Critical Review Form

Prognosis

BP and Clinical Outcomes in the International Stroke Trial, *Stroke* 2002; 33: 1315-1320

Objective: "To characterize BP in acute stroke, determine its relationship with outcome, and consider possible explanations." (p 1315).

Methods: Re-analysis of data from the IST involving 19,435 subjects with acute ischemic stroke from one of 467 hospitals in 36 countries randomized within 48-hours of stroke symptom onset to aspirin or subcutaneous heparin in a single-blinded, controlled 3x2 factorial design. Only 17,398 of these patients were included in the current analysis because they had CT-confirmed acute ischemic stroke (AIS). Outcomes included 14-day mortality, recurrent stroke, death or dependency at 6-months.

Guide		Comments
I.	**Are the results valid?**	
A.	**Was the sample of patients representative?** *In other words, how were subjects selected and did they pass through some sort of "filtering" system which could bias your results based on a non-representative sample. Also, were objective criteria used to diagnose the patients with the disorder?*	Potential *selection bias* in that IST subjects were excluded if a contraindication to ASA or heparin existed and some investigators may have excluded those with very high BP (perceived increased bleeding risk) or multiple co-morbidities. In general, though, this very large, geographically diverse RCT likely represents acute ischemic stroke subjects everywhere.
B.	**Were the patients sufficiently homogeneous with respect to prognostic risk?** *In other words, did all patients share a similar risk from during the study period or was one group expected to begin with a higher morbidity or mortality risk?*	No. The original IST trial (Table 1, p 1571 from Lancet 1997; 349: 1569-1581) did not list demographic or prognostic features among the various allocation groups, although "large numbers and central randomization ensured good balance" (p 1572). Differences between groups may have existed. Notably, total anterior circulation syndrome with very high prognostic risk was associated with low BP whereas lacunar syndrome (with a low prognostic risk) was associated with high BP.

C.	**Was follow-up sufficiently complete?** *In other words, were the investigators able to follow-up on subjects as planned or were a significant number lost to follow-up?*	The data were virtually complete with "negligible loss to follow-up" (p 1319).
D.	**Were objective and unbiased outcome criteria used?** *Investigators should clearly specify and define their target outcomes before the study and whenever possible they should base their criteria on objective measures.*	Death – definitive and unequivocal. Disability – need help from another person with daily activities. Somewhat subjective and possibly pre-dating the stroke. Ischemic stroke or symptomatic intracranial hemorrhage – confirmed by CT, MRI, or necropsy. Fairly unequivocal and generalizable. Note: 14 day outcome was not blinded. Death within 72 hours of CVA was presumed to be due to cerebral edema, if there was not another definable cause.

II.	**What are the results?** **How likely are the outcomes over time?**	• 82% of patients had elevated SBP (> 140 mm Hg) at a single measurement (median of 20 hours after symptom onset). <5% were hypotensive (sBP < 110 mm Hg). • By Day 14, 8.5% mortality and by 6-months 61.5% dead or dependent. • The OR with 95 CI for death within 14 days are: SBP<150 1.155 (1.095-1.216) SBP>150 1.048 (1.012-1.079) • In multivariate models (attempting to remove confounding influences) the following factors were independently associated with mortality, dependency, or recurrent stroke: age, total anterior circulation syndrome, early presentation, atrial fibrillation, and alertness. • U-shaped curve describes the relationship between baseline systolic BP and death or dependency at 6-months with a nadir ~ 150mm Hg. • Each 10 mm ↓ below 150 ↑ early death 17.9% and 6-month death/disability 3.6% ($p < 0.001$). • Each 10 mm ↑ above 150 mm Hg ↓ early death 3.8% ($p = 0.04$) and 6-month mortality 1.1% (not significant) and early stroke recurrence 4.2% ($p = 0.023$). • Neither symptomatic intracranial hemorrhage nor total recurrent strokes were associated with baseline systolic BP. • Most recurrent ischemic strokes occurred within 5-days (peak Day 1) and early recurrence was associated with early death and 6-month death or disability.

B.	**How precise are the estimates of likelihood?** *In other words, what are the confidence intervals for the given outcome likelihoods?*	Table 2 (p 1317) shows the 95% CI either cross or are very close to unity for the associations with HBP and poor outcome particularly at 6 months. The ORs are not impressive in any of the associations, but these are for increments of 10 mmHg differences, at BPs that are 30 or 40 Torr from the reference of 150, the results might be more meaningful.
III.	**How can I apply the results to patient care?**	
A.	**Were the study patients and their management similar to those in my practice?**	Some selection bias from RCT design, but the large number of subjects, countries, and institutions represented ensure that the study patients should be similar to most settings. The authors should have quantitatively described more demographic and prognostic factors from the study cohort.
B.	**Was the follow-up sufficiently long?**	For EM 6-months is sufficiently long, although for Internal Medicine or Neurology 6-months might be insufficient.
C.	**Can I use the results in the management of patients in my practice?**	Although this was not a study to assess the effect of BP alteration on stroke outcome, the study offers prognostic quantitative data to provide patients and family members at the time of acute ischemic stroke.

Limitations

1) **Selection bias possible from exclusion criteria of IST RCT design.**
2) **Only single systolic BP obtained by non-standardized means and no assessment of diastolic BP was performed.**
3) **IST was unblinded to treating clinicians opening the possibility of ascertainment or co-intervention bias.**
4) **Surrogate definition of cerebral edema was used (death within 3 days) without any verification.**

Bottom Line

Both high (> 150 mm Hg) and low (< 150 mm Hg) initial systolic BP are associated with poor outcomes following acute ischemic stroke. Over 80% of acute ischemic stroke patients present with initial systolic BP > 140 mm Hg and each 10 mm Hg increase above 150 mm Hg increases the 14 day mortality by 3.8% and early stroke recurrence by 4.2% without any significant impact on 6 month death or disability rates.