IMPACT OF ANTITHROMBOTIC AGENTS ON RADIOLOGICAL LESION PROGRESSION IN ACUTE TRAUMATIC BRAIN INJURY: A CENTER-TBI PROPENSITY-MATCHED ANALYSIS

François Mathieu1,4, Marc Maegele2, Hester Lingsma3, Virginia Newcombe4, David Menon4
1. Division of Neurosurgery, University of Toronto, Toronto, Canada
2. Institute for Research in Operative Medicine (IFOM), Universität Witten/Herdecke, Witten, Germany
3. Department of Public Health, Erasmus MC, Rotterdam, Netherlands
4. Division of Anaesthesia and Neurocritical Care, University of Cambridge, Cambridge, UK

Introduction
Population ageing in Europe and beyond has resulted in an increasing number of elderly patients being prescribed antithrombotic therapy for cardio- or cerebrovascular indications.1, 2 Although preinjury antiplatelet and anticoagulant treatment (APAC) have been linked to higher mortality and worse neurological outcomes after traumatic brain injury (TBI),3-7,33 whether these effects are mediated by an increased risk of intracranial hemorrhage progression is unclear.

Given the challenges involved in performing accurate serial measurements of traumatic lesions on neuroimaging, most of the literature has focused on associations with clinical outcomes and ignored effects on hemorrhagic progression. The few studies that did attempt to incorporate radiological outcomes generally used crude estimation of lesion burden such as binary assessment of progression versus stability by a medical expert or semi-quantitative classification systems such as the Marshall score.5, 8-10 In addition, the majority of these studies did not adequately control for confounding factors associated with antithrombotic agent therapy, including increased age and comorbidities, which are known to contribute to poor outcome in TBI.11-13 Understanding the mechanisms through which the use of APAC medication leads to worse outcomes after head trauma is important as it provides potential therapeutic targets to mitigate secondary injury.

The primary aim of this study was therefore to quantify the impact of antithrombotic agent use on radiological lesion progression in acute TBI using a novel, semi-automated approach at volumetric lesion measurement. As a secondary aim, we also compared clinical outcomes in a group of APAC users versus non-users, using a propensity-matched cohort design to control for factors associated with preinjury antithrombotic medication use.

Methods
Subjects were selected from a pool of patients enrolled in CENTER-TBI with computed tomography (CT) scan at admission and repeated within 7d of injury. In order to increase comparability between APAC users and non-users, a propensity matching procedure was performed to control for factors influencing the probability that a participant would require antithrombotic therapy in the pre-injury period. Patients were matched on the following demographic variables and risk factors: age, sex, body mass index (BMI), history of cardiological disease, NYHA classification, history of hypertension, hepatic disease, neurological disease and renal disease. We also included the following injury-related variables in the propensity score model to isolate best as possible the effect of APAC medication on radiological progression: injury cause, injury severity score (ISS), baseline total GCS, baseline motor GCS, baseline pupillary reactivity status, Brain Abbreviated Injury Scale (AIS), Face AIS, Thorax/chest AIS, Abdomen AIS, Extremities AIS, Pelvic AIS, External AIS, systolic and diastolic blood pressure upon arrival to the treatment site. A propensity score was generated for each of the eligible participant using a logistic regression model fitted with the variables described above. A one-on-one matching procedure between APAC and non-APAC users with a caliper of 0.05 was then performed.

Using a novel, semi-automated lesion segmentation approach based on a three dimensional convolutional neural network (3D CNN), we calculated absolute changes in volume of intraparenchymal (IPH), extra-axial (EAH), intraventricular (IVH) and total intracranial hemorrhage (ICH) between scans, and compared volume of hemorrhagic progression, proportion
of patients with significant degree of progression (>25% of initial volume), proportion with new intracranial hemorrhage on follow-up CT. We also assessed the following clinical outcomes: proportion of patients requiring intensive care unit (ICU) admission, ICU length of stay (LOS), total hospital LOS, need for neurosurgical intervention, death from any cause and death attributed to intracranial injuries and Extended Glasgow Outcome Scale (GOSE) at 6 months.

**Statistical analysis:** Comparisons of normally distributed variables between both patient groups were performed using the two-tailed Student’s t-test and non-parametric data were compared using the Mann-Whitney U test. For categorical variables, we used Chi-Square to assess for differences in proportions between the two groups. Mixed-effect logistic regression models were built to look at the influence of APAC use on hemorrhagic progression after accounting for initial lesion volume and timing of imaging studies, which have been shown to predict delayed lesion expansion.17-20

**Results**

**Patient characteristics:** A total of 316 patients (158 APAC users and 158 non-users) were successfully matched and included in the analysis. The mean age for the overall sample was 67.9 ± 12.2, 65 % were male, the median GCS score was 14 (range 3-15) with 10.5 % presenting with a pupillary abnormality. Comparative demographic and clinical characteristics between both patient groups including age, gender, mechanism of injury, baseline GCS and pupillary reactivity, injury severity score and systolic blood pressure on arrival to the study center were not statistically different between both groups (Table not shown).

There were no significant differences in the distribution of Marshall and Rotterdam scores for the initial CT scan, proportion of patients with a positive initial imaging study (87.6 versus 89.1 %, \(p = 0.72\)) and distributions of initial intracranial hemorrhage volumes in APAC users and non-users. Timing of the initial (3.6 ± 4.2 versus 4.0 ± 7.3 hour of injury, \(p = 0.57\)) and repeat CT scan (37.1 ± 36.5 versus 36.8 ± 43.5 hours from injury, \(p = 0.95\)) relative to time of injury were also comparable in both groups. 12 patients in the APAC group and 10 patients in the control group were excluded from the imaging analyses due to a technical inadequacy of either the initial or repeat imaging datafile.

Mean hemoglobin (13.1 vs 13.4 g/dL), international normalized ratio (INR) (1.1 versus 1.04), activated partial thromboplastin time (aPTT) (29 vs 28 seconds), platelet (205 vs 194 per nL) and fibrinogen (264.5 vs 282 mg/dl) levels were not statistically different between the groups. The presence of a coagulopathy on admission, broadly defined by conventional laboratory assays as an INR > 1.2 or aPTT > 35s or platelets < 100/nL or fibrinogen < 150 mg/dL was more frequent in APAC users (24.6% of APAC users versus 14.2% of non-users, \(p = 0.03\)). The breakdown of specific agents prescribed in the APAC group consisted of 70 patient on aspirin, 7 patients on clopidogrel, 13 patients on dual antiplatelet therapy, 6 patients on other forms of antiplatelet agent, 30 patients on vitamin K antagonists, 9 patients on direct oral anticoagulants (DOACs), 8 patients on unfractionated or low-molecular-weight-heparin (LMWH) and 3 patients on a combination of antiplatelet and anticoagulant medications. A summary of blood products and reversal agents received in each subgroup in the interval between admission and the repeat imaging study is available in a supplementary table (not shown here). 24 of the 30 patients (80.0%) on vitamin K antagonist were reversed using either fresh frozen plasma (FFP), prothrombin complex concentrate (PCC) and/or vitamin K. 7 of the 8 patients (87.5%) on unfractionated heparin or low-molecular heparin received some form of reversal consisting of FFP or PCC. Administration of protamine was however not recorded. In contrast, only 1 of 9 patients on direct oral anticoagulants received PCC and another was given tranexamic acid. 16 of 97 patients (16.5%) of patients on preinjury antiplatelet therapy received a platelet transfusion.

**Primary Outcome:** The mean volume of total intracranial hemorrhage (ICH) progression was 7.0 mL (± 21.3 mL) in APAC users and 6.0 mL (± 19.5 mL) in controls (\(p = 0.08\)) (see Table 1). APAC
users showed a higher mean growth volume for extra-axial hemorrhage (3.1 ± 16.0 mL versus 1.3 ± 11.5 mL, \( p = 0.01 \)). There were no significant between-group differences for intraparenchymal (3.8 ± 11.7 mL in APAC users versus 4.6 ± 16.0 in controls, \( p \) value =0.70) or intraventricular (0.2 ± 0.7 mL versus 0.0 ± 0.4, \( p \) value =0.79) lesions.

After accounting for initial lesion volume and timing of the initial CT scan, APAC status remained predictive of extra-axial hematoma expansion of 5mL or greater (odds ratio 2.14, \( p=0.039 \)) (Table not shown here). However, only initial hematoma size remained significant when looking at the smaller progression thresholds (>1mL, >2mL) for the extra-axial model. In contrast, initial lesion volume and short interval between injury and the first CT scan (odds ratio 1.09 and 0.77 respectively, \( p<0.001 \)), but not APAC status, were predictive of intraparenchymal hemorrhage expansion for all the different volume thresholds. We did not include IVH in these multivariate analyses given the negligible amount of interval change seen in both cohorts.

A breakdown of ICH progression volumes for each APAC agent subtype is presented in Supplementary Table (not shown here). Interestingly, patients on dual antiplatelet therapy, direct oral anticoagulants (DOACs) and patients on concurrent antiplatelet and anticoagulant therapy showed substantially larger progression volumes, but we cannot comment on statistical significance given the small subgroup sizes.

Of note, there was one outlier in the control group with an intraparenchymal progression volume of 159 mL. A sensitivity analysis excluding this datapoint brought the mean IPH progression to 3.6 ± 9.6 mL in controls (versus 3.8 ± 11.7 mL in APAC users), but the between-group difference still would not have reached significance. **Secondary radiological and clinical outcomes:** There were 79 patients (54.1 %) amongst APAC users who experienced significant hemorrhage progression compared to 55 (37.0%) in the control group (\( p = 0.003 \)) (Table 2). New intracranial hemorrhage was present on the repeat scan for 4 of the 18 APAC users who had a negative initial study and none of the non-users (\( p = 0.04 \)), but all of delayed hemorrhages were less than 2mL in size and none of these patients required neurosurgical intervention.

There were no significant differences in terms of need for ICU admission (64.4 versus 68.8%, \( p = 0.41 \)), ICU length of stay (10.7 versus 10.2 days, \( p = 0.78 \)), total hospital length of stay (19.3±35.6 versus 17.9±20.0 days, \( p = 0.33 \)) or rates of neurosurgical hematoma evacuation (24.4 versus 25.0%, \( p = 0.89 \)) between the two groups (Table 2). The median time from injury to hematoma evacuation was 6 hours for the APAC group (IQR: 3.75 to 10) and 6.5 hours for the control group (IQR: 3 to 20.25). The overall mortality rate at 6 months was 20.3 % (21.9 % in APAC users versus 18.8% in controls, \( p =0.51 \)). Extended Glasgow Outcome Scale (GOSE) distributions at 6 months were not statistically different between APAC users and non-users (Figure not shown).

**Conclusion**

We assessed the impact of preinjury antithrombotic therapy on radiological lesion progression in acute TBI patients. We found that APAC users experienced a significantly greater amount of hemorrhagic progression for extra-axial, but not for intraparenchymal or intraventricular lesions. To our knowledge, this is the first study quantifying the amount of lesion progression in this context by using a volumetric approach.

Preinjury use of antithrombotic agents was associated with greater expansion of extra-axial lesions, higher rates of significant hemorrhagic progression and higher risk of delayed traumatic intracranial hemorrhage, but this was not associated with worse clinical or functional outcomes. Future studies should attempt to delineate the differential effects of each APAC agent, ideally using a controlled, prospective and multicenter design. If such studies show significant adverse effects with specific agents, this would provide an impetus for optimization of targeted reversal strategies and a more thorough consideration of alternative antithrombotic regimen in patients with a high-risk profile for falls or other trauma mechanisms.
Tables and Figures

Figure 1: Semi-automated lesion segmentation maps

A: original image; B: automated lesion prediction; C: semi-automated lesion map after manual corrections by expert; Green label: extra-axial hemorrhage; Red label: intraparenchymal hemorrhage (contusion core); Blue label: edema; Yellow label: intraventricular hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>APAC (n=146)</th>
<th>Control (n= 148)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Intraparenchymal (mL)</td>
<td>3.8(11.7)</td>
<td>4.6(16.0)</td>
<td>0.70</td>
</tr>
<tr>
<td>Δ Extra-axial (mL)</td>
<td>3.1(16.0)</td>
<td>1.3(11.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Δ Intraventricular (mL)</td>
<td>0.2(0.7)</td>
<td>0.0(0.4)</td>
<td>0.79</td>
</tr>
<tr>
<td>Δ Total intracranial hemorrhage (mL)</td>
<td>7.0(21.3)</td>
<td>6.0(19.5)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Δ, change in volume between initial and repeat CT scan. Significant p-values are italicized.
<table>
<thead>
<tr>
<th></th>
<th>APAC</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiological outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of significant hemorrhage growth</td>
<td>79/146(54.1)</td>
<td>55/148(37.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>New intracranial hemorrhage</td>
<td>4/18(22.2)</td>
<td>0/16(0.0)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Clinical outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>101/158(63.9)</td>
<td>108/158(68.4)</td>
<td>0.41</td>
</tr>
<tr>
<td>ICU length of stay (days)</td>
<td>10.7(11.1)</td>
<td>9.6(9.6)</td>
<td>0.43</td>
</tr>
<tr>
<td>Total hospital length of stay (days)</td>
<td>19.3(35.7)</td>
<td>17.4(19.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>Neurosurgical hematoma evacuation</td>
<td>39/158(24.7)</td>
<td>39/158(24.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Mortality (6 months)</td>
<td>35/158(22.2)</td>
<td>30/158(19.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>Death attributed to intracranial injury</td>
<td>16/158(10.1)</td>
<td>10/158(6.3)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

ICU, intensive care unit. Significant p-values are italicized.
References


The work was performed in Toronto, Canada and Cambridge, United Kingdom between September 2018 to July 2019, as part of my research year (4th PGY year in the University of Toronto Neurosurgery residency program).

I designed the study, developed the semi-automated image-analysis pipeline, performed the imaging analyses, analysed the clinical data and wrote the manuscript.

David Menon and Virginia Newcombe acted as my primary and secondary research supervisors during my Master’s in Clinical Neuroscience at the University of Cambridge performed during my 4th PGY year.

Marc Maegele provided some guidance with regards to the CENTER-TBI data on antithrombotics use and patient’s coagulation profile.

Hester Lingsma reviewed the statistical analysis plan for the study and assisted with the propensity matching.