# ANTITHROMBOTIC MANAGEMENT IN ACUTE SUBDURAL HEMATOMA

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## Abstract

Traumatic brain injuries and cardiovascular deficiencies are two of the leading causes of death in the U.S. Antithrombotics are among the common medications used for the management of cardiovascular diseases. However, the nature of antithrombotic agents makes the management of any bleeding difficult. Therefore, they are either not given to patients with a risk of bleeding, or they are stopped immediately in cases of bleeding.

General guidelines in the case of intracranial hemorrhage (ICH) involve stopping the use of antithrombotics and then restarting them once the bleeding has stopped. However, unlike other types of intracranial hematomas, subdural hematomas (SDHs) are prone to rehemorrhage after a time (weeks or even months after the initial incident). Despite the prevalence of complications potentially caused by antithrombotic medications in the management of SDHs, this subject has yet to be fully investigated.

This research paper documents for the first time the effects of antithrombotic therapies on patients suffering from SDHs. More specifically, we study the management of antiplatelet aggregation agents and anticoagulants in patients with traumatic SDHs. Understanding the risks of antithrombotics at different SDH stages (e.g. presence of active bleeding, presence of small or large residuals, and absence of residuals) helps to prevent potentially critical hemorrhagic complications. This thesis is a retrospective research study of patients who were admitted to the Montreal General Hospital with an acute traumatic SDH and who needed antithrombotic therapy.

The study found that continuing therapeutic antiplatelet therapy while an SDH is still present, poses a high risk of rehemorrhage (45% for patients with a small residual SDH and up to 90% for those with a large residual SDH). The risk of rehemorrhage that will require neurosurgical intervention is 47%.

Our data also shows that withholding AAA therapy for an average of 50 days, while the SDH is still present, does not contribute to any significant adverse event.

We found similar results for anticoagulant therapy. The risk of rehemorrhage associated with restarting anticoagulant therapy if an SDH is not fully resolved is 28.5% and 62.5% for small and large residuals SDHs respectively. Our data shows that withholding anticoagulant therapy for an average of 67 days, while an SDH is still present, cause adverse events in only 1.1% of our study population.

In the majority of cases our findings suggest that the safest course is to wait until the subdural hematoma has completely resolved before reinitiating antithrombotic therapy. At the same time, the status of the SDH should be closely monitored, using CT-scans, so that therapy can be reinitiated as soon as is safe. For patients with a high risk of thrombo-embolic events, it might be wiser to restart antithrombotic therapy while closely following-up the SDH with help of CT-scan imaging.

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## Acronyms

AAA: Antiplatelet Aggregation Agents (Antiplatelet agents)

ACCP: American College of Clinical Pharmacy

ADP: Adenosine Diphosphate

AHA: American Heart Association

ASA: American Stroke association

BTF: Brain Trauma Foundation

CCU: Coronary Care Unit

COX: Cyclooxygenase

CT: Computed Tomography

DTI: Direct Thrombin Inhibitors

DVT: Deep Venous Thrombosis

EDH: Extradural Hemorrhage

FFH: Fall From Own /height

FFOH: Fall From Own Height

FFP: Fresh Frozen Plasma

GCS: Glasgow Coma Scale

GP iib/iiia: Glycoprotein IIa/IIIb

HMWH: High Molecular Weight Heparin

ICH: Intracranial Hemorrhage

ICP: Intra Cranial Pressure

INR: International Normalized Ratio

ISI: International Sensitivity Index

ISS: Injury Severity Score

LMWH: Low Molecular Weight Heparin

MGH: Montreal General Hospital

MI: Myocardial Infarction

MNPT: Mean Normal Platelet Time

MVA: Motor Vehicle Accident

PCC: Prothrombin Complex Concentrate

PDE: Phosphodiesterase

PED: Pedestrians hit by a car

PT: Prothrombin Time

REB: Research Ethics Board

SAH: Subarachnoid hemorrhage

SC: Subcutaneous

SDH: Subdural Hemorrhage

TIA: Transient Ischemic Attack

TBI: Traumatic Brain Injury

UFH: Unfractionated Heparin

# Chapter 1: Introduction and Problematic

In the United States, two of the most common causes of death are traumatic brain injury (TBI), and heart disease.

TBI is described as a blow, hit or penetrating injury to the brain that disrupts its function. A report shows that 1.7 million incidents of TBI are happening annually in the U.S. (Cattaneo, 2010). Similar report shows that TBI is a contributing factor to almost one-third of all injury-related deaths in United States. TBI is considered a high mortality rate pathology. Every year, 52,000 deaths occur due to TBI with fall being the most common cause (35.2%). Based on one's age, there is a higher risk of sustaining a TBI; adults aged 65 years and older, teenagers between 15 to 19 years old, and children between 0 to 4 years old (Cattaneo, 2010).

A survey done in the U.S. in 2014 (National Center for Health Statistics, 2015), indicates a morbidity rate from 10.9% of cardiac conditions[1] among adults aged 18 and over. This morbidity rate increases with age; increasing up to 24.6% among those aged 65 to 74 and 35.0% for those aged 75 and older.

This thesis aims to review the impact of cardiovascular disease (on antithrombotic therapy) on a common type of TBI, the subdural hematoma.

## SDH in Elderly Population

As stated earlier, both morbidity and mortality from TBI increases with increasing age (Seidler et al., 2010). Trauma induced ICHs are classified according to the location in which the

[1] Hypertension, coronary heart disease, angina (or angina pectoris), heart attack (or myocardial infarction), any other heart condition or disease not already mentioned, or a stroke.

bleeding occurs: epidural space (epidural hematoma), subdural space (SDH), subarachnoid space hemorrhage (SAH), and intraparenchymal collection (intracerebral hematoma) (ICH).

Among victims of TBIs, older populations are at a higher risk of SDH compared to younger victims, due to the reduction of the size of the brain in elderly population. Atrophy in the brain leads to both stretching of cerebral bridging veins and a larger subdural and subarachnoid space between the cranium and brain. The larger space results in greater movement of the brain within the cranium following a traumatic event. An older population is also more prone to other conditions (e.g. cardiovascular disease) that may further complicate TBI management (Asghar, Adhiyaman, Greenway, Bhowmick, & Bates, 2002).

Among all types of intracranial hemorrhage, SDH is the most common type of non-penetrating TBI (Taber, Warden, & Hurley, 2006). All TBI cases may face complications such as rebleeding and expansion of the lesion. (Rebleeding can occur within hours to few days after the initial incident. Traumatic SDHs (unlike other types of TBI) may take a long time (weeks or months) after the initiating TBI, to enlarge and become symptomatic (Bajsarowicz et al., 2015). This prolonged risk period makes the management of SDH challenging.

## Management of SDH in Patients with Cardiovascular Conditions

A common class of medications for cardiovascular conditions is the antithrombotic agents. Antithrombotics can be classified into three categories:

1. Antiplatelet Aggregation Agents (AAA) which limit the migration and aggregation of platelets,

2. Anticoagulants which limit blood clotting, and
3. Thrombolytic drugs which dissolve clots after their formation.

In this thesis we investigate the problems in management of antithrombotic therapy in patients with an SDH. We study the risk of resuming antithrombotic in patients with a residual hemorrhage to that of withholding antithrombotic until traumatic SDH is fully resolved. In patients with a recent SDH (similar to any other trauma), antithrombotic can cause rehemorrhage and therefore complicate the patient's condition. However, at the same time, patients may suffer from other conditions (e.g. cardiovascular disease) that require the use of antithrombotic. Therefore, it may be better to withhold the medication for a period of time after the trauma. However, the literature does not provide any clues regarding the duration of time to withhold antithrombotic therapy after a traumatic SDH.

To address this deficiency, we study in a retrospective fashion the complications and timing of AAA therapy and anticoagulant therapy for patients with an SDH.

# Chapter 2: Background and Hypothesis

This chapter reviews the current literature on the subject of TBI management and cardiovascular therapy. In particular, we study SDH and the role of antithrombotic medications in patients with concurrent cardiovascular disease.

## TBI Definition and Classification

Traumatic brain injury (TBI) may result in a spectrum of brain dysfunction, ranging from mild (with transient neurological impairments) to severe (permanent neurological deficits). The degree of severity of a TBI defined by the level of consciousness of the patient after the trauma.

Therefore, one of the very first approaches by clinicians upon admission of a patient with a TBI is to measure their “Glasgow Coma Score” (GCS). The “GCS” is a neurological scale which gives a reliable and objective way of measuring level of consciousness of a person. GCS measures the severity of neurological injuries based on three criteria: eye opening (score: 1 to 4), verbal ability (score: 1 to 5), and motor movement (score: 1 to 6) (Teasdale & Jennett, 1974) (Table 1).

According to the GCS, the severity of brain injury reflects the sum of scores for each of the three criteria. The lowest GCS is 3 (deep coma or death), while the highest is 15 (a fully awake person). A TBI is classified as 'severe' when GCS is between 3 and 8,'moderate' when between 9 and 12, and 'mild' when between 13 and 15.

Table 1: Glasgow Coma Scale

| | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Eye opening | Does not open eyes | Opens eyes in response to painful stimuli | Opens eyes in response to voice | Opens eyes spontaneously | N/A[2] | N/A |
| Verbal ability | Makes no sounds | Incomprehensible sounds | Utters inappropriate words | Confused, disoriented | Oriented, converses normally | N/A |
| Motor movement | No movement | Extension to painful stimuli (decerebrate response) | Abnormal flexion to painful stimuli (decorticate response) | Flexion / Withdrawal to painful stimuli | Localizes painful stimuli | Obeys commands |

## Intracranial Hemorrhage Classification in TBI

Intracranial hemorrhage (ICH) is a general term covering many different conditions where there is an extravascular accumulation of blood within intracranial spaces. Based on the location of the hematoma, an ICH can be classified as either intra-axial or extra-axial hemorrhage.

## TBI Among Elderly Population

TBI is one of the leading causes of intracranial hemorrhage, and therefore is a major public health problem especially among elderly people (70 years old or above). The number of traumatic brain injuries is increasing the elderly population (Seidler et al., 2010).

The Canadian population in general is growing older. Based on projections, 23%-25% of the population will be aged 65 years old and over by 2031 (Milan, 2007). The proportion of the population aged 80 years and over will increase dramatically from 5 million in 2011 to 10.4 million in 2036 (Milan, 2007). A study on patients admitted to the MGH, revealed that the ratio

[2] N/A: not applicable

of patients suffering a TBI and aged 70 years or older increased from 18% in 2000 to 48.5% in 2012 (De Guise et al., 2015).

## Recurrent TBI and Delayed Hemorrhage Expansion

A common problem associated with TBI is repeated traumatic brain injury. Hypertension management, including antithrombotic agents, possibly contributes to recurrent TBI (Berry et al., 2012; De Jong et al., 2013). The impact of different variables on traumatic brain injury has been studied in the literature (Berry & Miller, 2008; Currie, Lawson, Robertson, & Jones, 1984; Tinetti, Speechley, & Ginter, 1998; Graafmans et al., 1996; Campbell, Borrie & Spears, 1989; Thapa, Brockman, Gideon, Fought, & Ray, 1996; Nevitt, Cummings & Hudes, 1991; Aharon-Peretz, Kliot, Amye, 1997). However, the literature lacks specifics on the effect of these risks on the different subcategories of traumatic brain injury.

Intracranial bleeding such as an EDH, SDH or intracerebral hemorrhage have a risk of delayed expansion, especially within the first few hours of the injury. With the exception of SDHs, the risk of ICH expansion decreases sharply after a few hours and is very low after 24 hours (Narayan et al., 2008).

Although many subdural clots reabsorb spontaneously, the encapsulated fluid may slowly increase in volume, creating a chronic subdural hematoma. Also, a lack of parenchyma counterpressure in predisposed atrophied brain may permit further growth of a small hematoma that might otherwise resolved spontaneously (Bae, Doh, Bae, 1998; Maurice-Williams, 1999). This cerebral atrophy is almost exclusively seen in the elderly population, where we use the development of chronic subdural hematomas (Yang et al., 2012).

## Intracranial Hemorrhage Expansion and Blood Thinners

Studies show that the risk of an acute SDH increases among patients receiving anticoagulant therapy (Wintzen & Tijssen, 1982; Kawamata et al., 1995). Anticoagulation therapy increases the risk of atraumatic (idiopathic) SDH by up to 7 times normal in men and 26 times that of the non-anticoagulant community in women (Wintzen & Tijssen, 1982).

Among all types of traumatic intracranial hematomas, acute SDH carries the highest mortality rate (Shah & Kelly, 1999). Mortality rates of between 60-90% are reported in comatose patients presenting with traumatic acute SDHs (Richards, & Hoff, 1974; Ransohoff et al., 1971; Gutterman & Shenkin, 1970; Talalla & Morin, 1971). Mortality rates are higher among elder patients (60%) and in patients on anticoagulant therapy by (90% to 100%) (Kawamata et al., 1995).

Cardiovascular problems (see next section) are indications for antithrombotic therapy. Cardiovascular disease is a major cause of syncope which is the most common etiology of traumatic brain injury in geriatric patients, who may also be taking antithrombotic agents. Moreover, the management of patients suffering from TBI is more complicated when an active or new intracranial hemorrhage coincides with a serious need for antithrombotics (Nevitt et al., 1991; Currie et al. 1984; Tinetti et al., 1998; Graafmans et al., 1996; Campbell et al., 1989; Thapa et al., 1996; Sattin, 1992; Aharon-Peretz et al., 1997).

This review summarizes the current literature on the morbidity and mortality associated with premorbid non-steroidal anti-inflammatory drugs, aspirin, clopidogrel, warfarin, and heparinoids in the setting of traumatic head injury, and also examines the current strategies for reversal of these therapies.

## Antithrombotics

Antithrombotic medications are widely used for heart and vascular problems, as mentioned earlier. From stroke and prophylaxis in hypertension to reducing risk in serious conditions such as prostatic heart valves antithrombotics play a major role. Antithrombotic medications are classified into three categories: anti-platelet aggregation agents (AAA), anticoagulant agents, and thrombolytic medications. This thesis only covers AAA and anticoagulant agents and for each of these medications, their sub-types, mechanisms of action, indications and reversal management are further explained.

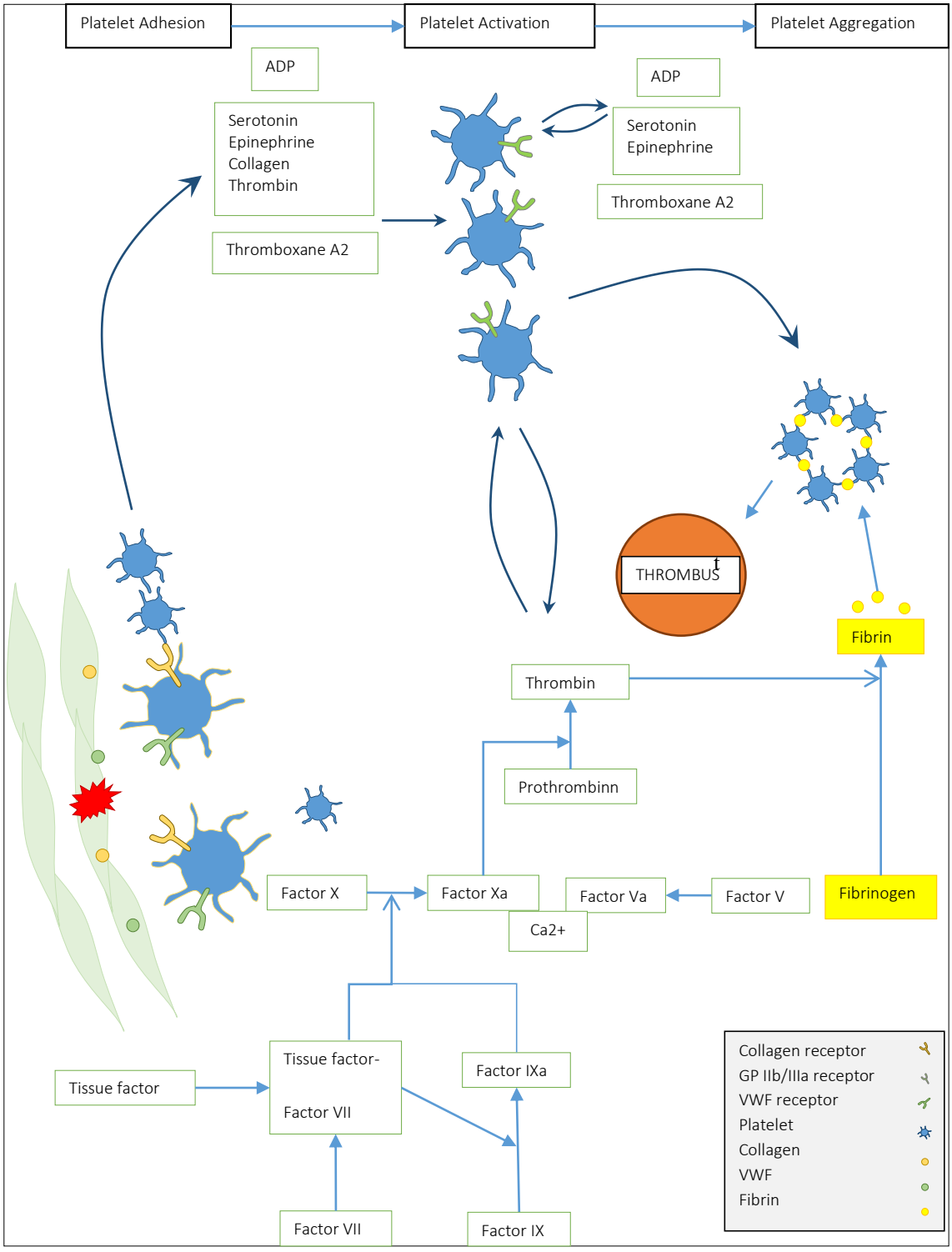
**AAA (anti-platelet aggregation agents).** AAA agents affect different stages of the clotting cascade, by decreasing platelet aggregation and/or adhesion and inhibiting thrombus formations (Gresele, Arnout, Deckmyn, &Vermylen, 1986; Schrör, 1996). These medications are mostly prescribed for treatment and prevention of those arterial and venous clots which are largely composed of platelets. Figure 1 illustrates the mechanism of thrombus formation. In the following section, we examine each of the AAA sub-types.

**COX inhibitors.** The medications in this class of antiplatelet agents are used as secondary prevention following myocardial infarction, unstable angina and cerebral transient ischemic attacks.

Cyclooxygenase (COX) inhibitors irreversibly inhibit thromboxane A2. Aspirin is an example of this group, which inhibits platelet activation and also has analgesic, anti-inflammatory and antioxidant effects. These properties along with being a low cost medication, makes aspirin the most widely used antiplatelet in cardiovascular patients (Frieden & Berwick, 2011; U.S. Preventive Services Task Force, 2009). Aspirin is widely used in the secondary prevention of cardiovascular and peripheral vascular diseases. A study shows that aspirin

reduces the risk of cardiovascular deaths, MIs and strokes by 25% (Awtry & Loscalzo, 2000).

Figure 1: The mechanism of thrombus formation (Franchi, & Angiolillo 2015; permission obtained)



**Glycoprotein IIb/IIIa.** These medications are monoclonal antibodies, which are injected under the close supervision of a specialist in a coronary care unit (CCU). They can be used only once as they naturalize the antibody to themselves. In addition, they can cause serious bleedings. Examples in this class are abciximab and tirofiban (Stangl & Lewis, 2010).

**Adenosine diphosphate (ADP) receptor inhibitors.** ADP is released from damaged vessels and red blood cells. It induces platelet aggregation through activation of GPIIb/ IIIa and fibrinogen binding. ADP mediates its action through binding to two G proteins (Gi and Gq), which are the main targets of antiplatelet medications (Schrör, 1997; Hollopeter et al., 2001). Also, platelets secrete ADP, which induces positive feedback on platelet aggregation. Clopidogrel is an example of this group.

For some patients, a combination of clopidogrel and aspirin is used to maximize the capacity to block complementary pathways of platelet activation (Schrör 1998). Combined therapy is recommended for at least four weeks after implementation of metal stents in coronary arteries and for longer periods in those with drug eluting stents (Terpening, 2009).

However, another study showed that this combined therapy increases the risk of major hemorrhage by approximately 2% per year (Reymond, Marbet, Radii, & Gratzl, 1992). This bleeding risk persists even if the daily dose of aspirin is less than 100mg (Campbell et al., 1989; Yusuf, 2001).

**Phosphodiesterase (PDE) inhibitors.** PDE inhibitors regulate platelet formation by limiting the intracellular level of cyclic nucleotides through catalyzing the hydrolysis of cAMP and cGMP1. Several nonselective or isoenzyme-selective PDE inhibitors have been developed, and some of them have entered clinical use as antiplatelet agents. Examples of this class of medications include dipyridamole (Gresele, Momi, & Falcinelli, 2011; Kalantzi et al., 2012).

**Antiplatelet reversal therapy.** The increasing use of antiplatelet agents raises concerns of inadequate platelet aggregation and hemostasis in the settings of acute hemorrhage. Antiplatelet agents have been associated with an increased risk for intracranial hemorrhage (ICH) as well as a secondary increase in ICH volume after the initial hemorrhage. The purpose of reversal therapy is rapid reversal of the antithrombotic medication, such as DDAVP and platelet concentrate transfusion (Frontera et al., 2015).

Trauma and emergency department clinicians are seeing more traumatic head injuries in patients already on antithrombotic therapy. These patients appear to be at increased risk of developing life-threatening intracranial hemorrhages. It is important therefore, trauma clinicians understand both the mechanism and duration of commonly prescribed antithrombotic in order to best assess and treat patients who develop intracranial hemorrhages.

## Anticoagulants

For many years, anticoagulants have been known to lower the rate of strokes in people prone to thrombosis (Shahpouri, 2012). However, they also prevent clotting in situations where clotting is indeed desirable. In other words, they can cause bleeding. This section reviews the major types of anticoagulant medication, their mechanism of action and reversal management.

**Medications that activate anticlotting factors.** (e.g. heparins) Antithrombin III inhibits thrombin and factor Xa, which are necessary factors in the final stages of the clotting cascade. Heparin is an anticoagulant agent that activates antithrombin III. There are two types of heparins, high molecular weight heparins (HMWH) and low molecular weight heparins (LMWH).

LMWHs, such as Daltaprin and Enoxaparin, consist of smaller fragments of heparin, and are prepared from unfractionated heparin (UFH) using controlled enzymatic or chemical depolymerization reaction (McLeod et al., 2001). LMWH has replaced heparin in most

conditions. See Table 2 for a more detailed list of advantages of LMWH over heparin (Goodman et al., 2000). The major side effect of LMWH is bleeding. However, a meta-analysis suggested that the risk of major bleeding is reduced with LMWH compared to unfractionated heparin (Andrassy, Eschenfelder, & Weber, 1994).

Heparin induced thrombocytopenia and osteoporosis are less common with LMWH compared to unfractionated heparin. LMWHs are preferred over UFHs for deep venous thrombosis (DVT) prophylaxis, as they have demonstrated a 45-70% lower relative risk of DVT patients undergoing total hip replacement (Geerts, et al., 2001). The American College of Clinical Pharmacy (ACCP) recommends LMWHs for DVT treatment (Hyers, et al., 2001).

Table 2: Advantages of LMWH over Heparin

| Pharmacokinetics | Advantages |
|---|---|
| Better bioavailability and longer half-life after subcutaneous injection | Can be given SC once or twice daily for both prophylaxis and treatment |
| Dose independent clearance | Simplified dosing |
| Predictable anticoagulant response | Coagulation monitoring is unnecessary in most patients |
| Lower risk of heparin-induced thrombocytopenia | Safer than heparin for short or long-term administration |
| Lower risk of osteoporosis | Safer than heparin for extended administration |

Reversal of UFH and LMWH is via Protamin sulfate (Hawksley, 1966; Lowary, Smith, Coyne, & Dunham, 1971) (Parkin & Kvale, 1949; Guffin et al., 1976). Also, recombinant factor VIIa is recommended when protamin sulfate is contraindicated or when not responsive after 4 doses (Parkin & Kvale, 1949; Dehmer, Haagen, Malloy, & Schmitz, 1987; Dehmer et al., 1996; Stafford-Smith, et al., 2005; Wolzt, et al., 1995).

**Direct thrombin inhibitors (DTIs).** Thrombin is an important factor in the clotting pathway, which makes it a good target for anticoagulant agents. Thrombin inhibitors bind to and inhibit the activity of thrombin, thereby preventing clot formation.

Thrombin inhibitors also inactivate free thrombin as well as fibrin-bound thrombin. Thrombin inhibitors can be used to prevent and treat arterial and venous thrombosis.

A study showed that for reversal of DTIs, Prothrombin Complex Concentrate (PCC) is the best available antidote (Eerenberg, et al., 2011; Marlu et al., 2012; Khoo et al., 2012).

**Vitamin K antagonists.** Warfarin, as an example of this group, is an oral anticoagulant that inhibits Vitamin K epoxide reductase. Vitamin K is an activator of coagulating factors II, VII, IX and X, so by decreasing the availability of Vitamin K, synthesis of these factors is decreased.

Regular blood monitoring by the international normalized ratio (INR) is done to check for effectiveness and safety. Warfarin is used to treat blood clots in cases of deep vein thrombosis or pulmonary embolism. It is also used to prevent thrombosis in patients at high risk, such as in atrial fibrillation, heart attack and knee or hip surgeries. For immediate reversal, PCC is preferred over fresh frozen plasma (FFP) (Fontera, et al., 2015).

A common indication for anticoagulation is the presence of a metallic cardiac valve. A meta-analysis of 13,088 patients and studying 53,647 patient-years found that anticoagulation decreases the risk of valve thrombosis from 1.7% to 0.2% per year and at the same time decreases the risk of embolism from 4% to 1% per year (Cannegieter, Rosendaal, and Briet, 1994). The same study also found that mitral heart valves have a 5-times higher risk of valve thrombosis and a 1.5-times higher risk of major embolism compared to aortic valves.

Another critical indication for anticoagulant medication is atrial fibrillation.

Anticoagulant therapy prevents strokes in patients with atrial fibrillation. The CHA2DS2VASc table helps to estimate the annual risk of stroke in atrial fibrillation, see Table 3 and Table 4 (Lip et al., 2009).

Table 3: CHA2DS2VASc score associated with different risk factors

| Risk factor | Score |
|---|---|
| CHF/ LV dysfunction | 1 |
| HTN | 1 |
| Age >75 | 2 |
| DM | 1 |
| Stroke/ TIA/ Thromboembolism | 2 |
| Vascular disease | 1 |
| Age 65-74 | 1 |
| Sex category (women) | 1 |
| Maximum possible score | 9 |

Table 4: Annual risk of strokes associated with different CHA2DS2VASc scores

| $CHA^2DS^2VASc$ score | Annual stroke risk (%) without anticoagulant therapy |
|---|---|
| 0 | 0 |
| 1 | 1.3 |
| 2 | 2.2 |
| 3 | 3.2 |
| 4 | 4 |
| 5 | 6.7 |
| 6 | 9.8 |
| 7 | 9.6 |
| 8 | 6.7 |
| 9 | 15.2 |

As mentioned above, monitoring the INR, is employed to check for effectiveness and safety of warfarin therapy. It was introduced due to delay in pharmacodynamics response time of Warfarin (the full effect may take **3-5 days** or more to occur).

In the absence of anticoagulant therapy INR typically ranges from 0.9 to 1.1. However,

the value will be higher among patients on therapeutic Warfarin (Baglin, Keeling, and Watson, 2005; Poller, L., 2004).

## Hypothesis of Our Study

This research investigates the effects of antithrombotic therapy on the management of SDH. The current literature has studied the associated risks of antithrombotic on TBIs in general. However, this is the first research that studies specifically SDHs and antithrombotic. The study intends to answer the following question: "What are the risks of antithrombotic therapy in the presence of an SDH?"

I aim to test the validity of the following questions:

Among patients with an SDH:

1. Is Antithrombotic therapy associated with hemorrhagic complications?
2. Are the risks associated with resuming antithrombotic therapy, is higher than those of withholding the medication?

Among patients with an SDH and on antithrombotic therapy:

3. Are the risks of rehemorrhage is correlated with the size of the residual SDH?
4. Does the amount of rebleeding correlate with the size of SDH residual? That is does a larger size of residual SDH at the time of restarting the therapy mean the larger the amount of rebleeding?
5. Does the severity of rebleeding correlate with the need for intervention? That is does a larger that is, does a requiring neurosurgical evacuation?

# Chapter 3: Methodology

In this chapter, characteristics of the study population, patient's management as well as the measurement used to assess the outcome, are discussed in detail. As this is a retrospective study we also discuss the sources and the methods of our data collection.

## Study Population

The study population included all patients who were diagnosed as having a traumatic SDH and who were admitted to the Montreal General Hospital (MGH), an adult tertiary trauma center (level 1), between January 2006 and January 2013.

The TBI database at MGH was used to identify patients with a traumatic SDH. The TBI program keeps a list of all admitted patients with a diagnosed TBI. The database includes many variables collected prospectively (date of trauma, age, gender, mechanism of trauma, GCS score on admission, severity of injury, surgical intervention(s), destination after discharge, and outcome at discharge).

We then performed a retrospective analysis on in-patient's hospital charts and out-patients' clinic notes to identify those patients on antithrombotic medications at the time of the injury, or shortly thereafter. Patients were excluded from our study:

- the patient died within 14 days of admission (due to the severity of the initial trauma). These patients were excluded because the time for observation of potential complications from withholding antithrombotic therapy is limited, which could potentially skew the conclusions towards a smaller risk of withholding the therapy,
- the patients had no indication for blood thinners pre-injury, and post-injury indications evolved only after a complete resolution of the traumatic SDH,
- the SDH was non-traumatic. This decision was made based on patient history and medical

documentation upon admission,

- the SDH was not acute,
- there was no SDH (incorrect data in the database),
- there was insufficient chart data (missing or incomplete data; no CT scan done at the time of admission or upon instituting antithrombotic).

Finally, this research was reviewed and approved by the institutional Research Ethics Board (REB).

## Assessing Patients' Management

All patients with a traumatic SDH were evaluated by the trauma team and by the neurosurgery service. As per the Brain Trauma Foundation (BTF) guidelines, patients who had any of the following conditions were taken to the operating room for immediate surgery.

- symptomatic SDH greater than 10mm;
- a midline shift[3] greater than 5mm;
- a deteriorating GCS score (by more than 1 point), as it may be a sign of impending herniation or increased ICP[4] (Bullock et al., 2006).

Conservative care was instituted based on the Brain Trauma Foundation guidelines and the clinical judgment of the attending neurosurgeon. For example, patients with a small SDH, patients with an asymptomatic SDH, or elderly patients with minimal symptoms, were kept under observation in a monitored setting. All patients with a GCS of 8 or less and an abnormal scan had an ICP monitor placed, as per the Brain Trauma Foundation guidelines (Bratton et al.,

[3] The midline shift which is associated with SDH

[4] Intracranial pressure is evaluated by inserting ICP monitor in place.

2007). Patients who had a non-surgical SDH upon admission but showed delayed clinical deterioration, (volume expansion of the SDH on imaging and associated symptoms) were treated by either burr hole evacuation when or by craniotomy.

## Data Collection

For each patient in our study, we collected demographic data (age and gender) and injury-related data (mechanism of trauma, initial GCS score). We also collected data such as history of falls or alcohol abuse, which are known to have a correlation with the rate of SDH rebleed (Bajsarowicz et al., 2015).

The following information was collected:

SDH maximum thickness and location (convexity, parafalcial, tentorial, or posterior fossa). We also looked at the CT scan characteristics of the SDH immediately after the trauma.

The specific AAA medication taken by the patient, as well as the medical indication(s) for its intake were recorded. We recorded how long the AAA or anticoagulant agent therapy was held after the injury.

The number of surgical evacuation(s) and the type of surgery (burr hole or craniotomy) prior to starting/restarting AAA therapy was also noted.

Based on these observations, patients were divided into two groups:

Group 1. The SDH had already completely resolved at the time of starting/restarting AAA therapy; Or

Group 2. The SDH remnant was still present[5].

[5] None of these patients had a significant midline shift; otherwise they would have been operated upon. There was no literature on this number (5mm thickness and 3 cm length) but large remnants are at higher risk of deterioration requiring surgery. This criterion is also used in a paper by Basjarowicz et al.

The latter group was further subdivided into two sub-groups:

Patients with large remnants: when either thickness is 5mm or more or length is 3cm or more (or both).

Patients with small or focal remnants: when remnant is not large (thickness and length are less than 5mm and 3cm respectively).

In this classification, midline shift was not taken into account since any patient with a large midline shift would have had been operated upon being considered in this classification. The classification by size is based on a study by Bajsarowicz et al. (2015), who found that SDH with 5mm thickness or more is at a higher risk of deterioration as of requiring surgery. SDH less than 5mm in thickness showed fewer and less severe complications. The remnant SDH was described as either acute rehemorrhage, sub-acute SDH or chronic SDH.

## Study Variables

We considered the following variables relevant to AAA and SDH:

The number of adverse events related to withholding therapy (e.g. MIs, transient ischemic attacks, strokes, etc.)

The number of times the SDH expanded while the patient was on blood thinners.

Hemorrhage expansion was classified into:

1. Small rehemorrhage: focal, not causing mass effect (see an example in Figure 2),
2. Large rehemorrhage: diffuse, causing new mass effect and altering management, e.g. withholding the medication again, hospitalization, etc.
3. Large rehemorrhage with complications requiring surgical intervention or leading to permanent neurological deficit or death.

4. The blood accumulated in the subdural space can cause mass effect and put pressure on the brain. The larger the mass (size of blood accumulation), the more likely for it to create pressure. Usually by the time of follow up any primary hematoma should have either resolved (in case of small residual) or have been surgically removed (in case of a large residual) (see Figure 2 and Figure 3). Therefore, if there was a large SDH at follow-up, it accumulated since the initial presentation and after treatment.

Figure 2: Small residual subdural hematoma

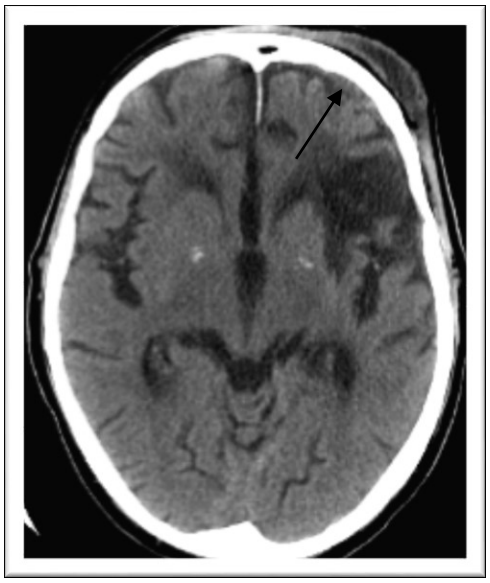
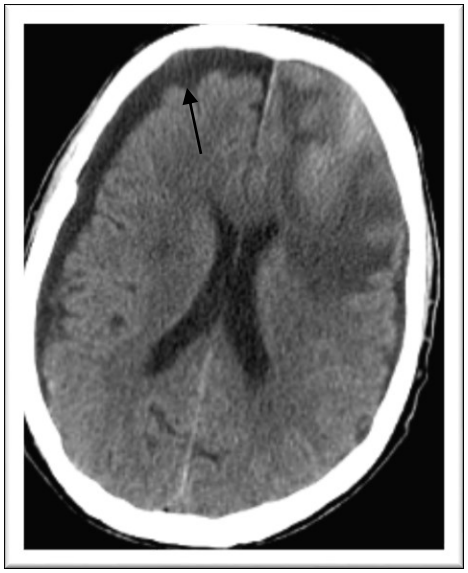


Figure 3: Large residual subdural hematoma



## Statistics

This research studies two groups of patients separately, each focusing on one class of antithrombotics. The first group consists of patients on AAA medications. The second group consists of patients taking anticoagulant medications. For each group we use statistical measures (e.g. mean, median and standard deviation) to compare numerical variables (e.g. bleeding rate, age of patients, etc.). We use chi-square test to evaluate the significance of our findings and correctness of our hypotheses.

# Chapter 4: Antiplatelet Therapy and SDH

This chapter studies the complications of antiplatelet (AAA) therapy on patients with an SDH. The first section describes patient's samples and characteristics, which include imaging characteristics, surgical treatment, reasons for anticoagulation therapy, timing and complications of therapeutic anticoagulation. Statistical analysis of gathered data is presented in the second section. The third section discusses our results and compares it with the literature. The fourth section offers our recommendations and conclusion.

## Patient Sample and Characteristics

The Montreal General Hospital (MGH) TBI and Trauma Registry databases hold 1919 patient charts coded as “traumatic SDH” for the studied period. There was no case of initiation of AAA therapy after a traumatic SDH. We found 279 patients who were already on AAA prior to their traumatic event. Out of the 279 patients, 63 were excluded, because either they died early from the severity of the injury, or the SDH was not acute, or data was insufficient. Furthermore, 14 patients never showed up for follow-up, therefore they were excluded from the study due to insufficient data. At the end, a total of 202 patients are included in this study.

Among 202 studied patients, 123 (61%) were male and 79 (39%) were female. The mean age was 74.6 years with a standard deviation of 12 years and a range between 23 and 96 years. The majority of patients (80.7%) were aged 65 years and above. The mean GCS on admission was 13.6 (see Table 5). The great majority of patients (88%) were suffering from a mild TBI (GCS between 13 and 15). For the studied patients, due to lack of data, we did not consider injury severity score (ISS) in our analysis.

Table 5: Glasgow Coma Scale (GCS) on admission, for patients on AAA.

| GCS Score | Number (total = 202) | Percentage (%) |
|---|---|---|
| 15 | 106 | 52.5 |
| 14 | 61 | 30.2 |
| 13 | 7 | 3.5 |
| 9-12 | 13 | 6.5 |
| 3-8 | 14 | 8 |

Table 6 shows details of the mechanisms of injury. In our study 55% of 202 patients had a TBI because of fall from own height. A fall from height was the second most common cause of TBI (29%). In addition, thirty-six patients (18%) had a history of alcohol abuse, while sixty-one (30%) had a history of recurrent falls.

Table 6: Mechanisms of injury for patients on AAA.

| Mechanism of Injury | Number (total = 202) | Percentage (%) |
|---|---|---|
| Fall from own height (FFOH) | 112 | 55.4 |
| Fall from height (FFH) | 59 | 29.3 |
| Motor vehicle accident (MVA) | 12 | 5.9 |
| Pedestrians hit by a car (PED) | 12 | 5.9 |
| Assault | 6 | 3 |
| Other | 1 | 0.5 |

**Imaging characteristics.** The thickness of the SDH on admission ranged from 1mm to 36mm with a mean of 8.6mm. The majority of cases (73.8%) measured 10mm or less. The locations of the SDHs were distributed as follows: 153 unilateral convexity (75.7%), 18 solely tentorial (8.9%), 17 bilateral convexity (8.4%), 10 parafalcial (5%), 2 convexity plus tentorial (1%), and 2 parafalcial plus tentorial (1%).

**Surgical treatment.** Fourteen patients (7%) required urgent evacuation of their SDH by either craniotomy (12 patients) or craniectomy (2 patients). Seven (3.5%) patients required an

intracranial pressure monitor (6 external ventricular drains and 1 intraparenchymal device) without evacuation of the SDH. Sixteen patients (8%) underwent burrhole evacuation of their SDH when it became chronic and prior to the institution of AAA therapy.

**Indications and types of AAA therapy.** Table 7 shows the list of indications for AAA therapy among patients prior to their injury. As for AAA therapy, the majority of patients (145 or 72%) only used ASA, while 23 (11.4%) took only clopidogrel. Thirteen (6.4%) used ASA in combination with an anticoagulant (warfarin) and one patient (0.5%) took a combination of clopidogrel and warfarin. Furthermore, nineteen patients (9.4%) used a combination of ASA and clopidogrel. Finally, one patient (0.5%) was on a combination of ASA, clopidogrel and warfarin.

Table 7: Primary indications for AAA

| Rationale | Number (total = 206) | Percentage (%) |
|---|---|---|
| Primary prevention | 125 | 62 |
| Coronary artery disease | 47 | 23.3 |
| Chronic heart failure | 8 | 4 |
| Stroke | 7 | 3.5 |
| Cardiac valvular disease | 4 | 2 |
| Atrial fibrillation | 9 | 4.5 |
| Previous Deep Venous thrombosis (DVT) | 2 | 1 |

**Timing and complications of AAA therapy.** AAA therapy was withheld on average 54.3 days (median of 50 days); ranging between 0 and 335 days. No adverse event was reported while AAA therapy was on hold.

For the majority of patients (84.2%), AAA was reintroduced once the SDH had completely resolved at follow-up CT scan. For the remaining thirty-two patients (15.8%), AAA was restarted while an SDH was still present on CT-scan.

The residual SDH was quantified as small in 22 patients and large in the remaining 10 patients when AAA was started. In the group of patients with a large residual SDH, one

(10%) had no rehemorrhage, one (10%) had a minor focal rebleed (not causing any mass effect) and eight (80%) suffered from diffuse rehemorrhage all causing a new mass effect requiring change of management, e.g. stopping AAA and hospitalization. Out of these 8 patients, one required neurosurgical intervention (12.5%) while no surgery was needed in the remaining 7 patients (78.5%).

Out of the 22 patients with small residual SDHs, 8 patients (36.36%) had a major rehemorrhage from which, 5 patients (22.7%) required neurosurgical intervention. The other three patients with a minor rehemorrhage did not require surgery. The remaining 11 patients (34%) resuming AAA when a SDH was present did not rebleed.

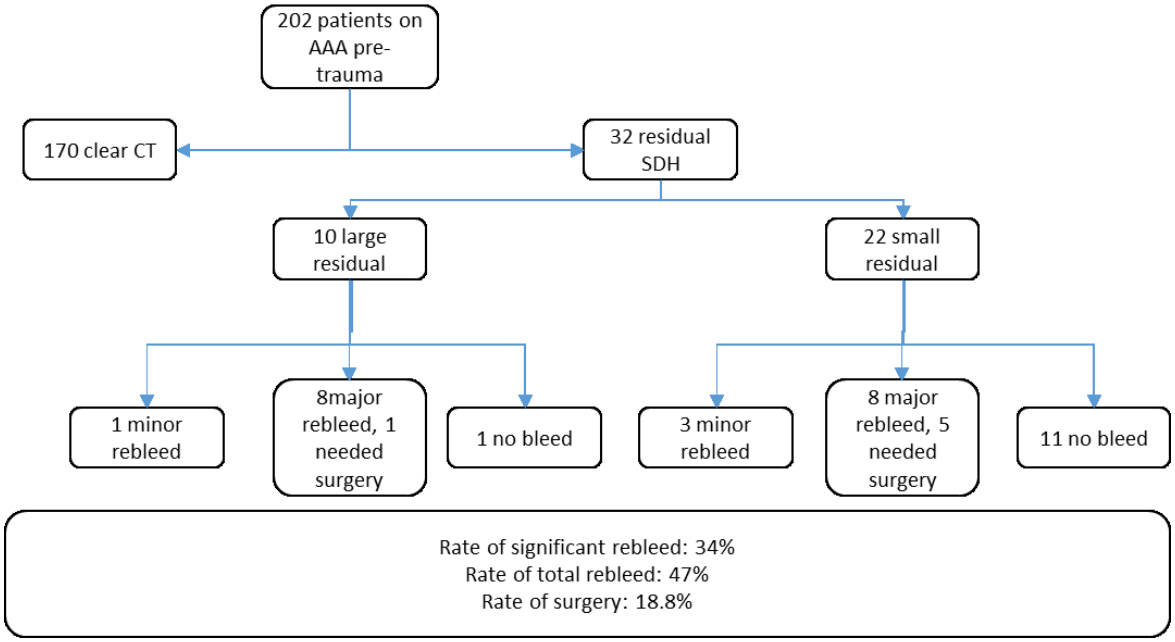
For the entire group of 32 patients with any size residual SDH, 15 patients (46.9%) suffered a rehemorrhage with 16 patients (49%) having a major rehemorrhage and 6 patients (18.8%) requiring surgical intervention (see Figure 4).

## Statistical Analysis

Chi-square testing was employed to validate each of the following 4 questions:

1. Is there a correlation between the size of the residual SDH and the risk of any rebleeding?
2. Is there is any correlation between the size of residual SDH and the risk of major rebleeding?
3. Is there any correlation between the size of residual SDH and the severity of rebleeding?
4. Is there any relationship between rebleeding and restarting anticoagulant therapy (for patients with a residual SDH)?

Figure 4: Risk of re-hemorrhage in traumatic SDH when taking AAA




First, we test whether there is a correlation between the size of the residual SDH and of any chance of rebleeding. Table 8 compares the number of patients with either small or large residual hematoma, against patients with and without further bleeding while taking AAA.

Table 8: The summary of observations taken from Figure AAA

| | Large Residual | Small Residual | Sum |
|---|---|---|---|
| No Bleeding | 1 | 11 | 12 |
| Bleeding | 9 | 11 | 20 |
| Sum | 10 | 22 | 32 |

The *null* hypothesis is that there is no relationship between the size of the residual (small or large) SDH and the chance of rebleeding. Table 9 shows the expected number of patients with and without bleeding given that the *null* hypothesis is true.

Table 9: Expected number of bleeding observations given that *null* hypothesis is true

| | Large Residual | Small Residual |
|---|---|---|
| No Bleeding | 3.75 | 8.25 |
| Bleeding | 6.25 | 13.75 |

The p-value (chi-square) on the two sets of numbers is 0.0303; and the *null* hypothesis is rejected at the 0.05 level of significance. We conclude that the size of the residual SDH on CT is significantly associated with rehemorrhage, with smaller residuals having less chance of rehemorrhage.

Second, we test whether there is a correlation between the chance of a major rehemorrhage and the size of residual SDH.

Table 10 compares the number of major bleeding events among patients with small and large residuals. The left table shows our observed data. The table on the right shows the expected values assuming that the two variants are independent (null hypothesis).

Table 10: The risk of major bleeding in small vs. large residuals

| | Observed | | |
|---|---|---|---|
| | Large Residual | Small Residual | Sum |
| Large Re-bleed | 8 | 8 | 16 |
| Other | 2 | 14 | 16 |
| Sum | 10 | 22 | 32 |

| Expected | |
|---|---|
| Large Residual | Small Residual |
| 5 | 11 |
| 5 | 11 |

The p-value calculated by the chi-square function on the two sets is 0.0221, therefore, we conclude that the size of residual blood on CT is significantly associated with the severity of rehemorrhage.

Next, we consider the severity of rehemorrhage: and compare no rebleeding, minor rehemorrhage, and major rehemorrhage with the size of the residual (Table 11). The left table shows observed data while the right table shows the expected values assuming that there is no relation between the two measures (null hypothesis).

Table 11: The severity of bleeding vs. the size of residual

| | Observed | | |
|---|---|---|---|
| | Large Residual | Small Residual | Sum |
| No Bleeding | 1 | 11 | 12 |
| Minor Bleeding | 1 | 3 | 4 |
| Major Bleeding | 8 | 8 | 16 |
| Sum | 10 | 22 | 32 |

| Expected | |
|---|---|
| Large Residual | Small Residual |
| 3.8 | 8.3 |
| 1.3 | 2.8 |
| 5 | 11 |

The p-value calculated by chi-square test on the two sets is 0.0601, therefore we do not have significant evidence (e.g. with 95% confidence) that the size of residual SDH is associated with the severity of rehemorrhage.

Finally, we test whether there is any correlation between rebleeding and restarting AAA therapy among patients with non-resolved residual SDHs.

Table 12 presents the incidences of bleeding with respect to continuation of anticoagulant therapy. The table on the left shows observation data while the numbers in the right table are the expected values assuming the null hypothesis is true.

The p-value calculated by chi-square test on the two sets is $< 0.0001$. Therefore, the data suggests a significant relationship between rehemorrhage and restarting AAA medication in patients having an SDH.

Table 12: Chance of bleeding on AAA

| | Stopped AAA until clearance of CT | Continued AAA despite residual presence | Sum |
|---|---|---|---|
| Major bleed | 0.00 | 16.00 | 16.00 |
| Minor bleed | 0.00 | 4.00 | 4.00 |
| No bleed | 170.00 | 12.00 | 182.00 |
| Sum | 170.00 | 32.00 | 202.00 |

| Expected | |
|---|---|
| 13.47 | 2.53 |
| 3.37 | 0.63 |
| 153.17 | 28.83 |

## Discussion

Many studies have looked at the interaction of AAA therapy in different neurosurgical pathologies, but only a few of them have concerned TBI.

The importance of studying the side effects of AAA therapy in patients with an SDH, lies with the differences of SDH from other types of ICHs, along with AAAs being widely used among the older population who have a higher risk of TBI.

Normally traumatic intracerebral contusions, subarachnoid hemorrhages or epidural hematomas do not progress beyond the first few days after the injury (Narayan, et al., 2008). However, SDHs can progress weeks or even months after the initial event, meaning its management is more challenging for the clinicians. Furthermore, the use of AAA therapy in patients with an SDH present makes the management even more complicated (Ananthasubramaniam et al., 2001; Asghar et al., 2002; Baglin et al., 2005; Broderick et al., 2007; Frontera et al., 2015; Jung et al., 2014; Kawamata et al., 1995; Bajsarowicz et al., 2015).

Our study shows that withholding AAA therapy (for an average of 54 days), did not result in any significant medical or neurological complication but that restarting AAA therapy among patients with non-resolved SDH (independent of the size of the residual) is associated with a high risk of rehemorrhage (47%). This rehemorrhage also increases the risk of future

surgical intervention (18.8%) needed for evacuation.

As indicated earlier, holding AAA therapy for an average of 54 days did not result in any symptomatic ischemic or embolic complications.

## Recommendations

In the majority of cases, we found that the safest course is to wait until the SDH is completely resolved before restarting AAA therapy. The SDH should be closely monitored with CT-scans so that the medication can be restarted as soon as the blood has completely resolved. Half of our study patients had a normal CT by 67 days. However, some cases of SDHs take a much longer time to resolve.

Those patients who have a greater chance of thrombo-embolic events, (e.g. those with a recent cardiac stent, a recent stroke or repetitive strokes, unstable angina, etc.), are more difficult to manage. For these patients, it may be wiser to restart AAA earlier (Beynon, Hertle, Unterberg, & Sakowitz, 2012), but to closely follow the SDH with the help of frequent computer tomography imaging.

## Conclusion

This is the first known study on the risk of AAA therapy in the setting of a traumatic SDH. This study found that continuing therapeutic AAA while an SDH is still present poses a high risk of rehemorrhage (47%) and therefore a higher risk of surgery to treat the rebleed. This study also found that the risk of rehemorrhage increases directly with size of the residual SDH.

The study also revealed that withholding AAA therapy for an average of 54 days was not associated with any significant adverse events. Regular imaging to monitor the SDH resolution, as well as close monitoring of patients with a high risk for ischemic sequela, is warranted.

# Chapter 5: Anticoagulant Therapy and SDH

This chapter studies complications of anticoagulant therapy on patients with SDH. The first section describes patient sample characteristics, which include imaging characteristics, surgical treatment, reasons for anticoagulation therapy, and timing and complications of therapeutic anticoagulation. The second section describes statistical analysis. The third section discusses our results in comparison with the literature. The fourth section offers our recommendations and we then end with my conclusion.

## Patient Samples and Characteristics

As stated in the previous chapter, the MGH TBI and Trauma Registry databases hold 1919 charts coded as "traumatic SDH" for the study period. We found 137 patients who were on anticoagulants prior to their traumatic event. Forty-four patients were excluded because either they died early from the severity of the injury (25 patients), the SDH was not acute (15 patients), or there was insufficient data (4 patients). There were 4 cases where anticoagulation therapy was not used before the traumatic SDH but was initiated post-trauma. Out of these, 3 cases were for DVT and 1 case for DVT plus PE. A total of 97 patients remained for analysis.

Among these patients seventy-three (75%) were male and twenty-four (25%) were female. The mean age was 74.4 with a standard deviation of 12 years and a range between 19 and 94 years of age. The majority of patients (83.2%) were aged 65 years and over. The mean GCS on admission was 13.4 (Table 13). The great majority (82%) of patients suffered a mild TBI (GCS between 13 and 15). The ISS was 25.7 on average and ranged from 16 to 50.

Table 13: Glasgow Coma Scale (GCS) on admission, for patients on anticoagulants

| GCS Score | Number (total = 99) | Percentage (%) |
|---|---|---|
| 15 | 50 | 51.5 |
| 14 | 25 | 26 |
| 13 | 5 | 5 |
| 9-12 | 7 | 7.2 |
| 3-8 | 10 | 10.3 |

Table 14 shows details of the mechanisms of injury. According to several studies a fall is the most common cause of TBI (Berry & Miller, 2008). In our study, 83 out of 97 patients' (85.6%) TBI was because of fall from their own height. The second most common cause of TBI was a fall from various heights for 6 out of the 97 patients (6.2%). Ten patients (10.3%) had a history of alcohol abuse, while 22 patients (22.7%) had a history of recurrent falls.

Table 14: Mechanism of injury (Anticoagulant group)

| Mechanism of Injury | Number (total = 97) | Percentage (%) |
|---|---|---|
| Fall from own height (FFOH) | 83 | 85.6 |
| Fall from height (FFH) | 6 | 6.2 |
| Motor vehicle accident (MVA) | 1 | 1.0 |
| Pedestrians hit by a car (PED) | 5 | 5.0 |
| Bike | 1 | 1.0 |
| Other | 1 | 1.0 |

**Imaging characteristics.** The SDH on admission had a mean thickness of 11.5mm, and a median of 10mm (ranging from 1mm to 43mm). The majority of cases (56.8%) measured 10mm or less. The locations of the SDH were distributed as follows: 86 (88.6%) over the convexity, 7 (7.2%) tentorial, and 4 (4.1%) parafalcial.

**Surgical treatment.** Fifteen patients (15.8%) required an urgent evacuation of their SDH by craniotomy and three (3.2%) required craniectomy for ICP control along with the evacuation

of the SDH. Fifteen patients (15.8%) underwent burrhole evacuation of their SDH when it became chronic and prior to the institution of therapeutic anticoagulation.

**Indications and types of anticoagulation therapy.** Table 15 lists the reasons for anticoagulation therapy prior to the injury. All patients used warfarin, except for one who used dabigatran. Twenty-nine patients (30.5%) used antiplatelet aggregation agents in combination with warfarin; 24 patients (25.3%) were taking acetylsalicylic acid; 3 patients (3.3%) were taking clopidogrel; and 2 patients (2.1%) were taking acetylsalicylic acid with clopidogrel and warfarin.

Table 15: Primary indication for Anticoagulant

| Rationale | Number (total = 93) | Percentage (%) |
|---|---|---|
| Atrial fibrillation | 24 | 25.8 |
| Cardiac valve prosthesis | 11 | 11.8 |
| Previous deep venous thrombosis/ pulmonary embolism | 11 | 11.8 |
| Chronic heart failure | 3 | 3.2 |
| Pacemaker | 6 | 6.4 |
| Coronary artery disease and peripheral vascular disease | 38 | 40.9 |

**Timing and complications of therapeutic anticoagulation.** Anticoagulation therapy was put on hold for an average of 105.6 days (median of 67 days; ranging from 0 to 868 days). During the time anticoagulation therapy was on hold, there was only one (1%) adverse event: a patient with a previous mitral valve replacement was found to have an atrial clot on surveillance echocardiogram on the 10th day following warfarin reversal. Therapeutic anticoagulation was reinitiated and the patient did not develop any embolic complications.

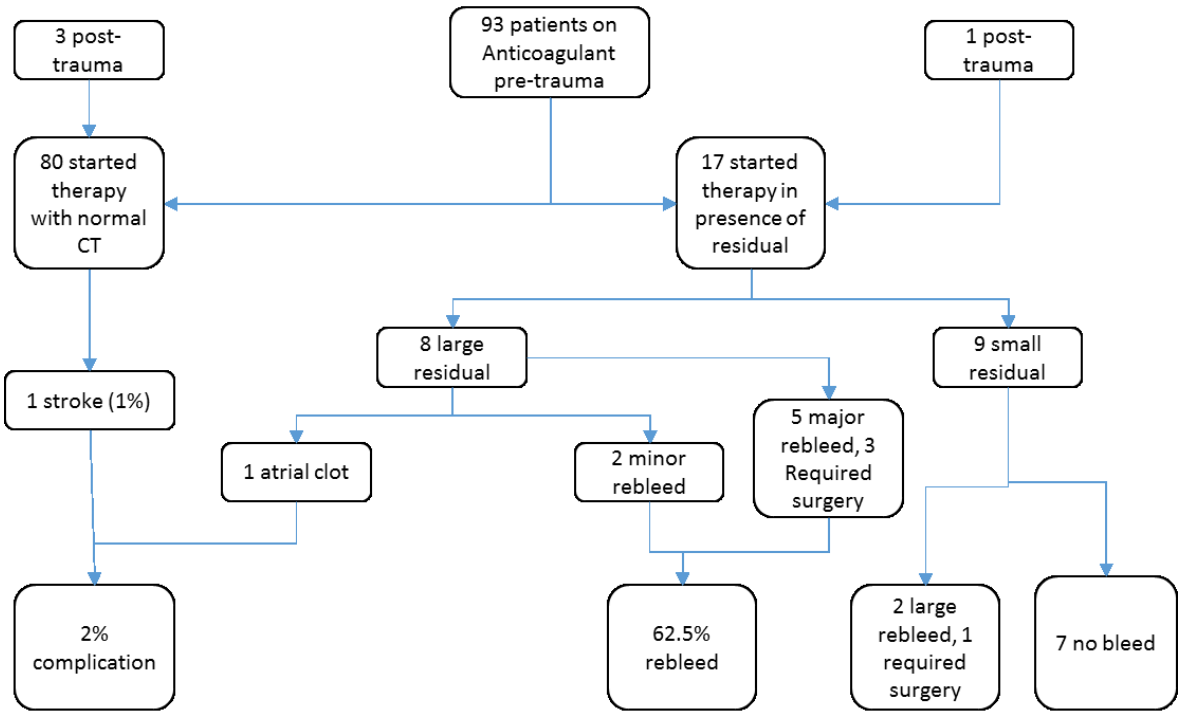
For 80 out of 97 patients (82.5%), therapeutic anticoagulation was reintroduced once the SDH had completely disappeared at a follow-up CT scan. In the remaining 17 patients (17.5%) therapeutic anticoagulation was restarted yet the SDH had not completely resolved on CT-scan.

The residual SDH was qualified as small in 9 patients and large in the remaining 8

patients. Within this latter group 5 patients (62.5%) suffered a rehemorrhage out of which 3 patients (37.5%) had a significant rehemorrhage requiring surgical evacuation. Two patients (25%) suffered from rehemorrhage but did not require any surgery and anticoagulation therapy was held again after the rehemorrhage incident.

In the group with a small remnant (9 patients), two patients (22.2%) had a rehemorrhage, out of which one (11.1%) required neurosurgical intervention. No problem was observed for the remaining 7 patients (77.8%). For the entire group of 17 patients with any residual SDH, 9 patients (53%) suffered a rehemorrhage with 4 patients (23.5%) requiring surgical intervention. One patient remained with a permanent neurological deficit (mild expressive dysphasia) after the rehemorrhage (see Figure 5 for the summary of the results).

Figure 5: Anticoagulant group, rebleeding and coagulation percentages



## Statistical Analysis

Chi-square testing was employed to validate each of the following gestation:

1. Is there any correlation between the size of the residual and the risk of rebleeding?
2. Is there any correlation between the size of residual and major rebleeding?
3. Is there any correlation between the size of residual and severity of rebleeding?
4. Is there any correlation between rebleeding and restarting of anticoagulant therapy (for patients with non-resolved residual SDH)?

First, we tested whether there is a correlation between the size of the residual SDH and the chance of rebleeding. Table 16 shows the number of patients starting or resuming anticoagulant therapy with either a small or large residual hematoma and it shows the number of patients with/without bleeding based on the size of the residual.

Table 16: The summary of observations taken from Figure A-COAG

| | Large Residual | Small Residual | Sum |
|---|---|---|---|
| No Bleeding | 1 | 1 | 2 |
| Bleeding | 7 | 2 | 9 |
| Sum | 8 | 3 | 11 |

The *null hypothesis* is that there is no relationship between the size of the residual and the chance of rebleeding. Table 17 shows the expected number of patients with and without bleeding given that the *null* hypothesis is true.

Table 17: Expected number of bleeding observations given residual size

| | Large Residual | Small Residual |
|---|---|---|
| No Bleeding | 1.5 | 0.5 |
| Bleeding | 6.5 | 2.5 |

The p-value returned by applying the chi-square function on the two sets of numbers (Table 16 and Table 17), is 0.042. Therefore, the null hypothesis is rejected as the probability of it being true is significantly small (less than 0.05). We conclude that the size of residual blood on computed tomography (CT scan) correlates with chance of bleeding, or in other words, a smaller residual has less chance of rehemorrhage.

Secondary, we tested whether there is a correlation between major rehemorrhage and size of residual SDH. Table 18 compares the risk of major bleeding among patients with small and large residuals. The left table shows observed data, whereas the table on the right shows the expected values if the two variants are independent (null hypothesis).

Table 18: The risk of major bleeding in small vs. large residuals

| | Observed | | | | Expected | |
|---|---|---|---|---|---|---|
| | Large Residual | Small Residual | Sum | | Large Residual | Small Residual |
| Large Re-bleed | 5 | 2 | 7 | | 3.23 | 3.70 |
| Other | 3 | 7 | 10 | | 4.70 | 5.29 |
| Sum | 8 | 9 | 17 | | | |

The p-value calculated by Chi-Square function on the two sets is 0.0921, therefore we do not have enough evidence (i.e. within the 95% confidence interval) to show that the size of residual blood is significantly associated with the size of rebleeding.

Next, we consider rebleeding: no rebleeding, minor, and major rebleeding, as a function of the size of the residual SDH. Table 19 presents the severity of bleeding against the size of residual. The left table shows our observed data while the right table shows the expected values.

Table 19: The severity of bleeding vs. the size of residual

| | Observed | | | Expected | |
|---|---|---|---|---|---|
| | Large Residual | Small Residual | Sum | Large Residual | Small Residual |
| No Bleeding | 1 | 7 | 8 | 3.8 | 4.2 |
| Minor Bleeding | 2 | 0 | 2 | 0.9 | 1.1 |
| Major Bleeding | 5 | 2 | 7 | 3.3 | 3.7 |
| Sum | 8 | 9 | 17 | | |

The p-value calculated by Chi-Square on the two sets is 0.0207; meaning that the size of residual SDH on computed tomography is significantly associated with the severity of bleeding. In those patients who have been restarted on anticoagulants.

Finally, we tested for any correlation between any rebleeding and restarting anticoagulation therapy among patients with non-resolved residuals. Table 20 presents the incidences of bleeding with respect to continuation of anticoagulant therapy. The table on the left shows our observation while the numbers in the right table are the expected values assuming that if there is no correlation between the two variants (null hypothesis).

Table 20: The chance of bleeding in patients on anticoagulants with presence vs absence of residual blood

| | Stopped | Continued | Sum |
|---|---|---|---|
| Major bleed | 0 | 3 | 3 |
| Minor bleed | 0 | 4 | 4 |
| No bleed | 82 | 10 | 92 |
| Sum | 82 | 17 | 99 |

| Expected | |
|---|---|
| 2.48 | 0.52 |
| 3.31 | 0.69 |
| 76.20 | 15.80 |

The p-value calculated by chi-square test on the two sets is <0.0001 suggesting a very strong correlation between the SDH rebleeding and restarting the anticoagulant medication.

## Discussion

Many studies have looked at the interaction of anticoagulation therapy in different neurosurgical pathologies but only a few of them have considered TBI. In addition, the studies enrolled a relatively small number of patients with traumatic SDHs. Hence, there is a need for more data on the management of anticoagulation therapy with SDH.

Comparing my result to the previous studies on the interaction of anticoagulation therapy in neurosurgical pathologies, my study shows a higher risk of rehemorrhage (41.2% in my study and 0% to 12% in other studies) when resuming anticoagulation therapy before the SDH is fully resolved. This discrepancy can be potentially explained by the fact that much of the literature is founded on the much broader category of ICH. These included only a small number of patients with a traumatic SDH. Kawamata et al. (1995) had 11 patients with an SDH and found a 0% risk of SDH rehemorrhage. Wijdicks et al. (1998), who had 20 patients with an SDH, also found 0% risk of SDH rehemorrhage. Byrnes et al. (2012), who had 13 patients with an SDH, found a 4% risk of SDH rehemorrhage. Jung, Jeon, Chang and Jung (2014), who had 5 patients, found a 21.1% risk of SDH rehemorrhage.

Presently our analysis based on 98 patients, is the largest cohort of SDH patients on anticoagulant therapy found in the literature. Our results show that withholding anticoagulant therapy for a median of 67 days resulted in a 1% complication rate. However, the risk of reinitiating anticoagulant therapy, when the SDH is not resolved, is associated with a 41.2% risk of rehemorrhage and a 17.6% risk of requiring surgical evaluation of the SDH, of these 6% will have a permanent neurological deficit related to the rehemorrhage. The risk of rehemorrhage was higher for larger residuals (62.5%) as compared to smaller residuals (22.2%). There is a high correlation between restarting anticoagulant therapy with an SDH present. The timing of and the

chance of rehemorrhage.

The timing of anticoagulation resumption in the literature varies from a few days to many weeks or even years. The average delay of anticoagulation therapy was 51 days in cases of acute SDH (Jung et al.,2014). None of the studies include the abnormalities formed on brain CT at the time of anticoagulation therapy resumption and there is little description on how follow-up or detection of rebleeding was investigated (Kawamata et al., 1995; Wijdicks et al., 1998; Byrnes et al., 2013; Jung et al., 2014).

The guidelines from the American Heart Association and the Stroke Council (AHA/ASA), suggests that interrupting anticoagulation for 7 to 10 days is safe for patients with indications for anti-coagulation (Broderick et al. 2007). This recommendation was supported by a study on interrupting anticoagulation for prosthetic heart valves which concluded that 2 weeks off anticoagulant therapy did not result in any adverse events (Ananthasubramaniam, Beattie, Rosman, Jayam, & Borzak, 2001).

However, another study on anticoagulation for prosthetic heart valves, who are at a high risk for thrombo-embolic events, found that the risk of complications increased over time (0.0% within the first 7 days, 10.53% within 14 days, and 38.49% within 30 days) (Jung, et al. 2014). Our results show only a 1.1% risk of thrombo-embolic complications, despite an average of two months interruption in anticoagulation therapy. This difference from Jung et al. can be explained partially by the fact that only 20% of our patients had a high-risk condition prostatic heart valve requiring therapeutic anticoagulation.

## Recommendations

For the majority of cases the safest course is to wait until the SDH is completely resolved before restarting anticoagulant therapy. On the other hand, to minimize thromboembolic

sequelae the SDH should be closely monitored, using CT-scans, so that anticoagulation can be reinitiated as soon as possible. Half of our studied patients had a normal CT by 67 days.

Patients with high risk of thrombo-embolic events (e.g. those with atrial fibrillation and a high CHA2DS2VASc score or those with a prosthetic mitral valve), are more difficult to manage. A rehemorrhage of the SDH may have less consequence than a large vascular territory stroke. Therefore, where the risk of ischemic stroke is very high (>40%) it might be worthwhile to restart anticoagulation before the SDH has completely cleared, but to monitor the SDH closely. These "at risk" patients might also benefit from closer follow-up with frequent cardiac ultrasound to detect the early presence of atrial clots or valve thrombosis (Roudaut, Serri, & Lafitte 2007). As was done for a patient in our study who was found to have an atrial clot.

If there is a SDH rehemorrhage, anticoagulation therapy must be reversed and held again (perhaps for a longer time). A more aggressive approach to a SDH in a patient at high risk of thromboembolic is surgical evacuation to reduce both the volume and the delay in SDH resolution. This might be justified in some asymptomatic patients, provided their surgical risk is not too high (Kawamata et al., 1995).

## Conclusion

This study found that continuing therapeutic anticoagulation while an SDH is still present poses up to 41% risk of rehemorrhage, and a 11% risk of surgery for the rebleed. The risk of rehemorrhage increases when the residual SDH is larger. Withholding anticoagulant therapy for an average of 67 days was associated with only a 1.1% risk of adverse events. Regular imaging to follow the SDH regression, as well as close monitoring of patients with a high risk of a thrombo-embolic event is warranted.

# Chapter 6: Limitations of Our Study

The first limitation of this study lies in the fact that it is retrospective (see below). The second limitation is the low number of participants with residual hemorrhage, which makes it more difficult to achieve a high degree of statistical confidence.

As per the nature of a retrospective study, there were problems with documentation. Specifically, there was missing and incorrect data in some of the patient's charts. Some patients did not show up for follow-ups, and it was not documented whether the patient recovered, had a rehemorrhage or presented to another facility. Another problem with documentation is the presence of errors in the written records. Some cases of ICH were mistakenly reported as an SDH. Some of the SDHs classified as acute, were found to be chronic in nature. Cases with known missing or incorrect data were excluded from this study, which resulted in an even smaller study group.

A limited number of cases with small and large residual SDH rebleeding, make it more difficult to achieve a high degree of statistical confidence. In the study on AAA, there were only 32 patients with non-resolved residuals (22 small and 10 large) while the study on anticoagulants found only 17 such patients (9 with small and 8 with a large residual). To achieve a higher degree of statistical confidence, future research is needed with larger sample sizes.

# Chapter 7: Conclusion

This thesis studied the effects of stopping and then restarting antiplatelet and anticoagulant therapy on traumatic SDHs. The aim of this study was to measure the risk of resuming antithrombotics in the presence of a residual subdural hemorrhage or withholding antithrombotics until the traumatic SDH fully resolved.

This retrospective study on subjects with an SDH and on antithrombotic therapy shows that there is a high risk (41%) of rehemorrhage if the SDH is still present. Almost 20% will need surgery to treat their rehemorrhage.

If patients are anticoagulated and suffer a SDH then (53%) will rebleed and almost a quarter (24%) of these will require surgery.

The study found that withholding AAA therapy after a traumatic SDH for an average of 54 days is not associated with any significant adverse events. Withholding anticoagulant therapy for an average of 67 days was associated with only a 1% risk of adverse events.

In both AAA and anticoagulant groups, the size of any residual hematoma at the time of restarting medication is directly associated with the risk of rehemorrhage. Patients with larger residuals have the highest risk of rehemorrhage and it is often the most severe. This risk of rebleeding for those who restarted AAA, in the presence of a large residual hemorrhage, was 90% and 50% for those with a small residual hemorrhage. The risk of rebleeding for those who restarted anticoagulants in the presence of a large residual hemorrhages was 88% and 22% for those with a small residual hemorrhage.

Based on these findings, I would recommend withholding antithrombotic medications until CT-imaging shows complete resolution of the SDH. In cases with a large residual hemorrhage, close follow up with appropriate clinical and imaging modalities is recommended. This frequent

monitoring of the lesion will help to detect complications before they become challenging to manage, or even life threatening.

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