Critical Review Form
Therapy

Rapid reduction of severe asymptomatic hypertension. A prospective, controlled trial. Arch Intern Med. 1989 Oct;149(10):2186-9.

<u>Objectives:</u> To determine, in emergency department (ED) patients with severe asymptomatic hypertension, "if antihypertensive loading is superior to initiation of maintenance therapy without loading." (p. 2186)

<u>Methods:</u> This randomized, placebo-controlled trial conducted at a large urban ED, included patients with sitting diastolic blood pressure (DBP) between 116 and 139 mmHg. Exclusion criteria included:

1) **Papilledema**
2) **Congestive heart failure**
3) **Encephalopathy**
4) **History of transient neurologic deficits**
5) **Serum creatinine level greater than 220 μmol/L (2.5 mg/dL)**
6) **Active urinary sediment**
7) **Angina or prior myocardial infarction**
8) **Any unstable medical condition**
9) **Potential fertility**
10) **Concomitant therapy with a tricyclic antidepressant or sedative-hypnotic**
11) **Considerable pain**

All patients were given 0.2 mg of clonidine and 25 mg of chlorthalidone initially. Patients were then randomized by a computer-generated sequence to one of 3 treatment arms: Group 1 patients were given clonidine 0.1 mg every hour up to 4 doses until DBP decreased by at least 20 mmHg or dropped below 105 mmHg; Group 2 patients were given placebo every hour for 4 doses, until either DBP decreased by at least 20 mmHg or fell below 105 mmHg, or until all 4 doses had been given; Group 3 patients received no further medication and were discharged immediately from the ED.

Upon discharge, patients in all 3 groups were given clonidine 0.2 mg and chlorthalidone 25 mg, each twice daily; patients whose systolic blood pressure (SBP) was ≤ 105 mmHg, or whose DBP was ≤ 70 mmHg after the initial 0.2 mg dose of clonidine were discharged on a regimen of clonidine 0.1 mg and chlorthalidone 12.5 mg, each twice daily. Follow-up occurred at 24, 48, and 72 hours, and at one week. At follow-up, patients whose SBP was ≤ 100 mmHg or whose DBP was ≤ 60 mmHg had their antihypertensive doses reduced to clonidine 0.1 mg and chlorthalidone 12.5 mg, each twice daily.

Seventy-four patients with asymptomatic hypertension were identified, of whom 44 completed the designated week of follow-up. An additional 20 patients completed 24-hour follow-up. Ten patients withdrew after the initial ED visits. Thirteen patients had newly diagnosed hypertension. Of the 64 patients with some follow-up data, 62 had clinical, laboratory, or historical evidence of chronic hypertension-related end-organ damage. All study subjects had no antihypertensive medications for at least 3 days prior to enrollment. No demographic data was provided.

The outcomes assessed included: 1) a comparison of the number of doses of clonidine vs. placebo and the amount of time required to achieve "acceptable" blood pressure control for groups 1 and 2; 2) a comparison of mean arterial pressure (MAP) between groups 1 and 2 every hour during the ED visit; 3) comparisons of reductions in SBP, DBP, and MAP after loading, and at 24 hours, 48-72 hours, and one week of follow-up for all 3 groups.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. A computer-generated sequence was used to randomize patients to one of 3 groups.
2.	Was randomization concealed (blinded)?	Unclear. It is unclear if the computer-generated sequence was performed beforehand or at the time of enrollment, and if the sequence could be subverted by the clinicians or investigators (allocation concealment).
3.	Were patients analyzed in the groups to which they were randomized?	Likely yes. The authors do not specifically mention whether an intention to treat analysis was used, but as all patients received the same outpatient therapy and the difference between groups lay in the initial management of their hypertension, it is reasonable to assume that patients were analyzed according to group. Compliance with outpatient therapy was measured by pill count, but the authors do not give data on rates of compliance.
4.	Were patients in the treatment and control groups similar with respect to known	No. Patients in group 1 had significantly higher initial SBP, DBP and MAP than those in groups 2 and 3 (Table 1). No additional demographic data was presented (prior diagnosis of hypertension, duration of hypertension, insurance status) which

<table>
<tr><td></td><td>prognostic factors?</td><td>could affect the outcomes (Consort Statement).

Table 1. Mean initial blood pressure (±SEM)<table><tr><td></td><td>Group 1
(n = 21)</td><td>Group 2
(n = 16)</td><td>Group 3
(n = 27)</td></tr><tr><td>SBP (mmHg)</td><td>192.9 ± 4.9</td><td>182.4 ± 4.4</td><td>181.9 ± 3.9</td></tr><tr><td>DBP (mmHg)</td><td>125.6 ± 1.8</td><td>124.1 ± 1.7</td><td>122.5 ± 1.1</td></tr><tr><td>MAP (mmHg)</td><td>148.7 ± 2.4</td><td>143.5 ± 2.0</td><td>142.3 ± 1.9</td></tr></table></td></tr>
<tr><td>B.</td><td>Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>Were patients aware of group allocation?</td><td>Yes and no. Patients in groups 1 and 2 were given either clonidine or placebo in the index ED visit, and would likely be unaware of group allocation. Patients in group 3 were discharged after the 1st dose of antihypertensive with no additional ED treatment, and could not be blinded to group allocation.</td></tr>
<tr><td>2.</td><td>Were clinicians aware of group allocation?</td><td>Yes and no. Investigators (who presumably cared for the patients at the follow-up visits) could not be blinded to allocation to group 3, but were blinded to allocation between groups 1 and 2.</td></tr>
<tr><td>3.</td><td>Were outcome assessors aware of group allocation?</td><td>Yes and no. Investigators could not be blinded to allocation to group 3, but were blinded to allocation between groups 1 and 2.</td></tr>
<tr><td>4.</td><td>Was follow-up complete?</td><td>No.</td></tr>
<tr><td>II.</td><td>What are the results (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>How large was the treatment effect?</td><td>There was no difference in the mean number of doses of clonidine or placebo required to achieve acceptable blood pressure control in groups 1 and 2 (2.0 ± 0.2 vs. 1.8 ± 0.3, respectively; p = 0.0299).

The mean MAP was similar between groups 1 and 2 after oral loading in the ED (5 hours after initiation of therapy): 110.1 ± 1.9 mmHg vs. 112.5 ± 3.2 mmHg (p = , although a larger mean</td></tr>
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<td>decline in MAP in was observed in group 1 (-38.6 ± 2.8 vs. -31.1 ±2.4, p < 0.05).

There was no significant difference in the mean reduction in SBP, DBP, or MAP between the 3 groups at 24 hours (Table 2), and no significant difference in the mean reduction in MAP at one week between groups 1, 2, and 3: -43.2±2.7 (95% CI -49.0 to -37.3) vs. -40.2±3.0 (95% CI -46.8 to -33.6) vs. -36.7±3.7 (95% CI -44.5 to -28.8), P = 0.689.

Table 2. Mean change in blood pressures at 24 hours (± SEM)
<table>
<tr><td></td><td>Group 1
(n = 21)</td><td>Group 2
(n = 16)</td><td>Group 3
(n = 27)</td></tr>
<tr><td>ΔSBP
mmHg
(95% CI)</td><td>-52 ± 6.3
(-65.0 to -38.9)</td><td>-45.4 ± 5.2
(-56.5 to -34.3)</td><td>-45.6 ± 4.9
(-55.7 to -35.5)</td></tr>
<tr><td>ΔDBP
mmHg
(95% CI)</td><td>-26.9 ± 2.2
(-31.6 to -22.3)</td><td>-29.6 ± 1.6
(-33.0 to -26.3)</td><td>-25.4 ± 2.2
(-29.9 to -20.9)</td></tr>
<tr><td>ΔMAP
mmHg
(95% CI)</td><td>-35.3 ± 3.3
(-42.1 to -28.5)</td><td>-34.9 ± 2.6
(-40.4 to -29.3)</td><td>-32.1 ± 2.9
(-37.9 to -26.2)</td></tr>
<tr><td colspan="4">P = 0.639 for ΔSBP mmHg
P = 0.395 for ΔDBP mmHg
P = 0.689 for ΔMAPmmHg</td></tr>
</table>
The incidence of recurrent severely elevated BP (DBP > 115 mmHg) at one week was similar in the 3 treatment groups: 4 of 21 (19%) in group 1, 1 of 16 (6.3%) in group 2, and 2 of 27 (7.4%) in group 3. All of these patients remained asymptomatic.

No patient experienced symptomatic hypotension or developed symptoms of cerebral hypoperfusion. Eleven patients required reduction in maintenance medication dosage due to relative hypotension during the loading (n=1) or follow-up (n=11) periods. The authors report that these were evenly distributed among the groups, but do not provide exact numbers. Six of these patients reported symptoms compatible with orthostasis.

Eighteen patients requested discontinuation of clonidine and chlorthalidone therapy due to side effects (impotence or sedation) at study completion.</td>
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<td>2.</td>
<td>How precise was the estimate of the treatment effect?</td>
<td>See above.</td>
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<td>III.</td>
<td>How can I apply the results to patient care (answer the</td>
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	questions posed below)?	
1.	Were the study patients similar to my patient?	No. While these patients were seen at a large, urban ED, there are differences affecting external validity: 1) The study was conducted in the 1980s. Management strategies for hypertension have changed both in the ED and in the outpatient setting. 2) All patients were provided medications and access to 24 hour and one-week follow-up. Many patients in our setting are unable to afford their prescribed medications or do not have access to follow-up care. 3) No demographic data was provided for patients. It is possible that there were differences with respect to age, sex, race, or past medical history that would make this group significantly different from our patient population.
2.	Were all clinically important outcomes considered?	No. The outcomes assessed were changes in BP measurements at 24 hours and one week, rather than patient-important outcomes (i.e. stroke, MI, renal failure, death). While long-term blood pressure control has been shown to improve these outcomes, short-term blood pressure differences may not have an effect.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While this study showed no difference in mean change in blood pressure at 24 hours and one week between patients receiving an oral clonidine load, placebo, or immediate ED discharge, they did not assess patient-important outcomes. Additionally, methodological flaws (i.e. a significant loss to follow-up, failure to provide demographic data) and issues with external validity make interpretation and application of the results difficult.

Limitations:

1) **Group 1 had higher mean initial systolic blood pressure and mean arterial pressures (prognostic imbalance).**

2) **Failure to adhere to Consort Statement:**

    a. **Did not provide demographic data.**

    b. **No primary outcome defined.**

3) **Inability to blind patients or clinicians to group 3 allocation**

4) **Failure to provide compliance data.**

5) **Significant loss to follow-up: 30 of 74 (40.5%) failed to complete one-week follow-up. While the authors state drop-outs were evenly distributed among the groups, they do not provide actual numbers (potential attrition bias).**

6) **Surrogate outcomes used rather than long-term patient-important outcomes (i.e. stroke, MI, renal failure, death).**

Bottom Line:

This randomized controlled trial assessed the effect of oral loading with clonidine in patients with asymptomatic severely elevated blood pressure in the ED on 24-hour and one week blood pressure measurements. They found no significant difference in the change in mean SBP, DBP, or MAP at either 24 hours or on week between groups who received oral loading of antihypertensives in the ED, oral loading with placebo in the ED, or immediate discharge. The study did not address the impact of these treatment measures on patient-important outcomes, such as stroke, MI, renal failure, or death. There were several issues with data reporting, including failure to provide demographic data or designate a primary outcome.