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Interaction between Antihypertensive Therapy Class and Pulse Pressure on Outcomes Following Acute Ischemic Stroke

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Abstract

Goal: The effect of pulse pressure and interactions with type of antihypertensive therapy on mortality after acute ischemic stroke has not been previously evaluated. Materials and Methods: A retrospective cohort study was conducted to evaluate the independent and interactive effects of pulse pressure and antihypertensive class (specifically angiotensin converting enzyme inhibitor/angiotensin type 1 receptor blocker, or beta blocker) on mortality following acute ischemic stroke. Findings/Conclusions: 343 patients were identified with 49 months of follow-up. Baseline pulse pressure was 64 mmHg and age was 66.5 years. Patients were divided at a pulse pressure of 70. Patients with pulse pressure $\geq$ 70 were older (p < 0.001) and had higher comorbid vascular burden (p = 0.031) than those with pulse pressure < 70. Pulse pressure did not remain a significant predictor of follow-up mortality after adjustment for baseline comorbidities. Angiotensin converting enzyme inhibitor/angiotensin type 1 receptor blocker based therapy was associated with lower follow-up mortality when beta blocker was not used in pulse pressure < 70 group (odds ratio 0.07, 95% confidence interval 0.01 - 0.48). Prospective analysis will be needed to confirm the protective effect of angiotensin converting enzyme inhibitor/angiotensin type 1 receptor blocker based on pulse pressure in acute ischemic stroke.

Keywords

Acute Ischemic Stroke, Pulse Pressure, Angiotensin Blockers, Beta Blockers, Outcomes

1. Introduction

The relationship between blood pressure (BP) control and short and long term outcomes in patients with acute ischemic stroke (AIS) is highly complex and not well understood with conflicting data. More than half of ischemic stroke patients had systolic blood pressure (SBP) above 160 mmHg within the first 48 hours of symptom onset in the International Stroke Trial (IST) [1]. However, the IST evaluation demonstrated a U-shaped relationship between SBP at both 14-day and 6 month outcomes. The most interesting was an increased risk of death at 14 days by 17.9% for every 10 mmHg SBP less than 150 mmHg compared to a 3.8% increased risk of death with each 10 mmHg increase above 150 mmHg (3.6% vs. 1.1% for 6 month death or dependency) [1]. On the other hand, recurrent AIS within 14-days was directly associated with increased SBP, which independently predicted the likelihood of AIS in a multivariate analysis [1].

Currently, the evidence does not support aggressive management of BP during AIS as a global strategy [2]. Although significantly elevated BP in AIS is deleterious, rapid reduction of SBP has been associated with a higher mortality [3] with cerebral hypoperfusion and increased cardiac events [4]. Reducing diastolic BP (DBP) by >20% also significantly increases the risk of death [5]. Citing conflicting evidence, the 2013 ACC/AHA Guidelines for the "Early Management of Patients with Acute Ischemic Stroke" did not specify BP targets and suggest using "best clinical judgment" and "to initially lower the SBP by 15% and monitor for neurological deterioration related to the (blood) pressure lowering" [2].

An important component of BP is the difference between SBP and DBP, or the pulse pressure (PP) [6]. Increased PP above a population norm has been associated with inferior outcomes in AIS [7] [8] [9] [10] [11], especially when PP exceeds 70 mmHg [7]. With the varying components of BP and the diversity of findings among the clinical trials of BP in AIS, the optimal approach to BP management in AIS remains unclear. Likewise, the choice of antihypertensive treatment in AIS and during follow-up has not been well established [12]. Angiotensin converting enzyme inhibitors (ACEI) were demonstrated to prevent recurrent strokes [13] and improve hospital [14] and follow-up survival [15]. Some studies suggested benefit with angiotensin II receptor blocker (ARB) [16] [17] [18] [19]; while calcium channel blocker (CCB) [5] [20] and beta-adrenergic blocker (BB) [21] [22] [23] therapies failed to show consistent reduction in mortality and prevention of recurrent stroke.

The effects of anti-hypertensive therapy on outcomes in patients with AIS and widened pulse pressure (WPP) have not been well studied previously. In this observational study, we examined whether treatment of hypertension modulates adverse effects of WPP in ischemic stroke. We have chosen to define WPP as a value of ≥70 mmHg as this cut point has been shown to be associated with poorer outcomes in previous studies [7].

2. Methods

2.1. Study Design and Patient/Variable Selection

Retrospective chart review was performed and follow-up outcomes (49.7 ± 22.4 months) were ascertained in 343 consecutive patients treated for AIS at a single tertiary care academic medical center, certified as Primary Stroke Center [24]. Patients were identified utilizing a hospital billing database, according to the discharge diagnosis code (ICD9 for acute stroke—434.xx, 435.xx, or 436.xx—in addition patients needed to have had an echocardiogram that was ordered to look for an embolic source).

The hospital's diagnostic evaluation and therapeutic interventions followed the 2003 "Guideline for The Management of Patients with Ischemic Stroke" [25]. Quality of care was ascertained according to the "Get With The Guidelines" [26] program criteria. During the study time period (2008 to 2011), the treating hospital was recognized for the performance achievement, with more than 85% of patients having received care according to the guideline, attesting to the quality and consistency of the care provided. Initial BP measurements were performed by properly trained Emergency Department triage RN in the supine patient, employing automated BP measurement unit with an appropriate size cuff for the patient's habitus. The discharge criterion for hypertension management was attaining BP of <140/90 mmHg, unless it could not be tolerated; this is consistent with the current "Evidence-Based Guideline for the Management of High BP in Adults: Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)" [27].

The choice of employed anti-hypertensive medications was determined by patient co-morbidities and the intensity of each required therapy. Treatment followed recommendation of "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" [28]. All medications were titrated to the maximal safe dosing to ensure goal BP management.

Outcomes were assessed until 2015 and were classified as in-hospital mortality in patients who expired during index admission, follow-up mortality in patients who expired during the follow-up period, and survivors. Outcomes and causes of death were determined through hospital charts and death certificates, and status was verified through the Social Security Death Index database [29] [30]. The study was approved by the institutional IRB at the Albany Medical College.

2.2. Statistical Analysis

Continuous variables were expressed as means and standard deviations. Differences in continuous variables were assessed with an unpaired t-test and non-parametric Kruskall-Wallis test, when appropriate. Categorical data was expressed as proportions and the differences in proportions were assessed with Chi-square analysis and Fisher's exact test, when appropriate.

Univariate logistic regression analysis was used to identify predictors of short

and follow-up mortality. Statistically significant univariable predictors of acute and follow-up mortality were subsequently entered in a multivariable logistic regression model to adjust for other risk factors. The dependent variables were hospital and follow up mortality and the independent variables were age, peripheral vascular disease, end-stage renal failure, Glasgow coma scale, PP ≥ 70 mmHg, and antihypertensive therapy utilized. An additional multivariable logistic regression was performed with ACEI or ARB therapy and Beta Blocker therapy as the dependent variables. The independent variables were sex, age, CAD, hypertension, diabetes, hyperlipidemia, peripheral arterial disease (PAD), end-stage renal disease, PP ≥ 70 mmHg, type of stroke and Glasgow coma scale. No data points were discarded; all patients alive at end of follow-up period were censored for long term outcomes assessment. For multivariable analysis, patients with missing data for the analysis were excluded.

P-value of <0.05 was used to indicate statistical significance and all p-values were two-tailed. All analyses were conducted with commercially available statistical software (JMP 7.0.2, SAS, NC, 2007).

3. Results

After inclusion and exclusion criteria were applied a total of 322 patients were identified for the study cohort (Table 1). The population was 43.8% female and the average age was 66.5 years. Table 1 also contains baseline demographic parameters for the cohort with baseline pulse pressure (PP) ≥ and <70. Patients with a PP ≥ 70 were older than those with PP < 70 (73.7 vs. 62.8 years, p < 0.001). Patients with PP ≥ 70 were more likely to have a history of hypertension (83.5 vs. 68.1%, p = 0.003), and PAD (67% vs. 54.6%, p = 0.031). The difference in PP between the two groups was driven by SBP. The first recorded SBP was 175.5 in patients with PP ≥ 70 and 133.7 in PP < 70 (p < 0.001); there was no difference between groups in first recorded DBP. The first recorded PP (in mmHg) was 49.8 and 89.6 in patients with PP < 70 and ≥70, respectively (p < 0.001). Patients with PP ≥ 70 were more likely to be placed on an ACEI/ARB or BB as compared to those with PP < 70 (53.9 vs. 31.9%, p < 0.001). Patients with PP ≥ 70 were less likely to be on monotherapy with BB therapy or not treated with BB at all.

Regarding the choice of antihypertensive class—ACEI/ARB or BB—patients in either of these two classes were similar in baseline comorbidity profile except for having a history of coronary artery disease without prior revascularization, which was more common in BB group (Table 2).

Outcomes

Overall in-hospital mortality was 5.3%. The average length of follow-up data was 49.7 months. Mortality during follow up for the overall cohort was 28.2% (Table 1). There was no difference between PP groups for in-hospital mortality. Follow-up mortality was significantly higher among those with a baseline PP > 70 (37.4 vs. 23.2%, p = 0.009) (Table 1). On univariate analysis, older age, the

Table 1. Demographic data and clinical parameters.

Parameter	Any PP N = 322	PP < 70 mmHg N = 207	PP ≥ 70 mmHg N = 115	Between group p-value
Females: n (%)	141 (43.8)	88 (42.5)	53 (46.1)	0.536
Age, years: mean ± SD	66.5 ± 15.6	62.8 ± 15	73.7 ± 13.4	<0.001
Age < 50 years old: n (%)	42 (13)	37 (17.9)	5 (4.3)	
Age 50 - 69 years old: n (%)	134 (41.6)	97 (46.9)	37 (32.2)	<0.001
Age 70 years or older: n (%)	146 (45.3)	73 (35.3)	73 (63.5)	
History of CAD: n (%)	81 (25.2)	46 (22.2)	35 (30.4)	0.104
No CAD history	241 (74.8)	161 (77.8)	80 (69.6)	
CAD w/o revascularization	41 (12.7)	27 (13)	14 (12.2)	
CAD with CABG history	21 (6.5)	9 (4.3)	12 (10.4)	0.110
CAD with PCI history	19 (5.9)	10 (4.8)	9 (7.8)	
History of hypertension: n (%)	237 (73.6)	141 (68.1)	96 (83.5)	0.003
History of diabetes: n (%)	94 (29.2)	60 (29)	34 (29.6)	0.913
History of dyslipidemia: n (%)	183 (56.8)	113 (54.6)	70 (60.9)	0.276
History of peripheral vascular disease: n (%)	190 (59)	113 (54.6)	77 (67)	0.031
Creatinine > 2 mg/dL or HD: n (%)	15 (4.7)	8 (3.9)	7 (6.1)	0.365
First recorded SBP, mmHg: mean ± SD	148.6 ± 29.7	133.7 ± 20.6	175.5 ± 24	<0.001
First recorded DBP, mmHg: mean ± SD	84.6 ± 17.2	83.9 ± 16.2	85.9 ± 18.8	0.331
First recorded pulse pressure, mmHg: mean ± SD	64 ± 23	49.85 ± 12	89.65 ± 14	<0.001
Pulse pressure ≥ 70 mmHg: n (%)	115 (35.7)			
Type of stroke: n (%)				
Embolic	191 (59.3)	120 (58)	71 (61.7)	
Lacunar	39 (12.1)	20 (9.7)	19 (16.5)	0.051
Transient ischemic attack	92 (28.6)	67 (32.4)	25 (21.7)	
Admission Glasgow coma scale, units: mean ± SD	13.6 ± 1.9	13.7 ± 1.7	13.4 ± 2	0.173
Beta-Blockers: n (%)	174 (54)	100 (48.3)	74 (64.3)	0.005
ACEI or ARB: n (%)	206 (64)	116 (56)	90 (78.3)	<0.001
ACEI or ARB with beta-blocker	128 (39.8)	66 (31.9)	62 (53.9)	
Beta-blocker without ACEI or ARB	46 (14.3)	34 (16.4)	12 (10.4)	
ACEI or ARB without beta-blocker	78 (24.2)	50 (24.2)	28 (24.3)	<0.001
No ACEI or ARB, no beta-blocker	70 (21.7)	57 (27.5)	13 (11.3)	
Diuretics: n (%)	33 (10.2)	20 (9.7)	13 (11.3)	0.642
Other anti-HTN Rx: n (%)	9 (2.8)	3 (1.5)	6 (5.2)	0.145
Interval to target blood pressure, days: mean ± SD	5.5 ± 8.4	1.7 ± 1.2	7.8 ± 10.2	0.355
In-hospital mortality: n (%)	17/322 (5.3)	9 (4.3)	8 (7)	0.316
Follow-up length, months: mean ± SD	49.7 ± 22.4	51.4 ± 21.9	47 ± 22.7	0.092
Follow-up mortality: n (%)	86/305 (28.2)	46/198 (23.2)	40/107 (37.4)	0.009

Abbreviations: SD—standard deviation; SBP—systolic blood pressure; DBP—diastolic blood pressure; BB—beta-adrenergic blockers; ACEI—angiotensin converting enzyme inhibitors; ARB—angiotensin receptor blockers; IV—intravenous; HTN—hypertension; Rx—therapy.

Table 2. Demographic and clinical parameters associated with anti-hypertensive medication utilization.

Parameter	ACEI or ARB (N = 215)		Beta-Blocker (N = 80)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Male gender	1.416 (0.912 - 2.199)	0.122	1.413 (0.921 - 2.167)	0.113
Age, per 10 years	1.337 (1.155 - 1.548)	0.001	1.507 (1.294 - 1.755)	<0.001
CAD (any)	2.340 (1.388 - 4.092)	0.003	3.451 (2.003 - 5.945)	<0.001
CAD w/o revascularization	1.543 (0.781 - 3.048)	0.212	3.615 (1.751 - 7.466)	<0.001
CAD—CABG history	3.060 (1.001 - 9.351)	0.049	3.013 (1.133 - 8.012)	0.027
CAD—PCI history	6.480 (1.472 - 28.518)	0.013	3.615 (1.276 - 10.244)	0.016
Hypertension	11.080 (6.352 - 19.327)	<0.001	3.886 (2.335 - 6.467)	<0.001
Diabetes	2.901 (1.683 - 4.999)	<0.001	1.789 (1.109 - 2.887)	0.017
Dyslipidemia	3.301 (2.092 - 5.209)	<0.001	1.706 (1.108 - 2.627)	0.015
Peripheral vascular disease	2.580 (1.644 - 4.048)	<0.001	2.076 (1.341 - 3.215)	0.001
Creatinine > 2 mg/dL or HD	1.995 (0.636 - 6.256)	0.236	1.703 (0.615 - 4.715)	0.305
Pulse pressure ≥ 70 mmHg	2.824 (1.677 - 4.756)	<0.001	1.931 (1.208 - 3.087)	0.006
Lacunar vs. embolic stroke	1.325 (0.649 - 2.703)	0.439	0.871 (0.537 - 1.413)	0.575
TIA vs. embolic stroke	0.883 (0.538 - 1.449)	0.623	1.185 (0.606 - 2.317)	0.619
Glasgow coma scale	1.004 (0.894 - 1.128)	0.941	0.952 (0.850 - 1.067)	0.401

Abbreviations: OR—odds ratio; ACEI—angiotensin converting enzyme inhibitors; ARB—angiotensin receptor blockers; CAD—coronary artery disease; CABG—coronary artery bypass graft surgery; PCI—percutaneous coronary intervention; TIA—transient ischemia attack.

presence of CAD without prior revascularization, presence of PAD, having a creatinine > 2 mg/dl or being on hemodialysis, having a Glasgow Coma Scale score > 9, PP > 70, requiring intravenous anti-hypertensive therapy during the hospitalization, and being on a BB based anti-hypertensive regimen were all significantly associated with increased follow-up mortality. In-hospital mortality was non-significantly lower for patients treated with ACEI/ARB compared to those not treated with ACEI/ARB (3.7% vs. 8.6%); follow up mortality was similar between the anti-hypertensive therapy groups (27.4% vs. 24.2%, p = 0.150). Looking at various combinations of ACEI/ARB and BB based therapy, being on an ACEI/ARB based therapy without BB was associated with lowest in-hospital and follow up mortality (2.5% and 16%, respectively, p = 0.003) (Table 3).

After adjustment for covariates in multivariate analysis (Table 4), PP > 70 was not independently associated with an elevated odds ratio (OR) of in-hospital or follow-up mortality. However, choice of antihypertensive therapy remained important in determining outcomes; there were also some subtle differences in the effects of antihypertensive therapy choice based on baseline PP. Being on an ACEI or ARB based antihypertensive regimen was associated with a lower probability of in-hospital mortality in both PP groups. When BB therapy was included in antihypertensive therapy with ACEI/ARB, the lowering of in-hospital mortality was attenuated in the PP > 70 group, but not in the PP < 70 group. Follow-up

Table 3. Effects of clinical parameters, pulse pressure, and anti-hypertensive medications on mortality.

Parameter	Category	N	Mortality: n (%)		p-value
			In-Hospital N = 19	Follow-Up N = 90	
Gender	Females	153	6 (3.9)	38 (24.8)	0.390
	Males	190	13 (6.8)	52 (27.4)	
Age group, years	<50	47	0 (0)	1 (2.1)	<0.001
	50 - 69	141	7 (5)	22 (15.6)	
	>70	155	12 (7.7)	67 (43.2)	
CAD	Yes	85	8 (9.4)	27 (31.8)	0.054
	No	258	11 (4.3)	63 (24.4)	
CAD with revascularization history	CAD-no CABG-PCI	44	5 (11.4)	22 (50)	<0.001
	CAD-CABG	21	2 (9.5)	3 (14.3)	
	CAD-PCI	20	1 (5)	2 (10)	
	No CAD	258	11 (4.3)	63 (24.4)	
Hypertension	Yes	247	16 (6.5)	68 (27.5)	0.272
	No	96	3 (3.1)	22 (22.9)	
Diabetes	Yes	99	3 (3)	30 (30.3)	0.286
	No	244	16 (6.6)	60 (24.6)	
Dyslipidemia	Yes	196	10 (5.1)	56 (28.6)	0.510
	No	147	9 (6.1)	34 (23.1)	
Peripheral vascular disease	Yes	202	17 (8.4)	64 (31.7)	<0.001
	No	141	2 (1.4)	26 (18.4)	
Cr > 2.0 mg/dL or HD	Yes	17	0 (0)	12 (70.6)	<0.001
	No	326	19 (5.8)	78 (23.9)	
Glasgow coma scale	<9	301	2 (0.7)	77 (25.6)	<0.001
	9-12	30	6 (20)	12 (40)	
	>12	12	11 (91.7)	1 (8.3)	
Pulse pressure group (mmHg)	≥70	115	8 (7)	40 (34.8)	0.020
	<70	207	9 (4.3)	46 (22.2)	
IV anti-HTN Rx	Yes	49	3 (6.1)	20 (40.8)	0.037
	No	294	16 (5.4)	70 (23.8)	
ACEI or ARBs	Yes	215	8 (3.7)	59 (27.4)	0.150
	No	128	11 (8.6)	31 (24.2)	
Beta-blockers	Yes	180	9 (5)	61 (33.9)	0.003
	No	163	10 (6.1)	29 (17.8)	
ACEI or ARB and beta-blocker group					
ACEI or ARB and beta-blocker		134	6 (4.5)	46 (34.3)	0.011
ACEI or ARB without beta-blocker		81	2 (2.5)	13 (16)	
Beta-blocker without ACEI or ARB		46	3 (6.5)	15 (32.6)	
No ACEI or ARB or beta-blocker		82	8 (9.8)	16 (19.5)	
Diuretics	Yes	36	2 (10.5)	7 (19.4)	0.613
	No	307	17 (5.5)	83 (27)	
Other anti-HTN Rx	Yes	10	0 (0)	3 (30)	0.957
	No	333	19 (6.5)	87 (26.1)	

Abbreviations: CAD—coronary artery disease; HTN—hypertension; Rx - therapy; IV—intravenous; ACEI—angiotensin converting enzyme inhibitor; ARB—angiotensin receptor blockers.

Table 4. Multivariate predictors of hospital and follow-up mortality.

Parameter	Hospital mortality		Follow-up mortality	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, per 10 years	1.140 (0.536 - 2.427)	0.734	2.244 (1.713 - 2.939)	<0.001
CAD-no revascularization*	1.157 (0.114 - 11.732)	0.902	2.81 (1.179 - 6.699)	0.019
CAD-CABG*	2.570 (0.067 - 99.294)	0.613	0.328 (0.081 - 1.333)	1.119
CAD-PCI*	1.028 (0.005 - 212.635)	0.992	0.207 (0.039 - 1.115)	0.067
Peripheral vascular disease	7.217 (0.816 - 63.849)	0.0756	1.584 (0.801 - 3.131)	0.186
Cr >2 mg/dL or HD	Insufficient cases		7.34 (1.885 - 28.573)	0.004
Glasgow coma scale 9 - 12†	33.809 (4.973 - 229.843)	<0.001	2.748 (0.948 - 7.967)	0.063
Glasgow coma scale >12†	3544.895 (150.124 - 83705.887)	<0.001	Insufficient cases	
Pulse pressure ≥ 70 mmHg	1.829 (0.239 - 13.985)	0.561	1.07 (0.533 - 2.149)	0.849
IV anti-HTN Rx	0.325 (0.008 - 13)	0.325	1.685 (0.693 - 4.095)	0.249
ACEI or ARB with BB††	0.078 (0.006 - 0.972)	0.078	0.652 (0.253 - 1.679)	0.375
ACEI or ARB w/o BB††	0.024 (0.001 - 0.763)	0.035	0.363 (0.129 - 1.019)	0.054
BB w/o ACEI or ARB††	0.105 (0.006 - 1.95)	0.130	0.983 (0.343 - 2.817)	0.974
Among those with PP < 70				
ACEI-ARB + BB	0.046 (0.006 - 0.335)	0.0023	0.74 (0.178 - 3.085)	0.6794
ACEI-ARB + No BB	0.083 (0.009 - 0.782)	0.0296	0.07 (0.01 - 0.477)	0.0066
No ACEI-ARB + BB	0.126 (0.009 - 1.813)	0.1280	0.867 (0.152 - 4.954)	0.8725

*) compared to outcomes in patients without CAD; †) compared to outcomes in patients with Glasgow Coma Scale <9; ††) compared to outcomes in patients not on ACEI or ARB or BB; **Abbreviations:** OR—odds ratio; IV—intravenous; HTN—hypertension; Rx—therapy; ACEI—angiotensin converting enzyme inhibitors; ARB—angiotensin receptor blockers; BB—beta blockers.

mortality was not influenced by choice of antihypertensive therapy (ACEI/ARB, BB, both ACEI/ARB and BB, or neither ACEI/ARB or BB) in the PP > 70 group (Table 4). Among patients with PP < 70, being on an ACEI/ARB based therapy without a BB was associated with a significantly lower follow-up mortality (OR 0.07, 95% confidence interval 0.01 - 0.477, p = 0.0066).

4. Discussion

In this retrospective cohort of patients admitted with a diagnosis of AIS, PP was not independently associated with short or long term mortality, but the use of an ACEI or ARB based antihypertensive regimen was associated with lower in-hospital among patients with PP <70 or ≥70. ACEI/ARB without BB was associated with lower follow-up mortality only those patients with baseline PP < 70.

A widened PP has been demonstrated in multiple analyses to be associated with a higher cardiovascular burden. Widened PP has been shown to correlate and associate with worse CV outcomes [31] [32]. The current analysis confirms that a widened PP is associated with increased mortality (p = 0.020), however this did not persist when adjusted for multiple comorbidities. The only other analy-

sis of PP on AIS outcomes demonstrated a significant association with weighted average PP (over 60 hours) on 3 month outcomes in the Glycine Antagonist in Neuroprotection International Trial; however, as with the current analysis, the baseline PP was not associated with follow-up outcomes after adjusting for comorbidities [7]. The association of average PP over the course of hospitalization with outcomes deserves further evaluation.

In contrast, choice of antihypertensive therapy remained significantly associated with outcomes with some notable differences based on baseline PP categorization. Regardless of baseline PP, being on an ACEI/ARB based antihypertensive therapy is associated with favorable in-hospital outcomes during AIS and including BB into the regimen attenuates the benefit. For long term mortality outcomes, ACEI/ARB based therapy was found to be beneficial in patients with PP < 70, with attenuation, again, from addition of BB. There was a reduction in mortality with ACEI/ARB based therapy, without BB, among patients with PP ≥ 70 however it did not meet statistical significance (OR 0.363, p = 0.054).

The Scandinavian Candesartan Acute Stroke Trial (SCAST) randomized patients with acute stroke (the majority of whom, ~85%, had AIS) to initial treatment with Candesartan or placebo for hypertension management. This was not a BP target study and no data on PP was provided. The investigators found no significant difference in the primary outcome at 6 months or 3 years [33]. A direct comparison between a randomized study and a retrospective study is not possible however the current analysis may suggest that PP may be an important consideration when analyzing the effect of antihypertensive therapy on AIS outcomes.

BB, on the other hand, were not associated with improved short and long term outcomes and attenuated some of the benefit seen with ACEI/ARB therapy. BB has been relegated to second line therapy in hypertension in general [27]. In regards to AIS, most of the data on BB therapy has been derived from retrospective studies. A recent analysis by Koton and colleagues looked at pre-stroke use of BB for hypertension management and post stroke outcomes [34]. These investigators found no effect on outcomes (stroke severity, recurrent stroke, or mortality) with the use of BB for pre-stroke hypertension therapy. Phelan and colleagues found a decrease in the in-hospital mortality in patients with AIS who had their home BB therapy continued during the first 3 days of AIS versus patients in whom BB therapy was discontinued [35]. This was despite a higher comorbid profile among patients on BB therapy [35]. Similarly, Tziomalos found worse in-hospital outcomes in patients treated with BB prior to AIS, than in those not treated with BB [36]. In contrast to our findings, Tziomalos and colleagues did not find a beneficial effect of ACEI or ARB therapy [36]. Similarly, Sykora and colleagues found improved in-hospital and 3-month AIS outcomes with the use of BB pre-stroke [37]. One important distinction from the current analysis is the duration of follow up; in our study, the duration of follow-up was significantly longer. In addition, distinctions in patient populations by PP have

not been previously reported. Given the disparate findings among data sets, a well-designed randomized controlled trial examining the role of BB therapy in improving post stroke outcomes may be warranted.

Several important limitations of the current analysis need to be acknowledged. The choice of antihypertensive therapy was left to the discretion of the provider and thus introduces indication bias that cannot be adequately addressed in the current format. In addition, there is no means to know how patients were treated after the point of discharge. Addition or subtraction of hypertensive medications may have led to muted effects seen in the various subgroup analyses. Finally, our study contained modest sample size and follow up period as a larger sample size with longer follow up would be beneficial in studying this matter.

5. Conclusion

Despite these limitations, the current analysis revealed important distinctions within patients who have suffered AIS. ACEI/ARB based antihypertensive management appears to provide the most favorable short and long term outcomes in patients with AIS. This seems to be most prominent among patients with AIS and PP < 70 at presentation. Future randomized controlled trials of patients with AIS should look at antihypertensive classes and PP interactions.

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