Timing of the resumption of antithrombotic agents following surgical evacuation of chronic subdural hematomas: a retrospective cohort study

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OBJECTIVE Antithrombosis (AT), defined here as either antiplatelets or anticoagulants, is a significant risk factor for the development of chronic subdural hematomas (cSDHs). Resuming AT following the evacuation of cSDH is a highly variable practice, with scant evidence in the literature for guidance. Here, a retrospective analysis of a cohort of patients from a single institution undergoing surgical drainage of cSDH was performed to evaluate postoperative complications and determine the optimal timing of the resumption of common antithrombotic agents.

METHODS This retrospective analysis was performed on 479 patients undergoing surgical evacuation of cSDH at St. Michael’s Hospital over a 5-year period (2007–2012). The collected variables included the type of AT agent, indications for AT, timing and type of postoperative complications, and the restart intervals for the AT agents, when available. Postoperative complications were classified as major hemorrhages, minor hemorrhages, or thromboembolic events.

RESULTS Among all 479 study patients, 71 experienced major hemorrhage (14.8%), 110 experienced minor hemorrhage (23.0%), and 8 experienced thromboembolism (1.67%) postoperatively. Patients on any type of preoperative AT regimen were at a higher risk of major hemorrhage (19.0% vs 10.9%; OR 1.93; 95% CI 1.15–2.71; p = 0.014). The type of AT agent did not affect the frequency of any postoperative complications. Patients on any preoperative AT regimen experienced earlier postoperative major hemorrhages (mean 16.2 vs 26.5 days; p = 0.052) and thromboembolic events (mean 2.7 vs 51.5 days; p = 0.036) than those patients without a history of AT; the type of AT agent did not affect timing of complications. Patients who were restarted on any AT therapy postoperatively were at decreased risk of major rebleeding following resumption than those patients who were not restarted (OR 0.06; 95% CI 0.02–0.2; p < 0.01).

CONCLUSIONS Patients with a history of preoperative AT experienced thromboembolic complications significantly earlier than those patients without AT, which peaked at 3 days postoperatively with no increase in hemorrhage risk when AT was restarted. Cursory evidence is presented that shows resuming AT early following the surgical evacuation of cSDH at 3 days postoperatively may be safe. However, much larger prospective studies are required prior to providing any definitive recommendations regarding the optimal timing and method of resumption of individual agents.

KEY WORDS anticoagulation; antiplatelet; antithrombosis; chronic subdural hematoma; vascular disorders

Chronic subdural hematoma (cSDH) is a disease of the elderly and demonstrates an incidence of approximately 3.4 patients per 100,000 persons younger than 65 years of age and 8 to 58 patients per 100,000 persons older than 65 years.1,4,9 The prevalence of cSDH is expected to rise as the percentage of the United States population older than 65 years grows from 12% in 2003 to a projected 20% by 2030.17 Other identified risk factors for the development of cSDH include male sex, history of falls, chronic alcohol use, and antiplatelet or anticoagulant therapy, with warfarin increasing the relative risk of developing cSDH by
The recurrence rates for cSDH in the recent literature range from 9% to 33%. The predictors of recurrence are highly variable but include patient characteristics such as age and bilateral cSDH, radiographic variables such as preoperative hematoma width and morphology, and surgical and perioperative factors such as operative technique and choice of drainage system.

The use of antithrombosis (AT), which is defined here as either antiplatelets or anticoagulants, is expanding with a progressive rise in the prevalence of patients with atherosclerotic risk factors, as well as thrombogenic cardiac arrhythmias which typically affect the elderly. Acute coronary syndromes affect more than 750,000 Americans per year, with dual antiplatelet therapy being the current standard of care. Atrial fibrillation afflicts more than 2.4 million Americans, and warfarin or targeted anticoagulants are used to treat those at high risk of arterial embolism. The use of any AT is known to predispose the patient to developing cSDH, and it is well accepted that these agents should be stopped at presentation and reversed in the case of warfarin. The impact of AT on recurrence following surgical drainage, however, is controversial. Balancing the risk of rebleeding with potential thromboembolic complications in these patients is an ongoing dilemma with scant evidence available to guide if and when therapeutic AT should be resumed postoperatively.

Here, we retrospectively analyzed a cohort of 479 patients who were treated surgically for cSDH at a single institution. We collected data on postoperative hemorrhagic and thromboembolic complications, when available, along with preoperative AT agents and indications. By analyzing one of the largest cohorts of cSDH patients in the literature, all of whom were from a single institution, underwent similar surgical techniques performed by 6 staff neurosurgeons, and have rates of recurrence and thromboembolism available, we hope to provide more robust evidence to guide the resumption of therapeutic AT as well as direct further definitive studies.

Methods

Patient Selection

The study subjects were collected from a database of patients admitted to St. Michael’s Hospital, Toronto, Canada, between 2000 and 2012. We searched the database for the following codes included in the ICD-10: codes I62 (other nontraumatic intracranial hemorrhage), S06.5 (traumatic subdural hemorrhage), S06.6 (traumatic subarachnoid hemorrhage), S06.8 (other intracranial injuries), S06.9 (intracranial injury, unspecified). The search was restricted to patients with electronic records and limited to those patients admitted after January 1, 2007. The records were then manually filtered to identify eligible patients. Study approval was obtained from the St. Michael’s Hospital Research Ethics Board.

Patients eligible for study inclusion included those older than 18 years of age with their first presentation to St. Michael’s Hospital, those with an isolated cSDH (defined as an untreated hematoma for > 3 weeks or a hypodense subdural hematoma on CT scan), and those treated surgically for the first time at this institution. Surgical drainage was performed via a single bur hole or craniotomy at the surgeon’s discretion, as dictated by the patient’s clinical and imaging findings. A minimum of 1 documented clinic follow-up visit was required.

Patients with nonhead injuries that might otherwise promote immobility and its associated thromboembolic complications, traumatic or aneurysmal subarachnoid hemorrhage, iatrogenic SDH, underlying coagulopathies, or platelet disorders (e.g., liver disease, myeloproliferative disorders) were excluded from the search.

The final search yielded 479 patients with spontaneous or posttraumatic cSDH. A clear history of trauma or fall could not be identified in all patients.

Data Collection

The collected variables included patient age, sex, number and type of surgical procedures, type of preoperative AT, indications for AT, time of AT discontinuation, reversal of AT, time of postoperative resumption of AT, time of postoperative complications, and follow-up interval. Preoperative patient comorbidities and functional status were not always readily identifiable and, hence, were not included in our data set. CT scans are not kept on the hospital imaging server for more than 2 years, and hematoma size was not always specified in the radiology reports; hence, data on preoperative hematoma size and morphology were not readily identifiable.

Antithrombotics were defined to include both anticoagulant and antiplatelet agents. The antiplatelets assessed in this study include acetylsalicylic acid (ASA; 81 mg or 325 mg daily), clopidogrel (75 mg daily), and dipyridamole (200 mg twice daily); anticoagulants included warfarin (dosed to the therapeutic international normalized ratio [INR] target), low-molecular-weight heparin (LMWH; dalteparin or enoxaparin administered at a weight-based therapeutic dosage), and targeted coagulation inhibitors (dabigatran, fondaparinux, rivaroxaban, or apixaban).

The indications for AT were categorized as primary prevention (the presence of hypertension, diabetes, hypercholesterolemia, and/or smoking history), atrial fibrillation, prior transient ischemic attack (TIA), or stroke, documented coronary artery disease (CAD; history of acute coronary syndrome or angiographic coronary disease, with or without surgical or endovascular revascularization), mechanical heart valve placement, arterial stent placement (coronary, carotid, or peripheral), active peripheral arterial/venous thrombosis or pulmonary embolism, venous thrombosis prophylaxis, or another indication. Reversal of AT was assessed only for patients on a regimen of warfarin with any combination of vitamin K, fresh-frozen plasma, or prothrombin complex concentrate. The reversal of other agents was attempted inconsistently, for instance with pooled platelet transfusions for antiplatelets. Given the lack of reliable efficacy, however, the reversal of agents other than warfarin was not assessed here.

Postoperative complications were classified as major hemorrhage, minor hemorrhage, or thromboembolic events. Major hemorrhage denotes a recurrent intracranial hemorrhage requiring either repeat operative drainage or

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readmission to the hospital for observation. Minor hemorrhage refers to residual subdural hematomas seen on outpatient postoperative imaging that necessitated further radiographic follow-up, but not readmission to hospital or reoperation. Thromboembolic events were categorized as peripheral venous thrombosis (including pulmonary embolism), peripheral arterial thrombosis, myocardial infarction, or TIA/stroke.

Our institution does not have guidelines for the routine administration of postoperative venous thromboprophylaxis to our patient cohort. Most patients were started on prophylactic subcutaneous heparin or LMWH at appropriate weight-based dosing on postoperative Day 2 or 3; however, there was significant variability across patients and staff neurosurgeons and, hence, this was not captured in our data set.

Data Analysis

The incidence of postoperative complications and timing were compared among patients on any AT regimen, patients off an AT regimen, and patients receiving ASA (81 mg or 325 mg daily), clopidogrel, or warfarin. The number of patients receiving other AT agents was too small to allow a stratified analysis. We found no differences in the complication incidence or timing between patients on preoperative ASA versus clopidogrel versus warfarin, and, hence, subsequent analyses following the resumption of AT were performed by pooling the patients on any of these 3 agents preoperatively in order to improve the statistical power.

Differences in complication timing between multiple (i.e., > 2) AT agents were assessed using Kruskal-Wallis 1-way ANOVA with Dunn’s multiple-comparisons tests. Comparisons between 2 groups of patients were made using the Mann-Whitney U-tests. Differences in complication frequencies among multiple (> 2) antithrombotics were analyzed using the chi-square tests; differences between 2 groups of patients were compared using the Fisher exact tests. Odds ratios and confidence intervals were computed for each test as appropriate. In order to obtain the cumulative hazard rates, differences in time-dependent outcomes (time to postoperative hemorrhage or thromboembolism) based on the timing of AT resumption were assessed by Cox proportional hazards regression using maximum likelihood methods. The significance level in all patients was set at \( p \leq 0.05 \).

All statistical analyses were performed using GraphPad Prism (GraphPad Software, Inc.).

Results

Patient Characteristics

The study patient characteristics are shown in Table 1. Patients had a mean age of 72.3 years, which was higher among those patients on preoperative AT (mean 76.4 years) than patients not receiving preoperative AT (mean 68.4 years), with significant male predominance. There were similar numbers of left- and right-sided cSDH. One-quarter of patients presented with bilateral hematomas; all but 5 of these patients required bilateral evacuation in their initial operation. The majority of patients underwent single bur hole drainage of their cSDH; a small subset underwent mini-cranietomy as their initial operation due to an acute-on-chronic or highly membranous appearance on CT imaging. The proportion of patients requiring initial mini-cranietomy was not affected by the use of preoperative AT. One patient underwent mini-cranietomy without replacement of the bone flap and hence was classified as a craniectomy. A closed subdural drainage system to thumb suction, using a Jackson-Pratt device, was placed in all 479 patients. The mean follow-up time was 3.1 months.

AT Profiles

Preoperative and postoperative AT use in our cohort is shown in Fig. 1. In total, 231 of 479 study patients (48%) were receiving AT therapy on admission: 127 patients were receiving 81 mg ASA (27%), 9 were receiving 325 mg ASA (2%), 28 were receiving clopidogrel (6%), 86 were receiving warfarin (18%), 8 were receiving LMWH (2%), 1 was receiving dabigatran (0.2%), and 6 were receiving dipyridamole (1%). Thirty-two patients were receiving multiple agents, and the majority were receiving either ASA+clopidogrel or ASA+warfarin; the former were typically on an AT regimen for recently implanted vascular stents, and the latter for atrial fibrillation and either primary prevention or known CAD. All patients on an AT regimen at presentation had their medication discontinued at or before surgery. The median time from discontinuation to initial operation was 1 day, with the exception of clopidogrel which was stopped a median of 3 days preoperatively. In total, 59 of 86 patients on warfarin (69%) un-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD in yrs</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>72.3 ± 13.6</td>
</tr>
<tr>
<td>Preop AT</td>
<td>76.4 ± 12.4</td>
</tr>
<tr>
<td>Restarted</td>
<td>76.0 ± 11.2</td>
</tr>
<tr>
<td>Not restarted</td>
<td>77.1 ± 14.1</td>
</tr>
<tr>
<td>No preop AT</td>
<td>68.4 ± 14.3</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>341 (71.2)</td>
</tr>
<tr>
<td>Female</td>
<td>138 (28.8)</td>
</tr>
<tr>
<td>Total</td>
<td>479 (100)</td>
</tr>
<tr>
<td>Side of cSDH</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>175 (36.5)</td>
</tr>
<tr>
<td>Right</td>
<td>184 (38.4)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>120 (25.1)</td>
</tr>
<tr>
<td>Initial surgical management</td>
<td></td>
</tr>
<tr>
<td>Bur hole</td>
<td>409 (84.9)</td>
</tr>
<tr>
<td>Craniotomy</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>72 (14.9)</td>
</tr>
<tr>
<td>Preop AT</td>
<td>38 (7.9)</td>
</tr>
<tr>
<td>No preop AT</td>
<td>34 (7.1)</td>
</tr>
<tr>
<td>Craniectomy</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

* Values are presented as the number of patients (%) unless stated otherwise.

Results
underwent some form of reversal, which generally included a combination of intravenous vitamin K and either fresh-frozen plasma or a prothrombin complex concentrate.

The indications for preoperative AT are shown in Fig. 2. Eighty-four patients were on an AT regimen for primary prevention due to atherosclerotic risk factors, 72 for atrial fibrillation, 34 for prior TIA or stroke, 45 for CAD with or without revascularization, 8 for mechanical cardiac valves, 13 for indwelling arterial stents (coronary, carotid, or peripheral), 14 for the treatment of active peripheral arterial/venous thrombosis or pulmonary embolism, 2 for deep venous thrombosis (DVT) prophylaxis, and 6 for other indications.

Early and More Frequent Major Hemorrhages With Preoperative AT

A summary of all postoperative complications encountered in our patient cohort, as stratified by pre- and postoperative AT use, is shown in Table 2. Among all study patients, postoperative major hemorrhage occurred in 71 of 479 patients (14.8%); of these, 64 patients required reoperation (16 of whom required a third procedure and 3 of whom required a fourth) and 7 patients were readmitted to the hospital for observation without further intervention. Patients on any AT preoperatively were more likely to have a major hemorrhage than those off AT (19.0% vs 10.9%; OR 1.93; 95% CI 1.15–2.71; p = 0.014). Subgroup analysis revealed that patients on preoperative ASA (OR 1.75; 95% CI 0.97–2.53; p = 0.083) or warfarin (OR 2.17; 95% CI 1.12–3.20; p = 0.023) were also more likely to rebleed than those patients off AT (Fig. 3). Patients on clopidogrel preoperatively did not rebleed at a significantly higher rate than patients off AT, but there was no statistical difference in the incidence of major hemorrhage.
rhage between patients on ASA versus clopidogrel versus warfarin (chi-square = 1.52; p = 0.47). Among patients on warfarin, preoperative reversal did not affect the rate of major hemorrhage.

Postoperative major hemorrhages occurred earlier in patients receiving any preoperative AT at a median interval of 16.2 days versus 26.5 days (Fig. 4). This just misses the level of statistical significance (p = 0.052). There was no difference in the timing of major rebleeds between patients receiving ASA versus clopidogrel versus warfarin (Fig. 4, lower), demonstrating median intervals of 14.2, 8.7, and 12.8 days, respectively.

Minor Hemorrhage Incidence and Timing Is Unaffected by Preoperative AT

Among all study patients, postoperative minor hemorrhage occurred in 110 of 479 patients (23.0%). There was no difference in the minor hemorrhage frequency between patients with or without a history of preoperative AT (23.8% vs 22.1%), or between patients on ASA versus clopidogrel versus warfarin preoperatively (chi-square = 3.06; p = 0.22) (Fig. 3). There was no statistical difference in the timing of minor hemorrhage between patients with or without a history of any AT (median 53.2 vs 46.4 days), nor between patients on ASA versus clopidogrel versus warfarin preoperatively (median 46.7 vs 40.0 vs 50.2 days, respectively) (Fig. 5).

Earlier Postoperative Thromboembolism With Preoperative AT

Thromboembolic complications occurred in 8 of 479 study patients (1.67%). Six of the 8 thromboembolic events occurred in patients on preoperative AT (Table 2): 2 myocardial infarctions in patients on ASA for known CAD, 1 DVT in a patient on warfarin for previous DVT, and 3 events unrelated to the indication for initial AT (1 in-hospital stroke in a patient on ASA+clopidogrel for coronary stents, and 2 radial artery thrombi in patients on AT for primary prevention or prior stroke). One in-hospital stroke and 1 DVT were seen in patients not on preoperative AT. No cases of stent thrombosis were seen. There was no statistical difference in the frequency of thromboembolism between patients with or without a history of preoperative AT (2.60% vs 0.81%; OR = 3.28; 95% CI 0.66–5.90; p = 0.16). There was also no statistical difference in thromboembolism frequency among patients on ASA versus clopidogrel versus warfarin preoperatively (chi-square = 7.08; p = 0.069); however, patients on clopidogrel demonstrated the highest postoperative thromboembolic rate (7.7%), which barely misses the level of significance (p = 0.052) (Fig. 3).

TABLE 2. Summary of the postoperative complications

<table>
<thead>
<tr>
<th>AT</th>
<th>Major Hemorrhage</th>
<th>Minor Hemorrhage</th>
<th>Thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prerestart</td>
<td>Postrestart</td>
<td>Prerestart</td>
</tr>
<tr>
<td>No AT preop (n = 248)</td>
<td>27</td>
<td>59</td>
<td>2</td>
</tr>
<tr>
<td>AT preop (n = 231)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA preop (n = 136)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restarted (n = 78)</td>
<td>7</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Downgraded to ASA (n = 14)†</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Not restarted (n = 58)</td>
<td>16</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Clopidogrel preop (n = 28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restarted (n = 7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not restarted (n = 21)</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Warfarin preop (n = 86)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restarted (n = 35)</td>
<td>2</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Not restarted (n = 51)</td>
<td>16</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

* The number of postoperative complications stratified by pre- and postoperative AT status are shown. The complications are categorized by their occurrence at pre- or postresumption of AT, where applicable.
† Patients in this category were on either clopidogrel or warfarin preoperatively and resumed ASA (81 mg) or ASA (325 mg) postoperatively.
Thromboembolic complications occurred significantly earlier in patients with a history of preoperative AT (median 2.7 vs 51.5 days; p = 0.036) (Fig. 6). There was no statistical difference in thromboembolism timing for patients on ASA versus clopidogrel versus warfarin preoperatively (median 3.5 vs 3.5 vs 2.0 days, respectively) (Fig. 6 lower).

**Postoperative AT Resumption Associated With Reduced Recurrence**

Of the 231 study patients on preoperative AT, 120 were restarted on a postoperative AT agent (51.9%), 106 on their home regimen. The remaining 14 patients resumed ASA or converted from either ASA+clopidogrel (typically for indwelling stents or CAD) or warfarin (typically for atrial fibrillation with questionable indications for therapeutic anticoagulation). No cases of inferior vena cava filter insertion in lieu of AT resumption were found.

The restart frequencies and intervals of all AT agents assessed in this study are shown in Table 3. AT was resumed at a median of 52 days postoperatively, and at >2 weeks in 75% of cases. Of all agents, clopidogrel was resumed least often and with the largest delay. No agent was resumed earlier than 3 days postoperatively. There was no difference in the rate of resumption of any agent between patients undergoing initial craniotomy versus bur hole evacuation (p = 0.52).

Fifty of 231 patients on preoperative AT suffered a major hemorrhage, of whom 15 resumed AT treatment postoperatively and in only 3 did the resumption of AT precede rebleeding (Table 2). Patients with a history of preoperative AT who were restarted on any AT had a reduced risk of rebleeding following resumption in comparison with those patients who did not resume AT (26.9% vs 2.2%; OR 0.06; 95% CI 0.02–0.2; p < 0.01) (Fig. 7 upper).

Of our cohort’s 6 total thromboembolic complications...
in patients receiving preoperative AT, 4 occurred in patients who resumed postoperative AT and all occurred prior to AT resumption. Patients who resumed AT did not show any difference in thromboembolism frequency prior to AT resumption relative to the patients who did not resume AT (3.3% vs 1.8%; OR 1.34; 95% CI 0.29–6.13; p = 0.89) (Fig. 7 lower). Cox proportional hazards regression of thromboembolism against time to resumption demonstrated a hazard ratio of 1.00 (95% CI 0.98–1.02; p = 0.86), indicating no influence of the resumption interval on the subsequent thromboembolism risk.

### Discussion

Antiplatelet and anticoagulant therapy are known risk factors for the development of cSDH, which are expected to rise in prevalence with the aging population that increasingly requires AT to treat the diseases that afflict it. The reported AT use in prior studies ranges from 18% to

### Table 3. Postoperative resumption of AT*

<table>
<thead>
<tr>
<th>Preop Agent</th>
<th>% Restarted</th>
<th>Early Restart</th>
<th>Late Restart</th>
<th>Median Restart Interval (range) in Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ATs</td>
<td>51.9% (120/231)</td>
<td>24.4%</td>
<td>75.6%</td>
<td>52 (3–801)</td>
</tr>
<tr>
<td>ASA</td>
<td>57.4% (78/136)</td>
<td>30.8% (24/78)</td>
<td>69.2% (54/78)</td>
<td>52 (3–187)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>25.0% (7/28)</td>
<td>0.0% (0/7)</td>
<td>100.0% (7/7)</td>
<td>67 (28–104)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>40.7% (35/86)</td>
<td>14.3% (5/35)</td>
<td>85.7% (30/35)</td>
<td>47 (4–801)</td>
</tr>
<tr>
<td>LMWH</td>
<td>37.5% (3/8)</td>
<td>33.3% (1/3)</td>
<td>66.7% (2/3)</td>
<td>17.5 (7–57)</td>
</tr>
<tr>
<td>Targeted anticoagulants</td>
<td>100.0% (1/1)</td>
<td>0.0% (0/1)</td>
<td>100.0% (1/1)</td>
<td>53 (53–53)</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>66.7% (4/6)</td>
<td>0.0% (0/4)</td>
<td>100.0% (4/4)</td>
<td>54 (32–66)</td>
</tr>
</tbody>
</table>

* The number and percentage of patients on a given preoperative agent restarted on the same agent postoperatively. Early/late restart refers to the percentage of restarts at ≤ 2 weeks (early) or > 2 weeks (late) from the time of the initial operation.
43% of patients with cSDH.\textsuperscript{3,7,11,27,29} Our cohort had slightly elevated numbers, with 48% of patients on any AT, 33% on antiplatelets, and 18% on warfarin.

The use of AT has not been as clearly associated with postoperative recurrence in the literature, although retrospective analyses reveal a recurrence rate as high as 33% for patients on AT at presentation versus as high as 15% for patients off AT.\textsuperscript{10} Forster et al. and Rust et al. showed increased recurrence with antiplatelets;\textsuperscript{11,25} Chon et al. found increased recurrence with anticoagulants,\textsuperscript{7} and several others found no increase in recurrence with either anticoagulants or antiplatelets.\textsuperscript{15,23,27,29} The overall recurrence rate of 14.8% in our cohort is consistent with prior studies. Our findings show increased major rehemorrhage in patients with a history of any preoperative AT (19% vs 10.9%), and specifically ASA and warfarin (17.7% and 20.9%, respectively). Interestingly, patients on clopidogrel did not show a proclivity to rebleed; we found no prior studies in the literature on the recurrence rates in the context of clopidogrel. In our cohort, clopidogrel was discontinued a median of 3 days prior to initial operation versus 1 day for both ASA and warfarin, which may partially explain this finding.

The incidence of thromboembolic complications in our cohort was 1.67%, which is consistent with previous reports. Few studies on cSDH have adequately evaluated thromboembolic complications in order to assess the relative rates in patients with and without a history of preoperative AT\textsuperscript{6} though the discontinuation/reversal of warfarin in 1 study did not increase the thromboembolism risk.\textsuperscript{15} Data on patients with any intracranial bleeding, without distinction of intra- and extraaxial hemorrhages or AT status, has shown equivalent hemorrhage and thromboembolism rates of roughly 6% to 7%.\textsuperscript{16} In our study there was a trend toward increased thromboembolism in patients on any preoperative AT (2.60% vs 0.81%), though this was not statistically significant. Patients on clopidogrel had the most thromboembolic complications; this may have been due partly to the cessation of clopidogrel earlier than ASA or warfarin. The indications for clopidogrel typically included arterial stents, which are thought to have a higher risk of thrombosis; however, none of our complications included stent thrombosis.

For cSDH in the context of AT, it is standard practice to discontinue AT at presentation and reverse warfarin prior to surgery where possible.\textsuperscript{15,18} The question then becomes if and when to resume AT postoperatively. While patients on a preoperative AT regimen in our cohort rebled earlier and more frequently than those patients off an AT regimen, at a median of 16.2 days versus 26.5 days, respectively, this by and large occurred irrespective of AT resumption, and, in fact, postoperative resumption was associated with a decrease in rehemorrhage. Patients on preoperative AT also experienced thromboembolic complications significantly earlier than those patients not receiving preoperative AT, at an average of 2.7 days versus 51 days, respectively, albeit the complications were unrelated to the original indication for AT in half of the cases. However, given the earlier onset of thromboembolism in patients on AT, with the apparently minimal risk of rebleeding following resumption, our data provide cursory evidence that resuming therapeutic AT early, starting at 3 days postoperatively, may be safe.

Multiple series have echoed the safety of resuming warfarin at 3 to 5 days for patients with mechanical valves with no increased risk of recurrence.\textsuperscript{6,15,18,31} Controversy remains regarding warfarin. Majeed et al. reported 10 to 30 weeks as the optimal restart interval, although this encompassed any instance of warfarin-related intracranial hemorrhage and included both operative and nonoperative cases.\textsuperscript{20} In a series of 343 cSDH, Torihashi et al. reported no increased risk of recurrence following the resumption of antiplatelets within 1 week postoperatively, though all patients were resumed and hence no comparison was made to patients who did not resume preoperative antiplatelets.\textsuperscript{20} Okano et al., in a large cohort of 448 cSDH patients, also reported no increase in recurrence for patients on preoperative antiplatelet agents who resumed postoperatively; however, the timing of resumption was not assessed.\textsuperscript{23} Neither study distinguished between types of antiplatelet agents. In smaller studies, Tahsim-Oglou et al. reported increased recurrence and reoperation rates for patients started on prophylactic dose LMWH (enoxaparin 40 mg daily) on postoperative Day 1, and Forster et al. reported increased recurrence in high-risk patients bridged postoperatively with therapeutically dosed nadroparin (also a LMWH).\textsuperscript{11,28} No studies assessing the recurrence risk with newer targeted anticoagulants were found.

Our finding of decreased recurrence risk following AT resumption is curious but was echoed previously by several other studies summarized in a systematic review by Chari et al.\textsuperscript{6} This finding may be due to differences in baseline hemorrhage risk across patients, with a tendency to restart AT on those patients perceived to be at lower risk for recurrence. Rehemorrhage risk stratification requires detailed data on patient comorbidities, neurological and functional status, including the risk of falls along with the preoperative radiological predictors of hematoma recurrence such as hematoma width and morphology. None of these data were available to us due to the retrospective nature of this study.

Other similar limitations exist in this study. The metrics of thromboembolic risk in atrial fibrillation, such as CHADS,\textsuperscript{2,3} and CHA\textsubscript{2}-DS\textsubscript{2}-VASc\textsuperscript{1,3,9} which are particularly important for warfarin and newer anticoagulants, were unavailable. Preoperative and postoperative INR for patients on warfarin were not always available. Our study was conducted at a tertiary referral center, and many patients were already reversed at the referring institution with an undocumented INR on admission. Postoperatively, many patients were restarted on warfarin in the hospital, but were subsequently discharged with their INR levels to be followed by their primary care physician. While the reversal of warfarin has been shown to reduce recurrence and improve outcome,\textsuperscript{10,15} the reversal of antiplatelet agents with desmopressin or platelet transfusions is controversial and was not captured here.\textsuperscript{3} Our sample sizes for newer anticoagulants, such as dabigatran or fondaparinux, were too limited to allow subgroup analyses of any antithrombotics other than ASA, warfarin, or clopidogrel. Our cohort size of 479 patients, while one of the largest series in the literature, remains too limited to allow a proper comparison of thromboembolic risk between patients with and without a history of AT. Based on our cohort, as well as the findings
in the literature and assuming a 2% thromboembolic risk in patients with a history of AT and 0.5% risk in those without AT, a study would require at least 860 patients to achieve 80% statistical power with an alpha level of 0.05. Lastly, no agent in our study was restarted prior to 3 days postoperatively, precluding the comparison of outcomes between resumption earlier or later than 3 days.

Conclusions

Patients receiving preoperative AT suffered hemorrhagic complications earlier and more frequently, but also experienced thromboembolic complications significantly earlier. Patients who were resumed on AT did not have an increased risk of recurrent hemorrhage. We provide cursory evidence that the resumption of preoperative antithrombotics at 3 days postoperatively may be safe; however, larger prospective studies are needed before any definitive recommendations can be made. The ultimate decision of whether, and how to resume AT should be tailored to individual patients and their unique risk profiles.

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**Disclosure**

Dr. Macdonald states that he has direct stock ownership in and is Chief Scientific Officer of Edge Therapeutics, Inc.

**Author Contributions**

Conception and design: Macdonald, Guha. Acquisition of data: Guha, Coyne. Analysis and interpretation of data: Guha. Drafting the article: Guha. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Statistical analysis: Guha. Administrative/technical/material support: Macdonald. Study supervision: Macdonald.

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