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Treatment of Blunt Cerebrovascular Injury - A Systematic Review and Meta-Analysis, Multicenter Retrospective Review, and Protocol for a Feasibility Randomized Controlled Trial

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ABSTRACT

Blunt cerebrovascular injury (BCVI) is an often-overlooked clinical problem that can result in stroke and cause devastating, potentially permanent, neurologic disabilities in young and otherwise healthy trauma patients. Early diagnosis and treatment of BCVI can reduce the risk of stroke and prevent disability, however, treatment also carries a risk of bleeding complications. More research is needed to understand the optimal management strategy to reduce the risk of stroke while minimizing bleeding complications.

The aim of this thesis is to review and critically appraise the literature to better understand the efficacy of various treatment strategies in preventing stroke following BCVI, evaluate current practice patterns and patient outcomes at Canadian Level I Trauma Centers, and create a feasibility randomized controlled trial protocol to assess practicability of a future randomized control trial determining the optimal dose of antiplatelet therapy in the treatment of BCVI.

Systematic review and meta-analysis of existing literature revealed a slightly lower risk of stroke with the use of antiplatelets compared to anticoagulants (4.5% vs. 5.2%; OR 0.57; 95% CI 0.33 – 0.96, p = 0.04), although there was no difference in stroke rate when evaluating the use of specific agents, acetylsalicylic acid (ASA) vs. heparin (OR 0.43; 95% CI 0.15 – 1.20, p = 0.11). Bleeding complications were significantly higher with the use of anticoagulants and led to more severe bleeding requiring invasive intervention, suggesting better tolerance of antiplatelets in the trauma population. Retrospective review of trauma registries at two Canadian Level I Trauma Centers revealed that patients were more likely to develop stroke after BCVI if they were injured as a result of a motor vehicle collision (MVC), had a lower initial Glasgow Coma Scale (GCS) and higher Injury Severity Scale (ISS), did not meet Denver screening criteria, or had carotid artery injuries. Patients who suffered a stroke were more likely to require intensive care. Treatment

interruptions or delays were not associated with increased risk of stroke, and the dose of therapy (81 mg ASA vs. 325 mg ASA) was not independently associated with an increase in stroke rate after adjustment for initial GCS, injury location, and grade of injury (OR 2.244; 95% CI 0.660-7.628).

Current research suggests that early detection and treatment of BCVI can significantly reduce the risk of stroke. ASA has shown similar efficacy as heparin for stroke risk reduction but was associated with less bleeding complications. Currently, the optimal dose of ASA is still unknown. Data from retrospective reviews suggests that there is no difference in stroke rates when using low-dose (81 mg) vs. high-dose (325 mg) ASA but no experimental studies exist to evaluate this question. A randomized controlled trial is required to further assess different doses of ASA to determine the optimal dose that reduces the risk of stroke while minimizing bleeding complications.

Keywords: blunt cerebrovascular injury (BCVI), blunt trauma, stroke, acetylsalicylic acid (ASA), heparin

LAY SUMMARY

Blunt cerebrovascular injury (BCVI) is injury to the blood vessels in the neck that deliver blood to the brain, which can occur after traumatic injury to the head, neck, or chest. If unrecognized or untreated, BCVI can lead to stroke, which can cause significant and sometimes permanent disability. Previous research has shown that early diagnosis and treatment are effective at reducing the risk of stroke. The most common treatment strategies are anticoagulation or antiplatelet medications, which are effective at decreasing the risk of stroke but may increase the risk of bleeding complications, especially in patients with multiple traumatic injuries. Currently, the optimal agent and dose of therapy to reduce the risk of stroke after BCVI while minimizing bleeding complications is unknown.

This thesis aims to investigate different management strategies for BCVI to find the best treatment strategy that reduces the risk of stroke while minimizing bleeding complications. To do this, we evaluated existing research and reviewed treatment patterns and outcomes at Canadian trauma centers. We showed that aspirin (ASA) and heparin, the two most commonly used treatment strategies for BCVI, are similarly effective at decreasing the risk of stroke. However, treatment with heparin is associated with more significant bleeding complications. Therefore, ASA should be the preferred treatment strategy. Patients treated with low dose ASA had similar risks of stroke compared to those treated with high dose ASA, however, risk of bleeding with different doses is unknown. Further experimental research is required to determine the best dose of therapy. We have created a protocol for a randomized controlled trial that evaluates the effects of different doses of ASA on the risk of stroke and bleeding complications, which is the first step in creating large trials evaluating this question and ultimately improving care for patients with BCVI.

CO-AUTHORSHIP

While this thesis represents my work, and I am responsible for all projects, data collection, analysis, and reporting, the co-authors listed below made important contributions to the project and deserve special mention.

Kelly Vogt, MD, MSc, FRCSC, acted as my supervisor and was instrumental in the design and realization of this thesis. From conception of the project, she provided direction and guidance on all aspects of the research process and manuscript writing. Dr. Vogt also assisted with article screening for Chapter 2, provided instruction on data analysis and interpretation, and critically reviewed and edited all components of the thesis.

Brad Moffat, MD, MSc, FRCSC; Ian Ball, MD, MSc, FRCSC; and Shane Smith, MD, MSc, CCFP, FRCSC, in their roles as committee members, provided invaluable contributions and feedback in critical review of the data and content of each chapter.

Laura Allen, MSc, was a vital team member and invaluable resource throughout the planning and data analysis components of various projects comprising this thesis. She assisted with data analysis and interpretation for Chapters 2 and 3 and championed the research ethics board (REB) and data sharing approval processes for Chapter 3.

Alla Iansavitchene, BSc, MLIS, proved exceptional in her role as clinical librarian with creation and validation of the search strategy, article acquisition and upload to the online screening platform, and assistance with writing the Methods section of Chapter 2.

Nouf Yassin, MBBS, SCFHS, GSSB; Eric Walser, MD, MSc, FRCSC; and Mella Kim, BMSc, assisted with article screening and data collection for Chapter 2.

Amy Makish, MN, NP, assisted with study design and data collection for Chapter 3.

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I am extremely fortunate to have an exemplary research committee that helped shape this thesis and make it immeasurably better. Dr. Brad Moffat, Dr. Ian Ball, and Dr. Shane Smith each

contributed invaluable insights, edits, and, on occasion, humorous comments, to early drafts. I am forever grateful for all their support.

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TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF FIGURES

Figure **Page**

LIST OF APPENDICES

Page

LIST OF ABBREVIATIONS

AC, anticoagulant

ACA, anterior cerebral artery

ACS, American College of Surgeons

ADAPTABLE, Comparative Effectiveness of Aspirin Dosing in Cardiovascular Disease Trial

AP, antiplatelet

ASA, acetylsalicylic acid

ATIII, antithrombin III

ATV, all-terrain vehicle

BCI, blunt carotid injury

BCVI, blunt cerebrovascular injury

BVI, blunt vertebral injury

CCA, common carotid artery

CENTRAL, Cochrane Central Register of Controlled Trials

CI, confidence interval

COX, cyclooxygenase

CTA, computed tomography angiography

DAI, diffuse axonal injury

DSA, digital subtraction angiography

DVT, deep venous thrombosis

EAST, Eastern Association for the Surgery of Trauma

ECA, external carotid artery

GCS, Glasgow Coma Scale

GI, gastrointestinal

GOS, Glasgow Outcome Scale

HR, hazard ratio

HIT, heparin-induced thrombocytopenia

ICA, internal carotid artery

ICH, intracranial hemorrhage

ICU, intensive care unit

IQR, interquartile range

ISS, Injury Severity Scale

IV, intravenous

LHSC, London Health Sciences Centre

MA, meta-analysis

MeSH, Medical Subject Headings

MRA, magnetic resonance angiography

MRI, magnetic resonance imaging

mRS, modified Rankin Scale

MVC, motor vehicle collision

OR, odds ratio

PCA, posterior cerebral artery

pRBC, packed red blood cells

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROOVIT, Prospective Observational Vascular Injury Trial

PS, prospective study

PTT, partial thromboplastin time

REB, Research Ethics Board

REDCap, Research Electronic Data Capture

RR, retrospective review

SCI, spinal cord injury

SD, standard deviation

SR, systematic review

STROBE, Strengthening the Reporting of Observational Studies in Epidemiology

TBI, traumatic brain injury

TIA, transient ischemic attack

TQIP, Trauma Quality Improvement Program

TREAT-CAD, Aspirin versus Anticoagulation in Cervical Artery Dissection Trial

TXA_2, thromboxane A_2

US, ultrasound

WTA, Western Trauma Association

CHAPTER 1
INTRODUCTION

CHAPTER 1. Introduction

1.1 Background

Blunt traumatic injury to the carotid (BCI) or vertebral arteries (BVI), jointly termed blunt cerebrovascular injury (BCVI), occurs due to blunt-force trauma to the head, face, neck, or chest.[1] BCVI occurs in approximately 1-3% of blunt traumas, usually following high-energy traumatic mechanisms, such as motor vehicle collisions, pedestrian versus vehicle collisions, and ATV/motorcycle crashes; as well as some low-energy mechanisms causing trauma to the head and neck, such as hanging and falls.[2-4]

BCVI can cause devastating and potentially permanent neurologic disabilities; if undiagnosed and untreated, BCVI can result in stroke or mortality. The risk of stroke is related to the severity (grade) of injury, however without treatment, stroke occurs in 20-28% of patients with BCVI, usually within the first 72 hours from injury.[4-7] BCVI-related mortality ranges from 1% to over 17% in some studies.[8,9] Patients who develop strokes as a result of BCVI suffer worse long-term outcomes and higher risks of mortality.[4,10-12]

Given the high rates of morbidity, potential long-term disability, and mortality associated with undiagnosed or inadequately treated BCVI, extensive research in recent years has led to the development of screening guidelines to improve early detection, enabling earlier intervention to reduce stroke occurrence. Once diagnosed, however, there is conflicting evidence and unclear guidance about optimal treatment strategies and modalities, and further research is needed to guide BCVI management.[13]

Anatomy

Injury to the carotid or vertebral arteries can impair blood flow to the brain and result in ischemic stroke, or cause embolization from thrombi within the injured vessels, resulting in thromboembolic stroke. Knowledge of anatomy is important for understanding injuries commonly associated with BCVI and the clinical presentation of strokes occurring as a result of BCVI.

The brain is supplied by the internal carotid arteries (ICAs), which arise from the common carotid arteries (CCAs), and the vertebral arteries, which branch off the subclavian arteries (Figure 1.1).[14-16] After bifurcation from the common carotid arteries, the internal carotid arteries enter the skull via the carotid canal of the temporal bone and branch into the anterior and middle cerebral arteries, together comprising the anterior circulation of the brain and supplying the cerebral hemispheres (except for the occipital lobes), which contain the frontal, parietal, and temporal lobes.[14,15] These areas are important for interpreting and integrating sensory and other information (frontal lobe), enabling hearing, speech, and declarative memory (temporal lobe), and coordinating sensory outputs (sensory cortex located in the postcentral gyrus of the parietal lobe) and motor function (motor cortex of the frontal lobe).[17]

The vertebral arteries branch off the subclavian arteries (running within the transverse foramina of the cervical vertebrae), and, together with the basilar artery and posterior cerebral arteries, comprise the posterior circulation to the brain. The posterior circulation provides blood flow to the brainstem, cerebellum, inferior aspect of the cerebral hemisphere and occipital lobe, and components of the limbic system. These areas are crucial for maintaining vital body functions, including regulating cardiovascular and respiratory functions, metabolic functions, and consciousness, coordinating movement, enabling vision, and allowing for interconnection between

the cerebellar hemispheres and the brainstem and thalami.[14,17] More details about head and neck vascular anatomy can be found in Appendix I.

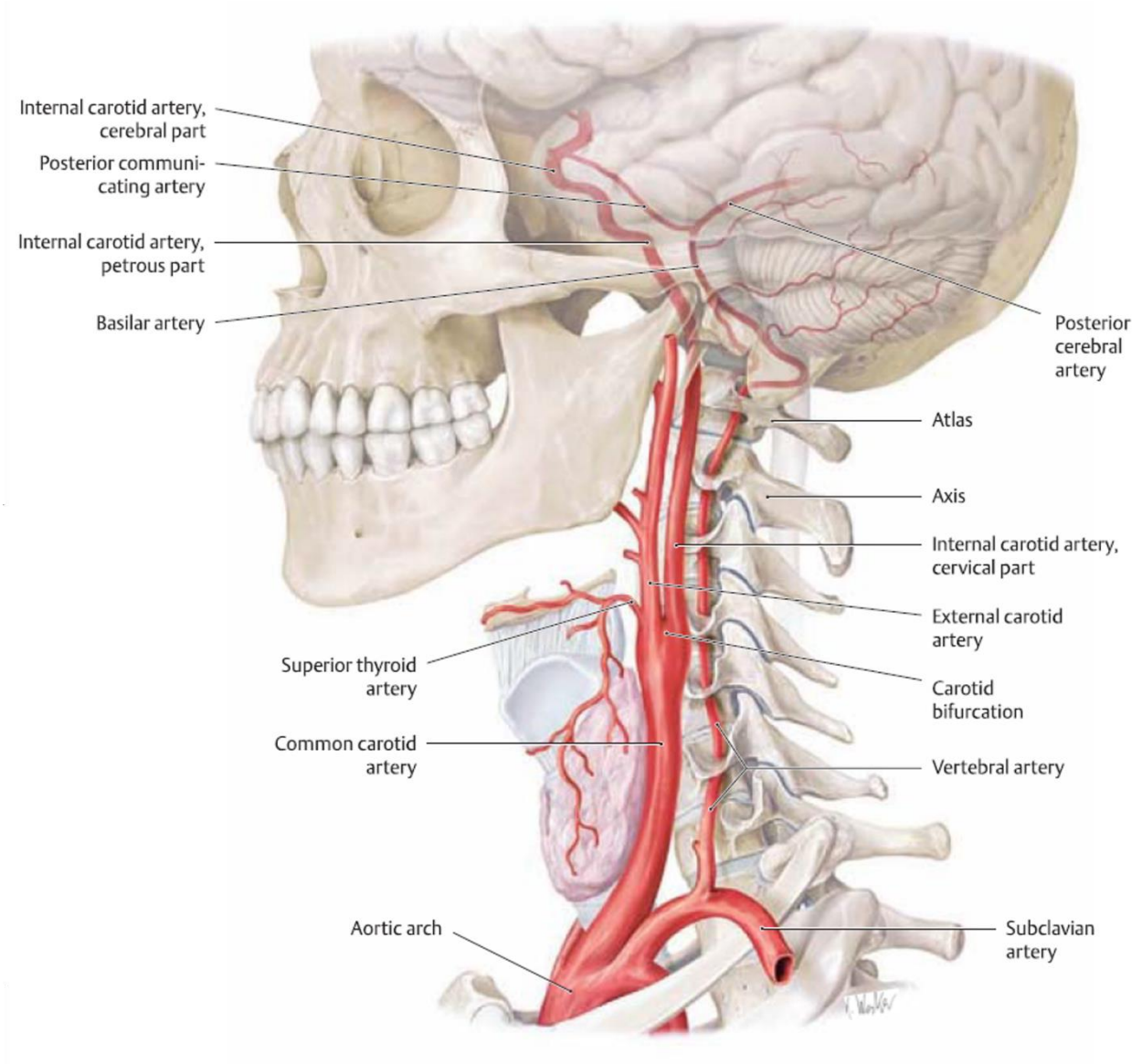

Figure 1.1. Vascular anatomy of the head and neck[15]

Image Credit: Schünke Michael, Schulte, E., Schumacher, U., Ross, L. M., Lamperti, E. D., Taub, E., Voll, M., & Wesker, K. (2010). Blood Vessels of the Brain. In *Atlas of Anatomy: Head and Neuroanatomy* (1st ed., pp. 246–265). Thieme.

Pathophysiology

Injury to the carotid and/or vertebral arteries occurs as a result of extreme neck rotation or hyperextension, direct blunt trauma to the artery, intraoral trauma, or injury from skull or vertebral fracture fragments.[18] Regardless of the underlying mechanism of injury, BCVI typically begins as an intimal disruption of the arterial wall, exposing the underlying subendothelial collagen, which promotes platelet aggregation, clotting, and subsequent embolization (Figure 1.2).[19,20] Arterial dissection can also cause intramural hematomas that impair blood flow, or result in partial or complete thrombosis, ultimately causing cerebral ischemia. In some cases, injury to the vessels can lead to pseudoaneurysms that compress the true vessel lumen, act as a source of embolization, or that eventually rupture and cause intra- or extracranial hemorrhage. In rare cases, injury causes complete transection through the artery, resulting in significant hemorrhage.[1,21,22]

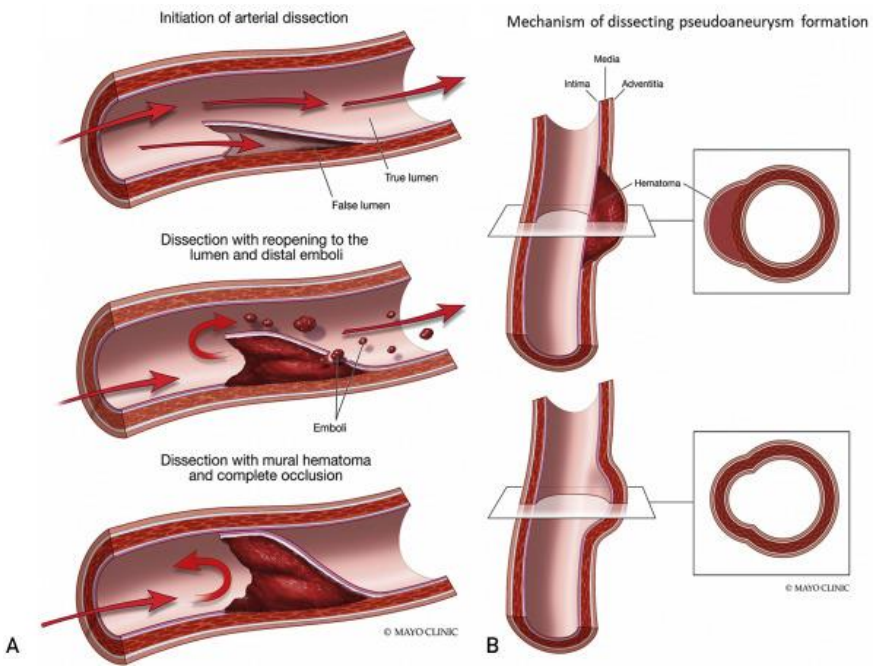

Figure 1.2. Pathophysiology of arterial dissection (A) and pseudoaneurysm formation (B)[19]

Image Credit: Keser, Z., Meschia, J. F., & Lanzino, G. (2022). Craniocervical Artery Dissections: A Concise review for Clinicians. *Mayo Clinic Proceedings*, 97(4), 777–783.

Injury can occur at any location along the artery. Most blunt carotid artery injuries occur along the distal internal carotid artery, near the skull base, typically as a result of neck hyperextension and stretching of the artery over the lateral articular processes of C1-C3.[23,24] Blunt vertebral artery injuries occur most commonly in the pars transversaria (V2), the cervical part of the artery which extends from the transverse foramen of C6 to C2, or the atlas loop (V3), ascending through the transverse foramen of C2, lateral to C2 and the C1-C2 articulation, to emerge from the transverse foramen of C1. [3,23,25,26]

Incidence and Risk of Stroke

BCVI is a rare injury. Initial studies suggested an incidence of less than 1 in 1000 blunt traumatic injuries (0.08%),[27] however, with greater awareness, increased screening, and improved imaging techniques and technology, the reported incidence has increased to 1-2.7%, and even up to 3% in high-risk patients.[3,28]

Once diagnosed with BCVI, patients should be started on treatment to reduce the risk of stroke. Treatment with antiplatelets or anticoagulation has been shown to significantly decrease the incidence of stroke, from 20-54% in untreated patients, to less than 1% to 3.9% in treated patients.[5,9,29,30] Amongst patients diagnosed with BCVI, higher risk of stroke has been associated with higher percentage of luminal stenosis and the presence of pseudoaneurysm (higher grade of injury), the presence of intraluminal thrombus on initial imaging, changing imaging features with repeat imaging (such as new intraluminal thrombus in carotid artery injuries or resolution of intraluminal thrombus in vertebral artery injuries), and lack/delay in treatment.[6,31,32] The majority of patients with BCVI who develop a stroke do so within 72 hours of admission, and most strokes are diagnosed within 72 hours to 1 week from injury.[7,33,34]

Clinical Presentation

Clinical presentation of BCVI is variable, depending on the injury site and severity, and ranges from asymptomatic injuries detected via screening (most common), to focal or global neurological deficits, to mortality. Early studies indicated that many patients with BCVI present with stroke at the time of diagnosis, with some studies showing up to 90% of patients with BCVI had suffered a stroke prior to BCVI diagnosis.[6] With increased recognition of BCVI and creation of screening protocols, most injuries are now detected before the onset of symptoms.[2] Signs suggestive of possible BCVI, including unexplained altered mental status or lateralizing neurologic signs, have been incorporated into screening criteria for detection of BCVI (Table 1.1).[34,35]

Injury to the carotid arteries can result in stroke within the anterior circulation (which supplies the cerebral hemispheres), resulting in classic stroke symptoms.[36] Injury to the vertebral arteries more commonly results in posterior circulation stroke, characterized by symptoms of oculomotor deficits, ataxia, "crossed" deficits (symptoms within cranial nerve territories on one side with sensory/motor deficits on the contralateral arm/leg), Horner's syndrome, etc.[36-39] Posterior circulation strokes, although less common, have a worse prognosis, result in worse functional outcomes, and are more difficult to detect clinically, potentially resulting in delayed diagnosis and treatment.[37,38]

Associated Injuries

Several injuries commonly occur with BCVI, and these associations have been used in the creation of screening guidelines to predict BCVI risk and need for imaging. Injuries associated with BCVI include cervical spine fractures (the strongest independent predictor for BCVI), especially fractures of C1-C3, fractures through the foramen transversarium, or fractures with

associated subluxation, basilar or complex skull fractures, fractures involving the petrous part of the temporal bone, occipital condyle fractures, mandibular fractures (especially displaced fractures or fractures of the mandibular condyle), Le Fort II or III midface fractures, and global signs of severe brain injury, such as Glasgow Coma Scale (GCS) ≤ 6.[1,21,29,34,40,41] Patients with blunt carotid injuries are more likely to have traumatic brain injury (TBI), facial fractures, or basilar skull fractures and tend to have a higher injury severity score (ISS) and lower GCS at presentation compared with patients with blunt vertebral artery injuries. Patients with vertebral artery injuries are more likely to have cervical spine injuries. In some series, cervical spine fractures were 22.9 times more likely to be present in patients with BCVI and were present in 67% of patients with vertebral artery injury.[6,42]

Of particular note are associated injuries that may increase the risk of bleeding complications with initiation of antiplatelet or anticoagulation treatment. These include traumatic brain injury or intracranial hemorrhage (ICH), and solid organ injuries, both of which commonly occur with BCVI.[33,40] Patients with TBI are at higher risk of BCVI, with an incidence of BCVI of 9.2% in patients with TBI, and TBI has been reported to accompany BCVI in over 40% of cases.[4] Patients with both TBI and BCVI are typically more seriously injured, with a higher ISS and higher incidence of hemodynamic shock at presentation.[40] Similarly, patients with solid organ injuries are at risk for delayed bleeding, requiring serial examinations, frequent bloodwork, and in some cases continuous cardiac monitoring.[33] These situations pose unique challenges as many physicians are understandably hesitant to initiate antiplatelet or anticoagulant therapy in these patients given the risk of exacerbating hemorrhage, which often leads to treatment delays. Multiple recent studies have shown that early treatment of BCVI in patients who have concomitant TBI or solid organ

injuries is safe and important to reduce the risk of BCVI-related stroke,[43-45] however, more research in this area is required to inform future care.

Imaging – Screening and Diagnosis

With improvements in recognition and implementation of screening protocols, more BCVIs are now diagnosed prior to stroke occurrence, enabling early treatment, and significantly reducing the risk of stroke.[3,46] Over the last several decades, increased use of imaging has led to a higher reported incidence of BCVI, with some institutions reporting an increase in incidence from 0.33% to 2%.[47] The incidence of stroke and BCVI-related mortality has declined from a stroke rate of 37% to 5%, and a mortality rate of 24%, to almost 0% in some small studies.[47] In larger studies, however, BCVI-related mortality ranges from 6% to 17.7%,[9,48] and BCVI stroke-related mortality is up to 40% in some studies.[12]

Screening for BCVI has dramatically altered outcomes for patients with this injury, however, many questions remain about optimal screening guidelines and modalities of screening. Several screening guidelines currently exist to assist physicians in determining which patients to screen.[3,41,49,50] The most widely recognized and commonly used screening guidelines are the Memphis[49] and expanded Denver[3,50] criteria; other prominent criteria include the Boston criteria[51] and the criteria set out in the EAST guidelines[13,41] and ACS TQIP guidelines[52] (Table 1.1).

Table 1.1. BCVI Screening Criteria

Denver Criteria[3,50]	
Signs/Symptoms of BCVI	**Risk Factors for BCVI**
Arterial hemorrhage from neck/nose/mouth	High energy transfer mechanism
Cervical bruit in patient < 50 years old	Displaced mid-face fracture (Le Fort II or III)
Expanding cervical hematoma	Mandible fracture
Focal neurological deficit – TIA, hemiparesis, vertebrobasilar symptoms, Horner's Syndrome	Complex skull fracture/basilar skull fracture/occipital condyle fracture
Neurologic deficit inconsistent with head CT	Severe Traumatic Brain Injury (TBI) with GCS < 6
Stroke on CT or MRI	Cervical spine fracture, subluxation, or ligamentous injury at any level
	Near hanging with anoxic brain injury
	Clothesline type injury or seat belt abrasion with significant swelling, pain, or altered mental status
	TBI with thoracic injuries
	Scalp degloving
	Thoracic vascular injuries
	Blunt cardiac rupture
	Upper rib fractures
Memphis Criteria[49]	
Cervical spine fracture	
Neurologic exam not explained by brain imaging	
Horner's syndrome	
Le Fort II or III fractures	
Skull base fractures involving the foramen lacerum	
Neck soft tissue injury (eg. seatbelt injury or hanging)	
Boston Criteria[51]	
1st Tier‡	**2nd Tier**†
Skull base fractures: petrous and basilar fractures	Complex facial fractures with midface instability
Any cervical spine fractures	DAI
Cervical spinal injury (cord, vertebral body, or ligaments)	Combined significant head and chest trauma
	Near-hanging
Soft tissue injury to the anterior neck with swelling/ecchymosis/hematoma/or bruit	Seat-belt abrasions on neck
Significant neurological deficit: lateralizing neurological deficit, TIA, Horner's syndrome	Other unexplained neurological deficits: vertigo, tinnitus, or GCS < 6
Evidence of brain infarct on CT	

TIA, transient ischemic attack; MRI, Magnetic Resonance Imaging; DAI, diffuse axonal injury
‡1st tier criteria indicate need for screening via CTA at the time of presentation
†2nd tier criteria indicate need for screening within 24-48 hours from presentation

Assessment of current screening guidelines repeatedly shows poor sensitivity and specificity of existing screening criteria.[49] Many patients with BCVI are missed because they do not have traditional risk factors.[49,53] Therefore, screening criteria continue to be expanded to include patients with traumatic brain injuries, scalp degloving, complex skull fractures, frontal skull fractures and orbital fractures, fractures of the petrous part of the temporal bone, mandibular fractures, upper rib fractures and other thoracic injuries, great vessel injuries, cardiac injuries, and multiple traumatic injuries.[3,30,53]

While expanded criteria have improved sensitivity,[13] as many as 21-53% of patients with BCVI are missed with existing guidelines.[29,30,53-57] As a result, many institutions have transitioned to universal screening in an effort to diagnose patients with BCVI who would not qualify for screening based on traditional screening criteria. Universal screening in some centers has increased the rates of BCVI diagnoses, with an incidence of BCVI as high as 7.6% in one study, more than double what has previously been reported in the literature.[53] In a Markov cost-benefit analysis of different screening criteria and strategies, universal screening was deemed to be the most cost-effective strategy.[58] Given the high morbidity, potential long-term disability, and high healthcare and societal costs associated with caring for patients with strokes, universal screening may be indicated to decrease the rate of missed BCVIs and subsequent BCVI-related strokes.[57]

Historically, the gold standard diagnostic modality for BCVI detection was four-vessel digital subtraction angiography (DSA).[41] DSA is sensitive and cost-effective in detecting BCVIs and reducing BCVI-related stroke,[11] however, DSA is an invasive procedure, and as such, carries risks of access-site complications, iatrogenic arterial injury/dissection, embolic stroke, bleeding complications, and infection. DSA is also limited in that it enables visualization of the vessel lumen

but does not allow for direct visualization of the vessel wall, potentially missing injuries involving wall hematomas or non-stricturing lesions.[21]

Recent improvements in CT imaging and adoption of high-resolution multi-slice CT scanners has led to a shift such that CT angiography (CTA) is now the primary modality employed in BCVI screening and diagnosis and is the recommended screening modality as per the American College of Surgeons (ACS) Trauma Quality Improvement Program (TQIP) Best Practice Guidelines.[52] Adoption of screening with CTA has led to significant reductions in both the time to diagnosis of BCVI and BCVI-related stroke.[59] Reported sensitivities for CTA range from 64-97.7%, with a specificity ranging from 95-100%,[60-64] compared to much lower sensitivities for other screening modalities, such as magnetic resonance angiography (MRA; sensitivity 61%, specificity 86%), or duplex ultrasonography (US; sensitivity 38.5-40%, specificity 99-99.7%).[65,66] Neither MRA nor Dupplex US have proven sensitive enough for reliable detection of BCVI and are not currently recommended screening modalities.[41]

Injury Grading

BCVI severity is classified using a grading scale developed by Biffl *et al*. in 1999 (Table 1.2).[67] The grade of injury has important implications for the risk of stroke and mortality. Use of this grading scale enables standardized characterization and helps guide management.

Table 1.2. Biffl *et al*. Injury Grading Scale for BCVI[67]

Injury Grade	Angiographic Characteristics
I	Luminal irregularity or dissection with < 25% luminal narrowing
II	Dissection or intramural hematoma with ≥ 25% luminal narrowing, intraluminal thrombus, or raised intimal flap
III	Pseudoaneurysm
IV	Occlusion
V	Transection with free extravasation

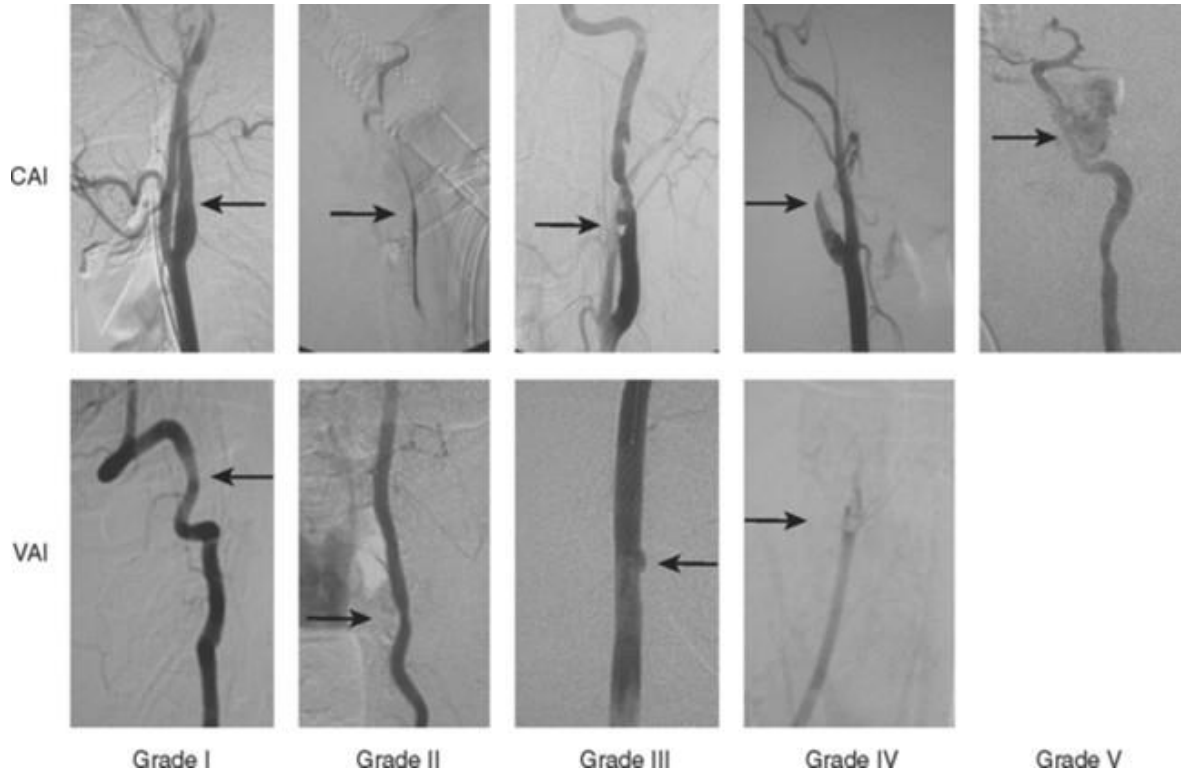

Figure 1.3. Representative DSA images of each injury grade[68]

Image Credit: Cothren, C. C., & Moore, E. E. (2005). Blunt cerebrovascular injuries. *Clinics*, 60(6), 489–496.

Risk of stroke correlates with injury severity, with greater correlation for carotid than vertebral artery injuries. Grade I carotid injuries carry an 8% risk of stroke, grade II injuries have a 14% risk of stroke, grade III injuries have approximately 26% risk of stroke, and grade IV injuries have a 50% risk of stroke. Grade I vertebral artery injuries carry a 6% risk of stroke, grade II

injuries a 38% risk of stroke, and grade III and IV injuries a 27-28% risk of stroke. Grade V injuries for both carotid and vertebral arteries have a 100% risk of stroke in most studies.[32]

Grade I injuries tend to have a good prognosis if detected and treated early, with over 50% of grade I injuries healing on follow up imaging. Approximately 8% of grade I injuries have been noted to progress to pseudoaneurysm formation, requiring more invasive treatment. Grade II injuries have significantly lower rates of healing, with some series reporting healing in only 8% of cases, and progression to pseudoaneurysm formation in 43%; overall improvement was noted in 22% of cases and worsening in 46%. Grade III injuries rarely healed on follow up imaging (only 3% healing rate in one study), grade IV injuries were rarely followed up, possibly due to poor healing rates, and grade V injuries were universally fatal in several studies.[6]

Treatment Options

Over the last 30 years, there has been significant progress in understanding and treatment of blunt cerebrovascular injuries. Early studies highlighting the importance of treatment to reduce stroke risk showed that treatment with heparin lead to improved survival and neurological outcomes.[69] Since then, several studies have evaluated different treatment strategies for BCVI, with most studies showing significant reductions in stroke risk following treatment with anticoagulation or antiplatelet agents.[2,5,9,29,70] Antiplatelet treatment usually consists of aspirin (81-325 mg daily) or clopidogrel (75 mg daily); the most common anticoagulation regimen is the use of unfractionated intravenous heparin (10 U/kg/h) without a bolus to target aPTT of 40-50 seconds.[32,50]

Although there are some indications for additional therapies, such as endovascular therapy (in the case of select higher grade injuries) or surgery, the mainstay of treatment is anticoagulation or antiplatelet agents for grade I-IV injuries.[22,32,71] Traditionally, grade I and II injuries are treated

with anticoagulation, typically intravenous (IV) heparin infusion with transition to warfarin, or antiplatelets, usually aspirin (ASA). Grade III-V injuries have historically required operative or endovascular management,[41] although recent data suggests that anticoagulation and/or antiplatelet therapy has an increasing role in even high grade BCVIs.[32] Endovascular stenting is rarely necessary, except in symptomatic or rapidly expanding pseudoaneurysms.[71-73] Grade V injuries require emergent operative or endovascular intervention to control hemorrhage and are often fatal despite treatment.[32] A summary of treatment strategies stratified by grade of injury is available in Table 1.3.

Table 1.3. Summary of Treatment Options Stratified by Grade of Injury[22,32,50]

	Medical Management	**Endovascular Therapy**	**Surgery**
Grade I	AP or AC first line therapy	Not indicated	Not indicated
Grade II	AP or AC first line therapy	Rarely needed, consider in the presence of neurologic symptoms or progression of dissection on repeat imaging	Rarely indicated
Grade III	AP or AC first line therapy	Indicated in some cases if aneurysm size > 1 cm or symptomatic	Rarely indicated
Grade IV	AP or AC first line therapy	Stenting usually not beneficial/indicated	Rarely indicated
Grade V	AP or AC indicated once stabilized*	Urgent stenting indicated for surgically inaccessible lesions	Urgent surgery if in an accessible location

AP, antiplatelets; AC, anticoagulants
*Dual antiplatelet therapy (ASA + clopidogrel) is required following stenting

Early treatment of asymptomatic patients is imperative to reduce stroke, with a recent systematic review showing that untreated patients have a 25% risk of stroke, while patients given any treatment have a stroke rate of 3%.[70] Delay in treatment and interruptions to treatment are associated with higher stroke rates.[74] Concomitant injuries are commonly cited as a reason for

withholding or delaying treatment with anticoagulation or antiplatelet therapy.[29,49] As many as 30% of patients with BCVI do not receive therapy or have delays in initiation of therapy due to associated traumatic brain injury, spinal cord injury (SCI) or need for spinal stabilization, solid organ injuries, pelvic fractures, or other orthopedic injuries due to concerns of exacerbating bleeding.[29]

Follow Up

Repeat imaging is required to evaluate healing or progression of blunt cerebrovascular injuries given high rates of change in injury grade noted on repeat imaging.[6] Repeat CTA is recommended at 7 to 10 days after BCVI diagnosis.[75] Many studies have shown that low-grade injuries (grade I or II) have a high rate of healing, allowing for discontinuation of therapy.[6,76,77] Grade II injuries have the potential to progress or develop into pseudoaneurysms, potentially necessitating endovascular intervention.[6] Higher-grade injuries (grade III and IV) rarely heal and require re-assessment to ensure there is no progression or indication for further intervention.[6,78-80] Persistent injuries require continued treatment with antiplatelets or anticoagulants, with repeat follow up imaging recommended at 3-6 months, before discontinuation of therapy.[75]

Despite absence of ischemic complications, many patients with BCVI have poor neurological prognosis, possibly due to TBI or other associated injuries.[81] Long-term clinical follow up reveals that most patients recover at least some neurological function, with many patients returning to normal or near-normal function.[10,75] Stroke due to BCVI was associated with worse functional outcomes, particularly impacting mobility and self-care.[4] Among patients who develop strokes, most strokes occur within the first week after injury (usually within the first 72 hours after injury), with very rare occurrence of strokes after 1 week.[7,81]

Current Guidelines

The most recent guidelines from the Western Trauma Association (WTA),[50] Eastern Association for the Surgery of Trauma (EAST),[13] and the Best Practice Guidelines from the Scandinavian Journal of Trauma[75] stress screening patients at high risk of BCVI using established criteria (Table 1.2). Once BCVI is identified, early treatment is recommended with either antiplatelets or anticoagulants, however, the most recent guidelines are unable to make specific recommendations as to the optimal treatment strategy and dose.[13] More research is required to determine the best treatment strategy to reduce BCVI-related stroke while minimizing bleeding complications.

1.2 Antiplatelets vs. Anticoagulants for Management of BCVI

Anticoagulation and antiplatelet medications (most commonly heparin and ASA) comprise the mainstay of BCVI treatment. Despite treatment of BCVI with anticoagulants and antiplatelets for several decades, there is little guidance about the optimal agent for therapy, required duration of therapy, risk of bleeding, and long-term follow up.

Commonly Used Antiplatelets and Anticoagulants – ASA vs. Heparin

Heparin is an anticoagulant containing a unique pentasaccharide sequence with high affinity for binding antithrombin III (ATIII), an anticoagulant that inhibits activated coagulation factor IIa (thrombin, which converts fibrinogen to fibrin), factor Xa, and, to lesser extents, factors XIIa and IXa.[82-85] Binding of heparin to ATIII increases its antithrombotic activity over 1000 fold,[83,84] resulting in decreased function of thrombin, thereby preventing fibrin formation and reducing thrombin-mediated activation of platelets and other coagulation factors (V and VIII).[82] Heparin exerts additional antithrombotic effects by binding to heparin cofactor II which further

catalyzes thrombin inactivation, as well as binding directly to platelets and inhibiting their function.[82,85]

Heparin, when administered intravenously, has a rapid onset of action, and is commonly used for treatment of venous thromboembolism.[86] Early studies showed that patients with BCVI treated with heparin had improved neurologic outcomes and reduced mortality compared to untreated patients.[69] Since then, heparin-based treatment protocols for BCVI have been developed,[6] and a heparin-based protocol is recommended by the most recent WTA guideline.[50] Heparin is preferred in the acute phase as it is reversible in the event of bleeding complications and may be more effective at reducing the risk of stroke compared to antiplatelets. However, a recent systematic review and meta-analysis has shown similar efficacy in terms of BCVI-related stroke reduction with antiplatelets vs. anticoagulants, although anticoagulants were associated with increased bleeding complications.[87] Many centers have transitioned to an aspirin-based treatment approach given its ease of administration and perceived decreased bleeding complications.[88,89]

ASA, or acetylsalicylic acid, is a cyclooxygenase (COX) inhibitor that irreversibly binds COX-1 and COX-2 within platelets, impairing conversion of arachidonic acid to thromboxane A_2 (TXA_2), which normally assists with platelet aggregation and vasoconstriction.[90,91] Inhibition of thromboxane production results in impaired platelet function and decreased clotting. Many studies have investigated the pharmacologic effects and relative efficacy in stroke prevention with different doses of ASA. These studies suggest that doses of 50-100 mg of ASA completely inhibit production of TXA_2 if taken daily,[90-92] although some studies report higher doses (300-500 mg) are required for complete inhibition in the acute setting.[93] ASA is rapidly absorbed by the gastrointestinal tract, resulting in measurable decreased platelet function within 60 minutes of administration (slower with enteric-coated formulations of ASA, which significantly delay

absorption). The half-life of ASA within the circulation is relatively short, approximately 20 minutes, but because platelets are irreversibly inhibited by ASA (unable to produce more COX), the effects of ASA persist for the duration of the lifespan of the inhibited platelets (approximately 7-10 days). After a single administered dose of ASA, platelet function recovers by about 10% each day as new platelets are being produced. With as little as 20% platelet function required for normal hemostasis, the effects of ASA are mostly reversed after approximately 2-3 days.[90] The pharmacokinetics of ASA have important implications when considering dosing for management of BCVI and understanding the implications of missed or delayed doses of therapy.

ASA has a long-standing history in use for both treatment and secondary prevention of vascular events following myocardial infarcts and strokes and is currently recommended for secondary prevention of vascular events (stroke, TIA, and myocardial infarct) by the 2020 Canadian Stroke Best Practice Recommendations,[94] as well as the American Heart Association and American Stroke Association 2021 Guidelines for the prevention of stroke and TIAs.[95]

Due to conflicting evidence on best practices for stroke prevention with ASA while minimizing bleeding complications, more research is needed to establish optimal ASA dosing for patients with vascular risk factors. ADAPTABLE, a recently conducted large randomized controlled trial comparing the effectiveness of low-dose ASA (81 mg daily) and high-dose ASA (325 mg daily) on the risk of the composite outcome of death, myocardial infarct, or stroke in patients with cardiovascular disease showed similar event rate for the major composite outcome (7.28% for ASA 81 mg vs. 7.51% for ASA 325 mg; HR 1.02; 95% CI 0.91 – 1.14), and no significant difference in bleeding complications between groups (0.63% for ASA 81 mg vs. 0.60% for ASA 325 mg; HR 1.18; 95% CI 0.79 – 1.77).[96] No study comparing different doses of ASA in stroke prevention and bleeding complications in the trauma population has been conducted.

Trauma patients are unique in that they are at increased risk of bleeding immediately post injury (eg. from delayed solid organ bleeding or intracranial hemorrhage) but also often incur increased thrombotic risk related to their injuries, as well as clotting secondary to the hypercoagulopathy that is associated with later stages of trauma-induced coagulopathy.[97] More research in this area is needed to better inform care of BCVI patients that are at particularly high risk of clotting resulting in stroke.

Antiplatelets vs. Anticoagulants – Evidence from the Non-Trauma Literature

Evidence from the non-trauma literature that describes stroke occurrence after spontaneous cervical artery dissection may offer further insight into stroke prevention with different medical management strategies. Spontaneous cervical artery dissection is the etiology for approximately 20% of strokes in young patients (occurring in 2.6-2.9 per 100,000 patients with mean age of diagnosis of 45) and the cause of 2.5% of all strokes.[98] The pathophysiology of cervical artery dissection is believed to be due to spontaneous intimal tears within the arterial walls resulting in aneurysmal dilation or intramural hematoma formation, similar to that of BCVI. Underlying arteriopathies or connective tissue disorders increase the risk of cervical artery dissection.[99]

The literature is mixed with respect to the relative efficacy of anticoagulation vs. antiplatelet therapy for stroke prevention following non-traumatic cervical artery dissection. A systematic review of existing literature until 2010 comparing the effects of anticoagulants vs. aspirin on death, disability, and risks of stroke and intracranial hemorrhage following carotid artery dissection revealed no significant difference in the occurrence of stroke or intracranial hemorrhage.[100] However, there was a non-significant trend towards decreased death and disability following treatment with anticoagulants. There were no completed randomized controlled trials included in the review, limiting the conclusions that could be drawn regarding the relative efficacy

and risk profile of antiplatelets vs. anticoagulants in the treatment of carotid artery dissection. Given the scarcity of high-quality data and small group sizes in preceding research which could bias results in either direction, a meta-analysis using Bayesian techniques was performed to compare the effects of antiplatelets and anticoagulants on the composite outcome of ischemic stroke, intracranial hemorrhage, and death.[101] The study found an advantage favouring antiplatelets in reducing the risk of the composite outcome (relative risk 0.32; 95% CI 0.12-0.63). However, when analyzing only studies of high methodological quality, the benefit was considerably less pronounced and no randomized controlled trials were included in the meta-analysis, again limiting the conclusions.

In response to the lack of high-quality evidence investigating this clinical issue, two multicenter randomized controlled trials were conducted. The CADISS trial, a randomized controlled trial of 250 patients investigating the effects of antiplatelet vs. anticoagulation therapy to reduce the risk of stroke recurrence following symptomatic spontaneous extracranial carotid and vertebral artery dissection showed no difference in ischemic stroke, TIA, death, or radiographic residual arterial narrowing with the use of antiplatelets or anticoagulants.[102] The event rate in the study was very low, however, and therefore the study was underpowered to answer this question. In part to address the issue of low event rate, TREAT-CAD, a subsequent randomized non-inferiority trail of 294 patients comparing use of aspirin and vitamin K antagonists (anticoagulants) in the treatment of cervical artery dissection, was conducted to evaluate efficacy in preventing the composite outcome of stroke, major hemorrhage, or death; the primary endpoint occurred in 23% of patients treated with aspirin and 15% of patients treated with anticoagulants, and non-inferiority of aspirin could not be proven, although absolute occurrences in both groups were low.[103]

Even within the non-trauma literature, there is conflicting evidence as to the best treatment strategies for stroke prevention, and many of the same challenges existing within the trauma literature (low event rates, variable treatment regimens, etc.) are present.

Antiplatelets vs. Anticoagulants for Treatment of BCVI

Observational studies evaluating BCVI demonstrate similarly conflicting data, with no definite conclusions as to the superiority of one treatment strategy over another.[5] An early retrospective review performed by Miller *et al*. of their center's experience with BCVI over a 4-year period identified 96 patients with a total of 139 BCVIs.[9] Of the 57 patients with carotid injuries who received medical management, 21% received heparin, 31% received aspirin, and 17% did not receive any treatment due to contraindications; the overall stroke rate in this population was 31% (23 of 75 patients suffered a stroke). Patients who received treatment had significantly fewer strokes than those not receiving any treatment; of those receiving treatment, patients treated with heparin had significantly better neurologic outcomes at discharge than those receiving aspirin or no treatment. Fifty patients in the study sustained vertebral artery injuries; 31 patients (62%) were treated with heparin, 13 (26%) were treated with aspirin, and 4 (8%) did not receive treatment due to contraindications. Patients who received treatment had a significantly lower rate of stroke development, with an overall stroke rate in this population of 14%. Patients treated with heparin had better neurologic outcomes at discharge than those treated with aspirin. Rates of hemorrhagic complications in all groups were minimal. Overall, treatment with either aspirin or heparin was effective at significantly reducing stroke following BCVI, with possible benefits in favour of heparin in terms of neurological status at the time of discharge.

A subsequent study by Cothren *et al*. directly compared efficacy of stroke reduction with antiplatelet vs. anticoagulant therapy following BCVI in 301 patients, with a cumulative 422

arterial injuries.[5] In this retrospective cohort study, treatment was initiated in 282 patients with asymptomatic BCVI, with either heparin, aspirin, or aspirin and clopidogrel; only one patient on treatment suffered a stroke after treatment with heparin for a grade II vertebral artery injury (stroke rate of 0.3%), compared to 50 strokes in patients not treated with antithrombotic or anticoagulation agents (stroke rate of 21%), and a resultant BCVI stroke-related mortality of 30% (15 of 50 patients). Eight patients in total receiving treatment had bleeding complications, in some cases requiring emergent surgery. Treatment with either antiplatelets or anticoagulants was effective in decreasing stroke rate, with infrequent complications and no mortalities related to complications. Overall, there was no significant difference in stroke risk or hemorrhagic complications between the groups.

Larger studies evaluating treatment with anticoagulants vs. antiplatelets for BCVI showed conflicting results. Hanna *et al*. conducted an analysis of the Nationwide Readmission Database investigating trauma patients with BCVI who had been discharged to evaluate the risks of readmission with stroke following treatment with either antiplatelets or anticoagulants.[104] Propensity score matching with a 1:1 ratio was conducted to control for patient demographics and other variables. The study showed that patients treated with anticoagulants were less likely to be readmitted with stroke within 6 months from discharge (1.8% vs. 5.72%, $p = 0.03$) and had a lower 6-month mortality rate (1.3% vs. 4.9%, $p = 0.03$). The following year, however, Bonow *et al*. published a large retrospective study evaluating 677 patients treated with ASA or anticoagulation over a span of 10 years which showed that patients treated with aspirin had a lower risk of stroke than those treated with anticoagulants.[105] Twenty-three of 600 patients (3.8%) treated with ASA suffered a stroke vs. 9 of 77 patients (11.7%) treated with anticoagulants; patients treated with anticoagulants had a higher likelihood of stroke (OR 3.01; 95% CI 1.00 – 8.21) and 15% higher

probability of sustaining a stroke compared to patients treated with aspirin in propensity-matched analysis. A prospective observational multicenter study conducted by Russo *et al*. evaluated 971 BCVIs identified from the PROspective Vascular Injury Treatment (PROOVIT) registry.[12] Patients treated with either antiplatelets or anticoagulation had a lower risk of stroke and death compared to untreated patients. Unfortunately, treatment with antiplatelets was not directly compared to treatment with anticoagulants, although univariate analysis of risk factors for stroke showed a significant reduction in stroke risk following use with antiplatelets but not anticoagulants.

A recent systematic review and meta-analysis conducted by Ku *et al*. comparing the risk-benefit profile of antiplatelets vs. anticoagulants in the treatment of BCVI to determine stroke risk and bleeding complications of each treatment strategy showed no significant difference in terms of stroke risk but did find a trend favouring decreased bleeding complications following antiplatelet treatment.[87] The review included 22 studies that reported treatment-stratified outcomes of anticoagulant and antiplatelet treatment of BCVI, as well as institutional experience at the study center, encompassing a total of 2044 patients with BCVI. There was significant heterogeneity in the treatment strategies and agents used in BCVI treatment across different centers. Antiplatelet regimens included aspirin (81 or 325 mg), clopidogrel, or treatment with dual antiplatelet agents (aspirin and clopidogrel). Anticoagulation regimens included heparin infusion, with or without subsequent transition to warfarin or other oral agents, or low-molecular weight heparins, such as dalteparin or enoxaparin. Stroke rate on antiplatelet therapy ranged from 0% to 7.5% (cumulative stroke rate 2.39%; 14 of 585 patients) and the stroke rate in the anticoagulation group ranged from 0% to 16.7% (cumulative stroke rate 2.24%; 8 of 357 patients); the stroke rate was not significantly different between groups (OR 1.27; 95% CI 0.40-3.99). Overall bleeding complications were

lower in the antiplatelet group than in the anticoagulation group (OR 0.38; 95% CI 0.15-1.00). When sub-divided to assess for intracranial vs. non-intracranial hemorrhage, the rates of intracranial hemorrhage were similar between treatment groups (OR 0.58; 95% CI 0.14-2.33), however, there was a trend towards decreased risk of non-intracranial hemorrhage in patients treated with antiplatelets (OR 0.37; 95% CI 0.12-1.16). Overall, this meta-analysis showed that risk reduction of stroke following BCVI is similar for antiplatelet and anticoagulant treatment regimens, however, there may be a higher risk of bleeding complications with use of anticoagulants in this patient population. This study was limited as it evaluated only broad treatment strategies, without providing information about specific agents or doses used, making it difficult to apply in practice. It remains unknown how the most commonly used treatment regimens (eg. IV heparin vs. ASA) compare in terms of stroke risk and bleeding complications, and which dose of therapy is best to balance the risks of stroke and bleeding complications.

Due in part to methodologic limitations, the body of literature to date remains inconclusive regarding the best medical management strategy in patients with BCVI. While the trauma literature seems to favor treatment with antiplatelet over anticoagulation therapy with respect to bleeding risk, key questions remain. The data, at present, do not definitely identify the optimal agent, and are not granular enough to determine the optimal agent or dose of therapy to both maximize stroke prevention and minimize bleeding risk.

1.3 Thesis Aims and Outline

This thesis aims to evaluate the risk of stroke with different treatment strategies for BCVI, as well as bleeding-associated risks with systemic anticoagulation vs. antiplatelet therapy (ASA) in severely injured trauma patients. To achieve this aim, a systematic review of the literature will be undertaken to evaluate and critically appraise the literature to better understand the efficacy of

various treatment strategies in preventing stroke following BCVI. A multicenter retrospective study of current practice in two Canadian trauma centres with respect to BCVI management and stroke rates will describe current treatment patterns and evaluate stroke risk following BCVI. This study will serve as the foundation for a larger prospective study aimed at determining the optimal treatment strategy and duration for BCVI. Finally, a pilot study will be proposed to assess feasibility of a future randomized control trial determining the optimal dose of antiplatelet therapy in the treatment of BCVI.

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CHAPTER 2

ANTIPLATELETS VERSUS ANTICOAGULANTS IN THE TREATMENT OF BLUNT CEREBROVASCULAR INJURY (BCVI)

A SYSTEMATIC REVIEW AND META-ANALYSIS

CHAPTER 2. Antiplatelets versus Anticoagulants in the Treatment of Blunt Cerebrovascular Injury (BCVI) – A Systematic Review and Meta-Analysis

2.1 Introduction

Blunt cerebrovascular injury (BCVI) occurs following 1-3% of blunt traumatic injuries and can result in stroke with significant long-term disability.[1-3] Overall, stroke occurs in approximately 20% of patients with BCVI, usually within hours to days of injury.[4-6] Increasing recognition and creation of screening guidelines have improved detection of BCVI, enabling early treatment to reduce the risk of stroke and prevent disability.[2,7] Once diagnosed, however, guidance about the optimal treatment strategy for BCVI is poor.

There are currently no randomized controlled trials investigating the most commonly used medical treatment strategies for BCVI and current guidelines are based on low-quality observational data.[8] Existing data synthesis studies have been limited by significant heterogeneity in treatment modality and dosing, as well as comparison groups. Studies evaluating the use of antiplatelets and anticoagulants in the treatment of BCVI show conflicting results. Some studies show equivalence in terms of stroke reduction and bleeding complications with the use of antiplatelets or anticoagulants,[4] while others suggest trends towards better neurologic function in patients receiving heparin instead of aspirin.[9] A recent systematic review and meta-analysis investigating the risk-benefit profile of antiplatelets versus anticoagulants in the treatment of BCVI showed similar stroke rates and slightly higher rates of bleeding complications with the use of anticoagulants, suggesting that antiplatelets may be a better treatment option.[10]

Given the conflicting results of previous reviews and the many differing strategies in the treatment of BCVI, further research is needed to determine the optimal treatment strategy to reduce

the risk of stroke while minimizing bleeding complications. The current study is designed to compare the use of antiplatelet vs. anticoagulant medications in reducing the risk of stroke following BCVI, as well as evaluating the risk of bleeding complications associated with treatment. The systematic review builds on previously performed reviews and comparative observational studies and will aim to answer the specific question of which treatment agent and dose (heparin, 325 mg aspirin, or 81 mg aspirin) is associated with the lowest risk of stroke and bleeding complications to enable better understanding of the risk-benefit profile of each treatment strategy.

2.4 Methods

Systematic Review

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[11] and was registered with the PROSPERO registry of systematic reviews and meta-analyses (CRD42023387148). The search protocol was created with the assistance of a professional medical librarian and the research question and outcomes of interest were determined *a-priori*.

Literature Search Strategy

A systematic literature search of published studies was conducted using MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases (using the OVID interface) from inception until October 19, 2022.

A sensitive search strategy was created using MeSH terms in MEDLINE and EMTree descriptors in Embase, using search keywords with alternative word spellings and endings, including “blunt cerebrovascular injury”, “BCVI”, “cerebrovascular trauma”, and “vertebral artery

injury", "carotid artery injury", or "cerebrocervical artery injury", "stroke", "transient ischemic attack", or "TIA", and "platelet aggregation inhibitors", "antiplatelet agents", "anticoagulants", or "treatments" to identify articles for screening. A full description of the search strategy can be found in Appendix II. The search strategy was validated by screening references from recent systematic reviews to ensure all relevant articles were included. A supplementary search was conducted using web-based search engines Google Scholar and PubMed to identify additional potentially relevant studies not indexed in bibliographic databases. Reference lists from included papers and conference abstracts for national and international trauma scientific meetings were searched by hand for additional relevant studies. The search was limited to studies reported in English.

Inclusion and Exclusion Criteria

Studies were eligible for inclusion if they reported treatment-stratified outcomes for at least 5 patients that had suffered a BCVI who were treated with antiplatelet or anticoagulation therapies, with comparison made between two different medical treatment strategies, and reported on the outcome of stroke. Studies reporting the use of combinations of medical management strategies (ie. anticoagulants and antiplatelets) only were excluded.

Conference abstracts and posters, case series with more than 5 patients, prospective and retrospective cohort studies, randomized controlled trials, and systematic reviews and meta-analyses were included for further review. Case reports and case series with less than 5 patients were excluded, as were animal studies and studies in pediatric patients (< 18 years of age). For studies that did not report treatment-stratified outcomes or included data for trauma and non-trauma patients in aggregate, the authors were contacted for more information; if unavailable, the studies were excluded. Cases involving penetrating trauma resulting in vascular injury were not included.

Article Selection

All studies underwent title and abstract screening using Covidence systematic review software (Veritas Innovation Ltd.; Melbourne, Australia), followed by full text screening. All screening was performed independently by two reviewers, with disagreements resolved independently by a third reviewer.

Outcomes

The primary outcome of this review was stroke following BCVI, with comparisons made based on treatment strategy. Strokes not related to BCVI, strokes present at the time of presentation to hospital, or strokes occurring prior to initiation of treatment for BCVI (and therefore not influenced by treatment type/dose), were not included in analysis. Secondary outcomes analysed included: bleeding complications and interventions required to manage complications, neurological outcome at discharge and follow up, radiographic healing and progression rates, and mortality. Bleeding complications were defined as new or worsening episodes of bleeding from existing intracranial or solid organ injuries, that may or may not require further intervention, as defined by the individual study authors. Neurologic function at discharge and follow up was assessed and reported according to the method reported in individual studies and categorized broadly as “good” or “poor” outcomes based on description of clinical outcome or stratification of outcome scales. Radiographic progression or healing of BCVI was defined as changes in the Biffl grade of injury on follow up imaging. Radiographic changes were stratified into categories to denote complete healing, improvement, stability, or worsening. Mortality was assessed based on overall mortality, BCVI-specific mortality, stroke-related mortality, and treatment-stratified mortality rates, where available.

Data Extraction and Analysis

Data extraction was performed in duplicate using a standardized data entry form. Extracted data included: study authors, year and journal of publication, study design, number, sex, and age of patients, mechanism of injury, Injury Severity Score (ISS), associated injuries, traumatic brain injury (TBI), number, Biffl grade, and location of BCVIs, treatment, time from injury to treatment and known missed doses, stroke, bleeding complications and interventions required for management of bleeding, radiographic changes, and mortality. Despite attempts to reach corresponding authors for supplemental information, no additional information was received beyond what was in the initial publication or abstract. Each study was critically evaluated to determine risk of bias using the Newcastle-Ottawa Score.[12]

Data were summarized using descriptive statistics. Meta-analysis was conducted by combining pooled estimates of odds ratios (OR) with a random-effects model using Mantel-Haenszel methods employing RevMan software (RevMan Version 5.4, The Cochrane Collaboration; Copenhagen, Denmark). Due to the number of studies with zero events in one or both groups, sensitivity analyses were completed to determine the impact of inclusion of these studies with a continuity correction versus excluding these studies from meta-analysis.

2.3 Results

Search Results

The search strategy and manual review of the literature identified a total of 4373 studies for review, from which 1058 duplicates were removed. A total of 3315 studies were screened, yielding 140 studies for full text review. Thirty-nine studies evaluated different medical management strategies for the treatment of BCVI and reported on stroke as an outcome and were therefore included in the final systematic review and meta-analysis (Figure 2.1).

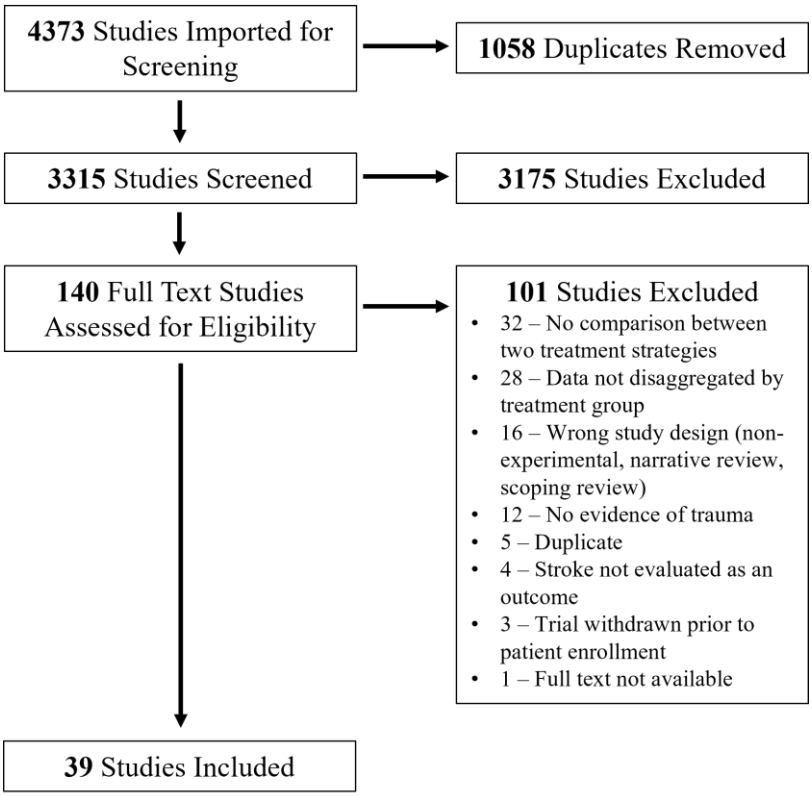

Figure 2.1. PRISMA diagram of study screening and selection; PRISMA, Preferred Reporting Items for Systematic Reviews

Study Characteristics

All primary research studies included in analysis were case series, retrospective observational studies, or prospective observational studies. There were three systematic reviews, two of which contained a meta-analysis as well as retrospective review component, and therefore the data from the retrospective reviews in these studies were included. There were no randomized controlled trials.

Overall, most studies were small to moderately sized, including a median of 104 patients per study (range 8-920), with twenty studies containing more than 100 patients. Included studies spanned from 1996 to 2022 and encompassed a total of 6552 patients, with at least 7655 BCVIs (some studies did not specify the number of BCVIs detected). Table 2.1 highlights key characteristics of included studies.

Table 2.1. Summary of Characteristics of Included Studies

Authors/ Year of Publication	Study Design	Number of Patients	Age	Sex (% Male)	ISS	Number of BCVI	BCVI Grade	Location of Injury	Treatment Groups	Stroke Rate	Bleeding Events	Mortality
Alterman et al., 2013[13]	RR	51	41.8	–	25.4	51	I – 12, II – 18, III – 2, IV – 18, V – 1	51 BVI	AP – 26, AC – 9, No Tx – 15	1 (1.9%)	–	Overall 8%
Biffl et al., 2000[14]	RR	38	38.9	M – 66%	25.5	59	I – 25, II – 9, III – 3, IV – 10	47 BVI	Heparin – 24, AP – 4, No Tx – 7	10 (26.3%)	Heparin – 2 hemorrhagic strokes	BCVI-related 8%
Biffl et al., 2002[15]	RR	171	35.6	M – 67%	27.7	254	I – 137, II – 52, III – 32, IV – 25, V – 8	157 BCI, 97 BVI	AP (ASA/Plavix), Heparin, No Tx	42 (24.5%)	Heparin – 22 bleeds	BCVI-related 10%
Bonow et al., 2021[16]	RR	677	–	M – 64%	–	908	I – 258, II – 224, III – 98, IV – 164, V – 2	290 BCI, 254 BVI	ASA – 600, AC – 77	32 (4.7%)	–	–
Colella et al., 1996[17]	RR	20	30	M – 45%	27	25	–	25 BCI	Heparin – 12, ASA – 2, Surgery – 4, No Tx – 2	3 (15%)	Heparin – 0, ASA – 0	Overall 20%
Cothren et al., 2004[18]	PS	114	34	M – 71%	29	150	I – 89, II – 30, III – 25, IV – 3, V – 3	150 BCI	Heparin – 56, AP – 17, No Tx – 41	19 (16.7%)	–	Overall 14%, Stroke-related 32%
Cothren et al., 2005[19]	PS	244	35	M – 68%	28	–	–	–	Heparin – 128, AP – 59	1 (0.5%)	–	BCI stroke-related 21% (overall 7%),

												BVI stroke-related 18% (overall 7%)
Cothren et al., 2009[4]	RR	301	37	M – 65%	27.0	422	I – 222, II – 70, III – 63, IV – 52, V – 15	210 BCI, 212 BVI	Heparin – 192, ASA – 67, ASA/Plavix – 23, No Tx – 107	57 (18.9%)	Heparin – 7, ASA/Plavix – 1	Overall 9%, Stroke-related 30%
D'Souza et al., 2022[20]	RR	186	49	M – 68%	–	–	–	–	ASA – 144, Plavix – 4, ASA/Plavix – 8, Heparin – 8, No Tx – 24	29 (15.6%)	–	Overall 12.9%
Daou et al., 2017[21]	RR	108	–	M – 48%	–	–	–	62 BCI, 42 BVI, 4 BCI + BVI	AP – 63, AC – 29, Combo – 11, No Tx – 5	32 (29.6%)	AP – 1, AC – 0, Combo – 1	Overall 3.1%
Edwards et al., 2007[22]	RR	110	37	M – 62%	30	133	–	–	Heparin – 48, AP – 42, Combo – 6	26 (23.6%)	Heparin – 2, AP – 0	Overall 26%, BCVI-related 6%
Esposito et al., 2022[23]	PS	777	–	M – 59%	–	777	–	332 BCI, 445 BVI	ASA – 485, Heparin – 76, AP – 494, AC – 47, Combo – 95	69 (8.9%)	–	–
Figueroa et al., 2021[24]	RR	38	45.6	M – 68%	–	46	–	25 BCI, 10 BVI, 3 BCI + BVI	AP – 25, AC – 3, Combo – 7, No Tx – 2	9 (23.7%)	No bleeding complication	Overall 7.9%
Hanna et al., 2020[25]	RR	725	–	M – 49%	12	725	–	384 BCI, 341 BVI	AP – 435, AC – 290	14 (1.9%)	–	Overall 4%
Harlan et al., 2021[26]	RR	91	40	M – 59%	22	–	–	–	AP – 71, AC – 20	6 (6.6%)	AP – 2, AC – 1	–
Hego et al., 2022[27]	RR	81	35	M – 68%	28	95	I – 28, II – 46,	57 BCI, 26 BVI	AP – 47, AC – 7,	11 (13.6%)	AP – 1, AC – 1	Overall 28.4%

							III – 8, IV – 11, V – 2		Combo – 3, No Tx – 25			
Hwang et al., 2010[28]	RR	67	32	M – 70%	–	67	I – 5, II – 15, III – 15, IV – 28, V – 4	33 BCI, 34 BVI	AP – 19, AC – 10, Combo – 6	22 (32.8%)	AP – 0, AC – 10	Overall 20%
Ku et al., 2021[10]	RR, SR, MA	149	46	–	31	269	–	–	AP – 40, AC – 16, Combo – 7, No Tx – 86	26 (17.4%)	AP – 2, AC – 2	–
Ku et al., 2022[29]	RR, SR, MA	149	–	–	–	269	–	–	AP – 40, AC – 23, No Tx – 86	18 (12.1%)	–	–
Kundi et al., 2021[30]	PS	51	–	–	–	–	III – 100%	–	Aspirin, ASA/Plavix, Heparin	8 (15.7%)	–	–
Lebl et al., 2013[31]	RR	42	56.4	M – 55%	24.4	46	–	–	AP – 8, AC – 8, Other Meds – 7, No Tx – 19	6 (14.3%)	–	Overall 26%
Leichtle et al., 2020[32]	RR	126	47	M – 64%	18	158	I – 43, II – 47, III – 43, IV – 25	81 BCI, 77 BVI	Heparin – 16, ASA – 77, ASA/Plavix – 6, Other Meds – 5	10 (7.9%)	Heparin – 2, ASA – 1, ASA/Plavix – 2, Other Meds – 0	Overall 12.7%
Lockwood et al., 2016[33]	RR	51	–	–	–	51	I/II – 25, III/IV/V – 26	51 BVI	AP – 35, AC – 5, No Tx – 11	4 (7.8%)	–	–
Makish et al., 2021[34]	RR	66	44	M – 73%	–	–	–	–	ASA 81 mg – 47, ASA 325 mg – 19	16 (24.2%)	–	Overall 11%
Malhotra et al., 2007[35]	PS	23	42	M – 70%	23.8	26	I – 10, II – 5, III – 5, IV – 1, V – 1	13 BCI, 13 BVI	AP – 7, AC – 5, No Tx – 10	1 (4.3%)	–	–

Miller et al., 2001[9]	RR	96	37	M – 60%	–	139	–	75 BCI, 64 BVI	AP, AC	32 (23.0%)	Heparin – 5	BCVI-related 17.7%
Miller et al., 2002[36]	PS	63	–	–	–	76	I/II – 49, III – 25	27 BCI, 49 BVI	AP – 38, AC – 20, No Tx – 6	9 (14.3%)	AP – 1, AC – 2	Overall 15.9%; BCVI-related 7.9%
Murphy et al., 2021[37]	SR	–	–	–	–	–	–	–	AP, AC, No Tx	–	–	–
Pujari et al., 2021[38]	RR	206	47	M – 65%	17	244	I – 94, II – 64, III – 11, IV – 63	244 BVI	AP, Heparin	4 (1.9%)	–	Overall 8.3%
Russo et al., 2021[39]	RR	920	–	–	–	971	I/II – 606, III – 134, IV – 214, V – 17	462 BCI, 509 BVI	AP – 630, AC – 448, Combo – 307, No Tx – 200	69 (7.5%)	–	Overall 12.8%, BCVI-related stroke 40%
Sack et al., 2009[40]	RR	8	26.8	M – 88%	–	8	–	8 BVI	ASA – 2, Heparin – 1, No Tx – 5	0 (0%)	ASA – 0, Heparin – 0	Overall 0%
Scott et al., 2014[41]	RR	120	36.1	M – 66%	–	152	–	152 BVI	AP – 80, AC – 4, Combo – 1, No Tx – 35	4 (3.3%)	–	Overall 3%
Scott et al., 2015[42]	RR	100	35	M – 71%	–	117	I – 54, II – 31	117 BCI	ASA – 54, Other Meds– 15, No Tx – 31	1 (1%)	–	Overall 9%
Scott et al., 2015[43]	RR	59	–	M – 59%	–	66	III – 23, IV – 43	66 BVI	AP – 45, AC – 2, No Tx – 1	4 (6.8%)	–	Overall 8.5%
Scott et al., 2015[44]	RR	49	–	M – 55%	–	58	III – 53, IV – 5	58 BCI	AP, Other Meds, No Tx	4 (8.2%)	–	Overall 12.2%
Stein et al., 2007[45]	RR	147	42	M – 58%	32	200	I – 51, II – 51,	132 BCI, 68 BVI	AP – 53, AC – 15,	22 (15.0%)	–	Overall 13%

							III – 46, IV – 50, V – 2		Combo – 27, No Tx – 32			
Wei et al., 2010[46]	RR	27	41.2	M – 67%	–	30	–	18 BCI, 12 BVI	AP – 10, AC – 1, Combo – 3, No Tx – 11	4 (14.8%)	–	Overall 14.8%
Yang et al., 2022[47]	PS	145	43	M – 65%	26	145	I – 145	145 BCI	ASA – 103, Heparin – 9	8 (5.5%)	–	–
Zeinneddine et al., 2022[48]	RR	156	–	–	–	172	I – 79, II – 39, III – 5, IV – 49	172 BVI	ASA – 135, Plavix – 1, Heparin – 2, No Tx – 18	3 (1.9%)	–	–

BCI, blunt cerebral injury; BVI, blunt vertebral injury; AP, antiplatelets; AC, anticoagulants; Combo, combination antiplatelets and anticoagulants; No Tx, no treatment; Other Meds, other medications; RR, retrospective review; PS, prospective study; SR, systematic review; MA, meta-analysis

Treatment for BCVI varied significantly, with the most common management strategies employing antiplatelets (usually 81 or 325 mg daily aspirin (ASA), 75 mg daily clopidogrel, or a combination of ASA and clopidogrel), anticoagulation (intravenous (IV) or subcutaneous heparin or enoxaparin with transition to warfarin or other oral anticoagulants), a combination or antiplatelets and anticoagulants, surgical/endovascular interventions (not included in analysis), or no treatment, most commonly due to contraindications to anticoagulation.

Critical appraisal of included studies using the Newcastle-Ottawa Score indicated that most studies were at a moderate to high risk of bias (Table 2.2).

Table 2.2. Critical Appraisal of Study Quality and Risk of Bias using the Newcastle-Ottawa Score

Authors	Study Design	Selection (4)				Comparability (2)		Outcome (3)			Total Score
		Representativeness of Exposed Cohort	Selection of Non-Exposed Cohort	Exposure Ascertainment	Absence of Outcome at Baseline	Adjusted for Key Confounders	Accounted for Other Confounders	Outcome Assessment	Length of Follow Up	Adequacy of Follow Up	
Alterman et al.[13]	RR	*	*	*	–	–	–	*	*	–	5
Biffl et al.[14]	RR	*	–	*	*	–	–	*	*	–	5
Biffl et al.[15]	RR	*	–	*	–	–	–	*	*	–	4
Bonow et al.[16]	RR	*	*	*	*	*	*	*	*	*	9
Colella et al.[17]	RR	*	*	*	*	–	–	*	*	–	6
Cothren et al.[18]	PS	*	–	*	–	–	–	–	*	–	3
Cothren et al.[19]	PS	*	–	*	*	–	–	*	*	–	5
Cothren et al.[4]	RR	*	–	*	*	–	*	–	*	–	5
D'Souza et al.[20]	RR	*	*	*	–	–	–	*	*	–	5
Daou et al.[21]	RR	*	*	*	–	*	*	*	*	–	7
Edwards et al.[22]	RR	*	–	*	–	–	–	*	*	–	4
Esposito et al.[23]	PS	*	*	*	–	*	*	*	*	–	7
Figueroa et al.[24]	RR	*	–	*	*	–	–	*	*	–	5
Hanna et al.[25]	RR	–	–	*	*	*	*	*	*	*	7
Harlan et al.[26]	RR	*	*	*	–	–	–	*	*	–	5
Hego et al.[27]	RR	*	*	*	–	–	–	*	*	–	5
Hwang et al.[28]	RR	*	*	*	*	–	–	*	*	–	6
Ku et al.[10]	RR/SR/MA	*	*	*	*	–	–	*	*	–	6
Ku et al.[29]	RR/SR/MA	*	*	*	–	–	–	–	*	–	4
Kundi et al.[30]	PS	*	*	*	–	–	–	–	*	–	4
Lebl et al.[31]	RR	*	*	*	*	–	–	*	*	–	6
Leichtle et al.[32]	RR	*	–	*	–	–	–	*	*	–	4
Lockwood et al.[33]	RR	*	*	*	*	*	*	*	*	–	8
Makish et al.[34]	RR	*	*	*	–	–	–	*	*	–	5
Malhotra et al.[35]	PS	*	*	*	–	–	–	*	*	–	5
Miller et al.[9]	RR	*	–	*	–	–	–	*	*	–	4
Miller et al.[36]	PS	*	–	*	*	–	–	*	*	–	5
Murphy et al.[37]	SR	*	*	*	–	–	–	*	*	–	5
Pujari et al.[38]	RR	*	–	*	*	–	–	*	*	–	5

Russo et al.[39]	RR	*	*	*	–	*	*	*	*	–	7
Sack et al.[40]	RR	*	*	*	–	–	–	*	*	*	6
Scott et al.[41]	RR	*	*	*	*	–	–	*	*	*	7
Scott et al.[42]	RR	*	*	*	*	–	–	*	*	*	7
Scott et al.[43]	RR	*	*	*	*	–	–	*	*	*	7
Scott et al.[44]	RR	*	*	*	*	–	–	*	*	*	7
Stein et al.[45]	RR	*	*	*	*	–	–	*	*	–	6
Wei et al.[46]	RR	*	*	*	*	–	–	*	*	–	6
Yang et al.[47]	PS	*	*	*	*	–	–	*	*	–	6
Zeinneddine et al.[48]	RR	*	*	*	*	–	–	*	*	–	6

Key confounders – Biffl injury grade, presence of intracranial hemorrhage or traumatic brain injury; RR, retrospective review; PS, prospective study; SR, systematic review; MA, meta-analysis

Primary Outcome – Stroke

There were 39 studies that evaluated different medical treatment strategies for BCVI and reported on the outcome of stroke. After exclusion of studies with overlapping cohorts, small studies with less than 5 patients in each treatment arm, systematic reviews, studies for which it was not possible to determine the number of strokes for each treatment arm, studies comparing only different doses of the same type of therapy or using combination therapy, and studies with no events in either treatment group, 24 studies were included in meta-analysis.

Overall, there were 567 strokes, with 188 strokes (33.2%) occurring on therapy. The stroke rate ranged from 0% to 32.8% amongst studies captured by the systematic review. Amongst studies included in the meta-analysis, there were a total of 405 strokes, with 141 (34.8%) occurring on therapy, for a total stroke rate of 4.5%. Patients treated with antiplatelets suffered 101 strokes, out of a total 2350 patients treated, resulting in a stroke rate of 4.3%. A total of 828 patients were treated with anticoagulants, of which 43 suffered a stroke (5.2% stroke rate). The stroke rate was lower for patients treated with antiplatelets compared to those treated with anticoagulants (OR 0.57; 95% CI 0.33 – 0.96, p = 0.04), Figure 2.2.

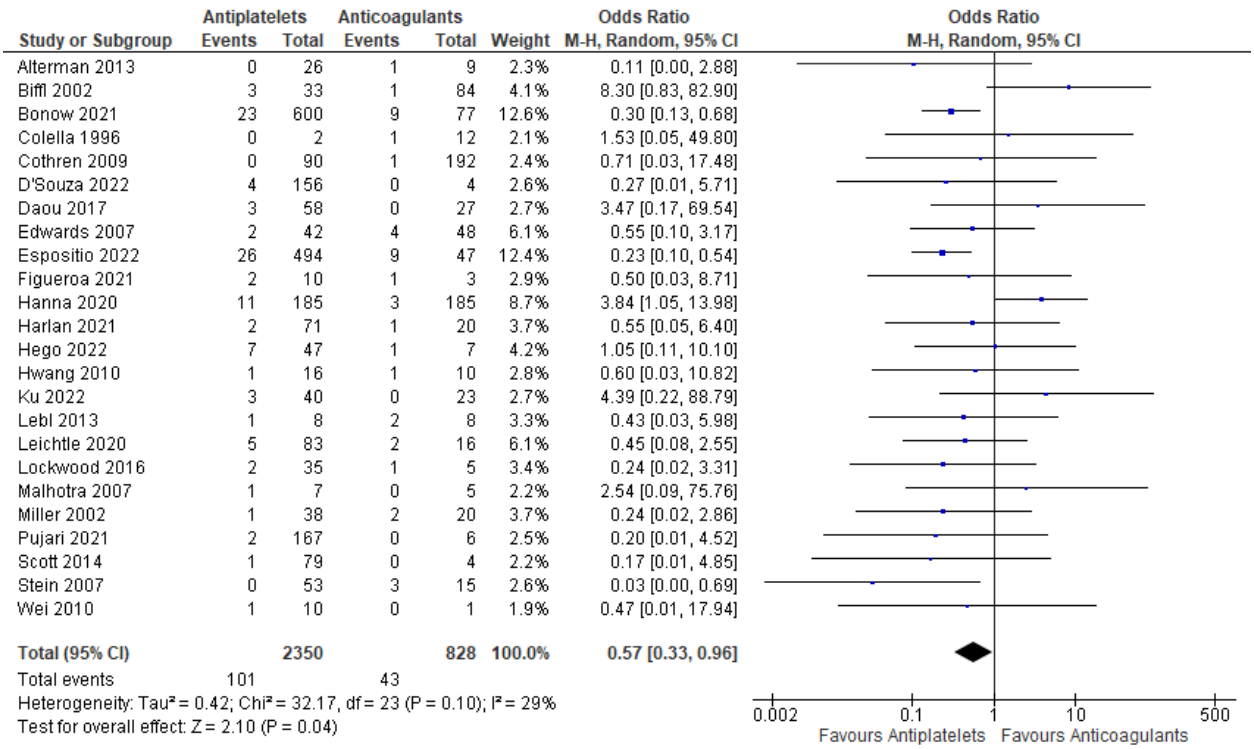

Figure 2.2. Forrest plot of meta-analysis of stroke rate for antiplatelets vs. anticoagulants

Twelve studies specifically evaluated stroke risk stratified by treatment with ASA vs. heparin. After exclusion of studies with overlapping cohorts, studies with less than 5 patients in both treatment arms, and studies with zero events in both arms, 9 studies remained for inclusion in the meta-analysis. Patients treated with ASA suffered 40 strokes, out of 904 patients treated, resulting in a stroke rate of 4.4%. Of the 396 patients treated with heparin, 29 suffered strokes, resulting in a stroke rate of 7.3%. The stroke rate was not significantly different for patients treated with ASA compared to those treated with heparin (OR 0.43; 95% CI 0.15 – 1.20, p = 0.11), Figure 2.3.

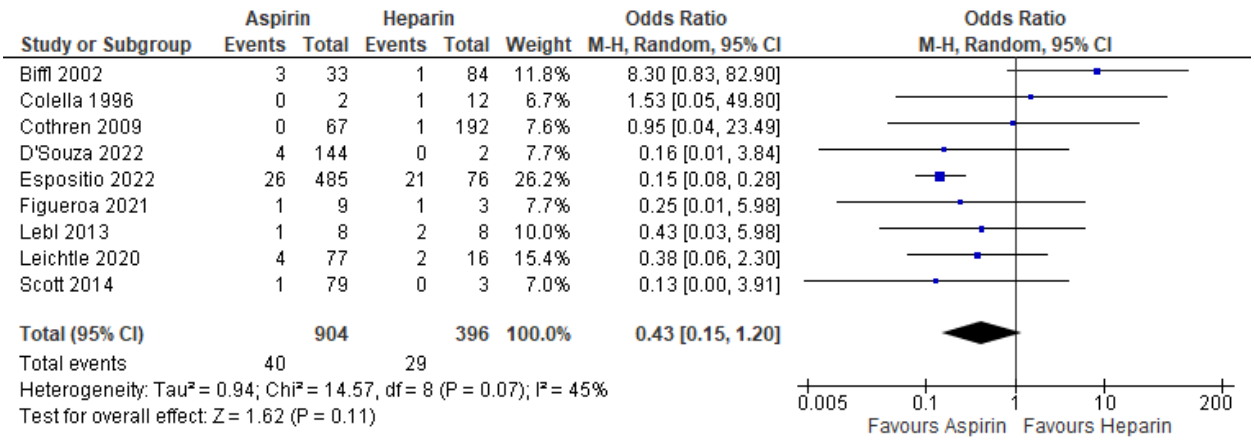

Figure 2.3. Forrest plot of meta-analysis of stroke rate for ASA vs. heparin

Further analysis of 4 studies reporting the efficacy of stroke prevention stratified by different doses of ASA (81 mg daily vs. 325 mg daily), available in Table 2.3, did not reveal a significant difference in stroke rate between the two treatment strategies (Figure 2.4), although this reflects only a small number of patients and studies.

Table 2.3. Stroke Rates following Treatment with ASA 81 mg daily vs. ASA 325 mg daily

Study	Year	Stroke Rate	
		ASA 81 mg	ASA 325 mg
Figueroa et al.[24]	2021	1/9 (11.1%)	0/15 (0%)
Leichtle et al.[32]	2022	2/20 (10%)	2/57 (3.5%)
Makish et al.[34]	2021	10/47 (21.3%)	6/19 (31.6%)
Pujari et al.[38]	2021	1.1%	0%

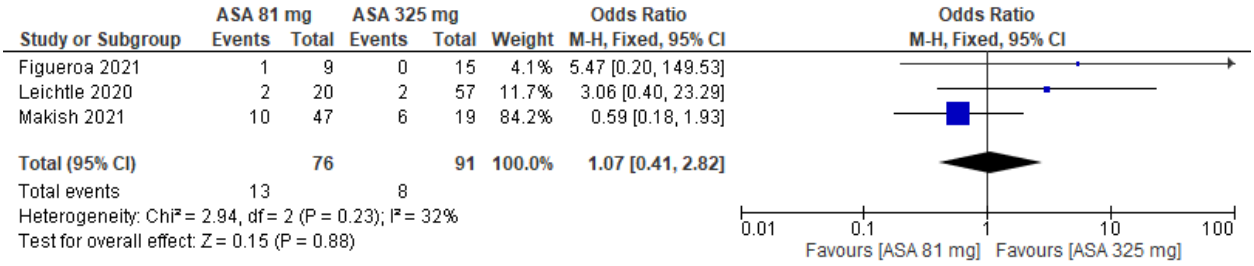

Figure 2.4. Forrest plot of meta-analysis of stroke rate for ASA 81 mg daily vs. ASA 325 mg daily

Studies with zero events in both treatment arms were excluded from analysis. To determine whether this impacts the results, a sensitivity analysis was performed using a continuity correction.

The results with and without correction were compared, with no significant difference in findings or conclusions.

Bleeding Complications

Sixteen studies evaluated bleeding complications, with direct comparison between antiplatelets vs. anticoagulants. After removal of studies with overlapping cohorts and studies with zero events in both treatment arms, 11 studies were included in the meta-analysis (Figure 2.5). Amongst patients treated with either antiplatelets or anticoagulants, the cumulative bleeding complication rate was 5.0% (54 bleeding events amongst 1072 patients). Overall, the rate of bleeding complications was lower in the group treated with antiplatelets vs. anticoagulants (OR 0.29; 95% CI 0.13 – 0.63, p = 0.002).

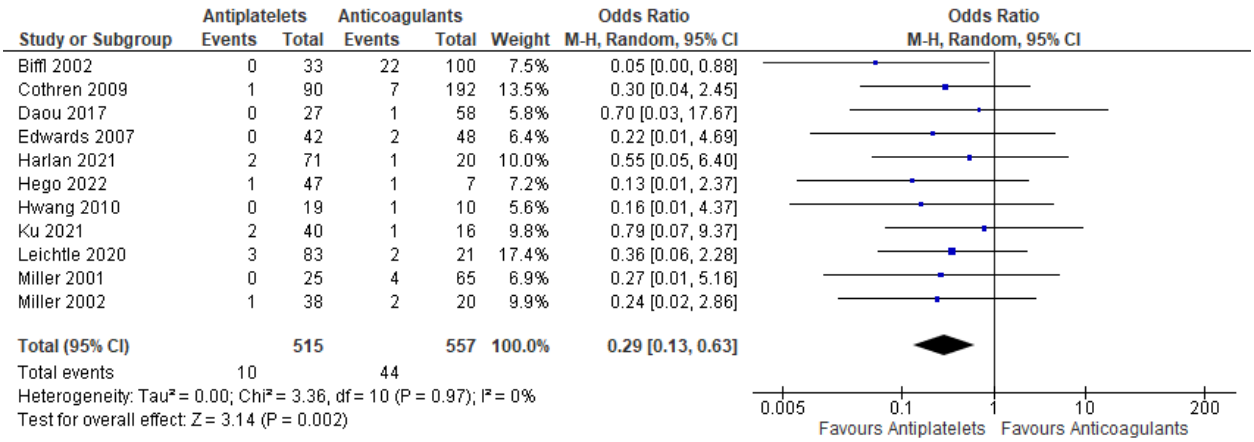

Figure 2.5. Forrest plot of meta-analysis of bleeding complications for antiplatelets vs. anticoagulants

Five studies evaluated rates of bleeding complications by comparing ASA and heparin. Amongst 216 patients treated with ASA, only 2 had bleeding complications (complication rate of 0.9%), compared with 16 of 294 patients treated with heparin (5.4% complication rate). Meta-analysis of bleeding complications amongst patients treated with ASA vs. heparin showed lower

rates of bleeding complications amongst patients treated with ASA (OR 0.16; 95% CI 0.04 – 0.58, p = 0.005), Figure 2.6.

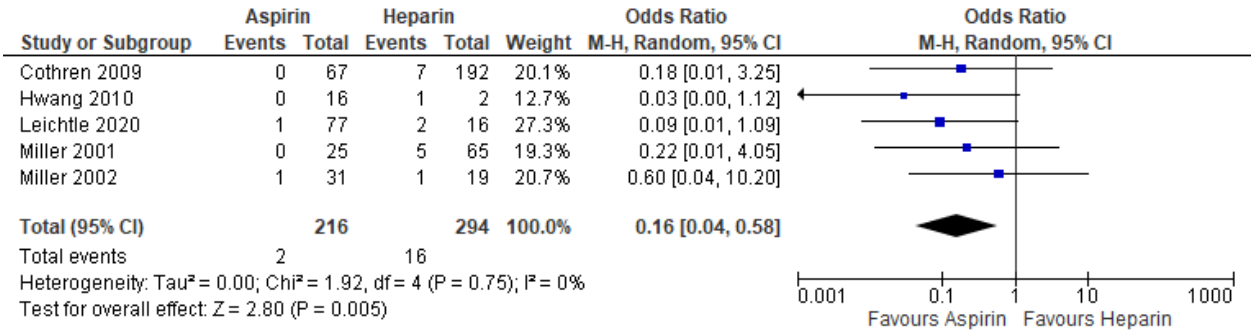

Figure 2.6. Forrest plot of meta-analysis of bleeding complications for ASA vs. heparin

Assessment of the severity of bleeding complications and subsequent interventions to address bleeding complications (Table 2.4) indicates that treatment with heparin led to a greater number, as well as greater severity, of bleeding complications. Use of heparin led to a cervical epidural hematoma resulting in quadriplegia in one patient,[28] severe intracranial hemorrhages in 15 patients, with 2 patients requiring craniotomies, and transfusion of a total of 17 units of packed red blood cells for all patients with bleeding complications.[4] Severe intracranial hemorrhage following administration of enoxaparin resulted in death in one patient.[36] Treatment with ASA and Plavix resulted in worsening intracranial hemorrhage in one patient, requiring repeat craniotomy,[32] while treatment with ASA only led to gastrointestinal bleeding in one patient requiring discontinuation of ASA therapy.[36]

Exclusion of studies with zero events in both arms and sensitivity analysis using a continuity correction did not result in a significant difference in findings or conclusions.

Table 2.4. Bleeding Complications and Required Interventions

Author	Year	Details of Bleeding Complications	Intervention for Bleeding
Biffl et al.[15]*	2002	Heparin: 10 bleeds at site of injury, 5 intra-cranial bleeds, 3 GI bleeds, 1 retroperitoneal bleed	–
Cothren et al.[4]	2009	Heparin: ICH x2 → craniotomy Heparin: recurrent epistaxis → nasal packing + 2 units pRBC Heparin: hepatic hematoma → 4 units pRBC Heparin: retroperitoneal hematoma (grade 1 kidney laceration) → 5 units pRBC Heparin: hemoglobin drop → 4 units pRBC Heparin: retroperitoneal bleed → 2 units pRBC ASA/Plavix: ICH → repeat craniotomy	Heparin: craniotomy x2, transfusion of 17 units pRBC ASA/Plavix: craniotomy
Daou et al.[21]	2017	3 major bleeds: 2 subarachnoid hemorrhages, 1 ICH	–
Edwards et al.[22]	2007	Heparin: ICH (supratherapeutic, PTT 100), no neurological deficits Heparin: GI hemorrhage → transitioned to antiplatelet therapy	–
Harlan et al.[26]	2021	3 bleeding complications	–
Hego et al.[27]	2022	2 bleeding complications: macroscopic hematuria, chronic subdermal hematoma → discontinuation of therapy (no stroke while therapy discontinued)	–
Hwang et al.[28]	2010	Heparin: cervical epidural hematoma resulting in quadriplegia	–
Ku et al.[10]	2021	Antiplatelets: hemoptysis, GI bleed Anticoagulation: GI bleed	–
Leichtle et al.[32]	2020	Heparin: 2 bleeds, ASA 81 mg: 0 bleeds, ASA 325 mg: 1 bleed, ASA/Plavix: 2 bleeds	–
Miller et al.[9]	2001	Heparin: subarachnoid hemorrhage x2 → discontinuation of anticoagulation Heparin: GI bleeding (gastritis) x2 → continue anticoagulation Heparin-induced thrombocytopenia (HIT) → discontinue heparin therapy	Heparin: discontinue therapy x3
Miller et al.[36]	2002	Enoxaparin: death due to severe ICH Heparin: significant epistaxis → discontinue anticoagulation ASA: GI bleed (gastric ulcer) → discontinue antiplatelet therapy	Heparin: discontinue therapy ASA: discontinue therapy

GI, gastrointestinal; ICH, intracranial hemorrhage; pRBC, packed red blood cells; HIT, heparin-induced thrombocytopenia
*20 of 22 bleeds with heparin occurred early in the study using a protocol administering a 70 unit/kg bolus of heparin, followed by an infusion with target PTT 60-80 sec; following changes to the protocol (no bolus, target PTT 40-50 sec), there were only 2 bleeding complications

Neurologic and Functional Outcomes

Twelve studies evaluated short and long-term functional outcomes following BCVI; 9 studies had disaggregated data enabling comparison of outcomes following treatment with antiplatelets vs. anticoagulants (Table 2.5). Overall, most patients who were treated for BCVI with either antiplatelets or anticoagulants had good outcomes. Most patients with strokes or neurologic deficits due to associated TBI or other injuries had some neurologic improvement after injury, with similar functional outcomes for those treated with antiplatelets and anticoagulants. Given the heterogeneity of outcome measures and follow up periods, meta-analysis could not be performed.

Table 2.5. Summary of Studies Evaluating Short and Long-Term Neurological and Functional Outcomes

Study	Outcome Measure	Good Outcome		Poor Outcome	
		AP	AC	AP	AC
Biffl et al.[14]	Severe vs. mild deficit vs. normal function	1/6	20/24	4/6 poor outcome 1/6 dead	1/24 poor outcome 3/24 dead
Biffl et al.[15]	Severe vs. mild deficit vs. normal function	2/5 improved	22/31 improved	3/5 unchanged	8/31 unchanged 1/31 worsened
Colella et al.[17]	Descriptive	2/2 normal function	10/12 normal function	–	2/12 dead
Cothren et al.[18]	Descriptive	2/3 improved	8/8 improved	1/3 dead	–
Daou et al.[21]	Modified Rankin Scale	57/63 mRS 0-2	27/29 mRS 0-2	6/63 mRS 3-6	2/29 mRS 3-6
Edwards et al.[22]	Glasgow Outcome Scale	17/23 GOS 4-5	18/24 GOS 4-5	6/23 GOS 1-3	5/24 GOS 1-3
Figueroa et al.[24]	Glasgow Outcome Scale – Extended	15/18 GOS-E 5-8	2/3 GOS-E 5-8	3/18 GOS-E 1-4	1/3 GOS-E 1-4
Hego et al.[27]	Descriptive	25/40	2/5	15/40	3/5
Sack et al.[40]	Descriptive	2/2	1/1	–	–

AP, antiplatelets; AC, anticoagulants; mRS, modified Rankin Scale; GOS, Glasgow Outcome Scale; GOS-E, Glasgow Outcome Scale – Extended

Radiographic Healing and Progression

A total of 19 studies evaluated radiographic healing and progression following BCVI; after removal of systematic reviews and studies for which it was not possible to determine progression or healing rates for different treatment strategies, 8 studies remained that allowed comparison of antiplatelets vs. anticoagulants (Table 2.6). Overall, most injuries either improved or remained stable on follow up imaging, which in most studies was performed within 7 to 14 days from injury. There was significant variation in reporting of radiographic progression, and many studies had disproportionate numbers of patients treated with antiplatelets or anticoagulants. Given the low follow up rate, range of follow up periods, small sample sizes, and heterogeneity in reporting, meta-analysis was not feasible.

Table 2.6. Summary of Studies Evaluating Radiographic Injury Progression and Healing

Study	Follow Up Period	Follow Up Percentage	Healed		Improved		Unchanged		Worsened	
			AP	AC	AP	AC	AP	AC	AP	AC
Biffl et al.[14]	7-10 days	21/47 BCVI (44.7%)	0/2	2/16	0/2	0/16	1/2	10/16	1/2	4/16
Biffl et al.[15]	7-10 days	132/171 patients (77.2%)	12/43	32/104	3/43	4/104	25/43	48/104	3/43	20/104
Cothren et al.[4]	10 ± 0.9 days	292/422 BCVI (69.2%)	–	–	27/62	53/100	28/62	76/100	7/62	19/100
Figueroa et al.[24]	1-9 months	8/38 patients (21.1%)	2/5	2/2	–	–	–	–	–	–
Harlan et al.[26]	7-14 days, up to 12 months	–	–	–	–	–	–	–	5/71	1/20
Malhotra et al.[35]	1 week – 1 year	11/23 patients (47.8%)	3/6	2/2	–	–	3/6	–	–	–
Scott et al.[41]	7-10 days (mean 40 days, range 7-291 days)	120 patients (100%), 152 injuries	67/106	–	9/106	–	23/106	3/3	7/106	–
Scott et al.[42]	7-10 days (mean 60 days, range 7-723 days)	100 patients (100%), 117 injuries	37/66	–	6/66	–	10/66	–	13/66	1/2

AP, antiplatelets; AC, anticoagulants

Mortality

Twenty-eight of 39 studies included in the review reported mortality rates (Table 2.1). Overall mortality rates ranged from 0% to 28.4%. Five studies reported BCVI-related mortality, ranging from 6% to 17.7%. Mortality after BCVI-related stroke ranged from 18% to 40%. No studies reported mortality rates stratified by treatment and therefore meta-analysis was not possible.

Publication Bias

Review of included studies and assessment for publication bias via visual inspection of funnel plots did not demonstrate significant bias (Figure 2.7).

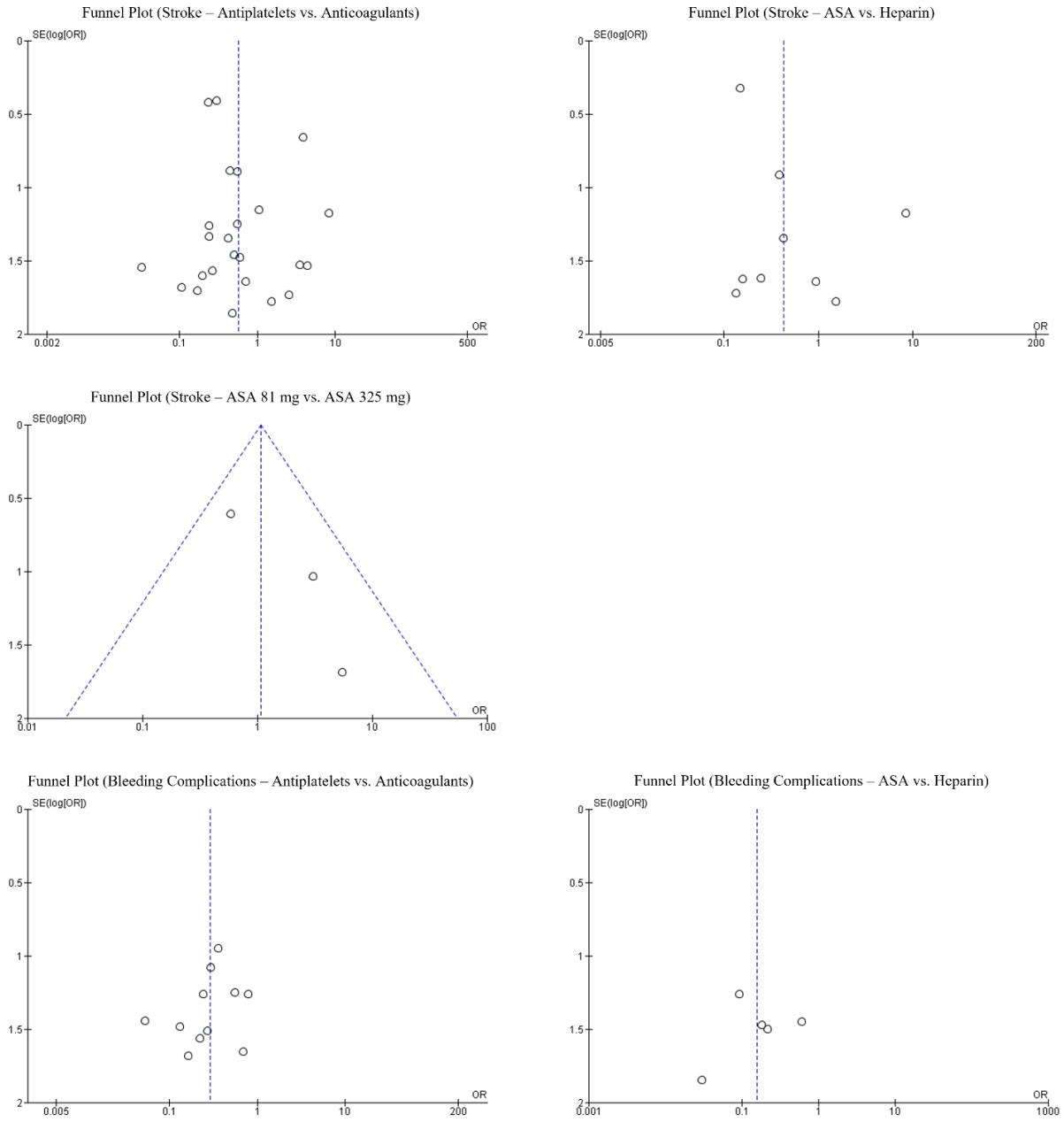

Figure 2.7. Funnel plots for the meta-analyses of stroke rate and bleeding complications

2.4 Discussion

Blunt cerebrovascular injury can lead to stroke and cause devastating disability and increased risk of mortality. With improved screening and prompt treatment, the rates of BCVI-related stroke have decreased significantly. This systematic review and meta-analysis evaluated different medical management strategies for treatment of BCVI to reduce the risk of stroke.

Secondary outcomes assessed included bleeding complications, functional/neurological outcome, radiographic progression, and mortality. We demonstrated a lower risk of stroke with the use of antiplatelets compared to anticoagulants. When assessing the most commonly used treatment modalities within each group (ASA vs. heparin), stroke rates were similar between groups. Very few studies evaluated different doses of ASA (81 mg vs. 325 mg daily), but meta-analysis of the few studies in which this comparison was possible showed no difference in stroke rate with low-dose vs. high-dose ASA. Bleeding complications were significantly lower with the use of antiplatelets vs. anticoagulants (as well as with the use of ASA vs. heparin), and the reported interventions required to address hemorrhagic complications were more invasive following the use of heparin and other anticoagulants.

Early evidence of the importance BCVI treatment showed that treatment with heparin improved survival and neurologic outcomes.[49] Since then, there have been a number of studies that have evaluated different treatment strategies for BCVI in order to prevent stroke occurrence, with conflicting results. Guidelines from the Western Trauma Association (WTA) for the screening and treatment of BCVI recommend use of IV heparin with a target PTT of 40-50 seconds, stating that heparin is more effective than antiplatelets and is reversible in the event of bleeding complications.[50] Other studies have suggested that anticoagulation and antiplatelets (ASA and/or clopidogrel) are equivalent or superior to heparin, and are associated with less hemorrhagic complications.[18,22,51] The most recent guidelines from the Eastern Association for the Surgery of Trauma reinforce the recommendation of early treatment of BCVI to reduce the risk of stroke but were unable to make specific recommendations as to the optional agent and dose.[8] Currently, there remains wide variation as to the preferred treatment strategy for BCVI across centers and trauma care providers.[52]

This study builds on previously conducted systematic reviews investigating different management strategies for BCVI. A recent review conducted by Murphy *et al*.[37] in 2021 investigating various treatment strategies (antiplatelets, anticoagulants, endovascular therapy, and surgery) for treatment of asymptomatic patients with BCVI found significantly lower rates of stroke following BCVI with any treatment regimen (3% stroke rate) compared to no treatment (25% stroke rate). Meta-analysis was not performed due to the heterogeneity of included studies, however, comparison of total stroke rates with the use of antiplatelets (8% stroke rate) vs. anticoagulants (7% stroke rate) showed similar rates of stroke with either treatment strategy. A systematic review and meta-analysis comparing the use of antiplatelets vs. anticoagulants for treatment of BCVI found no difference in stroke rates between the two treatment strategies but did find a statistically significant difference in the risk of bleeding complications favouring use of antiplatelets, suggesting that antiplatelets carry a lower risk in the trauma population.[10] These findings are similar to the findings of this study which, with the addition a several more studies published in the interim, was able to show a difference in stroke risk favouring use of antiplatelets, and similarly showed decreased risks of bleeding complications with the use of antiplatelets vs. anticoagulants. No meta-analyses were conducted evaluating the other outcomes of interest; however, previous systematic reviews have shown similar outcomes between groups.[10]

Trauma patients are at uniquely high risk of bleeding complications or worsening bleeding from existing intracranial or solid organ injuries.[53] In many cases, it is this concern about higher rates of bleeding complications with heparin and other anticoagulants that initially led some centers to adopt an ASA-based treatment approach.[34,38,54] The finding of lower bleeding risk with the use of ASA is further suggested by the results of this study. ASA has a long-standing history for use for both treatment and secondary prevention of vascular events following myocardial

infarcts and strokes, and is currently recommended for secondary prevention of vascular events (stroke, TIA, and myocardial infarct) by the 2020 Canadian Stroke Best Practice Recommendations,[55] as well as the American Heart Association and American Stroke Association 2021 Guidelines for the prevention of stroke and TIAs.[56] Though fewer data exists supporting optimal dosing of ASA in the setting of traumatic vascular injury, numerous studies in the non-trauma setting support that doses of 50-100 mg of ASA completely inhibit production of TXA_2 if taken daily,[57-60] and are associated with similar rates of cardiovascular complications when compared to higher ASA doses.[61] More research is needed to determine optimal doses of ASA for treatment of BCVI, specifically evaluating efficacy in stroke reduction and risk of bleeding complications.

This study has several important limitations. The quality of the meta-analysis is predicated on the quality of included studies. Most of the studies were relatively small retrospective reviews at moderate to high risk of bias, as per the Newcastle-Ottawa Score. There were no randomized controlled trials, and most studies had inherent limitations due to their non-experimental nature, retrospective design, and small sample size and event rate. The quality of data reporting, including inconsistent reporting of treatment modality and timing in relation to the onset of stroke, made it difficult to ascertain whether strokes occurred before treatment or to determine in which treatment group patients with stroke belonged. As a result, a high number of studies had to be excluded from the systematic review and meta-analysis. Many studies failed to report or account for key factors that may impact BCVI care or BCVI-related stroke risk, such as overall injury severity (ISS), presence of traumatic brain injury (TBI) or intracranial hemorrhage (ICH), and grade or location of BCVI (carotid vs. vertebral arteries), which may explain differences in stroke rates between treatment groups. There was an overrepresentation of data coming from a few large centers in the

United States that published prolifically on BCVI diagnosis and management, which may affect the generalizability of the results to other centers and populations. Many centers had pre-determined treatment protocols and, as treatment allocation was not randomized, this likely biased the results of the study. For example, some centers have established treatment protocols that use IV heparin unless patients are identified to be at high risk for bleeding, in which case they are treated with antiplatelets (ASA and/or clopidogrel) or observed if deemed too high risk for any treatment.[4,9,14,15,18,19,22,36] Other centers preferentially use antiplatelets for most cases,[34,38] and dual antiplatelets for patients with higher-grade injuries.[32] Preferential use of one treatment strategy over another biases the results as patients allocated to each treatment strategy likely have many factors that alter their risk of stroke or bleeding complications. Few studies reported changes or preferences in treatment strategy due to stroke, bleeding complications, or radiographic progression,[9,21-23,36,47] which further impairs determination of treatment-stratified risks of stroke and bleeding complications. The nature of bleeding complications and interventions (eg. surgery, transfusion, discontinuation of therapy) required to address complications were rarely reported. Finally, the low event rate of strokes and bleeding complications remains a limitation of this work. Sensitivity analysis demonstrated this did not significantly impact the results with respect to risk of stroke or bleeding complications.

Meta-analysis of other secondary outcomes, including short and long-term neurologic function, radiographic healing and progression, and mortality was not possible due to low numbers of studies reporting on these outcomes, and significant variability in how outcomes were reported. The search strategy and screening protocol were also not designed to capture all studies reporting on these outcomes. Further research is required to evaluate the impacts of different treatment strategies on each of these outcomes of interest.

2.5 Conclusions

This study evaluated the risk of stroke following BCVI and showed that treatment with antiplatelets is associated with lower risks of stroke and bleeding complications compared to treatment with anticoagulants. Treatment with ASA vs. heparin specifically was not associated with differences in stroke risk, but patients treated with ASA had fewer bleeding complications. The few available studies evaluating different doses of ASA did not show a difference in stroke rate. Similar outcomes were observed for other secondary outcomes of interest (neurologic outcomes and radiographic healing) between treatment groups; mortality could not be compared between groups. More research including randomized trials and better reporting are required to determine optimal treatment strategies for BCVI to reduce the risk of stroke while minimizing bleeding complications.

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CHAPTER 3

RETROSPECTIVE REVIEW OF CURRENT CANADIAN PRACTICE PATTERNS AND ASA DOSING IN THE TREATMENT OF BLUNT CEREBROVASCULAR INJURY (BCVI)

CHAPTER 3. Retrospective Review of Current Canadian Practice Patterns and ASA Dossing in the Treatment of Blunt Cerebrovascular Injury (BCVI)

3.1 Introduction

Blunt cerebrovascular injury, if unrecognized and untreated, can lead to stroke and increased morbidity and mortality.[1-2] Early diagnosis and treatment have been shown to reduce the risk of stroke and stroke-related mortality.[3-6] Recent guidelines on BCVI management recommend using established screening protocols to screen patients with high-risk mechanisms of injury or risk factors for BCVI to enable early detection and treatment.[7-9] Treatment with antiplatelets or anticoagulants is recommended, although there are no specific recommendations about the optimal agent and dose.[7] A recent systematic review and meta-analysis has demonstrated similar stroke rates with antiplatelets and anticoagulants, but less bleeding complications following treatment with antiplatelets, suggesting this may be the preferred strategy in the trauma population.[10]

Aspirin (ASA) is an oral antiplatelet agent commonly used for secondary stroke prevention in patients with cardiovascular disease. Many centers have transitioned to an ASA-based approach for treatment of BCVI given its lower risk of bleeding complications, as well as ease of administration, low cost, and lack of need for repeated bloodwork or monitoring.[11] The optimal dose of ASA, however, is under debate. Evidence from the non-trauma literature evaluating the use of ASA in secondary prevention of stroke following transient ischemic attacks (TIAs) or strokes suggests that ASA is beneficial in reducing the risk of recurrent stroke, especially in the early, acute phase.[12] Some studies report equivalence in terms of stroke reduction for cardiovascular events with 81 mg ASA vs. 325 mg ASA,[13] while other studies suggest efficacy may depend on the underlying pathophysiology, with minimum effective doses for stroke

prevention ranging from 75 mg daily for patients post myocardial infarct to 325 mg daily for patients with atrial fibrillation.[14]

The optimal dose for patients with cerebrovascular trauma has not been evaluated with any experimental trials, and there is significant variation across centers and trauma care providers in preferred treatment strategies.[15] Most published literature on BCVI comes from several large trauma centers in the United States, who use primarily anticoagulant-based management algorithms for patients with BCVI. There is relatively little data on current Canadian practice patterns, although many Canadian centers are using a primarily antiplatelet-based approach. Canada has unique challenges in providing rapid high-quality care to trauma patients. The population is spread over a large area and is serviced by only 32 level I or II trauma centers distributed throughout Canada, with significant rural-urban disparities in access to care and over one fifth of patients living more than one hour away from a level I or II trauma center.[16] Rapid and easy treatment strategies are even more imperative, and Canadian-specific data is needed. This multicenter retrospective review investigating BCVI management and outcomes at Lead Trauma Centers across Canada is an important first step. We specifically aim to describe current management patterns in the treatment of BCVI, and to evaluate whether low dose ASA (81 mg daily) vs. high dose ASA (325 mg daily) is associated with higher rates of stroke.

3.2 Methods

This study is a multicenter retrospective observational study, conducted and reported in accordance with STROBE guidelines.[17] The project was reviewed and approved by the Western University Research Ethics Board (REB# 118388) and data sharing agreements were granted by the Lawson Health Research Institute to participating sites. Collaborating centers obtained local institutional review board approval prior to participating.

Patient Selection

The current study represents data from two Lead Trauma Centers in Ontario Canada – London Health Sciences Centre and Hamilton Health Sciences. Patients with BCVI were identified from the prospectively collected trauma registries at these sites. All patients at least 18 years of age diagnosed with BCVI via CT angiography (CTA) from April 1, 2015, to March 31, 2022, were included in the study. Screening for BCVI was at the discretion of the treating trauma team leader at each site, as neither center had a universal screening protocol in place during the study period. Patients with penetrating neck injuries or pre-existing cerebrovascular disease impairing the ability to diagnose BCVI, and patients who died within 24 hours of their trauma were excluded from the study.

Data Collection

The following data were extracted from the trauma registry and patient electronic medical records: patient demographics (age and sex), prior medical conditions (previous TIA/stroke or use of antiplatelets or anticoagulants), time/date of injury and mechanism of injury, injury severity score (ISS), associated injuries, initial vitals and Glasgow Coma Scale (GCS), site and grade of BCVI (Table 1.2), treatment for BCVI (antiplatelets, anticoagulation, endovascular therapy, surgery), timing of therapy and stroke, bleeding complications related to treatment and necessary interventions to address complications, length of hospital stay, need for intensive care and ICU length of stay, discharge disposition, and mortality.

The need for CTA imaging for BCVI screening and diagnosis was at the discretion of the treating physician. The expanded Denver criteria (Table 1.1) were used to determine if patients met widely accepted criteria for screening. Patients who had CTA imaging during the same CT scan as the rest of the trauma imaging (with CTA results reported within 30 minutes of the rest of

the CT imaging) were considered as having CTA as part of initial trauma scan. All imaging was reviewed for diagnosis and grading of BCVI by experienced radiologists. Patients were followed throughout their stay in hospital, until discharge. Majority dose of treatment was defined as the dose of ASA received for over 50% of in-hospital doses. Delays in treatment were determined by review of the medication record to determine if patients had ordered doses of therapy that were held or not given. A delayed dose was recorded if there was a demonstrated delay of at least 2 hours. A missed dose was recorded if the dose was not given on the calendar day for which it was ordered to be given. Stroke was confirmed based on clinical documentation and final reporting by the radiologist of available neuroimaging (CT and/or MRI). All data was upload and stored on REDCap (Research Electronic Data Capture),[18] a secure online data entry and sharing platform.

Data Analysis

No formal sample size calculation was completed, as this sample represents a convenience sample of patients at participating lead trauma hospitals and there is very limited existing data to estimate the stroke risk with different doses of ASA. Data analysis was conducted with IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY., Version 29.0). Descriptive statistics were calculated to evaluate patient demographics, mechanisms of injury and associated injuries, BCVI characteristics and BCVI-specific treatments, and outcomes. Categorical data was analyzed and reported using frequencies (percentages) and continuous variables were analyzed using means (with standard deviations) and medians (with interquartile ranges), as appropriate. Continuous variables were compared using the Independent t-test for normally distributed data and the Mann Whitney U test for non-normally distributed data. The Chi-squared test and Fisher's exact test were used to compare categorical variables. Variables believed to impact the risk of stroke following BCVI were determined *a-priori* from the literature and entered into a multivariable

logistic regression analysis to identify the independent contribution of ASA dose to probability of stroke following BCVI. Data was reported using adjusted odds ratios with 95% confidence intervals and statistical significance set at $p < 0.05$. An alluvial flow chart (Figure 3.2) was created using RAWGraphs (Version 2.0 beta, accessed from https://app.rawgraphs.io/) to demonstrate treatment and outcome course for included patients.

3.3 Results

Throughout the study period, a total of 12,467 trauma patients were entered into the trauma registries at participating sites, with 199 patients diagnosed with BCVI (incidence of 1.6%). After review of patient charts, a total of 194 patients met inclusion criteria for the study (Figure 3.1).

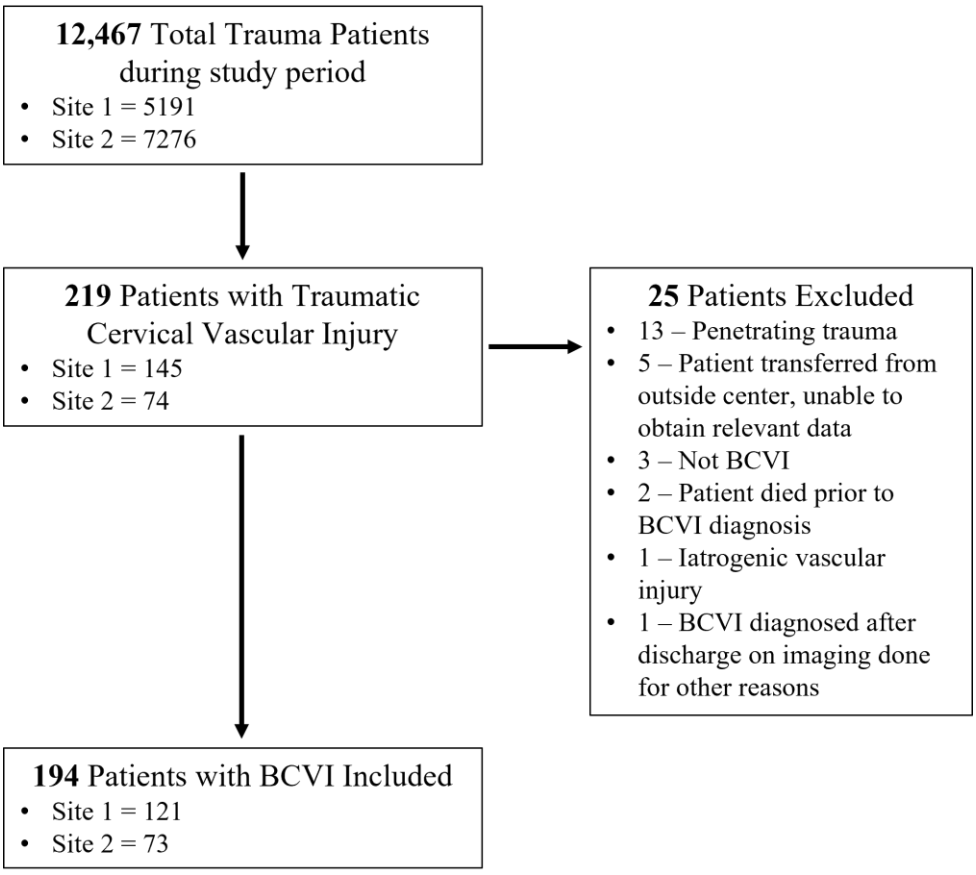

Figure 3.1. Flow chart of patients evaluated in the study

Approximately two thirds of the patients (123, 63.4%) were male, with half of patients (97, 50.0%) sustaining traumatic injuries as a result of motor vehicle collisions. Over 93% of patients met Denver criteria for BCVI screening based on injury mechanism and associated injuries, and 121 patients (62.8%) underwent CT angiography as part of their initial trauma workup. Only 12 patients were known to be on ASA and 3 patients on anticoagulants prior to injury. Additional information regarding baseline characteristics of included patients is available in Table 3.1.

Table 3.1. Characteristics of patients with blunt cerebrovascular injury, stratified by stroke

Characteristic	Value
Median Age (IQR)	47 (30-67)
Male Sex, n (%)	123 (63.4%)
Mechanism of Injury, n (%)	
MVC	97 (50.0%)
Pedestrian vs. vehicle	11 (5.7%)
Motorcycle collision	21 (10.8%)
ATV collision	6 (3.1%)
Bicycle vs. vehicle	6 (3.1%)
Fall	48 (24.7%)
Other	5 (2.6%)
Median Initial GCS (IQR)	14 (9-15)
Median ISS (IQR)	26 (17-35)
TBI, n (%)	93 (47.9%)
Prior Stroke, n (%)	3 (1.5%)
Did not meet Denver Criteria, n (%)	12 (6.2%)
CTA as Part of Initial Trauma Scan, n (%)	121 (62.8%)

MVC, motor vehicle collision; ATV, all-terrain vehicle; GCS, Glasgow Coma Scale; ISS, Injury Severity Scale; TBI, traumatic brain injury; CTA, computed tomography angiography; SD, standard deviation; IQR, interquartile range

CTA revealed a total of 254 BCVIs, with 109 carotid artery injuries and 145 vertebral artery injuries (Table 3.2). Most patients (147, 75.8%) had a single vessel injured, although 47 patients (24.2%) had an injury in two or more vessels (2 arteries injured in 38 patients; 3 arteries injured in 5 patients; 4 arteries injured in 4 patients).

Table 3.2. Summary of BCVI characteristics

Artery Injured	Number of Arteries Injured
Carotid Artery	**109**
Right carotid artery	49
Left carotid artery	60
Vertebral Artery	**145**
Right vertebral artery	69
Left vertebral artery	76

Treatment

Most patients (177, 91.2%) had pharmacologic treatment initiated for BCVI, with only 17 patients (8.7%) receiving no treatment during their hospitalization. The most common treatment modality for both initiation of therapy and maintenance therapy was ASA 81 mg daily, followed by ASA 325 mg daily. In some cases, 150 mg of ASA was administered rectally as a one-time dose for patients without oral access for medications, which was usually followed by maintenance therapy with either 81 mg or 325 mg ASA. Figure 3.2 illustrates the treatment and outcome pathways for included patients who were treated with ASA. Relatively few patients had cross-over between treatment strategies.

Twenty-three patients (13.0%) received other anticoagulation in addition to ASA. From the available data, 4 patients received IV heparin for treatment of BCVI-related stroke (3 patients), or treatment of grade IV BCVI (1 patient), 7 patients received Plavix (with either 150 mg or 300 mg loading doses, followed by 75 mg daily) due to BCVI stenting (5 patients), pre-injury use of Plavix (1 patient), and progression of BCVI grade to pseudoaneurysm formation (1 patient), and 4 patients received therapeutic levels of dalteparin for treatment of pulmonary embolism, deep vein thrombosis (DVT), or stroke. The most common reason for dual antiplatelet therapy with ASA and Plavix was stenting of BCVI; other common reasons for dual anticoagulation were treatment of pulmonary embolism, DVT, or stroke.

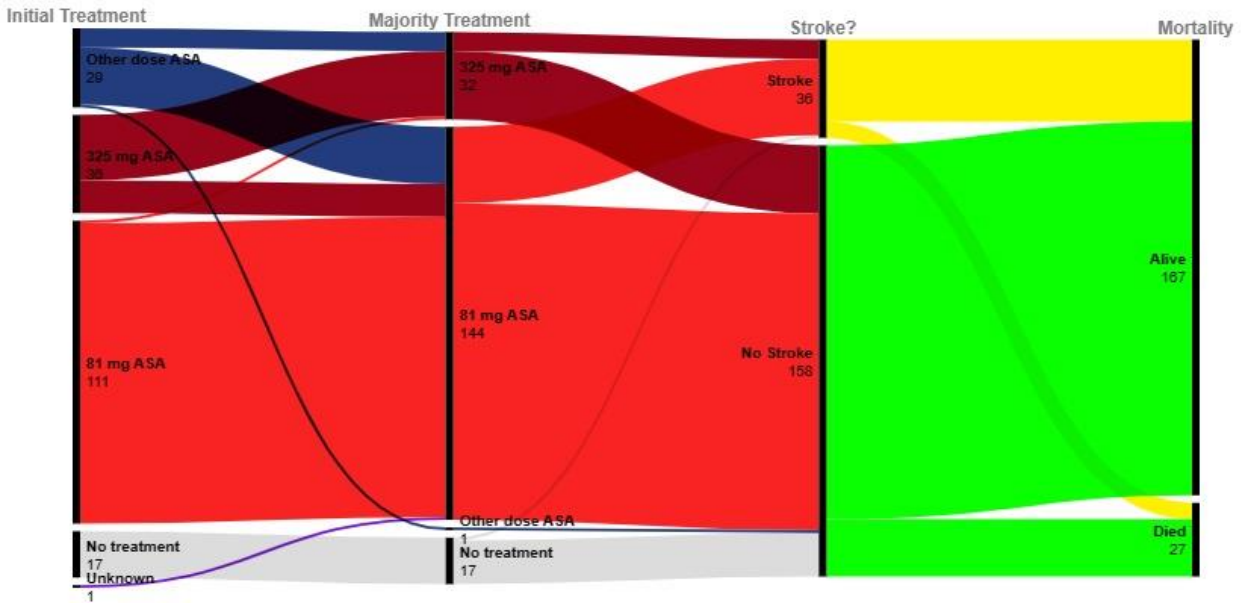

Figure 3.2. Alluvial diagram of initial treatment strategy, majority treatment strategy, stroke, and mortality

Treatment was initiated within a median time of 316 minutes, or 5.3 hours (IQR 149.75-880.5 minutes) from injury and approximately a third of patients (58, 31.9%) had a delay or interruption in treatment throughout their hospital stay.

Stroke

Overall, 36 (18.6%) patients had a stroke associated with their BCVI, of whom 18 (9.3% of total sample) had a stroke after receiving their first dose of pharmacologic therapy. Table 3.3 compares key patient and injury characteristics between those who did and did not have a stroke. Patients who had a stroke were more likely to have had an MVC, to have a lower initial GCS (median 11 vs. 14, $p = 0.019$), to have a higher ISS (median 34 vs. 25, $p = 0.012$), and to have not met the Denver criteria for screening (13.9% vs. 4.4%, $p = 0.049$).

Table 3.3. Patient characteristics, stratified by stroke vs. no stroke

	Stroke N = 36	**No Stroke N = 158**	**p Value**
Median Age (IQR)	35 (30-58.5)	49.5 (29-70.25)	p = 0.051
Male Sex, n (%)	23 (63.9%)	100 (63.3%)	p = 0.926
Mechanism of Injury, n (%)			
MVC	27 (75.0%)	70 (44.3%)	
Pedestrian vs. vehicle	1 (2.8%)	10 (6.3%)	
Motorcycle collision	4 (11.1%)	17 (10.8%)	
ATV collision	2 (5.6%)	4 (2.5%)	**p = 0.013**
Bicycle vs. vehicle	0	6 (3.8%)	
Fall	2 (5.6%)	46 (29.1%)	
Other	0	5 (3.2%)	
Median Initial GCS (IQR)	11 (6.5-15)	14 (10-15)	**p = 0.019**
Median ISS (IQR)	34 (22-42)	24.5 (17-34)	**p = 0.012**
TBI, n (%)	17 (47.2%)	76 (48.4%)	p = 0.898
Prior Stroke, n (%)	1 (2.8%)	2 (1.3%)	p = 0.462
Did not meet Denver Criteria, n (%)	5 (13.9%)	7 (4.4%)	**p = 0.049**
CTA as Part of Initial Trauma Scan, n (%)	23 (63.9%)	98 (62.8%)	p = 0.905

IQR, interquartile range; MVC, motor vehicle collision; AVT, all-terrain vehicle; GCS, Glasgow Coma Scale; ISS, Injury Severity Scale; TBI, traumatic brain injury; CTA, CT angiography

Subgroup analysis of patients not meeting Denver screening criteria revealed no statistically significant difference compared to those who did meet screening criteria in baseline patient demographics (age, sex), injury characteristics (ISS, GCS, TBI, presence of carotid artery injury), hospital length of stay, need for intensive care and ICU length of stay, or treatment characteristics, including time from diagnosis of BCVI to treatment, initial or majority dose of ASA, and time from initiation of treatment to stroke.

BCVI-specific associations with stroke are outlined in Table 3.4. BCVI site (carotid artery vs. vertebral artery vs. multiple arteries, p = 0.003), but not grade (p = 0.222), was associated with higher rates of stroke.

Table 3.4. BCVI-specific risk factors for stroke

	Overall	Stroke	No Stroke	p Value
Site of Injury, n (%)				
Carotid artery	46 (23.7%)	11 (30.6%)	35 (22.2%)	
Vertebral artery	101 (52.1%)	10 (27.8%)	91 (57.6%)	**p = 0.003**
Multiple	47 (24.2%)	15 (41.7%)	32 (20.3%)	
Highest Grade of BCVI, n (%)				
Grade I	54 (27.8%)	5 (13.9%)	49 (31.0%)	
Grade II	72 (37.1%)	16 (44.4%)	56 (35.4%)	p = 0.222
Grade III	25 (12.9%)	5 (13.9%)	20 (12.7%)	
Grade IV	43 (22.2%)	10 (27.8%)	33 (20.9%)	

IQR, interquartile range

For the 182 patients who received any ASA treatment, Table 3.5 outlines the associations between therapy and stroke. Overall, 19.4% of patients treated with ASA 81 mg for the majority of their treatment had a stroke, while 21.9% of patients treated with ASA 325 mg had a stroke, and only one patient who did not receive any treatment had a stroke. Neither initial dose nor majority dose was associated with a difference in stroke rate ($p = 0.502$ vs. $p = 0.755$). The timing of first dose was not significantly different between groups. 44% of patients who had a missed dose of ASA had a stroke, as compared to only 28.8% of patients who did not, but this result did not reach statistical significance ($p = 0.071$).

Specifically, amongst the 18 patients who had a stroke after receiving their first dose of ASA, 13 (9.0% of patients who received majority of doses as ASA 81 mg) had received ASA 81 mg and 5 (15.6% of patients who received majority of doses as ASA 325 mg) had received 325 mg ($p = 0.294$).

Table 3.5. Associations between ASA therapy and stroke

	Overall N = 182	**Stroke N = 36**	**No Stroke N=146**	**p Value**
Initial Dose of Therapy (ASA), n (%)				
81 mg	111 (63.1%)	21 (60.0%)	90 (63.8%)	
325 mg	36 (20.5%)	6 (17.1%)	30 (21.3%)	p = 0.502
Other	29 (16.5%)	8 (22.9%)	21 (14.9%)	
Majority Dose of Therapy (ASA), n (%)				
81 mg	144 (81.8%)	28 (19.4%)	116 (80.6%)	p = 0.755
325 mg	32 (18.2%)	7 (21.9%)	25 (78.1%)	
Timing of First Dose of ASA in minutes (IQR)	316.5 (149.75-880.5)	309 (243.75-903.5)	322 (132.5-885.5)	p = 0.318
Missed Doses of Therapy, n (%)	58 (31.9%)	16 (44.4%)	42 (28.8%)	p = 0.071

IQR, interquartile range

A logistic regression analysis was conducted to evaluate the independent association between majority dose of ASA and stroke, after adjusting for initial GCS, presence of carotid artery injury, and highest Biffl grade of injury (Table 3.6). The logistic regression explained 18.6% of variance (Nadelkerke $R^2 = 0.186$) and demonstrated that majority ASA dose (81 vs. 325 mg) was not independently associated with the risk of stoke (OR 2.244; 95% CI 0.660-7.628).

Table 3.6. Multivariate logistic regression analysis of factors associated with stroke after BCVI

Variable	**Odds Ratio**	**95% Confidence Interval**	**p Value**
GCS	0.906	0.803-1.022	p = 0.107
Carotid Injury	5.032	1.507-16.807	**p = 0.009**
Highest Biffl Grade of Injury	1.376	0.456-4.149	p = 0.571
Majority Dose of ASA	2.244	0.660-7.628	p = 0.195

GCS, Glasgow Coma Scale; ASA, acetylsalicylic acid

Outcomes

Other outcomes are outlined in Table 3.7. The median hospital length of stay for all patients was 12 days (5-23 days), with no significant difference between patients who had a stroke compared to those who did not have a stroke (p = 0.308). Patients who had a stroke were more likely to require intensive care (p = 0.030), although there was no difference between patients with

a stroke compared to those without a stroke in the length of stay in the ICU (p = 0.957). Most patients were discharged home (65, 38.9%) or to a subacute hospital (66, 39.5%) for continued recovery. Thirty-one patients (18.6%) required specialized rehabilitation services. Twenty-seven patients died as a result of their injuries, 6 of whom had suffered a stroke. Discharge disposition (p = 0.754) and mortality (p = 0.597) were not significantly different between groups that had a stroke compared to those that did not.

Table 3.7. Patient outcomes stratified by stroke

	Overall	**Stroke**	**No Stroke**	**p Value**
Median Hospital Length of Stay (IQR)	12 (5-23)	15 (7-29.25)	15 (6.5-27)	p = 0.308
ICU Stay, n (%)	125 (64.9%)	29 (80.6%)	96 (61.4%)	**p = 0.030**
Median ICU Length of Stay (IQR)	5 (2-11)	6 (2-9)	5 (2-13)	p = 0.957
Discharge Disposition, n (%)				
Home	65 (38.9%)	10 (33.3%)	55 (40.1%)	
Subacute hospital	66 (39.5%)	14 (46.8%)	52 (38.0%)	
Rehabilitation center	31 (18.6%)	6 (20.0%)	25 (18.2%)	p = 0.754
Long-term care	4 (2.9%)	0	4 (12.4%)	
Other	1 (0.7%)	0	1 (0.6%)	
Mortality, n (%)	27 (13.9%)	6 (16.7%)	21 (13.3%)	p = 0.597

ICU, intensive care unit; IQR, interquartile range

3.4 Discussion

Early diagnosis and treatment of blunt cerebrovascular injury is imperative to reduce the risk of stroke and stroke-related mortality. ASA has emerged as the preferred treatment modality at many centers,[11,19] however, there is still significant variability in ASA dosing practices and debate about the optimal dose to reduce stroke risk while minimizing bleeding complications. This multicenter retrospective review examined the use of 81 mg ASA compared to 325 mg ASA for treatment of BCVI to evaluate association with stroke. Overall, we demonstrated no difference in stroke risk with use of 81 mg ASA vs. 325 mg ASA in either univariable or multivariable analysis.

This study contributes to existing Canadian literature and builds on previously published retrospective reviews which similarly reported no difference in stroke rates following treatment with 81 mg ASA vs. 325 mg ASA,[20-22] with meta-analysis of these studies (Figure 2.4) revealing no significant difference between groups in terms of stroke risk. No experimental studies to date have evaluated the risks of stroke with different doses of ASA; this study represents the largest retrospective study aimed at answering this question.

Evidence from the basic science and non-trauma literature suggests that ASA doses of 50-100 mg per day are effective at irreversibly inhibiting cyclooxygenase-1 (COX-1), reducing production of thromboxane A_2 (TXA_2), and establishing antithrombotic effects.[23,24] Clinical studies comparing the effectiveness of 81 mg ASA vs. 325 mg ASA in prevention of cardiovascular events or death in patients with pre-existing atherosclerotic cardiovascular disease showed no significant difference in risk reduction of the composite outcome of death, myocardial infarct, or stroke.[13] While this study did not evaluate a difference in bleeding complications between groups, other studies have suggested that use of daily ASA increases risk of significant bleeding, particularly gastrointestinal bleeding,[25] and that higher doses of ASA are correlated with higher risks of bleeding complications.[26]

Treatment of BCVI with antiplatelets or anticoagulation is often balanced with bleeding risk in patients with multiple traumatic injuries. Bleeding risk is often cited as a reason for delaying or withholding therapy. It is therefore advisable to treat BCVI with the minimal effective dose of any medication that presents a bleeding risk, and the current study supports that 81 mg ASA may be sufficient for stroke prevention. Several studies addressing bleeding risk associated with BCVI treatment have shown that early treatment of patients with BCVI and concomitant intracranial, spinal cord, or solid-organ injuries using both antiplatelets and anticoagulants is safe and important

to reduce stroke risk.[21,26,27] Amongst 38 patients with both BCVI and TBI, treatment with antiplatelets and anticoagulants resulted in 7 patients sustaining a stroke (1 patient treated with ASA 81 mg + heparin, 1 patient treated with ASA 81 mg, 1 patient treated with heparin, 2 patients treated with ASA 325 mg + heparin, 1 patient treated with ASA + Plavix + heparin, and 1 patient treated with ASA + Plavix), while no patients had worsening of intracranial hemorrhage.[20] Other studies evaluating the use of 81 mg ASA vs. 325 mg ASA in 77 patients revealed that 2 patients in each treatment group developed strokes, while only one patient treated with 325 mg ASA had a bleeding complication.[21]

An important signal may be present in this study as it relates to delays and interruptions in therapy. Almost a third of patients had a delay in therapy or had at least one dose held during their hospital stay, and over a quarter of these patients suffered a stroke. It is not possible to determine whether the delay or missed doses resulted in stroke. While this study showed no significant difference in stroke rates between patients who had interruptions in therapy compared to those that did not, a previous multicenter study showed a significant increase in stroke risk in patients who had treatment interruptions (75% of patients with stroke had interruptions vs. 24% of patients with stroke without interruptions).[28] Withholding therapy has been associated with increased risk of stroke and death in several studies,[29,30] and it is likely that the current study is underpowered to answer this question. Understanding the reasons for, and implications of, withholding therapy is important to guide future investigations and build on areas of improvement.

Several additional important study limitations exist which must be considered when interpreting the results of this study. Most importantly, this was a retrospective study, and therefore the quality of data was dependent on the quality of clinical notes and chart review and was subject to missing or incomplete data. Of particular note, we were unable to reliably identify reasons for

withholding treatment, identify bleeding complications, or determine details of the stroke to confirm that it was in the territory supplied by the injured artery. This limits assessment of strokes due to BCVI compared to strokes occurring due to other causes, such as atrial fibrillation, atherosclerosis, etc., however, most patients included in the study were young and without pre-existing medical comorbidities predisposing to stroke, and therefore most strokes captured in the study were likely due to BCVI. Similarly, the cause of death was not recorded, and it is not possible to determine if any patients died as a result of BCVI-related stroke.

3.5 Conclusions

This study evaluated the use of 81 mg ASA vs. 325 mg ASA in the treatment of BCVI and the impact on stroke across Canadian Level I Trauma Centers. Treatment with low-dose vs. high-dose ASA did not result in a significant difference in stroke rates. Given the small sample size and retrospective nature of the study, no definite conclusions can be drawn about the optimal management strategy for BCVI, and more research is required to guide future care. To address this issue, a randomized controlled trial evaluating the use of 81 mg ASA vs. 325 mg ASA for BCVI treatment on stroke and bleeding complications is planned.

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CHAPTER 4

PROTOCOL FOR A FEASIBILITY RANDOMIZED CONTROLLED TRIAL EVALUATING THE USE OF 81 mg VS. 325 mg ASA FOR TREATMENT OF BLUNT CEREBROVASCULAR INJURY (BCVI)

CHAPTER 4. Protocol for a Feasibility Randomized Controlled Trial Evaluating the Use of 81 mg vs. 325 mg ASA for Treatment of Blunt Cerebrovascular Injury (BCVI)

4.1 Introduction

Background and Significance

Blunt cerebrovascular injury (BCVI), or injury to the carotid and vertebral arteries, occurs in 1-3% of blunt traumas, often as a result of injury to the head, neck, or chest.[1,2] BCVI is caused by arterial stretching or shearing, which leads to intimal disruption and exposure of the underlying subendothelial collagen.[3-5] Subsequent platelet aggregation and embolization can lead to stroke,[5] which occurs in approximately 20% of patients if untreated.[6] Stroke can lead to disability and poor long-term outcomes, and increases the mortality risk in patients with BCVI.[7-9]

Most strokes from BCVI occur within the first 72 hours from injury,[10] and therefore early diagnosis and treatment are imperative to reduce the risk of stroke. Expanded screening and improving imaging enable early diagnosis and treatment of BCVI, which has been shown to improve outcomes and decrease stroke rates.[11,12] Prompt treatment of BCVI is vital to decrease the risk of stroke.[3,6,13-16]

Currently, there is wide variation across centers and trauma care providers in treatment strategies for BCVI[17] and the most recent guidelines are unable to make specific recommendations about the optimal agent and/or dose or treatment to reduce the risk of stroke after BCVI while minimizing bleeding complications in patients with multiple traumatic injuries.[18] Recent reviews have suggested that stroke rates following treatment with antiplatelets vs. anticoagulants are similar, however, patients treated with anticoagulants experience more bleeding complications, suggesting that antiplatelets are better tolerated in the trauma population.[19] ASA is a commonly

used antiplatelet in the management of BCVI, and some centers have adopted an ASA-based approach to BCVI treatment.[20,21]

The optimal dose of ASA for stroke prevention and to minimize bleeding complications is unknown and more research is required to inform future care. Building on the systematic review and meta-analysis, as well as observational data presented thus far, the next step in further investigation of this issue is a feasibility randomized controlled trial to assess the practicality of conducting a larger randomized controlled trail investigating the efficacy of different doses of ASA (comparing 81 mg ASA vs. 325 mg ASA) in reducing stroke risk following BCVI. The feasibility trial will assess whether it is possible to enroll trauma patients to the study within 90 minutes of diagnosis of BCVI for randomization into low-dose or high-dose ASA groups. The study will assess the rate of enrollment of eligible participants, the feasibility of obtaining informed consent for data inclusion, and the contemporary rate and timing of stroke in this patient population on treatment, which will enable power calculations for future trials.

Rationale and Previous Work

Stroke after BCVI can cause significant disability and increased risk of mortality. Initial reports on the use of heparin in the treatment of BCVI showed improved survival and neurological outcomes compared to no treatment.[13] Several subsequent studies have shown significant reduction in stroke rates on therapy[3,6-9,12,14] and recent systematic reviews have shown that treatment of asymptomatic patients (before the onset of stroke) significantly reduces stroke rates.[19,22] Early recognition and treatment of BCVI have been identified as important interventions to reduce stroke and mortality, with the most recent guidelines recommending screening of patients at high risk of BCVI and treatment with antiplatelet or anticoagulation therapy.[18] Evaluation of the most commonly employed treatment strategies (anticoagulation and antiplatelets) suggests that efficacy

in stroke prevention is similar between the two treatment groups, however, there are fewer bleeding complications following treatment with antiplatelets (specifically ASA).[19] As a result, an ASA-based strategy is beginning to emerge in Canada.

Basic science research further supports use of antiplatelets for prevention of arterial thrombosis. Studies have shown that the composition of thrombi originating in the arterial system are different then those in the venous system, with arterial thrombi primarily composed of fibrin (43% of thrombus volume) and platelets (31%), while venous thrombi are composed primarily of red blood cells (63%) and fibrin (35%), with relatively few platelets.[23] Because arterial thrombosis appears to be primarily mediated by platelet aggregation while venous thrombosis is mediated the coagulation cascade pathway, arterial thrombi have traditionally been treated with antiplatelet agents, while venous thrombosis (eg. deep venous thrombosis) has been treated with anticoagulants.[24] Understanding the pathophysiology of BCVI, which is mediated by arterial injury and subsequent platelet aggregation and clotting,[5] supports that antiplatelets may be better treatment agents.

Research in the non-trauma literature has also evaluated the use of antiplatelets and anticoagulants in the treatment of spontaneous (non-traumatic) cervical artery dissection, which has several similarities to BCVI, to reduce the risk of stroke. Two randomized controlled trials were conducted investigating the efficacy of antiplatelets vs. anticoagulants in the treatment of cervical artery dissection. The Cervical Artery Dissection in Stroke Study (CADISS) evaluated recurrence rates of stroke or TIA in patients with previous symptomatic carotid artery dissection and showed no difference in the rates of recurrent stroke, bleeding, or death following use of antiplatelets vs. anticoagulants.[25] The Aspirin versus Anticoagulation in Cervical Artery Dissection (TREAT-CAD) trial, which investigated the use of ASA vs. vitamin K antagonists

(anticoagulants) in a non-inferiority randomized controlled trial evaluating the composite outcome of stroke, major hemorrhage, or death failed to show non-inferiority following treatment with ASA vs. anticoagulants (23% risk of primary endpoint with ASA compared to 15% risk with anticoagulants).[26] Bayesian meta-analysis of the use of antiplatelets vs. anticoagulants in the treatment of cervical artery dissection showed decreased ischemic stroke, intracranial hemorrhage, and death within the first 3 months after use of antiplatelets compared to anticoagulants.[27] More recent meta-analysis of clinical trials evaluating the use of oral anticoagulants vs. antiplatelets in the treatment of cervical artery dissection on the rates of recanalization on repeat imaging, stroke, or all-cause mortality did not show significant differences between groups in any of the primary outcomes.[28] Secondary outcomes (TIA and bleeding complications) appeared to occur more frequently in patients threated with anticoagulation, however, the results were not statistically significant.

There are no randomized controlled trials or meta-analyses on stroke rates with different doses of ASA in the treatment of cervical artery dissection, however, a recent randomized controlled trial evaluating the use of 81 mg ASA vs. 325 mg ASA on stroke prevention for patients with atherosclerotic cardiovascular disease, the Comparative Effectiveness of Aspirin Dosing in Cardiovascular Disease (ADAPTABLE) trial, showed no significant difference with different doses of ASA on the risk of cardiovascular events (stroke or myocardial infarct), bleeding complications, or death.[29] Meta-analysis of randomized controlled trials evaluating the risk of recurrent stroke or TIA with different doses of antiplatelets, specifically the use of ASA vs. dual antiplatelet agents (ASA + clopidogrel or ticagrelor), showed reduced rates of stroke but higher rates of bleeding complications with dual antiplatelet therapy.[30] Currently, antiplatelets, particularly ASA, are recommended and commonly used for secondary prevention to reduce

recurrent stroke or vascular events in patients with cardiovascular disease and previous strokes or myocardial infarcts.[31,32]

There appears to be evidence favouring use of ASA over anticoagulants in the treatment of BCVI, given recent systematic reviews, basic science understanding of arterial clotting pathophysiology, and similar research in the non-trauma literature. However, it is unknown whether these results can be applied to the BCVI population given the different underlying pathophysiology of BCVI compared to spontaneous cervical artery dissection or atherosclerotic cardiovascular disease. The presence of concomitant traumatic injuries and possible coagulopathy of trauma also puts BCVI patients at higher risk of both thrombosis and bleeding complications.[33] The trauma literature has significant variation in doses of ASA used during treatment, and many studies fail to report treatment doses at all. More research is required to further characterize the efficacy and safety profile of different doses of ASA for BCVI treatment. A feasibility randomized controlled trial is required to evaluate whether it is feasible to conduct a large-scale randomized controlled trial evaluating 325 mg vs. 81 mg ASA with respect to stroke rates and bleeding complications following BCVI.

Study Objectives

The primary aim of this study is to assess feasibility of conducting a randomized controlled trial investigating the use of ASA 81 mg daily vs. ASA 325 mg daily for treatment of patients with BCVI to evaluate the rates of stroke and bleeding complications. To this aim, feasibility will be defined as $\geq$ 70% enrollment rate of eligible patients within 90 minutes of BCVI diagnosis. Additional feasibility metrics will be assessed, as outlined below:

1. Evaluate efficiency and timeliness of establishing BCVI diagnosis/grade of injury and communicating this information to the treating (Trauma) team

2. Assess willingness of trauma team leaders to enroll patients to the study

3. Determine feasibility of enrolling eligible patients to the study within 90 minutes of diagnosis

    - Establish enrollment rate and assess willingness of patients/substitute decision makers to participate in the study; assess feasibility of obtaining informed consent using a deferred consent model with consent obtained within 24 hours of randomization, prior to second dose of therapy
    - Evaluate time to diagnosis, time to first dose of therapy, and number of patients giving consent to continue in the study
    - Determine rate of patient withdrawal from the study, reasons for withdrawal, and impact on cross-over to different dose of therapy after unblinding

4. Assess ability to coordinate care between different specialties to evaluate for potential contraindications to administration of antiplatelets

    - Evaluate buy-in from specialties involved in care of BCVI patients (Vascular Surgery, Neurosurgery) in rapid patient assessment and determination of contraindications to treatment

5. Identify personnel for data collection and evaluate data collection process to ensure accuracy of record keeping of all relevant patient data in the data collection software system (REDCap)

6. Evaluate efficacy of randomization process (ease of use, ability to maintain blinding to treatment allocation)

7. Ascertain ability to administer low dose (81 mg) vs. high dose (325 mg) ASA while maintaining blinding of the patient, treating physician and other members of the care team, and data collectors/analyzers

8. Ensure accuracy of data collection for stroke occurrence and timing in relation to start of therapy, missed doses, and reasons for delay of therapy

9. Determine rate of follow up via phone at 4 weeks from injury
    - Record patient disposition (eg. discharge home, transfer to other subacute hospital, admission to nursing or long-term care), time to discharge, mortality
    - Track events occurring after hospital discharge (eg. delayed stroke or bleeding)
    - Investigate reasons for loss to follow up

4.2 Methods

Study Design

This study is a feasibility trial with the goal of determining the feasibility of conducting a randomized controlled trial comparing different doses of ASA in the treatment of BCVI to reduce stroke rates (primary outcome). Bleeding complications as a result of treatment will be assessed as a secondary outcome.

Study Setting

This study will take place at Victoria Hospital, within the London Health Sciences Centre, a Canadian Level 1 Trauma Centre. Patients transferred from other hospitals will be eligible for inclusion in the study if they meet the eligibility criteria.

Study Duration

The feasibility trial will be conducted for approximately 1 year to assess feasibility of recruitment and randomization. During this time, stroke rate and bleeding complications will be recorded to access event rates and assist with power calculations for future studies.

Recruitment

Patients diagnosed with BCVI via CTA within 72 hours of injury will be eligible for inclusion in the study. To facilitate rapid intervention, a deferral of consent is being sought. Patients or substitute decision makers will be approached as early as possible and provided verbal information and written material regarding relevant background information about BCVI and the purpose of the study, their role and expectations as study participants, and their right to refuse or withdraw from the study at any point. Patients will be informed that their decision about participation in the study will not alter their care, patient questions will be answered, and written consent will be documented on the study consent form.

Recruitment markers will be recorded and assessed by the study team to determine feasibility of overall study recruitment, as well as to identify possible areas that can be addressed and improved. Relevant markers recorded are listed below:

- Total number of patients diagnosed with BCVI during the study period
- Patients diagnosed with BCVI within 72 hours of injury
- Proportion of patients meeting eligibility criteria approached for participation in the study
- Number of patients enrolled within 90 minutes of diagnosis
- Patients declining participation in the study and reasons for refusal

Eligibility Criteria

Inclusion Criteria

- Patients ≥ 18 years of age diagnosed with BCVI via CT angiography (CTA) within 72 hours of injury at a Level I Trauma Center

Exclusion Criteria

- Patients < 18 years of age
- Patients in whom the diagnosis of BCVI can not be made due to pre-existing disease (eg. carotid artery stenosis, previous carotid endarterectomy or stenting)
- Patients with stroke in the territory of BCVI before or at the time of BCVI diagnosis (eg. stroke on presentation to hospital or before BCVI diagnosis)
- Patients requiring additional treatment for BCVI (eg. endovascular therapy, surgery)
- Patients not willing to participate in the study or who are not able to give written informed consent in English

Sample Size

Sample size was calculated using a 1-tailed binomial exact test with an alpha (α) value of 0.05 and beta (β) of 0.2 based on accepted conventions and using established sample size reference tables[34] to determine the number of patients that must be approached for an adequately powered feasibility study. Using the RED-AMBER-GREEN framework of evaluating progression criteria proposed by Lewis et al.,[34] which stratifies cut-offs for trial progression based on the lower limit of what is deemed acceptable for progression (lower limit of GREEN zone) and the upper limit of what is considered unacceptable (upper limit of RED zone), values of 70% minimum enrollment (lower limit of GREEN zone) and 50% (upper limit of RED zone), 37 patients (round up to 38 to maintain even distribution between the two treatment arms) would need to be approached for participation in the study. Based on historical data, we anticipate 40 patients with BCVI to be evaluated annually, which provides rationale for the proposed study duration of 1 year.

Primary Outcome Measure and Progression Criteria

The feasibility of the study and progression to an efficacy randomized controlled trial will be determined based on our ability to enrol ≥ 70% of eligible patients with BCVI within 90 minutes of diagnosis. Enrollment of eligible participants will likely be influenced by the following factors:

- Buy-in from staff and trainees
- Communication between the radiology department and trauma team to enable rapid and accurate diagnosis of BCVI and identify possible study participants
- Willingness of patients to participate in the study
- Ability to promptly identify and contact substitute decision makers for consent for study participation in cases where patients are unable to provide consent within 24 hours of randomization (eg. intubated patients, patients with severe brain injury)

To address these potential issues, information about the study and roles of involved staff members/residents will be circulated ahead of time to ensure awareness of the study and required study protocol. Patient information packages will be available in the trauma bay, trauma unit, and intensive care unit to enable easy and rapid access for healthcare providers performing consent and enrollment. Data entry sheets for each participant and instructions for randomization using REDCap will be included in the study package to facilitate rapid randomization.

Process measures that allow for assessment of potential causes of enrollment challenges will also be recorded, including:

- Number/percentage of eligible BCVI patients approached for study participation
- Number/percentage of approached patients consenting to study enrollment and inclusion of data
- Number/percentage of patients withdrawing from the study

Additional secondary measures that will assist in determination of feasibility are treatment fidelity and rate of follow up at 4 weeks from the time of injury to determine stroke rate. Patients who do not consent to continuing in the study and receiving the study drug dose to which they are randomized will be asked for consent for inclusion of data in the study and will be treated according to the attending trauma physician's discretion (which may or may not change the dose of medication they are receiving but the administered dose will no longer be blinded). If consenting, this data will be included in final analysis during the pilot and eventual randomized controlled trial. Follow up will be assessed as a process measure to determine ability to reliably detect the presence of stroke at 4 weeks post injury in patients surviving to discharge.

Secondary Outcome Measures

This feasibility trial will inform whether it is possible to conduct a randomized controlled trial evaluating the effect of different doses of ASA on stroke and bleeding risk when used for the treatment of BCVI. As such, it will be imperative to determine whether it is possible to accurately record stroke and bleeding complication rates for all patients enrolled in the trial. Secondary outcome measures for this study will be stroke rate and bleeding complications following start of ASA therapy.

Randomization

Patients will be randomized to receive either 81 mg ASA daily or 325 mg ASA daily in a 1:1 ratio using randomization software on REDCap. To minimize risks of imbalanced randomization given the expected small sample size, patients will be randomized in random permuted blocks. Stratified randomization will be employed to reduce the risks of imbalanced randomization based on known risk factors that affect the likelihood of stroke following BCVI.

Patients will be stratified based on Biffl grade of injury at the time of initial BCVI diagnosis via CTA and will be classified as low risk for BCVI-related stroke (injury grades I-II) or high risk for BCVI-related stroke (grade III-IV).

Blinding

Patients, as well as all physicians and healthcare team members and data collectors/analysts, will be blinded to treatment allocation. The pharmacy team have been engaged for assistance with study drug allocation and creation of uniform pills to maintain blinding.

Study Protocol

Patients who are diagnosed with BCVI via CTA will be enrolled in the study and randomized to receive either 81 mg ASA daily or 325 mg ASA daily (within 90 minutes of diagnosis). Within 24 hours from diagnosis, the patient will be approached by the research team for continued participation in the study. If patients are not able to provide informed consent, a substitute decision maker will be identified from their chart and approached. Patients who consent to study participation will have basic data and identifiers entered into REDCap, a secure online data entry and study organization software, and will receive either 81 mg or 325 mg ASA daily, once deemed safe to begin antiplatelet therapy. Clearance for initiation of antiplatelet therapy will be at the discretion of the attending physician/trauma team. If concerns arise that require expertise from other services (eg. Neurosurgery input for patients with intracranial hemorrhage), decisions about starting antiplatelet therapy will be made jointly in consultation with the consulting service. Patients will be monitored throughout their hospital stay for the development of stroke in the territory of the injured vessel and bleeding complications. An outline of the study protocol is available in Figure 4.1.

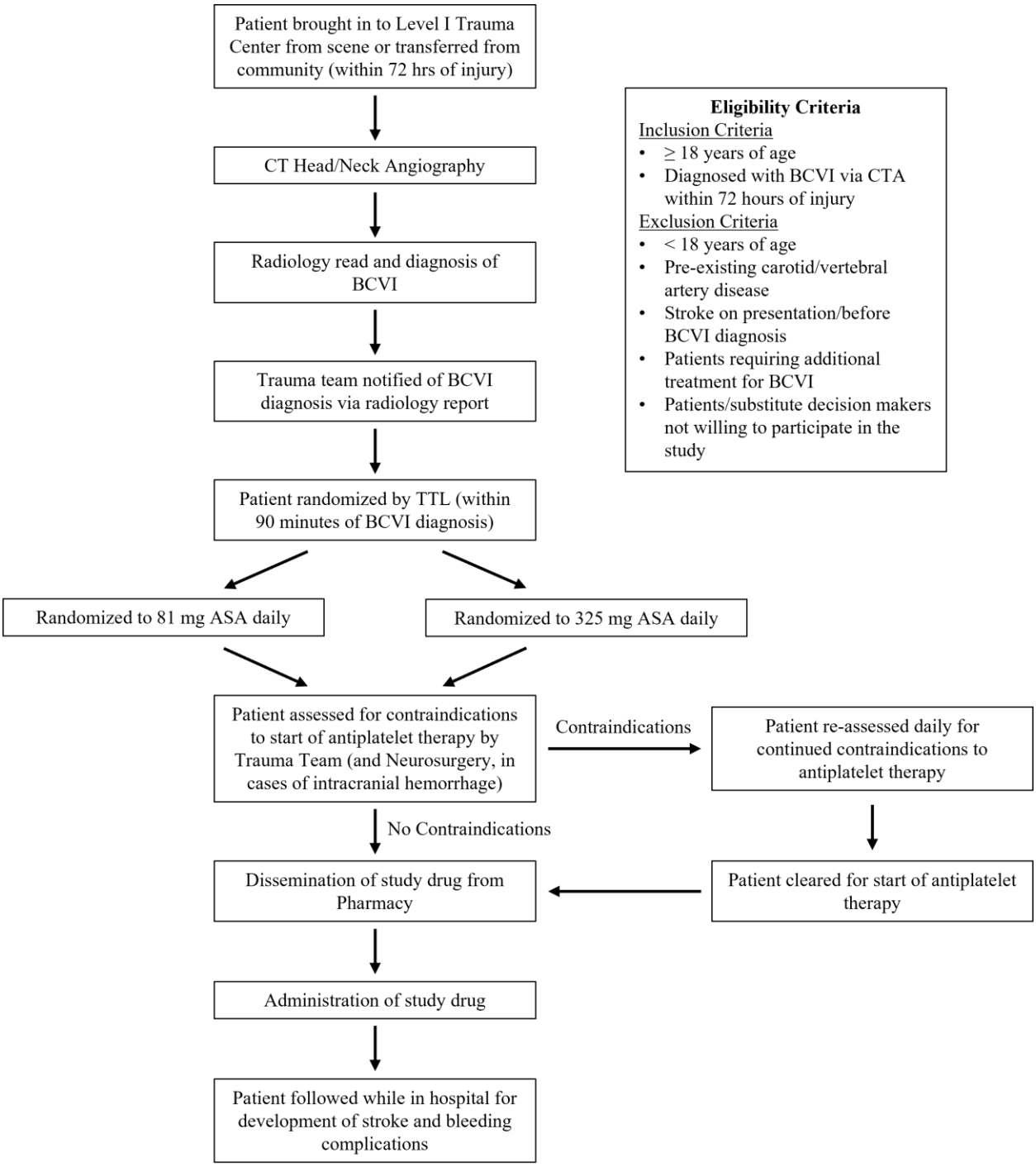

Figure 4.1. Study protocol flow chart. TTL, Trauma Team Leader; ASA, acetylsalicylic acid

Data Collection

All data will be collected and stored on REDCap, a secure online platform. The following data will be collected for all enrolled patients:

- Date and mechanism of trauma
- Direct admission to London Health Sciences Centre vs. transfer from other hospital
- Time of BCVI diagnosis
- Location and grade of BCVI, other treatments required for BCVI (stenting, surgery)
- Associated traumatic injuries (TBI, intra-cranial hemorrhage, intra-abdominal or retroperitoneal bleeding)
- Stroke diagnosis while admitted (location of stroke)
- Bleeding complications (new or worsening bleeding which may or may not require intervention)

Given the relatively low incidence of BCVI and BCVI-related stroke on therapy, patients enrolled in the feasibility trial will be included in future pilot and randomized controlled trials (Vanguard trial). All data required for future trials will be collected but not analyzed, and patient treatment allocation will remain blinded. Additional data collected for future trials includes:

- Age and sex of patient
- Medical comorbidities and pre-injury use of antiplatelets or anticoagulants
- Associated traumatic injuries (TBI, intra-cranial hemorrhage, intra-abdominal or retroperitoneal bleeding)
- Injury severity score (ISS)
- Need for operative intervention for traumatic injuries
- Hospital length of stay, ICU length of stay
- Type of bleeding complications, interventions required to address complications
- Stroke-related disability and neurological deficits at the time of stroke diagnosis
- Neurological function at discharge
- Radiographic characteristics of BCVI on follow up imaging

- Discharge disposition, need for specialized nursing care following discharge
- Mortality

Data Analysis

All collected data will be analyzed using simple descriptive statistics to determine feasibility. No comparative data will be presented given the planned inclusion of these patients in future trials.

Funding/Financial Support

Internal organizational grant applications will be submitted to assist with project funding for support staff and pharmacy costs.

4.3 Discussion

Given multiple challenges in creating a randomized controlled trial assessing different treatment strategies for BCVI, such as relatively low rates of BCVI in the trauma population[1,2] and low event rates (stroke and bleeding complications) on therapy,[3,6,9] a feasibility trial is required to assess whether it is possible to conduct a larger randomized controlled trial. A previously attempted randomized controlled trial aiming to evaluate the use of anticoagulants (heparin) vs. antiplatelets (ASA and Plavix) in the treatment of grade I-III BCVI (NCT00494156) was withdrawn prior to participant enrollment and randomization,[35] which highlights the need for feasibility testing prior to committing time and resources into the creation of future randomized controlled trials. If it is feasible to enroll enough participants, the next stage of trial planning will include a pilot randomized controlled trial evaluating stroke rates and bleeding complications which will help determine the required study size and timeline for a sufficiently powered large-scale randomized controlled trial.

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CHAPTER 5

SUMMARY OF RESULTS AND DISCUSSION

Chapter 5. Summary of Results and Discussion

5.1 Clinical Importance

Blunt cerebrovascular injury, although uncommon, causes significant morbidity and mortality, especially if unrecognized and untreated. Significant work over the last several decades has led to improvement in BCVI detection and treatment, which has contributed to decreased BCVI-related stroke and mortality.[1,2] Several treatment strategies have been described, however, there is still wide variability in practice among centers and trauma care providers,[3] and the most recent guidelines are unable to make specific recommendations as to the optimal treatment strategy and/or dose of therapy.[4] The aims of this thesis were to evaluate common medical treatment modalities used in the management of BCVI to reduce the risk of stroke, with particular focus on ASA and heparin. The results of this work will contribute to current knowledge of BCVI management to help inform future care and clinical guidelines, and act as a starting point for further experimental studies evaluating optimal treatment strategies.

5.2 Overview of Results

Systematic review and meta-analysis of the literature did not show a significant difference in stroke incidence following treatment with ASA or heparin, two of the most commonly used treatment strategies for BCVI, however, use of heparin was associated with a significantly higher risk of bleeding complications and more severe complications requiring invasive interventions. Meta-analysis was not possible for other outcomes of interest, including neurologic outcomes, radiographic healing, and mortality, although outcomes appeared similar between groups treated with antiplatelets and anticoagulants.

Overall, this study suggests this that ASA has a lower risk of bleeding following trauma and should be the preferred treatment modality for BCVI. However, the optimal dose of ASA is

still in question. Different doses of ASA for treatment of BCVI were evaluated by very few studies, which did not demonstrate a difference in stroke rates; no studies reported on differences in bleeding complications with high-dose vs. low-dose ASA. Further research is required to determine the optimal dose of ASA to reduce stroke rates while limiting bleeding complications.

Multi-center retrospective review evaluating the use of ASA for BCVI treatment demonstrated no difference in terms of stroke rates with the use of 81 mg ASA daily compared to 325 mg ASA daily. Factors associated with higher risk of stroke following BCVI included mechanism of injury, lower initial GCS and higher ISS, and not meeting Denver screening criteria. Carotid injuries were at higher risk of stroke, and patients who suffered a stroke were more likely to require intensive care, further highlighting the importance of early treatment to reduce stroke occurrence.

While useful for informing treatment approaches for BCVI based on existing literature and retrospective data, several limitations, including the retrospective and non-experimental nature of the data, preclude definite determination of which treatment modality and dose are best for BCVI management. The quality of data reporting and low event rate of stroke on therapy in many studies created limitations in review of existing literature, and, similarly, the retrospective nature and missing or incomplete data limited assessment of bleeding complications following treatment with different doses of ASA.

5.3 Future Directions

More research is required to determine the optimal dose of ASA, one of the most common treatment strategies in the management of BCVI. While previous non-experimental work suggests that there may be no difference in stroke rate with 81 mg ASA daily vs. 325 mg ASA daily, prospective, experimental studies are required to verify if this is the case and to help make

recommendations for future care. Part of this thesis included the creation of a protocol for a feasibility randomized controlled trial evaluating the use of 81 mg ASA daily vs. 325 mg ASA daily on BCVI-related stroke rate, which will assess whether it is possible to conduct a larger randomized controlled trial to evaluate the risk of stroke and bleeding complications with high-dose vs. low-dose ASA. The next steps for this project include conducting a pilot randomized controlled trial, and eventually, a large-scale randomized controlled trial.

5.4 References

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APPENDICES

APPENDIX I. Vascular Anatomy of the Neck, Head, and Brain

I. 1.1 Aortic Arch Anatomy

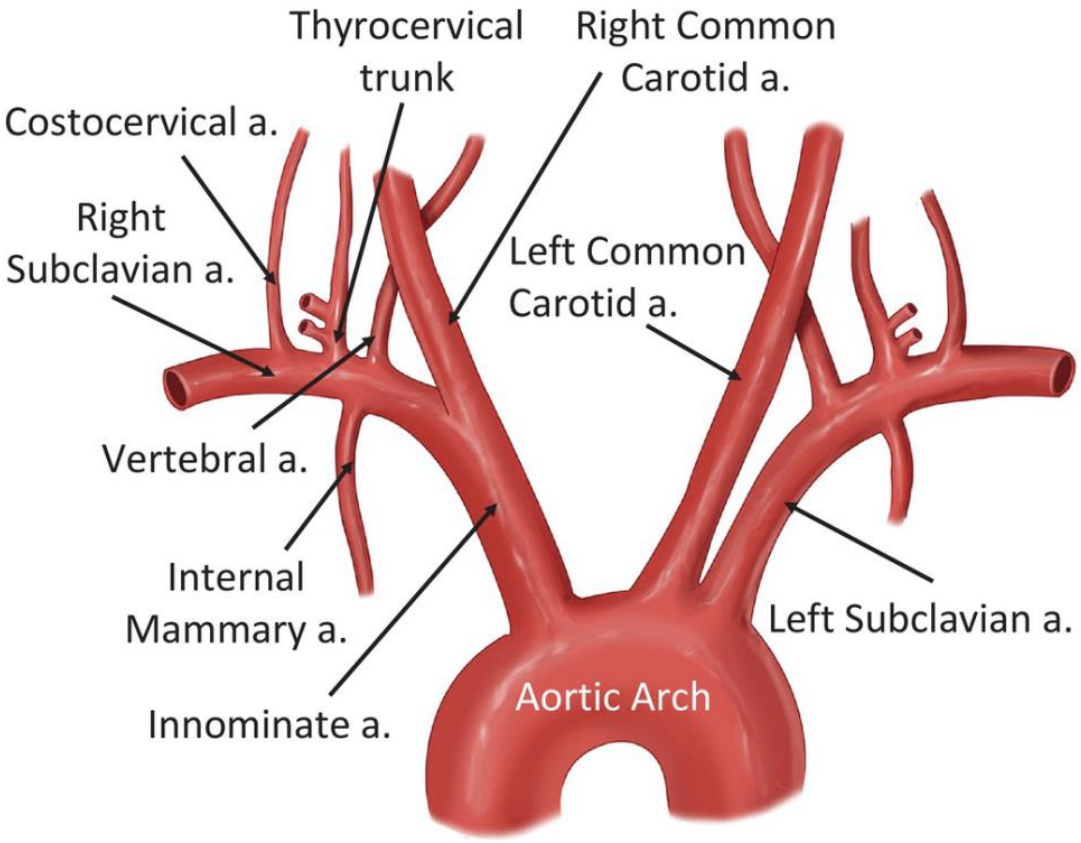

Figure I.1. Anatomy of the aortic arch and its branches

Image Credit: Demetrios, D., & Jennifer A. Smith, J.A. (2020). Subclavian Vessels. Atlas of Surgical Techniques in Trauma, Second Edition. (2nd ed., pp. 59–69) Cambridge Press.

The aortic arch is a continuation of the ascending aorta and gives off three branches, the innominate artery (or brachiocephalic trunk), which divides into the right common carotid and right subclavian arteries, the left common carotid artery, and the left subclavian artery. The vertebral arteries are the first branches of the subclavian arteries and travel upward toward the head along the back of the neck, within the transverse foramina of the first six cervical vertebrae (C6 to C1).[1] The common carotid arteries, which arise from the innominate artery on the right and directly

off the aortic arch on the left, travel up the neck within the carotid sheath, bifurcating into the internal and external carotid arteries at the level of the C3-4 intervertebral disc, roughly at the level of the superior border of the thyroid cartilage.[2] The internal carotid arteries enter the skull to supply the brain, while the external carotid arteries branch to supply the muscles and tissues of the face and head.

I. 1.2 Common and External Carotid Artery Anatomy

The left common carotid artery (CCA) originates from the aortic arch, the right common carotid artery originates from the innominate (brachiocephalic) artery; both arteries course upward within the neck, encased within the carotid sheath, until the level of the C3-4 intervertebral disc, where the common carotid arteries branch into the internal and external carotid arteries.[1-3]

The external carotid artery (ECA) gives rise to branches supplying the muscles and soft tissues of the neck, face, and scalp (Table I.1). The anterior branches include the superior thyroid artery, lingual artery, and facial artery, which supply the larynx and thyroid gland, the oral floor/cavity and tongue, and the face, respectively. The medial branch gives rise to the ascending pharyngeal artery, which supplies the dura and pharyngeal walls, and the posterior branches give rise to the occipital and posterior auricular arteries, which supply the scalp overlying the occiput and the structures of the inner and outer ear and parotid gland, respectively. The external carotid artery gives rise to two terminal branches, the maxillary artery, which has several branches supplying the muscles of mastication, the mandible, teeth and gums, the hard and soft palates, the palatine tonsils, and the pharyngeal wall, and the superficial temporal artery, which supplies the scalp of the forehead and vertex, and the soft tissues around the zygomatic arch and lateral orbital walls.[3]

Table I.1. Branches of the External Carotid Artery[3,4]

Primary Branches	Terminal Branches	Arterial Distribution
Superficial Thyroid Artery	Glandular branches	Thyroid gland
	Superior laryngeal artery	Larynx
	Sternocleidomastoid branch	Sternocleidomastoid muscle
Lingual Artery	Dorsal lingual branches	Base of tongue, epiglottis
	Sublingual artery	Sublingual gland, tongue, oral floor, oral cavity
	Deep lingual artery	Tongue
Facial Artery	Ascending palatine artery	Pharyngeal wall, soft palate, pharyngotympanic tube
	Tonsillar branch	Palatine tonsil
	Submental artery	Oral floor, submandibular gland
	Labial arteries (superior and inferior)	Lips and nasal septum
	Angular artery	Superior part of the cheek, inferior eyelid
Ascending Pharyngeal Artery	Pharyngeal branches	Pharyngeal wall
	Inferior tympanic artery	Mucosa of middle ear
	Posterior meningeal artery	Dura, posterior cranial fossa
Occipital Artery	Occipital branches	Scalp (occipital region to vertex)
	Descending branch	Posterior neck muscles
Posterior Auricular Artery	Stylomastoid artery	Facial nerve
	Posterior tympanic artery	Tympanic cavity
	Auricular branch	Auricle of ear and skin/scalp posterior to auricle
	Occipital branch	Occiput
	Parotid branch	Parotid gland
Maxillary Artery	Mandibular branch	Mandible, teeth, gums, dura, anterior and middle cranial fossae, TMJ, external auditory canal, tympanic cavity
	Pterygoid branch	Masseter muscle, temporalis muscle, pterygoid muscles, buccal muscles
	Pterygopalatine branch	Teeth, maxillary sinus, hard palate, soft palate, palatine tonsil, pharyngeal wall, nasal cavity and septum
Superficial Temporal Artery	Transverse facial artery	Soft tissues below zygomatic arch
	Frontal and parietal branches	Scalp (forehead and vertex)
	Zygomatico-orbital artery	Lateral orbital wall

TMJ, temporomandibular joint

Adapted from Blood Vessels of the Head and Neck, in *Atlas of Anatomy: Head and Neuroanatomy*[3] and Head in *Clinically Oriented Anatomy*[4]

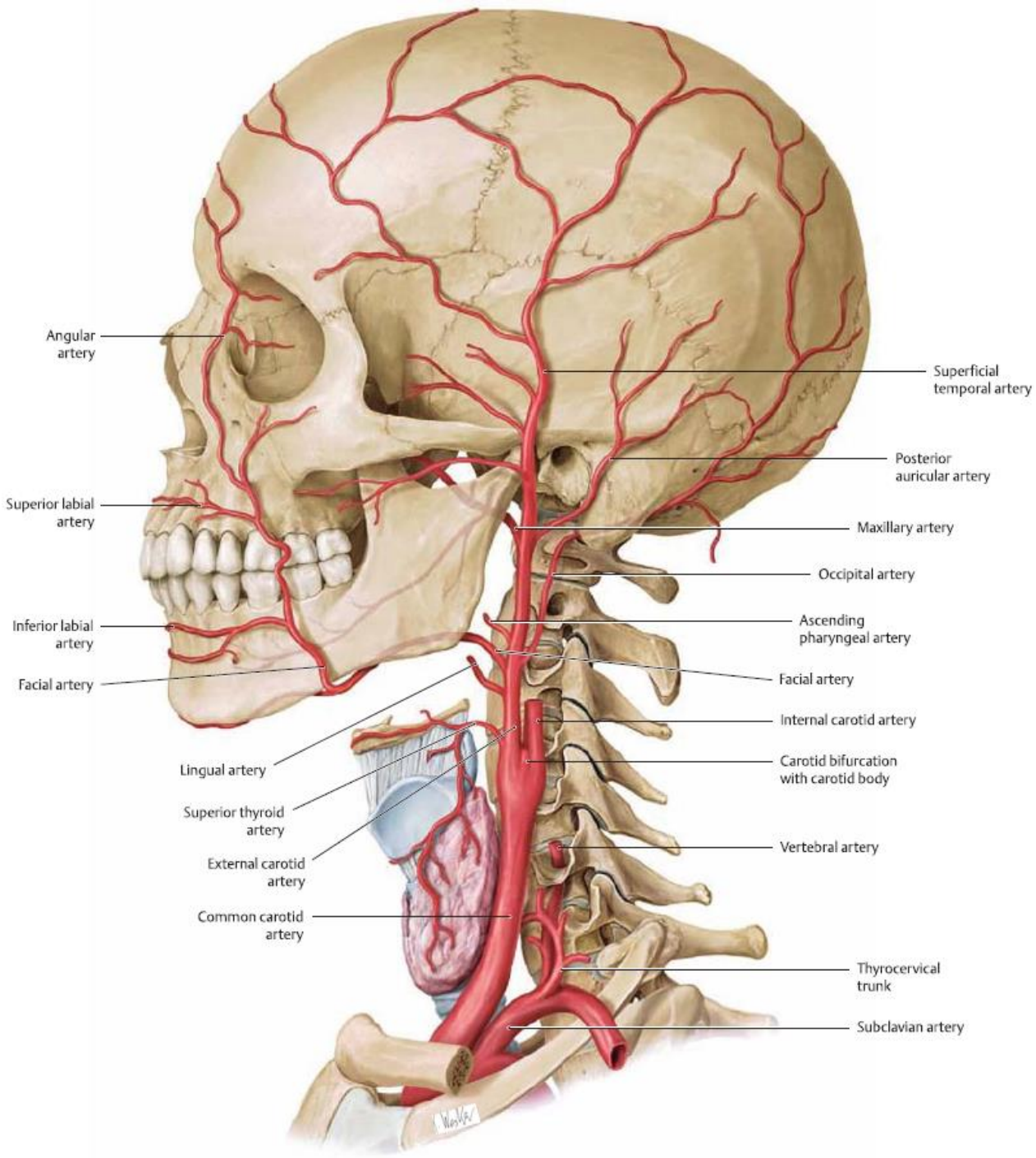

Figure I.2. Anatomy of the common and external carotid arteries

Image Credit: Schünke Michael, Schulte, E., Schumacher, U., Ross, L. M., Lamperti, E. D., Taub, E., Voll, M., & Wesker, K. (2010). Blood Vessels of the Head and Neck. In *Atlas of Anatomy: Head and Neuroanatomy* (1st ed., pp. 54–65). Thieme.

I. 1.3 Internal Carotid Artery Anatomy

The internal carotid arteries arise from the bifurcation of the common carotid arteries; they enter the skull via the carotid canal of the petrous part of the temporal bones, giving off several branches before terminating as the anterior and middle cerebral arteries, which supply the cerebral hemispheres (except the occipital lobes). There are several classification systems of the internal carotid artery segments. The Bouthiller classification (Table I.2),[5-7] describes seven segments according to the compartments within which they are located, with further numbering according to direction of blood flow.[6] Classification is often simplified into four anatomical divisions based on location within the head and neck, which includes the cervical, petrous, cavernous, and cerebral (supraclinoid) segments (Figure I.3, Table I.3).[3,8]

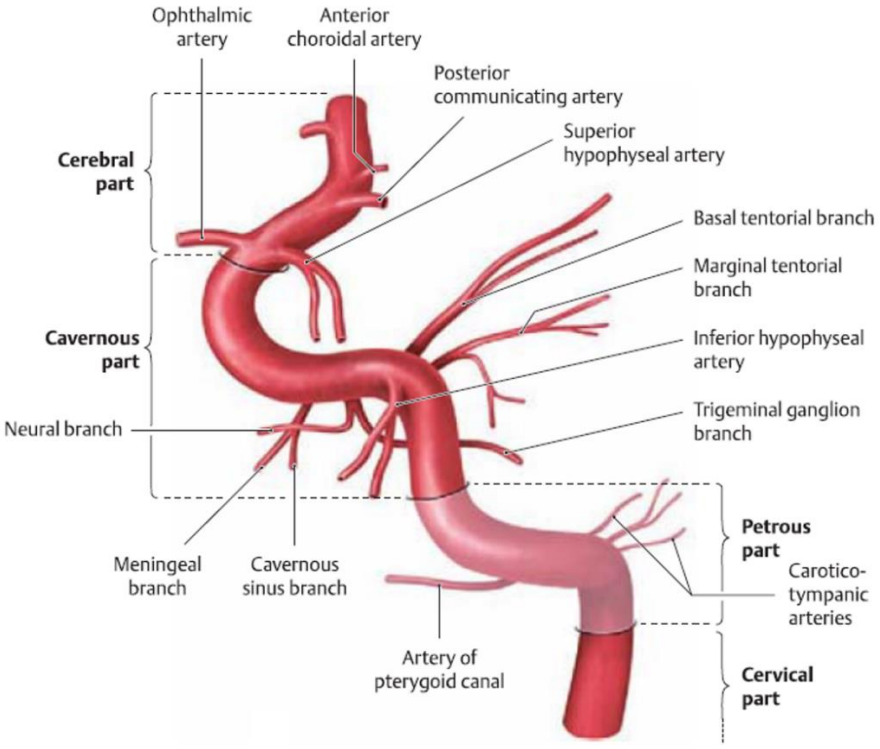

Figure I.3. Anatomy of the internal carotid artery[3]

Image Credit: Schünke Michael, Schulte, E., Schumacher, U., Ross, L. M., Lamperti, E. D., Taub, E., Voll, M., & Wesker, K. (2010). Blood Vessels of the Brain. In *Atlas of Anatomy: Head and Neuroanatomy* (1st ed., pp. 246–265). Thieme.

Table I.2. Bouthiller Classification System for the Segments of the Internal Carotid Artery[5-7]

Segment		Description of Anatomic Course	Branches
C1	Cervical	Runs within the carotid sheath from the common carotid artery bifurcation to the entrance of the carotid canal of the petrous bone, anterior to the jugular foramen	None
C2	Petrous	Continues from the entrance of the carotid canal to the posterior edge of the foramen lacerum ▪ Comprised of 3 parts – vertical portion, bend (posterior loop), and horizontal portion	Caroticotympanic artery Vidian artery
C3	Lacerum	Courses through periosteum from the posterior edge of the foramen lacerum to the superior margin of the petrolingual ligament	None
C4	Cavernous	Starts at the superior margin on the petrolingual ligament and terminates at the proximal dural ring (comprised of the junction of the medial and inferior periosteum of the anterior clinoid process) ▪ Comprised of 4 components – vertical portion, posterior bend, horizontal portion, anterior bend	Meningohypophyseal trunk Inferolateral trunk
C5	Clinoid	Short segment beginning at the proximal dural ring and ending at the distal dural ring	None
C6	Ophthalmic	Travels from the distal dural ring and extends to just proximal to the origin of the internal carotid bifurcation	Ophthalmic artery Superior hypophyseal artery
C7	Communicating	Last segment, from proximal to the origin of the posterior communicating artery, ending at the internal carotid bifurcation	Posterior communicating artery Anterior choroidal artery Anterior cerebral artery Middle cerebral artery

Adapted from Bouthillier *et al*.,[6] Charlick et al.,[5] and The Neurosurgical Atlas[7]

Table I.3. Segments of the Internal Carotid Artery[3,8]

Segment	Description	Risk of Injury
Cervical	Ascends in the neck within the lateral pharyngeal space, ventral to the transverse processes of C1-3	Distal cervical segment is at risk of stretch over the transverse processes of C1-3 during neck hyperextension
Petrous	Located within the carotid canal of the petrous portion of the temporal bone	At risk of injury with basilar skull fractures
Cavernous	Intracranial S-shaped segment coursing though the cavernous sinus	Lower risk of injury
Cerebral	Running through the subarachnoid space of the chiasmatic cistern, terminating as the anterior and middle cerebral arteries	Lower risk of injury

Adapted from Biffl *et al*.[8] and Blood Vessels of the Brain, in *Atlas of Anatomy: Head and Neuroanatomy*[3]

I. 1.4 Vertebral Artery Anatomy

The vertebral arteries branch from the subclavian arteries bilaterally, course upwards within the transverse foramina of C6 to C1, angle sharply around the lateral mass of the atlas to enter the skull through the dura mater in the foramen magnum, and unite with the contralateral vertebral artery at the anterior border of the pons to form the basilar artery (Figure 4).[4,9] The vertebral artery is divided into four segments based on anatomical location. The V1 segment is the stretch of artery from its origin to C6, V2 courses within the transverse foramen from C6 to C2, V3 is from C2 to the dura, and V4 is from the dura to the confluence creating the basilar artery.[10] The vertebral arteries, together with the basilar artery and posterior cerebral arteries, comprise the posterior circulation to the brain, providing blood flow to the brainstem, cerebellum, inferior aspect of the cerebral hemisphere and occipital lobe, and components of the limbic system. These structures are crucial for maintaining vital body functions, including regulating cardiovascular and respiratory functions, metabolic functions, and consciousness, coordinating movement, enabling

vision, and allowing for interconnection and communication between the cerebellar hemispheres and the brainstem and thalami.[4,11]

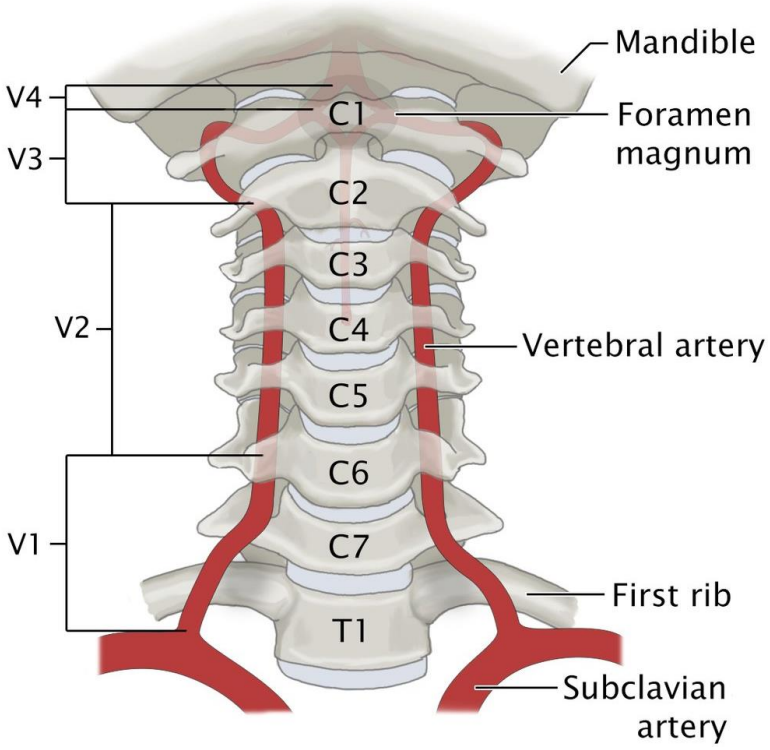

Figure I.4. Anatomy of the vertebral arteries[11]

Image Credit: ***Vertebral column - knowledge @ amboss*****. ambossIcon**. (2022, April 29). Retrieved January 29, 2023, from https://www.amboss.com/us/knowledge/Vertebral_column

I. 1.5 Anatomy of the Circle of Willis

The circle of Willis is an anastomotic network of arteries located at the skull base that connects the anterior circulation, primarily supplied by the internal carotid arteries, and the posterior circulation, primarily supplied by the vertebral arteries (Figure I.5).[3,13] The anterior part of the circle of Willis is formed by a connection between the right and left anterior cerebral arteries (ACAs), termed the anterior communicating artery.[13,14] The posterior component of the circle of Willis is comprised by the connection between the right and left posterior cerebral arteries, which are branches of the basilar artery. [13,14] After the vertebral arteries enter the skull through the

foramen magnum, they join to form the basilar artery, which bifurcates to form the right and left posterior cerebral arteries (PCAs).[13] The posterior cerebral arteries join the anterior circulation via the posterior communicating arteries bilaterally through anastomosis with the middle cerebral arteries (branches of the internal carotid arteries). [13,14]

The circle of Willis provides collateral flow to both the anterior and posterior circulations in the event of injury or thrombosis in one or more areas, protecting against brain ischemia. However, many variations exist in the anatomy of the circle of Willis, in both the size and presence of collaterals, which may become clinically significant in some cases of ischemia or injury.[4,13,15]

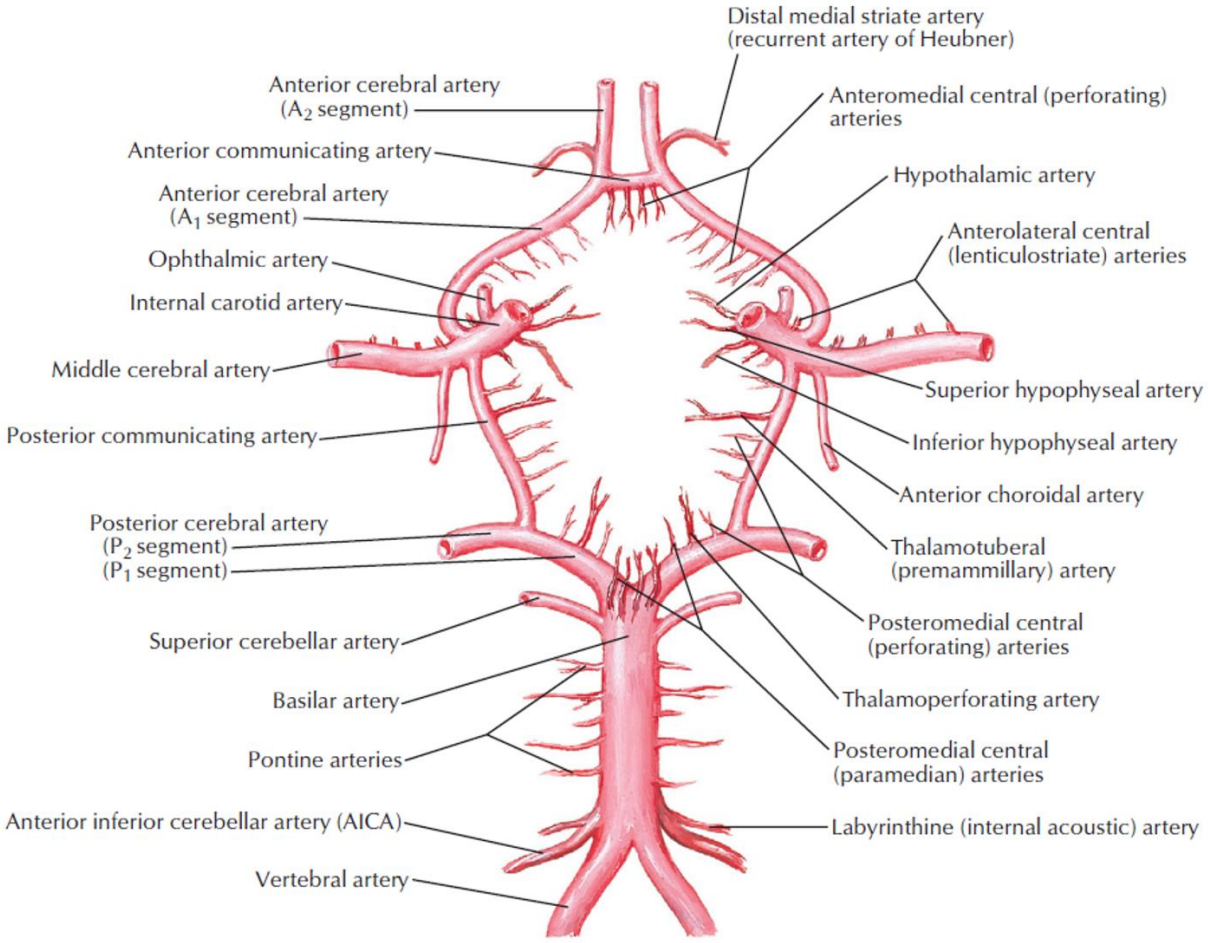

Figure I.5. Anatomy of the circle of Willis[15]

Image Credit: Hansen, J. T., & Netter, F. H. (2014). Head and Neck. In *Netter's Atlas of Human Anatomy* (6th ed.). Sanders Elsevier.

I. 1.6 Blood Supply to the Brain

The brain receives blood supply through the anterior circulation, comprised of the middle and anterior cerebral arteries (terminal branches of the internal carotid arteries), and the posterior circulation, comprised of the basilar, posterior cerebral, and posterior communicating arteries (arising from the vertebral arteries). The anterior circulation supplies the frontal cortex and the parietal and lateral temporal lobes of both hemispheres. The posterior circulation supplies the brainstem, cerebellum, occipital lobe, optic tract, internal capsule, and thalamus.[4]

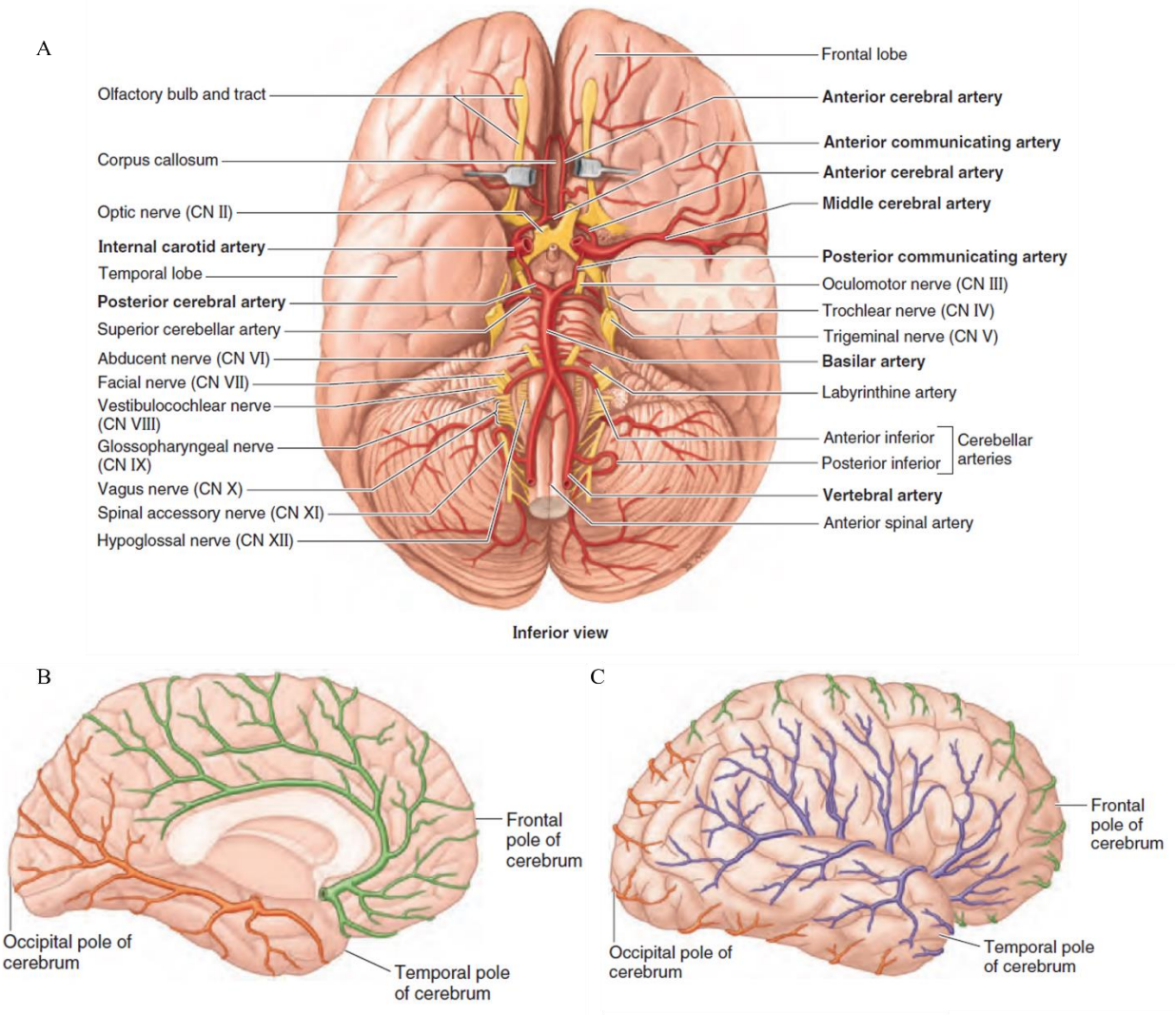

Figure I.6. Anatomy of the blood supply to the brain, inferior view (A), medial view of left hemisphere (B), right lateral view of right hemisphere (C)[3]

Image Credit: Schünke Michael, Schulte, E., Schumacher, U., Ross, L. M., Lamperti, E. D., Taub, E., Voll, M., & Wesker, K. (2010). Blood Vessels of the Brain. In *Atlas of Anatomy: Head and Neuroanatomy* (1st ed., pp. 246–265). Thieme.

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APPENDIX II. Systematic Review Search Strategy

II. 1.1 Ovid MEDLINE Database Search (1946 – Oct. 19, 2022)

1 exp cerebrovascular trauma/ (7874)

2 (vertebral artery/ or exp carotid artery/ or exp Carotid Artery Diseases/ or ((carotid$ or vertebral$ or vertebro$ or cervical$ or cervico$ or cerebrovascular$ or cerebro-vascular$) and (arterial$ or arter$)).tw,kf.) and (artery dissection/ or artery injury/ or (trauma$ or injur$ or resection$ or dissect*).tw,kf.) (30543)

3 ((trauma$ or injur$ or wound$ or resection$ or dissect* or rupture$ or transection$) adj5 (carotid$ or vertebral$ or vertebro$ or cervical$ or cervico$ or cerebrovascular$ or cerebro-vascular$)).tw,kf. (32593)

4 ((carot* or cerebr*) and (bcvi or tcvi)).tw,kf. (225)

5 (carot$ adj3 ((false adj aneurysm*) or pseudo?aneurysm*)).tw,kf. (662)

6 or/1-5 (51520)

7 exp Stroke/ or (stroke$ or ((cerebr$ or brain$) adj3 infarct$) or apoplex$).tw,kw. (352397)

8 Ischemic Attack, Transient/ or (transient$ and ((cerebr$ or brain$ or attack$) adj3 ischemi$)).tw,kw. or TIA.tw,kw. (38643)

9 or/7-8 (368638)

10 (((trauma$ or injur$ or wound$ or resection$ or dissect* or rupture$ or transection$) adj5 (carotid$ or vertebral$ or vertebro$ or cervical$ or cervico$ or cerebrovascular$ or cerebro-vascular$)) or (bcvi or tcvi)).ti. (14119)

11 6 and (trauma$ or injur$ or dissect$).ti. (21606)

12 or/10-11 (23431)

13 6 and 12 (23421)

14 exp Platelet Aggregation Inhibitors/ (133573)

15 ((antiplatelet$ or anti-platelet$) adj3 (drug$ or agent$ or therap$ or treat$ or medicat$ or profile$ or compar$)).tw,kf,nm. (28184)

16 (thienopyridine$ or aspirin$ or clopidogrel$ or cilostazol$ or Plavix or iscover or prasugrel$ or ticlopidine$ or brilinta or brilique or ticagrelor$ or ticlid or ticlodix or ticlodone$ or effient or efient).tw,kf,nm. (85736)

17 or/14-16 [antiplatelet agents] (168951)

18 exp anticoagulants/ or (anticoagul$ or anti-coagul$ or antithromb$ or anti-thromb$ or NOAC or DOAC or NOACs or DOACs).tw,kf,nm. (307726)

19 exp Vitamin K/ or (VKA or VKAs or (menadione$ adj2 antagonist$) or (anti?vitamin$ adj2 K) or (vitamin$ adj2 K)).tw,kf,nm. (30257)

20 (warfarin or acenocoumarol or coumadin or coumarin or phenprocoumon or sintrom or sinthrome or jantoven or marevan or waran or nicoumalone or dicoumarol or dicumarol or phenindione or dabigatran or ximelagatran or apixaban or rivaroxaban or edoxaban or betrixaban or idraparinux).tw,kf,nm. (60259)

21 exp Heparin/ or (liquaemin$ or heparin$ or LMWH).tw,kf,nm. or (enoxaparin$ or tinzaparin$ or dalteparin$ or danaparoid or fondaparinux or nadroparin or Fragmin or Lovenox or Innohep).tw,kf,nm. (114463)

22 or/18-21 [anticoagulants] (372667)

23 treatment$.mp. (5851324)

24 17 or 22 or 23 (6212451)

25 (antiplatelet$ or anti-platelet$ or (anticoagul$ or anti-coagul$ or antithromb$ or anti-thromb$ or NOAC or DOAC or NOACs or DOACs) or (liquaemin$ or heparin$ or LMWH) or (thienopyridine$ or aspirin$ or clopidogrel$ or cilostazol$ or Plavix or iscover or prasugrel$ or ticlopidine$ or brilinta or brilique or ticagrelor$ or ticlid or ticlodix or ticlodone$ or effient or efient) or (warfarin or acenocoumarol or coumadin or coumarin or phenprocoumon or sintrom or sinthrome or jantoven or marevan or waran or nicoumalone or dicoumarol or dicumarol or phenindione or dabigatran or ximelagatran or apixaban or rivaroxaban or edoxaban or betrixaban or idraparinux) or (enoxaparin$ or tinzaparin$ or dalteparin$ or danaparoid or fondaparinux or nadroparin or Fragmin or Lovenox or Innohep) or (therap$ or treat$ or medicat$)).ti. (2532462)

26 6 and 9 and (17 or 22) [concepts: BCVI PLUS Stroke PLUS Treatment focused on antiplatelets/anticoagulants] (1152)

27 6 and 9 and 25 [concepts: BCVI PLUS Stroke PLUS Treatment focused TITLE search] (832)

28 9 and 12 and 24 [concepts: BCVI focused TITLE search PLUS Stroke PLUS Treatment expanded] (1698)

29 12 and (17 or 22) [concepts: BCVI focused TITLE search (NO-Stroke) PLUS Treatment focused on antiplatelets/anticoagulants] (1623)

30 11 and 25 and (exp *Wounds, Nonpenetrating/ or Wounds, Nonpenetrating/ or (bcvi or tcvi or blunt).tw,kf.) (154)

31 26 or 27 or 28 or 29 or 30 (3467)

32 limit 31 to "all adult (19 plus years)" (1834)

33 limit 31 to "all child (0 to 18 years)" (393)

34 31 not (33 not (32 and 33)) (3299)

35 (pediatr$ or paediatr$ or child$ or adolescent$ or infan$ or newborn$ or neonat$).ti. (1531363)

36 34 not 35 (3214)

37 exp case-control studies/ or (case$ and control$).tw,kf. or (case$ and series).tw,kf. or cases.tw,kf. [Medline case series] (3432528)

38 case reports/ or case report$.mp. (2391261)

39 36 not (38 not (37 and 38)) (2426)

40 39 not case report.ti. [Removing case Reports and retaining Case Series] (2354)

41 40 not (exp Animals/ not (Human/ and exp Animals/)) (1856)

42 (animal$1 or mice or rat or rats or cat$1 or cattle$1 or dog$1 or goat$1 or horse$1 or rabbit$1 or sheep$1 or swine$1 or pig$1 or piglet* or canine$1 or feline$1 or porcine$ or calf or primate* or rodent$ or hamster$ or lamb$1 or monkey$1 or murine or veterinar*).ti. (2222031)

43 41 not 42 (1799)

44 limit 43 to English language (1600)

Total Article Count: 1600

II. 1.2 Ovid Embase Classic + Embase Database Search (1947 – Oct. 19, 2022)

1 carotid artery injury/ (5556)

2 (vertebral artery/ or exp carotid artery/ or exp *carotid artery disease/ or ((carotid$ or vertebral$ or vertebro$ or cervical$ or cervico$ or cerebrovascular$ or cerebro-vascular$) and (arterial$ or arter$)).tw,kw.) and (artery dissection/ or exp artery injury/ or (trauma$ or injur$ or resection$ or dissect*).tw,kw.) (45446)

3 ((trauma$ or injur$ or wound$ or resection$ or dissect* or rupture$ or transection$) adj5 (carotid$ or vertebral$ or vertebro$ or cervical$ or cervico$ or cerebrovascular$ or cerebro-vascular$)).tw,kw. (45103)

4 ((carot* or cerebr*) and (bcvi or tcvi)).tw,kw. (270)

5 (carot$ adj3 ((false adj aneurysm*) or pseudo?aneurysm*)).tw,kw. (862)

6 or/1-5 (73889)

7 exp cerebrovascular accident/ or (stroke$ or ((cerebr$ or brain$) adj3 infarct$) or apoplex$).tw,kw. (589982)

8 transient ischemic attack/ or (transient$ and ((cerebr$ or brain$ or attack$) adj3 ischemi$)).tw,kw. or TIA.tw,kw. (67800)

9 or/7-8 (612593)

10 (((trauma$ or injur$ or wound$ or resection$ or dissect* or rupture$ or transection$) adj5 (carotid$ or vertebral$ or vertebro$ or cervical$ or cervico$ or cerebrovascular$ or cerebro-vascular$)) or (bcvi or tcvi)).ti. (17677)

11 6 and (trauma$ or injur$ or dissect$).ti. (28571)

12 or/10-11 (30750)

13 6 and 12 (30738)

14 antithrombocytic agent/ (51108)

15 ((antiplatelet$ or anti-platelet$) adj3 (drug$ or agent$ or therap$ or treat$ or medicat$ or profile$ or compar$)).tw,kw. (47963)

16 (thienopyridine$ or aspirin$ or clopidogrel$ or cilostazol$ or Plavix or iscover or prasugrel$ or ticlopidine$ or brilinta or brilique or ticagrelor$ or ticlid or ticlodix or ticlodone$ or effient or efient).tw,kw. (150248)

17 or/14-16 [antiplatelet agents] (203027)

18 exp anticoagulant agent/ or (anticoagul$ or anti-coagul$ or antithromb$ or anti-thromb$ or NOAC or DOAC or NOACs or DOACs).tw,kw. (848399)

19 (VKA or VKAs or (menadione$ adj2 antagonist$) or (anti?vitamin$ adj2 K) or (vitamin$ adj2 K)).tw,kw. (28433)

20 *dabigatran/ or *rivaroxaban/ or *apixaban/ or (warfarin or acenocoumarol or coumadin or coumarin or phenprocoumon or sintrom or sinthrome or jantoven or marevan or waran or nicoumalone or dicoumarol or dicumarol or phenindione or dabigatran or ximelagatran or apixaban or rivaroxaban or edoxaban or betrixaban or idraparinux).tw,kw. (86923)

21 *heparin/ or exp *low molecular weight heparin/ or (liquaemin$ or heparin$ or LMWH).tw,kw. or (enoxaparin$ or tinzaparin$ or dalteparin$ or danaparoid or fondaparinux or nadroparin or Fragmin or Lovenox or Innohep).tw,kw. (162816)

22 or/18-21 [anticoagulants] (899173)

23 treatment$.ti. or treatment$.ab. /freq=2 (4128302)

24 17 or 22 or 23 (4888986)

25 (antiplatelet$ or anti-platelet$ or (anticoagul$ or anti-coagul$ or antithromb$ or anti-thromb$ or NOAC or DOAC or NOACs or DOACs) or (liquaemin$ or heparin$ or LMWH) or (thienopyridine$ or aspirin$ or clopidogrel$ or cilostazol$ or Plavix or iscover or prasugrel$ or ticlopidine$ or brilinta or brilique or ticagrelor$ or ticlid or ticlodix or ticlodone$ or effient or efient) or (warfarin or acenocoumarol or coumadin or coumarin or phenprocoumon or sintrom or sinthrome or jantoven or marevan or waran or nicoumalone or dicoumarol or dicumarol or phenindione or dabigatran or ximelagatran or apixaban or rivaroxaban or edoxaban or betrixaban or idraparinux) or (enoxaparin$ or tinzaparin$ or dalteparin$ or danaparoid or fondaparinux or nadroparin or Fragmin or Lovenox or Innohep) or (therap$ or treat$ or medicat$)).ti. (3444988)

26 6 and 9 and (17 or 22) [concepts: BCVI PLUS Stroke PLUS Treatment focused on antiplatelets/anticoagulants] (3089)

27 6 and 9 and 25 [concepts: BCVI PLUS Stroke PLUS Treatment focused TITLE search] (1480)

28 9 and 12 and 24 [concepts: BCVI focused TITLE search PLUS Stroke PLUS Treatment expanded] (2181)

29 12 and (17 or 22) [concepts: BCVI focused TITLE search (NO-Stroke) PLUS Treatment focused on antiplatelets/anticoagulants] (3380)

30 11 and 25 and (exp *blunt trauma/ or blunt trauma/ or (bcvi or tcvi or blunt).tw,kw.) (184)

31 26 or 27 or 28 or 29 or 30 (6158)

32 limit 31 to (adult <18 to 64 years> or aged <65+ years>) (3669)

33 limit 31 to (embryo <first trimester> or infant <to one year> or child <unspecified age>) (322)

34 31 not (33 not (32 and 33)) (5941)

35 (pediatr$ or paediatr$ or child$ or adolescent$ or infan$ or newborn$ or neonat$).ti. (1972146)

36 34 not 35 (5790)

37 exp case control study/ or (case$ and control$).tw,kw. or exp case study/ or (case$ and series).tw,kw. [EMBASE case series] (1279740)

38 case report/ or case report$.tw,kw. (2985680)

39 36 not (38 not (37 and 38)) (3605)

40 39 not case report.ti. (3563)

41 40 not ((exp animal/ or nonhuman/) not exp human/) (2949)

42 (animal$1 or mice or rat or rats or cat$1 or cattle$1 or dog$1 or goat$1 or horse$1 or rabbit$1 or sheep$1 or swine$1 or pig$1 or piglet* or canine$1 or feline$1 or porcine$ or calf or primate* or rodent$ or hamster$ or lamb$1 or monkey$1 or murine or veterinar*).ti. (2699298)

43 41 not 42 (2912)

44 limit 43 to English language (2645)

Total Article Count: 2645

II. 1.3 EBM Reviews – Cochrane Central Register of Controlled Trials Database Search (September 2022)

1 exp cerebrovascular trauma/ (39)

2 (vertebral artery/ or exp carotid artery/ or exp Carotid Artery Diseases/ or ((carotid$ or vertebral$ or vertebro$ or cervical$ or cervico$ or cerebrovascular$ or cerebro-vascular$) and (arterial$ or arter$)).tw.) and (artery dissection/ or artery injury/ or (trauma$ or injur$ or resection$ or dissect*).tw.) (764)

3 ((trauma$ or injur$ or wound$ or resection$ or dissect* or rupture$ or transection$) adj5 (carotid$ or vertebral$ or vertebro$ or cervical$ or cervico$ or cerebrovascular$ or cerebro-vascular$)).tw. (1451)

4 ((carot* or cerebr*) and (bcvi or tcvi)).tw. (7)

5 (carot$ adj3 ((false adj aneurysm*) or pseudo?aneurysm*)).tw. (5)

6 or/1-5 (1936)

7 exp Stroke/ or (stroke$ or ((cerebr$ or brain$) adj3 infarct$) or apoplex$).tw,kw. (66585)

8 Ischemic Attack, Transient/ or (transient$ and ((cerebr$ or brain$ or attack$) adj3 ischemi$)).tw,kw. or TIA.tw,kw. (4472)

9 or/7-8 (67324)

10 (((trauma$ or injur$ or wound$ or resection$ or dissect* or rupture$ or transection$) adj5 (carotid$ or vertebral$ or vertebro$ or cervical$ or cervico$ or cerebrovascular$ or cerebro-vascular$)) or (bcvi or tcvi)).ti. (512)

11 6 and (trauma$ or injur$ or dissect$).ti. (684)

12 or/10-11 (741)

13 6 and 12 (741)

14 exp Platelet Aggregation Inhibitors/ (15155)

15 ((antiplatelet$ or anti-platelet$) adj3 (drug$ or agent$ or therap$ or treat$ or medicat$ or profile$ or compar$)).tw. (6158)

16 (thienopyridine$ or aspirin$ or clopidogrel$ or cilostazol$ or Plavix or iscover or prasugrel$ or ticlopidine$ or brilinta or brilique or ticagrelor$ or ticlid or ticlodix or ticlodone$ or effient or efient).tw. (17768)

17 or/14-16 [antiplatelet agents] (28217)

18 exp anticoagulants/ or (anticoagul$ or anti-coagul$ or antithromb$ or anti-thromb$ or NOAC or DOAC or NOACs or DOACs).tw. (24145)

19 exp Vitamin K/ or (VKA or VKAs or (menadione$ adj2 antagonist$) or (anti?vitamin$ adj2 K) or (vitamin$ adj2 K)).tw. (2509)

20 (warfarin or acenocoumarol or coumadin or coumarin or phenprocoumon or sintrom or sinthrome or jantoven or marevan or waran or nicoumalone or dicoumarol or dicumarol or phenindione or dabigatran or ximelagatran or apixaban or rivaroxaban or edoxaban or betrixaban or idraparinux).tw. (8293)

21 exp Heparin/ or (liquaemin$ or heparin$ or LMWH).tw. or (enoxaparin$ or tinzaparin$ or dalteparin$ or danaparoid or fondaparinux or nadroparin or Fragmin or Lovenox or Innohep).tw. (14189)

22 or/18-21 [anticoagulants] (33589)

23 treatment$.mp. (907067)

24 17 or 22 or 23 (934937)

25 (antiplatelet$ or anti-platelet$ or (anticoagul$ or anti-coagul$ or antithromb$ or anti-thromb$ or NOAC or DOAC or NOACs or DOACs) or (liquaemin$ or heparin$ or LMWH) or (thienopyridine$ or aspirin$ or clopidogrel$ or cilostazol$ or Plavix or iscover or prasugrel$ or ticlopidine$ or brilinta or brilique or ticagrelor$ or ticlid or ticlodix or ticlodone$ or effient or efient) or (warfarin or acenocoumarol or coumadin or coumarin or phenprocoumon or sintrom or sinthrome or jantoven or marevan or waran or nicoumalone or dicoumarol or dicumarol or phenindione or dabigatran or ximelagatran or apixaban or rivaroxaban or edoxaban or betrixaban or idraparinux) or (enoxaparin$ or tinzaparin$ or dalteparin$ or danaparoid or fondaparinux or nadroparin or Fragmin or Lovenox or Innohep) or (therap$ or treat$ or medicat$)).ti. (457731)

26 6 and 9 and (17 or 22) [concepts: BCVI PLUS Stroke PLUS Treatment focused on antiplatelets/anticoagulants] (63)

27 6 and 9 and 25 [concepts: BCVI PLUS Stroke PLUS Treatment focused TITLE search] (70)

28 9 and 12 and 24 [concepts: BCVI focused TITLE search PLUS Stroke PLUS Treatment expanded] (47)

29 12 and (17 or 22) [concepts: BCVI focused TITLE search (NO-Stroke) PLUS Treatment focused on antiplatelets/anticoagulants] (48)

30 11 and 25 and (exp *Wounds, Nonpenetrating/ or Wounds, Nonpenetrating/ or (bcvi or tcvi or blunt).tw.) (12)

31 26 or 27 or 28 or 29 or 30 (136)

32 (pediatr$ or paediatr$ or child$ or adolescent$ or infan$ or newborn$ or neonat$).ti. (146458)

33 31 not 32 (134)

34 (animal$1 or mice or rat or rats or cat$1 or cattle$1 or dog$1 or goat$1 or horse$1 or rabbit$1 or sheep$1 or swine$1 or pig$1 or piglet* or canine$1 or feline$1 or porcine$ or calf or primate* or rodent$ or hamster$ or lamb$1 or monkey$1 or murine or veterinar*).ti. (6385)

35 33 not 34 (134)

36 limit 35 to English language (125)

Total Article Count: 125

APPENDIX III. Retrospective Review Research Ethics Board Approval

Western Research

Date: 12 January 2023

To: Dr. Brad Moffat

Project ID: 118388

Review Reference: 2023-118388-74772

Study Title: ASA dosing practices in the management of blunt cerebrovascular injury: A retrospective study

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

Date Approval Issued: 12/Jan/2023

REB Approval Expiry Date: 20/Jan/2024

Dear Dr. Brad Moffat,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

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

Western University 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); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; 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. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

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

Electronically signed by:

Ms. Jhananiee Subendran, Ethics Officer on behalf of Dr. P. Jones, HSREB Chair 12/Jan/2023 17:22

Reason: I am approving this document

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

APPENDIX IV. Letter of Information

Study Title: Randomized Controlled Trial Evaluating the Use of 81 mg ASA vs. 325 mg ASA for Treatment of Blunt Cerebrovascular Injury (BCVI)

Principal Investigator

Dr. Kelly Vogt, MD, MSc, FRCSC
Associate Professor, Department of Surgery
Victoria Hospital, London, ON

Introduction

You are being asked to participate in a study because you have been diagnosed with blunt cerebrovascular injury (BCVI).

This study examines the use of 81 mg ASA vs. 325 mg ASA in the treatment of BCVI to determine if there is any difference between treatment strategies and the risk of BCVI-related stroke. This form provides you with information to help you make an informed choice about participation in the study. Please read this document carefully and ask any questions that you may have. Participation in this study is voluntary. Deciding not to take part or to leave the study later will not alter your care or result in any penalty on your current of future health care.

Background Information

Blunt cerebrovascular injury (BCVI) is injury to the blood vessels in the neck that deliver blood to the brain. BCVI can lead to stroke if unrecognized or untreated. The current standard for treatment of BCVI is administration of a daily antiplatelet medication, called aspirin (ASA), which has been shown to reduce the risk of stroke after BCVI. Despite common use of this medication for treatment of BCVI, the optimal dose of therapy that reduces the risk of stroke while minimizing bleeding complications is unknown.

Purpose of this Study

The purpose of this study is to evaluate the safety and efficacy of using 81 mg ASA vs. 325 mg ASA in the treatment of BCVI. Several research studies have evaluated different treatment strategies for BCVI, but there have not been any experimental studies specifically addressing the optimal dose of ASA therapy. The optimal dose of therapy must balance the need to reduce the risk of stroke after BCVI, while minimizing bleeding complications.

What Will I Be Asked to Do?

You will be randomized to an intervention group that includes treatment with either 81 mg ASA or 325 mg ASA daily and will be observed while in hospital for the development of stroke or bleeding complications. You will have follow-up until 4 weeks from the time of injury, which will

include daily assessments while in hospital, a 2-week clinic follow up visit, and, if required, an additional phone call from study investigators at 4 weeks after injury.

Assignment to a Group

If you decide to participate, you will be "randomized" into one of the groups described below:

- Low-Dose ASA Group – administration of 81 mg ASA daily
- High-Dose ASA Group – administration of 325 mg ASA daily

Randomization means that assignment to a group is based on chance (like flipping a coin). You have an equal chance of being assigned to either group and it is not possible to predict which group you will be assigned to. During the study, you will not know which group you have been allocated to and the nurses and doctors taking care of you do not know which treatment group you are in.

What are the Benefits of Participating in this Study?

If you agree to participate in the study, the experimental intervention may or may not benefit you directly. However, the information learned by analysis of study results may provide benefits to other patients diagnosed with BCVI by enabling better understanding of the risks and benefits of different treatment doses.

What are the Risks or Potential Harms of Participating in this Study?

Although several studies have shown that that both 81 mg ASA and 325 mg ASA are effective at reducing the risk of stroke after BCVI, there is a chance that there is a difference in safety or efficacy of these two interventions. This may increase your risk of stroke or bleeding complications. Throughout your stay in hospital, you will be monitored for both stroke and bleeding complications and will have prompt treatment should either of these occur.

Do I have to Take Part in the Study?

Participation in this study is completely voluntary, and choosing not to participate will not impact the care you receive. If you agree to participate in the study, you can withdraw at any time. Withdrawing from the study means that the treatment group you are assigned to will be disclosed, and it will be up to the treating physician to determine your dose of therapy. If you withdraw from the study, you will still be followed while in hospital and during your regular scheduled follow-ups and will be asked for consent to the use of your study data. If you decline, no further data will be collected and existing data will be destroyed.

What is the Cost to Study Participants?

Participation in the study will not involve any additional costs to you or your private healthcare insurance.

Will Participants be Paid to be in the Study?

You will not be paid to participate in the study.

How Will Participant Information be Kept Confidential?

All information collected as part of this study will be handled in a confidential manner.

If you decide to participate in this study, the investigator(s) and staff will look at your personal information and collect only the information needed for the study.

"Personal health information" is information that can be used to identify you, including your:

- Name
- Address
- Telephone number
- Date of birth

You have the right to access, review, and request changes to your personal health information. Access to your personal health information will be under the supervision of the Principal Investigator.

Representatives of the Western University Health Sciences Research Ethics Board and/or the Lawson Quality Assurance and Education Program may review collected information to ensure it is correct and that the study is being conducted in accordance with the required laws and guidelines.

"Study data" is information collected for the purposes of the study, but that does not directly identify study participants.

A master list of all study participants will be kept in a password protected file on the Principal Investigator's secure computer, protected by firewalls, as per hospital policy. All study data will be stored on a secure online-based data collection software (REDCap). Paper-based signed consent forms will be kept in a locked cabinet in the Principal Investigator's office, which will be locked when not in use.

Study data that is sent outside the hospital will be used solely for the research purposes outlined in this document. All data will be de-identified prior to transfer.

The investigator(s), study staff, and other people involved in the collection and analysis of study data will keep the information they see or receive confidential. Even though the risk of identifying you from the data is very small, it can never be completely eliminated.

The Principal Investigator will keep any personal information about you in a secure and confidential location for 25 years, and then destroy it according to Lawson policy. When the results of this study are published, your identity will not be disclosed.

What are the Rights of Participants in a Research Study?

You have the right to receive information that could help you decide about participating in this study. You also have the right to ask questions about the study and your rights as a research participant, and have them answered to your satisfaction, before making a decision about participation in the study.

You have the right to be informed of the results of this study once the entire study is complete.

Conflict of Interest

There are no conflicts of interest to declare related to this study.

Contact Information

If you have any questions about this study, please contact the lead study investigator.

If you have any questions about your rights as a research participant or any ethical issues related to this study that you wish to discuss with someone not directly involved with the study, please contact the **LHSC Patient Relations Office.**

APPENDIX V. Consent Form

You will be given a copy of this consent form after it has been signed and dated by you and the study staff.

Full Study Title: Randomized Controlled Trial Evaluating the Use of 81 mg ASA vs. 325 mg ASA for Treatment of Blunt Cerebrovascular Injury (BCVI)

Name of Participant: _____

Participant

By signing this form, I confirm that:

- The research study has been explained to me and all of my questions have been answered to my satisfaction
- I understand the requirements of participating in this research study
- I have been informed of the risks and benefits, if any, of participating in this research study
- I have been informed of any alternatives to participating in this research study
- I have been informed of the rights of study participants
- I have read each page of this form
- I authorize access to my personal information and research study data
- I have agreed to participate in this research study

_____	_____	_____
Name of Participant (print)	Signature	Date

Name and Signature of Translator: (if applicable)	_____ Name	_____ Signature

Person Obtaining Consent

By signing this form, I confirm that:

- This study and its purpose have been explained to the participant named above
- All questions asked by the participant have been answered
- I will give a copy of this signed and dated document to the participant

_____	_____	_____
Name of Person Obtaining Or Witnessing Consent (print)	Signature	Date