Pharmacologic Treatment of Hypertensive Urgency in the Outpatient Setting: A Systematic Review

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BACKGROUND: Hypertensive urgency (HU), defined as acute severe uncontrolled hypertension without end-organ damage, is a common condition. Despite its association with long-term morbidity and mortality, guidance regarding immediate management is sparse. Our objective was to summarize the evidence examining the effects of antihypertensive medications to treat.

METHODS: We searched the PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Cochrane Database of Systematic Reviews, Web of Science, Google Scholar, and Embase through May 2016. Study selection: We evaluated prospective controlled clinical trials, case-control studies, and cohort studies of HU in emergency room (ER) or clinic settings. We initially identified 11,223 published articles. We reviewed 10,748 titles and abstracts and identified 538 eligible articles. We assessed the full text for eligibility and included 31 articles written in English that were clinical trials or cohort studies and provided blood pressure data within 48 h of treatment. Studies were appraised for risk of bias using components recommended by the Cochrane Collaboration. The main outcome measured was blood pressure change with antihypertensive medications. Since studies were too diverse both clinically and methodologically to combine in a meta-analysis, tabular data and a narrative synthesis of studies are presented.

RESULTS: We identified only 20 double-blind randomized controlled trials and 12 cohort studies, with 262 participants in prospective controlled trials. However, we could not pool the results of studies. In addition, comorbidities and their potential contribution to long-term treatment of these subjects were not adequately addressed in any of the reviewed studies.

CONCLUSIONS: Longitudinal studies are still needed to determine how best to lower blood pressure in patients with HU. Longer-term management of individuals who have experienced HU continues to be an area requiring further study, especially as applicable to care from the generalist.

INTRODUCTION

Hypertensive urgency (HU) is defined as systolic blood pressure of at least 180 mmHg and/or diastolic blood pressure of at least 110 mmHg, without associated end-organ damage.1 Patients with HU may be completely asymptomatic or may present with symptoms such as headache, epistaxis, faintness, malaise, psychomotor agitation, nausea, or vomiting.2

Up to 65 million Americans have hypertension; about 1% will have an episode of HU during their lives. The prevalence of HU in emergency room (ER) or office settings is estimated at 3–5%.3, 4 In a recent cohort study, cardiovascular events were found to occur in less than 1% of patients within a 6-month period.4

Guidance for immediate management of HU is unclear, since there is no consensus on the optimal target for acute blood pressure reduction or the time frame for achieving a normal blood pressure range. Most patients receive drug therapy for elevated blood pressure within the first 48 h of presentation.2–4 Knowledge of the effectiveness and safety of different medication choices and associated comorbidities is crucial for clinicians, especially generalists.

The aim of this systematic review is to summarize evidence of the benefits and harms associated with antihypertensive medications used to treat HU in adults, either in the clinic or ER. This systematic review is intended for a broad audience, including clinicians—especially general internists—along with policymakers and funding agencies, professional societies developing clinical practice guidelines, patients and their care providers, and researchers.

METHODS

Eligibility Criteria

We defined HU as severe hypertension without evidence of acute end-organ damage. We included studies with non-
pregnant adults with systolic blood pressure (SBP) > 179 mmHg or diastolic blood pressure (DBP) > 109 mmHg, with no end-organ damage. Because of inconsistent terminology, we selected studies based on the above blood pressure criteria. We included both clinic and ER settings in the search, but excluded studies where patients were hospitalized.

**Data Sources and Search.** Following the PRISMA guidelines, and in collaboration with a librarian (JT), two reviewers (CLC, KO) searched the literature using PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Cochrane Database of Systematic Reviews, Web of Science, Google Scholar, and Embase. The medical librarian created search strategies with standardized terms and keywords. We excluded case reports, letters, and editorials. Searches were limited to English-language publications and to human studies using the limits provided by the databases. The “human” filter recommended in the Cochrane Handbook for Systematic Reviews of Interventions was used in PubMed. Studies on pulmonary hypertension were excluded. The gray literature was also searched utilizing Google Scholar. In addition, one expert (PD) identified key literature for the review. All search results were exported to EndNote. Using the EndNote duplicate locator, 4861 duplicate articles were removed. The librarian updated the search in May 2016, and all searches were completed in July 2016. The full search strategy is shown in Appendix A.

Two evaluators (CLC and KO) independently identified and screened articles for inclusion. Reference lists of studies were manually scanned, and cited references were screened by each evaluator (Fig. 1).

**Study Selection.** Studies that 1) reported on adults with HU who received pharmacologic therapy in outpatient settings (clinic or ER) and 2) reported initial and subsequent blood pressure values within 48 h of medication administration were reviewed. Studies were excluded if they included animals, pediatric or pregnant patients, or the presence of acute end-organ damage. Because the U.S. Food and Drug Administration (FDA) prohibits the use of nifedipine for acute management of elevated blood pressure, articles that included only this drug were also excluded (532 studies).7

Primary outcome(s): Given the lack of consensus regarding the blood pressure reduction goal when treating HU, most studies did not report dichotomous outcomes. The primary measures of treatment efficacy were reduction in SBP, DBP, and mean arterial pressure (MAP; in mmHg) within 48 h of pharmacologic treatment.

Secondary outcomes: We extracted adverse effects including headache, dizziness, dry mouth, hypotension, stroke, transient ischemic attack, myocardial infarction, angina, heart failure, pulmonary edema, arrhythmia, renal impairment, new-onset proteinuria, and hospitalization. None of the studies reported on cardiovascular or all-cause mortality.

Data extraction: Using standardized Excel forms, four groups of two investigators each (JLW, AJC, DJ, CLC, AA, BB, CH) independently extracted data including the author, country, year, study type, setting, sample size, demographics, medications, details of treatment, primary outcome, adverse effects, and initial and subsequent blood pressure values. The team calculated MAP values when not explicitly calculated by the authors.

Two members of the team independently graded the strength of clinical data and subsequent recommendations for treatment of patients with HU according to the Oxford Centre for Evidence-Based Medicine levels of evidence. Any discrepancies were resolved after a joint review and discussion with a third reviewer. Levels of evidence were as follows: level 1A, systematic reviews (with homogeneity of randomized clinical trials); level 1B, individual randomized clinical
trials (with narrow confidence intervals); level 2A, systematic reviews (with homogeneity of cohort studies); and level 2B, individual cohort studies (including low-quality randomized clinical trials). Grades of recommendation are as follows: A = consistent level 1 studies; B = consistent level 2 or 3 studies, or extrapolations from level 1 studies; C = level 4 studies or extrapolations from level 2 or 3 studies; and D = level 5 evidence or inconsistent or inconclusive studies of any level. Studies with a high loss to follow-up were flagged.

**Risk of Bias Assessment**
For controlled trials, we used the Cochrane Risk of Bias Assessment tool. For cohort studies, we used the Newcastle-Ottawa Scale to assess study quality.

**Data Synthesis**
We could not combine results statistically because of heterogeneity among interventions and outcome measures. Furthermore, studies often lacked clearly defined primary outcomes. Therefore, we qualitatively synthesized results by antihypertensive medication class and created tables summarizing the evidence across all studies reviewed.

**RESULTS**
Our search strategy identified 11,223 published articles. We reviewed 10,748 titles and abstracts (after duplicates were removed) and identified 538 eligible articles. We identified 20 double-blind randomized controlled trials and 13 cohort studies, with 262 participants in prospective controlled trials (Fig. 1). After applying our eligibility criteria to the full texts of these articles, we included 31 English-language articles (Fig. 1). We included studies with nifedipine only if it was included as a comparison drug. We excluded the results of the nifedipine arm because of its black box warning in the management of HU.

The characteristics of included trials are summarized in Table 1. Studies were generally characterized by small sample size, different timing of the effects of antihypertensive therapies (0.17–24 h), and short-term follow-up. Most recent studies were conducted outside the United States.

We compiled the blood pressure effects by antihypertensive class (Table 2) and their reported side effects:

**Calcium Channel Blockers**
Seven calcium channel blockers were studied in 14 trials. Nicardipine and nifedipine were the most commonly studied (three trials and four trials, respectively). Isradipine and lacidipine each had two studies, and amlodipine, nitrendipine, and verapamil each had one study.

Amlodipine (5 or 10 mg PO) was evaluated in one small (n = 46) retrospective cohort. Both doses significantly reduced the MAP at 1 h (from 140 and 148 to 103 and 131, respectively). No side effects were reported. Isradipine was investigated in two trials, one a prospective cohort and the other an RCT, which found that PO doses ranging from 1.25 to 5 mg reduced SBP from 196–204 to 155–165 at 2 h. Reported side effects with isradipine were dizziness and nausea. In four trials, nitrendipine (4 mg, 10 mg, 20 mg), in SL or PO formulations, significantly reduced SBP, from 238–186 to 178–145, over 2–24 h. Four trials of nicardipine in various formulations significantly reduced SBP over 1–2 h, from 186–238 to 161–163. Reported side effects from nicardipine were mild headache, hypotension, or orthostasis, chest pain, and tachycardia. In single trials, nitrendipine 5 mg PO (n = 85) reduced SBP from 228 to 156 over 2–8 h, and verapamil SL reduced SBP significantly over 1–2 h, with 80 mg more effective than 40 mg. Reported side effects with verapamil were decreased heart rate and headache.

**ACE Inhibitors**
There were nine trials of ace inhibitors (one retrospective cohort, two prospective cohorts, five RCTs, one non-randomized controlled trial). All used captopril in doses ranging from 6.25 to 25 mg in both PO and SL formulations. SBP values were reduced from 244–198 to 177–144 at 0.17–12 h of captopril administration, with greater BP reduction seen using higher doses (25 mg).

Side effects reported with captopril were dizziness, headache, nausea and vomiting, dry mouth, vertigo, and flushing.

**Beta-Blockers**
There were five trials of beta blockers (three prospective cohorts and two RCTs). Labetalol was studied in doses ranging from 20 to 300 mg in both IV and PO formulations. Blood pressure values were reduced after 0.33–24 h of labetalol administration in all studies. Labetalol PO was investigated in only one small RCT (n = 10), which found that the mean PO dose of 221 mg reduced SBP from 195 to 154 at 4 h. Side effects reported with labetalol were dizziness, drowsiness, headache, bradycardia, and pain at the injection site.

**Centrally Acting Antihypertensives**
Two centrally acting agents, clonidine and ketanserin, were studied in seven trials. Clonidine was investigated in six trials (one prospective cohort, one retrospective cohort, four RCTs), which found that PO doses ranging from 0.1 to 0.6 mg reduced SBP from 204–196 to 165–155 at 2 h. Side effects reported with the use of clonidine were...
hypotension, orthostasis, impotence, sedation, dry mouth, mild transient drowsiness, and lower heart rate (average 6.2 beats/min). Ketanserin (unavailable in the U.S.) was studied in one RCT, also reducing BP after IV and SL administration. Somnolence was reported.

Table 1 Studies

| Trial, year, country | Medication(s) | Study design | Sample size | Age, years (mean) | Male, % | Ethnicity |
|---------------------|---------------|--------------|-------------|------------------|---------|-----------|
| Al-Waili, 1999, UAE | Verapamil | RCT | Verapamil 40 mg SL: n = 30  
Verapamil 80 mg SL: n = 30 | 42–70 | 56% | Not specified |
| Atkin, 1992, USA | Labetalol vs. Clonidine | RCT | Labetalol 200 mg: n = 18  
Clonidine 0.2 mg: n = 18  
Urapidil 103 mg IV: n = 9 | 47 | 58% | AA = 34  
W = 2 |
| Castro del Castillo, 1988, USA | Captopril | Prospective cohort | Captopril 12.5 mg SL: n = 41 | Not specified | Not specified | Not specified |
| Finnerty, 1963, USA | Diazoxide | Prospective cohort | Diazoxide 300 mg IV: n = 33 | Not specified | Not specified | Not specified |
| Garrett, 1982, USA | Diazoxide | Prospective cohort | Diazoxide 15 mg/min IV (300–1095 mg): n = 9  
Diazoxide 30 mg/min IV (300–1200 mg): n = 9 | 43 | 33% | AA = 13  
W = 5 |
| Gemici, 2003, Turkey | Captopril vs. Nifedipine | RCT | Captopril 25 mg SL: n = 15  
Nifedipine 10 mg SL: n = 13 | Captopril: 56 ± 11  
Nifedipine: Not specified | Not specified | Not specified |
| Greene, 1990, USA | Clonidine | Prospective cohort | Clonidine 0.1–0.2 mg oral: n = 13  
(then 0.1 mg/h as needed (average 0.24 mg) PO) | 50 | 46% | AA = 10  
W = 3 |
| Habib, 1995, USA | Nicardipine | RCT | Nicardipine 30 mg oral: n = 26  
Placebo: n = 27 | 48 ± 11 | 68% | AA = 43  
W = 10  
Not specified |
| Hirschl, 1998, Austria | Urapidil vs. Placebo | RCT | Urapidil 60 mg PO: n = 20  
Placebo: n = 20 | 59 | 40% | Not specified |
| Huey, 1988, USA | Labetalol | Prospective cohort | Labetalol 20–300 mg IV: n = 20 | 55 | 100% | AA = 12  
W = 8  
H = 5  
AA = 46 |
| Jaker, 1989, USA | Clonidine vs. Nifedipine vs. Labetalol | RCT | Clonidine 0.1 mg hourly up to 0.6 mg PO: n = 28  
Nifedipine 20 mg oral: n = 23  
Labetalol 0.5–1 mg/kg IV: n = 14  
Labetalol 0.1–0.2 mg and 0.1 hourly as needed PO: n = 32  
Nifedipine 10–20 mg oral: n = 35  
Grp 3: n = 27 | 48 | 39% | AA = 78  
W = 16 |
| Joekes, 1976, England | Clonidine vs. Nifedipine vs. Variety of drug therapies (Grp 3) | Retrospective cohort | Clonidine 0.1–0.2 mg oral: n = 23  
Nifedipine 10–20 mg oral: n = 35  
Grp 3: n = 27 | Not specified | Not specified | Not specified |
| Kaya, 2016, Turkey | Captopril | RCT | Captopril 25 mg SL: n = 108  
Captopril 25 mg PO: n = 104 | Captopril SL: 64 ± 11  
Captopril PO: 58 ± 12 | 46% | Not specified |
| Klocke, 1992, Germany | Nitrendipine vs. Clonidine | RCT | Nitrendipine 5 mg. If BP did not fall below 180/100 mmHg 60 min after administration, nitrendipine 5 mg was given: n = 140  
Clonidine 0.15 mg IV. If BP did not fall below 180/100 mmHg 60 min after administration, nitrendipine 5 mg was given: n = 139 | 58 ± 12 | 52% | Not specified |
| Komsuoglu, 1991, Turkey | Nicardipine vs. Captopril vs. Nifedipine | RCT | Nicardipine 20 mg SL: n = 22  
Captopril 25 mg SL: n = 20  
Nifedipine 20 mg bite & swallow: n = 23 | 62 | 51% | Not specified |
| Lechi, 1981, Italy | Labetalol | Prospective cohort | Labetalol 1 mg/kg IV bolus: n = 15  
Labetalol 1–4 mg/kg IV over 3 h: n = 6 | 25–60 | 57% | Not specified |

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| Trial, year, country | Medication(s) | Study design | Sample size | Age, years (mean) | Male, % | Ethnicity |
|---------------------|---------------|--------------|-------------|------------------|--------|-----------|
| Maleki, 2011, Iran  | Grp A - Nifedipine vs. Grp B - Captopril vs. Grp C - Nitroglycerin | RCT         | Grp A - Nifedipine 5 mg SL: n = 40 Grp B - Captopril 25 mg SL: n = 40 Grp C - Nitroglycerin SL: n = 40 | Grp A: 61 Grp B: 58 Grp C: 63 | 45%    | Not specified |
| McDonald, 1993, USA | Labetalol vs. Nifedipine | RCT         | Labetalol 200 mg oral 200 mg repeated if DBP was ≥120 mmHg: 100 mg given if DBP was >110 mmHg but ≤120 mmHg. Mean dose 221 mg: n = 10 Nifedipine 10 mg bite and swallow every hour up to a total dose of 20 mg: n = 10 | Labetalol: 46 Nifedipine: 48 | 50%    | AA = 20 |
| Panacek, 1995, Int. (mainly USA) | Fenoldopam vs. Nitroprusside | RCT         | Fenoldopam - IV starting dose 0.1 mcg/kg/min and increased in increments of ≤0.2 mcg/kg/min. Max rate 1.6 mcg/kg/min. Mean titrated dose 0.41 mcg/kg/min: n = 90 Nitroprusside - IV starting dose 0.5 mcg/kg/min and increased in increments of ≤1 mcg/kg/min. Max rate 8 mcg/kg/min. Mean titrated dose 1.67 mcg/kg/min: n = 93 | Fenoldopam: 46 ± 1 Nitroprusside: 48 ± 1 | 52%    | AA = 57 | W = 33 Nitroprusside: AA = 59 W = 33 Other = 4 |
| Peacock, 2011, USA | Nicardipine vs. Labetalol | RCT         | Nicardipine Dosing per physician discretion. Recommended 5 mg/h IV, increased every 5 min by 2.5 mg/h, until target SBP reached or max of 15 mg/h achieved. IV median titrated dose 3.1 mg: n = 110 Labetalol Dosing per physician discretion. Recommended 20 mg IV over 2 min, then repeated at 20, 40, or 80 mg injections every 10 min, until target SBP reached or max of 300 mg given. IV median titrated dose 40 mg: n = 116 | Nicardipine: 53 ± 15 Labetalol: 52 ± 14 | 47%    | AA = 172 W = 52 (2 patients withdrew) |
| Ram, 1979, USA     | Diazoxide     | Non-randomized controlled | Grp 1 - Diazoxide 105 mg IV, followed by 150 mg every 5 min until DBP of ≤110 mmHg or cumulative dose of 600 mg reached: n = 12 Grp 2 - Diazoxide 150 mg IV, followed by 150 mg every 5 min until DBP of ≤110 mmHg or cumulative dose of 600 mg reached: n = 20 | Grp 1 - Diazoxide 105 mg: 48 ± 2 Grp 2 - Diazoxide 150 mg: 46 ± 3 | Not specified | Not specified |
| Sahasranam, 1988, India Salkic, 2015, Bosnia | Captopril vs. Urapidil | Prospective cohort Non-randomized controlled | Captopril 12.5 mg SL: n = 16 Captopril 12.5 mg – 25 mg SL: n = 60 Urapidil 12.5 mg – 25 mg IV: n = 60 | Not specified | 58 ± 11 50% Not specified |
| Sanchez, 1999, USA | Lacidipine vs. Nifedipine | RCT         | Lacidipine 4 mg PO: n = 15 Nifedipine 20 mg PO: n = 14 | Not specified | 55 ± 11 31% Not specified |
| Saragoca, 1992, Brasil | Isradipine | RCT         | 1.25 mg SL: n = 10 2.5 mg SL: n = 10 5 mg SL: n = 7 | Not specified | Not specified Not specified |
| Saragoca, 1993, Brasil | Isradipine | Prospective cohort | Mean 3.9 mcg/kg/h IV: n = 10 | Not specified | Not specified Not specified |

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Vasodilators
Six vasodilators were studied across nine trials. Urapidil and diazoxide were the most commonly studied (three and two trials, respectively). Fenoldopam, nitroglycerin, and nitroprusside were each evaluated once. In three trials, urapidil in IV or PO formulations significantly reduced SBP from 215–165 to 179–132 over 0.5–12 h. Side effects reported with urapidil were nausea, vomiting, drowsiness, headache, and orthostatic hypotension.

Diazoxide (150–1290 mg IV) was investigated in two prospective cohort studies, which found that 150–1290-mg IV doses rapidly reduced SBP, from 214–225 to 187–159 in less than 1 h. Side effects reported with diazoxide were uremia, acute pulmonary edema, palpitations, transient hemiparesis, pain at the site of IV infusion, a mild increase in heart rate, atrial tachycardia, and chest pain. In single trials, IV fenoldopam (n = 90) at a mean dose of 0.41 mcg/kg/min reduced SBP from 212 to 178, hydralazine (n = 19) reduced MAP from 244 to 126 at 0.5 h, and nitroglycerin (n = 40) reduced SBP from 190 to 150 at 1 h.

Combinations of Antihypertensives
Combinations of agents were studied in two trials: labetalol plus furosemide and clonidine plus chlorthalidone. Labetalol 300 mg PO plus Lasix 20 mg IV was evaluated in one small (n = 16) prospective cohort, which showed a decrease in SBP from 206 to 154 at 3 h. Clonidine plus chlorthalidone was investigated in one RCT, which found that PO clonidine doses of 0.2–0.8 mg plus chlorthalidone 25 mg reduced SBP from 193–182 to 142–137 at 24 h.

Direct Comparisons
SL and PO nifedipine were the most commonly studied antihypertensives (four trials), with two comparisons against
Lacidipine (one prospective cohort, one RCT), one against ketanserin (RCT), and one against captopril and nitroglycerin (RCT). Captopril was evaluated in four comparative trials: with amlodipine, hydralazine and nifedipine (one retrospective cohort), urapidil (one RCT and one prospective cohort), and with nitroglycerin and nifedipine (one RCT). Clonidine was compared with labetalol (one RCT) and nitrendipine (one RCT).

### Table 2 Compiled Medication List

| Medication | Dose | Trial          | Study design       | Baseline | Follow-up |
|------------|------|----------------|--------------------|----------|----------|
| Calcium channel blockers | | | | SBP | DBP | MAP | Time (h) | SBP | DBP | MAP |
| Amlodipine | 5 mg PO | Sruamsiri | Retrospective cohort | * | * | 140 | 1 | * | * | 103 |
| | 10 mg PO | | | * | * | 148 | 1 | * | * | 131 |
| Isradipine | 1.25 mg SL | Saragoca, 1993 | Prospective cohort | 204 | 136 | 159 | 2 | 155 | 105 | 122 |
| | Mean 3.9 mcg/kg/h IV | | | * | * | 135 | 3 | * | * | 129 |
| | 1.25 mg SL | Saragoca, 1992 | RCT | 204 | 136 | 159 | 2 | 155 | 105 | 122 |
| | 2.5 mg SL | | | 214 | 132 | 159 | 2 | 165 | 97 | 120 |
| | 5 mg SL | | | 196 | 127 | 150 | 2 | 160 | 95 | 117 |
| Lacidipine | 4 mg SL | Zampaglione | Retrospective cohort | 208 | 125 | 153 | 0.5 | 178 | 110 | 133 |
| | 4 mg PO | Sanchez | RCT | 223 | 125 | 158 | 8 | 170 | 104 | 126 |
| | 20 mg SL | Komsuoglu | RCT | 238 | 134 | 169 | 2 | 161 | 98 | 119 |
| | 30 mg PO | | | 186 | 127 | 147 | 2 | 162 | 105 | 124 |
| Nitrendipine | 5 mg PO. If BP did not fall below 180/100 mmHg 60 min after administration, Nitrendipine 5 mg was given | | | | | | | |
| | Verapamil | 40 mg SL | Al-Waili | RCT | 200 | 127 | 151 | 1 | 177 | 95 | 122 |
| | | 80 mg SL | | | 201 | 129 | 153 | 1 | 150 | 91 | 111 |
| | | | | | 2 | 147 | 81 | 103 |
| Ace inhibitors | | | | | | | | |
| Captopril | 6.25 mg PO | Sruamsiri | Retrospective cohort | * | * | 137 | 0.5 | * | * | 122 |
| | 12.5 mg PO | Sahasranam | Prospective cohort | 198 | 130 | 153 | 0.5 | 162 | 106 | 125 |
| | 25 mg PO | Castro del Castillo | RCT | 211 | 110 | 144 | 12 | 159 | 88 | 112 |
| | 12.5 mg SL | Salkic | Non-randomized controlled | 213 | 130 | 158 | 0.5 | 177 | 112 | 134 |
| | 25 mg SL | | | 213 | 130 | 158 | 1 | 152 | 95 | 114 |
| Beta-blockers | | | | | | | | |
| Labetalol | 0.5–1 mg/kg IV | Joekes | Prospective cohort | 176 | 113 | 140 | 0.33–0.66 | 146 | 92 *
| | 1 mg/kg IV bolus | Lechi | Prospective cohort | 226 | 137 | 167 | 3 | 180 | 114 | 136 |
| | 1–4 mg/kg IV over 3 h | | | 216 | 128 | 157 | 3 | 177 | 112 | 134 |
| | 20–300 mg IV | Huey | Prospective cohort | 185 | 120 | 142 | 0.5 | 155 | 98 | 117 |
| | 200 mg PO; 200 mg repeated if DBP ≥120 mmHg; 100 mg given if DBP >110 mmHg but <120 mmHg. Mean dose 221 mg 200 mg, followed by hourly 200 mg, up to 1200 mg | McDonald | RCT | 195 | 127 | 150 | 4 | 154 | 100 | 118 |
| | | Atkin | RCT | 201 | 132 | 155 | 6 | 172 | 111 | 131 |

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One direct comparison study (RCT\textsuperscript{17}) evaluated fenoldopam and nitroprusside.

When captopril was compared to amlodipine, hydralazine, and nifedipine in a retrospective cohort study,\textsuperscript{14} there were no significant differences between these medications in their effect on BP reduction ($p = 0.513$). Captopril was superior to sublingual nitroglycerin in the first hour following administration ($p = 0.001$).\textsuperscript{26}

In two studies comparing captopril and urapidil,\textsuperscript{25, 29} both drugs were found to effectively lower blood pressure within 1 h\textsuperscript{29} and at 12 h\textsuperscript{25} ($p = 0.38/0.40$).

When fenoldopam and nitroprusside were compared\textsuperscript{17} the two antihypertensive agents were equivalent in controlling and maintaining BP. The adverse effect profiles of the drugs were similar: headache, dizziness, flushing, hypotension, nausea, vomiting, hyperhidrosis, and hypokalemia.

### Table 2. (continued)

| Medication | Dose | Trial | Study design | Baseline | Follow-up | | |
|------------|------|-------|--------------|----------|-----------| | |
| Clonidine | 0.15 mg IV. If BP did not fall below 180/100 mmHg 60 min after administration, Nitrendipine 5 mg was given 0.2 mg PO followed by hourly 0.1 mg, up to 0.7 mg. 0.1–0.2 mg, then 0.1 mg hourly as needed (average 0.24 mg) PO 0.1 mg and 0.1 hourly as needed PO | Klocke RCT 229 | 124 | 159 | 2 | 156 | 89 | 111 |
| | | | | | 6 | 155 | 88 | 110 |
| | | | | | 8 | 156 | 90 | 112 |
| Ketanserin | 20 mg SL 10 mg IV | Atkin RCT 190 | * * | 1 | 150 | * * | * | 129 |
| | | | | | 150 | 90 | 111 | 132 |
| Vasodilators | | | | | | | | |
| Diazoxide | | | | | | | | |
| | 15 mg/min IV (300–1095 mg) | Garrett Prospective cohort 214 | 145 | 168 | 0.35 | 159 | 103 | 122 |
| | 30 mg/min IV (300–1290 mg) | | | | | | | |
| | 150 mg IV followed by 150 mg every 5 min until DBP of ≤110 mmHg, cumulative dose of 600 mg IV achieved 150 mg followed by 150 mg every 5 min until DBP of ≤110 mmHg, cumulative dose of 600 mg IV achieved 300 mg IV | Ram Non-randomized controlled 216 | 139 | 165 | 0.25 | 186 | 111 | 136 |
| | | | | | 184 | 119 | 141 | 3 |
| | | | | | | | | |
| Fenoldopam | IV starting dose 0.1 mcg/kg/min and increased in increments of ≤0.2 mcg/kg/min. Max rate 1.6 mcg/kg/min. Mean titrated dose 0.41 mcg/kg/min | Panacek RCT 212 | 135 | 161 | 1 | 178 | 106 | 140 |
| | | | | | 6 | 173 | 106 | 128 |
| | | | | | End (24) | 183 | 106 | 132 |
| Hydralazine | 25 mg PO | Sruamsiri Retrospective cohort 175 | * | * | 144 | 0.5 | * | 126 |
| Nitroglycerin | SL | Maleki RCT 190 | * | * | 1 | 150 | * | * |
| Nitroprusside | IV starting dose 0.5 mcg/kg/min and increased in increments of ≤1 mcg/kg/min. Max rate 8 mcg/kg/min. Mean titrated dose 1.67 mcg/kg/min | Panacek RCT 210 | 133 | 159 | 1 | 165 | 101 | 122 |
| | | | | | 6 | 166 | 100 | 122 |
| | | | | | End (24) | 168 | 102 | 124 |
| Urapidil | 12.5 mg IV | Woisetschlaeger Non-randomized controlled 216 | 110 | 145 | 12 | 163 | 85 | 111 |
| Urapidil (con’t) | 12.5 mg IV 25 mg IV | Salkic RCT 213 | 130 | 158 | 0.5 | 179 | 110 | 133 |
| | | | | | 213 | 130 | 158 | 1 |
| | | | | | 213 | 130 | 158 | 1 |
| | | | | | 152 | 95 | 114 |
| | 60 mg PO | Hirschl RCT 165 | 89 | 114 | 12 | 132 | 79 | 96 |
| | 103 mg IV bolus | Bottorff Prospective cohort 190 | 126 | 147 | 0.2 | 164 | 105 | 125 |

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Clonidine and labetalol were compared in an RCT, with a similar reduction in blood pressure at 6 h and similar side effect profiles. Sedation, dizziness, orthostatic hypotension, and dry mouth were reported with clonidine; dizziness, drowsiness, and headache with labetalol.

Nitrendipine and IV clonidine were compared in one RCT, with similar reductions in BP up to 8 h. Side effects reported with nitrendipine were flushing and headache, and with clonidine were dizziness, somnolence, and bradycardia.

Risk of bias is summarized in Table 3. Most studies had unclear quality control standards regarding blood pressure measurements and excluded patients with significant comorbidities, such as chronic kidney disease, which are seen frequently in patients with hypertension. Among the controlled trials, only those by Komsuoglu, Woisetschlaeger, and Just had a low risk of bias for both the study design (random sequence generation and concealment of allocation) and the primary clinical outcome (blinding of outcome assessor).

**DISCUSSION**

In this systematic review of HU, the optimal choice of antihypertensive agent remains unclear (level 2B). Many agents demonstrated blood pressure-lowering benefit: captopril, labetalol, clonidine, amlodipine, verapamil, nitrendipine, isradipine, nifedipine, nitroglycerin, hydralazine, chlorothalidone, furosemide, diazoxide, nitroprusside, and fenoldopam. Other drugs that lowered blood pressure but are unavailable in the U.S. include lacidipine, ketanserin, and urapidil. Clinical choices in the setting of HU seemed to broaden as we conducted our extensive literature search. Side effects ranged from mild (dizziness, headache, nausea and vomiting, dry mouth, mild tachycardia, and sedation) to severe (hypotension, transient ischemic attack, uremia, and acute pulmonary edema).

Most studies limited data collection to the first few hours after initial presentation, which is not sufficient to assess morbidity and mortality. Studies were too clinically and methodologically diverse for a meta-analysis, and those that met our criteria for this systematic review included few patients. Most studies excluded patients with significant comorbidities, such as chronic kidney impairment; however, HU is a common complication in patients with associated comorbidities. In light of these factors, the generalizability of our findings is limited. Most studies that met our inclusion criteria provided only surrogate endpoint data, i.e. blood pressure lowering, and were short-term, lacking long-term morbidity and/or mortality outcomes, and providing statistical power only for differences in blood pressure lowering.

Our comprehensive systematic review regarding treatment of outpatient HU includes office and ER settings, limiting data to short-term observations of blood pressure (less than 24 h). This review also included studies based on blood pressure cut-offs, allowing us to distinguish studies that were mislabeled as urgencies or emergencies.

A limitation of this review is that it evaluated only English-language reports. However, Morrison et al. found no evidence of a systematic bias from language restrictions in systematic
review-based meta-analyses in conventional medicine. We attempted to minimize publication bias by searching the gray literature; we may have missed negative or small(er) studies.

The most recent systematic review of HU, by Souza in 2008, included studies in outpatient and inpatient settings. Their Cochrane Review was limited to randomized controlled trials of calcium channel blockers or angiotensin-converting enzyme inhibitors. Although they excluded commonly used agents (e.g. clonidine, hydralazine, and labetalol), many other reviews have demonstrated a benefit in blood pressure reduction from these agents. Side effects were problematic mainly for nifedipine and clonidine.

Intravenous medications, although effective, carry added costs, and therefore we do not recommend them; many available oral agents are appropriate alternatives. Some studies included in this review evaluated diuretics. However, since HU may be associated with hypovolemia, some recommend avoiding diuretics unless intravascular volume overload is present.

For HU, current data suggest that a 30-min rest may significantly decrease blood pressure. However, many studies in this review did not have patients rest for 30 min prior to intervention.

Most medications used in reports we review here were short-acting. Lowering blood pressure too rapidly in patients with HU may be harmful. In their review, Kessler and Joudeh noted that there appears to be no benefit in attaining goal blood pressure within hours to days, and that findings from the VALUE trial suggest that lowering blood pressure within a 6 month-period may be a better approach. Therefore, avoidance of rapid-acting agents such as clonidine and nifedipine should be considered.

Other studies have used long-acting antihypertensive agents which have demonstrated morbidity and mortality benefits in hypertension outcomes trials. One such study, conducted by Grassi et al., evaluated the long-acting dihydropyridine calcium channel blocker amlodipine and the ACE inhibitor perindopril in slowly lowering blood pressure toward goal for patients with HU. This study did not meet the inclusion criteria of our review, since it did not report changes in blood pressure within 48 h of treatment.

CONCLUSION
Additional longitudinal studies are needed to determine how best to safely decrease blood pressure in patients with HU. Larger and longer-term studies are also needed, including participants with other common comorbidities. Such research would hopefully provide more guidance to improve both short- and long-term cardiovascular outcome.

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Compliance with Ethical Standards:

Conflict of Interest: The authors declare that they have no conflict of interest.

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