Neurosciences Update

Cerebral revascularization for atherosclerotic disease. What is left after COSS?

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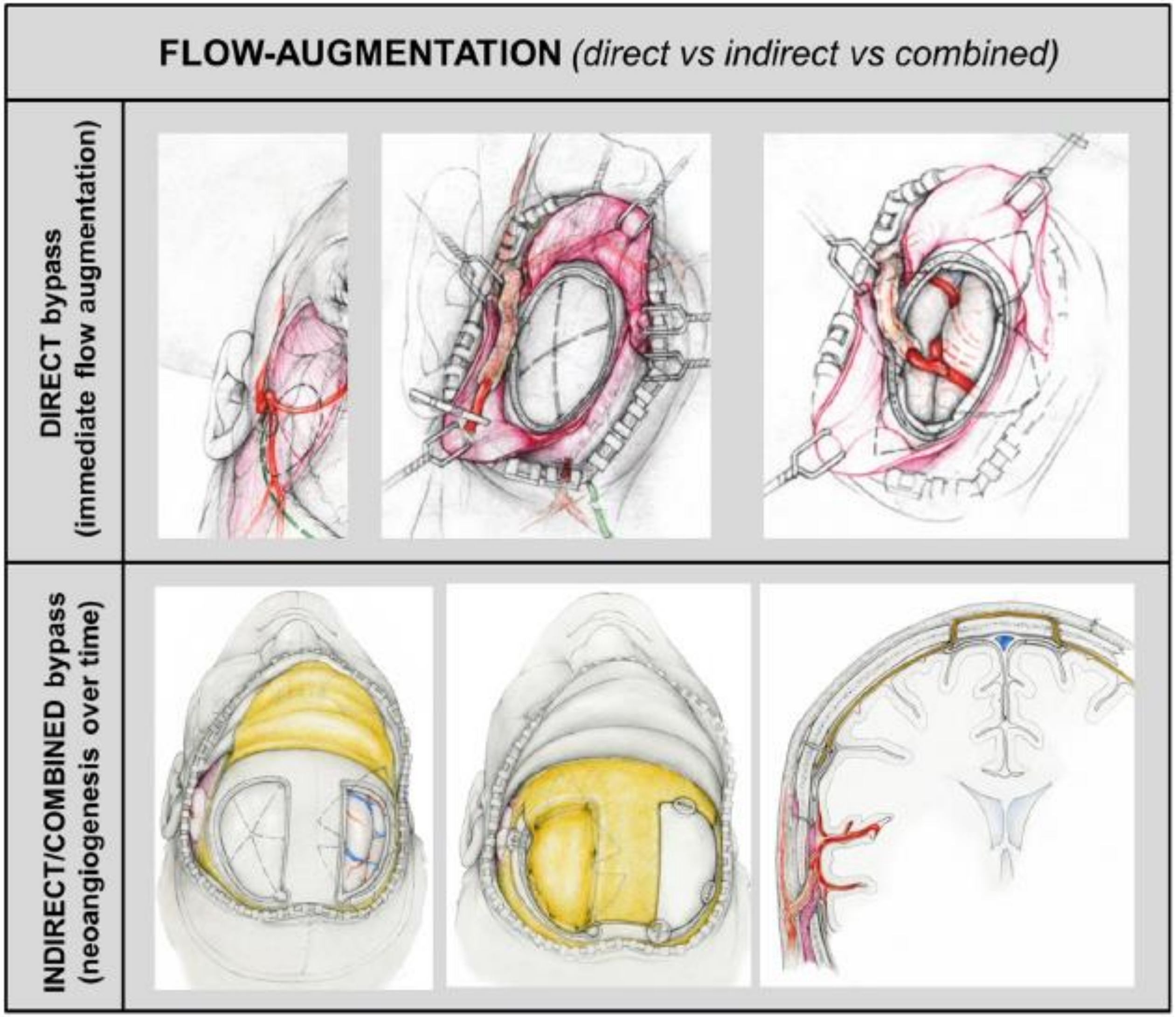
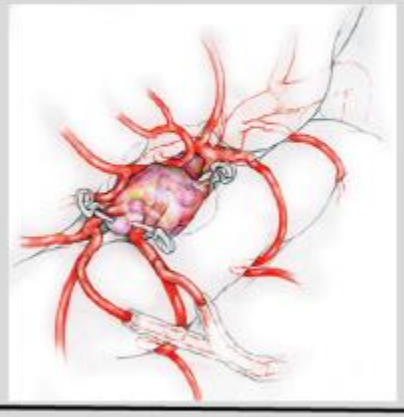
Atherosclerotic ICA occlusion

- 10% transient ischemic attacks (TIAs)
- 15-25% strokes
- 2 year risk of subsequent ischemic stroke while on medical therapy is 10-15%
- 1985: EC-IC bypass trial (1377 patients)

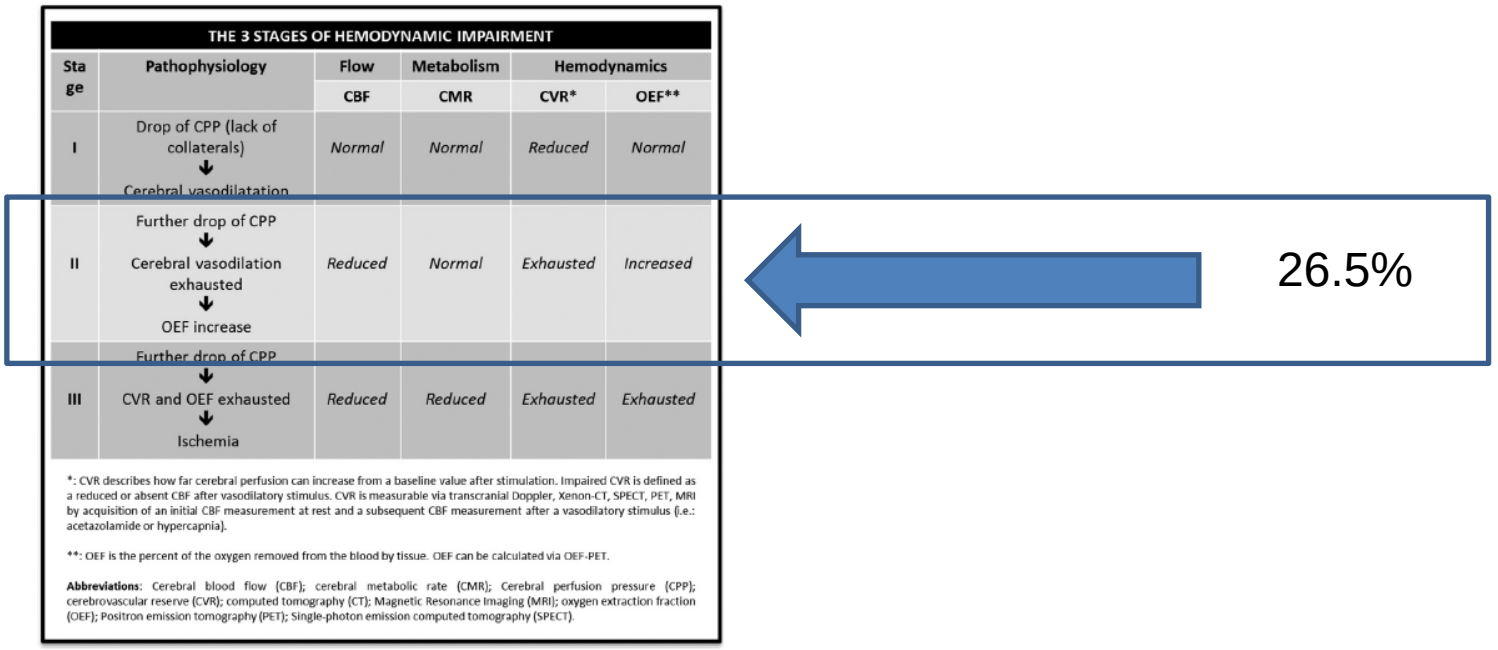

FLOW-AUGMENTATION (direct vs indirect vs combined)
DIRECT bypass
(immediate flow augmentation)
INDIRECT/COMBINED bypass
(neoangiogenesis over time)

FLOW-PRESERVATION

EC-IC bypass			IC-IC bypass	
No graft interposition		Graft interposition (long graft)	Graft interposition (short graft)	No graft interposition ("in situ" bypass)
				
Single-bypass	Double-bypass	Single-bypass (Occlusive VS Non-Occlusive-ELANA)		

STLCOS

- St Louis Carotid Occlusion Study
- OEF-PET



THE 3 STAGES OF HEMODYNAMIC IMPAIRMENT

Stage	Pathophysiology	Flow	Metabolism	Hemodynamics	
		CBF	CMR	CVR*	OEF**
I	Drop of CPP (lack of collaterals) ↓ Cerebral vasodilatation	*Normal*	*Normal*	*Reduced*	*Normal*
II	Further drop of CPP ↓ Cerebral vasodilation exhausted ↓ OEF increase	*Reduced*	*Normal*	*Exhausted*	*Increased*
III	Further drop of CPP ↓ CVR and OEF exhausted ↓ Ischemia	*Reduced*	*Reduced*	*Exhausted*	*Exhausted*

*: CVR describes how far cerebral perfusion can increase from a baseline value after stimulation. Impaired CVR is defined as a reduced or absent CBF after vasodilatory stimulus. CVR is measurable via transcranial Doppler, Xenon-CT, SPECT, PET, MRI by acquisition of an initial CBF measurement at rest and a subsequent CBF measurement after a vasodilatory stimulus (i.e.: acetazolamide or hypercapnia).

**: OEF is the percent of the oxygen removed from the blood by tissue. OEF can be calculated via OEF-PET.

Abbreviations: Cerebral blood flow (CBF); cerebral metabolic rate (CMR); Cerebral perfusion pressure (CPP); cerebrovascular reserve (CVR); computed tomography (CT); Magnetic Resonance Imaging (MRI); oxygen extraction fraction (OEF); Positron emission tomography (PET); Single-photon emission computed tomography (SPECT).

Extracranial-Intracranial Bypass Surgery for Stroke Prevention in Hemodynamic Cerebral Ischemia

The Carotid Occlusion Surgery Study Randomized Trial

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Context Patients with symptomatic atherosclerotic internal carotid artery occlusion (AICAO) and hemodynamic cerebral ischemia are at high risk for subsequent stroke when treated medically.

Objective To test the hypothesis that extracranial-intracranial (EC-IC) bypass surgery, added to best medical therapy, reduces subsequent ipsilateral ischemic stroke in patients with recently symptomatic AICAO and hemodynamic cerebral ischemia.

Design Parallel-group, randomized, open-label, blinded-adjudication clinical treatment trial conducted from 2002 to 2010.

Setting Forty-nine clinical centers and 18 positron emission tomography (PET) centers in the United States and Canada. The majority were academic medical centers.

Participants Patients with arteriographically confirmed AICAO causing hemispheric symptoms within 120 days and hemodynamic cerebral ischemia identified by ipsilateral increased oxygen extraction fraction measured by PET. Of 195 patients who were randomized, 97 were randomized to receive surgery and 98 to no surgery. Follow-up for the primary end point until occurrence, 2 years, or termination of trial was 99% complete. No participant withdrew because of adverse events.

Interventions Anastomosis of superficial temporal artery branch to a middle cerebral artery cortical branch for the surgical group. Antithrombotic therapy and risk factor intervention were recommended for all participants.

Main Outcome Measure For all participants who were assigned to surgery and received surgery, the combination of (1) all stroke and death from surgery through 30 days after surgery and (2) ipsilateral ischemic stroke within 2 years of randomization. For the nonsurgical group and participants assigned to surgery who did not receive surgery, the combination of (1) all stroke and death from randomization to randomization plus 30 days and (2) ipsilateral ischemic stroke within 2 years of randomization.

Results The trial was terminated early for futility. Two-year rates for the primary end point were 21.0% (95% CI, 12.8% to 29.2%; 20 events) for the surgical group and 22.7% (95% CI, 13.9% to 31.6%; 20 events) for the nonsurgical group ($P=.78$, Z test), a difference of 1.7% (95% CI, −10.4% to 13.8%). Thirty-day rates for ipsilateral ischemic stroke were 14.4% (14/97) in the surgical group and 2.0% (2/98) in the nonsurgical group, a difference of 12.4% (95% CI, 4.9% to 19.9%).

Conclusion Among participants with recently symptomatic AICAO and hemodynamic cerebral ischemia, EC-IC bypass surgery plus medical therapy compared with medical therapy alone did not reduce the risk of recurrent ipsilateral ischemic stroke at 2 years.

Trial Registration clinicaltrials.gov Identifier: NCT00029146

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ATHEROSCLEROTIC INTERNAL carotid artery occlusion (AICAO) causes approximately 10% of transient ischemic attacks (TIAs) and 15% to 25% of ischemic strokes in the carotid territory.[1,2] The 2-year risk of subsequent ipsilateral ischemic stroke while a patient receives medical therapy is 10% to 15%.[1-3] Extracranial-intracranial (EC-IC) arterial bypass surgery was developed to prevent subsequent stroke by improving hemodynamics distal to the occluded artery.[4] In 1985, a randomized trial demonstrated no benefit of this surgery in 808 patients with symptomatic carotid artery occlusion.[5] This trial was criticized for failing to identify the subgroup of patients with hemodynamic cerebral ischemia due to poor collateral circulation for whom surgical revascularization might be of greatest benefit.[6-8]

Subsequent advances in neuroimaging have made it possible to identify those with hemodynamic cerebral ischemia who are at high risk for subsequent stroke when treated medically.[3,9-11] We conducted the Carotid Occlusion Surgery Study (COSS) to determine whether EC-IC bypass surgery, added to best medical therapy, reduces subsequent ipsilateral ischemic stroke at 2 years in patients with recently symptomatic AICAO and hemo-

For editorial comment see p 2026.

Author Affiliations and a list of the Carotid Occlusion Surgery Study (COSS) Investigators appear at the end of this article.

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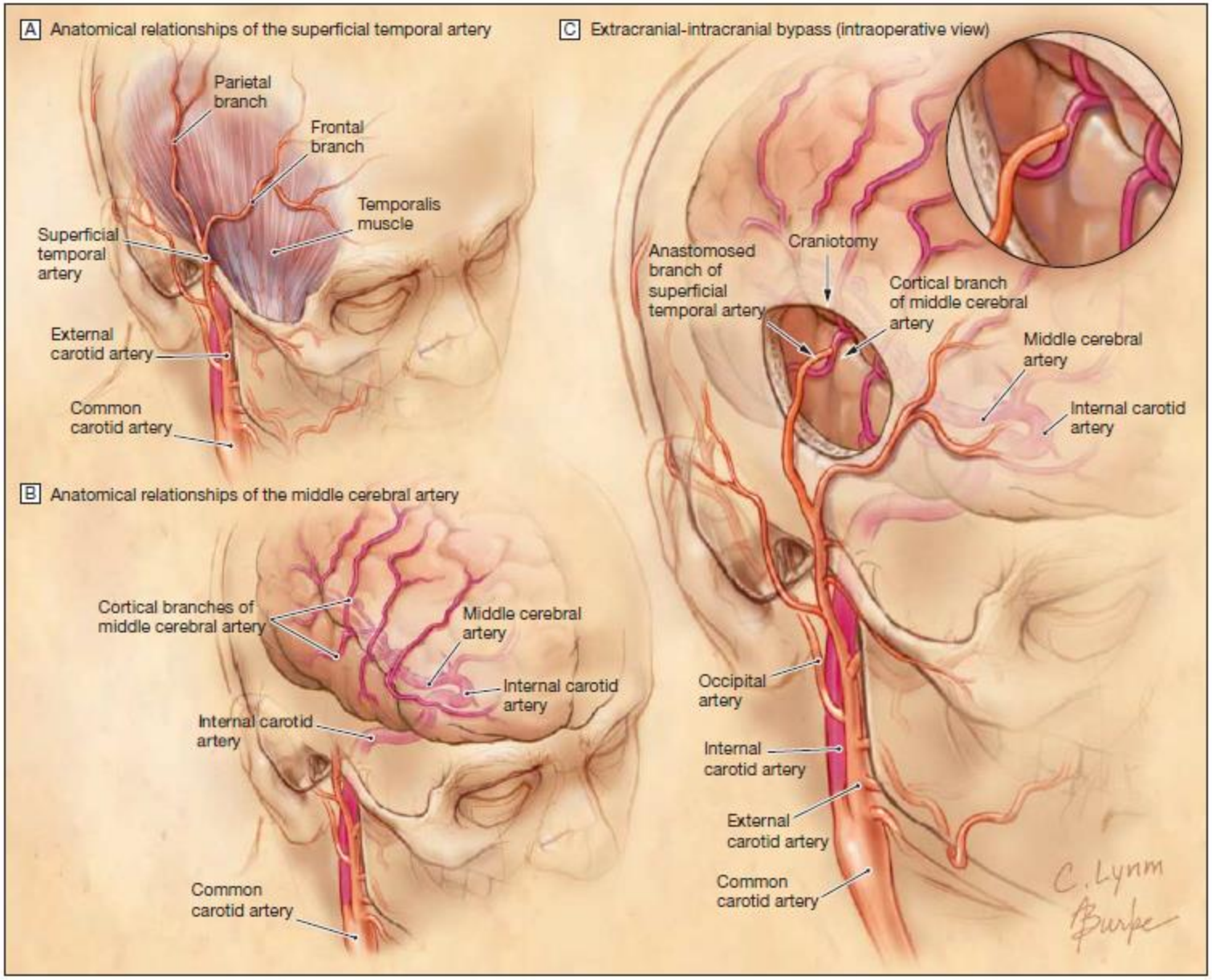
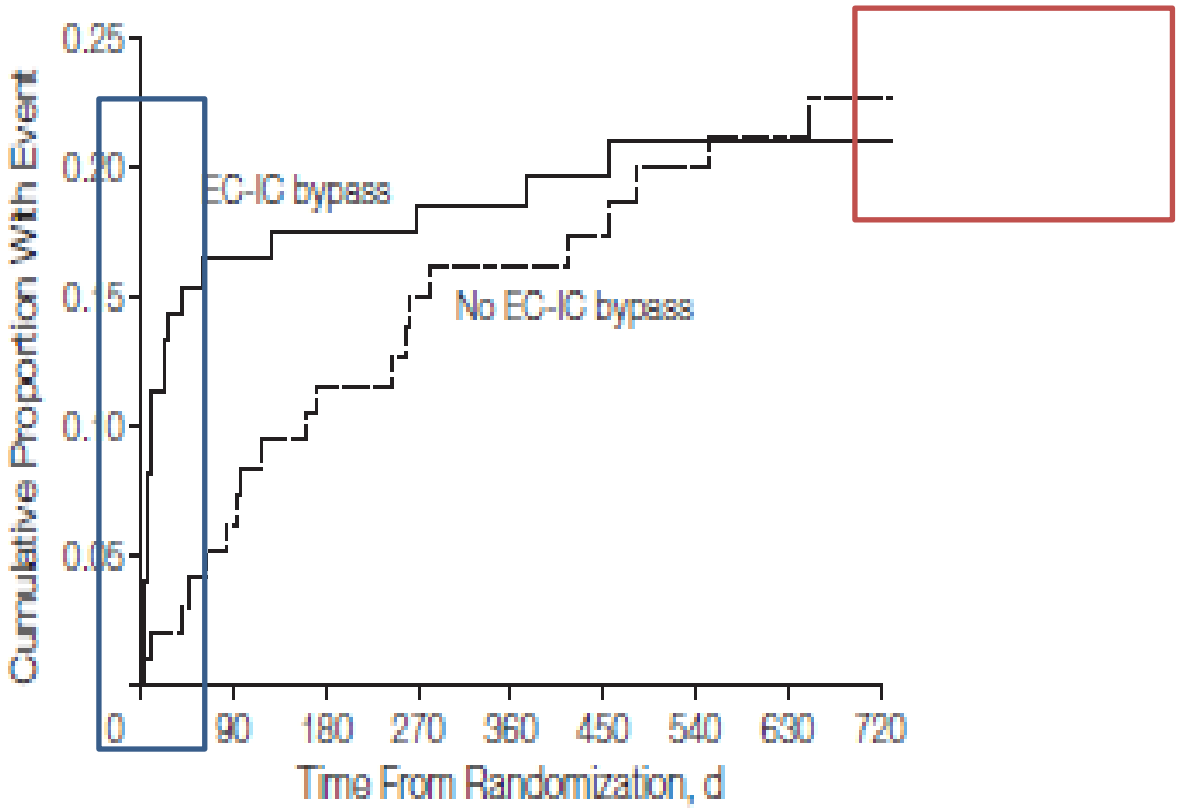
COSS

- 8 year randomized blinded adjudicated trial
- 195 patients: STA-MCA bypass vs. medical treatment (antiplatelet, BP 135/80, LDL <100, triglycerides <150, HbA1c <7%)
- Ipsilateral stroke within the next two years was the main outcome measure
- PET was used to identify hemodynamic cerebral ischemia
- Angiography


A Anatomical relationships of the superficial temporal artery
Parietal branch
Frontal branch
Temporalis muscle
Superficial temporal artery
External carotid artery
Common carotid artery
B Anatomical relationships of the middle cerebral artery
Cortical branches of middle cerebral artery
Middle cerebral artery
Internal carotid artery
Internal carotid artery
Common carotid artery
C Extracranial-intracranial bypass (intraoperative view)
Anastomosed branch of superficial temporal artery
Craniotomy
Cortical branch of middle cerebral artery
Middle cerebral artery
Internal carotid artery
Occipital artery
Internal carotid artery
External carotid artery
Common carotid artery
C. Lynn Burpe

Surgical arm

- 96% graft patency rate at last follow up
- Improved OEF
- Perioperative stroke rate of 12%
- Post-perioperative stroke rate 3% per year



No. at risk

EC-IC bypass (surgical group)	97	80	79	77	69	67	65	65	53
No EC-IC bypass (nonsurgical group)	98	87	81	74	69	65	62	57	51

JET

- Japanese EC-IC bypass trial
- Similar design as COSS
- 206 patients between 1998-2002
- Reduction from 14% to 5% in major stroke and death in by-pass group
- …CMOSS randomized clinical trial on the way in China
- …ERSIAS on the way in the US

CONCLUSION

- Level I evidence against EC-IC bypass for recently symptomatic carotid artery occlusion

- **Reduce perioperative complications** (anesthesia, ICU, nursing)
- Subgroups:
  - **Chronic retinal ischemia with progressive visual loss**
  - **Ongoing hemodynamic symptoms (orthostatic symptoms or limb shaking TIAs) despite optimal medical treatment**
  - **Acutesmall stroke with evolving symptoms due to penumbra**