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# Higher Stroke Risk with Lower Blood Pressure in Hemodynamic Vertebrobasilar Disease: Analysis from the VERiTAS Study

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## Abstract

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CONFLICTS OF INTEREST

SAH - material research support (no direct funds) from GE Healthcare and VasSol, Inc.

DSL - consultant for Stryker, Medtronic.

CPD - consultant for Microvention, Silk Road, Penumbra; serves on Scientific Advisory Board, Pulse Therapeutics; stock options in Pulse Therapeutics.

PBG - served as the founder and director/co-director of the Clinical Coordinating Center for the Lundbeck sponsored DIAS 4 trial of desmoteplase in acute ischemic stroke.

FTC - financial interest inVasSol, Inc.

**Background—**Despite concerns regarding hypoperfusion in patients with large artery occlusive disease, strict blood pressure (BP) control has become adopted as a safe strategy for stroke risk reduction.We examined the relationship between BP control, blood flow, and risk of subsequent stroke in the prospective Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS) Study.

**Methods—**VERiTAS enrolled patients with recent vertebrobasilar (VB) TIA or stroke and ≥50% atherosclerotic stenosis/occlusion of vertebral or basilar arteries. Hemodynamic status was designated as low or normal based on quantitative MRA. Patients underwent standard medical management and follow-up for primary outcome event of VB territory stroke. Mean BP during follow-up (<140/90 vs. ≥140/90 mm Hg) and flow status were examined relative to subsequent stroke risk using Cox proportional hazards analysis.

**Results—**The 72 subjects had an average of 3.8±1.2 BP recordings over 20±8 months of follow-up; 39 (54%) had mean BP of <140/90 mm Hg. The BP groups were largely comparable for baseline demographics, risk factors, and stenosis severity. Comparing subgroups stratified by BP and hemodynamic status, patients with both low flow and BP <140/90 mm Hg (n=10) had the highest risk of subsequent stroke with HR 4.5 (CI 1.3-16.0, p=0.02) compared to the other subgroups combined.

**Conclusions—**Among a subgroup of patients with VB disease and low flow, strict BP control (BP <140/90) may increase the risk of subsequent stroke.

### Keywords

blood flow; blood pressure; magnetic resonance imaging; magnetic resonance angiography; stroke; vertebrobasilar disease

## INTRODUCTION

Ischemic stroke guidelines advocate blood pressure (BP) control as an important component of primary and secondary stroke prevention(1, 2). However, the safety of aggressive BP management, and the optimal BP target, for patients with symptomatic large artery cerebrovascular occlusive disease remains debated, given potential concerns for hypoperfusion(3). Recently, secondary analyses from prospective cohorts with symptomatic intracranial stenosis(4) and carotid occlusion(5) have supported strict BP control as a safe and effective strategy for recurrent stroke risk reduction. Concern remains, however, for patients with proven hemodynamic compromise. We sought to examine the relationship between BP control, hemodynamic compromise, and risk of subsequent stroke in the prospective Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS) Study.

## METHODS

VERiTAS was a prospective multi-center blinded observational study conducted to test the hypothesis that patients with hemodynamic symptomatic vertebrobasilar (VB) disease as indicated by distal blood flow compromise measured by quantitative magnetic resonance angiography (QMRA) are at higher risk of subsequent posterior circulation stroke. The study

was conducted at five centers in North America from 2008 to 2014. The study protocol was approved by the institutional review boards at each participating site, and written informed consent was provided by each study participant. Details of the study design, characteristics of the cohort, and primary results indicating distal flow status as a predictor of subsequent stroke risk have been previously published(6-8).

All included patients had a posterior circulation transient ischemic attack (TIA) or stroke within the prior 60 days referable to ≥ 50% extracranial or intracranial atherosclerotic VB stenosis or occlusion, verified by conventional digital subtraction angiography (DSA) or computed tomographic angiography (CTA). All patients underwent QMRA at enrollment, using a standardized blinded protocol, and standard clinical evaluation(6). The QMRA blood flow measurements were reviewed centrally, and distal hemodynamic status was designated as low flow or normal flow based on a previously published algorithm defining hemodynamic compromise as > 20% reduction below the normative limits of posterior circulation vessel-specific flows(9). Pre-specified definitions for vascular risk factors were used(7), including hypertension defined as self-reported history or use of anti-hypertensive medication, hyperlipidemia defined as self-reported history or current treatment with lipid lowering therapy. diabetes mellitus defined as self-reported history or use of insulin or oral hypoglycemic treatment, and coronary artery disease defined as self-reported history of myocardial infarction, angina pectoris, positive stress test or cardiac surgery/intervention.

Patients were followed for a minimum of 12 months and up to 24 months. During the first12 months of follow-up, they were contacted monthly by telephone, and they were seen in person at 6 month intervals for the duration of the study. BP was measured at baseline and at each 6 month visit, with the participant sitting at rest for ≥ 5 minutes with the arm supported at the level of the heart. If the initial BP reading was >140/90 mmHg, a second reading was taken at the end of the visit and the lower of the two readings was recorded. Patients were managed at the discretion of their local treating physicians, who were requested to adhere to contemporary published guidelines for vascular risk factor management. For BP, the target goal was <140/90 based on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure(10), the guidelines operative at the time of the study.

The primary endpoint was fatal and nonfatal ischemic stroke in the VB territory, defined as new neurological symptoms or signs localizing to an area of the brain supplied by the VB arterial system lasting at least 24 hours, or lasting less than 24 hours but associated with new infarct on CT or MRI. All potential primary endpoints were submitted for adjudication, and designated as definite, probable, possible or no event based on pre-specified criteria by an independent panel of two stroke neurologists, blinded to the subject's hemodynamic data. In the event that the opinions differed, a third blinded stroke neurologist was consulted and the majority opinion prevailed. Only definite and probable events were included as primary endpoints for analysis.

## Statistical Analysis

Each patient's BP was averaged over the study period; only BPs recorded prior to a primary endpoint of VB territory stroke were included. For the analysis, we divided the cohort into

four groups based on BP above and below the target of 140/90 mmHg and based on the distal flow status as normal or low. Each patient was categorized in the ≥ 140/90 mmHg BP group if either the mean systolic or diastolic BP was above or equal to the target value. Spearman correlation analysis of flow status and BP at baseline and averaged over follow-up was performed. Comparison of baseline demographic, clinical, and angiographic features of disease based on the categorized BP variable was performed using unpaired t test or Wilcoxon rank sum test as appropriate for continuous variables and chi-square test for categorical variables. Similar comparisons were also performed specifically in low flow and normal flow status groups separately. Maximum follow-up included was 27 months to accommodate a 3-month time window around the planned maximum 24 months follow-up(8). Event rates for the primary endpoint were examined in the 4 subgroups of BP and flow status. The cumulative probability of the primary endpoint was examined using the product limit method. Cox proportional hazards regression was used to estimate hazard ratios (HR), for the highest risk subgroup in comparison to the others combined. HR were also examined after adjusting for identified predictors of stroke risk in this cohort(8), namely age, coronary artery disease, diabetes mellitus and physical activity (exercise enough to 'break a sweat' at least twice per week).

## RESULTS

### Patient characteristics

The enrolled cohort of 72 patients had a mean age of 65.6 ± 10.3 years, with 44% female, 25% black race and 11% Hispanic/Latino ethnicity; 93% had hypertension. The average BP over the 20 ± 8 months follow-up for the entire group was 141±17/79±9 mm Hg. The average number of BP recordings (including baseline BP) was 3.8±1.2. The majority of patients, 63 (87.5%), were on continuous antihypertensive therapy (at least one anti-hypertensive drug at every follow-up visit) throughout the study period.

Thirty-nine patients (54%) had average BP < 140/90 mm Hg. The BP groups were comparable for baseline demographics, risk factors, and stenosis severity (Table 1), except for baseline hyperlipidemia (p=0.04). However, hyperlipidemia was not a significant predictor for subsequent stroke in the cohort(8). The number of BP recordings (3.8±1.1 vs 3.7±1.3, p=0.79), the proportion of patients on continuous antihypertensive therapy (91% vs 85%, p=0.49) and the length of follow-up (19±7 vs 20±8 months, p=0.58) was also comparable between the ≥140/90 mm Hg BP group and <140/90 mm Hg groups, respectively.

Distal flow status at baseline was low in 18 (25%) of the cohort, with a very similar proportion between ≥140/90 mm Hg BP group (24%), and the <140/90 BP group (26%). Flow status was not correlated with BP at baseline (p=0.41) or with average BP during follow-up (p=0.89). Baseline characteristics were comparable between the BP groups when examined in the low flow status and in the normal flow status categories individually (data not shown).

### Stroke risk

Of 10 subsequent VB territory strokes, 7 occurred in patients with BP <140/90 mm Hg (17.9%) compared to 3 in patients with BP ≥ 140/90 mm Hg (9.1%) (p=0.33). Distal flow status was previously demonstrated to be a predictor of stroke (log rank, p=0.04) in this cohort(8). Among low flow status patients, those with BP <140/90 mm Hg had 4 events (40.0%) compared to 1 event (12.5%) in those with BP≥ 140/90 mm Hg (p=0.31) (Figure 1A). Among normal flow status patients, 3 events (10.3%) and 2 events (8.0%) occurred in the BP <140/90 mm Hg and BP≥ 140/90 mm Hg groups respectively (p=0.99) (Figure 1B).

When comparing subgroups stratified by BP and hemodynamic status, patients with both low flow status and BP <140/90 mm Hg (n=10) had the highest risk of subsequent stroke (Figure 2), with an event rate of 27.1 per hundred person-years (Table 2), and a HR of 4.5 (95% CI 1.3-16.0, p=0.02) when compared to all other subgroups combined. Adjusting for the previously identified risk factors for stroke in this cohort(8), the low flow and BP <140/90 mm Hg subgroup remained at significantly higher risk (HR 7.3, 95% CI 1.4 -37.9, p=0.02).

## DISCUSSION

Analysis of the VERiTAS cohort demonstrates that among patients with VB occlusive disease, those with hemodynamic compromise are at elevated risk of stroke when subject to strict BP control (<140/90 mm Hg). Large vessel VB disease is responsible for approximately one third of posterior circulation strokes,(11) and prior data indicate that 25-35% are associated with hemodynamic impairment, thus representing a clinically important subgroup.(8, 9) These results are the first to examine the effect of BP in relation to hemodynamic status in VB disease, and contrast with the well demonstrated importance of BP control in cardiovascular health and stroke risk reduction in general, with large studies supporting the benefits of more intensive BP management(12, 13). Studies examining BP specifically in patients with large artery cerebrovascular occlusive disease, however, are limited and concerns regarding promoting hypoperfusion and increased stroke risk exist. Such concerns are supported by data from trials of carotid stenosis, which have demonstrated significantly higher stroke risk among patients with bilateral carotid stenosis (≥ 70%) with lower systolic BP (<150 mm Hg)(3).

In contrast, however, analysis of the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) cohort of 567 patients with symptomatic intracranial stenosis demonstrated an increased risk of stroke in patients with increasing mean systolic and diastolic BP(4). Among the 206 patients with severe (≥70%) stenosis, however, increasing systolic BP was not associated with higher stroke risk, although SBP<140 was not associated with increased stroke risk either. In the analysis, the subgroup of patients with posterior circulation stenosis (n=243) was also examined and the same increase in stroke risk with higher BP was demonstrated. A post-hoc analysis of baseline angiographic collaterals in WASID patients found no interaction between collateral flow grade, baseline blood pressure, and stroke risk during follow-up(14), although it is important to note that no specific determination of hemodynamic status was performed in WASID, and that severity of stenosis alone is a poor surrogate for such a determination. Our previous analysis of blood flow in the VERiTAS

cohort(7) clearly demonstrates that distal hemodynamic status in the posterior circulation is not reliably predicted by the extent or severity of the disease. The algorithm for hemodynamic assessment used in the VERiTAS study intrinsically incorporates sources of collateral blood flow into its final designation of flow status, and as such, verifies the adequacy of collaterals, and is distinct from and supercedes simple anatomic measures such as stenosis severity or minimal residual diameter. Since hemodynamic compromise is present in only a relative minority of patients with cerebral occlusive diseases(9, 15), the relationship of increased stroke risk to increased BP noted in the WASID cohort may be a reflection of the generally detrimental effect of high BP in the majority of the flow compensated cohort, rather than an association that is equally applicable to all patients

The effect of BP on stroke risk has been studied in one population of patients with documented flow compromise: those with carotid occlusion and hemodynamic cerebral compromise based on increased oxygen extraction fraction (OEF) measured using positron emission tomography (PET) in the Carotid Occlusion Surgery Study(15) (COSS). Data form the nonsurgical cohort of 91 patients from this prospective randomized study was examined relative to subsequent stroke and average BP during follow-up. Lower BP (≤135/85) was associated with a reduced risk of ipsilateral ischemic stroke in this group of flow compromised patients(5). The results of our study, in contrast, demonstrate a clear trend towards increased stroke risk with lower BP, and certainly no evidence of a protective effect. Our cohort is specifically focused on the posterior circulation as compared to the COSS study, and it is possible that the characteristics of collateral networks and blood flow that are unique to the posterior vs anterior circulation are differentially susceptible to the effects of BP reduction. Also, the methods and definition of flow compromise differ between the studies, COSS using PET criteria and VERiTAS using QMRA criteria, although both have been demonstrated to be predictive of stroke risk.

### Limitations

Our cohort is small, and thus lacks sufficient power to demonstrate a significant difference when comparing BP management within the low flow group alone. Furthermore, additional analyses looking at different BP stratifications, or examining for possible confounding by a J curve phenomenon was not feasible. The number of BP measurements used to calculate average BP in our cohort was also relatively small and could lead to imprecision in our analysis. Additionally, blood pressure variability has recently emerged as an important predictor of stroke, independent of mean BP(16); however we lacked the number and frequency of BP measurements in this cohort to examine this aspect of BP in follow-up.

## CONCLUSION

Among a subgroup of patients with VB disease and low flow, strict BP control (BP <140/90 mm Hg) may increase the risk of subsequent stroke. This finding within a modest sized cohort suggests that among patients with posterior circulation occlusive disease and impaired flow, indiscriminate application of aggressive BP reduction goals may not be prudent. Further research to determine the optimal BP management in this subgroup of patients is warranted.

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## APPENDIX

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Biostatisticians: Xinjian Du, MD MPH, Hui Xie, PhD

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Participating sites ( in descending order of number of enrollees)

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Satellite Site

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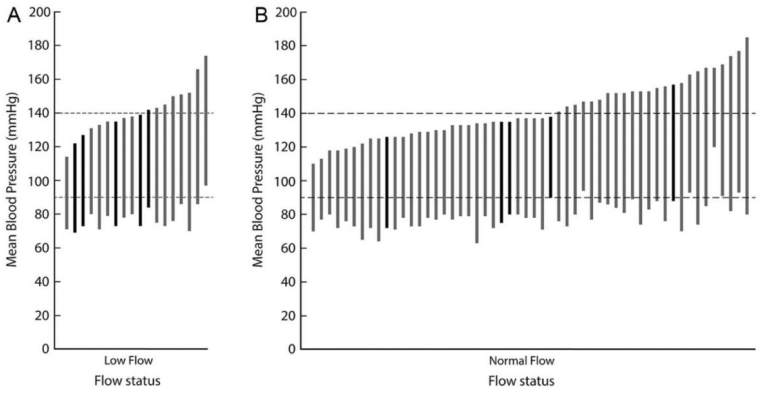


**Figure 1.**

Average systolic and diastolic BP in each individual subject. Black bars represent those experiencing the primary endpoint of VB territory stroke during follow-up. A. Low flow status subjects B. Normal flow status subjects

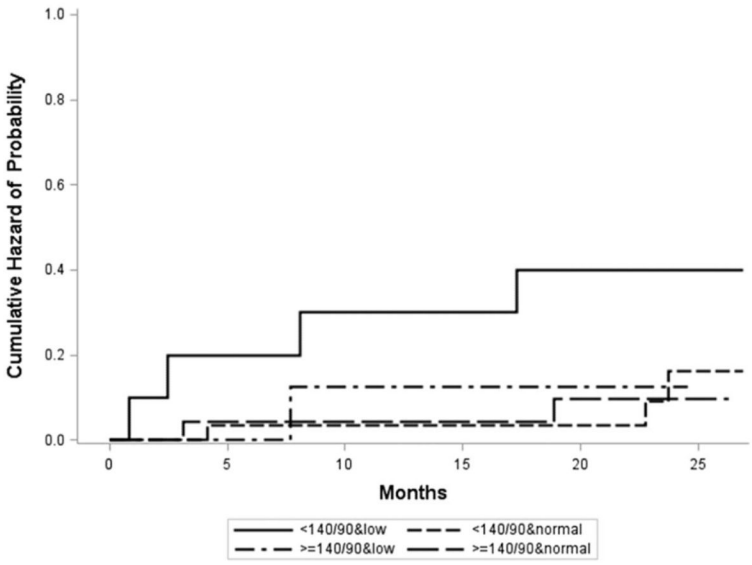


**Figure 2.**
Cumulative probability of vertebrobasilar territory stroke

## Table 1

### Patient Characteristics

| | All | ≥140/90 (n=33) | <140/90 (n=39) | P value |
|---|---|---|---|---|
| **Age, mean (SD), years** | 65.6(10.3) | 66.9(11.6) | 64.4 (9.0) | .30 |
| **Gender, n (%)** | | | | |
| Male | 40(56) | 19(58) | 21(54) | .75 |
| Female | 32(44) | 14(42) | 18(46) | |
| **Race, n (%)** | | | | |
| Black | 18(25) | 10(30) | 8(20) | .08 |
| Caucasian | 49(68) | 23(70) | 26(67) | |
| Other | 5(7) | 0(0) | 5(13) | |
| **Ethnicity, n (%)** | | | | |
| Hispanic or Latino | 8(11) | 4(12) | 4(10) | .99 |
| Not Hispanic or Latino | 64(89) | 29(88) | 35(90) | |
| **Qualifying event, n (%)** | | | | |
| Stroke | 52(72) | 24(73) | 28(72) | .64 |
| TIA | 20(28) | 9(27) | 11(28) | |
| **Days from qualifying event to enrollment, mean (SD)** | 38(53) | 20(61) | 18(46) | .22 |
| **Vascular risk factors, n (%)** | | | | |
| Hypertension | 67(93) | 32(97) | 35(90) | .37 |
| Diabetes Mellitus | 23(32) | 8(24) | 15(38) | .26 |
| Hyperlipidemia | 58(81) | 23(70) | 35(90) | .04 |
| Coronary artery disease | 16(22) | 6(18) | 10(26) | .45 |
| Chronic renal insufficiency/failure | 2(3) | 2(6) | 0(0) | .21 |
| Smoking (%) | | | | |
| Never | 31(43) | 16(48) | 15(38) | .56 |
| Former | 17(24) | 6(18) | 11(28) | |
| Current | 24(33) | 11(33) | 13(33) | |
| Alcohol | | | | |
| None | 44(61) | 19(58) | 25(64) | .54 |
| < 1 drink/day | 24(33) | 11(33) | 13(33) | |
| ≥ 1 drink/day | 4(6) | 3(9) | 1(3) | |
| BMI | | | | |
| Normal | 13(18) | 4(12) | 9(23) | .52 |
| Overweight | 33(46) | 16(48) | 17(44) | |
| Class(1-3) | 26(36) | 13(39) | 13(33) | |
| Physical activity | 24(33) | 11(33) | 13(33) | .99 |
| **Angiographic disease severity. n (%)** | | | | |
| Severe stenosis/occlusion (≥70%) | 56(78) | 25(76) | 31(79) | .70 |
| Stenosis location, extracranial only | 7(10) | 3(9) | 4(10) | .99 |
| **Flow status, n (%)** | | | | |

| | All | ≥140/90 (n=33) | <140/90 (n=39) | P value |
|---|---|---|---|---|
| Low flow | 18(25) | 8(24) | 10(26) | .89 |
| Normal flow | 54(75) | 25(76) | 29(74) | |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared): TIA, transient ischemic attack.

## Table 2

**Stroke event rates by blood pressure and flow status**

| Flow status and blood pressure status | n | No. Stroke events | Total PY of follow-up | Stroke event rate/100 PY | 95% CI |
|---|---|---|---|---|---|
| Normal flow status BP ≥140/90 | 25 | 2 | 41.64 | 4.80 | 1.20, 19.21 |
| Normal flow status BP<140/90 | 29 | 3 | 50.27 | 5.97 | 1.92, 18.51 |
| Low flow status BP ≥140/90 | 8 | 1 | 10.75 | 9.30 | 1.31, 66.01 |
| Low flow status BP<140/90 | 10 | 4 | 14.75 | 27.11 | 10.17, 72.23 |

Abbreviations: PY, person year