Cerebrovascular disorders: stroke
What is stroke?

- Suddenly (acutely) developing neurological deficit of vascular origin that lasts longer than 24 hours
- 80-85% ischemic
Stroke subtypes

Ischemic stroke ~ 80%

Haemorrhagic stroke ~ 20%

Prognosis of stroke

- Slight disabilities 57 %
- Moderate disabilities 9 %
- Severe disabilities 18 %
- Deceased 15 %

Transient ischemic attack (TIA)

- Sudden onset of (any kind) focal neurological sign that disappears within 24 hours
- Anything (weakness, numbness, dizziness, aphasia, visual disturbance (amaurosis fugax), double vision
TIA symptoms

• Sudden onset, usual duration is 5-20 min.
• Carotid artery symptoms:
  – Ipsilateral monocular visual loss (amaurosis fugax)
  – Contralateral paresis, sensory loss
  – Aphasia, agnosia, apraxia (dominant hemisphere)
  – Combination of the above
TIA symptoms

- Vertebrobasilar arteries:
  - Binocular visual loss
  - Vertigo, ataxia
  - Dysarthria, dysphagia (TGA)
  - Diplopia
Risk after TIA
1707 TIA’s patients, 90 days follow up

• **428 (25.1 %)** hospital readmission (for several reasons)
• 216 recurrent TIA – (12.7 %).
• 44 cardiovascularis events (2.6 %)
• 45 death (2.6 %),
Clinical groups - TIA

• 10% of all cerebrovasc. disorders
• 10% of all stroke patients have a history of prior TIA
• 1/3 of persons who had TIA will develop stroke within 5 years
EPIDEMIOLOGY of STROKE
Stroke

- A leading cause of serious, long-term disability (25-50% of stroke victims remains handicapped)
- 730,000 new or recurrent strokes occur per year in the US
- 40,000-50,000/year hospital admission due to stroke in Hungary (a new stroke in every 13th minute...!)
- Third leading cause of death after cardiovascular diseases and cancer
Distribution of mortality in Hungary

Stroke  hearth+periph.art.  other

Józán Péter: Agyérbetegségek, 1998. 4: 2-6, KSH 2001

Russia

BULGARIA

PORTUGAL

Hungary

Sveden

France

Józan Péter: Agyérbetegségek, 1998, 4: 2-6
Epidemiology

- Season differences: more frequent in winter and in spring
- Daily differences: most frequent at daybreak
- Sexual differences: Men > 2x > Women (stroke rates rise rapidly in menopausa)
Autoregulation of the brain circulation

CBF

Tension (Hgmm)

- Normal
- Hypertension
Thrombolysis in acute ischemic stroke

- In 90% of the cases occlusion of the intra/extracranial arteries can be detected
- Without reperfusion the majority of the ischemic damage is irreversible
- 80-85% of all strokes are ischemic
6:00 hours
Intravenous (or intra-arterial) administration of thrombolytic agents can achieve recanalization and improve outcome in carefully selected patients with acute ischemic stroke
Thrombolysis

- Iv. rt-PA (0.9mg/kg) with 10% of the dose in iv. bolus, followed by infusion lasting 60 min – within 3 hours of onset of ischemic stroke
- Iv. administration of streptokinase is dangerous
- Intra-arterial treatment of acute MCA occlusion in 6 hour time window is rec. (using pro-urokinase) – not registered
- Acut basilar occlusion may be treated with intra-arterial therapy – not registered
Before thrombolysis CT, no contrast
Before thrombolysis CT, no contrast
Before thrombolysis
MRI T2
Before thrombolysis: diffusion MRI
Before thrombolysis

MRI angiography
After 6 hours of thrombolysis: recanalisation
After 6 hours of thrombolysis

MRI T2
After 2 days of thrombolysis CT, no contrast
Acute Stroke Management

There are 5 mainstays in the treatment of acute stroke.

(1) Treatment of general conditions that need to be stabilised.

(2) Specific therapy directed against particular aspects of stroke pathogenesis, either recanalisation of a vessel occlusion or prevention of mechanisms leading to neuronal death in the ischaemic brain (neuroprotection).

(3) Prophylaxis and treatment of complications which may be either neurological (such as secondary haemorrhage, space-occupying oedema or seizures) or medical (such as aspiration, infections, decubital ulcers, deep venous thrombosis or pulmonary embolism).

(4) Early secondary prevention, which is aimed at reducing the incidence of early stroke recurrence.

(5) Early rehabilitation.
How to decrease consequences of stroke

Primary prevention

Acute stroke treatment

Secondary prevention Rehabilitation
## Risk factors

### Age

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Stroke risk/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 14</td>
<td>1 / 30 000</td>
</tr>
<tr>
<td>15 - 24</td>
<td>1 / 10 000</td>
</tr>
<tr>
<td>25 - 34</td>
<td>1 / 9000</td>
</tr>
<tr>
<td>35 - 44</td>
<td>1 / 5000</td>
</tr>
<tr>
<td>45 - 54</td>
<td>1 / 1000</td>
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<tr>
<td>55 - 64</td>
<td>1 / 300</td>
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<tr>
<td>65 - 74</td>
<td>1 / 100</td>
</tr>
<tr>
<td>75 - 84</td>
<td>1 / 50</td>
</tr>
<tr>
<td>85 +</td>
<td>1 / 30</td>
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</tbody>
</table>

*strong association with the age*
Risk factors of stroke

Non-modifiable
Age, Gender, Race, Heredity

Modifiable

Medical Conditions
Hypertension
Cardiac disease
Atrial fibrillation
Hyperlipidemia
Diabetes mellitus
Carotid stenosis

Behaviors
Cigarette smoking
Alcohol abuse
Physical inactivity
Primary prevention aims to reduce the risk of stroke in asymptomatic people. Recommendations concerning patients with TIAs are considered here as secondary prevention. Relative risk reduction (RRR), absolute risk reduction (ARR) and NNT to avoid 1 major vascular event per year are provided for each therapy in tables 5, 6, and 7.
Hypertension is the most important risk factor of stroke!

- Metaanalysis of 14 large randomized controlled trial showed, that decrease of diastolic blood pressure by 5-6 Hgmm decreases the relative risk of stroke by 42%

- Do not decrease the blood pressure in acute stroke! (200/100, 150/100 in hemorrhage)
Hypertonia megelőzése

- 40 év alatt kétévente vérnyomásmérés
- 40 év felett évente, 50 felett félévente vérnyomásmérés
- Hypertonia esetén 140/85 Hgmm alá kell a vérnyomást beállítani az életmód módosításával ill. gyógyszerrel (I. szintű evidencia)
**Primary Prevention**

*Diabetes mellitus*

Since there are other good reasons to treat diabetes appropriately, it seems prudent to do so in those at risk for stroke. Blood pressure should be lowered more aggressively in diabetics to achieve levels below 135/80 mm Hg [Turner et al., 1999].

The American Diabetes Association recommends using aspirin in primary prevention for anyone with diabetes older than 30 years with no known contra-indications [American Diabetes Association, 2000].
Cigarette Smoking

Cohort studies have shown cigarette smoking to be an independent risk factor for ischaemic stroke [Wolf et al., 1988] in men [Abbott et al., 1986] and women [Colditz et al., 1988]. A meta-analysis of 22 studies indicates that smoking doubles the risk of ischaemic stroke [Shinton et al., 1989]. Subjects who stop smoking reduce this risk by 50% [Colditz et al., 1988].
Alcohol Consumption

Heavy alcohol drinking (more than 60 g/day) increases the risk of stroke, while light or moderate alcohol consumption may be protective against all strokes and ischaemic strokes. Consumption of up to 12 g of alcohol per day was associated with an RRR of all strokes (RR: 0.83) and of ischaemic stroke (RR: 0.80). Moderate consumption (12–24 g/day) was associated with a reduced risk of ischaemic stroke (RR: 0.72) [Reynolds et al., 2003].

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Primary prevention

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Lifestyle Modification

In men, vigorous exercise was associated with a decreased risk of stroke [Lee et al., 1999]. The data suggested that this association was mediated through beneficial effects on body weight, blood pressure, serum cholesterol and glucose tolerance, and that, apart from these effects, physical activity had no influence on stroke incidence. Substantial evidence supports the use of diets high in non-hydrogenated unsaturated fats, whole grains, fruit and vegetables, fish once a month.
Primary prevention

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Hyperlipidaemia

Three primary or combined primary/secondary prevention trials were unable to show a significant reduction in stroke rate under pravastatin [ALLHAT Investigators, 2002; West of Scotland Coronary Prevention Study Group, 1998; Shepherd et al., 2002], despite a tendency (minus 11%) in men [WOSCOP Study Group, 1998]. In the larger Heart Protection Study [2002], the reduction in the event rate under simvastatin was significant even in those with low-density lipoprotein cholesterol below 3.0 mmol/l (116 mg/dl) or total cholesterol below 5.0 mmol/l (193 mg/dl). The annual excess of myopathies was 1 per 10,000 patients treated [Heart Protection Study, 2002].
Primary prevention

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Postmenopausal Oestrogen Replacement Therapy

Stroke rates rise rapidly in women once they become menopausal. However, in an analysis based on a 16-year follow-up of 59,337 postmenopausal women participating in the Nurses’ Health Study, there was only a weak association between stroke and oestrogen replacement [Grodstein et al., 2001]. According to the HERS II trial, hormone replacement in healthy women is associated with an increased risk of ischaemic stroke [Grady et al., 2002].
Aspirin in primary stroke prevention

Antithrombotic Therapy
A meta-analysis [Hart et al., 2000] of the 5 trials [Peto et al., 1988; Steering Committee of the Physicians Health Study Research Group, 1989; EDTRS Investigators, 1992; Hansson et al., 1998; Meade, 1998] comparing aspirin with no aspirin in 52,251 subjects with no aspirin in 52,251 subjects after a mean follow-up of 4.6 years found no effect on stroke rate. A further trial found that aspirin (100 mg per day) was associated with a non-significant reduction in stroke of 33% [de Gaetano, 2001]. No data are available on the use of other antiplatelet agents in primary prevention. There is no proof that aspirin is beneficial in patients with asymptomatic internal artery stenosis, but these patients being at increased risk for MI, there is a consensus to use aspirin.
Recurrence of stroke

*Ischemic stroke* (\(\%\))
- First year: 6-12
- In 5 years: 30-40

Myocardial infarction: 15
Vascular death: 15
Secondary Prevention

Antiplatelet Therapy

A meta-analysis of 287 trials [Antiplatelet Trialists Collaboration, 2002] showed a 25% relative reduction of serious vascular events (non-fatal myocardial infarction, non-fatal stroke or vascular death) under antiplatelet therapy in patients with previous ischaemic stroke or TIA: when 1,000 patients are treated for 2 years, 36 events are prevented among those with previous stroke or TIA, and this benefit substantially outweighs the absolute risks of major extra-cranial bleeding [Antiplatelet Trialists Cooperation, 2002].
Aspirin: 300-100 mg/day

Aspirin. Studies directly comparing the effects of different doses of aspirin failed to show differences in stroke recurrences [Algra and van Gijn, 1996; The Dutch TIA Study Group, 1991; Farrell et al., 1991]. The risk/benefit ratio of adding another antithrombotic drug to aspirin has not been fully studied.

(2) The incidence of gastro-intestinal disturbances with aspirin is dose dependent. Lower doses are safer. (3) The
Clopidogrel. Clopidogrel is slightly more effective than aspirin in preventing vascular events [CAPRIE Steering Committee, 1996]. It is the agent of choice in patients with contra-indications, or adverse effects, to aspirin and may be more effective in higher risk patients (i.e. with a previous stroke, peripheral artery disease, symptomatic coronary disease and diabetes) and after coronary surgery [Bhatt et al., 2000].
Dipyridamole Plus Aspirin. The ESPS II Study [Diener et al., 1996], a randomised, double-blind, placebo-controlled trial, showed that the combination of aspirin (50 mg) plus dipyridamole (400 mg) doubles the effect of aspirin alone and of dipyridamole alone: the RRR versus placebo were 37, 18 and 16%, respectively.
Oral anticoagulation

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Recommendations

1. Oral anticoagulation (INR 2.0–3.0) is indicated after ischaemic stroke associated with AF (level I). Oral anticoagulation is not advisable in patients with comorbid conditions such as falls, epilepsy, severe dementia, or gastro-intestinal bleedings.

2. Patients with prosthetic heart valves should receive long-term anticoagulation therapy with a target INR between 2.5 and 3.5 or higher (level II).

3. Patients with proven cardio-embolic stroke should be anticoagulated, if the risk of recurrence is high, with a target INR between 2.0 and 3.0 (level III).

4. Anticoagulation should not be used after non-cardio-embolic ischaemic stroke, except in some specific situations, such as aortic atheromas, fusiform aneurysms of the basilar artery or cervical artery dissection (level IV).
relative risk reduction for stroke of 60-65%, with a target international normalised ratio of 2.0-3.0
Cholesterol lowering therapy in secondary prevention of stroke

Cholesterol-Lowering Therapy

A significant reduction in stroke risk is seen across all treatment groups [Di Mascio et al., 2000]. Most of this effect was driven by trials involving patients with a prior vascular event using a statin, or where a reduction in total cholesterol levels of more than 10% was achieved. In secondary prevention, 57 patients would need to be treated with statins to prevent 1 stroke per year [Straus et al., 2002]. The MRC/BHF Heart Protection Study had a sub-
Hormone Replacement Therapy

In the Women’s Oestrogen for Stroke Trial, a placebo-controlled randomised trial of oestrogen replacement therapy for the secondary prevention of ischaemic stroke, the risk of fatal stroke was higher (not significant) with oestrogens, and non-fatal strokes were associated with worse functional outcomes [Viscoli et al., 2001].

Recommendation

1. There is no indication to use hormone replacement therapy for secondary stroke prevention in postmenopausal women (level II).
Smoking

Smoking cessation leads to an early reduction in risk of both coronary events and stroke at any age [Kawachi et al., 1993; Wannamethee et al., 1995; Colditz et al., 1988].

Recommendation

1. All smokers should stop smoking, especially patients who have had stroke (level IV).
Carotid endarterectomy (or stent?)

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Recommendations

1 Carotid surgery may be indicated for some asymptomatic patients with a 60–99% stenosis of the ICA. The carotid endarterectomy (CEA)-related risk of stroke or death must be less than 3%, and patients with a life expectancy of at least 5 years (or under the age of 80) may benefit from surgery (level II).

2 Carotid angioplasty, with or without stenting, is not routinely recommended for patients with asymptomatic carotid stenosis. It may be considered in the context of randomised clinical trials.
**Table 5.** RRR, ARR and NNT to avoid 1 stroke per year in patients who undergo surgery for ICA stenosis (modified from Hankey and Warlow [1999])

<table>
<thead>
<tr>
<th>Disease</th>
<th>RRR</th>
<th>ARR/year</th>
<th>NNT to avoid 1 stroke/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic (60–99%)</td>
<td>53</td>
<td>1.2</td>
<td>85</td>
</tr>
<tr>
<td>Symptomatic (70–99%)</td>
<td>65</td>
<td>3.8</td>
<td>27</td>
</tr>
<tr>
<td>Symptomatic (50–69%)</td>
<td>29</td>
<td>1.3</td>
<td>75</td>
</tr>
<tr>
<td>Symptomatic (&lt;50%)</td>
<td></td>
<td>no benefit</td>
<td>no benefit</td>
</tr>
</tbody>
</table>


Extracranial-Intracranial Anastomosis

Anastomosis between the superficial temporal and middle cerebral arteries is not beneficial in preventing stroke in patients with MCA or ICA stenosis or occlusion [The EC/IC Bypass Study Group, 1985].
Clinical manifestations of atherothrombosis

Ischaemic stroke

Transient ischaemic attack

Myocardial infarction

Angina:
- Stable
- Unstable

Peripheral vessel diseases

Adapted from: Drouet L. Cerebrovasc Dis 2002; 13(suppl 1): 1–6.
Small artery occlusive stroke

- 15-20% of thrombotic stroke
- Lipohyalinosis, local arteriosclerosis of small penetrating arteries
- Etiology: long standing hypertension or diabetes
- Typical localisation: basal ganglia, thalamus, pons, internal capsule
- Infarction are smaller than 1,5 cm in diameter
- Gradual progression
Lacunar infarction
Symptoms

- Pure motor paresis (internal capsule, pons)
- Pure sensory deficit (thalamus, corona radiata)
- Dysarthria-clumsy hand (pons, internal capsule)
- Ataxic hemiparesis (internal capsule)
- Multiple infarction are associated with vascular dementia
Cerebral embolism

• 20% of ischemic stroke
• Younger patients
• Acute onset, maximal severe deficit, quickly improvement
• Recurrent stroke (more than one vascular territory)
• Cortical infarction
• Cardiac diseases in the anamnesis
Cerebral embolism

Intracardial thrombus

Vegetation on the aortic valve
Etiology

- Atrial fibrillation (most important risk factor of stroke in elderly women)
- AMI – stroke complicates 2-4%, usually in the first 4-5 weeks (mural thrombus)
- Ventricular aneurysm
- Valve disorders
- Prosthetic valve
- Infective endocarditis
- Intracardial tumors
- Cardiac procedures (angiography, bypass, PTCA)
Hemodynamic stroke

• Global reduction of the CBF
• Cardiac dysfunction, hypotension, hypoxia, hypoglycemia, severe carotid artery stenosis
• Multifocal ischemic lesions (cortex, anterior-posterior watershed infarction
Intracerebral hemorrhage

- 10-14% of all strokes, typical age 50-70 years
- Overall mortality vary between 25-60%
- Etiology: history of hypertension: 72-81%
- The chronic hypertension is associated with fibrinoid degeneration of small arteries of the brain (Charcot-Bouchard microaneurysm)
A. Microaneurysm formed in parenchymal artery of brain as result of hypertension. Lenticulostriate vessels (shown) most commonly involved, but similar process may occur in other parts of brain, especially lobar white matter, thalamus, pons and cerebellum.

B. Microaneurysm ruptures, causing pressure on adjacent (satellite) vessels.

C. Satellite vessels rupture.

D. Amount of blood extravasated into brain tissue depends on tissue turgor opposed to intravascular blood pressure.
Etiology

• Vascular malformations (aneurysm, AVM, cavernous angioma)
  – Leading cause of stroke in younger age group (female predominance)
  – Typical lobar hemorrhage (temporal-frontal)
  – Cavernous angiomas are often located in the subcortical white matter and in the pons
  – Clinical presentation: seizures (30-70%), ICH (10-30%), progressive neurological deficit (35%)
Etiology of ICH

- Intracranial tumors
  - Less than 10% of ICH (glioblastoma, metastases)
- Bleeding disorders: hemophilia, ITP, leukemia
- Anticoagulant (10%) and fibrinolytic treatment
  - Slowly progressive course is typical, large volume hematomas, high mortality
- Cerebral amyloid angiopathy (selective deposition of amyloid in cerebral vessels (cortex-leptomeninges)
  - Elderly, nonhypertensive patients, recurrent lobar ICH or SAV
  - Association with histopathological features of Alzheimer’s disease, progressive dementia
Etiology of ICH

• Granulomatosus angitis (vasculitis)
  – Monocular inflammation in the wall of intracranial arteries

• Hemorrhagic transformation of cerebral infarction (cerebral embolism)

• Trauma: hematoma occurs in surface of brain, often multiple

• Sympathomimetic agents (amphetamines, cocain)
  – Subcortical white matter localisation
Clinical manifestation

- Sudden onset, followed by progression
- Symptoms of elevated ICP (headache, vomiting, depressed level of consciousness)
- Focal neurological deficit, rarely seizures
- Size of hematoma:
  - small: <1cm - good prognosis
  - Medial: 1-3 cm - prognosis is related on localisation
  - Large: 3-5 cm – poor prognosis
  - Extralarge: >5cm - fatal
Anatomical forms of ICH

- Putaminal: 35%, mortality: 37%
- Caudate: 5%, mortality: 10%
- Thalamic: 10-15%, mortality: 30%
- Lobar: 25% mortality: 30%
- Cerebellar: 5-10%, mortality: 20%
- Pontin: 5%, paramedian: mortality: 80%
- Mesencephalic: rare
- Medullary: rare, mortality: 100%
- Intraventricular: secondary form (caudate, thalamic, putaminal, lobar), primary form: subependymal malformation
Subarachnoid haemorrhage

- Incidence: 15/100,000/year
- 6-10% of all strokes
- Etiology: a) intracranial aneurysm (75%), b) arteriovenousus malformation (5%) c) other
- Pathogenesis:
  - Classification of aneurysm: morphological:
    1. saccular, 2. fusiform, 3. dissecting
  - Size: <3mm, 3-6 mm, 7-10 mm, 11-25 mm, >25 mm (giant)
  - Origin: congenital (90%)-arise from defects in the muscular layer of cerebral arteries?, degenerative changes? Both ?
  - Other origin: arteriosclerotic, septic-mycotic, traumatic, neoplastic
  - Location_ arterial bifurcation of the circle of Willis
Clinical symptoms of SAV

- **A: unruptured aneurysm:**
  - Anterior comm. artery- visual field defects
  - Posterior comm. artery- oculomotor nerv palsy
  - Middle cerebral artery- aphasia, hemiparesis, seizures

- **B: ruptured aneurysm:**
  - Sudden oncet headache, often extremly severe, womiting
  - Meningeal sign
  - Neurological deficit
  - Depressed level of consciousness
Hunt –Hess clinical score

- Grade 0: unruptured aneurysm
- Grade I: asymptomatic or mild headache
- Grade II: moderate or severe headache, nuchal rigidity, cranial nerve palsy
- Grade III: drowsiness, mild deficit
- Grade IV: stupor, moderate to severe hemiparesis, vegetative disturbances
- Grade V: deep coma, decerebrate rigidity, moribund state
Potential complications of SAV

• Rebleeding (10-30%) (prevention of rebleeding: endovascular occlusion of the aneurysm, as soon as possible)
• Delayed ischaemia related to vasospasm 3-14 days
• Cerebral oedema
• Acut obstructive hydrocephalus
• Delayed communicating hydrocephalus
• Intracerebral, subdural haematoma