REVIEW

# Management of Patients With Hypertensive Urgencies and Emergencies

## A Systematic Review of the Literature

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***BACKGROUND:*** **Hypertensive urgencies and emergencies are common clinical occurrences in hypertensive patients. Treatment practices vary considerably to because of the lack of evidence supporting the use of one therapeutic agent over another. This paper was designed to review the evidence for various pharmacotherapeutic regimens in the management of hypertensive urgencies and emergencies, in terms of the agents' abilities to reach predetermined ''safe'' goal blood pressures (BPs), and to prevent adverse events.**

***METHODS:*** **MEDLINE was searched from 1966 to 2001, and the reference lists of all the articles were retrieved and searched for relevant references, and experts in the field were contacted to identify other relevant studies. The Cochrane Library was also searched. Studies that were eligible for inclusion in this review were systematic reviews of randomized control trials (RCTs) and individual RCTs, all-or-none studies, systematic reviews of cohort studies and individual cohort studies, and outcomes research. No language restrictions were used.**

***RESULTS:*** **None of the trials included in this review identified an optimal rate of BP lowering in hypertensive emergencies and urgencies. The definitions of hypertensive emergencies and urgencies were not consistent, but emergencies always involved target end-organ damage, and urgencies were without such damage. Measures of outcome were not uniform between studies. The 4 hypertensive emergency and 15 hypertensive urgency studies represented 236 and 1,074 patients, respectively. The evidence indicated a nonsignificant trend toward increased efficacy with urapidil compared to nitroprusside for hypertensive emergencies (number needed to treat [NNT] for urapidil to achieve target BP, 12; 95% confidence interval [95% CI], number of patients needed to harm [NNH], 5 to NNT, 40 compared to nitroprusside). Several medications were efficacious in treating hypertensive urgencies, including: nicardipine (NNT for nicardipine compared to plabebo, 2 in one study [95% CI, 1 to 5] and 1 in another [95% CI, 1 to 1]); lacidipine (NNT, 2; 95% CI, 1 to 8 for lacidipine vs nifedipine) or urapidil (NNT for urapidil compared to enalaprilat and nifedipine, 4; 95% CI, 3 to 6); and nitroprusside and fenoldopam (all patients reached target BP in 2 studies). The studies reported 2 cases of cerebral ischemia secondary to nifedipine.**

***CONCLUSIONS:*** **Many effective agents exist for the treatment of hypertensive crises. Because of the lack of large randomized controlled trials, many questions remain unanswered, such as follow-up times and whether any of the studied agents have mortality benefit.**

***KEY WORDS:*** **hypertensive urgency; hypertensive emergency; hypertensive crisis.**
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Hypertensive urgencies and emergencies are common clinical occurrences that may account for as many as 27.5% of all medical emergencies presenting to the emergency department[1] and 3% of all emergency room visits,[2] and that may affect as many as 1% of hypertensive patients.[3,4] However, clinical treatment practices for the management of hypertensive urgencies and emergencies vary considerably.[1] This practice variability is in part because of the lack of evidence supporting the use of one therapeutic agent over another. This paper was designed to review the evidence for various pharmacotherapeutic regimens in the management of hypertensive urgencies and emergencies in terms of the agents' ability to reach a predetermined "safe" target blood pressure (BP) and to prevent adverse events.

For this paper, we used the following definitions for hypertensive urgencies and emergencies, which were taken from the literature: in a *hypertensive emergency*, a patient has evidence of target end-organ damage, such as encephalopathy, unstable angina, stroke, or a dissecting aortic aneurysm. The absolute level of BP in this situation is not as important as the evidence of end-organ damage.[1] In *hypertensive urgencies*, the patient has elevated BP but has no evidence of end-organ damage.

## METHODS

### Search Strategy

We searched MEDLINE from 1966 to 2001 using the terms *hypertensive urgency*, *hypertensive emergency*, *hypertensive crisis*, *uncontrolled hypertension*, *refractory*

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*hypertension*, *poorly responsive hypertension*, *poorly responsive blood pressure*, and *malignant hypertension*. We also used *search terms* for finding systematic reviews.[5] We then retrieved the references of all the articles and searched the bibliographies for additional relevant references. Experts in the field were contacted to identify any relevant studies. We also searched the Cochrane Library using the terms *hypertension* and *malignant hypertension*. Studies that were eligible for inclusion in this review were systematic reviews of randomized control trials (RCTs) and individual RCTs, all-or-none studies, systematic reviews of cohort studies and individual cohort studies, and outcomes research, i.e., Level 1 or 2 evidence. We did not include any language restrictions in the literature search. Our study included all classes of antihypertensive agents. The agents could have been given via sublingual (SL), oral (PO), or parenteral (IV) routes, depending on the agent and the setting.

The articles were appraised by 2 independent reviewers who assessed their level of evidence on the basis of the definitions that can be found in Table 1. Levels of evidence are useful in assessing the validity of evidence and in interpreting evidence. They have been designed to identify the specific methods that maximize the validity of a study's conclusions and structure them into a hierarchy of study types with the most valid at the forefront.[6] Only those articles with Level 1 or 2 evidence were included in this review. Number needed to treat (NNT) and relative risk (RR) calculations were performed using the Mount Sinai Hospital Center for Evidence Based Medicine statistics calculator[7] and were included for comparative purposes. The NNT calculations were given, when possible, for the most effective agent in trials comparing more than 1 antihypertensive. The RR calculations were also performed, when possible, to give an estimate of the likelihood of the less-effective agent reaching the target BP.

**Table 1. Levels of Evidence/Therapy Studies[6]**

| Level of Evidence | Study Design |
|---|---|
| 1a | Systematic review of RCTs |
| 1b | Individual RCT |
| 1c | All or none[6,*] |
| 2a | Systematic review of cohort studies |
| 2b | Individual cohort study |
| 2c | Outcomes research[6,†] |
| 3a | Systematic review of case control study |
| 3b | Individual case control study |
| 4 | Case series |
| 5 | Expert opinion, consensus meeting |

* *Met when all patients died before the treatment became available, but some now survive on it; or when some patients died before the treatment became available, but none now die on it.*

† *Outcomes research uses data to understand how well treatments work in the real world, in specific patient populations and under specific conditions (i.e., the end result of healthcare practices and interventions).*

*RCT, randomized control trial.*

## Study Participants

Study participants were over the age of 18 years and had had a hypertensive emergency or urgency at the time of their enrollment in the study. Exclusion criteria were varied and included the very elderly (>80 years old),[8,9] pregnancy and lactation,[8–19] history of organ transplantation,[8,17] immunosuppression,[17–19] acute[8,9,17,18] or chronic renal failure,[8,11,12,17,18,20] dialysis,[17–19] valvular heart disease,[11,12,14,21] recent stroke,[11,12,14,21,22] acute myocardial infarction,[9,11,12,14–16,21] coronary bypass surgery or congestive heart failure,[11,12] "bilateral stenosis"[9] or arrhythmia,[15–20] or a known secondary cause of hypertension such as pheochromocytoma.[8,17–19] Other exclusion criteria included hypothyroidism,[19] hepatic[14,15,17–19] or hematological disease,[14,17,18] asthma or chronic obstructive pulmonary disease,[16] alcohol intoxication,[12] parenteral analgesia,[17,18] dopamine antagonists[17–19] or "considerable pain."[13] Patients with signs of end-organ involvement were excluded in the hypertensive urgency studies. Signs of end-organ involvement (acute myocardial infarction, aortic dissection, and focal neurological deficits) aside from hypertensive changes in the retina were exclusion criteria in 1 study of hypertensive emergencies.[10]

## RESULTS

Six hundred hypertensive urgency or hypertensive emergency abstracts were identified in the literature. Most of these studies were excluded because they were nonhuman studies, did not involve patients with high enough BP to qualify as an urgency or an emergency, were safety/tolerability studies, or were case-series or case reports. We were left with 39 studies after excluding all of the above. Ten studies were then excluded because they did not include a target BP and were therefore of limited usefulness to clinicians and could not be compared to other agents in terms of NNT or RR. Other studies were excluded because they were methodologically flawed in their randomization (5 studies) or because the target BP was arbitrarily described as an appropriate target BP according to the treating physician (1 study). Methodologically flawed RCTs were excluded because they were of a lower quality and level of evidence compared to some of the well-designed cohort studies that we evaluated. Other reasons for exclusion were that the study involved nonpharmacological interventions (e.g., coffee and cigarette smoking or concurrent hemodialysis)[2] or that the study was a follow-up of patients who had already been treated for a hypertensive emergency or urgency[1] or who had had a run-in period with other drugs (1 study), making the interpretation of the results very difficult in terms of the drug of interest. Nineteen trials met the criteria for Level 1 or 2 evidence. The 4 hypertensive emergency and 15 hypertensive urgency studies represented 236 and 1,074 patients, respectively.

Eight of the 19 trials included in this review were open label or did not mention if the trial was

blinded.[8–10,16,17,19,23,24] We included these studies because they met our review's inclusion of Evidence Level 1 or 2. In addition, the number of studies of this quality is limited and the further exclusion of studies would further limit the conclusions of this review.

The definitions of hypertensive emergencies and urgencies did vary in the studies with respect to specific BP measurements, but emergencies always involved hypertension with target end-organ damage, and urgencies without such damage. Moreover, measures of outcome were not uniform between studies. Some studies used the diastolic blood pressure (DBP) as the endpoint to indicate success, and either used a specific blood pressure (usually 95 to 110 mm Hg),[8] a percentage reduction in blood pressure[20] or a numeric (20 mm Hg)[13,20] fall in the DBP. Fewer studies used the systolic blood pressure (SBP) as the goal.

Many of the studies included in this review used adverse effects as outcome measures as well. None of the studies used immediate or long-term mortality endpoints. In addition, in the hypertensive emergency studies, resolution of end-organ dysfunction did not figure prominently as outcome measures in all the studies.

## Treatment for Hypertensive Emergencies

We were unable to identify any prospective studies that addressed the questions of how quickly BP should be controlled in a hypertensive emergency or when maintenance therapy with antihypertensive medications should begin. We identified 3 small, level 2b trials and one level 1b trial that compared various therapies in patients with hypertensive emergencies (Table 2).[8,10,21,23] Each of the 3 level 2b trials used different entry criteria. One study included patients with increased SBP and/or increased DBP and any evidence of target end-organ damage.[8] They found that nitroprusside led to a faster response (49%) than did urapidil (20%) in the first 15 minutes of therapy ($P < .001$). However, due to the short half-life of nitroprusside, this difference was not seen at 4 hours.[8] Nitroprusside was associated with more adverse side effects, including 2 episodes of hypotension, although none of them was associated with clinical sequelae (23% vs 11%; $P < .04$). In addition, nitroprusside requires invasive monitoring. Another study included patients with an elevated DBP and hypertensive retinopathy and found that nitroprusside achieved the target BP more slowly than did nifedipine,[10] while a third study included patients with DBP >120 mm Hg but did not provide explicit information about target organ damage.[23] This last study looked at 120 patients who were randomized to 1 of 4 treatment groups including: 10 mg nifedipine SL; 50 mg captopril SL; 0.15 mg clonidine IM; or 10 mg nifedipine SL and 40 mg furosemide IV. No significant blood pressure differences were found between the 4 groups after treatment.

The last study, by Angeli et al., found that 7 of 10 patients treated with captopril or 5 of 10 treated with nifedipine were complete responders (not significant).[21] This study also found that the duration of action for the 2 drugs was similar.

## Treatment for Hypertensive Urgencies

We were unable to identify any high-quality studies that addressed what blood pressure defines a hypertensive urgency, how quickly blood pressure should be decreased in a hypertensive urgency, when maintenance therapy should be started, or whether patients with hypertensive urgencies should be treated in observed settings. We found 15 prospective trials representing levels 1b and 2b evidence that addressed therapy in patients with hypertensive urgencies (Table 3). Although many of these studies defined hypertensive urgencies differently, the most consistently used definition was a DBP of >120 mm Hg. Methodological problems in the trials included small sample size,[11,13,14,16,25] open label design,[9,16,17,19,24] lack of follow-up in most of the studies, and contamination.[14] In addition, few studies looked at outcomes more than 24 hours after randomization, and follow-up ranged from only 15 minutes to 1 week. Moreover, the trials used various definitions of "therapeutic response" and none looked at long-term blood pressure control or important cardiovascular endpoints.

In one study comparing nicardipine to placebo, nicardipine therapy led to effective blood pressure control in 65% of patients compared to 22% of patients in the placebo group ($P = .002$).[26] This is one of the few therapies that have been evaluated in a randomized control trial, and demonstrated statistical superiority over placebo.[26] In another study, nifedipine was more effective at lowering the SBP at 30 minutes when compared with captopril, clonidine, and furosemide ($P < .02$), but this difference was no longer seen after 30 minutes.[11] Three dosage regimens of labetalol were compared in another study and differed only in their response at 2 hours, when the 200-mg dose was associated with significantly less tachycardia than either the 100-mg or 300-mg doses.[20] In a study comparing long- and short-acting calcium channel blockers, long-acting lacidipine was more effective than nifedipine at keeping the blood pressure controlled at 24 hours ($P = .001$).[25] In addition, 1 patient had a stroke syndrome 30 minutes after taking nifedipine (see Table 3). When compared with clonidine, nifedipine controlled blood pressure significantly more quickly.[12] In a study by Rutledge et al., enalaprilat was significantly better at reducing blood pressure than placebo in the moderate hypertension group defined arbitrarily as a DBP of 100 to 114 mm Hg.[14] Interestingly, 58% of patients assigned to the placebo group responded to hospitalization and no active medications. When enalaprilat was compared with furosemide, the 2 agents did not differ in terms of efficacy.

Hirschl et al. showed that urapidil had a significantly higher rate of response when compared with nifedipine after a single dose (92% vs 70%; $P < .04$). This response was

**Table 2. Hypertensive Emergencies**

| Author | Patients | Intervention | Outcomes | NNT | AE* | RR |
|---|---|---|---|---|---|---|
| Hirschl et al.,[8] (Evidence 2b) | SBP >200 mm Hg and/or DBP >110 mm Hg and evidence of target organ damage ($n$ = 81). | NTP 0.5 μg/kg/min increased every 15 min vs URP 12.5 mg every 15 min | 1. BP 185/95 mm Hg at 90 min and no re-elevation at 4 hrs<br>2. Major adverse effects (hypotension) | 1. NNT 12 (95% CI, NNH 5 to NNT 40) for URP<br>2. NNH 3 (95% CI, NNH 3 to NNT 22) | 7 major AE (hypotension) in NTP group, 2 in URP (hypotension) ($P$ = .04) | RR of NTP achieving target BP 0.507 (95% CI, 0.19 to 0.29) |
| Franklin et al.,[10] (Evidence 2b) | DBP >130 mm Hg and eye ground changes ($n$ = 15). | NTP 0.5 μg/kg/min increased by 0.25 μg/kg/min every 15 min vs NIF PO 10 mg and again at 2 and 6 hr until DBP ≤120 mm Hg | Time at which DBP was ≤120 mm Hg | 14.2 ± 12.6 hr in NTP group vs 4.5 ± 4.5 hr in NIF group ($P$ < .05) | 1 hypotensive effect in NTP group | NA |
| Pascale et al.,[23] (Evidence 2b) | DBP >120 mm Hg and patients with target organ damage not explicitly excluded ($n$ = 120). | NIF SL 10 mg vs CPL SL 50 mg vs NIF SL 10 mg and CLN IM 0.15 mg vs NIF SL 10 mg and FSM IV 40 mg | 1. Change in blood pressure<br>2. Adverse effects | No significant differences between blood pressures in any groups | CPL patients complained of a bad taste | NA |
| Angeli et al.,[21] (Evidence 1b) | DBP ≥140 mm Hg after 20 min of bedrest ($n$ = 20). | NIF 10 mg SL compared to CPL 25 mg SL (all patients received SL placebo). | 1. DBP of ≤120 mm Hg and complete resolution of symptoms at 60 min<br>2. Adverse effects | 1. 7/10 in the CPL group were complete responders and 5/10 patients in the nifedipine group were complete responders; NNT for CPL 5 compared to NIF (95% CI, NNH 2 to NNT 5).<br>2. Hypotensive effect of equal duration (4 ± 2 hr) | No hypotension was observed with either drug; NIF associated with headache (1 patient) and flushing (2 patients) | RR for NIF to reach the goal BP 0.65 (95% CI, 0.67 to 2.94) |

** Comparing adverse effects was difficult because of the inconsistent methods of reporting adverse effects among different studies. AEs, when documented, were included in Tables 2 and 3. BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; NNT, number needed to treat; NNT is the number of patients needed to treat in order to prevent 1 negative outcome; in the context of this study, the NNT is the number of patients needed to treat in order for 1 patient to achieve the target blood pressure; NNH, number needed to harm; NNH is the number of patients needed to treat in order to harm 1 patient inadvertently; in the context of this study, the NNH is the number of patients needed to treat in order for 1 patient to miss achieving the target blood pressure; RR, relative risk; AE, adverse effects; SBP, systolic blood pressure; DBP, diastolic blood pressure; NTP, nitroprusside; NIF, nifedipine; CPL, captopril; CLN, clonidine; URP, urapidil; FSM, furosemide; SL, sublingual; IM, intramuscular; NA, not applicable.*

100% and 50%, in the urapidil and nifedipine groups, respectively, after a second dose in those patients who did not respond to the first dose.[24] In addition, urapidil was associated with a shorter stay in the emergency room (83 vs 113 minutes; $P < .05$). The studies that compared oral nifedipine with oral labetalol, and oral nifedipine with oral nitrendipine found the agents to be of similar efficacy.[15,16]

In the 3 studies that examined fenoldopam in comparison to nitroprusside, the drugs were of comparable efficacy and all resulted in the achievement of the target BP in either the initial infusion phase or the maintenance phase (depending on the trial).[17–19] The agents also had similar adverse event profiles. Nitroprusside was found to have an accumulation of thiocyanate metabolites, but did not result in clinical toxicity.[19]

In the study by Hirschl et al.,[9] urapidil was found to be almost uniformly successful when compared to the 70% to 72% response rates in the nifedipine or enalaprilat groups (NNT for urapidil of 4). In addition, the RR for nifedipine or enalaprilat to reach the target BP compared to urapidil was significantly less than 1. One nifedipine patient in this study had a transient ischemic attack (TIA). In the study by Wallin et al., the second placebo-controlled trial involving nicardipine concluded that the drug is a more successful antihypertensive than placebo,[22] but this study involved both hypertensive urgencies and emergencies, as opposed to the study by Habib et al., which involved only hypertensive urgencies.[26]

## DISCUSSION

After reviewing all of the available evidence, the best choice of hypertensive agent in urgencies and emergencies remains unclear. In emergencies, the most desirable NNT is for urapidil,[8] although nitroprusside, captopril, and clonidine are likely acceptable choices as well. Comparing nitroprusside and urapidil with captopril and clonidine is difficult because no head-to-head studies have ever been done with these agents.

Hypertensive urgencies can also be treated with a variety of agents, including nicardipine,[26] lacidipine,[25] and urapidil,[9] and nitroprusside or fenoldopam,[17–19] which have the most favorable NNT profiles. Nifedipine can be used, but has rapid blood pressure–lowering properties that are not necessary in this nonemergent situation. This agent therefore shouldn't be used in the treatment of urgencies. In addition, nifedipine was associated with a TIA in 2 hypertensive urgency studies,[9,25] and has been implicated by others as a cause of cardiovascular morbidity and mortality.[27] No other antihypertensive agent in the studies we reviewed was associated with this complication. This association has been debated in medical literature and is still of uncertain significance.[28,29]

These recommendations must be viewed with caution and are meant to show what is known, and what is not known, about hypertensive urgencies and emergencies. The studies included in this review have many limitations. First, tremendous variation and inconsistency exists in the definitions and cutoffs for urgencies and emergencies and for target blood pressures. Second, long-term outcomes were not well studied, and important clinical outcomes were often not measured. Third, studies were often underpowered, leading to wide confidence intervals with respect to treatment efficacy. Further, as demonstrated in Tables 2 and 3, the confidence intervals were so wide that they gave both NNT and number of patients needed to harm (NNH) data, indicating that the various agents may have either harmed or benefited patients. In addition, the small numbers of patients in the studies limited their power to detect differences in mortality and morbidity, and may also account for some of the inconsistencies found in the results. Finally, the reporting of adverse effects was not consistent, making comparison of adverse effects difficult (Tables 2 and 3), and the small study sizes may also have limited the ability to detect important differences in adverse effect profiles.

When faced with hypertensive urgencies and emergencies, the clinician has to not only select an appropriate antihypertensive agent but also assess how rapidly the blood pressure must be lowered. Unfortunately, the literature does not have data to support one timetable over another. Therefore, clinical judgement must be used in order to set a goal for the rate of decline of blood pressure, as well as for the target blood pressure. Clinical practice guidelines for the management of hypertensive emergencies suggest that the mean arterial blood pressure be reduced by $\leq$25% within 2 hours and to 160/100 mm Hg by 6 hours.[30–32] In hypertensive urgencies, the goal blood pressure should be achieved over hours to days. Avoiding excessive reductions in blood pressure is advised because this can precipitate renal, cerebral, or coronary ischemia.[9,25] Frequent monitoring of blood pressure response to treatment (every 15 to 30 minutes) is also recommended. As some authors have pointed out,[8] the rate of blood pressure lowering should be considered in the context of the patient's clinical condition, and does have clinical significance; patients with an aortic dissection, for example, require more rapid blood pressure control,[33–35] compared to a patient with a hypertensive emergency and cerebrovascular symptoms, where a sudden drop in blood pressure might be dangerous.

Finally, many important questions remain unanswered. Future studies need to be consistent with respect to their operational definitions and cutoffs for urgencies and emergencies and for target blood pressures. This may serve as a better guide for clinicians. Second, studies need to follow patients over a period of time long enough to gather outcome data, such as cardiovascular morbidity and mortality, reduction in the number of hospitalizations, and length of stay information. The studies included in this review are of limited value because they use the surrogate endpoint of blood pressure control. Third, it remains unknown as to when patients with hypertensive crises should start maintenance therapy after

**Table 3. Hypertensive Urgencies**

| Authors | Patients | Intervention | Outcomes | NNT | AE* | RR |
|---|---|---|---|---|---|---|
| Habib et al.,[26] (Evidence 1b) | DBP >120 mm Hg ($n$ = 53) | NCN PO 30 mg vs placebo | Goal: DBP <100 mm Hg | 1. NNT 2 (95% CI, 1 to 5) for NCN | No increase AE in NCN group | RR for placebo to achieve target BP compared to NCN, 0.45 (95% CI, 0.25 to 0.78) |
| Komsuoglu et al.,[11] (Evidence 1b) | DBP ≥120 mm Hg ($n$ = 66) | NIF PO 20 mg vs NCN PO 20 mg vs C PO 25 mg | 1. DBP ≤110 mm Hg<br>2. Adverse effects | NIF vs NCN NNT 24 (95% CI, NNH 5 to NNT 9)<br>NCN vs CPL NNT 18 (95% CI, NNH 4 to NNT 9)<br>NIF vs CPL NNT 77 (95% CI, NNH 5 to NNT 6) | No difference in adverse effects except NIF increased heart rate compared with other agents | 1. RR for NIF vs NCN, 1.91 (95% CI, 0.19 to 19.63) $P$ = .97<br>2. RR for NIF vs captopril, 0.87 (95% CI, 0.14 to 5.62) |
| Gonzalez et al.,[20] (Evidence 1b) | DBP 110 to 140 mm Hg ($n$ = 36) | LBL PO 100 mg vs LBL PO 200 mg vs LBL PO 300 mg | DBP ≤100 mm Hg or 30 mm Hg reduction in DBP | 1. 100 vs 200 mg: NNT 6 (95% CI, NNH 1 to NNT 4)<br>2. 100 vs 300 mg: NNT 12 (95% CI, NNH 2 to NNT 3) | No adverse events | 1. RR for LBL 100 mg vs 200 mg dose, 1.2 (95% CI, 0.5 to 2.88)<br>2. RR for LBL 100 mg vs 300 mg dose, 1.5 (95% CI, 0.56 to 4.0) |
| Sanchez et al.,[25] (Evidence 1b) | DBP ≥120 mm Hg ($n$ = 29) | LCN PO 4 mg vs NIF PO 20 mg | 1. Decrease in DBP >25% of baseline at 8 and 24 hr<br>2. Adverse effects | NNT 2 (95% CI, 1 to 8) for LCN | 1 Patient in NIF group had a stroke 30 min after the dose, blood pressure decreased from 210/125 mm Hg to 120/80 mm Hg | RR for NIF compared to LCN to reach the target BP, 0.37 (95% CI, 0.15 to 0.92) |
| Jaker et al.,[12] (Evidence 1b) | DBP ≥120 mm Hg ($n$ = 51) | NIF PO 20 mg vs CLN PO 0.1 mg repeated every hr | 1. DBP ≤100 mm Hg<br>2. Adverse effects | NNT 2 (95% CI, 1 to 2) for NIF | Significant increase in heart rate in NIF group, no clinical sequelae; 59% sedation in CLN patients | RR for NIF compared to CLN to reach the target BP, 0.2 (95% CI, 0.03 to 1.57) |
| Zeller et al.,[13] (Evidence 1b) | DBP 116 to 139 mm Hg ($n$ = 15). | 3 Different combinations of chlorthalidone and CLN | Fall in DBP of 20 mm Hg or DBP <105 mm Hg | No differences between groups | 11 Patients had hypotension evenly distributed in 3 groups, no clinical sequelae | No difference |
| Rutledge et al.,[14] (Evidence 1b) | DBP 100 to 114 mm Hg ($n$ = 65). | Moderate hypertension group (DBP 100 to 114): ENL 1.25 mg IV every 6 hr vs placebo; severe hypertension (DBP 115 to 130): ENL 1.25 mg IV every 6 hr vs FSM | DBP <95 mm Hg | NNT 4 (95% CI, NNH 1 to NNT 19) for ENL | 2 Patients in severe hypertension stratum treated with ENL developed hypotension, had no clinical sequelae | 1. RR for placebo compared to ENL to reach the target BP at 24 hr, 0.58 (95% CI, 0.33 to 1.04) and 0.61 (95% CI, 0.26 to 1.4) at 48 hr<br>2. RR for FSM compared to ENL to reach the target BP at 24 hr, 0.82 (95% CI, 0.5 to 1.33) and 0.69 (95% CI, 0.2 to 2.41) |
| Hirschl et al.,[24] (Evidence 1b) | SBP >200 mm Hg and/or DBP >110 mm Hg ($n$ = 53) | URP IV 25 mg, then 12.5 mg if no response vs NIF sublingual 10 mg, repeated if no response | SBP<180 mm Hg or DBP <100 mm Hg | NNT 5 (95% CI, 2 to 55) for URP | No AE. | RR for NIF compared to URP to achieve target BP, 0.12 (95% CI, 0.01 to 2.04) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Rohr et al.,[15] (Evidence 2b) | SBP 200 to 250 mm Hg or DBP 110 to 140 mm Hg ($n$ = 161) | NIF PO 10 mg vs NIT PO 5 mg | Decrease of ≥20 mm Hg SBP and of ≥15 mm Hg DBP | NNT 1,000 (95% CI, NNH 7 to NNT 7) for NIT | No major AE | 83% of patients had effective blood pressure control in 4 hr in both groups |
| McDonald et al.,[16] (Evidence 2b) | DBP ≥120 mm Hg ($n$ = 20) | NIF PO 10 mg repeated 2 times if necessary vs LBL PO 200 mg followed by 100 mg or 200 mg at 2 hr if necessary | DBP ≤110 mm Hg | NNT 6 (95% CI, NNH 2 to NNT 10) for NIF | No AE | RR for LBL to reach the target BP compared to NIF, 0.2 (95% CI, 0.01 to 3.71) |
| Panacek et al.,[17] (Evidence 2b) | DBP ≥120 mm Hg ($n$ = 183). | FNP 0.1 μg/kg/min vs NTP 0.1 μg/kg/min and titrated to target BP of DBP<140 mm Hg or maximum reduction of 40 mm Hg in DBP | 1. Time to reach the initial goal induction DBP<br>2. BP reduction during 6- to 24-hr maintenance phase<br>3. Adverse effects | No significant difference in time to reach goal DBP: 1 hr, 25 min in FNP-treated group, vs 1 hr, 34 min in NTP-treated group (NS) | 22 Patients (10 FNP, 12 NTP) withdrawn due to clinical events: hypotension in 5 FNP patients and 11 NTP patients (NS). None had clinical sequelae from the hypotension | |
| Pilmer et al.,[18] (Evidence 1b) | DBP ≥120 mm Hg ($n$ = 33) | FNP 0.1 μg/kg/min vs NTP 0.1 μg/kg/min and titrated to target BP of DBP 95 to 110 mm Hg or maximum reduction of 40 mm Hg in DBP | 1. Time to reach the initial goal induction DBP<br>2. BP reduction during 6- to 24-hr maintenance phase<br>3. Adverse effects | 1. All patients reached goal DBP during initial 6-hr titration period<br>2. No significant difference in time to reach goal DBP: 1.5 ± 1.4 hr in FNP-treated group, vs 2 ± 2.5 hr in NTP-treated group (NS).<br>3. Re-elevation in DBP 1 hr after NTP infusion termination (103 ± 1.8 mm Hg vs 111 ± 3.0 mm Hg) $P < .03$ | 4 Patients (2 FNP, 2 NTP) withdrawn due to hypotension (NS). None had clinical sequelae from the hypotension | NA |
| Reisin and Huth,[19] (Evidence 2b) | DBP ≥120 mm Hg and <170 mm Hg ($n$ = 18) | FNP 0.1 μg/kg/min vs NTP 0.5 μg/kg/min and titrated to target BP of DBP <110 mm Hg if initial DBP 120 to 149 mm Hg or by at least 40 mm Hg if initial DBP was 150 to 190; after goal DBP achieved, maximum infusion rate maintained for at least 2 hr then titrated off over 2 hr | 1. Compare the efficacy of FNP vs NTP in DBP reduction<br>2. Adverse effects | 1. All patients reached goal DBP by the end of the maintenance period<br>2. No mention of any difference in time to reach goal DBP or re-elevation in DBP infusion termination | No patients had hypotension due to FNP or NTP. 2 NTP patients had toxic thiocyanate levels but no clinical manifestations of toxicity | NA |

*(Continued)*

**Table 3. (Continued)**

| Authors | Patients | Intervention | Outcomes | NNT | AE* | RR |
|---|---|---|---|---|---|---|
| Hirschl et al.,[9] (Evidence 2b) | SBP >210 mm Hg or DBP >110 mm Hg or patients with DBP >100 mm Hg AND evidence of end-organ dysfunction (~1:1 ratio of urgencies and emergencies) ($n$ = 168) | ENL 5 mg IV vs URP 25 mg IV or NIF 10 mg capsule SL or NIF 10 mg SL spray | SBP <180 mm Hg and DBP <95 mm Hg and resolution of end-organ dysfunction in hypertensive emergencies | NNT for URP compared to ENL and NIF 4 (95% CI, NNT 3 to NNT 6) | 1 NIF patient had hypotension and a TIA | RR for ENL/NIF to reach the goal BP compared to URP, 0.73 (95% CI, 0.64 to 0.83) |
| Wallin et al.,[22] (Evidence 1b) | SBP >200 mm Hg or DBP >120 mm Hg; study included a mixture of urgency and emergency patients ($n$ = 123) | NCN IV 5.0 mg/hr with titration vs placebo | SBP ≤160 mm Hg or DBP ≤110 mm Hg or decrease DBP ≥25 mm Hg | NNT for NCN compared to placebo 1 (95% CI, 1 to 1) | 7 NCN patients developed hypotension, 4 had to stop drug, 2 had dose decreased (no clinical sequelae) | RR for placebo to reach goal BP compared to NCN, 0.01 (95% CI, 0.001 to 0.017) |

** Comparing adverse effects was difficult due to the inconsistent methods of reporting adverse effects among different studies. AEs, when documented, were included in Tables 2 and 3. SBP, systolic blood pressure; DBP, diastolic blood pressure; TIA, transient ischemic attack; NNT, number needed to treat; NNT is the number of patients needed to treat in order to prevent 1 negative outcome; in the context of this study, the NNT is the number of patients needed to treat in order for 1 patient to achieve the target blood pressure; NNH, number needed to harm; NNH is the number of patients needed to treat in order to harm 1 patient inadvertently; in the context of this study, the NNH is the number of patients needed to treat in order for 1 patient to miss achieving the target blood pressure; RR, relative risk; AE, adverse effects; SBP, systolic blood pressure; DBP, diastolic blood pressure; CLN, clonidine; FNP, fenoldopam; NTP, nitroprusside; NIT, nitrendipine; NIF, nifedipine; URP, urapidil; LCN, lacidipine; FSM, furosemide; ENL, enalaprilat; NCN, nicardipine; SL, sublingual; IM, intramuscular; NA, not applicable.*

initial blood pressure control is accomplished in the emergency room. Another issue that has not been explored is how quickly the blood pressure should be lowered in this context. Finally, none of the studies we reviewed evaluated which patients should be admitted to the hospital and for how long, and which patients should be managed as outpatients. In addition, it is unclear whether these patients can be triaged outside of the emergency department in such settings as physicians' offices or over the phone. We believe that there is more research to be done in this area, and hope that future collaborative, multicenter, randomized double-blind controlled trials will be performed to address these issues.

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