Original Article

OPEN

INFOGRAPHIC

Effect of intravenous antihypertensives on outcomes of severe hypertension in hospitalized patients without acute target organ damage

Lama Ghazi[a], Fan Li[b], Michael Simonov[a], Yu Yamamoto[a], James T. Nugent[a,c], Jason H. Greenberg[a,c], Christine Y. Bakhoum[a,c], Aldo J. Peixoto[d,*], and F. Perry Wilson[a,*]

See editorial on page 220

Background: Treatment of severe inpatient hypertension (HTN) that develops during hospitalization is not informed by guidelines. Intravenous (i.v.) antihypertensives are used to manage severe HTN even in the absence of acute target organ damage; however they may result in unpredictable blood pressure (BP) reduction and cardiovascular events. Our goal was to assess the association between i.v. antihypertensives and clinical outcomes in this population.

Methods: This is a multihospital retrospective study of adults admitted for reasons other than HTN who develop severe HTN during hospitalization without acute target end organ damage. We defined severe HTN as BP elevation of systolic >180 or diastolic >110 mmHg. Treatment was defined as receiving i.v. antihypertensives within 3 h of BP elevation. We used overlap propensity score weighted Cox models to study the association between treatment and clinical outcomes during index hospitalization.

Results: Of 224 265 unique, nonintensive care unit hospitalizations, 20 383 (9%) developed severe HTN, of which 5% received i.v. antihypertensives and 79% were untreated within 3 h of severe BP elevation. In the overlap propensity weighted population, patients who received i.v. antihypertensives were more likely to develop myocardial injury (5.9% in treated versus 3.6% in untreated; hazard ratio [HR]: 1.6 [1.13, 2.24]). Treatment was not associated with increased risk of stroke (HR: 0.7 [0.3, 1.62]), acute kidney injury (HR: 0.97 [0.81, 1.17]), or death (HR: 0.86 [0.49, 1.51]).

Conclusions: Intravenous antihypertensives were associated with increased risk of myocardial injury in patients who develop severe HTN during hospitalization. These results suggest that i.v. antihypertensives should be used with caution in patients without acute target organ damage.

Graphical abstract: http://links.lww.com/HJH/C125

Keywords: antihypertensive treatment, electronic health records, inpatient hypertension

Abbreviations: AKI, acute kidney injury; BP, blood pressure; CT, computed tomography; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; EHR, electronic health record; HR, hazard ratio; i.v., intravenous; KDIGO, Kidney Disease: Improving Global Outcomes; MAP, mean arterial pressure; MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drugs; YNHHS, Yale New Haven Health System

INTRODUCTION

Acute severe hypertension, systolic blood pressure (BP) >180 or diastolic BP >110 mmHg, is associated with increased morbidity and mortality, regardless of whether patients present with end organ damage (hypertensive urgency or hypertensive emergency) [1,2]. These acute severe BP elevations frequently occur during hospitalization for other reasons. In fact, 10% of nonintensive care unit hospitalized patients, admitted for reasons other than hypertension, have been found to develop incident severe hypertension [3,4]. These high BPs, though often not causing symptoms, usually prompt healthcare providers to administer antihypertensives, commonly intravenous (i.v.) medications, despite no substantive evidence that antihypertensive medications improve outcomes in the absence of acute target organ damage [5].

Treatment of acute severe hypertension during hospitalization may be harmful due to unpredictable BP reductions, subsequent end organ injury, or the concomitant effect of specific antihypertensives given [6–8]. We have previously shown that treatment with i.v. antihypertensives was associated with a 38% greater risk (hazard ratio [HR]: 1.38 [1.15, 1.67]) of severe BP reduction (mean arterial pressure reduction of ≥30%) compared to no treatment among inpatients who develop severe hypertension [3]. However, it is unknown whether treatment of acute severe BP elevation might lead to worse clinical outcomes. Other studies have

Journal of Hypertension 2023, 41:288–294

[a]Department of Internal Medicine, Clinical and Translational Research Accelerator, Yale University, [b]Department of Biostatistics, Yale School of Public Health, [c]Section of Nephrology, Department of Pediatrics, Yale University School of Medicine and [d]Department of Internal Medicine, Section of Nephrology, Yale School of Medicine, and the Hypertension Program, Yale New Haven Hospital Heart and Vascular Center, New Haven, Connecticut, USA

Correspondence to F. Perry Wilson, MD, MSCE, 60 Temple St, Ste 6C, New Haven, CT 06510, USA. Tel: +1 203 737 1704; fax: +1 203 764 8373; e-mail: francis.p.wilson@yale.edu

*Aldo J. Peixoto and F. Perry Wilson contributed equally to this work.

Received 18 July 2022 **Revised** 26 September 2022 **Accepted** 18 October 2022

DOI:10.1097/HJH.0000000000003328

demonstrated that treatment of inpatient hypertension, across the BP spectrum, with antihypertensives was associated with greater risk of ischemic events and mortality [4,9]. These studies however, only included noncardiovascular disease (CVD) admissions, used a wide range of BPs to define hypertension, and did not adjust for medications besides antihypertensives that could influence BPs. Given that both chronic and acute severe BP elevations are associated with worse clinical outcomes [2], understanding the clinical implications of severe hypertension development during hospitalization and the effect of treatment on clinical outcomes in this population is critical to guide future management recommendations. Therefore, the goal of this study was to evaluate the effect of i.v. antihypertensive treatment on clinical outcomes in patients who develop severe hypertension (acute severe BP elevations) without acute target organ damage during hospitalization.

METHODS

Study population

This is a retrospective study of adult patients admitted to Yale New Haven Health System (YNHHS) network hospitals between 6 January 2016 and 31 March 2020 who were hospitalized for $\geq$2 and $\leq$30 days. We excluded patients hospitalized with hypertensive emergency and patients admitted to a maternity ward, an intensive care unit, or a research unit. Patients who received vasopressors 6 h before severe inpatient hypertension development (expanded upon below) were excluded from the analysis (Fig. 1). For patients with multiple admissions during the study period, we only included data from the first admission. We excluded all patients who had missing data on any of the covariates (0.83%). The study was approved by the Yale Human Investigation Committee (HIC # 2000028801). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. Electronic health record data (EHR) was collected from the YNNHS data warehouse (EPIC, Verona, WI).

Severe inpatient hypertension

We defined severe inpatient hypertension as the first documented severe BP elevation (systolic BP > 180 or diastolic BP > 110 mmHg) after admission and did not include BPs captured in the emergency department. To exclude falsely elevated measurements, we excluded patients whose BP decreased to systolic BP <180 mmHg or diastolic BP <110 mmHg within 1 h of the index severe BP elevation without administration of antihypertensive medications over the same interval. If no repeat BP measurement was available within 1 h of severe BP elevation, we considered the patient to have severe hypertension

Antihypertensive treatment

We defined i.v. antihypertensive treatment as receiving any of four intravenous medications: (hydralazine, labetalol, metoprolol, or nicardipine) on our inpatient formulary within 3 h of developing severe hypertension.

Covariates

Demographics, vital signs, body mass index, ward, comorbidities prior to admission [defined by the Elixhauser

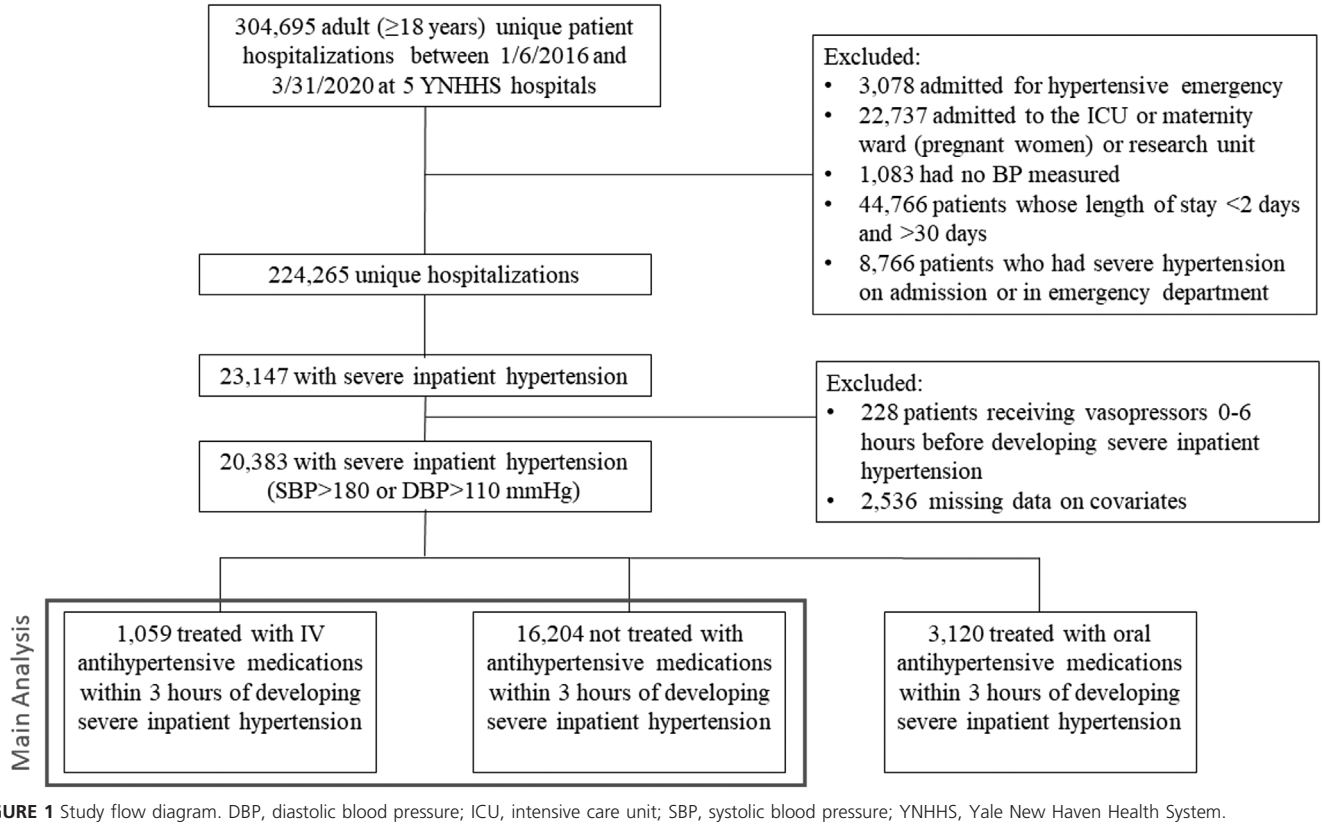

FIGURE 1 Study flow diagram. DBP, diastolic blood pressure; ICU, intensive care unit; SBP, systolic blood pressure; YNHHS, Yale New Haven Health System.

comorbidity index based on International Classification of Diseases (ICD)-10 codes [10]], antihypertensive medications, and laboratory results were extracted from the EHR. Estimated glomerular filtration rate (eGFR) was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equation that estimates eGFR without race [11]. We defined mean arterial pressure (MAP) as 1/3 systolic BP + 2/3 diastolic BP. We also included use of narcotics, sedatives, benzodiazepines, nonsteroidal anti-inflammatory drugs (NSAID), corticosteroids, and crystalloid i.v. fluids; these are indirect markers of pain, anxiety, inflammation, or volume status and have been associated with BP effects [12–15]. Race and ethnicity were extracted from the patient-reported demographic information in the EHR and were included as they have been independently associated with hypertension [2].

Outcomes

Our main outcomes of interest included myocardial injury, stroke, acute kidney injury (AKI) and inpatient death. All events were considered only if they occurred 3 h or more after developing severe inpatient hypertension to reduce the risk of reverse causality. We defined myocardial injury as evidence of newly elevated troponin (serum troponin concentration above the 99th percentile). If the patient had AKI before troponin elevation, they were excluded from the myocardial injury outcome analysis. Timing of the event was determined by the time the blood sample (troponin) was drawn. Stroke was considered present if the patient had an ICD-10 code for stroke (I60–I69) and magnetic resonance imaging (MRI) or computed tomography (CT) brain imaging was completed. Timing of stroke was determined by the time imaging was performed. AKI was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria. AKI was defined as an increase in serum creatinine of $\geq$0.3 mg/dl (26.5 μmol/l) within 48 h or 1.5 times the lowest measured serum creatinine within the previous 7 days [16]. Finally, death was ascertained using EHR data. Based on our chart review of 100 random records, we have a 98% sensitivity in identifying the correct BP measurements and other baseline covariates and a 95% sensitivity in identifying our outcomes.

Statistical analysis

Characteristics between treated and untreated severe hypertensive patients were presented as median and interquartile range or proportions. To account for confounders between treated and untreated patients, we used overlap propensity score weighting, which has been demonstrated to be more statistically efficient than inverse probability weighting and more robust than extreme propensity scores [17–21]. A propensity score is the probability that each patient will be assigned to receive antihypertensive treatment given the measured covariates [22]. We calculated the propensity score for antihypertensive treatment using a multivariable logistic regression model containing demographics, comorbidities, laboratory measures on admission, medications besides antihypertensives that affect BP given before severe inpatient hypertension development (e.g. NSAID, corticosteroid, i.v. crystalloid fluid), vitals on admission and BP at time of severe hypertension development. Each patient was then weighted by the overlap weights, which correspond to the probability of that patient being assigned to the opposite group [19]. In other words, treated patients are weighted by the probability of not receiving treatment (1 − propensity score) and untreated patients are weighted by the probability of receiving treatment (propensity score). We further assessed covariate balance between treated and untreated groups using the full cohort and, in the overlap propensity score weighted cohort, with standardized mean difference of 0 as evidence of balance. Finally, we used a complete case analysis and fit an overlap propensity score-weighted Cox regression model to study the association between antihypertensive treatment and clinical outcomes.

In a sensitivity analysis, we studied the association of treatment on outcomes among cardiovascular and non-CVD admissions (i.e. excluded patients admitted for cerebrovascular events, myocardial infarction, heart failure or abdominal aortic aneurysm) and explored differences by treatment route in each group to compare our findings with those in the literature [4,9]. These were determined based on whether a new, not historical, ICD-10 code for any cerebrovascular events, myocardial infarction, heart failure or abdominal aortic aneurysm during hospitalization were coded during hospitalization. We further studied the association of treatment on outcomes by admission ward (surgical versus medical). Additionally, we assessed the effect of treatment with i.v. antihypertensives compared to receiving no treatment or oral antihypertensives only within 3 h of developing severe inpatient hypertension. We also compared the risk of developing clinical outcomes among those treated with i.v. antihypertensives versus oral antihypertensives. Finally, in an exploratory analysis we studied the association of treatment on clinical outcomes based on the most common admission diagnoses.

We conducted our analyses using R, version 4.0.0 (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Cohort characteristics

Of the 304 695 hospitalization events, we identified 224 265 admissions fitting our inclusion and exclusion criteria, of which 20 377 (9%) developed severe hypertension (Figure 1). Of those, 5% received i.v. antihypertensives and 79% did not receive any antihypertensive medications within 3 h of developing severe hypertension. Median number of BP measurements was 29 [16, 52]. Additionally, median time from admission to first recorded elevated BP was 6.5 [1.2, 44.3] h and 6.7 [1.0, 46.9] h among treated and untreated severe hypertensive patients. Regardless of treatment status, patients who developed severe hypertension were elderly (median age: 73), had a history of hypertension (78%), and had similar lab values on admission (Table 1). Patients who received i.v. antihypertensives compared to those who did not receive any treatment had a higher BP upon admission (BP: 162/84 in treated and 154/81 mmHg in untreated patients, respectively) and higher BP at time of severe hypertension development (BP: 191/93 in treated and 185/89 mmHg in untreated patients, respectively). The standardized mean differences between these groups

TABLE 1. Characteristics of patients with severe inpatient hypertension in baseline population and propensity weighted patients (using standardized overlap weights)

	Baseline population			Overlap propensity weighted population[a]	
	Treated $N = 1059$	Untreated $N = 16\,204$	SMD	Treated $N = 1059$	Untreated $N = 16\,204$
Demographics					
Age	74 (62, 86)	73 (60, 84)	0.080	73 (60, 85)	73 (60, 84)
Black	229 (22%)	3094 (19%)	0.063	211 (20%)	3079 (19%)
Male sex	447 (42%)	7166 (44%)	0.041	477 (45%)	7129 (44%)
Hispanic or Latino	92 (9%)	1636 (10%)	0.060	95 (9%)	1620 (10%)
Location					
Surgical ward	309 (29%)	3005 (19%)	0.251	222 (21%)	3079 (19%)
Comorbidities					
Congestive heart failure	293 (28%)	4735 (29%)	0.034	318 (30%)	4699 (29%)
Cardiac arrhythmia	408 (39%)	6511 (40%)	0.034	424 (40%)	6482 (40%)
Valvular disease	213 (20%)	3332 (21%)	0.011	223 (21%)	3402 (21%)
Pulmonary circulation disorder	109 (10%)	1900 (12%)	0.046	127 (12%)	1945 (12%)
Peripheral vascular disease	252 (24%)	4056 (25%)	0.029	275 (26%)	4051 (25%)
Hypertension	825 (78%)	12 731 (79%)	0.016	847 (80%)	12 639 (78%)
Paralysis	49 (5%)	752 (5%)	0.001	42 (4%)	810 (5%)
Other neurological disorders	278 (26%)	4436 (27%)	0.025	275 (26%)	4375 (27%)
Chronic pulmonary disorders	310 (29%)	5952 (37%)	0.159	402 (38%)	5833 (36%)
Diabetes	420 (40%)	6603 (41%)	0.022	445 (42%)	6643 (41%)
Hypothyroidism	231 (22%)	3634 (22%)	0.015	232 (22%)	3564 (22%)
Renal failure	318 (30%)	4991 (31%)	0.017	329 (31%)	5023 (31%)
Liver disease	30 (13%)	2358 (15%)	0.055	159 (15%)	2269 (14%)
Peptic ulcer disease	53 (5%)	847 (5%)	0.010	53 (5%)	810 (5%)
AIDS/HIV	12 (1%)	252 (2%)	0.037	21 (2%)	324 (2%)
Cancer	199 (19%)	3239 (20%)	0.030	222 (21%)	3241 (20%)
Rheumatoid arthritis/collagen	70 (7%)	1291 (8%)	0.052	84 (8%)	1296 (8%)
Coagulopathy	120 (11%)	2141 (13%)	0.057	127 (12%)	2106 (13%)
Obesity	198 (19%)	4023 (25%)	0.149	275 (26%)	3889 (24%)
Weight loss	181 (17%)	2947 (18%)	0.029	190 (18%)	2917 (18%)
Fluid and electrolyte disorder	524 (49%)	8276 (51%)	0.032	540 (51%)	8264 (51%)
Blood loss anemia	60 (6%)	1233 (8%)	0.078	95 (9%)	1296 (8%)
Iron deficiency anemia	205 (19%)	3367 (21%)	0.035	233 (22%)	3402 (21%)
Alcohol abuse	140 (13%)	2127 (13%)	0.003	138 (13%)	2106 (13%)
Drug abuse	134 (13%)	2255 (14%)	0.037	138 (13%)	2268 (14%)
Psychosis	47 (4%)	1021 (6%)	0.083	53 (5%)	972 (6%)
Depression	327 (31%)	5395 (33%)	0.052	350 (33%)	5347 (33%)
Labs on admission					
Sodium	139 (136, 141)	139 (136, 141)	0.038	139 (136, 141)	139 (136, 141)
Potassium	4.1 (3.8, 4.6)	4.2 (3.8, 4.6)	0.015	4.2 (3.8, 4.6)	4.2 (3.8, 4.6)
Chloride	102 (98, 105)	102 (98, 105)	0.031	101 (97, 105)	102 (98, 105)
Bicarbonate	25 (22, 27)	25 (22, 27)	0.044	25 (22, 27)	25 (22, 27)
BUN	20 (15, 30)	20 (14, 31)	0.023	20 (14, 30)	20 (14, 31)
eGFR	63 (39, 87)	66 (40, 89)	0.084	65 (40, 91)	65 (40, 89)
White blood cell count	9 (6.8, 12.0)	9 (6.8, 12.1)	0.027	9.4 (6.9, 12.6)	9 (6.8, 12.1)
Platelet count	224 (178, 288)	224 (174, 284)	0.024	226 (180, 289)	224 (175, 284)
Hemoglobin	12.3 (10.7, 13.7)	12.1 (10.5, 13.6)	0.075	12.2 (10.8, 13.6)	12.1 (10.5, 13.6)
Hematocrit	38 (33, 42)	37 (33, 41)	0.068	38 (33, 42)	38 (33, 42)
Medications given 6 h before onset of severe inpatient hypertension					
NSAID	13 (1%)	372 (2%)	0.014	21 (2%)	324 (2%)
Crystalloid	172 (16%)	2392 (15%)	0.062	180 (17%)	2431 (15%)
Narcotics	184 (17%)	2557 (16%)	0.043	180 (17%)	2592 (16%)
Sedatives	60 (6%)	1165 (7%)	0.051	85 (8%)	1134 (7%)
Steroids	40 (4%)	724 (5%)	0.011	42 (4%)	648 (4%)
Admission characteristics					
Systolic BP	162 (140, 182)	154 (135, 173)	0.061	153 (132, 172)	154 (135, 174)
Diastolic BP	84 (72, 97)	81 (70, 92)	0.012	80 (69, 94)	81 (70, 92)
MAP	111 (96, 124)	106 (93, 118)	0.039	106 (90, 118)	106 (94, 118)
Heart rate	82 (71, 96)	83 (71, 97)	0.044	83 (70, 98)	83 (71, 97)
BMI	27 (22, 32)	27 (23, 33)	0.034	28 (23, 33)	27 (23, 32)
BP at time of severe inpatient hypertension development					
Systolic BP	191 (183, 107)	185 (181, 190)	0.078	185 (181, 192)	185 (181, 190)
Diastolic BP	93 (83, 107)	89 (80, 107)	0.130	93 (82, 111)	89 (80, 107)
MAP	126 (119, 134)	122 (115, 129)	0.101	123 (117, 131)	122 (115, 129)

Values are presented as count (%) or median (IQR).
BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; NSAID, non-steroidal anti-inflammatory; SMD, standardized mean difference.
[a]For overlap propensity weighted population, SMD converge to 0.

converge to zero and all covariates are balanced in the overlap propensity weighted cohort [17,19]. Additionally, there was sufficient overlap between treated and untreated groups (Figure S1, Supplemental Digital Content, http://links.lww.com/HJH/C105).

Inpatient outcomes

The median systolic BP, diastolic BP and MAP at discharge among treated and untreated patients were 141 [128, 155], 74 [67, 82], 97 [89, 104] mmHg and 140 [126, 154], 73 [66, 82], 96 [88, 104] mmHg (*P*-value: 0.05, 0.43, 0.09), respectively. Figure S2, Supplemental Digital Content, http://links.lww.com/HJH/C105 and Figure S3, Supplemental Digital Content, http://links.lww.com/HJH/C105 show BP reduction in treated and untreated groups over 12 h from time of severe hypertension development. The median time to develop myocardial injury, stroke, AKI and death in the treated group was: 7.1 [3.2, 17.9], 26.8 [9.6, 43.3], 45.2 [24.8, 84.4] and 155.4 [123.1, 175.5] h from the time that follow up started (3 h post severe hypertension development). In the untreated group, the median time to develop myocardial injury, stroke, AKI and death was 8.5 [3.9, 26.6], 32.6 [7.1, 62.4], 47.1 [24.1, 94.1] and 132.5 [69.5, 266.5] h. Patients who received i.v. antihypertensives were more likely to have myocardial injury compared to those who were untreated (5.9% in treated versus 3.6% in untreated, overlap propensity weighted HR, 95% confidence interval [CI]: 1.52 [1.08, 2.14]). In the unadjusted analysis, patients treated with i.v. antihypertensives were more likely to develop AKI and death compared to untreated patients (23.1 versus 17.7% for AKI and 2.6 versus 1.3% for death). After overlap propensity weighting, there was no increased risk in AKI or death in treated patients (HR: 0.7 [0.30, 1.62] for AKI and 0.86 [0.49, 1.51] for death). We did not observe any difference in stroke between groups (Table 2).

Sensitivity analysis

Among both cardiovascular and non-CVD admissions, treated patients were more likely to develop myocardial injury and AKI in unadjusted analysis (Table S2, Supplemental Digital Content, http://links.lww.com/HJH/C105). However, after overlap propensity weighting there was no increased risk in either outcome among patients treated with i.v. antihypertensives. Additionally, patients admitted to a medical ward who developed severe hypertension and were treated with i.v. antihypertensive had 74% HR: 1.74 [1.17, 2.59] greater risk of developing myocardial injury. This was not observed in patients admitted to a surgical ward (Table S3, Supplemental Digital Content, http://links.lww.com/HJH/C105). Even when we compared patients who received i.v. antihypertensives to those who did not receive treatment or received only oral antihypertensives, we found that i.v. treatment resulted in greater risk of myocardial injury (HR: 1.59 [1.13, 2.24]) (Table S4, Supplemental Digital Content, http://links.lww.com/HJH/C105). Similar to the main results, patients treated with i.v. antihypertensives had greater risk of myocardial injury compared to those treated with oral antihypertensives (HR: 1.91 [1.1, 3.16]) (Table S5, Supplemental Digital Content, http://links.lww.com/HJH/C105). In our exploratory analysis, we found that patients admitted for kidney reasons (based on admission ICD-10 codes) had greater risk of acute kidney injury with i.v. antihypertensive treatment. We also found that patients admitted for neurological reasons (based on admission ICD-10 codes) had greater risk of myocardial injury with i.v. antihypertensive treatment (Tables S6 and S7, Supplemental Digital Content, http://links.lww.com/HJH/C105). Finally, there was no clinically relevant difference in median length of stay for i.v. treatment versus untreated patients despite statistical significance (5.6 [3.7, 9.4] days and 5.7 [3.8, 9.1] days, $P < 0.001$, respectively).

DISCUSSION

We observed that in a large healthcare system, 9% of hospitalized adults admitted for reasons other than hypertension developed severe hypertension and 5% received i.v. antihypertensives within 3 h of severe hypertension development. After using overlap propensity weighting to balance treated and untreated patients, we found that patients who received i.v. antihypertensives were more likely to develop myocardial injury during hospitalization compared to those who did not receive treatment and/or received oral antihypertensives. There was no difference in overlap propensity weighted risk of stroke, AKI or death and absolute length of stay was comparable between groups.

Rastogi *et al.* [4] found that among adults admitted for non-CVD reasons, 78% had an elevated systolic BP reading (≥140 mmHg), 33% were treated of which 26% received i.v. antihypertensives, though timing of treatment was not determined. They found that treatment with i.v. antihypertensives was associated with greater odds of myocardial

TABLE 2. Inpatient outcomes for treated versus untreated patients by treatment route hazard ratio (HR) calculated while accounting for overlap propensity weights

	Events in treated	Events in untreated	Unweighted crude HR [95% CI]	Overlap propensity weighted HR [95% CI]
Myocardial Injury				
i.v. versus no treatment	62 (5.9%)	591 (3.6%)	1.63 [1.25, 2.11]	1.52 [1.08, 2.14]
Stroke				
i.v. versus no treatment	7 (0.7%)	107 (0.7%)	1.00 [0.47, 2.15]	0.70 [0.30, 1.62]
Acute kidney injury				
i.v. versus no treatment	245 (23.1%)	2876 (17.7%)	1.06 [0.93, 1.21]	0.97 [0.81, 1.17]
Death				
i.v. versus no treatment	28 (2.6%)	208 (1.3%)	1.08 [0.72, 1.60]	0.86 [0.49, 1.51]

95% CI, 95% confidence interval.

injury (odds ratio [OR]: 2.27 [1.17, 4.68]) and AKI (OR: 1.47 [1.16, 1.87]). Another study by Mohandas *et al.* [9] found that among patients who received "as-needed" antihypertensives in addition to their chronic medications during hospitalization, treatment was associated with greater odds of AKI, stroke, and mortality. When stratified by antihypertensive route, they found that i.v. antihypertensives (93% of all as-needed medications) resulted in an increase in adverse clinical outcomes, while oral antihypertensives were not associated with AKI or death. Their study excluded patients in the intensive care unit, pregnant adults, and those who had a history of acute CVD or end stage kidney disease. These results are also consistent with previous studies that described the risks of treating acute BP elevations in the hospital with i.v. antihypertensives [6–8]. In all, we have found that treatment with i.v. antihypertensives and not oral antihypertensives resulted in greater risk of myocardial injury. This suggests that i.v. antihypertensives should be used with caution, if at all. In fact, current guidelines solely recommend the adjustment of chronic therapy, not any acute intervention with short acting agents, either intravenous or oral [2].

Our study focused on the hospitalized period. Similar to our findings, a study assessing inpatient hypertension (systolic BP $\geq$ 140 mmHg) among non-CVD admissions found that treatment did not affect the length of stay [4]. On the contrary, as-needed antihypertensives in patients admitted to the hospital with no previous history of CVD or end stage kidney disease, resulted in an increase in hospital length of stay. These inconsistencies might be due to differences in patient populations, whether it is excluding patients with certain comorbidities or including only non-CVD admissions or using a wide range of BP thresholds to determine effect of treatment on outcomes. Future studies are needed to assess the impact of treatment of severe hypertension not only on discharge BP but also on BP in the outpatient setting in a large cohort of adults of all age ranges and admitted for multiple reasons.

Previous studies demonstrating the adverse effect of inpatient hypertension treatment have included patients with any degree of hypertension [4,9], yet providers may be most likely to treat patients with severely increased hypertension [4]. Our study on the other hand uses a set cut point to define and assess severe hypertension using both systolic and diastolic BP. Other strengths of these analyses include: we have a large well characterized cohort of patients admitted to several large hospitals for various reasons. This allowed us to account for several confounders that might affect why patients who developed severe hypertension were treated or not; we validated our data with manual chart review; finally, we used overlap propensity score weighting which confers additional strengths in balancing treated and untreated patients than inverse probability weighting and in improving precision of the treatment effect estimates. Overlap weights also mimic characteristics of a randomized controlled trial as it emphasizes the population with most clinical equipoise [17–20].

Our study has several limitations. We did not account for outpatient BP before hospitalization. Therefore, we are unable to account for baseline BP or hypertension control. However, we accounted for history of hypertension. Additionally, we studied the effect of antihypertensive medications on outcomes irrespective of dose or indication. However, by limiting our analysis to i.v. antihypertensives given within 3 h of severe hypertension elevation we could assume these medications were not routine medications and were given for treatment of severe BP elevation. Knowing that BP management might be different for patients with CVD diagnoses, we stratified our analysis by CVD admission. Among non-CVD admissions (62%), we found that even though myocardial injury was more common in those treated with i.v. antihypertensives compared to untreated patients, there was no increased risk of the event with treatment. This might be due to small number of cases in those treated with i.v. antihypertensives. Additionally, in our exploratory analysis we assessed the effect of treatment on clinical outcomes by admission diagnoses grouping. We did not find adverse effects of i.v. antihypertensives in patients admitted for fractures or injuries, or for gastrointestinal and genitourinary reasons or those admitted for infectious reasons. We did however find adverse effects with i.v. antihypertensives among those admitted for kidney and neurological reasons. These results only give a general overview of the possible impact of treatment in patients hospitalized for different reasons, as admission diagnoses are prone to error and often change over the course of hospitalization [23]. Moreover, we were unable to assess how BP was measured, that is which device was used, cuff placement or patient positioning. Treatment practices, such as choice of antihypertensive class and route, may reflect prevalent practices at our institution and may be different at other institutions. Therefore, findings from this study – at one single healthcare system – may not be generalizable to other hospitals. Also, relying on one BP measurement to define severe hypertension may bias our findings. However, by excluding patients who had a spontaneous drop in BP without treatment within 1 h of the severe BP measurement allowed us to exclude any falsely elevated BP measurements. Finally, other unmeasured covariates might confound the association between treatment of severe hypertension and outcomes. For example, this may include the clinical decision-making reasoning behind treating BP elevations. Through overlap propensity score weighting, however, we have to the extent possible balanced patients who were treated and untreated based on important factors that are believed to influence whether providers will treat severe hypertension (e.g. comorbidities, type of ward, demographics).

In summary, we found that among hospitalized adults, 9% develop severe hypertension, and 5% receive i.v. antihypertensives within 3 h of severe BP elevation. Treatment with i.v. antihypertensives resulted in greater risk of myocardial injury, but not stroke, AKI, or death. Our findings suggest that acute treatment of severe hypertension in the absence of acute target organ damage should be approached cautiously, and preferentially i.v. antihypertensives should be avoided. Further studies and randomized clinical trials to determine which patients should be treated, if any, and which antihypertensives (class and route) to administer upon the development of severe hypertension in the hospital setting are needed.

ACKNOWLEDGEMENTS

Disclosures: None.

Sources of funding: This work was funded by the American Heart Association (AHA) Postdoctoral Fellowship award (829804). C.Y.B. is funded by AHA Grant 857722 and NIDDK K23 DK129836. F.P.W. is funded by National Institutes of Health grants P30DK079310, R01HS027626 and R01DK113191.

Contributors: We would like to thank Aditya Biswas, MS, Jonathan Hanna, MD, and Tayyab Shah, MD for their help with the data analysis and validating data using manual chart review.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Peixoto AJ. Acute severe hypertension. *N Engl J Med* 2019; 381:1843–1852.
2. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2018; 138:e426–e483.
3. Ghazi LLF, Chen X, Simonov M, Yamamoto Y, Biswas A, Hanna J, *et al.* Severe inpatient hypertension prevalence and blood pressure response to antihypertensive treatment. *J Clin Hypertens (Greenwich)* 2022; 24:339–349.
4. Rastogi R, Sheehan MM, Hu B, Shaker V, Kojima L, Rothberg MB. Treatment and outcomes of inpatient hypertension among adults with noncardiac admissions. *JAMA Intern Med* 2021; 181:345–352.
5. Axon RN, Garrell R, Pfahl K, Fisher JE, Zhao Y, Egan B, *et al.* Attitudes and practices of resident physicians regarding hypertension in the inpatient setting. *J Clin Hypertens (Greenwich)* 2010; 12:698–705.
6. Campbell P, Baker WL, Bendel SD, White WB. Intravenous hydralazine for blood pressure management in the hospitalized patient: its use is often unjustified. *J Am Soc Hypertens* 2011; 5:473–477.
7. Lipari M, Moser LR, Petrovitch EA, Farber M, Flack JM. As-needed intravenous antihypertensive therapy and blood pressure control. *J Hosp Med* 2016; 11:193–198.
8. Weder AB, Erickson S. Treatment of hypertension in the inpatient setting: use of intravenous labetalol and hydralazine. *J Clin Hypertens (Greenwich)* 2010; 12:29–33.
9. Mohandas R, Chamarthi G, Bozorgmehri S, Carlson J, Ozrazgat-Baslanti T, Ruchi R, *et al.* Pro Re Nata antihypertensive medications and adverse outcomes in hospitalized patients: a propensity-matched cohort study. *Hypertension* 2021; 78:516–524.
10. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, *et al.* Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005; 43:1130–1139.
11. Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, *et al.* A unifying approach for GFR estimation: recommendations of the NKF-ASN Task Force on reassessing the inclusion of race in diagnosing kidney disease. *Am J Kidney Dis* 2022; 79:268–288; e1.
12. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol* 2020; 16:223–237.
13. Booth JN, Li J, Zhang L, Chen L, Muntner P, Egan B. Trends in prehypertension and hypertension risk factors in US adults: 1999–2012. *Hypertension* 2017; 70:275–284.
14. Parikh NI, Pencina MJ, Wang TJ, Benjamin EJ, Lanier KJ, Levy D, *et al.* A risk score for predicting near-term incidence of hypertension: the Framingham Heart Study. *Ann Intern Med* 2008; 148:102–110.
15. Kshirsagar AV, Chiu YL, Bomback AS, August PA, Viera AJ, Colindres RE, *et al.* A hypertension risk score for middle-aged and older adults. *J Clin Hypertens (Greenwich)* 2010; 12:800–808.
16. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int 2012; 2(Suppl):1–138.
17. Li F, Thomas LE. Addressing extreme propensity scores via the overlap weights. *Am J Epidemiol* 2019; 188:250–257.
18. Zeng S, Li F, Hu L, Li F. Propensity score weighting analysis of survival outcomes using pseudo-observations. arXiv preprint arXiv:2103.00605.
19. Li F MK, Zaslavsky AM. Balancing covariates via propensity score weighting. *J Am Stat Assoc* 2018; 113 (521):390–400.
20. Thomas LE, Li F, Pencina MJ. Overlap weighting: a propensity score method that mimics attributes of a randomized clinical trial. *JAMA* 2020; 323:2417–2418.
21. Cheng C, Li F, Thomas LE, Li F. Addressing extreme propensity scores in estimating counterfactual survival functions via the overlap weights. *Am J Epidemiol* 2022; 91:1140–1151.
22. Haukoos JS, Lewis RJ. The propensity score. *JAMA* 2015; 314:1637–1638.
23. Hussain F, Cooper A, Carson-Stevens A, *et al.* Diagnostic error in the emergency department: learning from national patient safety incident report analysis. *BMC Emerg Med* 2019; 19:77.