Critical Review Form

Meta-analysis

High Blood Pressure in Acute Stroke & Subsequent Outcome: A Systematic Review, *Hypertension* 2004; 43: 18-24.

Objectives: **To perform a SR of observational studies of BP and outcome to assess the relation between the two.**

Methods: **One investigator conducted literature search using 10 key words in exploring PUBMED and EMBASE with the addition of articles obtained from reviewing reference lists of electronic database findings. Articles were excluded if they were randomized trials (authors feel selection bias inherent to RCT limits external validity), used outcomes other than Barthel's Index or Rankin Scale disability or stroke-related death, were duplicate publications, or had insufficient data reporting.**

Two authors independently extracted data with a third author resolving all discrepancies related to data extraction. The earliest BP reading was used and data were dichotomized into high (systolic BP > 150, diastolic BP > 90 mm Hg or MAP > 110 mm Hg) where not continuous. Dichotomous data were analyzed as Odds Ratio and continuous data as weighted mean difference. Statistical assessment of heterogeneity occurred with Cochran's Q-test Chi-square analysis with causes of heterogeneity explored with sensitivity analysis. Publication bias was assessed with Egger's asymmetry test (funnel plot).

Guide	Question	Comments
I	***Are the results valid?***	There is significant design and measurement heterogeneity between studies, most studies showed a worse outcome with hypertension in acute stroke, but some were neutral and 3 showed improved outcomes with higher initial BP.
1.	Did the review explicitly address a sensible question?	Yes, does initial blood pressure impact outcomes of ischemic, hemorrhagic, or mixed strokes?

2.	Was the search for relevant studies detailed and exhaustive?	No, only two electronic databases (PUBMED and EMBASE) were searched. Additional electronic databases include CINAHL, LILACS, and the Cochrane registry. Furthermore, the authors failed to contact investigators or industry experts to identify unpublished or ongoing clinical trials.
3.	Were the primary studies of high methodological quality?	Since the authors fail to grade the evidence using any established grading scales (like Jadad for RCT's) and they specifically excluded the highest tier of evidence among single trials (RCT's), the reader cannot be certain of the quality of evidence represented by the individual trials or how much weight each should carry. In general, however, there was considerable variability in methodology including timing and reporting of BP measurements, definition of hypertension (SBP ranging from 150 mmHg-200 mm Hg), timing of outcome determination (ranging from 6 days to 6 years) and definitions of outcomes (death, death or dependency, death or deterioration, recurrent stroke, hematoma expansion). Also 11 studies focused on primary intracerebral hemorrhage (PICH), 5 on ischemic stroke and the remainder looked at both.
4.	Were the assessments of the included studies reproducible?	Two investigators abstracted data but no assessment of abstract accuracy or study quality was reported in an inter-rater reliability assessment (Kappa).

II.	*What are the results?*	
1.	What are the overall results of the study?	• 32 observational studies totaling 10, 892 patients were included. • Studies had variable patient populations, outcome measures, follow-up intervals, methods of measuring BP, and ranged from 1949-2001. Important to consider time range here because of technological advancements. Specifically, how did a physician clinically distinguish an ischemic and a hemorrhagic stroke in 1949 prior to CT? Answer: The referenced 1949 paper by Tennent used a scale of history, physical exam and LP findings derived by Aring & Merritt in 1935 with reported 92% accuracy! • Incomplete, inconsistent Forest Plots are reported on page 19. • No publication bias was detected. • Most studies evaluated primary intracranial hemorrhage (PICH) • The strongest associations (Tables 2-4, pp 21-22) were with MAP for death (weighted mean difference 11.4, 95% CI 8.2-14.6, $p < 0.01$) and death/disability composite (WMD 9, 95% CI 0.92-17.1, $p = 0.03$) for **all** strokes. • In PICH, systolic BP and MAP have significant OR's (3.55 for sBP and 2.26 for MAP) for death, whereas based upon two studies ischemic stroke has an insignificant association with any BP parameter. • Elevated diastolic BP in ischemic stroke has two-fold increased risk of early recurrent stroke (authors fail to define "early").
2.	How precise are the results?	The statistically significant heterogeneity between studies (as measured by Cochrane's Q-test Chi square on Figure 1, p 19) suggest meta-analysis should probably not be performed. However, meta-analysis was performed with lack of precision as noted by above CI's.

3.	Were the results similar from study to study?	As mentioned above, there were significant differences for OR for death as well as death/disability between studies that primarily included PICH versus those looking at ischemic stroke. Most studies showed worse outcome with elevated BP, although some studies were neutral, and *3 showed improved outcomes*.

III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	Observational studies of variable design suggestion an association between elevated BP and poor outcomes following hemorrhagic stroke. A cause-effect relationship and benefit of BP lowering cannot be answered based upon this paper. Furthermore, this review does not answer when, how much, and how long to lower the BP.
2.	Were all patient important outcomes considered?	Most studies looked at death, dependency, deterioration, or a combined endpoint. Rarely were neurologic assessment scales used to quantify deterioration.
3.	Are the benefits worth the costs and potential risks?	N/A. This was not an interventional study nor was any hypothetical risk/benefit analysis discussed. The current study is simply observations upon which to base prognosis and future therapeutic trials.

Limitations

1) **Significant study-to-study heterogeneity limiting ability to conduct meta-analysis.**
2) **Observational trials only suggest association, not cause-effect. The current data only allows us to hypothesize about cause-effect and potential therapeutic interventions.**
3) **Lack of assessment of study quality.**
4) **Poor overall search strategy. The results of a Systematic Review or Meta-analysis depend entirely upon what evidence one includes. Identifying all potentially relevant data with a valid assessment of individual study quality are therefore crucial to optimizing SR quality.**
5) **The study neither references nor follows standardized guidelines for Systemic Reviews of Observational Studies known as the MOOSE Guidelines (Stroup DF et al, *JAMA* 2000; 283: 2008-2012).**

Bottom Line

One SR of observational trials suggests an association between elevated MAP (> 110) and systolic BP (>150) with death or the composite of death/disability in acute hemorrhagic stroke. Although an elevated diastolic BP (>90) is associated with a two-fold increased risk of early recurrent stroke in ischemic stroke, there is no significant association between acute ischemic stroke presenting BP parameters with death, disability, or deterioration based upon the current data.