Hypertensive Emergencies and Urgencies


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Conflict of Interest Statement

SEK has through the past 10 years or so received (to institution) SC honoraria for working with several RCTs (NORDIL, HOT, INSIGHT, LIFE, ASCOT, VALUE, ACCOMPLISH), and ad hoc honoraria (with regular tax reporting) for consulting or speaking for Abbott, AZ, Bayer, Berlin Chemie, Boehringer Ingelheim, BMS, Leo, Menarini, Merck, Merk, Nycomed, Novartis, Pharmcia, Phizer, Recordati, Sanofi-Aventis, Sankyo, Schering-Plough, Servier, Takeda
Guidelines

2007 Guidelines for the Management of Arterial Hypertension

The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

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Contribution of Risk Factors to Burden of Disease Mortality*

Prevalence of hypertension in different regions of the world: Actual figures for 2000 - predicted for 2025

Rate of hypertension %

<table>
<thead>
<tr>
<th>Region</th>
<th>2000 Men</th>
<th>2000 Women</th>
<th>2025 Men</th>
<th>2025 Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established Market Economies</td>
<td>116.2</td>
<td>123.3</td>
<td>147.9</td>
<td>161.8</td>
</tr>
<tr>
<td>Former Socialist Economies</td>
<td>40.8</td>
<td>52.5</td>
<td>44.0</td>
<td>59.7</td>
</tr>
<tr>
<td>India</td>
<td>107.3</td>
<td>106.2</td>
<td>102.1</td>
<td>98.5</td>
</tr>
<tr>
<td>Latin America &amp; the Caribbean</td>
<td>57.8</td>
<td>60.0</td>
<td>80.4</td>
<td>80.4</td>
</tr>
<tr>
<td>Middle Eastern Crescent</td>
<td>35.9</td>
<td>37.9</td>
<td>72.2</td>
<td>80.4</td>
</tr>
<tr>
<td>China</td>
<td>98.5</td>
<td>83.1</td>
<td>151.7</td>
<td>147.5</td>
</tr>
<tr>
<td>Other Asia &amp; Islands</td>
<td>35.9</td>
<td>33.0</td>
<td>67.3</td>
<td>62.1</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>38.2</td>
<td>41.6</td>
<td>73.6</td>
<td>77.1</td>
</tr>
</tbody>
</table>

Kearney et al Lancet 2005
"The Silent killer"

Hypertensive Emergency or Urgency at the Emergency Department of St. Imre Hospital in Hungary

In 2010
No. of population covered by the hospital………….. 900,000
No. of cases……………………………………………..….1451
No. of cases with hypertensive emergency or urgency…..155
No. of hospitalised patients for hypertensive crisis………..123

C. Farsang, Personal Communication 2011
Hypertensive Emergencies

- Hypertensive emergencies - severe forms of high BP are associated with acute damage to target organs
- Such emergencies are rare but can be life threatening
- In these conditions, the management of hypertension must be rapid
- Avoid extremely rapid falls in BP - may be associated with complications such as under-perfusion of the brain and cerebral infarction or damage to the myocardium and kidneys
- Excessive or rapid reductions in BP should be avoided in acute stroke

Hypertensive Emergencies

- Hypertensive left ventricular failure
- Hypertension with myocardial infarction
- Hypertension with unstable angina
- Hypertension and dissection of the aorta
- Severe hypertension associated with subarachnoid haemorrhage or cerebrovascular accident
- Crisis associated with phaeochromocytoma
- Use of recreational drugs such as amphetamines, LSD, cocaine or ecstasy
- Hypertension perioperatively
- Severe pre-eclampsia or eclampsia
- Hypertensive encephalopathy - MALIGNANT HYPERTENSION

Malignant Hypertension

- In most developed societies malignant hypertension is seen infrequently and mostly in economically deprived strata
- Malignant hypertension embraces a syndrome of severe elevation of arterial BP (diastolic BP usually >140mmHg) with vascular damage that can be particularly manifest as retinal haemorrhages, exudates and/or papilloedema
- Severe or poorly treated essential hypertension is usually the cause of malignant hypertension, although the presence of secondary cause of hypertension has probably been underestimated
- Blacks are known to be more frequently affected than Caucasians
- The prevalence of malignant hypertension has diminished as a result of earlier treatment of hypertension and more efficient antihypertensive drugs

Malignant Hypertension

- In malignant hypertension there is **breakdown of auto-regulation** as a result of the arterial wall being continuously exposed to extremely high BP.
- Pathological studies of the vascular wall demonstrate that there is **myointimal proliferation** and **fibrinoid necrosis**.
- The severity of the **proliferative response** parallels the severity and length of exposure to the high BP.
- The **fibrinoid necrosis** represents spasm and forced dilatation of small arterioles.
- The **leaking of fluid** into the extracellular space is associated with **small haemorrhages**.

Malignant Hypertension

- The most dangerous condition associated with malignant hypertension is **encephalopathy** - headache, disturbed mental status and visual impairment.
- Also associated with this condition is **deterioration in renal function**, with more severe forms of renal failure being associated with reduced life expectancy despite prompt and effective management of the hypertension.
- Malignant phase hypertension is also associated with **haemolysis and evidence of disseminated intravascular coagulation**.
- When malignant hypertension is **untreated**, its prognosis is extremely **poor**, with 50% of individuals dying within 12 months.
- With **modern antihypertensive drugs survival is better** and reflects not only improved BP control, but also identification of secondary causes and more widely available services such as renal dialysis and Tx.

Chapter 32

HYPERTENSIVE EMERGENCIES AND URGENCIES

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Grade I-II hypertensive retinopathy
Papillo-edema
TREATMENT OF HYPERTENSIVE URGENCIES AND EMERGENCIES

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²1st Department of Internal Medicine, St. Emeric Hospital, Budapest, Hungary

Agabiti-Rosei E, Salvetti M, Farsang C. J Hypertens 2006; 24:2477–2485
Table 1. Hypertensive emergencies

**Hypertensive encephalopathy**

- Severe hypertension associated to acute target organ damage:
  - acute coronary syndromes
  - pulmonary oedema
  - acute aortic dissection
  - intracerebral haemorrhage, subarachnoid haemorrhage
  - acute brain infarction
  - acute or rapidly progressing renal failure

**Severe hypertension after thrombolysis for ischaemic stroke**

**Pheochromocytoma crisis**

**Guillain-Barré syndrome**

**Spinal cord injury**

**Drugs related hypertension (sympathomimetics, cocaine, phencyclidine, phenylpropanolamine, lysergic acid diethylamide, cyclosporine, antihypertensive treatment withdrawal, interaction with MAO inhibitors)**

**Eclampsia**

**Postoperative bleeding**

**Post coronary artery bypass hypertension**
Table 2. Diagnostic workup

Repeated blood pressure measurements (first measurements at both arms)

Clinical history and physical examination:
- cardiovascular
- CNS
- **fundus oculi**

Selected laboratory studies:
- urinalysis, creatinine, urea, electrolytes, and a full blood count
- when a secondary form of hypertension is suspected, a sample for plasma renin activity, aldosterone, and eventually catecholamines should also be drawn

Electrocardiography

Chest X rays

Further investigations (according to the clinical presentation):
- echocardiography (TT, TE)
- brain CT scan or MRI
- abdominal ultrasonography
- thoraco-abdominal CT scan or MRI
- vascular ultrasound
The goal is to bring DBP down to 100–110 mmHg over 24 hours. **Exceptions:** Acute LV failure, dissection of aortic aneurysm - controlled hypotension is recommended.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium nitroprussiate</td>
<td>0.25–10 μg/kg/min</td>
<td>Immediate</td>
<td>1–2 min</td>
<td>Hypotension, vomiting, cyanate toxicity</td>
</tr>
<tr>
<td>Labetalol</td>
<td>20–80 mg bolus 1-2 mg/min infusion</td>
<td>5–10 min</td>
<td>2–6 h</td>
<td>Nausea, vomiting, heart block, bronchospasm</td>
</tr>
<tr>
<td>Glyceryl trinitrate</td>
<td>5–100 μg/min</td>
<td>1–3 min</td>
<td>5–15 min</td>
<td>Headache, vomiting</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>1.25–5.00 mg bolus</td>
<td>15 min</td>
<td>4–6 h</td>
<td>Hypotension, renal failure, angioedema</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40–60 mg</td>
<td>5 min</td>
<td>2 h</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>0.1–0.6 μg/kg/min</td>
<td>5–10 min</td>
<td>10–15 min</td>
<td>Hypotension, headache</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>2–10 mg/h</td>
<td>5–10 min</td>
<td>2–4 h</td>
<td>Reflex tachycardia, flushing</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>10–20 mg bolus</td>
<td>10 min</td>
<td>2–6 h</td>
<td>Reflex tachycardia</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>5–10 mg/min</td>
<td>1–2 min</td>
<td>3–5 min</td>
<td>Reflex tachycardia</td>
</tr>
<tr>
<td>Urapidil</td>
<td>25–50 mg bolus</td>
<td>3–4 min</td>
<td>8–12 h</td>
<td>Sedation</td>
</tr>
</tbody>
</table>
Hypertensive Urgencies

• Hypertensive urgencies are characterized by severe elevations in BP (>180/120 mmHg) without evidence of acute TOD. In hypertensive urgencies BP can usually be reduced in the emergency department by orally administered drugs without hospital admission and with ambulatory follow-up.

VALUE: Patient Characteristics

**Associated Risk Factors**

- Increased serum creatinine: 3.6%
- LVH: 12.2%
- Proteinuria: 22.5%
- Active smoker: 24.0%
- Diabetes: 31.6%
- High Cholesterol: 33.3%

**Associated Diseases**

- LVH with Strain: 6.1%
- PAD: 13.9%
- Stroke: 19.8%
- CAD: 45.8%

LVH = left ventricular hypertrophy.
PAD = peripheral artery disease; CAD = coronary artery disease.
VALUE: Analysis of Results Based on BP Control at 6 Months

Pooled Treatment Groups

- Fatal/Non-fatal cardiac events
- Fatal/Non-fatal stroke
- All-cause death
- Myocardial infarction
- Heart failure hospitalisations

Hazard Ratio 95% CI

Controlled patients* (n = 10755)
Non-controlled patients (n = 4490)

*SBP < 140 mmHg at 6 months.
**P < 0.01.

VALUE: Analysis of Results Based on Immediate Response*

Pooled Treatment Groups

Fatal/Non-fatal cardiac events
Fatal/Non-fatal stroke
All-cause death
Myocardial infarction
Heart failure hospitalisations

Immediate responders* (n = 9336)
Non-immediate responders (n = 5663)

Odds Ratio 95% CI

*Those not on previous tx: SBP Δ ≥10 mmHg at one month;
those on previous tx: SBP ≤ baseline at one month.
**P < 0.05; †P < 0.01.

Medication that rapidly lowers BP in an uncontrolled way, particularly *sublingual nifedipine*, should be avoided because an excessive fall in BP leads to ischemic symptoms, including angina pectoris and myocardial infarction.
Elevated Blood Pressure in Acute Stroke

• 75% of patients with acute stroke have systolic blood pressure ≥140 mm Hg\(^1,2\)

• Elevated blood pressure in the acute phase is associated with poor short- and long-term outcome\(^2\)

• There are no large-scale trials to guide clinical practice

• Animal studies and one clinical study (ACCESS)\(^3\) have shown promising results of the angiotensin receptor blocker candesartan in acute stroke

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\(^3\) Schrader J et al. *Stroke* 2003; 34: 1699
Cumulative event rate
Kaplan Meier Curve

Secondary – Vascular Events

Log Rank 4,99   p=0,0255

Schrader J & al. Stroke 2003;34:1699-1703
The ISH statement on the management of blood pressure in acute stroke was finalized after presentation and discussion at the World Health Organization and International Society of Hypertension (WHO–ISH) Meeting on Stroke and Blood Pressure, held in Melbourne, Australia, 5–7 December 2002. The meeting was conducted under the auspices of the Austin Hospital Medical Research Foundation, Melbourne. *J Hypertens* 21:665–672 © 2003 Lippincott Williams & Wilkins.

Journal of Hypertension 2003, 21:665–672

Keywords: stroke, ischaemic stroke, primary intracerebral haemorrhage, blood pressure management, hypertension, International Society of Hypertension

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SCAST Study Group

- 146 centres, 9 European countries
- 2,029 pts with acute stroke and elevated blood pressure (2005-2010)
- Recruitment was stopped early on administrative grounds (target: 2,500 pts)

## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Candesartan n = 1,017</th>
<th>Placebo n = 1,012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender, n (%)</td>
<td>405 (40)</td>
<td>448 (44)</td>
</tr>
<tr>
<td>Age, years (mean, SD)</td>
<td>70.8 ± 11.2</td>
<td>71.0 ± 11.0</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg (mean, SD)</td>
<td>171.2 ± 19.0</td>
<td>171.6 ± 19.2</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg (mean, SD)</td>
<td>90.3 ± 13.9</td>
<td>90.6 ± 14.2</td>
</tr>
<tr>
<td>Duration of symptoms, hrs (mean, SD)</td>
<td>17.6 ± 8.1</td>
<td>17.9 ± 8.1</td>
</tr>
<tr>
<td>SSS score (mean, SD)</td>
<td>40.6 ± 12.3</td>
<td>40.5 ± 12.6</td>
</tr>
<tr>
<td>Pre-morbid mRS score (median, IQR)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Qualifying event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke, n (%)</td>
<td>862 (85)</td>
<td>871 (86)</td>
</tr>
<tr>
<td>Haemorrhagic stroke, n (%)</td>
<td>144 (14)</td>
<td>130 (13)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>9 (1)</td>
<td>11 (1)</td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>676 (69)</td>
<td>670 (70)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>163 (16)</td>
<td>157 (16)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>190 (19)</td>
<td>186 (19)</td>
</tr>
<tr>
<td>Previous stroke or TIA, n (%)</td>
<td>252 (25)</td>
<td>204 (21)</td>
</tr>
<tr>
<td>Current use of an ACE inhibitor, n (%)</td>
<td>270 (27)</td>
<td>264 (27)</td>
</tr>
<tr>
<td>Thrombolytic treatment before inclusion</td>
<td>69 (8)</td>
<td>82 (9)</td>
</tr>
</tbody>
</table>
Blood Pressure in Treatment Period

<table>
<thead>
<tr>
<th>Day</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>152</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>160</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>152</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>147</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>147</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>147</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>147</td>
<td>82</td>
</tr>
</tbody>
</table>

\[\Delta \text{SBP} = 0.4, 3.3, 3.7, 5.0, 4.9, 5.7, 4.9\]

\[P\text{-value} = 0.62, 0.001, <0.001, <0.001, <0.001, <0.001, <0.001\]
Composite Vascular Endpoint (Vascular Death, Myocardial Infarction or Stroke)

Candesartan: 120 (11.7%)
Placebo: 111 (11.3%)

Adjusted HR 1.09, 95% CI 0.84–1.41; p=0.52
Functional Outcome (mRS)

Adjusted common OR 1.17, 95% CI 1.00-1.38; p=0.048

(non-significant, due to the use of two co-primary effect variables)
Meta-analysis of trials of >100 pts: Effect on death or dependency

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Favours treatment</th>
<th>Control</th>
<th>Risk Ratio IV, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>Weight</td>
</tr>
<tr>
<td>1.1.1 Previous trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BEST 1988</td>
<td>93 201</td>
<td>43 100</td>
<td>6.0% 1.08 [0.82, 1.41] 1988</td>
</tr>
<tr>
<td>ASCLEPIOS 1990</td>
<td>47 116</td>
<td>44 114</td>
<td>4.5% 1.05 [0.76, 1.45] 1990</td>
</tr>
<tr>
<td>Norms 1994</td>
<td>39 90</td>
<td>42 79</td>
<td>4.7% 0.82 [0.60, 1.12] 1994</td>
</tr>
<tr>
<td>Kaste 1994</td>
<td>44 175</td>
<td>31 172</td>
<td>2.9% 1.40 [0.93, 2.10] 1994</td>
</tr>
<tr>
<td>VENUS 1995</td>
<td>63 223</td>
<td>57 225</td>
<td>4.8% 1.12 [0.82, 1.52] 1995</td>
</tr>
<tr>
<td>Squire 1996</td>
<td>32 69</td>
<td>32 63</td>
<td>3.8% 0.91 [0.64, 1.30] 1996</td>
</tr>
<tr>
<td>INWEST 2000</td>
<td>138 195</td>
<td>56 100</td>
<td>10.1% 1.26 [1.04, 1.54] 2000</td>
</tr>
<tr>
<td>ACCESS 2003</td>
<td>45 173</td>
<td>35 166</td>
<td>3.2% 1.23 [0.84, 1.82] 2003</td>
</tr>
<tr>
<td>IMAGES 2004</td>
<td>826 1188</td>
<td>858 1198</td>
<td>32.4% 0.97 [0.92, 1.02] 2004</td>
</tr>
<tr>
<td>INTERACT pilot 2008</td>
<td>95 203</td>
<td>95 201</td>
<td>9.3% 0.99 [0.81, 1.22] 2008</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2633</td>
<td>2418</td>
<td>81.6% 1.04 [0.95, 1.14]</td>
</tr>
<tr>
<td>Total events</td>
<td>1422</td>
<td>1293</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.01; Chi² = 13.15, df = 9 (P = 0.16); I² = 32%
Test for overall effect: Z = 0.92 (P = 0.36)

1.1.2 SCAST

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Favours treatment</th>
<th>Control</th>
<th>Risk Ratio IV, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>Weight</td>
</tr>
<tr>
<td>SCAST 2010</td>
<td>348 1000</td>
<td>331 1004</td>
<td>18.4% 1.06 [0.93, 1.19] 2010</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1000</td>
<td>1004</td>
<td>18.4% 1.06 [0.93, 1.19]</td>
</tr>
<tr>
<td>Total events</td>
<td>348</td>
<td>331</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.39)

Total (95% CI) 3633 3422 100.0% 1.04 [0.97, 1.12]
Ischemic Penumbra: Hypoperfused Area of Focal Ischemia Can Be Salvaged by Timely Intervention

- Infarct: <8 mL/100 g/min
- Penumbra: 8–23 mL/100 g/min
- Normal: 50 mL/100 g/min

Impaired Function
No Structural Damage

Summary: Hypertensive Emergencies and Urgencies

- Treatment of hypertension in people with established CV or renal disease ("high risk") or target organ damage is always a matter of urgency – SBP control (SBP<140 mmHg) within 1 month (or earlier) lowers death and prevents CV endpoints
- In people with hypertensive emergency the goal is to bring DBP down to 100–110 mmHg over 24 hours
- Controlled hypotension is recommended in acute LV failure and dissection of aortic aneurysm
- Malignant hypertension/encephalopathy/papillo-edema is uncommon in modern societies but should be treated with iv drugs and careful titration of BP to targets
- High BP should not be lowered in acute stroke (first week)