TIA/Mild Stroke Management

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Epidemiology - Canada

- Estimate
  - 70,000 adults have ischemic stroke annually
  - 300,000 Stroke survivors
    - Great variations in morbidity
- Additional 24,000 have TIA
- Of patients with TIA and mild stroke a significant percentage go onto have a stroke with functional disability.

- Old definition
  - TIA - Sx for < 24 hours
  - Stroke - Sx for > 24 hours
- MR imaging
  - Sx can last for < 1 hour with definite infarct
    - 30% sx < 24 hrs have infarct
  - Sx can last for > 24 hrs with no residual infarct
  - Can have no Sx and have infarct
- Pathophysiological mechanism the same
- No real difference – Treat the same
- Recommendations apply to TIA/minor stroke equally

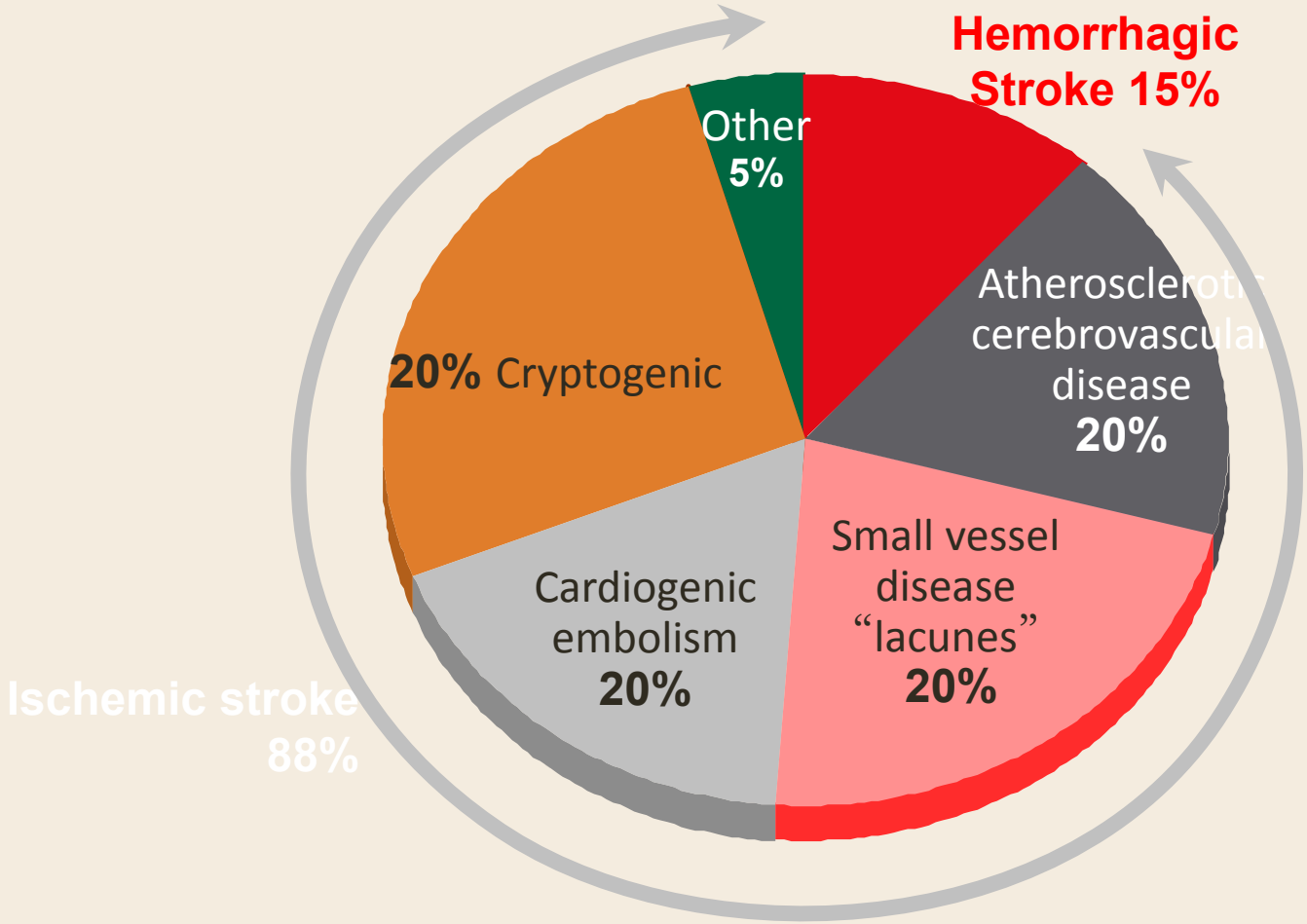
What is the Difference Between a Mild Stroke and a TIA?

- Transient Ischemic Attack
  - Traditional - Focal deficit clearing clinically within 24 hours
  - BUT – MRI imaging shows
    - A third of patients with symptoms clearing < 24 hrs have infarction
    - Many patients with symptoms clearing > 24 hour do not have infarction
- Current Definition
  - TIA: Focal neurological deficit without imaging evidence of infarction
- Stroke:
  - Focal neurological deficit with evidence of infarction (MRI, clinical, pathological)
- Distinction is artificial - They share pathophysiological mechanisms and prognosis

Ischemic Stroke - Subtypes

1. Large vessel atherothrombotic (extracranial or intracranial)
2. Cardioembolic
3. Small vessel disease
4. Other known causes (dissection, patent foramen, vasculitis, hypercoagulable state, ….)
5. Cryptogenic
6. Silent Infarction

Stroke Types & Incidence

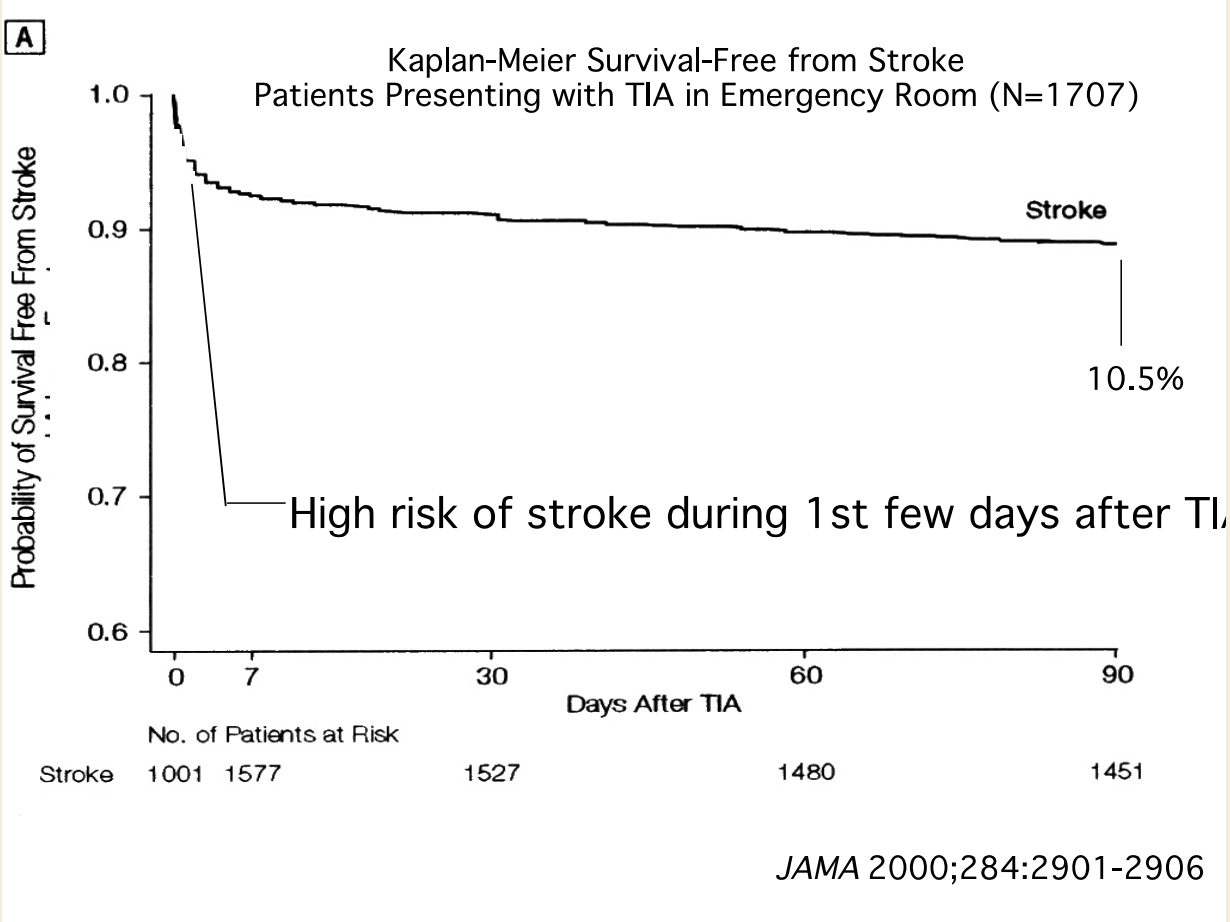


Albers GW, et al. Chest 2004; 126 (3 Suppl): 438S–512S.
Thom T, et al. American Heart Association. Circulation 2006; 113: e85–e151.

Stroke Mimics

- Migraine aura
- Epilepsy – focal seizures with postictal weakness
- Preexisting conditions causing weakness or deficit + acute systemic illness
- Hypoglycemia
- Tumour
- Subdural
- Behavioural

Stroke Risk Following TIA Seen in ER in 2000

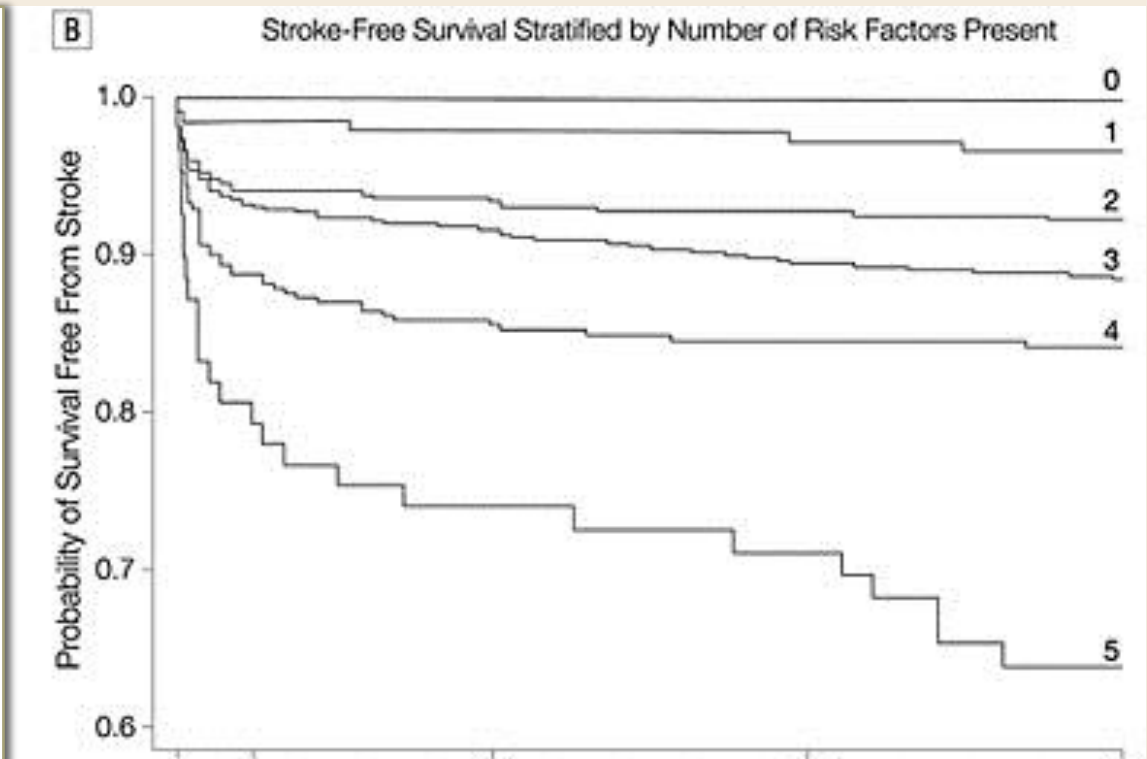


JAMA 2000;284:2901-2906

Plot of Survival Free State for 90 Days Following ER Visit for TIA – Risk Factors

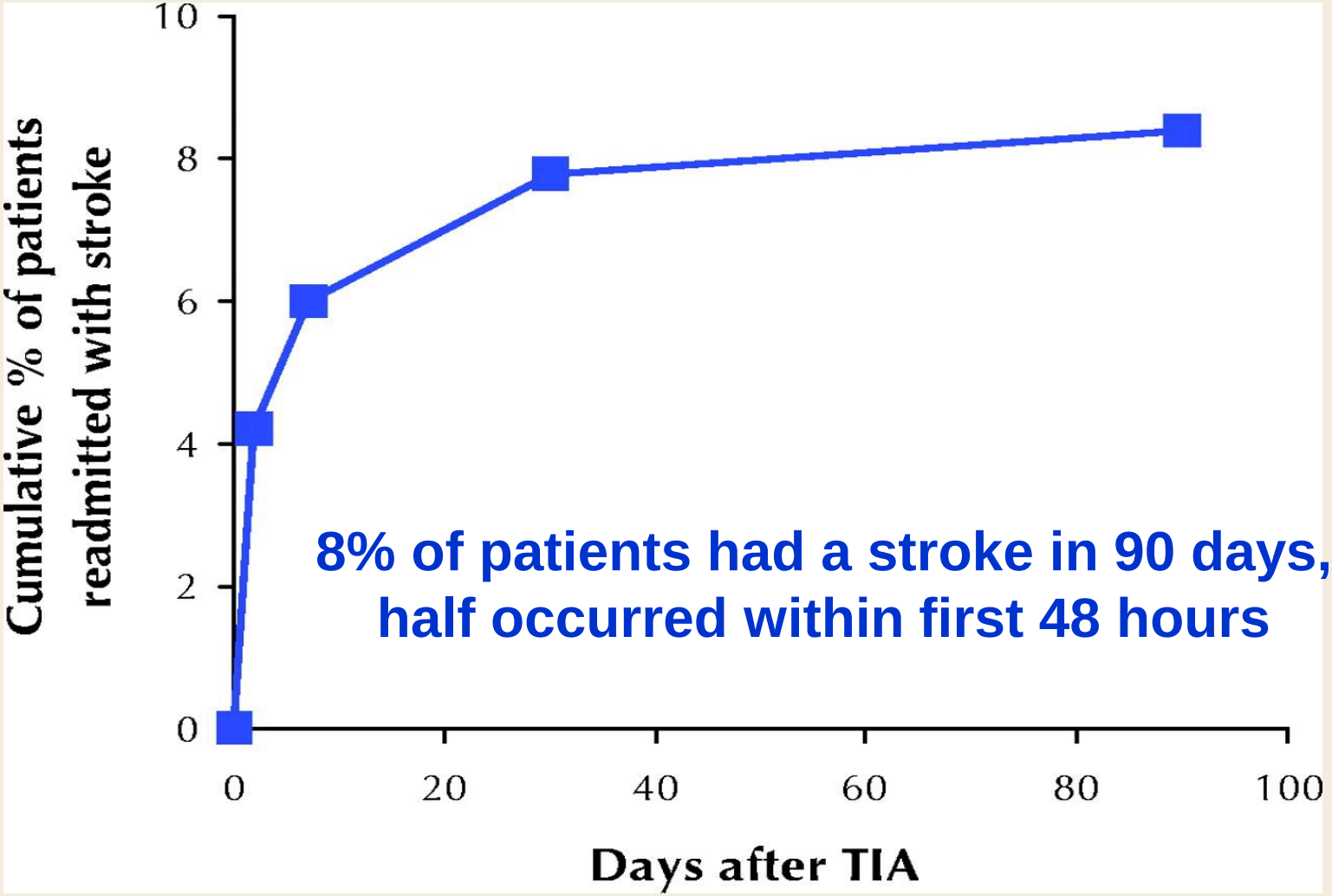
Risk factors

1. Age > 60
2. Diabetes
3. Sx > 10 minutes
4. Weakness
5. Speech



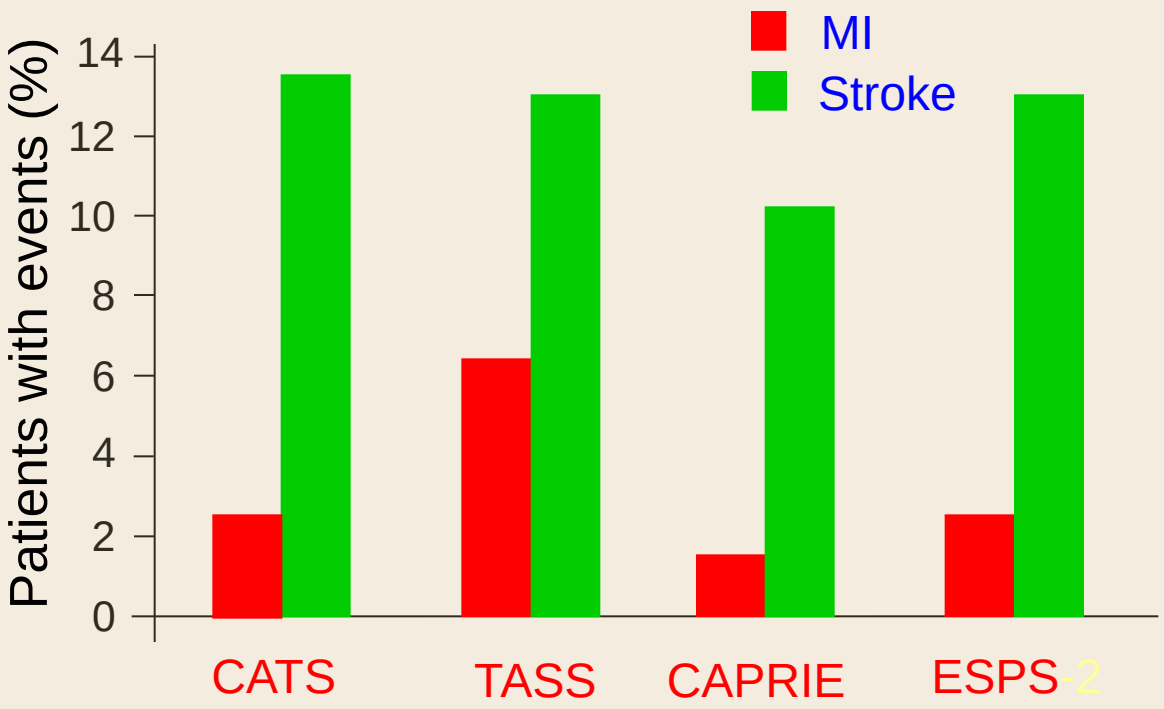
No. of Risk Factors	No. of Patients at Risk				
0	1	20	20	20	20
1	53	177	171	167	166
2	282	479	474	466	459
3	363	541	525	506	494
4	245	299	283	270	268
5	57	61	54	51	44

Ontario Demonstration Sites –
Time to Stroke after TIA



Gladstone D CMAJ 2004

Risk of Vascular Events After Stroke or TIA



CATS = Canadian American Ticlopidine Study
TASS = Ticlopidine Aspirin Stroke Study
CAPRIE = Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
ESPS-2 = European Stroke Prevention Study 2

Albers GW *Neurology* 2000;**54**:1022-1028

Hypertension

- THE MOST IMPORTANT RISK FACTOR FOR ISCHEMIC STROKE
- THE MOST IMPORTANT INTERVENTION
- Present in 70% of ischemic stroke
- Use conventional definition 140/90
- However:
  - Population studies assign increasing risk of primary stroke (and presumably recurrent stroke) beginning at SBP 115-120

Blood Pressure Management Following TIA/Minor Stroke

- First 24/48 hours – no intervention
  - Unless BP > 220 mm Hg - intervention (e.g. with IV labetalol)
    - Target BP 185 systolic
  - No benefit in treating elevated BP in setting of acute stroke
  - Aggressive hypotensive treatment can be harmful (perfusion)
  - Follow

- After 24 -48 hours
  - Initiate or reintroduce antihypertensive therapy if established BP>140 and diastolic >90 mm Hg

- How low – Recommended Target AHA 140/90
  - For lacunar infarct – target SBP 130 vs 150
  - DM no benefit lowering BP <120 vs <140

- No evidence of a J curve

- Choice of drugs - ? Diuretic + ACE

PROGRESS Trial – Perindopril +/- Indipamide following Stroke

Initial SBP	Decrease in SBP mmHg	RRR Stroke
>160	11.1	39%
140-159	9.2	31%
120-139	7.6	14%
<119	7.4	0%

Dyslipidemia and Stroke

- Elevated LDL-C associated with increased risk of thrombotic stroke
- Statin use reduced ischemic stroke risk in cardiovascular trials
- BUT Low LDL-C => increased risk of ICH – (inconclusive)
- Aggressive statin use may stabilize stenosis & reduce intra-plaque hemorrhage - Unstable stenosis
- Some evidence of plaque regression with high dose

Dyslipidemia – SPARCL Trial

- Secondary Stroke Prevention
  - Following TIA/Mild stroke
  - Subjects LDL 2.6 -4.9
  - No cardiac disease
  - 80 mg atorvastatin – 4.9 yrs
- SPARCL Trial Results:
  - 23% reduction in TIA/ischemic stroke over 5 years
  - 33% Reduction in major cardiovascular events
  - No particular target for LDL
  - For those with >50% reduction in LDL levels 35% reduction in combined risk of fatal and non fatal stroke
  - Small (1%) increase in hemorrhagic stroke
  - All subgroups benefited

Dyslipidemia

- SPARCL –Additional considerations
  - Benefits probably underestimated
  - 22% placebo patients switched to a statin
  - Drug started up to 6 months post TIA/stroke
- Other lipid indices associated with risk of thrombotic stroke
  - Elevated Triglycerides
  - Low HDL
  - Elevated lipoprotein a
- No proof of benefit in non statin treatment
  - (e.g. Niacin + anti flushing agent, fibrates)
- Statin therapy is associated with plaque stabilization
- **RECOMMENDATIONS:**
  - Early statin use with intensive lipid lowering effects and LDL-C>2.5
  - If statin intolerant – alternative –eg fibrates
  - Lifestyle modification
  - Dietary recommendations

Large Artery Atherosclerosis

Symptomatic Extracranial Carotid Disease

- Carotid - Greater than 70% stenosis
  - Carotid endarterectomy + medical therapy for symptomatic patients with high grade stenosis
  - 30 day stroke in death rate 7.1% - (currently 6%)
  - Timing – within two weeks – benefit falls off after 2 weeks
- 50-69% stenosis –
  - Recurrent stroke
    - Medical – 22.2%
    - Surgical - 15.7%
- Gender issues - females higher risk of unfavorable outcome
- BUT medical therapy has improved and
- Surgical therapy has improved

- **Carotid Artery Stenting – Equivalent benefit**

Large Artery Atherosclerosis
Intracranial Stenosis

- High Risk of recurrent stroke esp if >70% stenosis
- Trials of
  - EC-IC bypass
  - Angioplasty and stenting
- Uniformly negative – Trials ongoing
- Aggressive Medical Therapy
  - ASA+Clopidogrel x 3 months
  - High intensity statin
  - BP <140 mmHg

Large Artery Atherosclerosis
Vertebrobasilar Disease

- Interventions-
  - Angioplasty/Stenting
  - Open Revascularization

- Limited trial data
  - Low periproceduaral complication rate
  - No proof of efficacy

- Recommendation of ASA:
  - Aggressive medical therapy
  - Interventions justified if medical therapy fails

Stroke and Disorders of Glucose Metabolism

- Diabetes
  - DM Type 1
  - Prediabetes
  - Diabetes type 2
  - Prediabetes defined by HbA1c
- Patients with Diabetes
  - increased risk of stroke (1.5-3.7X)
  - Increased stroke severity
  - Increased risk of recurrence (60%)
- Patients with Stroke
  - 28% have prediabetes
  - 25-45% have overt diabetes

Stroke and Disorders of Glucose Metabolism

- No direct studies of secondary stroke prevention by interventions for improved glucose metabolism
- More intensive glycemic control (ie, HbA1c <6% or <6.5%) may be modestly effective for preventing nonfatal CHD events, particularly MI, compared with current targets (ie, HbA1c <7%–8%)
- **RECOMMENDATION**
  - All patients TIA/minor stroke should be screened for DM
    - Fasting glucose
    - HbA1c
  - Follow ADA guidelines for glycemic control
  - Unclear the long term benefit of improved glycemic control for stroke prevention

Role of Diabetes Medications

- Pioglitazone therapy (PROactive)
  - 47% RR reduction in recurrent stroke (HR, 0.53; 95% CI, 0.34–0.85) and a 28% RR
  - 28% Reduction in stroke, MI, or vascular death

(Also metformin & linagliptin)

Wilcox Stroke 2007;38:865

Obstructive Sleep Apnea (OSA)

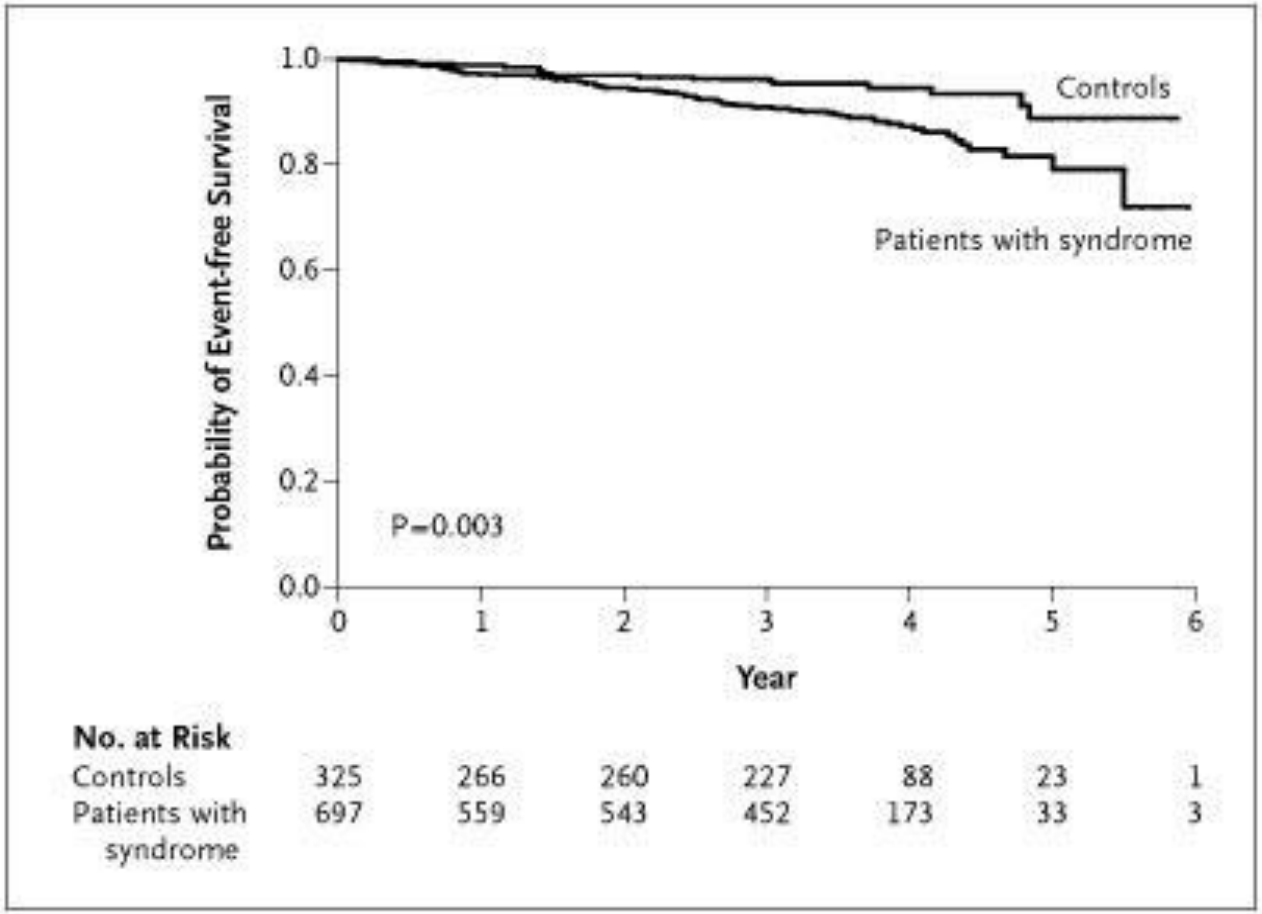
- AHI (Apnea Hypopnea Index)
  - Cessation in breathing > 10 sec
  - Associated with decrease in blood oxygen
- Normal <4/hr
- Moderate-severe SDB (AHI >20/hr) independent risk factor for first ever stroke in four years
- Severe SDB independent risk factor for fatal and non fatal cardiovascular events

Effects of OSA

- Diabetes
- Accelerates microangiopathic change
- Vascular reactivity impaired
- Associated with impaired cognition
- Associated with refractory hypertension
- Standard physical features absent
  - BMI inaccurate for predicting OSA
  - Thick neck
  - Sleepiness
  - Questionnaires
- Increased risk of:
  - Cerebral infarctions
  - Cardiovascular disease

Figure 1. Kaplan–Meier Estimates of the Probability of Event-free Survival among Patients with the Obstructive Sleep Apnea Syndrome and Controls

TIA , Stroke, and Death



Yaggi HK et al. N Engl J Med 2005;353:2034-2041.

OSA Severity Causing Stroke/Death

3 Year Follow-up

Severity	Stroke or Death	# Patients	Hazard Ratio
AHI <4	13	271	1.00
AHI 4-12	21	258	1.75
AHI 13-36	20	243	1.74
AHI >36	34	250	3.30

Trend Analysis: Relationship Between OSA Severity and Outcome – Stroke/Death

Yaggi et al NEJM 2005 353:2034

Sleep Apnea in Acute Stroke

- Apnea Hypoxia Index (AHI)
- Meta-analysis of 2343 Stroke pts
  - 72% sleep apnea (>4 events/hr)
  - 38% > 20 events/hr
  - 93% OSA - 7% central
- OSA 4% in general population

Johnson J Clin Sleep Med 2010 ;6:131

OSA in the Post Stroke Patient

Associated with poorer outcomes

- Higher Mortality
- Delirium
- Reduced motivation,
- Decreased cognitive capacity
- Worse functional impairment
- Longer Rehabilitation
- Longer hospital stays
- Increase the risk of recurrent stroke and death
- DOES CPAP IMPROVE OUTCOME???

Am J Resp CC Med 2009; 180:36
Arch Int Med 2008; 297-301

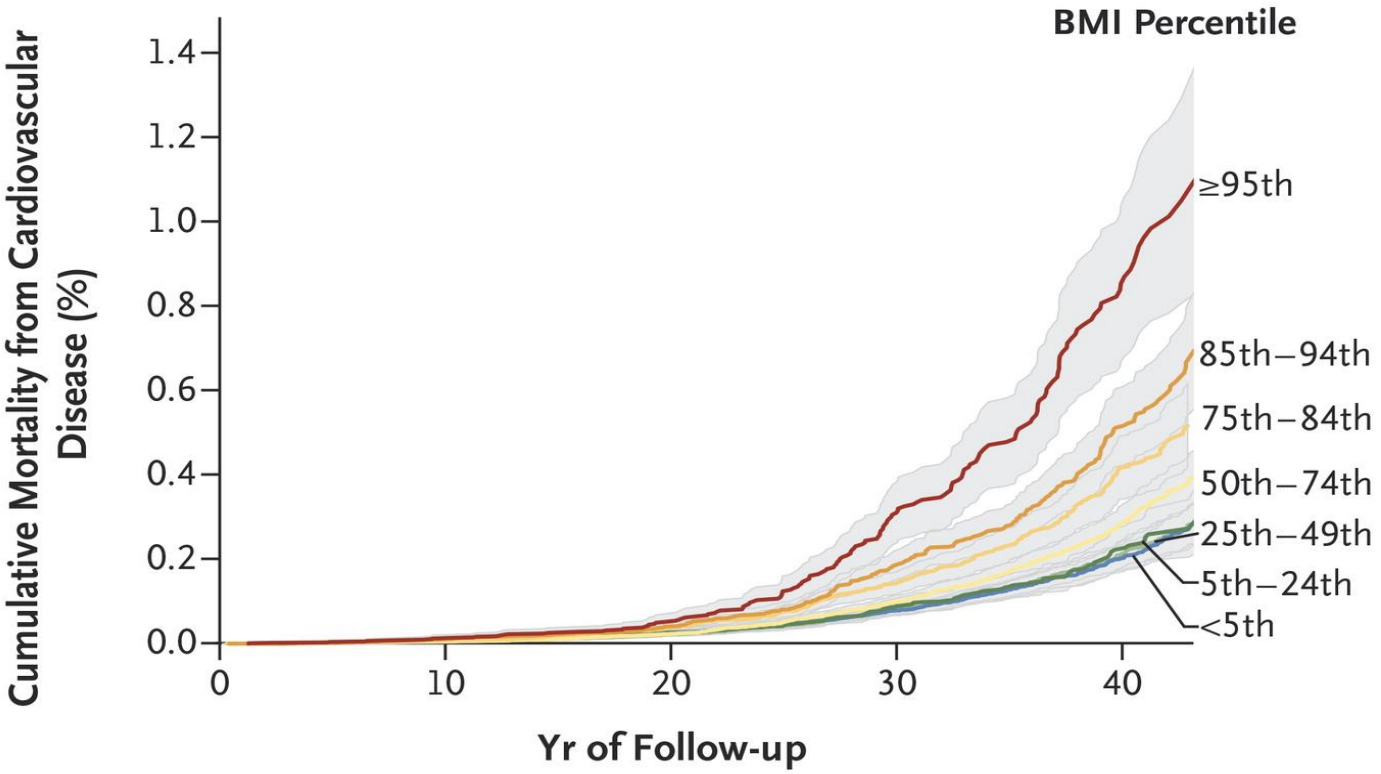
Obesity

- Long recognized as risk factor for stroke
- Risk of ischemic stroke increases in a near- linear fashion starting at a BMI of 20 kg/m2
- 1 kg/m2 is associated with 5% increase in stroke risk
- Probably via intermediary of increased risk factors
- Obesity paradox
- No quality trials to evaluate weight loss as a specific treatment for stroke prevention
- One trial of bariatric surgery: (SOS) (Primary prevention)
  - Stroke reduced 34% (p=0.008)
  - MI reduced 29%
- No secondary prevention trials

Adolescent BMI and Stroke Risk

- Israeli population study all 17 year olds
- Followed for 40 years
- Of 32,127 deaths
  - 2918 (9.1%) were from cardiovascular causes
  - 1497 from coronary heart disease, 893 from sudden death
  - 528 from stroke

Mass Index (BMI) during Adolescence and Subsequent Cardiovascular Mortality.



No. at Risk

Participants at risk	1,712,018	1,042,018	540,636	160,145
Cumulative person-yr	17,201,301	30,718,320	38,472,521	41,926,636
Cumulative cardio-vascular deaths	185	609	1,577	2,676

NEJM

Twig G et al. N Engl J Med 2016;374:2430-2440.

Nutrition

- Recommend a Mediterranean type diet rather than a low fat diet
  - Vegetables, fruits, whole grains and low fat dairy products, poultry, fish
  - Limit red meats, sweets,
  - Low salt
- Supplementation with various vitamins not recommended (possibly folic acid)

Atrial Fibrillation

- Common – increasing with age
  - <0.1% under age of 50
  - 10% Over age of 80
- Risk for stroke following TIA/Stroke without risk factors 7-10%/yr
- 72% on AC by CHADS2
- 90% require AC by CHA2DS2
- Following TIA Stroke – All patientd without contraindications

- Primary Prevention
  - AC recommended for ALL NVAF patients except:
  - 0 score reasonable for No AC
  - 1 consider AC
  - = and >2 Recommend NOAC, then warfarin, then antiplatelets

- CHADS2 not particularly reliable for short term

Atrial Fibrillation

- The risk of recurrence of AF related strong is as high and this 8% he the first two weeks
- Early Initiation of treatment within 1 to 2 days.
- If large infarction, hemorrhagic transformation, or other bleeding risk factors (HAS-BLED) may delay
- But with a TIA/ minor stroke reasonable to initiate within 24 to 48 hours
- Suspect Cardioembolic
  - Large vessel occlusion.
  - Wedge shaped cortical infarct
  - No other obvious explanation

CHADS Score and Stroke Risk

	Points		Total Points	Annual Stroke Risk
Congestive Heart Failure - History	+1		0	1.9%
Hypertension	+1		1	2.8%
Age >65-75 yrs	+1		2	4.0%
Diabetes	+1		3	5.9%
Stroke/TIA/Thromboemboli	+2		4	8.5%
			5	12.5%
			6	18.2%

CHA2DS2 - Vasc Score and Stroke Risk

Risk Factors	Points		Total Points	Annual Stroke Risk
Congestive Heart Failure - History	+1		0	0
Hypertension	+1		1	1.3%
Age >65-75 yrs	+1		2	2.2%
Age >75	2		3	3.2%
Diabetes	+1		4	4.0%
Stroke/TIA/Thromboembolli	+2		5	6.7
Vascular Disease	1		6	9.8%
Female Sex	1		7	9.6%
			8	6.7%
			9	15.2%

Occult AF – Following TIA/Stroke

- 10% patients will have new AF detected during hospital admission
- Additional 11% if monitored for 2-4 weeks
- Occult AF detected during routine monitoring for cardiological conditions have an increased incidence of strokes
- What is the accepted AF activity?
  - One run of 30 sec???

Non Pharmacological Approaches

- Non-Pharmacological approaches
- Various devices have been trialed to occlude the left atrial appendage, or other means to terminate AF.
- In view on the efficacy and safety of the oral anticoagulants and the long term efficacy of these devices use is limited.

- Mechanical valves NO
- Moderate/severe MS - no

New Oral Anticoagulants

- Dabigatran
  - 150 mg and 110 mg
- Rivaroxaban
  - 15 and 20 mg
- Apixaban
  - 5 mg

Other Ischemic Stroke Mechanisms

- Cardiac
  - E.g. Cardiomyopathy
  - Patent FO
  - Valvular heart disease
  - Prosthetic heart valves
  - ASA /warfarin usually

Other:

e.g. Dissection

Vasculitis

Prothombotic conditions

Inherited thrombophilias

HAS-BLED - Risk of bleeding with AF

Condition	Points
Hypertension >160 mmHg	1
Abnormal - Liver Function Renal/Function	1 1
Stroke/TIA	1
Bleeding Predisposition	1
Labile INR	1
Elderly >65	1
Drug predisposing medications Drug/Alcohol abuse	1 1
Total Possible	**9**

Antithrombotic therapy

- ASA and Clopidogrel
- Either/or but not both
- MATCH trial slight benefit of decreased ischemic strokes balanced by increased hemorrhagic strokes

- Prior use of antithrombotics decreases stroke severity

  (Smith Stroke 2016 >500,000 pts)

- Rarely used
  - Ticlopidine
  - Aggrenox

Dual Antiplatelet Therapy Following TIA/Minor Stroke

- ASA 81 mg + Plavix 75 mg
- Meta-analysis 10 trials (8969 pts)
- Significant reduction of recurrent stroke
- RRR = .65
- p= > 0.00001
- No significant subgroups
- Similar risk of intracranial hemorrhage

- Yang Lui J Neurol; ePub Aug 2016

Cigarette Smoking

- Important independent risk factor for first ischemic stroke
- Increased risk of silent infarction
- Two fold increase in risk of recurrence of stroke.
- Now evidence of ”Secondhand smoke” increased risk
- No direct evidence cessation is beneficial – but much indirect
- Smoking Cessation a priority

- References 30, 53 316

Alcohol Consumption

- Increased stroke risk - ischemic/hemorrhagic Heavy alcohol use,
  - Binge drinking
  - Acute alcohol ingestion
- Protective effect for ischemic stroke for light to moderate consumption (J shaped curve)
  - ~ two drinks per day/ males
  - ~ one drink per day/females
- Hemorrhagic stroke- greater risk with increased use - linear

Thanks For Your Attention