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# Outcomes in Traumatic Brain Injury Patients on Preinjury Anticoagulation and Antiplatelet Agents

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## INTRODUCTION

Traumatic brain injury (TBI) affects an estimated 1.7 million people a year. Around 75% of these cases are mild. Falls and motor vehicle accidents are among the leading causes for TBI, with falls accounting for 60.7% of occurrences in populations 65 years or older<sup>1</sup>. As the general population continues to expand both in age and in size, the risk of falls will increase. This poses a problem particularly in light of the pervasive use of anticoagulants and antiplatelet agents for this population, both of which increase the bleeding risk.

Anticoagulants and antiplatelet agents are used for a variety of conditions, including deep venous thrombosis, atrial fibrillation, pulmonary embolism and coronary artery disease. They are also given postoperatively for prosthetic heart valves or stent placement. An estimated 597,689 deaths in 2010 were due to cardiovascular disease, with 80% above the age of 65<sup>2</sup>. Stroke caused 129,476 deaths. The use of anticoagulants and antiplatelet agents for prevention of cardiovascular and cerebrovascular events is irrefutable, but little literature has touched on its effects on morbidity and

mortality in those with traumatic brain injury. This article summarizes the current literature on the pre-TBI use of anticoagulants and antiplatelet agents and the associated morbidity and mortality.

## CASE

A 68-year-old man with a past medical history of myocardial infarction 6 months ago with stent placement (now on aspirin and plavix), HTN, DM, obesity and 40 pack year smoking complained of an intense headache immediately prior to falling while getting up to go to the bathroom. After the fall, his wife called the paramedics. Shortly after arriving in the emergency department, he became unresponsive and was emergently intubated. CT scan showed ICH (Figure 1). His ICH score upon admission was 4. His coagulation profile was normal. His platelets were decreased at 110,000/uL.

## DISCUSSION

A large percentage of the population sustaining traumatic brain injury due to falls are also those that are likely to be on chronic antiplatelet or anticoagulation therapy. The increased risk of bleeding with these agents after TBI then becomes worrisome, as increased morbidity and mortality has been shown to occur with any volume of bleeding, with larger volume hemorrhages having the worst prognosis.<sup>7,8</sup> A small number of papers to date have looked at warfarin, aspirin or clopidogrel use in mild TBI patients and mortality. These studies are summarized below and in Table 1.

### Warfarin

Warfarin is a vitamin K antagonist, and works by inhibiting the enzyme vitamin K epoxide reductase, which is responsible for carboxylating a glutamic acid residue. This is necessary for calcium binding, allowing connection to phospholipids surfaces to promote clotting.

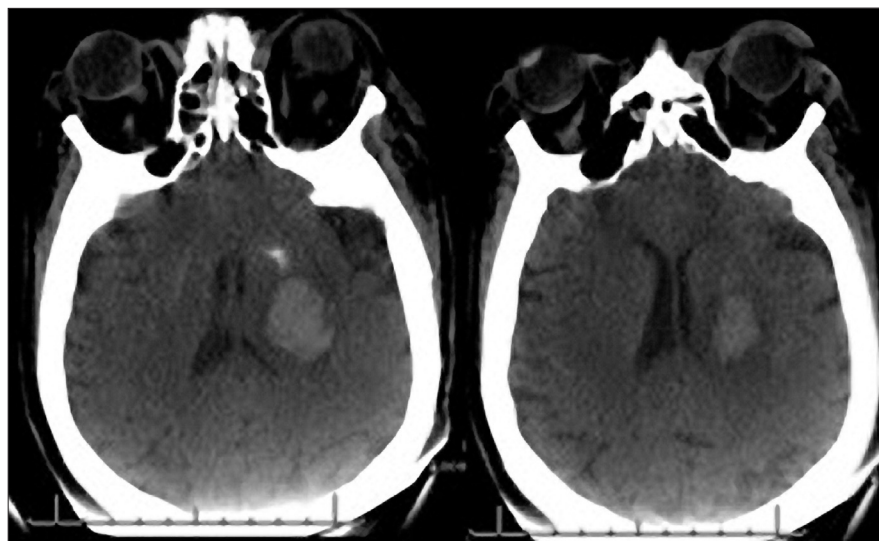


Figure 1

Axial CT scans demonstrating intracerebral hemorrhage.

**Table 1. Summary Of Studies On The Effects Of Anticoagulation Or Antiplatelet Therapy In Patients With Traumatic Brain Injury**

Study	Therapy	Number of Subjects	Mortality	Major findings
Wojcik et al., 2001	Warfarin	416	7.5% warfarin 8.2% control	No difference between mortality, ICU stay, LOS, or discharge disposition
Mina et al., 2002	Warfarin Aspirin Clopidogrel	19	47% aspirin 33% warfarin 8% control	Aspirin and warfarin significantly increased mortality
Spektor et al., 2003	Aspirin	110	Not recorded	No increased incidence of ICH in patients treated with low-dose aspirin
Lavoie et al., 2004	Warfarin	35	40% warfarin 21% control	Higher frequency of isolate head trauma, more severe head injuries and death
Ohm et al., 2005	Aspirin Clopidogrel	90	23% antiplatelet 8% control	Antiplatelet use in patients with ICH increased mortality
Jones et al., 2006	Clopidogrel	43	7% clopidogrel	Increased morbidity and blood transfusion requirement
Franko et al., 2006	Warfarin	159	23.9% 4.9% control	Mortality with warfarin greater than control Age a separate predictor of death
Pieracci et al., 2007	Warfarin	1,511	21.9% warfarin 15.2% control	Increased risk of mortality in patients using warfarin before ICH compared with controls
Wong et al., 2008	Clopidogrel	111	14% clopidogrel 3% aspirin	Clopidogrel increases long-term disability and mortality
Ahmed et al., 2009	Warfarin Aspirin Clopidogrel Heparin	29	20% warfarin 12.5% antiplatelet 20.6% control	No difference in mortality
Fortuna et al., 2009	Warfarin Aspirin Clopidogrel	166	6% clopidogrel 13% aspirin 17% warfarin 20% controls	No difference in mortality
Major et al., 2009	Aspirin Clopidogrel	287	1.4% aspirin	Mortality rate of 21% in patients with ICH on antiplatelet therapy
Bachelani et al., 2011	Aspirin	84	Not recorded	Aspirin did not increase risk of ICH progression or poor outcome
Bonville 2011	Warfarin Aspirin Clopidogrel	271	12.3% aspirin 9.3% clopidogrel	Warfarin increased mortality, aspirin and clopidogrel did not

Warfarin is cleared by the cytochrome P450 system in the liver and therefore has the potential to interact with a number of drugs. Warfarin is indicated for prophylaxis and treatment of venous thrombosis, pulmonary embolism, atrial fibrillation, post valve replacement, stroke or systemic embolization after myocardial infarction. It is monitored closely with PT and INR due to variable individual responses. Therapeutic levels usually fall between 2-3 for thromboembolism or atrial fibrillation or 2.5-3.5 with mechanical heart valves that are in the mitral position.<sup>28</sup>

Use of warfarin has been associated with increased risk of intracranial hemorrhage, more severe head trauma and increased mortality.<sup>12</sup> Studies have shown that higher INR levels at admission are associated with hemorrhage progression and subsequent risk of mortality.<sup>29-31</sup> The risk of mortality in a patient anticoagulated on warfarin with an ICH after head injury ranges in the literature from 16-80%.<sup>13-15</sup> Mina et al. found a 33% (4/12) mortality rate in TBI patients taking warfarin prior to injury versus 8% (3/37) of controls. The severity of the injury,

irrespective of anticoagulation use also seemed to impact mortality, with the majority of the deaths occurring in those falling down stairs.<sup>10</sup> Franko et al. also found a significant increase in mortality in patients that were anticoagulated, 23.9% versus controls, 4.9%.<sup>19</sup> Pieracci et al. demonstrated increased risk of mortality in patients using warfarin before ICH compared with patients who did not.<sup>20</sup> Only one study looked at the development of ICH after TBI in patients taking warfarin and found that it was increased compared to controls (57.1% vs. 30.5%).<sup>21</sup> In contrast, there

have also been studies that have not found an increase in mortality from warfarin use. Ahmed et al. and Fortuna et al. found no correlation between preinjury warfarin use and mortality.<sup>22,23</sup> Wojcik et al. also found no significant differences between warfarin and the control group with respect to mortality, ICU stay or LOS and discharge disposition.<sup>24</sup>

### Aspirin

Aspirin, also known as acetylsalicylic acid, is a non-steroidal anti-inflammatory agent with antipyretic, anti-inflammatory, analgesic and antiplatelet effects. It works by irreversibly binding and inhibiting cyclooxygenase-1 (COX-1) and inhibiting the production of thromboxane A2 (TXA2), which is normally involved in platelet aggregation. The effects of aspirin persist for the lifetime of the platelet (8-12 days).

The USPSTF currently recommends the use of aspirin to decrease the risk of myocardial infarction and stroke in men and women respectively. Aspirin use has been reported to be as high as 61% in adults  $\geq 65$  years old.<sup>3</sup>

One of the earliest papers (1992) looking at aspirin and hemorrhage in patients with head injuries found that aspirin was a risk factor in developing chronic subdural hematomas.<sup>9</sup> More recent papers have documented the increased risk of death with aspirin therapy in patients with radiographic evidence of intracranial injury.<sup>10,11</sup> Mina et. al found a statistically significant mortality rate (47%) in those taking aspirin compared with controls (8%).<sup>10</sup> Another study by other authors at the same institution found almost a threefold increase of death in patients taking either aspirin, clopidogrel or combination antiplatelet therapy compared with controls. However, they did not match comorbid conditions between cases and controls, with 71.1% of cases manifesting three or more conditions, compared with 34.8% in the control.<sup>11</sup> The greater number of comorbid conditions may have had an impact on the increased mortality seen in the cases. In contrast, a study by Spektor et. al found no correlation between low-dose aspirin consumption and the frequency or type of intracranial hemorrhage.<sup>17</sup> Neither did Bonville et. al.<sup>21</sup> It should be noted that in these studies, aspirin use was either patient-reported or gathered from outpatient pharmacy records. There were no bleeding times or platelet function tests done to confirm the degree of platelet inhibition.

Misclassification of exposure therefore may have occurred, skewing results and potentially explaining why certain studies were unable to see an effect of aspirin on mortality.

### Clopidogrel

Clopidogrel is a thienopyridine, along with Ticlopidine and Prasugrel. Their mechanism of action involves inhibiting the ADP receptor, P2Y12 on platelets. ADP is stored in platelets and released upon platelet activation and promotes further platelet activation. Clopidogrel was first approved by FDA in 1997 after the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial in 1996 found that clopidogrel was more effective than aspirin in reducing cardiovascular events. Clopidogrel is currently FDA-approved for use in reducing the risk of heart attack and stroke and PAD. It is also used in conjunction with aspirin in patients with stents to decrease the risk for in-stent thrombosis.<sup>4-6</sup>

Studies looking at clopidogrel use are lacking and to date, there is no consensus as to whether or not preinjury clopidogrel use increases mortality in patients with TBI. A retrospective chart review by Jones et. al did not find a statistically significant difference in mortality between those on clopidogrel and controls, but did find an increased morbidity and requirement for blood transfusions in patients receiving preinjury clopidogrel.<sup>16</sup> These findings agreed with those of Wong et. al, which found that prior clopidogrel use in TBI increased long-term disability and mortality.<sup>18</sup>

More recent studies have looked at reversing the antiplatelet effects of aspirin and clopidogrel with platelet transfusions in post-TBI patients.<sup>25</sup> No clear guidelines currently exist for antiplatelet reversal. A metaanalysis by Batchelor et al. found no clear benefit with regards to survival in administering platelets to those with antiplatelet-associated ICH.<sup>26</sup> Some studies have even found those receiving transfusions may predict worse outcomes than those that did not receive anything.<sup>27</sup> Recent development of assays to measure the degree of platelet inhibition such as P2Y12 or the Aspirin Response Test may help to establish recommendations for antiplatelet reversal. These assays may also help accurately assess the degree of platelet inhibition and can provide a more solid cause and effect relationship between antiplatelet use and TBI.

### CONCLUSION

Traumatic brain injury is a common cause of death in young individuals, but the incidence of mortality from TBI is also increasing among the elderly. Hemorrhage progression has been associated with poor outcomes and patients on anticoagulation or antiplatelet therapy coming in with TBI need to be closely monitored for the first few days. With a growing portion of the population on anticoagulation and antiplatelet therapy, the risk of hemorrhage progression will increase and so will mortality. Studies have already demonstrated that coagulopathies are associated with an increased risk of mortality that is likely secondary to hemorrhage progression. A consensus however, still has yet to be reached regarding mortality risk and patient reported anticoagulant or antiplatelet use in traumatic brain injury patients. The benefits of stroke or myocardial infarction prevention have to be weighed against the risk of hemorrhage and death in those at increased risk for traumatic brain injury from a variety of causes. Randomized clinical control trials need to be carried out in order to accurately assess the cause and effect relationship between these agents and development of intracranial bleeding, progression of bleeding and mortality. RCT will also help determine the utility of administering FFP or platelets for reversal of coagulopathies and the effects on morbidity.

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