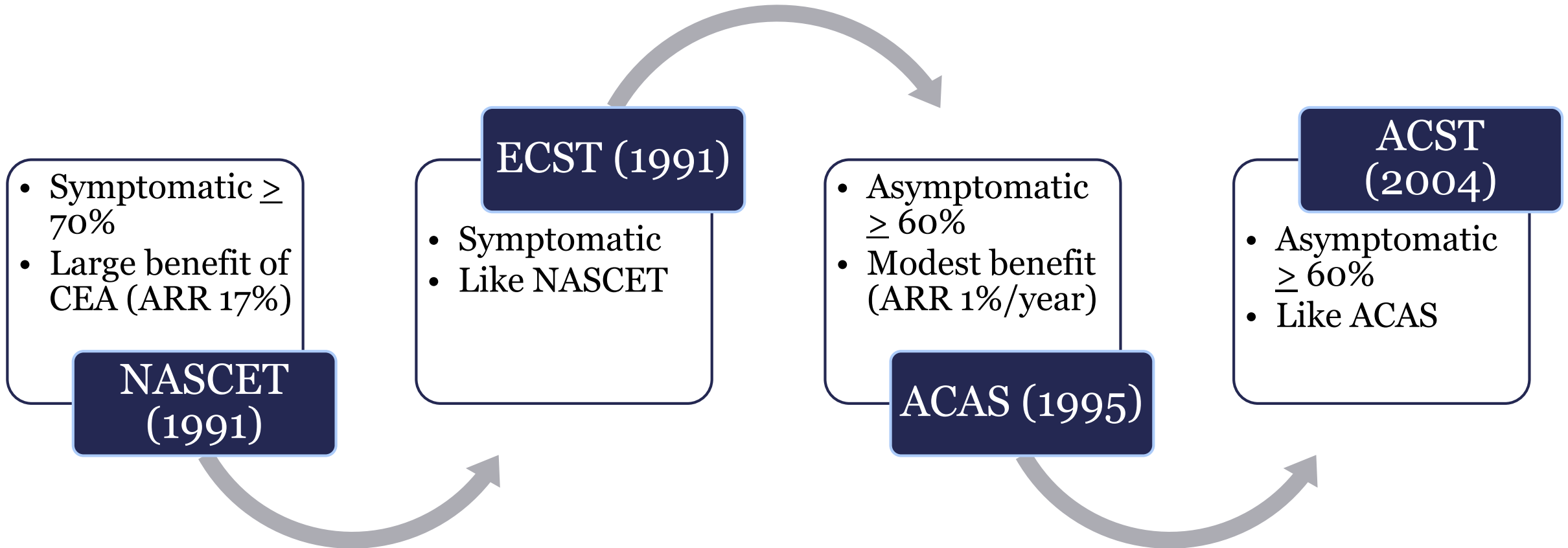
1950s – DeBakey & Eastcott pioneer carotid endarterectomy (CEA)

2000s – Advent of carotid artery stenting (CAS); clinical equipoise over equivalence

1990s – Early trials (NASCET etc.) establish CEA benefit in symptomatic and select asymptomatic patients

Now – Evolving paradigm from surgery/stent to optimal medical therapy + intervention

Early Trials – CEA vs Medical Therapy



North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med.* 1991;325:445–453.

European Carotid Surgery Trialists' Collaborative Group. *Lancet.* 1991;337:1235–1243.

Asymptomatic Carotid Atherosclerosis Study Group. *JAMA.* 1995;273:1421–1428.

Halliday A et al. *Lancet.* 2004;363:1491–1502.

Early Trials – CEA vs "Medical Therapy"

- Established CEA as **standard of care** for symptomatic $\geq 70\%$ stenosis and modest improvement for asymptomatic $> 60\%$ stenosis
- High stroke risk population \approx **5-6% per year**
- **Modern medical therapy was not yet at the forefront**



Aspirin only
(No DAPT/AC)



Limited Statin Use
(LDL $> 130-150$)

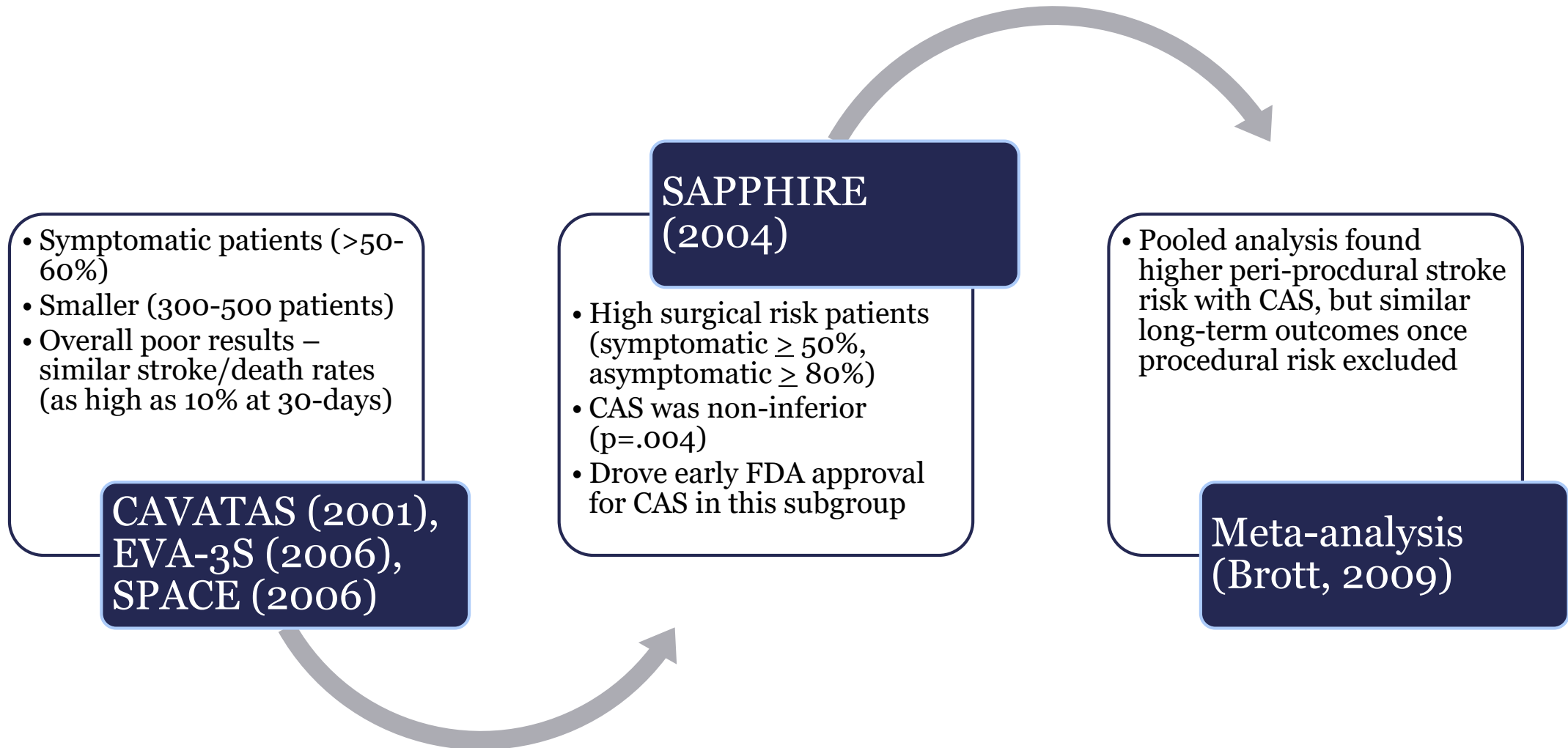


No BP Targets
(Mean 140-160 mmHg)



No Lifestyle Counseling
(Tobacco use common)

Early Trials - CAS vs CEA



CAVATAS Investigators. *Lancet*. 2001;357:1729–1737.

Yadav JS et al. *N Engl J Med*. 2004;351:1493–1501.

Mas JL et al. *N Engl J Med*. 2006;355:1660–1671.

SPACE Collaborative Group. *Lancet*. 2006;368:1239–1247.

Early Trials - **CEA vs CAS** in the **CREST-1 Trial** (NEJM 2010)

Population:

- 2,500 patients from 132 centers in USA and Canada
- **Symptomatic (> 50%) or asymptomatic ($\geq 60\%$) carotid stenosis**

Intervention:

- Randomized 1:1 CAS with embolic protection vs conventional CEA
- All patients received optimal medical therapy

Outcomes:

- Primary- Composite stroke, MI, or death within 30 days + ipsilateral stroke up to 4 years

CREST-1 Results

Outcome	CEA	CAS	p-value
Primary composite endpoint	6.8 %	7.2 %	NS
Periprocedural stroke or death	2.3 %	4.4 %	0.005
Periprocedural MI	2.3 %	1.1 %	0.03
Long-term ipsilateral stroke (to 4 yrs)	2.4 %	2.0 %	NS
Age interaction	—	CAS favored <70 yrs; CEA favored ≥70 yrs	Significant

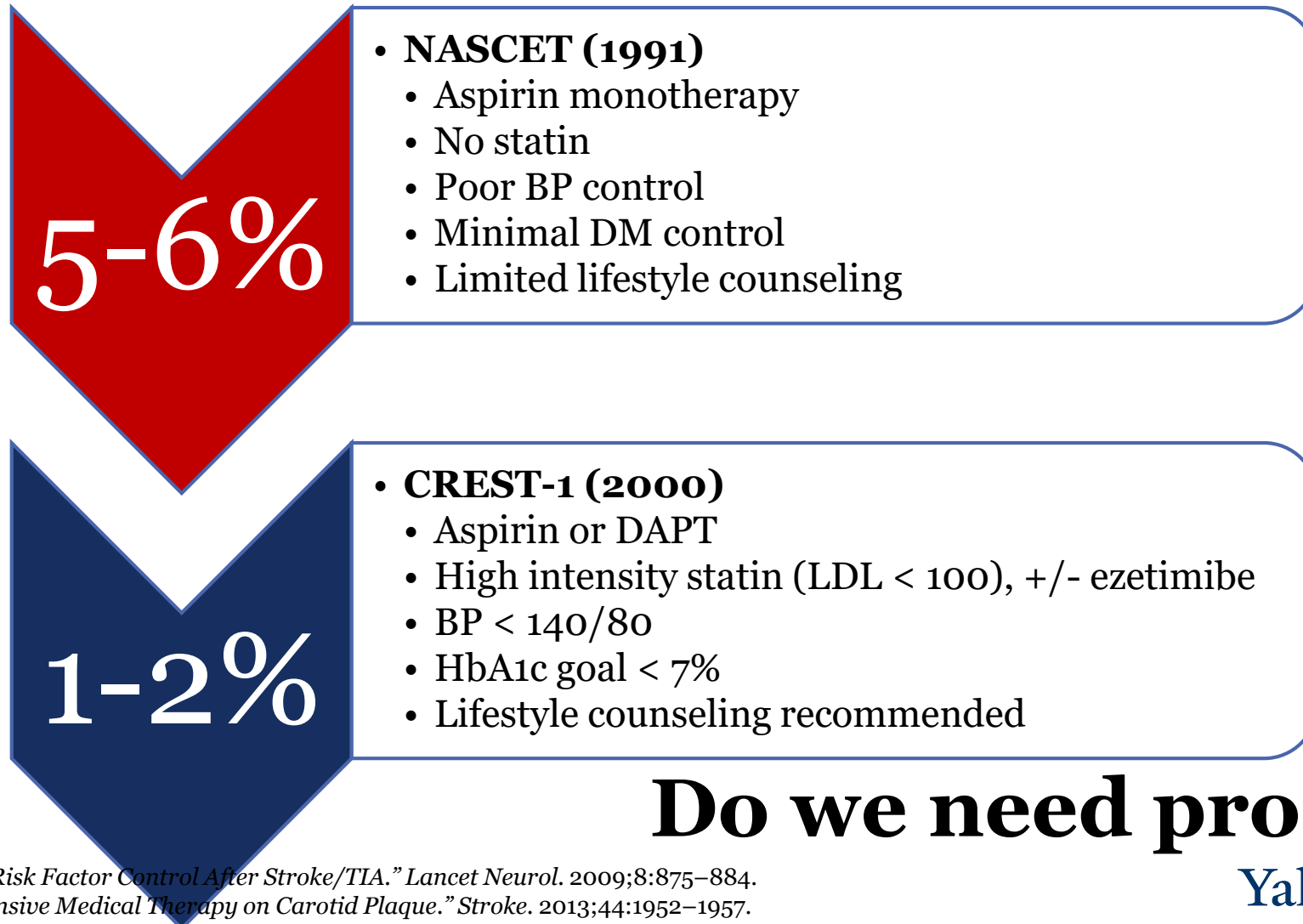
Operator experience: Surgeons - 12 CEA per year, Interventionalists – 30 CAS or training

Periprocedural mortality: 0.7 % in CAS and 0.3 in CEA.

QOL: CAS patients recovered faster at 2 weeks; equalized by 6 months.

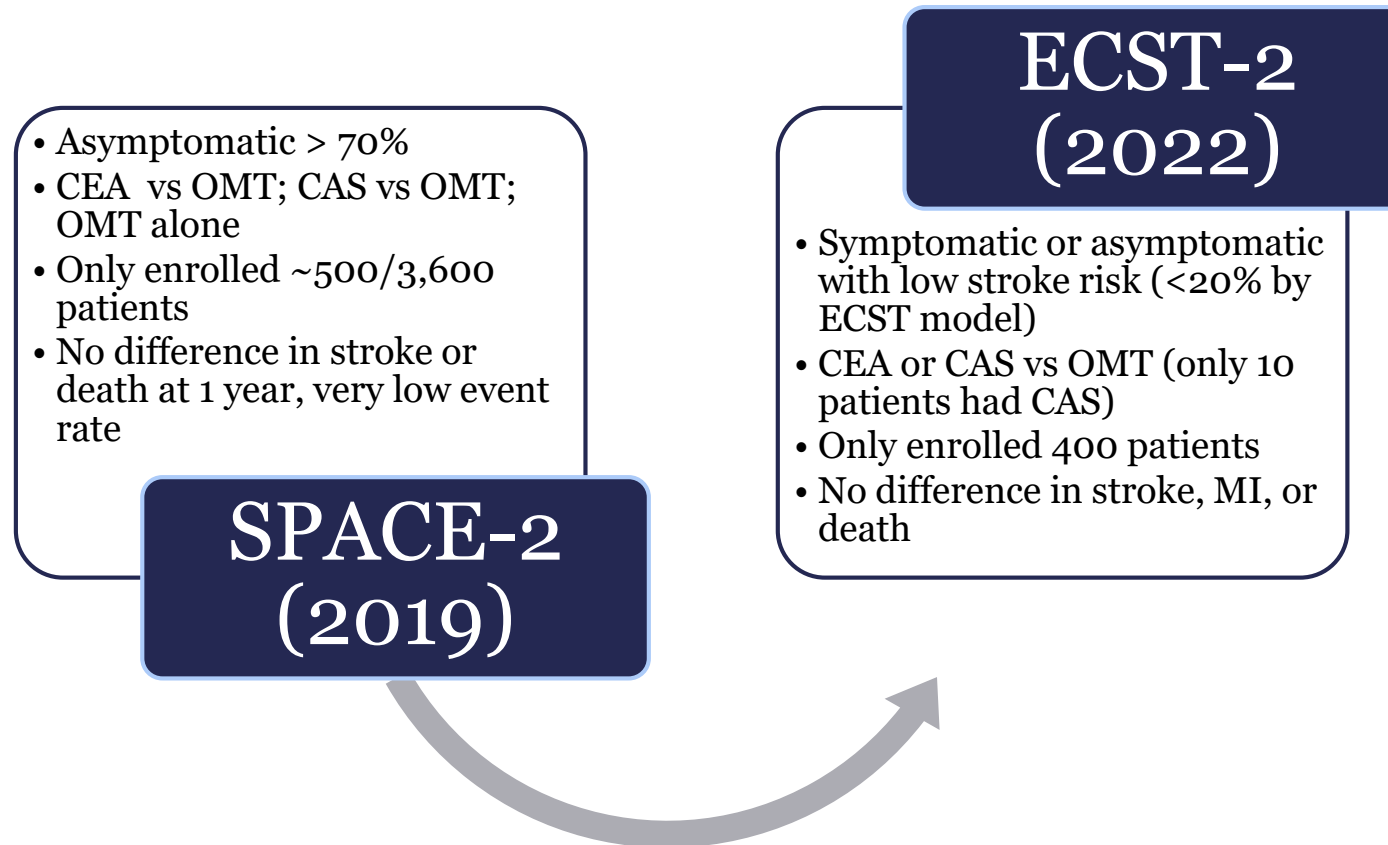
The Impact of Medical Therapy

Annual Stroke Risk



Do we need procedures?

Recent Trials – Intervention (CEA or CAS) vs Medical Therapy



2021 AHA/ACC Guidelines for the Prevention of Stroke after Stroke/TIA

COR	RECOMMENDATIONS
1	1. In patients with a TIA or nondisabling ischemic stroke within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis, carotid endarterectomy (CEA) is recommended to reduce the risk of future stroke, provided that perioperative morbidity and mortality risk is estimated to be <6%.
1	2. In patients with ischemic stroke or TIA and symptomatic extracranial carotid stenosis who are scheduled for carotid artery stenting (CAS) or CEA, procedures should be performed by operators with established periprocedural stroke and mortality rates of <6% to reduce the risk of surgical adverse events.
1	3. In patients with carotid artery stenosis and a TIA or stroke, intensive medical therapy, with antiplatelet therapy, lipid-lowering therapy, and treatment of hypertension, is recommended to reduce stroke risk.
1	4. In patients with recent TIA or ischemic stroke and ipsilateral moderate (50%–69%) carotid stenosis as documented by catheter-based imaging or noninvasive imaging, CEA is recommended to reduce the risk of future stroke, depending on patient-specific factors such as age, sex, and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6%.
2a	5. In patients ≥70 years of age with stroke or TIA in whom carotid revascularization is being considered, it is reasonable to select CEA over CAS to reduce the periprocedural stroke rate.
2a	6. In patients in whom revascularization is planned within 1 week of the index stroke, it is reasonable to choose CEA over CAS to reduce the periprocedural stroke rate.

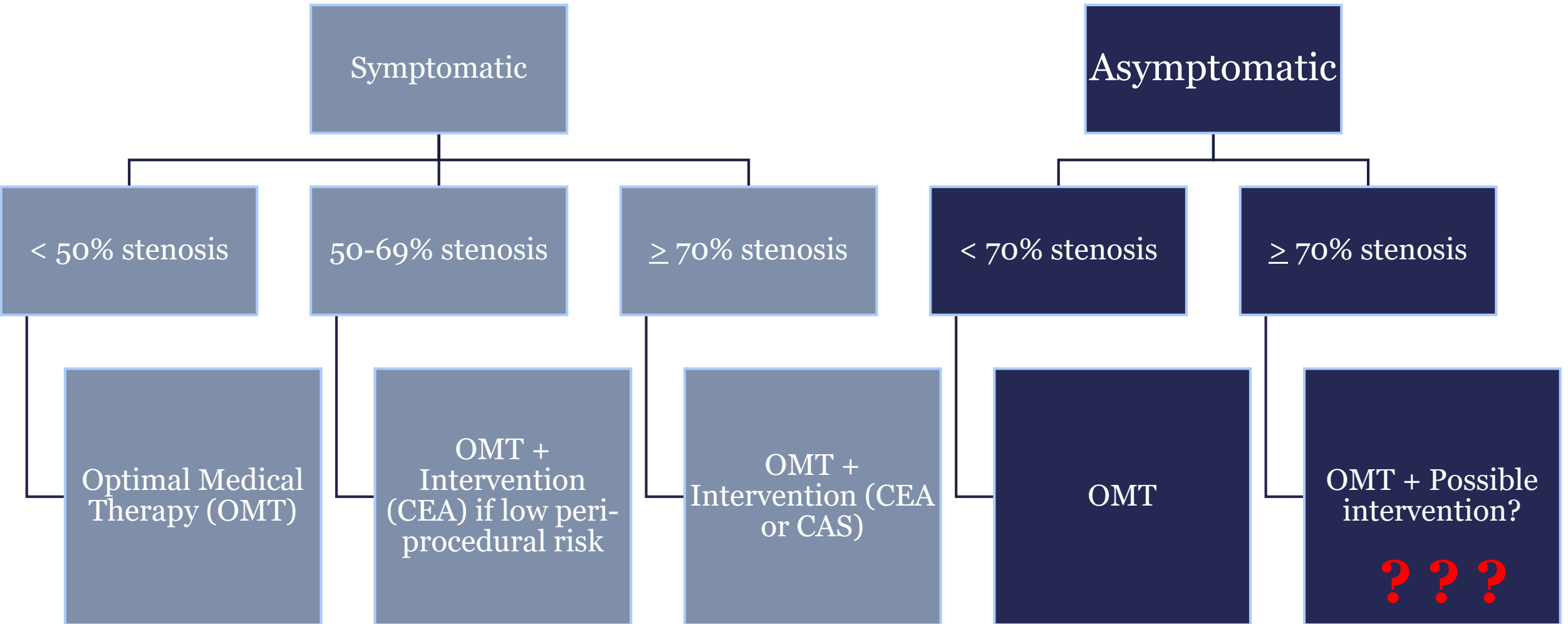
2021 AHA/ACC Guidelines for the Prevention of Stroke after Stroke/TIA

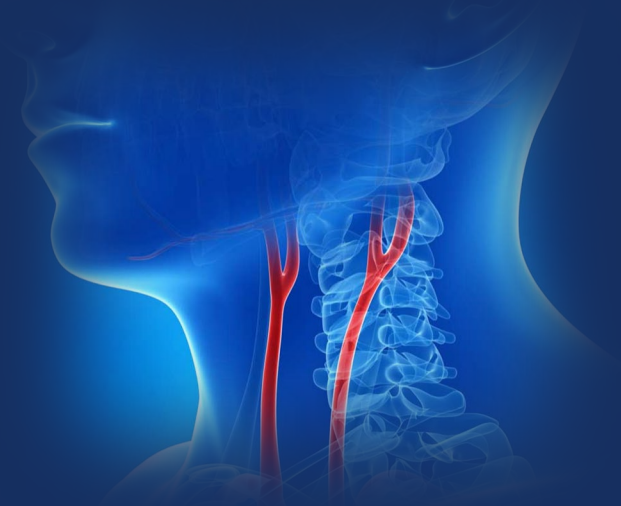
COR	RECOMMENDATIONS
2a	7. In patients with TIA or nondisabling stroke, when revascularization is indicated, it is reasonable to perform the procedure within 2 weeks of the index event rather than delay surgery to increase the likelihood of stroke free outcome.
2a	8. In patients with symptomatic severe stenosis ($\geq 70\%$) in whom anatomic or medical conditions are present that increase the risk for surgery (such as radiation-induced stenosis or restenosis after CEA) it is reasonable to choose CAS to reduce the periprocedural complication rate.
2b	9. In symptomatic patients at average or low risk of complications associated with endovascular intervention, when the internal carotid artery stenosis is $\geq 70\%$ by noninvasive imaging or $>50\%$ by catheter-based imaging and the anticipated rate of periprocedural stroke or death is $>6\%$, CAS may be considered as an alternative to CEA for stroke prevention, particularly in patients with significant cardiovascular comorbidities predisposing to cardiovascular complications with endarterectomy.
2b	10. In patients with a recent stroke or TIA (past 6 months), the usefulness of transcarotid artery revascularization (TCAR) for prevention of recurrent stroke and TIA is uncertain.
3: No Benefit	11. In patients with recent TIA or ischemic stroke and when the degree of stenosis is $<50\%$, revascularization with CEA or CAS to reduce the risk of future stroke is not recommended.
3: No Benefit	12. In patients with a recent (within 120 days) TIA or ischemic stroke ipsilateral to atherosclerotic stenosis or occlusion of the middle cerebral or carotid artery, extracranial intracranial bypass surgery is not recommended.

Guideline Recommendations for Asymptomatic Disease

- **All guidelines agree:**
 - No routine **screening** for asymptomatic carotid stenosis
 - **Best medical therapy** for everyone (statins, antiplatelet, BP, DM, lifestyle)
- **SVS 2022:** CEA (or CAS/TCAR) reasonable for **asymptomatic carotid stenosis $\geq 70\%$** in low-risk, good-life-expectancy patients
- **ESVS 2023:** Revascularization may be considered for **asymptomatic $\geq 60-70\%$** stenosis only in **highly selected** high-risk patients
- **AHA/ACC 2021:** Focuses on symptomatic disease; for asymptomatic emphasizes individualized decisions and aggressive risk-factor control

Current Management Pathway





CREST-2 Trial Results

CREST-2 Trial (NEJM, 2025)

- Enrolled 1,485 patients from 155 centers across 5 countries
- **Yale was a top 10 enrolling site**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Medical Management and Revascularization for Asymptomatic Carotid Stenosis

T.G. Brott,¹ G. Howard,² B.K. Lal,³ J.H. Voeks,⁴ T.N. Turan,⁴ G.S. Roubin,⁵ R.M. Lazar,⁶ R.D. Brown, Jr.,⁷ J. Huston III,⁸ L.J. Edwards,² M. Jones,⁹ W.M. Clark,¹⁰ Á. Chamorro,¹¹ L. Llull,¹¹ C. Mena-Hurtado,¹² D. Heck,¹³ R.S. Marshall,¹⁴ V.J. Howard,¹⁵ W.S. Moore,¹⁶ K.M. Barrett,¹ B.M. Demaerschalk,¹⁷ N. Sangha,¹⁸ H. Aronow,¹⁹ M. Foster,²⁰ W.C. Sternbergh III,²¹ F. Shawl,²² G. Lanzino,²³ J. Rapp,²⁴ H.S. Tran,²⁵ R. Ecker,²⁶ A. Mackey,²⁷ V. Ali,²⁸ C. Given II,²⁹ P. Teal,³⁰ V.S. Kashyap,³¹ D. Mukherjee,³² M. Harrigan,³³ S. Silverman,³⁴ M. Koopmann,³⁵ V.G. Wadley,³⁶ Y. Zhang,² J.D. Rhodes,² S. Chaturvedi,³⁷ and J.F. Meschia,¹ for the CREST-2 Investigators*

CREST-2 Trial

- **Background**

- Systematic reviews of older studies have shown a reduction in mortality and near two-fold risk reduction in ipsilateral stroke for revascularization of asymptomatic disease
- As intensive medical therapy has evolved, recent trials, including ESCT-2 and SPACE, comparing medical therapy to revascularization have challenged this paradigm
- CREST-2 was designed to investigate best treatment option: revascularization and intensive medical therapy (IMM) or IMM alone.

CREST-2

• Methods

- Two parallel studies: CEA vs. BMT and transfemoral CAS vs. BMT
 - No direct comparison between CEA and CAS
- Multicenter, randomized, observer-blinded study

Inclusion Criteria

Age 35+

No symptoms in last 180 days (can have prior TIA for example)

>70% stenosis on ultrasound and any of the following:

- PSV > 230 cm/s
- EDV 100+ cm/s
- Internal/common carotid velocity ratio > 4 or
- CTA or MRA confirming stenosis >70%

OR

>70% stenosis by angiogram alone

Exclusion Criteria

Previous disabling stroke (mRS 2 or higher)

Unstable angina

Atrial fibrillation prompting anticoagulation

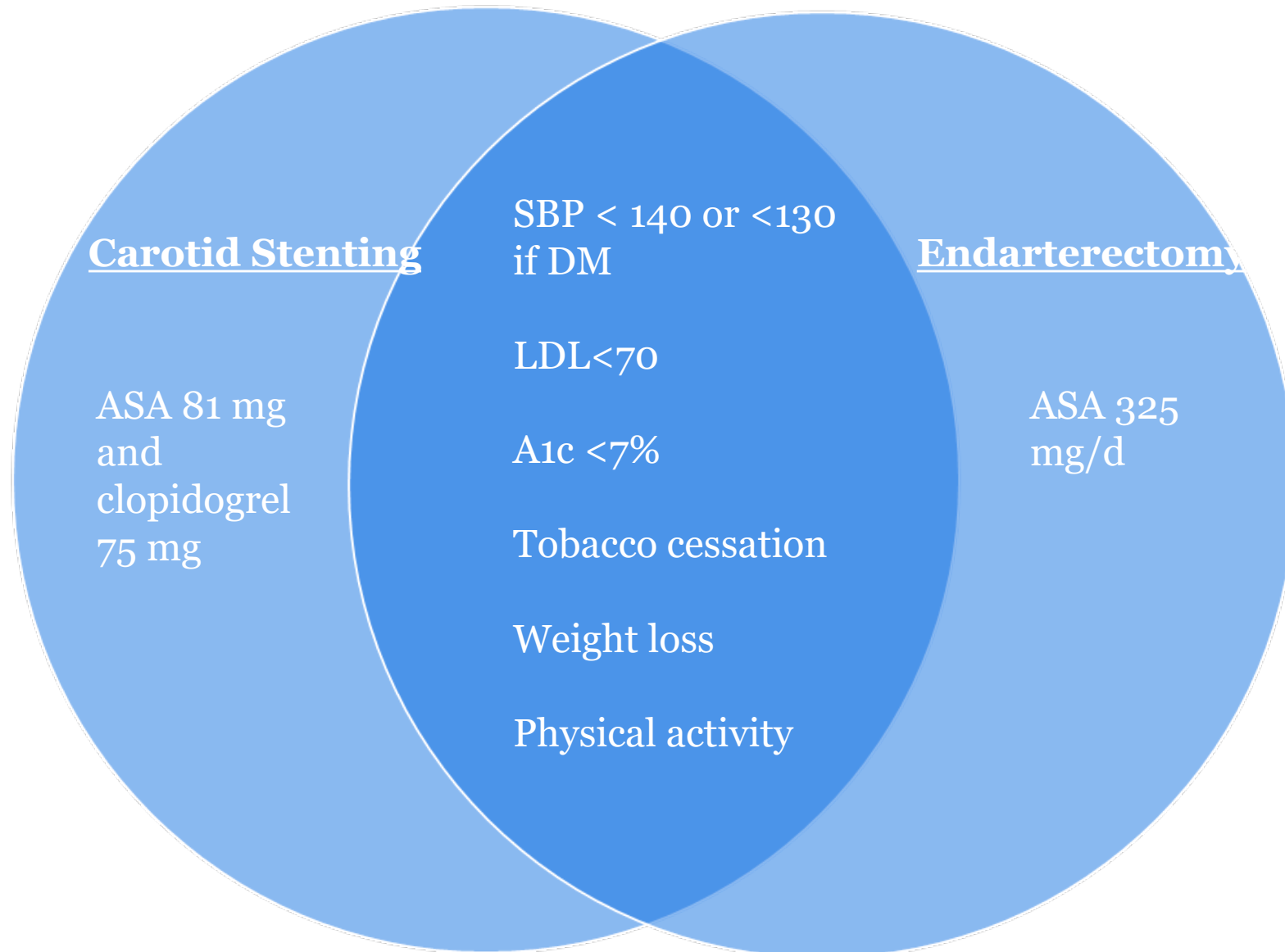
Other high-risk sources of emboli

CKD (Cr >2.5 or GFR <50)

CHF (EF 30% or less)

Contralateral common or internal carotid occlusion

CREST-2 Intensive Medical Management



CREST-2

- **Primary outcome**

- 4-year composite rate of:

- Any stroke or death from randomization to 44 days (periprocedural period)

- PLUS

- Ipsilateral ischemic stroke thereafter

- **Secondary outcomes**

- Primary composite outcome plus contralateral stroke after 44 days

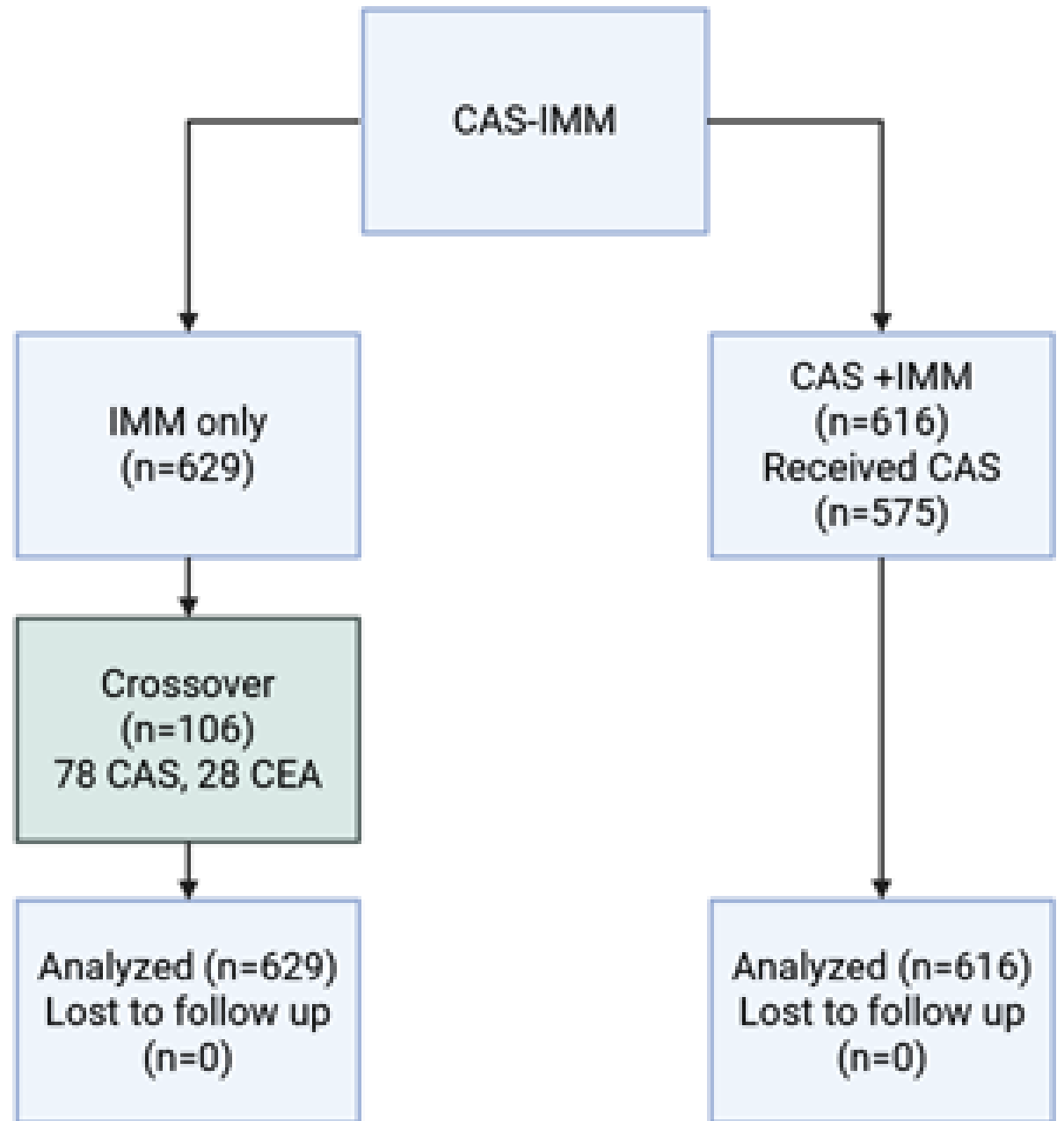
- **Statistical analysis**

- Intention-to-treat

- Kaplan-Meier to estimate event rates

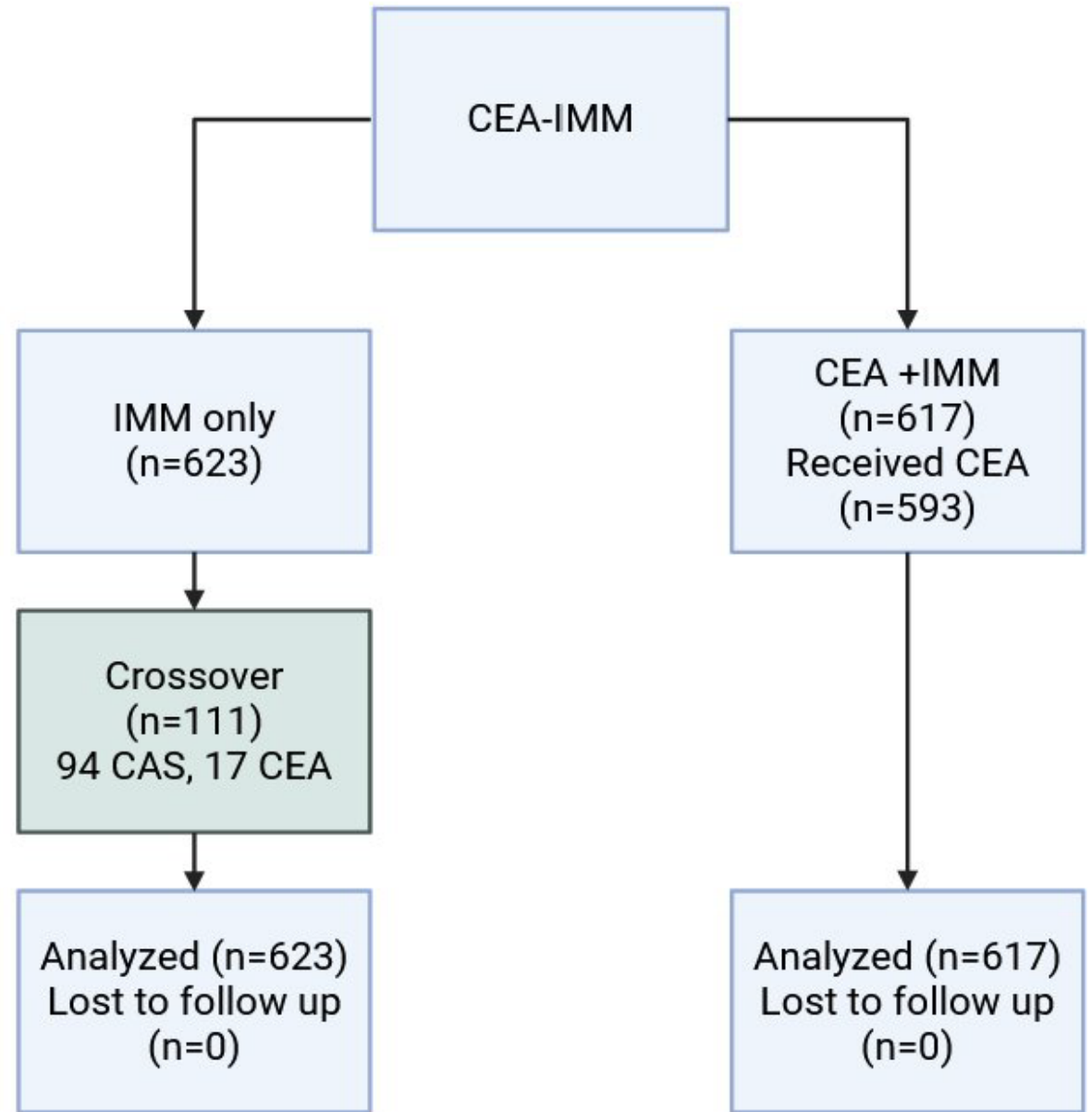
- Treatment differences were tested using a re-randomization (permutation) test with 10,000 repeats to handle low event rates.

CREST-2 Results- CAS Cohort



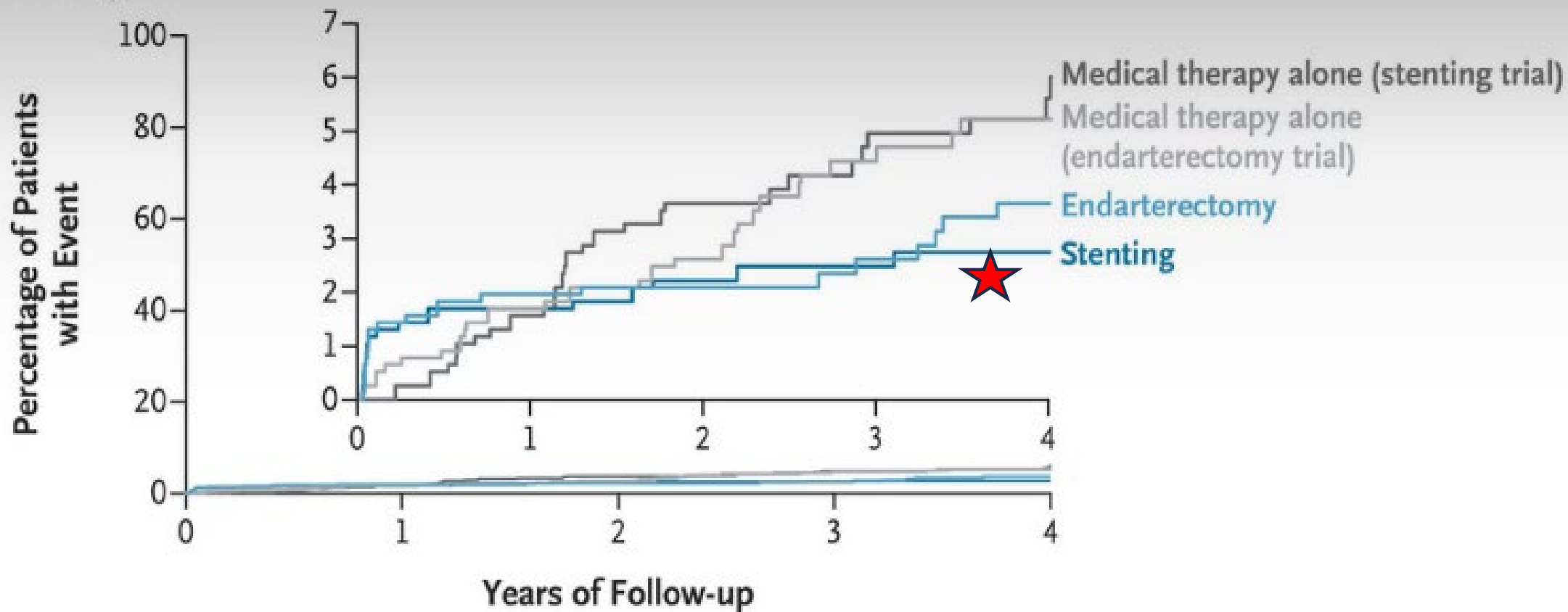
CREST-2 Results- CEA Cohort***

Switch CAS/CEA nu



	CAS-IMM Trial		CEA-IMM Trial	
Characteristic	IMM	CAS	IMM	CEA
Age- yr	69.7 ± 7.7	69.3 ± 8.1	70.4 ± 7.6	70.7 ± 7.8
Female (%)	38.2	36.9	39.0	35.3
White Race (%)	90.1	92.9	88.3	90.0
HTN (%)	87.4	88.0	84.9	85.1
DM (%)	37.8	40.7	38.0	34.4
HLD (%)	93.3	92.0	90.0	91.5
Current smoking (%)	54.5	53.7	43.3	44.3
CAD (%)	54.5	53.7	43.3	44.3
Peak systolic velocity ≥ 389 cm/s (%)	33.5	31.1	32.9	37.2
Contralateral stenosis >50% (%)	34.4	37.0	37.2	35.7

A Primary-Outcome Analysis



No. of Patients

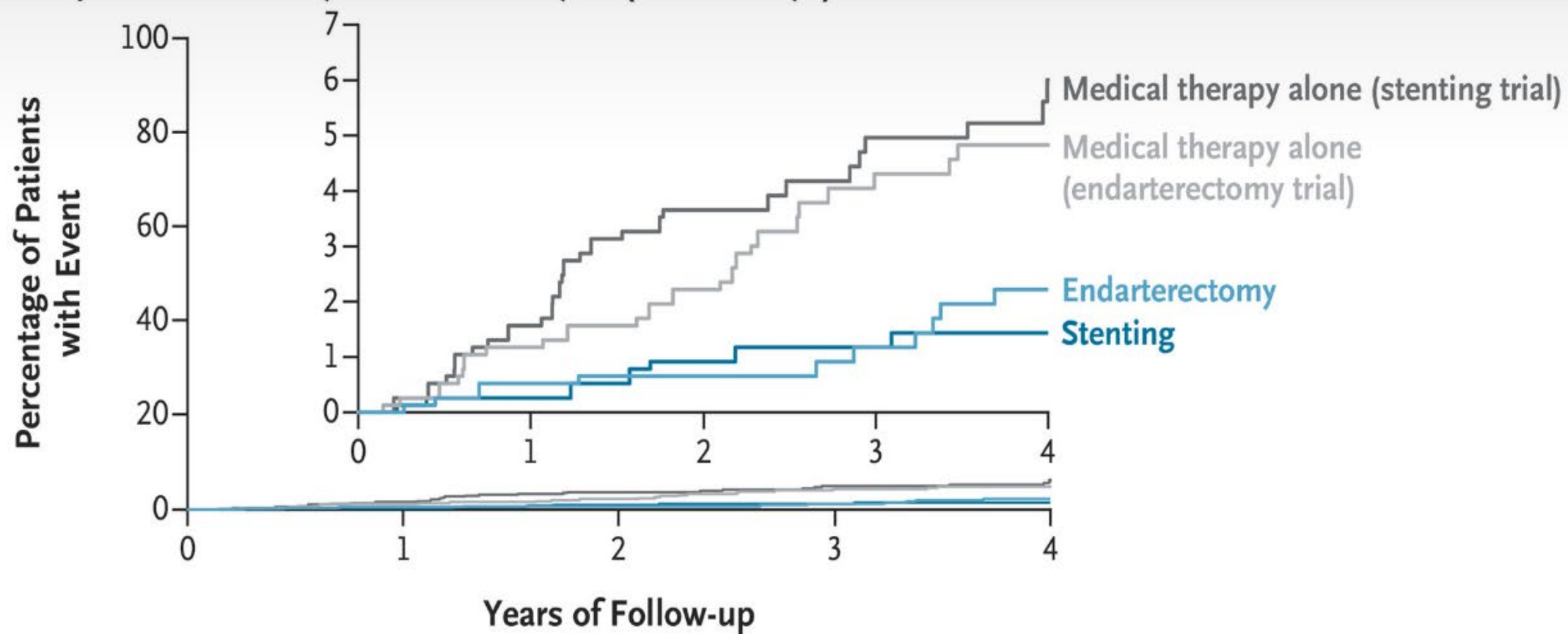
Stenting trial

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

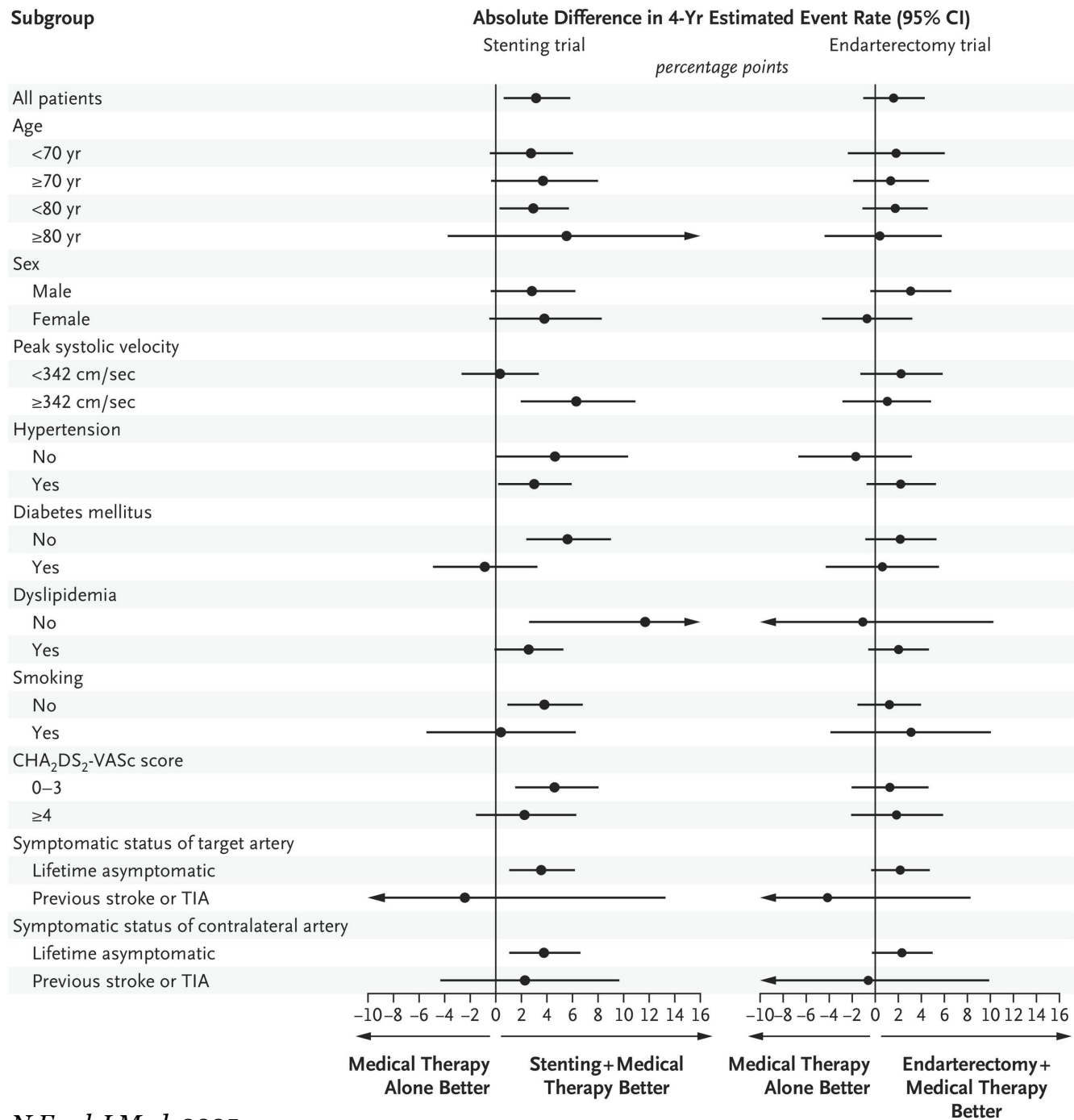
C Postprocedural Component of Primary-Outcome Analysis (after 44 days)



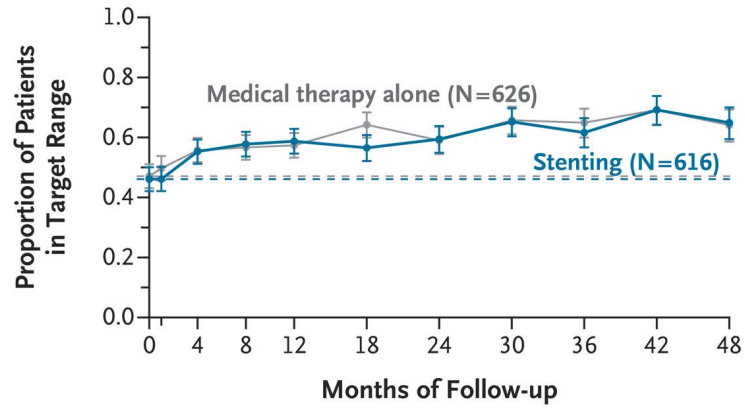
No. of Patients

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

	CAS-IMM Trial		CEA-IMM Trial	
Primary 4-Yr Outcome	IMM	CAS	IMM	CEA
Event Rate (95% CI) (%)	6.0 (3.8, 8.3)	2.8 (1.5, 4.3)	5.3 (3.3, 7.4)	3.7 (2.1, 5.5)
Absolute Risk Difference (%)	3.2 (0.6, 5.9)		1.6 (-1.1,4.3)	
P-Value	0.02		0.24	
RR (95% CI)	2.13 (1.15, 4.39)		1.43 (0.78, 2.72)	
Components of Primary Outcome				
Periprocedural stroke or death (0-44 days)	0/629	8/616	3/623	9/617
Postprocedural ipsilateral stroke (>44 days)	28/600	7/582	23/600	10/596
RR for postprocedural stroke (95% CI)	4.07 (1.78, 9.31)		2.38 (1.13,5.0)	

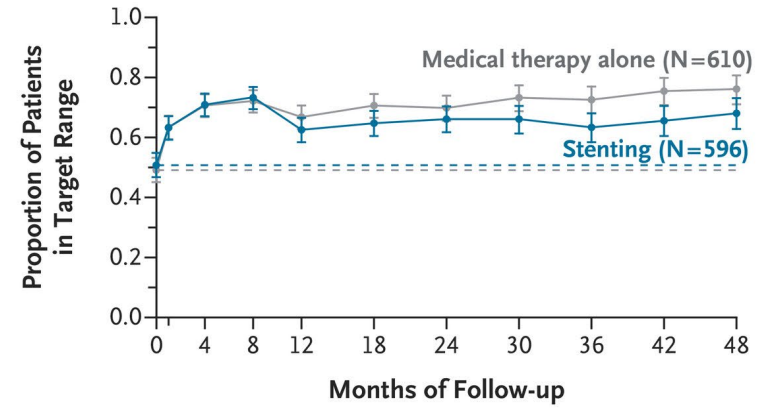


A Stenting Trial: Systolic Blood Pressure



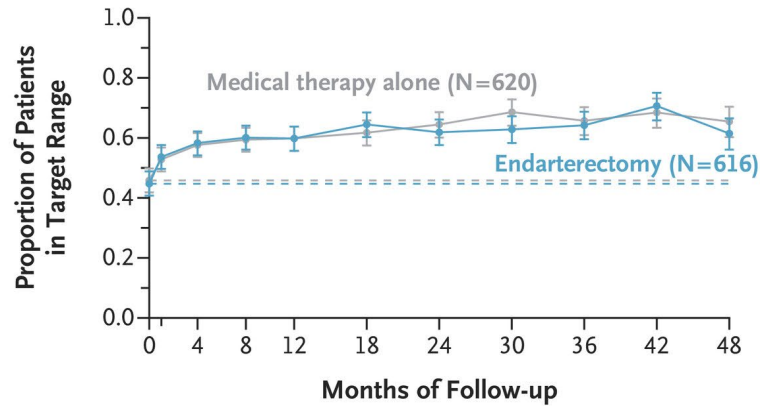
No. of Patients	0	4	8	12	18	24	30	36	42	48
Medical therapy alone	615	597	587	575	528	474	421	399	360	323
Stenting	607	595	583	570	531	478	425	396	370	336

B Stenting Trial: LDL Cholesterol



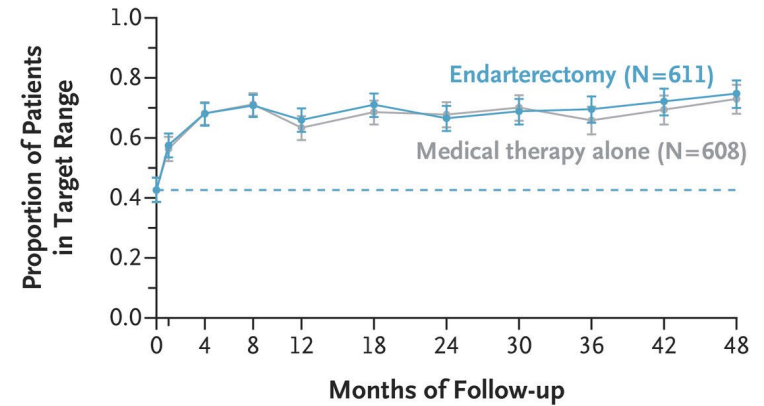
No. of Patients	0	4	8	12	18	24	30	36	42	48
Medical therapy alone	607	595	585	573	526	472	419	399	360	323
Stenting	596	586	577	567	529	476	425	396	370	336

C Endarterectomy Trial: Systolic Blood Pressure

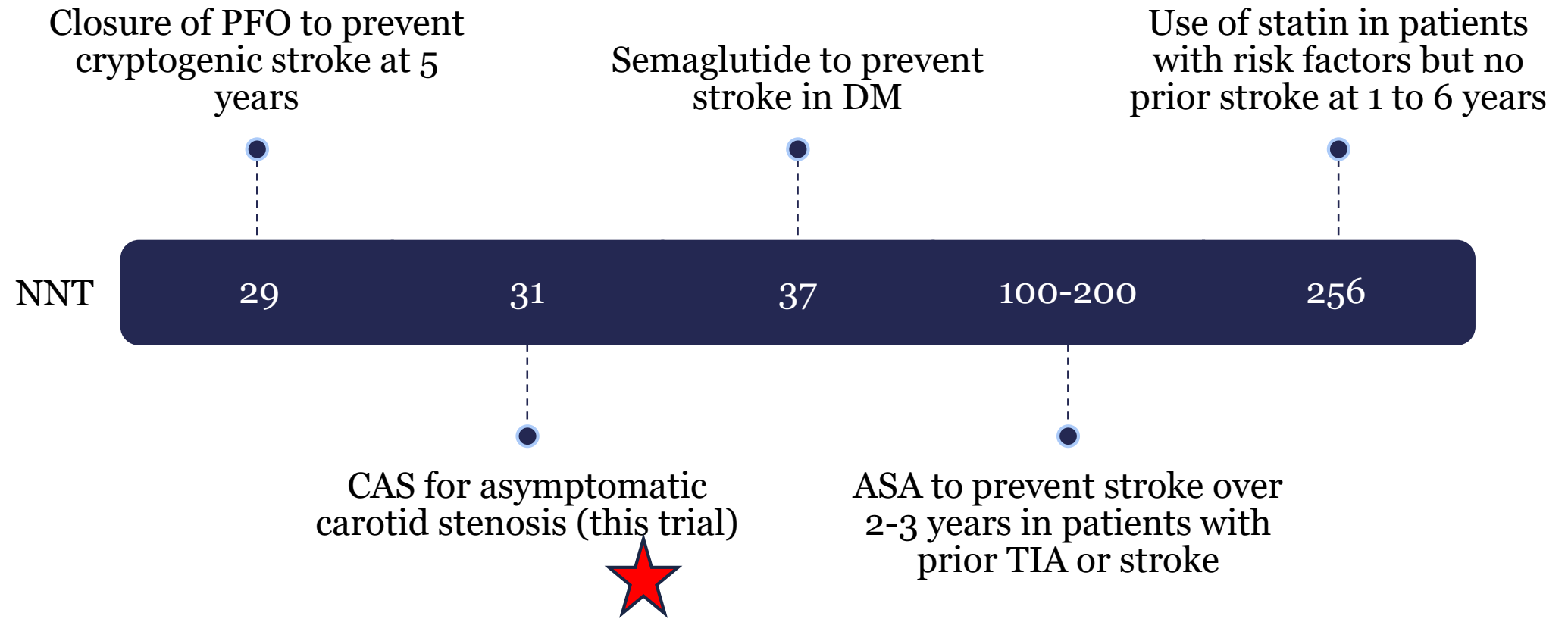


No. of Patients	0	4	8	12	18	24	30	36	42	48
Medical therapy alone	613	607	590	580	542	498	459	420	377	353
Endarterectomy	611	609	605	586	549	515	466	437	399	358

D Endarterectomy Trial: LDL Cholesterol

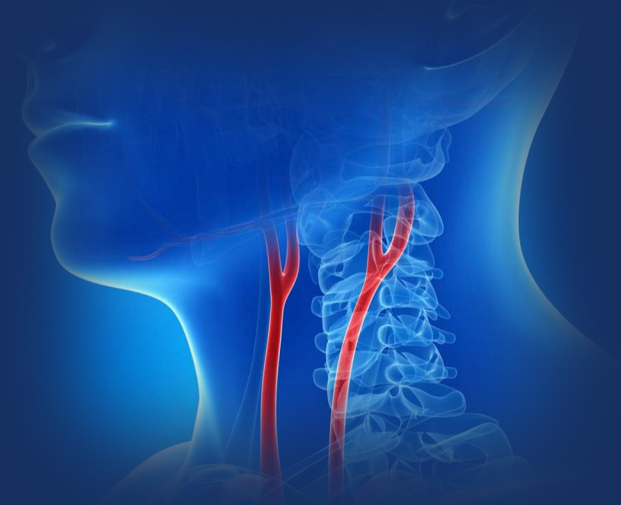


No. of Patients	0	4	8	12	18	24	30	36	42	48
Medical therapy alone	608	604	588	579	541	497	459	420	377	353
Endarterectomy	610	610	606	586	549	515	466	437	399	358



CREST-2 Summary

- In patients without recent symptoms and appropriate anatomy, the addition of **stenting to intensive medical management** led to a **lower risk of a composite of perioperative stroke or death plus ipsilateral stroke** at 4 years in patients with severe, **asymptomatic** carotid stenosis when stenting was performed by an experienced operator.
 - Similar benefits were not observed for carotid endarterectomy
- **Future Directions**
 - **CREST-H** – cognitive outcomes
 - **Imaging studies**



Case Conclusion

Back to our patient...

After a shared decision-making discussion, he was enrolled in the **CREST-2 trial (CAS-IMM)**

He was randomized to the **medical therapy (IMM)** arm

He underwent medical optimization with **blood pressure optimization** and **lifestyle counseling**

Four years later...

History of Present Illness

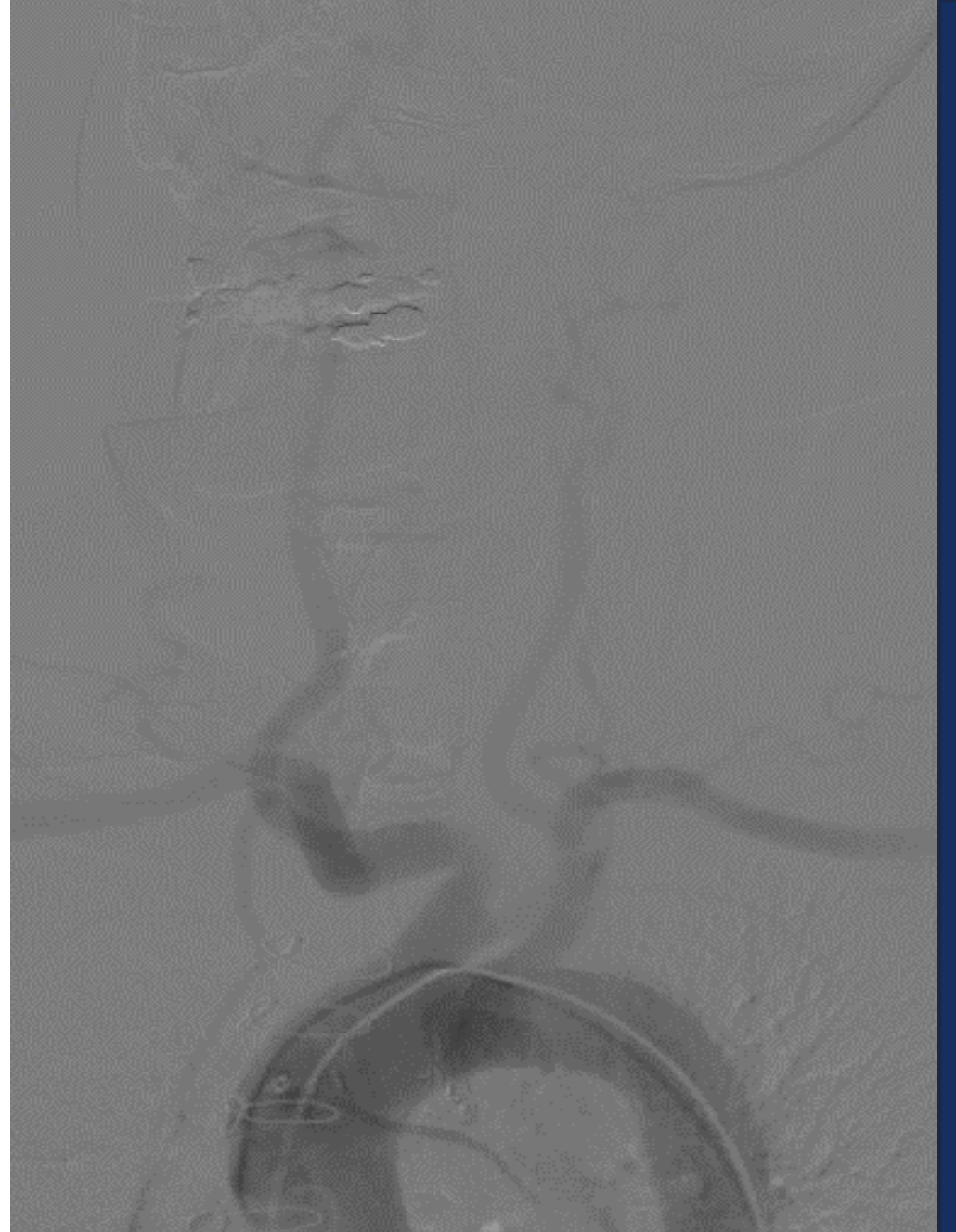
- Patient presented with 10 minutes of sudden onset slurred speech
- No weakness, facial droop, headache, or visual symptoms
- Similar episode 6 months prior

Imaging

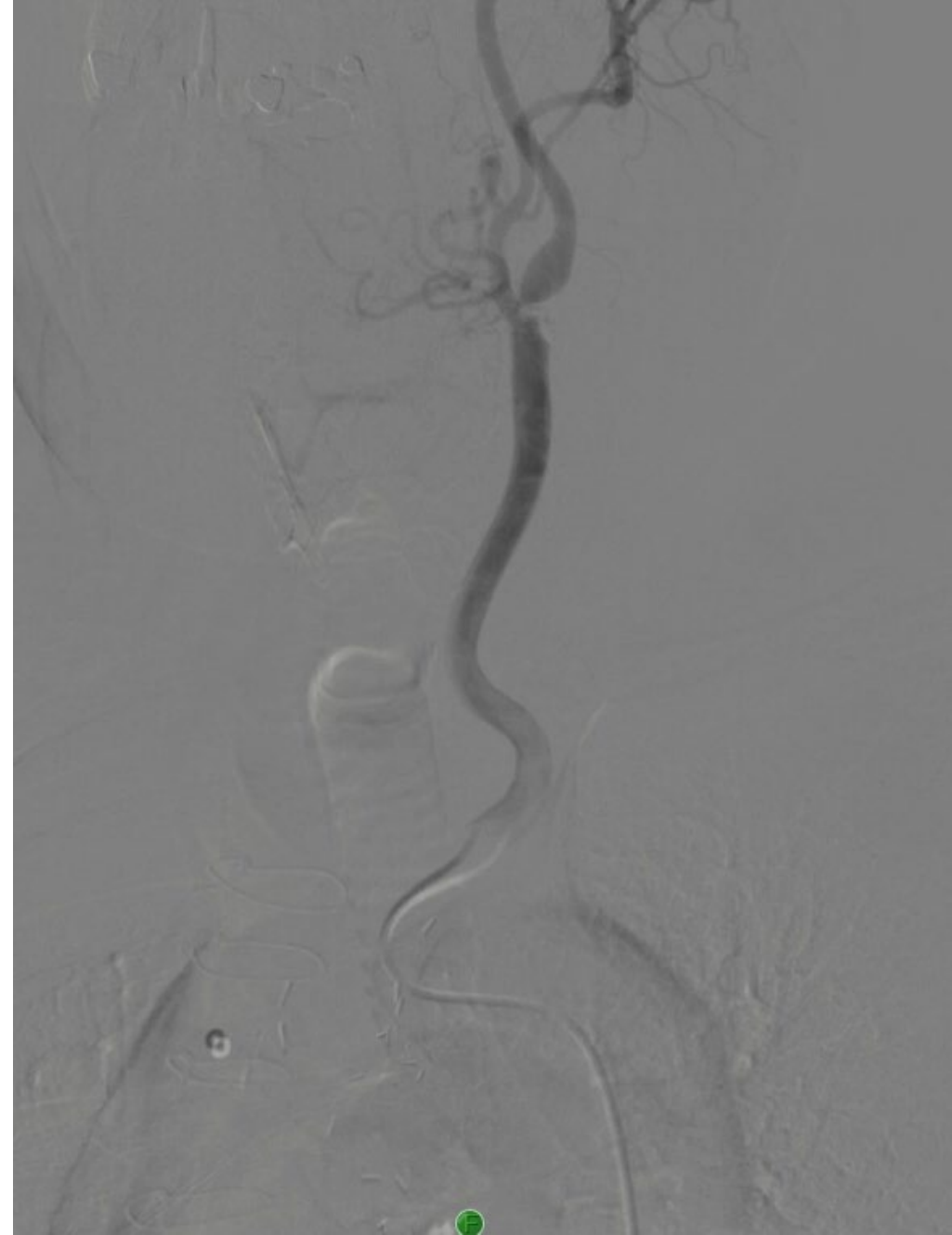
- **MRA Brain** – No acute infarct
- **CTA Head/Neck** – Redemonstration of severe (80–90%) left ICA stenosis at proximal segment; no dissection or ulceration

Clinical Course

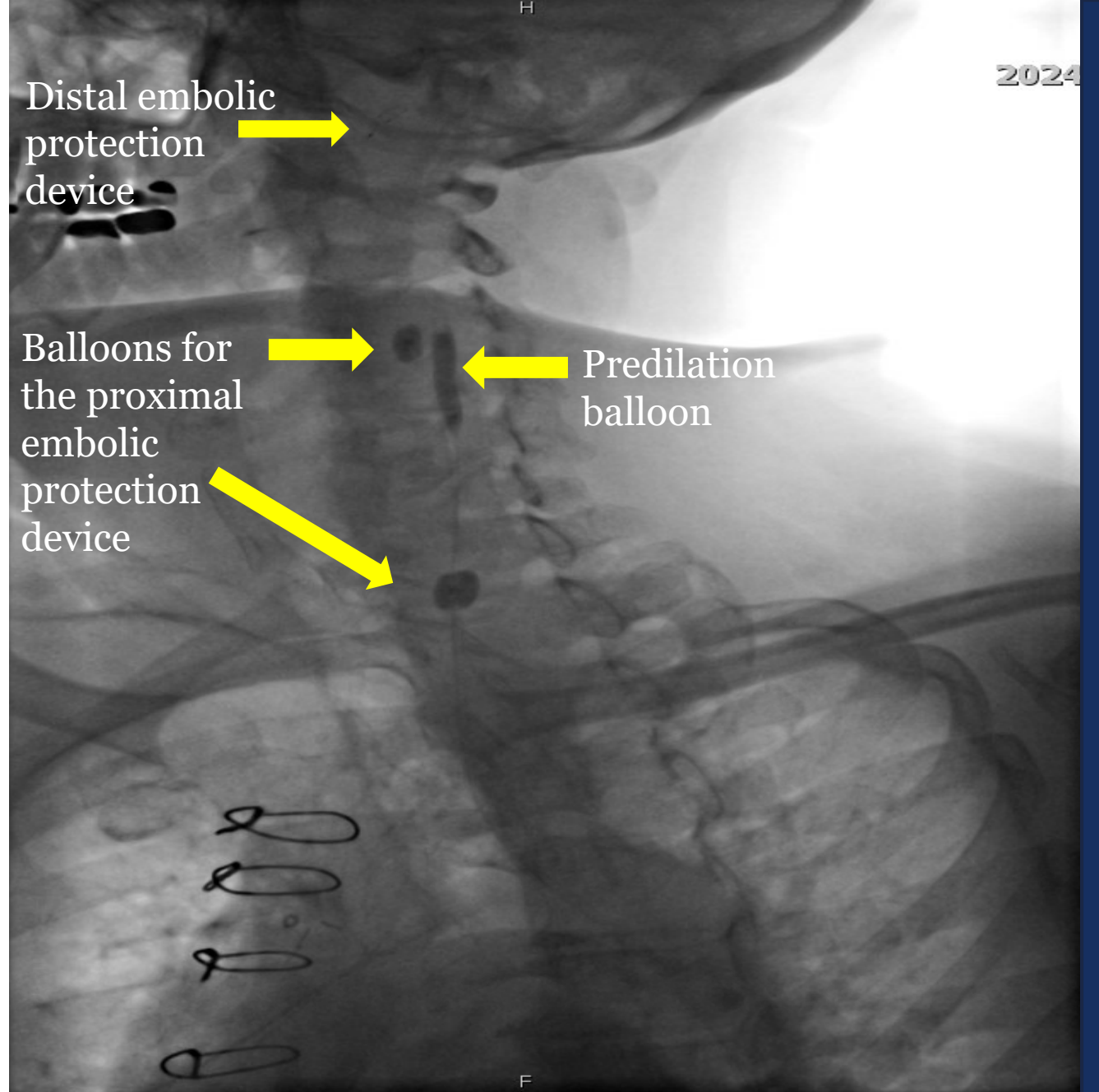
- **Carotid artery stenting**
chosen due to young age
and prior neck radiation
(poor surgical candidate)
- Transfemoral access
- Proximal and distal
embolic protection



Clinical Course



Clinical Course



Clinical Course

- **Carotid artery stenting** chosen due to young age and prior neck radiation (poor surgical candidate)



Clinical Course



Clinical Course Continued



No persistent
neurologic deficits



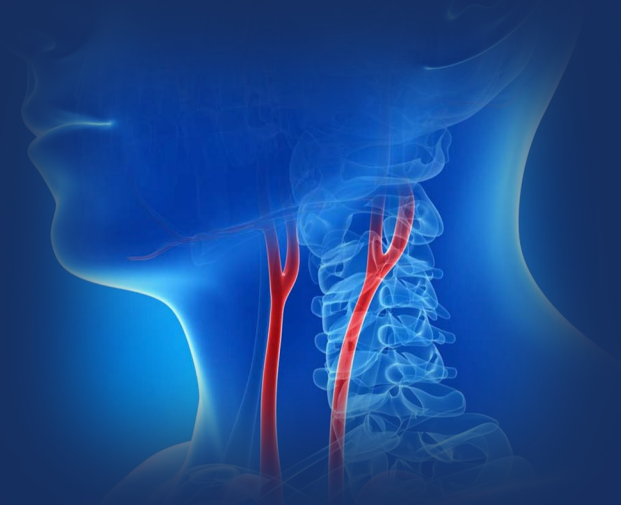
Follow up
ultrasound showed
patent stent



Seen in clinic last
month, doing well



Acknowledgements



Thank you