Prevention and Management of hypertensive stroke

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4 Dec 2006

Content

- How does HT cause stroke?
- What are the clinical and radiological manifestations for HT-related stroke?
- How should we lower BP in acute stroke?
- What is the current concepts in anti-hypertensive therapy for prevention of first and recurrent stroke?
How does HT cause stroke?

Lipohyalinosis

Fibrinoid degeneration

Atherosclerosis
Cortical infarction

MCA territory infarction
ACA territory infarction

PCA territory infarction
Lacunar Infarct
Lacunar Infarct

Binswanger’s disease
Binswanger’s disease

- Subcortical arteriosclerotic encephalopathy
- Chronic small vessel disease
- Vascular parkinsonism
- Lower half parkinsonism

- Apathy
- Gait apraxia
- Small step gait
- Hyperreflexia
- Extensor plantar reflexes
- Subcortical dementia – cognitive slowing
Cardioembolic stroke

Atrial Fibrillation

hypertensive hemorrhage
Basal ganglia haemorrhage

Pontine haemorrhage
Antiplatelet agents

Aspirin

- small benefit in reducing the death and recurrent stroke rate
- net decrease of 9 deaths or occurrences of further stroke per 1000 patients (level Ia)
**IV thrombolysis**

- FDA approval 1996
- iv tPA < 3 hr
- Improved outcome at 3 months

**NINDS**

TPA-treated group were at least 30% more likely to have minimal or no disability at 3 months.

Benefit were consistent regardless of age, stroke subtype or prior use of aspirin.
6.4% tPA vs. 0.6% in placebo 
(within 36hrs)

Mortality rate in both treatment group was similar at 3mo & at 1 year
Intra-arterial thrombolysis

MERCI balloon guide catheter

FDA  August 11, 2004

1st medical device specifically indicated to -
retrieve blood clots from the brain in ischemic stroke for -
patients who fail or are ineligible for iv tPA
BP lowering in acute phase

Ischaemic penumbra

Ischemic penumbra
(gradient of necrotic death, apoptotic death, and tissue survival)

Ischemic core
(necrotic cell death)

Anterior cerebral artery (collateral flow)

Middle cerebral artery

Embolus
Ischaemic penumbra

Cerebral autoregulation
Cerebral autoregulation

BP management in acute ischaemic stroke

- CBF is pressure dependent in ischaemic brain regions
- Further reduction
  - irreversibly injure the ischaemic penumbra
  - increase stroke volume
BP management in acute ischaemic stroke

- Transient HT – common after acute ischaemic stroke

- Causes:
  - anxiety
  - pain
  - neuroendocrine factors
  - stroke location
  - compensatory response to brain hypoxia or increased ICP

BP management in acute ischaemic stroke

- Manage stress responses, pain, nausea and vomiting, bladder distension or other sources of anxiety

- Early BP elevations often decline spontaneously during the first minutes to hours

- May not require pharmacologic Rx
Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome

Castillo J, Leira R, Garcia MM, Serena J, Blanco M, Davalos A.

Power Grade 3/5

Power Grade 1/5

Anti-HT Drug for BP 180/90
“Stroke in evolution”? 

Non-specific

- Failure of collateral circulation
- Systemic hypotension
- Cardiac arrhythmia
- Embolization or propagation of thrombus
- Progressive occlusion of vessel lumen
- Psychological depression
- Sepsis
- Seizures

Any conditions deserve BP lowering?

- AMI
- Aortic dissection
- Hypertensive encephalopathy
- Severe left heart failure
- Post-thrombolysis
Consensus for BP Mx (not eligible for thrombolysis)

<table>
<thead>
<tr>
<th>SBP &lt;220 mm Hg or DBP &lt;120 mm Hg</th>
<th>Observe BP unless end organ involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP &gt;220 mm Hg or DBP 121–140 mm Hg</td>
<td>Labetalol OR nicardipine (target 10%–15% reduction)</td>
</tr>
<tr>
<td>DBP &gt;140 mm Hg</td>
<td>Sodium nitroprusside 0.5 µm/kg per min IV with continuous BP monitoring (target 10%–15% reduction)</td>
</tr>
</tbody>
</table>


Resume previous anti-HT Rx?

Those already taking anti-HT Rx:
→ Resume drugs to avoid rebound HT

→ Maintain:

SBP 180–220 mm Hg
DBP < 120 mm Hg
Labetolol

- Selective $\alpha_1$ antagonist
- $\beta_1$ & $\beta_2$ antagonist
- Decrease systemic vascular resistance through $\alpha$ blockade
- Beta-blocking reflex tachycardia induced by vasodilatation

Labetolol

Does not affect cerebral blood flow

Dosing regimen 10-20mg iv (over 1-2 min) every 15-20min

Doubling of each subsequent dose is recommended
Sublingual Nifedipine

- Should be avoided
- Cause precipitous reduction in BP

Adalat 5mg S.L. stat

Bring home message:

Don’t lower BP in acute ischaemic stroke if

SBP < 220 mm Hg

or

DBP < 120 mm Hg
Managing HT in ICH

- limited observational data
- no data from randomized clinical trials
- left with consensus opinion and our best judgement
- balancing the two competing issues:
  - Rebleeding
  - Secondary brain injury
- BP lowering to limit hematoma expansion, non-nervous system organ injury

AHA Scientific Statement
Guidelines for the Management of Spontaneous ICH
*Stroke.* 1999;30:905-915

<table>
<thead>
<tr>
<th>SBP &gt;230 mm Hg</th>
<th>Nitroprusside</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP &gt;140 mm Hg</td>
<td>on 2 readings 5 minutes apart</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SBP 180 to 230 mm Hg</th>
<th>IV labetalol, esmolol, enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP 105 to 140 mm Hg</td>
<td>or MAP 130 mm Hg on 2 readings 20 minutes apart</td>
</tr>
<tr>
<td>or MAP 130 mm Hg on 2 readings 20 minutes apart</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SBP &lt;180 mm Hg</th>
<th>Observe</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP &lt;105 mm Hg</td>
<td></td>
</tr>
</tbody>
</table>

If ICP monitoring is present
- Keep cerebral perfusion pressure > 70mmHg
Primary prevention
Risk factors for stroke

Non-modifiable
- Non-white ethnicity
- Male sex
- Older age
- Positive family history

Modifiable
- HT
- Smoking
- Excessive alcohol intake (>60g/d)
- Obesity
- Dyslipidaemia
- DM
- Carotid artery disease
- AF
- CHF

Blood Pressure and Stroke: An Overview of Published Reviews
Carlene M.M. Lawes, Derrick A. Bennett, Valery L. Feigin, and Anthony Rodgers
Stroke 2004 35: 776 - 785
BP level & risk of vascular disease

- JNC VII
- Risk begins at 115/75 mmHg
- No limits below this point
- No J-curve response

Classification of BP by JNC 7

- Normal
- Prehypertension
- Stage 1 HT
- Stage 2 HT

SBP vs. DBP graph
Which drug should we use?

Any class effect?

Comparison with placebo

<table>
<thead>
<tr>
<th>Trials</th>
<th>Events/participants</th>
<th>Difference in BP* (Mean, mm Hg)</th>
<th>Relative risk</th>
<th>p (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi vs placebo*</td>
<td>5</td>
<td>473/9111 660/9118 -5/-2</td>
<td>0.72 (0.64–0.81)</td>
<td>0.33</td>
</tr>
<tr>
<td>CA vs placebo</td>
<td>4</td>
<td>78/3794 119/3688 -8/-4</td>
<td>0.62 (0.47–0.82)</td>
<td>0.90</td>
</tr>
<tr>
<td>More vs less</td>
<td>4</td>
<td>140/7494 261/13394 -4/-3</td>
<td>0.77 (0.63–0.95)</td>
<td>0.15</td>
</tr>
<tr>
<td>Total mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi vs placebo*</td>
<td>5</td>
<td>839/9111 951/9118 -5/-2</td>
<td>0.88 (0.81–0.96)</td>
<td>0.04</td>
</tr>
<tr>
<td>CA vs placebo</td>
<td>4</td>
<td>239/3794 263/3688 -8/-4</td>
<td>0.80 (0.75–1.05)</td>
<td>0.30</td>
</tr>
<tr>
<td>More vs less</td>
<td>5</td>
<td>404/8034 549/13394 -4/-3</td>
<td>0.96 (0.84–1.09)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

### Direct comparison between anti-HT regimen

<table>
<thead>
<tr>
<th>Stroke</th>
<th>Trials</th>
<th>Events/participants</th>
<th>Difference in BP* (mean, mm Hg)</th>
<th>Relative risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI vs D/B</td>
<td>5</td>
<td>584/20195</td>
<td>1178/26358 +2/0</td>
<td>1.09 (1.00-1.18)</td>
<td>0.13</td>
</tr>
<tr>
<td>CA vs D/B</td>
<td>9</td>
<td>999/31031</td>
<td>1358/37418 +1/0</td>
<td>0.93 (0.85-1.00)</td>
<td>0.67</td>
</tr>
<tr>
<td>ACEI vs CA</td>
<td>5</td>
<td>701/12952</td>
<td>622/12541 +1/-1</td>
<td>1.12 (1.01-1.25)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total mortality</th>
<th>Trials</th>
<th>Events/participants</th>
<th>Difference in BP* (mean, mm Hg)</th>
<th>Relative risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI vs D/B</td>
<td>6</td>
<td>2178/20631</td>
<td>3067/26799 +2/0</td>
<td>1.00 (0.95-1.05)</td>
<td>0.76</td>
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<tr>
<td>CA vs D/B</td>
<td>9</td>
<td>2527/31031</td>
<td>3437/37418 +1/0</td>
<td>0.99 (0.95-1.04)</td>
<td>0.71</td>
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<tr>
<td>ACEI vs CA</td>
<td>6</td>
<td>1763/12958</td>
<td>1683/12541 +1/-1</td>
<td>1.04 (0.98-1.10)</td>
<td>0.68</td>
</tr>
</tbody>
</table>


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### Size does matter

**Type of anti-HT Rx**

**Size (intensity) of BP ↓**
### Compelling reasons & recommendations

<table>
<thead>
<tr>
<th></th>
<th>Diuretic</th>
<th>B-blocker</th>
<th>ACEI</th>
<th>ARB</th>
<th>CCB</th>
<th>Aldosterone Antagonist</th>
</tr>
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<tbody>
<tr>
<td>CHF</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Post-MI</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>High CHD risk</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>DM</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CRF</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Recurrent CVA</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
Stage 2 HT
Stage 1 HT
Prehypertension
Normal

Lifestyle modification

Compelling indications? Y treat

Treat with thiazide
ACEI, ARB, BB, CCB, or combination
Stage 2 HT
Stage 1 HT
Prehypertension
Normal

SBP
160
140
120
80 90 100
DBP

✓ Lifestyle modification

2 drugs combinations
Thiazide + ACEI/ARB/BB/CCB

Central Pontine Myelinolysis
What are the risk factors for thiazide induced hyponatremia?

- Age
- Low body mass
- Hypokalemia

Stroke prevention in Diabetics

- 40 – 60% adult with type 2 DM have HT
- Any difference in BP management for this special group of patients to prevent stroke?
UKPDS Event Rates for Select Endpoints With Tight vs Less Tight Blood Pressure Control

- **Any DM-related endpoint**: Tight (n=758) mean achieved BP 144/82 mmHg, Less tight (n=390) mean achieved BP 154/87 mmHg
- **DM-related death**: P=0.02
- **Stroke**: P=0.01
- **Microvascular complications**: P=0.009


UKPDS Relative Risk Reduction for Intensive vs Less Intensive Glucose Control

- **Microalbuminuria at 12 yrs**: -33% (P<0.01)
- **Microvascular complications**: -28% (P=0.02)
- **Retinopathy**: -31% (P=0.05)
- **Myocardial Infarction**: -16% (P=0.03)
- **Any DM endpoint**: -12% (P=0.03)

Over 10 years, HbA1c was 7.0% (6.2-8.2) in the intensive group (n=2,729) compared with 7.9% (6.9-8.8) in the conventional group (n=1,138).

**UKPDS Findings:**

**Tight BP Control vs. Intensive Glucose Control**

- **Tight vs. Less tight BP control reduces risk of**
  - Any diabetes-related endpoint: 24% (*P*=0.005)
  - Microvascular complications: 37% (*P*=0.009)
  - Stroke: 44% (*P*=0.01)

- **Intensive vs. Conventional glucose control policy reduces risk of**
  - Any diabetes-related endpoint: 12% (*P*=0.03)
  - Microvascular complications: 25% (*P*<0.01)
  - Myocardial infarction: 16% (*P*=0.05)

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"**Is ACEI/ARB better for diabetics?**"

Diagram showing the renin-angiotensin system (RAS) with ACE inhibition, showing the relative effects of ACE inhibitors (ACE) vs. other non-ACE inhibitors.
Is ACEI superior to other agents in the prevention of cardiovascular events in hypertensive type 2 diabetics?

<table>
<thead>
<tr>
<th></th>
<th>Size</th>
<th>ACEI</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCD</td>
<td>470</td>
<td>enalapril</td>
<td>nisoldipine</td>
</tr>
<tr>
<td>CAPPP</td>
<td>572</td>
<td>captopril</td>
<td>Diuretic or BB</td>
</tr>
<tr>
<td>FACET</td>
<td>380</td>
<td>fosinopril</td>
<td>amlodipine</td>
</tr>
<tr>
<td>UKPDS</td>
<td>758</td>
<td>captopril</td>
<td>atenolol</td>
</tr>
</tbody>
</table>


Relative Risk Reduction With ACEIs in ABCD, CAPPP and FACET

- AMI: -63, P < 0.001
- CVS Event: -51
- All-cause Mortality: -43, P = 0.01
- Stroke: -24, NS

MICRO-HOPE sub-studies of DM patients

**Ramipril (n = 3,577)**

- **Combined primary endpoint**
  - RR = 25%  
  - P < 0.001

- **Stroke**
  - RR = 33%  
  - P = 0.007

- **Myocardial infarction**
  - RR = 22%  
  - P = 0.01

- **Cardiovascular death**
  - RR = 37%  
  - P < 0.001

*The occurrence of myocardial infarction, stroke or cardiovascular death


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**LIFE Study Diabetes Subgroup**

(Lorsartan)

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>No. of events</th>
<th>P value</th>
<th>Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>242</td>
<td>0.031</td>
<td></td>
</tr>
<tr>
<td>CV Death</td>
<td>99</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>116</td>
<td>NS</td>
<td>21%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>91</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Total Mortality</td>
<td>167</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

Implications

- Tight control of HT with ACEI or ARB treatment reduces the risk of stroke in persons with DM

- Glycemic control reduces microvascular complications, but evidence showing a reduction in stroke risk with tight glycemic control is lacking

ASA/AHA 2006 recommendation
Primary stroke prevention for Diabetics

- Tight BP control
- Keep BP < 130/80 mmHg
- Consider ACEI/ARB
Case scenario

Chan Tai Man  M/52

BP 145/85 p70  Hslix 2hr pp 16.3

Hypertension

Primary Prevention

Stroke

Secondary Prevention

Stroke
ACEI for 2\textsuperscript{nd} stroke prevention?

- **HOPE**
  - **Ramipril** vs. Placebo
  - for 1013 patients with Hx of stroke/TIA
  - 24% RR (95% CI, 5 – 40) stroke, MI or vascular death; (n =1013)
  - BP lowering 3/2mm Hg (Office BP)

- **HOPE substudy (Ambulatory BP)**
  - 10/4 mmHg reduction over 24hr
  - 17/8 mmHg reduction during nighttime
  - $\rightarrow$ BP lowering effect leading to stroke risk reduction?

Comparative Effects of Ramipril on Ambulatory and Office Blood Pressures
Par Svensson; Ulf de Faire; Peter Sleight; Salim Yusuf; Jan Östergren
Hypertension. 2001;38:626

PROGRESS (perindopril)

- N = 6105
- Hx of stroke or TIA
- ACEI, ACEI + indapamide

- Recurrent CVA:
  - 43% RRR (95% CI 30 – 54); 12/5 mmHg $\downarrow$

- Recurrent major CVS events:
  - 40% RRR (95% CI 29 – 49)

- No benefit when ACEI was given alone
- Benefit also shown in normotensive patients

PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack.
AHA/ASA Guideline 2006
Secondary Prevention of Stroke

All patients with ischaemic stroke or TIA

- How much?
  - Benefit seen in reduction of ~10/5 mmHg
  - Normal BP < 120/80 mmHg by JNC-7
AHA/ ASA Guideline 2006
Secondary Prevention of Stroke

- Which drug?
- Optimal regimen – uncertain
- Available data support:
  - Diuretic
  - Diuretic + ACEI
- Individualized with patient characteristics

Key message

- Benefit for HT Rx is clear
- Choice of agent must be individualized
- Reduction of BP is generally more important than specific agent
- “Size does matter!”