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Mean Arterial Pressure in Acute Ischemic Stroke Study

Abstract

Background. There is little, if any, evidence available on the validation of blood pressure (BP) measurements obtained in the acute care setting. Despite this, acute stroke practitioners trust and rely on non-invasive blood pressure (NIBP) devices to guide acute ischemic stroke (AIS) patients' treatment. Although systolic blood pressure (SBP) has been found to be the most unreliable measurement displayed on NIBP devices, treatment decisions for AIS are based on them. Today, 25 years after the FDA's approval of alteplase, practitioners continue to use BP parameters of 185/110 and 180/105 to guide the initiation of alteplase bolus and infusion, although the shift to the use of NIBP devices challenges the validity of these dated parameters. Theoretically, by inserting the inclusion and exclusion systolic and diastolic blood pressure thresholds into the mean arterial pressure (MAP) equation, one could deduce the exclusion threshold for MAP to be > 130 . Furthermore, if a MAP of 130 mmHg were to be adopted as the threshold for treatment, many patients who would otherwise be excluded, would receive alteplase treatment. A clear understanding of MAP in relation to SBP and diastolic blood pressure (DBP) in patients with AIS, which is now exclusively measured with NIBP devices, is critical for safe and effective alteplase management. **Study Aims.** To understand agreement between SBP, DBP, and MAP measured by NIBP and measured manually in alteplase-treated AIS patients. An additional secondary study aim was to investigate the relationship between MAP and outcomes in alteplase-treated AIS patients. **Methods.** Two trained examiners from three comprehensive stroke centers and four primary stroke centers measured five sets of manual-derived BP and NIBP-derived SBP, DBP, and MAP in 95 acute ischemic stroke patients treated with alteplase for a total of 475 paired sets of measures. The two examiners used a dual-auditory stethoscope to ensure accuracy of the manual measures. To avoid interruption of acute stroke care, all measurements occurred during the 24 hours following the alteplase infusion. The data was analyzed using Bland-Altman analysis for measures of agreement. **Results.** Our study found no agreement in SBP, DBP, and MAP for 475 paired manual and NIBP measurements, with SBP and MAP manual and NIBP measures showing the least agreement between methods. Although DBP-paired measures did not agree, they were in closer agreement than SBP and MAP measures on Bland-Altman (BA) analysis for measures of agreement, and 44% of DBP measures fell within 5 mmHg of each other. NIBP measures were consistently higher than manual measurements and differed from manual measurements as much as 50 mmHg for SBP, 40 mmHg for DBP, and 44 mmHg for MAP. We found that the higher the systolic blood pressure, the greater the disagreement. Additionally, we analyzed the percentage of measurements that fell within a difference of 5, 10, 15, and 20 mmHg for SBP, DBP, and MAP separately. For SBP, 39% of the 475 sets of measures fell within 5 mmHg and 62% fell within 10 mmHg. For DBP, 44% fell within 5mmHg and 72% fell within 10 mmHg. For MAP, 34% fell within 5 mmHg and 62% fell within 10 mmHg. **Conclusion.** Despite the widespread use of NIBP devices, few clinicians are familiar with their fundamental operating principles and the potential for inaccuracies and disagreement between manual and NIBP measurements. Clinically acceptable limits of agreement for SBP, DBP, and MAP in AIS patients should be defined a priori based on clinical necessity, biological considerations, and treatment goals. Additionally, our study takes an important first step in reframing AIS treatment context toward consideration of MAP as a key measure to guide the initiation of alteplase treatment and ongoing patient management. It is likely that stroke guidelines are silent regarding MAP because the information to understand safe MAP levels in AIS patients during and after alteplase administration is lacking. The safe MAP for AIS patients receiving alteplase treatment is not yet known, but work must continue in this area.

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**Mean Arterial Pressure in Acute
Ischemic Stroke Study**

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Anne W. Alexandrov, PhD

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The University of Tennessee*

in

*Nursing Science
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DEDICATION

I dedicate this dissertation to my loving husband, Sam Grove, for his unconditional love, support, and belief in me during this journey and throughout our life together.

To my friends and family, for their prayers and encouragement during the last five years. A special thank you to my sister, Patty Antonelli, for always being there to offer encouragement and assistance when it was most needed.

And to my parents, Iris C. Rabasca, Ph.D., an English Professor, and Michael J. Rabasca, a history teacher—both humble, faith-filled, and life-long learners who taught their six children the importance of loving God and family, and the value of higher education.

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ABSTRACT

Background. There is little, if any, evidence available on the validation of blood pressure (BP) measurements obtained in the acute care setting. Despite this, acute stroke practitioners trust and rely on non-invasive blood pressure (NIBP) devices to guide acute ischemic stroke (AIS) patients' treatment. Although systolic blood pressure (SBP) has been found to be the most unreliable measurement displayed on NIBP devices, treatment decisions for AIS are based on them. Today, 25 years after the FDA's approval of alteplase, practitioners continue to use BP parameters of 185/110 and 180/105 to guide the initiation of alteplase bolus and infusion, although the shift to the use of NIBP devices challenges the validity of these dated parameters. Theoretically, by inserting the inclusion and exclusion systolic and diastolic blood pressure thresholds into the mean arterial pressure (MAP) equation, one could deduce the exclusion threshold for MAP to be ≥ 130 . Furthermore, if a MAP of 130 mmHg were to be adopted as the threshold for treatment, many patients who would otherwise be excluded, would receive alteplase treatment. A clear understanding of MAP in relation to SBP and diastolic blood pressure (DBP) in patients with AIS, which is now exclusively measured with NIBP devices, is critical for safe and effective alteplase management.

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Methods. Two trained examiners from three comprehensive stroke centers and four primary stroke centers measured five sets of manual-derived BP and NIBP-derived SBP, DBP, and MAP in 95 acute ischemic stroke patients treated with alteplase for a total of 475 paired sets of measures. The two examiners used a dual-auditory stethoscope to ensure accuracy of the manual measures. To avoid interruption of acute stroke care, all measurements occurred during the 24 hours following the alteplase infusion. The data was analyzed using Bland-Altman analysis for measures of agreement.

Results. Our study found no agreement in SBP, DBP, and MAP for 475 paired manual and NIBP measurements, with SBP and MAP manual and NIBP measures showing the least agreement between methods. Although DBP-paired measures did not agree, they were in closer agreement than SBP and MAP measures on Bland-Altman (BA) analysis for measures of agreement, and 44% of DBP measures fell within 5 mmHg of each other. NIBP measures were consistently higher than manual measurements and differed from manual measurements as much as 50 mmHg for SBP, 40 mmHg for DBP, and 44 mmHg for MAP. We found that the higher the systolic blood pressure, the greater the disagreement. Additionally, we analyzed the percentage of measurements that fell within a difference of 5, 10, 15, and 20 mmHg for SBP, DBP, and MAP separately. For SBP, 39% of the 475 sets of measures fell within 5 mmHg and 62% fell within 10 mmHg. For DBP, 44% fell within 5mmHg and 72% fell within 10 mmHg. For MAP, 34% fell within 5 mmHg and 62% fell within 10 mmHg.

Conclusion. Despite the widespread use of NIBP devices, few clinicians are familiar with -their fundamental operating principles and the potential for inaccuracies and disagreement between manual and NIBP measurements. Clinically acceptable limits of agreement for SBP, DBP, and MAP in AIS patients should be defined a priori based on clinical necessity, biological considerations, and treatment goals. Additionally, our study takes an important first step in reframing AIS treatment context toward consideration of MAP as a key measure to guide the initiation of alteplase treatment and ongoing patient management. It is likely that stroke guidelines are silent regarding MAP because the information to understand safe MAP levels in AIS patients during and after alteplase administration is lacking. The safe MAP for AIS patients receiving alteplase treatment is not yet known, but work must continue in this area.

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LIST OF ABBREVIATIONS

AAMI	Association for the Advancement of Medical Instrumentation
AHA	American Heart Association
AIS	acute ischemic stroke
ANSI	American National Standards Institute
APN	advanced practice nurse
aPTT	activated partial thromboplastin time
ASA	American Stroke Association
ATP	adenosine triphosphate
BA	Bland-Altman
BBB	blood-brain barrier
BHS	British Hypertension Society
BP	blood pressure
CA	cerebral autoregulation
CBF	cerebral blood flow
CCC	concordance correlation coefficients
CI	confidence interval
CO	cardiac output
CPB	cardiopulmonary bypass
CPP	cerebral perfusion pressure
CT	computed tomography
CVP	central venous pressure
DAMPs	damage-associated molecular patterns
DBP	diastolic blood pressure
DINAMAP	Device for Indirect Noninvasive Automatic Mean Arterial Pressure
DM	diabetes mellitus
DO	Doctor of Osteopathy
ECASS	European Cooperative Acute Stroke Study
ECT	ecarin clotting time
ED	emergency department
ESH	European Society of Hypertension
GE	General Electric
HgbA1C	glycated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act Authorization
HMH	Hackensack Meridian Health
HR	heart rate
HTN	hypertension
ICP	intracranial pressure
INR	international normalized ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	intravenous
LCL	lower confidence limit
LoA	limits of agreement

LVO	large vessel occlusion
MAP	mean arterial pressure
MD	medical doctor
mmHg	millimeters of mercury
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
mRS	modified Rankin Score
NIBP	non-invasive blood pressure
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
NJ	New Jersey
PAC	pulmonary artery catheter
PP	pulse pressure
RN	registered nurse
rt-PA	recombinant tissue plasminogen activator
SBP	systolic blood pressure
SD	standard deviation
sICH	symptomatic intracerebral hemorrhage
SvO ₂	mixed venous oxygen saturation
SVR	systemic vascular resistance
TICI	thrombolysis in cerebral infarction
TN	Tennessee
tPA	tissue plasminogen activator
TT	thrombin time
UCL	upper confidence limit
UTHSC	University of Tennessee Health Science Center

CHAPTER 1. INTRODUCTION

Overview

Each year in the United States, 795,000 persons experience new or recurrent strokes. Early stroke symptom recognition is essential for seeking timely care. Unfortunately, knowledge of stroke warning signs and risk factors in the United States remains poor.¹ Strokes account for one of every twenty deaths, are fifth among all causes of death, and are the leading cause of serious long-term disability.² Eighty-seven percent are acute ischemic strokes (AIS) resulting from arterial blockage, whereas 13% are classified as a hemorrhagic stroke that results from arterial rupture.³

Primary risk factors for stroke include high blood pressure, diabetes mellitus, atrial fibrillation, high cholesterol, smoking, obesity, and family history.² Of these risk factors, blood pressure is the most powerful determinant of risk for both ischemic and hemorrhagic stroke. Antihypertensive therapy is associated with a reduction in stroke incidence. An average 10 mmHg decrease in systolic blood pressure (SBP) reduces the risk of stroke by 41%.²

Landmark Study

The National Institute of Neurological Disorders and Stroke (NINDS) Tissue Plasminogen Activator in Acute Ischemic Stroke Study⁴ took place from 1991-1994. Investigators reported favorable functional outcomes at 90 days and at one year in patients treated with intravenous recombinant tissue plasminogen activator (rt-PA) (now known as “alteplase”). The results of this randomized, double-blind placebo-controlled trial and the later European Cooperative Acute Stroke Study (ECASS)-3⁵ serve worldwide as the basis for evidence-based, guideline-directed treatment of AIS up to 4.5 hours from symptom onset.

In the original NINDS study,⁴ eligibility for enrollment included a clinical diagnosis of ischemic stroke with a clearly defined time of onset, a deficit measurable on the National Institute of Health Stroke Scale (NIHSS), and a baseline noncontrast brain computed tomography (CT) scan that showed no evidence of intracranial hemorrhage.⁴ Since a fibrinolytic agent would be used to break up blood clots occluding brain arteries, the investigators recognized the need for controlling severe hypertension to reduce the risk of intracranial hemorrhage. The NINDS investigators selected blood pressure (BP) parameters at the time of alteplase bolus to be less than 185/110 mmHg, with a further reduction to less than 180/110 mmHg by the time the alteplase continuous infusion began.⁴ Interestingly, these BP parameters were not established from pilot work but instead were suggested with the thought that BP should not be maintained too low because this may stifle flow through partially occluded vessels, thereby exacerbating brain ischemia. Additionally, only manual sphygmomanometer BP monitoring was allowed during the NINDS study because of concerns for bruising from noninvasive

automatic oscillometric BP (NIBP) cuffs. Blood pressure monitoring by arterial line was not advocated for the study because this approach would be impractical in an Emergency Department setting, would increase time to treatment, and arterial puncture could result in severe bleeding in an alteplase treated patient. Notably, criteria regarding a goal mean arterial pressure (MAP) parameter was not included in the study.

MAP and Acute Ischemic Stroke

Since the publication of the NINDS study in 1995,⁴ NIBP devices have become standard of care in hospitals in the United States and throughout most of the world. These devices have an added feature of simultaneously displaying the patient's heart rate (HR) and MAP with the SBP and diastolic BP (DBP). Although NIBP MAP is readily available, this parameter is disregarded by acute stroke practitioners because parameters for MAP were never established. Stroke treatment guidelines are silent regarding MAP because information to understand safe MAP values for maintenance of BP during and after alteplase administration is lacking, and MAP in relation to stroke has had very little attention because of widespread international acceptance of the NINDS study's established SBP and DBP treatment parameters.

Interestingly, MAP in patients with sepsis and septic shock has been studied extensively and found to be a more useful measurement to guide treatment.⁶⁻⁹ While perfusion of critical organs, such as the brain or kidney, may be protected from systemic hypotension by autoregulation of regional perfusion, below a threshold MAP, tissue perfusion becomes linearly dependent on arterial pressure.^{7,9} To date, findings supporting the use of MAP in clinical practice, and in particular in patients undergoing NIBP monitoring have not been adopted for stroke patients largely because previous studies have been deemed irrelevant since they were not obtained in rt-PA-treated stroke patients.

The acceptable limits for the parameters of SBP and DBP are informed by the American Heart Association/American Stroke Association's (AHA/ASA) 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke,^{1,10} the 2019 Updates to the 2018 guidelines,^{10(p. e369)} and by the NINDS Tissue Plasminogen Activator in Acute Ischemic Stroke Study⁴. *"Patients who have elevated BP and are otherwise eligible for treatment with IV Alteplase should have their BP carefully lowered so that their systolic BP <185mmHg and their diastolic BP is <110 mmHg before IV fibrinolytic therapy is initiated."*^{1(p. e17),10(p. e369)} Because BP parameters can vary significantly throughout the 24 hours after alteplase treatment, patients that were initially, "blood pressure in bounds" for alteplase, may have "out-of-bounds" periods where hypertension may ensue placing the patient at high risk for post-treatment hemorrhagic transformation. Therefore, as per the previously cited guidelines, acute stroke practitioners are to manage the BP during and after alteplase therapy to maintain the BP <180/105 mmHg.^{1,10}

Although MAP is readily available from NIBP devices commonly used by acute stroke practitioners to monitor BP in AIS patients, no recommendations about MAP parameters are made in current guidelines. Therefore, this parameter has not been of interest to acute stroke practitioners. Theoretically, by inserting the exclusion and inclusion SBP and DBP thresholds into the MAP equation of $DBP + .333(P)$, one could deduce the exclusion threshold for MAP. By using this formula, the patient would be excluded from receiving the alteplase bolus and infusion if their MAP is ≥ 135 mmHg and ≥ 130 mmHg, respectively (**Table 1-1**). Furthermore, if a MAP of < 135 mmHg is adopted as the threshold for treatment, many patients who would otherwise be excluded, would receive alteplase treatment. For instance, if a patient presents with an elevated, exclusion SBP of 210 and within-guideline DBP of 88, applying the equation $DBP + .333(P)$, their MAP would be 130 mmHg. Additionally, if the patient's presenting SBP is within guidelines for treatment at 170 mmHg but with an elevated, exclusion DBP of 106 mmHg, their MAP would also be 130 mmHg. In other words, many combinations of SBPs and DBPs could mathematically produce a MAP of 130 mmHg. However, many of these may be outside the traditional BP treatment parameters that state SBP should be less than 180 mmHg, and DBP should be less than 105 mmHg (**Table 1-2**).

Today, 21 years after the U.S. approval of alteplase, acute stroke practitioners continue to use the original parameters proposed in the NINDS study.⁴ However, their shift to the use of NIBP devices challenges the validity of these dated parameters. Firstly, the MAP is considered the most reliable measurement from an NIBP device. In fact, the SBP and DBP measurements displayed on these devices are derived from the MAP using a proprietary algorithm. Secondly, there is much heteroscedasticity among study results that examined agreement between SBP, DBP, and MAP parameters derived from manual sphygmomanometry/cuff and NIBP devices.

Of the few papers that address MAP and AIS in general,¹¹⁻¹⁴ none address MAP in relationship to alteplase treatment guidelines. There is a critical need to understand MAP on NIBP monitoring in patients undergoing alteplase treatment, to inform clinical practice of acceptable parameters that may be more beneficial than NIBP derived SBP and DBP values, which show little agreement to actual pressures.

Study Aims

Primary Study Aims

1. Understand agreement between SBP and DBP measured by NIBP device and manual sphygmomanometry in AIS patients treated with alteplase.
2. Understand agreement between MAP measured by NIBP device and calculated MAP (from manually obtained SBP and DBP) in AIS patients treated with alteplase.

Table 1-1. MAP in relation to current “in-bounds” SBP and DBP for initiation of alteplase bolus and alteplase infusion in acute ischemic stroke patients.

Initiation of Alteplase	Systolic Blood Pressure (SBP)	Diastolic Blood Pressure (DBP)	Pulse Pressure (PP)	Mean Arterial Pressure (MAP)
Bolus	<185	<110	75	<135
Infusion	<180	<105	75	<130

Notes: MAP = DBP + .333(PP); “in-bounds” = blood pressure threshold based on current acute ischemic stroke guidelines for initiation of alteplase bolus and infusion.

Table 1-2. MAP in relation to theoretical combination of “in-bounds” and “out-of-bounds” SBP and DBP for initiation of alteplase infusion in acute ischemic stroke patients.

Initiation of Alteplase	Systolic Blood Pressure (SBP)	Diastolic Blood Pressure (DBP)	Pulse Pressure (PP)	Mean Arterial Pressure (MAP)
Infusion	170	106*	66	128
Infusion	210*	88	122	129
Infusion	166	110*	56	129
Infusion	220*	80	140	127

Notes: MAP = DBP + .333(PP); * = “out-of-bounds” blood pressure based on current acute ischemic stroke guidelines for initiation of alteplase infusion.

Secondary Study Aim

1. Investigate the relationship between MAP and outcomes in alteplase treated AIS patients

Significance of Study

Stroke Centers are evaluated and ultimately certified by how closely the interventions they provide to AIS patients are in agreement with the Guidelines for the Early Management of Patients with Acute Ischemic Stroke.^{1,10} The American Heart Association/American Stroke Association (AHA/ASA) publication is regularly updated to ensure the guidelines stay current with findings from new clinical research that influence AIS treatment. In the 2018 guidelines,¹ the panel added the recommendation that hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support organ function.

In instances where supporting evidence based on clinical trial research is not available, recommendations from the panel of subject matter expert authors are made on the basis of pathophysiological reasoning and expert practice experience. If there are no clinical trials to inform recommendations, the panel applies rules of evidence and strength of recommendations to inform the guideline.¹⁵ The panel's recommendation for safe BP parameters in patients with AIS is an example of the use of expert opinion because of the lack of supporting evidence from clinical research. This may explain why current stroke guidelines^{1,10} remain essentially noncommittal with regard to evidence-based recommendations:

The blood pressure (BP) level that should be maintained in patients with AIS to ensure best outcome is not known. Some observational studies show an association between worse outcomes and lower BPs, whereas others have not. No studies have addressed the treatment of low BP in patients with stroke. In a systematic analysis of 12 studies comparing colloids with crystalloids, the odds of death or dependence were similar. Clinically important benefits or harms could not be excluded. There are no data to guide volume and duration of parenteral fluid delivery. No studies have compared different isotonic fluids.^{1(p. 35)}

These statements reflect the heterogeneity of AIS, and that systemic vascular and cardiac pathology may require and tolerate very different thresholds of pressure to maintain and/or enhance perfusion.

Symptomatic Intracerebral Hemorrhage

For BP management during fibrinolytic therapy, the AHA/ASA stroke guidelines provide more specific guidance. To inform their recommendations, guideline authors

used methodology from the 1991-1995 NINDS study,⁴ as well as results from research conducted since the NINDS study,¹⁶ showing that elevated BP levels before or during alteplase infusion may be related to adverse outcomes, including a higher risk of symptomatic intracranial hemorrhage (sICH) and a lower likelihood of complete recanalization and three-month favorable functional outcome.¹⁷ Several studies, in particular, have shown an association between elevated systolic BP (SBP) and sICH¹⁸⁻²⁰, with the best outcomes associated with an SBP of 141 to 150 mmHg.^{15,20}

Of note, sICH remains the most feared complication of alteplase treatment²¹ with a reported 50% mortality.²² It is defined as a local or remote parenchymal hemorrhage type 2 noted within 36 hours post-alteplase treatment, in combination with a National Institute of Health Stroke Scale (NIHSS) increase of 4 points or more from baseline or from the lowest NIHSS value measured, or clinical worsening that leads to death.^{18,21} In the NINDS study,⁴ the incidence of sICH was 6.4%; however, the definition used for sICH was very different from the current definition listed above. Subsequent studies that used the new definition show a lower sICH incidence that has not exceeded 3% in large clinical trials.^{18,19,23,24} The risk for sICH after alteplase administration is clearly associated with BP parameters.¹⁶ Therefore, the AHA/ASA guidelines recommend maintaining BP <180/105 mmHg and delaying the administration of aspirin until 24 hours after alteplase treatment. However, in the presence of concomitant conditions for which such treatment given in the absence of alteplase is known to provide a substantial benefit or withholding such treatment is known to cause substantial risk, earlier administration of aspirin and/or other antiplatelet therapy may be considered.¹

Elevated blood pressure is common during acute ischemic stroke¹⁵ and is often higher in acute stroke patients with a history of hypertension than in those without premorbid hypertension. In an observational study, SBP was >139 mmHg in 77% and >184 mmHg in 15% of patients on arrival to the ED.²⁵ During the acute phase of ischemic stroke BP may decrease spontaneously, starting within 90 minutes after the onset of stroke symptoms,¹⁵ however, this has not been well studied in relation to vascular imaging changes over time. In other words, in cases where the residual clot is not retrieved or lysed, BP may remain elevated in an attempt to augment downstream perfusion through collateral arterial channels. But again, to fully understand changes in BP in relation to clot burden, more work in this area is needed.

Mean Arterial Pressure

Mean arterial pressure (MAP) is the average arterial pressure during one cardiac cycle. It is considered a better indicator of perfusion to vital organs than SBP.²⁶ Normal MAP values generally lie between 70 and 110 mmHg, with recent guidelines recommending maintenance of MAP at more than 65 mmHg to ensure adequate tissue perfusion and to avoid shock.⁹ A MAP of 60 mmHg provides the internal organs with the necessary supply of blood, but prolonged hypotension with a MAP of less than 60 to 65 mmHg is associated with poor outcomes.⁸ Perfusion of critical organs such as the brain or kidney is safeguarded by autoregulation in the event of systemic hypoperfusion,

however below a MAP threshold, tissue perfusion becomes linearly dependent on the arterial pressure to prevent shock.⁹ In ischemic states, such as AIS, the loss of autoregulatory capacity results in passive vasomotor dilation, making blood flow passively dependent on mean arterial pressure.²⁷

Oscillometric Blood Pressure Monitors (Non-invasive Blood Pressure Devices)

The DINAMAP brand of oscillometric blood pressure monitors was introduced in the mid-1970s. DINAMAP is an acronym for “Device for Indirect Noninvasive Automatic Mean Arterial Pressure”.²⁸ The first generation of these devices only measured MAP. Subsequent models added SBP and DBP as well as HR measurements.²⁹ These devices were designed, in part, to answer the need for more accurate measurement of BP, allowing clinicians to non-invasively monitor and maintain acceptable MAP parameters, especially in critically ill, hypotensive patients. Since their introduction, validity and reliability testing has been conducted, first on animals, then on humans.^{28,30} By the late 1980s and early 1990s, after 20 plus years of research, NIBP devices achieved widespread trust as acceptable measures of blood pressure, despite variability in study results which examined accuracy and/or agreement between NIBP device measurements of SBP, DBP, and MAP and arterial line monitoring measurements³¹⁻³⁵ the gold standard for BP and MAP accuracy,³⁶⁻³⁸ and between manual sphygmomanometer readings.^{31,39-43}

Studies have shown that oscillometric devices overestimate SBP, and underestimate DBP compared with sphygmomanometers.^{39,41,42} Therefore, it is very possible that current alteplase treatment is being managed at pressures that are, in reality, lower than thresholds set by the original NINDS study.⁴ This is significant because poor management of blood pressure in AIS patients is associated with worse outcomes.¹⁵

Additionally, since NIBP cuffs deflate at a manufacturer-specific speed that assumes a regular pulse,⁴⁴ use of NIBP monitoring is not recommended in patients with atrial fibrillation or other highly irregular heart rhythms, because the device has been found to be highly inaccurate.²⁸ However, widespread adoption of the device around the world in numerous patient populations demonstrates that this advice is largely ignored.

Conceptual Framework

Ischemic Penumbra

Through a series of events called the ischemic cascade, an AIS causes one zone of injury and one zone of potential injury, referred to respectively as: 1) the ischemic core and 2) the ischemic penumbra. The ischemic core is the area of the brain most affected by severe ischemia, with most tissue in the region irreversibly injured and, ultimately, infarcted. Ischemic penumbra, of which the conceptual framework is the focus of this

study, is brain tissue potentially destined for infarction, but not yet irreversibly injured.^{17,45}

Ischemic Cascade

The ischemic cascade, rather than a chain of events, is actually multiple processes occurring simultaneously. Cell hypoperfusion and resulting cell hypoxia cause neurons to lose their ability to create energy in the form of adenosine triphosphate (ATP) through aerobic metabolism. With the marked reduction/absence of oxygen, energy is instead produced by anaerobic metabolism, which produces approximately 15 times less energy than that produced by ATP. A by-product of anaerobic metabolism is lactic acid, which in high enough quantities, disrupts the normal acid-base balance within brain cells (glial cells and neurons).⁴⁶ Consequently, ATPase-dependent ion transport mechanisms become dysfunctional, contributing to increased intracellular and mitochondrial calcium levels, cell swelling, rupture, and, ultimately, cell death.⁴⁷ Simultaneously, the sodium and calcium pump within the cells stops functioning normally, resulting in an influx of calcium in the cell that stimulates neuronal depolarization. This excessive depolarization causes excitotoxicity⁴⁸ and an excessive release of neurotoxic glutamate from presynaptic nerve terminals.⁴⁹

Cell death ensues through a variety of mechanisms, including excitotoxicity, as noted above, as well as through ionic imbalance, oxidative/nitrosative stress, inflammation, apoptosis, and peri-infarct depolarization.⁵⁰ Under normal circumstances, cerebral blood flow (CBF) is maintained at a relatively constant rate of 50 mL/100 g/min. As cerebral perfusion pressure (CPP) decreases, CBF gradually declines. When CBF decreases to less than 20 to 25 mL/100 g/min, a massive loss of oxygen and glucose, two vital nutrients for neurons and supportive glial cells, occurs. Below a CBF of 10 mL/100 g/min, neuronal depolarization occurs and, within a few minutes, will result in the death of core neurons and causing necrosis⁵¹ unless CBF is restored.⁵²

Disruption of the Blood Brain Barrier

The Blood-Brain Barrier (BBB) separates the bloodstream from tissue in the brain and central nervous system. This protective barrier is vital for the prevention of infection and injury. Four to six hours after an AIS, the blood-brain barrier starts to break down, resulting in an inflammatory reaction in the ischemic area around the infarct. Vasogenic edema occurs from proteins and water leaking out of endothelial cells in the capillaries and into the extracellular space. This edema adds to cytotoxic edema, which is already in the area and can result in a mass effect where brain swelling displaces surrounding brain tissue. The swelling increases over a few days and peaks 3-5 days post-stroke.⁵³ The enhanced permeability of the vascular wall, because of prolonged ischemia and hypoxia caused by vascular compression, greatly increases the chances of hemorrhagic transformation, making cautious BP management critically essential.⁵⁴

The occurrence of sICH after administration of alteplase may also be associated with disruption of the blood-brain barrier. Although oxygen to brain cells is restored upon reperfusion after administration of alteplase, a surge in the generation of reactive oxygen species occurs, and pro-inflammatory neutrophils infiltrate ischemic tissues actually exacerbating the ischemic injury. Thus, consideration of the integrity of the blood-brain barrier should also guide BP treatment decisions.²²

Prolonged ischemia leads to brain cell death. While neurons die, they release damage-associated molecular patterns (DAMPs), which are signals which trigger the inflammatory response by activating inflammatory cells called macrophages. Macrophages cause more inflammation by activating immune cells. Collectively, this stimulates liquefactive necrosis. Neutrophils in the area release digestive enzymes called hydrolases that breakdown dead cells and create a cavity of soft, liquefied necrotic cell debris.⁵³ If the stroke and resulting necrotic area are small, it can be contained and removed by macrophages. A larger necrotic area creates a large cavity in the brain, which is permanent and will not regenerate, ultimately filling with cerebrospinal fluid once the dead tissue has been carried off.⁵³

Cell processes and changes during the ischemic cascade, where different areas within the ischemic region evolve into irreversible brain injury over time, were first identified in animal studies.⁵⁵⁻⁵⁸ Additional studies^{56,59-63} involving AIS patients using CT, magnetic resonance imaging and angiography (MRI and MRA), and post-mortem evaluation of brain tissue, contributed to the development of the ischemic penumbra conceptual framework, of which the construct is the *Ischemic Cascade*. Concepts include the *Ischemic Core*, *Ischemic Penumbra*, *Cerebral Autoregulation*, *Cerebral Perfusion Pressure*, *Cerebral Blood Flow*, and *Blood Pressure* (**Appendix A**).

Assumptions for the Penumbra Conceptual Framework are: 1) Penumbra is ischemic brain tissue potentially destined for infarction, but not yet irreversibly injured;^{17,45,61} 2) Cerebral blood flow is dependent on vascular conductance and mean arterial pressure;^{64,65} and 3) The absence of autoregulatory capabilities in the ischemic penumbra, the area which is at risk of being recruited into stroke, results in vasomotor relaxation with passive vascular dilation, a state that is fully dependent on mean arterial pressure to ensure perfusion.⁶⁵

Because the penumbra is hypoperfused tissue surrounding the ischemic core, in which blood flow is too low to maintain electric activity but sufficient to preserve ion channels, the area is subjected to the wave of deleterious metabolic processes⁶⁶ which occurs during the ischemic cascade (excitotoxicity, spreading depression, oxidative stress, and inflammatory response), however, since the penumbra is still potentially salvageable, it is the target of acute therapies.^{17,67}

Findings show that this evolution is most critically linked to the severity of the decline in CBF, which is dependent on vascular resistance and arterial BP. Cerebral autoregulation is the inherent ability of blood vessels to keep CBF relatively constant over a wide range of systemic BP levels by means of complex myogenic, neurogenic, and

metabolic mechanisms.⁶⁴ However, because cerebral autoregulation is lost within the ischemic penumbral territory, understanding BP in relation to penumbral salvage with therapies such as alteplase is essential to optimizing patient outcomes in acute ischemic stroke.

The penumbral concept states that different areas within the ischemic region evolve into irreversible brain injury over time. It is necessary to ensure adequate CBF in the penumbral region of vasomotor relaxation while protecting tissue that is friable and vulnerable to hemorrhage because of ischemic injury. Therefore, a clear understanding of MAP in relation to SBP and DBP in patients with AIS, which is now exclusively measured with NIBP devices, is critical for safe and effective alteplase management.

CHAPTER 2. LITERATURE REVIEW

Blood Pressure in Acute Ischemic Stroke (AIS)

Ischemic stroke can be divided into two broad groups of patients, those with large vessel occlusions (LVO), who make up approximately 30% of cases, and those with small vessel (lacunar) strokes, who make up a considerably larger group.²⁷ LVO can occur from embolization from a proximal source or less commonly in situ atherosclerosis,^{27,68} both of which lead to an abrupt fall in regional cerebral blood flow (CBF).⁶⁸

Large Vessel Occlusion (LVO) and Ohm's Law

In a small observational study, cases of LVO treated with alteplase with higher systolic blood pressure (SBP) on presentation were associated with lower revascularization rates.⁶⁹ This finding is well supported by Ohm's law of electricity, which has been applied to hemodynamics. Ohm's original work suggested the following: $(U \text{ (voltage)} = I \text{ (current)} \times R \text{ (resistance)})$.⁷⁰ Applying Ohm's law to the pathophysiology of vessel occlusion, where BP (pressure differences) is analogous to voltage, cardiac output (CO) to current, and systemic vascular resistance (SVR) to resistance,⁷⁰ the hemodynamic equation is expressed as $Q \text{ (blood flow)} = (P^1 - P^2 \text{ (pressure difference)}) / R \text{ (resistance)}$. In other words, the difference between pressures at two different points, divided by resistance, produces blood flow. Therefore, higher SBP in LVO patients may, in fact, represent persisting occlusion with an attempt to overcome a high resistant state.

Small Vessel Occlusion (Lacunar Strokes)

Lacunar strokes are small (0.2 to 15 mm in diameter) noncortical infarcts caused by occlusion of a single penetrating branch of a large cerebral artery.⁷¹ The primary risk factor for lacunar strokes is hypertension⁷². Hypertension results in lipohyalinosis, a segmental arteriolar wall disorganization that causes wall thickening and diameter reduction of the small vessel.⁷¹ Although no large-scale trial has systematically studied blood pressure (BP) management in either LVO or lacunar strokes to provide clear guidance, recent findings in lacunar stroke patients suggest that it is likely safe to lower BP well below the guideline-recommended values.^{73,74}

Blood Pressure Management in Acute Ischemic Stroke

With each update in the *Guidelines for the Early Management of Patients With Acute Ischemic Stroke*,^{1,10} recommendations regarding optimal BP in AIS patients to ensure the best outcome have been noncommittal. Both the 2018 guidelines¹ and the 2019 updated guidelines¹⁰ state that an absolute target BP level for AIS patients is not known. This lack of absolutes naturally leaves room for clinician interpretation and

thus variation among acute stroke centers' BP management. Illustrating this, a retrospective study⁷⁵ that sought to describe practice patterns for BP management in patients with AIS among emergency department (ED) physicians in Midwest academic and community hospitals found that antihypertensive therapy was often given despite patients not meeting guideline treatment criteria. Additionally, reduction in SBP exceeded guideline recommendations in one in four cases, while one in three cases that met guideline criteria for BP treatment did not receive antihypertensives.⁷⁵

Blood Pressure Management in Acute Ischemic Stroke Patients Receiving Alteplase

For AIS patients receiving alteplase, clinical guidelines for SBP and diastolic blood pressure (DBP) parameters have been specified and are based on the limits established for the NINDS rt-PA Stroke Study.⁴ The guidelines state that patients who have elevated BP and are otherwise eligible for treatment with intravenous alteplase should have their BP carefully lowered to a systolic BP <185 mmHg and diastolic BP <110 mmHg prior to the alteplase bolus. In addition, the BP should be further lowered to <180 mmHg SBP and <105 mmHg DBP prior to initiation of the alteplase continuous infusion.¹ Strict control of BP is essential in the alteplase-treated patient, and BP protocol violations are independently associated with a higher likelihood of sICH and worse patient outcome. In a retrospective cohort study that analyzed 510 patients with ischemic stroke treated with alteplase within 3 hours from stroke onset over a previous 10-year period, sICH occurred in 31 patients (6.1%);¹⁶ BP protocol violations were present in a total of 63 patients (12.4%) and were more frequent in patients with sICH (26% versus 12%; $P = 0.019$). However, as discussed previously, the BP parameters cited in the guidelines were not derived through systematic study but instead were based on the expert consensus of the NINDS rt-PA Stroke Study trialists.

Mean Arterial Pressure in Acute Ischemic Stroke Patients

Although BP is one of the easiest cardiovascular measures to quantify, it only provides indirect information regarding the patient's cardiovascular status.⁷⁰ Because MAP is the average effective arterial pressure that propels blood through the vasculature, its value is important in the management of patients with systemic blood flow limitations, thus making it a more useful and common parameter in systemic conditions for assessment of tissue and organ perfusion.^{27,70} However, in previous or current stroke guidelines, goal MAP parameters have never been set or even mentioned despite its significant effect on CBF in the face of cerebral autoregulatory collapse.²⁷ Moreover, and ironically, MAP is not utilized for monitoring patients' response to care despite the fact that it is readily available to providers with point-of-care non-invasive oscillometric BP (NIBP) devices. Furthermore, no studies have yet to investigate the relationship between MAP and outcomes in AIS patients who have received alteplase. Interestingly, of the few papers that address MAP and AIS in general, none address MAP in relationship to treatment guidelines.

Calculation of Mean Arterial Pressure

The mathematical formula for MAP in patients with central⁷⁰ and arterial line invasive monitoring is: $(CO \times SVR) + \text{central venous pressure (CVP)}$. In patients without central monitoring, MAP can be calculated from blood pressure cuff measurements using the empirical formula which states: MAP equals the sum of diastolic pressure (DP) and one-third of the pulse pressure (PP), where PP is the difference between the systolic and diastolic pressure.^{76,77} Thus $MAP = DP + 0.333(PP)$. This standard equation assumes that diastole persists for 2/3 and systole for 1/3 of each cardiac cycle.⁷⁶

Ischemic Penumbra

The concept of an ischemic penumbra is based on the theory that downstream perfusion from an infarct determines the fate of tissue lying in that region. Within that downstream region, a “potentially viable” area, the ischemic penumbra, that is likely most relevant to the degree to which patients with LVO stroke recover from their ischemic event.

The human brain constitutes only 2% of the body weight but receives 15% of total cardiac output.⁷⁸ Autoregulation is the mechanism responsible for maintaining blood flow relatively constant in the brain and other vital organs and, as such, plays a critical role in maintaining blood flow and tissue viability to the brain during AIS. Furthermore, its role in maintaining the viability of the ischemic penumbra could determine the degree of permanent disability.

Cerebral autoregulation (CA) is best described by the relationship between MAP and mean CBF.⁷⁹ In normal states of perfusion, CA enables relatively constant CBF despite variation in arterial pressure, actively constricting when pressures are elevated to limit blood flow, and dilating arterial segments when MAP drops to maximize blood flow.⁸⁰ In the case of AIS, increased intracranial pressure (ICP) is rare because of cerebral atrophy that affords room within the skull. When increased ICP occurs, it is generally a late event occurring between 48-96 hours post-stroke onset. Therefore, cerebral perfusion pressure (CPP), which is the product of MAP less ICP, or $MAP - ICP = CPP$, is generally expected to be no more than 10-15 mmHg less than MAP in AIS. Because it is energy dependent, CA is generally well maintained within a MAP of 60-150 mmHg.⁸¹ However, in the event of an AIS, CA is dramatically impaired due to failure of cellular adenosine triphosphate (ATP) dependent systems, resulting in acidosis and passive vasomotor relaxation that produces maximal arteriole dilatation.⁸² The consequence of this dilatation is that CBF becomes passively dependent on MAP.⁸³ In the case of LVO stroke, precipitous drops in BP may further devastate perfusion of penumbral tissue, thereby recruiting it into infarction.

It is difficult to understand why MAP has been a neglected value in patients with stroke. Most stroke patients today are managed using NIBP monitoring, and even though

these devices provide a MAP value, it is largely ignored by stroke practitioners. Given the physiologic significance of MAP, an improved understanding of its relevance in the management of AIS is warranted.

MAP in Relation to Systemic Conditions

MAP in Sepsis

Optimal MAP in sepsis has been widely studied.^{6,8} During standard treatment for septic shock, the most important hemodynamic variables predicting 30-day outcomes are MAP and lactate for the first 6 hours and MAP, mixed venous oxygen saturation (SvO₂), and CVP for the first 48 hours. The best predictive threshold levels for mortality in sepsis were 65 mmHg for MAP and 70% for SvO₂.⁸ A retrospective study of 111 patients found that a target MAP of 65 mmHg is usually sufficient in patients with septic shock. However, a MAP of around 75 to 85 mmHg may reduce the development of acute kidney injury in patients with chronic arterial hypertension.⁶ Based on results of these and other studies examining optimal MAP while on vasopressor agents, the Society of Critical Care Medicine's *Surviving Sepsis International Guidelines for the Management of Patients with Sepsis and Septic Shock: 2016*⁷ gave a strong recommendation for an initial target MAP of 65 mmHg in patients with septic shock. Overall recommendations suggest that a target MAP of 65 mmHg, when compared to higher MAP targets (i.e., 85 mmHg), results in lower risk of atrial fibrillation, lower vasopressor requirements, and similar mortality among patients with septic shock.⁷

MAP during Cardiac Surgery

Currently, there is no consensus for the optimal MAP for patients during cardiopulmonary bypass (CPB),⁸⁴ but based on results from a series of studies; the accepted range appears to lie between 50 – 80 mmHg. In a 1990 study of 504 patients' neurologic and renal outcomes in relation to MAP during coronary artery bypass grafting, a target MAP of >50 mmHg was recommended, with findings that this MAP did not adversely affect renal or cerebral function⁸⁵. However, in a 1995 randomized trial comparing intraoperative high versus low MAP during CPB, patients who were maintained at a MAP of 80 mmHg had significantly less (8.1%) morbidity and mortality than those managed at usual MAPs of 50–60 mmHg.⁸⁶ In 1998, researchers assessed the efficacy and safety of the pharmacological protocol used to achieve and maintain target MAP to 80 mmHg in the 1995 study and reported that findings support the protocol as both efficacious and safe.⁸⁷

In 2007, researchers further expanded on the findings of the 1995 study by evaluating whether tailoring the MAP target for the period of CPB to the patient's usual (pre-surgery) MAP would reduce major morbidity and mortality and improve quality of life more than using a target MAP of 80 mmHg for all patients. They found there were

no statistically significant differences in the combined outcome of mortality, cardiac, neurologic or cognitive complications, and deterioration in the quality of life.⁸⁸

The John Hopkin's *Textbook of Cardiothoracic Surgery*⁸⁹ advises that MAP range during CPB lies between 50 and 80 mmHg, based on patient's coexisting conditions:

Perfusion of the brain is normally protected by autoregulation, which appears to be lost somewhere between 55 and 60 mmHg during CBP at moderate hypothermia and 24 percent hematocrit. This pressure is thus generally regarded to be the lowest safe pressure for routine CBP. In older patients, who may have vascular disease and/or hypertension, mean arterial blood pressure is generally maintained between 70 and 80 mmHg at 37°C. Higher pressures are undesirable because collateral blood flow to the heart and lungs increases blood in the operative field.^{89(p. 348)}

Recommendations on setting MAP parameters in cardiac diseases can be summarized as “tailored to the vascular dynamics of the patient.” This is logical in that hemodynamic diseases are highly heterogeneous, often requiring very different approaches to management to ensure optimal blood flow. Given that AIS is more similar to myocardial infarction than to other neurologic diseases, once MAP is systematically studied as a measure of flow and subsequently used more routinely to monitor BP, the resulting data may similarly suggest establishing an acceptable range rather than a single target value or use of a tailored approach.

Non-Invasive Blood Pressure (NIBP)

As described earlier, $(CO \times SVR) + CVP = MAP$.⁹⁰ However, an arterial line and pulmonary artery catheter (PAC) are needed to directly measure CO, SVR, and CVP. Such instrumentation requires invasive procedures that would delay care to patients warranting time-sensitive emergent stroke treatment. Additionally, the risk of bleeding in the alteplase treated patient with an arterial line and PAC would be substantial. Therefore, the use of non-invasive technology has become the standard of care for the management of acute stroke patients.

Original research on the indirect oscillometric measurement of BP dates to 1876,⁹¹ years before Korotkoff (1905) described the sounds that measure systolic and diastolic arterial pressure levels for the auscultatory method.⁹²⁻⁹⁵ Research and development for NIBP oscillometric measurements increased in the 1960s as a method to measure BP on animals, whose Korotkoff sounds are difficult to detect.⁹³ In 1969, Posey and Geddes showed that the point of maximum oscillation corresponds to true MAP,^{92,96} with continued work showing points in the oscillometric envelope that correlated not only with MAP but also with SBP and DBP. SBP correlated with a cuff pressure in the oscillogram when the oscillations reached about 50% of their ultimate peak, and DBP correlated with oscillations that were at about 80% of peak.⁹⁶ In 1979, an early NIBP

device was tested using measures on the bicep and ankle in 28 studies of 17 subjects with intra-arterial catheters. Investigators concluded that NIBP produced good results regardless of clinical condition.²⁹ With the award of a US patent in 1982 for the DINAMAP (a synonym for Device Noninvasive Measurement of Arterial Pressure) to Ramsey III (Johnson & Johnson, assignee),⁹⁷ automatic oscillometric point of care patient monitoring entered the clinical arena. The original device only measured and displayed MAP. In 1988, a second patent was awarded to Ramsey III et al. (Critikon, assignee), for a newer generation DINAMAP capable of measuring and displaying SBP and DBP along with MAP.⁹⁸

NIBP devices in use today determine MAP by measuring cuff pressure oscillations as the cuff pressure is reduced by discrete increments.²⁹ The small oscillations of intra-cuff pressure, which are caused by heartbeat-induced pulse volume changes, are sensed by the cuff and measured by a pressure transducer.⁹⁹ Cuff deflation in discrete increments, instead of continuously, allows the oscillation data obtained at each cuff pressure to be tested for artifacts and averaged, greatly enhancing artifact-rejection ability.²⁹ MAP is selected as the lowest cuff pressure at which the oscillation amplitude is a maximum.²⁹ SBP and DBP values are then algorithmically derived from the MAP^{99,100}. Because it correlates directly with the maximum oscillations detected by the system, the MAP is accepted as the most accurate value derived from NIBP measurements.³² Since cuff pressure oscillations continue when cuff pressure falls beneath diastolic blood pressure, the endpoint for diastolic pressure is indistinct.³¹

Like any instrument, the usefulness of its measurements is dependent first upon its validity and second its reliability. This is especially so for NIBP measures such as SBP and DBP that are derived from the MAP reported on the device. Differing clinical validation protocols for automated non-invasive oscillometric devices have been established by the American National Standards Institute (ANSI) and the US Association for the Advancement of Medical Instrumentation (AAMI), the International Organization for Standardization (ISO), the British Hypertension Society (BHS), and the European Society of Hypertension (ESH) Working Group on Blood Pressure (BP) Monitoring.^{101,102} ANSI/AAMI first published their joint standards and recommended practices in 1987,¹⁰³ with periodic updates released since then. The most recent version of the ANSI/AAMI/ISO standard was released in 2019.¹⁰⁴

The ANSI/AAMI/ISO protocol determines the accuracy of BP monitoring devices using the mean error and the standard deviation of error obtained from 255 measurements. This standard requires the mean error to fall within 5 mmHg and a standard deviation of error to fall within 8 mmHg.¹⁰³⁻¹⁰⁵

In the “interest of science, patients, consumers, and manufacturers”, the AAMI, ESH and ISO experts agreed to develop a universal standard protocol for device validation.¹⁰¹ Consensus is based on the evidence from previous validation studies using the AAMI, BHS, ESH-IP, and ISO protocols, new statistical analyses on power of study sample and subgroups, and expert opinion.¹⁰¹ Current key aspects of the validation procedure are that at least 85 subjects are required for the validation study, the

auscultatory standard is retained for reference BP measurement with measurements taken simultaneously by 2 trained observers blinded to each other's readings and to the measurements taken with the test device.¹⁰³ As soon as the AAMI/ESH/ISO standard is fully developed, it will be regarded as the single universal standard and will replace all other previous standards/protocols. This was expected to be finalized in 2018,^{101,106} however, as of this writing, the full document is not yet published.

Clinicians should understand that NIBP measurements are the end-product of company-owned proprietary computer algorithms. Therefore algorithms, testing, and validation procedures differ from one device to another¹⁰³ and are scattered in many different publications or patents.¹⁰⁵ Most practical algorithms used in commercially available devices are closely guarded trade secrets that are not subject to independent critique and validation. Hence the best way to determine systolic and diastolic arterial pressures from cuff pressure oscillations remains an open scientific problem.³¹ Because of this situation, claims and findings of accuracy and agreement for one NIBP device brand cannot be generalized to other brands.

Studies of Agreement

Benefits of oscillometric measurement include the elimination of observer variability¹⁰⁷ and the need for a stethoscope, which makes NIBP less susceptible to external noise (excluding low-frequency mechanical vibration).¹⁰⁸ Use of NIBP monitoring has become a substitute for invasive intra-arterial BP measurements, reducing bleeding and infection risk, and these devices are now found throughout the hospital.³⁶ Additionally, NIBP monitoring may also decrease erroneous BP measurements as a result of an auscultatory gap, which is often present in older patients with a wide pulse pressure. With auscultatory gaps, Korotkoff sounds may become inaudible between systolic and diastolic pressure, and reappear as cuff deflation continues; this may also occur because of fluctuations of intra-arterial pressure and is likely in subjects with target organ damage.¹⁰⁹

Study findings^{31-33,110-112} vary with regard to agreement between BP measures from an NIBP device compared to measures from an arterial line and manual sphygmomanometer. Per the 2013 ANSI/AAMI/ISO standard,¹⁰³ for clinical use, the current acceptable limit of the difference is approximately 5mmHg.^{43,99,103} Many studies used these limits to analyze and report findings of accuracy.

NIBP Agreement with Arterial Line Measurement

Concerning agreement between NIBP device and arterial line measures, both animal^{33,111,112} and human studies have shown that NIBP devices accurately and consistently measure MAP with acceptable agreement of the displayed MAP from arterial line monitoring.³¹⁻³³ MAP has also been found to be more reliable than the displayed SBP and DBP readings.⁴³ Interestingly, diastolic NIBP values have shown closer agreement

with arterial line diastole, whereas NIBP systolic pressures may differ considerably from arterial line systole.³³

In anesthetized surgical patients, NIBP devices showed an acceptable agreement and were interchangeable with invasive arterial pressure monitoring for MAP during normotensive conditions.³⁴ However, during induction of anesthesia, and when the arterial pressure was low, there was less agreement. Thus interchangeability between readings was not achieved. Investigators concluded that NIBP device measures are not statistically equivalent to invasive monitoring during all periods of anesthesia, but they may be a useful additional arterial pressure monitor.³⁴

Since the amplitude of the oscillations depends on several factors other than BP, and oscillometric measurement is not continuous, in some patient conditions, measurements were found to be inaccurate when compared to gold-standard intra-arterial monitoring. For example, MAP may be significantly underestimated^{41,43} in patients with stiff, atherosclerotic arteries and wide pulse pressures. Additionally, in patients with dysrhythmias, such as atrial fibrillation, oscillometric device measurements were found to be unreliable.²⁸ When the cuff is inflated, and the artery is partially or fully occluded, pressure oscillations created by the expansion of the arterial wall during each heartbeat are sensed by the cuff and measured by the device's hardware and software.⁹⁹ Therefore, the irregularity in heart rate, strength, and rhythm that occur with atrial fibrillation decrease the reliability of the displayed parameters.

Independent studies by Pagonas et al. in 2013¹¹³ and Lakhal et al. in 2015¹¹⁴ and 2017¹¹⁵, offer a differing opinion on the generalized belief that NIBP measurements are inaccurate in patients with arrhythmias. These investigators submit that most available studies^{116,117}, which addresses the reliability of NIBP measurements during arrhythmia, is misleading since the auscultatory method was used as the reference gold standard¹¹⁷ rather than arterial line measurement. They add that during an arrhythmia, the auscultatory method is exposed to inter- and intra-observer bias owing to the beat-to-beat variability of pulse pressure and thereby of Korotkoff sounds.¹¹⁵

In studies of agreement, Pagonas et al.¹¹³ compared NIBP measures with intra-arterial measurements in ICU or intermediate care unit patients with atrial fibrillation and sinus rhythm. Lakhal et al.^{114,115} compared NIBP measures with intra-arterial measurements in ICU patients with atrial fibrillation, atrial flutter, and frequent extra systoles. Both Pagonas et al. and Lakhal et al. used the ANSI/AAMI/ISO validation criteria of accuracy (mean BP difference ≤ 5 mm Hg) and precision ($SD \leq 8$ mm Hg).¹⁰³ In all three studies, the investigators found that arrhythmias did not significantly impact the agreement of NIBP measures with intra-arterial measures, and did not significantly affect the accuracy of oscillometric measurements as long as three repeated measures of the mean are averaged.¹¹³⁻¹¹⁵

Cuff size and upper arm circumference have been found to affect the accuracy of NIBP oscillometric devices.^{118,119} Using 1494 pairs of simultaneous oscillometric and invasive arterial MAP measurements collected in 38 critically ill patients over 72 hours,

Bur and colleagues found that use of inotropic support and the position of the cuff did not affect the accuracy of the oscillometric method; however, the relation between cuff size and upper-arm circumference contributed substantially to the differences between oscillometric and invasive arterial MAP measurements. NIBP oscillometric MAP measurement in patients who had smaller than the recommended cuff sizes resulted in smaller discrepancies between invasive and noninvasive MAP measurement compared with the recommended cuff sizes.¹¹⁸

NIBP Agreement with Manual Sphygmomanometer Measurement

Studies have also demonstrated the underestimation of BP measurement by NIBP devices at increasing BP levels.^{40,43} A retrospective review of 30 studies which examined the accuracy of BP measurement by oscillometric ambulatory devices (12 studies) and non-ambulatory devices (18 studies) performed between 1993-2003, the accuracy of BP measurement, particularly SBP, decreased at increasing blood pressure levels.⁴³ Reviewers speculated whether this finding could be due to the oscillometric method of BP measurement, or whether the decrease in accuracy could be explained by increasing blood pressure variability at increasing blood pressure, and the use of sequential measurements.⁴³

With regard to SBP agreement between NIBP and manual mercury sphygmomanometry, a study by Coe et al. found opposite results in that the NIBP device over-read SBP by a mean of 8.38 mmHg, and under-read DBP by a mean of 1.68 mmHg, when compared with manual readings. Although the NIBP readings were found to be clinically reliable at normotensive values, the error increased at borderline hypertensive levels and higher. Investigators summarized that 6.5% of the study participants would have been inappropriately diagnosed as hypertensive from the NIBP device readings, and thus potentially rejected from day surgery and inappropriately referred to their general practitioner. Due to this finding, investigators conclude with a recommendation to recheck the BP using a manual sphygmomanometer for any hypertensive reading by an NIBP device.¹²⁰

Similar findings were reported by Keavney et al.⁴⁰ where NIBP measures were less accurate than manual sphygmomanometry. The proportion of NIBP readings that differed from the observers' readings by 5 and 10 mmHg was higher with the oscillometric technique than with manual sphygmomanometry. Higher SBPs were under-estimated by the NIBP device, while lower SBPs tended to be over-estimated. Interestingly, the crossover point occurred at approximately 150 mmHg. These trends were not discernible for the differences between DBP measurements.⁴⁰ MAP was not addressed in this study.

Kiers et al.¹²¹ compared the MAP measured with an NIBP oscillometric device with the MAP calculated using the SBP and DBP measured by auscultation using the formula $DBP + 1/3 \text{ Pulse Pressure}$. Results showed a significant difference between

measured MAP and calculated MAP ($p < 0.001$) and therefore, concluded that measured, and calculated MAP cannot be used interchangeably.¹²¹

Araghi et al.¹²² compared arterial blood pressure (ABP) with NIBP measurements obtained using both auscultatory and oscillometric methods in 54 overweight critically ill patients and concluded that NIBP in this patient population could be inaccurate. Oscillometric BP measurements underestimated ABP readings regardless of patient body mass index, whereas auscultatory measurements underestimated SBP and overestimated MAP and DBP.

In a study that used two geometric models for numerical analysis, one a cylinder-shaped ideal model, and the other an anatomic model reconstructed from CT scan images of an upper arm segment, researchers investigated the mechanical response of soft tissues to cuff pressurization and found that a thickened subcutaneous fat layer in obese subjects significantly reduced the effective pressure transmitted to the brachial artery.¹²³ They postulated that this might explain why blood pressure overestimation occurs more frequently in obese subjects in NIBP measurement.¹²³

Despite questions of accuracy, NIBP devices have become the clinical standard, in large because of a decrease in training requirements.⁹⁹ Of the parameters displayed on NIBP devices, patient medical management is guided mostly by SBP and DBP. It is likely that most clinicians are not aware that the design of the devices, as well as the preponderance of study results, support the MAP as the most accurate of the displayed measures. Additionally, few clinicians understand the issues and procedures which may affect the accuracy of these devices.

As technology has evolved, newer, proprietary algorithms boost improved sensitivity to differences in pulse pressure and arterial stiffness.³¹ In 2012, biomedical engineers published a paper that detailed the development of an algorithm that predicts cuff pressure oscillations produced during NIBP oscillation measurements and allows accurate extraction of systolic and diastolic pressures in the presence of varying arterial stiffness or varying pulse pressure. Unlike the closely held trade secret³¹ of most NIBP device proprietary algorithms, the engineers placed their algorithm in the public domain and invited others to independently test and refine their approach.³¹

Best Practice for Measurement of BP by Manual Sphygmomanometry and NIBP

With both manual sphygmomanometry and NIBP devices, the most common error in BP measurement is the use of inappropriate cuff size. Too narrow or too short a cuff bladder (undercuffing) results in an overestimation of BP and too wide or too long a bladder (overcuffing) results in an underestimation of BP.¹²⁴ The bladder length recommended by the American Heart Association is 80 percent of the patient's arm circumference, and the ideal width is at least 40 percent.¹²⁵ Error is minimized when the cuff width is 46 percent of the arm circumference. In obese patients, longer, wider cuffs are needed to compress the brachial artery adequately. If there is uncertainty regarding

correct cuff size, clinicians should refer to a table that details recommended cuff sizes based on arm circumference.¹²⁵

Best practice also includes placing the lower edge of the cuff 2-3 cm above the antecubital fossa, squeezing all of the residual air out of the cuff before applying it to the arm or leg, wrapping the cuff snugly around the arm, instructing the patient to refrain from talking or moving, letting nothing press against the cuff during measurement, and ensuring that the cuff and heart are at the same horizontal level.¹²⁶

Additionally, a minimum of two readings should be taken, and the average of those readings should be used to represent the patient's BP. If there is more than 5 mmHg difference between two consecutive readings, additional readings should be performed, and their average should be used. At least a 1-minute interval should be adopted between the two consecutive readings.¹⁰⁵

Manual Sphygmomanometry (Korotkoff) Technique

The Korotkoff technique requires the use of both a sphygmomanometer (inflatable cuff with a pressure gauge) and a stethoscope to link pressure changes with the return of blood flow. As the cuff inflates, the artery is occluded. As the cuff deflates, the blood flow generated produces the turbulence needed to produce Korotkoff sounds. In extremely large patients, in those with excessively calcified (and rigid) arteries,¹²⁷ and in patients with severe hypotension, this technique may fail secondary to the inability to hear Korotkoff sounds.

The proper technique for blood pressure measurement using cuff and sphygmomanometer is described by Pickering et al. in the AHA Scientific Statement for Recommendations for Blood Pressure Measurement in Humans and Experimental Animals.¹²⁵ The examiner should first palpate the brachial artery in the antecubital fossa and place the midline of the bladder of the cuff on the patient's upper bare arm so that it is just above the brachial arterial pulsation. To allow room for placement of the stethoscope, the lower end of the cuff should be 2 to 3 cm above the antecubital fossa. If the cuff touches the stethoscope, artifactual noise will be generated. The cuff is first inflated without auscultation until the pulse is no longer apparent on palpation; this identifies the level of suspected systolic pressure. The cuff should initially be inflated to at least 30 mmHg above the point at which the radial pulse disappears. The rate of deflation has a significant effect on blood pressure determination. Deflation rates >2 mm per second can lead to a significant underestimation of systolic and overestimation of diastolic blood pressure.¹²⁵ As the cuff is gradually deflated, pulsatile blood flow is re-established and accompanied by Korotkoff sounds, phase 1 sounds indicating SBP, and phase 5 sounds indicating DBP. Neither the examiner nor the patient should talk during the measurement.¹²⁵

The key to good measurement is the use of a high-quality stethoscope with clean earpieces and short tubing. Inexpensive stethoscopes may lack good tonal transmission properties required for accurate auscultatory measurement.^{124,125} Korotkoff sounds are best heard using the bell of the stethoscope over the palpated brachial artery in the

antecubital fossa. However, it probably does not matter much if the bell or diaphragm is used in routine blood pressure measurement, provided the stethoscope is placed accurately.¹²⁴

BP measurements should initially be taken on both arms. If reproducible differences greater than 20 mmHg for systolic or 10 mmHg for diastolic pressure are present on consecutive readings¹²⁴, the presence of a cardiovascular abnormality should be considered. During emergency care of a patient, clinical judgment should be used when deciding whether the difference is significant enough to warrant delay of treatment to work-up the potential cause of the difference.

In older patients with a wide pulse pressure, the Korotkoff sounds may become inaudible between systolic and diastolic pressure, and reappear as cuff deflation is continued. This phenomenon is known as the auscultatory gap. In some cases, this may occur because of fluctuations of intra-arterial pressure and is most likely to occur in subjects with target organ damage.¹⁰⁹ The auscultatory gap often can be eliminated by elevating the arm overhead for 30 seconds before inflating the cuff and then bringing the arm to the usual position to continue the measurement. This maneuver reduces the vascular volume in the limb and improves inflow to enhance the Korotkoff sounds.¹²⁵ If a wide variation in BP measurements is recorded, clinicians should consider the auscultatory gap and/or cardiac dysrhythmias as possible culprits.

BP examiners should be assessed for eye/hand/ear coordination, which is required to ensure proper technique for manual sphygmomanometer BP Monitoring. They should be able to see the dial of the manometer at eye level without straining or stretching and see the sphygmomanometer from three feet away. Additionally, the examiner must be able to hear the appearance and disappearance of Korotkoff sounds.

Benefits of manual sphygmomanometer BP monitoring are that the equipment is often inexpensive, lightweight, and portable. Additionally, the gauge will function in any position, as long as the examiner is able to view it directly. Limitations include multiple opportunities for major sources of error, including inappropriate cuff size, incorrect stethoscope placement, examiner error via inadequate hearing acuity or incorrect technique, and rapid cuff deflation.

NIBP Oscillometric Technique

The physical requirements for the examiner using an NIBP oscillometric device are much less than with a manual sphygmomanometer, so the importance of eye/hand/ear coordination is markedly reduced. As noted earlier, initial training is required for the selection of the correct cuff size and placement, proper patient positioning¹²⁵, and ensuring that the cuff is at heart level.

Since development for each brand of NIBP device is proprietary, examiners should refer to the user's manual for their specific device. As noted earlier,

ANSI/AAMI/ISO has published validation criteria to check for the accuracy of the NIBP device.¹⁰³ In addition, the organization has published environmental standards for safety and performance, which include maintaining ranges for temperature (10-40°C), humidity (15-90% noncondensing), and altitude (-170 to 1,700 m referenced to sea level). For safety, the maximum cuff pressure should never exceed 330 or 30 mmHg above the upper limit of the instrument's manufacturer-specified operative range, whichever is higher. Only devices independently validated according to standard protocols should be used, and individual calibration is recommended.¹⁰³

CHAPTER 3. MATERIALS AND METHODS

Research Design

The purpose of this prospective observational study was to examine the agreement of systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) measurements derived from a non-invasive blood pressure (NIBP) device with the same measurements obtained through traditional manual auscultatory methods in acute ischemic stroke (AIS) patients treated with alteplase. Additionally, this deductive study examined the relationship of MAP and outcomes in AIS patients who have received intravenous alteplase. A total of seven medical centers (three comprehensive stroke centers – two in New Jersey (NJ) and one in Tennessee (TN); and four primary stroke centers in NJ served as the sites for this study.

Institutional Review Board (IRB) Approval

Investigators received approval from the Institutional Review Board (IRB) at the University of Tennessee Health Science Center (UTHSC) and at Hackensack Meridian Health (HMH), a healthcare system in New Jersey. A waiver of informed consent and a waiver of the Health Insurance Portability and Accountability Act Authorization (HIPAA) was granted by both IRBs. Study protocol and procedures did not interfere with evidence-based standard of care treatment for AIS patients. Additionally, formal data-sharing agreements between the UTHSC and HMH's study sites were obtained.

Study Inclusion and Exclusion Criteria

Patients eligible for enrollment in the study were those who met current inclusions without exclusions for treatment with alteplase as set forth in the *2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke*¹ and the 2019 guideline updates¹⁰ that follow:

Inclusion Criteria

- Age ≥ 18 years old.
- Diagnosis of ischemic stroke.
- Onset of symptoms < 4.5 hours before beginning treatment.
- Baseline computed tomography scan of the brain negative for hemorrhage.
- Alteplase bolus and infusion received within the previous 24 hours.

Exclusion Criteria

- Significant head trauma, intracranial or spinal surgery in the previous 3 months.
- Suspected subarachnoid hemorrhage.
- Current intracranial hemorrhage.
- Known conditions that could increase the risk for hemorrhage (i.e. intracranial neoplasm, arteriovenous malformation, or aneurysm).
- Inability to control blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg) with intravenous antihypertensive agents (i.e., labetalol bolus or nicardipine infusion).
- Active internal bleeding.
- Acute bleeding diathesis, including but not limited to:
 - Platelet count <100 000/mm³.
 - Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal.
 - Current use of warfarin with INR >1.7 or PT >15 seconds.
 - Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays).

Study Specific Exclusion Criteria

Our study also adopted the following exclusion criteria that go beyond what is specified in the 2018 Guidelines and 2019 updates.^{1,10}

- Patients in atrial fibrillation or atrial flutter. (Oscillometric NIBP readings taken from patients in these rhythms are difficult to interpret due to significant beat-to-beat variation in MAP.^{28,30})
- Patients with upper arm circumference that exceeded the sizing recommendations¹²⁵ for either the NIBP or manual obese cuff parameters. (NIBP device measurements have been shown to be inaccurate in patients with ill-fitting blood pressure cuffs.)
- Patients on any form of isolation/contact precautions.

Protocol

Acute ischemic stroke patients who met inclusions without exclusions as detailed in the *2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke*¹ and the 2019 guideline updates,¹⁰ were eligible for study participation. Baseline pre-alteplase infusion SBP, DBP, MAP, and pre-treatment National Institute for Health Stroke Scale (NIHSS) scores were recorded, along with standard demographic variables, stroke arterial territory, antihypertensive medications used for treatment, and the dose prescribed, along with stroke mechanism. Medical conditions affecting the

cardiovascular system were also recorded, along with the dose of alteplase administered. Any additional treatment by thrombectomy was recorded along with Post-Treatment Thrombolysis in Cerebral Infarction (TICI) recanalization scores. Patient outcome measure after reperfusion including discharge modified Rankin Score (mRS) and the discharge NIHSS scale^{5,23} were also recorded.

Two examiners simultaneously measured BP readings with the use of a dual-auditory stethoscope following the technique described by Pickering, et al. in the *AHA Scientific Statement for Recommendations for Blood Pressure Measurement in Humans and Experimental Animals*¹²⁵ (refer to study process steps below). In addition, the design of the study protocol was informed by the ANSI/AAMI/ISO protocol from their 2013 publication: *Non-Invasive sphygmomanometers - Part 2: Clinical Validation of automated measurement*¹⁰³ and by the AAMI/ESH/ISO 2018 *Collaborative Statement: A Universal Standard for the Validation of Blood Pressure Measuring Devices*.¹⁰¹

Study Instruments and Supplies

The instruments and supplies used for the study, were as follows:

- General Electric Brand oscillometric NIBP device with valid and current biomedical inspection at the time of the study – supplied and used by all NJ study sites.
- Drager oscillometric NIBP device with a valid and current biomedical inspection at the time of the study – supplied and used by TN study site.
- Prestige Medical Clinical I Teaching Edition, dual auditory stethoscopes were purchased from Amazon and supplied to each study site.
- Disposable WIN TAPE 1 Meter 40" Paper Tape Measures for measurement of each patients' arm circumference were purchased from Amazon and supplied to each study site.
- Standard blood pressure cuffs (small/child, average, and large) supplied by each hospital study site.
- Hospital approved cleaning agent for reusable blood pressure cuffs supplied by each study site.

Study Process Steps

Blood Pressure Measurements

Two trained examiners measured five sets of manual-derived BP and NIBP-derived SBP, DBP, and MAP in acute ischemic stroke patients treated with alteplase. For the manual measures, the two examiners used a dual-auditory stethoscope to ensure accuracy of the measurement. The manual measurement was followed within 5-10 minutes by the NIBP measurement. To avoid interruption of acute stroke care, all measurements occurred during the 24 hours following the alteplase infusion. There was

no specific time during the 24 hours for the 5 sets of paired measurements to be completed.

The patient's arm circumference was measured with the disposable paper measuring tape, which was provided to each study site by the investigators. All seven study sites used the same brand of measuring tape. Appropriate BP cuff size was guided by Recommended Cuff Sizes for Accurate Measurement of Blood Pressure⁵ (**Table 3-1**).

Manual Blood Pressure Measurement

1. With the use of a dual-auditory stethoscope, two examiners, referred to as Examiner 1 and Examiner 2, first took a manual BP measurement, followed within 5-10 minutes by an NIBP measurement
2. Prior to initiation of manually derived blood pressure measurements, Examiner 1 explained to the patient the purpose of the set of blood pressure measurements with the dual-auditory stethoscope and the NIBP device using the following IRB-approved script:

The two of us are taking your blood pressure with a stethoscope that has 2 sets of ears. With this type of stethoscope, both of us can listen to your blood pressure at the same time to make sure we both hear the same blood pressure. We will write your blood pressure down on this form
(Examiner will show the Case Report Form).

We will then take your blood pressure with this blood pressure machine and write your blood pressure from the machine on the form as well. We will use these numbers in a study to find out whether the blood pressures we hear with the stethoscope matches the blood pressure from the machine. We also want to understand what the third number on the blood pressure machine means in relation to the top and bottom blood pressure numbers.
(Examiner will point to the MAP on the NIBP device). (Note: Examiner may say “systolic and diastolic” if the patient understands what these words mean.)

3. The Examiners followed the technique described by Pickering et al. in the American Heart Association's *Scientific Statement for Recommendations for Blood Pressure Measurement in Humans and Experimental Animals*.¹²⁵ The technique is further described in Step 5 of the Technique for Manual BP Measurement below. This technique was modified only for two examiners utilizing a dual-auditory stethoscope.

Table 3-1. Recommended cuff sizes for accurate measurement of blood pressure.

Adult Arm Size Circumference	Recommended Cuff Size (cm)
22 to 26 cm	12 x 22 cm (small adult)
27 to 34 cm	16 x 30 cm (adult)
35 to 44 cm	16 x 36 cm (large adult)

Data Source: Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation*. 2005;111.

Non-invasive Blood Pressure (NIBP) Measurement

NIBP measurements are a routine part of the standard of care treatment for acute ischemic stroke patients.

1. Both manual BP and NIBP measurements were taken from the same arm. After the Examiners recorded the SBP and DBP manual measurements, the manual cuff was removed, and the appropriate-sized NIBP device cuff was placed using standard of care technique.
2. Each of the two measurement-methods were taken within 5-10 minutes of each other to allow time for the patient's arm to fully revascularize and relax between measurements; otherwise, the data from the NIBP device would likely have been erroneous.

Additional Information Regarding Manual BP and NIBP Device Measurement

1. To avoid potential bias from NIBP device BP measurement results, the manual BP was always taken before the NIBP measurement.
2. The manual BP and NIBP taken as part of the study protocol did not guide patient treatment.
3. The clinician guiding the AIS patient's treatment was permitted to ask for the study BPs from the Examiners at any time.
4. If the clinician decided to use a study BP measurement to guide treatment, rather than the BP obtained as normal standard of care, from that point on, the patient would be excluded from the study. As this was an observational study only, this stipulation ensured that no treatments were based on measures obtained as part of the study protocol.

(Note: There was no instance of this occurring during the study period.)

Technique for Manual BP Measurement

Examiner 1 and Examiner 2 listened for the SBP and DBP using a dual-auditory stethoscope. All examiners were health care providers, i.e., Registered Nurses (RNs), Advanced Practice Nurses (APNs), and/or Physicians (MDs or DOs) trained and experienced in taking manual BPs from the technique described in the American Heart Association's *Scientific Statement for Recommendations for Blood Pressure Measurement in Humans and Experimental Animals*.¹²⁵ This technique was modified only in regard to two examiners utilizing a dual-auditory stethoscope.

1. Examiner 1 palpated the brachial artery in the antecubital fossa and placed the midline of the bladder of the cuff on the patient's upper bare arm so that it is just above the brachial arterial pulsation. To allow room for placement of the stethoscope, the lower end of the cuff was positioned 2 to 3 cm above the antecubital fossa.

2. Examiner 1 first identified the level of the suspected SBP by palpating the patient's pulse at the brachial or radial artery while inflating the cuff without auscultation. The level where the pulse is no longer palpable is the suspected SBP.
3. Both Examiner 1 and Examiner 2 prepared to listen for the BP measurement by placing their respective ends of the dual auditory stethoscope in their ears.
4. Examiner 1 placed the stethoscope over the brachial artery. To avoid artifactual noise, both examiners ensured that the stethoscope did not touch the cuff.
5. Examiner 1, who initially determined the level of the SBP, inflated the cuff to at least 30 mmHg above the point at which the radial pulse was determined to disappear.
6. To avoid significant underestimation of systolic and overestimation of DBP, Examiner 1 deflated the cuff at a rate of ≤ 2 mm per second.
7. As the cuff was gradually deflated and pulsatile blood flow re-established, both examiners listened for the appearance of Korotkoff sounds. Phase 1 Korotkoff sound is characterized by a clear, repetitive tapping sound, coinciding with the reappearance of a palpable pulse.¹²⁸ The initial appearance of phase 1 sounds is equal to the SBP. The point at which the repetitive tapping disappears is considered to be the phase 5 Korotkoff sound, which indicates the DBP.
8. Neither the examiners nor the patient should talk during the measurement.¹²⁵

Valid and Invalid Blood Pressure Measurements

1. Examiner 1 and Examiner 2 reported to each other the SBP and DBP they heard. For this study, a "valid BP measurement" was achieved when less than a 4 mmHg difference between the SBP and DBP between the Examiners' measures was reported. The SBP and DBP heard by Examiner 1 was the measurement used for the study, and thus was recorded on the CRF. However, if a difference of more than 4 mmHg existed between either the SBP or DBP from Examiner 1 and Examiner 2's reported measurements, then the BP measurement was considered "invalid".
2. In cases where "invalid BP measurements" were found, the Examiners waited at least five minutes before repeating another "set" of blood pressure measurements.
3. This process was repeated until a total of 5 "valid" sets of manual and NIBP measurements were recorded within 24 hours of the patient receiving the alteplase bolus and infusion. There were no set times in which the measurements must be taken; however, they must all have occurred within 24 hours after the patient received alteplase.

Data Collection

Patient enrollment and data collection took place over 13 months. Study site-specific investigators ensured inclusion and exclusion criteria were satisfied before enrolling an AIS patient in the study. Patient study variables were recorded on a case

report form (**Appendix B**) then de-identified and transferred to a research database maintained in an Excel spreadsheet. A unique identifier was assigned to each study patient by the principal investigator.

Data Analysis

Data from five sets of manual-derived BP and NIBP-derived measures for SBP, DBP, and MAP were collected from 95 patients from seven hospitals: six hospitals based in NJ, and one hospital in TN. Data was exported from an Excel research database to IBM SPSS Statistics 22.0 for descriptive analysis, tests of significance (parametric and non-parametric *t*-test), and normality analysis. NCSS Statistical Software (2020) was used for Bland-Altman analysis for measures of agreement and Lin's concordance correlation coefficients were used to analyze agreement between the paired readings.

CHAPTER 4. RESULTS

Between February 2019 and February 2020, seven medical centers (two comprehensive stroke centers in New Jersey [NJ], one comprehensive stroke center in Tennessee [TN], and four primary stroke centers in NJ) enrolled alteplase-treated AIS patients in this prospective, observational study. Our study population consisted of 95 AIS patients: 62 from NJ and 33 from TN, with mean age 69; 61% men, and 76% with a history of hypertension (**Table 4-1**).

Bland-Altman Analysis for Measures of Agreement

To test for agreement between the manual and NIBP measures, analyses were run using the Bland-Altman (BA) analysis for measures of agreement.¹²⁹⁻¹³² The BA analysis is a technique used to compare two measurements of the same variable. The question to be answered is whether the two methods of BP measurement are comparable to the extent that one might replace the other with sufficient accuracy for the intended purpose of BP measurement.¹²⁹ The analysis incorporates the Bland-Altman (BA) scatter plot, descriptive statistics, test of normality, significance of bias, and limits of agreement, and assumption plots.

Bland and Altman's technique for measuring agreement was first introduced in 1983. Since that time, the method has evolved, with the authors, in a series of articles published between 1983-2007 further refining, clarifying, and defining alternate and additional techniques researchers may consider based on the type and quantity of the data collected, and the method of data collection.

What follows are BA statistical tests for the analysis of measures of agreement for 475 sets of manual BP and NIBP-derived SBP, DBP, and MAP from 95 patients. The differences between SBP, DBP, and MAP measurements, and prediction limits for the difference between pairs of future measurements, known as the limits of agreement are shown.¹³³ For this analysis, each of the 475 sets of measures were treated independently.

The Bland-Altman Scatter Plot

In their introductory article; "Measurement in Medicine: The Analysis of Method Comparison Studies,"¹³⁰ Altman and Bland state that the mandatory first step for method comparison studies is to plot the data. As an integral part of the analysis, this visual tool is often simply referred to as a Bland-Altman Plot (BA plot). The BA plot is essentially a standard scatter plot with the addition of limits of agreement (LoA) and a difference (bias) line. It consists of a plot of the difference between paired readings of two variables (i.e. manual BP measures and NIBP device measures) over the average of these readings, with 2 standard deviation (SD) lines (confidence interval [CI]) parallel to the mean difference line.¹³⁴

Table 4-1. Demographic/Baseline characteristics of the study population.

Variables	All Study Sites (n = 95)	TN Values (n = 33)	NJ Values (n = 62)	p-Value (<i>t</i> -test, chi-square, and median test)
Age, mean (SD)	69 (14)	65 (12.3)	71 (14.6)	<0.05*(0.04)
Gender				p = ns (0.41)
Male, n (%)	58 (61)	22 (67)	36 (58)	
Female, n (%)	37 (39)	11 (33)	26 (42)	
Ethnicity				<0.05**(0.000)
Caucasian, n (%)	61 (64)	9 (27)	52 (84)	
African American, n (%)	30 (32)	23 (70)	7 (11)	
Hispanic, n (%)	4 (4)	1 (3)	3 (5)	
Hypertension, n (%)	72 (76)	24 (73)	48 (77)	p = ns (0.61)
Diabetes mellitus, n (%)	33 (35)	14 (42)	19 (31)	p = ns (0.25)
HgbA1c, mean (SD)	6.4 (1.6)	6.5 (1.8)	6.3 (1.4)	p = ns (0.58)
Smoking, n (%)	30 (32)	11 (33)	19 (31)	p = ns (0.79)
Previous Stroke, n (%)	25 (27)	13 (41)	12 (19)	<0.05* (0.03)
Baseline NIHSS, Median (Q1, Q3)	5 (3, 11)	5 (3, 7)	6 (3.25, 13)	<0.05* (0.04)
Pre-Stroke Modified Rankin Score, Median (Q1, Q3)	0 (0, 1)	0 (0, 2)	0 (0, 1)	p = ns (0.99)

Notes: p = ns refers to non-significant; p-value*<0.05; p-value**<0.001. For categorical variables (gender, ethnicity, HTN, DM, smoking, previous stroke) chi-square test was used. For continuous variables (age, A1C), a student's *t*-test was used. For baseline NIHSS and baseline mRS, non-parametric median test for difference in the medians.

The difference in the readings from the two methods, manual BP and NIBP measurements, are plotted on the y-axis, and the average of the readings from the two methods are plotted on the x-axis. The data cluster around a regression line by definition regardless of the agreement.¹²⁹ The BA plot's visual format makes it easier to assess the magnitude of disagreement, spot outliers, and determine if a trend exists in the data. It displays four types of data misbehavior: (1) systematic error (mean offset), (2) proportional error (trend), (3) inconsistent variability, and (4) excessive or erratic variability.¹³⁴

To make a determination that no remarkable data misbehavior is present, the measurement points should center about difference = 0, provide a reasonable confidence interval, and remain in the same general pattern for all horizontal axis values.¹³⁴ Only about 5% of the data should lie outside the plus-minus CI, and these points should not be dramatically far outside the confidence interval. If too many points lie outside, then the data are erratically variable.¹³⁴

Descriptive Statistics

Descriptive statistics of the *count*, *mean*, *standard deviation* (SD) and *95% CI*, *bias*, and *LoA* for manual and NIBP measured SBP, DBP, and MAP were generated for our measurement data.

Test of Normality of Differences

To test for normality of the distribution of the variables and to test the statistical significance of the bias, the Shapiro Wilk parametric test was used.

Assumptions Plots

A histogram, normal probability plot of difference, and a linear scatter plot) were generated to show the behavior of the data from the manual measures in relation to NIBP measures. These plots facilitate visual assessment for whether a data set is approximately normally distributed.

Lin's Concordance Correlation Coefficients (CCC)

Lin's CCC were also computed to provide a further understanding of the data's behavior. CCCs are used to evaluate the agreement between paired readings when the variable of interest is continuous.^{135,136} Values near +1 indicate strong concordance between x and y; values near -1 indicate strong discordance, and values near zero indicate no concordance.¹³⁷ However, researchers have various interpretations. Altman interprets the correlation with <.20 as poor and >.80 as excellent,^{138,139} whereas McBride suggests

the following interpretation: <0.90: poor; 0.90 to 0.95: moderate; 0.95 to 0.99: substantial; and >0.99 almost perfect.^{139,140}

Additional Tests

In addition to the BA analyses, parametric tests, non-parametric tests, and further descriptive statistics were run for additional data comparison.

Systolic Blood Pressure

Bland-Altman Scatter Plot for SBP

The Bland-Altman scatter plot for SBP (**Figure 4-1**) illustrates the difference between the two methods (manual minus NIBP) against the average of the two methods (manual plus NIBP)/2. The figure shows the center dotted line ($y = 0$) and the line of bias (mean difference). Here, the bias is the mean difference and is equal to -3.75 points or mmHg. This indicates the average NIBP device readings were higher than the manual readings. The lower control limit (LCL) ($\text{mean} - 1.96 \times \text{SD}$) and upper control limit (UCL) ($\text{mean} + 1.96 \times \text{SD}$) lines show the limits of agreement (LoA). The points that lie out of the LoA lines are outliers.

Descriptive Statistics, Bias, and Limits of Agreement for SBP

Table 4-2 shows the *count, mean, standard deviation (SD), and 95% CI of the difference* for SBP measured by the two methods. The mean (SD) for manual SBP was 138(21) mmHg, and mean (SD) for NIBP SBP was 142(22) mmHg. The mean (SD) of the bias (difference) between the two methods was -3.75 (12.8) mmHg. The NIBP measure was subtracted from the manual BP measure. The negative result indicates that the NIBP SBP readings were higher than manual SBP measures. The value for LCL was -28.9 and UCL was 21.4. Note the width of the confidence interval of 50.3 mmHg between the LCL and UCL.

Test of Normality for SBP

The Shapiro–Wilk test for normality of the difference between the two methods of SBP measurements (manual SBP minus NIBP SBP) yielded a value of 0.990 ($p=0.0025$); thus, the hypothesis of normality is rejected.

Figure 4-1. Bland–Altman plot of the 475 manual SBP versus NIBP SBP measures.

The dotted line indicates difference of manual *minus* NIBP SBP (y-axis) = 0, the line of perfect average agreement. The red line is the line of bias (the actual difference of manual *minus* NIBP SBP). a) The points center about the difference = 0 and are in the same general pattern for all horizontal axis values. b) The mean is offset, lying below zero, suggesting a mean bias (a systematic error). c) 2.1 percent (~10 of 475) of the data points lie above and below the confidence limits. d) Most of the outliers fall beyond an average reading of approx. 130 mmHg SBP.

Table 4-2. Descriptive statistics for SBP.

Variables	Descriptive Statistics			95% CI of the Difference	
	Count	Mean	SD	Lower	Upper
MAP Manual	475	138.1	20.9	136.3	140
MAP NIBP	475	141.9	21.7	139.9	143.8
Difference	475	- 3.75	12.8	-4.91	-2.59
Lower LoA	475	-28.91	1.0	-30.9	-26.9
Upper LoA	475	21.41	1.0	19.41	23.39

Notes: Based on 475 sets of measures from 95 patients. LoA = Limits of Agreement and CI = Confidence Intervals.

Assumption Plots for SBP

Figure 4-2 shows the histogram, the normal probability plot of difference, and the linear scatter plot for SBP measurements. These plots clearly show that the data is skewed, not normally distributed, and there exists a large difference in the SBP manual and NIBP measures.

Lin's CCC for SBP

CCC was 0.82.

Diastolic Blood Pressure

Bland-Altman Scatter Plot for DBP

The Bland-Altman Scatter Plot (**Figure 4-3**) for DBP illustrates the difference between the two methods (manual *minus* NIBP) against the average of the two methods (manual *plus* NIBP)/2. The figure shows the center dotted line ($y = 0$) and the line of bias (mean difference). Here, the bias is the mean difference and is equal to -1.06 points or mmHg. This indicates the average NIBP device readings were higher than the manual readings. The LCL and UCL lines show the LoA. The points that lie out of the limits of agreement lines are outliers.

Descriptive Statistics, Bias, and Limits of Agreement for DBP

Table 4-3 shows the *count, mean, standard deviation (SD), and 95% CI of the difference* for DBP measured by the two methods. The mean (SD) for manual DBP was 73(12) mm/Hg, and mean(SD) for NIBP DBP was 74(13) mm/Hg. The mean (SD) of the bias (difference) between the two methods was -1.06(10.2) mmHg. The NIBP measure was subtracted from the manual measure. The negative result indicates that the NIBP DBP readings were higher than manual DBP measures. The value for LCL was -21.0, and UCL was 19.0. Note the width of the confidence interval of 40.0 mmHg between the LCL and UCL.

Test of Normality for DBP

The Shapiro–Wilk test for normality of the difference between the two methods of DBP measurements (manual DBP minus NIBP DBP) yielded a value of 0.993 ($p = 0.0273$); thus, the hypothesis of normality is rejected.

Figure 4-2. Assumption plots for normality (histogram, normal probability plot, and linear plot) for SBP.

a) The histogram is skewed left and thus is not normally distributed. b) The normal probability plot of the difference shows longer than expected tails with the data points skewed from the extremes, indicating the distribution of the data was not normal. c) The linear scatter plot where manual and NIBP readings are plotted against each other on an x and y-axis (centerline is the $y = x$ line). Data points are deviating (scattered) from the centerline of equality and are widely dispersed, indicating that the linear relationship is not strong. The points that are away from the centerline indicate that there is a difference in the manual and NIBP readings. The drawn line connecting one point to the y-axis and the x-axis illustrates that there is a difference in the manual and NIBP readings. Here, the SBP NIBP (y-axis) is approximately 165, and the manual SBP (x-axis) is approximately 135.

Figure 4-3. Bland–Altman plot of the 475 manual DBP versus NIBP DBP measures.

The dotted line indicates difference of manual *minus* NIBP DBP (y-axis) = 0, the line of perfect average agreement. The red line is the line of bias (the actual difference of manual *minus* NIBP DBP). a) The points center about the difference = 0 and are in the same general pattern for all horizontal axis values. b) The mean is offset, lying below zero, suggesting a mean bias (a systematic error). c) 3.4 percent (~16 of 475) of the data points lies above and below the confidence limits. d) Most of the outliers fall below an average reading of 80 mmHg DBP.

Table 4-3. Descriptive statistics for DBP.

Variables	Descriptive Statistics			95% CI of the Difference	
	Count	Mean	SD	Lower	Upper
DBP Manual	475	73.2	12.4	72.1	74.3
DBP NIBP	475	74.3	13.4	73.0	75.5
Difference	475	-1.06	10.2	-1.98	0.14
Lower LoA	475	-21.0	0.80	22.6	-19.5
Upper LoA	475	19.0	0.80	17.3	20.5

Notes: Based on 475 sets of measures from 95 patients. LoA = Limits of Agreement and CI = Confidence Intervals.

Assumption Plots for DBP

Figure 4-4 shows the histogram, the normal probability plot of difference, and the linear scatter plot for DBP measurements. These plots clearly show that the data is skewed, not normally distributed, and there exists a large difference in the DBP manual and NIBP measures.

Lin's CCC for DBP

CCC was 0.69.

Mean Arterial Pressure

Bland-Altman Scatter Plot for MAP

The Bland-Altman scatter plot (**Figure 4-5**) for MAP illustrates the difference between the two methods (manual *minus* NIBP) against the average of the two methods (manual *plus* NIBP)/2. The figure shows the center dotted line ($y = 0$) and the line of bias (mean difference). Here, the bias is the mean difference and is equal to -5.49 points or mmHg. This indicates the average NIBP device readings were higher than the manual readings. The LCL and UCL lines show the LoA. The points that lie out of the LoA lines are outliers.

Descriptive Statistics, Bias, and Limits of Agreement for MAP

Table 4-4 shows the *count, mean, standard deviation (SD), and 95% CI of the difference* for MAP measured by the two methods. The mean (SD) for manual MAP was 95(13) mm/Hg, and mean (SD) for NIBP MAP was 100(17) mmHg. The mean (SD) of the bias (difference) between the two methods was -5.49(11) mmHg. The NIBP measure was subtracted from the manual measure. The negative result indicates that the NIBP MAP readings were higher than manual DBP measures. The value for LCL was -27.5, and UCL was 16.5. Note the width of the confidence interval of 44 mmHg between the LCL and UCL.

Test of Normality for MAP

The Shapiro–Wilk test for normality of the difference between the two methods of MAP measurements (manual MAP minus NIBP MAP) yielded a value of 0.992 ($p=0.0105$); thus, the hypothesis of normality is rejected.

Figure 4-4. Assumption plots for normality (histogram, normal probability plot, and linear plot) for DBP.

a) The histogram is skewed left and thus is not normally distributed. b) The normal probability plot of the difference shows that the data points are skewed, meaning the distribution was not normal. c) The linear scatter plot where manual and NIBP readings are plotted against each other on an x and y-axis (centerline is the $y = x$ line). Data points are deviating (scattered) from the centerline of equality and are widely dispersed, indicating that the linear relationship is not strong. The drawn line connecting one point to the y-axis, and the x-axis illustrates that there is a difference in the manual and NIBP readings. Here, the DBP NIBP (y-axis) is approximately 105 and the manual DBP (x-axis) is approximately 62.

Figure 4-5 Bland–Altman plot of the 475 manual MAP versus NIBP MAP measures.

The dotted line indicates difference of manual *minus* NIBP MAP (y-axis) = 0, the line of perfect average agreement. The red line is the line of bias (the actual difference of manual *minus* NIBP MAP). a) The points center about the difference = 0. b) There is a negative linear association between the difference and the average. c) A trend or error proportional to the size of measure is seen (cluster of points moves to below the median line as the mean MAP increases). d) The mean is offset, lying below zero, suggesting a mean bias (a systematic error). e) 4.7 percent (~22 of 475) of the data points lie above and below the confidence limits. Since nearly 5% lie outside the plus-minus CI, this suggests a skew in the data and variability. f) Most of the outliers (14 of 22) fall below the average MAP reading of 124 mmHg.

Table 4-4. Descriptive statistics for MAP.

Variables	Descriptive Statistics			95% CI of the Difference	
	Count	Mean	SD	Lower	Upper
MAP Manual	475	94.8	13.4	93.6	96.0
MAP NIBP	475	100.3	17.2	98.8	101.9
Difference	475	-5.49	11.2	-6.50	-4.48
Lower LoA	475	-27.5	0.9	-29.2	-25.8
Upper LoA	475	16.5	0.9	14.8	18.2

Notes: Based on 475 sets of measures from 95 patients. LoA = Limits of Agreement and CI = Confidence Intervals.

Assumption Plots for DBP

Figure 4-6 shows the histogram, the normal probability plot of difference, and the linear scatter plot for MAP measurements. These plots clearly show that the data is skewed, not normally distributed, and there exists a large difference in the MAP manual and NIBP measures.

Lin's CCC for MAP

CCC was 0.76.

Non-Parametric and Parametric Findings

Since the difference between the two SBP, DBP, and MAP measurements did not follow a normal distribution, additional testing of the significance of bias using both non-parametric and parametric student's *t*-test was performed

Non-Parametric: One-Sample Wilcoxon Signed Rank Test

As the normality assumptions for 475 sets of measures for all SBP, DBP, and MAP were rejected, the non-parametric One-Sample Wilcoxon Signed Rank Test was used to determine if the bias (difference) in the median of the measures (null hypothesis: median test value = 0) was significant. All three null hypotheses were rejected for SBP $p = .000$, for DBP $p = .049$, and for MAP $p = .000$.

Parametric: One Sample Student's *t*-Test

As the sample size was adequate, the parametric one-sample student's *t*-test was used to determine if the bias (difference) in the mean of the measures (null hypothesis: mean test value = 0) was significant for 475 sets of measures for all SBP, DBP, and MAP. All three null hypotheses were rejected: SBP ($p = .000$), DBP ($p = .024$), and MAP ($p = .000$).

Other Findings

Each of the 475 paired sets of measures (manual and NIBP) were further analyzed to determine how far each of the SBP, DBP, and MAP measurements fell from each other. The differences of these measurements are presented in percentage terms.

Figure 4-6. Assumption plots for normality (histogram, normal probability plot, and linear plot) for MAP.

a) The histogram is skewed left and thus is not normally distributed. B) The Normal Probability Plot of the Difference shows that the data points are dispersed at both extremes indicating the distribution was not normal. c) The Linear Plot: manual and NIBP readings plotted against each other on an x and y-axis (centerline is the $y = x$ line). Data points are deviating from the line of equality. The points that are away from the centerline show the difference in the readings as measured by the 2 methods. The drawn line connecting one point to the y-axis and the x-axis illustrates that there is a difference in the manual and NIBP readings. (Here, the MAP NIBP (y-axis) is approximately 150, and the manual MAP (x-axis) is approximately 112.

Percent Difference in mmHg Between Manual and NIBP Device

Table 4-5 shows the percentage of measurements that fell within a difference of 5, 10, 15 and 20 mmHg for SBP, DBP and MAP separately. Eighty percent of measures should fall within 5 mmHg and 95% should fall within 10 mmHg for clinical agreement to be considered acceptable.¹⁴¹ Thus, values with a width greater than 10 mmHg (+/- 5 mmHg) are considered clinically different.

For SBP, 39% of the 475 sets of measures fell within 5 mmHg and 62% fell within 10 mmHg. For DBP, 44% fell within 5mmHg and 72% fell within 10 mmHg. For MAP, 34% fell within 5 mmHg and 62% fell within 10 mmHg.

Other SBP Findings

As explained earlier in chapter 1, for patients who present with AIS, the acceptable limits for the parameters of SBP for initiation of alteplase bolus are <185 mmHg, and <180 mmHg for alteplase infusion. In the chapter, these SBP parameters were referred to as “in bounds” and “out of bounds” for alteplase treatment. Having this in mind, each of the 475 paired SBP measures were further analyzed to determine the number of manual and NIBP measurements that fell within the in-bounds and out-of-bounds SBP limits for initiation of alteplase. **Table 4-6** shows that in 11 instances, manual SBP was >180 mmHg, compared to 22 instances when NIBP SBP was >180 mmHg.

Other DBP Findings

For patients who present with acute ischemic stroke, DBP “in-bounds” and “out-of-bounds” limits for initiation of alteplase bolus are <110 mmHg, and for alteplase infusion <105 mmHg. Having this in mind, each of the 475 paired DBP measures were further analyzed to determine the number of manual and NIBP measurements that fell within the in-bounds and out-of-bounds DBP limits for initiation of alteplase treatment. **Table 4-7** shows that in no instances did manual DBP identify values <105 mmHg compared to six when NIBP DBP was >105 mmHg.

Other MAP Findings

Chapter 1 includes a discussion introducing MAP as a parameter to guide AIS treatment potentially. Chapter 2 provides evidence that MAP is the value most closely associated with NIBP accuracy. Applying the SBP and DBP out-of-bounds values (>180 and >105 mmHg, respectively) for initiation of alteplase infusion into the calculated MAP equation produces an in-bounds MAP <130 and out-of-bounds MAP $\geq$ 130 mm Hg. Having this in mind, each of the 475 paired MAP measures were further analyzed to determine the number of manual and NIBP measurements that fell within the in-bounds and out-of-bounds MAP limits for initiation of alteplase treatment. **Table 4-8** shows in

Table 4-5. Percent difference in mmHg between manual and NIBP device.

Variable (n = 475)	+/- ≤5 mmHg	+/- ≤10 mmHg	+/- ≤15 mmHg	+/- ≤20 mmHg	Mean +/- SD of the Difference (mmHg)
SBP	39%	62%	76%	86%	-3.75 ± 12.84
DBP	44%	72%	86%	95%	-1.06 ± 10.28
MAP	34%	62%	78%	89%	-5.49 ± 11.22

Table 4-6. The number of SBP measures <180 and ≥180 mmHg.

SBP (mmHg)	Manual	NIBP
<180	463	453
≥180	11	22

Note: SBP for each of 475 measurements from 95 patients. All measurements were taken during the 24-hours after alteplase infusion.

Table 4-7. The number of DBP measures <105 and ≥105 mmHg.

DBP (mmHg)	Manual	NIBP
<105	475	469
≥105	0	6

Note: DBP for each of 475 measurements from 95 patients. All measurements were taken during the 24-hours after alteplase infusion.

Table 4-8. The number of MAP measures <130 and ≥130.

MAP Range (mmHg)	Manual	NIBP
<130	471	442
≥130	2	30

Note: MAP for each of 475 measurements from 95 patients. All measurements were taken during the 24-hours after alteplase infusion.

two instances that manual MAP was ≥ 130 mmHg compared to 30 instances when NIBP MAP was ≥ 130 mmHg.

Secondary Study Aim Results for MAP and Outcomes

Following are our results from investigating the relationship between MAP and outcomes in alteplase-treated AIS patients

Ultimately the data were insufficient to analyze this study aim adequately. Like current reported statistics, only 3% of our study population (3 patients) developed symptomatic intracranial hemorrhage (sICH). Of the 95 patients, three patients died before hospital discharge, one of which was attributed to post-alteplase sICH. Overall, for the entire sample, the median NIHSS at admission was 5, and at discharge or day 7, median NIHSS was 1 (**Table 4-9**). The baseline median modified Rankin score (mRS) before stroke onset was 0 for the sample. Median mRS at discharge or day 7 for those without sICH was 1; for 3 patients with sICH, median mRS at discharge or day 7 it was 5 ($p = ns$). Of the 3 sICH patients, 1 died before hospital discharge.

A total of 90 patients had mRS documented at hospital discharge or day 7. These patients were dichotomized into groups based on achievement of an mRS of ≤ 2 indicating favorable outcome at the time of hospital discharge vs. those with mRS > 2 indicating poor functional outcome. Manual and NIBP-derived SBP, DBP, and MAP were analyzed for differences based on hospital discharge functional outcome (**Table 4-10**).

Table 4-9. Outcomes for median NIHSS at baseline and 24 hours, and median mRS at pre-stroke and discharge or day 7.

NIHSS - Baseline	NIHSS -24-hr	mRS - Pre-stroke Score	mRS - Discharge or Day 7
5 (3, 11)	2 (0, 6.25)	0 (0, 1)	1 (0, 4)

Notes: NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Score. Results for median (Q1, Q3)

Table 4-10. Comparison of manual and NIBP for SBP, DBP, and MAP between patients with favorable outcomes and poor outcomes at discharge or day 7.

Means	Favorable Outcomes (mRS $\leq$ 2) at Discharge or Day 7	Poor Outcomes (mRS $>$ 2) at Discharge or Day 7	p-Value (Independent Samples <i>t</i> -Test)
Manual SBP	136	141.8	$<0.05^*(0.004)$
Manual DBP	73.6	72.6	p = ns (0.45)
Manual MAP	94.4	95.7	p = ns (0.30)
NIBP SBP	139.7	145.3	$<0.05^*(0.008)$
NIBP DBP	75	73.6	p = ns (0.29)
NIBP MAP	100.2	100.8	p = ns (0.74)

Notes: mRS = modified Rankin Score. Favorable outcomes include 56 patients; 280 observations. Poor outcomes were patients who developed sICH and/or in-hospital death before discharge. Poor outcomes include 34 patients with 170 observations. Discharge mRS was not documented in the medical record for 5 patients – thus could only run analysis on 90 patients, not 95.

CHAPTER 5. DISCUSSION AND CONCLUSIONS

Our study found no agreement in SBP, DBP, and MAP for 475 paired manual and NIBP measurements, with MAP manual and NIBP measures showing the least agreement between methods. Although DBP paired measures did not agree, they were in closer agreement than SBP and MAP measures using Bland-Altman (BA) analysis, and 44% of DBP measures fell within 5 mmHg of each other. Importantly, our results show that NIBP measures were consistently higher than manual measurements and differed from manual measurements as much as 50 mmHg for SBP, 40 mmHg for DBP, and 44 mmHg for MAP.

Understanding Agreement

When the two methods for measuring blood pressure are compared, neither provides an unequivocally correct measurement, so testing is performed to assess the degree of agreement.¹³⁰ Additional considerations (beyond closeness of the numerical readings) include whether the two measurement methods produce the same mean, whether there is any relative bias (differences), and whether variability (SD) between the measurement methods exists.¹²⁹ Even with all this in place, clinically acceptable limits of agreement for SBP, DBP, and MAP in AIS patients must be defined a priori in order to understand if the two measures adequately agree in the specific patient population undergoing testing.

Determination of Acceptable Limits of Agreement

As noted above, a vital first step is to determine the acceptable bias (acceptable limits of agreement [LoA] between measurement methods. The LoA estimates the interval within which a proportion of the differences between measurements lie. The LoA includes both systematic (bias) and random error (precision) and provides a useful measure for comparing the likely differences between individual BP results measured by manual and NIBP methods.¹⁴² For example, if we had determined that an acceptable bias between the manual and NIBP measures was 5 mmHg, then the bias would have been tested for the test value of 5. Since stroke guidelines are silent regarding an acceptable bias in the AIS patient population, we tested whether significant bias was present compared to the test value of zero. In other words, part of the determination of agreement was based on how far from zero the mean difference of the NIBP test method fell from the reference method, manual BP (i.e., mean manual BP minus mean NIBP).

The BA analysis only defines the intervals of agreement; it does not determine whether those limits are acceptable (or not) from a clinical standpoint. In other words, how far apart measurements can be to maintain their acceptability in clinical use is a question of judgment that must be considered by the investigators.¹³⁰ We suggest that

clinically acceptable LoA for SBP, DBP, and MAP in AIS patients should be defined a priori in all vascular diseases based on clinical necessity, biological considerations, and treatment goals.¹⁴³ Our findings highlight the need for guideline-specified clinically acceptable LoA between manual and NIBP measures, particularly since NIBP is almost exclusively used today, yet, the BP goals for treatment with alteplase were originally established to support BP measurement by manual cuff.

Many Factors Affect the Agreement Decision

In our study, the Shapiro-Wilks test was used first to test the normality of the distribution of the SBP, DBP, and MAP, and normality was rejected for all 3 BP parameters ($p < 0.05$). The non-parametric one-sample Wilcoxon signed rank test was used to determine the significance of the difference using the null hypothesis for each of the BP parameters; median test value = 0. All three null hypotheses were rejected for the difference in SBP, DBP, and MAP measures. The parametric one-sample student's *t*-test was used to determine if the bias was significant for each of the BP parameters (mean test value = 0); again, all three null hypotheses were rejected ($p < 0.05$). Additionally, the SD for the mean difference of SBP was 12.8, for DBP was 10.2, and for MAP was 11.2, and the width of the CIs was quite large for all three BP parameters. For example, the SBP LCL was -28.9 mmHg, and UCL was 21.4 mmHg; therefore, the width between the LCL and UCL comprised 50.3 mmHg for SBP. Similarly, the width between DBP LCL and UCL was 40.0 mmHg, and the width between MAP LCL and UCL was 44 mmHg. With such a significant variation between mean manual and mean NIBP measures, a determination that the two methods of measurements are in agreement would be questionable.

Using SBP as an example, poor agreement is evident in both the SBP's 50-point range in CIs and the BP data points wide dispersion and deviation from the centerline of equality on the linear scatter plot. Interestingly, the error increased at approximately 130 mmHg levels, and this trend continued as the SBP increased. Because AIS patients commonly present with severe hypertension that requires treatment with antihypertension agents before thrombolysis can be initiated, it may be likely that in hyperacute ischemic stroke the error between manual and NIBP devices may be quite substantial. Undoubtedly this error impacts clinical treatment decisions and the subsequent management required to provide safe patient care, and it may also result in clinicians maintaining BP much lower than the original limits of 180/105 mm Hg.

Investigators who also studied agreement between NIBP and manual or arterial measurements^{40,43,114,115,119,144} evaluated their results based on the limits set by the Association for the Advancement of Medical Instrumentation (AAMI).¹⁰³ However, the AAMI procedure is intended for validation of an individual NIBP device's accuracy prior to placing the device into clinical use. The AAMI procedure involves testing the mean error and the SD of the error for a total of 255 pairs of measurements (three sets of manual BP and NIBP measures) from 85 patients. Per the AAMI, an acceptable limit is when the difference of the means between manual and NIBP measures < 5 mmHg with

SD <8. Should BP investigators and clinicians consider AAMI protocol to be the gold standard for patient treatment decisions as well? Or should acceptable LoA, mean difference, and SD be studied, evaluated alongside the clinical condition in question, and ultimately agreed upon by subject matter experts? AAMI seems to support the latter, stating in their 2013 publication of recommendations for the basic safety and essential performance of automated non-invasive sphygmomanometers:

...the application of a standard or recommended practice is solely within the discretion and professional judgment of the user of the document. A standard or recommended practice is limited, however, in the sense that it responds generally to perceived risks and conditions that may not always be relevant to specific situations. A standard or recommended practice is an important reference in responsible decision-making, but it should never replace responsible decision-making.^{103(p. 2)}

A related problem in relying on AAMI procedures to determine accuracy and agreement of readings between manual and NIBP measurements is that algorithms, testing, and validation procedures differ from one device to another¹⁰³ and are scattered in many different publications or patents.¹⁰⁵ This means that claims and findings of accuracy and agreement for one NIBP device brand cannot be generalized to other brands. Babbs,³¹ an NIBP device engineer, confirms this situation when reporting that accurate extraction of systolic and diastolic pressure oscillations remains an open problem in biomedical engineering. To resolve this problem, he developed an algorithm based on physics and physiology and then shared it in the public domain for NIBP device manufacturers and engineers to review and use.

Many clinicians are unaware that NIBP devices are engineered in a way that *should* make the MAP the most accurate measurements from these devices. Similar to Kiers et al.,¹²¹ we also found a relatively large range in the difference between calculated and measured MAP between manual and NIBP measures. Kiers et al.¹²¹ and our results challenge the well-held belief that MAP is the most accurate measure from the NIBP, unless we are to accept that manual measurement in and of itself is flawed and inaccurate. Even if we were to accept the NIBP MAP as the most valid measure, this still presents the problem that SBP and DBP values differ significantly, with hundreds of combinations of SBP and DBP values possible from a single MAP measurement.

An Alternate Approach to Measure Agreement

The British Hypertension Society (BHS) introduced a protocol for evaluating NIBP devices' accuracy by using the percentage of differences within certain limits.^{131,141} The BHS protocol is quite complex, and similar to the AAMI procedure, its intent is to evaluate the accuracy of an NIBP device prior to placing it into service. The NIBP device is graded A, B, C, or D based on percentages of readings within 5, 10, and 15 mmHg. The BHS protocol also includes an instruction to determine whether the mean

differences and SD fall within the AAMI recommendations of <5 mmHg and ≤ 8 mmHg, respectively.

We adapted a portion of the BHS protocol to determine in percentage terms how far each of the 475 paired manual and NIBP measurements fell from each other. We also evaluated our findings with an adaptation of the protocol guidelines that stipulates that 80% of measures should fall within 5 mmHg, and 95% should fall within 10 mmHg.¹⁴¹ We found only 39% of the 475 sets of SBP manual and NIBP measures fell within 5 mmHg of each other, 62% fell within 10 mmHg, and 86% fell within 20 mmHg of each other. For DBP, 44% fell within 5 mmHg of each other, 72% fell within 10 mmHg, and 95% within 20 mmHg each other. For MAP, 34% fell within 5 mmHg of each other, 62% fell within 10 mmHg, and 89% within 20 mmHg of each other. Importantly, none of the 3 BP parameters had 80% of their paired measures falling within 5 mmHg and 95% within 10 mmHg of each other.

Statistical and Clinical Significance of Our Study

In their 1986 article “Statistical Methods for Assessing Agreement Between Two Methods of Clinical Measurement,” Bland and Altman wrote:

It is most unlikely that different methods will agree exactly, by giving the identical result for all individuals. We want to know by how much the new method is likely to differ from the old: if this is not enough to cause problems in clinical interpretation we can replace the old method by the new or use the two interchangeably.^{130(p 308)}

Clinical Significance of NIBP Measure

Alteplase significantly improves the overall odds of a good stroke outcome when delivered within 4.5 hours of stroke onset, with earlier treatment associated with greater proportional benefits.¹⁴⁵ Progressive disappearance of the ischemic penumbra is the major factor that accounts for the declining benefit with time.¹⁴⁶ Therefore, it is imperative that clinicians understand and consider the origins of NIBP device readings so that treatment is not unnecessarily delayed. Per stroke guidelines, a clinician should hold the alteplase bolus until the patient’s SBP is <185 mm Hg and DBP is <110 mm Hg, and BP should be further lowered to SBP <180 mm Hg and DBP <105 mm Hg by the time the alteplase infusion begins. Depending on the point in the AIS clinical pathway that the patient’s BP is measured, the presence of bias between the means can be *either clinically significant or clinically insignificant*. For example, an SBP of 180 mm Hg from an NIBP device in a clinically stable AIS patient on arrival to the emergency department is likely *clinically insignificant* in that an alteplase treatment decision is yet to be made, with guidelines suggesting that AIS patients can be managed up to an SBP of 220 mm Hg and DBP of 120 mm Hg when alteplase is withheld; therefore, there is no real concern if the NIBP measurement is falsely elevated. On the other hand, the lack of agreement is

arguably *clinically significant* at the point in the clinical pathway when the patient is deemed appropriate for alteplase treatment because an SBP that is higher than recommended stroke guideline treatment thresholds will trigger potential delays in alteplase treatment due to the need for administration of intravenous antihypertensives. Interestingly, higher NIBP readings may be causing practitioners to keep BP much lower than the original alteplase treatment BP targets without their knowledge of doing so. In a similar study of agreement between manual and NIBP measures of pre-assessment of outpatient surgery patients, Coe et al.¹²⁰ surmised that 6.5% of their study participants would have been inappropriately diagnosed as hypertensive from the NIBP device readings, and thus potentially rejected from day surgery and inappropriately referred to their general practitioner. In agreement with Cole's suggestion, it would be reasonable for acute stroke practitioners to recheck an acute AIS patient's BP using a manual sphygmomanometer for any hypertensive reading by an NIBP device.¹²⁰

To further examine the potential influence manual and NIBP measures may have on clinical decision making, we analyzed our paired measures to determine the number of measurements that fell within the in-bounds and out-of-bounds limits for initiation of alteplase. For SBP, 11 manual and 22 NIBP measures were >180 mmHg, meaning that alteplase treatment would have been delayed more often in the NIBP group due to SBP >180 mmHg. None of the DBP values we measured for either manual or NIBP exceeded the guideline's 105 mm Hg threshold.

Currently, MAP is not cited in the guidelines as a measure requirement for determining alteplase treatment thresholds; however, it can be calculated from the 180/105 mmHg exclusion boundary for alteplase treatment at 130 mm Hg. Whether MAP of >130 mm Hg is the "true" high limit for alteplase treatment remains unknown since even the guideline's 180/105 mmHg values were not derived through any systematic study of alteplase-treated patients or animals. However, assuming 130 mm Hg to be the upper limit, 2 manual and 30 NIBP MAP measures in our study exceeded this value.

Ultimately our data were insufficient to analyze the impact of MAP on patient outcomes. Similar to current reported performance of alteplase, only 3% of our study population (3 patients) developed sICH. We did find that sICH patients had clinically important but not statistically significant differences in NIHSS and mRS at discharge or 7 days, with the lack of statistical significance attributed to the small sample size. Of the 95 patients, 1 patient died, which was attributed to post-alteplase sICH. Collectively for 5 patients (3 sICH of which 1 died, plus 2 other patients that died), there were no recorded manual MAP >130 mmHg, but there were 3 recorded NIBP MAP >130 mmHg in 1 of the 5 patients who died in hospital but did not have a sICH; however, the overall mean for this small group's NIBP MAP was <130 mm Hg.

We also dichotomized patients into groups based on favorable (mRS ≤ 2) or poor (mRS 3-6) outcomes, finding significantly higher SBP on both manual ($p = 0.04$) and NIBP ($p = 0.08$) readings in patients with poor functional outcome at discharge or day 7. This is similar to what others have found in their examination of BP and outcome, in that significantly higher BP is associated with worse functional outcome.^{147,148}

Additional Considerations Regarding NIBP Devices

As explained in chapter 1, the NINDS study protocol required BP to be measured manually.⁴ Ultimately, recommendations in the original AIS guidelines were informed by the NINDS study protocol. Interestingly, subsequent updates to the AIS guidelines have yet to address and formally recommend the use of an NIBP device as an option for BP measurement. However, the reality of clinical practice today is that manual BP cuffs are rarely used or even available when an alteplase treatment decision is being made or during the peri-treatment period when BP should be closely monitored and managed. Additionally, whether NIBP devices are being used in an evidence-based manner is debatable, given that many clinicians are not aware of the need to revert to manual BP when a patient presents with common NIBP exclusions such as atrial fibrillation.

NIBP's convenience, ease of use, and vast quantity and availability in hospitals make it unrealistic to expect clinicians to return to and rely solely upon manual BP measurements for the initiation of alteplase. Many clinicians who were practicing before and during the 1990s when manual BP measurement was standard of care are no longer at the bedside. Today's clinicians are likely to question why it matters whether BP is obtained via manual or NIBP methods, as their training included instruction on NIBP devices.

When NIBP devices were first introduced into acute care hospitals and ambulatory clinics, training consisted of placing the cuff, turning on the device, pressing start, and possibly learning to set automatic repeat BP measures. Even today, training on the use of NIBPs does not include how devices are engineered to generate the measures or how to routinely assess whether clinically important differences between manual and NIBP might be present. Therefore few clinicians realize that 1) certain medical conditions make NIBP measures unreliable, 2) NIBP devices are engineered using tightly held, proprietary algorithms, 3) MAP is accepted as the most accurate value derived from NIBP measurements³² because SBP and DBP are algorithmically derived from the MAP^{99,100} and 4) NIBP DBP more closely agrees with manual measurements, than SBP. We surmise that still today, little has changed regarding clinicians' degree of understanding of NIBP measures, particularly pertaining to how well measures from the NIBP device actually agree with manual BP measurements.

During the time that the NINDS study protocol and subsequent AIS guidelines were written,⁴ research examining optimal MAP in AIS patients was scarce, and BP measurements by manual sphygmomanometer were standard of care. Additionally, few neurologists managed BP in acute stroke patients during the 1990s, instead relying on internal medicine and emergency specialists to oversee the general medical management needs of AIS patients. Certainly, these two factors likely contributed to a lack of awareness of the value of MAP and its absence from mention in current guidelines. However, since then, NIBP devices that display MAP alongside SBP and DBP have become standard of care in hospitals throughout the United States and most of the world, although to date, most stroke clinicians fail to pay attention to the MAP measure, instead favoring SBP and DBP for treatment parameters. Despite the universal adoption of NIBP

devices over the last 25 years, there continues to be a paucity of literature related to a goal MAP in AIS patients. To further this area of research, it will also be necessary to understand more about practitioners' overall physiologic knowledge of BP-derived variables, as well as to understand the availability of manual devices in settings where NIBP now dominates.

Study Limitations

Our study has limitations that must be acknowledged. First, we deliberately did not interfere with alteplase treatment in our collection of study data, choosing to obtain our sets of measures at a time that did not slow our stroke team members' delivery of the bolus and intravenous infusion. Additionally, we did not obtain continuous measures over the 24-hour period as this would have been significantly labor-intensive. Because of this, we do not have BP values collected at the time of clinical deterioration in our 3 sICH patients, and this limited our understanding of what may have been important BP changes during the hemorrhage period. However, continuous measurement of BP values was not necessary to meet our study objective. Therefore, we would argue that for this phase of study, our methods were acceptable.

A second limitation with our methods was that NIBP device brands differed between the NJ and TN study sites, which arguably affects the generalizability of this study. However, 100% of our study's devices had been approved for use by biomedical engineering and displayed current labels showing the monitoring time period for which they were approved. We believe that while this is a limitation, it is also reflective of "real life" monitoring, as there will always be differences in the devices used at different hospitals. Essentially the recognition of this limitation shines a light on the fact that AIS treatment decisions are based on device-dependent measurements that will always vary from hospital to hospital. Past AAMI recommendations¹⁰³ and the recent Association for the Advancement of Medical Instrumentation/European Society of Hypertension/International Organization for Standardization (AAMI/ESH/ISO) Collaborative Statement¹⁰¹ summarizes nine key aspects for healthcare institutions to follow for the validation procedure for NIBP devices. The procedure calls for three sets of manual and NIBP measures in 85 patients for a total of 255 pairs of measurements. It is doubtful that health care sites are validating all of their NIBP devices in this way before placing them into service, and even less doubtful that specific populations of patients, for example AIS, are used as part of a validation process within hospitals. Therefore, we chose to focus our study methods on ensuring the accuracy of BP measurement techniques for both manual and NIBP measures, and further ensured accuracy by using a dual-auscultation stethoscope for all manual measures.

Lastly, while arterial line measurement of BP is commonly referred to as the "gold standard" for determination of "true" SBP, DBP, and MAP values, we chose to use manual sphygmomanometry as the point of comparison with NIBP. While this may be considered a shortcoming in our approach, it is consistent with the methods used in the original NINDS rt-PA Stroke Study, which established the BP parameters that are still in

use today for alteplase treatment. Additionally, arterial lines are deliberately not inserted in patients that have received alteplase. In fact, guidelines recommend avoiding arterial and even venous punctures due to the fibrinolytic action of the drug, which could result in unnecessary blood loss. It also would have been unrealistic to consent patients and perform arterial line insertion prior to administration of alteplase as this would have delayed time to alteplase treatment substantially, as well as increased the risk for bleeding from failed arterial line insertion attempts. Therefore, to answer the agreement question, we believe that our approach was realistic, in the patient's best interest, and consistent with the original clinical trial methods that led to use of guideline BP thresholds.

Conclusion

Despite the widespread use of NIBP devices, few clinicians are familiar with its fundamental operating principles and of the potential for inaccuracies and disagreement between manual and NIBP measurements.¹⁴⁹ In their 2019 scientific statement, the American Heart Association (AHA) wrote that there is little, if any, evidence available on the validation of BP measurements obtained in the acute care setting.¹⁵⁰ Despite the AHA's acknowledgment of lack of knowledge regarding BP monitoring, acute stroke practitioners trust and rely on NIBP devices to guide AIS patient treatment. Our results show that NIBP measures are consistently higher than, and may differ from manual measurements as much as 50 mmHg for SBP, 40 mmHg for DBP, and 44 mmHg for MAP, and that this disagreement may cause treatment delays due to the need to manage hypertension.

The safe MAP for AIS patients receiving alteplase treatment is not yet known, but work must continue in this area. Acute stroke practitioners are encouraged to begin exploration of MAP due to their use of and reliance on NIBP to guide AIS treatment.¹⁵⁰ This research must be guided by consensus for acceptable levels of BP agreement as well as determination of validation methods that realistically fit within the current treatment and monitoring paradigm and do not disrupt time to alteplase administration. It is likely that stroke guidelines are silent regarding MAP because the information to understand safe MAP levels in AIS patients during and after alteplase administration is lacking. Our study takes an important first step in reframing AIS treatment context toward consideration of MAP as a key measure to guide the initiation of alteplase treatment and ongoing patient management.

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APPENDIX A. CONCEPTUAL FRAMEWORK – ISCHEMIC PENUMBRA

APPENDIX B. CASE REPORT FORM

SIDE 1

IDENTIFYING INFORMATION									
ACCOUNT #			LOCATION:				UNIQUE IDENTIFIER		
<div style="border: 1px solid black; width: 100px; height: 20px;"></div>			☐ BHC ☐ LFC ☐ HJHC ☐ DMC ☐ RMC ☐ SEMC				<div style="border: 1px solid black; width: 100px; height: 20px;"></div>		
Patient Identifier Information is not included in study MAP In Stroke Study (MAPSS) CASE REPORT FORM									
DEMOGRAPHICS									
1. AGE (in yrs)		8. ETHNICITY:		6. NEWS ON ADMISSION:		7. PRE-MORBIID PRIOR STROKE EVENT:		9. WEIGHT (lbs)	
<div style="border: 1px solid black; width: 40px; height: 20px;"></div>		☐ Caucasian ☐ Hispanic ☐ Other ☐ Black ☐ Asian		<div style="border: 1px solid black; width: 40px; height: 20px;"></div>		☐ No ☐ Yes		<div style="border: 1px solid black; width: 40px; height: 20px;"></div>	
2. GENDER:		4. STROKE ONSET DATE:		5. STROKE ONSET TIME:		On No Symptoms On No Sig. Disability On Slight Disability On Moderate Disability On Most Severe Disability On Severe Disability On Dead		10. BMI	
☐ Male ☐ Female		<div style="border: 1px solid black; width: 100px; height: 20px;"></div>		<div style="border: 1px solid black; width: 100px; height: 20px;"></div>				<div style="border: 1px solid black; width: 40px; height: 20px;"></div>	
PAST MEDICAL HISTORY									
16. HISTORY OF HYPERTENSION:		18. HISTORY PREVIOUS MI:		20a. CARDIAC VASCULAR DISEASE?		20b. IF YES, TREATED BY VALVULOPLASTY?		20c. IF YES, TREATED BY VALVE REPLACEMENT?	
☐ No ☐ Yes		☐ No ☐ Yes		☐ No ☐ Yes		☐ No ☐ Yes		☐ No ☐ Yes	
17. CONCURRENT MYOCARDIAL INFARCTION		19. CONCURRENT CORONARY HEART FAILURE?		21. ASCENDING AORTIC ARCH RECONSTRUCTION?		22. PERIPHERAL VASCULAR DISEASE?		23. CAROTID ARTERY ATHEROSCLEROSIS?	
☐ No ☐ Yes		☐ No ☐ Yes		☐ No ☐ Yes		☐ No ☐ Yes		☐ No ☐ Yes	
24. PROVIDES CAROTID RECONSTRUCTION?		25a. DIABETES MELLITUS?		25b. IF POS DM TYPE 1?		25c. IF POS DM TYPE 2?		26. PREVIOUS STROKE?	
☐ No ☐ Yes		☐ No ☐ Yes		☐ No ☐ Yes		☐ No ☐ Yes		☐ No ☐ Yes	
SOCIAL HISTORY									
11. SMOKING HISTORY:		12. PACKS PER DAY:		13. YRS SMOKED:		14. PACE YEARS:		15a. ILLICIT DRUG USE:	
☐ No ☐ Yes		<div style="border: 1px solid black; width: 40px; height: 20px;"></div>		<div style="border: 1px solid black; width: 40px; height: 20px;"></div>		<div style="border: 1px solid black; width: 40px; height: 20px;"></div>		☐ No ☐ Yes	
								15b. TYPE OF DRUG:	
LABS									
27. ADMISSION BUN		28. ADMISSION PTT		29. ADMISSION TROPONIN I		30. ADMISSION FIRST RECORDED BODY TEMP		31. ALKALIC DURING HOSPITALIZATION	
<div style="border: 1px solid black; width: 100px; height: 20px;"></div>		<div style="border: 1px solid black; width: 100px; height: 20px;"></div>		<div style="border: 1px solid black; width: 100px; height: 20px;"></div>		<div style="border: 1px solid black; width: 100px; height: 20px;"></div>		<div style="border: 1px solid black; width: 100px; height: 20px;"></div>	
r-t-P-A									
32a. r-t-P-A DILUS TIME		32b. r-t-P-A DILUS DOSE		32c. r-t-P-A DILUS INFUSION TIME		32d. r-t-P-A DILUS INFUSION DOSE		32e. ENTIRE r-t-P-A DOSE RECEIVED?	
<div style="border: 1px solid black; width: 100px; height: 20px;"></div>		<div style="border: 1px solid black; width: 100px; height: 20px;"></div>		<div style="border: 1px solid black; width: 100px; height: 20px;"></div>		<div style="border: 1px solid black; width: 100px; height: 20px;"></div>		☐ No ☐ Yes	
								32f. r-t-P-A TOTAL CALCULATED DOSE	
								<div style="border: 1px solid black; width: 100px; height: 20px;"></div>	
THROMBECTOMY					ANTIHYPERTENSIVES				
36. ADDITIONAL TREATMENT BY THROMBECTOMY?		37. FINAL TICI SCORE POST THROMBECTOMY:		38a. ANTIHYPERTENSIVE GIVEN FOR r-t-P-A?		38b. IF YES, WHAT TYPE OF ANTIHYPERTENSIVE WAS GIVEN?		38c. IF ANSWERED 4 or 5, WHAT ANTIHYPERTENSIVE GIVEN?	
☐ No ☐ Yes		<div style="border: 1px solid black; width: 40px; height: 20px;"></div>		☐ No ☐ Yes		☐ No ☐ Yes		☐ No ☐ Yes	
ADVERSE EVENTS									
39. SYMPTOMATIC INTRACRANIAL HEMORRHAGE?		40. NON-SYMPTOMATIC HEMORRHAGIC TRANSFORMATION?		41. OROPHARYNGEAL ANGIOEDEMA?		42. SYSTEMIC NON-INTRACRANIAL HEMORRHAGE?		43. TRANSFUSION TREATMENT REQUIRED?	
☐ No ☐ Yes		☐ No ☐ Yes		☐ No ☐ Yes		☐ No ☐ Yes		☐ No ☐ Yes	
NIHSS					mRS		DISCHARGE		
44. NEWS AT 24 HOURS FROM TIME COMPUTED r-t-P-A SURVEILLANCE		45. NEWS AT DISCHARGE OR DAY 7		46. NEWS AT DISCHARGE OR DAY 7:		47. LENGTH OF STAY (IF OF DATA)		48. DISCHARGE DISPOSITION:	
<div style="border: 1px solid black; width: 100px; height: 20px;"></div>		<div style="border: 1px solid black; width: 100px; height: 20px;"></div>		<div style="border: 1px solid black; width: 100px; height: 20px;"></div>		<div style="border: 1px solid black; width: 100px; height: 20px;"></div>		<div style="border: 1px solid black; width: 100px; height: 20px;"></div>	
				On No Symptoms On No Sig. Disability On Slight Disability On Moderate Disability On Most Severe Disability On Severe Disability On Dead				On Home On Home Plus Outpatient Rehab On Inpatient Rehab On Skilled Nursing Facility On Palliative Care On Dead	

SIDE 2

MR#:

Unique Identifier (assigned by PI):

MAP In Stroke Study (MAPSS)											
Measure #	DUAL AUDITORY MANUAL READING					NIBP					
	Circle Arm Used (use same arm as manual)	Arm Circumference	Cuff Size Used (circle one)	Time Measured	SBP (manual)	DBP (manual)	Circle to CONFIRM this is the SAME ARM as Manual	Time NOTE: Documented time MUST BE between 5 and 10 minutes AFTER manual BP	SBP (NIBP)	DBP (NIBP)	MAP (NIBP)
1st Set	L		Sm Adult				L	Make sure NIBP is taken between 5-10 minutes AFTER manual time			
	R		Lg Adult				R				
2nd Set	L		Sm Adult				L	Make sure NIBP is taken between 5-10 minutes AFTER manual time			
	R		Lg Adult				R				
3rd Set	L		Sm Adult				L	Make sure NIBP is taken between 5-10 minutes AFTER manual time			
	R		Lg Adult				R				
4th Set	L		Sm Adult				L	Make sure NIBP is taken between 5-10 minutes AFTER manual time			
	R		Lg Adult				R				
5th Set	L		Sm Adult				L	Make sure NIBP is taken between 5-10 minutes AFTER manual time			
	R		Lg Adult				R				

VITA

Mary Angela Grove was born in 1961 on Long Island, New York. She earned a Bachelor of Science in Nursing in 1983 at D'Youville College, and a Master of Science in Nursing in 1989 at State University of New York at Stony Brook, where her concentration was Adult Health and Critical Care Medicine. She is certified by the American Nurses Credentialing Center as both an Acute Care Nurse Practitioner and an Adult Nurse Practitioner. She is board certified as a Neurovascular Registered Nurse by the Association of Neurovascular Clinicians. She is trained as a Lean Six Sigma Black Belt. Mary is a former Major in the United States Air Force Reserves, where she served as a flight nurse leading medical teams on worldwide missions. While a doctoral student at the University of Tennessee Health Science Center, she co-authored *Back to Basics: Adherence with Guidelines for Glucose and Temperature Control in an American Comprehensive Stroke Center Sample*. During the International Stroke Conference 2017 in Houston, Texas, she presented a poster entitled *Stress-Mediated Hyperglycemia or Undiagnosed Diabetes?* Mary was awarded her Doctor of Philosophy in July 2020.