BLOOD PRESSURE MANAGEMENT IN THE EARLY PHASE OF ANEURYSMAL SUBARACHNOID HEMORRHAGE: BELIEFS, PRACTICES, AND THE RELATIONSHIP WITH CLINICAL OUTCOMES

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Abstract

This thesis investigates the relationship between elevated blood pressure and aneurysm rebleeding in aneurysmal subarachnoid hemorrhage (aSAH) while also exploring clinicians' practices and beliefs surrounding blood pressure management. With the aim of establishing a program of research evaluating blood pressure management during the early phase of aSAH, the objectives of this thesis were threefold: 1) To review the existing literature on blood pressure and aneurysm rebleeding via a systematic review; 2) To describe clinicians' practices and beliefs through a national survey; and 3) To analyze actual blood pressure management practices via a retrospective cohort study. While no clear relationship between elevated blood pressure and rebleeding was found, the evidence is biased and exclusively observational. Clinicians' self-reported blood pressure targets are consistent prior to securing the aneurysm but otherwise vary; this aligns with actual practice. These findings will inform the design of a clinical trial to assess the safety/efficacy of blood pressure lowering in early aSAH.

Authors' Contributions

Manuscript 1: Systematic Review

Terrett LA, Reszel J, Ameri S, Turgeon AF, McIntyre L, English SW. *Elevated blood pressure and culprit aneurysm rebleeding during the unsecured period of aneurysmal subarachnoid hemorrhage: A systematic review*. *Neurocrit Care*. Accepted with revisions. May 31, 2024.

LT conceptualized this systematic review, collected and analyzed the data, created the original draft of the manuscript and generated subsequent revisions. JR assisted with the methodology, data collection, and review of manuscript drafts. SA performed data collection and reviewed and edited manuscript drafts. AFT assisted with the methodology and reviewed and edited manuscript drafts. LM provided supervision, assistance with methodology, and reviewed and edited the manuscript drafts. SWE provided supervision, assistance with methodology, and reviewed and edited the manuscript drafts.

Manuscript 2: National Cross-Sectional Survey

Terrett LA, McIntyre L, O'Kelly C, Ramsay T, Turgeon AF, English SW. *Blood Pressure Management in Early Aneurysmal Subarachnoid Hemorrhage: A National Cross-Sectional Survey of Canadian Intensivists and Cerebrovascular Neurosurgeons. Neurocrit Care*. 2024 Jun 11. doi: 10.1007/s12028-024-02011-4. Epub ahead of print. PMID: 38862709.

LT conceived and designed the study, with support from the other authors. LT performed the literature review, data collection, data analysis, created the tables and figures, drafted the manuscript, and performed subsequent revisions. SWE, LM, AFT, TM, CO reviewed and revised

the manuscript drafts and provided individual content expertise at all phases of the study when required.

Manuscript 3: Retrospective Cohort

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LT conceived and designed the study, with support from the other authors. LT performed the literature review, data collection, data analysis, created the tables and figures, and drafted the manuscript, and performed subsequent revisions. SWE, LM, AFT, and TM, reviewed and revised the manuscript drafts and provided individual content expertise at all phases of the study when required.

List of Required Approvals

Manuscript 1: Systematic Review

Elevated blood pressure and culprit aneurysm rebleeding during the unsecured period of aneurysmal subarachnoid hemorrhage: A systematic review.

Ethics approval: not required

Manuscript 2: National Cross-Sectional Survey

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Manuscript 3: Retrospective Cohort

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1 Chapter 1 – Introduction

1.1 Rationale

Aneurysmal subarachnoid hemorrhage (aSAH) is a subtype of hemorrhagic stroke that occurs due to rupture of an intracranial aneurysm. Rebleeding of the culprit aneurysm is a catastrophic event associated with significant morbidity and mortality. Treatment and avoidance of acute elevations in blood pressure has been a mainstay of therapy to prevent rebleeding. However, it is unclear if this strategy is effective in reducing the rebleed risk and may paradoxically increase the risk of cerebral ischemia and infarction, leading to worse clinical outcomes. Additionally, the current beliefs and practice patterns, with respect to blood pressure management in the Canadian setting, are not described in the literature. This information is vital to the design and development of future prospective studies that aim to understand the relationship between blood pressure, aneurysmal rebleeding, and other patient-important aSAH outcomes.

1.2 Objectives

The objectives of this thesis were the following:

1) To conduct a systematic review which evaluates the current evidence base to determine the relationship between elevated blood pressure and the risk of aneurysm rebleeding during the pre-secured period in aSAH.
2) To identify the current self-reported beliefs and approaches to blood pressure management during the early phase (first 72 hours; including both the pre-secured and post-secured periods) of aSAH within Canadian hospitals.

3) To determine actual clinical patterns of practice with respect to blood pressure management during the early phase of aSAH.

1.3 Overview of thesis and included manuscripts

Chapter 2: Background

A brief overview of the epidemiology of aSAH is presented to provide context to the thesis material. Next, the role of elevated blood pressure in rebleeding of the culprit aneurysm is discussed in the setting of the contemporary literature and current practice management guidelines. What is known about clinicians' current beliefs and patterns of practice with respect to blood pressure management in aSAH is described. Finally, key knowledge gaps are presented and discussed.

Chapter 3: Systematic Review of the Literature

A systematic review of the existing literature for blood pressure management in the early phase of aSAH was undertaken with two objectives:

1. To determine if elevated blood pressure is independently associated with increased risk of aneurysm rebleeding during the pre-secured period (prior to aneurysm treatment) in aSAH.
2. To determine if elevated blood pressure during the early phase (first 72 hours) is associated with other secondary outcome measures including mortality, delayed cerebral ischemia, cerebral infarction, and cerebral edema.

I present the manuscript *Elevated blood pressure and culprit aneurysm rebleeding during the unsecured period of aneurysmal subarachnoid hemorrhage: A systematic review* (**Terrett LA**,

Reszel J, Ameri S, Turgeon AF, McIntyre L, English SW. *Neurocrit Care*. Accepted with revisions. May 31, 2024).

Chapter 4: Cross-Sectional Survey of Clinicians

A cross-sectional survey of Canadian critical care physicians and neurosurgeons was performed with the following objectives:

1. To define the self-reported practice pattern of blood pressure management in the early phase of aSAH.
2. To identify reported predictors for the selection of higher or lower blood pressure targets in the early phase of aSAH.
3. To describe reported barriers to implementation of the desired blood pressure targets in the early phase of aSAH.

I present the manuscript *Blood Pressure Management in Early Aneurysmal Subarachnoid Hemorrhage: A National Cross-Sectional Survey of Canadian Intensivists and Cerebrovascular Neurosurgeons* (**Terrett LA**, McIntyre L, O'Kelly C, Ramsay T, Turgeon AF, English SW. *Neurocrit Care*. Jun 11. doi: 10.1007/s12028-024-02011-4. Epub ahead of print. PMID: 38862709.).

Chapter 5: Retrospective Cohort Study

To examine the current (actual) practice patterns of treating clinicians with respect to blood pressure management during the early unsecured phase of aSAH, we undertook a single-centre, retrospective cohort study at the Ottawa Hospital in the form of a patient medical record review. I present the manuscript, *Blood Pressure Management During the Early Phase of Aneurysmal*

Subarachnoid Hemorrhage: A Retrospective Cohort from a Single Academic Centre. (**Terrett LA**, McIntyre L, Ramsay T, Turgeon AF, English SW. Prepared for Submission).

Chapter 6: Discussion

The key findings of the three component studies are presented and discussed with an emphasis on their relevance to the overarching objectives of this thesis and the future direction of this program of research.

2 Chapter 2 – Background

2.1 Aneurysmal subarachnoid hemorrhage: Epidemiology

Aneurysmal subarachnoid hemorrhage (aSAH) occurs due to rupture of a cerebral aneurysm. It is a type of hemorrhagic stroke that affects a relatively young population (mean age of approximately 60 years) with a female predominance (greater than 60% of patients).[1–4] Over the past two decades, despite advances in the technical aspects of treatment and improvements in critical care, mortality in aSAH has remained high, with a 30-day case fatality rate of 22-33% and a 1 year case fatality rate of 37-43%.[2–5] Morbidity is also a significant consequence of aSAH with 15% of survivors having a poor functional outcome (defined as a modified Rankin Score of 3-5) at one year.[5] Additionally, up to 40% of survivors are unable to return to work and those that do, often work fewer hours and in roles with reduced responsibility.[6] Many survivors are left with cognitive impairment across a variety of domains, including memory, executive function, and language, which remain present three years after their event.[6] In nearly half of patients, overall recovery and level of function can be further complicated by persistent depression, anxiety, fatigue, and sleep disturbances.[6] Lastly, the financial cost to the healthcare system and society in general is significant: The mean total cost per patient with subarachnoid hemorrhage is nearly twice that of intracerebral hemorrhage ($92,794 vs $53,491; 2017 Canadian dollars) and the mean total cost per survivor is $136,098 for subarachnoid hemorrhage vs $94,857 for intracerebral hemorrhage (2017 Canadian dollars).[7]

2.2 Timeline (phase) in aSAH and corresponding blood pressure management

The natural evolution of aneurysmal subarachnoid hemorrhage is divided into 2 phases: an early phase (during the first 72 hours), where early brain injury predominates: and a late phase

(beyond 72 hours), where vasospasm and delayed cerebral ischemia predominate.[8–10] Early brain injury is a complex process that has not been fully elucidated. It is hypothesized that cerebral ischemia occurring in the minutes following the initial aneurysm rupture initiates a variety of pathophysiologic changes, including: 1) Physiologic (elevated intracranial pressure, decreased cerebral perfusion pressure, decreased cerebral blood flow, and impaired autoregulation); 2) Ionic (electrolytes influx and homeostatic abnormalities and spreading cortical depolarizations); 3) Mechanical and Biochemical (including increased extracellular glutamate and hydrocephalus); 4) Molecular (including increased inflammation, oxidative stress, alteration in nitric oxide metabolism, platelet activation and aggregation, and cell death); and 5) Pathological (including both vascular and cellular injury and abnormalities).[9] The early phase can be further subdivided into a "pre-secured period" (where the ruptured aneurysm has not yet been treated) and a "post-secured period" (where the ruptured aneurysm has been surgically or endovascularly occluded or excluded). Classically, the teaching surrounding blood pressure management has differed between these phases: During the pre-secured period, efforts are typically made to maintain blood pressure below specific target thresholds, with the goal of preventing rebleeding of the culprit aneurysm. Once the aneurysm has been secured and the risk of rebleeding has been eliminated, more liberal blood pressure parameters are often allowed. This is especially true with increasing time from rupture, as the risk for vasospasm and delayed cerebral ischemia increases.

2.3 Elevated blood pressure, rebleeding, and the impact on outcome in aSAH

Rebleeding is an important contributor to both morbidity and mortality, with up to 60% of patients who rebleed subsequently dying and a large proportion of survivors suffering significantly worse functional outcome.[11,12] Elevated blood pressure prior to securing the

aneurysm may increase the risk of rebleeding by increasing transmural pressure across the "clotted/temporarily sealed" rupture site.[13] Consequently, lowering blood pressure, or preventing blood pressure elevation prior to securing the aneurysm, could reduce the risk of rebleeding but may unfortunately put the already injured brain at risk for further ischemia.

2.4 Potential risks of lowering blood pressure during the early phase of aSAH

Lowering blood pressure during the early phase in aSAH is not without risk. Early brain injury is highly prevalent in aSAH. A cohort study published in 2021 evaluated CT scans during the first 72 hours from aneurysm rupture using selective sulcal volume (above the lateral ventricles) as a marker of global cerebral edema and early brain injury.[14] Based on a reduced selective sulcal volume below 5 mL, they found that 61% of patients in the cohort had global cerebral edema.[14] Early brain injury leads to variety of abnormalities including reduced cerebral blood flow, impaired autoregulation of cerebral blood flow, increased brain tissue hypoxia, and increased brain tissue metabolic distress.[9,15–18] Reducing blood pressure could further exacerbate these abnormalities leading to ischemia, infarction, and ultimately worse outcomes. A recent retrospective cohort, using a database from a single centre in the USA, evaluated 202 patients with aSAH from 2007 to 2016.[19] The authors evaluated systolic blood pressure (SBP) at 4 hour intervals during the first 24 hours of admission. The outcome measure was a dichotomized modified Rankin scale score (good outcome = 0-2; Poor outcome = 3-6). There were two key findings: First, hypotension (defined as a minimum SBP $\leq$ 90 mmHg) was associated with a poor outcome and second, an increased minimum systolic blood pressure was associated with a good outcome (for every 1 mmHg increase in minimum SBP there was a 3% increase in the odds of a good outcome).[19] Importantly, the authors identified that the key time period for preventing

hypotension was early, during the first 10-16 hours after rupture.[19] Other studies have produced similar findings **(Table 1)**. In general, these studies show that a higher blood pressure (mean arterial pressure [MAP] or SBP) during the period from admission to 24 hours was associated with improved outcomes, including decreased mortality, reduced incidence of vasospasm and delayed cerebral ischemia, and improved functional outcomes. Aggressive blood pressure lowering, in an attempt to prevent aneurysm rebleeding, could cause hypotension during the critical time period and lead to worse clinical outcomes.

2.5 Existing evidence base for blood pressure lowering to prevent rebleeding

Three previous systematic reviews (two published in 2014 and another in 2022) identified elevated blood pressure during the pre-secured period as one among many potential risk factors for aneurysm rebleeding. [20–22] However, these reviews have several limitations affecting their interpretation in guiding clinicians in the management of blood pressure. These reviews were limited in their scope: The single metric they evaluated was SBP, only two SBP thresholds were included (140 mmHg and 160 mmHg), and only one of the reviews included studies reporting SBP as a continuous outcome **(Table 2)**. They also suffered from a number of methodological flaws: Two of the reviews included one or more studies that only recorded pre-existing hypertension (as opposed to elevated blood pressure from presentation to aneurysm securing), two of the reviews performed a meta-analysis that combined adjusted and unadjusted results, and none of the reviews evaluated different effect measures separately **(Table 2)**. Lastly, one of the reviews included a study with a different SBP threshold than the one they were evaluating.[21] In light of these important limitations, clinical decision-making should not rely on the results of these reviews.

2.6 Practice Management Guidelines

The current aSAH management guidelines from the American Heart Association/American Stroke Association (AHA/ASA) and the Neurocritical Care Society (NCS) were both released in 2023 **(Table 3).**[23,24] They recognise the absence of quality evidence to guide decision-making and consequently no longer recommend specific blood pressure targets prior to securing the aneurysm.[23,24] The NCS guidelines state "There is insufficient evidence to recommend a blood pressure reduction goal for the treatment of hypertension before aneurysm treatment in aSAH."[24] This decision was based on three cohort studies with an overall quality of evidence rated as "very low" using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework.[24] Similarly, the AHA/SAS guidelines state that the "…available evidence is insufficient to recommend any specific BP target" but they do recommend avoiding extremes of blood pressure (strong recommendation; consensus of expert opinion).[23] Additionally, the AHA/ASA guidelines recommend taking patient-specific factors ("…blood pressure at presentation, brain swelling, hydrocephalus, and history of hypertension and renal impairment…") into account if/when selecting blood pressure target thresholds (strong recommendation, consensus of expert opinion).[23]

Historic management guidelines from the AHA/ASA, the NCS, and the European Stroke Organisation (ESO) were similarly based on this limited, poor quality evidence **(Table 3).**[25–27] They provided differing recommendations for blood pressure management during the pre-secured period: The AHA/ASA guidelines recommended keeping systolic blood pressure below 160 mm Hg (Class IIa; Level of Evidence C), the ESO guidelines recommend taking patient-specific factors into account and a "prudent" systolic blood pressure target of < 180 mmHg

(Good Clinical Practice), and the NCS recommended treating only extreme blood pressure elevations (systolic blood pressure > 160 mmHg or mean arterial pressure > 110 mmHg) (Low Quality Evidence; Strong Recommendation).[25–27]

2.7 Current blood pressure management practices in the early phase of aSAH

Our best understanding of the contemporary reported practices of blood pressure management in early aSAH comes from a 2017 survey.[28] This self-directed, web-based quantitative survey of 128 critical care physicians practicing in the USA identified significant variability with respect to the reported upper and lower blood pressure targets in both the pre- and post-secured periods of aSAH.[28] The results highlight a lack of consensus and the wide variability that currently exists with respect to blood pressure management during the early phase of aSAH.

2.8 Knowledge gaps in the existing literature

There are multiple unknowns surrounding BP management during the early phase of aSAH: Whether there is an association between elevated blood pressure and rebleeding, the potential impact of lowering blood pressure on the rate of rebleeding, the optimal blood pressure targets to utilize both before and after the aneurysm is secured, the potential for inadvertent hypoperfusion and ischemia due to over-aggressive blood pressure lowering, and whether there is a minimum blood pressure that should be maintained to limit additional cerebral injury and improve outcomes.

The two most pressing questions that need to be answered are: 1) Does lowering blood pressure during the early phase of aSAH lead to decreased rebleeding and improved outcomes and 2) What magnitude of blood pressure lowering is required to achieve these improved

outcomes without conversely causing harm. [13,29] While a randomized controlled trial is required to more thoroughly answer these questions, there are a number of other important knowledge gaps to be addressed by our program of research.

The association between elevated blood pressure during the pre-secured period and aneurysm rebleeding is not clear. Importantly, the blood pressure threshold associated with increased rebleeding has not been definitively identified. In chapter 3, I present the results of a systematic review of the existing literature that describes the relationship between elevated blood pressure during the pre-secured period and rebleeding of the culprit aneurysm. This review also explores the relationship between elevated blood pressure during the early phase of aSAH and a variety of other clinical and radiological outcomes.

In the absence of consensus regarding the optimal blood pressure targets during the pre-secured phase of aSAH, an understanding of contemporary practice patterns is essential. In chapter 4, I present a cross-sectional survey of Canadian clinicians who care for patients with aSAH with the purpose of identifying the self-reported blood pressure management practices. In addition, this survey identifies predictors of using a higher or lower blood pressure target as well as any potential barriers to blood pressure target implementation. This information will assist with the design of a future clinical trial.

Finally, the actual practice of blood pressure management in this population is unclear. This information will be vital to the design of a future clinical trial. In chapter 5, I present a retrospective cohort that aims to describe the blood pressure targets in actual practice, the techniques used to lower and maintain blood pressure, and the degree of success in achieving the desired targets.

2.9 Tables and Figures

Table 1. Studies reporting maintenance of higher BP or higher minimum BP during first 24 hours and association with a "good" outcome.

Study	Design	Patients	BP metric	Outcome	Unadjusted results	Adjusted results
Ascanio 2020[19]	Retrospective Cohort	202	SBP (minimum SBP during first 24 hrs)	Good mRS (0-2) at last follow-up	Good outcome: 108.4+/-13.3 mmHg Poor outcome: 101.4+/-14.1 mmHg p<0.001	1 mmHg increase in minimum SBP: OR 1.03 (95% CI: 1.001-1.064) P=0.04
Duran 2013[30]	Retrospective Cohort	200	MAP (highest reading over first 6 hrs)	Hospital mortality	Survivors MAP: 106.4+/-15.3 mmHg Non-survivors MAP: 102.3 +/-16.4 mmHg P=0.026	NR
Gathier 2022[31]	Retrospective Cohort	1167	Lowest MAP 24 hrs preceding DCI	DCI in ICU	NR	Reference MAP: 100 (aHR 1) MAP 50: aHR 2.59 (1.12-5.96) MAP 60: aHR 1.79 (0.99-3.24) MAP 70: aHR 1.25 (0.81-1.93)
Roederer 2014[32]	Retrospective Cohort	81	MAP (day 1 post bleed max value)	Vasospasm (angiographic)	VS+: 107.52 mmHg VS-: 122.87 mmHg Mean difference: 15.35 mmHg (95% CI: 2.99-27.72) p=0.018	NR
Zhou 2023[33]	Retrospective Cohort	1420	MAP (admission)	Hospital mortality	MAP <82 mmHg: HR 2.17 (95% CI: 1.43-3.30) p<0.001	MAP <82 mmHg: HR 1.67 (95% CI: 1.08-2.57) p<0.021

BP: blood pressure; DCI: delayed cerebral ischemia; ICU: intensive care unit; MAP: mean arterial pressure; mRS: modified Rankin score; SBP: systolic blood pressure; VS: vasospasm.

Table 2. Description/limitations of existing systematic reviews evaluating elevated blood pressure and rebleeding.

Review ID	Studies reporting BP	SBP thresholds (mmHg)	Continuous BP also evaluated?	BP metrics other than SBP evaluated?	Included studies using pre-existing hypertension?	Meta-analysis mixed unadjusted and adjusted results?	Evaluated multiple effect measures (eg OR, HR, RR) separately	Narrative description of studies with no SBP thresholds
Tang 2014[20]	5	140, 160	no	no	yes[a]	yes	no	no
Alfotih 2014[21]	4	160[b]	no	no	yes[c]	no	no	no
Doherty 2022[22]	7	140, 160	yes	no	no	yes	no	no

BP: blood pressure; SBP: systolic blood pressure.
[a] Cha KC et al, 2010[34] and Demarchis GM et al 2014[35]
[b] One of the included studies used an SBP threshold of 140 mmHg (Cong et al 2012[36])
[c] Cha KC et al, 2010[34]

Table 3. Guidelines for blood pressure lowering during the pre-secured period in aneurysmal subarachnoid hemorrhage.

Organization	Year	Recommendations (summary)	Strength/level of evidence
Current			
AHA/ASA[23]	2023	"…available evidence is insufficient to recommend any specific BP target."	COR: 1 (strong recommendation).
		"…In patients with aSAH and unsecured aneurysm, frequent blood pressure (BP) monitoring and BP control with short-acting medication(s) is recommended to avoid severe hypotension, hypertension, and BP variability."	LOE: C-EO (Consensus of expert opinion).
NCS[24]	2023	"There is insufficient evidence to recommend a blood pressure reduction goal for the treatment of hypertension before aneurysm treatment in aSAH."	Quality of Evidence (GRADE): Very low.
Historical			
AHA/ASA[25]	2012	"The magnitude of blood pressure control to reduce the risk of rebleeding has not been established, but a decrease in systolic blood pressure to < 160 mm Hg is reasonable."	Class IIa: weight of opinion favours treatment. Level of evidence C: consensus opinion of experts.
NCS[26]	2011	"Treat extreme hypertension in patients with an unsecured, recently ruptured aneurysm. Modest elevations in blood pressure (mean blood pressure <110 mmHg) do not require therapy. Pre-morbid baseline blood pressures should be used to refine targets…"	Strong recommendation/Low quality evidence.
ESO[27]	2013	"Until coiling or clipping, systolic blood pressure should be kept below 180 mm Hg; this may be already achieved by applying analgesics and nimodipine." "If systolic pressure remains high despite these treatments further lowering of blood pressure should be considered."	Good Clinical Practice. Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion. Level C: possibly effective, ineffective, or harmful

AHA/ASA: American Heart Association/American Stroke Association; NCS: Neurocritical Care Society; ESO: European Stroke Organisation; aSAH: aneurysmal subarachnoid hemorrhage; BP: blood pressure; COR: class of recommendation; LOE: level of evidence; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations.

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3 Chapter 3 - Systematic Review of the Literature

Title:
Elevated blood pressure and culprit aneurysm rebleeding during the unsecured period of aneurysmal subarachnoid hemorrhage: A systematic review.

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3.1 Abstract:

Objective:

In aneurysmal subarachnoid hemorrhage (aSAH), rebleeding prior to securing the culprit aneurysm leads to significant morbidity and mortality. Elevated blood pressure has been identified as a possible risk factor. In this systematic review, we evaluated the association between elevated blood pressure and aneurysm rebleeding during the unsecured period.

Methods:

We searched MEDLINE, Embase + Embase Classic, and CENTRAL, from inception to March 8th, 2024. We included studies of adults with aSAH reporting at least 1 blood pressure measurement during the unsecured period and a measure of association with rebleeding. Results were stratified by blood pressure thresholds, effect measure, and adjustment for confounding. Separate meta-analyses were performed for each of these groups.

Results:

For the primary outcome of aneurysmal rebleeding, 15 studies were included in our review. All studies were observational in design and at moderate or high risk of bias. Meta-analysis of the unadjusted results produced mixed findings across the systolic blood pressure (SBP) thresholds: SBP > 140 mmHg, unadjusted Odds Ratio (uOR]) 1.03; 95% CI, 0.55-1.93; I^2 = 66%; SBP > 160 mmHg, uOR, 3.35; 95% CI, 1.44-7.81; I^2 = 83%; SBP > 180 mmHg, uOR, 1.52; 95% CI, 0.40-5.81; I^2 = 89%; SBP > 200 mmHg, uOR, 7.99; 95% CI, 3.60-17.72; I^2 = 0%. Meta-analysis of adjusted results was only possible at a SBP > 160 mmHg; adjusted Hazard Ratio (aHR), 1.13; 95% CI, 0.98-1.31; I^2 = 0%. There was no clear dose effect with increasing blood pressure. The

overall quality of evidence as assessed by the Grading of Recommendations, Assessment, Development and Evaluations tool was rated as very low.

Conclusions:

Based on very low-quality evidence, elevated blood pressure during the unsecured period is not associated with an increased risk of culprit aneurysm rebleeding.

3.2 Introduction:

Aneurysmal subarachnoid hemorrhage (aSAH) is a form of hemorrhagic stroke that results from a ruptured cerebral aneurysm. It occurs in patients who are relatively young, mainly female, and has a high mortality rate.[1–4] A quarter of survivors remain functionally dependent and a large proportion are left with cognitive impairment across various domains.[1,5] Additionally, the financial impact on society and the healthcare system is significant, as aSAH has the highest hospital costs of all stroke subtypes.[6]

Rebleeding of the culprit aneurysm after aSAH is associated with significant morbidity and mortality.[7] Elevated blood pressure prior to securing the aneurysm may be a risk factor for rebleeding, by increasing transmural pressure across the "temporarily sealed" rupture site.[8] Consequently, lowering blood pressure prior to securing the aneurysm may reduce the risk of rebleeding and was recommended in previous management guidelines.[9–11] However, these recommendations were based on an extremely small number of observational studies and expert consensus. Recent management guidelines from the American Heart Association/American Stroke Association and the Neurocritical Care Society recognize the absence of high-quality evidence and no longer recommend keeping blood pressure below a specific target.[12,13] Importantly, any decision to lower blood pressure must be weighed against the risks of reduced cerebral perfusion, increased ischemia, and worsened clinical outcomes.[14–16]

We aimed to conduct a systematic review of the existing literature to evaluate the association of elevated blood pressure during the unsecured period with the incidence of aneurysmal rebleeding in hospitalized adult patients with acute aSAH. A secondary objective was to examine the association of blood pressure during the early phase of aSAH with clinically relevant and experimental outcomes.

3.3 Methods:

Our study protocol was developed a priori using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [17,18] and registered on PROSPERO (CRD42022319563).[19] Our results are reported in accordance with the PRISMA 2020 reporting guidelines **(Supplemental Data: Appendix 1).**[20]

Study identification:

The search strategy was developed with the assistance of an Information specialist **(Supplemental Data: Appendix 2)**. We searched MEDLINE, Embase, and CENTRAL from inception to March 8th, 2024.

Study Selection:

We included interventional and observational studies that were published in English or French. Studies were eligible if they; 1) included adults (≥ 18 years) who presented to hospital with aSAH and reported a minimum of 1 blood pressure measurement either prior to intervention to secure the aneurysm (primary outcome) or during the first 72 hours of admission (secondary outcomes); 2) reported on either rebleeding of the culprit aneurysm (primary outcome) or any clinically relevant or experimental outcome (secondary outcomes); and 3) reported or provided sufficient data to calculate a measure of association. Studies were excluded if they exclusively reported blood pressure values either prior to hospital presentation or >72 hours from presentation. For a complete list of inclusion/exclusion criteria, please see **Supplemental Data: Appendix 3**.

Using Covidence Data Extraction 2.0 (Veritas Health Innovation, Melbourne, Australia. www.covidence.org), duplicate citations were removed and each record was independently screened by two reviewers (LT, SA, JR). Full texts of potentially relevant articles were retrieved and independently screened by two reviewers (two of LT, SA, SMG, JR). Disagreements were resolved through consensus, in consultation with a third author as needed.

Outcome Measures:

The primary outcome is defined as rebleeding of the culprit aneurysm prior to definitive treatment. The secondary outcomes included the following: clinical outcomes (e.g. mortality, functional outcomes, delayed cerebral ischemia (DCI), Length of stay, etc), radiographic outcomes (e.g. vasospasm, cerebral infarction), and any experimental outcomes (e.g. serum biomarkers, nuclear medicine investigations, etc).

Data Extraction:

We developed a data extraction form using the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of prognostic factor studies (CHARMS-PF)[21] **(Supplemental Data: Appendix 4)**. Two reviewers (any combination of LT, SA, SMG, JR) independently extracted the data for the primary outcome and a single reviewer (LT) extracted the data for the secondary outcomes. For each included study we extracted information on demographics, participants, primary and secondary outcomes, blood pressure information, other prognostic factors, missing data, analysis methods, results, and interpretation.

Risk of Bias and Quality Assessment:

We used the Quality in Prognosis Studies (QUIPS) tool,[22] operationalized for our review, to assess the risk of bias **(Supplemental Data: Appendix 5).**[23] A single reviewer (LT) conducted the risk of bias assessments. As a quality control measure, 25% of the studies had the risk of bias assessment performed in duplicate by another reviewer (JR or SA). To assess the quality of evidence for the primary outcome, we used the GRADE system (Grading of Recommendations, Assessment, Development and Evaluations), adapted for narrative reviews. [24] A single reviewer (LT) performed the GRADE assessment.

Data Synthesis/statistical analysis:

Primary Outcome

Following established methodology,[21] we performed a stratified analysis of pre-defined systolic blood pressure (SBP) thresholds: 140 mmHg, 160 mmHg, 180 mmHg, and 200 mmHg where data was available. Studies were grouped by their reported effect measure (OR, RR, HR). For each blood pressure threshold, we assessed the unadjusted (univariate) and the adjusted (multivariate) association of blood pressure with rebleeding. A priori, we identified 6 key confounders: poor clinical grade (Hunt and Hess or World Federation of Neurological Societies score IV or V), large aneurysm size (>10 mm), posterior circulation location, radiographic grade (modified fisher score ≥3 or presence intraparenchymal/Intraventricular hematoma), age, and sex.[25,26] Studies that performed multivariable modelling needed to adjust for at least one of these confounders to be included in a meta-analysis.

We planned to conduct meta-analyses of both unadjusted and adjusted results using a random effects model with an inverse-variance method. When meta-analysis was deemed inappropriate (due to an insufficient number of studies for a given blood pressure threshold or

inadequate adjustment for confounding), studies were still included in a forest plot with the pooled estimate suppressed.[27] Between-study heterogeneity was evaluated using the I^2 statistic and defined as follows: Low when I^2 was less than 50% and moderate to high when I^2 was greater than or equal to 50%.[28] Publication bias was assessed by visual inspection of funnel plots, which were generated when there were 10 or more studies for a specific blood pressure threshold. A p value less than 0.05 was considered statistically significant. We conducted the analysis and generated forest plots using Review Manager 5.4.1 (The Cochrane Collaboration, 2020).

Secondary outcomes

We anticipated extensive differences between the studies with respect to the nature and timing of the measurement for both the exposure and the outcome. Therefore, we planned to group the studies by outcome and perform a narrative, descriptive analysis.

3.4 Results:

We identified 5109 unique citations, of which 46 met eligibility and were included in the final review (**Figure 1 and Supplemental Data: Appendix 6**). Twelve studies[29–40] evaluated only the primary outcome, 29 studies[14,15,41–69] evaluated one or more of the secondary outcomes and three studies[16,70,71] evaluated both.

Primary outcome:

The 15 studies reporting the primary outcome (aneurysm rebleeding) were all observational in design **(Supplemental Data: Appendix 7).** Over half of the studies (8/15) evaluated only a

single blood pressure reading at presentation to hospital[29,31,33,34,36,38–40] while the remainder (7/15) measured blood pressure over a specific time interval or reported a metric of blood pressure variability[16,30,32,35,37,70,71] **(Supplemental Data: Appendix 8)**. A single study compared management strategies and BP targets at 2 different centers.[70] Three studies did not define BP thresholds and presented only continuous data.[33,35,71]

*SBP > 140 mmHg **(Figure 2 and Table 1)***

Six studies[16,29,34,36,37,40] examined the association between elevated SBP > 140 mmHg with rebleeding. Meta-analysis of unadjusted results from the five studies reporting odds ratios showed no association with rebleeding (unadjusted Odds Ratio [uOR], 1.03; 95% CI, 0.55-1.93; I^2 = 66%). None of these five studies reported adjusted results from a multivariate model. A single study[16] evaluated time to event data and presented a hazard ratio adjusted for 5/6 of the pre-specified confounders. An SBP > 140 mmHg in the 6 hours prior to censoring or rebleeding was not associated with a risk of rebleeding (aHR, 0.89; 95% CI, 0.72-1.10).

*SBP > 160 mmHg **(Figure 3 and Table 1)***

Six studies[16,32,37–40] examined the association between elevated SBP > 160 mmHg with rebleeding. Meta-analysis of unadjusted results from the 4 studies reporting odds ratios showed an association with rebleeding (uOR, 3.35; 95% CI, 1.44-7.81; I^2 = 83%). One of these studies[32] presented adjusted results from a multivariable model, which after adjustment for 3/6 key confounders (age, sex, and clinical grade), showed that there is 3.34 times the odds of rebleeding if the SBP is greater than 160 mmHg (OR, 3.34; 95% CI, 1.73-7.74; $p < 0.001$). In contrast, two recent (2022), large cohorts presented results from multivariable models that were adjusted for

5/6 key confounders.[16,39] Meta-analysis of these 2 studies showed no association between SBP > 160 mmHg and rebleeding (adjusted Hazard Ratio [aHR], 1.13; 95% CI, 0.98-1.31; I^2 = 0%)

SBP > 180 mmHg ***(Figure 4 and Table 1)***

Four studies[16,30,34,37] examined the association of an SBP > 180 mmHg with rebleeding. Meta-analysis of unadjusted results from 3 studies reporting odds ratios showed that an SBP > 180 mmHg was not associated with an increased odds of rebleeding (uOR, 1.52; 95% CI, 0.40-5.81; I^2 = 89%) A single study[16] presented results from a multivariable model, adjusted for 5/6 key confounders, which did not demonstrate an association between SBP > 180 mmHg and rebleeding (aHR, 1.21; 95% CI, 0.84-1.74).

SBP > 200 mmHg ***(Figure 5 Table 1)***

Two studies[31,37] examined the association of an SBP > 200 mmHg with rebleeding. Meta-analysis of unadjusted results from these 2 studies suggests a strong association with rebleeding (uOR, 7.99; 95% CI, 3.60-17.72; I^2 = 0%). One of these studies present multivariable results[31] which does not show an association when adjusting for 2/6 key confounders (OR, 1.41: 95% CI, 0.68-2.91).

Non-categorized studies

A single comparative study[70] from 2022 assessed cohorts from two centers with different SBP management strategies (intensive: SBP ≤ 140 mmHg vs Liberal: SBP ≤ 200 mmHg). They evaluated blood pressure from admission to aneurysm occlusion, rebleeding, or death. An intensive strategy did not result in reduced risk of rebleeding (aHR, 0.66; 95% CI, 0.23-1.92).

Three additional studies[33,35,71] evaluated the association of blood pressure as a continuous variable and rebleeding. The first study[33] is a retrospective cohort that found a 2% increase in rebleeding for every 1 mmHg increase in SBP, when adjusted for 2/6 key confounders (OR, 1.02; 95% CI, 1.00-1.04; $p = 0.050$). The second study[35] is a case-control design that evaluated the association of rebleeding with both mean SBP and SBP variability over the unsecured period. On univariate analysis, elevated mean SBP was not associated with rebleeding (mean SBP rebleed, 137.2+/-20.9; mean SBP no rebleed, 132.1+/-18.7; $p = 0.423$) but increased SBP variability was associated with rebleeding (SBPV-SD; rebleed, 14.3+/-2.9; no rebleed, 10.9+/-3.4; $p <0.001$). Increased SBP variability was associated with rebleeding in multivariable modeling (SBP-SD, OR, 1.254; 95% CI, 1.13-1.39; $p = <0.001$), when adjusted for 2/6 key confounders. The third study[71] is a retrospective cohort that found no association between the maximum SBP during the unsecured period and symptomatic rebleeding (OR, 1.00; 95% CI, 0.99-1.01; p=0.06).

Mean Arterial Pressure

Two studies[16,71] reported on the association of MAP and rebleeding. In the first study, a MAP < 100 mmHg during a specified timeframe (1, 3, or 6 hours) prior to the rebleeding event was associated with a decreased risk of rebleeding (e.g. within 6 hours of rebleeding and for a MAP = 80 mmHg; aHR, 0.30; 95% CI, 0.11-0.80). The second study[71] found no association between maximum MAP during the unsecured period and aneurysm rebleeding after adjustment for confounders (Unadjusted analysis; OR, 1.01; 95% CI, 1.00-1.03; p = 0.001; Adjusted analysis; not significant, results not reported).

Secondary Outcomes:

Thirty-four studies[14–16,41–65,65,66,68–71] evaluated an association of elevated blood pressure during the early phase (first 72 hours) of aSAH with various outcomes **(Supplemental Data: Appendices 9 and 10)**. Five studies were prospective cohorts[42,46,62,65,67] and the remainder were retrospective cohorts, including 4 studies[48,50,57,60] that were post-hoc analyses of patients enrolled in a group of clinical trials. Heterogeneity between the studies, with respect to timing and measurement of both the exposure and the outcome, is displayed in a matrix table format. **(Supplemental Data: Appendix 11)**.

Mortality

Six studies[15,42,44,54,68,69] examined the association between elevated blood pressure and mortality and reported variable results.

mRS

Nine studies[14,44,46,48,51,61,65,67,71] examined the association between elevated blood pressure and functional outcome as measured by the Modified Rankin Scale (mRS). Multivariable modelling was performed in seven studies with variable results.

Glasgow outcome scale

Eight studies[43,45,56,58,60,62,63,66] examined the association between elevated blood pressure and functional outcome as measured by the Glasgow Outcome Scale (GOS). The follow-up varied from hospital discharge to 1 year from treatment. Five studies[43,56,58,60,66] performed multivariable modelling. Four of these studies found an association between elevated blood pressure and poor outcome. The size of the effect measures was extremely small (OR $\leq$ 1.02), with the exception of

a single study.[66] This study found that an SBP > 135.6 mmHg on admission, when compared to an SBP < 120.9 mmHg, was associated with 2.8 times the odds of a poor outcome (OR, 2.8; 95% CI, 1.1-6.9; p = 0.024).

Delayed cerebral ischemia/Vasospasm

Ten studies[16,41,49,52,53,55,57,59,63,70] examined the association between elevated blood pressure and the incidence of DCI or vasospasm. Seven studies[16,41,52,53,55,57,70] performed multivariable modelling and present adjusted results that were variable.

Cerebral infarction

Two studies[50,63] examined the association between elevated blood pressure and the incidence of cerebral infarction. One of these[50] performed multivariable modeling but the results were not significant and were not reported.

Other outcomes

Three studies examined additional outcomes: Hospital discharge disposition[47,68] and ICU length of stay.[64]

Risk of Bias Assessment:

Primary Outcome

All studies were rated as either moderate (n=12) or high (n=3) overall risk of bias **(Figure 6)**. Publication bias could not be assessed using a funnel plot as there were less than 10 studies per blood pressure threshold strata.

Secondary Outcomes

With the exception of a single study[48] that was rated as low risk of bias, all studies were rated as either moderate (n=23) or high (n=10) overall risk of bias **(Supplemental Data: Appendix 12).**

Quality of Evidence:

Overall, the quality of evidence as assessed by GRADE for the primary outcome of rebleeding was rated as very low. There were serious concerns in all the certainty domains (**Table 2 and Supplemental Data: Appendix 13)**.

3.5 Discussion:

In our systematic review, we did not find an association between elevated blood pressure and rebleeding of the culprit aneurysm during the unsecured period in aSAH. While the results of the unadjusted meta-analyses are mixed across the various BP thresholds, there are inadequate numbers of studies reporting adjusted results at each of the BP thresholds to perform a meta-analysis, with the exception of an SBP > 160 mmHg, which shows no association with rebleeding (aHR, 1.13; 95% CI, 0.98-1.31; I^2 = 0%). Additionally, there is no consistent dose effect observed as blood pressure increases between the thresholds. The evidence base is comprised of exclusively observational data that is at moderate or high risk of bias. The overall quality of evidence is rated as very low for the primary outcome. Further, we did not find an association between elevated blood pressure during the early phase and any of the secondary outcomes.

Our results are in contrast to three previous systematic reviews[25,26,72] that reported an association between elevated SBP > 160 mmHg and aneurysmal rebleeding. These previous reviews did not account for multivariable results (adjusted for confounders) in the context of included studies that are exclusively observational in design and at moderate to high risk of bias. Using an SBP > 160 mmHg as an example, the meta-analysis of four studies that report unadjusted results seems to suggest a strong association between elevated blood pressure and rebleeding.[32,37,38,40] However, only one of these reports adjusted results from a multivariable model.[32] In contrast, the meta-analysis of two recent studies, which report hazard ratios from multivariable models adjusted for 5/6 pre-specified confounders, did not find an association with rebleeding .[16,39] While it is tempting to use unadjusted results to draw conclusions about the association of elevated BP and the risk of rebleeding, this could be misleading, especially in the context of purely observational data at moderate to high risk of bias. The apparent association of elevated SBP and rebleeding using unadjusted results alone may be entirely due to confounding.

In our review, 10 of the 15 studies were designed using multivariable modelling, but only 2 found a statistically significant association between elevated systolic blood pressure and rebleeding.[32,33] There are important limitations in the methodology of these 2 studies that reduces the validity of their results. The first study[32] only adjusted for 3/6 key confounders and there were important differences in how data on SBP was collected between groups. The exposure was not the same for the entire cohort, potentially introducing significant bias into study. The second study[33] only adjusted for 2/6 key confounders and the clinical significance is questionable: the effect size is very small (OR, 1.020) and the confidence interval includes 1 (95% CI, 1.000-1.041).

Most of the included studies (8/15) use a single blood pressure value from the time of presentation to hospital. While this is reflective of the physiologic condition at the time of presentation, it does not reflect the impact of elevated blood pressure over the unsecured period. More importantly, this single value should not influence blood pressure management during this timeframe. In contrast to previous systematic reviews, our findings support the absence of specific blood pressure target recommendations found in the newly published guidelines.[12,13] Lastly, we cannot draw any conclusions from the secondary outcome analyses due to the large amount of clinical and methodological diversity amongst the studies, the moderate to high risk of bias, and the variable results reported.

The findings of our systematic review are strengthened by its methodologic rigor including clear definition of the exposure relevant to the review question, reporting a variety of BP metrics, and using additional pre-specified BP thresholds to examine if there was a dose effect of BP on rebleeding. This systematic review has several limitations, many of which relate to the limitations of the individual studies themselves, including study design and risk of bias. The absence of reported multivariable results limited the meta-analyses to unadjusted results at all BP thresholds, with the exception of an SBP > 160 mmHg. There is a significant timespan from the first to the last included study (35 years), during which time, much has changed within the management of critically ill patients, specifically those with aSAH. Most studies used a single admission blood pressure as opposed to a measure that incorporates the entire unsecured period. This decreases the potential relevance of the measurement and allows for introduction of bias into the results (as it is unclear what the BP was during the remainder of the unsecured period). The small number of studies within each blood pressure threshold strata limited the ability to examine the causes of heterogeneity. In our protocol we had planned to explore the

etiologies of heterogeneity by performing both subgroup analysis and meta-regression, but this was not feasible. Additionally, the small number of studies prevented us from generating a funnel plot to assess publication bias and small study effects. Lastly, as all studies included for the primary outcome were at moderate or high risk of bias, and due to the small overall number of studies, we did not perform the pre-specified sensitivity analysis removing high risk of bias studies.

3.6 Conclusions:

We did not observe an association between elevated blood pressure during the unsecured period of aSAH and aneurysmal rebleeding. The existing literature is exclusively observational, at moderate to high risk of bias, and of very low quality overall. Current evidence does not support the use of a specific blood pressure strategy for the management of aSAH. Importantly, there are no interventional studies examining the impact of blood pressure reduction on the risk of rebleeding. A large-scale, randomized clinical trial is needed to address this question.

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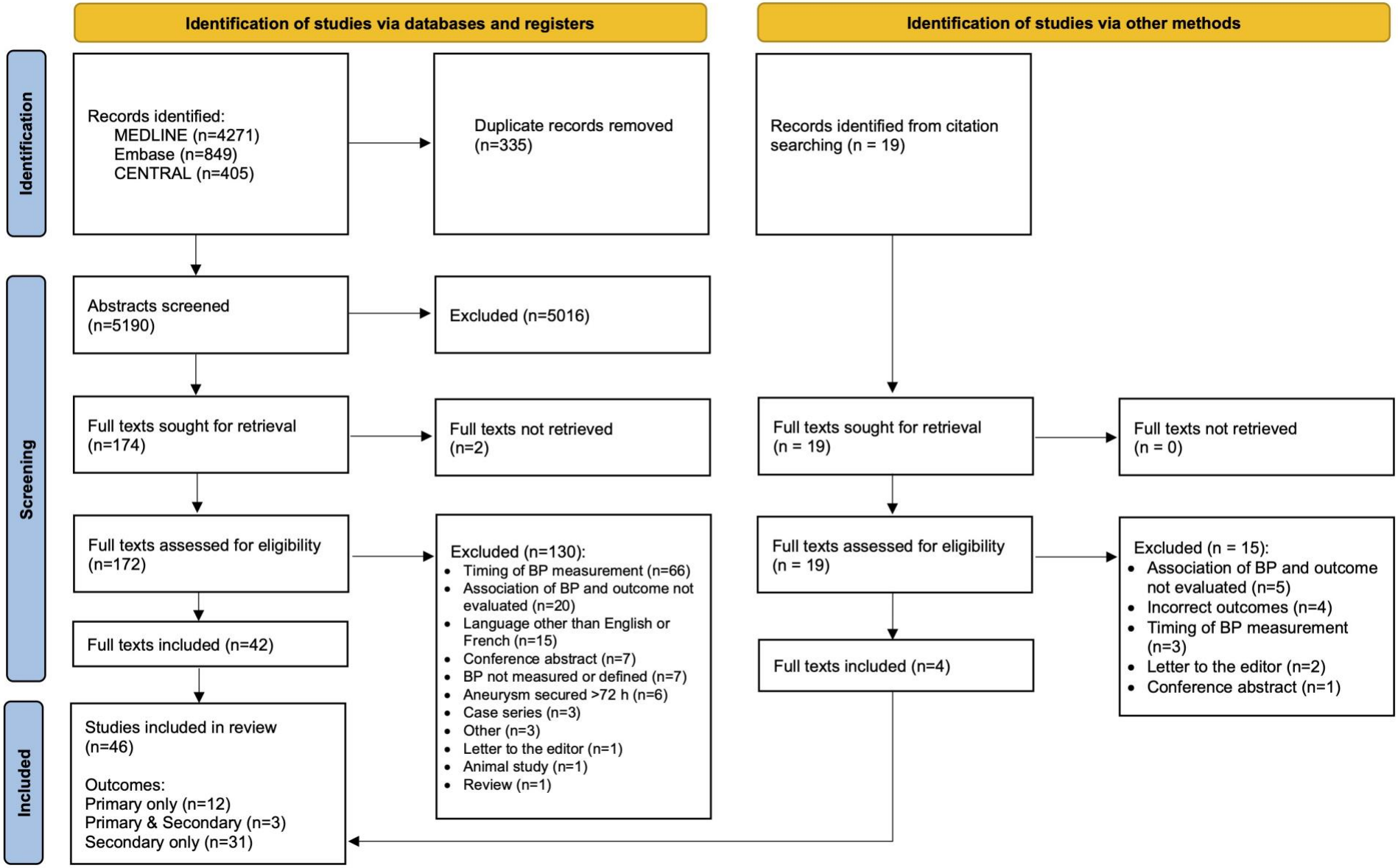
3.8 Figure and tables:

Figure 1. PRISMA Flow Diagram



Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

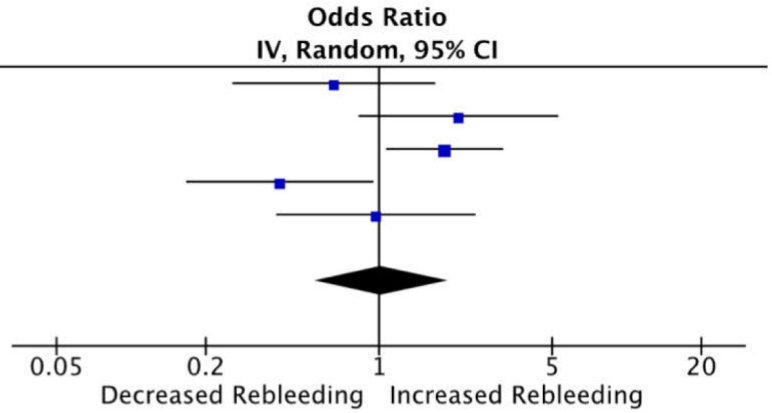
Figure 2. Forest Plots of Systolic Blood Pressure and Risk of Rebleeding: SBP > 140 mmHg

A.

Study or Subgroup	SBP > 140 Events	SBP > 140 Total	SBP < 140 Events	SBP < 140 Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Inagawa 1987	22	114	8	30	18.3%	0.66 [0.26, 1.67]	1987
Ohkuma 2001	31	199	6	74	18.5%	2.09 [0.83, 5.24]	2001
Cong 2012	32	174	31	284	25.1%	1.84 [1.08, 3.14]	2012
Oheda 2015	14	225	10	70	19.5%	0.40 [0.17, 0.94]	2015
Liu 2021	6	36	64	375	18.6%	0.97 [0.39, 2.43]	2021
Total (95% CI)		**748**		**833**	**100.0%**	**1.03 [0.55, 1.93]**	
Total events	105		119				

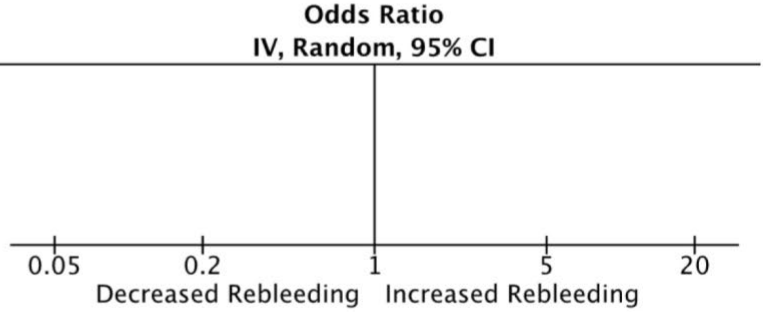
Heterogeneity: $Tau^2 = 0.33$; $Chi^2 = 11.93$, df = 4 (P = 0.02); $I^2 = 66\%$

Test for overall effect: Z = 0.09 (P = 0.93)



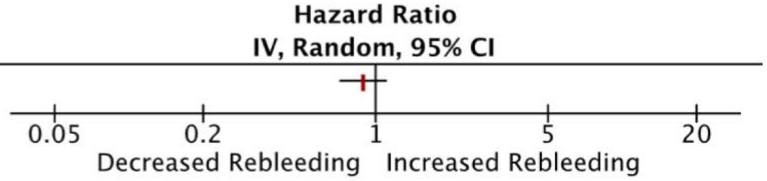
B.

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Random, 95% CI	Year
Inagawa 1987	0	0	Not estimable	1987
Ohkuma 2001	0	0	Not estimable	2001
Cong 2012	0	0	Not estimable	2012
Oheda 2015	0	0	Not estimable	2015
Liu 2021	0	0	Not estimable	2021



C.

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Random, 95% CI	Year
Gathier 2022	-0.1165	0.1082	0.89 [0.72, 1.10]	2022



A. Unadjusted Odds Ratio; B. Adjusted Odds Ratio; C. Adjusted Hazard Ratio

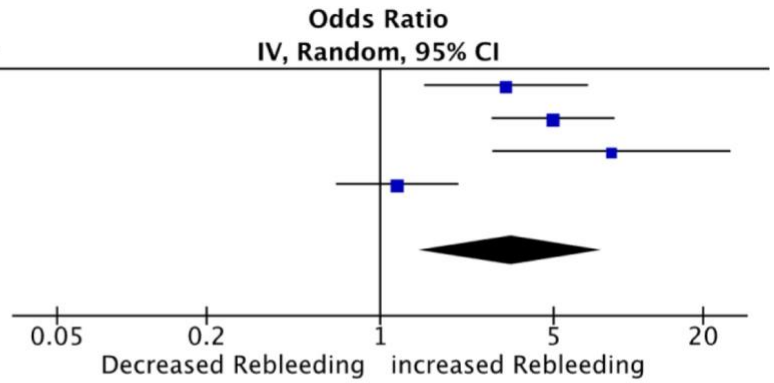
Figure 3. Forest Plots of Systolic Blood Pressure and Risk of Rebleeding: SBP > 160 mmHg

A.

Study or Subgroup	SBP > 160 Events	SBP > 160 Total	SBP < 160 Events	SBP < 160 Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Ohkuma 2001	26	126	11	147	24.9%	3.21 [1.52, 6.81]	2001
Guo 2011	44	109	26	217	27.3%	4.97 [2.84, 8.71]	2011
Solanki 2016	26	30	73	169	20.4%	8.55 [2.86, 25.57]	2016
Liu 2021	49	276	21	135	27.3%	1.17 [0.67, 2.05]	2021
Total (95% CI)		**541**		**668**	**100.0%**	**3.35 [1.44, 7.81]**	
Total events	145		131				

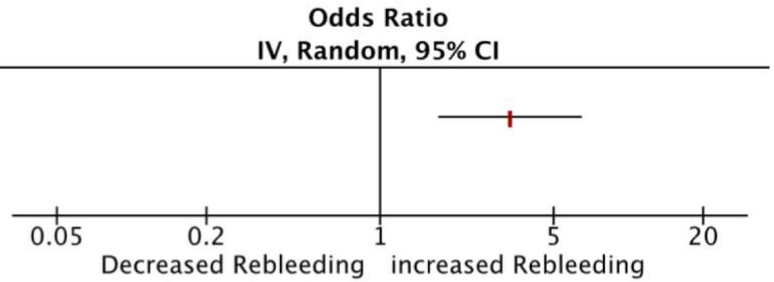
Heterogeneity: $Tau^2 = 0.60$; $Chi^2 = 17.47$, df = 3 (P = 0.0006); $I^2 = 83\%$

Test for overall effect: Z = 2.81 (P = 0.005)



B.

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Random, 95% CI	Year
Ohkuma 2001	0	0	Not estimable	2001
Guo 2011	1.2054	0.3342	3.34 [1.73, 6.43]	2011
Solanki 2016	0	0	Not estimable	2016
Liu 2021	0	0	Not estimable	2021

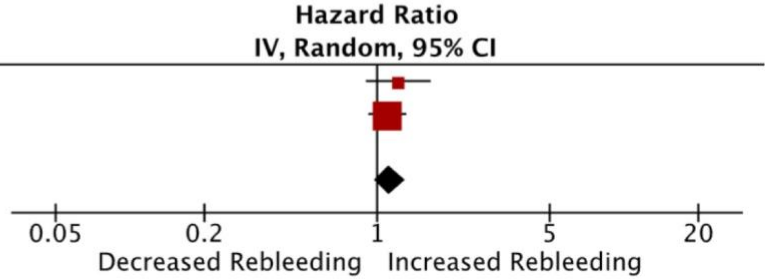


C.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
van Lieshout 2022	0.1989	0.1496	24.7%	1.22 [0.91, 1.64]	2022
Gathier 2022	0.0953	0.0857	75.3%	1.10 [0.93, 1.30]	2022
Total (95% CI)			**100.0%**	**1.13 [0.98, 1.31]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.36$, df = 1 (P = 0.55); $I^2 = 0\%$

Test for overall effect: Z = 1.63 (P = 0.10)



A. Unadjusted Odds Ratio; B. Adjusted Odds Ratio; C. Adjusted Hazard Ratio

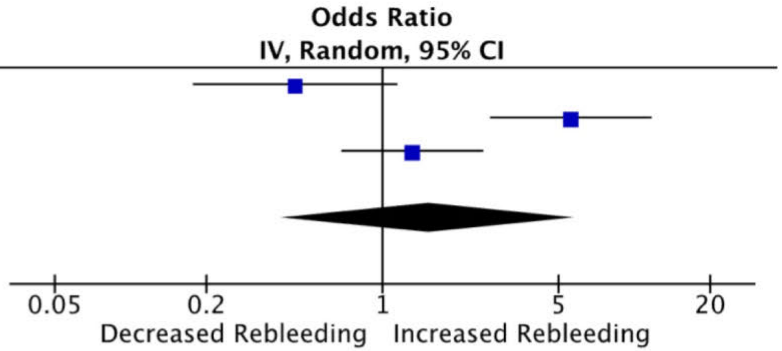
Figure 4. Forest Plots of Systolic Blood Pressure and Risk of Rebleeding: SBP > 180 mmHg

A.

Study or Subgroup	SBP > 180 Events	SBP > 180 Total	SBP < 180 Events	SBP < 180 Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Inagawa 1987	7	53	23	91	31.8%	0.45 [0.18, 1.13]	1987
Ohkuma 2001*	20	61	17	212	33.7%	5.60 [2.70, 11.60]	2001
Darkwah Oppong 2018	13	180	45	804	34.5%	1.31 [0.69, 2.49]	2018
Total (95% CI)		**294**		**1107**	**100.0%**	**1.52 [0.40, 5.81]**	
Total events	40		85				

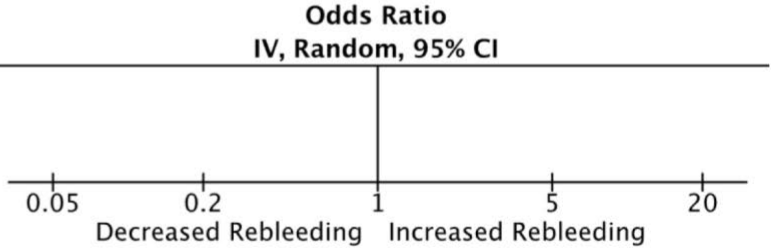
Heterogeneity: $Tau^2 = 1.25$; $Chi^2 = 18.82$, df = 2 ($P < 0.0001$); $I^2 = 89\%$

Test for overall effect: Z = 0.62 (P = 0.54)



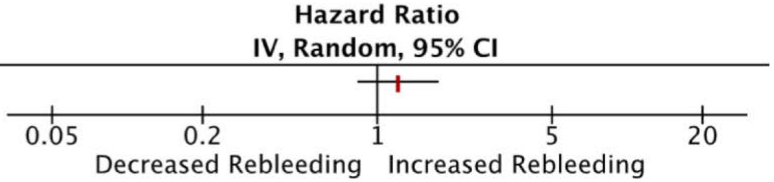
B.

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Random, 95% CI	Year
Inagawa 1987	0	0	Not estimable	1987
Ohkuma 2001*	0	0	Not estimable	2001
Darkwah Oppong 2018	0	0	Not estimable	2018



C.

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Random, 95% CI	Year
Gathier 2022	0.1906	0.1862	1.21 [0.84, 1.74]	2022



A. Unadjusted Odds Ratio; B. Adjusted Odds Ratio: C. Adjusted Hazard Ratio

* SBP > 182 mmHg

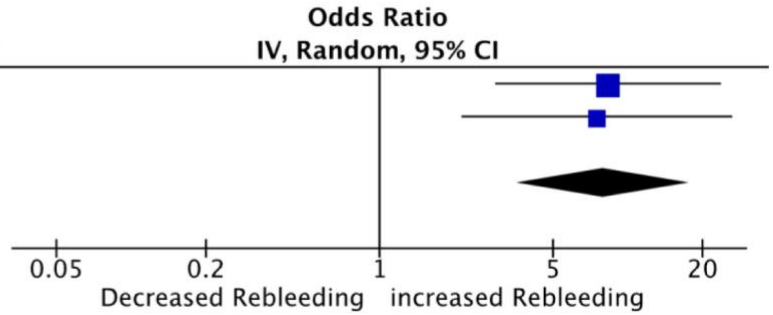
Figure 5. Forest Plots of Systolic Blood Pressure and Risk of Rebleeding: SBP > 200 mmHg

A.

Study or Subgroup	SBP > 200 Events	SBP > 200 Total	SBP < 200 Events	SBP < 200 Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Fujii 1996	10	18	21	161	59.1%	8.33 [2.96, 23.50]	1996
Ohkuma 2001	6	11	31	225	40.9%	7.51 [2.16, 26.10]	2001
Total (95% CI)		**29**		**386**	**100.0%**	**7.99 [3.60, 17.72]**	
Total events	16		52				

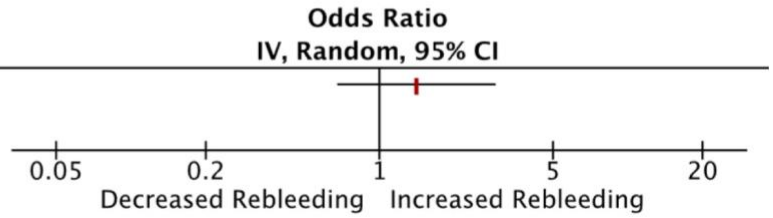
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 (P = 0.90); $I^2 = 0\%$

Test for overall effect: Z = 5.11 (P < 0.00001)



B.

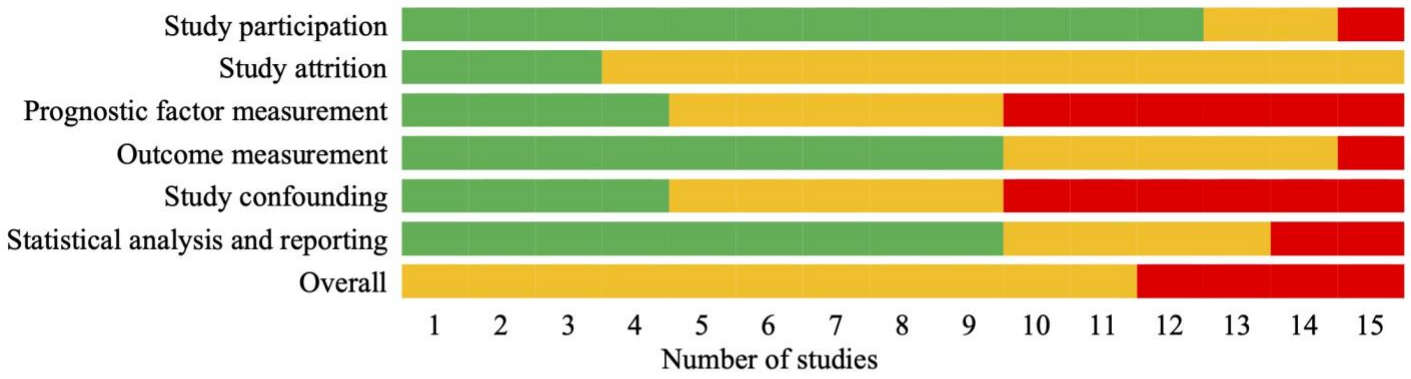
Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Random, 95% CI	Year
Fujii 1996	0.3436	0.3698	1.41 [0.68, 2.91]	1996
Ohkuma 2001	0	0	Not estimable	2001



A. Unadjusted Odds Ratio; B. Adjusted Odds Ratio

Figure 6. Risk of Bias Assessment

A.



B.

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall rating
Calviere 2022	Low	Moderate	Low	Moderate	High	Low	Moderate
Cong 2012	Low	Low	Moderate	Moderate	Low	Low	Moderate
Darkwah Oppong 2018	Low	Moderate	Moderate	Low	High	Low	Moderate
Fujii 1996	Low	Low	High	Low	Moderate	Low	Moderate
Gathier 2022	Moderate	Low	Moderate	Low	Low	Low	Moderate
Guo 2011	Low	Moderate	High	Low	Low	Moderate	Moderate
Haripottawekul 2024	Low	Moderate	Low	Low	Moderate	High	Moderate
He 2019	Low	Moderate	Moderate	Low	Moderate	Low	Moderate
Inagawa 1987	Moderate	Moderate	High	Low	High	High	High
Lin 2016	Low	Moderate	Low	Low	Moderate	Low	Moderate
Liu 2021	Low	Moderate	High	Moderate	High	Moderate	High
Oheda 2015	Low	Moderate	Low	Low	High	Low	Moderate
Ohkuma 2001	Low	Moderate	High	High	High	Moderate	High
Solanki 2016	Low	Moderate	High	Moderate	Moderate	Low	Moderate
Van Lieshout 2022	High	Moderate	Moderate	Moderate	Low	Moderate	Moderate

Low risk of bias Moderate risk of bias High risk of bias

A. Risk of bias presented by QUIPS domain across all included studies (primary outcome = rebleeding)
B. Risk of bias by QUIPS domain and overall for each included study (primary outcome = rebleeding)

4 Chapter 4 – Cross-Sectional Survey of Clinicians

Title:
Blood Pressure Management in Early Aneurysmal Subarachnoid Hemorrhage: A National Cross-Sectional Survey of Canadian Intensivists and Cerebrovascular Neurosurgeons

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4.1 Abstract:

Background/Objective:

In aneurysmal subarachnoid hemorrhage, rebleeding of the culprit aneurysm is associated with significant morbidity and mortality. Blood pressure reduction to specific target levels, with the goal of preventing rebleeding, has been a mainstay of care prior to definitively securing the aneurysm. Clinical practice guidelines have recently changed and no longer recommend specific blood pressure targets. This survey aims to identify the reported practice patterns and beliefs regarding blood pressure management during the early phase of aSAH

Methods:

We conducted a self-administered, web-based survey of critical care physicians and cerebrovascular neurosurgeons practicing in Canada. The questionnaire contained 21 items, including 3 case-based scenarios to elicit blood pressure target selection, both pre- and post-aneurysm securing.

Results:

In the pre-secured period, a systolic blood pressure of 160 mmHg (50% [144/287]) and 140 mmHg (42% [120/287]) were the most frequently selected upper limit targets. In the post-secured period, a systolic blood pressure of 180 mmHg (32% [93/287]) was the most frequently selected upper limit target but there was a wide distribution of targets selected across all three cases ranging from 100 mmHg to > 200 mmHg. A mean arterial pressure of 65 mmHg was the most common lower limit target in both the pre- and post-secured periods. There was little change in blood pressure targets with increasing clinical severity. Predictors of higher or lower

blood pressure target selection and barriers to implementation of the desired target were identified.

Conclusions:

During the pre-secured period, nearly half of the reported upper limit blood pressure targets are lower than previous guideline recommendations. These targets remain consistent despite increasing clinical severity and could potentially exacerbate cerebral ischemia and negatively impact clinical outcomes. In the post-secured period, there is wide variation in the reported blood pressure targets. A clinical trial is urgently needed to guide decision-making.

4.2 Introduction

Aneurysmal subarachnoid hemorrhage (aSAH), resulting from the rupture of a cerebral aneurysm, is a devastating form of stroke. It affects a relatively young population (mean age of 60 years), mainly women, and is associated with significant morbidity and mortality.[1–5] Rebleeding of the culprit aneurysm prior to treatment is a catastrophic complication.[6] In theory, any increase in transmural pressure across the aneurysm can lead to "re-opening" of the initially "clotted" rupture site.[7] Previous studies evaluating predictive factors for pre-treatment aneurysmal rebleeding have identified elevated blood pressure (BP) as an important risk factor.[8–10]

Blood pressure (BP) control during the pre-secured period of aSAH has been recommended in management guidelines from the American Heart Association/American Stroke Association (AHA/ASA), the European Stroke Organization (ESO), and the Neurocritical Care Society (NCS).[11–13] In contrast, other more recent guidelines acknowledge the absence of high quality evidence and recognize that lowering BP must be balanced against the risks of hypotension, hypoperfusion, and exacerbation of early brain injury.[14,15] Importantly, lowering BP to specific targets prior to securing the aneurysm is no longer recommended. The extent to which the previous recommendations of tight BP control has influenced current clinical practice is not known.

In the USA, a web-based, self-directed survey of 128 critical care physicians identified significant practice variability with respect to BP management in the aSAH population.[16] In the Canadian context, the practice pattern and beliefs are unclear. The objectives of this study are

threefold: First, to describe the self-reported practice patterns of early BP management by clinicians who care for aSAH patients in the Canadian setting. Second, to identify predictors for the selection of specific BP targets. And finally, to explore potential barriers to specific BP target implementation.

4.3 Methods

Questionnaire Development

In accordance with established survey methodology,[17,18] we conducted a self-administered, web-based survey of cerebrovascular neurosurgeons and critical care physicians who care for patients with aSAH and currently practice in Canada. A team of experts was established which included three neurointensivists (LT, SWE, AFT), two intensivists with expertise in survey methodology (LM, AFT), a cerebrovascular neurosurgeon (CO), and a statistician (TR). Using expert opinion and a review of the contemporary literature, questionnaire items were generated iteratively and grouped under specific themes: demographic data, BP targets (both pre and post aneurysm securing), predictors of higher or lower BP target selection, and barriers to BP target implementation. Once saturation of each theme was achieved, items were reduced using a modified Delphi process.[19] Items were structured to minimize respondent burden and to maximize response rate. The questionnaire was then placed into the final web-based format utilizing SurveyMonkey (SurveyMonkey Inc., San Mateo, California, USA. www.surveymonkey.com) and pre-piloted by three members of the core team to ensure both content- and face-validity. Lastly, the questionnaire was pilot-tested by three critical care fellows to confirm the time required for completion, as well as the clarity of the questions and the overall

structure and flow of the survey. Approval was obtained from the University of Ottawa Research Ethics Board (certificate number H-11-22-8598).

Questionnaire Content

The final questionnaire consisted of 21 questions organized within the following themes: demographic data, BP targets (both pre and post aneurysm securing), predictors of higher or lower BP target selection, and barriers to BP target implementation **(appendix 1)**. To elicit BP target selection, the survey contained three case scenarios representing a typical patient with aSAH but with progressive clinical severity from case 1 to case 3 **(appendix 2)**. In brief, case 1 represents a good grade presentation (World Federation of Neurosurgical Societies [WFNS] I with thin SAH, no external ventricular drain [EVD] and normal vital signs except for elevated BP). Case 2 represents an intermediate grade presentation (WFNS II, thick SAH, no EVD, normal vital signs except for elevated BP). Case 3 represents a poor grade presentation (WFNS V, intubated, EVD in situ, mild cerebral edema, other vitals normal except for elevated BP).

Study Population

We aimed to survey, in entirety, the Canadian cerebrovascular neurosurgeon and critical care physician communities who care for patients with aSAH during the early phase of illness (first 72 hours). To achieve this, we created a custom database using publicly available information from hospital and university web sites, informal networks of colleagues, and input from departmental administrators when required. The sampling frame included all attending cerebrovascular neurosurgeons (n=49) and critical care physicians (n=244) who practice in Canadian centers (n=21) and who could potentially care for adult patients with aSAH. In

accordance with the American Association For Public Opinion Research, a complete survey was defined as having at least 80% of questions answered.[20]

Dissemination

The survey was distributed using SurveyMonkey and followed evidence-based strategies to increase the overall response rate.[21] An initial, personalized, introductory email was sent to all of the potential respondents identified in our database with a link to the survey. This was followed by reminder emails at 2 and 4 weeks. SurveyMonkey allows for tracking which respondents have completed the survey without linking this to their responses. This allows for targeted follow-up emails to be generated while maintaining anonymity. There was no financial incentive provided and completion of the survey was voluntary. Responses were collected from March 3rd, 2023 to April 30th, 2023.

Statistical analysis

Data was downloaded and cleaned using Microsoft Excel for Mac (version 16.77.1, Microsoft Corporation, 2023). Figures were generated using Microsoft Excel. Data analysis was completed using SAS studio (release 3.8 Enterprise Edition, SAS institute Inc., Cary, NC, USA). All response options were created in a categorical format to facilitate accurate responses. Categorical variables are presented as frequency and percent. Results were displayed graphically in bar charts.

4.4 Results

One hundred and five clinicians (36%) responded to the survey. Three did not provide care to aSAH patients and were excluded, leaving responses from 102 clinicians included in the final analysis **(Table 1)**. Of these, 85% (87/102) were complete. Eighty-five percent (87/102) of respondents were critical care physicians and 15% (15/102) were cerebrovascular neurosurgeons. Sixteen percent (14/87) of respondents had additional subspecialty training in neurocritical care. There was a broad distribution in years of practice with representation in all categories. Ninety-one percent (79/87) worked in centers that cared for 25 or more cases of aSAH per year and 92% (80/87) worked in centers that offered both surgical clipping and endovascular coiling. A majority of respondents, 61% (53/87), reported working at centers that leveled the arterial BP transducer at the tragus during concurrent intracranial pressure monitoring (ICP) monitoring.

Blood pressure target selection

Ninety-eight percent (100/102) of respondents completed case 1, Ninety-five percent (97/102) of respondents completed case 2, and eighty-eight percent (90/102) of respondents completed case 3. There was a total of 287 responses across all three cases.

Pre-secured period

In the period before the culprit aneurysm is secured (pre-secured period), the most frequently selected systolic BP (SBP) upper limit target across all three cases was 160 mmHg (50% [144/287]) followed by 140 mmHg (42% [120/287]) **(Figure 1A)**. A mean arterial pressure (MAP) lower limit target of 65 mmHg was most frequently selected by respondents (39% [111/287]). However, there was a wide range of lower limit MAP targets selected (from a MAP < 65 mmHg to a MAP = 110 mmHg) **(Figure 1B)**.

Of those respondents who chose an SBP upper limit target of 140 mmHg in good-grade aSAH (case 1), 84% (37/44) subsequently selected the same target in intermediate-grade aSAH (case 2) and 78% (32/41) selected the same target in poor-grade aSAH (case 3) **(Table 2A)**. Of those respondents who chose an SBP upper limit target of 160 mmHg in good-grade aSAH (case 1), 96% (46/48) selected the same target in intermediate-grade aSAH (case 2) and 86% (38/44) chose the same target in poor-grade aSAH (case 3) **(Table 2B)**.

Post-secured period

In the period following securing of the culprit aneurysm (post-secured period), the most frequently selected SBP upper limit target across all three cases was 180 mmHg (32% [93/287]) **(Figure 2A)**. There was a wide distribution of targets selected, ranging from 100 mmHg to > 200 mmHg. The MAP lower limit target most frequently selected by respondents across all three cases was 65 mmHg (42% [121/287]) **(Figure 2B)**.

Cerebral perfusion pressure targets:

The most frequently selected CPP lower limit target was 60 mmHg, in both the pre-secured (49% [44/90]) and post-secured periods (44% [40/90]) **(figure 3)**.

Predictors of setting a higher or lower BP target selection:

The main predictor of setting a higher BP target was evidence of cerebral edema or elevated ICP (90% of respondents) **(Figure 4A)**. Conversely, the main predictor for lower BP target selection was larger aneurysm size (76% of respondents) (**(Figure 4B)**.

Barriers to BP target implementation:

Of the four barriers to BP target implementation that were presented to respondents, the most frequently selected was disagreement with another provider (sometimes = 41%, often/always = 14%) **(Figure 4C)**.

4.5 Discussion

Our national survey of cerebrovascular neurosurgeons and critical care physicians shows uniformity in the reported upper-limit BP targets selected during the pre-secured period, with an SBP of either 140 mmHg or 160 mmHg as the most common choice. In the post-secured period, there is wide variation in the reported SBP upper limit target. The lower limit MAP targets mentioned are similar in both the pre- and post-secured periods. Interestingly, there is little change in either the upper or lower limit targets selected (in both the pre- and post-secured periods) with increasing clinical severity across the cases (from good grade to poor grade) even though evidence of cerebral edema or elevated ICP was identified by most respondents as being an important factor in setting BP targets. The main reported barrier to implementation of the desired BP target was disagreement with another provider.

Our findings are congruent with those in a 2017 survey of clinicians from the USA.[16] In that study, the most frequently selected SBP targets during the pre-secured period were 140 mmHg and 160 mmHg. These reported practices are more aggressive than the management guidelines from the American Heart Association/American Stroke Association and the Neurocritical Care Society in place at the time of this survey. Those guidelines identify that there is no clear

consensus on the magnitude of BP reduction required to reduce rebleeding, however, they state it is reasonable to treat an SBP > 160 mmHg (or a MAP > 110 mmHg).[11,12] Newly released guidelines published last year from both organizations identify the absence of high quality evidence to support BP lowering as a measure to prevent rebleeding and consequently no longer recommend any specific targets.[14,15] Blood pressure reduction must be weighed against the risks of hypoperfusion and ischemia and the potential for worsening clinical outcomes.[22–24]

In the post-secured period, the wide variation in the reported targets is in keeping with the 2017 survey from the USA. importantly, there is not the same uniformity in reported target selection as there was in the pre-secured period. Ten percent or more of respondents selected a response ranging from 160 mmHg to >200 mmHg. With the risk of rebleeding eliminated, it is likely that clinicians are comfortable tolerating much higher BP. Additionally, as the time course of the illness moves into the late phase (beyond 72 hours) where there is a risk of vasospasm and delayed cerebral ischemia (DCI), it is possible that treating clinicians view higher BP as potentially protective. Another possibility is that this wide variation in reported BP targets could be partially due to factors that were not explored in the case scenarios (e.g. type of repair, late presentation, associated hematoma/ischemia/infarction, myocardial dysfunction, etc).

The most frequently selected MAP target across all three cases was 65 mmHg. This did not change meaningfully with increasing case severity or between the pre-secured period and the post-secured period. This likely reflects the typical minimum MAP (65 mmHg) utilized in critical care environments in the setting of shock management.[25] As these were all early phase and prior to the onset of vasospasm/DCI, this target may be entirely appropriate. In the setting of

cerebral edema (case 3), one may have expected the respondents to target a higher MAP with the goal of maintaining cerebral perfusion and preventing ischemia. In this case, it is possible that the concurrent ICP monitoring and resulting CPP target would override the minimum MAP target selected by the respondents. The degree to which the previous guideline recommendations around BP targets influenced the responses to minimum MAP in this survey are not known.

A key purpose of this survey was to assist with the design of a future clinical trial. Previous trials evaluating BP reduction in ICH had a number of challenges with the design and implementation that are relevant to a future trial of BP reduction in aSAH.[26,27] These include timing and location of patient recruitment, time to achieve target BP, transient BP elevations with spontaneous recovery, and heterogeneity of both BP treatment, BP targets, and other medical care. Stratification of disease severity, between intervention arms, was identified as a key issue in the INTERACT2 and ATACH-2 trials.[26,27] Based on our survey, it would be important to ensure that the top-ranked reported predictors for using a higher or lower BP target, are balanced between the intervention arms. Many of these, including clinical grade, radiologic grade, and age, are also predictors of outcome in aSAH, further necessitating balanced study arms. Another important issue is non-standardized management post-enrolment.[26] As identified in our survey, there is wide variability in the reported lower blood pressure targets between providers during the pre-secured period and both the upper and lower BP targets in the post-secured period. Depending on the timing of the outcome selected in a future clinical trial, this variability could play a significant role in influencing the outcome. Either management will need to be standardized or the outcome will need to be proximal to the intervention to limit the impact of this variability.

The main reported barrier to implementation of the desired BP target was identified as provider disagreement. This highlights the strongly held beliefs of providers and the absence of high-quality evidence to guide decision-making. Newly released management guidelines, which no longer make specific BP reduction recommendations, highlight the need for a clinical trial to guide management.[14,15] These new recommendations could help to soften people's beliefs and facilitate increased comfort with patient randomization to different BP management strategies in a clinical trial. Additionally, our group has conducted a systematic review (submitted for publication; protocol available at PROSPERO; CRD42022319563) evaluating the relationship between elevated blood pressure and aneurysm rebleeding during the pre-secured period. There was no clear association of elevated blood pressure with aneurysm rebleeding. All the included studies were observational in design and at moderate to high risk of bias. There were no interventional studies evaluating BP reduction during the pre-secured period. These results could further help to alleviate concern with using "different" BP targets and increase provider comfort with enrolment in a clinical trial.

Our study has a number of strengths. We created a custom database in an attempt to identify the entire population of cerebrovascular neurosurgeons and critical care physicians who care for aSAH across Canada. This differs from the prior study which only distributed the survey to a subset of the overall population.[16] The inclusion of a case-based approach to elicit responses to varying clinical severity also differs from the 2017 survey. This adds clinical context to the decision-making, with the goal of the stated response more closely aligning with actual clinical practice. Lastly, our study assessed predictors for using a higher or lower BP target and perceived

barriers to target implementation in clinical practice. As discussed above, these will provide valuable guidance for the design of further prospective studies of blood pressure control in early aSAH.

Our study also has important limitations. First, the overall response rate was 36% (105/293) which seems low and may lead one to question whether the results are appropriately representative of the population of interest. However, this response rate is in keeping with the average of neurosurgical surveys in the post-COVID era.[28] Importantly, with the creation of our custom database, we included any clinician who could potentially care for adult patients with aSAH. It is highly likely that many recipients of the survey invitation did not care for this patient population and thus did not respond, artificially lowering the response rate. Notably, of the 102 respondents who started the survey, 85% (87/102) completed the questionnaire. Second, small or absent number of responses in some cells limits our ability to apply statistical testing for group comparisons. However, this was not the stated aim of the study, which was to describe the reported practices of clinicians. Finally, recall bias is a potential source of error within our survey.[29] We attempted to minimize this by surveying actively practicing providers. The majority reported working at high-volume centers, which hopefully ensured the recall period would be relatively short.

4.6 Conclusions

In our survey, we report the stated practice patterns of ICU physicians and cerebrovascular neurosurgeons in Canada, with respect to BP management during the early phase of aSAH. Practices appear entrenched with little change in targets as clinical severity increases from good

grade to poor grade. Nearly half of respondents report using more aggressive (lower) BP targets then previous guidelines recommended. There is potential that this pattern of practice may increase the risks of cerebral ischemia and infarction, leading to worse clinical outcomes. A clinical trial is urgently needed to determine the optimal BP targets in aSAH. Our results will inform the design and development of a future prospective study.

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4.8 Tables and Figures

Table 1: Respondent demographic information (n=102)*

	Variable		Total respondents	Frequency (%)
Respondent Characteristics	Specialty		102	
		Critical Care Medicine		87 (85)
		Neurosurgery		15 (15)
	NCC fellowship training (yes)		87	14 (16)
	Years in clinical practice (yrs)		87	
		0-5		20 (23)
		6-10		15 (17)
		11-15		19 (22)
		16-20		11 (13)
		21-25		11 (13)
		26-30		6 (7)
		>30		5 (6)
Centre Characteristics	Yearly aSAH cases at the respondent's centre (count)		87	
		<25		8 (9)
		25-50		35 (40)
		>50		44 (51)
	Procedural capability of respondent's centre		87	
		Surgical clipping		85 (98)
		Endovascular therapy		82 (94)
		Both		80 (92)
	Anatomic level of ABP monitor during concurrent ICP monitoring		87	
		Tragus/EAM		53 (61)
		Phlebostatic axis		25 (29)
		Unsure		5 (6)
		other		4 (5)

Variables presented as frequency (counts) and percentage (%)
*15 missing responses for all demographic variables except Specialty (0 missing)
ABP: Arterial Blood Pressure; aSAH: aneurysmal Subarachnoid Hemorrhage; EAM: External auditory meatus; ICP: Intracranial Pressure; NCC: Neurocritical Care

Table 2: BP target selection in subsequent cases by respondents who selected either 140 mmHg or 160 mmHg in Case 1.

2A. Case 1 SBP 140 mmHg

Case 2	Frequency (%)
Higher	4 (9.1)
Same (140 mmHg)	37 (84.1)
Lower	3 (6.8)
Case 3	
Higher	5 (12.2)
Same (140 mmHg)	32 (78.0)
Lower	3 (7.3)
Would not use an SBP target	1 (2.4)

2B. Case 1 SBP 160 mmHg

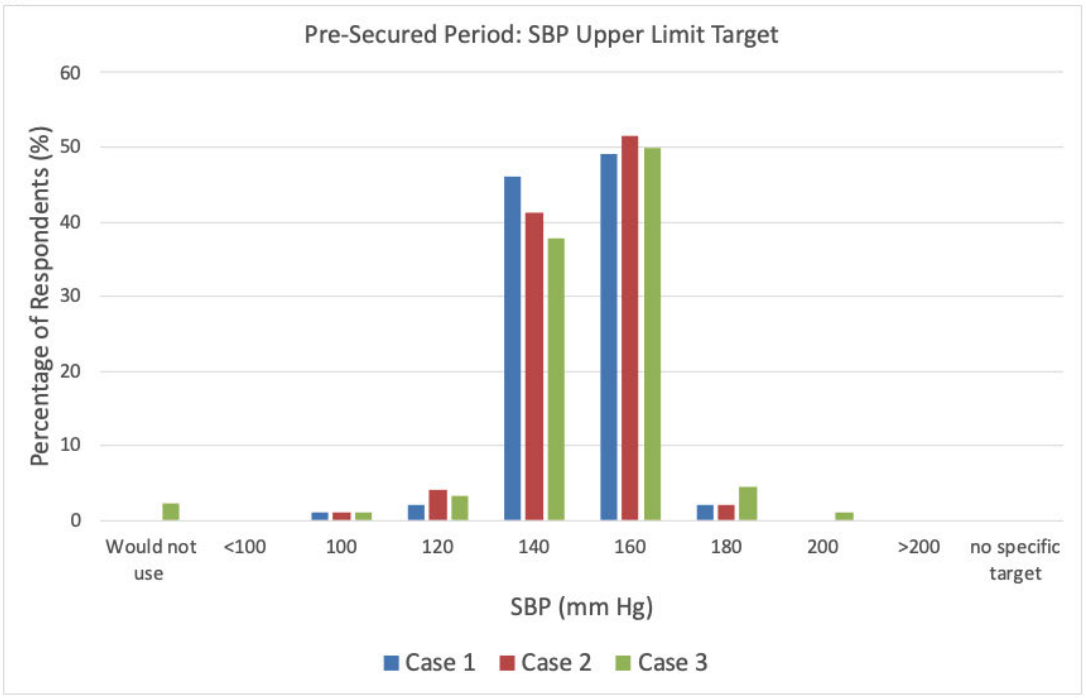
Case 2	Frequency (%)
Higher	0 (0)
Same (160 mmHg)	46 (95.8)
Lower	2 (4.2)
Case 3	
Higher	4 (9.1)
Same (160 mmHg)	38 (86.4)
Lower	1 (2.3)
Would not use an SBP target	1 (2.3)

SBP: systolic blood pressure

Figure 1: Pre-secured period blood pressure targets (percentage of respondents).

Figure 1: Pre-secured period blood pressure targets (percentage of respondents).

A.



B.

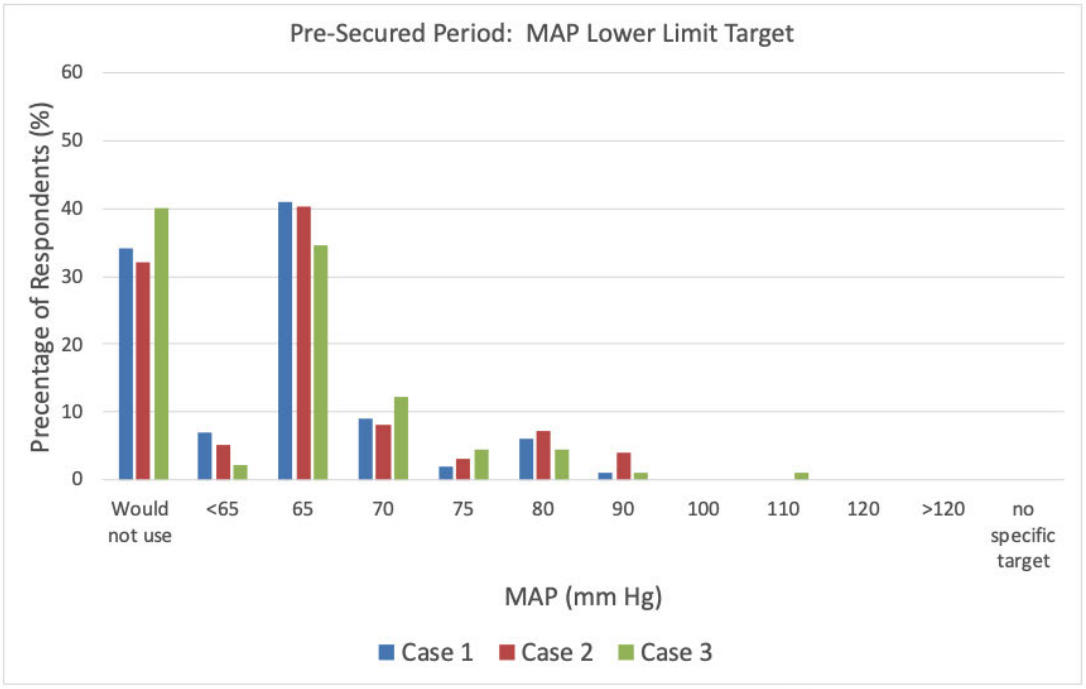


Figure 1A: Pre-secured period: SBP upper limit target
Figure 1B: Pre-secured period: MAP lower limit target
SBP: Systolic blood pressure; MAP: Mean arterial pressure

Figure 2: Post-secured period blood pressure targets (percentage of respondents).

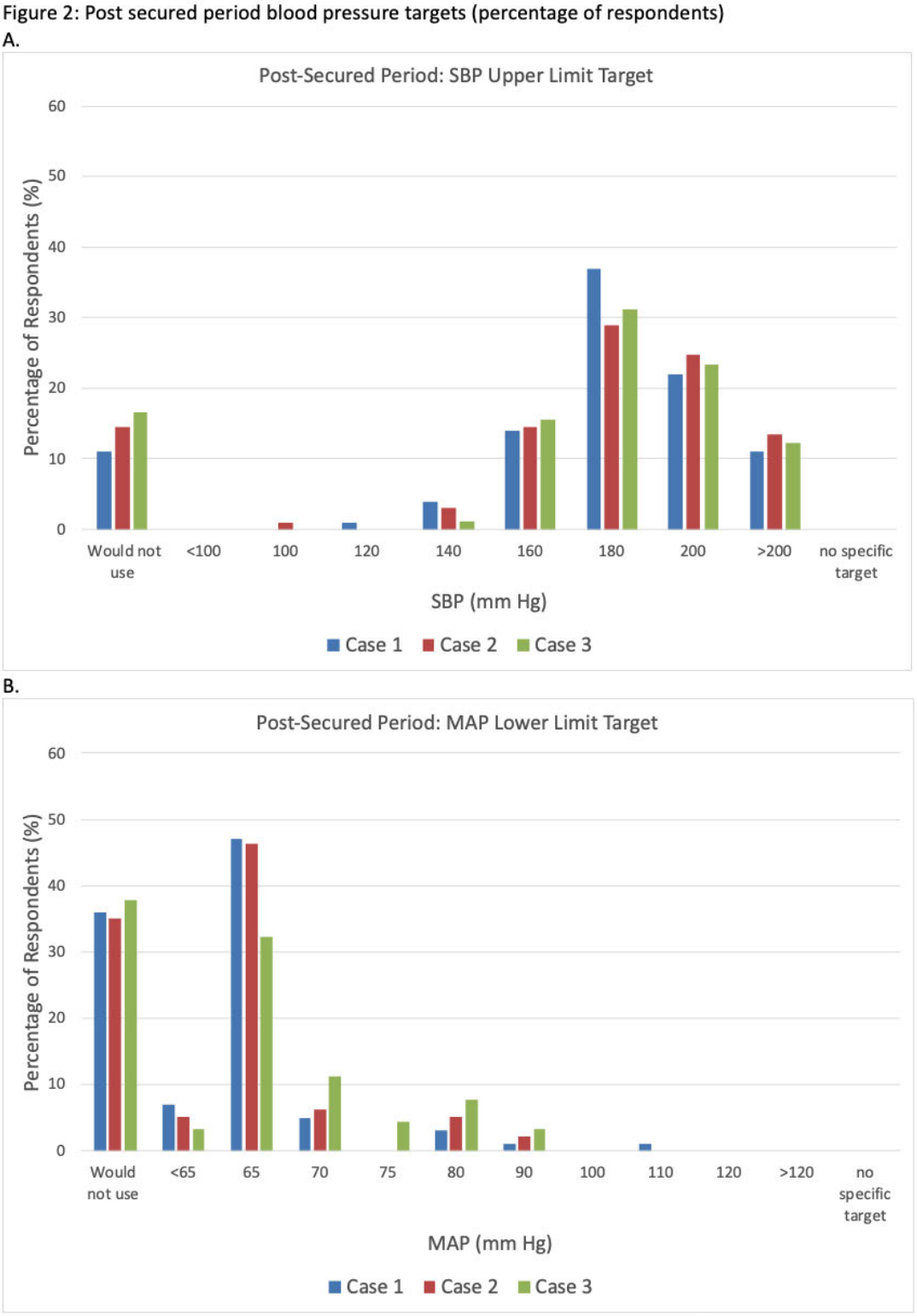
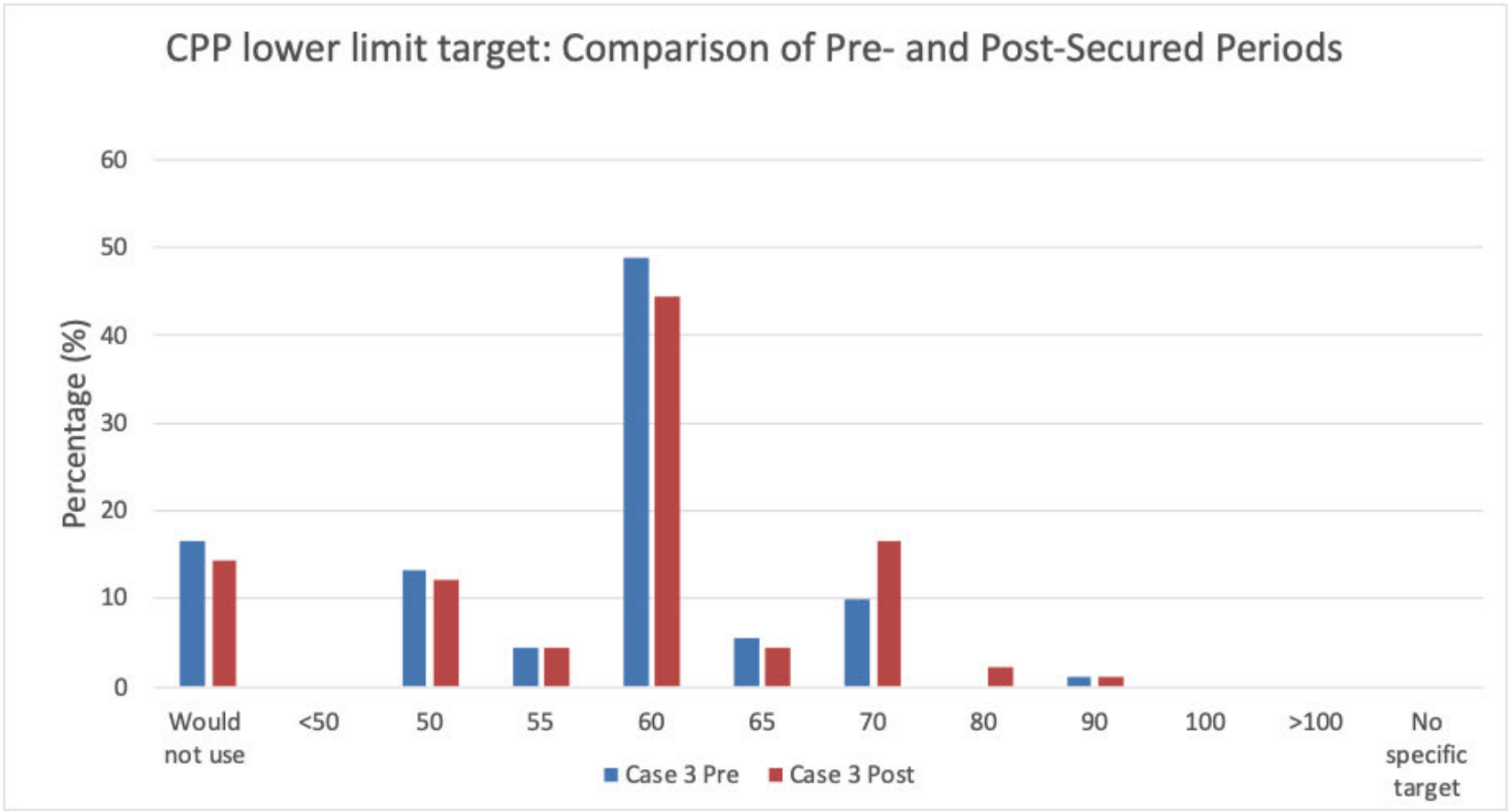


Figure 2A: Post-secured period: SBP upper limit target
Figure 2B: Post-secured period: MAP lower limit target
SBP: Systolic blood pressure; MAP: Mean arterial pressure

Figure 3: Cerebral perfusion pressure (CPP) targets pre vs post secured period (percentage of respondents)

Figure 3: Cerebral perfusion pressure (CPP) targets pre vs post secured period (percentage of respondents)



Values are in mmHg; CPP: Cerebral perfusion pressure

Figure 4: Predictors for higher/lower BP target selection and perceived barriers to BP target implementation

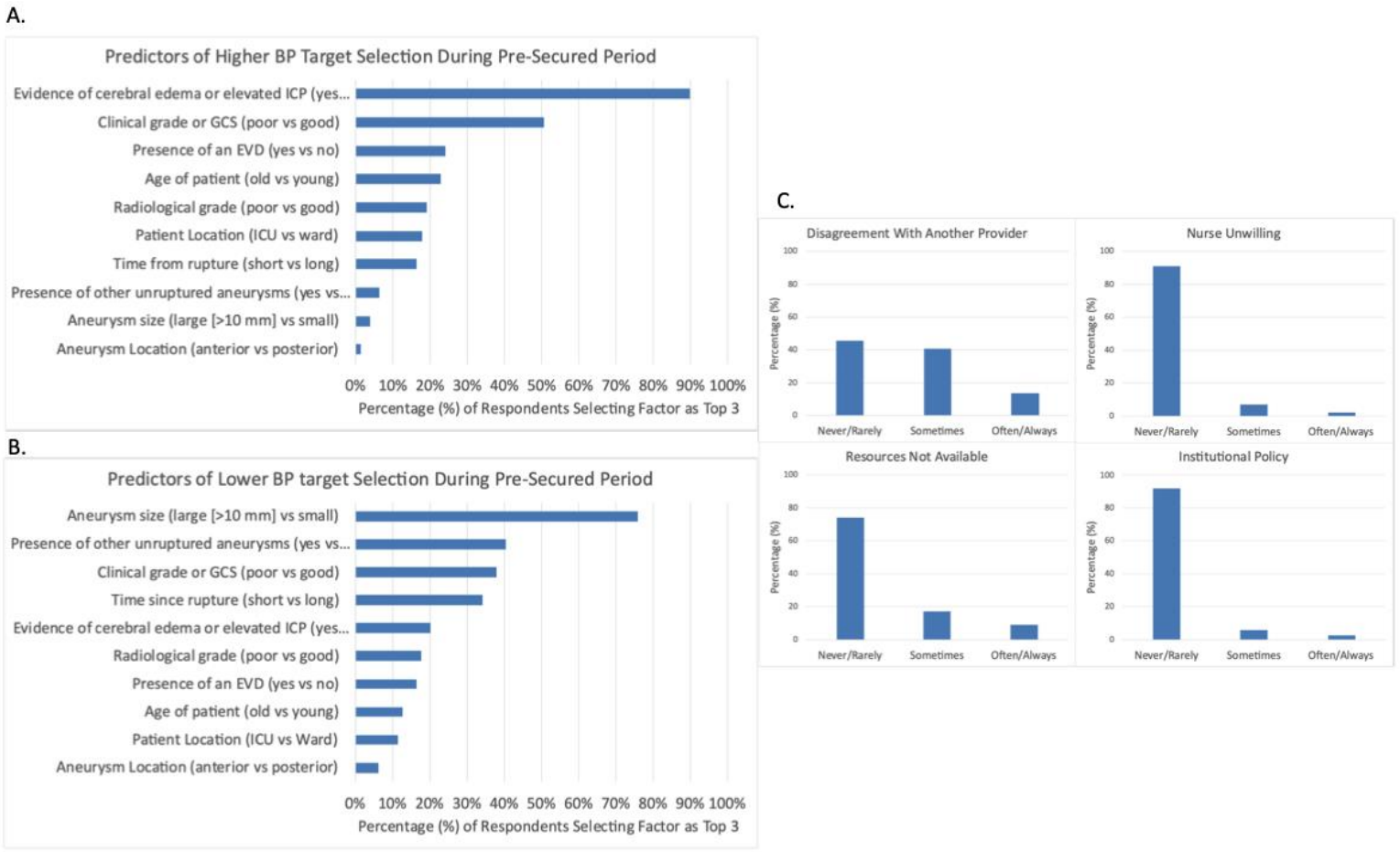


Figure 4A: Predictors of higher BP target selection during pre-secured period
Figure 4B: Predictors of lower BP target selection during pre-secured period
Figure 4C: Perceived barriers to BP target implementation
BP: Blood pressure; GCS: Glasgow coma score; ICP: Intracranial pressure

5 Chapter 5 – Retrospective Cohort Study

Title:
Blood Pressure Management During the Early Phase of Aneurysmal Subarachnoid Hemorrhage: A Retrospective Cohort from a Single Academic Centre.

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5.1 Abstract

Background/Objective:

In aneurysmal subarachnoid hemorrhage (aSAH), it is unclear if blood pressure (BP) lowering prior to securing the culprit aneurysm should be undertaken. To inform the design of a future clinical trial we aimed to describe the actual practices of BP control, including the specific targets prescribed, the techniques used for BP control, and the success in achieving the targets.

Methods:

We conducted a retrospective cohort study of patients admitted to a single academic, tertiary care centre from October 1st, 2019 to September 30th, 2020. Patients were identified from the screening logs of a clinical trial in aSAH. We included patients with a first episode of aSAH, who presented to hospital within 24 hours of aneurysm rupture. Patients who did not have aneurysm treatment attempted because they were not expected to survive were excluded. Data were collected by a single trained abstractor using a pilot-tested data collection form and included the following: baseline demographic data, BP readings from admission until the aneurysm was secured, BP target data (both upper and lower targets), and medications used to control BP. Time beyond target and number of episodes defined success in managing BP. Descriptive statistics summarized the data.

Results:

Forty-three patients were assessed for eligibility and 29 of these were included in the final cohort. The median age was 63 years (IQR 58-71) and 25 patients (86%) were female. The median World Federation of Neurological Societies score was II (IQR I-IV) and the median

modified Fisher score was 4 (IQR 3-4). The median time from hospital presentation to aneurysm repair was 12 hours (IQR 7-20 hours). Fourteen patients (48%) were admitted to an intensive care unit. All patients (n = 29) had an upper limit BP target prescribed. Eighteen patients (62%) deviated above this target but only 11 patients (38%) received antihypertensive treatment. The remaining 7 patients (24%) returned to below target without intervention. The most commonly prescribed medications were labetalol (25 patients [86%]) and hydralazine (20 patients [69%]). Seven patients (24%) had a lower limit BP target prescribed. Deviations below this target (or a mean arterial pressure below 65 mmHg) occurred in 9 patients (31%). Patients with invasive arterial BP monitoring or those admitted to the ICU spent less time (both total and percentage) beyond their target (upper or lower) and had shorter deviation episode durations. The majority of both high (52/53 [98%]) and low (21/25 [84%]) BP readings occurred during the first 12 hours of hospitalization.

Conclusions:

Blood pressure deviations, both high and low, occur frequently and early during the pre-secured period in aSAH. Lower limit BP targets are infrequently prescribed but low BP episodes occurred in nearly one third of patients (9 [31%]), potentially risking cerebral ischemia. Admission location and intensity of monitoring/treatment may reduce the duration of BP deviations and increase the success of meeting BP targets. These findings will inform the design of a clinical trial of BP management in aSAH.

5.2 Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a type of stroke that affects relatively young population (mean age of 60 years), leading to significant life years lost and a high burden of disability in survivors.[1–5] The costs to society are significant as aSAH is associated with the highest hospital costs of all types of stroke.[6] Rebleeding of the aneurysm is a catastrophic event that is associated with significant morbidity and mortality.[7] Securing the aneurysm by endovascular coiling or surgical clipping is the definitive treatment. During the pre-secured period, elevated blood pressure (BP) may increase the risk of re-rupture and bleeding due to increased transmural pressure across the rupture site.[8] Lowering BP during this period is also not without risk. Early brain injury is highly prevalent during the early phase of aSAH.[9] In this setting, reduced BP could impair cerebral blood flow leading to increased cerebral ischemia and ultimately worse clinical outcomes.[10–12]

Historic management guidelines recommended BP reduction to specific targets, with a focus on reducing the risk of rebleeding.[13,14] However, these recommendations were based on expert consensus opinion and observational studies, which are at increased risk of bias.[15,16] Consequently, newly released guidelines from the same organizations no longer recommend specific BP targets during the pre-secured period.[17,18]

A 2017 electronic, self-directed survey of 128 critical care physicians in the USA identified that the reported practice patterns of BP management during the early phase of aSAH were highly variable.[19] Systolic blood pressure (SBP) targets ranged from 140 mmHg to 180 mmHg prior to securing the aneurysm with a small percentage (approximately 5%) not setting a maximum SBP

target. In light of these findings, we conducted a retrospective cohort study with the aims of describing the actual practices of setting BP targets in aSAH, the techniques used for control, and the degree of success in achieving the desired targets.

5.3 Methods

Study design and objectives:

We conducted a retrospective cohort study at a single tertiary care teaching hospital. The objective of this study was to describe the current practices of BP management prior to securing the aneurysm, including the specific BP targets prescribed, the characteristics of deviations beyond the targets, and the techniques used to manage BP. A secondary objective was to gather information to assist with the design of a clinical trial. Research Ethics board approval was obtained and informed consent was not required due to the nature of the study.

Patient selection:

Consecutive patients who presented to The Ottawa Hospital with aSAH during a one-year period from October 1st, 2019 to September 30th, 2020 were identified using the screening logs of a randomized controlled trial of aSAH (Aneurysmal Subarachnoid Hemorrhage - Red Blood Cell Transfusion and Outcome [SAHaRA]: A Randomized Controlled Trial; NCT03309579). The screening logs contain a complete list of prospectively identified admitted patients from March 11th, 2018 to July 10th, 2023 with primary subarachnoid hemorrhage. In our cohort, we included adults (≥ 18 years) with subarachnoid hemorrhage (confirmed on imaging or CSF analysis) of aneurysmal etiology (confirmed on vascular imaging), who presented to hospital within 24 hours of rupture. Rupture was defined as time of symptom onset identified by the patient or bystanders.

If the patient or bystanders were not able to identify symptom onset or the event was unwitnessed, the "last seen well" time was used as the time of rupture. Patients were excluded if they had non-aneurysmal subarachnoid hemorrhage (i.e. traumatic SAH, iatrogenic SAH, or SAH due to an arteriovenous malformation), if it was not a first episode of aSAH, and if no treatment of the culprit aneurysm was attempted because the patient was not expected to survive.

Patient management:

The Ottawa Hospital is an academic tertiary care centre with neurosurgical and neuro-interventional services. Patients were admitted to either a level 3 intensive care unit (ICU) or to a level 2 high-dependency unit (HDU), if more stable. Management of patients was in keeping with the current aSAH management guidelines in place at the time of hospitalization.[13,14] This included endovascular or surgical treatment of the ruptured aneurysm, rapid treatment of hydrocephalus, and management of elevated intracranial pressure.

Data Collection:

A case report form was created and pilot-tested by a single author on three patient medical records to ensure completeness, clarity, and ease of use. A single author (LT) collected data from the patient electronic medical record. Data collected included the following; Age on admission, sex, admission and discharge dates, aneurysm location (anterior vs posterior), aneurysm size (from imaging), GCS on presentation to hospital, presenting clinical grade (World Federation of Neurological Societies [WFNS]), presenting radiologic grade (modified Fisher [mFisher]), timing data (rupture, presentation to The Ottawa Hospital, repair), placement of an EVD prior to repair of the aneurysm, evidence of elevated ICP or cerebral edema prior to repair, the type of

repair performed (surgical clipping vs coiling), herniation at presentation, and the presence of an arterial line for BP monitoring during the unsecured period. If the WFNS or mFisher scores were not provided, they were calculated using the admission note and the first CT scan at presentation, respectively.

The prescribed BP targets were identified in the admission orders. The prescribing service (Critical Care vs Neurosurgery) and upper and lower BP targets were collected, including the parameter (systolic blood pressure [SBP], mean arterial pressure [MAP], and diastolic blood pressure [DBP]) and the specific value (e.g. 140 mmHg). If a required time duration (e.g. 15 min) beyond target prior to initiation of BP treatment was ordered, this was captured.

All recorded BP readings from presentation to hospital until the aneurysm was repaired were collected. For the purpose of this study, we defined the pre-secured period as the time from the first BP recorded on presentation to hospital until the last BP reading prior to leaving the ward/ICU to have the aneurysm secured (time of repair). The number and duration of discreet episodes of blood pressure outside of the prescribed target range were recorded. The start of an episode was defined as the first BP reading outside of the target range and the end of an episode was defined as the first reading back in the target range. Details of the technique used to control BP (specific medication, dose, route, and delivery) were collected. Lastly, to assess individual BP readings, all recorded BP values from hospital presentation until time of repair were extracted from each patient and a new dataset was created, with the date and time for each reading.

Outcomes

The key outcome measures comprising "compliance" with the prescribed BP target are the following: 1) Number of deviation episodes; 2) The median episode duration in minutes; 3) The total time beyond target (equal to the sum of the duration of deviations beyond target); 4) The percentage of total time beyond target (equal to the total time beyond target divided by total time of the unsecured period). An important assumption is that all deviation readings being produced would be recorded and that the first blood pressure reading back in the normal range would also be recorded.

Subgroups

Additional comparisons were performed for the following subgroups: 1) Upper and lower BP limits based on guidance from the literature; 2) Patients with BP deviations receiving BP treatment vs not receiving BP treatment; 3) Admission location (ICU vs HDU); 4) Low BP episodes without a prescribed lower limit target compared to those with a target; 5) Type (intensity) of BP monitoring. For the patients without prescribed lower-limit targets, a MAP of 65 mmHg was used as a threshold to identify these patients, as this is commonly used in critical care environments.[20]

Statistical analysis:

Analysis was performed using SAS studio (release 3.8 Enterprise Edition, SAS institute Inc., Cary, NC, USA). Descriptive statistics summarized the study data. Continuous variables are presented as medians and interquartile ranges. Categorical variables are presented as frequencies and percentages. Missing data was managed by deletion.

The extracted individual BP readings were displayed graphically in scatterplots with upper and lower BP target limit lines overlayed. The upper limit target was selected based on the guideline recommendations in place at the time of hospitalization (SBP 160 mmHg).[13,14] A MAP of 65 mmHg was selected as the standard lower limit based on existing critical care guidelines.[20] A second lower limit MAP (80 mmHg) was also overlayed in the scatterplot, in accordance with the evidence suggesting a higher MAP may improve outcomes in aSAH.[11,21]

5.4 Results

Forty-three consecutive patients were screened for enrollment **(Appendix 1)**. Data was available within the hospital medical records for 42 patients. Thirteen were excluded leaving 29 patients in the final cohort. The most common reason for exclusion was time of presentation to hospital greater than 24 hours from rupture (7 patients). Three patients had no SAH on imaging, two were deemed not salvageable/not offered treatment and one patient had no aneurysm identified.

The median age of the cohort was 63 years (Interquartile Range (IQR) 58-71 years) (**Table 1**). Twenty-five patients (86%) were female. On presentation, the median Glasgow Coma (GCS) was 14 (IQR 9-15) the median clinical grade (WFNS) was II (IQR I-IV) and the median radiologic grade (modified Fisher score [mFisher]) was 4 (IQR 3-4). The median aneurysm size was 5mm (IQR 4-7mm) and in 4 patients (14%), the culprit aneurysm was located in the posterior circulation. Twelve patients (41%) had an EVD placed during the unsecured period. Fourteen patients (48%) were admitted to ICU with the remaining 15 (52%) admitted to an HDU. Invasive arterial BP monitoring during the pre-secured period occurred in 10 patients (34%). The median SBP on presentation was 154 mmHg (IQR 129-169). The median time from

rupture to presentation to the tertiary care centre was 3 hours (IQR 1-6). The median time from hospital presentation to repair was 12 hours (IQR 7-20) and the median time from rupture to repair was 19 hours (IQR 9-24).

Blood pressure targets:

Upper limit targets

BP targets during the pre-secured period were prescribed by the neurosurgical team in 27 patients (93%) (**Table 2**). An upper limit target was prescribed in all 29 patients (100%). The most frequently prescribed upper limit target was an SBP of 160 mmHg (26 patients [90%]). An upper limit MAP target was not prescribed for any patient. None of the patients had a time trigger for treatment ordered.

Eighteen patients (62%) had at least one deviation above the prescribed BP target (**Table 3**). The median number of episodes per patient was 1 (IQR 1-2). The median total time above the target was 71 minutes (IQR 35-216) and the median percentage of total time above the target was 12% (IQR 2-28). The median episode duration was 46 minutes (IQR 21-135) with a median maximum SBP of 178 mmHg (167-185) over the pre-secured period.

Lower limit targets

For deviations below the prescribed target, a lower limit target was not prescribed for 22 (%) participants leaving 7 patients included in the analysis (**Table 3).** Five patients (71%) had at least one episode below the prescribed lower-limit target. The median number of episodes per patient was 4 (IQR 2-6). The median total time below the target was 87 minutes (IQR 60-148) and the

median percentage of total time spent below the target was 8% (IQR 4-21). The median episode duration was 30 minutes (IQR 25-44). The median minimum SBP was 111 mmHg (IQR 86-136) and the median minimum MAP was 53 mmHg (IQR 36-70). None of the patients had a time trigger for treatment ordered.

Interventions to manage blood pressure:

Interventions to keep BP below upper-limit target

Of the 29 patients who had an upper BP target prescribed, 18 (62%) had a BP deviation above the prescribed target and 11 (38%) required intervention to lower BP (**Table 4A**). In seven patients (24%), the BP returned below the target without antihypertensive administration. Patients that did not have a recorded BP elevation did not receive antihypertensive medication.

Twenty-five patients (86%) had an antihypertensive medication ordered: Labetalol (25 patients [86%]) and hydralazine (20 patients [69%]) were the two medications most frequently ordered (**Table 4B**). Nineteen patients (66%) had both labetalol and hydralazine ordered and 2 patients (7%) received both medications. Eleven patients (38%) received treatment with an antihypertensive medication. Labetalol was administered to 10 patients (34%) and hydralazine was administered to 3 patients (10%). The median number of bolus doses of medication administered per patient was 1 (IQR 1-3). Of the patients receiving treatment, two (18%) received antihypertensive infusions.

Interventions to keep BP above lower-limit target

Of the 7 patients who had a lower BP target prescribed, 5 (71%) had a BP deviation below the prescribed target and 4 (57%) required intervention to raise BP (**Table 4A**). In 1 patient (14%) the BP returned above the target without vasopressor administration. Four patients (57%) had a vasopressor ordered: Phenylephrine (2 patients [29%]) and norepinephrine (3 patients [43%]) were the only two vasopressors ordered. Four patients received treatment with a vasopressor: Two patients (29%) received phenylephrine and 4 patients (57%) received norepinephrine (57%). One patient received norepinephrine in the absence of an order. Two patients without prescribed lower limit BP targets had vasopressors ordered and 1 of these patients received vasopressor treatment (**Appendix 2**)

Subgroup comparison: Upper and lower BP limits based on guidance from the literature: From the entire cohort of 29 patients, there was a total of 648 extracted BP observations during the unsecured period **(Table 5)**. For SBP, two observations had missing data leaving 646 included in the analysis. For MAP, 132 observations were missing data leaving 516 included in the final analysis.

SBP > 160 mmHg

Over the entire period, 53/646 readings (8%) exceeded the SBP upper limit threshold of 160 mmHg **(Figure 1A)**. Forty-seven out of fifty-three (89%) occurred during the first 6 hours and 52/53 (98%) occurred during the first 12 hours.

MAP < 65 mmHg

Over the entire period, 25/516 readings (5%) exceeded the MAP lower limit threshold of 65 mmHg **(Figure 1B)**. Thirteen out of twenty-five (52%) occurred during the first 6 hours and 21/25 (84%) occurred during the first 12 hours.

MAP < 80 mmHg

Over the entire period, 131/516 readings (25%) exceeded the MAP lower limit threshold of 80 mmHg **(Figure 1B)**. Sixty-three out of one-hundred and thirty-one (48%) occurred during the first 6 hours and 96/131 (73%) occurred during the first 12 hours.

Subgroup comparison: Patients with BP deviations receiving treatment vs not:

Deviations above the prescribed target (n=18)

Eleven patients (61%) received antihypertensive treatment to bring their BP back below the target **(Table 6)**. Patients receiving treatment had a greater median number of BP episodes above target (2 [IQR 1-3] vs 1 [IQR 1-2]), a longer median time spent above the target (166 minutes [IQR 37-285] vs 39 minutes [IQR14-63]), a greater median percentage of their total pre-secured time above the target (27% [IQR 11-42] vs 3% [2-8]) and a greater median episode duration (72 minutes [37-159] vs 28 minutes [14-39]). The median maximum SBP was similar between the two groups (178 mmHg [167-185] vs 177 mmHg [160-196]).

Deviations below the prescribed target (n=5)

Four patients (80%) received vasopressor treatment to bring their BP back above the target. Compared with a single patient who did not receive treatment, patients receiving vasopressor therapy had a greater median number of episodes below the target (5 [IQR 3-6] vs 2), longer

median time spent below the target (118 minutes [IQR 58-209] vs 60 minutes), a greater median percentage of their total pre-secured time below the target (13% [IQR 4-31] vs 8%), but similar median episode durations (34 minutes [IQR 16-44] vs 30 minutes).

Subgroup comparison: Admission location (ICU vs HDU):

Deviations above the prescribed target

Compared with patients admitted to the ICU, patients admitted to the HDU had a greater median number of episodes above the target (2 [IQR 1-3] vs 1 [IQR 1-2]), a longer median time spent above the target (159 minutes [IQR 63-285] vs 37 minutes [IQR 14-79]), a greater median percentage of total time spent above the target (14% [IQR 3-27] vs 8% [IQR 2-39]), and a longer median episode duration (55 minutes [IQR 39-159] vs 35 minutes [IQR 14-72]) **(Table 7)**. The median maximum SBP was similar between the two groups. Similar numbers of patients received treatment in each location (ICU = 5/9 [56%] vs HDU = 6/9 [67%]) but patients in the ICU received more doses of antihypertensive medication (3 [IQR 1-3] vs 1 [1-3]).

Deviations below the prescribed target

All patients with deviations below the prescribed target were admitted to the ICU preventing comparison.

Subgroup comparison: Low BP episodes without a prescribed target:

Nine patients had deviations either below a prescribed target (n=5) or a MAP of 65 mmHg (n=4) **(Table 8)**. Compared to patients with a prescribed target, those without a target who deviated below a MAP of 65 mmHg were more frequently admitted to the HDU (3/4 [75%] vs 0/5 [0%]),

had fewer recorded median episodes of low blood pressure (1 [IQR 1-1] vs 4 [IQR 2-6]), had a higher median minimum MAP (59 mmHg [IQR 55-63] vs 53 [IQR 36-70]), and did not receive vasopressor therapy (0/4 [0%] vs 4/5 [80%]. The other episode characteristics were similar except for the median episode duration which was longer in the patients with no prescribed target (93 minutes [IQR 63-143] vs 30 minutes [IQR 25-44]).

Subgroup comparison: Type (intensity) of blood pressure monitoring:

Deviations above the prescribed target

Patients with invasive arterial BP (ABP) monitoring were more frequently admitted to the ICU compared to those with non-invasive BP (NIBP) monitoring (ABP: 9/10 [90%] vs NIBP: 5/19 [26%]) **(Table 9)**. Evaluating BP deviations above the set target, a greater proportion of patients with ABP monitoring had at least one deviation (7/10 [70%] vs 11/19 [58%]). However, patients monitored invasively by ABP had a lower median number of episodes (1 [IQR 1-3] vs 2 [IQR1-3]), a shorter median total time above the target (37 minutes [IQR14-216] vs 135 minutes [IQR 39-275), a lower median percentage of total time above the target (8% [IQR 2-27] vs 14% [IQR 2-39]), and a shorter median episode duration (35 minutes [IQR 14-53] vs 79 minutes [IQR21-159]). The median maximum SBP was similar between the groups (177 mmHg [IQR 169-195] vs 181 mmHg [IQR 163-185]).

Deviations below the prescribed target

A greater proportion of patients with ABP monitoring, as compared to NIBP monitoring, had deviations below the prescribed lower limit target or a MAP < 65 mmHg (ABP: 5/10 [50%] vs NIBP: 4/19 [21%]). Patients with ABP monitoring had a greater median number of episodes

below the target (4 [IQR 2-6] vs 1 [IQR 1-2]) but a similar median total time below the target (87 minutes [IQR 60-148] vs 93 minutes [IQR 63-143]). Patients with ABP monitoring had a lower median percentage of total time below the target (4% [IQR 4-21] vs 7% [IQR 4-13] and a shorter median episode duration (44 minutes [IQR 25-45] vs 93 minutes [IQR 48-143]). The median minimum MAP was similar between the groups (59 mmHg [IQR 45-67] vs 56 mmHg [IQR 54-61]).

5.5 Discussion

In this single centre retrospective cohort of patients with aSAH, prescribed upper BP limits were much more common than lower BP limits in the period prior to securing the aneurysm. All 29 patients had an upper limit BP target prescribed during the pre-secured period, with the most frequent target being an SBP of 160 mmHg. Deviations above the prescribed upper limit BP target were common (62% of patients), occurred early (98% within 12 hours of presentation), and required specific antihypertensive treatment (61%). While very few patients had a lower BP target prescribed (< 25%), nearly one third (31%) of patients experienced relative hypotension. Patients with increased intensity of monitoring and treatment, represented by invasive arterial BP monitoring and ICU admission, showed increased compliance with their BP targets: They had a shorter median episode duration, a shorter total time above or below target, and spent a smaller percentage of time above or below target.

The observed management practice for acutely elevated BP is aligned with the management guidelines from the American Heart Association/American Stroke Association and the Neurocritical Care Society in place at the time the patients were treated.[13,14] Patients with BP

episodes above the prescribed target, but not receiving treatment, had fewer and shorter episodes. While it is possible that these resolved spontaneously with observation, it is unclear how a decision to treat would be initiated at the bedside: The patient populations had similar max SBP (178 mmHg [167-185] vs 177 mmHg [160-196]) and none of the patients had an ordered time duration above target to initiate therapy. Alternatively, non-recorded interventions (e.g. administration of analgesia or sedation) may have contributed to the BP returning below target, but we are not able to determine this from our data.

The admitting location (ICU vs HDU) appeared to be an important factor affecting upper limit BP deviations. Compared with patients in the ICU, those admitted to the HDU who had BP deviations above the upper limit target had twice as many episodes, a longer episode duration, and a greater total time and percentage of time spent above the upper limit target. Less intense monitoring (only 1 patient admitted to the HDU had invasive arterial BP monitoring) likely played an important role, as reduced frequency of blood pressure readings may have delayed treatment and created longer episodes. It is also possible that reluctance to administer antihypertensive therapy in the HDU setting was another contributing factor: Patients in the HDU received a lower median number of antihypertensive doses (1 [IQR 1-3]) compared with patients admitted to the ICU (3 [IQR 1-3]). There is the possibility that the severity of aSAH is a potential confounder of these findings: Patients with more severe brain injury may have had more frequent and severe BP deviations but would also have been more likely admitted to ICU. Our data is insufficient to describe this relationship in detail. This discrepancy between admitting locations has important implications for a clinical trial: Study arms will need to be balanced with

respect to admitting location and efforts will need to be made to ensure timely recognition and treatment of BP deviations in the non-ICU setting.

Invasive arterial blood pressure monitoring also appeared to impact the characteristics of BP deviations. Compared to patients who had NIBP monitoring, those with ABP monitoring spent less time (both total and percentage of total) above or below their target and had shorter episode durations. Interestingly, patients with ABP monitoring had a greater number of low episodes. While this is possibly a function of increased monitoring and identification, it is unclear if these differences are from the ABP monitoring itself or if they arise from a difference in admission location and severity of clinical condition: Ninety percent of patients with ABP monitoring were admitted to ICU.

In our cohort, very few patients (7/29 [24%]) had lower BP targets explicitly prescribed: This potentially exposes over three quarters of the cohort to episodes of low BP. Early brain injury, which can significantly impair cerebrovascular autoregulation, is highly prevalent in aSAH.[9] Reduced BP in the setting of altered cerebrovascular autoregulation could lead to decreased cerebral blood flow, ultimately leading to ischemia and further injury.[22] It is possible that the common practice of intervening on a MAP below 65 mmHg, which is frequently used in critical care environments, may have in fact influenced management of this cohort.[20] As a result, an "assumed" minimum target could have been present for all patients. To explore this further, we compared patients who deviated either below a MAP of 65 mmHg or their prescribed target. We observed that patients with a prescribed target had more identified low episodes and a shorter median episode duration **(Table 8)**. This potentially highlights the importance of a formally

prescribed lower limit BP target for both identification and management of low BP episodes. Alternatively, these findings may reflect intensity of monitoring and treatment, as all patients with a prescribed lower BP target were admitted to the ICU (5/5 [100%]).

Our study has a number of strengths. We used the screening logs from the SAHaRA clinical trial to identify all presentations of aSAH our institution, ensuring our cohort screened all consecutive presentations over a one-year time period. We collected all BP readings entered into the patient electronic medical record during the entire pre-secured period, ensuring complete capture of the available data. Our study also has a number of limitations. The cohort was derived from a single academic centre and contained only 29 patients, and therefore may not be representative of other centres. There were additional features that may impact the generalizability of this cohort to other populations: Eighty-six percent of the patients were female and sixty-six percent had a modified fisher score of 4, although these characteristics are similar to a previously conducted multicentre cohort of patients with aSAH in Canada.[23] Only the data entered into the patient's electronic medical record by the bedside provider was available for analysis. BP readings were usually recorded hourly which created a number of potential concerns. First, if blood pressure was only checked hourly, it is possible that BP deviations could have occurred without being identified, recorded, or treated. Second, when treating a blood pressure deviation, the return to the normal range may have been observed but not recorded into the medical record until the next hour. This may have created artificially long BP deviation episodes. We recognize this is an important limitation of our data and future studies will require more frequent and consistent data recording. We defined the pre-secured period as the first BP reading at presentation until the patient left their admitting location for aneurysm treatment. This left a period (potentially several

hours) unaccounted for, which included induction of anesthesia and initial aspects of the procedure/surgery until actual aneurysm occlusion. However, we viewed intraoperative BP management as a separate question, and we intentionally chose not to address this in the present study. While we evaluated blood pressure targets and the success in achieving them, we did not attempt to determine if BP deviations themselves are actually associated with adverse clinical outcomes (rebleeding, ischemia, infarction, mortality, etc). Finally, other treatments that could have influenced (or been used to "treat") BP, such as analgesia, sedation, or fluid blouses, were not collected as part of the study and should be considered in future studies.

5.6 Conclusions

In this small, single-centre cohort of patients with aSAH, we describe the actual management practices for high and low BP during the pre-secured period. Management of elevated BP is in keeping with guidelines in place at the time of patient presentation. BP deviations above the prescribed target happen early in the hospital admission. Over half of patients had episodes of elevated BP but many of these resolved without treatment. The majority of patients, over three-quarters, did not have lower-limit BP targets ordered. Nearly one third of patients had episodes of low BP potentially risking cerebral ischemia. Admission location, and intensity of monitoring and treatment, may influence the identification and management of BP deviations (both high and low), and are important considerations for additional studies. These findings will help inform the design and conduct of a future clinical trial.

5.7 References

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5.8 Tables and figures

Table 1: Baseline characteristics of included patients (n=29)

	Variable		Median (IQR)	Frequency (%)
Patient Characteristics	Age (years)		63 (58-71)	
	Female sex			25 (86)
	GCS on presentation		14 (9-15)	
	Clinical grade on presentation (WFNS)		II (I-IV)	
		I		13 (45)
		II		4 (14)
		III		1 (3)
		IV		4 (14)
		V		7 (24)
	Radiographic grade on presentation (mFisher)		4 (3-4)	
		1		3 (10)
		2		4 (14)
		3		3 (10)
		4		19 (66)
	Aneurysm size (mm)		5 (4-7)	
	Aneurysm location = posterior circulation			4 (14)
	Endovascular repair			20 (69)
	EVD placed during unsecured period			12 (41)
	Admitting location	ICU		14 (48)
		HDU		15 (52)
Blood Pressure	Arterial BP monitoring during unsecured period			10 (34)
	Blood pressure on presentation (mmHg)			
		SBP	154 (129-169)	
		DBP	87 (77-94)	
		MAP†	92 (75-121)	
Timing	Timing (hours):			
	Rupture to presentation*ˆ		3 (1-6)	
	Presentation to repair		12 (7-20)	
	Rupture to repair*		19 (9-24)	

Continuous variables presented as median and interquartile range (IQR); Categorical variables presented as frequency (counts) and percentage (%).
†n=10 (data missing from 19 participants)
*n=24 (data missing from 5 participants)
ˆPresentation to tertiary care centre
WFNS: world federation of neurological societies; mFisher: modified fisher scale; EVD: external ventricular drain; HDU: high dependency unit; ICU: intensive care unit; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure.

Table 2: Physician Prescribed Blood Pressure Targets

Variable		BP (mmHg)	Frequency (%)
Blood Pressure Targets:	Upper limit prescribed		29 (100)
	SBP upper limit	160	26 (90)
		150	2 (7)
		140	1 (3)
	MAP upper limit	any	0 (0)
	Lower limit prescribed		7 (24)
	SBP lower limit	140	1 (3)
		120	2 (7)
	MAP lower limit	80	1 (3)
		75	1 (3)
		65	2 (7)
Ordering service:	Neurosurgery		27 (93)
	ICU		0 (0)
	Unclear†		2 (7)
Ordered time trigger until BP treatment (minutes)		none	29 (100)
Deviations above target: number of patients			18 (62)
Deviations below target: number of patients*			5 (71)

Categorical variables presented as frequency (counts) and percentage (%);
† either neurosurgery or ICU
* n=7 (target not set for 22 participants: no lower limit BP target explicitly set)
BP: blood pressure; SBP: systolic blood pressure; MAP: mean arterial pressure; ICU: intensive care unit

Table 3. Blood pressure characteristics in patients with deviations beyond prescribed target

		Deviations above prescribed target		Deviations below prescribed target	
Variable		**Median (IQR)**	**Frequency (%)**	**Median (IQR)**	**Frequency (%)**
Number of patients with ≥ 1 deviation beyond prescribed target:*			18/29 (62%)		5/7 (71%)
Characteristics of patients with deviations:					
Number of episodes per patient		1 (1-2)		4 (2-6)	
Total time beyond target (minutes)		71 (35-216)		87 (60-148)	
Percentage of total time beyond target (%)		12 (2-28)		8 (4-21)	
Episode duration (minutes)		46 (21-135)		30 (25-44)	
Max or Min pressure (mmHg)	SBP	178 (167-185)		111 (86-136)	
	MAP			53 (36-70)	

Categorical variables presented as frequency (counts) and percentage (%); Continuous variables presented as median and interquartile range (IQR).
BP: blood pressure; SBP: systolic blood pressure; MAP: mean arterial pressure;
* Upper target prescribed in 29 patients (100%); Lower target prescribed in 7 patients (24%)

Table 4: Interventions to maintain blood pressure within target range.

Table 4A: Patients with blood pressure deviations and medication administration

Variable		Medication Administered*	Frequency (%)
BP above target:	≥ 1 episode (n=18)	Yes	11 (38)
		No	7 (24)
	No episodes (n=11)	Yes	0 (0)
		No	11 (38)
BP below target:†	≥ 1 episode (n=5)	Yes	4 (57)
		No	1 (14)
	No episodes (n=2)	Yes	0 (0)
		No	2 (29)

Table 4B: Medications ordered vs administered.

	Specific medication	Patients with Medication Ordered	Patients with Medication Administered
Upper limit target (n=29):	Any antihypertensive	25 (86)	11 (38)
	Labetalol	25 (86)	10 (34)
	Hydralazine	20 (69)	3 (10)
	Ace inhibitor	4 (14)	0 (0)
	Other beta blocker	1 (3)	0 (0)
	Labetalol and Hydralazine (both)	19 (66)	2 (7)
Bolus doses administered per patient^	Any antihypertensive		1 (1-3)¥
Patients receiving infusion^			2 (18)
Lower limit target (n=7):	Any vasopressor	4 (57)	4 (57)
	Phenylephrine	2 (29)	2 (29)
	Norepinephrine	3 (43)	4 (57)¶

Categorical variables presented as frequency (counts) and percentage (%); Continuous variables presented as median and interquartile range (IQR).
*antihypertensive for BP above target range or vasopressor for BP below target range
† n=7 (lower target not prescribed in 22 patients = not included in analysis)
^ n=11 (Antihypertensive medication not administered in 18 patients = not included in analysis)
¥ median (IQR)
¶ norepinephrine was administered in 1 patient where there was no recorded order.
BP: blood pressure; SBP: systolic blood pressure; MAP: mean arterial pressure; ICU: intensive care unit

Table 5. Extracted blood pressure readings for entire unsecured period (n=648) exceeding standardized upper and lower BP target limits

	Upper Limit	**Lower Limit**	
	SBP > 160 mmHg	**MAP < 65 mmHg**	**MAP < 80 mmHg**
BP readings outside of target for select time period, presented as a proportion of readings in the time period:			
0 - 6 hours	47/334 (14.1%)	13/255 (5.1%)	63/255 (24.7%)
0 - 12 hours	52/486 (10.7%)	21/382 (5.5%)	96/382 (25.1%)
Entire unsecured period*	53/646 (8.2%)	25/516 (4.8%)	131/516 (25.4%)
BP readings outside of target for select time period, presented as a proportion of all readings beyond of target:			
0 – 6 hours	47/53 (88.7%)	13/25 (52.0%)	63/131 (48.1%)
0 - 12 hours	52/53 (98.1%)	21/25 (84.0%)	96/131 (73.3%)

Categorical variables presented as frequency (counts) and percentages (%)
BP: blood pressure; MAP: mean arterial pressure; SBP: systolic blood pressure
* There was a total of 646 SBP readings and 516 MAP readings recorded in the patient records

Table 6. Subgroup comparison: Deviations beyond target receiving treatment vs not receiving treatment

		Treated		**Not Treated**	
		Median (IQR)	**Frequency (%)**	**Median (IQR)**	**Frequency (%)**
Deviations above prescribed targets (n=18):					
Number of patients with ≥ 1 deviation			11/18(61%)		7/18 (39%)
Number of episodes per patient		2(1-3)		1(1-2)	
Total time above target (minutes)		166 (37-285)		39 (14-63)	
Percentage of total time above target (%)		27 (11-42)		3 (2-8)	
Episode duration (minutes)		72 (37-159)		28 (14-39)	
Maximum SBP (mmHg)		178 (167-185)		177 (160-196)	
Deviations below prescribed targets (n=5):					
Number of patients with ≥ 1 deviation			4/5(80%)		1/5 (20%)
Number of episodes per patient		5 (3-6)		2*	
Total time below target (minutes)		118 (58-209)		60*	
Percentage of total time below target (%)		13 (4-31)		8*	
Episode duration (minutes)		34 (16-44)		30*	
Minimum pressure (mmHg)	SBP	86*		136*	
	MAP	53 (36-70)			

Categorical variables presented as frequency (counts) and percentage (%); Continuous variables presented as median and interquartile range (IQR).
MAP: mean arterial pressure; SBP: systolic blood pressure
* Single patient.

Table 7. Subgroup comparison: Blood pressure characteristics in patients with deviations beyond prescribed target: Admitting location (ICU vs HDU)

		Upper limit target prescribed (n=29)		Lower limit target prescribed (n=7)	
Variable		**HDU**	**ICU**	**HDU**	**ICU**
Patients with ≥ 1 deviation beyond prescribed target*		9/15 (60%)	9/14 (64%)	0/1 (0%)	5/6 (83%)
Characteristics of patients with deviations:					
Number of episodes per patient		2 (1-3)	1 (1-2)		4 (2-6)
Total time beyond target (minutes)		159 (63-285)	37 (14-79)		87 (60-148)
Percentage of total time beyond target (%)		14 (3-27)	8 (2-39)		8 (4-21)
Episode duration (minutes)		55 (39-159)	35 (14-72)		30 (25-44)
Max or Min pressure (mmHg)	SBP	181 (163-185)	177 (169-182)		111 (86-136)
	MAP				53 (36-70)
Medications received by patients with deviations:					
Received antihypertensive medication		6/9 (67%)	5/9 (56%)		2/5 (40%)
Number of antihypertensive doses received		1 (1-3)	3 (1-3)		4 (3-5)
Received vasopressor medication		0/9 (0%)	2/9 (22%)		4/5 (80%)

Categorical variables presented as frequency (counts) and percentage (%); Continuous variables presented as median and interquartile range (IQR).
BP: blood pressure; HDU: high dependency unit; ICU: intensive care unit; SBP: systolic blood pressure; MAP: mean arterial pressure;
* Upper target prescribed in 29 patients (100%); Lower target prescribed in 7 patients (24%)

Table 8. Subgroup comparison: Patients with low BP episodes (n=9) defined as either MAP < 65 mmHg or deviation below prescribed lower limit target

		Deviation below MAP of 65 mmHg (n=4)		Deviation below prescribed target (n=5)	
Variable		**Median (IQR)**	**Frequency (%)**	**Median (IQR)**	**Frequency (%)**
Admitting Location:	ICU		1/4 (25%)		5/5 (100%)
	HDU		3/4 (75%)		0/5 (0%)
Number of episodes per patient		1 (1-1)		4 (2-6)	
Total time below target (minutes)		93 (63-143)		87 (60-148)	
Percentage of total time below target (%)		4 (3-11)		8 (4-21)	
Episode duration (minutes)		93 (63-143)		30 (25-44)	
Minimum BP (mmHg):	MAP	59 (55-63)		53 (36-70)	
	SBP			111 (86-136)	
Patients receiving ≥ 1 vasopressor dose			0/4 (0%)		4/5 (80%)
Patients receiving ≥ 1 antihypertensive dose			0/4 (0%)		2/5 (40%)

Categorical variables presented as frequency (counts) and percentage (%); Continuous variables presented as median and interquartile range (IQR).
BP: blood pressure; ICU: intensive care unit; HDU: high dependency unit; SBP: systolic blood pressure; MAP: mean arterial pressure;

Table 9. Subgroup comparison: Arterial blood pressure monitoring vs non-invasive blood pressure monitoring

Variable		**ABP (n=10)**	**NIBP (n=19)**
Admitting location	ICU	9/10 (90%)	5/19 (26%)
	HDU	1/10 (10%)	14/19 (74%)
Characteristics of patients with ≥1 deviation above target:			
Number of patients		7/10 (70%)	11/19 (58%)
Number of episodes per patient		1 (1-3)	2 (1-3)
Total time beyond target (minutes)		37 (14-216)	135 (39-275)
Percentage of total time beyond target (%)		8 (2-27)	14 (2-39)
Episode duration (minutes)		35 (14-53)	79 (21-159)
Maximum pressure (mmHg)	SBP	177 (169-195)	181 (163-185)
	MAP		
*Characteristics of patients with ≥ deviation below target:**			
Number of patients		5/10 (50%)	4/19 (21%)
Number of episodes per patient		4 (2-6)	1 (1-2)
Total time beyond target (minutes)		87 (60-148)	93 (63-143)
Percentage of total time beyond target (%)		4 (4-21)	7 (4-13)
Episode duration (minutes)		44 (25-45)	93 (48-143)
Minimum pressure (mmHg)	SBP	86 ¶	136 ¶
	MAP	59 (45-67) †	56 (54-61) ¥

Categorical variables presented as frequency (counts) and percentage (%); Continuous variables presented as median and interquartile range (IQR).
ABP: arterial blood pressure (measured by intra-arterial catheter); BP: blood pressure; HDU: high dependency unit; ICU: intensive care unit; NIBP: non-invasive blood pressure; SBP: systolic blood pressure; MAP: mean arterial pressure;
* lower target either prescribed or set at MAP < 65 mmHg
¶ A single patient in in each group had a lower limit SBP target prescribed
† Four patients
¥ Three patients

Figure 1: Extracted blood pressure readings

Figure 1A. Systolic blood pressure during the unsecured period vs. time from presentation to hospital.

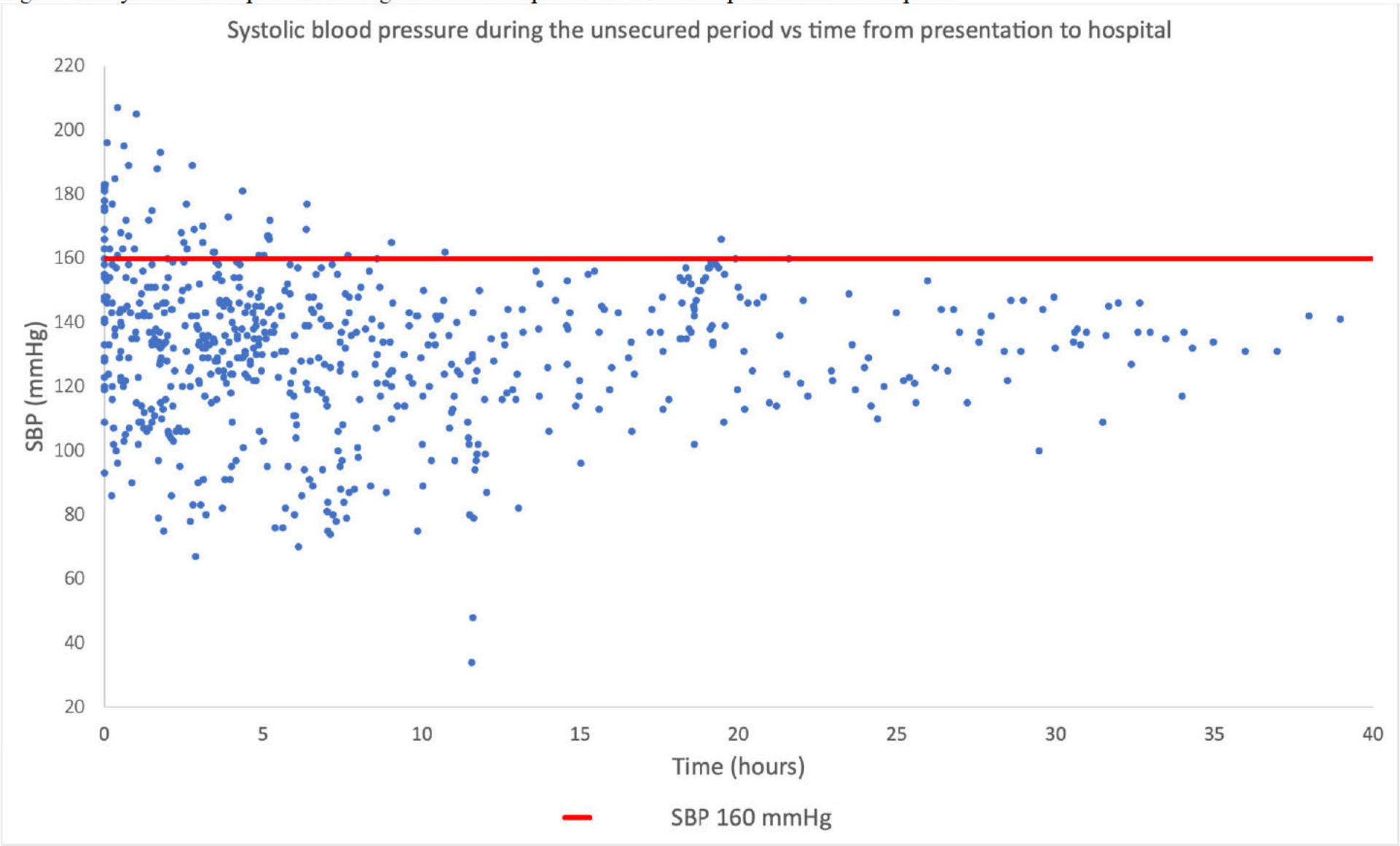
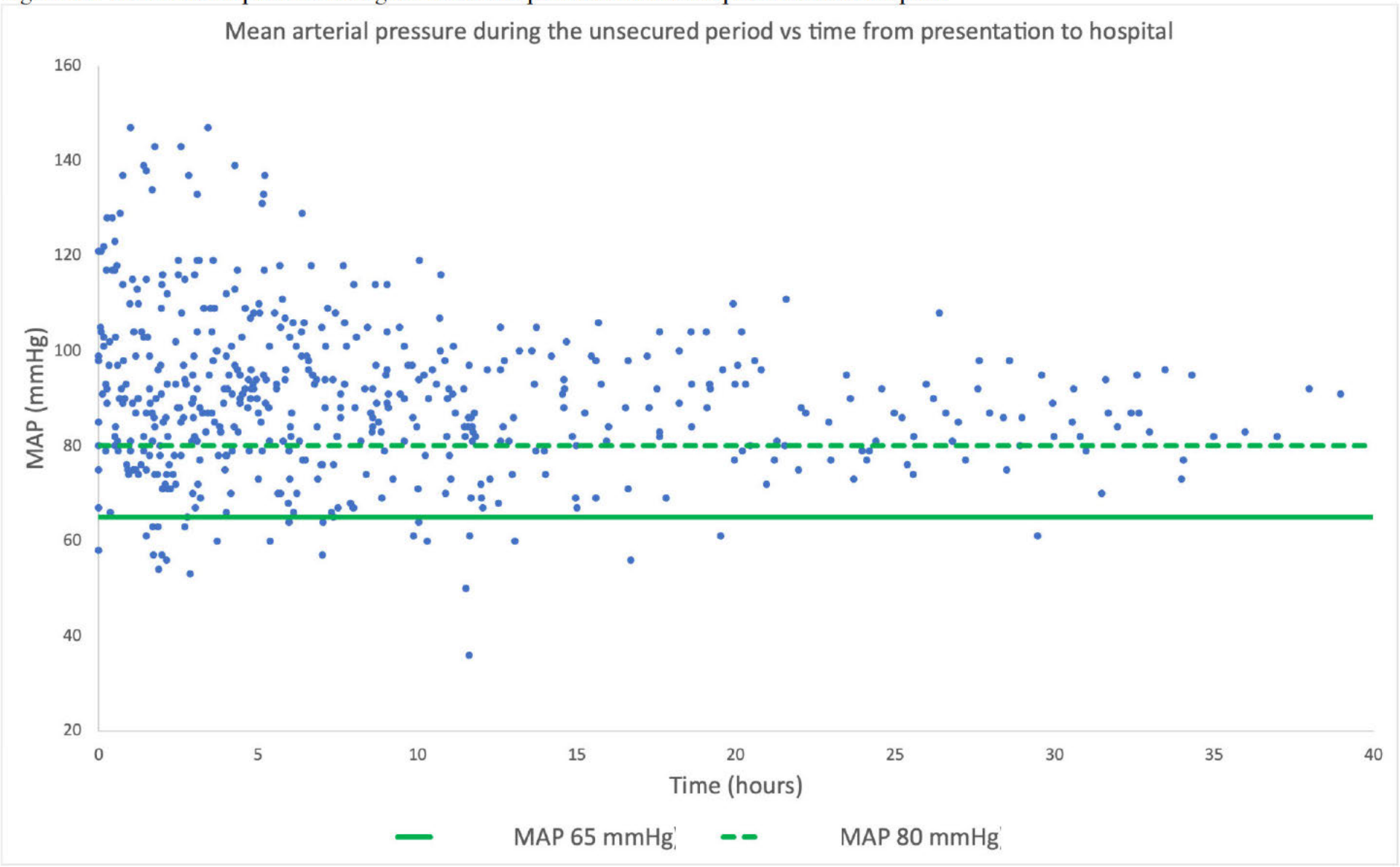


Figure 1B. Mean arterial pressure during the unsecured period vs. time from presentation to hospital.



6 Discussion

6.1 Summary

Rebleeding of the culprit aneurysm in aSAH is associated with increased mortality and poor outcomes. Elevated blood pressure prior to securing the aneurysm is a possible risk factor for rebleeding. For decades, management guidelines have recommended lowering blood pressure below specific thresholds to mitigate the risk of rebleeding in this period.[1-3] These recommendations have changed with newly released guidelines by the AHA/ASA and the NCS, which no longer recommend blood pressure lowering to specific targets and concurrently identify the potential for cerebral hypoperfusion and ischemia that can occur with blood pressure lowering in the setting of early brain injury.[4,5]

The objectives of this thesis were threefold: first, to understand the contribution of elevated blood pressure to aneurysm rebleeding during the pre-secured period as reported within the existing literature; second, to identify clinicians' beliefs and self-reported practices of blood pressure management during the early phase of aSAH; and third, to determine the actual blood pressure management practice during the pre-secured period in aSAH.

Chapter 3 presents a systematic review, the results of which failed to detect a consistent association between elevated blood pressure during the pre-secured period and our primary outcome of aneurysm rebleeding. In our meta-analysis of unadjusted results, the absence of a "dose response", exemplified by a systolic blood pressure greater than 160 mmHg showing an association with rebleeding, but a systolic blood pressure greater than 180 mmHg not showing an association, suggests physiologic impossibility in this blood pressure range. It is possible that an extremely elevated systolic blood pressure (greater than 200 mmHg) is associated with rebleeding, as the pooled effect estimate was quite large. However, this was an unadjusted result.

Importantly, very few studies reported results adjusted for confounders. A systolic blood pressure of 160 mmHg was the only threshold in our meta-analysis where comparison between unadjusted and adjusted results was possible: While the unadjusted results showed an association, the adjusted results did not, suggesting that confounding played a role. This is important, as all the included studies were observational in design and at moderate or high risk of bias due to missing data, differences in the nature and measurement of the exposure, and failure to adequately account for confounding. Furthermore, the majority of included studies only evaluated a single blood pressure value at hospital presentation, which was not reflective of the exposure to elevated blood pressure over pre-secured period. Overall, the certainty in the evidence was rated as very low. And finally, there was no clear relationship between elevated blood pressure during the early phase (first 72 hours) of aSAH and any of the secondary outcomes assessed.

Chapter 4 presents a cross-sectional survey that examined the beliefs and self-reported practices of blood pressure management during the early phase of aSAH amongst intensivists and neurovascular interventionalists/surgeons across Canada. Clinicians responding to the survey reported uniform upper-limit blood pressure targets during the pre-secured period. However, nearly half of respondents reported using a target that was more aggressive (lower) than recommended by the practice guidelines in place at the time of the survey. Reported post-secured period targets and lower-limit targets varied widely. Reported blood pressure target selection did not change in clinical scenarios with increasing severity (from good grade to poor grade presentations). Respondents reported the main perceived barrier to implementation of their desired blood pressure target was disagreement with another provider. The most frequently selected predictor for using a higher blood pressure target was evidence of cerebral edema or

elevated ICP, and the most frequently selected predictor for using a lower blood pressure target was a larger aneurysm size (> 10 mm).

Chapter 5 presents a single centre retrospective cohort study that described the actual practice of blood pressure management during the pre-secured period in aSAH. The majority of both high and low blood pressure readings occurred early, within the first 12 hours of admission. All patients had an upper limit blood pressure target prescribed during the pre-secured period with an SBP of 160 mmHg being the most common target. Deviations above the target blood pressure were common but many patients returned below the target without pharmacologic intervention (eg: antihypertensive treatment). Patients who required antihypertensive treatment had a greater number of episodes above target, a longer episode duration, and spent a greater amount of time (both total and percentage of total) above their prescribed targets. Labetalol and hydralazine with the two most common antihypertensives ordered and the only antihypertensives administered. While all patients had an upper limit blood pressure target prescribed, very few patients (less than 25%) had lower limit blood pressure targets prescribed, potentially risking hypoperfusion and ischemia. Admission location and invasive arterial BP monitoring influenced the success of achieving the prescribed targets: Patients admitted to a high dependency unit (compared to an Intensive care unit) had a greater number of blood pressure deviations above the prescribed target, a longer median episode duration, and a greater median total and percentage of time above target, while patients with invasive arterial blood pressure monitoring had more deviation episodes but spent less time (both total and percentage) above or below their target and had a shorter median episode duration.

6.2 Importance of findings

In contrast to prior systematic reviews,[6-8] we failed to detect a clear association between elevated blood pressure during the pre-secured period and rebleeding of the culprit aneurysm. The existing literature is observational in nature and at moderate to high risk of bias. Over half of the studies included in our systematic review measured only a single blood pressure value from admission, which is not representative of exposure to elevated blood pressure during the pre-secured period. As a result, the data may be insufficient to detect an association between elevated blood pressure and rebleeding. Despite this, clinicians' self-reported practices of blood pressure management during the pre-secured period are quite uniform. Nearly half of clinicians reported the selection of an upper-limit blood pressure target that was more aggressive (lower) than recommended by the management guidelines in existence at the time the survey was completed,[1-3] potentially risking ischemic injury. This contrasts with the post-secured period where there was more variability in the reported blood pressure targets selected. This variability likely arose due to an absence of studies to support decision-making in this period and is reflected in clinical practice guidelines, both historic[1-3] and current[4,5], that do not provide guidance for blood pressure management after the aneurysm is secured.

The clinical severity of the aSAH presentation did not appear to impact the self-reported blood pressure target selection in our survey. This was an unexpected finding, as patients with a poor clinical grade have higher incidence of cerebral edema and disturbed cerebrovascular autoregulation, which may necessitate increased blood pressure to maintain adequate perfusion and prevent cerebral ischemia.[9] Contrary to this self-reported practice, clinicians reported the two main predictors for selection of a higher blood pressure target were 1) evidence of cerebral edema/elevated intracranial pressure and 2) a poor clinical grade. However, their self-reported

blood pressure targets did not change meaningfully in the presence of these predictors within the presented cases. One potential explanation is that the cases in the survey were not different or severe enough to reach the clinician's threshold for changing a blood pressure target. Alternatively, it is possible that beliefs surrounding blood pressure targets are very firmly held and are not actually influenced by the reported predictors. And finally, it is possible that clinicians' actual practice is discordant with their self-reported practice.

In our survey, self-reported lower-limit blood pressure targets were highly variable and did not change appreciably in the pre- or post- aneurysm treatment periods or with increasing clinical severity. This suggests a uniform approach to a heterogeneous population. These results also highlight both an absence of consensus regarding the optimal lower-limit target and the paucity of evidence to guide clinician decision-making. In actual practice, lower-limit blood pressure targets were infrequently prescribed in our cohort. It may be that clinicians' default to using the generic lower limit target of a MAP of 65 mmHg, which is commonly used in critical care environments.[10] However, it potentially indicates that clinicians are not giving consideration to the risks associated with hypoperfusion and ischemia.[11–15]

This thesis forms the foundation for a program of research into blood pressure management in early aSAH. A major goal of this program is the development and conduct of a clinical trial evaluating blood pressure lowering during the pre-secured period in aSAH. Relevant challenges from previous trials of blood pressure lowering in intracerebral hemorrhage[16,17] combined with key findings from our cohort and survey, will inform the design of a future clinical trial. In our cohort, the majority of high blood pressure readings occurred during the first six hours after presentation to hospital prior to securing the aneurysm. Patient recruitment will need to occur rapidly after presentation to hospital, likely in the emergency department, and

blood pressure lowering will need to be initiated immediately after assignment to a treatment arm. To achieve this, the trial will likely need to use a deferred consent model. Spontaneous resolution of elevated blood pressure (without antihypertensive treatment) occurred in 7/18 (39%) of patients with elevated blood pressure in the cohort study. This phenomenon has the potential to affect the actual treatment received within an intervention arm. It will be important to account for this during recruitment, potentially with a brief period of observation (e.g. 15-20 min) and repeated blood pressure readings to confirm persistent blood pressure elevation prior to enrolment in the trial. Intensity of monitoring and treatment, represented by admission location (HDU vs ICU) and invasive arterial blood pressure measurement, appeared to influence both the frequency and duration of blood pressure deviation episodes in our cohort. Either randomization would need to be stratified by admission location or the trial could only enrol patients from the ICU. Similarly, our survey identified and ranked a number of potential predictors for blood pressure target selection (which are also known predictors of aneurysm rebleeding and other outcomes). To ensure balanced study arms, randomization will need to be stratified by these covariates. Disagreement between providers was reported as the major barrier to implementation of the desired blood pressure target in our survey. Establishing consensus and agreement to both enrol patients and comply with the assigned targets could be a significant challenge in a trial. This may be facilitated by the most recent guidelines (which no longer recommend lowering blood pressure to a specific target) as well as the publication of our systematic review which highlights absence of quality evidence. Wide variability in the reported lower blood pressure targets was identified in our survey, and our cohort showed that less than a quarter of patients had lower limit blood pressure targets prescribed. Despite this, thirty-one percent of patients had

low blood pressure episodes, potentially risking cerebral ischemia and infarction. These episodes will need to be minimized, possibly through protocolized care, in a clinical trial.

6.3 Strengths and limitations

In this thesis, I have built the foundation for a research program evaluating blood pressure management during the early phase of aSAH through three component studies: a literature review, a survey of clinicians' beliefs and practices, and an evaluation of blood pressure management in clinical practice.

The systematic review (Chapter 3) was methodologically rigorous, with clear definitions of exposure and outcomes, and used pre-specified blood pressure target thresholds. The survey (Chapter 4) identified all potential clinicians caring for aSAH in the acute setting (via the creation of a custom database). It used a case-based approach to mirror the actual practice of blood pressure target selection while also identifying predictors and barriers to selection of the desired target. The retrospective cohort (Chapter 5) used screening logs from a randomized clinical trial to ensure all aSAH patients were identified and collected comprehensive blood pressure data from medical records.

Each component has limitations. The systematic review (Chapter 3) is impacted by the limitations of the included studies, which had large differences in the measurement and definition of both the exposure and the outcomes. Very few studies reported results adjusted for confounders and all the included studies (with a single exception) were at moderate or high risk of bias. There were very few studies included at each blood pressure target threshold preventing assessment of publication bias and limiting our ability to perform sensitivity analyses to explore heterogeneity. The survey (Chapter 4) had a 36% response rate, which appears low but aligns

with response rates of neurosurgical surveys in the post-COVID era.[18] The cohort (Chapter 5) had a small sample size (n=29) and was not powered for hypothesis testing. It may not represent practices in other centers and had non-granular blood pressure data with widely spaced readings. Other interventions influencing blood pressure were not accounted for, which future studies should consider.

6.4 Future directions

Additional important questions have arisen over the course of this thesis. The lack of uniformity in reported upper-limit blood pressure targets during the post-secured period should be investigated further. Rationale for this variation could be explored in a dedicated survey of providers or potentially through other qualitative studies. Another question to address is the wide variability in reported lower-limit blood pressure targets and the absence of formal orders prescribing lower-limit targets in actual clinical practice. A large multicentre prospective cohort study could effectively answer this question, as well as many others, and could be facilitated by the existing infrastructure of the SAHaRA trial (Aneurysmal Subarachnoid Hemorrhage - Red Blood Cell Transfusion and Outcome [SAHaRA]: A Randomized Controlled Trial; NCT03309579).

The findings within this thesis support the need for a clinical trial to determine if blood pressure lowering is safe and effective at reducing aneurysm rebleeding during the pre-secured period in aSAH and concurrently provided the groundwork upon which to build this trial. The next steps will be the conduct of a multicentre cohort study (which expands on the single centre cohort) and the concurrent design of a multicentre pilot randomized controlled trial to determine the feasibility of a larger study. This project proposal will be presented at a national meeting of

Canadian critical care researchers with the goal of obtaining support and collaboration for further development.

6.5 Conclusions

This thesis demonstrates that the existing literature does not establish a relationship between elevated blood pressure during the pre-secured period and culprit aneurysm rebleeding prior to treatment in aSAH. Furthermore, the currently available literature does not demonstrate a relationship between elevated blood pressure during the early phase of aSAH and any clinically or radiologically relevant outcomes. This evidence base is exclusively observational in nature and at moderate to high risk of bias. Clinicians self-reported blood pressure targets are uniform for upper limit blood pressure targets during the pre-secured period but widely variable after the aneurysm is secured and for lower limit blood pressure targets across both periods. This self-reported practice aligns with actual practice with respect to upper limit blood pressure targets. However, very few lower limit targets were prescribed, potentially risking hypoperfusion and ischemia. Key results from this thesis will be used to design a clinical trial to test the safety and efficacy of blood pressure lowering in aSAH prior to securing the aneurysm.

6.6 References

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7 Appendices

7.1 Ethics approvals

The Ottawa Hospital | L'Hôpital d'Ottawa
RESEARCH INSTITUTE | INSTITUT DE RECHERCHE

uOttawa

UNIVERSITY OF OTTAWA HEART INSTITUTE
INSTITUT DE CARDIOLOGIE DE L'UNIVERSITÉ D'OTTAWA

Ottawa Health Science Network Research Ethics Board (OHSN-REB) / Conseil d'éthique de la recherche du réseau de science de la santé d'Ottawa (CÉR-RSSO)

Date:	May 26, 2023
Principal Investigator:	Dr. Shane English, TOH/OHRI
Protocol ID:	20230326-01H
Study Title:	Blood Pressure Management in Early Aneurysmal Subarachnoid Hemorrhage: A Retrospective Cohort Examining Clinical Practice at a University-Affiliated Tertiary Care Centre.
Submission Type:	Initial Application
Review Type:	Delegated Review Secondary Use of Information
Date of Approval:	May 26, 2023
Study Approval Expiry Date:	May 26, 2024

Dear Dr. English,

An **Institutional approval (OHRI) letter is required prior to the conduct of the study** at this site. The institutional approval letter is an indication that you have satisfied ethics, contracts, departmental notifications, as applicable.

Thank you for submitting the above referenced study. The Ottawa Health Science Network Research Ethics Board (OHSN-REB) has reviewed the application and granted approval for your study. This approval is granted until the expiration date noted above. This research study is to be conducted by the investigator noted above.

The **OHSN-REB ethics approval** is applicable only for The Ottawa Hospital.

Documents Approved:

Document Name	**Document Version Date**
Protocol	May 24, 2023

No deviations from, or changes to, the protocol should be initiated without prior written approval of an appropriate amendment from the OHSN-REB, except when necessary to eliminate immediate hazard(s) to study participants.

REB members involved in the research project do not participate in the review, discussion or decision.

If the study is to continue beyond the expiry date noted above, a Continuing Review Form must be received by the OHSN-REB on or prior to the full board submission deadline date of the meeting scheduled to occur a minimum of 30 days prior to the study expiry date. If the study has been completed by the expiry noted above, a Study Closure Report must be received by the OHSN-REB.

The OHSN-REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2); Part C, Division 5 of the Food and Drug Regulations; or with the definition in the Interim Order Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations; and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. OHSN-REB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

Please do not hesitate to contact us if you have any questions.

Sincerely,

[redacted]

Raphael Saginur, M.D.
Chairperson
Ottawa Health Science Network Research Ethics Board

/iw

Civic Campus, Box 675, 725 Parkdale Avenue, Ottawa, Ontario, K1Y 4E9
613-798-5555 extension 16719 Fax: 613-761-4311 http://www.ohri.ca/ohsn-reb

The Ottawa Hospital Research Institute | L'Hôpital d'Ottawa Institut de recherche

June 01, 2023

Dr. Shane English

The Ottawa Hospital, General Campus
501 Smyth Road
Room L1285
Ottawa, ON
K1H 8L6

Re: OHRI Institutional Approval for Ottawa Health Science Network Research Ethics Board (OHSN-REB) Submission

Protocol ID#: 20230326-01H;

Blood Pressure Management in Early Aneurysmal Subarachnoid Hemorrhage: A Retrospective Cohort Examining Clinical Practice at a University-Affiliated Tertiary Care Centre.

Dear Dr. Shane English,

This letter serves as **Ottawa Hospital Research Institute (OHRI)** Institutional Approval for the above-referenced study. Please maintain this documentation in your investigator study file.

Based on the information you provided about this study through the Clinical Research Registration Form, you have satisfied the requirements for institutional (OHRI) approval. This includes initial research ethics approval by OHSN-REB, appropriate departmental/service area notifications and execution (fully signed versions) of all agreement(s) required to begin the study locally. Please note there may be additional agreement(s) pending execution that are required to send funds, samples, or data to external sites, but are not required for you to begin your study locally.

Changes and/or additions to your study that may require additional agreement(s) or revisions to existing agreement(s) must be communicated to the OHRI Contracts Office. This should be undertaken simultaneously with any related OHSN-REB amendment submission.

Changes and/or additions to your study that affect various hospital/institution departments (e.g., pharmacy, Department of Medical Imaging, EORLA, EEG, etc.) must be communicated to the relevant departments.

As mentioned in the 'Response' tab of the Ethics application, you have 3 months from the date of initial OHSN-REB approval to submit French documents including the translation certificate to OHSN-REB through the Translated Documents section of the ethics application (if applicable).

Should you have any questions, please contact REBadministration@ohri.ca or 613-798-5555 extension 16719.

Penny Phillips
Director, Clinical Research Administration
Ottawa Hospital Research Institute | Institut de recherche de l'Hôpital d'Ottawa

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21/06/2023

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

Lettre d'approbation administrative | Letter of administrative approval

Numéro de dossier / Ethics File Number	H-06-23-9212
Titre du projet / Project Title	Blood Pressure Management in Early Aneurysmal Subarachnoid Hemorrhage: A Retrospective Cohort Examining Clinical Practice at a University-Affiliated Tertiary Care Centre.
Type de projet / Project Type	Thèse de maîtrise / Master's thesis
CÉR primaire / Primary REB	Réseau de science de la santé d'Ottawa (RSSO) / Ottawa Health Science Network (OHSN)
Statut du projet / Project Status	Approuvé / Approved
Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)	21/06/2023
Date d'expiration (jj/mm/aaaa) / Expiry Date (dd/mm/yyyy)	26/05/2024

Équipe de recherche / Research Team

Chercheur / Researcher	Affiliation	Role
Luke TERRETT	Département d'épidémiologie et santé publique / Department of Epidemiology and Public Health	Chercheur Principal / Principal Investigator
Shane ENGLISH	Département de médecine / Department of Medicine	Superviseur / Supervisor
Lauralyn MCINTYRE		Co-superviseur / Co-supervisor

Conditions spéciales ou commentaires / Special conditions or comments:

Received uOttawa approval via email on June 14, 2023

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01/12/2022

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

CERTIFICAT D'APPROBATION ÉTHIQUE | CERTIFICATE OF ETHICS APPROVAL

Numéro du dossier / Ethics File Number	H-11-22-8598
Titre du projet / Project Title	Blood Pressure Management in Early Aneurysmal Subarachnoid Hemorrhage: A Cross-Sectional Survey of Canadian Clinicians.
Type de projet / Project Type	Thèse de maîtrise / Master's thesis
Statut du projet / Project Status	Approuvé / Approved
Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)	01/12/2022
Date d'expiration (jj/mm/aaaa) / Expiry Date (dd/mm/yyyy)	30/11/2023

Équipe de recherche / Research Team

Chercheur / Researcher	Affiliation	Role
Luke TERRETT	Département d'épidémiologie et santé publique / Department of Epidemiology and Public Health	Chercheur Principal / Principal Investigator
Shane ENGLISH	Département de médecine / Department of Medicine	Superviseur / Supervisor
Lauralyn MCINTYRE		Co-superviseur / Co-supervisor

Conditions spéciales ou commentaires / Special conditions or comments

This approval is solely for the cross-sectional survey of the project. A separate application will be submitted at a later date for the retrospective cohort study.

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7.2 Supplementary Data: Systematic Review

Table of contents

Page

Appendix 1: PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p.1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p.3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p.5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p.5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	pp.5-6 Appendix 3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p.5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	pp.5-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p.6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p.6 Appendix 4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Appendix 4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p.6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	pp.6-7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	p.6-7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	pp.6-7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	pp.6-7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	pp.6-7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	pp.6-7

Section and Topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	pp.6-7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p.7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	p.6
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p.7 Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Appendix 6
Study characteristics	17	Cite each included study and present its characteristics.	Appendix 7 Appendix 8 Appendix 9 Appendix 10
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 6 Appendix 12
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 2-5 Appendix 8 Appendix 10
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	pp.7-10
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figure 2-5 pp.6-9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	p.10 Table 1 Appendix 13
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	pp.10-11
	23b	Discuss any limitations of the evidence included in the review.	pp.10-11
	23c	Discuss any limitations of the review processes used.	pp.10-11
	23d	Discuss implications of the results for practice, policy, and future research.	p.11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p.5

Section and Topic	Item #	Checklist item	Location where item is reported
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p.5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	pp.6-10
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p.2
Competing interests	26	Declare any competing interests of review authors.	p.2
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Appendix 4

Appendix 2: Search Strategy

Ovid MEDLINE(R) ALL <1946 to March 8, 2024>

1 exp Subarachnoid Hemorrhage/
2 (subarachnoid* adj2 haemorrhag*).ti,ab,kf.
3 (subarachnoid* adj2 hemorrhag*).ti,ab,kf.
4 SAH.ti,ab,kf.
5 aSAH.ti,ab,kf.
6 (subarachnoid* adj2 bleed*).ti,ab,kf.
7 or/1-6
8 Blood Pressure/
9 blood pressure*.ti,ab,kf.
10 ((Systolic* or diastolic*) adj2 pressure*).ti,ab,kf.
11 mean arterial pressure*.ti,ab,kf.
12 exp Hypertension/
13 hypertension*.ti,ab,kf.
14 exp Hypotension/
15 hypotension*.ti,ab,kf.
16 or/8-15
17 7 and 16
18 exp animals/ not humans.sh.
19 17 not 18

Embase Classic+Embase <1947 March 8, 2024>

1 exp Subarachnoid Hemorrhage/
2 (subarachnoid* adj2 haemorrhag*).ti,ab,kw.
3 (subarachnoid* adj2 hemorrhag*).ti,ab,kw.
4 SAH.ti,ab,kw.
5 aSAH.ti,ab,kw.
6 (subarachnoid* adj2 bleed*).ti,ab,kw.
7 or/1-6
8 Blood Pressure/
9 blood pressure*.ti,ab,kw.
10 ((Systolic* or diastolic*) adj2 pressure*).ti,ab,kw.
11 mean arterial pressure*.ti,ab,kw.
12 exp Hypertension/
13 hypertension*.ti,ab,kw.
14 exp Hypotension/
15 hypotension*.ti,ab,kw.
16 or/8-15
17 7 and 16
18 exp animals/ not humans.sh.
19 17 not 18

EBM Reviews - Cochrane Central Register of Controlled Trials <1991 to February 2024>

1 exp Subarachnoid Hemorrhage/
2 (subarachnoid* adj2 haemorrhag*).ti,ab,kw.
3 (subarachnoid* adj2 hemorrhag*).ti,ab,kw.

4 SAH.ti,ab,kw.
5 aSAH.ti,ab,kw.
6 (subarachnoid* adj2 bleed*).ti,ab,kw.
7 or/1-6
8 Blood Pressure/
9 blood pressure*.ti,ab,kw.
10 ((Systolic* or diastolic*) adj2 pressure*).ti,ab,kw.
11 mean arterial pressure*.ti,ab,kw.
12 exp Hypertension/
13 hypertension*.ti,ab,kw.
14 exp Hypotension/
15 hypotension*.ti,ab,kw.
16 or/8-15
17 7 and 16
18 exp animals/ not humans.sh.
19 17 not 18

Appendix 3: Eligibility Criteria

	Inclusion criteria	Exclusion criteria
Population	• Adults ≥18 years • Patients with aneurysmal subarachnoid hemorrhage • Patients admitted to hospital • Patents who have not yet had aneurysm secured	• Patients <18 years • Patients with traumatic SAH • Patients not yet admitted to hospital
Index prognostic factor	• Blood pressure (systolic blood pressure, mean arterial pressure, diastolic blood pressure, blood pressure variability)	
Comparator prognostic factors	• May include any of: age, sex, aneurysm size, aneurysm location (anterior vs posterior), clinical grade at presentation, and one of radiographic grade (Fisher grade), presence of hematoma or intraventricular hemorrhage	

Outcome(s)	• Primary outcome: rebleeding during unsecured phase
	• Secondary outcomes:
	  • Mortality
	  • Functional (GOS, mRS)
	  • Delayed Cerebral Ischemia or Vasospasm
	  • Cerebral infarction
	  • Any other clinical outcomes
	  • Serum Biomarkers (any)
		• Does not report on any of the primary or secondary outcomes

Timing	• Reports blood pressure measurement taken between presentation to hospital and securing aneurysm • Reports rate of rebleeding between hospital admission and securing aneurysm	• Only reports blood pressure measurements taken before hospital admission • Only reports blood pressure measurements taken after aneurysm secured (for primary outcome only) • Only reports blood pressure measurements taken intraoperatively • >72 hours between admission and securing aneurysm
Setting	• All hospital settings	• Not a hospital setting
Other criteria	• Explores an association between blood pressure and pre-defined outcomes • Studies using prospective or retrospective design • Any year • Language: English, French • Full text available	• Case studies • Case series • Commentaries, editorials, reviews • Conference abstracts

Appendix 4: Data Extraction Template

study #
Sources of data
study ID (1st author, year)
title
lead author contact details
country
study funding
stated purpose
study design
participants
consecutive participants enrolled (y/n)
location/setting
number of centres
inclusion criteria
exclusion criteria
participant description (focus on 6 key confounders)
details of treatment received
study dates (start, end)
outcomes to be predicted
definition and method for measurement of outcomes (each outcome)
was the same outcome definition (and method of measurement) used in all participants?
types of outcomes (single or combined)
were the outcomes assessed without knowledge of other candidate prognostic factors (blinded)
were the candidate prognostic factors part of the outcome (when using panel or consensus outcome measurement)
time of outcome occurrence or summary of duration of follow-up
prognostic factors
which of the six key confounders in our protocol are included in the study? (Age, Sex, Clinical grade, aneurysm size, aneurysm location, fisher grade (ICH or IVH)
definition and method for measurement of prognostic factors

timing of prognostic factor measurement (admission, first 24 hours, 48, unsecured only, beyond etc)
were prognostic factors assessed blinded for outcome and for each other (if relevant)?
handling of prognostic factors in the analysis (continuous, linear, transformed, categorized, etc)
Sample Size
was a sample size calculation conducted? If so, how?
number of 1) participants 2) outcomes (events)
events per variable (for candidate prognostic factors only)
Missing data
number of participants with any missing value (prognostic factors or outcomes only)
number of participants with missing data for prognostic factor of interest (blood pressure)
details of attrition (loss to follow-up_ and for time to event data, the number of censored observations)
handling of missing data
Analysis
modelling method (linear or logistic regression, cox regression, etc)
how modelling assumptions were checked (important for time to event data and hazard ratios)
method for selection of prognostic factors for inclusion in multivariable modelling (eg all candidate prognostic factors considered, preselection of established prognostic factors, retain only those significant from univariable analysis)
method/criteria for slection or exclusion of prognostic factors during multivariable modelling
method for handling of each continous prognostic factor including cutpoints used and their justification (dichotomization, categorization, linear, non-linear, etc)
Results
blood pressure categories used in the study
outcomes evaluated and outcome measures

unadjusted prognostic factor estimates (OR, RR, HR, mean diff) with 95% CI (or SE, SD if continuous)
adjusted estimates (from multivariate model)
set of adjustment factors used (other variables in model)
Interpretation and Discussion
interpretation of presented results
Comparison with other studies, discussion of generalizability, strengths, limitations
Other
comments and notes

Appendix 5: Quality in Prognosis Studies (QUIPS) Risk of Bias Assessment Tool (adapted for this study)

QUIPS Risk of Bias Tool			
Domain	**What is being assessed**	**Rating**	**Explanation**
Study participation	Is the study sample representative of the population of interest?	Low	All of: • Used consecutive or random sampling from target population; cases and controls are from similar population • Participants represent population of interest (people with aSAH presenting to hospital) • At least one inclusion and one exclusion criterion are given
		Moderate	• There may be differences between participants and non-participants; however, there was insufficient information to judge as high or low
		High	Any of: • Sample was selectively recruited; cases and controls from different source populations • Participants do not represent population of interest (people with aSAH presenting to hospital) • No inclusion and exclusion criteria described
Study attrition	Are the participants who completed the study representative of the baseline sample?	Low	Any of: • <10% missing data, or • Reasons for missing data unlikely to be related to true outcome (missing at random)
		Moderate	Any of: • 10-20% missing data • There may be differences between completing and non-completing participants; however, there was insufficient information to judge as high or low
		High	Any of: • >20% missing data • Reasons for missing data likely to be related to true outcome or prognostic factor
Prognostic factor measurement	Was blood pressure measurement adequate?	Low	All of: • Blood pressure clearly defined/described • Methods and settings for blood pressure measurement were the same for all participants • Continuous variable used or cutpoints used and justified
		Moderate	• There may be differences in blood pressure measurement between rebleed cases and non-rebleed cases; however, there was insufficient information to judge as high or low
		High	Any of: • Methods and settings for blood pressure measurement were not the same for all participants (e.g., different approaches for participants with different outcomes) • Cutpoints used and not justified
Outcome measurement	Was rebleeding measurement adequate?	Low	All of: • Rebleeding clearly defined/described • Follow up period defined and is adequate for outcome to occur (72 hours or until aneurysm is secured) • Rebleeding measured similarly for all participants • Valid and reliable measurement used to determine rebleeding (clinical AND radiographic)
		Moderate	• There may be differences in how rebleeding was measured for different blood pressure levels; however, there was insufficient information to judge as high or low

QUIPS Risk of Bias Tool			
Domain	**What is being assessed**	**Rating**	**Explanation**
		High	Any of: • Follow up period inadequate for outcome to occur (i.e., follow up is less than 72 hours after admission or ends prior to aneurysm being secured) • Rebleeding measured differently across participants • No valid and reliable measurement used to determine rebleeding (i.e., only clinical, only radiographic, or neither)
Confounding	Are key adjustment factors accounted for? (from our 6)	Low	• More than 2 confounding variables (of the 6) considered in multivariate analysis (or accounted for in study design through matching, stratification)
		Moderate	• Up to 2 confounding variables (of the 6) considered in multivariate analysis (or accounted for in study design through marching, stratification)
		High	Any of: • No confounding variables (of the 6) considered in multivariate analysis (or accounted for in study design through matching, stratification); or no multivariate analysis done
Statistical analysis and reporting	Is statistical analysis and reporting appropriate and adequate?	Low	All of: • Enough data is presented to assess whether analysis was adequate • Model building strategy was appropriate • No selective reporting of results (i.e., the variables identified in the methods section are included in the results section)
		Moderate	• Possible bias in analysis and reporting of results; however, there was insufficient information to judge as high or low
		High	Any of: • Not enough data is presented to assess whether analysis was adequate • Model selected was inadequate or not described; analysis approach was inadequate or not described • Selective reporting of results (i.e., not all of the variables identified in the methods section are included in the results section)
OVERALL ROB RATING		**LOW**	• All domains classified as having low RoB, or up to one moderate RoB
		MODERATE	• If one domain is high risk, or moderate risk for at least two domains
		HIGH	• High risk for at least two domains

Appendix 6: Excluded studies (n=140) and full texts not retrieved (n=2)

Author, Year	Citation	Reason for Exclusion
Aires 2022	Aires R, Galafassi G, Pinho MCV, et al. Preoperative scale proposal based on clinical outcome for elderly patients with ruptured intracranial aneurysms undergoing microsurgery. The International journal of neuroscience. 2022;(gs4, 0270707):1-7. doi:10.1080/00207454.2022.2070488	Blood pressure measurement taken before hospital admission
Aleman-Rivera 2001	Aleman-Rivera A, Camacho-Gomez A. [The results of surgical treatment in 100 patients operated on for intracranial aneurysms of the anterior circulation]. Revista de neurologia. 2001;32(12):1128-1131.	Language other than English or French
AMPASStudyGrp 2016	AMPAS Study Grp, Zhao B, Fan Y, et al. Aneurysm rebleeding after poor-grade aneurysmal subarachnoid hemorrhage: Predictors and impact on clinical outcomes. JOURNAL OF THE NEUROLOGICAL SCIENCES. 2016;371:62-66. doi:10.1016/j.jns.2016.10.020	Blood pressure measurement taken before hospital admission
Aoyagi 1996	Aoyagi N, Hayakawa I. Study on early re-rupture of intracranial aneurysms. Acta neurochirurgica. 1996;138(1):12-18.	Does not explore a potential association between blood pressure and outcomes
Ascanio 2020	Ascanio LC, Enriquez-Marulanda A, Maragkos GA, et al. In Reply: Effect of Blood Pressure Variability During the Acute Period of Subarachnoid Hemorrhage on Functional Outcomes. Neurosurgery. 2020;87(3):E430-E431. doi:10.1093/neuros/nyaa238	Letter to Editor
Banos-Gonzalez 2011	Banos-Gonzalez M, Cantu-Brito C, Chiquete E, et al. [Systolic blood pressure and functional outcome in patients with acute stroke: a Mexican registry of acute cerebrovascular disease (RENAMEVASC)]. Archivos de cardiologia de Mexico. 2011;81(3):169-175.	Language other than English or French
Bautista 2019	Bautista AF, Lenhardt R, Yang D, et al. Early Prediction of Prognosis in Elderly Acute Stroke Patients. Critical care explorations. 2019;1(4):e0007. doi:10.1097/CCE.0000000000000007	Blood pressure measurement taken before hospital admission
Bazowski 1992	Bazowski P, Gamrot J, Rudnik A, Konopka M. [Analysis of selected prognostic factors in patients with ruptured cerebral aneurysms operated-on in the early period]. Neurologia i neurochirurgia polska. 1992;Suppl 1(nyf, 0101265):25-28.	Language other than English or French
Beseoglu 2010	Beseoglu K, Unfrau K, Steiger HJ, Hanggi D. Influence of blood pressure variability on short-term outcome in patients with subarachnoid hemorrhage. Central European neurosurgery. 2010;71(2):69-74. doi:10.1055/s-0029-1237725	Blood pressure measurement after 72 hours
Botia 1996	Botia E, Vivancos J, Leon T, Segura T, Fernandez-Garcia C, Lopez-Lopez F. [Predictive mortality factors and the development of major complications in non-traumatic subarachnoid hemorrhage]. Revista de neurologia. 1996;24(126):193-198.	Language other than English or French
Brandt 1991	Brandt L, Saveland H, Romner B, Ryman T. Does nimodipine eliminate arterial hypertension as a prognostic risk factor in subarachnoid haemorrhage?. British journal of neurosurgery. 1991;5(5):485-489.	Blood pressure measurement taken before hospital admission

Bromowicz 1979	Bromowicz J, Bryniarska D, Koniar-Danilewicz H, Danilewicz B. [Effectiveness of antifibrinolytic, edema-preventing and hypotensive agents in the prevention of recurrent bleeding from intracranial aneurysms]. Neurologia i neurochirurgia polska. 1979;13(6):647-651.	Language other than English or French
Calviere 2018	Calviere L GC Rafk M, Koopman I, Rousseau V, Albucher JF, Geeraerts T, Rinkel GJE, Olivot JM, Vergouwen MDI. Rebleeding rate in two comprehensive stroke units using different blood pressure management. 2018;13(2 Supplement 1):54.	Conference abstract
Chongruksut 2020	Chongruksut W, Limpastan K, Jetjumnong C, et al. Age as a prognostic factor of 30-day mortality in hemorrhagic stroke patients: A Thai large tertiary care referral center. Asian journal of surgery. 2020;43(10):991-995. doi:10.1016/j.asjsur.2019.11.010	Does not explore a potential association between blood pressure and outcomes
Chotai 2013	Chotai S, Ahn SY, Moon HJ, et al. Prediction of outcomes in young adults with aneurysmal subarachnoid hemorrhage. Neurologia medico-chirurgica. 2013;53(3):157-162.	Blood pressure measurement taken before hospital admission
Chua 2016	Chua MH, Griessenauer CJ, Thomas AJ, Ogilvy CS. Who is Likely to Present in Poor Neurologic Condition After Aneurysmal Subarachnoid Hemorrhage? Risk Factors and Implications for Treatment. World neurosurgery. 2016;92(101528275):113-119. doi:10.1016/j.wneu.2016.04.123	Blood pressure measurement taken before hospital admission
Cinotti 2019	Cinotti R, Putegnat JB, Lakhal K, et al. Evolution of neurological recovery during the first year after subarachnoid haemorrhage in a French university centre. Anaesthesia, critical care & pain medicine. 2019;38(3):251-257. doi:10.1016/j.accpm.2018.10.002	Does not explore a potential association between blood pressure and outcomes
Claassen 2002	Claassen J, Carhuapoma JR, Kreiter KT, Du EY, Connolly ES, Mayer SA. Global cerebral edema after subarachnoid hemorrhage: frequency, predictors, and impact on outcome. Stroke. 2002;33(5):1225-1232.	Does not explore a potential association between blood pressure and outcomes
Conway 2001	Conway JE, Tamargo RJ. Cocaine use is an independent risk factor for cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke. 2001;32(10):2338-2343.	Blood pressure measurement taken before hospital admission
DarkwahOppong 2022	Darkwah Oppong M, Steinwasser L, Ries C, et al. Blood pressure and outcome after aneurysmal subarachnoid hemorrhage. Scientific reports. 2022;12(1):8006. doi:10.1038/s41598-022-11903-4	Blood pressure measurement after 72 hours
Disney 1988	Disney L, Weir B, Grace M. Factors influencing the outcome of aneurysm rupture in poor grade patients: a prospective series. Neurosurgery. 1988;23(1):1-9.	Blood pressure measurement after 72 hours
Doerfler 2018	Doerfler S, Faerber J, McKhann GM, et al. The Incidence and Impact of Secondary Cerebral Insults on Outcome After Aneurysmal Subarachnoid Hemorrhage. World neurosurgery. 2018;114(101528275):e483-e494. doi:10.1016/j.wneu.2018.02.195	Blood pressure measurement after 72 hours

Duan 2016	Duan G., Yang P., Li Q., et al. Prognosis predicting score for endovascular treatment of aneurysmal subarachnoid hemorrhage a risk modeling study for individual elderly patients. Medicine (United States). 2016;95(7):e2686. doi:10.1097/MD.0000000000002686	Blood pressure measurement taken before hospital admission
Duangthongphon 2019	Duangthongphon P, Souwong B, Munkong W, Kitkhuandee A. Results of a Preventive Rebleeding Protocol in Patients with Ruptured Cerebral Aneurysm: A Retrospective Cohort Study. Asian journal of neurosurgery. 2019;14(3):748-753. doi:10.4103/ajns.AJNS_32_19	Does not explore a potential association between blood pressure and outcomes
Eskesen 1987	Eskesen V, Rosenorn J, Schmidt K, Ronde F. Pre-existing arterial hypertension in subarachnoid haemorrhage: an unfavourable prognostic factor. British journal of neurosurgery. 1987;1(4):455-461.	Blood pressure measurement taken before hospital admission
Ezawa 1972	Ezawa K., Shimizu T., Watanabe R. Natural history and prognosis of spontaneous subarachnoid hemorrhage. Tokyo Jikeikai Medical Journal. 1972;87(3):380-391.	Language other than English or French
Fontana 2015	Fontana J, Scharf J, Weis C, Schmieder K, Barth M. The spontaneous arterial blood pressure rise after aneurysmal subarachnoid hemorrhage - a biphasic phenomenon. Clinical neurology and neurosurgery. 2015;137(df4, 7502039):22-27. doi:10.1016/j.clineuro.2015.06.014	Blood pressure measurement after 72 hours
Fontana 2016	Fontana J, Wenz H, Schmieder K, Barth M. Impairment of Dynamic Pressure Autoregulation Precedes Clinical Deterioration after Aneurysmal Subarachnoid Hemorrhage. Journal of neuroimaging : official journal of the American Society of Neuroimaging. 2016;26(3):339-345. doi:10.1111/jon.12295	Does not explore a potential association between blood pressure and outcomes
Foroohar 2000	Foroohar M, Macdonald RL, Roth S, Stoodley M, Weir B. Intraoperative variables and early outcome after aneurysm surgery. Surgical neurology. 2000;54(4):304-315.	Blood pressure measurement taken before hospital admission
Fortuny 1980	Fortuny LA, Adams CB, Briggs M. Surgical mortality in an aneurysm population: effects of age, blood pressure and preoperative neurological state. Journal of neurology, neurosurgery, and psychiatry. 1980;43(10):879-882.	>72 hours from from admission to securing aneurysm
French 1950	French L.A., Blake P.S. Subarachnoid haemorrhages and intracranial aneurysms. Journal-lancet. 1950;70(12):459-466.	Case series
Frontera 2006	Frontera JA, Claassen J, Schmidt JM, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery. 2006;59(1):21-27.	Conference abstract
Fujita 1993	Fujita K, Lin XP, Masumura M, Ebara K, Asada M, Tamaki N. [Risk factors for severe subarachnoid hemorrhage following aneurysmal rupture]. No shinkei geka Neurological surgery. 1993;21(10):885-889.	Language other than English or French
Garton 2020	Garton ALA, Gupta VP, Giantini Larsen AM, Kamel H, Knopman J, Stieg PE. Letter: Effect of Blood Pressure Variability During the Acute Period of Subarachnoid Hemorrhage on Functional Outcomes. Neurosurgery. 2020;87(3):E428-E429. doi:10.1093/neuros/nyaa230	Letter to Editor

Ge 2021	Ge XB, Yang QF, Liu ZB, Zhang T, Liang C. Increased blood pressure variability predicts poor outcomes from endovascular treatment for aneurysmal subarachnoid hemorrhage. Arquivos de neuro-psiquiatria. 2021;79(9):759-765. doi:10.1590/0004-282X-ANP-2020-0167	Blood pressure measurement taken after aneurysm secured
Gomis 1994	Gomis P, Rousseaux P, Jolly D, Graftieaux JP. [Initial prognostic factors of aneurysmal subarachnoid hemorrhage]. Neuro-Chirurgie. 1994;40(1):18-30.	No full text available
Goncalves 2022	Goncalves B, Rynkowski C, Turon R, et al. Clinical Characteristics and Outcomes of Patients with Aneurysmal Subarachnoid Hemorrhage: A Prospective Multicenter Study in a Middle-Income Country. Neurocritical care. 2022;(101156086). doi:10.1007/s12028-022-01629-6	Blood pressure measurement taken before hospital admission
Gonzalez 2007	Gonzalez NR, Boscardin WJ, Glenn T, Vinuela F, Martin NA. Vasospasm probability index: a combination of transcranial doppler velocities, cerebral blood flow, and clinical risk factors to predict cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Journal of neurosurgery. 2007;107(6):1101-1112.	Blood pressure measurement taken before hospital admission
Graetz 2010	Graetz D, Nagel A, Schlenk F, Sakowitz O, Vajkoczy P, Sarrafzadeh A. High ICP as trigger of proinflammatory IL-6 cytokine activation in aneurysmal subarachnoid hemorrhage. Neurological research. 2010;32(7):728-735. doi:10.1179/016164109X12464612122650	Does not explore a potential association between blood pressure and outcomes
Gross 2014	Gross BA, Rosalind Lai PM, Frerichs KU, Du R. Aspirin and aneurysmal subarachnoid hemorrhage. World neurosurgery. 2014;82(6):1127-1130. doi:10.1016/j.wneu.2013.03.072	Does not explore a potential association between blood pressure and outcomes
Hamdan 2014	Hamdan A, Barnes J, Mitchell P. Subarachnoid hemorrhage and the female sex: analysis of risk factors, aneurysm characteristics, and outcomes. Journal of neurosurgery. 2014;121(6):1367-1373. doi:10.3171/2014.7.JNS132318	Does not explore a potential association between blood pressure and outcomes
Hammer 2018	Hammer A, Steiner A, Ranaie G, et al. Impact of Comorbidities and Smoking on the Outcome in Aneurysmal Subarachnoid Hemorrhage. Scientific reports. 2018;8(1):12335. doi:10.1038/s41598-018-30878-9	Blood pressure measurement taken before hospital admission
Henderson 1977	Henderson W.G., Torner J.C., Nibbelink D.W. Intracranial aneurysms and subarachnoid hemorrhage: report on a randomized treatment study. IV-B. Regulated bed rest: statistical evaluation. Stroke. 1977;8(5):579-589.	>72 hours from from admission to securing aneurysm
Hijdra 1988	Hijdra A, van Gijn J, Nagelkerke NJ, Vermeulen M, van Crevel H. Prediction of delayed cerebral ischemia, rebleeding, and outcome after aneurysmal subarachnoid hemorrhage. Stroke. 1988;19(10):1250-1256. doi:10.1161/01.str.19.10.1250	Does not explore a potential association between blood pressure and outcomes
Hirashima 2005	Hirashima Y, Hamada H, Kurimoto M, Origasa H, Endo S. Decrease in platelet count as an independent risk factor for symptomatic vasospasm following aneurysmal subarachnoid hemorrhage. Journal of neurosurgery. 2005;102(5):882-887.	Blood pressure measurement taken before hospital admission
Hitchcock 1984	Hitchcock ER, Tsementzis SA, Dow AA. Short- and long-term prognosis of patients with a subarachnoid haemorrhage in relation to intra-operative period of hypotension. Acta neurochirurgica. 1984;70(3-4):235-242.	intraoperative blood pressure only

Hori 2022	Hori S, Kashiwazaki D, Akioka N, et al. Predictive Factors of Functional Outcome in World Federation of Neurosurgical Societies Grade V Subarachnoid Hemorrhage. World neurosurgery. 2022;165(101528275):e216-e222. doi:10.1016/j.wneu.2022.05.135	Blood pressure measurement taken before hospital admission
Horie 2019	Horie N, Sato S, Kaminogo M, et al. Impact of perioperative aneurysm rebleeding after subarachnoid hemorrhage. J Neurosurg. Published online 2019:1-10. doi:10.3171/2019.6.JNS19704	hypertension not defined
Hosmann 2020	Hosmann A, Klenk S, Wang WT, Koren J, Sljivic S, Reinprecht A. Endogenous arterial blood pressure increase after aneurysmal subarachnoid hemorrhage. Clinical neurology and neurosurgery. 2020;190(df4, 7502039):105639. doi:10.1016/j.clineuro.2019.105639	Blood pressure measurement after 72 hours
Hostettler 2020	Hostettler IC, Pavlou M, Ambler G, et al. Assessment of the Subarachnoid Hemorrhage International Trialists (SAHIT) Models for Dichotomized Long-Term Functional Outcome Prediction After Aneurysmal Subarachnoid Hemorrhage in a United Kingdom Multicenter Cohort Study. Neurosurgery. 2020;87(6):1269-1276. doi:10.1093/neuros/nyaa299	Blood pressure measurement taken before hospital admission
Huang 2023	Huang, Qiu-Yu MMa; Huang, Qing MDb; Lin, Shao-Wei MMc; Wang, Fan MMb; Sun, Yi MDc; Zeng, Yi-Le MMb; Liu, Bang MMc; Cai, Ying-Ying MMc; Chen, Ze-Long MBd; Wu, Si-Ying MDc,*. Prognostic factors affecting the ruptured intracranial aneurysms: A 9-year multicenter study in Fujian, China. Medicine 102(40):p e34893, October 06, 2023. | DOI: 10.1097/MD.0000000000034893	Blood pressure measurement taken before hospital admission
Huang 2020	Huang H, Lai LT. Incidence and Case-Fatality of Aneurysmal Subarachnoid Hemorrhage in Australia, 2008-2018. World neurosurgery. 2020;144(101528275):e438-e446. doi:10.1016/j.wneu.2020.08.186	Blood pressure measurement taken before hospital admission
IglesiasPosadilla 2015	Iglesias Posadilla D, Gero Escapa M, Gonzalez Robledo J, et al. Outcomes of spontaneous subarachnoid hemorrhage (SAH) in neurocritical care unit: a multicenter study. 2015;3(no pagination). doi:10.1186/2197-425X-3-S1-A773	Conference abstract
Ikawa 2020	Ikawa F, Michihata N, Iihara K, et al. Risk Management of Aneurysmal Subarachnoid Hemorrhage by Age and Treatment Method from a Nationwide Database in Japan. World neurosurgery. 2020;134(101528275):e55-e67. doi:10.1016/j.wneu.2019.09.015	Blood pressure measurement taken before hospital admission
Kanamaru 2020	Kanamaru H, Kawakita F, Asada R, et al. Prognostic factors varying with age in patients with aneurysmal subarachnoid hemorrhage. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2020;76(dpi, 9433352):118-125. doi:10.1016/j.jocn.2020.04.022	Blood pressure measurement taken before hospital admission
Katsuki 2020	Katsuki M, Kakizawa Y, Nishikawa A, Yamamoto Y, Uchiyama T. Easily created prediction model using deep learning software (Prediction One, Sony Network Communications Inc.) for subarachnoid hemorrhage outcomes from small dataset at admission. 2020;11. doi:10.25259/SNI6362020	Does not explore a potential association between blood pressure and outcomes
Kienzler 2016	Kienzler J, Marbacher S, Remonda L, et al. Outcome after In-Hospital Rebleeding of Rupture of Intracranial Aneurysms. Journal of neurological surgery Part A, Central European neurosurgery. 2016;77(3):207-221. doi:10.1055/s-0035-1570007	Does not explore a potential association between blood pressure and outcomes

Kim 2021	Kim KH, Koo HW, Lee BJ, Sohn MJ. Analysis of risk factors correlated with angiographic vasospasm in patients with aneurysmal subarachnoid hemorrhage using explainable predictive modeling. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2021;91(dpi, 9433352):334-342. doi:10.1016/j.jocn.2021.07.028	Blood pressure measurement taken before hospital admission
Kim 2022	Kim YJ, Lee SH, Jeon JP, Choi HC, Choi HJ. Clinical Factors Contributing to Cognitive Function in the Acute Stage after Treatment of Intracranial Aneurysms: A Cross-Sectional Study. Journal of clinical medicine. 2022;11(17). doi:10.3390/jcm11175053	Blood pressure not measured
King 2009	King A.T., Mcmahon C., Tyrrell P., et al. Outcome after Subarachnoid haemorrhage - A SAH cohort study. British Journal of Neurosurgery. 2009;23(2):119. doi:10.1080/02688690902858607	Conference abstract
Kirkness 2009	Kirkness CJ, Burr RL, Mitchell PH. Intracranial and blood pressure variability and long-term outcome after aneurysmal sub-arachnoid hemorrhage. American journal of critical care : an official publication, American Association of Critical-Care Nurses. 2009;18(3):241-251. doi:10.4037/ajcc2009743	Mixed population and unable to extract aSAH data specifically
Konar 2019	Konar SK, Ramesh S, Christopher R, et al. The Correlation of Endothelial Nitric Oxide Synthase (eNOS) Polymorphism and Other Risk Factors with Aneurysmal Subarachnoid Hemorrhage: A Case-Control Study. Neurology India. 2019;67(4):1006-1012. doi:10.4103/0028-3886.266231	Blood pressure measurement taken before hospital admission
Koopman 2022	Koopman I, van Wijngaarden PB, Rinkel GJE, Vergouwen MDI. Devastating delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Frontiers in neurology. 2022;13(101546899):1016111. doi:10.3389/fneur.2022.1016111	Does not explore a potential association between blood pressure and outcomes
Kozak 2016	Kozak N, Bereczki D, Szabo S. Predictors of Symptomatic Vasospasm After Subarachnoid Hemorrhage: A Single Center Study of 457 Consecutive Cases. Turkish neurosurgery. 2016;26(4):545-549. doi:10.5137/1019-5149.JTN.14408-15.1	hypertension not defined
Kuroiwa 1994	Kuroiwa T, Tanabe H, Arai M, Ohta T. [Measurement of serum neuron-specific enolase levels after subarachnoid hemorrhage and intracerebral hemorrhage]. No shinkei geka Neurological surgery. 1994;22(6):531-535.	Does not explore a potential association between blood pressure and outcomes
Kusumi 2005	Kusumi M, Yamada M, Kitahara T, et al. Rerupture of cerebral aneurysms during angiography--a retrospective study of 13 patients with subarachnoid hemorrhage. Acta neurochirurgica. 2005;147(8):831-837.	Incorrect outcomes
Lebedev 1986	Lebedev VV, Kholodov SA, Platonova TK, Shelkovskii VN, Krylov VV. [Prediction of recurrent hemorrhages from ruptured arterial aneurysms in the acute period]. Zhurnal nevropatologii i psikhiatrii imeni SS Korsakova (Moscow, Russia : 1952). 1986;86(9):1281-1284.	Language other than English or French
Lindbohm 2019	Lindbohm JV, Kaprio J, Korja M. Survival bias explains improved survival in smokers and hypertensive individuals after aSAH. Neurology. 2019;93(23):e2105-e2109. doi:10.1212/WNL.0000000000008537	Blood pressure measurement taken before hospital admission
Massei 1998	Massei R, Tavola M, Mottura G, Ciceri R, Pontiggia M. [Subarachnoid hemorrhage: protective hypotension in delayed surgery]. Minerva anestesiologica. 1998;64(5):209-210.	Language other than English or French

McGirt 2007	McGirt MJ, Woodworth GF, Ali M, Than KD, Tamargo RJ, Clatterbuck RE. Persistent perioperative hyperglycemia as an independent predictor of poor outcome after aneurysmal subarachnoid hemorrhage. Journal of neurosurgery. 2007;107(6):1080-1085.	Blood pressure measurement taken before hospital admission
Meyer-Leddin 1957	Meyer-Leddin H. The prognosis of spontaneous subarachnoid bleeding. Medizinische Klinik. 1957;52(41):1788-1791.	Language other than English or French
Miyakoshi 2010	Miyakoshi K., Mori K., Iai S., Watanabe T., Hadeishi H. Prediction model of functional outcome in patients with acute subarachnoid hemorrhage using stepwise regression analysis. Cerebrovascular Diseases. 2010;29(SUPPL. 2):267. doi:10.1159/000321266	Conference abstract
Mocco 2006	Mocco J, Rose JC, Komotar RJ, Mayer SA. Blood pressure management in patients with intracerebral and subarachnoid hemorrhage. Neurosurgery clinics of North America. 2006;17 Suppl 1(bjt, 9008004):25-40.	Review
Nagasawa 1988	Nagasawa S, Ohtsuki H, Yonekawa Y, Handa H. [Clinical analysis of 60 aged patients with ruptured intracranial aneurysms]. No shinkei geka Neurological surgery. 1988;16(1):17-21.	Language other than English or French
Naidech 2005	Naidech AM, Janjua N, Kreiter KT, et al. Predictors and impact of aneurysm rebleeding after subarachnoid hemorrhage. Arch Neurol. 2005;62(3):410-416. doi:10.1001/archneur.62.3.410	Blood pressure not measured
Nibbelink 1975	Nibbelink DW, Torner JC, Henderson WG. Intracranial aneurysms and subarachnoid hemorrhage. A cooperative study. Antifibrinolytic therapy in recent onset subarachnoid hemorrhage. Stroke. 1975;6(6):622-629.	>72 hours from from admission to securing aneurysm
Nichols 2021	Nichols L, Gall S, Stankovich J, Stirling C. Associations between socioeconomic status and place of residence with survival after aneurysmal subarachnoid haemorrhage. Internal medicine journal. 2021;51(12):2095-2103. doi:10.1111/imj.15044	Blood pressure measurement taken before hospital admission
O'Neill 1988	O'Neill P, West CR, Chadwick DW, et al. Post-ictal blood pressure in aneurysmal subarachnoid haemorrhage. British journal of neurosurgery. 1988;2(2):153-159.	Blood pressure measurement after 72 hours
Ohman 1991	Ohman J, Servo A, Heiskanen O. Risks factors for cerebral infarction in good-grade patients after aneurysmal subarachnoid hemorrhage and surgery: a prospective study. Journal of neurosurgery. 1991;74(1):14-20.	Blood pressure measurement taken before hospital admission
Panni 2023	Panni P, Riccio L, Cao R, Pedicelli A, Marchese E, Caricato A, Feletti A, Testa M, Zanatta P, Gitti N, Piva S, Mardighian D, Semeraro V, Nardin G, Lozupone E, Paiano G, Picetti E, Montanaro V, Petranca M, Bortolotti C, Scibilia A, Cirillo L, Lanterna AL, Ambrosi A, Mortini P, Beretta L, Falini A. Clinical Impact and Predictors of Aneurysmal Rebleeding in Poor-Grade Subarachnoid Hemorrhage: Results From the National POGASH Registry. Neurosurgery. 2023 Sep 1;93(3):636-645. doi: 10.1227/neu.0000000000002467. Epub 2023 Apr 3. PMID: 37010298.	Blood pressure measurement taken before hospital admission
Pereira 2007	Pereira AR, Sanchez-Pena P, Biondi A, et al. Predictors of 1-year outcome after coiling for poor-grade subarachnoid aneurysmal hemorrhage. Neurocritical care. 2007;7(1):18-26.	Blood pressure measurement taken before hospital admission

Placek 2015	Placek MM, Wachel P, Czosnyka M, Soehle M, Smielewski P, Kasprowicz M. Complexity of cerebral blood flow velocity and arterial blood pressure in subarachnoid hemorrhage using time-frequency analysis. Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Annual International Conference. 2015;2015(101763872):7700-7703. doi:10.1109/EMBC.2015.7320176	Blood pressure measurement after 72 hours
Platz 2011	Platz J, Guresir E, Vatter H, et al. Unsecured intracranial aneurysms and induced hypertension in cerebral vasospasm: is induced hypertension safe?. Neurocritical care. 2011;14(2):168-175. doi:10.1007/s12028-011-9510-2	>72 hours from from admission to securing aneurysm
Qi 2021	Qi M, Jiang L, Xu Y, et al. Risk Factors for Prognosis in Elderly Patients with Severe Aneurysmal Subarachnoid Hemorrhage: A Retrospective Study. Advances in therapy. 2021;38(1):249-257. doi:10.1007/s12325-020-01531-7	Blood pressure measurement taken before hospital admission
Qian 2014	Qian Z, Peng T, Liu A, et al. Early timing of endovascular treatment for aneurysmal subarachnoid hemorrhage achieves improved outcomes. Current neurovascular research. 2014;11(1):16-22.	No full text available
Rautalin 2022	Rautalin I, Juvela S, Martini ML, Macdonald RL, Korja M. Risk Factors for Delayed Cerebral Ischemia in Good-Grade Patients With Aneurysmal Subarachnoid Hemorrhage. Journal of the American Heart Association. 2022;11(23):e027453. doi:10.1161/JAHA.122.027453	Blood pressure measurement taken before hospital admission
Rinaldo 2016	Rinaldo L, Rabinstein AA, Lanzino G. Elderly age associated with poor functional outcome after rupture of anterior communicating artery aneurysms. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2016;34(dpi, 9433352):108-111. doi:10.1016/j.jocn.2016.05.006	Blood pressure measurement taken before hospital admission
RiveroRodriguez 2017	Rivero Rodriguez D, Scherle Matamoros C, Fernandez Cue L, Miranda Hernandez JL, Pernas Sanchez Y, Perez Nellar J. Factors associated with poor outcome for aneurysmal subarachnoid haemorrhage in a series of 334 patients. Neurologia (Barcelona, Spain). 2017;32(1):15-21. doi:10.1016/j.nrl.2014.12.006	Language other than English or French
RiveroRodriguez 2015	Rivero Rodriguez D, Scherle Matamoros C, Cue LF, Miranda Hernandez JL, Pernas Sanchez Y, Perez Nellar J. Predictor's of Mortality in Patients with Aneurysmal Subarachnoid Haemorrhage and Reebleding. Neurology research international. 2015;2015(101543314):545407. doi:10.1155/2015/545407	Rebleeding is one of the inclusion criteria
RiveroRodriguez 2016	Rivero Rodriguez D, Scherle Matamoros C, Fernandez Cue L, Miranda Hernandez JL, Pernas Sanchez Y, Perez Nellar J. [Re-bleeding predictors in patients with aneurysmal subarachnoid haemorrhage and delayed neurosurgical treatment]. Neurocirugia (Asturias, Spain). 2016;27(2):51-56. doi:10.1016/j.neucir.2015.05.004	Language other than English or French
Rodholm 2002	Rodholm M, Starmark JE, Ekholm S, von Essen C. Organic psychiatric disorders after aneurysmal SAH: outcome and associations with age, bleeding severity, and arterial hypertension. Acta neurologica Scandinavica. 2002;106(1):8-18.	Blood pressure measurement taken before hospital admission
Roganovic 2001	Roganovic Z, Pavlicevic G, Tadic R, Djirkovic S. [Risk factors for the onset of vasospasm and rebleeding after spontaneous subarachnoid hemorrhage]. Vojnosanitetski pregled. 2001;58(1):17-23.	Language other than English or French

RonneEngstrom 2023	Ronne Engstrom E, Baldvinsdottir B, Aineskog H, et al. The impact of previous health on the mortality after aneurysmal subarachnoid hemorrhage: analysis of a prospective Swedish multicenter study. Acta neurochirurgica. 2023;165(2):443-449. doi:10.1007/s00701-022-05464-8	Blood pressure measurement taken before hospital admission
Rosenwasser 1983	Rosenwasser RH, Delgado TE, Buchheit WA, Freed MH. Control of hypertension and prophylaxis against vasospasm in cases of subarachnoid hemorrhage: a preliminary report. 1983;12(6):658. doi:10.1227/00006123-198306000-00012	Incorrect outcomes
Ryttlefors 2007	Ryttlefors M, Howells T, Nilsson P, Ronne-Engstrom E, Enblad P. Secondary insults in subarachnoid hemorrhage: occurrence and impact on outcome and clinical deterioration. Neurosurgery. 2007;61(4):704-705.	Blood pressure measurement after 72 hours
Sadasivam 2023	Sadasivam AS, Nathan B, Anbazhagan SP. Clinical Profile and Outcome in Patients with Spontaneous Subarachnoid Hemorrhage from a South Indian Tertiary Centre: A Prospective Observational Study. Asian J Neurosurg. 2023 Mar 27;18(1):80-87. doi: 10.1055/s-0043-1761234. PMID: 37056879; PMCID: PMC10089737.	Blood pressure measurement taken before hospital admission
Saito 2021	Saito N, Nishikawa T, Ota T. Impact of blood pressure on the outcomes of inpatients with Subarachnoid hemorrhage: A retrospective cross-sectional study. Medicine (Baltimore). 2021;100(7):e24761. doi:10.1097/MD.0000000000024761	Blood pressure measurement taken before hospital admission
Saveland 1994	Saveland H, Brandt L. Which are the major determinants for outcome in aneurysmal subarachnoid hemorrhage? A prospective total management study from a strictly unselected series. Acta neurologica Scandinavica. 1994;90(4):245-250.	Blood pressure measurement taken before hospital admission
Savla 2022	Savla P, Marino MA, Marotta DA, et al. Magnesium Levels and Diastolic Blood Pressure (DBP) as a Vasospasm Prediction Metric in Patients With Aneurysmal Subarachnoid Hemorrhage (SAH). Cureus. 2022;14(3):e23161. doi:10.7759/cureus.23161	Blood pressure measurement after 72 hours
Schneck 1964	Schneck S.A. On the relationship between ruptured intracranial aneurysm and cerebral infarction. Neurology. 1964;14(1-8):691-702.	Does not explore a potential association between blood pressure and outcomes
Sebastian 2011	Sebastian J., Derksen C., Khan K., et al. Demographic, clinical and transcranial doppler parameters for predicting clinical and angiographic cerebral vasospasm in aneurysmal subarachnoid hemorrhage patients. Journal of Neuroimaging. 2011;21(1):100. doi:10.1111/j.1552-6569.2010.00558.x	Conference abstract
Shi 2017	Shi JK, Yuan XC, Sun J, Liu DH. Adiponectin Single Nucleotide Polymorphisms and Serum Levels Are Relevant to Prognosis of Patients With Aneurysmal Subarachnoid Hemorrhages. American journal of therapeutics. 2017;24(3):e308-e316. doi:10.1097/MJT.0000000000000437	Blood pressure measurement taken before hospital admission
Silverman 2019	Silverman A, Kodali S, Strander S, et al. Deviation From Personalized Blood Pressure Targets Is Associated With Worse Outcome After Subarachnoid Hemorrhage. Stroke. 2019;50(10):2729-2737. doi:10.1161/STROKEAHA.119.026282	Does not explore a potential association between blood pressure and outcomes

Simonato 2022	Simonato D, Gaugain S, Le Dorze M, et al. Early Cerebral Infarction After Aneurysmal Subarachnoid Hemorrhage Is Associated with Prior Global Cerebral Hypoperfusion. World neurosurgery. 2022;168(101528275):e546-e554. doi:10.1016/j.wneu.2022.10.022	Does not explore a potential association between blood pressure and outcomes
Soehle 2008	Soehle M, Czosnyka M, Chatfield DA, Hoeft A, Pena A. Variability and fractal analysis of middle cerebral artery blood flow velocity and arterial blood pressure in subarachnoid hemorrhage. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2008;28(1):64-73.	Blood pressure measurement taken after aneurysm secured
Solar 2020	Solar P, Klusakova I, Jancalek R, Dubovy P, Joukal M. Subarachnoid Hemorrhage Induces Dynamic Immune Cell Reactions in the Choroid Plexus. Frontiers in cellular neuroscience. 2020;14(101477935):18. doi:10.3389/fncel.2020.00018	Animal study
Sui 2022	Sui J, Wang N, Jiang P, et al. Validation of the predictive accuracy of "clinical + morphology nomogram" for the rebleeding risk of ruptured intracranial aneurysms after admission. Chinese neurosurgical journal. 2022;8(1):5. doi:10.1186/s41016-022-00274-4	hypertension not defined
SvedungWettervik 2022	Svedung Wettervik T, Hanell A, Howells T, Ronne-Engstrom E, Lewen A, Enblad P. Intracranial pressure- and cerebral perfusion pressure threshold-insults in relation to cerebral energy metabolism in aneurysmal subarachnoid hemorrhage. Acta neurochirurgica. 2022;164(4):1001-1014. doi:10.1007/s00701-022-05169-y	Does not explore a potential association between blood pressure and outcomes
SwissSOSStudyGrp 2018	Swiss SOS Study Grp, Stienen M, Germans M, et al. Predictors of In-Hospital Death After Aneurysmal Subarachnoid Hemorrhage: Analysis of a Nationwide Database (Swiss SOS [Swiss Study on Aneurysmal Subarachnoid Hemorrhage]). STROKE. 2018;49(2):333-340. doi:10.1161/STROKEAHA.117.019328	Does not explore a potential association between blood pressure and outcomes
Tabuchi 2006	Tabuchi S, Hirano N, Tanabe M, et al. Relationship of hypotension and cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage. Neurological research. 2006;28(2):196-199.	Blood pressure measurement after 72 hours
Tanno 2007	Tanno Y, Homma M, Oinuma M, Kodama N, Ymamoto T. Rebleeding from ruptured intracranial aneurysms in North Eastern Province of Japan. A cooperative study. Journal of the neurological sciences. 2007;258(1-2):11-16.	Case series
Tappura 1962	Tappura M. Prognosis of subarachnoid haemorrhage. a study of 120 patients with unoperated intracranial arterial aneurysms and 267 patients without vascular lesions demonstrable in bilateral carotid angiograms. Acta medica Scandinavica. 1962;173(SUPPL. 392):85-91.	Does not explore a potential association between blood pressure and outcomes
Tewari 2015	Tewari M, Aggarwal A, Mathuriya S, Gupta V. The outcome after aneurysmal sub arachnoid hemorrhage: a study of various factors. Annals of neurosciences. 2015;22(2):78-80. doi:10.5214/ans.0972.7531.220205	Blood pressure measurement taken before hospital admission
Thongrong 2020	Thongrong C, Kasemsiri P, Duangthongphon P, Kitkhuandee A. Appropriate Blood Pressure in Cerebral Aneurysm Clipping for Prevention of Delayed Ischemic Neurologic Deficits. Anesthesiology research and practice. 2020;2020(101532982):6539456. doi:10.1155/2020/6539456	intraoperative blood pressure only

Togashi 2015	Togashi K, Joffe AM, Sekhar L, et al. Randomized pilot trial of intensive management of blood pressure or volume expansion in subarachnoid hemorrhage (IMPROVES). Neurosurgery. 2015;76(2):125-135. doi:10.1227/NEU.0000000000000592	Blood pressure measurement taken after aneurysm secured
Tommasino 2018	Tommasino N, Saravia M, Rodriguez A, Mizraji R. Epidemiologic and Evolutionary Profile of Patients With Subarachnoid Hemorrhage With Glasgow Coma Scale Score of 8 or Less Who Entered the Follow-Up Program of the National Institute of Donation and Transplantation. Transplantation proceedings. 2018;50(2):405-407. doi:10.1016/j.transproceed.2017.12.047	hypertension not defined
Torner 1981	Torner J.C., Kassell N.F., Wallace R.B., Adams Jr. H.P. Preoperative prognostic factors for rebleeding and survival in aneurysm patients receiving antifibrinolytic therapy: Report of the cooperative aneurysm study. Neurosurgery. 1981;9(5):506-513.	>72 hours from from admission to securing aneurysm
Urciuoli 1984	Urciuoli R, Liboni W, Lo Russo G, Pisani R, De Mattei M. [Endocranial biophysical parameters (intracranial pressure, flow velocity, blood pressure, cerebral perfusion pressure) in the complications of subarachnoid hemorrhage]. Agressologie: revue internationale de physio-biologie et de pharmacologie appliquees aux effets de l'agression. 1984;25(6):679-682.	Case series
Uzunkaya 2021	Uzunkaya F, Idil Soylu A. Predictors of full functional recovery in endovascularly treated patients with aneurysmal subarachnoid hemorrhage. Turkish journal of medical sciences. 2021;51(4):2000-2006. doi:10.3906/sag-2103-3	Blood pressure measurement taken before hospital admission
vanDonkelaar 2015	van Donkelaar C, Bakker N, Veeger N, et al. Predictive Factors for Rebleeding After Aneurysmal Subarachnoid Hemorrhage Rebleeding Aneurysmal Subarachnoid Hemorrhage Study. STROKE. 2015;46(8):2100-2106. doi:10.1161/STROKEAHA.115.010037	Blood pressure measurement taken before hospital admission
VanKessel 2011	Van Kessel M.A., Heijenbrok-Kal M.H., Verhagen A.P., Van Kooten F., Stam H.J., Ribbers G.M. Long-term functional outcome after subarachnoid hemorrhage: A systematic review on prognostic determinants. Cerebrovascular Diseases. 2011;31(SUPPL. 2):182. doi:10.1159/000329448	Conference abstract
Varelas 2010	Varelas PN, Abdelhak T, Wellwood J, et al. Nicardipine infusion for blood pressure control in patients with subarachnoid hemorrhage. Neurocritical care. 2010;13(2):190-198. doi:10.1007/s12028-010-9393-7	Does not explore a potential association between blood pressure and outcomes
Vidal 2016	Vidal A, Perez M, Juez A, et al. Have SAH prognostic factors changed in the era of endovascular intervention? 2016;4(no pagination). doi:10.1186/s40635-016-0100-7	Conference abstract
Vitosevic 2022	Vitosevic F, Milosevic Medenica S, Kalousek V, et al. CLINICAL CHARACTERISTICS AND MORPHOLOGICAL PARAMETERS ASSOCIATED WITH RUPTURE OF ANTERIOR COMMUNICATING ARTERY ANEURYSMS. Acta clinica Croatica. 2022;61(2):284-294. doi:10.20471/acc.2022.61.02.15	Incorrect outcomes
Wang 2023	Bang-Yue Wang, Chao Peng, Hong-Sheng Jiang, Zhong-Hong Yang, Yan Zhao, Yun-Fei Song, Jian Li, Yi-Fan Yang, Zhen Wang, Heng-Rui Zhang, Zhuo-Lin Wu, Jian-Zhong Cui, Xin-Yu Yang, Fu-Guang Hu, The survival and outcome of older patients with primary aneurysmal subarachnoid haemorrhage: a	Blood pressure measurement taken before hospital admission

	2-year follow-up, multi-centre, observational study, *Age and Ageing*, Volume 52, Issue 11, November 2023, afad202, https://doi.org/10.1093/ageing/afad202	
Wang 2023	Wang J, Li R, Li S, et al. Intraoperative arterial pressure and delayed cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage after surgical clipping: A retrospective cohort study. Frontiers in neuroscience. 2023;17(101478481):1064987. doi:10.3389/fnins.2023.1064987	intraoperative blood pressure only
Wang 2011	Wang T, Zhang JH, Qin X. Analysis on death-associated factors of patients with subarachnoid hemorrhage during hospitalization. Acta neurochirurgica Supplement. 2011;110(Pt 1):219-223. doi:10.1007/978-3-7091-0353-1_38	Blood pressure measurement taken before hospital admission
Wartenberg 2006	Wartenberg KE, Schmidt JM, Claassen J, et al. Impact of medical complications on outcome after subarachnoid hemorrhage. Critical care medicine. 2006;34(3):617-624.	Blood pressure measurement after 72 hours
Weir 1975	Weir B, Rothberg C, Grace M, Davis F. Relative prognostic significance of vasospasm following subarachnoid hemorrhage. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques. 1975;2(2):109-114.	Incorrect outcomes
Wijdicks 1990	Wijdicks EF, Vermeulen M, Murray GD, Hijdra A, van Gijn J. The effects of treating hypertension following aneurysmal subarachnoid hemorrhage. Clinical neurology and neurosurgery. 1990;92(2):111-117.	>72 hours from from admission to securing aneurysm
Winn 1982	Winn HR, Richardson AE, Jane JA. The late morbidity and mortality in ruptured single anterior circulation aneurysms treated by non-surgical therapy. Acta neurochirurgica. 1982;63(1-4):71-81.	Does not explore a potential association between blood pressure and outcomes
Yang 2023	Yang Y, He K, Liu L, et al. Risk Factors for Cerebral Infarction After Microsurgical Clipping of Hunt-Hess Grade 0-2 Single Intracranial Aneurysm: A Retrospective Study. World neurosurgery. 2023;171(101528275):e186-e194. doi:10.1016/j.wneu.2022.11.124	Blood pressure measurement taken before hospital admission
Yao 2017	Yao PS, Chen GR, Zheng SF, Kang DZ. Predictors of Postoperative Cerebral Ischemia in Patients with Ruptured Anterior Communicating Artery Aneurysms. World neurosurgery. 2017;103(101528275):241-247. doi:10.1016/j.wneu.2017.04.007	Blood pressure measurement taken before hospital admission
Yarlagadda 2006	Yarlagadda S, Rajendran P, Miss JC, et al. Cardiovascular predictors of in-patient mortality after subarachnoid hemorrhage. Neurocritical care. 2006;5(2):102-107.	Blood pressure measurement after 72 hours
Yin 2011	Yin L, Ma CY, Li ZK, Wang DD, Bai CM. Predictors analysis of symptomatic cerebral vasospasm after subarachnoid hemorrhage. Acta neurochirurgica Supplement. 2011;110(Pt 2):175-178. doi:10.1007/978-3-7091-0356-2_32	Blood pressure measurement taken before hospital admission
Yoshikawa 2022	Yoshikawa MH, Rabelo NN, Telles JPM, et al. Microsurgery versus embolization: different risk factors for short- and longterm outcomes of patients with ruptured aneurysms. Acta cirurgica brasileira. 2022;37(8):e370806. doi:10.1590/acb370806	Blood pressure measurement taken before hospital admission

Yousef 2015	Yousef KM, Balzer JR, Bender CM, et al. Temporal Profiles of Cerebral Perfusion Pressure After Subarachnoid Hemorrhage. The Journal of neuroscience nursing : journal of the American Association of Neuroscience Nurses. 2015;47(4):E2-9. doi:10.1097/JNN.0000000000000145	Does not explore a potential association between blood pressure and outcomes
Yu 2019	Yu Z., Zheng J., Ma L., You C., Hao L. Prediction of rebleeding after aneurysmal subarachnoid hemorrhage. Journal of Neurosurgery. 2019;131(5):1679-1680. doi:10.3171/2018.12.JNS183460	Letter to Editor
Yue 2016	Yue Q, Liu Y, Leng B, et al. A Prognostic Model for Early Post-Treatment Outcome of Elderly Patients With Aneurysmal Subarachnoid Hemorrhage. World neurosurgery. 2016;95(101528275):253-261. doi:10.1016/j.wneu.2016.08.020	Blood pressure measurement taken before hospital admission
Zafar 2018	Zafar SF, Postma EN, Biswal S, et al. Electronic Health Data Predict Outcomes After Aneurysmal Subarachnoid Hemorrhage. Neurocritical care. 2018;28(2):184-193. doi:10.1007/s12028-017-0466-8	Blood pressure not measured
Zhang 2023	Zhang Y, Zeng H, Zhou H, Li J, Wang T, Guo Y, Cai L, Hu J, Zhang X, Chen G. Predicting the Outcome of Patients with Aneurysmal Subarachnoid Hemorrhage: A Machine-Learning-Guided Scorecard. *Journal of Clinical Medicine*. 2023; 12(22):7040. https://doi.org/10.3390/jcm12227040	Blood pressure measurement taken before hospital admission
Zhang 2017	Zhang F, Li P, Zhang C, Wang L, Jing SQ. The Prognosis Factors for Endovascular Coiling of Aneurysm in Patients With Ruptured Intracranial Aneurysm. The Journal of craniofacial surgery. 2017;28(6):e535-e539. doi:10.1097/SCS.0000000000003818	Blood pressure measurement taken before hospital admission
Zhang 2021	Zhang J, Lo YL, Li MC, Yu YH, Wu SY. Risk of Re-Rupture, Vasospasm, or Re-Stroke after Clipping or Coiling of Ruptured Intracranial Aneurysms: Long-Term Follow-Up with a Propensity Score-Matched, Population-Based Cohort Study. Journal of personalized medicine. 2021;11(11). doi:10.3390/jpm11111209	Does not explore a potential association between blood pressure and outcomes
Zhao 2022	Zhao J, Zhang S, Ma J, Shi G, Zhou J. Admission rate-pressure product as an early predictor for in-hospital mortality after aneurysmal subarachnoid hemorrhage. Neurosurgical review. 2022;45(4):2811-2822. doi:10.1007/s10143-022-01795-3	Does not explore a potential association between blood pressure and outcomes
Zheng 2019	Zheng J, Xu R, Guo Z, Sun X. Small ruptured intracranial aneurysms: the risk of massive bleeding and rebleeding. Neurological research. 2019;41(4):312-318. doi:10.1080/01616412.2018.1563737	Blood pressure measurement taken before hospital admission
Zhou 2023	Zhou X, Bates AH, Mahajan UV, et al. Racial differences in time to blood pressure control of aneurysmal subarachnoid hemorrhage patients: A single-institution study. PloS one. 2023;18(2):e0279769. doi:10.1371/journal.pone.0279769	Blood pressure is an outcome variable
Zorin 2021	Zorin M, Kazantseva V. [PREDICTORS OF RE-BLEEDING IN THE ACUTE PERIOD OF RUPTURE OF CEREBRAL ARTERIAL ANEURYSMS]. Georgian medical news. 2021;(320):120-126.	Language other than English or French

Appendix 7: Description of Included Studies Reporting the Primary Outcome (n = 15)

First author, Year	Study country	Study design	Enrollment years	Overall sample size	# of rebleeds	Overall rate of rebleeding	Mean age (years)	Sex (% female)
Calviere 2022	France, The Netherlands	Retrospective cohort	Site 1: 2013-2015 Site 2: 2009-2014	522	33	6.3%	Site 1: 54[a] Site 2: 57.6[a]	Site 1: 62.4%[a] Site 2: 71.3%[a]
Cong 2012	China	Retrospective cohort	2005-2008	458	63	13.8%	Rebleed: 55[b] Non-rebleed: 53[b]	Rebleed: 49.2% Non-rebleed: 62.8%
Darkwah Oppong 2018	Germany	Retrospective cohort	2003-2016	984	58	5.9%	Rebleed: 58.9 Non-rebleed: 54.5	Rebleed: 65.5% Non-rebleed: 67.0%
Fujii 1996	Japan	Retrospective cohort	1990-1994	179	31	17.3%	NR	Rebleed: 64.5% Non-rebleed: NR
Gathier 2022	The Netherlands	Retrospective cohort	2003-2011	1167	45	3.9%	Total sample: 56 Site 1: 55 Site 2: 57	Total Sample: 69% Site 1: 69% Site 2: 69%
Guo 2011	China	Retrospective cohort	2002-2010	326	70	21.5%	Rebleed: 58.2 Non-rebleed: 52.07	Rebleed: 55.7% Non-rebleed: 61.3%
Haripottawekul 2024	USA	Retrospective cohort	2016-2023	324	34	10.5%	Rebleed: 59.1 Non-rebleed: 56.8	Rebleed: 55% Non-rebleed: 64%
He 2019	China	Retrospective cohort	2016-2019	245	35	14.3%	Rebleed: 56.7 Non-rebleed: 55.0	Rebleed: 65.7% Non-rebleed: 68.1%
Inagawa 1987	Japan	Retrospective cohort	1980-1986	150	33	22.0%	Total sample: 41% over 60 years[c]	Total sample: 54.7%[c]
Lin 2016	China	Case control	2010-2015	612	61	10.0%	Rebleed: 55.3 Non-rebleed: 52.1	Rebleed: 55.3% Non-rebleed: 59.2%

First author, Year	Study country	Study design	Enrollment years	Overall sample size	# of rebleeds	Overall rate of rebleeding	Mean age (years)	Sex (% female)
Liu 2021	China	Retrospective cohort	2018-2020	411	70	17.0%	Rebleed: 54.0 Non-rebleed: 54.8	Rebleed: 54.3% Non-rebleed: 62.2%
Oheda 2015	Japan	Retrospective cohort	2008-2013	309	24	7.8%	Rebleed: 55 Non-rebleed: NR Total sample: 62.2	Rebleed: 54.2% Non-rebleed: NR Total sample: 69.6%
Ohkuma 2001	Japan	Prospective cohort	1989-1998	273	37	13.6%	Rebleed: 61.2 Non-rebleed: 58.6	Rebleed: 54.1% Non-rebleed: 69.1%
Solanki 2016	India	Case control	2010-2014	199	99	N/A[d]	Rebleed: 47.75 Non-rebleed: 47.72	Rebleed: 57.6% Non-rebleed: 60%
Van Lieshout 2022	Germany, The Netherlands	Retrospective cohort	1998-2020	2075	269	7.7%	Total sample: 55.0	Total sample: 66.3%

Abbreviations: **N/A**: not applicable; **NR:** not reported

[a] Data reported by study site, not by rebleed group versus non-rebleed group

[b] Median age

[c] Data reported for total sample, not by rebleed group versus non-rebleed group

[d] 99 rebleed cases matched with 100 controls

Appendix 8: Results of Individual Studies – Primary Outcome (n = 15)

	Blood pressure (BP)		Rebleeding		Reported results			
First author, Year	BP measured	BP categories used	Follow-up period	Rebleed rates by BP group	Unadjusted results	MV model with BP	Key confounders included in model	Adjusted results
Calviere 2022	SBP	Continuous	24h after admission	Site 1: 4/149[a] Site 2: 29/373[a]	HR 0.35 (95% CI: 0.12-0.99)	Yes	Age, Size, Clinical grade	HR 0.66 (95% CI: 0.23-1.92)
Cong 2012	SBP	≤140 >140	30 days after admission	≤140: 31/284 >140: 32/174	p=0.026	Yes	Sex, Clinical grade, ICH/IVH	NS (p=0.089) NR
Darkwah Oppong 2018	SBP	Max SBP > 182[b]	During hospital admission	**Max SBP > 182[c]** Rebleed: 23.08% Non-rebleed: 17.89%	OR 1.38 (95% CI: 0.7-2.69); p=0.35	No	-	-
Fujii 1996	SBP	0-150 150-200 >200	24h after admission	0-150: 11/78 150-200: 10/83 >200: 10/18	p<0.05	Yes	Clinical grade, ICH/IVH	OR 1.41 (95% CI: 0.68-2.91) p=0.354
Gathier 2022	SBP MAP	SBP: 120, 140, 160, 180 MAP: 60-160 in 10 mmHg increments Note: we only present a portion of the data	ICU admission	NR	NR	Yes	Age, Sex, Location, Clinical grade, Radiologic grade	highest SBP or MAP < 6h prior to rebleeding: **SBP** 140: aHR 0.89 (0.72-1.10) 160: aHR 1.10 (0.93-1.31) 180: aHR 1.21 (0.84-1.73) **MAP** 80: aHR 0.27 (0.10-0.73)
Guo 2011	SBP	≤160 >160	72h from initial SAH	≤160: 26/217 >160: 44/109	p=0.002	Yes	Age, Size, Clinical grade	OR 3.338 (95% CI: 1.734-7.737) p<0.001
Haripottawekul 2024	SBP MAP	Continuous	24 hours after aneurysm secured	NR	**Max MAP**	Yes	Clinical grade (others = not described)	**Max MAP** NS NR

	Blood pressure (BP)		Rebleeding		Reported results			
First author, Year	BP measured	BP categories used	Follow-up period	Rebleed rates by BP group	Unadjusted results	MV model with BP	Key confounders included in model	Adjusted results
	DBP				OR 1.01 (95% CI: 1.00-1.03); p = 0.001 **Max SBP** OR 1.00 (95% CI: 0.99-1.01); p=0.06 **Max DBP** NR			**Max SBP** NS NR **Max DBP** NR
He 2019	SBP DBP	Continuous	Until coiling or clipping	**SBP**[d] Rebleed: 159.8 ± 34.8 Non-rebleed: 143.5 ± 22.8 **DBP**[d] Rebleed: 90.2±18.1 Non-rebleed: 83.4 ± 13.3	**SBP** p=0.011 **DBP** p=0.008	Yes	Clinical grade, ICH/IVH	**SBP** OR 1.020 (95% CI: 1.000-1.041) p=0.050 **DBP** OR 1.002 (95% CI: 0.967-1.038) p=0.910
Inagawa 1987	SBP DBP	**SBP** ≤139 140-179 ≥180 **DBP** ≤99 ≥100	2 weeks or until death or operation	**SBP** ≤139: 8/30 140-179: 15/61 ≥180: 7/53 **DBP** ≤99: 15/65 ≥100: 13/68	NS[e]	No	-	-
Lin 2016	SBP SBPV-SD	Continuous	Within 3 days of ictus	**Mean SBP**[d] Rebleed: 137.2±20.9 Non-rebleed: 132.1±18.	**Mean SBP** p=0.423 **SBPV-SD**	Yes (SBPV-SD and SBPV-SV)	Size, Clinical grade	**SBPV-SD** OR 1.254 (95% CI: 1.131-1.391) p<0.001 **SBPV-SV**

	Blood pressure (BP)		Rebleeding		Reported results			
First author, Year	BP measured	BP categories used	Follow-up period	Rebleed rates by BP group	Unadjusted results	MV model with BP	Key confounders included in model	Adjusted results
	SBPV-SV			**SBPV-SD[d]** Rebleed: 14.3±2.9 Non-rebleed: 10.9±3.4 **SBPV-SV[d]** Rebleed: 16.9±3.8 Non-rebleed: 13.7±4.2	p<0.001 **SBPV-SV** p<0.001			OR 1.131 (95% CI: 1.039-1.231) p=0.0.004
Liu 2021	SBP and DBP combined	**Admission** BP > 160/90 **Before event** BP > 140/80	During hospital admission	**Admission** <160/90: 21/135 >160/90: 49/276 **Before event** <140/80: 64/375 >140/80: 6/36	**Admission** P=0.578 **Before event** P=0.951	No	-	-
Oheda 2015	SBP	≤140 >140	ED arrival to aneurysm obliteration	≤140: 10/70 >140: 14/239	p=0.04	No	-	-
Ohkuma 2001	SBP	≥120 ≥140 ≥160 ≥180 ≥200	24h from initial SAH	≥120: 35/256 ≥140: 31/199 ≥160: 26/126 ≥180: 20/61 ≥200: 6/11	≥120: OR 1.2 (95% CI: 0.3-5.4) p>0.9999 ≥140: OR 2.1 (95% CI: 0.8-5.2) p=0.1090 ≥160: OR 3.1 (95% CI: 1.5-6.8) p=0.0016 ≥180: OR 5.6 (95% CI: 2.7-11.6) p<0.0001 ≥200: OR 8.9 (95% CI: 2.6-31.0) p=0.0012	No	-	-

	Blood pressure (BP)		Rebleeding		Reported results			
First author, Year	BP measured	BP categories used	Follow-up period	Rebleed rates by BP group	Unadjusted results	MV model with BP	Key confounders included in model	Adjusted results
Solanki 2016	SBP DBP	SBP ≥ 160 DBP ≥ 90	3 years	**SBP** <160: 73/169 ≥160: 26/30 **DBP** <90: 73/169 ≥90: 65/104	**SBP** p<0.0001 **DBP** p=0.00016	Yes	Age, Sex, Clinical grade, Size, Location, ICH/IVH	**SBP** NS NR **DBP** OR 0.906 (95% CI: 0.842-0.975) p=0.008
Van Lieshout 2022	SBP	SBP > 160	72h[g]	NR	NR	Yes	Age, Sex, Clinical grade, Radiologic grade, Size	HR = 1.22 (0.91 1.63) p=0.187

Abbreviations: **BP:** blood pressure; **CI:** confidence interval; **DBP:** diastolic blood pressure; **ED:** Emergency Department; **ICH:** intracerebral hemorrhage; **IVH:** intraventricular hemorrhage; **MV:** multivariate; **NS:** not significant; **NR:** not reported; **OR:** odds ratio; **SAH:** subarachnoid hemorrhage; **SBP:** systolic blood pressure; **SBPV-SD:** systolic blood pressure variability standard deviation; **SBPV-SV:** systolic blood pressure variability successive variation.

[a] Group 1: applied a strict BP management protocol targeting SBP ≤140 mmHg; Group 2: elevated BP typically not treated unless above 180-200 mmHg.
[b] 182 mmHg cutpoint used based on ROC curve.
[c] Study data presented as percentages, rather than counts
[d] Blood pressure presented as continuous data by rebleed versus non-rebleed group.
[e] No p value reported.
[f] Data entered in this table as presented in published study. However, the reported rebleeding cases in the two DBP blood pressure categories are greater than the total 99 rebleeding cases in the study. DBP data is presumed incorrect.
[g] Exact timing not clearly reported

Appendix 9: Description Of Included Studies Reporting Secondary Outcomes (n = 31)

First author, Year	Study country	Study design	Enrollment years	Sample size (n)	Outcome	# of events (n)	Rate of outcome (%)	Mean age +/- SD (years)	Sex (% female)	Admission Clinical Grade (WFNS or H&H 4-5)
Aldakkan 2017	Canada	Retrospective cohort	Not described	191	Clinical DCI	78	40.8%	51.3 +/- 11.6	84.4%	NR
Al-Mistarehi 2022	Sudan	Prospective cohort	2013	40	Mortality at 3 weeks	16	40.0%	53.46+/-6.93	62.5%	NR
Ascanio 2020	USA	Retrospective cohort	2007-2016	202	Dichotomized mRS at last follow-up:	57	28.9%	Good: 54.1 +/- 12.7 Poor: 63.3 +/- 16.0	Good: 66.2% Poor: 66.7%	Good: 27 (18.6%) Poor: 39 (68.4%)
Cai 2018	China	Retrospective cohort	2011-2014	345	Dichotomized GOS at hospital discharge	35	10.1%	57.4 +/- 11.2	66.1%	37/345 (10.7%)
Cai 2017	China	Retrospective cohort	2011-2016	67	1) Dichotomized mRS at discharge and 6 months 2) Mortality at 6 months	29	43.2%	57.2 +/- 12	58.2%	100%
Calviere 2022	France and the Netherlands	Retrospective cohort	2009-2015	522 T: 149 U: 373	Clinical deterioration due to DCI	T: 27 (18%) U: 93 (25%) Total: 120	23.0%	T: 54 +/- 14.8 U: 7.6 +/- 12.8	T: 62% U: 71.3%	T: 30/149 (20.1%)[a] U: 107/373 (28.7%)[a]
Cha 2010	South Korea	Retrospective cohort	1995-2007	35	Dichotomized GOS at 6 months	21	60%	52.5 +/- 11.3	48.6%	Good: 0/14 (0%) Poor: 1/21 (4.8%)
Claassen 2004	USA	Prospective cohort	1996-2002	413	Dichotomized mRS at 3 months	167	40.4%	54 +/- 15 years	71.0%	139 (33.7%)
Dowlati 2021	USA	Retrospective cohort	2017-2019	174	Poor disposition at discharge	45	25.9%	55.0 +/- 15.9	41.3%	43/174 (25.3%)

First author, Year	Study country	Study design	Enrollment years	Sample size (n)	Outcome	# of events (n)	Rate of outcome (%)	Mean age +/- SD (years)	Sex (% female)	Admission Clinical Grade (WFNS or H&H 4-5)
Duran 2013	Turkey	Retrospective cohort	2009-2012	200	Hospital mortality	90	45%	57.0 +/- 14.9	58.0%	61/200 (30.5%)
Eagles 2020	Canada	Retrospective cohort	2005-2006	301	mRS >2 at 12 weeks post SAH	67	22.2%	51 (44,59)[b]	70.1%	0/301 (0%)
Faust 2014	Gemany	Retrospective cohort	Not described	98	Vasospasm (Angiographic)	50	51.0%	VS+: 52+/-12 VS-: 21+/-11	VS+: 62.0% VS-: 71%	VS+: 10/50 (20%) VS-: 17/48 (35.4%)
Ferguson 2007	Canada	Retrospective cohort	1991-1997	2741	Cerebral infarction	707	25.8%	Infarction: 53+/-13 No Infarction: 51 +/-13	Infarction: 74.7% No Infarction: 82.8%	Infarction: 27.3% No Infarction: 16.4%
Gathier 2022	The Netherlands	Retrospective cohort	2003-2011	1167	DCI during ICU stay	110	9%	56 +/- 13	68.9%	567 (49%)
Haripottawekul 2024	USA	Retrospective cohort	2016-2023	324	Dichotomized mRS (poor=4-6) 3 months from discharge	124	38.3%	Fav: 55.6+/-12.7 Poor :59.7+/-14.7	Fav: 58% Poor: 69%	Fav: 27 (14%) Poor: 79 (64%)
Inamasu 2015	Japan	Retrospective cohort	2008-2013	312	Dichotomized mRS 30 days post admission	NR	1. <140: 30% 2. 140-180: 26% 3. 185-219: 35% 4. ≥220: 54%	62.7 +/- 14.1	68.9%	NR
Kelly 2022	USA	Retrospective cohort	2000-2020	528	Vasospasm	309	58.5%	55 (45, 64)[b]	68.6%	172 (32%)
Khan 2022	Qatar	Retrospective cohort	2007-2016	259	Vasospasm	87	37%	VS+: 48 +/- 13 VS-: 46 +/- 12	VS+: 31.7% VS-: 68.3%	VS+: 31/87 (35.6%) VS-: 37/172 (21.5%)

First author, Year	Study country	Study design	Enrollment years	Sample size (n)	Outcome	# of events (n)	Rate of outcome (%)	Mean age +/- SD (years)	Sex (% female)	Admission Clinical Grade (WFNS or H&H 4-5)
Lantigua 2015	USA	Retrospective cohort	1996-2009	1200	Hospital mortality	216	18%	55 +/- 15	67.3%	353/1200 (29.4%)
Liu 2020	China	Retrospective cohort	2013-2019	887	DCI	224	25.3%	NR	63.4%	123/887 (13.9%)
Liu 2023	China	Retrospective cohort	2014-2022	1169	Dichotomized GOS at D/C	406	34.7%	53[b]	56.5%	NR
MacDonald 2003	USA	Retrospective cohort	1991-1997	3567	Vasospasm (symptomatic)	NR	30%	52 +/- 14	83%	23%
Nastasovic 2019	Serbia	Retrospective cohort	2009-2014	262	Dichotomized GOS at 3 months	156	156	Unfav: 54.37 +/- 10.56 Fav: 49.13 +/- 10.77	Unfav: 63.5% Fav: 59.4%	Unfav = 129 (82.7%)[c] Fav = 42 (39.6%)[c]
Roederer 2014	USA	Retrospective cohort	2001-2011	81	Vasospasm (angiographic, treated with IA vasodilators)	35	43.2%	VS+: 56.4 +/- 14.4 VS-: 50.8 +/- 9.3	VS+: 76.1% VS-: 62.9%	VS+: 27/46 (58.7%) VS-: 14/35 (40.0%)
Rosengart 2007	Canada and USA	Retrospective cohort	1991-1997	2695	Dichotomized GOS at 3 months	666	24.7%	NR	82.3%	521/2695 (19.3%)
Sirataranon 2022	Thailand	Retrospective cohort	2013-2018	457	Dichotomized mRS at 1 year	121	26.5%	54.5	60.2%	152/457 (33.3%)
Soehle 2007	UK	Prospective cohort	Not described	29	Dichotomized GOS at 1 year	19	66%	51 +/- 13	58.6%	12/29 (41%)
Stulberg 2023	USA	Retrospective cohort	2001-2012	504	1. Hospital mortality 2. Favorable Discharge disposition	NR	NR	NR	NR	NR
Teping 2018	Germany	Retrospective cohort	2011-2014	115	1. GOS at 3 months 2. GOS at discharge 3. Clinical DCI	1. NR 2. NR 3. 54	1. N/A 2. N/A 3. 47.0%	54.7 +/- 13.0	80.0%	38/115 (33%)

First author, Year	Study country	Study design	Enrollment years	Sample size (n)	Outcome	# of events (n)	Rate of outcome (%)	Mean age +/- SD (years)	Sex (% female)	Admission Clinical Grade (WFNS or H&H 4-5)
					4. Functional DCI 5. Cerebral infarction	4. 52 5. 38	4. 45.2% 5. 33.0%			
Witiw 2013	Canada	Retropsective cohort	2005-2006	413	ICU LOS	N/A	N/A	51.0 +/- 10.8	70.0%	100 (24.2%)
Yan 2021	China	Prospective cohort	2017-2018	1577	Dichotomized mRS at 6 months	216	13.7%	56.7 +/- 13.5	60.9%	NR
Yang 2019	China	Retrospective cohort	2015-2018	303	Dichotomized GOS at discharge	124	41%	57.0 +/- 12.5	48.8%	85/303 (28.1%)
Zhang 2011	China	Prospective cohort	2003-2005	156	Dichotomized mRS at discharge	19	12.2%	52.9 +/- 12.1	57.7%	NR
Zhou 2023	China	Retrospective cohort	2014-2015	1420	Hospital mortality	201	14.2%	≥ 65 years: 40.4%	46.2%	NR

Abbreviations: **DCI**: delayed cerebral ischemia; **Fav**: favourable; **GOS**: Glasgow outcome score; **HH**: Hunt and Hess; **ICU**: intensive care unit; **LOS**: length of stay; **mRS**: modified Rankin scale; **N/A**: not applicable; **NR**: not reported; **PAASH**: Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage; **T**: Toulouse; **U**: Utrecht; **VS**: vasospasm; **WFNS**: World Federation of Neurological Societies;

[a] Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage (PAASH) score used
[b] Median (IQR)
[c] Reported HH 3-5

Appendix 10: Results Of Individual Studies – Secondary Outcomes (n = 31)

Appendix 10A: Mortality

	Blood pressure (BP)		Mortality		Reported results			
First author, Year	BP measurement and timing	BP categories used	Follow-up period	Mortality rates by BP group	Unadjusted results	MV model with BP	Key confounders included in model	Adjusted results
Al-Mistarehi 2022	SBP single admission value	SBP > 140	3 weeks from admission	Survived: 10/24 (41.6%) had high BP Died: 15/16 (93.8%) had high BP P<0.001	52.2% mean difference P<0.001	No	-	-
Cai 2017	SBP over 24h post coiling	1) continuous 2) Mean SBP 120-140 3) SBPV-SV	6 months	-	SBP-SV: HR 1.07 (95% CI: 1.02-1.12) p=0.003 MSBP120-140: HR 0.25 (95% CI: 0.06-1.11) p=0.068	Yes	Age, Clinical grade, Radiologic grade	SBP-SV: HR 1.10 (95% CI: 1.04-1.17) p=0.001
Duran 2013	MAP highest value from first 6 hourly readings at admission	Continuous	In Hospital	-	Survivors MAP: 106.4+/-15.3 Non-survivors MAP: 102.3 +/-16.4 P=0.026	No	-	-
Lantigua 2015	SBP single admission value	Continuous	In Hospital	Survivors SBP: 154 (132–178)[a] Died SBP: 164 (131–196)[a] P= 0.003	Difference in group medians of 10 mmHg P=0.003	Unclear	-	NR
Stulberg 2023	SBP variability First 72 from admission	Continuous	In Hospital	NR	NR	Yes	Age, Sex	SBP variability: OR 3.6 (95% CI: 1.2-10.5) p=0.02

	Blood pressure (BP)		Mortality		Reported results			
First author, Year	BP measurement and timing	BP categories used	Follow-up period	Mortality rates by BP group	Unadjusted results	MV model with BP	Key confounders included in model	Adjusted results
Zhou 2023	MAP Admission	Quartiles: <82 82-93 93-103 >103	In Hospital	<82: 66 (18.9%) 82-93: 33 (9.2%) 93-103: 32 (8.7%) >103: 70 (20.2%) P<0.001	<82: HR 2.17 (95% CI: 1.43-3.30) p<0.001 82-93: Reference 93-103: HR 1.01 (95% CI: 0.62-1.64) p=0.975 >103: HR 2.34 (95% CI: 1.54-3.53) p<0.001	Yes	Age	<82: HR 1.67 (95% CI: 1.08-2.57) p<0.021 82-93: Reference 93-103: HR 1.16 (95% CI: 0.70-1.92) p=0.557 >103: HR 2.13 (95% CI: 1.38-3.29) p<0.001

Abbreviations: **BP**: blood pressure; **CI**: confidence interval; **HR**: haard ratio; **MAP**: mean arterial pressure; **MV**: multivariate; **NR**: not reported; **SBP**: systolic blood pressure; **SV:** successive variation.

[a] Median (IQR)

Appendix 10B: Modified Rankin Score (mRS)

	Blood pressure (BP)		mRS		Reported results			
First author, Year	BP measurement and timing	BP categories used	Follow-up period	mRS categories	Unadjusted results	MV model with BP	Key confounders included in model	Adjusted results
Ascanio 2020	SBP Admission to 24h	Continuous Mean, max, min, peak, trough, SD, SV, CV	Last clinical follow-up	Good: 0-2	Min SBP (mean, SD): good outcome: 108.4+/-13.3 Poor outcome: 101.4+/-14.1 p<0.001	Yes	Age, Clinical grade	Minimum SBP: OR 1.03 (95% CI: 1.001-1.064) P=0.04
Cai 2017	SBP 1) Admission 2) Over 24h post coiling 3) SBPV-SV	1) Continuous 2) Mean SBP 120-140 (MSBP 120-140) 3) Continuous	Discharge 6 months	Fav: 0-2	1) SBP admission: Outcome at D/C: Fav: 153.8+/-21.5 Unfav: 149.9+/-26.5 P=0.52 2) MSBP120-140: Fav outcome at D/C: OR 5.45 (95% CI: 1.8-16.4) p=0.046 Fav outcome at 6 months: OR 3.60 (95% CI: 1.14-11.4) p=0.03 3) SBPV-SV: Fav outcome at D/C: OR 0.87 (95% CI: 0.78-0.97) p=0.015 Fav outcome at 6 months: OR 0.86 (95% CI: 0.76-0.98) p=0.018	Yes	Age, Clinical grade, Radiologic grade	1) SBP admission: Not performed 2) MSBP120-140: Fav outcome at D/C: OR 7.1 (95% CI: 2.0-25.4) p=0.002 Fav outcome at 6 months: Not an independent predictor 3) SBPV-SV: Fav outcome at D/C: Not an independent predictor Fav outcome at 6 months OR 0.87 (95% CI: 0.78-0.97) p=0.011

	Blood pressure (BP)		mRS		Reported results			
First author, Year	BP measurement and timing	BP categories used	Follow-up period	mRS categories	Unadjusted results	MV model with BP	Key confounders included in model	Adjusted results
Claassen 2004	MAP Admission to 24h	<70 70-130 >130	3 months	Poor: 4-6	Poor outcome: MAP <70: 11/15 (73%) MAP 70-130: 83/269 (31%) MAP >130: 69/116 (59%) P<0.001	Yes	Unclear	MAP < 70 or >130: OR 1.7 (95% CI: 1.0-2.9)
Eagles 2020	SBP Admission	Continuous Admission SBP > 150	12 weeks post aSAH	Poor: > 2	OR 1.01 (95% CI: 1.00-1.24)	Yes	Age, Sex, Location, Radiologic grade	Continuous: OR 1.01 (95% CI: 1.00-1.03) SBP > 150: OR 3.99 (95% CI: 1.92-8.32)
Haripottawekul 2024	SBP MAP DBP Admission	Continuous	3 months from discharge	Poor: 4-6	Max MAP: OR 1.01 (95% CI: 1.002-1.025) p=0.025 Max SBP: OR 1.00 (95% CI: 0.99-1.02) p=0.23 Max DBP: OR 1.02 (95% CI: 1.005-1.03) p=0.006	Yes	Clinical grade (others unclear)	Max MAP: NS NR Max DBP: NS NR
Inamasu 2015	SBP Admission	<140 140-184 185-219 >=220	30 days from admission	Poor: 5-6	Poor outcome: <140: 30% 140-184: 26% 185-219: 35% >=220: 54% P<0.05 for ≥ 220 group	No	-	-
Sirataranon 2022	SBP Admission	>160	1 year from treatment	Poor: 4-6	Poor outcome:	Yes	Age, Sex, Clinical grade, Radiologic	SBP > 160: OR 1.18 (95% CI: 0.64-2.16)

	Blood pressure (BP)		mRS		Reported results			
First author, Year	BP measurement and timing	BP categories used	Follow-up period	mRS categories	Unadjusted results	MV model with BP	Key confounders included in model	Adjusted results
					SBP > 160: OR 1.48 (95% CI: 0.93-2.34)		grade, location, size	
Yan 2021	SBP Admission	<100 100-149 150-200 >200	6 months from onset	Poor: 2-5	NR	Yes	Age, Sex, Size, Location, Radiologic grade	OR 0.68 (95% CI: 0.53-0.86) p=0.002
Zhang 2011	SBP DBP Pulse Pressure (PP) Admission (mean of 3 BP readings)	PP: < 50 50-69 ≥ 70	Hospital Discharge	Poor: > 2	Mean SBP: no difference p=0.760 PP 50-69: OR 0.436 (95% CI: 0.129-1.477) p=0.182 PP ≥ 70: OR 0.718 (95% CI: 0.221-2.328) p=0.581	Yes	Age, Sex	PP 50-69: OR 0.406 (95% CI: 0.086-1.911) p=0.254 PP ≥ 70: OR 0.411 (95% CI: 0.080-2.096) p=0.284

Abbreviations: **BP**: blood pressure; **CI**: confidence interval; **DBP**: diastolic blood pressure; **HR**: hazard ratio; **MAP**: mean arterial pressure; **MV**: multivariate, **NR**: not reported; **OR**: odds ratio; **PP**: pulse pressure; **SBP**: systolic blood pressure; **SV**: successive variation.

Appendix 10C: Glasgow Outcome Score (GOS)

	Blood pressure (BP)		GOS		Reported results			
First author, Year	Type of BP measured and timing	BP categories used	Follow-up period	GOS categories	Unadjusted results	MV model with BP	Key confounders included in model	Adjusted results
Cai 2018	SBP Admission SBP and DBP Post coiling over 24h	Continuous Median SBP on admission Post coiling mean SBP, DBP, and variability parameters	Hospital discharge	Unfav: 1-3	Median admission SBP: Unfavourable: 149.8+/-27.5 Favourable: 147.2+/-22.6 P=0.757 Variability Parameters: Increased variability associated with favourable outcome (multiple parameters)	Yes	Age, Clinical grade	NS NR
Cha 2010	SBP Admission	continuous	6 months from event	Unfav: 1-3	Admission SBP Favourable: 152.1+/-23.6 Unfavourable: 151.0+/-17.3 P=0.864	No	-	-
Liu 2023	SBP Admission	continuous	Hospital discharge	Poor: 1-3	Admission SBP: Poor: 153.5, Good: 144.0, P<0.001 OR 1.013 (95% CI: 1.008-1.018) P<0.001	Yes	Age, Clinical grade, Radiologic grade, Size	OR 1.008 (95% CI: 1.002-1.014) p=0.012
Nastasovic 2019	SBP Admission	Continuous	3 months from SAH	Unfav: 1-3	Unfavourable: 156.57+/-23.35 Favourable: 137.36+/-21.28 P<0.001	Yes	Age, Sex, Clinical Grade	OR 1.020 (95%CI: 1.002-1.038) p=0.03
Rosengart 2007	SBP Admission	Continuous SBP: 130-139	3 months	Unfav: 1-3	NR	Yes	Age, Sex	SBP: OR 1.01 (95% CI: 1.00-1.01) p=0.003 SBP130-139: HR 0.98 (95% CI: 0.73-1.31) p=0.89

	Blood pressure (BP)		GOS		Reported results			
First author, Year	Type of BP measured and timing	BP categories used	Follow-up period	GOS categories	Unadjusted results	MV model with BP	Key confounders included in model	Adjusted results
		140-159 160-179 180-209 ≥210						SBP140-159: HR 1.29 (95% CI: 1.03-1.63) p=0.026 SBP160-179: HR 1.21 (95% CI: 0.92-1.59) p=0.18 SBP180-209: HR 1.25 (95% CI: 0.89-1.77) p=0.20 SBP ≥ 210: HR 1.47 (95% CI: 0.81-2.65) p=0.20
Soehle 2007	MAP Admission	MAP > 95	1 year after SAH	Unfav: 1-3	NS NR P=0.080	No	-	-
Teping 2018	SBP MAP Days 0-3	1) 25 mmHg SBP increase 2) ≥160 mmHg sustained (3h)	3 months	Unfav: 1-3	NS	No	-	-
Yang 2019	SBP DBP Multiple variability parameters Admission – 24 hrs	Tertiles	Hospital discharge	Unfav: 1-3	SBP mean: Favourable: 126.3 +/-14.7 Unfavourable: 135.9 +/-16.8 p<0.001 Not shown: Essentially all variability params and DBP have significant difference between groups	Yes	Age, radiologic grade, Clinical grade	SBP mean: ref=T1 (<120.9) T2 (SBP 120.9-135.6): OR 1.6 (95% CI: 0.7-4.0) p=0.295 T3 (SBP > 135.6): OR 2.8 (95% CI: 1.1-6.9) p=0.024 All SBP variability parameters significantly associated with unfavourable outcome DBP variability parameters not associated with unfavourable outcome

Abbreviations: **BP**: blood pressure; **CI**: confidence interval; **DBP**: diastolic blood pressure; **HR**: hazard ratio; **MAP**: mean arterial pressure; **MV**: multivariate, **NR**: not reported; **NS**: not significant; OR: odds ratio; **PP**: pulse pressure; **SBP**: systolic blood pressure; **SV**: successive variation.

Appendix 10D: DCI/Vasospasm

	Blood pressure (BP)		DCI/Vasospasm		Reported results			
First author, Year	Type of BP measured and timing	BP categories used	Follow-up period	DCI or Vasospasm	Unadjusted results	MV model with BP	Key confounders included in model	Adjusted results
Aldakkan 2017	SBP Admission	Continuous	NR	Development of clinical DCI	OR 0.99 (95% CI: 0.97-1.01) p=0.181	Yes	Age, Sex, Clinical grade, Radiologic grade, Size, Location	OR 0.99 (95% CI: 0.97-1.01) p=0.364
Calviere 2022	SBP 1) Admission 2) 4h 3) Last measurement 4) delta SBP admission to 4h	2 center comparison: Utrecht = liberal BP Tolouse = tight BP control	In hospital	DCI	DCI : Utrecht = 25% Tolouse = 18% OR 0.65 (95% CI: 0.40–1.03)	Yes	Age, Sex, Size	OR 0.68 (95% CI: 0.41–1.11)
Faust 2014	SBP, DBP, MAP Averaged hourly and daily	continuous Mean daily values over first 3 days	In hospital	Vasospasm (>33% narrowing of vessels)	**VS+ versus VS- groups** **Mean Daily MAP** Day 1: P=0.21; Day 2: P=0.86; Day 3: P=0.55 **Mean Daily DBP** Day 1: P=0.96; Day 2: P=0.45; Day 3: P=0.36 **Mean Daily SBP** Day 1: P=0.40; Day 2: P=0.97; Day 3: P=0.43	No	-	-

	Blood pressure (BP)		DCI/Vasospasm		Reported results			
First author, Year	Type of BP measured and timing	BP categories used	Follow-up period	DCI or Vasospasm	Unadjusted results	MV model with BP	Key confounders included in model	Adjusted results
Gathier 2022	MAP 0-48 hours of ICU admission	50, 60, 70 Lowest MAP 12 or 24 hours preceding DCI	ICU admission	DCI	Not provided	Yes	Age, Sex, Location, Clinical grade, Radiologic grade	**Lowest MAP in 24 hours prior to DCI** Reference MAP = 100 (aHR = 1) MAP 50, aHR = 2.59 (1.12-5.96) MAP 60, aHR = 1.79 (0.99-3.24) MAP 70, aHR = 1.25 (0.81-1.93) **Lowest MAP in 12 hours prior to DCI** MAP 50, aHR = 1.59 (0.61-4.20) MAP 60, aHR = 1.40 (0.71-2.76) MAP 70, aHR = 1.23 (0.80-1.90)
Kelly 2022	SBP admission	Continuous	In hospital	Vasospasm	SBP: Median (IQR) VS-: 142 (126-155) VS+: 145 (130-165) P=0.078	Yes	Age, Sex, Clinical grade, Radiologic grade	HR = 1.18; 95% CI 1.05–1.35; p = 0.008
Khan 2022	SBP admission	Continuous	Not described	Vasospasm	SBP: Mean +/- SD VS+: 167.1+/-33.8 VS-:154.4+/-34.9 P=0.007	Yes	Age, Clinical grade	OR 1.008 (95% CI: 1.000-1.017) p=0.046
Liu 2020	BP Admission	≥ 140/90	In hospital	DCI	OR 1.97 (95% CI: 1.25-3.11) p=0.003	Yes	Age, Clinical grade, Location, Radiologic grade	OR 1.63 (95% CI: 1.00-2.65) P=0.049

	Blood pressure (BP)		DCI/Vasospasm		Reported results			
First author, Year	Type of BP measured and timing	BP categories used	Follow-up period	DCI or Vasospasm	Unadjusted results	MV model with BP	Key confounders included in model	Adjusted results
MacDonald 2003	SBP Admission	Continuous	In hospital	Vasospasm (symptomatic)	10 mmHg increase in admission SBP: OR 1.03 (95% CI: 1.00-1.06) P=0.027	Yes	Age, Sex, Clinical grade, Radiologic grade, Size	NS NR
Roederer 2014	MAP Post bleed day 1 maximum MAP value	Continuous	In hospital	Vasospasm	Max MAP: VS+: 107.524 VS-: 122.874 Mean difference: 15.35 (95% CI: 2.99-27.72) p=0.018	-	-	-
Teping 2018	SBP MAP Days 0-3 (phase 1)	1) 25 mmHg SBP increase 2) ≥160 mmHg sustained (3h)	In hospital	Clinical DCI (cDCI) Functional DCI (fDCI)	Phase 1 SBI: Increased fDCI: approx 65% vs 40% (Fig. 5a:) $p < 0.05$ Phase 1 EPH: More likely to develop cDCI (Fig. 7a: $p < 0.05$)	No	-	-

Abbreviations: **BP**: blood pressure, **CI**: confidence interval; **cDCI**: clinical delayed cerebral ischemia; **DBP**: diastolic blood pressure; **DCI**: delayed cerebral ischemia; **fDCI**: functional (radiographic) delayed cerebral ischemia; **HR**: hazard ratio; **MAP**: mean arterial pressure; **MV**: multivariate; **NR**: not reported; **OR**: odds ratio; **PP**: pulse pressure; **SBP**: systolic blood pressure; **SBI**: spontaneous blood pressure increase; **SV**: successive variation; **VS**: vasospasm.

Appendix 10E: Cerebral Infarction

	Blood pressure (BP)		Cerebral Infarction		Reported results			
First author, Year	Type of BP measured and timing	BP categories used	Follow-up period	Cerebral Infarction	Unadjusted results	MV model with BP	Key confounders included in model	Adjusted results
Ferguson 2007	SBP Admission	≤ 129 130-139 140-159 160-179 180-209 ≥ 210	In hospital	Imaging	SBP (10mmHg): OR 1.01 (95% CI: 1.00-1.01) p=0.0023 SBP 130-139: OR 1.07 (95% CI: 0.81-1.40) SBP 140-159: OR 1.35 (95% CI: 1.09-1.69) SBP 160-179: OR 1.38 (95% CI: 1.05-1.81) SBP 180-209: OR 1.09 (95% CI: 0.75-1.60) SBP >=220: OR 2.22 (95% CI: 1.14-4.35)	Yes	Age, Clinical grade, Radiologic grade, Size	NS NR
Teping 2018	SBP MAP Days 0-3 (phase 1)	1) 25 mmHg SBP increase 2) ≥160 mmHg sustained (3h)	In hospital	Imaging	25 mmHg SBP increase: increased infarction = approx 65% vs 35% p < 0.05 (Fig. 5a:)	No	-	-

Abbreviations: **BP**: blood pressure; **CI**: confidence interval; **DBP**: diastolic blood pressure; **HR**: hazard ratio, **MAP**: mean arterial pressure; **MV**: multivariate; **NR**: not reported; **OR**: odds ratio; **SBP**: systolic blood pressure.

Appendix 10F: Other outcomes

	Blood pressure (BP)		Other outcomes		Reported results			
First author, Year	Type of BP measured and timing	BP categories used	Follow-up period	Outcome	Unadjusted results	MV model with BP	Key confounders included in model	Adjusted results
Dowlati 2021	SBP, DBP, PP Multiple variability parameters Admission to 24 hours	Continuous	In Hospital	Disposition at discharge: Good vs poor Poor = nursing home, hospice, death	SBP mean: p=0.45 Poor: 135.36+/-17.8; Good: 133.54+/-12.25 SBP var: p=0.014 Poor: 19.9+/-7.9; Good: 16.94+/-6.48 DBP mean: p=0.67 Poor: 66.09+/-11.1; Good: 65.41+/-8.48 DBP var: p=0.24 Poor: 10.91+/-4.6; Good: 9.83+/-5.5 PP mean: p=0.62 Poor=69.18+/-16.4; Good=68.03+/-12.12 PPvar: p=0.042 Poor: 14.6+/-6.3; Good: 12.8+/-4.7	Yes (SBP only)	Age, Clinical grade, Radiologic grade	SBP var: OR 1.07 (95% CI: 1.01-1.14) p=0.019 PP var: OR 1.110 (95% CI: 1.023-1.212) p=0.015
Stulberg 2023	SBP variability First 72 from admission	Continuous	In Hospital	Disposition at discharge: Poor = nursing home or hospital	NR	yes	Age, sex	OR 0.6 (95% CI: 0.3-1.3) p=0.19
Witiw 2013	MAP admission	Continuous	ICU stay	ICU LOS	HR 1.00 (95% CI: 0.99-1.01) p=0.996	No	-	-

Abbreviations: **BP**: blood pressure; **CI**: confidence interval; **DBP**: diastolic blood pressure; **HR**: hazard ratio, **LOS:** length of stay; **MAP**: mean arterial pressure; **MV**: multivariate; **NR**: not reported; **OR**: odds ratio; **PP**: pulse pressure; **SBP**: systolic blood pressure; **SV**: successive variation.

Appendix 11: Matrix tables displaying timing and measurement of exposure (blood pressure) and secondary outcomes.

Appendix 11A: Mortality

			Mortality		
Exposure variable	Timeframe	Category	3 weeks from admission	In hospital	6 months
SBP	Single admission value	Continuous		Lantigua 2015	
		SBP > 140	Al-Mistarehi 2022		
	Post coiling over 24 hours	Mean SBP 120-140			Cai 2017
		SBPV-SV			Cai 2017
	Admission to 72 hours	SBPV (SD, ARV, rSD)		Stulberg 2023	
MAP	Admission	Single reading		Zhou 2023	
	Admission to 6 hours	Highest reading		Duran 2013	

Abbreviations: **MAP**: mean arterial pressure; **SBP:** systolic blood pressure; **SBPV-SV:** systolic blood pressure variation – successive variation.

Appendix 11B: Modified Rankin Score (mRS)

			mRS						
Exposure variable	Timeframe	Category	Discharge	30 days	12 weeks	3 months	6 months	1 year	Last clinical follow-up
SBP	Single admission value	Continuous	Cai 2017		Eagles 2020				
		SBP > 150			Eagles 2020		Yan 2021*		
		SBP > 160						Sirataranon 2022	
		SBP ≥ 220		Inamasu 2015					
	Admission: mean of 3 readings	Continuous (mean)	Zhang 2011						
	Admission to 24 hours	Mean							Ascanio 2020
		Max							Ascanio 2020
		Min							Ascanio 2020
		Peak							Ascanio 2020
		Trough							Ascanio 2020
		SD							Ascanio 2020
		CV							Ascanio 2020
		SV							Ascanio 2020
	Admission until aneurysm secured	Max SBP				Haripottawekul 2024			
	Post coiling over 24 hours	Mean SBP 120-140	Cai 2017				Cai 2017		
		SBPV-SV	Cai 2017				Cai 2017		
MAP	Admission to 24 hours	MAP < 70				Claassen 2004			
		MAP 70-130				Claassen 2004			
		MAP > 130				Claassen 2004			
	Admission until aneurysm secured	Max MAP				Haripottawekul 2024			
DBP	Admission: mean of 3 readings	Continuous (mean)	Zhang 2011						
	Admission until aneurysm secured	Max DBP				Haripottawekul 2024			
PP	Admission: mean of 3 readings	Continuous (mean)	Zhang 2011						
		<50	Zhang 2011						

		50-69	Zhang 2011						
		≥70	Zhang 2011						

Abbreviations: **CV:** coefficient of variation; **DBP**: diastolic blood pressure; **MAP**: mean arterial pressure; **mRS**: modified rankin score; **PP**: pulse pressure; **SBP**: systolic blood pressure; **SD**: standard deviation; **SV**: successive variation.

Appendix 11C: Glasgow Outcome Score (GOS)

			GOS			
Exposure variable	Timeframe	Category	Discharge	3 months	6 months	1 year
SBP	Single admission value	Continuous	Liu 2023	Nastasovic 2019 Rosengart 2007	Cha 2010	
		SBP 130-139		Rosengart 2007		
		SBP 140-159		Rosengart 2007		
		SBP 160-179		Rosengart 2007		
		SBP 180-209		Rosengart 2007		
		SBP ≥ 210		Rosengart 2007		
	Admission to 24 hours	Mean	Yang 2019			
		Max	Yang 2019			
		Min	Yang 2019			
		Max-min	Yang 2019			
		SD	Yang 2019			
		CV	Yang 2019			
		SV	Yang 2019			
	Admission to day 3 (day 0-3)	SBP increase ≥ 25		Teping 2018		
	Admission to day 3	SBP >160		Teping 2018		
	Post coiling over 24 hours	Mean	Cai 2018			
		SBPV-SV	Cai 2018			
		SBPV-SD	Cai 2018			
MAP	Admission	MAP > 95				Soehle 2007
DBP	Admission to 24 hours	Mean	Yang 2019			
		Max	Yang 2019			
		Min	Yang 2019			
		Max-Min	Yang 2019			
		SD	Yang 2019			
		CV	Yang 2019			
		SV	Yang 2019			
	Post coiling over 24 hours	Mean DBP	Cai 2018			
		DBP-SD	Cai 2018			

		DBP-SV	Cai 2018			

Abbreviations: **CV**: coefficient of variation; **DBP**: diastolic blood pressure; **MAP**: mean arterial pressure; **GOS**: Glasgow outcome score; **PP**: pulse pressure; **SBP**: systolic blood pressure; **SD**: standard deviation; **SV**: successive variation.

Appendix 11D: Vasospasm/Delayed Cerebral Ischemia (DCI)

			DCI/Vasospasm		
Exposure variable	Timeframe	Category	In Hospital	In ICU	Not described
SBP	Single admission value	Continuous	Calviere 2022 Kelly 2022 Macdonald 2003		Aldakkan 2017 Khan 2022
		SBP > 140	Liu 2020		
	Admission to day 3 (day 0-3)	SBP increase ≥ 25	Teping 2018		
	Admission to day 3	SBP >160	Teping 2018		
		Daily Mean	Faust 2014		
	4 hours post admission	Continuous	Calviere 2022		
	Last measurement	Continuous	Calviere 2022		
	Delta SBP admission to 4 hours	Continuous	Calviere 2022		
MAP	post bleed day 1 max MAP value	Max	Roederer 2014		
	Admission to day 3	Daily Mean	Faust 2014		
	0-48 hours in ICU	During 12 hrs before event MAP = 50		Gathier 2022	
		During 12 hrs before event MAP = 60		Gathier 2022	
		During 12 hrs before event MAP = 70		Gathier 2022	
		During 24 hrs before event MAP = 50		Gathier 2022	
		During 24 hrs before event MAP = 60		Gathier 2022	
		During 24 hrs before event MAP = 70		Gathier 2022	
DBP	Single admission value	DBP > 90	Liu 2020		
	Admission to day 3	Daily Mean	Faust 2024		

Abbreviations: **DBP**: diastolic blood pressure; **ICU**: intensive care unit; **MAP**: mean arterial pressure; **mRS**: modified Rankin score; **SBP**: systolic blood pressure.

Appendix 11E: Cerebral Infarction

			cerebral infarction
Exposure variable	timeframe	category	In hospital
SBP	Single admission value	Continuous	
		SBP ≤ 129	Ferguson 2007
		SBP 130-139	Ferguson 2007
		SBP 140-159	Ferguson 2007
		SBP 160-179	Ferguson 2007
		SBP 180-209	Ferguson 2007
		SBP ≥ 210	Ferguson 2007
	Admission to day 3 (day 0-3)	SBP increase ≥ 25	Teping 2018
	Admission to day 3	SBP >160	Teping 2018

Abbreviations: **SBP**: systolic blood pressure.

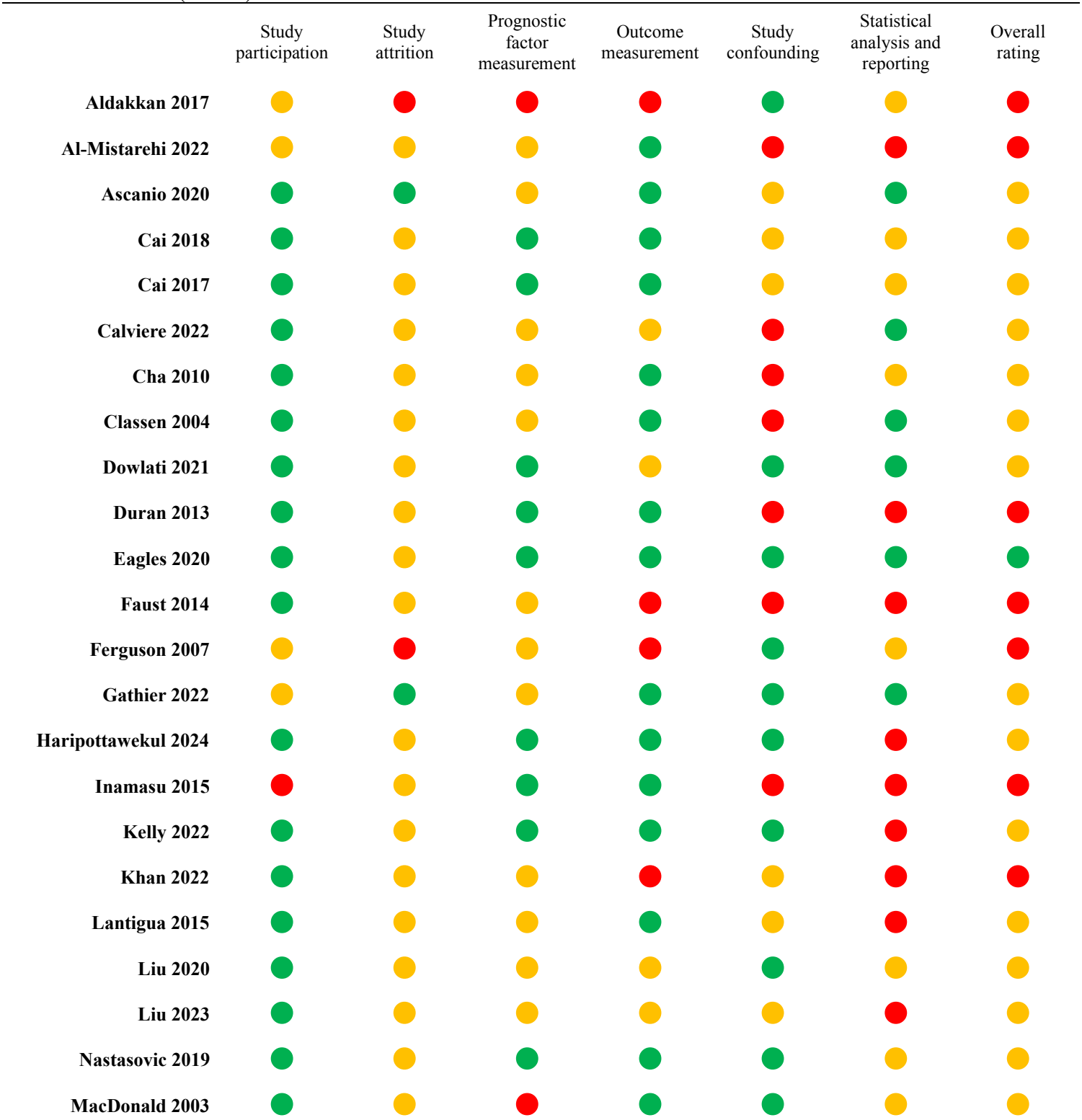
Appendix 11F: Other Outcomes

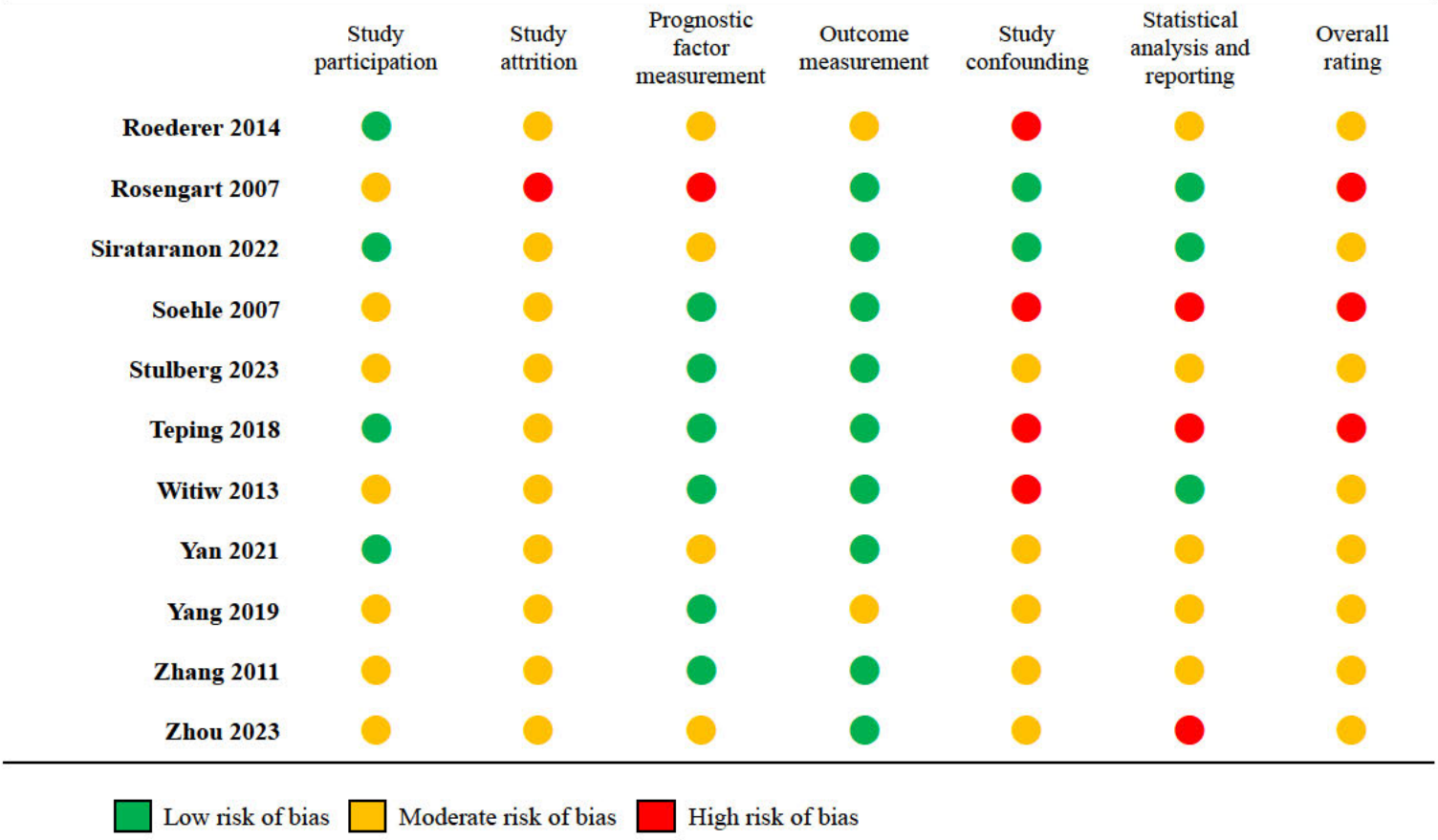
			Other	
Exposure variable	timeframe	category	ICU LOS	disposition
SBP	Admission to 24 hours	Mean		Dowlati 2021
		SD		Dowlati 2021
	Admission to 72 hours	SBP variability (SD, ARV, rSD)		Stulberg 2023
MAP	Single admission value	continuous	Witiw 2013	
DBP	Admission to 24 hours	Mean		Dowlati 2021
		SD		Dowlati 2021
PP	Admission to 24 hours	Mean		Dowlati 2021
		SD		Dowlati 2021

Abbreviations: **DBP**: diastolic blood pressure; **ICU**: intensive care unit; **MAP**: mean arterial pressure; **mRS**: modified Rankin score; **PP**: pulse pressure; **SBP**: systolic blood pressure; **SD**: standard deviation.

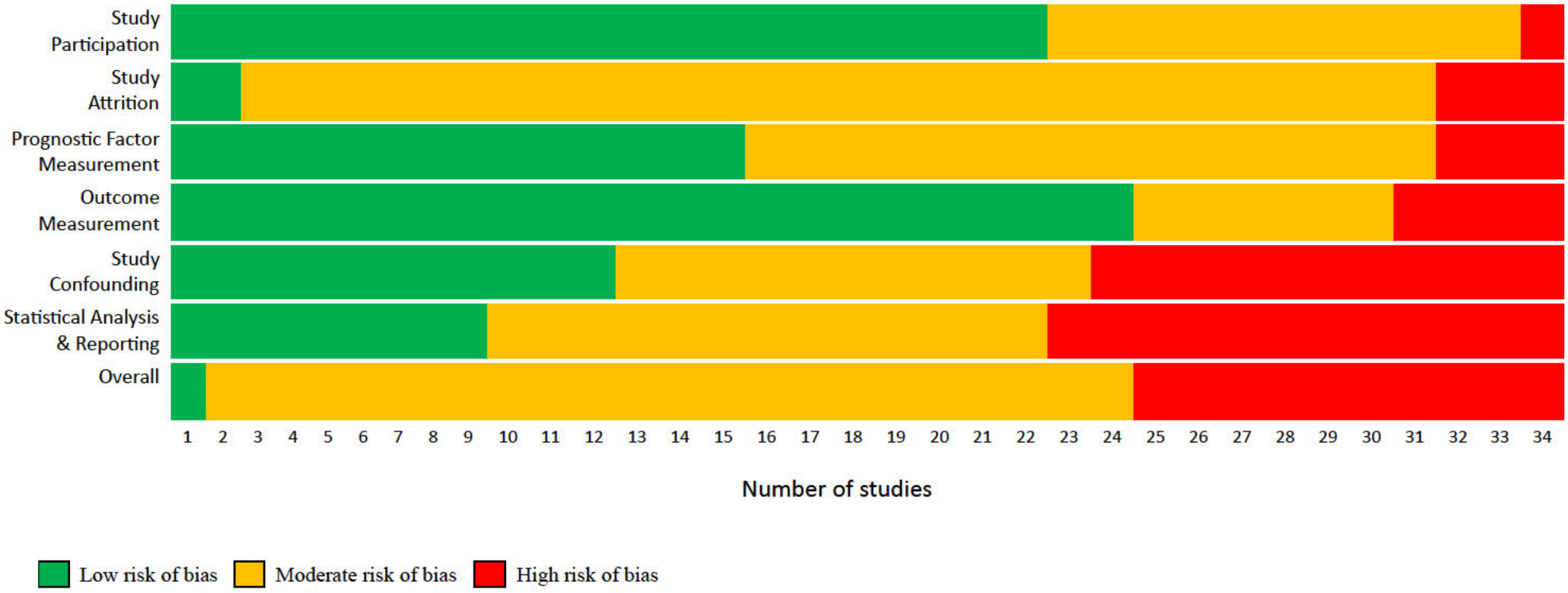
Appendix 12: Risk Of Bias - Secondary Outcomes

Appendix 12A: Risk of Bias by QUIPS domain and overall for each included study – secondary outcomes (n = 34)




Study participation
Study attrition
Prognostic factor measurement
Outcome measurement
Study confounding
Statistical analysis and reporting
Overall rating
Roederer 2014
Rosengart 2007
Sirataranon 2022
Soehle 2007
Stulberg 2023
Teping 2018
Witiw 2013
Yan 2021
Yang 2019
Zhang 2011
Zhou 2023
Low risk of bias
Moderate risk of bias
High risk of bias

Appendix 12B: Risk of bias presented by QUIPS domain across all included studies – secondary outcomes (n = 34)



Appendix 13: Justification for Grading of Recommendations, Assessment, Development and Evaluations (GRADE) - Primary Outcome (Rebleeding)

GRADE assessment justification details: Primary Outcome (aneurysmal rebleeding)

GRADE Domain	Judgement	Concerns about certainty domains
Risk of bias	All 15 studies included in our review are observational. None of the studies were judged to have low risk of bias. Twelve studies were at moderate risk of bias and 3 studies were at high risk of bias. The most common reasons for high risk of bias ratings were failure to account for confounders and lack of consistency in prognostic factor (exposure) measurement. Overall, we judged the studies to have serious limitations in this domain.	Serious
Indirectness	The population was similarly defined across studies as adults with aneurysmal SAH. The measurement and timing of the exposure (elevated blood pressure) varied between the studies: Over half (n = 8/15) of the studies only measured a single blood pressure at admission (29,31,33,34,36,38–40), which does not truly reflect the impact of blood pressure over the time period of interest. The remaining 7 studies measured different blood pressure metrics across variable time periods (16,29,31,34,36,70,71). The outcome of rebleeding was similarly defined across most of the studies with the use of CT scan and clinical deterioration, except for Okhuma et al, which had limitations in the outcome measurements. Finally, studies differed in their clinical protocols and use of blood pressure management interventions (e.g., tranexamic acid, nimodipine or more intensive surveillance) which may have influenced the outcome of interest.	Serious
Imprecision	There were a total of 962 rebleed events across the 15 studies. The largest studies did not show significant results when adjusted for confounders (Darkwah Oppong et al, Gathier et al, and Van Lieshout et al). Smaller studies without adjustment for confounders often reported significant results. We therefore judged the evidence to have serious imprecision.	Serious
Inconsistency	The direction and magnitude of the effect estimates varied between the studies. There was no clear dose response effect across the different blood pressure target thresholds. At the target threshold of 160 mmHg there appears to be a strong unadjusted effect of blood pressure on rebleeding but this is lost moving up to a target threshold of 180 mmHg. Unadjusted results were often significant while adjusted results were not. Also, there was selective reporting of adjusted results in three studies (Cong et al, Solanki et al, Haripottawekul et al). They presented significant effect estimates on the unadjusted analysis but did not report the subsequent non-significant adjusted effect estimates.	Serious
Publication bias	A funnel plot was not generated, due to a limited number of studies at each blood pressure target and the different effect estimates used (OR and HR). Included studies reported both negative and positive results. In addition, we conducted a comprehensive search that included some protocol registries. Overall, we did not suspect significant publication bias.	Not suspected

7.3 Survey Appendix 1 (Questionnaire)

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Blood Pressure Management in Early Aneurysmal Subarachnoid Hemorrhage: A Cross-Sectional Survey of Canadian Clinicians.

Consent Form/Participation information

Dear Colleagues,

You are invited to participate in a national survey of blood pressure management during the early phase (first 72 hours) of aneurysmal subarachnoid hemorrhage (aSAH).

Purpose of the Study:

1) To describe the current practice patterns of clinicians managing aSAH patients in the Canadian setting.
2) To identify predictors for selection of specific blood pressure targets.
3) To explore potential barriers to blood pressure target implementation.

Participation:

Participation will consist of completion of a self-directed, online questionnaire, which takes **5-10 minutes to complete.**

Benefits:

Current evidence is limited to observational studies. Clinical practice guidelines are based on this data and recommend differing targets. A recent survey of practitioners in the USA shows highly heterogeneous practice patterns. The information obtained from this survey will help inform the development of a prospective clinical trial in the near future.

Risks:

This survey is minimal risk.

Confidentiality and Privacy:

Survey data will be collected anonymously using the online platform "SurveyMonkey" (www.surveymonkey.com). In order to minimize the risk of security breaches and to help ensure confidentiality, it is recommended that standard safety measures are used, such as signing out of your account, closing your browser, and locking your device when it is no longer in use or once the study is completed.

Conservation of Data:

Data will be encrypted and stored on servers based in Canada. Access will be password protected. Data that is downloaded from these servers will be stored in an encrypted format and password protected on a single computer (belonging to the Principal investigator). Research records will be kept for 5 years and then permanently deleted or destroyed.

Voluntary Participation:

Participation is voluntary. You can withdraw at any time prior to submitting the survey

and all your data will be removed from the study. After submission of the survey, it will not be possible to remove your data from the study because it was collected anonymously, which prevents the researchers from identifying individual datasets.

This project is being conducted independently from the organizations from which participants may be recruited. If you have any questions about the study, you may contact the researchers. If you have any questions regarding the ethical conduct of this study, you may contact the Office of Research Ethics and Integrity via email (ethics@uottawa.ca) or telephone (613-562-5387).

University of Ottawa Ethics File Number: H-11-22-8598

Luke A. Terrett
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University of Alberta

Alexis F. Turgeon
Professor, Department of Anesthesiology and Critical Care Medicine, Université Laval
Scientist, Population Health and Optimal Health Practices U

* 1. By clicking "I agree", I am consenting to participate in this survey

☐ I agree

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* 2. In your clinical practice, do you care for adult patients (age 18 years or older) with aneurysmal subarachnoid hemorrhage (aSAH)?

- ◯ Yes
- ◯ No

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* 3. Which of the following specialties do you practice (select all that apply)?

- [ ] Critical Care Medicine
- [ ] Neurosurgery
- [ ] Neither of these specialties

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Self-reported blood pressure target selection:

The following section will present 3 hypothetical case scenarios where **you are writing the admission orders**. Please consider the blood pressure targets (i.e. the maximum and minimum allowable values) that you would select. If you would not use a given parameter (e.g. upper limit MAP), please identify this by selecting "would not use". The timeframe for all cases is divided into an unsecured phase and a secured phase (lasting up to 72 hours from rupture)

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Blood Pressure Management in Early Aneurysmal Subarachnoid Hemorrhage: A Cross-Sectional Survey of Canadian Clinicians.

CASE 1

Consider an otherwise healthy 55 year old female who has just been admitted with aneurysmal subarachnoid hemorrhage (aSAH). She is 3 hours post rupture. The plan is to secure the aneurysm within the next 24 hours:

- World Federation of Neurological Societies (WFNS) grade I
- Glasgow Coma Score (GCS) 15, no neurologic deficits.
- Not intubated.
- CT scan = thin SAH without intraventricular hemorrhage (IVH) or intracerebral hemorrhage (ICH) (i.e. Modified Fisher grade 1).
- No external ventricular drain (EVD).
- Normal vital signs, except elevated blood pressure = 185/100 (128) mmHg.

* 4. **Prior to securing the aneurysm:**

For this patient, what would you typically select as your blood pressure targets? If you would not use a specific parameter, please select the response option "would not use".

SBP = Systloic Blood Pressure
MAP = Mean Arterial Pressure

	SBP (mm Hg)	MAP (mm Hg)
Upper Limit		
Lower Limit		

Other (please specify)

* 5. **After the aneurysm is secured (and within 72 hours post rupture):**

For this patient, what would you typically select as your blood pressure targets? If you would not use a specific parameter, please select the response option "would not use".

SBP = Systloic Blood Pressure
MAP = Mean Arterial Pressure

	SBP (mm Hg)	MAP (mm Hg)
Upper Limit		
Lower Limit		

Other (please specify)

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CASE 2

Now consider a different 55 year old female who has just been admitted with aSAH. She is 3 hours post rupture. The plan is to secure the aneurysm within the next 24 hours:

- WFNS grade II.
- GCS 13, no neurologic deficits.
- Not intubated.
- CT scan shows = thick SAH without IVH or ICH (Modified Fisher grade 3).
- No EVD.
- Normal vital signs, except elevated blood pressure = 185/100 (128) mmHg.

* 6. **Prior to securing the aneurysm:**

For this patient, what would you typically select as your blood pressure targets? If you would not use a specific parameter, please select the response option "would not use".

SBP = Systloic Blood Pressure
MAP = Mean Arterial Pressure

	SBP (mm Hg)	MAP (mm Hg)
Upper Limit		
Lower Limit		

Other (please specify)

* 7. **After the aneurysm is secured (and within 72 hours post rupture):**

For this patient, what would you typically select as your blood pressure targets? If you would not use a specific parameter, please select the response option "would not use".

SBP = Systloic Blood Pressure
MAP = Mean Arterial Pressure

	SBP (mm Hg)	MAP (mm Hg)
Upper Limit		
Lower Limit		

Other (please specify)

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CASE 3

In this final case, consider another 55 year old female who has just been admitted with aSAH. She is 3 hours post rupture. The plan is to secure the aneurysm within the next 24 hours:

- WFNS Grade V (poor grade)
- GCS 6
- She is intubated/ventilated.
- EVD = placed for hydrocephalus and functioning properly.
- CT scan = EVD in good position, resolving hydrocephalus, subtle signs of diffuse cerebral edema.
- Intracranial Pressure (ICP) = 13 mmHg.
- Other vital signs normal, except elevated blood pressure = 185/100 (128) mmHg.

* 8. **Prior to securing the aneurysm:**

For this patient, what would you typically select as your blood pressure targets? If you would not use a specific parameter, please select the response option "would not use".

SBP = Systloic Blood Pressure
MAP = Mean Arterial Pressure
CPP = Cerebral Perfusion Pressure

	SBP (mm Hg)	MAP (mm Hg)	CPP (mm Hg)
Upper Limit			
Lower Limit			

Other (please specify)

* 9. **After the aneurysm is secured (and within 72 hours post rupture):**

For this patient, what would you typically select as your blood pressure targets? If you would not use a specific parameter, please select the response option "would not use".

SBP = Systloic Blood Pressure
MAP = Mean Arterial Pressure
CPP = Cerebral Perfusion Pressure

	SBP (mm Hg)	MAP (mm Hg)	CPP (mm Hg)
Upper Limit			
Lower Limit			

Other (please specify)

Blood Pressure Management in Early Aneurysmal Subarachnoid Hemorrhage: A Cross-Sectional Survey of Canadian Clinicians.

10. From the following list, please select the **top 3** factors that would push you to use a **higher** blood pressure target during the early unsecured phase of aSAH **(within 72 hours from rupture and prior to securing the aneurysm).**

- [ ] Aneurysm size (large [>10 mm] vs small)
- [ ] Presence of other unruptured aneurysms (yes vs no)
- [ ] Clinical grade or GCS (poor vs good)
- [ ] Radiological grade (poor vs good)
- [ ] Time from rupture (short vs long)
- [ ] Age of patient (old vs young)
- [ ] Patient Location (ICU vs ward)
- [ ] Presence of an EVD (yes vs no)
- [ ] Evidence of cerebral edema or elevated ICP (yes vs no)
- [ ] Aneurysm Location (anterior vs posterior)

Blood Pressure Management in Early Aneurysmal Subarachnoid Hemorrhage: A Cross-Sectional Survey of Canadian Clinicians.

11. Please rank your choices from most important (1) to least important (3)

- Aneurysm size (large [>10 mm] vs small)
- Presence of other unruptured aneurysms (yes vs no)
- Clinical grade or GCS (poor vs good)
- Radiological grade (poor vs good)
- Time from rupture (short vs long)
- Age of patient (old vs young)
- Patient Location (ICU vs ward)
- Presence of an EVD (yes vs no)
- Evidence of cerebral edema or elevated ICP (yes vs no)
- Aneurysm Location (anterior vs posterior)

Blood Pressure Management in Early Aneurysmal Subarachnoid Hemorrhage: A Cross-Sectional Survey of Canadian Clinicians.

12. From the following list, please select the **top 3** factors that would push you to use a **lower** blood pressure target during the early unsecured phase of aSAH **(within 72 hours from rupture and prior to securing the aneurysm).**

- [ ] Aneurysm size (large [>10 mm] vs small)
- [ ] Presence of other unruptured aneurysms (yes vs no)
- [ ] Clinical grade or GCS (poor vs good)
- [ ] Radiological grade (poor vs good)
- [ ] Time since rupture (short vs long)
- [ ] Age of patient (old vs young)
- [ ] Patient Location (ICU vs Ward)
- [ ] Presence of an EVD (yes vs no)
- [ ] Evidence of cerebral edema or elevated ICP (yes vs no)
- [ ] Aneurysm Location (anterior vs posterior)

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13. Please rank your choices from most important (1) to least important (3)

- Aneurysm size (large [>10 mm] vs small)
- Presence of other unruptured aneurysms (yes vs no)
- Clinical grade or GCS (poor vs good)
- Radiological grade (poor vs good)
- Time since rupture (short vs long)
- Age of patient (old vs young)
- Patient Location (ICU vs Ward)
- Presence of an EVD (yes vs no)
- Evidence of cerebral edema or elevated ICP (yes vs no)
- Aneurysm Location (anterior vs posterior)

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14. (optional question)

How does a measured ICP affect your BP target prescribing in early a SAH (within 72 hours from rupture)?

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* 15. Do you experience barriers to the implementation of a specific BP target during the early phase of aSAH (first 72 hours)?

	Never	Rarely	Sometimes	Often	Always
Disagreement with another physician/surgeon regarding the BP target	○	○	○	○	○
Nursing staff unwilling to implement the target	○	○	○	○	○
Appropriate staff, equipment, or bed location not available	○	○	○	○	○
Institutional policy prevents implementation of your preferred target	○	○	○	○	○

Other (please specify)

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* 16. Have you completed a formal fellowship in neurocritical care (at least 1 year of advanced training in a specialized neurocritical care unit)

- ◯ Yes
- ◯ No

* 17. How many years have you been in clinical practice (since completion of your training)

- ◯ 0-5
- ◯ 6-10
- ◯ 11-15
- ◯ 16-20
- ◯ 21-25
- ◯ 26-30
- ◯ greater than 30

* 18. What is your gender

- ◯ Man
- ◯ Non-binary (not exclusively a man or a woman, for example agender, fluid, queer, or two-spirit)
- ◯ Woman
- ◯ Prefer to self describe

* 19. At the centre where you practice, what is the approximate number of yearly aSAH patients?

- ◯ < 25
- ◯ 25 to 50
- ◯ > 50

* 20. Which aneurysm treatment option(s) is/are available at your centre (select one or both)?

- ☐ Open neurosurgical clipping
- ☐ Endovascular therapy

21. For patients receiving ICP monitoring **at your centre**, which anatomic level is blood pressure typically measured at (i.e. where is the arterial line transducer placed)?

- ◯ Tragus/external auditory meatus (middle cranial fossa)
- ◯ Phlebostatic axis/mid-axillary line (right atrium)
- ◯ unsure/I don't know
- ◯ Other (please specify)

7.4 Survey Appendix 2 (Case Descriptions)

Case 1:

Consider an otherwise healthy 55 year old female who has just been admitted with aSAH. She is 3 hours post rupture. The plan is to secure the aneurysm within the next 24 hours:

- World Federation of Neurological Societies (WFNS) grade I
- Glasgow Coma Score (GCS) 15, no neurologic deficits.
- Not intubated.
- CT scan = thin SAH without Intraventricular hemorrhage (IVH) or intracerebral hemorrhage (ICH) (i.e. Modified Fisher grade 1).
- No external ventricular drain (EVD).
- Normal vital signs, except elevated blood pressure = 185/100 (128) mmHg.

Case 2:

Now consider a different 55 year old female who has just been admitted with aSAH. She is 3 hours post rupture. The plan is to secure the aneurysm within the next 24 hours:

- WFNS grade II.
- GCS 13, no neurologic deficits.
- Not intubated.
- CT scan shows = thick SAH without IVH or ICH (Modified Fisher grade 3).
- No EVD.
- Normal vital signs, except elevated blood pressure = 185/100 (128) mmHg.

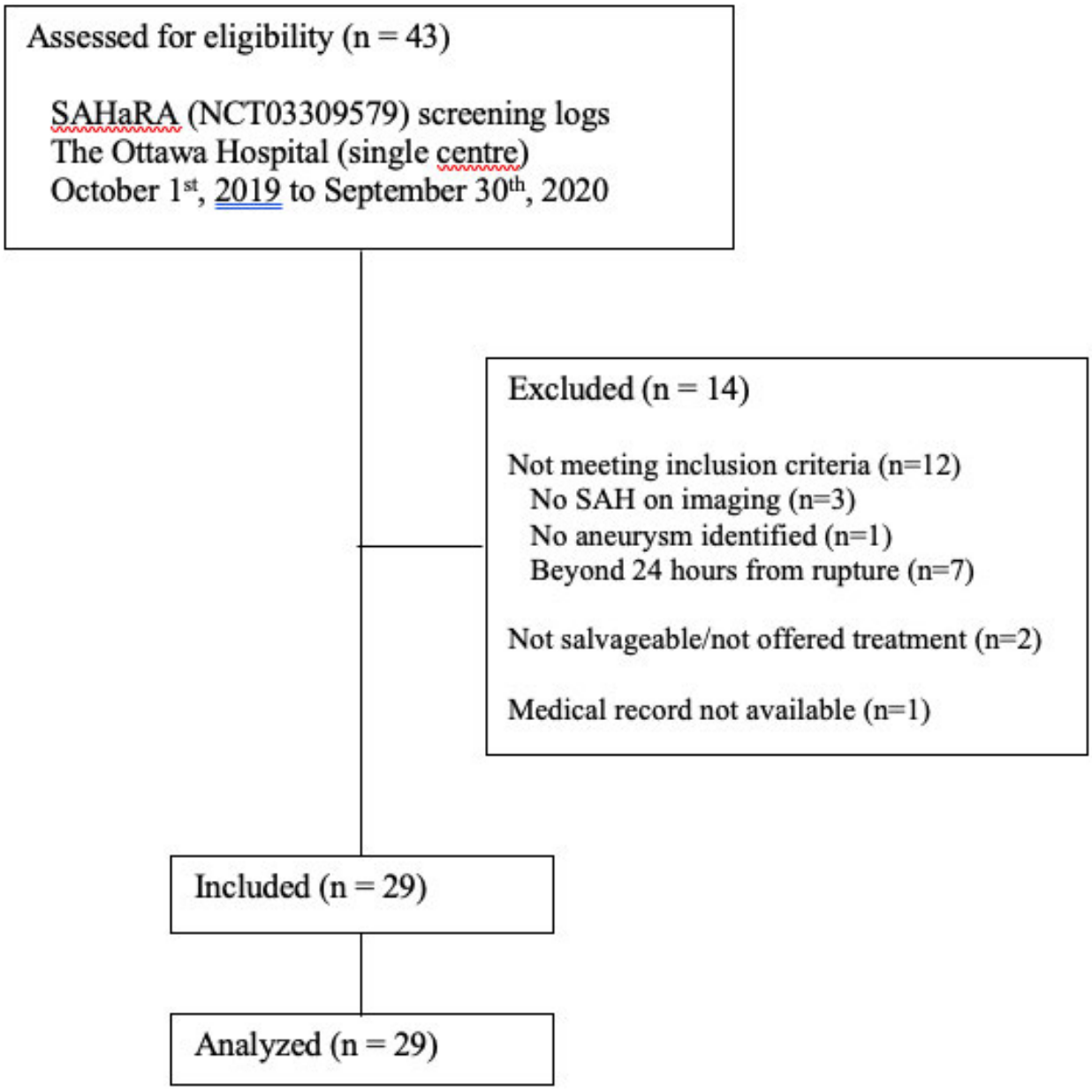
Case 3:

In the final case, consider another 55 year old female who has just been admitted with aSAH. She is 3 hours post rupture. The plan is to secure the aneurysm within the next 24 hours:

- WFNS Grade V (poor grade)
- GCS 6
- She is intubated/ventilated.
- EVD = placed for hydrocephalus and functioning properly.
- CT scan = EVD in good position, resolving hydrocephalus, subtle signs of diffuse cerebral edema.
- ICP = 13 mmHg.
- Other vital signs normal, except elevated blood pressure = 185/100 (128) mmHg.

7.5 Retrospective Cohort Appendix 1

Appendix 1: STROBE Flowchart



7.6 Retrospective Cohort Appendix 2

Appendix 2: Vasopressors ordered and administered for patients with no prescribed lower limit BP target (n=22)

	Medication Ordered Frequency (%)		
Medication Administered Frequency (%)	**No**	**Yes**	**Total (%)**
No	20 (91%)	1 (5%)	21 (95%)
Yes	0	1 (5%)	1 (5%)
Total (%)	20 (91%)	2 (9%)	22 (100%)

7.7 Confirmation of Status of Systematic Review (Accept with Revisions)

From: **Neurocritical Care (NECA)** em@editorialmanager.com
Subject: Decision on your Manuscript #NECA-D-24-00234 - [EMID:0c98ae88d68dadac]
Date: May 31, 2024 at 3:59 PM
To: Luke Terrett [redacted]

Dear Dr Terrett:

Several reviewers and editors have evaluated your manuscript.
We are interested in publishing your manuscript if you can make some revisions.
Prior to a final decision, I would like you to address the issues raised during the review, discussed in the comments below. Should you adequately address those issues, I expect to be able to accept the paper for publication. Please send a revision within 6 weeks or notify me if more time is needed.

Your responses to the reviewers and list of changes must be uploaded as a file in addition to your revised manuscript.
When uploading your revised files, please make sure only to submit your editable source files (e.g., Word, txt). When submitting your revised manuscript please upload 2 files, one of the original submission with the changes indicated (track changes) and a second of the final text of the revised version.

Submit your revised manuscript at:
https://www.editorialmanager.com/neca/

You can obtain your Username/Password by using the "Send Login Details" link available on the login page.
Click "Author Login" to submit your revision.

Thank you for submitting your work to our journal.

With kind regards,

Michael Diringer
Editor-in-Chief
Neurocritical Care