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The Treatment of Intracranial Stenosis

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Conflict of Interest Disclosure

Disclosure

Editorial Advisory Board, Medscape Neurology
Stroke Adjudication Committee, CREST 2 Trial
Medical Advisory Board, Coherex Medical
National Leader, Bristol-Meyers Squibb, PHRI
Consultant, St. Jude Medical/Abbott

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Stroke Facts

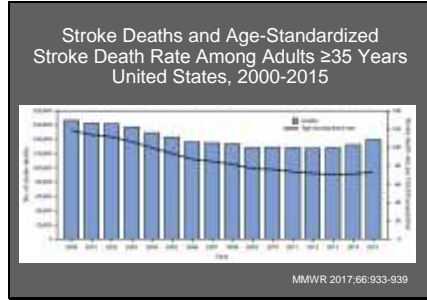
- Stroke has moved down to the fifth leading cause of death in the US
 - Was in third place until 2008

Leading Causes of Death in the US

- Heart disease
- Cancer
- Chronic lower respiratory diseases
- Accidents (unintentional injuries)
- Stroke**

CDC.gov

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Intracranial Stenosis

- May be the most common cause of stroke worldwide

Stroke 2008; 39: 2396-2399

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Outline: Intracranial Stenosis

- Evolution in management through clinical trials
 - Warfarin versus aspirin
 - Stenting
 - Risk factor management
 - Potential future directions
- Methods applied to the management of carotid stenosis

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Case
A 75 year old woman presents with 3 episodes of word-finding difficulty over a month and new right sided weakness.

She has been taking aspirin, 81 mg, daily.
Her blood pressure is 157/79 and her LDL (bad cholesterol) is 134 mg/dL (3.47 mmol/L).

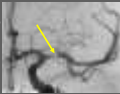
The carotid arteries and evaluation of the heart were normal.

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Case
75 year old woman with 2 episodes word finding difficulty
Has severe left middle cerebral artery stenosis

Management?

- a) Antiplatelets vs. anticoagulation?
- b) Should a stent be placed?
- b) Does aggressive treatment of risk factors make a difference?



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Warfarin Aspirin Symptomatic Intracranial Disease Trial (WASID) Trial: 2005

Included patients with TIA or stroke caused by intracranial stenosis of 50-99%

- Compared warfarin and aspirin in the prevention of ischemic stroke, brain hemorrhage and vascular death
- Did not specify how risk factors should be treated

N Engl J Med 2005;352:1305-1316

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WASID Trial Results 2005

- Warfarin provided no benefit over aspirin in preventing strokes and caused more major hemorrhages
- In those with stenosis of 70-99%, nearly a quarter had recurrent strokes at two years

Risk of stroke at 2 years in 2005

Category	Percentage
Risk of stroke at 2 years in 2005	24%

N Engl J Med 2005;352:1305-1316; Stroke 2015;46:2562-2567

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Risk Factor Control in WASID

Blood pressure

- 53% had blood pressures <140 mmHg at 2 years

Lipids

- Only 10% achieved an LDL target of <70 mg/dL (1.81 mmol/L)

Neurology 2007;69:2063-2068

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Stents Explored for the Treatment of Intracranial Stenosis

- High rates of successful stent placement
- Risk of stroke associated with the procedure
- Unclear how stents would fare against medical treatment alone

Stroke 2004;35:1388-1392; Neurology 2008;70:1518-1524

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**Trial To Explore
Stenting Versus Medical Therapy**


SAMMPRIS: Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis

- Patients with stroke or TIA within 30 days attributed to high grade stenosis of a major intracranial artery
- Study compared stenting plus aggressive medical management to aggressive medical management alone
- Outcomes were stroke or death within 30 days, or strokes in the territory of the qualifying artery beyond 30 days

NEJM 2011;365:993-1003; Lancet 2014;383:333-41

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Metro Areas with SAMMPRIS Sites




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SAMMPRIS Randomized Trial

Enrollment halted for high 30-day stroke/death rate in stenting group after 451 patients were in the trial

30-Day Stroke and Death Rate



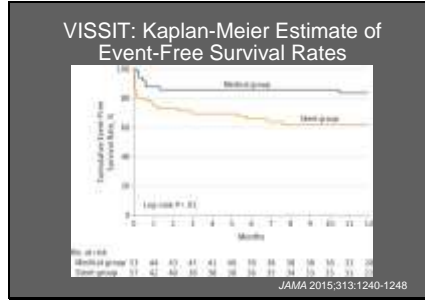
Group	30-Day Stroke and Death Rate
Stenting	14.70%
Risk factor control alone	5.80%

p=0.002

- Patients continued to be followed

NEJM 2011;365:993-1003

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Choice of Stents?

Chinese Registry, n=300

- Patients with symptomatic, within 90 days, intracranial stenosis ($\geq 70\%$) combined with poor collaterals
 - Excluded if acute infarct within 3 weeks
- Treated either with balloon-mounted stent or with balloon predilation plus self-expanding stent
- The 30-day rate of stroke, transient ischemic attack, and death was 4.3%

Stroke 2015;46:2822-29

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More Careful Patient Selection?

WEAVE Registry

- FDA mandated registry to evaluate stroke and death rate within 72 hours in patients treated with the Wingspan Stent System
- Primary analysis group (on-label)
 - 70-99% stenosis
 - Refractory to medical management (any medication)
 - 7 days post stroke
 - Recurrent (2 or more) strokes
 - Age 22-80, mRS 3 or less

International Stroke Conference Los Angeles, January 2018

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More Careful Patient Selection?

WEAVE Registry Results

- Study stopped early after interim analysis and 152 on-label patients treated
- Target event rate of 4% for 150 on-label patients met

	On-label, n=152	Off-label, n=46
Stroke or death within 72 hours	2.6% (4/152)	23% (11/46)

International Stroke Conference Los Angeles, January 2018

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More Careful Patient Selection?

Off-label subjects, WEAVE and SAMMPRIS

Off Label Reason (n=46)	WEAVE %	SAMMPRIS %
>80 years old	4%	0%
Not refractory to meds	22%	37% (not on antithrombotic)
<2 strokes	26%	74%
mRS>3	35%	0%
≤7 days post stroke	50%	50% within 9 days (range 1-34 days)
Extracranial disease	4%	0%
Intracranial dissection	4%	0%

International Stroke Conference L.A., January 2018; NEJM 2011;365:993-1003

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More Careful Patient Selection?

Early stenting – is it risky?

- Theoretical risk of reperfusion hemorrhage and peri-procedural stroke due to “hot plaque”
- However, time from the qualifying event to stenting did not differ in SAMMPRIS in those with and without ischemic or hemorrhagic strokes within 30 days of the procedure (stented at median of 9 days)

International Stroke Conference L.A., January 2018; Stroke 2012;43:2682-8, supplemental material

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Impact of Operator Experience?

Experienced interventionalists in WEAVE

- Only 24 centers versus 50 in SAMMPRIS
- Mean number of Wingspan cases prior to enrolling first patient was 37 stents versus 10 for SAMMPRIS
- However, interventionalists credentialed with less Wingspan experience in SAMMPRIS did not have higher rates of peri-procedural strokes (higher enrolling sites did have fewer hemorrhagic strokes)

International Stroke Conference Los Angeles, January 2018;
J Neurointerv Surg 2013;5:528-33.

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Angioplasty Alone

Phase I study of submaximal angioplasty

- Single center, 24 patients
- Balloon undersized to approximately 50-70% of the non-diseased vessel diameter
- No strokes within 30 days and 5.6% (1 patient) at 1 year

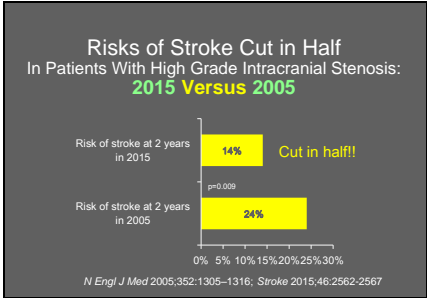
J Neurosurg 2016;064-71

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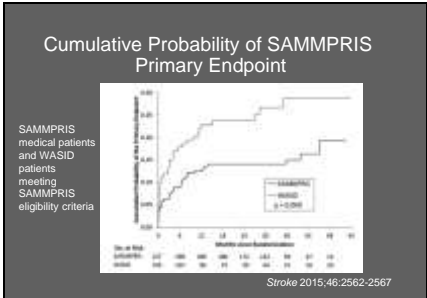
What Really Contributed to the SAMMPRIS Results?

- Risks in the stenting group were higher than expected
- Risks in those that received medical management alone were much lower than expected!
 - The rigorous medical treatment and risk factor control likely explain this

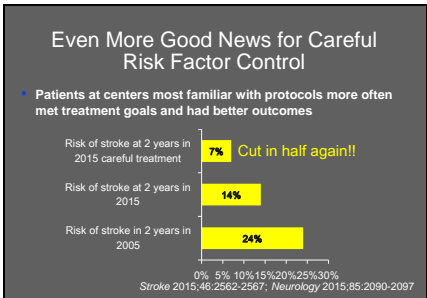
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Implementing Aggressive Medical Management

Antiplatelet agents

- Aspirin for entire follow-up, clopidogrel for 90 days


Aggressive risk factor management

- Systolic blood pressure <140 mm Hg
- Low density lipoprotein (LDL) <70 mg/dl (1.81 mmol/L)
- Diabetes control, Hemoglobin A1C <7.0%
- Lifestyle modification
 - Exercise, smoking cessation, weight management

Lancet 2014;383:333-41; Stroke 2014;45:2160-2236

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High Blood Pressure Treatment Algorithm



Circ Cardiovasc Qual Outcomes 2012; 5: e51-e60.

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Clopidogrel and Aspirin for Intracranial Stenosis

Thirty-day findings suggest antiplatelet role

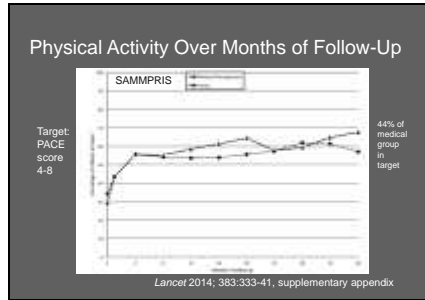
- The 30-day stroke or death rate in the medical group of SAMMPRIS was 5.8% versus 10.7% in similar patients in WASID
- Rapidity of reduction faster than what would be expected for risk factor reduction

Other support for dual antiplatelet use

- Reduction in microemboli seen with transcranial Doppler compared to aspirin alone in intracranial and carotid stenosis

NEJM 2011;365:993-1003; Lancet Neurol 2010;9:489-497

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- Implementing Aggressive Medical Management
- **Antiplatelet agents**
 - Aspirin for entire follow-up, clopidogrel for 90 days
 - **Aggressive risk factor management**
 - Systolic blood pressure <140 mm Hg
 - Low density lipoprotein (LDL) <70 mg/dl (1.81 mmol/L)
 - Diabetes control, Hemoglobin A1C <7.0%
 - Lifestyle modification
 - Exercise, smoking cessation, weight management
- Lancet 2014;383:333-41; Stroke 2014;45:2160-2236

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Back to Our Case

A 75 year old woman with 3 episodes of word-finding difficulty and right sided weakness with severe left middle cerebral artery stenosis.

Management?

- a) Antiplatelets vs. anticoagulation? **Antiplatelets**
- b) Should a stent be placed? **Not currently**
- b) Does aggressive treatment of risk factors make a difference? **YES!**

She was treated with dual antiplatelet therapy for 3 months and then with aspirin and risk factor control

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Potential Future Directions

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Trials of Transient Limb Ischemia 

- **Bilateral arm ischemic preconditioning (BAIPC)**
 - 5 brief cycles followed by reperfusion; twice daily over 300 consecutive days
 - BAIPC group (n=38) had lower recurrent stroke risk and more reperfusion than controls (n=30) (p<0.01)
- Ongoing trial in China of 3000 patients with symptomatic intracranial stenosis of 50-99%
 - Bilateral treatment (200 mmHg) once daily for 12 mos
 - Primary outcome: Time from randomization to first occurrence of stroke

Neurology 2012;79:1853-61; Int J Stroke 2016;11:831-8; ClinicalTrials.gov

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Genetic Contributions

Ring finger protein 213 (RNF213) gene variant

- Susceptibility locus for moyamoya disease in East Asian populations
- RNF213 has been associated with intracranial stenosis in studies of Japanese and Han Chinese patients without signs of moyamoya disease

Stroke 2012;43:3371-74; Brain Circulation 2018;4:33-39

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Applications to the Carotid Artery

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Asymptomatic Carotid Stenosis:
Risks Low on Current Medical Therapy

Oxford Vascular Study of ≥50% asymptomatic carotid stenosis

- 101 patients recruited consecutively from 2002-2009
- Intensive medical treatment
 - Aspirin +/- clopidogrel x 30 days then Aggrenox, BP <130/80, statin
- Mean follow-up 3 years
- Average annual event rate **0.34%** for any ipsilateral ischemic stroke (1.78% for ipsilateral TIA)

Stroke 2010;41:e11-e17

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Asymptomatic Carotid Stenosis:
Carotid Occlusion Risk Has Decreased

Detection of new carotid artery occlusion during annual monitoring with carotid ultrasound

- In the database, 316 asymptomatic patients developed occlusions from 1995-2012
 - Most (80.4%) of new occlusions occurred before 2002
 - Only 4 patients had ipsilateral strokes, one at time of occlusion (1.2%)
- Risks of progression of stenosis to occlusion below those of carotid endarterectomy or stenting
 - Have decreased markedly with more intensive medical therapy

JAMA Neurol 2015;72:1261-7

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SAMMPRIS Approach Relevant for Asymptomatic Carotid Stenosis?


CREST 2 trial enrolling (NINDS funded):

- Asymptomatic carotid artery stenosis
- Revascularization plus intensive medical management versus medical management alone



ClinicalTrials.gov

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Thank you!
