경동맥 동맥경화증의 진단 및 치료

허 성 혁

경희대학교병원 신경과

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overview

- Mechanism of carotid atherosclerosis
- Diagnosis of carotid atherosclerosis
- Primary and secondary prevention of stroke d/t carotid atherosclerosis
  - Guidelines
  - Large clinical trials about CEA vs. stent
  - Medical Tx

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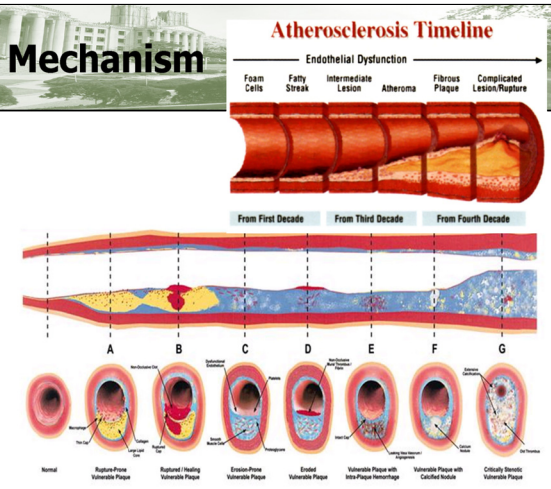
Mechanism



2008, Venkatesan

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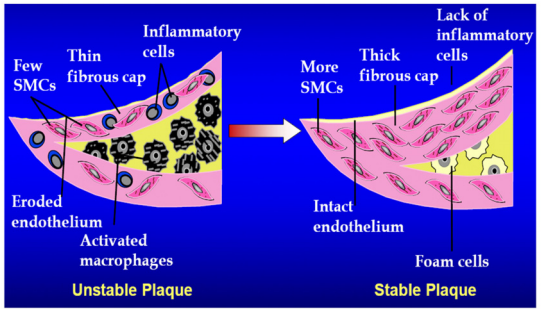
atherosclerosis

- Atherosclerosis involves more than just lipids



Circulation. 1995;91:2844-2850

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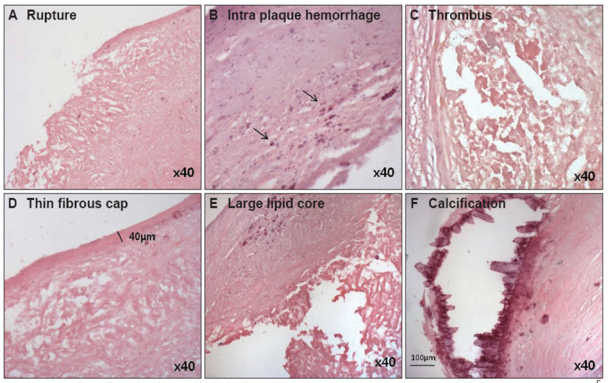
Histologic analysis

Heo SH et al. J Clin Neurol, 2011



Supplementary Fig. 1. Examples of plaque histological features in cartid endarterectomy specimens (hematoxylin and eosin stain, ×40).

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- Atherosclerosis is an inflammatory disease
  - Essential components of atherogenesis
    - Injury to the vessel wall
    - The associated inflammatory response to injury
    - → response-to-injury hypothesis of atherosclerosis

Stroke. 2003;34:2518-2532
NEJM. 1999;340:115-126
Circulation. 1999;100:e20-e28

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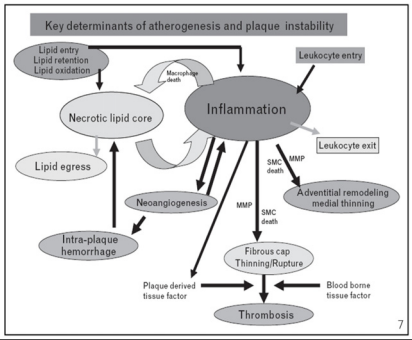
Molecular mechanism of carotid syndrome

Molecular mechanisms of plaque instability
Prediman K. Shah Curr Opin Lipidol 2007;18:492-499

Schematic shows various steps involved in atherogenesis highlighting the role of inflammation in events leading to plaque instability, plaque rupture and thrombosis. MMP, matrix-degrading metalloproteinase; SMC, smooth muscle cell.



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Considering factors

- Intervention trials evaluating the effect of treatment of this patient group
  - Local factors
    - Degree of narrowing
    - the morphology of lesion
  - Hemodynamic factors
    - Collateral compensation
  - Systemic factors
    - Asymptomatic or symptomatic
    - Accompanying diseases – IHD, PAD
    - Level of risk factor control

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Active coronary plaque vs MI

Plaque Stabilization: Can We Turn Theory into Evidence?

Peter Libby, MD,[a,b,*] and William Sasiela, PhD[c]

Previous concepts viewed atherosclerosis primarily as a progressive lipid storage and smooth muscle proliferative disease. Its clinical manifestation (ie, plaque accumulating along the artery wall and eventually obstructing the lumen, thereby constricting blood flow and causing coronary events) has been regarded principally as a mechanical phenomenon.[1] However, subsequent research has demonstrated that many coronary events do not arise from lesions with critical stenosis. For example, in a study involving 92 patients, Giroud and associates[2] observed that 78% of myocardial infarctions (MIs) occurred in arteries that did not have significant stenosis in previous angiograms. Furthermore, only modest improvements in arterial stenosis accompany the significant reductions in coronary events achieved by lipid-lowering drugs (eg, 3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors, or statins). Indeed, recent work indicates that inflammation participates importantly in plaque development, and that acute coronary syndromes (ACS), including MI and unstable angina, usu-

- Am J Cardiol 2006;98(suppl):26-33
- Nat Med 2002;8(11):1257-62
- Am J Cardiol 1992;69:729-732

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Active carotid plaque vs ischemic stroke

JAMA®
Online article and related content current as of July 20, 2008.

Extracranial Thrombotically Active Carotid Plaque as a Risk Factor for Ischemic Stroke

Luigi Giusto Spagnoli; Alessandro Mauriello; Giuseppe Sangiorgi; et al.

JAMA. 2004;292(15):1845-1852 (doi:10.1001/jama.292.15.1845)

Table 2. Thrombotically Active Plaques, Cap Rupture, and Cap Erosion by Study Group

	No. of Plaques (%)			*P* Value		
	Patients With Major Ipsilateral Stroke (n = 96)	Patients With TIA (n = 91)	Asymptomatic Patients (n = 82)	Stroke vs TIA	Stroke vs Asymptomatic	TIA vs Asymptomatic
Thrombotically active plaque	71 (74.0)	32 (35.2)	12 (14.6)	<.001	<.001	.002
Cap rupture	64 (66.7)	21 (23.1)	11 (13.4)	<.001	<.001	.004
Cap erosion	7 (7.3)	11 (12.1)	1 (1.2)	.51	.09	.03

Abbreviation: TIA, transient ischemic attack.

Table 3. Thrombosis Related to the Time Interval Between Symptom Onset and Surgery in Patients With Stroke

	Time Interval Between the Acute Cerebral Event and Carotid Endarterectomy, No. (%)				
	0-2 mo (32 Cases)	3-6 mo (18 Cases)	7-12 mo (15 Cases)	13-24 mo (13 Cases)	25-30 mo (18 Cases)
Thrombotically active plaque	32 (100)	13 (72.2)	11 (73.3)	7 (53.8)	8 (44.4)
Only organized thrombosis	0	4 (22.2)	4 (26.7)	5 (38.5)	10 (55.6)
No thrombosis	0	1 (5.6)	0	1 (7.7)	0

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overview

- Mechanism of carotid atherosclerosis
- Diagnosis of carotid atherosclerosis
- Primary and secondary prevention of stroke d/t carotid atherosclerosis
  - Guidelines
  - Large clinical trials about CEA vs. stent
  - Medical Tx

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Diagnostic tools

- Various diagnostic tools
  - Carotid bruit
  - CT angiography
  - MR angiography
  - Carotid ultrasound
  - TCD air-bubble test
  - TFCA (conventional angiography)
  - PET CT
- Considering factors
  - Invasiveness
  - Urgency
  - Cost
  - Purpose
    - Plaque burden
    - Routine follow-up
    - Operability or intervention
  - Patient's factor
    - Contrast allery
    - Renal function
    - Co-operation

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Overflowing tests

- 며칠 전 타과 consult
  - 53세, 남자. Rt neck pain
  - Both carotid stenosis (20-30%)
  - Clinical impression : myofascial pain synd (자전거포)
- Check order
  - Routine lab (including HAV, HCV, TFT, vitD)
  - X-ray : chest, C-T-L spine, knee, abdomen
  - Ultrasound : carotid, extremities (both arm/leg), abdomen/pelvis
  - CT: chest, cardiac angio CT
  - MRI: brain MRI/MRA with DWI
- U.S. Preventive Services Task Force (US PSTF)
  - Recommend against screening for carotid artery stenosis in those without symptoms (2014 Ann Int Med)

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Carotid bruit

- A weak predictor of stroke (JAMA 1981, NEJM 1980)

Carotid bruits as a prognostic indicator of cardiovascular death and myocardial infarction: a meta-analysis

Christopher A Pickett, Jeffrey L Jackson, Brian A Hemann, J Edwin Atwood

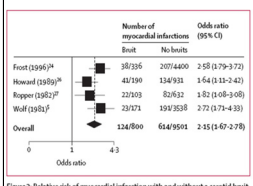

Figure 3: Relative risk of myocardial infarction with and without a carotid bruit

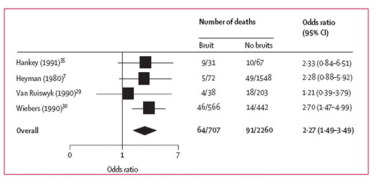

Figure 5: Relative risk of cardiovascular death with and without a carotid bruit

Lancet 2008; 371: 1587–94

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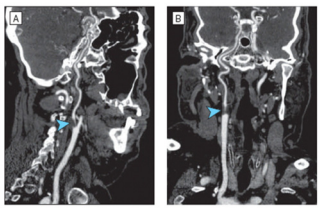
CTA

- From cross-sectional images
- Rapid
- Show marked calcification
- Crude for measuring stenosis degree
- f/u after CAS



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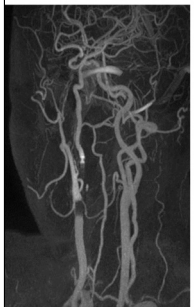
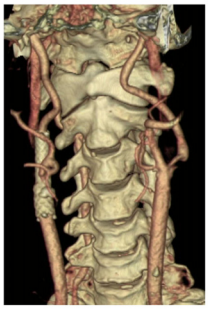
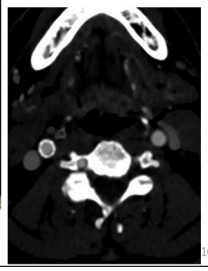
CTA

- F/U after CAS







MRA CTA

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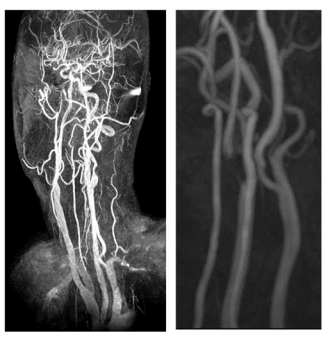
MRA (TOF vs. CE)

- Image quality
  - CE>TOF
- Contrast
  - TOF<CE
- High cost
- Long elapsed time
- Loud noise, claustrophobia



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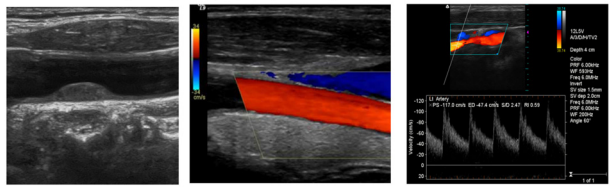
Carotid ultrasound

- Most common test for diagnosing carotid a disease
- Non-invasive, painless
- B -mode
  - 혈관의 구조
- Pulse wave Doppler
  - 혈류 속도와 파형
  - 1~10 MHz 음파
- 고밀도의 조직은 밝게 , 저밀도의 조직은 회색



Carotid IMT

- Subclinical atherosclerosis
  - Surrogate marker for atherosclerosis

Ultrasound Imaging of Cerebrovascular Disease 11

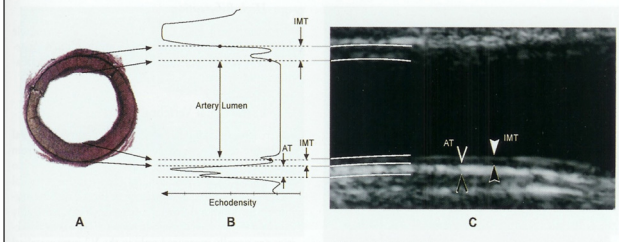
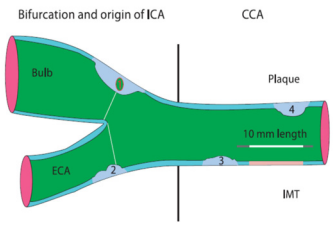


FIGURE 1-7. Histologic and ultrasonic correlation of intima-media thickness (IMT). **A.** The sets of two arrows at the top and bottom outline the IMT between the luminal border of the intima and the junction of the media and adventitia (AT). **B.** Graph depicting the echogenicity profiles of the AT, media, intima, and arterial lumen. **C.** The IMT and AT are respectively outlined by the closed and open arrowheads. 19

Mannheim carotid IMT consensus



1: thickness > 1.5 mm
2: lumen encroaching > 0.5 mm
3, 4: > 50% of the surrounding IMT value

Cerebrovasc Dis 2007;23:75–80 20

Carotid USG for estimating risk by carotid plaque

- Stenosis degree & flow velocity
- Plaque surface morphology
- Plaque composition
  - Echogenicity
  - Heterogeneity
- Others
  - Plaque area
  - Plaque volume (3D)
  - Fibrous cap thickness
  - Intraplaque neovascularization

Risk factor for symptomatic carotid stenosis

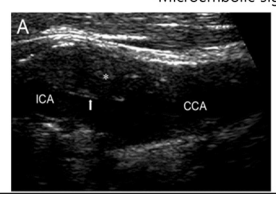
•Stenosis > 90%
•History of neurological events
•Progression of stenosis
•Echolucent plaques (Duplex sono)
•Hypertension

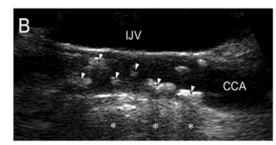
stroke, 2001

•Degree of stenosis
•Brain infarction on neuroimaging
•Plaque ulceration (angiography)
•Echolucent plaque

Int angio.1995

•Unstable plaque (circulation 2002)
•Microembolic signals (stroke, 2002)





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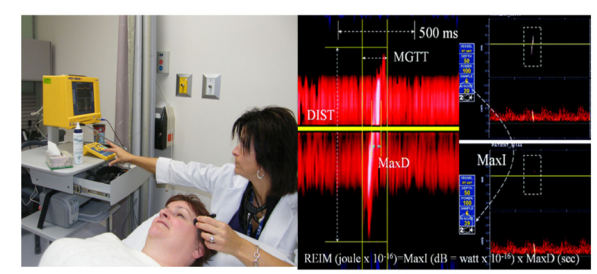
TCD air-bubble test

- Check vulnerability of proximal vessel to MCA



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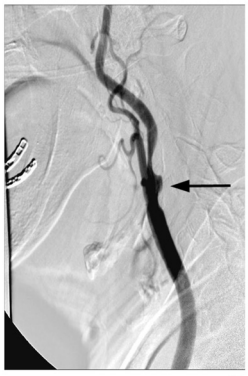
TFCA

- Gold standard
- Can take best information
  - Exact stenosis deg
  - Collateral circulation
  - Plaque morphology & calcification
- Invasive & small risk of serious Cx
- 0.5-1.0% risk of stroke, MI, arterial injury, or retroperitoneal bleeding



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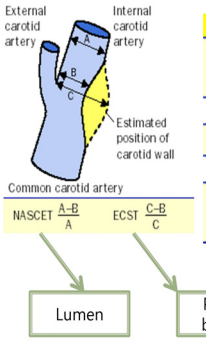
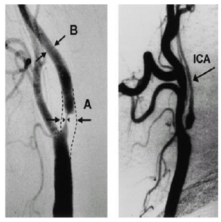
Measuring method



NASCET	ECST
30	65
40	70
50	75
60	80
70	85
80	91
90	97



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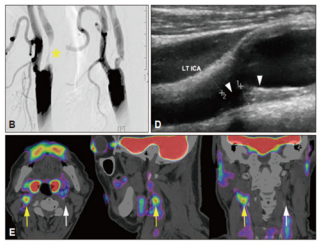
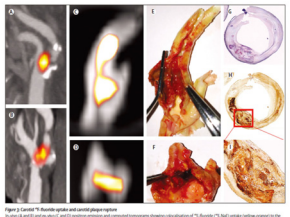
Future diagnostic image

-^{18}F-FDG PET/CT vs. -^{18}F-fluoride PET/CT





J Clin Neurol, 2013

Lancet, 2014

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overview

- Mechanism of carotid atherosclerosis
- Diagnosis of carotid atherosclerosis
- Primary and secondary prevention of stroke d/t carotid atherosclerosis
  - Guidelines (ASA 2014, EUSI 2008)
  - Large clinical trials about CEA vs. stent
  - Medical Tx

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Guideline -USA

(*Stroke.* 2014;45:3754-3832.)

Primary prevention

1. Patients with asymptomatic carotid stenosis should be prescribed daily aspirin and a statin. Patients should also be screened for other treatable risk factors for stroke, and appropriate medical therapies and lifestyle changes should be instituted (*Class I; Level of Evidence C*).
2. In patients who are to undergo CEA, aspirin is recommended perioperatively and postoperatively unless contraindicated (*Class I; Level of Evidence C*).
3. It is reasonable to consider performing CEA in asymptomatic patients who have >70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low (<3%). However, its effectiveness compared with contemporary best medical management alone is not well established (*Class IIa; Level of Evidence A*).
4. It is reasonable to repeat duplex ultrasonography annually by a qualified technologist in a certified laboratory to assess the progression or regression of disease and response to therapeutic interventions in patients with atherosclerotic stenosis >50% (*Class IIa; Level of Evidence C*).
5. Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum, 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established (*Class IIb; Level of Evidence B*).
6. In asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS, the effectiveness of revascularization versus medical therapy alone is not well established (*Class IIb; Level of Evidence B*).
7. Screening low-risk populations for asymptomatic carotid artery stenosis is not recommended (*Class III; Level of Evidence C*).

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Guideline -USA

Stroke. 2014;45:2160-2236

Secondary prevention

1. For patients with a TIA or ischemic stroke within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis as documented by noninvasive imaging, CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6% (*Class I; Level of Evidence A*).
2. For patients with recent TIA or ischemic stroke and ipsilateral moderate (50%–69%) carotid stenosis as documented by catheter-based imaging or noninvasive imaging with corroboration (eg, magnetic resonance angiogram or computed tomography angiogram), CEA is recommended depending on patient-specific factors, such as age, sex, and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6% (*Class I; Level of Evidence B*).
3. When the degree of stenosis is <50%, CEA and CAS are not recommended (*Class III; Level of Evidence A*).
4. When revascularization is indicated for patients with TIA or minor, nondisabling stroke, it is reasonable to perform the procedure within 2 weeks of the index event rather than delay surgery if there are no contraindications to early revascularization (*Class IIa; Level of Evidence B*).

CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the ICA is reduced by >70% by noninvasive imaging or >50% by catheter-based imaging or noninvasive imaging with corroboration and the anticipated rate of periprocedural stroke or death is <6% (*Class IIa; Level of Evidence B*). (Revised recommendation)

It is reasonable to consider patient age in choosing between CAS and CEA. For older patients (ie, older than ≈70 years), CEA may be associated with improved outcome compared with CAS particularly when arterial anatomy is unfavorable for endovascular intervention. For younger patients, CAS is equivalent to CEA in terms of risk for periprocedural complications (ie, stroke, MI, or death) and long-term risk for ipsilateral stroke (*Class IIa; Level of Evidence B*). (New recommendation)

Among patients with symptomatic severe stenosis (≥70%) in whom anatomic or medical conditions are present that greatly increase the risk for surgery or when other specific circumstances exist such as radiation-induced stenosis or restenosis after CEA, CAS is reasonable (*Class IIa; Level of Evidence B*). (Revised recommendation)

8. CAS and CEA in the above settings should be performed by operators with established periprocedural stroke and mortality rates of <6% for symptomatic patients, similar to that observed in trials comparing CEA to medical therapy and more recent observational studies (*Class I; Level of Evidence B*). (Revised recommendation)
9. Routine, long-term follow-up imaging of the extracranial carotid circulation with carotid duplex ultrasonography is not recommended (*Class III; Level of Evidence B*). (New recommendation)
10. For patients with a recent (within 6 months) TIA or ischemic stroke ipsilateral to a stenosis or occlusion of the middle cerebral or carotid artery, EC/IC bypass surgery is not recommended (*Class III; Level of Evidence A*).
11. For patients with recurrent or progressive ischemic symptoms ipsilateral to a stenosis or occlusion of a distal (surgically inaccessible) carotid artery, or occlusion of a midcervical carotid artery after institution of optimal medical therapy, the usefulness of EC/IC bypass is considered investigational (*Class IIb; Level of Evidence C*). (New recommendation)
12. Optimal medical therapy, which should include antiplatelet therapy, statin therapy, and risk factor modification, is recommended for all patients with carotid artery stenosis and a TIA or stroke, as outlined elsewhere in this guideline (*Class I; Level of Evidence A*).

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Guideline -USA

Stroke. 2014;45:2160-2236

Secondary prevention

Section	2014 Recommendation	Description of Change From 2011
Carotid disease	CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by >70% by noninvasive imaging or >50% by catheter-based imaging or noninvasive imaging with corroboration and the anticipated rate of periprocedural stroke or death is <6% *(Class IIa; Level of Evidence B)*.	Class changed from I to IIa based on outcome findings reported in a meta-analysis of comparative trials
	It is reasonable to consider patient age in choosing between CAS and CEA. For older patients (ie, older than ≈70 years), CEA may be associated with improved outcome compared with CAS, particularly when arterial anatomy is unfavorable for endovascular intervention. For younger patients, CAS is equivalent to CEA in terms of risk for periprocedural complication (ie, stroke, MI, or death) and long-term risk for ipsilateral stroke *(Class IIa; Level of Evidence B)*.	New recommendation
	CAS and CEA in the above settings should be performed by operators with established periprocedural stroke and mortality rates of <6% for symptomatic patients, similar to that observed in trials comparing CEA to medical therapy and more recent observational studies *(Class I; Level of Evidence B)*.	Class changed from IIa to I
	Routine, long term follow-up imaging of the extracranial carotid circulation with carotid duplex ultrasonography is not recommended *(Class III; Level of Evidence B)*.	New recommendation
	For patients with recurrent or progressive ischemic symptoms ipsilateral to a stenosis or occlusion of a distal (surgically inaccessible) carotid artery, or occlusion of a midcervical carotid artery after institution of optimal medical therapy, the usefulness of EC/IC bypass is considered investigational *(Class IIb; Level of Evidence C)*.	New recommendation

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CLINICAL DECISIONS
INTERACTIVE AT WWW.NEJM.ORG

Management of Carotid Stenosis — Polling Results

Autumn Klein, M.D., Ph.D., Caren G. Solomon, M.D., M.P.H., and Mary Beth Hamel, M.D., M.P.H.

2008, NEJM

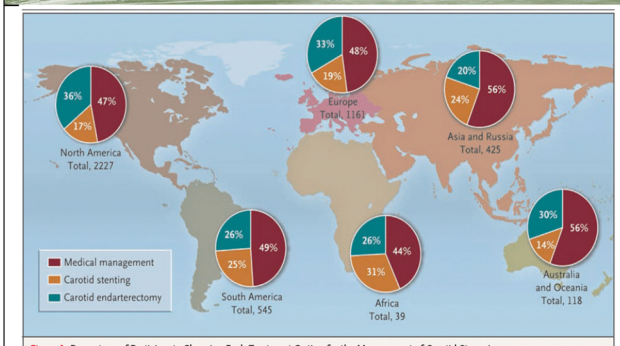

Figure 1. Percentage of Participants Choosing Each Treatment Option for the Management of Carotid Stenosis.
The total number of participants who voted and the percentage who selected each option are shown for each continent or region. The percentages did not vary substantially according to continent or region. An interactive graphic that includes the total numbers of votes and percentages according to country is available at www.nejm.org.

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Expert's opinion

JAMA®
Online article and related content current as of June 28, 2009.

A 70-Year-Old Man With a Transient Ischemic Attack: Review of Internal Carotid Artery Stenosis

Louis R. Caplan

JAMA. 2008;300(1):81-90 (doi:10.1001/jama.299.21.jrr80004)

- Mr. V
  - 70-yr-old man
  - Hx of coronary dis, s/p coronary stent (2006), pph vascular dis, GI bleeding d/t clopidogrel, HT, HL
  - Acute onset slurred speech & Lt facial droop
  - Onset: 4hr ago
  - Language: improving within 5min
  - ED NIHSS-2

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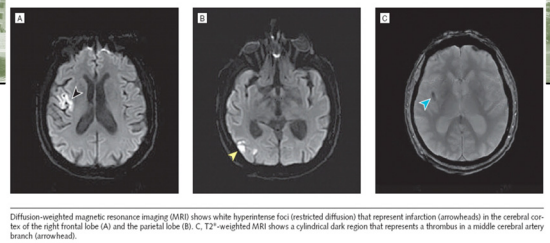
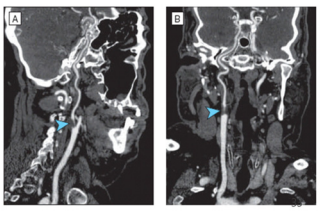
Figure 2. Mr V's Diffusion-Weighted and T2*-Weighted MRI Scan



Diffusion-weighted magnetic resonance imaging (MRI) shows white hyperintense foci (restricted diffusion) that represent infarction (arrowheads) in the cerebral cortex of the right frontal lobe (A) and the parietal lobe (B). C, T2*-weighted MRI shows a cylindrical dark region that represents a thrombus in a middle cerebral artery branch (arrowhead).

- Decision making
  - Medical Tx:
    - Severe carotid stenosis
    - Onset <2wks
  - CEA :
    - MI risk
  - Carotid stent:
    - pph vascular dis

Figure 1. Views of a Computed Tomography Angiogram in Mr V



overview

- Mechanism of carotid atherosclerosis
- Diagnosis of carotid atherosclerosis
- Primary and secondary prevention of stroke d/t carotid atherosclerosis
  - Guidelines
  - Large clinical trials about CEA vs. stent
    - Short-term outcome
    - Long-term outcome
    - RCTs in aSx patients
  - Medical Tx

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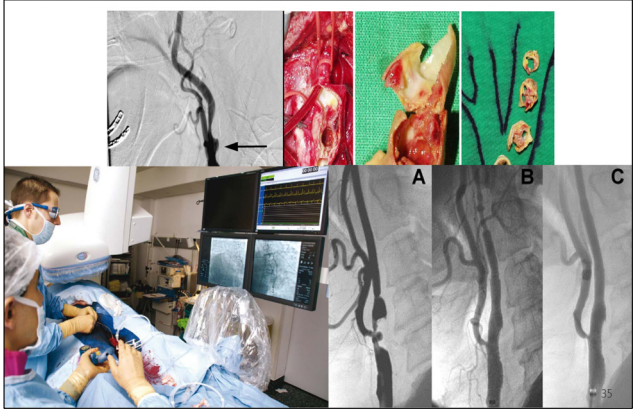
CEA vs. stent



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RCTs

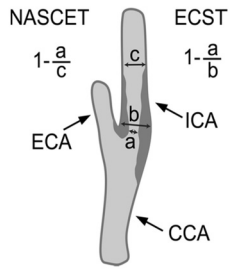
- 1995: ACAS(JAMA)
- 1998: NASCET(NEJM), ECST(Lancet)
- 2001: CAVATAS(Lancet), WALLSTENT(Stroke)
- 2004: SAPPHIRE(NEJM), ACST(Lancet)
- 2006: EVA-3S(NEJM), SPACE(Lancet)
- 2008-9: EVA-3S 4yr, SPACE 2yr, CAVATAS long (Lancet Neurol), SAPPHIRE long(NEJM)
- 2010: ICSS interim(Lancet), CREST(NEJM), ACST-1(Lancet)
- 2014: ICSS(Lancet)

- vs. medical Tx
- aSx patients
- Sx patients
- Both

36

Measuring method

- NASCET vs. ECST

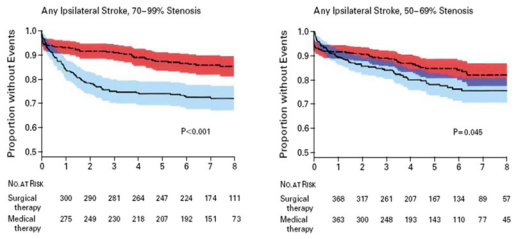


NASCET	ECST
30	65
40	70
50	75
60	80
70	85
80	91
90	97

37

NASCET

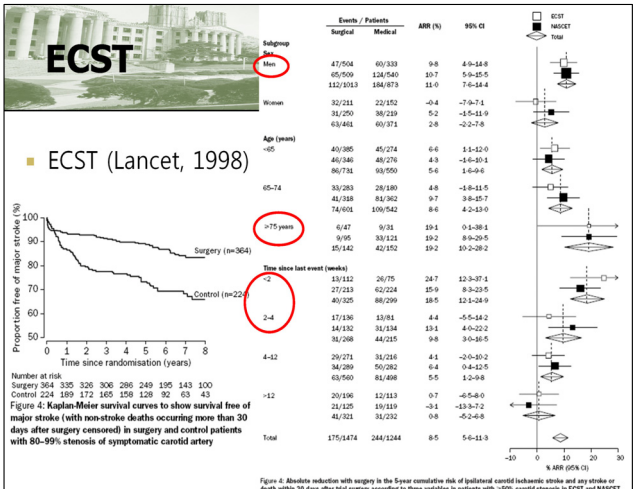
- NASCET (NEJM, 1998)



38

ECST

- ECST (Lancet, 1998)



(Lancet, 2004) 39

Previous RCTs

- CAVATAS (2001, Lancet)
  - 1st large RCT in Europe, Australia, Canada
  - Sx>90%
  - No difference in endovascular Tx (25/251, 10%) vs. CEA (25/253, 10%)
- SAPPHIRE (2004, NEJM)
  - High risk patients
  - Sx<30%
  - Primary outcome
  - (death, stroke or MI at 30d +ipsilat stroke or stroke-related death within 31d to 1yr)
    - CAS (20/167, 12.2%) vs. CEA (32/167, 20.1%) : p=0.05
- SPACE (2006, Lancet)
  - CAS (41/599, 6.84%) vs. CEA (37/584, 6.34%) : p=0.09 for non-inferiority
- EVA-3S (2006, NEJM)
  - CAS (23/261, 8.8%) vs. CEA (7/259, 2.7%) : p=0.004

Criteria for high risk (at least one factor required)
Clinically significant cardiac disease (congestive heart failure, abnormal stress test, or need for open-heart surgery)
Severe pulmonary disease
Contralateral carotid occlusion
Contralateral laryngeal-nerve palsy
Previous radical neck surgery or radiation therapy to the neck
Recurrent stenosis after endarterectomy
Age>80 yr

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ICSS-interim (2010, Lancet)

- **Multicenter, international, randomized controlled trial with blinded adjudication of outcomes**
  - Primary outcomes; the 3 years rate of fatal or disabling stroke in any territory
  - Interim analysis; the 120 days after treatment of composite outcomes
  - composite outcome ; procedural stroke, myocardial infarction, or death

- The composite outcome within the first 120 days of treatment in the ITT(P=0.006)
  CAS (72, 8.5%) vs. CEA (44, 5.2%)
- The risk within 30 days of treatment in the PP analysis (p=0·003)
  CAS (7·4%) vs CEA (4·0%)
  - Higher number of non-disabling stroke in CAS (36 vs. 11 within 30days)
  - the rate of disabling stroke or death did not differ significantly (26 vs. 18)

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ICSS-interim (2010, Lancet)

- Enrolled period; May 2001~October 2008
- 50 centers
- 1713 pts (CAS, n=855, CEA, n=858)

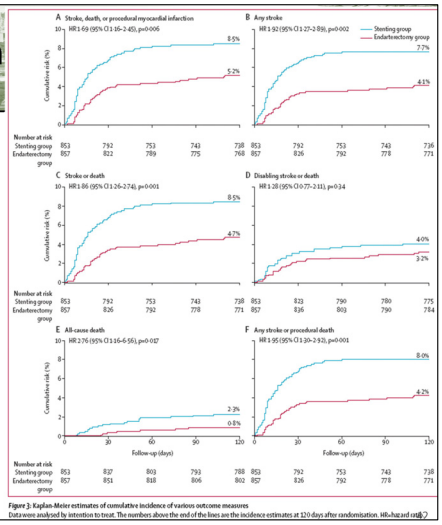
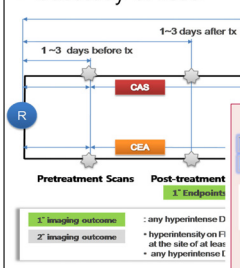


Figure 3: Kaplan-Meier estimates of cumulative incidence of various outcome measures
Data were analysed by intention to treat. The numbers above the end of the lines are the incidence estimates at 120 days after randomisation. HR=hazard ratio

ICSS-MRI study (2010, Lancet Neurol)

- Substudy of ICSS



Result – Clinical outcome within 30 d

	Carotid stenting (n=124)	Carotid endarterectomy (n=107)	OR (95% CI)	p*
Any stroke or death	11 (9%)	5 (5%)	1·99 (0·70–5·66)	0·300
All cause death	1 (1%)	0	..	..
Any stroke	10 (8%)	5 (5%)	1·79 (0·62–5·17)	0·423
Stroke pathology				
Ischaemic	10 (8%)	3 (3%)	..	..
Haemorrhagic	0	2 (2%)	..	..
Stroke severity				
Non-disabling	7 (6%)	2 (2%)	..	..
Disabling	3 (2%)	3 (3%)	..	..
Fatal	0	0	..	..
TIA	3 (2%)	0	..	..
Ischaemic stroke or TIA	13 (10%)	3 (3%)	4·06 (1·20–13·63)	0·035

Data are number (%). TIA=transient ischaemic attack. *Fisher's exact test.

Table 3: Clinical outcome within 30 days of treatment

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Primary outcome ; New DWI lesions

	Carotid stenting (n=124)	Carotid endarterectomy (n=107)	OR (95% CI)	p*
At least one new lesion	62 (50%)	18 (17%)	4·94 (2·67–9·16)†	<0·0001
			5·21 (2·78–9·79)‡	<0·0001
Single lesion	18 (15%)	9 (8%)	..	..
Multiple lesions	44 (35%)	9 (8%)	..	..
Location of lesions				
Ipsilateral carotid circulation only	34 (27%)	14 (13%)	..	..
Ipsilateral carotid and non-ipsilateral (contralateral carotid or vertebrobasilar) circulations	22 (18%)	3 (3%)	..	..
Non-ipsilateral (contralateral carotid or vertebrobasilar) circulations only	6 (5%)	1 (1%)	..	..
Ischaemic events in patients with new DWI lesions§	9 (7%)	3 (3%)	..	..
Hemispheric stroke	8 (6%)	3 (3%)	..	..
Retinal infarct	1 (1%)	0	..	..
TIA	0	0	..	..
None	53 (43%)	15 (14%)	..	..

Data are number (%). DWI=diffusion-weighted imaging. TIA=transient ischaemic attack. *Logistic regression. †Unadjusted. ‡Adjusted for interval between treatment and post-treatment scan. §Events occurring between start of treatment and post-treatment scans only. No ischaemic event occurred between the start of treatment and the post-treatment scan in patients without new DWI lesions.

Table 4: New DWI lesions on post-treatment scans

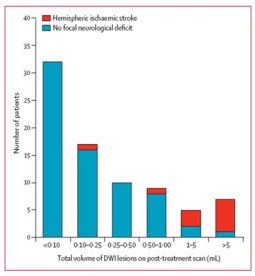

Figure 2: Distribution of DWI lesion volumes on post-treatment scans according to whether or not focal neurological deficits occurred
DWI=diffusion-weighted imaging.

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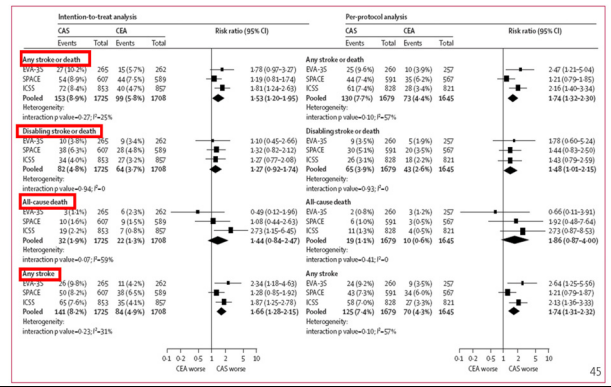
Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data

Carotid Stenting Trialists' Collaboration*

Lancet 2010; 376: 1062-73



45

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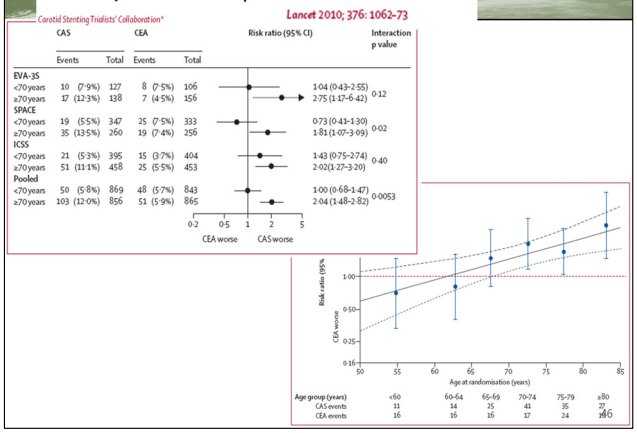

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overview

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Long-term outcome

- SPACE 2yr f/u (2008, Lancet Neurol)
  - Ipsilateral stroke or vascular death : HR 1.11 (95% CI 0.77-1.60)

	CAS	CAE	Hazard ratio (95% CI)	p value
Sex				
Women	14/171 (8·3%)	11/167 (6·7%)	1·30 (0·59–2·85)	0·68
Men	42/436 (9·9%)	39/422 (9·6%)	1·07 (0·42–2·74)	
Age at randomisation				
<68 years	14/293 (5·0%)	25/284 (9·0%)	0·54 (0·28–1·03)	0·004
≥68 years	42/314 (13·7%)	25/305 (8·6%)	1·80 (0·96–3·40)	

Recurrent carotid stenoses of 70% or more
ITT: 10.7% vs. 4.6% (p=0.0009)
PPA: 11.1% vs. 4.6% (p=0.0007)

- EVA-3S 4yr f/u (2008, Lancet Neurol)
  - Any stroke : HR 1.97 (95% CI, 1.06-3.67)
- SAPPHIRE long; 3yr f/u (2008, NEJM)
  - Major adverse event : CAS(24.6%) vs. CEA (26.9%) p=0.27
- CAVATAS long; median 5 yrs (2009, Lancet Neurol)
  - Disabling stroke or death : 1.02 (95% CI: 0.79-1.32)

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Time for a moratorium?

Poor outcomes after endovascular treatment of symptomatic carotid stenosis: time for a moratorium

Peter M Rothwell
John Radcliffe Hospital, Oxford, UK

Lancet Neurol (2009)

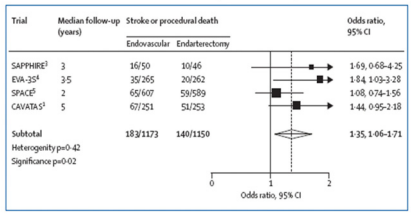

Figure: Meta-analysis of data on long-term risk of any stroke after randomisation and non-stroke periprocedural death from all published randomised trials of endovascular treatment versus endarterectomy for symptomatic carotid stenosis
The SAPPHIRE trial composite outcome also included periprocedural myocardial infarction and death and only ipsilateral ischaemic stroke at more than 30 days after the procedure.

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CREST (2010, NEJM)

- Dec, 2000 ~ July, 2008
- 117 centers in USA & Canada
- Symptomatic & asymptomatic(47.2%)
  - Asymptomatic pts included after 2005
- 2502 pts (CAS=1262, CEA=1240)
- Primary outcome
  - Stroke, MI, death from any cause during the periprocedural period or any ipsilateral stroke within 4 years

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CREST (2010, NEJM)

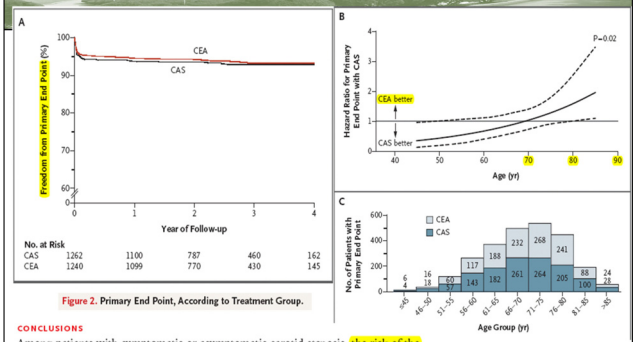

Figure 2. Primary End Point, According to Treatment Group.

CONCLUSIONS

Among patients with symptomatic or asymptomatic carotid stenosis, the risk of the composite primary outcome of stroke, myocardial infarction, or death did not differ significantly in the group undergoing carotid-artery stenting and the group undergoing carotid endarterectomy. During the periprocedural period, there was a higher risk of stroke with stenting and a higher risk of myocardial infarction with endarterectomy. (ClinicalTrials.gov number, NCT00004732.)

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ICSS (2014, Lancet)

	Stenting (n=853)			Endarterectomy (n=857)			Hazard ratio* (95% CI)	Absolute risk difference (95% CI)	
	Number of events*	Cumulative 1-year risk (SE)†	Cumulative 5-year risk (SE)†	Number of events*	Cumulative 1-year risk (SE)†	Cumulative 5-year risk (SE)†		At 1 year	At 5 years
Fatal or disabling stroke (primary outcome measure)	52	3·9% (0·7)	6·4% (0·9)	49	3·2% (0·6)	6·5% (1·0)	1·06 (0·72 to 1·57)	0·7% (-1·0 to 2·5)	-0·2% (-2·8 to 2·5)
Any stroke	119	9·5% (1·0)	15·2% (1·4)	72	5·1% (0·8)	9·4% (1·1)	1·71 (1·28 to 2·30)‡	4·4% (1·9 to 6·9)	5·8% (2·4 to 9·3)
Procedural stroke or procedural death or ipsilateral stroke during follow-up	95	9·0% (1·0)	11·8% (1·2)	57	4·7% (0·7)	7·2% (0·9)	1·72 (1·24 to 2·39)‡	4·2% (1·9 to 6·6)	4·6% (1·6 to 7·6)
All-cause death	153	4·9% (0·7)	17·4% (1·5)	129	2·3% (0·5)	17·2% (1·5)	1·17 (0·92 to 1·48)	2·6% (0·8 to 4·4)	0·2% (-4·0 to 4·4)

*Calculated as the first relevant event between randomisation and the end of follow-up. †Calculated from randomisation onwards. ‡p<0·001. §p=0·01.

Table 2: Intention-to-treat analysis of cumulative risks and hazard ratios of main outcome events

	Stenting (n=752)			Endarterectomy (n=811)			Hazard ratio* (95% CI)	Absolute risk difference (95% CI)	
	Number of events*	Cumulative 1-year risk (SE)*	Cumulative 5-year risk (SE)*	Number of events*	Cumulative 1-year risk (SE)*	Cumulative 5-year risk (SE)*		At 1 year	At 5 years
Fatal or disabling stroke	24	0·9% (0·4)	3·4% (0·8)	27	1·4% (0·4)	4·2% (0·9)	0·93 (0·53 to 1·60)	-0·5% (-1·5 to 0·6)	-0·9% (-3·2 to 1·4)
Any stroke	56	2·9% (0·6)	8·9% (1·2)	39	1·8% (0·5)	5·8% (1·0)	1·53 (1·02 to 2·31)†	1·1% (-0·4 to 2·6)	3·1% (0·0 to 6·2)
Ipsilateral carotid stroke	28	1·4% (0·4)	4·7% (0·9)	23	1·1% (0·4)	3·4% (0·8)	1·29 (0·74 to 2·24)	0·2% (-0·9 to 1·3)	1·2% (-1·1 to 3·6)
Contralateral carotid or vertebrobasilar stroke	29	1·4% (0·4)	4·6% (0·9)	16	0·5% (0·3)	2·5% (0·7)	1·92 (1·04 to 3·52)†	0·9% (-0·1 to 1·8)	2·1% (-0·2 to 4·3)
Severe carotid restenosis (≥70%) or occlusion	72/737	6·9% (1·0)	10·8% (1·3)	62/793	5·3% (0·8)	8·6% (1·1)	1·25 (0·89–1·75)	1·7% (-0·8 to 4·1)	2·2% (-1·1 to 5·4)

*Calculated from the end of the procedural period (30 days after completed treatment) for the first four outcomes and from immediately after completed treatment for the last outcome, until the end of follow-up. †p<0·05.

Table 3: Per-protocol analysis of cumulative risks and hazard ratios of main outcome events

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ICSS (2014, Lancet)

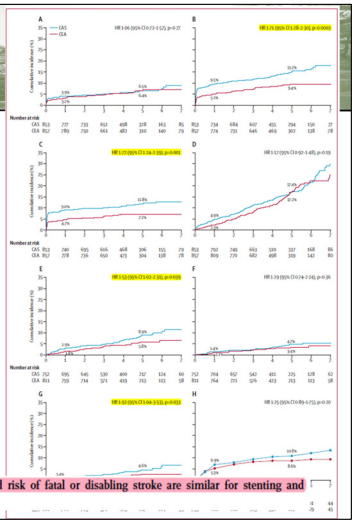

Figure 2: Kaplan-Meier estimates of cumulative incidence for major outcomes
(A) Fatal or disabling stroke. (B) Any stroke. (C) Procedural stroke or procedural death or ipsilateral stroke during follow-up. (D) All-cause death. (E) Any stroke more than 30 days after treatment. (F) Ipsilateral stroke more than 30 days after treatment. (G) Contralateral carotid or vertebrobasilar stroke more than 30 days after treatment. (H) Ipsilateral severe (at least 70%) carotid stenosis after completed treatment, generated by life-table analysis. Panels A–D show

Interpretation Long-term functional outcome and risk of fatal or disabling stroke are similar for stenting and endarterectomy for symptomatic carotid stenosis.

IHD is a major cause of death after ischemic stroke

- Meta-analysis (2005, Stroke)
  - 65,996 patients. Mean f/u for 3.5 yrs
  - Annual fatal MI : **1.1%**
- Northern Manhattan study (2006, Neurology)
  - 655 patients. Mean f/u for 4 yrs
  - 5-yr fatal cardiac events : **6.4%** (fatal stroke 3.7%)
- SPARCL (2010, Stroke)
  - 4,731 patients. Mean f/u for 4.9 yrs
  - Major coronary events : **5.1%**
- In Korean single hospital study (2012, Stroke)
  - 3,278 patients. Mean f/u for 3.4 yrs
  - Fatal IHD : **3.3%** (fatal stroke 12.3%)

➔ about **1%** of stroke TIA patients died of IHD every year

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overview

- Mechanism of carotid atherosclerosis
- Diagnosis of carotid atherosclerosis
- Primary and secondary prevention of stroke d/t carotid atherosclerosis
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  - Large clinical trials about CEA vs. stent
    - Short-term outcome
    - Long-term outcome
    - RCTs in aSx patients
  - Medical Tx

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ACST (2004, Lancet)

- 3120 aSx patients
- >60% carotid st on US
- No stroke or TIA within 6 months
- Immediate CEA vs indefinite deferral of any CEA
- Main outcome :
  - Perioperative mortality and morbidity
  - Non-perioperative stroke

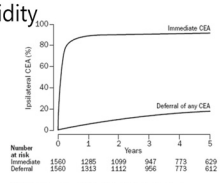

Figure 2: **Proportion with ipsilateral CEA by time from randomisation in ACST, with numbers alive and still under observation at various times**

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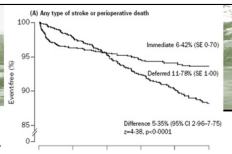
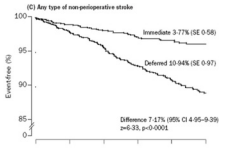
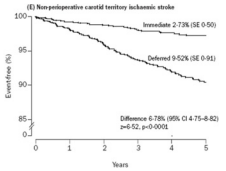
ACST (2004, Lancet)







	Allocated immediate CEA (n=1560)	Allocated deferral of any CEA (n=1560)
Surgical compliance		
Number of patients with any CEA	1348	229
Proportion (life-table) with CEA (%)		
Within 1 year	89·3%	6·9%
Within 5 years	91·8%	20·0%
Contralateral CEA	69	44
Proportion (life-table) with CEA (%)		
Within 1 year	2·9%	0·8%
Within 5 years	5·7%	3·9%
Ipsilateral CEA	1336	201
Proportion (life-table) with CEA (%)		
Within 1 year	88·5%	6·2%
Within 5 years	91·1%	17·7%
Number (%) with ipsilateral CEA preceded in trial by ipsilateral symptoms [stroke+TCI]*	7 [1+6] (0·5%)	93 [13+80] (46·3%)
Perioperative mortality and morbidity (ie, within 30 days of CEA)		
Stroke deaths†	10	2
Disabling strokes	9	3
Non-disabling strokes	16	6
Cardiac deaths	5	0
Non-fatal myocardial infarctions	10	0
Other deaths	0	0
Any perioperative stroke or death	40	11‡
% of number of CEAs (95% CI)	2·8% (2·0–3·9)	4·5% (2·2–8·0)

TCI=transient cerebral ischaemia. *Of these 14 strokes, one versus 11 were ipsilateral. †Of these 12 strokes, none versus two caused death more than 30 days after CEA. ‡Seven had been operated on for ipsilateral symptoms (one stroke, six TCI), one in conjunction with cardiac surgery, and three because the doctor or patient changed their mind.

Table 1: **Surgical compliance, mortality, and morbidity during first 5 years after randomisation**

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ACST-1 (2010, Lancet)

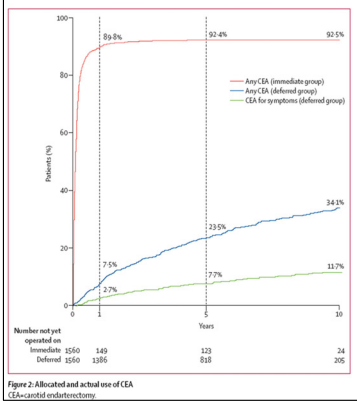

Figure 2: **Allocated and actual use of CEA**
CEA=carotid endarterectomy.

	Immediate CEA (n=1560)	Deferral of any CEA (n=1560)
Surgical compliance		
Number of patients with any CEA	1425 (91·3%)	407 (26·1%)
Proportion with any CEA (%)*		
Within 1 year	89·8%	7·5%
Within 5 years	92·4%	23·5%
Within 10 years	92·5%	34·1%
Proportion with non-symptomatic CEA (%)*		
Within 1 year	89·7%	4·8%
Within 5 years	92·1%	16·5%
Within 10 years	92·2%	23·5%
Proportion with ipsilateral CEA (%)*		
Within 1 year	88·9%	6·9%
Within 5 years	91·5%	21·3%
Within 10 years	91·6%	29·8%
Proportion with contralateral CEA (%)*		
Within 1 year	2·9%	0·8%
Within 5 years	5·5%	4·0%
Within 10 years	7·7%	7·5%
Perioperative mortality and morbidity		
Total number of CEAs†	1532	447
Stroke death	11	2
Cardiac death	5	0
Other death	1	1
Disabling stroke	9	5
Non-disabling stroke	18	8
Non-fatal myocardial infarction	10	1
Any perioperative stroke or death	44	16
% of total number of CEAs (95% CI)	2·9% (2·1–3·8)	3·6% (2·2–5·7)

This table includes only CEAs done within 10 years of randomisation. CEA=carotid endarterectomy. *Kaplan-Meier time-dependent percentages; denominators at these times are shown in figure 2. †Ipsilateral or contralateral (bilateral=two CEAs) first or subsequent CEAs.

Table: **Surgical compliance, mortality, and morbidity**

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ACST-1 (2010, Lancet)

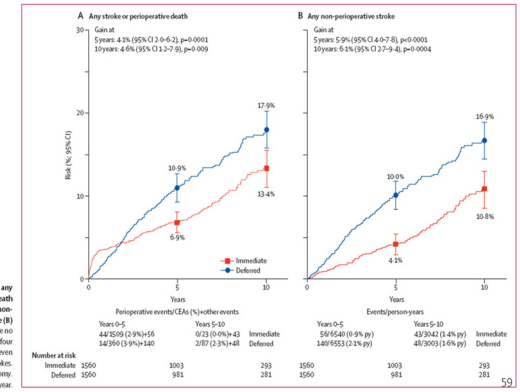

Figure 3: 10-year risk of any stroke or perioperative death (A) and any non-perioperative stroke (B)
After year 10 there were no perioperative strokes and four immediate versus seven deferred first strokes. CEA=carotid endarterectomy. py=per year.

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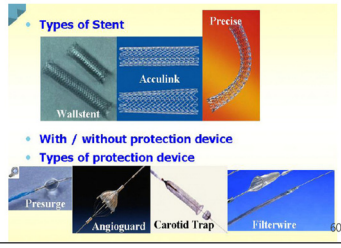
Debate on CEA & CAS method

- Various Results d/t CAS results
  - Learning curve (especially EVA-3S)
  - Method (type of stent, protection device)
  - Selection of case for CAS
    - Age, gender, etc
- CEA method
  - GA vs. LA
  - Patch
  - Shunt



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CEA outcome with or without neurologists involvement

Temporal Trends in the Risks of Stroke and Death due to Endarterectomy for Symptomatic Carotid Stenosis: An Updated Systematic Review

K. Rerkasem [a], P.M. Rothwell [b,*] Eur J Vasc Endovasc Surg (2009) 37, 504–511

Results: Of 494 studies, only 53 reported operative risks for patients with symptomatic stenosis separately. In keeping with the findings of our previous review, the pooled operative risk of stroke and death reported in studies published by surgeons alone (3.9%, 95% confidence interval (CI): 3.4–4.3) was significantly lower ($p < 0.001$) than that reported in studies that involved neurologists (5.6%, 95% CI: 5.1–6.2). The pooled ratio of operative stroke:operative death was 4.0 (range: 3.6–4.5) in studies involving neurologists or stroke physicians and 2.7 (range: 2.1–3.9) in studies involving only surgeons ($p = 0.002$). We found no evidence of a reduction in published risks of death or stroke and death due to CEA for symptomatic carotid stenosis between 1985 and 2008. Indeed, the 1.4% (range: 1.2–1.6%) pooled operative mortality in studies published during 2001–2008 was significantly higher than that reported in ECST and NASCET (1.0%, 95% CI: 0.9–1.1%). However, the average age of patients having CEA has continued to increase during this period.

Summary of intervention

	CEA vs. CAS
Short-term outcome in Sx patients	CEA >> CAS
Long-term outcome in Sx patients	CEA ≥ CAS
Asymptomatic stroke [DWI(+)] in Sx patients	CEA >> CAS
Mortality	CEA ≥ CAS
Outcome in aSx & Sx patients	CEA ≥ CAS
Outcome in aSx & Sx High risk patients	CEA ≤ CAS
MI	CEA << CAS
Anesthesia	CEA ≤ CAS
Contrast allergy	CEA >> CAS
Cranial neuropathy	CEA << CAS
Op scar vs. femoral pucture	CEA << CAS
Inaccessible site	CEA << CAS
Hospitalization period	CEA << CAS
Cost (J Vasc Surg 2006;44:270-6)	CEA(12,100$) >> CAS(17,400$)
Restenosis	CEA ≥ CAS

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overview

- Mechanism of carotid atherosclerosis
- Diagnosis of carotid atherosclerosis
- Primary and secondary prevention of stroke d/t carotid atherosclerosis
  - Guidelines
  - Large clinical trials about CEA vs. stent
    - Short-term outcome
    - Long-term outcome
    - RCTs in aSx patients
  - Medical Tx

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Medical treatments

- Guidelines
  - ESO 2008
    - ASA/clopidogrel combination immediately before and for at least 1 month (Class IV, GCP)
    - Based on the observation of coronary trials
      - Combination ASA/clopidogrel up to 12 months; CREDO
  - ASA/AHA 2014
    - Patients with aSx carotid stenosis should be prescribed daily aspirin and a statin (Class I; LOE C)
    - In patients who are to undergo CEA, aspirin is recommended perioperatively and postoperatively unless contraindicated (Class I; LOE C)
    - CAS and CEA should be performed by operators with established periop stroke and mortality rates <6% for Sx patients, similar to that observed in trials comparing CEA to medical Tx and more recent observational studies (Class I, LOE B)

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Medical treatments

- Medical arm of large clinical trials
  - NEJM 1991, 1998
    - 70-99% stenosis: 26% vascular events at 2 years (vs. 9% in CEA group)
    - 50-69% stenosis: 22.2% vascular events at 5 years (vs. 15.7% in CEA group)
- Aspirin plus clopidogrel
  - Suggested by many **cardiac trials** (CURE, CREDO)
  - No additive effects documented by **MATCH** and **CHARISMA** trials
  - Subgroup analysis of CHARISMA (Bhatt et al., Circulation 2007)
    - 9,478 patients with **documented prior MI, ischemic stroke, or symptomatic PAD**
    - Composite endpoints: 7.3% versus 8.8% (HR 0.83, p = 0.01).

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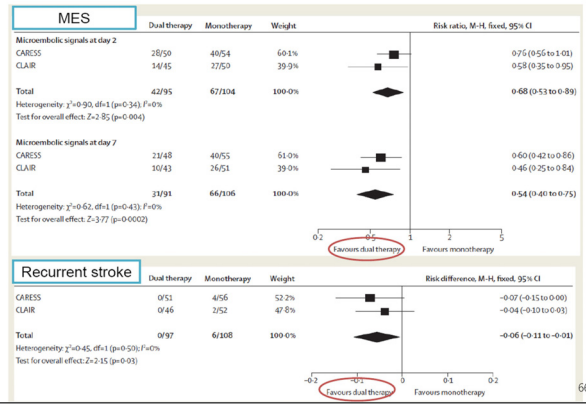
CARESS (2005, Circulation) & CLAIR (2010, Lancet Neurol)



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Atherosclerotic regression by long-term medical Tx?

- By surrogate marker (carotid IMT)
  - Statins
    - Lovastatin, Pravastatin, Fluvastatin, Simvastatin, Atorvastatin, Rosuvastatin, Pitavastatin
  - Niacin (NEJM, 2009)
  - PPAR-γ agonists (ATVB, 2004/ Circulation, 2005)
    - (Pioglitazone, Rosiglitazone)
  - Antihypertensives (Circulation, 2001)
    - ACE inhibitors, ARB, CCB, Beta blockers
  - PDE inhibitors
    - Cilostazol (Circulation, 2010)

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Impact of advances in medical Tx

- Advances in medical Tx for stroke prevention
  - Potentially erase or reduce the benefit of invasive treatments (CEA or CAS)
  - Paucity of data on stroke rates in patients with carotid stenosis who receive an aggressive Tx regimen with statins, newer antiplatelet agents, and targeted blood pressure lowering
  - New trial of "Best medical Tx" vs. "CEA or CAS" is pending

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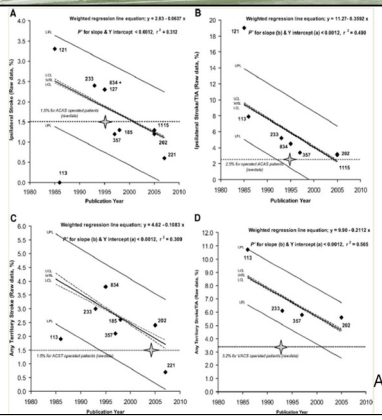
Annual Stroke rate of non-CEA arm in aSx carotid stenosis



- Trends over time
  - Smaller events rate
  - More effective medical Tx
- CEA/CAS ➔ Medical Tx

Abbott AL, et al(Stroke, 2009)

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Take home message

- Mechanism of carotid syndrome
  - In situ thrombosis vs. borderzone infarction vs. a-to-a embolization
  - Atherosclerosis ← chronic inflammation
    - Endothelial dysfunction & vascular smooth muscle cell apoptosis
    - Plaque rupture & thrombus formation
- w/u of carotid stenosis
  - Various tools for specific patients' condition
  - Accurate: TFCA, noninvasive: carotid USG

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Take home message

- Medical Tx
  - Dual antiplatelet in acute stages
  - Statin, bp control, antiplatelets, PPAR-γ agonist
- Surgical Tx
  - Symptomatic carotid stenosis
    - Perioperative: CEA>CAS
    - Long-term: CEA≥CAS, but individual consideration
  - 60-99% asymptomatic carotid stenosis
    - Long-term : CEA ≥ stent or medical Tx in selected patients
    - Experienced surgeon (periop risk<3%)

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