Hypertension associated with functional status early after hospitalization for ischemic stroke: A cohort study

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Abstract

Background

Permissive hypertension in the hyperacute phase of acute ischemic stroke (AIS) is an accepted standard of care; optimal strategies for hypertension management among patients in the post-acute care phase are unknown. This study aimed to identify the association of hypertension management on functional outcomes during the post-acute care phase.

Methods

This retrospective cohort study at a comprehensive stroke center included adults age ≥ 18 with a primary diagnosis of AIS who were discharged to home or an inpatient rehabilitation facility (IRF). The primary outcome was functional improvement defined as an increase of modified Rankin Scale (mRS) by 1 or more point between discharge and follow-up. Univariate analyses with the Chi-square test and t-test assessed differences between baseline characteristics between the home and IRF groups. Covariates and functional improvement associations were assessed with multivariable logistic regression.

Results

Patients with hypertension discharged to IRF had a higher odds of no functional improvement between hospital discharge and clinic follow-up (OR 2.53, 95% CI: 1.02-6.59) compared to those without hypertension. Patients discharged to IRF prescribed any antihypertensives had a higher odds of no functional improvement (OR 2.36, 95% CI 1.08-5.34) compared to those not prescribed antihypertensives.

Conclusions

Patients with a hypertension diagnosis discharged to IRF after AIS are less likely to have functional improvement compared to patients discharged home which may be associated with the prescription of antihypertensive medications.

Introduction

Hypertension often requires active medical management during acute care hospitalizations for acute ischemic stroke (AIS), but optimal strategies for management in the early post-acute care phase after hospital discharge are uncertain. For example, permissive hypertension in the hyperacute phase of AIS is a widely accepted standard of care, with long-term systolic blood pressure (SBP) targets clearly delineated in national clinical practice guidelines (1, 2). Early aggressive treatment with antihypertensives to low SBP targets may impair collateral circulation supporting penumbral tissue, leading to expansion of cerebral infarcts (3–6). Prior studies suggest that patients with prior hypertension and stroke may have altered autoregulatory curves; thus, these patients may be more susceptible to worsening or growing infarct if high SBPs are treated excessively (7). This uncertainty may result in harm in transitions of care from the acute hospitalization to home environments and inpatient rehabilitation facilities (IRF) if

medication plans are not clearly delineated or if targets are not established, potentially leading to overtreatment. Overzealous blood pressure management could precipitate a drop in SBP that ultimately under perfuses recovering tissue, and either delays or halts a patient's functional recovery.

Patients with AIS in closely supervised post-acute care settings such as IRFs may be more likely to undergo assertive changes in their risk factor management medications (e.g. up titration of antihypertensive dosage or frequency) than patients discharged home due to more frequent blood pressure measurement and interactions with medical professionals. To better understand the potential impact of hypertension and its management during the post-acute care phase after AIS on recovery outcomes, we assessed their associations with changes in the modified Rankin Scale (mRS) between hospital discharge and first outpatient Stroke Clinic evaluations in patients discharged home versus those discharged to IRFs.

Methods

Study Population

This was a retrospective cohort study including patients age ≥ 18 hospitalized at a comprehensive stroke center (Tufts Medical Center) with a primary diagnosis of AIS between 1/1/2018–12/31/2019 and who followed up in the outpatient neurology or neurosurgery clinic. Patients discharged with a provisional diagnosis (e.g. "possible AIS") or AIS as part of differential were excluded. Only patients discharged home (e.g. "home" or "home with services") or to an inpatient rehabilitation facility (IRF) who returned for a follow-up appointment were included in the analysis. This study was approved by the IRB of Tufts Medical Center.

Covariates

Data obtained from the electronic health record included basic demographics (age, sex, race, ethnicity), past medical history, substance use, first documented systolic blood pressure (SBP), fingerstick blood glucose, stroke admission severity (admission NIHSS), acute revascularization treatment (IV thrombolysis, IVT; endovascular therapy, EVT), hemoglobin A1c (HbA1c), and discharge destination. The patient's antihypertensives prescribed at hospital discharge was also recorded ("no antihypertensives prescribed at discharge", "antihypertensives restarted but not completely at discharge", or antihypertensives prescribed or restarted at goal dose"). This data was collected to identify variability in antihypertensive management following hospital discharge.

Outcomes

The primary outcome was the magnitude of change of the mRS between hospital discharge and first clinic follow-up. Each mRS was retrospectively estimated by two members of the research team (MEP, KEC, EJP, YA) trained in the mRS assessment using information from discharge summaries, physical therapy and occupational therapy notes, and outpatient neurology/neurosurgery notes. Discrepancies in the estimated mRS were resolved by a third team member (LYL).

Statistical Analysis

Chi-square and t-test were used for univariate analyses according to the structure of the data. To assess the differences in recovery trajectories based on the magnitude of change in mRS, multivariate logistic regression was applied to two samples of patients stratified by their discharge destination (home versus IRF). The outcome was dichotomized as change in mRS ≥ 1 or no change in mRS. Two models were used: Model 1 included only variables selected based on clinical expertise that were considered major determinants of stroke recovery outcomes (demographics, acute revascularization treatment, NIHSS) and hypertension. Model 2 included additional clinical measurements and stroke risk factors (admission BP, fingerstick glucose, diabetes, atrial fibrillation) that might affect post-hospitalization medication management and thus alter recovery trajectories. Chi-square test was also performed on antihypertensive resumption plans for patients with hypertension in each discharge group. A secondary analysis was performed to assess the effect of antihypertensive medication prescription on mRS change. Statistical significance was defined as $p < 0.05$. All analyses were conducted in R (version 1.4.1106, Vienna, Austria) as complete case analyses, provided that the extent of missingness for included variables was less than 5%.

Results

Two hundred and twenty-three patients with AIS that returned for outpatient follow-up were included with 130 discharged home and 93 discharged to an IRF (Supplemental Appendix Fig. A.1). The average time from discharge to outpatient follow-up was 43.5± 29.0 days. With regards to baseline characteristics and treatment, white race, atrial fibrillation, EVT, and NIHSS were all lower among patients discharged home (Table 1). There were no differences in diagnosis of hypertension or diabetes, SBP, or admission glucose; none of these were associated with the mRS at discharge (not shown). Discharge mRS and first clinic follow-up mRS were lower among patients discharged home, but the magnitude of change in mRS was higher among patients discharged home.

Table 1
Baseline characteristics.

	Home (N = 130)	Rehab (N = 93)	p-value	Overall (N = 223)
Sex				
Female	51 (39.2%)	44 (47.3%)	0.256	95 (42.6%)
Male	79 (60.8%)	49(52.7%)		128 (57.4%)
Age (years)				
Mean (SD)	64.45 (14.75)	66.62 (15.89)	0.294	65.35 (15.24)
Median [IQR]	65.0 [55.3, 74.0]	69.0 [58.0, 78.0]		67.0 [56.50, 75.0]
Race				
White	68 (52.3)	67 (72.0)	0.001	135 (60.5)
Black/African American	11 (8.5)	12 (12.9)		23 (10.3)
Asian	43 (33.1)	8 (8.6)		51 (22.9)
Other	4 (3.1)	2 (2.2)		6 (2.7)
Not Specified	4 (3.1)	4 (4.3)		8 (25.6)
Diabetes	33 (25.4%)	24 (25.8%)	1.00	57 (25.6%)
Hypertension	85 (65.4%)	63 (67.7%)	0.823	148 (66.4%)
Hyperlipidemia	62 (47.7%)	35 (37.6%)	0.175	97 (43.5%)
Atrial Fibrillation	17 (13.1%)	26 (28.0%)	0.009	43 (19.3%)
Coronary Artery Disease or MI				
Coronary Artery Disease or MI	13 (10.0%)	8 (8.6%)	0.905	21 (9.4%)
Congestive Heart Failure				
Congestive Heart Failure	5 (3.8%)	8 (8.6%)	0.228	13 (5.8%)
Former Tobacco Smoker				
Former Tobacco Smoker	37 (28.5%)	16 (17.2%)	0.074	53 (23.8%)
Current Tobacco Smoker				
Current Tobacco Smoker	32 (24.6%)	26 (28.0%)	0.685	58 (26.0%)
HbA1c on Admission (%)				

	Home (N = 130)	Rehab (N = 93)	p-value	Overall (N = 223)
Sex				
Mean (SD)	6.05 (1.06)	6.09 (1.29)	0.816	6.07(1.16)
Median [IQR]	5.80 [5.50, 6.30]	5.70 [5.30, 6.32]		5.80 [5.40, 6.30]
Systolic BP on admission (mmHg)				
Mean (SD)	147.53 (24.42)	147.63 (27.67)	0.977	147.57 (25.75)
Median [IQR]	150 [130.25,162.0]	148.0 [129.0, 163.3]		149.0 [129.3, 163.0]
Fingerstick Glucose on Admission (mg/dL)				
Mean (SD)	123.08 (42.13)	135.25 (69.37)	0.108	128.22 (55.49)
Median [IQR]	108 [98.5,134.0]	115 [99.00, 149.00]		111.0 [99.0, 138.5]
IVT	28 (21.5)	23 (24.7)	0.691	51 (22.9%)
EVT	11 (8.5)	24 (25.8)	0.001	35 (15.7%)
NIHSS				
Mean (SD)	3.77 (5.14)	10.79 (7.47)	< 0.001	6.74 (7.13)
Median [IQR]	2.00 [1.0, 4.0]	10.0 [4.0, 17.5]		4.00 [1.0, 11.0]
Discharge mRS				
Mean (SD)	1.78 (1.25)	4.13 (0.92)	< 0.001	2.76 (1.61)
Median [IQR]	1.00 [1.00, 3.00]	4.00 [4.00, 5.00]		3.00 [1.0, 4.0]
First Clinic Follow-up mRS				
Mean (SD)	1.28 (1.07)	2.82 (1.19)	< 0.001	1.92 (1.35)
Median [IQR]	1.00 [1.00, 2.00]	3.00 [2.00, 4.00]		2.00 [1.0, 3.0]
Difference in mRS from Discharge to Follow-up				
Mean (SD)	0.51 (0.50)	0.27 (0.45)	< 0.001	0.41 (0.49)

	Home (N = 130)	Rehab (N = 93)	p-value	Overall (N = 223)
Sex				
Median [IQR]	1.00 [0, 1.00]	0 [0, 1.00]		0 [0, 1.00]
Days to Follow-up				
Mean (SD)	40.01 (23.24)	49.20 (35.67)	0.020	43.67 (29.10)
Median [IQR]	34.00 [28.00, 48.50]	35.00 [27.00, 57.00]		34 [28,50.25]
Hemoglobin A1c (HbA1c), NIH Stroke Scale (NIHSS), Modified Rankin Scale (mRS), Intravenous Thrombolytic (IVT), Endovascular Therapy (EVT)				

In the regression analysis (Model 1) assessing the effect of hypertension on recovery trajectories among patients discharged home, a diagnosis of hypertension was not associated with fixed mRS (Table 2). However, among patients discharged to IRFs, a diagnosis of hypertension was associated with no change in mRS between hospital discharge and outpatient follow-up (OR 2.53, 95% CI: 1.02–6.59). The second model demonstrated a similar association between hypertension and no change in mRS (OR 3.83, 95% CI 1.40–11.6) among patients discharged to IRFs (not shown). The distribution of mRS among patients in each group are shown in Supplemental Appendix Fig. A.2.

Table 2. Association between hypertension and no change in mRS between hospital discharge and outpatient follow-up.

A. Discharge to home.

	OR	2.50%	97.50%
Hypertension	0.853	0.320	2.233
NIHSS	0.418	0.104	1.528
Sex (male)	0.825	0.350	1.916
Age	0.996	0.966	1.026
Race	1.049	0.806	1.393
EVT	3.685	0.654	25.075
IVT	1.076	0.379	3.167

B. Discharge to IRF.

	OR	2.50%	97.50%
Hypertension	2.526	1.022	6.591
NIHSS	1.681	0.744	3.874
Sex (male)	1.070	0.502	2.301
Age	1.002	0.975	1.030
Race	0.952	0.722	1.251
EVT	1.044	0.423	2.577
IVT	1.196	0.476	3.020

Inpatient Rehabilitation Facility (IRF), NIH Stroke Scale (NIHSS), Modified Rankin Scale (mRS), Intravenous Thrombolytic (IVT), Endovascular Therapy (EVT)

The distribution of strategies for antihypertensive medication prescription upon discharge differed between the two groups (p = 0.02). Compared to patients discharged home, patients discharged to IRFs had a larger proportion with prior prescribed antihypertensives partly restarted (25.00% IRF vs 7.04% home, p = 0.005) and fewer with no antihypertensive medication started (14.29% IRF vs 22.54% home, p = 0.24). Most patients in both groups had prior prescribed antihypertensives completely restarted at the time of discharge (60.71% IRF vs 70.04% home, p = 0.25).

A secondary analysis was performed to assess the effect of antihypertensive prescription practices on the recovery outcomes of patients with hypertension discharged home and to IRFs. There was no association of antihypertensive resumption and no change in mRS among patients with hypertension discharged home (Supplemental Appendix Table A.1). Patients with hypertension discharged to IRFs with antihypertensives, either completely restarted or restarted at a lower dose, had greater odds of no change in mRS (OR 2.36, 95% CI: 1.08–5.34) compared to those discharged without antihypertensives.

Discussion

To our knowledge, this is the first study assessing the relationship between stroke risk factors modifiable in the early post-acute care phase and their effects on anticipated stroke recovery trajectories. We found that both hypertension and the prescription of antihypertensive medications were associated with a blunted recovery trajectory (no change in mRS between discharge and follow-up) among patients discharged to IRFs. Importantly, hypertension was not associated with mRS at discharge, suggesting that the divergence of outcomes occurred after the acute care hospitalization. Prior natural history studies have demonstrated parallel curves in recovery from AIS across stroke severity, so differences in stroke severity between patients discharged home versus IRF are unlikely to explain this lack of clinical improvement among patients discharged to IRFs (6). This could be due to overtreatment in settings with more frequent blood pressure monitoring and opportunities compared to home. Two-thirds of patients

with AIS in our study had hypertension, highlighting the need to refine management in the early post-acute care phase.

Our study adds to the current literature arguing against early initiation of antihypertensive medications in the post-acute care phase of AIS. While ample evidence suggests that antihypertensive medications reduce the risk of long-term stroke recurrence, there is limited evidence examining antihypertensive treatment in the early post-acute care phase and its association with stroke recovery. Several of these studies do not support early initiation of antihypertensive medications. IMWEST concluded that at day 21, diastolic blood pressure lowering 20% increased the risk of death or dependency(8). PRoFESS reported that treatment with telmisartan had no difference in mortality or clinical dependency by day 15 post-treatment initiation compared to placebo (9). CATIS found patients whose antihypertensives were discontinued during hospitalization did not have a significant difference in mRS at 3-month follow-up compared to groups whose hypertension was actively managed during hospitalization (10). Finally, VENTURE suggested that patients with valsartan initiation within 48 hours of stroke onset had no significant difference in death or dependency in comparison to patients with no antihypertensive treatment (11). Altogether, these studies and our findings may suggest that a longer delay in antihypertensive resumption is reasonable for the sake of preserving early stroke recovery potential. Current guidelines set by the American Heart Association-American Stroke Association (AHA/ASA) suggest that it is reasonable to resume antihypertensive medications when blood pressure is above 140/90, but no specific medication, dose, or timing is recommended for most patients(12). There remains a knowledge gap regarding how and when to resume antihypertensive medications in the post-acute care phase with our findings highlighting that there may be risk of harm.

This study has several strengths and limitations. First, the population was relatively diverse with a broad range of age, race, and stroke severity, and a high proportion of patients with HTN and treatment with IVT or EVT. This Comprehensive Stroke Center has a broad catchment area drawing from socioeconomically and demographically diverse neighborhoods and regions in Eastern Massachusetts and New England. Second, most patients with ischemic stroke (78%) returned for outpatient follow-up, which is relatively high for real-world clinical practice. This allowed for mRS assessment in the post-acute care phase. Third, the proportion of patients discharged home versus IRF were well balanced. With regards to limitations, the standard outpatient follow-up time at our center is 4-6 weeks post-discharge, an assessment time that differs from many stroke outcomes studies (e.g. 90 days). Nonetheless, this earlier outcome assessment time point should be able to assess patients with stroke during the steepest part of their anticipated recovery trajectories. It was outside the scope of this study to perform a direct neuroimaging review or volumetric analysis of infarcts or white matter hyperintensities, so this study cannot account for imaging markers of vascular brain injury that may be due to pre-existing hypertension and may affect stroke recovery. Also, the study did not control for stroke etiology across discharge destinations which could account for differences in the impact of antihypertensive medications. While mRS is commonly used to assess clinical improvement in AIS patients, it cannot comprehensibly account for the many social factors that can impact an ability's patient to functionally recover. Our study controls for a variety of demographic risk factors standard for use of mRS as an outcome variable. Additionally, the 64 patients

lost to follow-up across both discharge destinations could have been lost to reasons that would have impacted their antihypertensive management and outcomes of this study. Finally, we did not have the ability to assess the magnitude or timing of blood pressure measures, specific modifications to antihypertensive medications, or medication adherence during the period between hospital discharge and outpatient follow-up. Future studies with prospective assessment of these measures will be needed to confirm these associations of hypertension and early post-acute care antihypertensive treatment with blunted stroke recovery.

Discharge to IRFs and the prescription of antihypertensive medications at IRFs are associated with blunted recovery. As this may suggest that hypertension is being overtreated in IRFs, further studies will be needed to clarify the effect of specific SBP goals and antihypertensive medication classes during this phase of recovery.

Declarations

Data Availability

The data that supports the findings of this study are openly available in Harvard Dataverse at https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/HTNOXC.

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Author Contributions

Study design, analysis, and interpretation of results, manuscript draft preparation and editing were performed by Pudlo and Leung. Data collection was performed by Coté, Jost-Price, and Pudlo. Leung contributed to study conception. All authors have reviewed and approve of the final manuscript.

Ethical Approval

This study was approved by the Tufts Medical Center IRB. This manuscript follows STROBE guidelines for observational cohort studies.

Competing Interests

The authors have no conflicts of interest.

References

1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for

the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344-e418.

2. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2021;52(7):e364-e467.
3. Jeong HG, Kim BJ, Kim H, Jung C, Han MK, Liebeskind DS, et al. Blood Pressure Drop and Penumbral Tissue Loss in Nonrecanalized Emergent Large Vessel Occlusion. Stroke. 2019;50(10):2677–84.
4. Ko SB, Yoon BW. Blood Pressure Management for Acute Ischemic and Hemorrhagic Stroke: The Evidence. Semin Respir Crit Care Med. 2017;38(6):718–25.
5. Rusanen H, Saarinen JT, Sillanpää N. The association of blood pressure and collateral circulation in hyperacute ischemic stroke patients treated with intravenous thrombolysis. Cerebrovasc Dis. 2015;39(2):130–7.
6. Douiri A, Grace J, Sarker SJ, Tilling K, McKevitt C, Wolfe CD, et al. Patient-specific prediction of functional recovery after stroke. Int J Stroke. 2017;12(5):539–48.
7. Maïer B, Gory B, Lapergue B, Sibon I, Richard S, Kyheng M, et al. Effect of Baseline Antihypertensive Treatments on Stroke Severity and Outcomes in the BP TARGET Trial. Stroke. 2022:STROKEAHA121037548.
8. Ahmed N, Näsman P, Wahlgren NG. Effect of intravenous nimodipine on blood pressure and outcome after acute stroke. Stroke. 2000;31(6):1250–5.
9. Bath PM, Martin RH, Palesch Y, Cotton D, Yusuf S, Sacco R, et al. Effect of telmisartan on functional outcome, recurrence, and blood pressure in patients with acute mild ischemic stroke: a PRoFESS subgroup analysis. Stroke. 2009;40(11):3541–6.
10. He J, Zhang Y, Xu T, Zhao Q, Wang D, Chen CS, et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. JAMA. 2014;311(5):479–89.
11. Oh MS, Yu KH, Hong KS, Kang DW, Park JM, Bae HJ, et al. Modest blood pressure reduction with valsartan in acute ischemic stroke: a prospective, randomized, open-label, blinded-end-point trial. Int J Stroke. 2015;10(5):745–51.
12. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2018;49(3):e46-e110.

Supplementary Files

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- SupplementalAppendixAFigureA.1.docx
- SupplementalAppendixFigureA.2.docx
- SupplementalAppendixTableA.1.docx