ANTITHROMBOTICS AND TRAUMATIC BRAIN INJURY IN THE ELDERLY POPULATION: HEMORRHAGE PATTERNS AND OUTCOMES

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Abstract

In the elderly population, use of antithrombotic therapy (AT), antiplatelets (AP – aspirin, clopidogrel) and/or anticoagulants (AC – warfarin, DoAC – Dabigatran, Rivaroxaban, Apixaban), to prevent thrombo-embolic events must be carefully weighed against the risk of intracranial hemorrhage (ICH) with trauma. We hypothesize that for all patients 65yro+ presenting to the emergency room with head trauma, those on AT will be more likely to sustain a traumatic brain injury (TBI), ICH, and poorer outcomes.

Data was collected from all head trauma patients 65yo+ presenting to our supraregional tertiary trauma center over a 24-month period; age, gender, injury mechanism, provenance, medical history, medications, International Normalized Ratio, Glasgow Coma Scale (GCS) upon presentation, ICH presence and type, hospital admission, reversal therapy, surgery, discharge destination, Extended Glasgow Outcome Scale score (GOSE) at discharge and mortality.

1365 patients were identified; 724 on AT (413 AP, 151 AC, 59 DoAC, 48 2AP, 38 AP+AC, 15 AP+DoAC) and 641 not (non-AT). When adjusted for covariates, AP was associated with more TBIs ($p=0.0035$). Of the TBI patients, those using ATs had higher rates of ICH ($p=0.0004$), hemorrhage progression ($p=0.00094$), more invasive surgical interventions (craniotomies and craniectomies vs burr hole; $p=0.0188$), functional dependency at discharge ($GOSE\leq4$; $p<0.0001$) and mortality ($p<0.0001$). Risk of mortality was not associated with single antiplatelet use but was notably high with 2AP (OR 5.74; $p=0.0003$) and AP+AC (OR 4.12; $p=0.0118$).

Elderly trauma patients on ATs, especially combination therapy, have elevated risks of TBI, ICH and poor outcomes compared to those who are not.

Résumé

Parmi les personnes âgées, un traitement antithrombotique (AT) comme des antiplaquettaires (AP - aspirine, clopidogrel) ou des anticoagulants (AC - Warfarine, DoAC - Dabigatran, Rivaroxaban, Apixaban) pour prévenir les événements thromboemboliques doit être pesé contre le risque d'hémorragie intracrânienne avec un traumatisme. Nous émettons l'hypothèse que pour tous les patients 65 ans et plus qui se présentent à la salle d'urgence avec un traumatisme crânien, ceux sur AT seront plus susceptibles de subir un traumatisme crânio-cérébral (TCC), une hémorragie intracrânienne (HIC) et des résultats médicaux moins favorables.

Les données ont été recueillies auprès de tous les patients ayant subi un traumatisme crânien de 65 ans et plus et se présentant à notre centre de traumatologie tertiaire suprarégional pendant une période de 24 mois : âge, sexe, mécanisme des blessures, provenance, antécédents médicaux, médicaments, rapport normalisé international, échelle de Glasgow lors de la présentation, présence et type de l' hémorragie intracrânienne, hospitalisation, renversement du traitement antithrombotique, chirurgie, destination au congé, l'échelle de devenir de Glasgow et la mortalité.

1365 patients ont été identifiés; il y avait 724 patients prenant des AT (413 AP, 151 AC, 59 DoAC, 48 2AP, 38 AP + AC, 15 AP + DoAC) et 474 ne prenant pas d'AT. Après ajustement pour les covariables, les AP ont été associés à plus de TCC ($p = 0,0035$). Parmi les patients qui ont eu un TCC, ceux qui ont pris les ATs avaient des taux élevés de HIC ($p = 0,0004$), de progression de l'hémorragie ($p = 0,00094$), d'interventions chirurgicales plus invasives (craniotomies et craniectomies contre trou de trépan, $p = 0,0188$), de dépendance fonctionnelle

au congé de l'hôpital (GOSE ≤4, p <0,0001) et de mortalité (p <0,0001). Le risque de mortalité n'était pas associé avec l'utilisation d'un seul antiplaquettaire, mais était particulièrement élevé avec 2AP (OR 5,74, p = 0,0003) et AP + AC (OR 4,12, p = 0,0118).

Les patients âgés souffrant de traumatismes qui prennent des AT, en particulier les polythérapies, présentent des risques élevés de TCC, d'HIC et de mauvais résultats par rapport à ceux qui n'en prennent pas.

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Author Contributions

This master's project was initially conceived by Dr. Judith Marcoux[1] and Dr. Elaine de Guise[2]. In consultation with Pasquale Scotti[3] and Dr. Jean-Marc Troquet[1], the study goals and methodology were clearly defined. Ms. Mitra Feyz[4] and Dr. Troquet[5] provided access to the medical records of head trauma patients who presented and/or were admitted to the Montreal General Hospital. Under the supervision of Dr. Marcoux[1], Pasquale Scotti[3] reviewed all hospital charts and radiological scans, conducted data analysis, and produced all written materials, figures and tables. Dr. Marcoux[1] also reviewed all the records to determine which sustained a traumatic brain injury as well as many of the radiological images to confirm the presence and type of hemorrhage. Dr. Chantal Séguin[6] and Dr. Benjamin W. Lo[1] were appointed to Pasquale Scotti's[3] advisory committee and reviewed his work at regular intervals, providing feedback and assistance with the interpretation of the results.

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Acronyms

AC: Anticoagulant

A-fib: Atrial Fibrillation

ANOVA: Analysis of Variance

AP: Antiplatelet

ASA: Acetyl Salicylate Acid

AT: Antithrombotic

CI: Confidence Interval

COX 1: Cyclooxygenase 1

CT: Computed Tomography

DOAC: Direct Oral Anticoagulant

EDH: Epidural Hematoma

GCS: Glasgow Coma Scale

GOSE: Glasgow Outcome Scale Extended

HIT: Heparin-Induced Thrombocytopenia

ICH: Intracranial Hemorrhage

ICP: Intracranial Pressure

INR: International Normalized Ratio

IPH: Intra-parenchymal Hemorrhage

LMWH: Low Molecular Weight Heparin

MGH: Montreal General Hospital

MRI: Magnetic Resonance Imaging

OR: Odds Ratio

PPT: Partial Thromboplastin Time

PT: Prothrombin Time

REB: Research Ethics Board

RR: Relative Risk

SAH: Subarachnoid Hematoma

SD: Standard Deviation

SDH: Subdural Hematoma

TBI: Traumatic Brain Injury

TXA2: Thromboxane A2

VKORC1: Vitamin K Epoxide Reductase

Chapter 1: Introduction

As a result of increasing life expectancy, the proportion of elderly adults (≥65 years old) in the population is rapidly growing both in Canada and worldwide. Elders constituted 8% of the global population in 2015, and that figure is projected to reach 14% by 2040 (Melorose et al., 2015). Furthermore, as the mean age is increasing within this subpopulation so too is the frequency of fall-related injuries (54% increase between 2005 and 2013) and those falls are more likely to cause a traumatic brain injury (TBI) (Do et al., 2015; Hukkelhoven et al., 2003). The average hospitalization rate for TBI among elders is nearly four times greater than that of younger patients (<65 years old), and falls account for 82% of TBI-related hospitalizations among the elderly compared to only 32% among younger patients (Fu et al., 2015).

One reason seniors are more prone to TBI is that they have a significantly higher risk of sustaining an intracranial hemorrhage (ICH) with head trauma. Anatomical changes within the skull that occur with ageing, namely cerebral atrophy, increased adherence of the dura to the skull, and cerebrovascular atherosclerosis, facilitate the tearing of bridging veins in response to an external force, predisposing elders to subdural hemorrhages (SDH) (Asghar et al., 2002). In tandem with the growing proportion of seniors in the population, SDH is projected to become the most common cranial neurosurgical condition among adults by the year 2030, surpassing brain tumors (Balser et al., 2015).

To complicate matters, older patients have a high prevalence of heart and cardiovascular disease and thus antithrombotic (AT) agents, antiplatelet (AP) and/or anticoagulant (AC) therapy, are more frequently used in this subpopulation to reduce the risk or to prevent the onset of thrombo-embolic events (Andreotti et al., 2015). The most important adverse effect of this

class of medication is the risk of bleeding, especially in trauma (Fitzmaurice et al., 2002). This has led many to investigate the impact of AT therapy on head trauma to ascertain the role of these agents with respect to ICH and outcomes, however findings have been conflicting.

Chapter 2: Background Information

2.1. TBI Definition

A traumatic brain injury is defined as a traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force. It is indicated by new onset or worsening of at least one of the following clinical signs immediately following the event:

1. any period of loss of or a decreased level of consciousness
2. any loss of memory for events immediately before or after the injury (posttraumatic amnesia)
3. any alteration in mental state at the time of the injury (e.g., confusion, disorientation, slowed thinking, alteration of consciousness/mental state)
4. neurological deficits (e.g., weakness, loss of balance, change in vision, praxis, paresis/plegia, sensory loss, aphasia) that may or may not be transient
5. intracranial lesion

(Menon et al., 2010)

TBI injuries can be focal or diffuse; intracranial hemorrhages are considered focal injuries whereas widespread axonal injury and hypoxic-ischemic injury are considered diffuse (Mckee et al., 2015). Focal injuries are a result of direct collision forces on the skull causing

compression at the site of impact (coup) and/or on the opposite side of the impact (contre-coup). Diffuse injures are attributed to rapid acceleration/deceleration forces which produces shear stress on vasculature and brain parenchyma (Andriesson et al., 2010). These injuries are not mutually exclusive. In fact, most TBI's are heterogeneous with both focal and diffuse components (Greenfield et al., 2008). In one study, among moderate to severe TBIs, both focal and diffuse injuries were found in 50% of patients (Skandsen et al., 2010).

2.2. Measuring TBI Severity: The Glasgow Coma Scale

The *Glasgow Coma Scale* (GCS) is used to grade TBIs of adults on a 15 point scale and categorizes cases as mild (13-15), moderate (9-12), or severe (3-8). The GCS is a sum of three separate measures: degree of eye opening (1-4), verbal capacity (1-5), and motor response (1-6). The severity of TBI approximately reflects the patient's level of consciousness. This is a quick and standardized measurement and is routinely used in emergency rooms (Teasdale & Jennett., 1974; Teasdale et al., 2014).

TABLE 1: The Glasgow Coma Scale (GCS)

	1	**2**	**3**	**4**	**5**	**6**
Eye	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	-	-
Verbal	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	-
Motor	Makes no movements	Decerebrate response: Extension to painful stimuli	Decorticate response: Abnormal flexion to painful stimuli	Flexion / Withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

Adapted from Teasdale & Jennett., 1974

Some have argued against its use due to low inter-rater reliability (Rowley et al., 1991; Gill et al., 2004; Wijdicks et al., 2005). For example, in one study, GCS scores were the same in just 38% of cases and were 2 or more points apart in 33% (Gill et al., 2004). However, a recent systematic review demonstrated that GCS was adequately reliable when only considering studies with high methodological quality (85% of kappa values; 100% Intraclass Correlation Coefficient (ICC)), and that studies demonstrating low reliability are methodologically flawed (Reith et al., 2016).

An alternative to the GCS is the *FOUR score* which consists of four components; eye response, motor response, brainstem reflex, and respiration, each of which is scored between 0-4. The potential strengths of this approach are that it is easier to test in neurologically critically ill patients who are intubated and that it further characterizes the severity of the comatose state in patients with the lowest GCS scores (Wijdicks et al., 2005). Reliability of the FOUR score is comparable but not superior to GCS (Sadaka et al., 2012; McNett et al., 2014).

2.3. Types of Intracranial Hemorrhage in TBI

An intracranial hemorrhage can be either intra-axial (Intrapenchymal Hemorrhage - IPH) or extra-axial (outside brain parenchyma along the meninges). Extra-axial hematomas include epidural hematoma (EDH), subdural hematoma (SDH), and subarachnoid hematoma (SAH). An *epidural hematoma* (EDH) is a collection of blood between the cranium and periosteal dura due to lacerations of arterial meningeal vessels via collision forces. A *subdural hematoma* (SDH) is a collection of blood between the dural and arachnoid meninges due to lacerations of bridging veins via acceleration/deceleration forces (Kim et al., 2011).

TABLE 2: Differences between Epidural and Subdural Hematomas

Epidural Hematoma (EDH)	Subdural Hematoma (SDH)
Usually at injury site ("coup")	Usually opposite to injury site ("contre-coup")
Usually linked to tearing of meningeal artery via collision forces	Usually linked to tearing of bridging veins via acceleration/deceleration forces
Usually associated with skull fracture	Not necessarily linked to skull fracture
Lentiform-shaped collection of blood	Crescent-shaped collection of blood
Confined by suture lines	Not confined by suture lines
Usually in temporal or temporoparietal regions	Usually over cerebral convexities
Not confined by falx or tentorium cerebelli	Confined by falx and tentorium cerebelli
Mass effect directly related to size of hematoma	Mass effect more often associated with underlying parenchymal injury
Acute emergency	May be chronic condition

Table adapted from Kim et al., 2011 and Parizel et al., 2001

A *subarachnoid hematoma* (SAH) is a collection of blood between the arachnoid and pia meninges. It occurs in ~40% of patients with moderate to severe injury and is usually associated with other types of intracranial hemorrhage (Murray et al., 1999). In the context of TBI, it occurs as a result of direct laceration of the small cortical vessels, intraventricular hemorrhage exiting the fourth ventricular outflow foramen, or direct extension from a cortical hematoma. Hydrocephalus and elevated intracranial pressure are common complications of SAH; acutely, this is due to blood in the intraventricular space and/or inflammatory arachnoiditis, and chronically, it is due to decreased resorption of CSF (Kim et al., 2011).

For SDH, current guidelines recommend surgery when there is a thickness greater than 10 mm or a midline shift greater than 5 mm on CT scan, regardless of the patient's GCS. Patients

with a GCS<9, SDH less than 10 mm thick, and a midline shift less than 5 mm may undergo surgical evacuation of the lesion only if the GCS score decreased between the time of injury and hospital admission by 2 or more points on the GCS and/or the patient presents with asymmetric or fixed and dilated pupils and/or the ICP exceeds 20 mm Hg (Bullock et al., 2006). For IPH, surgery is recommended for patients with GCS scores 6-8 with frontal or temporal contusions greater than 20 cm^3 in volume with midline shift of at least 5 mm and/or cisternal compression on CT scan as well patients with any lesion greater than 50 cm^3 in volume (Bullock et al., 2006).

2.4. Identifying and Classifying Intracranial Hemorrhages: The CT Marshall Score

A *Computed Tomography (CT) scan* can be used to detect both focal and diffuse brain injuries and differentiate them, a task that is difficult with clinical examination alone due to the similarity of signs and symptoms (Andriesson et al., 2010). It is performed in every patient with a moderate or severe TBI (GCS < 13). For mild head injuries (GCS 13-15), CT scans are performed when at least one of the following criteria is met:

1. GCS score <15 at 2 h after injury
2. Suspected open or depressed skull fracture
3. Any sign of basal skull fracture (haemotympanum, ‘racoon’ eyes, cerebrospinal fluid otorrhoea/rhinorrhoea)
4. Vomiting ≥ two episodes
5. Age ≥ 65 years
6. Amnesia before impact >30 min

7. Dangerous mechanism (pedestrian struck by motor vehicle, occupant ejected from motor vehicle, fall from height >3 feet or five stairs)

(Stiell et al., 2001)

Hematomas appear as hyperdense (brighter) compared to surrounding tissue due to the aggregation of globin molecules and hematocrit which attenuates (removes photons from) x-ray beams more than brain parenchyma. With active bleeding, the mass is complex, non-homogeneous and not yet clotted; thus hyperacute hemorrhages may appear heterogeneous on CT imaging (Parizel et al., 2001). With hemorrhagic contusions, detection can be confounded by the partial volumes between dense microhemorrhages (Newcombe et al., 2013; Iaccarino et al., 2014) and edema (hypodense) which can isoattenuate the signal (McKee et al., 2015). Repeat CT scan hours after injury is recommended not only to monitor the bleed but also to account for these technical issues (Brown et al., 2007). Another factor to consider is that if a patient is anemic (less hemoglobin) or if CSF (hypodense) is mixed with the blood, the hematoma may appear isodense compared to surrounding tissue (Kim et al., 2011).

Diffuse injuries and hemorrhages are categorized on CT scans by the *Marshall classification* (Marshall et al., 1991).This classification system is widely used and standardized (Saatman et al., 2008). It has a stronger correlation with mortality rate than physical examination measures (Marshall et al., 1991) and has an even higher prognostic value when considered in combination with the presence/absence of traumatic subarachnoid or intraventricular hemorrhage and different types of mass lesions (Maas et al., 2005).

TABLE 3: The CT Marshall Classification System

Diffuse Injury Type	**Characteristics**
I	No visible intracranial pathological processes
II	Cisterns are present Midline shift 0-5mm Lesion densities present No high- or mixed-density lesion >25mL May include bone fragments and foreign bodies
III/Swelling	Cisterns are compressed or absent Midline shift 0-5mm No high- or mixed-density lesion >25mL
IV/Shift	Midline shift >5mm No high- or mixed-density lesion >25mL
V/Evacuated mass lesion	Any lesion surgically evacuated
VI/Non-evacuated mass lesion	High- or mixed-density lesion >25mL not surgically evacuated

Adapted from Marshall et al., 1991

Compared to *Magnetic Resonance Imaging (MRI)*, an alternative imaging technique, CT scans are more available and cost effective, require shorter imaging time and are easier to perform on patients who are on ventilator support, in traction, or agitated, and thus are the imaging modality of choice in the first 24 hours post-TBI (Lee et al., 2005). Furthermore, it is adequately sensitive to detect hematomas, contusions, and swelling (Saatman et al., 2008). One advantage MRI has over CT is increased sensitivity in detecting non-hemorrhagic contusions, diffuse axonal injury, and edema (Gentry et al., 1988; Hesselink et al., 1988).

2.5. Neurological Outcome: The Glasgow Outcome Scale Extended

The *Extended Glasgow Outcome Scale (GOSE)* is an ordinal measure of disability. It is scored based on a structured interview that can be conducted face-to-face or by telephone. It has five categories: death, vegetative state, severe disability, moderate disability, and good recovery. The latter three categories are further divided into "lower" and "upper" categories, making it an 8-point scale (Wilson et al., 1998). It was designed to assess how functional a patient is in his or her respective community; however it can also be reliably used at the time of discharge. This scale has a high inter-rater reliability and its measures also correlate closely with those of widely-used quality of life assessments, including the SF-36 (generic to all patients) and the Quality of Life After Brain Injury (specific to TBI patients) (McMillan et al., 2012).

TABLE 4: The Glasgow Outcome Scale Extended (GOSE)

GOSE Score	Functional Condition
1	Dead
2	Vegetative: Unawareness with reflex responses and periods of spontaneous eye opening.
3	Lower Severe Disability: Fully dependent for all activities of daily living. Requires assistance to be available constantly. Unable to be left alone at night.
4	Upper Severe Disability: Can be left at home for up to eight hours but remains dependent. Unable to use public transport or shop by themselves.
5	Lower Moderate Disability: Able to return to work in sheltered workshop or non-competitive job. Rarely participates in social and leisure activities. Ongoing daily psychological problems (quick temper, anxiety, mood swings, depression).
6	Upper Moderate Disability: Able to work but at a reduced capacity. Participates in social and leisure activities half as often. Weekly psychological problems.
7	Lower Good Recovery: Return to work. Participates in social and leisure activities a little less and has occasional psychological problems.
8	Upper Good Recovery: Full recovery with no recurring problems relating to the injury.

Adapted from Honeybul et al., 2013

2.6. The Effect of Ageing on TBIs

Physiological changes associated with ageing include increased dural adherence to skull, cerebral atrophy, and cerebrovascular atherosclerosis, elevating risk of cerebrovascular injury and particularly SDH in the elderly population. The increased intracranial space allows for more stretching of bridging veins in response to acceleration/deceleration forces. Furthermore, there is elevated susceptibility to delayed hemorrhagic expansion which can occur days or weeks after initial trauma due to mass effect on brain parenchyma further stretching bridging veins and/or re-bleeding from neovessels formed within the organized wall of the old hematoma membranes (Ashgar et al., 2002). Compared to younger patients, seniors who experience TBI's have longer hospital stays (Pentland et al., 1986), slower rates of functional recovery (Frankel et al., 2006), are more likely to experience delayed neurological decline (Pennings et al., 1993), and have higher mortality rates (Susman et al., 2002). Elderly people also have decreased free radical clearance which amplifies oxidative stress, potentially leading to more neuronal cell death (Thompson et al., 2006). This may also contribute to longer hospital stays and poorer outcomes.

2.7. Antithrombotic Medications

There are two types of antithrombotic medications*; Antiplatelet Agents (AP)*, which decrease platelet aggregation and/or adhesion to stop thrombus *formation*, and *Anticoagulants (AC)*, which inhibit clotting mechanisms to stop thrombosis *progression*. APs are prescribed to prevent the formation of arterial and venous clots in patients at high risk for myocardial infarction and stroke (e.g. personal or family history of cardiovascular disease or infarct, angina, intermittent claudication) or who are post-operative for coronary bypass, angioplasty, or stenting. They are also used to treat acute myocardial infarctions and strokes by reducing further platelet

activation and adhesion. ACs are prescribed to prevent embolus formation secondary to atrial fibrillation (A-fib) or prosthetic heart valves as well as to treat deep vein thrombosis, pulmonary embolism, and myocardial infarction with unstable angina.

Antiplatelet Agents (AP) include:

1. Cyclooxygenase 1 inhibitors (Acetyl Salicylate Acid/ASPIRIN): Acetyl Salicylate Acid (ASA) irreversibly binds and inhibits the enzyme cyclooxygenase (COX) 1 in platelets, blocking the production and release of thromboxane A2 (TXA2), an agent that activates adjacent platelets. Platelets cannot regenerate COX 1 and have a 7-10 day turnover period. In addition to its antiplatelet property, ASA is also used for its analgesic and antipyretic effect. Furthermore, it is the only medication in its class that is available over-the-counter.

   A recent systematic review shows that while ASA use for primary prevention does statistically decrease the risk of nonfatal myocardial infarction, it does not decrease the rate of stroke or all-cause mortality. In addition, the rates of bleeding events with ASA use are consistently elevated in the literature (Brotons et al., 2015; Antithrombotic Trialists' (ATT) Collaboration., 2009). On the other hand, a meta-analysis of eight trials including 25,570 patients on ASA demonstrated a 21% decreased mortality rate from colorectal cancer (Rothwell et al., 2011).

   The Japanese Primary Prevention Project (JPPP) was a clinical trial that included 14,464 individuals aged 60-85 years old who were considered at high risk for thrombo-embolic events as defined by having hypertension, dyslipidemia, or diabetes. Patients were randomized to ASA 100 mg o.d. or no ASA and kept that regimen over a period of

five years before the trial was discontinued. There was no difference in risk of cardiovascular death, myocardial infarction or stroke between these two groups. In this same study, more patients treated with aspirin had intracerebral or subarachnoid hemorrhage (31) than those not receiving aspirin (14) (Ikeda et al., 2014).

2. Thienopyridines/ADP Receptor Inhibitors (Clopidogrel/PLAVIX, Ticlopidine/TICLID): these are orally bioavailable prodrugs. The active metabolite irreversibly binds and inhibits P_2Y_{12} receptors (a G-protein coupled receptor) on platelets. This competes with ADP binding to decrease platelet aggregation. It is the standard of care up to one year after acute coronary syndrome (Yusuf et al., 2001) and elective percutaneous coronary intervention (Steinhubl et al., 2002). It is often co-prescribed with ASA because they have distinct mechanisms of action, maximizing the antiplatelet effect. However, in the elderly population (65 years or older) this combination significantly increased the incidence of major bleeding compared to aspirin alone (Relative Risk = 1.38, 95% CI 1.13–1.67; P=0.001) (Yusuf et al., 2001). A more recent systematic review has confirmed this elevated risk of hemorrhage; the review also demonstrated an overall reduction in myocardial infarction incidence but showed no effect on mortality with respect to lacunar strokes (Palacio et al., 2012).

   Ticagrelor is a *reversible* inhibitor of P_2Y_{12} receptors. It is recommended in preference to clopidogrel in patients with non ST-elevation acute coronary syndrome or segment T elevation myocardial infarction managed with primary percutaneous coronary intervention (Andreotti et al., 2015).

Anticoagulants include:

1. Indirect Thrombin Xa inhibitor (Heparin): Heparin is a sulfated glycosaminoglycan, administered either intravenously (immediate action) or subcutaneously (action in ~60 minutes). It allosterically activates antithrombin III, an endogenous inhibitor of factor Xa and thrombin. There are two formulations of heparin: *unfractionated* and *low molecular weight (LMWH)*. Unfractionated heparin has a longer glycosaminoglycan chain which stabilizes the interaction between antithrombin III and thrombin. In contrast, LMW heparin has a shorter chain and so it cannot stabilize the interaction between antithrombin III and thrombin; only factor Xa is inhibited, leading to a more predictable anticoagulant response. Other advantages of LMW heparin include increased bioavailability and dose-dependent renal clearance which simplifies dosing regimens. LMW heparin has replaced its unfractionated counterpart for most indications unless there is severe renal impairment (Andreotti et al., 2015).

   Heparin use, as well as anticoagulant use in general, elevates the risk of hemorrhage, especially in the elderly population (Hutton et al., 1999). Another important side effect is heparin-induced thrombocytopenia (HIT); IgG antibodies bind to heparin/platelet factor 4 complexes to activate platelets and produce a hypercoagulable state. Thrombosis in HIT is associated with a mortality of approximately 20–30% and an equal percentage of patients becoming permanently disabled by limb amputation or stroke. The highest incidence of HIT has been observed in trauma and post-surgery patients (1-5%) (Linkins et al., 2015; Ahmed et al., 2007). Long-term heparin use is also linked to osteoporosis (Mazziotti et al., 2010).

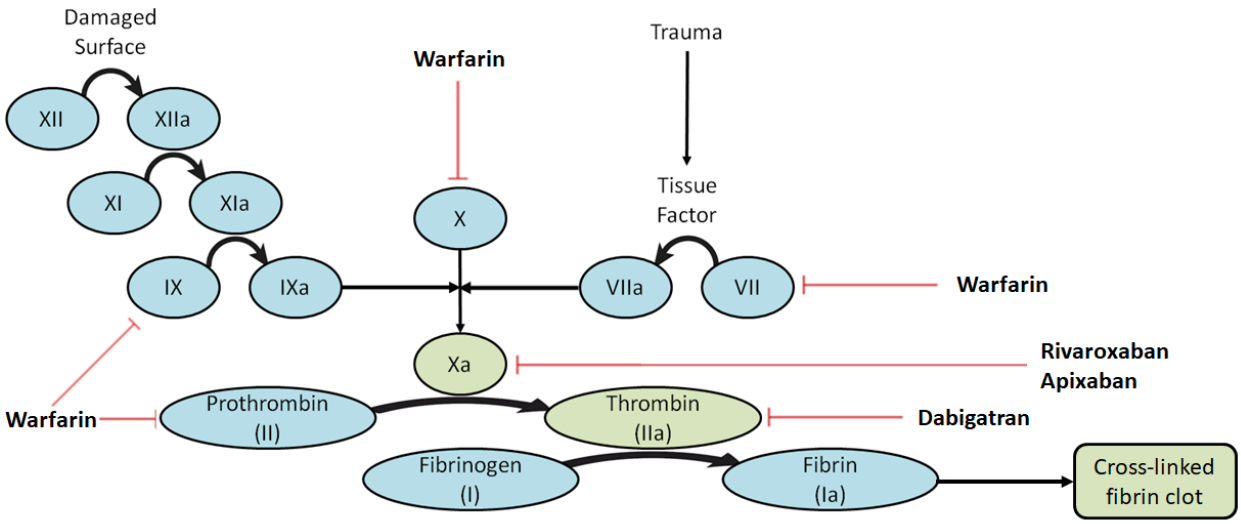
2. Vitamin K Inhibitors (Warfarin/COUMADIN): Warfarin is orally bioavailable, however this route of administration leads to a slower onset of action (days) compared to heparin (<1 hour). It is a competitive inhibitor of vitamin K epoxide reductase (VKORC1), the enzyme that catalyzes the reduction of vitamin K. Reduced vitamin K activates a carboxylase which in turn activates factors II, VII, IX, and X, as well as proteins C and S. The carboxylated forms of these factors and proteins have a higher affinity for platelets than their un-carboxylated forms. Warfarin activity leads to significantly less factor carboxylation and thus fewer assemblies are formed on platelets for fibrin or thrombin synthesis.

    Warfarin has a very narrow therapeutic index and requires monthly monitoring of coagulation profile as measured by the *international normalized ratio (INR)*. Another important consideration is that warfarin has many interactions with common foods and drugs that can further increase the anticoagulation (Nutescu et al., 2011). Newer oral anticoagulants, such as direct factor Xa inhibitors and direct thrombin inhibitors, have been developed specifically to address the shortcomings of warfarin therapy. They do not require INR monitoring. Furthermore, both have been FDA approved for the prevention of stroke and systemic embolism in nonvalvular A-fib patients as well as to prevent and treat deep vein thrombosis and pulmonary embolism. However, a major drawback of newer oral anticoagulants is the lack of a reliable antidote. This is particularly dangerous in the context of intracranial bleeds as the anticoagulant effect can persist for 12-24 hours after the last dose was taken, potentially increasing hematoma volume, elevating the risk of an acute re-bleed, and delaying surgical intervention.

3. Direct Thrombin Inhibitor (Dabigatran Etexilate/PRADAXA): This class of anticoagulants can also be used for the treatment of HIT (Ho et al., 2016). One important consideration is that it is 80% cleared through the renal system, thus the dose must be carefully adjusted in patients with impaired renal function (creatinine clearance <30mL/min).

   The RE-LY trial randomized 18,113 A-fib patients to receive either dabigatran or warfarin for a median follow-up of 2.0 years. Compared to warfarin, dabigatran users were at a significantly lower risk of intracranial bleeds: for 110 mg dose, RR (95% CI) = 0.30 (0.19–0.45), P<0.001 and for 150 mg dose, RR (95% CI) = 0.42 (0.29–0.62), P<0.001. This effect is irrespective of age (Eikelboom et al., 2011).

FIGURE 1: Mechanisms of Action for Anticoagulant Medications



4. Direct Factor Xa Inhibitor (Rivaroxaban/XARELTO, Apixaban/ELIQUIS): They are both mainly eliminated via liver metabolism, bile, and feces; however dose reductions in patients with impaired renal function are recommended (Andreotti et al., 2015). In a

recent randomized crossover study, apixaban demonstrated less intersubject variability in exposure and fewer fluctuations in plasma concentration than rivaroxaban, suggesting a more constant and predictable anticoagulation response (Frost et al., 2014).

ROCKET AF was a double-blinded clinical trial where 14,264 nonvalvular A-fib patients at elevated risk for stroke were randomly assigned either rivaroxaban or warfarin. 44% of the patients in this cohort were 75 years or older. There were significant reductions in intracranial hemorrhage (0.5% vs. 0.7%, P = 0.02) and fatal bleeding (0.2% vs. 0.5%, P = 0.003) in the rivaroxaban group (Patel et al., 2011). Among patients 75 years and older, the findings were similar but not statistically significant (Halperin et al., 2014).

One controversy regarding direct factor Xa inhibitors is that there may be rebound hypercoagulability/thrombosis due to hematological counter-regulatory mechanisms that are not immediately reversed once administration ceases. In the ROCKET AF trial, the number of strokes and non-CNS embolic events was higher following rivaroxaban discontinuation than warfarin discontinuation but this was not a statistically significant difference (Patel et al., 2013).

2.8. Measuring Anticoagulation: The International Normalized Ratio

The international normalized ratio (INR) is used to measure coagulation with warfarin use. It is based on prothrombin time (PT), a blood test whereby tissue factor is added to a patient's plasma and clotting time is measured. PT evaluates the tissue factor/extrinsic pathway. INR = (PTpatient/PTnormal)xISI, where ISI is the international sensitivity index, a value that depends on the particular batch of tissue factor used. In the absence of warfarin therapy, INR

usually ranges from 0.9 to 1.1. The desired range with therapy is 2-3; if higher values are found, the dosage must be adjusted, a dose must be withheld, or reversal therapy with vitamin K must be administered. If INR is <2, use of a booster dose should be considered.

2.9. Reversing Anticoagulation

Table 5: Recommended Reversal Therapy for each Anticoagulant

Anticoagulant	**Reversal Therapy**
Heparin	Protamine Sulfate to bind and inhibit the anticoagulant activity of heparin; dosing depends on whether the formulation is unfractionated or LMW and pTT values Severe/life-threatening bleed: consider recombinant factor VIIa
Warfarin	INR > 10 without serious bleed: hold warfarin and give oral vitamin K and prothrombin complex concentrate (BERIPLEX or OCTAPLEX) Severe/life-threatening bleed: hold warfarin, administer vitamin K slow infusion IV, and give prothrombin complex concentrate
Direct Thrombin Inhibitor & Direct Factor Xa Inhibitor	No specific guidelines exist. If there is no bleeding, holding the medication is usually the only intervention required. If a bleed is suspected, the use of fluid and blood product replacement should be considered. Oral activated charcoal may be used to neutralize ingestion of over-dose quantities if less than 2 hours has passed. Administration of factor replacement may be considered.

(Christos et al., 2016; Thigpen et al., 2013)

Chapter 3: Rationale and Hypothesis

An association between warfarin use and ICH incidence has been clearly demonstrated (Pieracci et al., 2007; Franko et al., 2006; Karni et al., 2001) but results are less clear for other agents. Many studies have shown that AT therapy elevates the risk of mortality with head trauma, however they are inconsistent with regards to which medications are more dangerous (Tollefson et al., 2018; Narum et al., 2016; Grandhi et al., 2015; Peck et al., 2014; Fortuna et al., 2008; Wong et al., 2008; Ivascu et al., 2008; Pieracci et al., 2007; Franko et al., 2006; Ohm et al., 2005; Lavoie et al., 2004). Other studies have been unable to confirm a significant relationship between AT use and elevated rates of ICH and/or mortality (Julien et al., 2016; Cull et al., 2015; Dunham et al., 2014; Ahmed et al., 2009; Kennedy et al. 2000).

Direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, and apixaban, are increasingly replacing warfarin as AC of choice as they do not require monthly monitoring and have shorter half-lives, lower risks of fatal bleeding, as well as fewer drug and food interactions (Andreotti et al., 2015; Halperin et al., 2014; Eikelboom et al., 2011). DOAC use is associated with decreased mortality compared to warfarin use in the context of spontaneous ICH (Inohara et al., 2018), however the benefit of DOAC in the context of traumatic ICH is still unclear (Prexl et al., 2018; Kobayashi et al., 2017; Maung et al., 2016; Pozzessere et al., 2015).

Methodological differences may account for some of these discrepancies. Several investigations only included patients who sustained a traumatic ICH and thus only considered the severity of bleeds but not their elevated incidence as the underlying mechanism precipitating poorer outcomes (Grandhi et al., 2015; Peck et al., 2014; Ahmed et al., 2009; Fortuna et al., 2008; Wong et al., 2008; Ohm et al., 2005; Karni et al. 2001). Others have cohorts consisting

solely of admitted patients, not considering patients with only minor injury (Tollefson et al., 2018; Julien et al., 2016; Cull et al., 2015; Dunham et al., 2014). These studies therefore have a selection bias towards more severe injuries. Furthermore, many studies only investigated the impact of APs without considering the effects of concomitant AC therapy (Cull et al., 2015; Fabbri et al., 2013; Ohm et al., 2005; Ivascu et al., 2008) and vice-versa (Pierracci et al., 2007; Franko et al., 2006; Lavoie et al., 2004; Wojcik et al., 2001; Karni et al., 2001; Kennedy et al., 2000; Ferrera et al. 1999).

We hypothesize that for all elderly patients (65yro+) seen in the ER with head trauma, those taking AT medications will be more likely to sustain a TBI, and that among the TBI patients medication use will lead to more ICHs, hemorrhagic expansion and/or new hemorrhage on follow-up imaging and poorer outcomes (unfavorable discharge destination, functional dependency at discharge and mortality).

Chapter 4: Methodology

4.1. Data Collection

This study was conducted at the Montreal General Hospital, a supraregional level 1 trauma center, and received full approval by the institutional Research Ethics Board (REB 2017-2894). We retrospectively reviewed the electronic medical records of all patients presenting to the emergency room between April 2014 and March 2016 with a history of acute head trauma and aged 65 or older. Exclusion criteria were known coagulopathies and head trauma secondary to hemorrhagic stroke. Admitted head trauma patients were identified through our institutional trauma registry. Non-admitted head trauma patients were identified via the emergency room information system and database, MedUrge, on the basis of patient history and head CT requests.

Each case was reviewed by a neurosurgeon to determine if a TBI was sustained, as per the TBI definition (Menon et al., 2010).

The following data were collected from electronic medical records: age, gender, mechanism of trauma, medical history, use of antithrombotic agents and which ones, International Normalized Ratio (INR) and Partial Thromboplastin Time (pTT) values upon presentation, Glasgow Coma Scale (GCS) score upon presentation, CT scan findings, hospital admission and length of stay, use of reversal therapy, surgical intervention and type of surgery, discharge destination, Extended Glasgow outcome Scale score (GOSE) at discharge (non-admitted patients were classified as functionally independent), and mortality.

As per the Canadian CT head rule, the standard practice is that all patients aged 65 and older, even with only minor head trauma, are at significant risk for neurological intervention and are required to undergo a head CT (Stiell et al., 2001). Thus, all patients in our cohort had head CTs which were reviewed and the findings were validated by institutional radiology reports. We identified whether there was an intracranial hemorrhage (ICH) or not, the type of ICH, be it epidural (EDH), subdural (SDH), subarachnoid (SAH), or intraparenchymal (IPH), and the severity of the bleed as per the Marshall grade, midline shift (cm), SDH width (cm), SDH extent (<3 lobes or ≥3 lobes), SAH pattern (focal or diffuse), and IPH pattern (focal or multifocal). Each follow-up scan was also reviewed to determine if there was ICH progression, defined as hematoma expansion or development of new hemorrhage.

4.2. Statistical Analysis

On univariate analysis, continuous variables were analysed using the T-test and Analysis of Variance (ANOVA) and categorical variables were analysed with the $\chi 2$ likelihood ratio test.

On multivariate analysis, continuous variables were analysed via standard least square models and categorical variables were analysed via multivariable logistic regression models. Age, gender, mechanism of trauma, provenance, and GCS score were all analyzed in relation to each dependent variable via univariate methods to determine if they should be included as covariates in the final multivariate model. Those continuous variables which followed an approximately normal distribution were represented as means with standard deviations. Categorical variables were reported as incidence rates as well as Wald based odds ratios (OR) with 95% confidence interval (CI) whenever the outcome was binary. Significance was defined a priori as a p value of less than 0.05. All statistical analyses were carried out using JMP version 13.0.0 (SAS Institute Inc., Cary, NC, USA).

Chapter 5: Results

5.1. Study Population and Demographics

A total of 1365 patients were identified according to the inclusion criteria over the 24 month period. Of this cohort, 724 (53.0%) were taking oral AT therapy pre-injury and 641 (47.0%) were not (FIG 2). Patient demographics, mechanisms of trauma, clinical information, and outcomes are described in TABLE 6. The underlying cardiovascular conditions and risk factors that prompted the use of antithrombotic therapy in our cohort are detailed in FIGURE 3.

FIGURE 2: Flowchart of medication groups

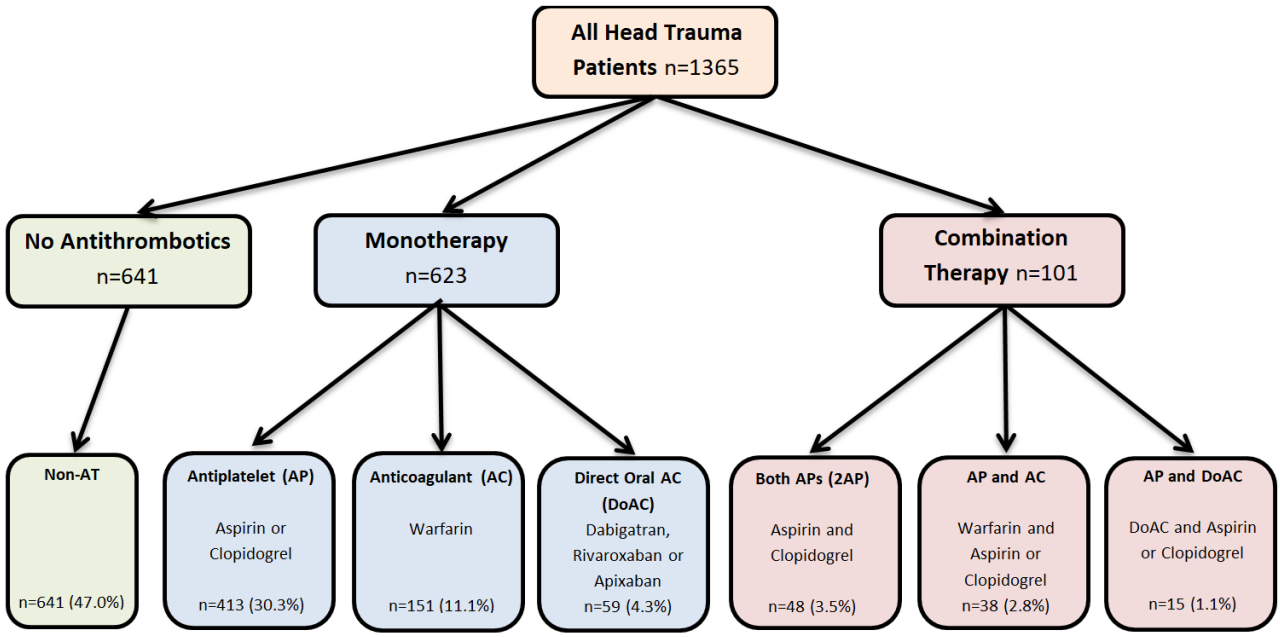
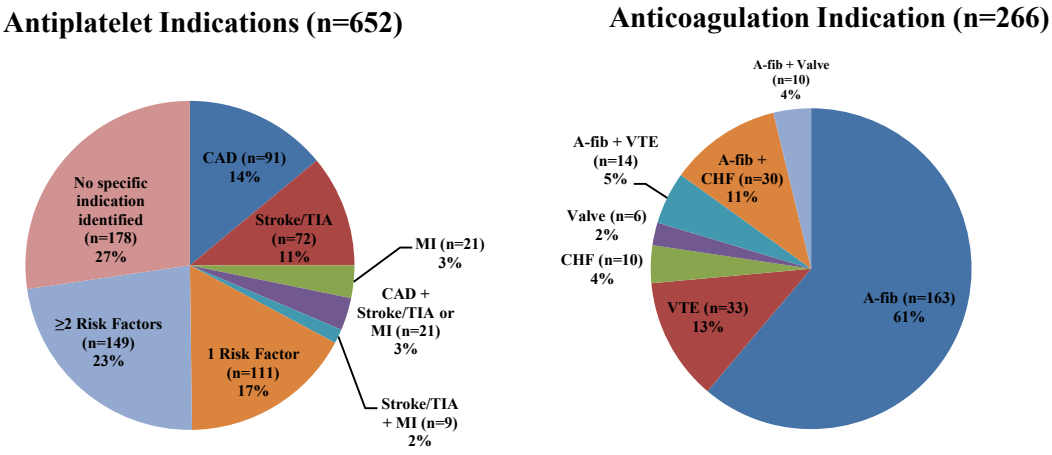


FIGURE 3: Indications for antiplatelet and anticoagulation therapy



CAD = coronary artery disease; TIA = transient ischemic attack; MI = myocardial infarct. Risk factor groups represent patients at risk for CAD/stroke/TIA/MI but who have not developed the disease – those factors included hypertension, dyslipidemia, diabetes mellitus and obesity. A-fib = atrial fibrillation; VTE = venous thrombus embolism (pulmonary embolism or deep vein thrombosis); CHF = congestive heart failure; valve = mechanical valve replacement.

TABLE 6: Demographic and clinical characteristics of all head trauma patients

Demographic/Clinical Characteristic	Total (n=1365)	Non-AT (n=641)	AT (n=724)	P
Age in years, mean (SD)	79.5 (8.1)	78.02 (8.7)	80.9 (7.9)	<0.0001[a*]
Gender, n (%)				0.0006[b*]
- Male	672 (49.2%)	284 (44.3%)	388 (53.6%)	
- Female	693 (50.8%)	357 (55.7%)	336 (46.4%)	
Mechanism, n (%)				<0.0001[b*]
- Fall from own height	993 (77.8%)	426 (66.5%)	567 (78.3%)	
- Fall down stairs	130 (9.5%)	63 (9.8%)	67 (9.3%)	
- Pedestrian/cyclist hit by vehicle	69 (5.1%)	49 (7.6%)	20 (2.8%)	
- Motor vehicle collision	46 (3.6%)	31 (4.84%)	15 (2.1%)	
- Cycling accident	21 (1.5%)	16 (2.5%)	5 (0.7%)	
- Assault	17 (1.2%)	12 (1.9%)	5 (0.7%)	
- Fall from height ≤ 5ft	16 (1.2%)	4 (0.6%)	12 (1.7%)	
- Fall from height = 5-10 ft	12 (0.9%)	5 (0.8%)	7 (1.0%)	
- Fall from height > 10 ft	5 (0.4%)	2 (0.3%)	3 (0.4%)	
- Other	56 (4.1%)	33 (5.1%)	23 (3.2%)	
Provenance, n (%)				<0.0001[b*]
- Directly to trauma center	920 (67.40%)	479 (74.73%)	441 (60.91%)	
- Transfer from external site	445 (32.60%)	162 (25.27%)	283 (39.09%)	
Intl Normalized Ratio, mean (SD)	1.26 (0.64)	1.04 (0.10)	1.42 (0.81)	<0.0001[a*]
Glasgow Coma Scale, mean (SD)	14.1 (2.3)	14.3 (1.8)	13.9 (2.6)	0.0005[a*]
TBI Diagnosis, n (%)				0.0023[b*]
- All TBI	731 (53.6)	315 (49.1)	416 (57.5)	
- Mild TBI (GCS 13-15)	623 (45.6)	280 (43.8)	343 (47.4)	
- Moderate TBI (GCS 9-12)	45 (3.3)	19 (3.0)	26 (3.6)	
- Severe TBI (GCS 3-8)	63 (4.6)	16 (2.5)	47 (6.5)	
Intracranial Hemorrhage, n (%)				<0.0001[b*]
- All types	564 (41.3)	208 (32.5)	356 (49.2)	
- Subdural Hemorrhage	395 (28.9)	144 (22.5)	251 (34.7)	
- Subarachnoid Hemorrhage	238 (17.4)	94 (14.7)	144 (19.9)	
- Intraparenchymal Hemorrhage	151 (11.1)	46 (7.2)	105 (14.5)	
Combination Hemorrhage, n (%)	200 (35.5)	68 (32.7)	132 (37.1)	0.2921[b]
CT Marshall Grade, mean (SD)	1.9 (1.4)	1.7 (1.3)	2.1 (1.5)	<0.0001[a*]
Hospital Admission, n (%)	437 (32.0)	165 (25.7)	272 (37.6)	<0.0001[b*]
Surgical Intervention				0.0093[b*]
- All types	144 (10.6)	54 (8.4)	90 (12.4)	
- Burr hole	78 (5.7)	38 (5.9)	40 (5.5)	
- Craniotomy	46 (3.4)	11 (1.7)	35 (2.6)	
- Craniectomy	20 (1.5)	5 (0.4)	15 (2.1)	
Discharge Home, n (%)	926 (67.8)	492 (76.8)	434 (59.9)	<0.0001[b*]
GOSE ≤ 4 at discharge, n (%)	228 (16.7)	68 (10.6)	160 (22.1)	<0.0001[b*]
Mortality, n (%)	84 (6.2)	19 (3.0)	65 (9.0)	<0.0001[b*]

*Statistically significant difference ($p \leq 0.05$)

[a]Compared using T-Test

[b]Compared using $\chi 2$ Likelihood Ratio Test

5.2. Initial Presentation: TBI Diagnosis, TBI Severity and Intracranial Hemorrhage

Of the 1365 head trauma patients presenting to our emergency room, 731 (53.6%) were diagnosed with a traumatic brain injury (TBI). On univariate analysis, medication group was significantly correlated to TBI diagnosis ($p<0.0001$). Among the TBI patients, the mean GCS score was lower for those on antithrombotics (13.2, SD 3.3) than those who were not (13.8, SD 2.4) ($p=0.0052$). Furthermore, the proportion of antithrombotic users with TBI whose injury was categorized as severe (GCS 3-8) was more than double that of non-users (11.3% vs 5.1%, $p=0.0090$). However, there weren't any between-group differences among the medication categories for either GCS score or TBI severity.

When adjusting for age, gender, mechanism of trauma, and provenance, pre-injury AT group was still a significant predictor of TBI diagnosis among head trauma patients who presented to the emergency room ($p=0.0035$). Antiplatelet use was associated with significantly elevated risk of TBI compared to the non-AT group, both with a single agent or the aspirin and clopidogrel combination. The use of an anticoagulant alone, either warfarin or a DoAC, was not associated to TBI risk (TABLE 2). Medication group was not significantly associated to GCS score or to TBI severity when adjusting for covariates.

Intracranial hemorrhage (ICH) was more prevalent with TBI patients on AT therapy than those not on therapy (85.6% vs 65.7%, $p<0.0001$) with significant between-group differences ($p<0.0001$) on univariate analysis. In the same comparison, there was a significantly elevated incidence of subdural hemorrhage (SDH; 60.3% vs 45.7%, $p<0.0001$) and intraparenchymal hemorrhage (IPH; 25.2% vs 14.6%, $p=0.0004$) as well as between-group differences for both (SDH; $p=0.0002$, IPH; $p=0.0137$). Antithrombotic use was not correlated to subarachnoid hemorrhage or combination hemorrhage (2 or more types) incidence on univariate models.

When adjusting for age, gender, mechanism of trauma, provenance, and GCS score, differences between pre-injury AT group continued to be a significant predictor of ICH (p=0.0006). Compared to non-users, the risk of sustaining an ICH with TBI was elevated for single AP users and for warfarin users, and ten-fold higher for patients on both an antiplatelet and warfarin (TABLE 7). Pre-injury AT use continued to be significant predictor of SDH (p=0.0145) and IPH (p=0.0176), however the between-group differences were non-significant.

TABLE 7: Multivariate Analysis of TBI diagnosis and Hemorrhage by Medication Group

Medication Group	TBI in head trauma patients presenting to ER				Risk of ICH with TBI			
	Incidence (%)	OR	95% CI	p	Incidence (%)	OR	95% CI	p
None	49.1	-	-	-	65.7	-	-	-
AP	57.7	1.42	1.05-1.92	0.0238*	81.8	2.07	1.29-3.31	0.0027*
AC	52.7	1.07	0.69-1.65	0.7641	91.1	3.89	1.60-9.45	0.0027*
AP AC	73.7	1.68	0.70-4.05	0.2483	96.4	10.32	1.30-82.09	0.0274*
2AP	77.1	2.39	1.06-5.40	0.0366*	89.2	2.12	0.64-7.00	0.2176
DOAC	41.3	0.56	0.52-2.24	0.0924	91.7	3.60	0.71-18.34	0.1229
AP DOAC	86.7	6.45	1.27-32.80	0.0247*	69.2	0.89	0.21-3.79	0.8735

*Statistically significant difference ($p \leq 0.05$)

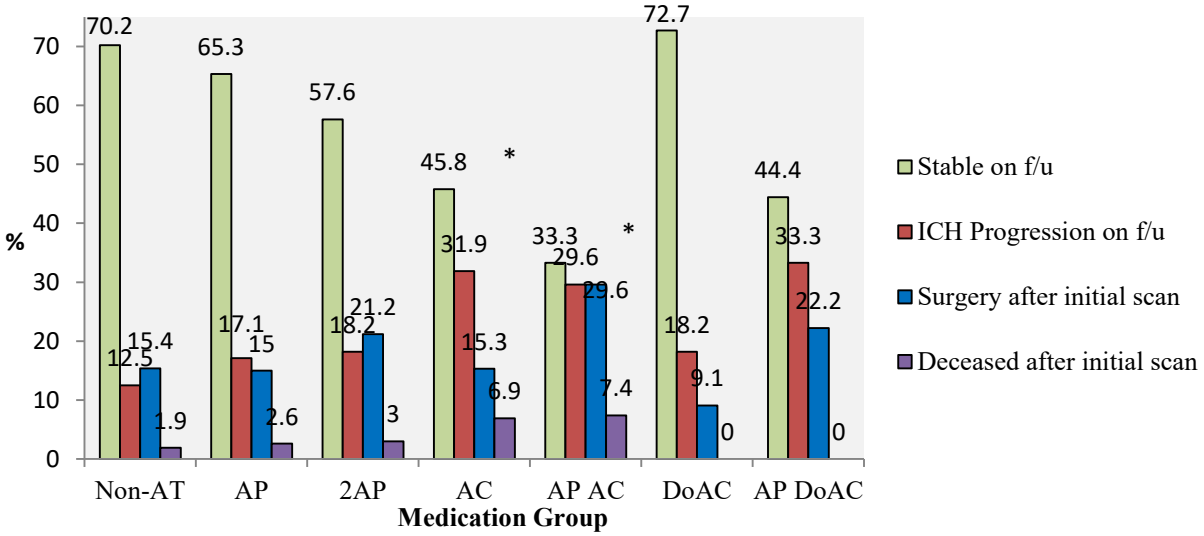
When adjusting for the same covariates, pre-injury AT group was not a predictor of any measure of ICH severity; marshall grade in CT scans, midline shift, SDH width (cm), SDH extent (<3 lobes or ≥3 lobes), SDH bilateralness, SAH pattern (focal vs diffuse), and IPH pattern (single vs multiple hemorrhages).

5.3. Hemorrhage Progression

Of the 564 cases where ICH was identified on CT scan, 353 (62.6%) remained stable on follow-up imaging, 102 (18.1%) showed progression of ICH on follow-up imaging either as an expansion of an existing hematoma or a new hemorrhage, 91 (16.1%) required surgical intervention immediately after the initial scan, and 17 (3.0%) died after the initial scan. Comparing ICH patients on pre-injury AT therapy to those who were not, more AT patients showed ICH progression on follow-up scan (21.6% vs 12.5%), were taken to the operating room

immediately after the initial scan (16.6% vs 15.4%,) or died after the initial scan (3.7% vs 1.9%) (p=0.0126). The incidences for each medication group are detailed in FIGURE 4. Between-group differences with respect to ICH progression category were statistically significant on multivariate analysis (p=0.0094). A subset analysis of all patients with ICH who were not deceased and did not require surgical intervention before follow-up CT scan showed that warfarin use, but not AP only or DOAC use, was a significant predictor of ICH progression, both as monotherapy [OR 5.30, 95% CI 2.48-11.31, p<0.0001] and in combination with an AP [OR 6.15, 95% CI 2.07-18.26, p=0.0011].

FIGURE 4: ICH Progression Categories



*Statistically significant difference (p≤0.05)

5.4. Surgical Intervention

On univariate analysis, antithrombotic users who sustained a TBI had a higher but non-significant rate of surgery than non-users with TBI (21.6% vs 17.1%, p=0.1286). However, of those who did undergo surgery, AT users had a statistically higher rate of craniotomies (39.9% vs 20.4%) and craniectomies (16.7% vs 9.3%) compared to the less invasive burr holes (44.4% vs 70.4%) (p=0.0093), with significant between-group differences among the medication

categories (p=0.0239). Provenance and GCS score were both unadjusted predictors of type of surgery and thus applied as covariates in the multivariate model, after which pre-injury AT use continued to be a significant predictor of type of surgery (p=0.0322). However, the between-group differences were non-significant.

5.5. Outcomes: Discharge Destination, Neurological Disability and Mortality

Among the TBI patients, those on ATs were compared to those not on therapy and were found to be less likely to be discharged home (33.7% vs 55.6%), more likely to suffer poorer function outcomes as defined by GOSE≤4 at discharge (38.0% vs 20.6%) and had more than double the mortality rate (15.4% vs 5.7%) (p<0.0001). There were significant between-group differences for each outcome (p<0.0001). Age, gender, mechanism of trauma, provenance, GCS score, and medication group were all unadjusted predictors of each outcome and applied as covariates in the multivariate models (TABLE 8 and TABLE 9). On multivariate analysis, pre-injury medication group was a significant predictor of discharge destination (p=0.0002), GOSE ≤4 (p<0.0001) and mortality (p=0.0003) in TBI patients. Associations of demographics and clinical characteristics to in-hospital mortality are described in TABLE 8.

All non-DoAC groups were significantly less likely to be discharged home; compared to non-AT patients, AP and AC TBI patients were approximately half as likely [AP OR 0.64, 95% CI 0.23-0.81, p=0.0293; AC OR 0.44, 95% CI 0.23-0.81, p=0.0093] and the combination groups were approximately 1/5 as likely [2AP OR 0.21, 95% CI 0.08-0.56, p=0.0018; AP+AC OR 0.18, 95% CI 0.06-0.56, p=0.0029]. These groups were also predictors of discharge with GOSE≤4; the risk of this outcome was particularly high with AP+AC combination therapy compared to non-users [OR 6.42, p<0.0001] (TABLE 9).

TABLE 8: Multivariate Analysis of In-Hospital Mortality among TBI Patients

Variable	OR	95% CI	p
Age, per year	1.04	1.01-1.08	0.0230*
Male sex	1.48	0.81-2.71	0.1968
Provenance – Trauma Center	2.16	1.18-3.70	0.0129*
GCS Score, per pt lost	1.40	1.35-1.46	<0.0001*
Pre-injury AT use	2.05	1.38-3.04	0.0003*
SDH	1.69	0.92-3.14	0.0931
- ≥3 vs <3 lobes	1.83	0.83-4.03	0.1350
SAH	2.21	1.24-3.93	0.0071*
- Diffuse vs Focal	4.15	1.89-9.12	<0.0001*
IPH	3.49	1.89-6.45	<0.0001*
- Multifocal vs Focal	1.20	0.38-3.82	0.7556
Marshall score, per pt	1.84	1.52-2.24	<0.0001*
ICH Progression[1]	4.62	2.12-10.03	<0.0001*
Length of Stay, per day[2]	0.97	0.95-0.99	0.0028*

[1]Subset analysis on patients with ICH who were not deceased and did not require surgical intervention before follow-up CT scan (n=456)
[2]Subset analysis on admitted patients (n=437)
*Statistically significant difference (p≤0.05)

TABLE 9: Multivariate Analysis of Outcomes of TBI Patients by Medication Group

Medication Group	Functional Dependency (GOSE ≤4) at Discharge				Mortality (GOSE=1)			
	Incidence (%)	OR	95% CI	p	Incidence (%)	OR	95% CI	p
None	20.7	-	-	-	5.7	-	-	-
AP	32.6	1.60	1.02-2.51	0.0404*	11.9	2.04	0.95-4.37	0.0665
AC	46.8	2.90	1.59-5.31	0.0005*	22.8	5.81	2.38-14.19	0.0001*
AP AC	60.7	6.42	2.59-15.91	<0.0001*	17.9	3.67	1.02-13.26	0.0470*
2AP	48.7	3.35	1.52-7.40	0.0028*	21.6	5.46	1.79-16.65	0.0029*
DOAC	25.0	0.95	0.31-2.93	0.9298	20.8	6.20	1.21-13.94	0.0064*
AP DOAC	23.1	0.76	0.15-3.71	0.7322	0	-	-	-

*Statistically significant difference (p≤0.05)

The use of a single antiplatelet agent (aspirin or clopidogrel) was not a significant predictor of mortality, however the combination of both aspirin and clopidogrel was [OR 5.46, p=0.0029]. The AC, AP AC and DoAC groups all also had significantly higher risk of death when compared to nonusers. Surprisingly, the odds were higher in patients taking warfarin alone [OR 5.81, p=0.0001] compared to warfarin and an antiplatelet [OR 3.67, p=0.0470]. The monotherapy group had a higher mean INR (2.43, SD 0.09) than the combination group (2.18, SD 0.18), however this was a non-significant difference when these two groups were directly

compared (p=0.2168). DOAC use was also associated with mortality and is comparable to warfarin use. There were no deaths in the small AP DoAC group (n=13) (TABLE 9).

5.6. Reversal Therapy

Of the patients on antithrombotic therapy, 137 (18.9%) received reversal therapy (platelets for antiplatelet reversal; Vitamin K, prothrombin complex concentrate, fresh frozen plasma for anticoagulation reversal), 235 (32.5%) had their medication held, and 352 (48.6%) were not held or reversed. Reversal therapy was most frequently employed when the patient was on warfarin pre-injury, either alone or in combination with an antiplatelet (TABLE 10). Reversal therapy was associated to a higher mean Marshall score [3.3 (SD 1.7) vs 3.0 (SD 1.5) for hold and 2.5 (SD 1.7) for none; p=0.0004] as well as elevated rates of ICH progression [29.3% vs 21.5% for hold and 18.0% for none; p=0.0061) and mortality [22.6% vs 14.9% for hold and 11.2% for none; p=0.0355], reflecting its higher likelihood of use with critical hemorrhages compared to milder ones. When stratifying by each medication group, reversal category was not associated to any variables.

TABLE 10: Reversal categories for medication groups

Category	AP	AC	AP AC	2AP	DoAC	AP DoAC
None, n (%)	247 (59.8)	31 (20.5)	5 (13.2)	16 (33.3)	33 (55.9)	7 (46.7)
Hold, n (%)	144 (34.8)	22 (22.8)	11 (28.9)	25 (52.1)	19 (32.2)	5 (33.3)
Reversal, n (%)	22 (5.3)	76 (50.3)	22 (57.9)	7 (14.6)	7 (11.9)	3 (20.0)

Chapter 6: Discussion

6.1. Overview of Findings

In the current study, pre-injury AP use leads to higher rates of TBI among the head trauma patients who presented to the ER. Of the patients who sustained a TBI, those taking AT medications were more likely to sustain an ICH and that risk was notably high for patients on both an antiplatelet and warfarin. The initial ICHs were not more severe for the therapy groups compared to the non-therapy group; however, the odds of hemorrhagic expansion or new hemorrhage on follow-up scan were significantly elevated with warfarin use. AT patients who sustained a TBI had higher rates of admission, more invasive surgical interventions, discharge to a long-term care facility, discharge in a state of functional dependency, and mortality.

6.2. The Role of Mechanism of Injury

A larger proportion of AT patients presented to the ER with head trauma following a fall from their own height, the least severe mechanism of injury, compared to non-AT patients (78% vs 67%, $p<0.0001$), which is consistent with similar studies (Tollefson et al., 2018; Prexl et al., 2018; Narum et al., 2016; Maung et al., 2016; Peck et al., 2014). This suggests that seniors on these medications who fall may sustain more severe head injuries requiring medical intervention than those who are not. Furthermore, while more patients in the AT group sustained injury from low kinetic mechanisms, they had higher rates of TBIs (58% vs 49%, p=00023) and ICHs (49% vs 33%, $p<0.0001$) compared to non-AT patients. This is likely attributable to both the antithrombotic activity of the medications as well as the age and health of patients in this group. AT users were on average three years older than non-users (81 vs 78 yo) and had more

cardiovascular risks and diseases necessitating AT use. Thus, more advanced cerebral atrophy and poorer cerebral reserves are probable contributing factors to this finding.

6.3. The Severity of TBI upon Initial Presentation

There was no difference in severity of the TBIs upon initial presentation for any medication group. Presence of ICH is a diagnostic criterion for TBI, thus ATs produce more TBIs by increasing the likelihood of ICHs with trauma. Many patients with ICH, particularly those with minor bleeds, present either asymptomatically or with minor neurological perturbations. As such, those TBIs are classified as "mild" per the GCS scale. TBI severity not varying significantly across medication groups is consistent with ICH severity also not varying significantly.

6.4. The Risk of Intracranial Hemorrhage

An association between warfarin use and ICH in head trauma patients has been clearly demonstrated in previous studies (Dossett et al., 2011; Pieracci et al., 2007; Franko et al., 2006; Karni et al., 2001). The current study replicates this finding and provides evidence that antiplatelet use also elevates ICH risk when there is a TBI. While no differences in the severity of the initial bleeds were found among the different groups, pre-injury warfarin use was associated to significantly higher rates of radiological changes on follow-up scans compared to non-users. Similarly, warfarin use, but not AP use, was significantly correlated to radiological changes compared to non-users in Tollefson et al. (40% vs 11%; p=0.004) and Peck et al. (adjusted relative rate ratio [aRRR], 3.23; 95% confidence interval [CI], 1.21-8.62; p = 0.02) (Tollefson et al., 2018; Peck et al., 2014). Grandhi et al.'s analysis of 1552 patients with traumatic ICH also reported higher rates of hemorrhage progression among warfarin users

compared to non-users (34% vs 23%), however this relationship was non-significant on multivariable analysis (p=0.43) (Grandhi et al., 2015).

6.5. Surgical Intervention and Discharge Destination

Our finding that pre-injury AT use does not predict if surgical intervention will be required is consistent with similar studies (Prexl et al., 2018; Grandhi et al., 2015; Wong et al., 2008). However, we demonstrated that among those who required surgery, pre-injury AT use elevates the rates of the more invasive procedures, craniotomies and craniectomies, used to remove acute, thick blood, compared to burr holes, used to evacuate chronic, thinner blood. Our finding that AT users are less likely to be discharged home and have higher rates of transfer to long-term care facilities compared to non-users has been consistently reported in the literature (Peck et al., 2014; Fortuna et al., 2008; Ahmed et al., 2009; Wong et al., 2008; Karni et al., 2001).

6.6. The Risk of Neurological Disability

In the current study, both AP and warfarin use were associated to a higher likelihood of functional dependency (GOSE≤4) at discharge and the combination of both produced a six-fold risk compared to non-users. Julien et al.'s analysis of 982 TBI patients also used GOSE score at discharge as an outcome measure and likewise found that AT use was associated with poor functional outcomes; however this effect was only significant for partial thromboplastin time (PTT) values reaching 60 and above (Julien et al., 2016). A limitation of that study is that they did not report the individual effects of AP or AC use. Tollefson et al. found that in a prospective cohort of 184 moderate to severe TBI patients, functional dependency among survivors (GOSE

2-4) at 6 months post-injury was significantly correlated to warfarin use (OR 5.61, 95% CI 1.77-17.75, p=0.003) but not AP use (OR 1.88, 95% CI 0.81-4.35, p=0.141) (Tollefson et al., 2018).

6.7. The Risk of Mortality

Several studies have demonstrated that among patients who sustained a traumatic ICH, those who were on warfarin preinjury, but not those who were on a single AP preinjury, were at higher risk of in-hospital mortality compared to non-users (Tollefson et al., 2018; Narum et al., 2016; Grandhi et al., 2015; Bonville et al., 2011; Fortuna et al., 2008). Our analysis which included all patients who sustained a TBI and not ICH specifically yielded the same result, with the addition that patients on both AP agents (aspirin and clopidogrel) preinjury also had higher rates of mortality. In contrast, Peck et al.'s study on 353 patients with traumatic ICH found that AP users, but not warfarin users, had higher rates of in-hospital mortality compared to non-users in spite of warfarin use being the key predictor of hemorrhage progression or new hemorrhage on follow-up scan (Peck et al., 2014).

In the current study, the rates of ICH and mortality were comparable between the warfarin and DOAC groups, although the effect on ICH was non-significant for DOACs. Several large studies have also shown no significant difference in ICH rate or mortality when comparing preinjury warfarin use to preinjury DOAC use in the context of trauma (Kobayashi et al., 2017; Maung et al., 2016; Pozzessere et al., 2015). In contrast, the report by Prexl et al. on 186 TBI patients found that while there was a higher incidence of ICH progression in their warfarin group than their DOAC group (59.4% vs 24.2%, p=0.023), as it is in the current study, the mortality rate was also higher with warfarin (22% vs 3%, p=0.047) (Prexl et al., 2018). However, their analysis was univariate only.

6.8. The Role of Reversal Therapy

Consistent with previous studies, reversal therapy was most often employed to reverse warfarin anticoagulation and sparsely used to reverse antiplatelet activity or anticoagulation by other agents, likely due to the immediacy and reliability of vitamin K and factor replacement in warfarin-anticoagulated patients (Prexl et al., 2018; Kobayashi et al., 2017). Neither antiplatelet reversal (platelet transfusion) nor anticoagulation reversal (prothrombin complex, fresh frozen plasma and/or vitamin K) improved outcomes, as commonly reported (Kobayashi et al., 2017; Grandhi et al., 2015; Fortuna et al., 2008; Ivascu et al., 2008; Karni et al., 2001). A potential reason for this is that there is variability with respect to criteria and timing of reversal therapy administration both between and within hospitals (Pandya et al., 2018; Gulseth et al., 2016; Christos et al., 2016; Le Roux et al., 2014). Antidotes for DOACs, such as idarucizumab, were not available during the study period.

One study that showed a protective effect of warfarin reversal was Ivascu et al., whereby the rates of ICH progression and mortality among warfarin-anticoagulated patients with traumatic ICH were low (11% and 10% respectively) using a protocol where rapid confirmation of ICH with expedited head CT scan was followed by immediate reversal (Ivascu et al., 2005). It is important to note that the sample size for that particular study was small (n=19). Pandya et al.'s study on 276 traumatic ICH patients on preinjury AP therapy reported that those who did not develop ICH progression on follow-up scan had a shorter average time to platelet transfusion compared to those who did (319 vs 354 minutes from hospital presentation), however the effect was non-significant (p=0.44) (Pandya et al., 2018).

6.9. The Mechanistic Role of Antithrombotic Agents

One point of debate is whether poorer outcomes following trauma among AT users are due to the medications per se or the underlying medical conditions (Dossett et al., 2011). The fact that rates of ICH and ICH progression were elevated among AT users compared to nonusers suggests a mechanistic role of ATs in outcomes. However, we must also consider that AT users tend to be older and thus have more cerebral atrophy, which also predisposes ICHs. Previous studies on the effect of warfarin in head trauma corroborate the mechanistic role, reporting that the risk of mortality increases with increasing degrees of anticoagulation as measured by INR values (Pierracci et al., 2007; Franko et al., 2006).

6.10. Antithrombotic Therapy Benefits vs Risks and Recommendations

There is significant variability with respect to which patients are prescribed ATs and during what time-frame (Vandiver et al., 2018; Coccheri et al., 2017; So et al., 2016; Caterina et al., 2014). This is due in part to the individualized needs of patients as well as the lack of re-evaluation at regular intervals (Vandiver et al., 2018). By comparing the benefits of AT therapy to its risks, we can consider the following recommendations as a general framework for their use.

While the net clinical benefit of aspirin use in patients with cardiovascular disease is clear, its value in primary prevention remains controversial (Brotons et al., 2015; Ikeda et al., 2014; Antithrombotic Trialists' (ATT) Collaboration., 2009). Yet, aspirin continues to be frequently prescribed to low-risk populations (Coccheri et al., 2017). Among the patients in our cohort who sustained a TBI, those taking an AP had elevated rates of ICH and functional dependency at discharge compared to non-users. In patients at low risk for cardiovascular disease, stroke or myocardial infarction, antiplatelet use for primary prevention is not

recommended. Modest benefits for patients at high risk have been shown in some trials (Brotons et al., 2015), however this must be carefully weighed against each individual patient's risk of fall. The combination of both aspirin and clopidogrel is appropriate following percutaneous coronary intervention in acute coronary syndrome patients for up to 12 months, depending on bleeding and/or trauma risks (Bavishi et al., 2017).

The POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) trial was a large prospective study that compared dual antiplatelet therapy to monotherapy in acute secondary prevention of recurrent ischemic events (stroke or myocardial infarction) for stroke patients. 4881 acute minor ischemic stroke patients or high-risk TIA patients were treated within 12 hours of symptom onset and were kept on the therapy for 90 days. During the first 30 days of treatment, dual antiplatelet therapy significantly reduced the chance of recurrent ischemic event compared to monotherapy (5% for 2AP, 6.5% for 1AP, HR 0.75 [95% CI, 0.59–0.95], P=0.02) (Johnston et al., 2018). In a trial that recruited patients up to 3 months post-TIA/stroke with treatment and follow-up of 18 months, no benefits of dual therapy over monotherapy were demonstrated (Diener et al., 2004). Similarly, another trial which recruited patients up to 6 months post-stroke with a mean follow-up duration of 3.4 years also failed to show a significant reduction of ischemic events with dual therapy (Palacio et al., 2012). In the current study, we demonstrate that patients on two antiplatelet agents had much higher risks of neurological disability and mortality than those on a single agent. Therefore, dual antiplatelet intervention may be appropriate for secondary prevention in stroke patients who are not at high risk for trauma and should be started shortly after symptom onset, be confined to the first month, then be transitioned to monotherapy.

The combination of antiplatelet and anticoagulation therapy is frequently utilized in spite of the lack of appropriate indication (Caterina et al., 2014). This combination is usually recommended in patients with mechanical cardiac valves as well as A-fib patients who have undergone percutaneous coronary intervention and/or had an acute coronary syndrome within the last year. The combination is generally not indicated for primary prevention of stable coronary artery disease, peripheral artery disease or stroke, nor should it be used for A-fib without additional indications for antiplatelet therapy (Vandiver et al., 2018). In patients with both A-fib and either coronary artery disease or diabetes mellitus, AP+AC therapy does not significantly reduce the risk of ischemic events compared to anticoagulation alone, but it does elevate the risk of major bleeding (So et al., 2016).

This study demonstrated that patients on AP+AC who sustained a TBI had considerably higher rates of ICH, ICH progression and neurological disability at discharge compared to those on AC alone. As such, if more than one year has elapsed since an A-fib patient has had a stent insertion or acute coronary syndrome, the antiplatelet agent should, in most cases, be discontinued. Likewise, if A-fib develops in a patient already taking aspirin or clopidogrel for primary prevention of ischemic events, discontinuation of the antiplatelet therapy is recommended if an anticoagulant is prescribed. In more complex cases that don't clearly fit the inclusion/exclusion criteria, careful clinical judgment should be exercised before prescribing this combination with a thorough assessment of the patient's fall or trauma risk.

DOACs are at least as effective as warfarin in preventing thromboembolic events in patients with A-fib, history of venous thromboembolism or bio-prosthetic heart valves (Lowenstern et al., 2018; Abdulaali et al., 2017; Avezum et al., 2015), however they have been shown to be less effective for patients with a mechanical heart valve (Eikelboom et al., 2013).

Based on our work and the findings of others, rates of ICH and mortality are similar between TBI patients taking DOACs and those taking warfarin (Kobayashi et al., 2017; Maung et al., 2016; Pozzessere et al., 2015). Furthermore, we found that DOAC users had lower rates of ICH progression and functional dependency at discharge than warfarin users in the context of head trauma. As more antidotes for reversal of DOAC anticoagulation are being developed and become readily available, the prognosis of TBI patients on DOACs is expected to improve (Pollack et al., 2017). Thus, DOACs are an effective and safe alternative to warfarin in most patients requiring anticoagulation, except for those with a mechanical heart valve or who have seriously impaired renal function (Lutz et al., 2017).

6.11. Limitations

Some limitations in the current study should be noted. As this study is retrospective, the classification of medication groups is based on self-reporting and completeness of electronic medical records. Thus, some AT users may have been misclassified as non-users, meaning the true effects of ATs may be underestimated. We also did not have exhaustive data on patient characteristics, such as co-morbidities or premorbid functional status, which are important contributing factors to the outcomes. Platelet function assays and thrombelastogrophies were not routinely performed and thus we were unable to confirm or measure the degree of platelet activity among AP users. Furthermore, the AP/DOAC combination had a very small sample population (n=15) compared to the other groups and so results pertaining to that group should be interpreted with caution. Finally, the present study only reports on outcomes at discharge in the present study; significant functional recovery as measured by GOSE can be observed up to 12 months post-injury (Sandhaug et al., 2015). Conversely, some patients may deteriorate if they develop chronic SDHs, for which pre-injury AT therapy is a risk factor (Rust et al., 2006).

Chapter 7: Conclusion

Head trauma patients presenting to the ER were more likely to be diagnosed with a TBI if they were on AP therapy pre-injury compared to other or no ATs. While both AP monotherapy and warfarin groups (alone and in combination with an AP) were associated with significantly elevated odds of sustaining an ICH among TBI patients, only warfarin use was a predictor of hemorrhage progression on follow-up scans. The use of a single AP was not associated with mortality, however anticoagulation therapy and the combination of both aspirin and clopidogrel were. Patients on DOAC therapy were significantly less likely to have hemorrhage progression on follow-up scan and be functionally dependent at discharge compared to those on warfarin, however the overall mortality rates were similar. Further study is required to determine if DOACs are safer than warfarin and if reversal therapy is beneficial in the context of head trauma.

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