Blood pressure changes in acute ischemic stroke and outcome with respect to stroke etiology

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ABSTRACT

Objective: Previous research suggested that proper blood pressure (BP) management in acute stroke may need to take into account the underlying etiology.

Methods: All patients with acute ischemic stroke registered in the ASTRAL registry between 2003 and 2009 were analyzed. Unfavorable outcome was defined as modified Rankin Scale score >2. A local polynomial surface algorithm was used to assess the effect of baseline and 24- to 48-hour systolic BP (SBP) and mean arterial pressure (MAP) on outcome in patients with lacunar, atherosclerotic, and cardioembolic stroke.

Results: A total of 791 patients were included in the analysis. For lacunar and atherosclerotic strokes, there was no difference in the predicted probability of unfavorable outcome between patients with an admission BP of <140 mm Hg, 140–160 mm Hg, or >160 mm Hg (15.3% vs 12.1% vs 20.8%, respectively, for lacunar, $p = 015$; 41.0% vs 41.5% vs 45.5%, respectively, for atherosclerotic, $p = 075$), or between patients with BP increase vs decrease at 24–48 hours (18.7% vs 18.0%, respectively, for lacunar, $p = 0.84$; 43.4% vs 43.6%, respectively, for atherosclerotic, $p = 0.88$). For cardioembolic strokes, increase of BP at 24–48 hours was associated with higher probability of unfavorable outcome compared to BP reduction (53.4% vs 42.2%, respectively, $p = 0.037$). Also, the predicted probability of unfavorable outcome was significantly different between patients with an admission BP of <140 mm Hg, 140–160 mm Hg, and >160 mm Hg (34.8% vs 42.3% vs 52.4%, respectively, $p < 0.01$).

Conclusions: This study provides evidence to support that BP management in acute stroke may have to be tailored with respect to the underlying etiopathogenetic mechanism. ***Neurology*® 2012; 79:1440–1448**

GLOSSARY

ASTRAL = Acute STroke Registry and Analysis of Lausanne; **BP** = blood pressure; **CHUV** = Central University Hospital of Vaud; **CI** = confidence interval; **DBP** = diastolic blood pressure; **MAP** = mean arterial pressure; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **SBP** = systolic blood pressure.

After many years of debate[1,2] and numerous small studies,[3] the management of blood pressure (BP) in the acute phase of stroke remains an issue of controversy. Several studies revealed the presence of a U-shaped curve describing the association between BP in acute stroke and outcome[4–6]; recently, results from the GIFA study showed that admission systolic BP between 120 and 180 mm Hg is associated with lower in-hospital mortality and better cognitive and functional performance at discharge.[7] Still, many studies failed to confirm the importance of baseline BP on prognosis.[3] Moreover, studies yielded inconsistent results about the prognostic significance of spontaneous or therapeutic BP change during the acute phase of stroke.[8]

A plausible explanation for these inconsistent results is that stroke is caused by heterogeneous mechanisms and affects patients with different cardio-cerebrovascular comorbidities. These diversities probably influence the tolerability of the ischemic penumbra to BP dynamics during the acute phase. For example, the typical patient with lacunar stroke usually has chronic

Supplemental data at www.neurology.org

Supplemental Data

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hypertension with subsequent arterial stiffness[9] and shift of the cerebral autoregulatory curve to the right[10]; these structural and pathophysiologic changes may help tolerate elevated BP in acute stroke more efficiently with only minimal risk of hemorrhagic transformation due to the small size of infarct.[11] A patient with atherosclerotic stroke may have extended atherosclerotic occlusions throughout the vascular tree which compromise the patency of collateral circulation; therefore, such a patient may need significantly elevated BP to maintain the perfusion of penumbra from the collaterals, which however may induce cerebral edema and increase the risk of hemorrhagic transformation and stroke recurrence.[5] Conversely, a patient with cardioembolic stroke may only have atrial fibrillation without arterial hypertension or significant atherosclerotic disease; such a patient may have patent collateral circulation and therefore may need only moderately elevated BP to promote perfusion of penumbra via collaterals. These examples emphasize the notion that BP management in the acute phase of stroke may need to take into consideration not only baseline BP values[12] but also other parameters like the underlying etiopathogenetic mechanism and arterial pathology. This was already suggested by the finding that spontaneous BP variation in the acute stroke varies between different stroke types.[13]

We designed this study to investigate the interaction of baseline BP with subsequent BP change in the acute phase of stroke to predict outcome with respect to the underlying etiology.

METHODS The dataset comprised all patients who were registered in the Acute STroke Registry and Analysis of Lausanne (ASTRAL) between January 1, 2003, and December 31, 2009. ASTRAL is the prospective registry of all consecutive patients admitted to the stroke unit or intensive care unit of the Central University Hospital of Vaud (CHUV) with acute ischemic stroke within 24 hours after last proof of well-being.[14] The methods applied to collect and register patient data, and the definitions used in ASTRAL, were previously described.[14]

Prestroke modified Rankin Scale score (mRS) and NIH Stroke Scale score (NIHSS) were evaluated at admission by mRS certified medical personnel. Stroke pathophysiology was classified according to the TOAST classification.[15] Hematologic parameters and vital signs were recorded at admission usually in the emergency room (termed as "acute" values), and at 24–48 hours after stroke onset (termed as "subacute" values), usually in the intermediate care stroke unit. BP measurements were performed with fully automatic arm blood pressure monitors with the patient lying supine. In case of serial subacute BP measurements available, the first recording was taken into account for the analysis. Mean arterial pressure (MAP) was calculated from systolic (SBP) and diastolic (DBP) values according to the following formula: MAP = DBP + (SBP − DBP)/3. The endpoint was unfavorable outcome defined as mRS >2 at 3 months and assessed by mRS-certified medical personnel in the outpatient clinic or during a structured telephone interview.

All patients were treated according to the current European Stroke Organization guidelines.[16] Blood pressure was moderately reduced with IV labetalol or diltiazem or nitroglycerin when >220/120 mm Hg, or >185/110 if patient was eligible for thrombolysis. Low blood pressures were not therapeutically elevated. Prestroke antihypertensive treatment was discontinued at admission except for β-blockers or if patient had history of cardiac failure.

Statistical analysis. Continuous variables are summarized by median and interquartile range. Prespecified thresholds were defined in order to exclude outliers. We did not apply ad hoc imputation techniques for missing data. To test whether the dataset that was finally included in the analysis (791 observations) was representative of the overall population (1,910 observations), comparison of the outcome's and covariates' distribution of both populations was carried out using a bootstrap version of the univariate Kolmogorov-Smirnov test for continuous variables and a χ^2 test for categorical ones. Logistic regression including the covariates presented in the table with backward elimination of the main effects was used for inferential purpose. The predicted probability of unfavorable outcome was expressed as a function of SBP and MAP measurements (at admission and 24–48 hours difference) defined on a rectangular grid. A local polynomial surface algorithm was used to assess the effect of SBP and MAP (considered as continuous variable) on the endpoint in patients with lacunar, atherosclerotic, and cardioembolic stroke. In areas with relatively low density of observations (patients), the fitted model was used to predict the outcome response by extrapolating data from areas with higher density of observations (Kernel smoothing surface methodology). All analyses were performed with R 2-12-0.

Standard protocol approvals, registrations, and patient consents. The scientific use of ASTRAL data was approved by the local ethics committee.

RESULTS A total of 2,050 patients with acute ischemic stroke were admitted to CHUV during the study period. Of them, 140 patients (6.8%) were excluded because there was no assessment of stroke etiology (n = 23, 1.1%) or endpoint (n = 117, 5.7%). From the remaining 1,910 patients, 1,142 (60.0%) were excluded due to missing data in any of the covariates considered (figure 1). The final dataset included 791 patients and was comparable to the parent population regarding any of the examined variables. Among them, 124 (16%) had lacunar stroke, 105 (13%) atherosclerotic, and 252 (32%) cardioembolic, whereas there were 310 (39%) patients with stroke of some other cause or of undetermined etiology. The main characteristics of the study

Table Patient characteristics[a]

Patient characteristics	All (n = 1,910)	Finally included in the analysis (n = 791)	Lacunar (n = 124)	Atherosclerotic (n = 105)	Cardioembolic (n = 252)
Demographics, time intervals					
Age, y	72.6 ± 21.7	71.0 ± 21.2	68.3 ± 15.0	71.1 ± 18.2	74.6 ± 18.4
Female sex	846 (44)	326 (41)	28 (22.6)	43 (41.0)	118 (46.8)
Prehospital modified Rankin Scale score = 0	1,116 (58)	520 (66)	91 (73.4)	61 (58.1)	152 (60.3)
Stroke onset-to-admission time, min	208 ± 578	180 ± 446	165 ± 323	405 ± 743	146 ± 331
Vital signs					
Temperature (°C) at admission	36.4 ± 0.8	36.4 ± 0.8	36.4 ± 0.8	36.4 ± 0.7	36.3 ± 0.8
At 24–48 h	36.8 ± 0.9	36.8 ± 0.9	36.9 ± 0.9	36.5 ± 0.9	36.9 ± 0.9
Systolic blood pressure (mm Hg) at admission	158 ± 36	159 ± 40	160 ± 36	169 ± 42	155 ± 35
At 24–48 h	140 ± 29	139 ± 26	145 ± 24	147 ± 30	138 ± 30
Diastolic blood pressure (mmHg) at admission	89 ± 21	90 ± 21	90 ± 21	98 ± 22	90 ± 24
At 24–48 h	69 ± 19	68 ± 19	70 ± 22	71 ± 17	68 ± 22
Mean arterial pressure (mm Hg) at admission	111 ± 26	113 ± 25	114 ± 25	120 ± 25	112 ± 25
At 24–48 h	92 ± 20	92 ± 20	93 ± 20	95 ± 18	91 ± 22
Heart rate (min^{-1}) at admission	78 ± 22	78 ± 22	80 ± 22	76 ± 19	80 ± 25
At 24–48 h	77 ± 23	75 ± 24	77 ± 22	71 ± 18	80 ± 27
Laboratory values					
Glucose (mmol/L) at admission	6.5 ± 2.1	6.6 ± 2.0	6.8 ± 2.7	6.2 ± 2.1	6.7 ± 1.9
At 24–48 h	5.7 ± 1.6	5.6 ± 1.6	5.8 ± 1.8	5.4 ± 1.5	5.6 ± 1.6
Serum creatinine (μmol/L)	89 ± 32	88 ± 28	85 ± 25	86 ± 29	89 ± 25
Total cholesterol (mmol/L)	5.3 ± 1.7	5.3 ± 1.6	5.6 ± 2.0	5.7 ± 1.6	5.0 ± 1.5
White blood cell count ($10^3/mm^3$)	8.0 ± 3.5	8.0 ± 3.3	8.8 ± 3.8	7.1 ± 2.2	7.9 ± 3.4
Hemoglobin (g/L)	139 ± 22	141 ± 21	143 ± 20	140 ± 19	140 ± 20
Platelet count, $\times 10^3$/L	221 ± 81	217 ± 77	219 ± 76	220 ± 59	213 ± 68
Brain parenchymal/arterial imaging					
Acute ischemic lesion at admission	609 (32)	261 (33)	52 (42)	13 (12)	95 (38)
Previous stroke at neuroimaging	524 (27)	250 (32)	46 (37)	39 (37)	86 (34)
Leukoaraiosis	414 (21)	158 (20)	26 (21)	29 (28)	51 (20)
Significant arterial pathology	832 (43)	410 (52)	116 (94)	7 (7)	135 (54)
Complete recanalization at 24–48 h	142 (7)	71 (9)	9 (7)	2 (2)	35 (14)
Clinical examination					
NIHSS at admission	6 ± 11	7 ± 12	8 ± 12	4 ± 3	10 ± 12
Risk factors and medical history					
Previous cerebrovascular event	196 (25)	532 (28)	40 (32)	19 (18)	58 (23)
Hypertension	1,291 (67)	535 (68)	93 (75)	82 (78)	167 (66)
Atrial fibrillation	495 (26)	199 (25)	1 (1)	2 (2)	165 (65)
Dyslipidemia	1,269 (66)	565 (71)	105 (85)	89 (85)	157 (62)
Diabetes mellitus	309 (16)	141 (18)	30 (24)	23 (22)	47 (19)
Mechanical or biological valve	60 (3)	20 (3)	0 (0)	0 (0)	16 (6)
Coronary artery	293 (15)	106 (13)	10 (8)	11 (10)	50 (20)
Active smoking	453 (23)	191 (24)	44 (35)	32 (30)	39 (15)
Peripheral artery disease	104 (5)	39 (5)	17 (14)	4 (4)	4 (2)
Low ejection fraction (<30%)	89 (5)	33 (4)	0 (0)	1 (1)	29 (12)

—Continued

Table Continued

Patient characteristics	All (n = 1,910)	Finally included in the analysis (n = 791)	Lacunar (n = 124)	Atherosclerotic (n = 105)	Cardioembolic (n = 252)
Previous treatment					
Antiplatelets	690 (36)	264 (33)	44 (35)	37 (35)	91 (36)
Anticoagulants	195 (10)	66 (8)	1 (1)	1 (1)	46 (18)
Antihypertensives	1,061 (55)	418 (53)	58 (47)	51 (49)	157 (62)
Oral hypoglycemic agents	200 (10)	95 (12)	19 (15)	18 (17)	30 (12)
Lipid-lowering drugs	442 (23)	187 (24)	31 (25)	21 (20)	66 (26)
Thrombolysis (mostly IV)	350 (18.1)	143 (18.1)	32 (26)	9 (9)	65 (26)

Abbreviation: NIHSS = NIH Stroke Scale.
[a] Values are median ± interquartile range for continuous variables and absolute count (%) for categorical variables.

groups are summarized in the table. Of interest, there was a relatively high proportion of patients with cardioembolic stroke. The distribution of observations for each subgroup with regards to acute SBP and SBP change at 24–48 hours is presented in figure e-1 on the *Neurology*® Web site at www.neurology.org. The results of the logistic regression analysis were previously presented in another analysis of the same dataset.[12] Applying a backward elimination procedure in a logistic regression model including the covariates presented in the table resulted in a model with 8 significant main effects, i.e., age, prior use of antidiabetics, NIHSS score at admission, prestroke mRS, acute ischemic lesion on CT/MRI, CT/MRI lesions unrelated to stroke, arterial recanalization, and admission glucose level. The significance of all 2-way interactions in that model was assessed and 3 were found significant at the 5% level: NIHSS score at admission by recanalization, prestroke mRS by antidiabetics, and acute ischemic lesion on CT/MRI by CT/MRI lesions unrelated to stroke. Therefore, the final model used for predictions purposes contains 8 main effects and 3 interaction terms.

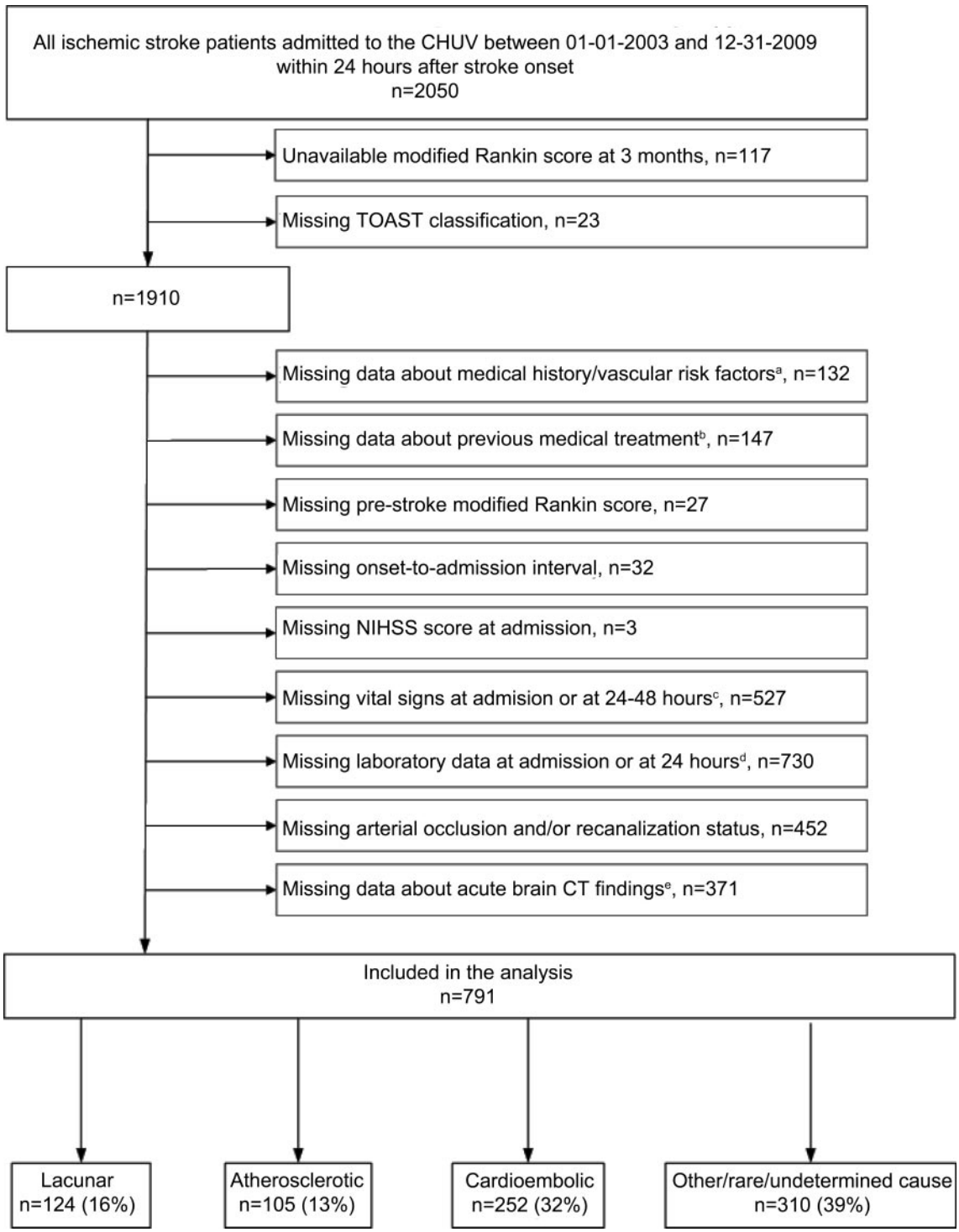
In patients with lacunar stroke, the mean predicted probability of unfavorable outcome was generally low (18.1%, 95% confidence interval [CI] 15.3–21.1, figures 2 and 3) with the exception of patients with a BP increase at 24–48 hours. There was no statistically significant difference in the mean predicted probability of unfavorable outcome between patients with an admission BP of ≤140 mm Hg, 140–160 mm Hg, and >160 mm Hg (15.3%; 95% CI 12.5%–18.9% vs 12.1%; 95% CI 9.2%–15.3% vs 20.8%; 95% CI 17.8%–23.9%, respectively, $p = 015$) or between patients with an increase vs decrease of BP at 24–48 hours (18.7%; 95% CI 15.2%–23.0% vs 18.0%; 95% CI 15.3%–21.0%, respectively, $p = 0.84$). Of notice, there was no patient with lacunar stroke and low BP at admission (<110 mm Hg) (figure e-1), so no estimations can be done for the effect of BP change on outcome in this patient subgroup.

Patients with atherosclerotic stroke had a higher mean probability of unfavorable outcome (43.6%; 95% CI 39.6%–47.5%, figures 2 and 3). Similar to patients with lacunar stroke, there was no statistically significant difference in the mean predicted probability of unfavorable outcome between patients with an admission BP of ≤140 mm Hg, 140–160 mm Hg, and >160 mm Hg (41.0%; 95% CI 37.0%–44.8% vs 41.5%; 95% CI 36.9%–45.9% vs 45.5%; 95% CI 41.4%–49.6%, respectively, $p = 075$) or between patients with an increase vs decrease of BP at 24–48 hours (43.4%; 95% CI 38.9%–47.5% vs 43.6%; 95% CI 39.6%–47.8%, respectively, $p = 0.88$).

In patients with cardioembolic stroke, the mean probability of unfavorable outcome was similar to the patients with atherosclerotic stroke (44.5%; 95% CI 39.6%–47.5%, figures 2 and 3). However, in contrary to patients with atherosclerotic or lacunar stroke, patients with a cardioembolic stroke and an increase of BP at 24–48 hours had a higher probability of unfavorable outcome compared to those with a decrease of BP (53.4%; 95% CI 50.3%–56.2% vs 42.2%; 95% CI 39.4%–45.1%, respectively, $p = 0.037$). Also, the predicted probability of unfavorable outcome was significantly different between patients with an admission BP of ≤140 mm Hg, 140–160 mm Hg, and >160 mm Hg (34.8%; 95% CI 32.1%–37.4% vs 42.3%; 95% CI 39.3%–45.3% vs 52.4%; 95% CI 49.2%–55.9%, respectively, $p < 0.01$).

DISCUSSION This study investigates the interaction of baseline BP and subsequent BP changes to predict stroke outcome with respect to stroke etiology. We found that in patients with lacunar or atherosclerotic stroke, there is no significant difference in predicted probability of unfavorable outcome between those with an admission BP of ≤140 mm Hg, 140–160 mm Hg, or >160 mm Hg, or between

Figure 1 Flow diagram of the study participants

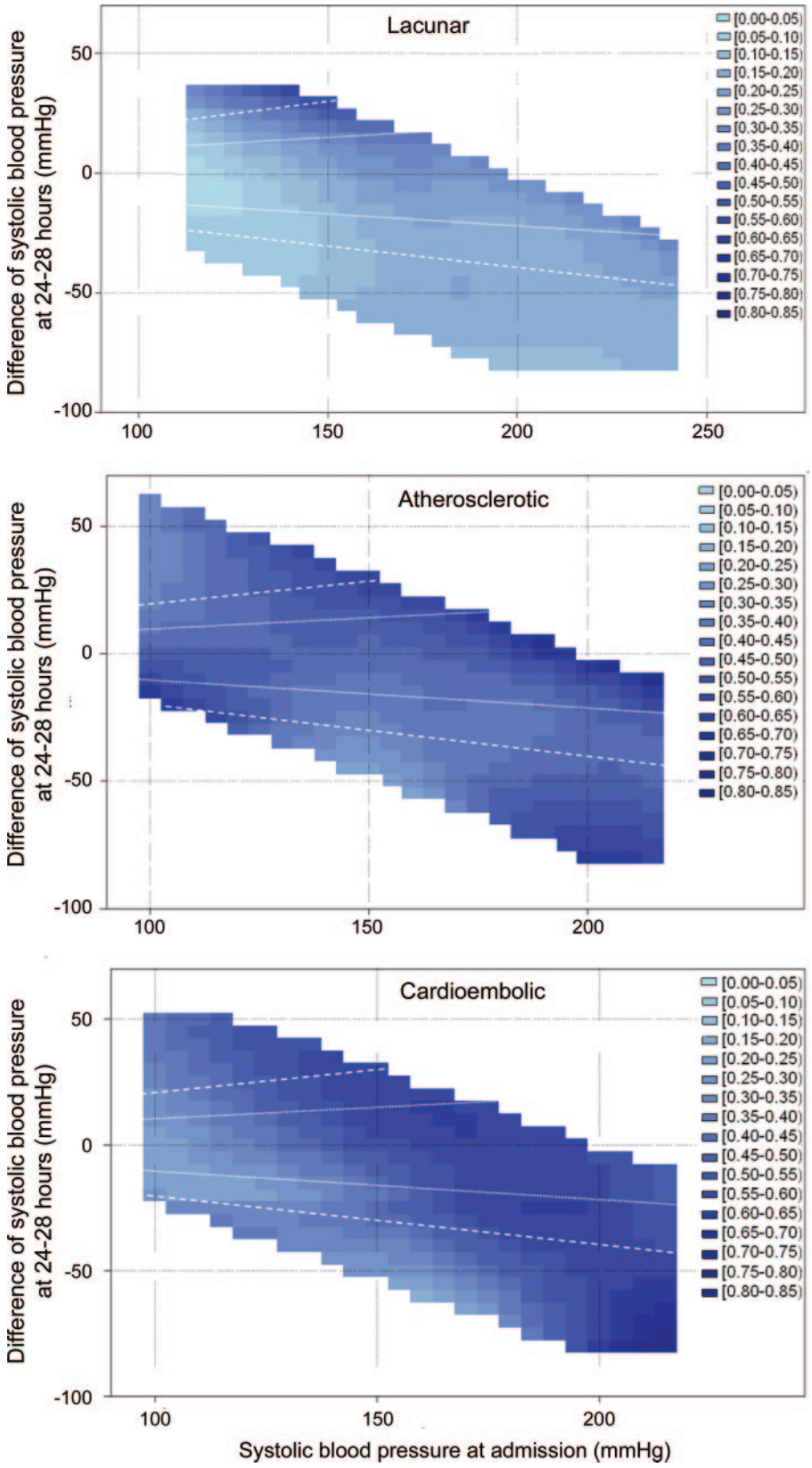


For [a], [b], [c], [d], and [e], n indicates number of missing observations (not patients) for the following parameters: [a] Arterial hypertension, diabetes mellitus, atrial fibrillation, active smoking, dyslipidemia, coronary artery disease, peripheral artery disease, low ejection fraction (<30%), mechanical/biological valve. [b] Antihypertensives, antiplatelets, antidiabetics, anticoagulants, lipid-lowering drugs. [c] Temperature, systolic/diastolic blood pressure, heart rate. [d] Glucose, creatinine, cholesterol, hemoglobin, white blood cell count, platelet count. [e] Acute ischemic changes, hemorrhagic transformation, old lesions, leukoaraiosis. CHUV = Central University Hospital of Vaud; NIHSS = NIH Stroke Scale.

those with increase or decrease of BP at 24–48 hours. On the contrary, in patients with cardioembolic stroke, the predicted probability of unfavorable outcome increases significantly with increasing levels of admission BP, and is also higher when BP increases at 24–48 hours.

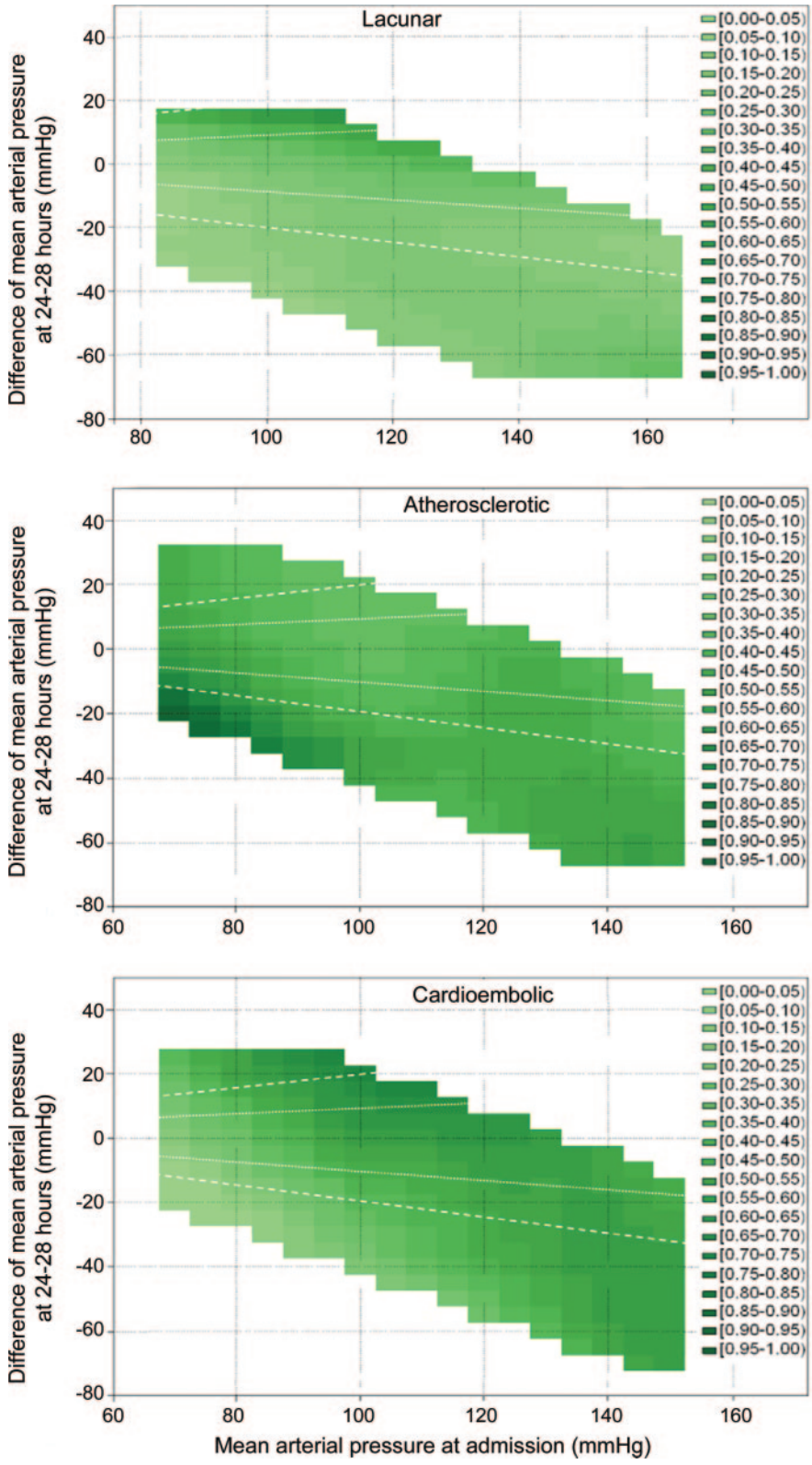
Patients with atherosclerotic or lacunar stroke frequently have chronic hypertension (79% and 81%,

Figure 2 Systolic blood pressure (SBP) at admission and predicted probability of unfavorable outcome



Color intensities (and corresponding numbers) represent predicted probability of unfavorable outcome in patients with lacunar (upper figure), atherosclerotic (middle figure), and cardioembolic stroke (lower figure) with regards to SBP at admission and 24–48 hours SBP difference. Dotted lines indicate a 10% change of SBP at 24–48 hours, whereas dashed lines indicate a 20% change.

Figure 3 Mean arterial pressure at admission and predicted probability of unfavorable outcome



Color intensities (and corresponding numbers) represent predicted probability of unfavorable outcome in patients with lacunar (upper figure), atherosclerotic (middle figure), and cardioembolic stroke (lower figure) with regards to mean arterial pressure (MAP) at admission and 24–48 hours MAP difference. Dotted lines indicate a 10% change of MAP at 24–48 hours, whereas dashed lines indicate a 20% change.

respectively, in our sample) which shifts the autoregulation of cerebral blood flow to the right.[10] As a result, baseline BP values that are usually considered normal for the general population (<140 mm Hg) may be actually inadequate to perfuse the ischemic brain of such patients. Taken also into account that these patients usually have significant atherosclerotic burden and may have diffuse stenotic lesions in the cerebral circulation, high BP may be warranted to enhance perfusion of the ischemic penumbra via collaterals and potentially improve outcome,[17] especially in elderly patients who may have pseudohypertension[18–20] and cerebral arterial hypertensive hypertrophy which shifts autoregulation of cerebral blood flow to the right.[21] In accordance with these considerations, our study showed that in patients with atherosclerotic or lacunar stroke the probability of unfavorable outcome was not higher in patients with high BP levels (compared to lower BP levels) or in patients whose BP increases at 24–48 hours (compared to patients whose BP decreases). On the contrary, the frequency of arterial hypertension in our population was lower in patients with cardioembolic stroke; cardioembolic strokes are usually of larger volume and therefore pose a significant risk of hemorrhagic transformation and cerebral edema when BP remains at high levels[22,11]; these considerations could explain our finding that patients with cardioembolic stroke and high admission BPs or elevation of BP at 24–48 hours have a higher probability of unfavorable outcome.

One may argue that it is difficult to determine stroke etiology at admission or during the first hours after. In this case, the individual tailoring of BP management with respect to the underlying etiopathogenetic mechanism would not be feasible in daily clinical practice. However, a study performed in 1993 showed that early (within 12 hours after stroke onset) clinical diagnosis of stroke etiology may be very accurate.[23] This is even more feasible nowadays, especially in centers which offer advanced multimodal imaging at admission.[14]

One of the strengths of the study is the wide set of demographic, clinical, laboratory, and neuroimaging variables which were used for outcome adjustment. Also, the baseline BP measurements were performed early after stroke onset (median onset-to-admission interval was 180 minutes). Moreover, we did not apply ad hoc imputation techniques for missing data but rather included in the analysis only patients with complete dataset which preserved the original associations of the covariates which were included in the analysis. It is possible that this approach may have introduced selection bias; however, the dataset that was finally included in the analysis was not significantly different from the parent population. Finally, SBP and MAP were analyzed as continuous variables preventing loss of information and reduction of the statistical power.[24]

The present study is limited by the fact that the timing of subacute BP measurements was not predefined and standardized with the time window being relatively wide due to the retrospective nature of the study; still, most subacute BP measurements were close to the 24th hour after the initial measurement. Also, we did not capture data regarding the use of antihypertensive medications during the first hours of cerebral ischemia in patients with extremely elevated BP levels, and as a result, outcome was not adjusted for the classes of drugs used to control BP and their putative pleiotropic effects, as was implied by the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study.[25] Furthermore, we did not assess BP variability during the acute phase which may influence clinical outcome.[26] Also, the analysis did not include data about arterial patency, recanalization, and the size of initial infarct and penumbra, which would potentially provide further insight into the association of BP with the underlying pathophysiology. The relatively high proportion of cardioembolic strokes could perhaps reflect the decreased incidence of lacunar and atherosclerotic strokes due to more efficacious primary stroke prevention by better BP control and increasing use of statins. Finally, the statistical power of our analysis may be limited by the relatively small size of the patient groups that were studied; therefore, these results should be regarded as hypothesis-generating and interpreted with caution.

This study investigates the interaction of baseline BP and subsequent BP changes to predict stroke outcome with respect to stroke etiology. These hypothesis-generating results provide further evidence to support that BP management in the acute stroke may need to take into consideration the underlying etiopathogenetic mechanism. More data from currently ongoing randomized controlled trials like ENOS are needed to confirm these findings.

AUTHOR CONTRIBUTIONS

Dr. Ntaios: study concept and design, analysis and interpretation, preparation of the manuscript. Dr. Lambrou: analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Michel: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision.

DISCLOSURE

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