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Stella Aslanyan, Christopher J. Weir and Kennedy R. Lees

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# Research Report

## Elevated Pulse Pressure During the Acute Period of Ischemic Stroke Is Associated With Poor Stroke Outcome

Stella Aslanyan, MD; Christopher J. Weir, PhD; Kennedy R. Lees, MD, FRCP; for the GAIN International Steering Committee and Investigators

**Background**—It is controversial which component of blood pressure (BP) during acute period of stroke best predicts outcome. We hypothesized that elevated pulse pressure (PP), the difference between systolic BP (SBP) and diastolic BP (DBP), is independently associated with poor stroke outcome at 3 months.

**Methods**—We analyzed both treatment groups from the Glycine Antagonist (Gavestinel) in Neuroprotection (GAIN) International trial (1455 ischemic stroke cases of mostly moderate severity). Cox proportional hazards and logistic regression modeling corrected for demography, medical history, heart rate, stroke severity, and clinical subtype.

**Results**—Elevated weighted average PP during the first 60 hours was associated with poor outcome by mortality, Barthel index, National Institutes of Health Stroke Score (NIHSS) and Rankin scores. Elevated baseline PP was associated with Barthel index and Rankin score.

**Conclusion**—Elevated PP is associated with poor stroke outcome at 3 months. (*Stroke*. 2004;35:e153-e155.)

**Key Words:** ischemia ■ stroke ■ outcome

Pulse pressure (PP), the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP), is a pulsatile component of the blood pressure (BP) curve as opposed to mean BP (MBP) (the sum of two thirds of DBP and one third of SBP), its steady component.

SBP and DBP increase after stroke.<sup>1</sup> They decrease spontaneously by 12 and 7 mm Hg in the first 24 hours (PP decreases by 5) and by 22 and 12 mm Hg in the first week (PP decreases by 10), but no further thereafter.<sup>2</sup>

There is controversy about the role of different components of BP during the acute phase of stroke on outcome. Low SBP<sup>2</sup> and DBP<sup>3,4</sup> and elevated SBP, DBP, and MBP<sup>5</sup> have been shown to be associated with poor stroke outcome. A J-shaped relationship was observed between SBP and outcome.<sup>6</sup> PP has been shown to be associated with 1-year mortality,<sup>7</sup> whereas others failed to see this effect.<sup>5</sup> We have shown previously that elevated weighted average (WA) MBP was associated with mortality at 3 months in the Glycine Antagonist (Gavestinel) in Neuroprotection (GAIN) International trial<sup>8</sup> population.<sup>9</sup> In the present study, we aim to investigate the effect of baseline and WAPP (the area under the curve describing PP over the course of the measurement divided by its duration) after ischemic stroke using the same trial data. In addition, we aim to compare the effects of PP with MBP, SBP, and DBP on stroke outcome. We hypothesize that elevated baseline and WAPP are associated with poor stroke outcome, and that this can be partly explained by the opposite effects of SBP and DBP.

### Subjects and Methods

We studied patients with ischemic stroke (mostly moderate severity) from both treatment groups, because gavestinel did not have an effect on stroke outcome and did not significantly alter BP.<sup>8,9</sup> Inclusion criteria tolerated a wide range of BP on admission, including systolic hypertension, but excluded malignant hypertension defined by DBP >130 mm Hg. BP was measured at baseline, at 30 minutes, and at 4, 12, 12.25, 60, and 60.25 hours after the start of the randomized treatment. The outcomes were mortality during 3 months, Barthel activities of daily living index (dead or 0 to 55 versus 60 to 90 versus ≥95), National Institutes of Health Stroke Score (NIHSS) scale and modified Rankin scale (dead or ≥2 versus 0 to 1) at 3 months, consistent with the GAIN statistical analysis plan.

### Statistical Analysis

Logistic regression and Cox proportional hazards modeling identified the association between baseline and WAPP and outcome in univariate fashion and after correcting for prognostic factors (baseline NIHSS score, age, gender, treatment group, heart rate, stroke risk factors, and stroke subtype). All linear logistic models were compared with generalized additive models using analysis of variance to rule out a nonlinear relationship.

We did not combine MBP, SBP, and DBP into 1 model with PP because of their high intercorrelations. To compare these similar entities, we standardized the variables (subtracted the mean and divided by the standard deviation) and fitted each in a separate model. The resulting log-odds ratios (ORs) and log-hazard ratios (HRs) were compared.

### Results

Descriptive statistics of the sample of 1455 ischemic stroke patients were presented earlier.<sup>9</sup> The median (interquartile

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From Division of Cardiovascular and Medical Sciences (S.A., C.J.W., K.R.L.) and Robertson Centre for Biostatistics (C.J.W.), University of Glasgow, Scotland.

Correspondence to Dr S. Aslanyan, Gardiner Institute, Western Infirmary, Glasgow G11 6NT, UK. E-mail stella\_s\_aslanyan@hotmail.com  
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**Odds Ratios and Hazard Ratios (95% CI) of Pulse Pressure Predicting Poor Outcome per Additional 10 mm Hg**

	WAPP		Baseline PP	
	Univariate	*	Univariate	*
Mortality, HR	1.18 (1.11–1.26)	1.12 (1.04–1.20)	1.05 (1.00–1.11)	1.04 (0.99–1.10)
Barthel index	1.28 (1.21–1.36)	1.13 (1.05–1.22)	1.08 (1.04–1.13)	1.06 (1.00–1.12)
NIHSS score	1.22 (1.13–1.31)	1.12 (1.02–1.23)	1.05 (0.99–1.10)	1.05 (0.98–1.13)
Rankin scale	1.23 (1.14–1.32)	1.11 (1.01–1.22)	1.07 (1.02–1.13)	1.09 (1.01–1.17)

\*After correcting for prognostic factors.

WAPP indicates weighted average pulse pressure.

range) of baseline PP and WAPP was 70 (59 to 80) mm Hg and 69 (57 to 79) mm Hg, respectively.

Elevated WAPP was associated with poor outcome by all outcome measures in univariate analyses and after correcting for prognostic factors (Table). Elevated baseline PP was associated with Barthel index and Rankin score. There was no significant evidence that these associations were different in patients with and without atrial fibrillation.

The Figure presents log-ORs and log-HRs of standardized WA and baseline PP, MBP, DBP, and SBP in predicting poor stroke outcome after correcting for prognostic factors. Although there is a trend for higher values of WASBP and low values of baseline DBP to be associated with poor stroke outcome, this was not statistically significant in many of the models.

## Discussion

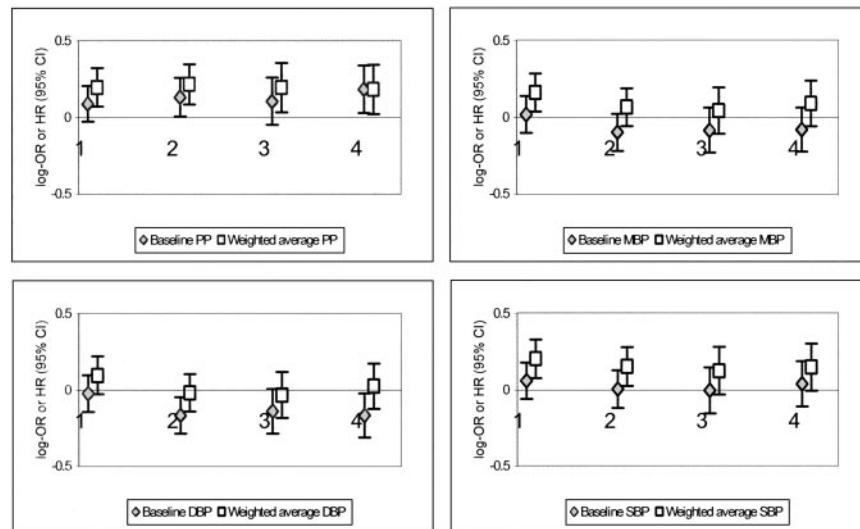
Our findings showed a clear linear logistic relationship between high baseline PP and WAPP and poor stroke outcome: there was no significant difference between the models that we have presented or generalized additive models that allow any shape of relationship.

The opposite effects of WASBP and baseline DBP on outcome might explain some of the effect of PP on the outcome. Our study confirmed the association of low baseline DBP with poor outcome presented earlier,<sup>3,4</sup> but it failed to show any effect of baseline SBP. The effect of WASBP was consistent with the effect of beat-to-beat SBP.<sup>5</sup> The confi-

dence intervals for the effect sizes of standardized PP, MBP, DBP, and SBP on outcome overlap substantially (Figure). Thus, we found no evidence of any one BP component being more strongly associated with outcome than the others. WAPP, however, was the only BP component to be consistently associated with all 4 outcome measures, in comparison to 2 for baseline DBP and WASBP and 1 for WA MBP. Therefore, the role of PP should not be underestimated.

Exclusion criteria controlled only for high DBP, thus we could have encountered a selection bias of PP. The mean PP was higher (74 mm Hg, n=92<sup>5</sup>) in the study that failed to detect PP effect in comparison to our results (72 mm Hg). In a subgroup of patients with SBP <180 at baseline (n=1088), after correcting for prognostic factors, ORs and HRs of PP were not statistically significant, but their confidence intervals overlapped with the results of the entire sample. Reasons for this might be smaller sample and PP range and exclusion of patients with poor prognosis because of extremely high SBP.

Having an observational nature, our study cannot prove a causal relationship of PP with stroke outcome: high PP may be the consequence of potential poor outcome rather than its cause. Results might not directly apply to the general hospital-based population. Medications can selectively alter different components of BP, and thus clarification of their effect is important for BP management in acute stroke care. In conclusion, elevated PP during the acute period of ischemic stroke is independently associated with poor stroke outcome



Log-ORs and HRs (95% CI) of standardized BP components when predicting poor outcome after correcting for prognostic factors. 1 indicates mortality, HR; 2, Barthel index; 3, NIHSS score; 4, Rankin scale.

at 3 months after correcting for baseline NIHSS score, age, gender, treatment group, heart rate, stroke risk factors, and stroke type.

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