

Timing of Agent Resumption and Therapeutic Targets in the Pathophysiology of Traumatic Brain Injuries

Abdurrahman F. Kharbat^{1§}, Drashti Patel^{2§}, Kiran Sankarappan³, Raja Al-Bahou², Faisal Alamri⁴, Anjali Patel², Rajvi Thakkar², Ryan D. Morgan⁵, Kishore Balasubramanian³, Brandon Lucke-Wold^{*6} 

¹Department of Neurosurgery, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA.

²College of Medicine, University of Florida, Gainesville, FL, USA.

³College of Medicine, Texas A and M University, Houston, TX, USA.

⁴King Salman Hospital, Riyadh, Kingdom of Saudi Arabia.

⁵Division of Neurosurgery, Texas Tech University Health Sciences Center, Lubbock, TX, USA.

⁶University of Florida, Department of Neurosurgery, Gainesville, Florida, USA.

§A.K. and D.P. contributed equally to this paper.

Correspondence to: Brandon Lucke-Wold, University of Florida, Department of Neurosurgery, Gainesville, Florida, USA.

Received date: March 28, 2024; **Accepted date:** April 05, 2024; **Published date:** April 15, 2024

Citation: Kharbat AF, Patel D, Sankarappan K, et al. Timing of Agent Resumption and Therapeutic Targets in the Pathophysiology of Traumatic Brain Injuries, *IJMRS @ PubScholars Group* 2024;1(3):10-19

Copyright: ©2024 Kharbat AF, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

ABSTRACT

An estimated 69 million people worldwide suffer from traumatic brain injuries each year. Direct head trauma can cause traumatic brain hemorrhage, which can be life-threatening if not treated quickly. Current studies suggest the use of antithrombotic therapy for treatment, but the optimal duration of such therapy in neurosurgery remains controversial. This article critically reviews recommendations regarding the ideal timing of antiplatelet and anticoagulant therapy for diseases such as subarachnoid hemorrhage, subdural hematoma, skull fractures, brain contusions, and diffuse axonal injury. Additionally, the role of these agents in the context of prosthetic valves and stents will be examined, and their effects on bleeding time and platelet aggregation will be evaluated. This review highlights possible directions for future research in this area and highlights the limitations inherent in the current literature. In the case of hemorrhage in TBI, the standard of care is to resume appropriate AAT at intervals to reduce the risk of ICH, but timing and treatment vary among clinicians. Various studies have shown that restarting AAT reduces the long-term risk of thrombotic events and ischemic stroke. However, this benefit should be weighed against the risk of developing ICH if AAT is restarted too soon. Timing of resumption of AAT should be determined based on multidisciplinary risk stratification considering patient risk factors and comorbidities that may predispose to thromboembolic complications due to prolonged discontinuation of AAT cessation.

Keywords:

Traumatic brain injury, Subarachnoid hemorrhage, Subdural hematoma, Aspirin, Clopidogrel, Antiplatelet and anticoagulant therapy.

Abbreviations:

TBI: Traumatic Brain Injury; SAH: Subarachnoid Hemorrhage; SDH: Subdural Hematoma; DAI: Diffuse Axonal Injury; ICH: Intracranial Hemorrhage; AAT: Antiplatelet and Anticoagulant Therapy; CT: Computerized Tomography; CATE: Secondary Cardiogenic Arterial Thromboembolism; DAPT: Dual Antiplatelet Therapy; CFR: Cyclic Flow Reduction; NOAC: Novel Oral Anticoagulants; DOAC: Direct Oral Anticoagulants

Introduction

Traumatic brain injury (TBI) refers to a devastating and complex medical condition that can cause death or severe disability [1]. TBI typically arises from direct physical trauma to the head, and it is alarmingly prevalent, with an estimated 69 million individuals worldwide suffering from TBI annually. Individuals in Asia and the Western Pacific experience the greatest burden of disease, including more severe symptoms and an increased mortality rate; however, Europe and North America have the highest number of recorded TBI cases [2].

Traumatic brain bleeds can occur in TBI due to various mechanisms, such as blunt force trauma, penetrating injuries, or acceleration-deceleration forces, leading to damage to the brain vasculature [3]. When traumatic brain hemorrhage occurs in association with traumatic brain injury, treatment of these injuries becomes even more complex. Two examples of traumatic brain hemorrhage commonly seen in TBI patients are subarachnoid hemorrhage (SAH) or subdural hematoma (SDH) [4]. SAH is most commonly caused by TBI, and traumatic SAH can lead to progressive neurological deterioration and increased patient morbidity and mortality [5]. Similarly, SDH is another possible consequence of TBI. 11% of mild to moderate TBIs and 20% of severe TBIs present with SDH [6]. SDH further compounds the challenges faced by patients with TBI, as evidenced by the 60% of patients who either die or become severely disabled following SDH [7]. This highlights the important role played by the cerebrovascular system in maintaining the health of nervous tissue. Damage to these blood vessels can lead to life-threatening complications. Along with SAH and SDH, other complications of TBI may also result in traumatic brain bleeds, including skull fractures, cerebral contusions, and Diffuse Axonal Injury (DAI). Notably, skull fractures resulting from TBI serve as a significant predictor of Intracranial Hemorrhage (ICH) [8]. One study by Lukas

Leitner, et al. assessed over 1700 patients with TBI and found a statistically significant correlation between skull fractures and ICH, as well as ICH-related outcomes [8]. Survival rates for patients with ICH remain distressingly low, with less than 50% of patients surviving to the one-year mark [9]. Those who do survive face the sequelae of complications resulting from traumatic brain bleeds, substantially compromising their quality of life. Cerebral contusion, another complication associated with TBI, is also linked to ICH. These contusions inflict permanent damage to cerebral tissue, stemming from the absorption of kinetic energy during direct head trauma. This trauma results in hemorrhagic lesions that can expand and worsen over time. Potential complications of contusions include seizures, hydrocephalus, severe disability, coma, and death [10]. DAI is also a TBI-related complication with many adverse effects, the most prominent of which is dysautonomia [11]. Overall, damage resulting from TBI varies greatly and has the potential

to culminate into life-threatening traumatic brain bleeds.

Traumatic cerebral hemorrhage can cause various sequelae that require emergency treatment to improve patient prognosis. Elevated blood pressure is associated with poor prognosis in traumatic cerebral hemorrhage, with an additional risk of contributing to hematoma expansion [12]. Although the use of antithrombotic therapy (AAT) is often indicated for the treatment of traumatic cerebral hemorrhage, there are a number of patient factors that need to be considered before initiating AAT, as shown in Figure 1. For example, given the high prevalence of traumatic brain injury in the elderly, many patients may have other comorbidities such as atrial fibrillation and deep vein thrombosis, and may be at risk for stroke or blood clots. AAT is required to reduce the risk of associated events [13-17]. The usefulness of AAT in other such diseases may complicate its use in the treatment of traumatic cerebral hemorrhage.

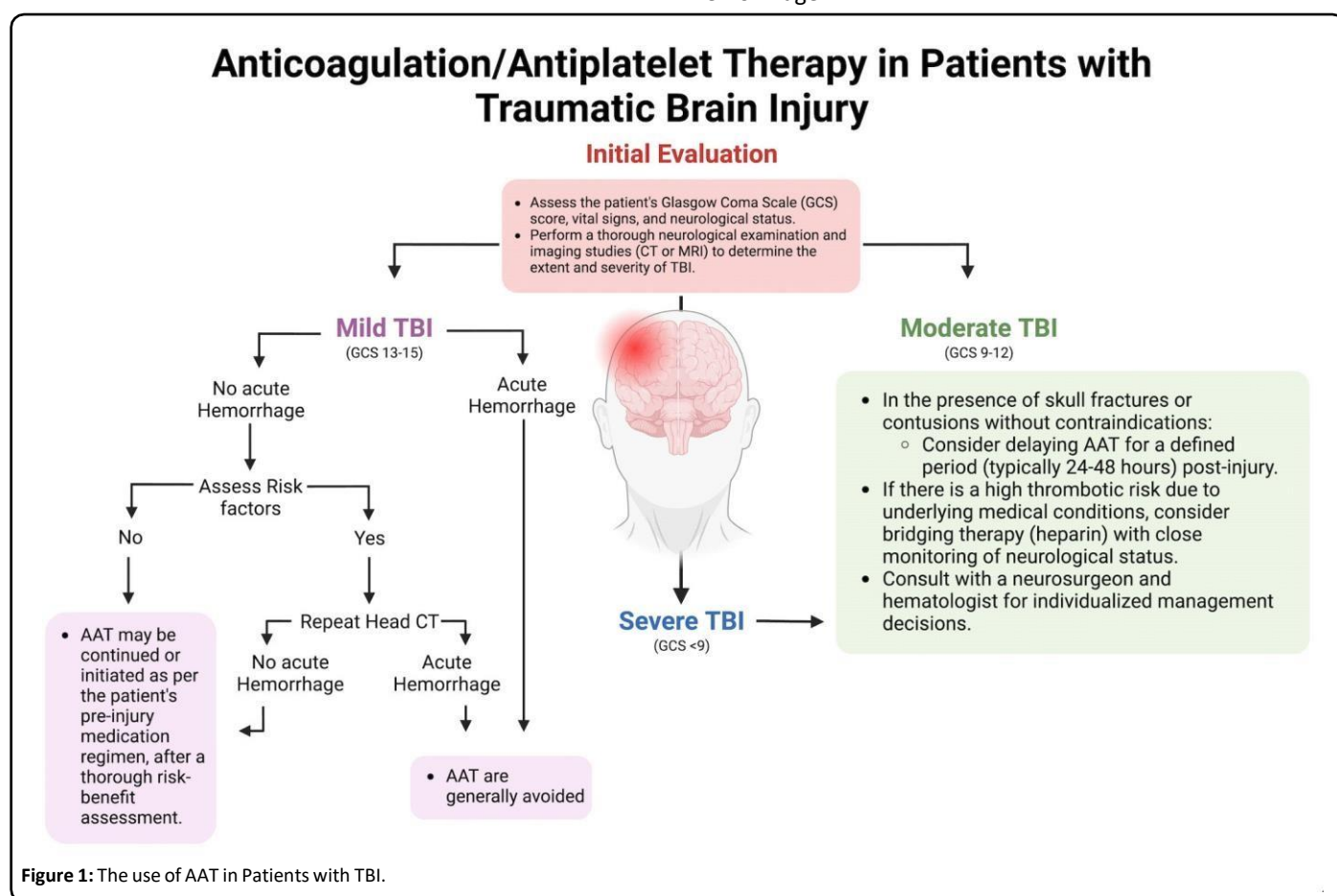


Figure 1: The use of AAT in Patients with TBI.

If a patient sustains a traumatic brain injury while taking AAT, these drugs can affect the blood's ability to clot, increasing the risk of brain hemorrhage. Furthermore, excessive use of AAT may also falsely induce hypotension, which may reduce cerebral blood flow [12, 18]. Therefore, medical professionals should continue or use these medications during the acute phase of TBI treatment, striking a delicate balance between preventing further intracerebral hemorrhage and minimizing the risk of blood clot-related complications. The benefits and risks of discontinuation must be carefully weighed [19].

This paper aims to review the literature to better ascertain the

appropriate duration of AAT in the context of traumatic brain bleeds. Our aim is to provide a comprehensive review of the current literature regarding the ideal duration of AAT administration after traumatic SAH and in acute or chronic SDH. Additionally, we examine the optimal duration of antiplatelet therapy and its impact on patient care in skull fractures, brain contusions, and DAI. We will also look at the impact of AAT on prosthetic valves and stents, and the impact of AAT on bleeding time and platelet aggregation. Our discussion will extend to the potential future implications for research concerning the utility of AAT in the context of traumatic brain bleeds, emphasizing the existing limitations within the current

body of research on this topic.

AAT Duration in Traumatic SAH and Acute or Chronic SDH

Researchers have long endeavored to elucidate and support the specific decision-making processes involved in deciding whether a patient should continue AAT after traumatic SAH [20]. This is an increasingly common topic, with many research

papers finding an association between administration of the oral anticoagulant warfarin and increased risk of ICH, prompting further research on this topic [21].

Additionally, antiplatelet drugs such as aspirin are being studied for their role in preventing inflammation and aneurysm rupture, as shown in Figure 2.

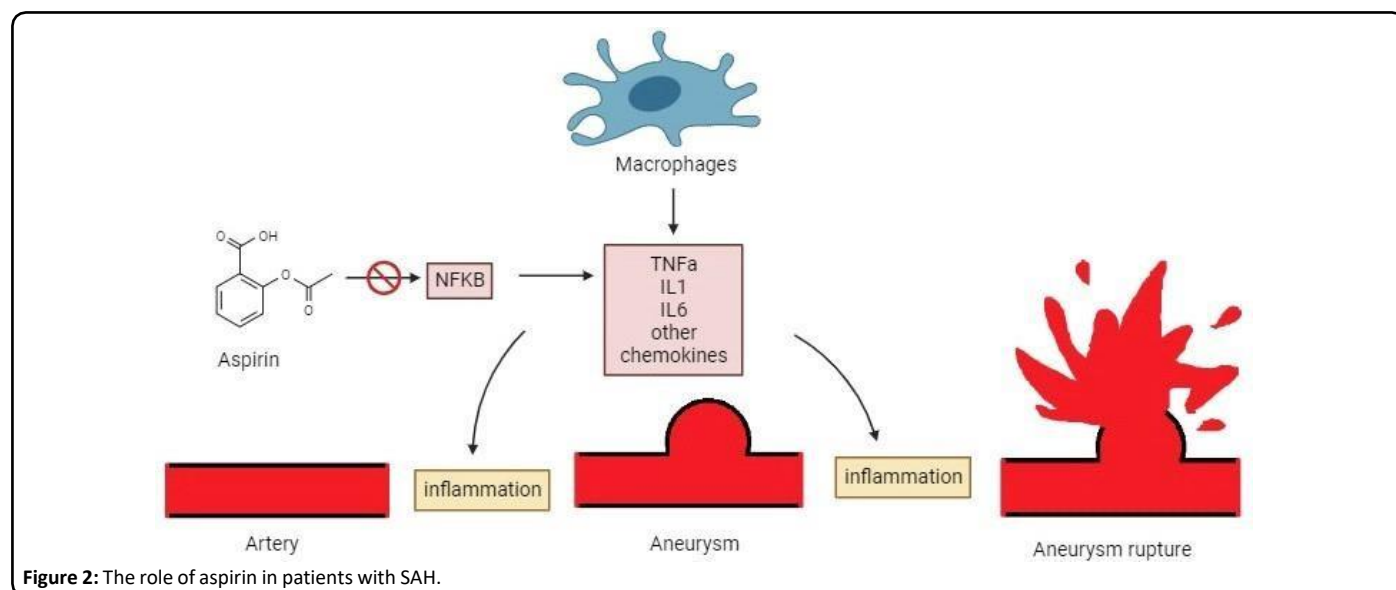


Figure 2: The role of aspirin in patients with SAH.

The Role of Aspirin in Patients with SAH

The optimal timeframe for initiating oral anticoagulation therapy depends on numerous personalized patient factors. Taking this into account, Yan-Huang Li, et al. proposed a straightforward three-step model for determining the ideal timing of AAT administration [20].

- A patient's risk of developing further thromboembolism or ICH is evaluated by considering a variety of factors, including history of atrial fibrillation, mechanical valve defects, and previous experience of deep vein thrombosis or pulmonary embolism. The decision to weigh the pros and cons of continuous anticoagulation therapy depends on the patient's specific brain disease [20].
- The correct AAT is chosen, and the optimal timing for therapy is determined based on the conclusions drawn from step one. It is essential to recognize that the decision to initiate AAT should be a multidisciplinary effort, with the involvement of neurologists, neurosurgeons, and interventional cardiologists, promoting a team-based approach to patient care [20].
- Clinicians take additional measures to manage any chronic comorbidities that the patient may be experiencing, such as hypertension, heart failure, or diabetes [20].

The first step of this model focuses on evaluating risk scores for thromboembolism and ICH, which can prove to be a complicated process. For instance, one study by Vivien H Lee, et al. established a simple scoring system known as the HAIR score (Hunt and Hess score, age, intraventricular hemorrhage, re-bleed) [22]. This scoring system, ranging from 0 to 8, offers insight into the various risks associated with SAH and was formulated

based on data from 400 patients suffering from traumatic SAH and acute and chronic SDH. The study found that a higher HAIR score was associated with increased hospital mortality among their patients [22]. Another study examined the aneurysmal rupture risk scores in patients with SAH in a large prospective study involving a cohort of 319 patients. Surprisingly, this team of researchers concluded that the aneurysmal risk scores did not correlate with a patient's increased risk for mortality or intracranial bleeding [23]. This discrepancy between studies calls for more research in the development of models that accurately predict a patient's risk assessment in order to draw better conclusions regarding the duration of AAT.

The Optimal Timing for AAT in SAH and SDH

A retrospective study by Yana Puckett aimed to determine the best timing for resuming AAT in 256 patients with TBI between 2009 and 2012. The study reported that resuming AAT between 7 and 9.5 days after TBI may lead to fewer adverse events when compared to previous recommendations of 3-10 days. The study analyzed patient metrics, such as coagulation studies, type of TBI, treatment, and AAT resumption timing, and it evaluated patient outcomes during a six-month follow-up. Rates of complications were also assessed, including mortality, myocardial infarction, stroke, re-bleeding, venous thromboembolism, and pneumonia. Adverse events were least observed (10%) in the group restarting AAT between 7-14 days, while the group not resuming AAT had the highest rate of adverse events (68.8%). One limitation of this study was low statistical power due to follow-up limitations and a patient cohort with shorter hospital observation periods and more benign brain injuries [17]. Further research should focus on patients with more severe TBIs with longer durations of hospitalization.

Another review article by Jochen A. Sembill concluded that

physicians typically initiated AAT as early as one week for patients without significant risk factors like atrial fibrillation or a history of thromboembolism [24]. For patients with other relevant medical histories, the timing of re-initiation was adjusted based on individual risk factors. On the other hand, a survey of multiple neurosurgeons by Yan Xu et al. revealed a lack of consensus regarding the timing of re-initiating therapy, with 40% of physicians preferring to recommence treatment between 14 days and 3 months after the initial injury [25]. In conclusion, the literature offers varying recommendations, with some favoring re-initiation of therapy within one week, others suggesting a 1-2 week delay, and still others advocating for even longer intervals exceeding one month [17,24-29].

Lastly, in terms of how long AAT should be administered, one study by Hormuzdiyar H Dasenbrock, et al. found that long-term AAT was associated with several significant benefits, including shorter hospital stays, reduced risk of venous thrombotic events, and a decreased likelihood of cardiac complications [30]. Similarly, another study concluded that the long-term administration of this therapy (>2 weeks) substantially lowered the overall incidence of delayed cerebral ischemia, particularly when it was concurrently applied with endovascular treatment [31]. Moreover, it was associated with improved patient outcomes and reduced mortality rates. Conversely, a retrospective review study conducted by Ben King, et al. examined the guidelines for resuming anticoagulant therapy and demonstrated the potential risks of hemorrhage and thrombosis [32]. Consequently, these divergent findings suggest that there is an identifiable optimal timing for resuming therapy that falls within the current window for re-initiation.

AAT indications for other complications of TBI

Skull fractures, anterior cranial and temporal bone contusions, and administration of AAT after DAI are topics of ongoing research and clinical discussion. However, the lack of strong research such as randomized controlled trials has limited the availability of evidence-based clinical recommendations in this area [19]. Decisions regarding the management of AAT administration are complex and multifactorial, taking into account the patient's general health status, injury severity and location, and risk of thromboembolic and hemorrhagic events. Therefore, the approach to managing these patient cohorts is highly dependent on the empirical assessment and clinical experience of the physicians. This reliance on clinical judgment may contribute to the lack of an established protocol for determining the optimal time frame for resumption of AAT in patients after TBI [14, 17, 19].

AAT Indications for Minor TBI and Skull Fractures

The current literature presents a range of recommendations concerning the duration of AAT following TBI. For instance, in cases of minor skull fractures or minor TBI with negative Computerized Tomography (CT) images, there is typically no recommended reversal of AAT. Instead, it is advised to monitor the patient in the intensive care unit and perform repeat scans to rule out any potential bleeding [13,19]. If the subsequent scans do not reveal any bleeding, the resumption of AAT may be considered within a matter of days to weeks, contingent

upon other clinical and radiological assessments. However, the optimal duration of AAT for patients with skull fractures remains a topic of ongoing research. This highlights the need for further clinical trials and consensus guidelines to provide clearer recommendations to healthcare practitioners managing these complex cases [16].

AAT Indications for Severe TBI, Cerebral Contusions, and DAI

In cases involving severe TBIs characterized by extensive contusions or DAI, the potential benefits of AAT must be carefully weighed against the associated bleeding risks. This decision often requires multidisciplinary collaboration among neurologists, neurosurgeons, and hematologists to optimize patient outcomes while minimizing complications. However, rapid AAT reversal is recommended in patients with ICH, with platelet transfusion being the suggested approach for reversing aspirin or clopidogrel therapy [13, 19]. In cases of warfarin-induced coagulopathies, effective treatment can typically be achieved with fresh frozen plasma and intravenous vitamin K. However, the use of recombinant activated factor VII in warfarin-associated traumatic ICH remains uncertain, mainly due to limited clinical benefits, cost considerations, and safety concerns in trauma cases [13].

Albrecht, et al. conducted a retrospective investigation into the risk of adverse outcomes in TBI patients hospitalized for one year. They compared those who resumed warfarin therapy to those who did not, revealing a reduced risk of thrombotic events (RR, 0.77; 95% CI, 0.67–0.88) and hemorrhagic or ischemic strokes (RR, 0.83; 95% CI, 0.72–0.96) associated with warfarin resumption. However, warfarin resumption was also linked to an increased risk of hemorrhagic events (RR, 1.51; 95% CI, 1.29–1.78). These findings suggest an overall net benefit in resuming anticoagulation for most patients [33].

Another study, which included 3355 participants, reviewed the outcomes related to neurological deterioration or progression of hemorrhagic TBI on repeat head CT scans in patients who received anticoagulation within 60 days post-injury. The median administration time for anticoagulation after injury was found to be 9 days, and there were no indications of neurological decline attributable to the administration of anticoagulation; however, 6 patients exhibited an advancement of hemorrhagic TBI in follow-up head CT scans. Furthermore, multiple logistic regression analysis revealed that patients aged 65 and older were significantly linked to the advancement of hemorrhagic TBI following therapeutic anticoagulation (odds ratio, 15.2; 95% confidence interval, 1.1-212.7; P=0.04) [34].

Tykocki and Guzek, et al. also reported a relatively low risk of hemorrhagic complications in the early resumption of antithrombotic therapy within 3-17.5 days after TBI. Furthermore, their findings indicate that the risk of such complications may be even lower when non-vitamin K antagonist oral anticoagulants are used, compared to vitamin K antagonists [35].

Antiplatelet Therapies

The Effects of AATs on Prosthetic Valves and Stents

AAT therapy is also indicated for use in traumatic brain bleeds for patients with prosthetic valves and stents. For instance,

one study by Makkar, et al. found that clopidogrel and aspirin therapy significantly reduced thrombus formation in ex vivo porcine models with deployed nitinol stents in external arteriovenous shunts. The study investigated the acute actions of these regimens and found that a combination of clopidogrel and aspirin demonstrated significant effects for reducing acute thrombus formation over the deployed stents, even at low doses. Aspirin showed synergistic effects when combined with clopidogrel, enhancing its anti-thrombotic effects, but models treated with aspirin alone had almost complete obliteration of the stent by the thrombus. Similarly, pigs treated with clopidogrel alone had an insignificant level of diminished thrombosis unless given in relatively high doses when compared to the combined treatment regimen [36].

In another study involving a rabbit model, the combined regimen was assessed in ex vivo heart valves and compared with the acute effects of warfarin. The study found that clopidogrel and aspirin therapy resulted in a greater reduction of thrombus over the heart valves than warfarin or control groups [37].

Similarly, in a different experiment involving baboons, Harker, et al. examined the efficacy of clopidogrel and aspirin in preventing platelet depositions on externally placed arteriovenous shunts with stainless steel stents. The study examined the cumulative effect of clopidogrel in inhibiting platelet depositions over six days on the hypercoagulable stent; it studied low doses of the clopidogrel and examined the additive effects of aspirin when combined with clopidogrel. The study also investigated heparin in an ex vivo placed stent, both alone and in combination with clopidogrel. The study demonstrated that heparin did not significantly reduce platelet depositions over the placed stent unless it was combined with clopidogrel. The study also found that the combination of these regimens did not significantly increase the bleeding time when compared to clopidogrel alone [38].

McKellar, et al. also contrasted the effects of clopidogrel and aspirin with dalteparin in preventing thrombus formation over various periods of time. The study involved a post-mortem analysis of thrombus size over implanted aortic valves. The researchers studied swine for 30 days divided into three treatment groups: 1. combined treatment with clopidogrel and aspirin, 2. single treatment with clopidogrel, aspirin, or dalteparin, or 3. non-treated group. Swine receiving Dual Antiplatelet Therapy (DAPT) had a drastic reduction in thrombus size in comparison to the control group. Additionally, swine treated with single therapies had a larger thrombus size when compared to the DAPTs, but their effects were deemed to be insignificant. The swine receiving dalteparin had the largest thrombus size compared to the other treatment groups, followed by aspirin and clopidogrel. Dalteparin-treated swine had a thrombus size nearly three times larger than DAPTs. DAPTs were also compared to the control group over 150 days. Mean thrombus size in the aspirin and clopidogrel combined group was significantly smaller than the control group, with a four times greater size reduction. Interestingly, there were no reported deaths due to thromboembolic events in the short-term, long-term, or non-treated group [39]. Hence, it can be concluded that a combination of aspirin and clopidogrel is the most effective treatment for thrombi in prosthetic valves and stents.

The Effects of AATs on Intravascular Thrombosis

The debate regarding AAT also extends to the topic of intravascular thrombosis. For instance, one double-blinded randomized control trial studied two groups of cats receiving either aspirin or clopidogrel to investigate the incidence of Secondary Cardiogenic Arterial Thromboembolism (CATE). The researchers found that clopidogrel-treated cats had a significantly decreased likelihood of recurrent CATE and an increased median time for the event to occur. Additionally, the clopidogrel group was less likely to die due to cardiac causes [40].

The aforementioned study by Harker, et al. also found that although heparin and clopidogrel significantly reduced platelet aggregation on the placed stent, they did not decrease the platelet deposition on a vascular graft when compared to clopidogrel alone. Contrastingly, clopidogrel combined with aspirin diminished graft platelet depositions dramatically [38]. Another study measured the acute Cyclic Flow Reduction (CFR) in the coronary arteries of pigs with induced unstable angina and its relation to clopidogrel and aspirin when used alone or combined. These researchers found that clopidogrel and aspirin together, even at low doses, exhibited rapid and effective action in decreasing the CFR whilst inhibition of platelet aggregation was delayed. In fact, aspirin or clopidogrel alone with the same doses did not show any effects at all [41].

The antithrombotic effects of clopidogrel, ticlopidine, and prasugrel were singly compared in rat models after induction of carotid arterial thrombosis in a different study. The study measured vessel occlusion time after induction of thrombosis and treatment in comparison to the non-treated group. Prasugrel displayed more potent and faster actions, compared to clopidogrel and ticlopidine, in keeping patent vessels and reducing thrombus formation [42]. Moreover, these drugs were examined for their ability to prevent arteriovenous shunt thrombosis in rats; their results were strikingly similar to the previously mentioned study [42,43]. In another experiment involving rat models, aspirin, clopidogrel, enoxaparin, and heparin were compared with each other as single therapies or in combination with aspirin for the inhibition of CFR post-induction of carotid artery thrombosis. This study concluded that clopidogrel combined with aspirin was more effective than enoxaparin and aspirin or heparin and aspirin in the reduction of thrombus formation [44]. Combined therapy with aspirin and clopidogrel is more effective in treating intravascular thrombosis than other combination or stand-alone treatment regimens.

The Effects of AATs on Platelet Aggregation

Clopidogrel substantially inhibits ADP-induced platelet aggregation in a dose-dependent manner; however, it has no effect on collagen-induced aggregation. Contrastingly, aspirin prevents collagen-dependent aggregation in a dose-dependent pattern with a minimal effect on ADP-induced aggregation. A combination of both regimens resulted in a delayed effect on ADP-dependent aggregation without a significant effect on collagen-induced aggregation [41]. On the other hand, prasugrel displayed stronger and faster inhibition of platelet aggregation in both mechanisms, and its inhibitory effects increased when combined with aspirin, even at low doses [45,46].

The Effects of AATs on Bleeding Time

The aforementioned study by H. J. Daykin, et al. compared bleeding time in association with the administration of AAT alone or in combination with aspirin. The tail bleeding times associated with heparin and enoxaparin were significantly increased at higher doses when compared to aspirin or clopidogrel alone. Combining anticoagulants with aspirin further increased bleeding time in contrast to the combination of clopidogrel and aspirin [44]. Similarly, rivaroxaban had a minor increase in bleeding time compared to clopidogrel with aspirin, but no statistically significant differences were found [47]. Clopidogrel and prasugrel also had no significant difference in the bleeding time [46]. Further research should focus on assessing bleeding time with combination therapies with larger sample sizes.

Ticagrelor, Prasugrel, and Clopidogrel

Another experimental study involved ex vivo and in vivo rat and dog models to compare ticagrelor therapy to clopidogrel and compounds 072 and 105, chemical compounds identical to prasugrel and its active metabolite, respectively. J.J.J. van Giezen, et al. found that ticagrelor has distinguishing chemical properties when compared to both prasugrel and clopidogrel. For instance, ticagrelor is an active compound that does not need to be converted by the liver to exert its effects, unlike thienopyridines. Additionally, the high affinity of ticagrelor saturates active sites and leaves it able to more rapidly reach equilibrium when compared to clopidogrel and prasugrel [48]. Ticagrelor is also capable of reversibly binding to the active site,

unlike prasugrel and clopidogrel. Additionally, in vivo and ex vivo studies revealed no significant difference in bleeding time and thrombus formation between ticagrelor and prasugrel [49]

Future Implications for Research on the Use of AATs in Traumatic Brain Bleeds

Duality of Efficacy and Side Effects

The core concern when administering AAT in cases of traumatic brain bleeds revolves around the balance between potential therapeutic benefits and associated risks. These medications are invaluable for mitigating the danger of thrombotic events such as ischemic strokes. However, their mechanism of action also significantly elevates the risk of further hemorrhagic complications such as increased intracranial pressure, brain herniation, neurological deficits, epilepsy, and cerebral edema [50]. While it is widely accepted that platelets regulate primary hemostasis, the impact of antiplatelet medications on subdural hematomas or subarachnoid hemorrhages remains an area of active investigation [51]. However, antiplatelet use has been associated with an increased risk of acute ICH post-head trauma, albeit with a low risk for delayed ICH [52-54]. Thus, immediate head CT imaging is recommended for all such patients [55]. In clinical scenarios where anticoagulation is crucial for the patient, such as in atrial fibrillation or specific cardiac conditions, the decision to recommence treatment should be more meticulously calculated. Overall, the drugs that are currently in use in the context of traumatic brain bleeds are outlined in Table 1.

Table 1: Drugs commonly used to manage coagulopathy in traumatic brain bleeds.

Drug	Mechanism	Side Effects	Drug interactions	Reversal agents
Warfarin	Vitamin K Antagonist	Bleeding, Bruising	NSAIDs, Antibiotics	Vitamin K, FFP
Dabigatran (Pradaxa)	Direct thrombin inhibitor	GI Upset, Bleeding	Antiplatelets	Idarucizumab
Rivaroxaban (Xarelto)	Factor Xa inhibitor	Bleeding, Liver dysfunction	NSAIDs, Antiplatelets	Andexanet alfa
Apixaban (Eliquis)	Factor Xa inhibitor	Bleeding, Nausea	NSAIDs, Antiplatelets	Andexanet alfa
Heparin	Antithrombin activator	Bleeding, HIT	Antiplatelets	Protamine Sulfate
Enoxaparin (Lovenox)	Low molecular weight heparin	Bleeding, Bruising	NSAIDs, Antiplatelets	Protamine Sulfate
Clopidogrel (Plavix)	ADP receptor inhibitor	Bleeding, GI Upset	PPIs, Other antiplatelets	None
Lisinopril	ACE Inhibitor	Cough, Elevated blood K+	NSAIDs, Diuretics	None
Amlodipine	Ca2+ Channel blocker	Edema, Headache	Grapefruit juice	None
Metoprolol	Beta-Blocker	Fatigue, Bradycardia	Antiarrhythmics	Glucagon
Levetiracetam	SV2A modulation	Irritability, Dizziness	Other CNS depressants	None

Drug Interactions in Patients with Multiple Comorbidities

In patients with multiple comorbidities, polypharmacy is a prevalent issue that further complicates the use of AAT. This polypharmacy environment significantly heightens the potential for drug interactions, making it an area requiring comprehensive study. Certain medications, such as NSAIDs and specific antibiotics, can interact with anticoagulants to exacerbate the risk of bleeding. These drug interactions are not merely additive but can often produce synergistic effects, amplifying the risks associated with each medication [56].

Duration of Therapy

As noted earlier, optimal duration for which AAT should be

administered in the context of traumatic brain bleeds remains controversial. Majeed et al. concluded that the optimal timing for restarting anticoagulation should be between 10 and 30 weeks after the intracranial bleeding (55% had ICH), based on the high risk of recurrent hemorrhage in the first 10 weeks that decreased over time, and a rise in ischemic complications beyond 30 weeks [57]. Meanwhile, Park et al. proposed that OAC be reinitiated after 2 weeks to avoid the overriding effect of intracranial hemorrhage recurrence on the prevention of systemic thromboembolism and ischemic stroke [58]. Current practice is largely empirical and there is a need for prospective, randomized trials that compare short-term vs long-term therapy to determine which provides an ideal risk-to-benefit ratio.

Alternative Therapies

While current AAT has proven efficacious in various settings, their limitations, and associated risks in the context of traumatic brain hemorrhage illustrate the need for innovative pharmacological strategies. The development of drugs with targeted mechanisms of action that provide anticoagulant benefits without increasing the risk of hemorrhage is of paramount importance. Promising therapeutics include Novel Oral Anticoagulants (NOACs), next-generation antiplatelet agents, antihypertensive medications, antiepileptics, and statins.

NOACs such as dabigatran etexilate mesylate, rivaroxaban, and apixaban represent a significant leap forward. A 2022 meta-analysis revealed that Direct Oral Anticoagulants (DOACs) cut the risk of ICH by nearly half compared to Vitamin K antagonists, with dabigatran 110 mg identified as the safest DOAC in terms of ICH risk [59-61]. Another study from 2020 found that despite DOACs being reversed at nearly half the rate of warfarin, patients with traumatic ICH on warfarin had higher 6-month mortality rates, suggesting a potential survival advantage for DOACs in this population [62]. As such, NOACs are increasingly becoming first-line options for stroke prevention in atrial fibrillation patients at high risk for ICH [63].

Next-generation antiplatelet agents, such as cangrelor and ticagrelor, hold significant promise in the management of patients who have experienced traumatic brain bleeds [64]. Unlike traditional antiplatelet drugs like clopidogrel, these newer agents offer more targeted and controllable platelet inhibition. For example, cangrelor is an intravenous P2Y₁₂ inhibitor with rapid onset and offset of action, providing clinicians with the ability to quickly titrate its effects [65]. Ticagrelor, on the other hand, is an oral agent that also acts on the P2Y₁₂ receptor but offers the benefit of reversibility [66]. These features balance the need for antithrombotic efficacy with a minimized risk of further hemorrhagic complications. This adaptability offers clinicians greater flexibility in tailoring therapy to individual patient needs, which can be particularly beneficial in scenarios requiring surgical intervention or when there is a high risk of recurrent hemorrhage.

The utilization of antihypertensive agents like ACE inhibitors, calcium channel blockers, and beta-blockers, although somewhat controversial, offers another strategy to mitigate the risk of recurrent bleeds by maintaining optimal blood pressure levels. Antiepileptic medications, such as levetiracetam, may be utilized prophylactically to prevent seizures, which can elevate intracranial pressure and potentially exacerbate bleeding [67]. While not directly aimed at reducing the risk of bleeding, some clinicians consider the use of statins for their neuroprotective effects, although further research is needed to validate their efficacy in this context [68]. Lifestyle modifications also serve as adjunctive strategies and should be monitored rigorously. These include smoking cessation, alcohol limitation, and dietary changes aimed at vascular health.

Strengthening Data Regarding the Duration of AAT Use

To refine our understanding of optimal anticoagulation duration in the context of traumatic brain bleed, a comprehensive, multifaceted approach is essential. This would serve to elevate the quality of evidence, allowing clinicians to deliver evidence-

based care that maximizes therapeutic benefits while minimizing adverse outcomes. Strategies for achieving this involve the design of rigorous randomized clinical trials, longitudinal cohort studies, meta-analyses, standardization of outcome metrics, and patient risk stratification.

Randomized clinical trials remain the gold standard in clinical research, providing robust evidence on the efficacy and safety of interventions. However, longitudinal cohort studies offer complementary insights into longer-term outcomes and potential late complications associated with varying treatment durations. Such studies could provide critical information on the longitudinal safety and efficacy of anticoagulant regimens in brain hemorrhage patients. Additionally, meta-analyses, which synthesize data from multiple independent studies, offer more reliable estimates of treatment effects which is valuable when individual studies yield small or conflicting results. Outcome standardization is another pivotal aspect. Clear definitions of what constitutes a successful outcome such as clot resolution, absence of rebleeding, or reduced morbidity would facilitate comparability across studies.

A notable deficiency in the current state of research is the lack of patient-stratified studies, which would consider individual risk factors like age, comorbidities, and the specific nature of the brain hemorrhage. For instance, anticoagulant therapy poses a unique risk/benefit profile for elderly, stroke-prone patients compared to younger cohorts [59]. Patient stratification could pave the way for more individualized treatment plans, allowing for the optimized use of anticoagulants and antiplatelets while minimizing adverse outcomes.

Conclusion

As treatments for traumatic cerebral hemorrhage continue to evolve, the need for comprehensive comparative studies increases. Advances in personalized medicine are creating new opportunities for personalized treatment plans that take into account variables such as drug interactions, genetic predisposition, and comorbidities. This multifaceted approach should include not only evaluation of the optimal duration of AAT, but also evaluation of new pharmacological alternatives such as NOACs and next-generation antiplatelet agents.

In the case of hemorrhage in TBI, the standard of care is to resume appropriate AAT at intervals to reduce the risk of ICH, but timing and treatment vary among clinicians. Various studies have shown that restarting AAT reduces the long-term risk of thrombotic events and ischemic stroke. However, this risk must be weighed against the risk of developing ICH if AAT is restarted too soon. The timing of resuming AAT should be determined based on multidisciplinary risk stratification considering patient risk factors and comorbidities that may lead to thromboembolic complications with long-term discontinuation of AAT cessation.

Traumatic brain injury encompasses a spectrum of injuries that can have significant and far-reaching consequences in the short and long term. Achieving an accurate diagnosis and implementing appropriate management strategies, including decisions related to AAT, should be based on the most up-to-date research and customized to meet the specific needs of each patient whilst taking into consideration co-morbidities and

clinically complicating factors. The continually evolving body of literature on this subject highlights the critical importance of ongoing research efforts aimed at generating robust evidence to guide the management and treatment of TBIs, especially in the context of continued AAT.

Conflicts of Interest

The author have no conflicts of interest to report.

Funding

No.

References

- Capizzi A, Woo J, Verduzco-Gutierrez M. Traumatic Brain Injury: An Overview of Epidemiology, Pathophysiology, and Medical Management. *Med Clin North Am.* 2020;104(2):213-238.
- Dewan MC, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg.* 2018;130(4):1080-1097.
- Georges A, J MD. Traumatic Brain Injury. StatPearls. Treasure Island (FL):2023.
- Monson KL, Converse MI, Manley GT. Cerebral blood vessel damage in traumatic brain injury. *Clin Biomech (Bristol, Avon).* 2019;64:98-113.
- Griswold DP, Fernandez L, Rubiano AM. Traumatic Subarachnoid Hemorrhage: A Scoping Review. *J Neurotrauma.* 2022;39(1-2):35-48.
- Al-Mufti F, Mayer SA. Neurocritical Care of Acute Subdural Hemorrhage. *Neurosurg Clin N Am.* 2017;28(2):267-278.
- Yokobori S, Nakae R, Yokota H, et al. Subdural hematoma decompression model: A model of traumatic brain injury with ischemic-reperfusional pathophysiology: A review of the literature. *Behav Brain Res.* 2018;340:23-28.
- Leitner L, El-Shabrawi JH, Bratschitsch G, et al. Risk adapted diagnostics and hospitalization following mild traumatic brain injury. *Arch Orthop Trauma Surg.* 2021;141(4):619-627.
- Puy L, Parry-Jones AR, Sandset EC, Dowlatsahi D, Ziai W, Cordonnier C, et al. Intracerebral haemorrhage. *Nat Rev Dis Primers.* 2023;9(1):14.
- Pellot JE, De Jesus O. Cerebral Contusion. StatPearls. Treasure Island (FL):2023.
- Mesfin FB, Gupta N, Hays Shapshak A, et al. Diffuse Axonal Injury. StatPearls. Treasure Island (FL):2023.
- Caceres JA, Goldstein JN. Intracranial hemorrhage. *Emerg Med Clin North Am.* 2012;30(3):771-794.
- McMillian WD, Rogers FB. Management of prehospital antiplatelet and anticoagulant therapy in traumatic head injury: a review. *J Trauma.* 2009;66(3):942-950.
- Beynon C, Hertle DN, Unterberg AW, et al. Clinical review: Traumatic brain injury in patients receiving antiplatelet medication. *Crit Care.* 2012;16(4):228.
- Peck KA, Calvo RY, Schechter MS, et al. The impact of preinjury anticoagulants and prescription antiplatelet agents on outcomes in older patients with traumatic brain injury. *J Trauma Acute Care Surg.* 2014;76(2):431-436.
- Wong H, Lovett N, Curry N, et al. Antithrombotics in trauma: management strategies in the older patients. *J Blood Med.* 2017;8:165-174.
- Puckett Y, Zhang K, Blasingame J, et al. Safest Time to Resume Oral Anticoagulation in Patients with Traumatic Brain Injury. *Cureus.* 2018;10(7):e2920.
- Morgenstern LB, Hemphill JC, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2010;41(9):2108-2129.
- Wiegele M, Schochl H, Haushofer A, et al. Diagnostic and therapeutic approach in adult patients with traumatic brain injury receiving oral anticoagulant therapy: an Austrian interdisciplinary consensus statement. *Crit Care.* 2019;23(1):62.
- Li YG, Lip GYH. Anticoagulation Resumption After Intracerebral Hemorrhage. *Curr Atheroscler Rep.* 2018;20(7):32.
- Liotta EM, Prabhakaran S. Warfarin-associated intracerebral hemorrhage is increasing in prevalence in the United States. *J Stroke Cerebrovasc Dis.* 2013;22(7):1151-1155.
- Lee VH, Ouyang B, John S, et al. Risk stratification for the in-hospital mortality in subarachnoid hemorrhage: the HAIR score. *Neurocrit Care.* 2014;21(1):14-19.
- Lignon P, Gariel F, Marnat G, et al. Prospective assessment of aneurysmal rupture risk scores in patients with subarachnoid hemorrhage: a multicentric cohort. *Neuroradiol.* 2022;64(12):2363-2371.
- Sembill JA, Kuramatsu JB, Schwab S, et al. Resumption of oral anticoagulation after spontaneous intracerebral hemorrhage. *Neurol Res Pract.* 2019;1:12.
- Xu Y, Shoamanesh A, Schulman S, et al. Oral anticoagulant re-initiation following intracerebral hemorrhage in non-valvular atrial fibrillation: Global survey of the practices of neurologists, neurosurgeons and thrombosis experts. *PLoS One.* 2018;13(1):e0191137.
- Nagano N, Tabata H, Hashimoto K. Anticoagulant-related intracerebral hemorrhage in patients with prosthetic heart valves--report of two cases. *Neurol Med Chir (Tokyo).* 1991;31(11):743-745.
- Kawamata T, Takeshita M, Kubo O, et al. Management of intracranial hemorrhage associated with anticoagulant therapy. *Surg Neurol.* 1995;44(5):438-442.
- Crawley F, Bevan D, Wren D. Management of intracranial bleeding associated with anticoagulation: balancing the risk of further bleeding against thromboembolism from prosthetic heart valves. *J Neurol Neurosurg Psychiatr.* 2000;69(3):396-398.
- Phan TG, Koh M, Wijidicks EF. Safety of discontinuation of anticoagulation in patients with intracranial hemorrhage at high thromboembolic risk. *Arch Neurol.* 2000;57(12):1710-1713.
- Dasenbrock HH, Yan SC, Gross BA, et al. The impact of aspirin and anticoagulant usage on outcomes after aneurysmal subarachnoid hemorrhage: a Nationwide Inpatient Sample analysis. *J Neurosurg.* 2017;126(2):537-547.
- Cagnazzo F, Derraz I, Lefevre PH, et al. Antiplatelet Therapy in Patients with Aneurysmal SAH: Impact on Delayed Cerebral Ischemia and Clinical Outcome. A Meta-Analysis. *AJNR Am J*

Neuroradiol. 2019;40(7):1201-1206.

32. King B, Milling T, Gajewski B, et al. Restarting and timing of oral anticoagulation after traumatic intracranial hemorrhage: a review and summary of ongoing and planned prospective randomized clinical trials. *Trauma Surg Acute Care Open.* 2020;5(1):e000605.
33. Albrecht JS, Liu X, Baumgarten M, et al. Benefits and risks of anticoagulation resumption following traumatic brain injury. *JAMA Intern Med.* 2014;174(8):1244-1251.
34. Matsushima K, Inaba K, Cho J, et al. Therapeutic anticoagulation in patients with traumatic brain injury. *J Surg Res.* 2016;205(1):186-191.
35. Tykocki T, Guzek K. Anticoagulation Therapy in Traumatic Brain Injury. *World Neurosurg.* 2016 ;89:497-504.
36. Makkar RR, Eigler NL, Kaul S, et al. Effects of clopidogrel, aspirin and combined therapy in a porcine ex vivo model of high-shear induced stent thrombosis. *Eur Heart J.* 1998;19(10):1538-1546.
37. Schlitt A, Hauroeder B, Buerke M, et al. Effects of combined therapy of clopidogrel and aspirin in preventing thrombus formation on mechanical heart valves in an ex vivo rabbit model. *Thromb Res.* 2002;107(1-2):39-43.
38. Harker LA, Marzec UM, Kelly AB, et al. Clopidogrel inhibition of stent, graft, and vascular thrombogenesis with antithrombotic enhancement by aspirin in nonhuman primates. *Circulation.* 1998;98(22):2461-2469.
39. McKellar SH, Thompson JL, Garcia-Rinaldi RF, et al. Short- and long-term efficacy of aspirin and clopidogrel for thromboprophylaxis for mechanical heart valves: an in vivo study in swine. *J Thorac Cardiovasc Surg.* 2008;136(4):908-914.
40. Hogan DF, Fox PR, Jacob K, et al. Secondary prevention of cardiogenic arterial thromboembolism in the cat: The double-blind, randomized, positive-controlled feline arterial thromboembolism; clopidogrel vs. aspirin trial (FAT CAT). *J Vet Cardiol.* 2015;17 Suppl 1:S306-S317.
41. Bierbach B, Horstick G, Berg O, et al. Potent low dose platelet inhibitory effects of clopidogrel and aspirin on coronary thrombus formation in an animal model of acute unstable angina. *Thromb Haemost.* 2006;95(2):354-361.
42. Niitsu Y, Sugidachi A, Ogawa T, et al. Repeat oral dosing of prasugrel, a novel P2Y12 receptor inhibitor, results in cumulative and potent antiplatelet and antithrombotic activity in several animal species. *Eur J Pharmacol.* 2008;579(1-3):276-282.
43. Sugidachi A, Asai F, Ogawa T, et al. The in vivo pharmacological profile of CS-747, a novel antiplatelet agent with platelet ADP receptor antagonist properties. *Br J Pharmacol.* 2000;129(7):1439-1446.
44. Daykin HJ, Sturgeon SA, Jones C, et al. Arterial antithrombotic effects of aspirin, heparin, enoxaparin and clopidogrel alone, or in combination, in the rat. *Thromb Res.* 2006;118(6):755-762.
45. Niitsu Y, Jakubowski JA, Sugidachi A, et al. Pharmacology of CS-747 (prasugrel, LY640315), a novel, potent antiplatelet agent with in vivo P2Y12 receptor antagonist activity. *Semin Thromb Hemost.* 2005;31(2):184-194.
46. Brandt JT, Payne CD, Wiviott SD, et al. A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J.* 2007;153(1):66e9-66e16.
47. Becker EM, Perzborn E, Klipp A, et al. Effects of rivaroxaban, acetylsalicylic acid and clopidogrel as monotherapy and in combination in a porcine model of stent thrombosis. *J Thromb Haemost.* 2012;10(12):2470-2480.
48. van Giezen JJ, Berntsson P, Zachrisson H, et al. Comparison of ticagrelor and thienopyridine P2Y(12) binding characteristics and antithrombotic and bleeding effects in rat and dog models of thrombosis/hemostasis. *Thromb Res.* 2009;124(5):565-571.
49. Sugidachi A, Ohno K, Ogawa T, et al. A comparison of the pharmacological profiles of prasugrel and ticagrelor assessed by platelet aggregation, thrombus formation and haemostasis in rats. *Br J Pharmacol.* 2013;169(1):82-89.
50. Divito A, Kerr K, Wilkerson C, et al. Use of Anticoagulation Agents After Traumatic Intracranial Hemorrhage. *World Neurosurg.* 2019;123:e25-e30.
51. Uccella L, Zoia C, Bongetta D, et al. Are Antiplatelet and Anticoagulants Drugs A Risk Factor for Bleeding in Mild Traumatic Brain Injury? *World Neurosurg.* 2018;110:e339-e45.
52. Beynon C, Potzy A, Sakowitz OW, et al. Rivaroxaban and intracranial haemorrhage after mild traumatic brain injury: A dangerous combination? *Clin Neurol Neurosurg.* 2015;136:73-78.
53. Uccella L, Zoia C, Perlasca F, et al. Mild Traumatic Brain Injury in Patients on Long-Term Anticoagulation Therapy: Do They Really Need Repeated Head CT Scan? *World Neurosurg.* 2016;93:100-103.
54. Savioli G, Ceresa IF, Luzzi S, et al. Rates of Intracranial Hemorrhage in Mild Head Trauma Patients Presenting to Emergency Department and Their Management: A Comparison of Direct Oral Anticoagulant Drugs with Vitamin K Antagonists. *Medicina (Kaunas).* 2020;56(6):308.
55. Alter SM, Mazer BA, Solano JJ, et al. Antiplatelet therapy is associated with a high rate of intracranial hemorrhage in patients with head injuries. *Trauma Surg Acute Care Open.* 2020;5(1):e000520.
56. Gulati S, Solheim O, Carlsen SM, et al. Risk of intracranial hemorrhage (RICH) in users of oral antithrombotic drugs: Nationwide pharmacoepidemiological study. *PLoS One.* 2018;13(8):e0202575.
57. Majeed A, Kim YK, Roberts RS, et al. Optimal timing of resumption of warfarin after intracranial hemorrhage. *Stroke.* 2010;41(12):2860-2866.
58. Park YA, Uhm JS, Pak HN, et al. Anticoagulation therapy in atrial fibrillation after intracranial hemorrhage. *Heart Rhythm.* 2016;13(9):1794-1802.
59. Hart RG, Diener HC, Yang S, et al. Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: the RE-LY trial. *Stroke.* 2012;43(6):1511-1517.
60. Hankey GJ, Stevens SR, Piccini JP, et al. Intracranial hemorrhage among patients with atrial fibrillation anticoagulated with warfarin or rivaroxaban: the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for

prevention of stroke and embolism trial in atrial fibrillation. *Stroke*. 2014;45(5):1304-1312.

61. Lv M, Wu T, Jiang S, et al. Risk of Intracranial Hemorrhage Caused by Direct Oral Anticoagulants for Stroke Prevention in Patients With Atrial Fibrillation (from a Network Meta-Analysis of Randomized Controlled Trials). *Am J Cardiol*. 2022;162:92-99.

62. Billings JD, Khan AD, McVicker JH, et al. Newer and Better? Comparing Direct Oral Anticoagulants to Warfarin in Patients With Traumatic Intracranial Hemorrhage. *Am Surg*. 2020;86(9):1062-1066.

63. Chatterjee S, Sardar P, Biondi-Zoccai G, et al. New oral anticoagulants and the risk of intracranial hemorrhage: traditional and Bayesian meta-analysis and mixed treatment comparison of randomized trials of new oral anticoagulants in atrial fibrillation. *JAMA Neurol*. 2013;70(12):1486-1490.

64. Alvikas J, Myers SP, Wessel CB, et al. A systematic review and meta-analysis of traumatic intracranial hemorrhage in patients

taking prehospital antiplatelet therapy: Is there a role for platelet transfusions? *J Trauma Acute Care Surg*. 2020;88(6):847-854.

65. Sible AM, Nawarskas JJ. Cangrelor: A New Route for P2Y₁₂ Inhibition. *Cardiol Rev*. 2017;25(3):133-139.

66. James S, Akerblom A, Cannon CP, et al. Comparison of ticagrelor, the first reversible oral P2Y₁₂ receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. *Am Heart J*. 2009;157(4):599-605.

67. Angriman F, Tirupakuzhi Vijayaraghavan BK, Dragoi L, et al. Antiepileptic Drugs to Prevent Seizures After Spontaneous Intracerebral Hemorrhage. *Stroke*. 2019;50(5):1095-1099.

68. Imai T, Sugiyama T, Iwata S, et al. Levetiracetam, an Antiepileptic Drug has Neuroprotective Effects on Intracranial Hemorrhage Injury. *Neurosci*. 2020;431:25-33.