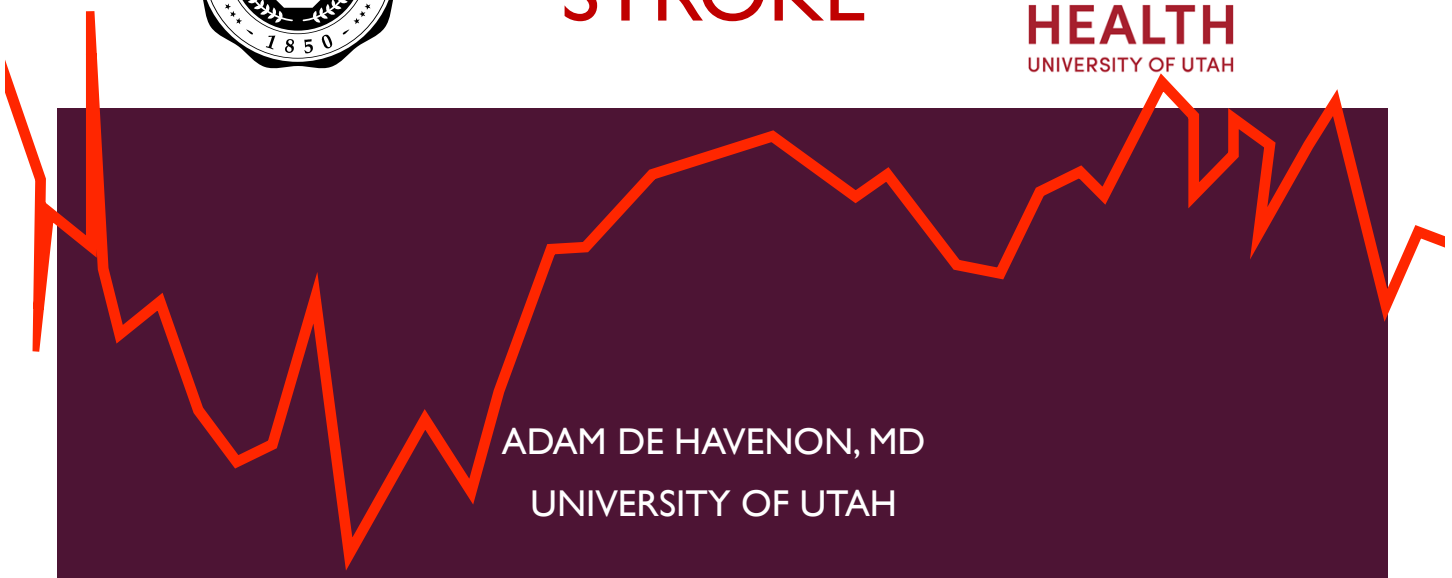
BLOOD PRESSURE VARIABILITY AND STROKE



ADAM DE HAVENON, MD

UNIVERSITY OF UTAH

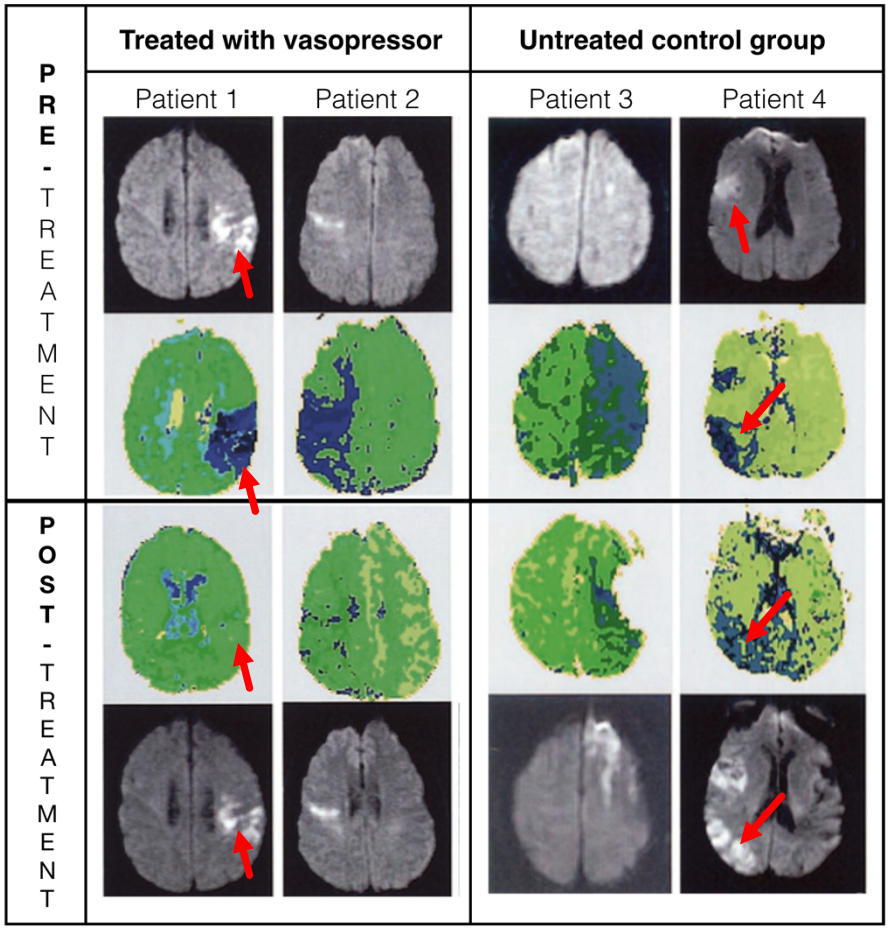
OBJECTIVES

- Why blood pressure variability (**BPV**)?
- Measurement of BPV
- Association with outcome after stroke
- Association with incident or recurrent stroke
- Mechanisms and etiology of BPV
- Treatment to reduce BPV

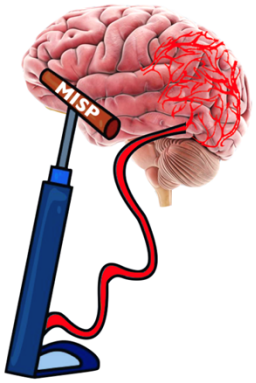
THIS ALL STARTED WITH INDUCED HYPERTENSION

- Induced hypertension is thought to improve collateral flow and, thus, cerebral blood flow
- Rats, rabbits, gerbils, and monkeys subjected to middle cerebral artery occlusion + induced hypertension
  - Results were positive, with smaller infarct sizes, better survival, and less neurologic injury
- Case reports and series in humans suggested similar benefit

Rordorf et al. *Stroke*. 1997;28(11):2133–2138.



Hillis AE, et al. *Neuroradiology* 2004;46(1):31–9.



We have given you this booklet because the neurologist taking care of you thinks you may be a good candidate for MISP. A member of the study team is available to answer any questions you may have about the study or what participation means for you personally.

We cannot guarantee you any personal benefit from your participation in this study. However, the information from this study will help us learn the best way to treat strokes in other people like you.

If you choose not to participate, your doctor will still work toward providing you with the best medical care to suit your needs.

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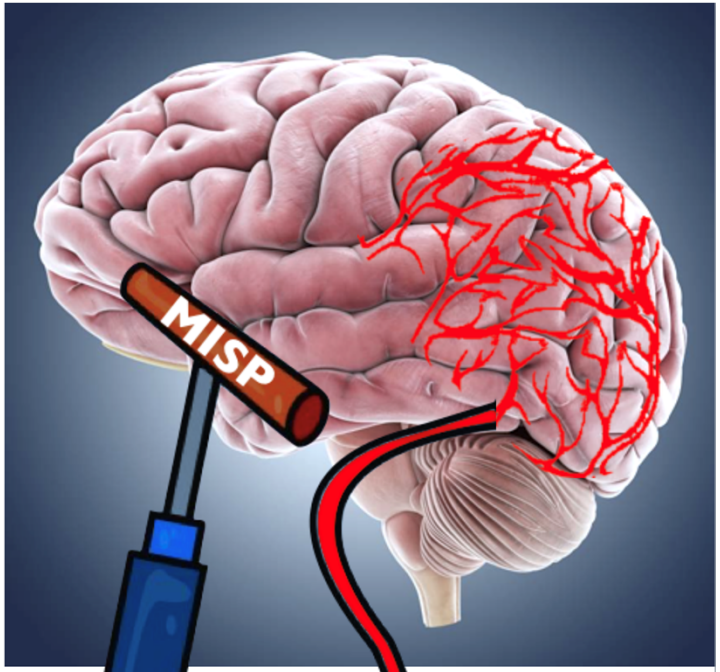
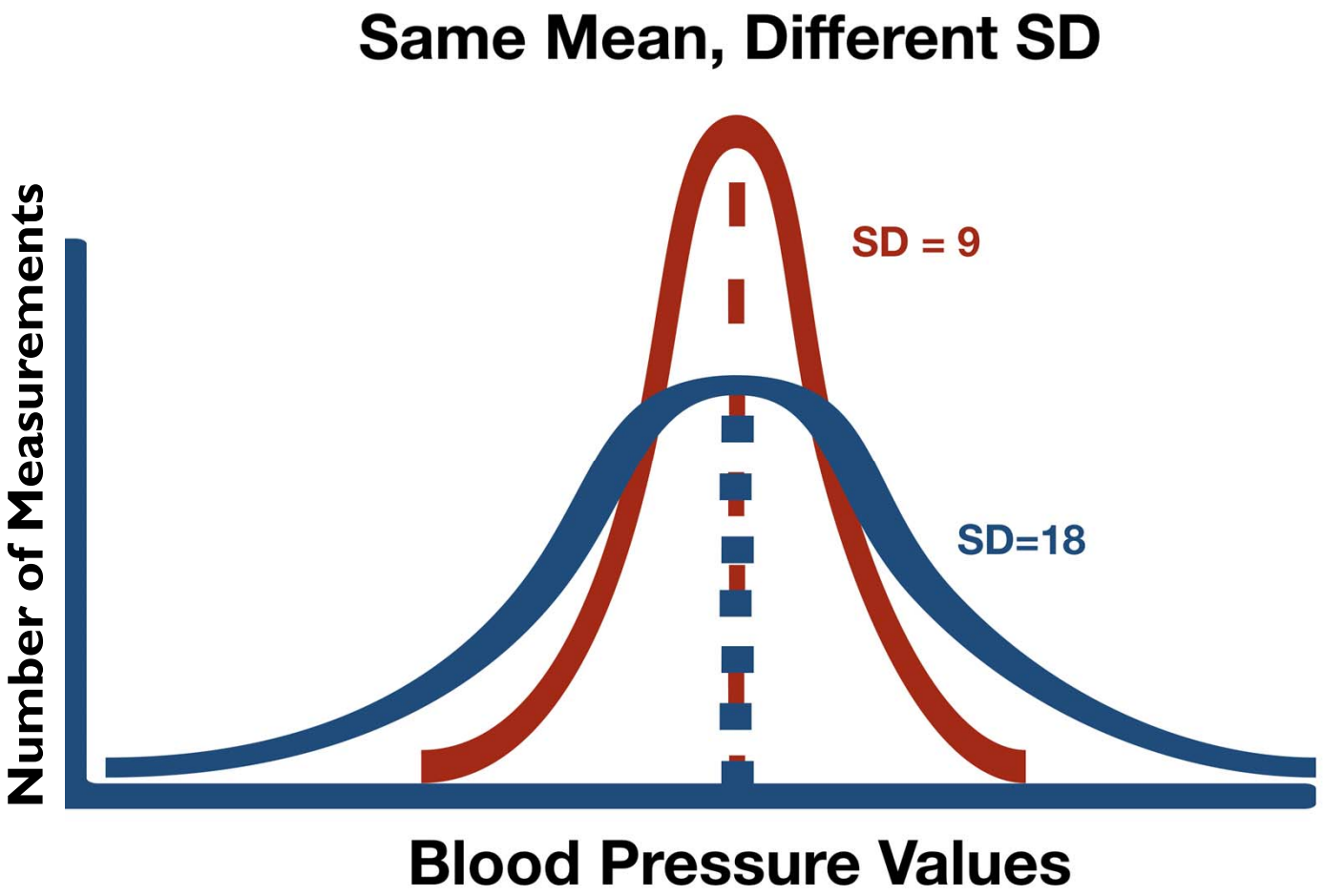


MISP

Midodrine for Ischemic Stroke with Penumbra

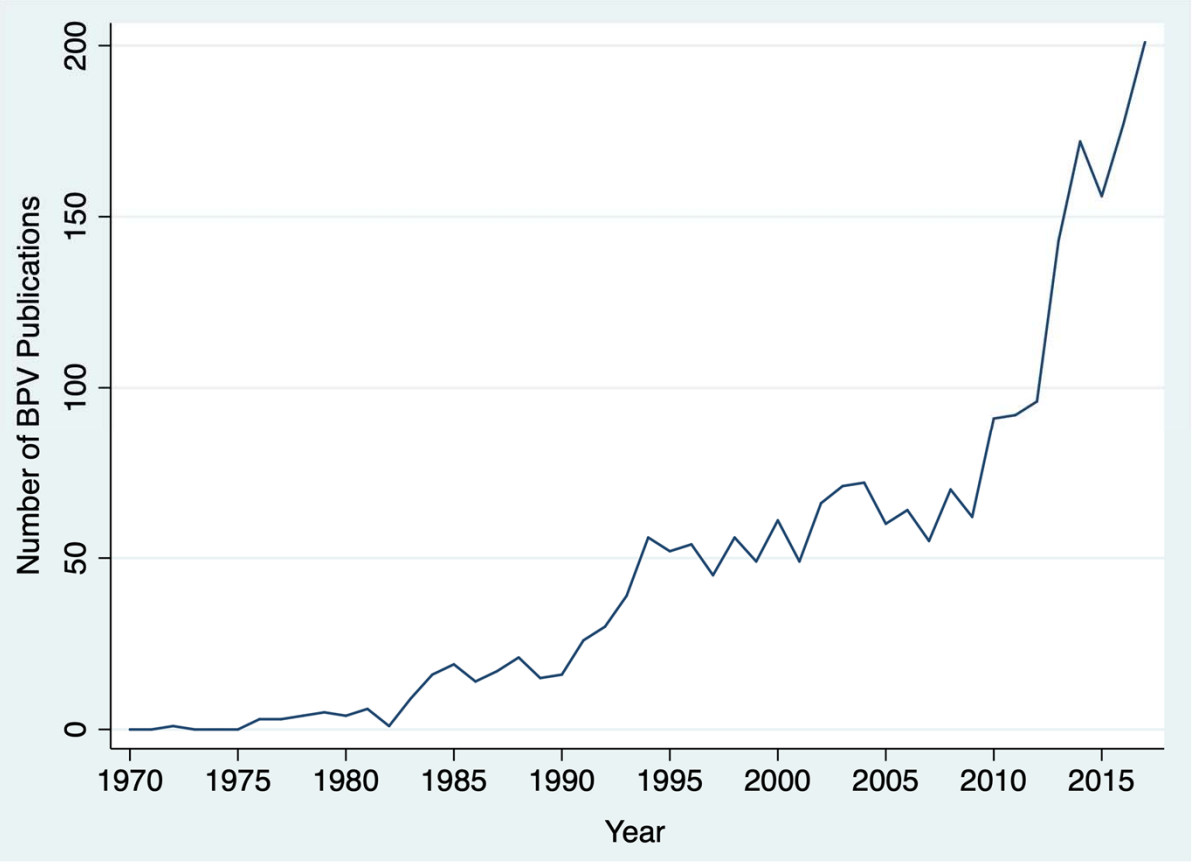

Same Mean, Different SD
SD = 9
SD=18
Number of Measurements
Blood Pressure Values

PRIOR BPV RESEARCH

- Increased blood pressure variability (BPV) after acute ischemic stroke (AIS) and intracranial hemorrhage (ICH) has been associated with:
  - Worse clinical outcome
  - Death
  - Failure to respond to therapeutic interventions

Endo K, Kario K, Koga M, et al. *Stroke*. 2013;44(3):816-818.
Manning L, et al. *The Lancet Neurology*. 2014;13:364–373.
de Havenon A, et al. *Stroke*. 2018;49:1981–1984.

PUBLICATIONS ABOUT BPV ARE INCREASING EVERY YEAR



BPV IS INCREASED AFTER STROKE

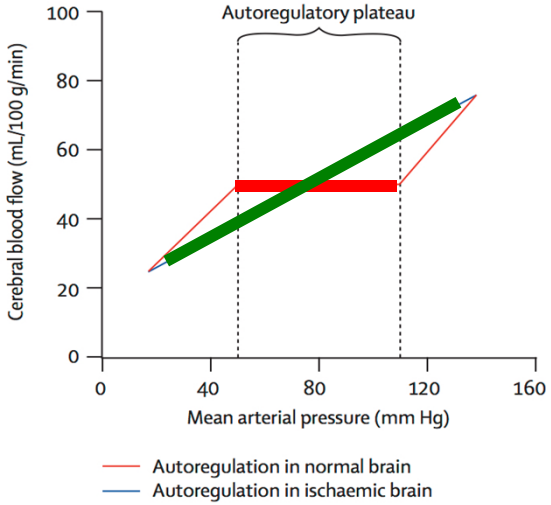
- In healthy patients there is a spectrum of BPV
  - Dependent on mechanisms ranging from the normal diurnal variation, medications, comorbid disease processes and behavioral or humoral factors.
- After stroke, both blood pressure and BPV increases for reasons that are not fully understood

	Patients with stroke (n=32)	**Healthy controls (n=15)**
SBP SD (mean±SD)	9.5±4.8	6.4±2.6

Wong KH, de Havenon A, ISC 2018, Poster Presentation.

PATHOPHYSIOLOGY: TARGETED DAMAGE

- Following AIS and ICH, the cerebrovasculature loses its ability to autoregulate
- Thus, high BPV can have **direct effects on the still viable penumbral tissue** surrounding the stroke core
- But we don't know specifically why BPV would harm the brain

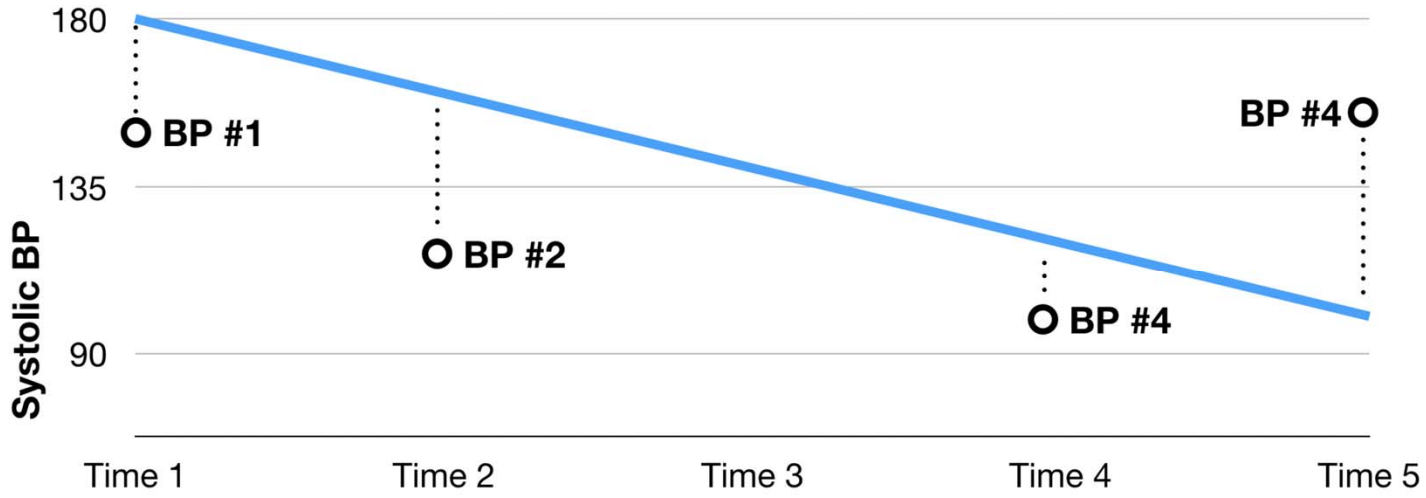


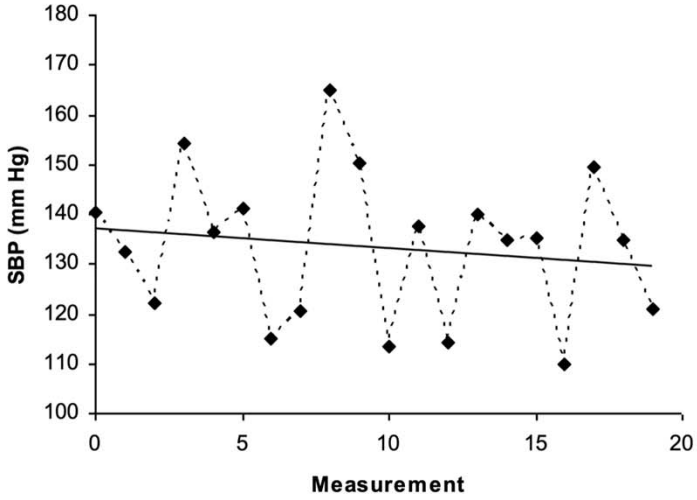
Tikhonoff V. Lancet Neurol. 2009 Oct;8(10):938–48.

PROBLEMS WITH PRIOR BPV RESEARCH

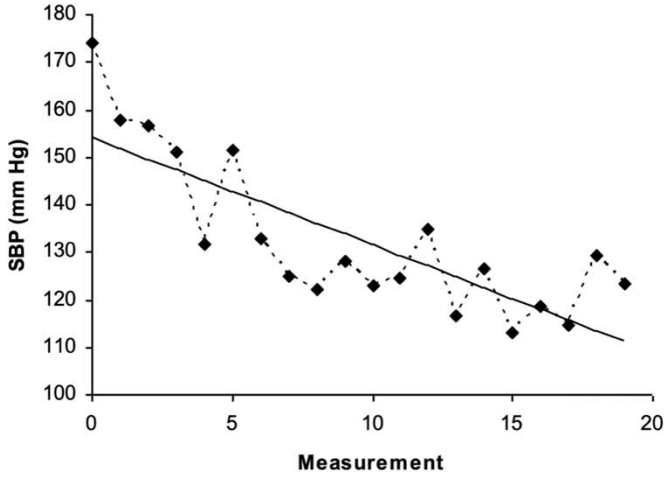
- Almost all studies have been retrospective
- Small total number of blood pressure readings
- Diverse stroke phenotypes
- Neurologic outcome and confounders not well adjudicated
- Appropriate statistical methodologies not routinely employed
- As a result, the association of elevated BPV and worse outcome after stroke is not widely accepted as causal

SO HOW DO YOU MEASURE VARIABILITY?





SD = 15.0 ARV = 19.6
rSD = 15.2 SV = 23.2



SD = 16.1 ARV = 9.9
rSD = 10.3 SV = 11.7

n.neurology.org/highwire/filestream/132069/field_highwire.../1/Appendix_e-2.doc

FIRST STUDY OF 215 STROKE PATIENTS

Research Article

Increased Blood Pressure Variability Is Associated with Worse Neurologic Outcome in Acute Anterior Circulation Ischemic Stroke

Adam de Havenon,[1] Alicia Bennett,[1] Gregory J. Stoddard,[2] Gordon Smith,[1] Haimei Wang,[1] Jana Wold,[1] Lee Chung,[1] David L. Tirschwell,[3] and Jennifer J. Majersik[1]

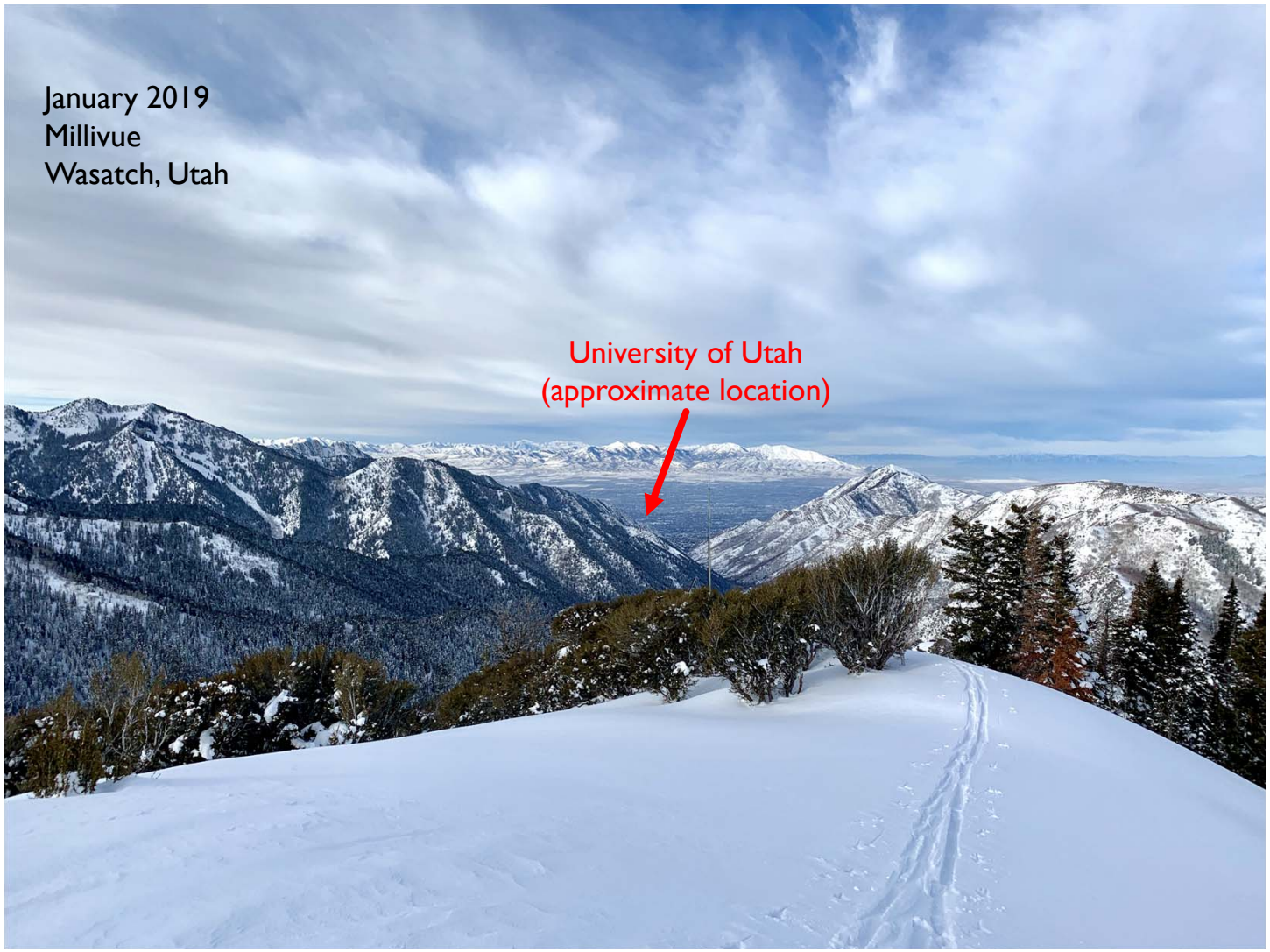
[1]*Department of Neurology, University of Utah, Salt Lake City, UT, USA*
[2]*Department of Internal Medicine, University of Utah, Salt Lake City, UT, USA*
[3]*Department of Neurology, University of Washington, Seattle, WA, USA*

Ordinal logistic regression models with predictor variables of systolic BPV and mean SBP fitted to the outcomes of a one point shift in mRS at follow-up

Variable	OR for 1 point mRS shift	95% CI	p value	Adjusted OR for 1 point mRS shift*	95% CI	p value
0-24 Hours (n=215)						
SBP CV	2.32	1.35-4.00	0.002	2.06	1.09-3.92	0.03
SBP SD	1.99	1.34-2.96	0.001	1.61	1.02-2.55	0.04
SBP SV	1.83	1.32-2.54	<0.001	1.83	1.22-2.74	0.01
Mean SBP	1.02	1.00-1.03	0.02	1.00	0.99-1.02	1.00
0-72 Hours (n=202)						
SBP CV	3.38	1.73-6.59	<0.001	2.32	1.03-5.21	0.04
SBP SD	2.56	1.55-4.23	<0.001	1.70	0.95-3.04	0.08
SBP SV	2.45	1.48-4.07	0.001	2.18	1.20-3.96	0.01
Mean SBP	1.01	1.00-1.03	0.08	1.00	0.99-1.02	0.72
0-120 Hours (n=186)						
SBP CV	4.33	1.94-9.69	<0.001	3.16	1.25-7.94	0.02
SBP SD	3.07	1.72-5.49	<0.001	1.98	1.05-3.74	0.04
SBP SV	2.88	1.57-5.29	0.001	2.32	1.20-4.49	0.01
Mean SBP	1.01	0.99-1.02	0.20	1.00	0.98-1.02	0.96

* Adjusted for admission NIHSS, patient age, history of atrial fibrillation, history of diabetes mellitus, endovascular therapy, IV tPA administration, and premorbid mRS

de Havenon A, et al. *Stroke Research and Treatment*. 2016.


January 2019
Millivue
Wasatch, Utah
University of Utah
(approximate location)

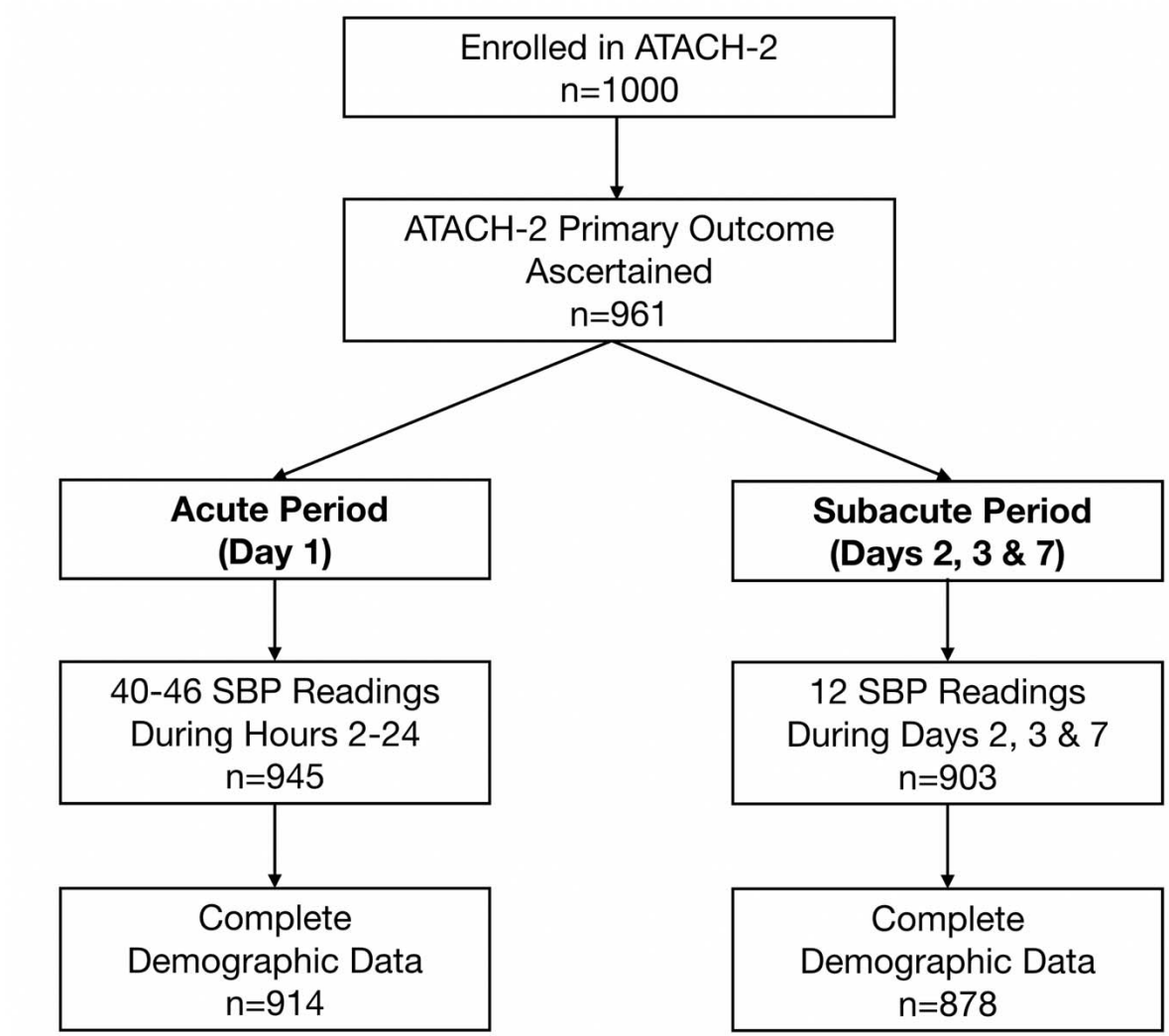
Increased Blood Pressure Variability Contributes to Worse Outcome After Intracerebral Hemorrhage

An Analysis of ATACH-2

Adam de Havenon, MD; Jennifer J. Majersik, MD, MS; Gregory Stoddard, MPH, MBA; Ka-Ho Wong, BS; J. Scott McNally, MD, PhD; A. Gordon Smith, MD; Natalia S. Rost, MD, MPH; David L. Tirschwell, MD, MSc

Conclusions—In this secondary analysis of ATACH-2, we show that increased systolic BPV is associated with worse long-term neurological outcome. Additional research is needed to find techniques that allow early identification of patients with an expected elevation of BPV and to study pharmacological or protocol-based approaches to minimize BPV. **(*Stroke*. 2018;49:1981-1984. DOI: 10.1161/STROKEAHA.118.022133.)**

de Havenon A. *Stroke*. 2018;49:1981–1984.


Enrolled in ATACH-2
n=1000
ATACH-2 Primary Outcome
Ascertained
n=961
Acute Period
(Day 1)
Subacute Period
(Days 2, 3 & 7)
40-46 SBP Readings
During Hours 2-24
n=945
12 SBP Readings
During Days 2, 3 & 7
n=903
Complete
Demographic Data
n=914
Complete
Demographic Data
n=878

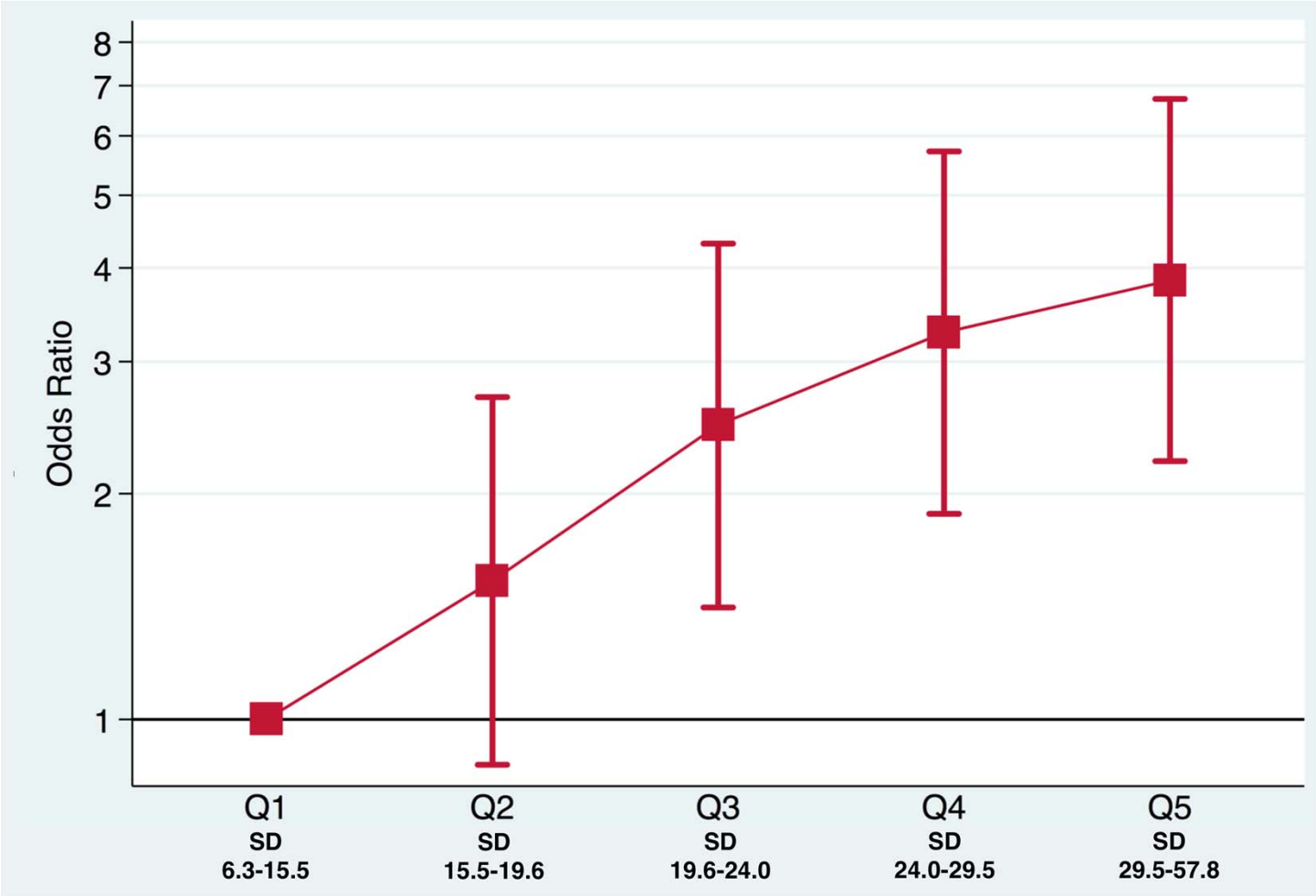
Odds ratio of an unfavorable neurological outcome (mRS 4-6).

	Unadjusted Model		Adjusted Model*	
	OR (95% CI)	p value	OR (95% CI)	p value
Acute Period				
Mean	1.11 (1.01, 1.22)	0.035	1.49 (1.25, 1.78)	<0.001
SD	1.72 (1.30, 2.26)	<0.001	1.74 (1.30, 2.32)	<0.001
CV	2.03 (1.37, 3.02)	<0.001	1.91 (1.28, 2.85)	0.001
ARV	1.37 (1.11, 1.69)	0.004	1.33 (1.07, 1.65)	0.011
SV	1.38 (1.15, 1.65)	0.003	1.34 (1.11, 1.61)	0.002
RSD	1.65 (1.24, 2.19)	0.001	1.65 (1.24, 2.19)	0.001
Subacute Period				
Mean	1.05 (0.93, 1.19)	0.402	1.11 (0.98, 1.27)	0.116
SD	1.92 (1.60, 2.30)	<0.001	1.83 (1.52, 2.20)	<0.001
CV	2.49 (1.91, 3.24)	<0.001	2.28 (1.75, 2.99)	<0.001
ARV	1.58 (1.39, 1.81)	<0.001	1.54 (1.35, 1.76)	<0.001
SV	1.48 (1.32, 1.66)	<0.001	1.45 (1.29, 1.62)	<0.001

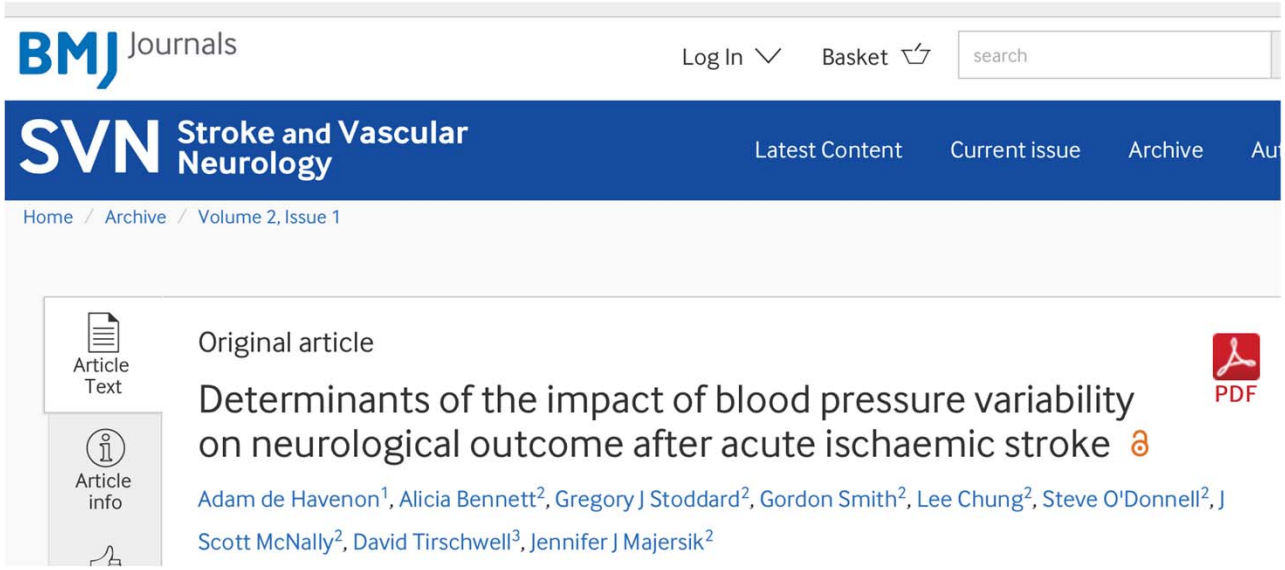
*Adjusted for patient age, sex, and treatment arm.


December 2018
Meadows Chutes
Wasatch, Utah

Odds ratio for poor outcome (mRS 4-6) in quintiles of increasing BPV



DETERMINANTS OF BPV'S EFFECT



de Havenon A, et al. *Stroke Vasc Neurol*. 2017;2:1–6.

Odds ratios for a one point shift in mRS at follow-up

BPV Indice	OR*	95% CI	p value	BPV Indice	OR*	95% CI	p value
Proximal Vessel Occlusion (n=58)				**No Proximal Occlusion (n=52)**			
SBP SD	5.38	1.44-20.2	0.013	SBP SD	1.63	0.53-5.03	0.398
SBP SV	3.47	1.05-11.4	0.041	SBP SV	3.55	0.91-13.8	0.068
Good Collaterals (n=60)				**Bad Collaterals (n=50)**			
SBP SD	5.78	1.23-27.2	0.027	SBP SD	1.85	0.60-5.74	0.289
SBP SV	3.82	1.15-12.7	0.029	SBP SV	2.09	0.58-7.47	0.258
Higher Lesion Core Volume (n=55) (mean±SD = 72.7±39.2 mL)				**Lower Lesion Core Volume (n=55) (mean±SD = 15.1±10.3 mL)**			
SBP SD	9.27	2.36-36.3	0.001	SBP SD	0.74	0.21-2.63	0.643
SBP SV	18.9	3.69-97.1	<0.001	SBP SV	1.27	0.44-3.66	0.664
Higher Hypoperfused Volume (n=55) (mean±SD = 121.3±44.9 mL)				**Lower Hypoperfused Volume (n=55) (mean±SD = 30.5±17.6 mL)**			
SBP SD	5.41	1.24-23.6	0.025	SBP SD	0.85	0.23-3.10	0.804
SBP SV	4.09	0.99-16.9	0.052	SBP SV	1.63	0.52-5.08	0.402

* Adjusted for admission NIHSS, patient sex, tPA administration, symptomatic intracranial hemorrhage, and admission glucose value.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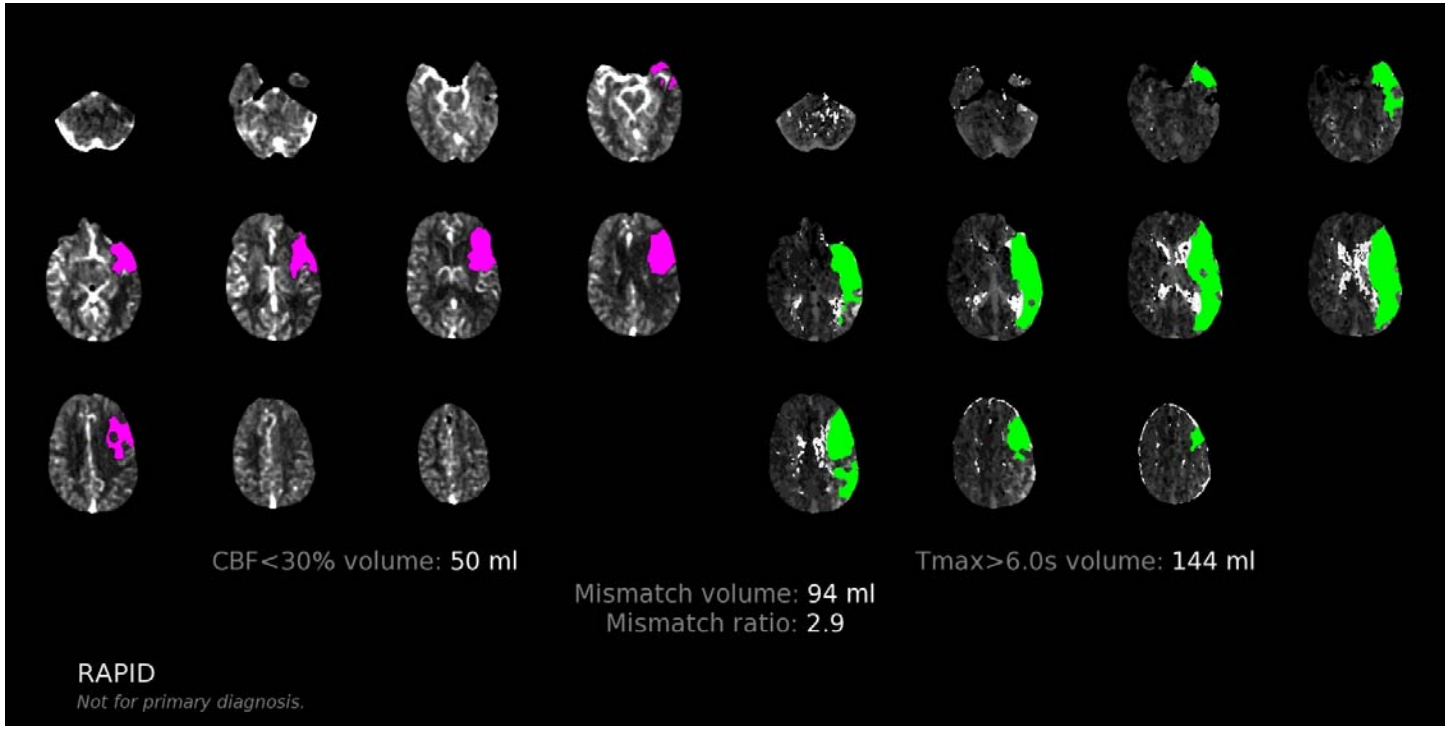
Silver Spoon
Wasatch, Utah

Mismatch Like This:



EXPANDING TO POST-THROMBECTOMY

Ischemic stroke

ORIGINAL RESEARCH

Increased blood pressure variability after endovascular thrombectomy for acute stroke is associated with worse clinical outcome

Alicia E Bennett,[1] Michael J Wilder,[2] J Scott McNally,[3] Jana J Wold,[4] Gregory J Stoddard,[4] Jennifer J Majersik,[4] Safdar Ansari,[4] Adam de Havenon[5]

Bennett AE… de Havenon A. *J Neurointerv Surg*. 2018 Jan 19.

Odds Ratio for a One-Point Increase in Modified Rankin Score Comparing Those with Sufficient vs. Insufficient Recanalization.

Sufficient Recanalization (TICI 2b-3), n=100				Insufficient Recanalization (TICI 0-2a), n=82			
BPV Indice	Adjusted OR*	95% CI	p value	BPV Indice	Adjusted OR*	95% CI	p value
0-24 Hours (n=182)							
SBP SD	1.66	0.81-3.41	0.166	SBP SD	2.56	1.04-6.26	0.040
SBP SV	1.70	0.83-3.48	0.147	SBP SV	5.86	1.82-18.85	0.003
0-72 Hours (n=163)							
SBP SD	1.28	0.58-2.81	0.536	SBP SD	2.89	1.04-8.05	0.042
SBP SV	1.64	0.72-3.77	0.240	SBP SV	6.34	1.58-25.35	0.009

* Adjusted for admission NIHSS, patient age, admission glucose and BUN, tPA administration, prior stroke, symptomatic ICH, and premorbid mRS

Bennett AE… de Havenon A. *J Neurointerv Surg*. 2018 Jan 19.

December 2018
Maybird Headwall
Wasatch, Utah

WHAT ABOUT LONGITUDINAL STROKE RISK?

- We recently found that increased visit-to-visit BPV correlated with risk of stroke in:
  - Secondary Prevention of Small Subcortical Strokes (**SPS3**)
  - The Atherosclerosis Risk in Communities Study (**ARIC**)
- We also found that BPV in the 24 hours after ischemic stroke onset correlated with death in 1,891 patients in the Virtual International Stroke Trials Archive (**VISTA**) cohort
- Unfortunately, all those results are embargoed until the International Stroke Conference in 2019

PRoFESS TRIAL SECONDARY ANALYSIS

- We were interested in visit-to-visit BPV and the risk of recurrent stroke
- We obtained the data from the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial
- The study exposure was BPV during the first year of PRoFESS
- The outcome was ischemic or hemorrhagic stroke or cardiovascular death during the remainder of the trial
- The final cohort included 16, 916 patients

Association of systolic BPV with stroke outcomes in 16,916 PRoFESS patients

	Recurrent Stroke (events = 753)		Ischemic stroke (events = 654)		Hemorrhagic stoke (events = 70)	
BPV Variable, 10 unit change	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**P Value**
Systolic Mean	1.01 (0.97, 1.05)	0.69	1.00 (0.95, 1.05)	0.98	1.09 (0.95, 1.26)	0.23
Systolic SD	1.14 (1.01, 1.28)	0.03	1.16 (1.02, 1.31)	0.02	1.03 (0.69, 1.54)	0.87
Systolic ARV	1.10 (1.00, 1.20)	0.05	1.13 (1.02, 1.24)	0.01	0.95 (0.69, 1.31)	0.75
Systolic SV	1.10 (1.02, 1.19)	0.02	1.12 (1.03, 1.22)	0.008	0.99 (0.75, 1.31)	0.94
Systolic rSD	1.26 (1.11, 1.42)	<.001	1.31 (1.15, 1.49)	<.001	0.91 (0.58, 1.41)	0.66
Systolic VIM	1.13 (1.00, 1.27)	0.05	1.15 (1.01, 1.31)	0.03	1.01 (0.67, 1.52)	0.95

**All outcomes (control for competing risk of all cause mortality. Adjusted for patient age, sex, race, smoking, TOAST classification of index stroke, and diabetes. Coefficients represent a 10 point change in blood pressure variability.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Football Field
Wasatch, Utah

Association of systolic BPV with death outcomes in 16,916 PRoFESS patients

	Death from cardiovascular causes or recurrent stroke (events = 1,220)		Death from other causes (events = 771)	
BPV Variable, 10 unit change	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**P Value**
Systolic Mean	1.02 (0.98, 1.05)	0.28	0.99 (0.95, 1.03)	0.66
Systolic SD	1.15 (1.05, 1.26)	0.002	1.22 (1.09, 1.36)	<.001
Systolic ARV	1.11 (1.03, 1.19)	0.004	1.13 (1.04, 1.24)	0.005
Systolic SV	1.11 (1.04, 1.18)	0.002	1.13 (1.05, 1.22)	0.002
Systolic rSD	1.17 (1.06, 1.29)	0.002	0.99 (0.87, 1.13)	0.89
Systolic VIM	1.15 (1.04, 1.26)	0.004	1.22 (1.09, 1.37)	<.001

**Adjusted for patient age, sex, race, smoking, TOAST classification of index stroke, and diabetes. Coefficients represent a 10 point change in blood pressure variability.


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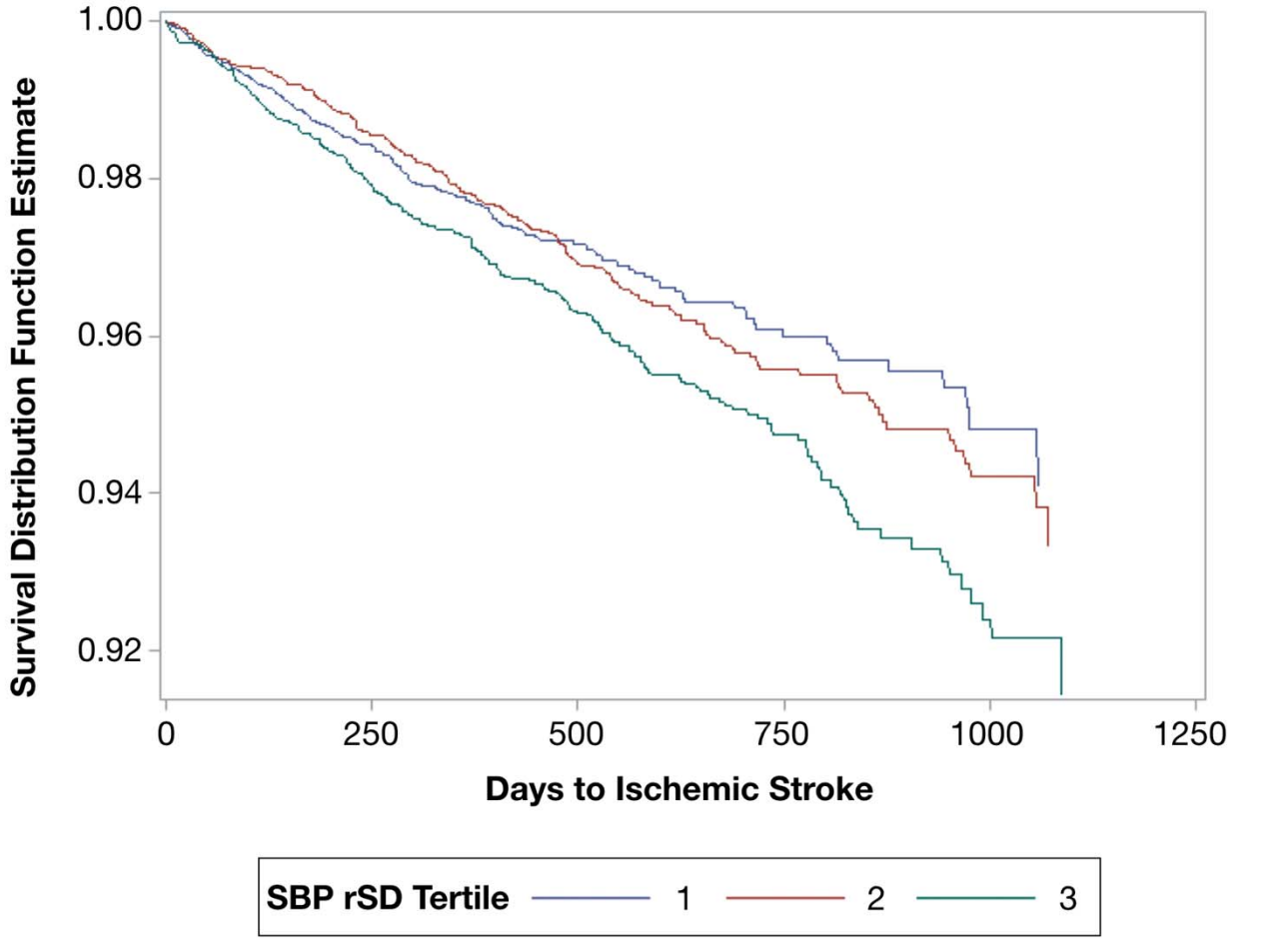
Wasatch, Utah

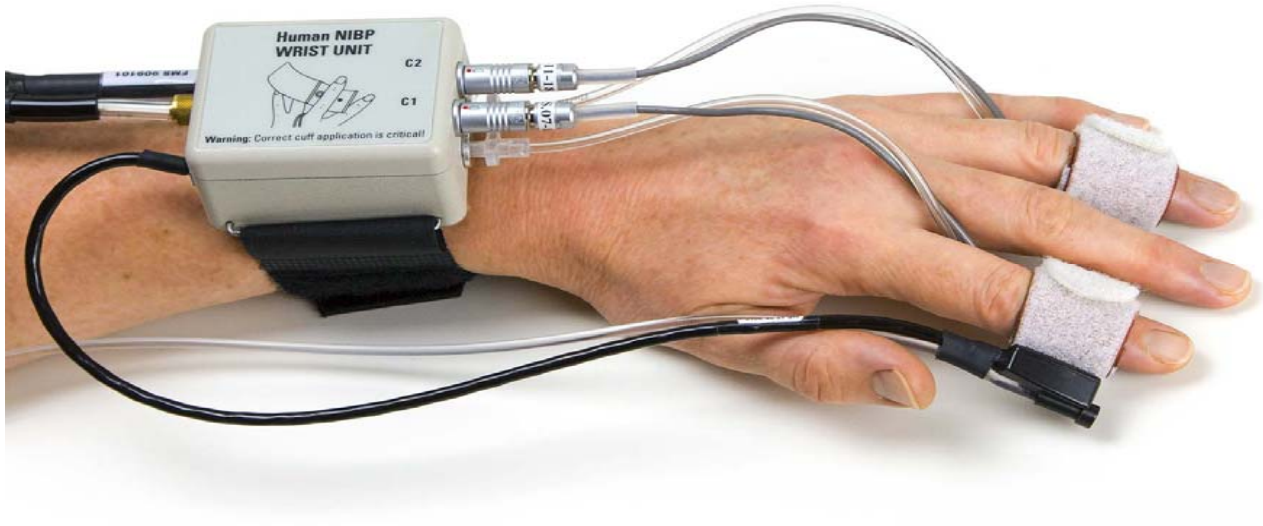

1.00
0.98
0.96
0.94
0.92
Survival Distribution Function Estimate
0
250
500
750
1000
1250
Days to Ischemic Stroke
SBP rSD Tertile
1
2
3

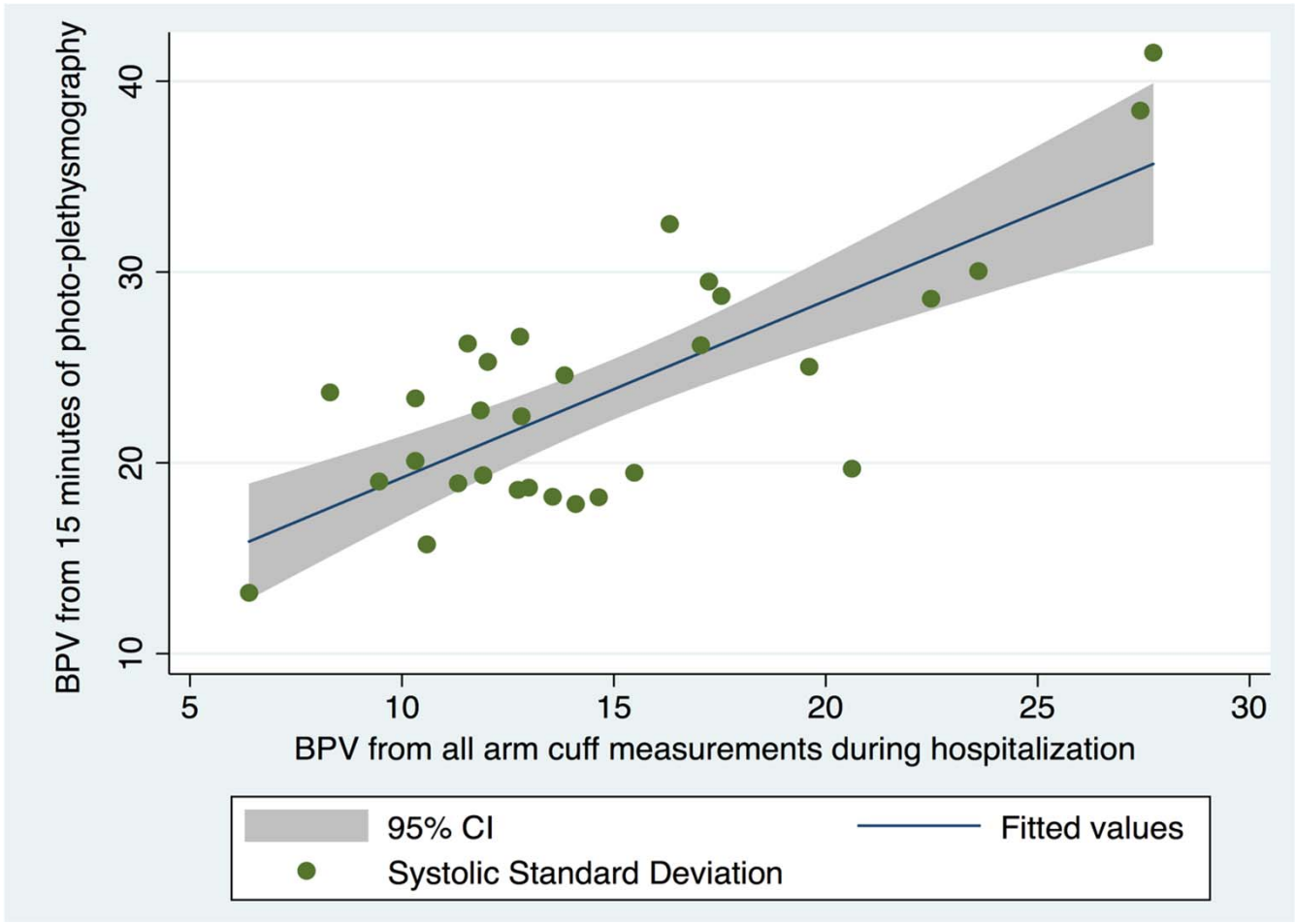
NEXT STEPS

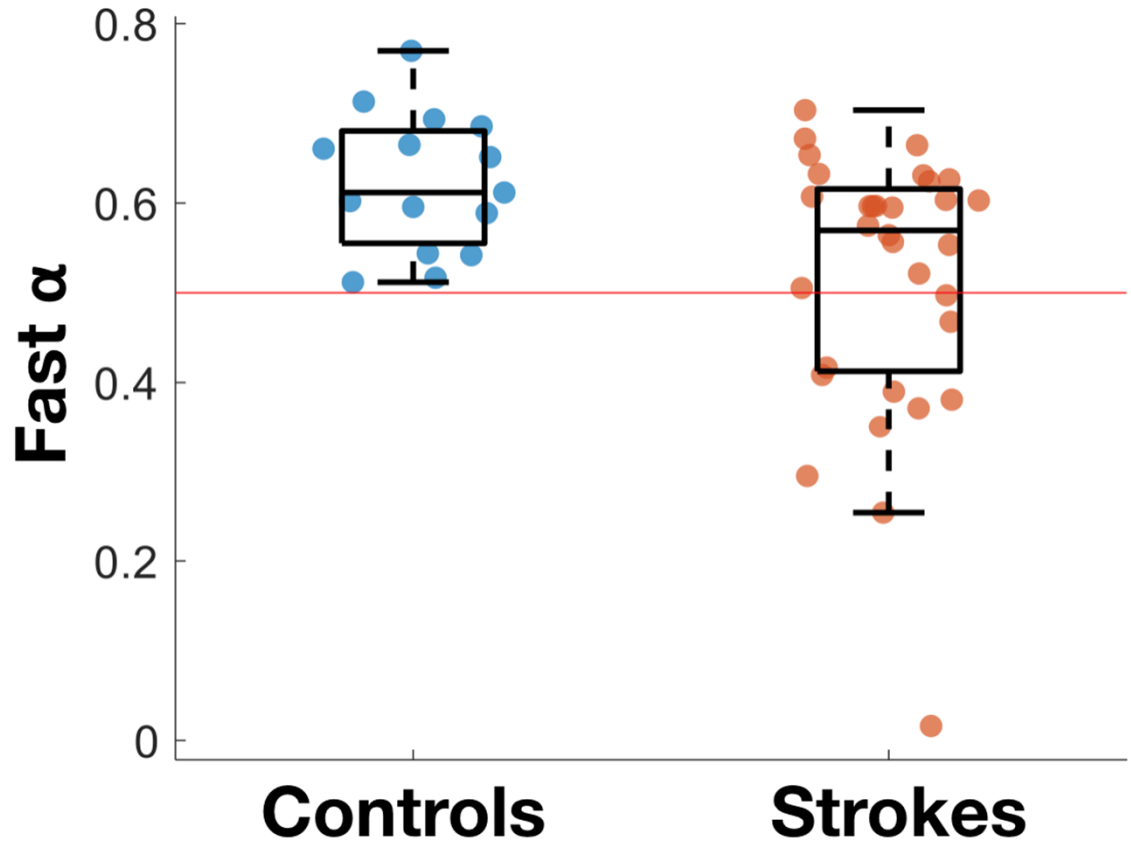
- Prior BPV research in stroke patients has relied on retrospective datasets or is limited by suboptimal methodology
- As a result, the association of elevated BPV and worse outcome after stroke is not widely accepted as causal
- Additional challenges include:
  - How to identify patients who WILL have elevated BPV
  - How to reduce BPV in acute stroke patients

IDENTIFYING AT-RISK PATIENTS

- Accurate measurement of BPV requires multiple measurements of BP



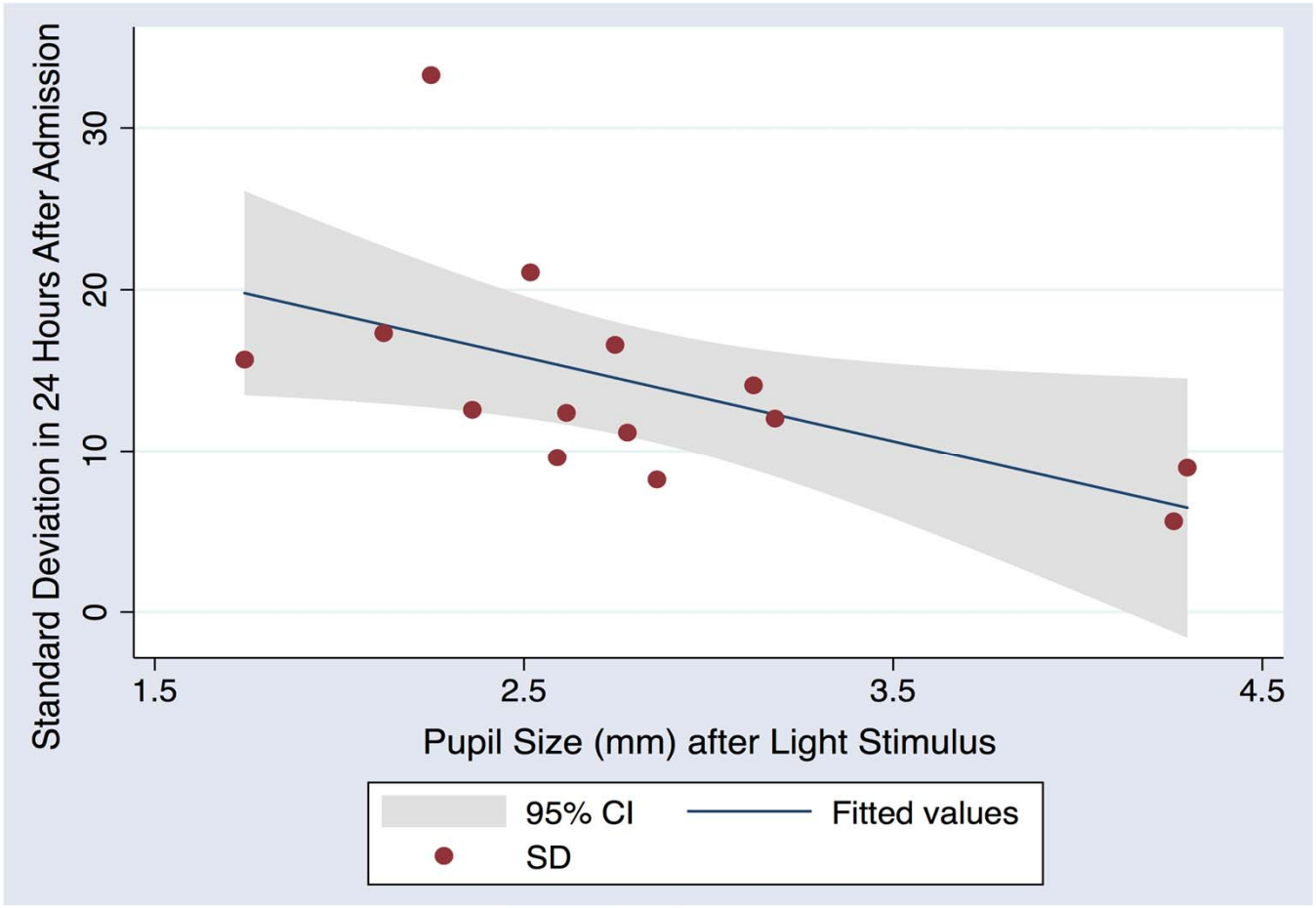

BPV from 15 minutes of photo-plethysmography
10
20
30
40
5
10
15
20
25
30
BPV from all arm cuff measurements during hospitalization
95% CI
Fitted values
Systolic Standard Deviation


0.8
0.6
0.4
0.2
0
Fast α
Controls
Strokes

MECHANISTIC UNDERSTANDING OF BPV AFTER STROKE

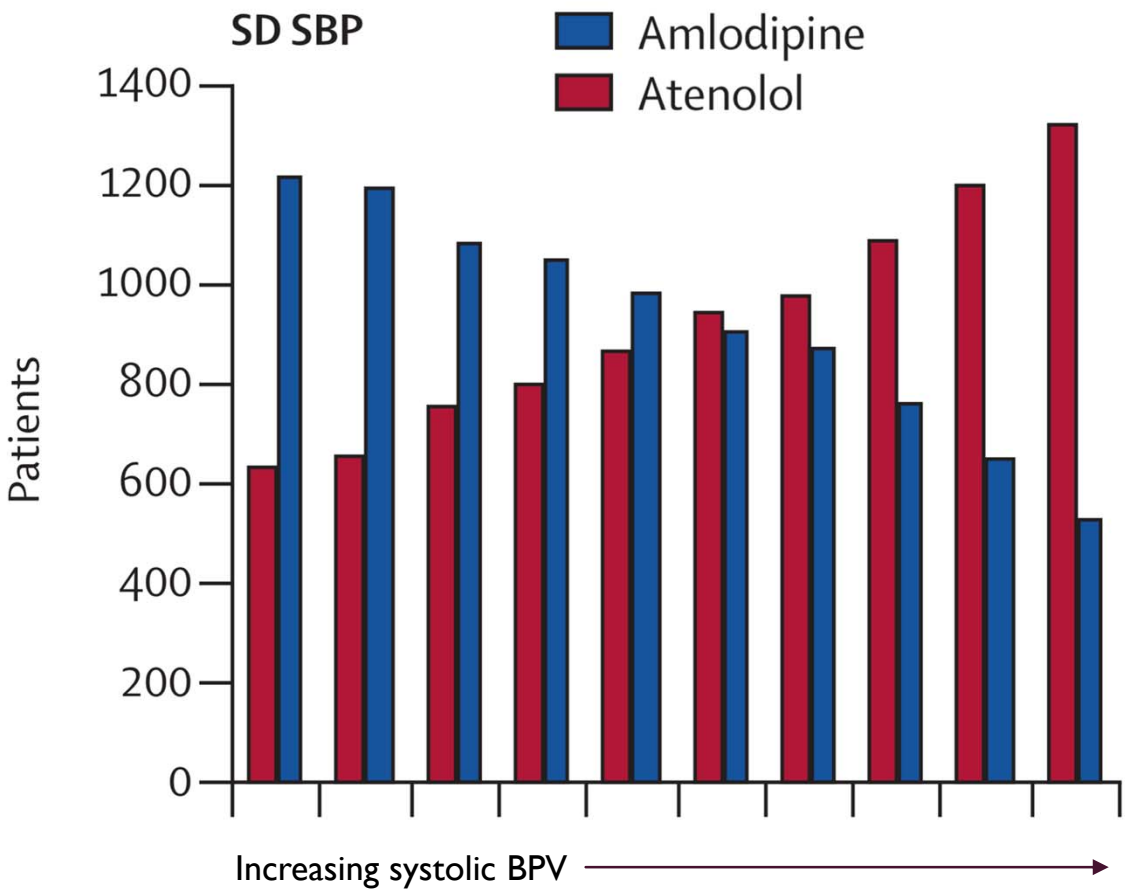
- Theories are speculative
  - Autonomic dysfunction
  - Disturbed cerebral autoregulation
  - Damage or compression of brain regions that regulate blood pressure
  - Neuroendocrine disturbance
  - Nonspecific mechanisms such as headache, urine retention, infection, and psychological stress.
- Improved understanding of the underlying pathophysiology is important for future trials of targeted treatment

Rothwell PM. *The Lancet.* 2015;385:582–585.



Blackman JA, et al. *Arch Neurol* 2004;61:321–8

Rothwell PM, et al. *The Lancet.* 2010;375:895–905.



FUTURE DIRECTIONS

- Prospectively correlate multiple statistical representations of BPV with modified Rankin Scale at 90 days from stroke onset, after adjustment for baseline NIH stroke scale, stroke location/volume, age, sex, and stroke interventions
- Collect quantitative pupillary light reflexes to co-localize the physiologic dysfunction that causes elevated BPV after stroke
- Validate finger photoplethysmography, a non-invasive and safe continuous blood pressure measurement tool, to identify future risk of elevated BPV
- Conduct a protocol-based intervention to reduce BPV with a rapidly titratable medication.

UTAH'S WASATCH AVERAGES OVER 500 INCHES OF SNOW A YEAR!

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