Acute Medical Management

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UR MEDICINE

Stroke Treatment Alliance of Rochester
STAR-NY

Outline

- Head-of-bed position
- Blood pressure management
- Antiplatelet therapy
- Anticoagulation
- Statin therapy
- Rehabilitation and recovery

Head-of-bed position

- **HeadPoST** (*International Stroke Conference* 2017)
  - Designed to compare lying flat *vs.* sitting up in first 24 hours
  - 11,094 patients with AIS or ICH from 114 centers in 9 countries
  - No difference in functional outcomes at 90 days
  - Median NIHSS score 4 (0-42)

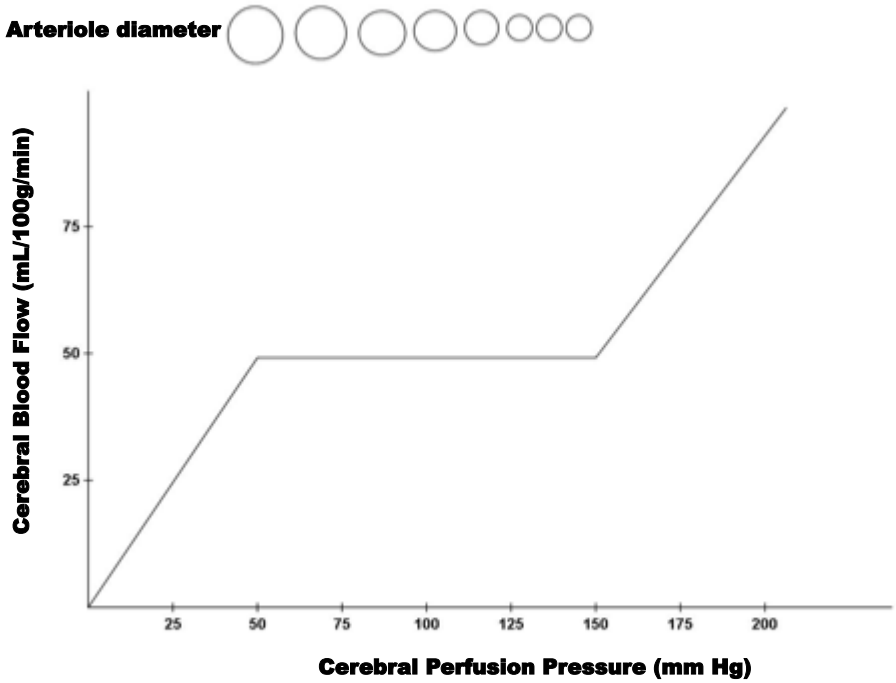
Blood pressure management

- Defining the problem:
  - Stroke is heterogeneous.
  - Optimal BP management remains unclear.
    - Should we raise or reduce the BP?
    - What threshold should we use to treat the BP?
    - How long after stroke should we start treatment?
    - How aggressive should the treatment be?
    - Should we stop or continue home antihypertensives?

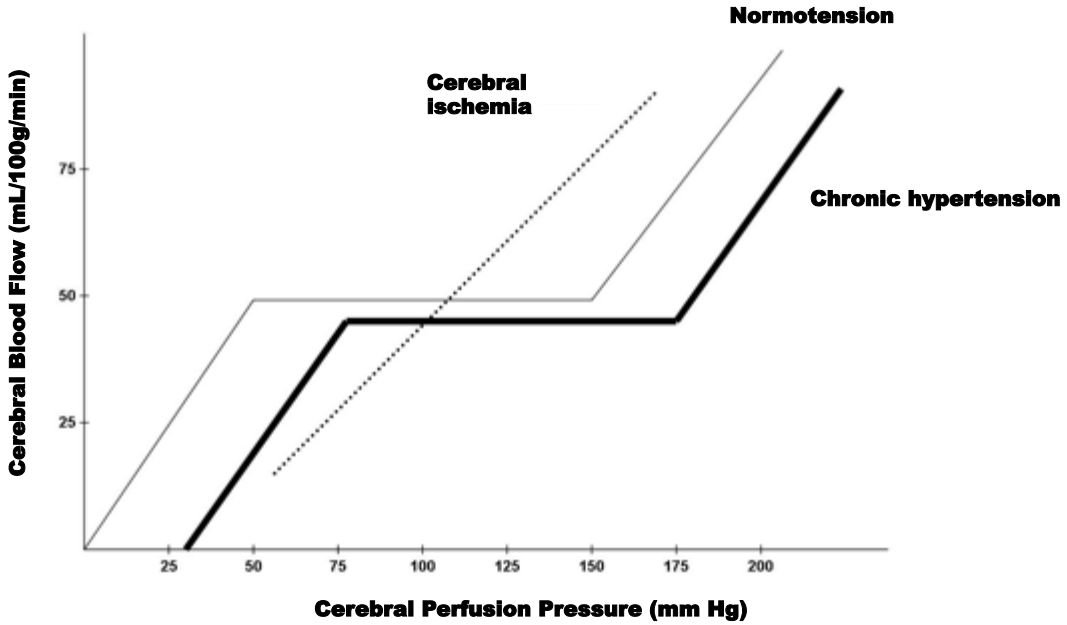
Cerebral autoregulation

- Maintenance of constant CBF despite changes in CPP
- CPP = MAP – ICP
  - CPP: Cerebral perfusion pressure
  - MAP: Mean arterial pressure
  - ICP: Intracranial pressure
- CPP and MAP have a linear relationship with slope = 1.

Cerebral autoregulation



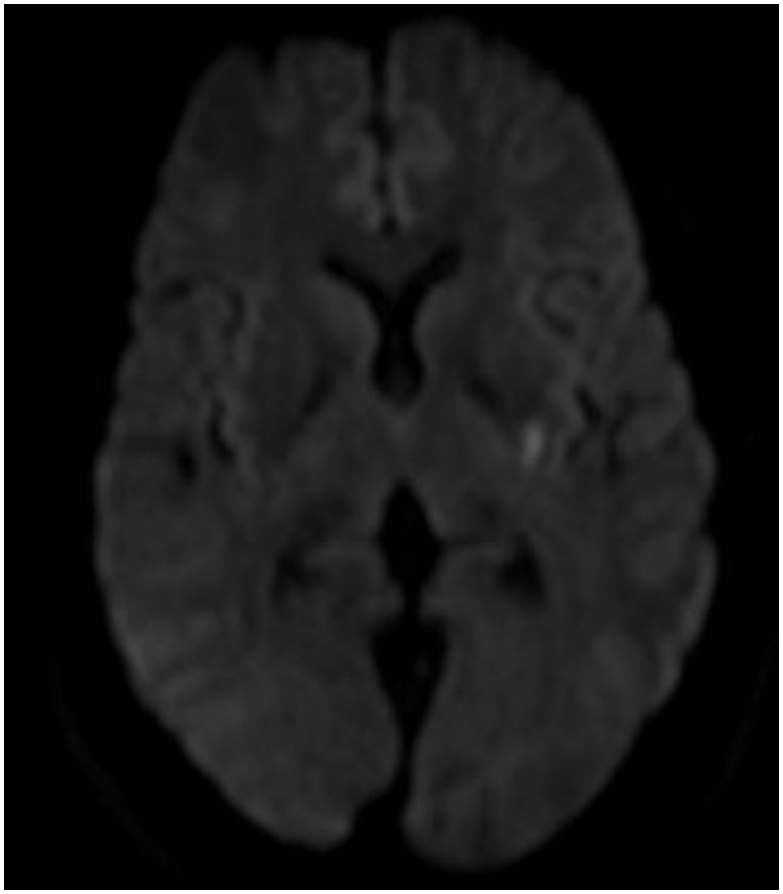
Cerebral autoregulation



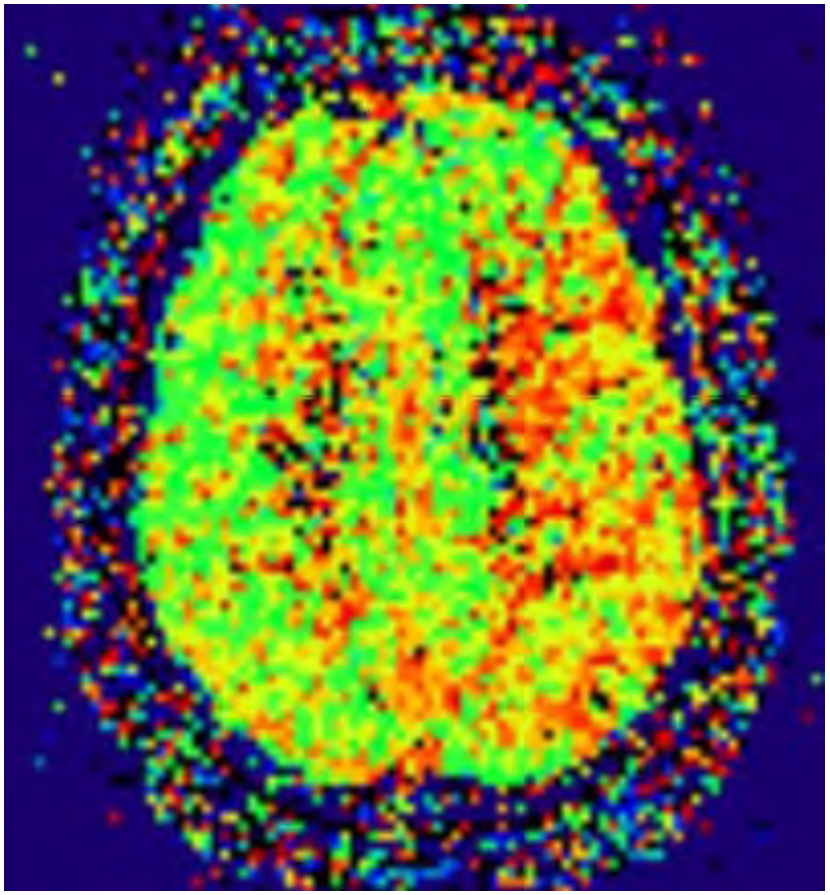
Case 1

- 56-y.o. woman with smoking and dyslipidemia
- Diagnosed with hypertension and started on treatment
- Recurrent right-sided weakness and speech difficulties
- BP 120/77 mm Hg on arrival

Case 1



Case 1



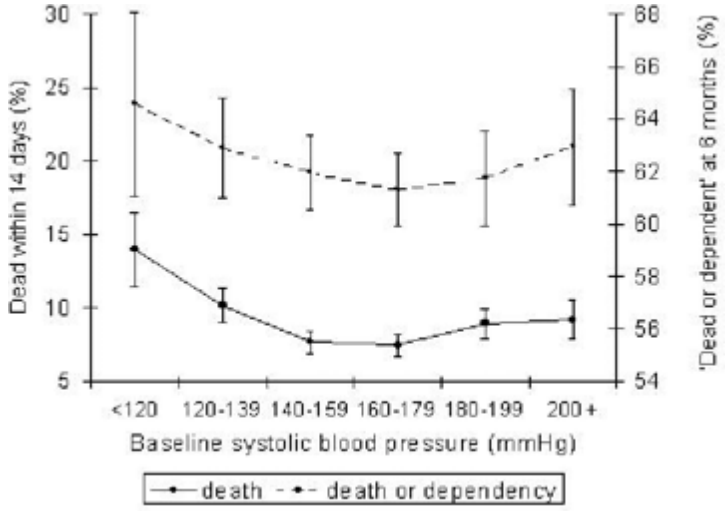
Case 1

Natural history

- 3/4 patients present with elevated BP.
- BP tends to normalize in the first 7 days.
- 1/3 of patients experience a reduction in first 24 hours.
- Indirect evidence for poor outcome if BP too high or low.

Observational data

- **IST**
  - In first 48 hours, 54% of patients had SBP > 160.
  - U-shaped relationship between BP and mortality
  - Excess mortality 3.8% for every 10 mm Hg above SBP 150
  - Excess mortality 17.9% for every 10 mm Hg below SBP 150



Empirical data

- **INWEST**
  - Designed to test neuroprotective effect of nimodipine in stroke
  - Planned enrollment 600 at 34 centers
  - Patients enrolled within 24 hours of stroke onset
  - Randomized to placebo *vs.* 1 or 2 mg/hr followed by 30 mg q6h
  - 2 mg/hr group had significantly worse outcomes than placebo.
  - 1 mg/hr group also had worse outcomes, though not significant.
  - Stopped early after enrolling 295 patients

Empirical data

- **ACCESS**
  - Designed to assess safety of 10-15% BP reduction first 24 hrs after acute ischemic stroke
  - Planned enrollment 500 at 53 centers
  - SBP/DBP ≥ 200/110 within 6-24 hours, or SBP/DBP ≥ 180/105 within 24-36 hours
  - Randomized to candesartan *vs.* placebo on day 1
  - Followed by candesartan +/- other agent(s) on day 7
  - Stopped early after analysis of 342 randomized patients
    - No difference in BP between groups
    - No difference in functional outcome at 3 months
    - Lower 1-year mortality and event rate in candesartan group

Schrader *et al.* Stroke 2003;34(7):1699-703.

Empirical data

- **CHHIPS**
  - Designed to test feasibility, safety, and efficacy of two agents
  - 179 patients with AIS (80%) or ICH (20%) and SBP > 160
  - Randomized 2:1 to lisinopril, labetalol, or placebo within 36 hours for 14 days
  - All patients placed on ACE inhibitor at 14 days
  - Target SBP 145-155, or 15 mm Hg reduction from baseline
  - 21 *vs.* 11 mm Hg drop in SBP in first 24 hours in treated *vs.* placebo ($p = 0.004$)
  - No difference in death or dependency at 2 weeks
  - No early neurologic deterioration or SAE seen with BP reduction
  - Treated group had 50% RRR in mortality at 3 months ($p = 0.05$).

Empirical data

- **COSSACS**
  - Designed to test safety and efficacy of stopping or continuing home BP medications
  - 763 patients presenting with AIS (92%) or ICH (8%)
  - Randomized to continue or stop BP medications for 2 weeks
  - Difference of 13 mm Hg in SBP and 8 mm Hg in DBP at 2 weeks ($p < 0.0001$)
  - No difference in death or dependency at 2 weeks
  - No difference in serious adverse events
  - No difference in mortality at 6 months

Empirical data

- **SCAST**
  - Designed to test effectiveness of BP reduction in acute stroke
  - 2029 patients with AIS (86%) or ICH (14%) and SBP > 140
  - Randomized to candesartan *vs.* placebo within 30 hrs for 7 days
  - Primary endpoints:
    - Composite endpoint of vascular death, MI, or stroke at 6 months
    - Functional outcome at 6 months (mRS)
  - Target SBP 145-155, or 15 mm Hg reduction from baseline
  - 147/82 *vs.* 152/84 in candesartan *vs*. placebo ($p < 0.0001$)
  - No difference in composite vascular outcome at 6 months
  - Higher risk of poor functional outcome at 6 months in candesartan group (OR 1.17, 95% CI 1.00-1.38, $p = 0.048$)

Empirical data

- **Effect of Blood Pressure Lowering in Early Ischemic Stroke**
  - Meta-analysis of trials published between 1966 and 2015
  - 13 randomized trials including 12,703 subjects
  - All studies started BP lowering within 3 days of AIS onset
  - Primary outcome: death or dependency at 3 months
  - Secondary outcome: recurrent vascular events
  - Early BP lowering had no effect on primary or secondary outcome

Empirical data

- **Induced hypertension: Randomized pilot study**
  - 15 patients randomized 2:1 to iHTN *vs.* standard care
  - Inclusion: AIS ≤ 7 days and DWI-PWI mismatch > 20%
  - MAP increased by 10-20 mm Hg in iHTN arm (max 140 mm Hg)
    - Stopping antihypertensives
    - Administering IV fluids
    - Administering IV phenylephrine
  - Target improvement in NIHSS score ≥ 2
  - NIHSS scores better in iHTN arm, day 3 (5.6 *vs.* 12.3, $p = 0.01$).
  - By week 6 to 8, NIHSS scores were 2.8 *vs.* 9.7 ($p < 0.04$).
  - No significant adverse events, 6 of 9 treated patients were responders.

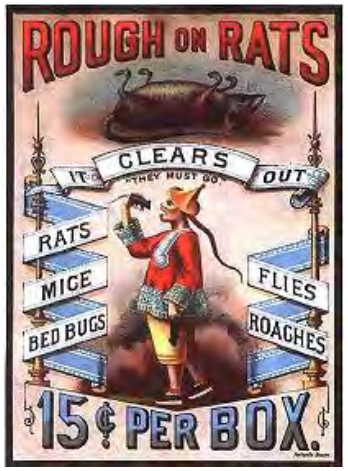
Current guidelines

- Benefits of treating BP in AIS not well established
  - (Class IIb; Level of Evidence C)
- If BP markedly elevated, a 15% reduction is reasonable in first 24 hours. Consider treatment for SBP ≥ 220, or DBP ≥ 110.
  - (Class I; Level of Evidence C)
- Resuming BP medications in patients with hypertension after 24 hours is reasonable.
  - (Class IIa; Level of Evidence B)
- No clear evidence for choice of medications to lower BP
  - (Class IIa; Level of Evidence C)

Antiplatelet therapy

- **IST** (*Lancet* 1997)
  - 19,435 randomized within 48 hours to ASA 300 mg *vs.* "avoid ASA" for up to 14 days.
  - Primary endpoint: death within 14 days, death or dependency at 6 months.
  - Results:
    - 4 fewer deaths per 1000 at 14 days in ASA group
    - 11 fewer deaths or nonfatal strokes per 1000 at 14 days in ASA group
    - Lower death and disability at 6 months if adjusted for prognosis
- **CAST** (*Lancet* 1997)
  - 21,106 randomized within 48 hours to ASA 160 mg *vs.* placebo for up to 4 weeks.
  - Primary endpoint: Death or dependence at discharge, or death at 4 weeks.
  - Results:
    - 5.4 fewer deaths per 1000 at 4 weeks in ASA group
    - 9 fewer deaths or nonfatal strokes per 1000 at 4 weeks in ASA group
    - 13 fewer dead or dependent per 1000 at discharge
- **Conclusion:** ASA therapy results in about 10 fewer deaths or recurrent strokes per 1000 in first few weeks, so start ASA as soon as possible after acute ischemic stroke.

Anticoagulation



- **TOAST** (*JAMA* 1998)
  - 1,281 randomized to ORG 10172 *vs.* placebo for 7 days.
  - No difference in functional outcomes at 30 days.
  - Increased ICH risk (14 *vs.* 4, $p = 0.05$), esp. in those with NIHSS score > 15
  - Subgroup analysis suggested benefit in those with large vessel disease.
  - Heparin for “hot carotid” hypothesis
- **HAEST** (*Lancet* 2000)
  - 449 with AF randomized within 30 days of AIS to dalteparin *vs.* ASA 160 mg
  - Primary endpoint: Recurrent ischemic stroke in first 14 days
  - Recurrent stroke occurred in 8.5% of dalteparin *vs.* 7.5% of ASA group.
  - No difference in symptomatic ICH or functional outcomes at 14 days or 3 months
- **CADISS** (*Lancet* 2015)
  - 250 with cervical ICA or VA dissection randomized to antiplatelet *vs.* warfarin within 7 days
  - Primary endpoint: Ischemic stroke attributable to dissection, or death
  - No difference in outcomes or adverse events

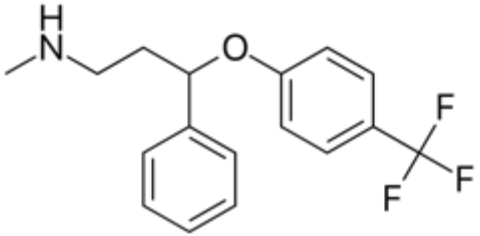
Statin therapy

- **SPARCL** (*NEJM* 2006)
  - 4,731 randomized within 6 months to atorvastatin 80 mg *vs.* placebo
  - Primary outcome: Recurrent stroke over 5 years
    - Occurred in 11.2% of those on atorvastatin *vs.* 13.1% on placebo
    - ARR 2.2% and RRR 16% over 5 years
    - LDL reduced to 73 *vs.* 129 with atorvastatin *vs.* placebo
- **ASSORT** (*International Stroke Conference* 2017)
  - 257 randomized to statin therapy within 24 hours *vs.* 7 days
  - Primary endpoint: 90-day disability by mRS
  - Results: No harm or benefit with early initiation
  - Statins used: atorvastatin 20 mg, rosuvastatin 5 mg, pitavastatin 4 mg

- **Conclusion:** High-dose, high-potency statin therapy reduces recurrent stroke risk in the long run. Unclear how soon statin therapy needs to be started after ischemic stroke, but starting immediately does not appear to confer significant risk at 90 days.

Rehabilitation and recovery

- **FLAME** (*Lancet* 2011)
  - 118 with AIS randomized within 5-10 days to 90-day course of fluoxetine 20 mg *vs.* placebo
  - Primary outcome: Change in FMMS score over 90 days
  - Improvement of 34.0 vs. 24.3 points (p = 0.003) in FMMS score in fluoxetine group
  - More depression in placebo group
- **AVERT** (*Lancet* 2015)
  - 2,014 with AIS and ICH randomized to frequent, higher-dose, very early mobilization (within 24 hours) *vs.* usual stroke unit care
  - Primary endpoint: mRS score ≤ 2 at 3 months
  - 92% *vs.* 59% mobilized within 24 hours in VEM *vs.* usual care group
  - Median time to mobilization 18.5 *vs.* 22.4 hours in VEM *vs.* usual care group
  - Fewer favorable outcomes in VEM group at 3 months (46% *vs.* 50%, p = 0.004)



Summary

- Head of bed elevation probably harmless unless exam position-dependent.
- With blood pressure and AIS, one size does not fit all.
- Start antiplatelet and statin therapy as soon as possible.
- No role for acute anticoagulation in most cases.
- Consider fluoxetine in patients with severe hemiparesis.
- Very early and aggressive mobilization may be harmful.