

Early Intervention and Prevention of Stroke

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Learning Objectives

- Outline steps to improve the acute management of brain attacks.
- Evaluate the evidence for selecting an antiplatelet agent for the secondary prevention of stroke.
- Describe future therapies for the early intervention and prevention of stroke.

Outline

- Introduction
 - Definitions
 - Stroke in perspective
 - Primary prevention
- Acute management
 - Trials with thrombolytic agents
- Stroke prevention
 - Secondary prevention with antiplatelet agents
- Future therapy

Commonly used definitions

- Disease or Syndrome ?
- Transient Ischemic Attack (TIA)
 - Deficits last < than 24 hours (minutes)
- Completed Stroke
 - Deficits persist
- Stroke-in-Evolution
 - Worsening of neurologic deficits over minutes or hours

Migraine versus TIA

Migraine

- Time course is 10 to 30 minutes
- Build-up
- Symptoms develop over minutes
- Migration of symptoms

TIA

- Time course is < 10 minutes
- Abrupt onset
- Symptoms develop over seconds
- No migration

Striking reality

- 1 episode of stroke every minute
- 1 death every 3 minutes
- Third leading cause of death (160,000 Americans /year)
- 750,000 new or recurrent cases (30%) per year
- 4,000,000 stroke survivors
- Approximately one-third of all stroke survivors will have another stroke within five years
- From 1986 to 1996, stroke death rate decreased but actual number of stroke deaths rose

Striking reality

- Over the course of a lifetime, 4 out of every 5 American families will be touched by stroke
- Largest single cause of permanent disability
 - 33% need help caring for themselves
 - 20% need help walking
 - 75% will be vocationally impaired after 7 years
- Second cause of dementia
- 40 Billion \$ in overall cost

Striking reality

- Stroke risk increases with age (age > 55)
- Over age 65, the risk of dying from stroke is seven times that of the general population
- Two thirds of all strokes occur in people over age 65.
- Stroke belt

Striking evidence

- Most preventable of all catastrophic conditions
- Stroke is an emergency
- Time is brain

Risk factors

Non-modifiable	Modifiable (relative risk)
• Age	• Hypertension (4-5x)
• Male sex (> 20%)	• Atrial fibrillation (5-15x)
• African-American (2.5x) & Hispanic ethnic origin	• Tobacco smoking (2-3x)
• Family history	• Diabetes (2-3x)
	• Hypercholesterolemia (2x)

Stroke Prevention & Hypertension

- Hypertension (43 M) - prevalent but modifiable
- Studies have detected HTN in 60% of elderly
- Tx achieve < 140/90 mmHg in less than 30%
- 5-6 mmHg reduction decreases risks by 40%
- Systolic Hypertension in the Elderly Program (SHEP): TX decreased stroke by 36%
- Reduction of isolated systolic hypertension to < 140 mmHg in the elderly (Syst-Eur Trial): 42% reduction
- Hope Trial (ramipril vs placebo in high risk patients): Reduction: Any stroke (30%), Fatal stroke (60%)

Stroke Prevention & Hypertension

• Hope Trial (2000) (ramipril vs placebo) in high risk patients):	• Progress Trial (2001) (Perindopril +/- indapamide vs placebo)
• Vascular disease or DM + 1 RF (4.5 yrs)	• Stroke or TIA w/ or w/o HTN (4 yrs)
• Reduction:	• Reduction:
– Any stroke (30%)	– Any stroke (40%) with combination therapy
– Fatal stroke (60%)	

Stroke Prevention & Diabetes

- Death is significantly increased with DM
- Intensive treatment of both type I and II DM reduces microvascular complications (DCCT & UK Prospective Diabetes Trials)
- No evidence that blood glucose control alone decreases risk of stroke
- Aggressive treatment of blood pressure in type II diabetes reduces the risk of stroke by 44% (UK Prospective Diabetes Study Group)

Stroke Prevention & Life Style

- Lifestyle factors:
 - Cigarette smoking, Heavy use of alcohol
- Lipid-Lowering therapy
 - In CAD, lipid-lowering therapy decreases stroke by 20% to 30% in primary and secondary prevention trial for coronary artery disease
 - Ongoing trial for primary and secondary prevention for TIA and stroke

Stroke Prevention & Atrial-Fibrillation

- 2 M Americans have nonvalvular atrial fibrillation
- Causes 36% of stroke in patients between 80-89
- Coumadin if :
 - Age (>60-65), TIA or stroke, HTN, CHF, DM
 - Coumadin decreases risks of stroke by 68%
 - Aspirin decrease risks of stroke by 21%
 - Consider Aspirin if no risk factors or 65-75 with no other risk factors, or > 75 with risks of hemorrhage

Rational for thrombolytic Therapy

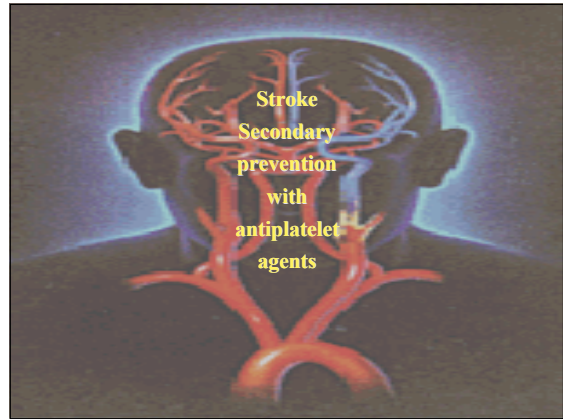
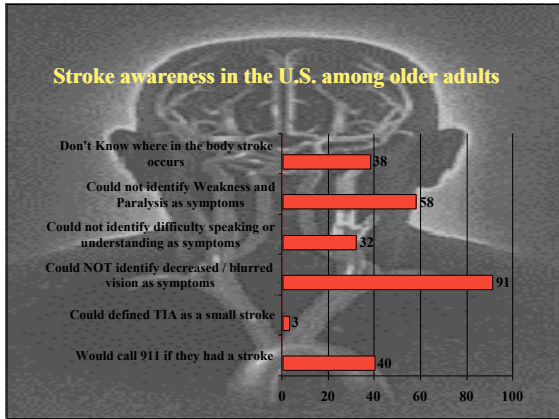
- Angiographic studies
- Animal studies
- Experience with MI and PE

Thrombolytic Trials with r-tPA

Studies	N	Window (Hr)	Symptomatic ICH (tPA / Placebo)	Mortality (tPA / Placebo)	Neuro. benefits
NINDS	624	< 3	6.4% / 0.6%	17.4% / 20.6%	Yes
ECASS I	620	< 6	19.8% / 6.5	22% / 15.6%	Yes
ECASS II	800	< 6	8.8% / 3.4%	10.5% / 10.7%	Yes
Atlantis -B	547	3-5	7% / 1.1%	11% / 6.9%	Yes

About using streptokinase ?

Study	N	Window	Symptomatic ICH	Mortality
MAST-Italy	622	< 6 hours	6% / 0.6%	27% / 12% At 10 days 34% if ASA
MAST-Europe	270	< 6 hours	17.5% / 3%	35% / 18% At 10 days
ASK-Australia	340	< 4	Poorly reported	43.4% / 22.1%



- ### Prevalence of another stroke after a TIA or a completed stroke
- Of all 500,000 stroke survivors / year:
 - 20% will have another stroke within 1 year
 - Recurrence occurs within 30 days in 33%
 - The rate of recurrence is 10% / year
 - TIA's
 - precede stroke in 60%
 - 35% will develop a stroke within 5 yrs if untreated

- ### ASA as a treatment of reference
- Antiplatelet Trialists (Meta-analysis)
 - Stroke, MI and vascular death reduced by 22%
 - Meta-analysis (Algra and van Gijn)
 - Stroke, MI or vascular death reduced by 16%
 - Meta-analysis (Johnson et al.)
 - Stroke reduced by 15%
 - SALT
 - 17% relative risk reduction for stroke, MI or vascular death

Low vs High dose ASA ASA Carotid Endarterectomy Trial

Event	81-325 mg (1,395)	650-1300 mg (1,409)	NNT
Stroke or MI	6.2 %	8.4 %	46
Death	4.2 %	10 %	17

- ### ASA Summary
- | | |
|--|---|
| <h4>Primary Prevention</h4> <ul style="list-style-type: none"> British Doctors' Trial (n=5139) US Physicians' Health Study (n=22,071) <ul style="list-style-type: none"> 44% in RR for MI No difference in stroke Increased risk of hemorrhagic stroke | <h4>Secondary Prevention</h4> <ul style="list-style-type: none"> Antiplatelet Trialist's Collaboration <ul style="list-style-type: none"> 15-20% in RR for stroke 25% in RR for Stroke, MI, PVD in high risk patients |
|--|---|

Thienopyridines

Mechanism of action
Pharmacodynamics
Clinical implications

<p>Ticlopidine</p> <ul style="list-style-type: none"> Tx stopped in 4% due to diarrhea or skin rash Less GI bleed than ASA (60%) Neutropenia in up to 2% (w/in 3 months) TTP in 0.05% (2-12 wks) 	<p>Clopidogrel</p> <ul style="list-style-type: none"> Neutropenia similar to ASA TTP (12 cases reported) (within 2 wks)
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Clopidogrel vs Ticlopidine

Event	CAPRIE (1996) (n=6,431)	CATS (1989) (n=1053)	TASS (1989) (n=3,069)
Stroke	8% (p=0.28)		21% (p=0.02)
Stroke, MI, Vascular death	7.3% (p=0.26)	30% (p=0.01)	9% (p=0.20)

European Stroke Prevention Studies Dipyridamole-ASA Combination

<p>ESPS-1 (1990)</p> <ul style="list-style-type: none"> DP 75 mg & ASA 330 mg tid versus placebo Secondary prevention for 2 yrs (n=2,500) Results: <ul style="list-style-type: none"> - 38% reduction in stroke 	<p>ESPS-2 (1996)</p> <ul style="list-style-type: none"> ER-DP 200 mg & ASA 25 mg bid versus ASA, DP or Placebo Secondary prevention for 2 yrs (n=6,602) Results: <ul style="list-style-type: none"> 37% reduction in stroke (ER-DP/ASA versus placebo)
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Results of ESPS-2

Treatment	Stroke (all) Risk Reduction (%)	P value	Death (all) Risk Reduction (%)	P value
ASA vs Placebo	18.1	.01	10.9	.20
ER-DP vs Placebo	16.3	.04	7.3	.45
ASA/ER-DP vs Placebo	37.0	<.001	8.5	.32
ASA/ER-DP vs ER-DP	24.7	.002	1.3	.82
ASA/ER-DP vs ASA	23.1	.01	-2.7	.78

Reported side effects in ESPS-2

Side effects (%)	Placebo (n=1649)	ASA (n=1649)	ER-DP (n=1654)	ASA/ER-DP (n=1650)
Any	56.6	60	62.5	64
GI (Any) (Diarrhea)	28.2	30.4	30.5	32.8
Headache	32.4	33.1	37.2	38.2
Bleeding (any) (moderate/severe)	4.5 (29.7%)	8.2 (39.3)	4.7 (31.2)	8.7 (41.7)
Dizziness	30.9	29.2	30.1	29.5

Comparison of the efficacy of alternative antiplatelet agents vs ASA

Event	ASA/ER-DP	Ticlopidine	Clopidogrel
Stroke/MI/Vascular Death	22	9	7.3
Stroke	23	21	8

Schools of Thoughts (Relative efficacy, safety and cost)

- “I like to use ASA, it has been proven effective for many years and it is cheap.”
- “I like to use ticlopidine, it is more effective than ASA. I just need to monitor patients more closely for 3 months”
- “I like to use Clopidogrel, it is safer and easier to tolerate than Ticlopidine. It is probably as effective as ticlopidine since it works the same way.”
- “I like to use ASA/ER-DP combination. It is more effective than all currently available agents.”

Sixth ACCP Consensus Conference on Antithrombotic Therapy

- Acute ischemic stroke
 - r-tPA if < 3 hours and no exclusion criteria
 - IA r-tPA for MCA occlusion if >3 and < 6 hrs
 - If not eligible for thrombolysis
 - Anticoagulation can be considered
 - ASA within 48 hours (CAST & IST Trials)
- Stroke prevention
 - Antiplatelet agents
 - Caution with oral anticoagulant (INR < 3)
- Cerebral venous sinus thrombosis

New antiplatelet drug: Cilostazole Stroke Prevention Study

- Inhibition of cAMP phosphodiesterase
 - Inhibit aggregation secondary to ADP, collagen, epi and arach. Acid & Enhance prostacyclin effects
- MC, R, DB, Placebo-controlled (Available in Japan since 1988)
- N=1,095
- Population: Cerebral infarction within 1-6 months
- Major exclusion: Cardiogenic cerebral embolism
- Primary end point: Recurrence of stroke
- Secondary end point: Other vascular events and death

Gotoh F, et al. J Stroke Cerebrovasc Dis 2000;9:147-57.

New antiplatelet drug: Cilostazole Stroke Prevention Study

- | <u>Efficacy results (900 pt-yrs)</u> | <u>Safety results</u> |
|--|---|
| • Cerebral infarction <ul style="list-style-type: none">• 3.3 vs 5.8 events/year• 42% RR, p=0.015 | • Headache <ul style="list-style-type: none">– 12.8% vs 3.2%, p<0.0001 |
| • Lacunar infarction <ul style="list-style-type: none">• 3 vs 5.3• 43% RR, p=0.037 | • Palpitations <ul style="list-style-type: none">– 5.3% vs 0.4%, p<0.0001 |
| | • Increase in pulse rate <ul style="list-style-type: none">– 19% vs 7.9%, p<0.0001 |
| | • Decrease in triglyceride |
| | • Increase in HDL |

Gotoh F, et al. J Stroke Cerebrovasc Dis 2000;9:147-57.

Unanswered questions

- Should ASA be considered as the treatment of reference for secondary prevention
- What if stroke /TIA occurs despite ASA?
- Aggrenox was compared to 50 mg daily. In the U.S., standard dose is 81 - 325 mg. Will the effect be comparable ?
- There are no direct comparisons among all agents

Discussion

- What would be your agent of choice for a first time TIA / Stroke ?
- What is the most cost-effective agent?
- Can you combine Clopidogrel and ASA?
- What is the latest about using a neuroprotective agent during the acute phase of a stroke?



References to have in your stroke file

- ✓ Albers GW, et al. Antithrombotic and thrombolytic therapy for ischemic stroke. *Chest* 2001;119:300S-320S.
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- ✓ Hankey GJ, et al. Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and population. *Lancet* 1999;354:1457-63.
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