**Current Practice Trends for Use of Early Venous Thromboembolism Prophylaxis After Intracerebral Hemorrhage**

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**BACKGROUND:** Venous thromboembolism (VTE) is common after intracerebral hemorrhage (ICH). Guidelines recommend early VTE prophylaxis.

**OBJECTIVE:** To determine characteristics associated with early chemoprophylaxis (CP) after ICH in the Get With The Guidelines-Stroke registry.

**METHODS:** In this observational cohort study, we identified patients with ICH between January 1, 2009 and September 30, 2013, who (1) were non-ambulatory and/or not comfort care measures by hospital day 2; (2) were not transferred to another acute care facility; and (3) had known VTE prophylaxis status at end of hospital day 2. Categories for VTE prophylaxis were as follows: (1) mechanical non-CP or (2) CP with or without mechanical prophylaxis. Early prophylaxis was defined as occurring by hospital day 2. Using multivariable logistic regression, we assessed patient, hospital, and geographic factors independently associated with early CP use.

**RESULTS:** Among 74,283 patients with ICH from 1358 hospitals, 5929 (7.9%) received early CP, 66,444 (89.4%) received early mechanical/non-CP, and 1910 (2.6%) had no prophylaxis, mechanical or CP, within the first 2 days. There was no increase in early CP use over the study period; 60% of hospitals provided early CP to <9% of patients. In multivariable analysis, female sex, atrial fibrillation, diabetes, coronary, carotid, and peripheral artery disease, prior ischemic stroke or transient ischemic attack, hospital size >500 beds, and geographic region were independently associated with early vs no early CP use.

**CONCLUSION:** Nationally, the large majority of ICH patients receive early mechanical VTE prophylaxis only, without CP. Patient comorbidities and hospital characteristics such as geographic location are determinants of higher use of early CP.

**KEY WORDS** Anticoagulants, Pulmonary embolism, Intracranial hemorrhage, Prevention and control, Venous thrombosis

Deep vein thrombosis (DVT) and pulmonary emboli (PE) are preventable and common causes of morbidity and mortality after intracerebral hemorrhage (ICH). Rates of venous thromboembolism (VTE) are as much as 4 times higher in ICH than in ischemic stroke. Rates of symptomatic VTE after ICH range from 1% to 10%, with rates between 20% and 80% for asymptomatic VTE, detected by duplex ultrasound, fibrinogen scanning, or MRI.

According to the American Heart Association/American Stroke Association guidelines for ICH management, pneumatic compression devices are recommended (class I, level of evidence B) in all patients, while low-dose subcutaneous unfractionated heparin or low-molecular weight heparin (LMWH) may be
considered (class IIb, level of evidence B) after documented cessation of bleeding within 1 to 4 days from ICH onset in high-risk (eg, bed bound, hemiparetic) individuals.\textsuperscript{1} There are limited data on contemporary practice of VTE prophylaxis after ICH. We sought to determine the type and timing, temporal trends, and patient and hospital characteristics associated with early chemo prophylaxis (CP) after ICH, using Get With The Guidelines (GWTG)-Stoke registry.

**METHODS**

**Data Source**

The GWTG-Stroke registry is a nationwide in-hospital quality improvement program for stroke care that promotes consistent adherence to the latest scientific management guidelines. Since its initiation in 2003, 2491 hospitals have entered more than 3.4 million patient records into the GWTG-Stroke database. VTE prophylaxis has been a consistently reported measure since 2009. Hospitals enter data via a web-based Patient Management Tool (Quintiles Inc., Cambridge, Massachusetts) to collect clinical data, access decision support, and provide real-time online reporting of quality care measures. Under the common rule, sites are granted a waiver of informed consent, as the data are mainly used locally for quality improvement. Data analysis was done by a centralized research institute with local institutional review board approval.

**Data Collection and Study Population**

Using the GWTG-Stroke registry, we identified patients admitted with ICH at participating hospitals between January 1, 2009 and September 30, 2013, who (1) were not ambulatory at the end of hospital day 2; (2) did not transfer out to another facility; (3) did not have comfort care measures initiated before hospital day 2; and (4) and had complete data on VTE prophylaxis category and timing, including whether prophylaxis was initiated by hospital day 2, and if CP, mechanical, or both were used.

**Primary Variable of Interest**

The type and timing of VTE prophylaxis following ICH were the primary variables of interest. Categories for VTE prophylaxis included CP (ie, low-dose unfractionated heparin or LMWH) with or without mechanical prophylaxis, or mechanical prophylaxis (ie, pneumatic compression boots) alone. We further assessed timing of VTE prophylaxis and categorized early initiation as occurring on or before the end of hospital day 2 such that the categories of interest were as follows: early CP, early mechanical prophylaxis only, and prophylaxis after hospital day 2 ("no early prophylaxis"). Due to the way data are collected in the GWTG-Stroke registry, patients with missing documentation of VTE prophylaxis (ND) and those who never receive any form of VTE prophylaxis (no prophylaxis) are coded as one group and could not be separated for analysis.

**Patient Characteristics**

Demographic data included age, gender, race/ethnicity, health insurance status, and arrival and admission information. Medical history included the presence of atrial fibrillation/flutter, coronary artery disease, carotid stenosis, diabetes mellitus, heart failure, hypertension, prosthetic heart valve, peripheral vascular disease, smoking status, prior stroke/transient ischemic attack (TIA), and ambulatory status prior to admission. Information regarding hospital characteristics including geographic region, the number of beds, hospital type, number of years participating in GWTG-Stroke registry, and the type of care unit (eg, Stroke Unit, neurology admission, or other service admission) was also collected.

**Exploratory Outcomes**

VTE, defined as DVT or PE, during hospital stay and in-hospital mortality were evaluated as exploratory outcomes to measure the impact of early VTE prophylaxis categories on short-term outcomes.

**Statistical Analysis**

Baseline patient and hospitals characteristics were described overall and compared by type of VTE prophylaxis (CP vs non-CP). Categorical variables were presented as counts and proportions, and the difference between groups was tested using a Chi-square test. Continuous variables were presented as medians with 25th and 75th percentiles for non-parametric variables, and the difference between groups was tested using the Kruskal-Wallis test, while means, standard deviations, minima, and maxima of parametric continuous variables were compared using the Student t-test.

The use of VTE prophylaxis over the study period was described by reporting the number (proportion) of ICH patients for whom VTE prophylaxis was performed. These counts and proportions were reported by prophylaxis type, timing of prophylaxis (hospital day with admission day referred to as day 0, and study year. The proportions over the study period were plotted by type and timing of prophylaxis.

An adjusted multinomial logistic regression model fit with generalized estimating equations (GEE) methods and robust variance estimates to account for in-hospital clustering was created for early CP vs other categories of VTE prophylaxis following ICH. Variables in the main model included age, gender, race, medical history, admission information, hospital characteristics, and date of prophylaxis. The linearity between the continuous variables and outcomes was examined using lack-of-fit tests to compare between a linear fit model and a nonlinear fit model. Appropriate transformation was used to achieve linearity, such as log transformation or linear splines. Collinearity was assessed by checking variance inflation factors. Single imputation was used for missing values. Missing values for continuous variables was imputed to the median. Missing values for categorical variables was imputed to the most frequent category. Hospital characteristics were not imputed. If a patient had missing medical history, it was assumed that the medical condition did not occur. If variables had a missing rate of >15%, they were not included in the model. In a sensitivity analysis for early CP use, we adjusted for National Institutes of Health Stroke Scale (NIHSS) score as a continuous independent variable. Finally, we explored the relationship between type and timing of VTE prophylaxis and the occurrence of VTE in the hospital stay and in-hospital mortality, adjusting for relevant covariates, using logistic regression and GEE methods. \( p \)-value < .05 was considered significant in the final models. All statistical analyses were performed using SAS Version 9.3 software (SAS Institute, Cary, North Carolina). STROBE reporting guidelines were implemented for the manuscript.
RESULTS

Participants

During the study period, 74,283 patients with ICH from 1358 hospitals met inclusion criteria (Figure 1) and received some form of prophylaxis (CP, mechanical, or both) during their admission; 68,202 (91.8%) received mechanical/non-CP, and 6081 (8.1%) received CP. By VTE timing (Table 1), 72,373 (97.4%) received some form of early prophylaxis (5929 [7.98%] early CP; 66,444 [89.5%] early mechanical prophylaxis only).

Descriptive Data

Due to the large sample size, nearly all demographic categories were significant between prophylaxis groups (Table 2). However, several differences were notable. Interhospital transfer was more common in the CP group (36.3% vs 31.1 and 33.5%, \(P < .001\)) as compared to mechanical/non-CP or no early prophylaxis, respectively (Table 2). The median time in minutes from last known well to arrival at the GWTG hospital at which the patient was entered into the registry was 293 for Emergency Medical Services (EMS) from home/scene vs 1020 for transfers from other hospitals \((P < .001)\). The percentage of patients arriving on a weekend vs weekday was not different between groups \((P = .34)\). More patients in the no early prophylaxis group resided in a chronic health care facility at the time of symptom onset than in CP or early mechanical/non-CP groups (8.1% vs 8.0 and 6.3%, \(P < .001\)). The median number of beds was lower for the no early prophylaxis group than CP or mechanical/non-CP groups, respectively (434 vs 468 and 441, \(P < .001\)). Early CP use occurred more frequently at academic hospitals (73.1% vs 64.6% and 69.2%, \(P < .001\)) and with neurology service admissions (49.4% vs 36.4% and 37.2%, \(P < .001\)). Early CP use was less frequent when associated with stroke consult (53.16% vs 60.74% and 63.56%, \(P < .001\)).

Main Results

There was no increase in CP use over the study period (Figure 2), with rates ranging from 7.3% to 9.0% \((P = .17)\). Hospital-level variation suggested that the majority of hospitals \((\geq 60\%)\) provided early CP to <9% of ICH patients, while a small minority \((5\%)\) of hospitals provided early CP routinely in nearly all ICH patients (Figure 3). In multivariable analysis, several factors pertaining to patient, hospital, and geographic characteristics were independently associated with early vs no early CP use (Table, Supplemental Digital Content). Patients with coronary artery disease \((\text{adjusted odds ratio [OR]} 1.11, \text{confidence interval [CI]} 1.04-1.18)\), diabetes \((\text{adjusted OR} 1.18, \text{CI} 1.11-1.25)\), peripheral artery disease \((\text{adjusted} 1.22, \text{CI} 1.06-1.40)\), atrial fibrillation or flutter \((\text{adjusted OR} 1.25, \text{CI} 1.16-1.34)\), carotid stenosis \((\text{adjusted OR} 1.27, \text{CI} 1.08-1.49)\), prior TIA \((\text{adjusted OR} 1.13, \text{CI} 1.01-1.27)\), and stroke \((\text{adjusted OR} 1.17, \text{CI} 1.10-1.25)\) were more likely to receive early CP. Rates of early CP varied by hospital size as follows: 7.48% for hospitals with less than 300 beds, 6.52% with 301–396 beds, 5.97% with 397–519 beds, 10.30% with 520–719 beds, and 9.66% with 720–2204 beds. There were also several regional differences noted, with hospitals in the Northeast and South being more likely to use early CP than hospitals in the Midwest or West. A secondary analysis in the subset of patients in whom an NIHSS score was recorded (Table, Supplemental Digital Content) did not find that NIHSS score \((P = .065)\) significantly related to early CP use.

Other Analyses

There were 2721 VTE events during the study period and 18,463 deaths. In prespecified secondary analysis of in-hospital outcomes, the adjusted OR for the occurrence of VTE between early VTE prophylaxis and no early VTE prophylaxis was 0.93 \((95\% \text{ CI} 0.70-1.24, P = .63)\). The adjusted OR for VTE occurrence comparing early CP with all other categories was 1.18 \((95\% \text{ CI} 1.01-1.39, P = .038)\). Comparing mortality rates between groups, early CP was associated with lower mortality \((\text{adjusted OR} 0.74, 95\% \text{ CI} 0.67-0.81, P < .0001)\) compared to all other groups.

DISCUSSION

Key Results

In this analysis of the GWTG-Stroke registry, we observed that nearly 90% patients with ICH receive early mechanical VTE prophylaxis, while utilization of early CP occurs in <10% of patients. We found that patient and hospital characteristics such as medical comorbidities and hospital size and location correlate with early utilization of CP after ICH. Use of CP did not change over the 4-yr study period.

Interpretation

Current rates of CP are consistent with the existing American Heart Association guidelines which indicate a class IIb recommendation. Recent guidelines published in Neurocritical Care also reflect the paucity of high-quality data on the subject. While use of mechanical prophylaxis received a strong recommendation, use of CP within 48 h of hospital admission was given a weak recommendation. A survey of HERE Canadian neurosurgeons and intensivists, two-thirds of whom practiced in an academic setting, reported a majority starting anticoagulation within 48 h, although there was significant practice variation. More experienced physicians with specialization in stroke, neurocritical care, or vascular neurosurgery may be more likely to work at larger urban and academic hospitals, and have personal experience with safe initiation of early CP after ICH. Our finding that patients cared for at academic centers and on neurology services had higher rates of early CP use may support this assertion, as does our finding that patients not on a primary neurology service \(\text{(ie, stroke consults)}\) had lower rates of early CP.

While we cannot be certain about clinical factors that influenced clinician decision making, those with vascular
FIGURE 1. Flowchart of inclusion/exclusion criteria for assembly of final analyzed cohort.
TABLE 1. Type and Timing of VTE Prophylaxis in Patients With the GWTG-Stroke Cohort of ICH Included for Analysis

<table>
<thead>
<tr>
<th>Prophylaxis type</th>
<th>Early VTE prophylaxis</th>
<th>No early VTE prophylaxis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical/non-CP</td>
<td>66,444/74,283 (89.45%)</td>
<td>17,587/74,283 (2.37%)</td>
<td>68,220</td>
</tr>
<tr>
<td>Any CP</td>
<td>59,297/74,283 (7.98%)</td>
<td>15,283/74,283 (0.20%)</td>
<td>60,881</td>
</tr>
<tr>
<td>CP only</td>
<td>27,004/74,283 (3.63%)</td>
<td>10,173/74,283 (0.14%)</td>
<td>28,177</td>
</tr>
<tr>
<td>Chemo- and mechanical</td>
<td>32,297/74,283 (4.35%)</td>
<td>5,173/74,283 (0.00069%)</td>
<td>32,870</td>
</tr>
<tr>
<td>Total</td>
<td>72,373</td>
<td>1910</td>
<td>74,283</td>
</tr>
</tbody>
</table>

TABLE 2. Select Factors Associated With Early CP Use

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjusted OR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>1.08</td>
<td>1.03</td>
<td>1.14</td>
<td>.002</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>1.25</td>
<td>1.16</td>
<td>1.34</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Coronary artery disease/prior MI</td>
<td>1.11</td>
<td>1.04</td>
<td>1.18</td>
<td>.002</td>
</tr>
<tr>
<td>Carotid stenosis</td>
<td>1.27</td>
<td>1.08</td>
<td>1.49</td>
<td>.004</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.18</td>
<td>1.11</td>
<td>1.25</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>1.22</td>
<td>1.06</td>
<td>1.40</td>
<td>.006</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1.17</td>
<td>1.10</td>
<td>1.25</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>1.13</td>
<td>1.01</td>
<td>1.27</td>
<td>.030</td>
</tr>
<tr>
<td>Hospital size (per 10 beds up to 500)</td>
<td>0.87</td>
<td>0.79</td>
<td>0.97</td>
<td>.001</td>
</tr>
<tr>
<td>Hospital size (per 10 beds above 500)</td>
<td>1.08</td>
<td>1.02</td>
<td>1.14</td>
<td>.011</td>
</tr>
<tr>
<td>Region Midwest vs Northeast</td>
<td>0.65</td>
<td>0.47</td>
<td>0.89</td>
<td>.008</td>
</tr>
<tr>
<td>Region West vs Northeast</td>
<td>0.64</td>
<td>0.46</td>
<td>0.91</td>
<td>.012</td>
</tr>
</tbody>
</table>

*The OR for hospital size is per 10 beds increase (up to 500 or above 500); joint P-value of the 2 splines is .005.

Multivariable logistic regression model showing selected ORs and 95% CI for significant patient, hospital, and geographic characteristics associated with early CP (n = 5929) vs no early CP (n = 75,899).

comorbidities (eg, atrial fibrillation, coronary or peripheral artery disease, and prior stroke) were more likely to receive early CP perhaps due to heightened risk of VTE in those with greater comorbidities. The GWTG-Stroke registry clearly delineates VTE prophylactic drugs from anticoagulants for stroke prevention, which eliminates the continuation of premorbid anticoagulation as a potential confounding factor. Furthermore, it is highly implausible that therapeutic anticoagulation would be continued in the first 2 days after ICH. While the registry does not record information on ICH location or size, we were unable to find an association between clinical severity as measured by NIHSS score, a reasonable proxy for size and location, and early CP use.

CP in the hyperacute setting is often postponed due to the risk of hematoma expansion, which occurs in 15% to 38% of ICH patients within the first 24 h,10-14 but after which hematoma expansion is uncommon (<5% occurrence).14-17 Prior small studies examining early CP use in ICH patients have consistently found the practice to be safe, with lower rates of VTE. In a prospectively randomized study, initiation of LMWH after 48 h was not associated with increased hematoma growth compared to the mechanical prophylaxis only group but VTE rates were similar between groups (3 and 1 DVTs, respectively).18 In another study, the incidence of pulmonary embolism was significantly decreased (OR 9.2, CI 1.1-75) in patients started on low-dose heparin on hospital day 2 as compared to day 4 or 10 without an increase in rebleeding.19 In a study that retrospectively evaluated the effects of treatment with enoxaparin 20 mg daily
vs no treatment (compression stockings were not used), rates of 3-mo mortality, symptomatic thromboembolic complications, and hematoma expansion were similar between groups. A fourth study found that usage of subcutaneous heparin for VTE prophylaxis after ICH was safe, though not superior to elastic stockings in preventing VTE. A meta-analysis of CP compared to other treatments for VTE prevention after ICH found that rates of PE were significantly decreased in the CP group, while rates of DVT were non-significantly decreased. Rates of hematoma expansion, however, in the CP group were non-significantly increased.

Lacking a definitive randomized controlled trial assessing early CP after ICH, physicians may be less compelled to change practice away from mechanical prophylaxis only. Though a meta-analysis suggested a number needed to treat of 22 for DVT prevention and 181 for PE prevention in medically ill patients, the feasibility of conducting such a trial in ICH patients may be limited if randomization to either treatment is perceived as unethical or lacking equipoise. Most hospitals in our study observed either 0% or 100% early CP use. In one study examining what level of clinical equipoise justifies a randomized controlled clinical trial, authors found that when 70% of experts favored one treatment, 50% of potential subjects preferred receiving that treatment as opposed to being randomized in a trial. Given that only 15% of hospitals in our study observed rates of early CP use in the cited range (30%-70%), initiation of a randomized controlled trial would be challenging, as potential subjects at the most institutions would have to be enrolled by clinicians with strong but opposing preferences to either initiate or avoid early CP after ICH.

**Limitations**

There are several limitations to our study. First, whether early CP is more effective than mechanical prophylaxis at preventing VTE cannot be determined with certainty using our data. While the prevalence of VTE was slightly higher in patients treated with early CP, we cannot rule out confounding by indication (ie, that CP was more likely to be prescribed in patients at higher risk).
CONCLUSION

Our study is one of the largest to assess trends for VTE prophylaxis after ICH. Though the majority of patients received early mechanical VTE prophylaxis, early CP was infrequently utilized after ICH. Given the high morbidity and mortality associated with VTE after ICH and several small prospective trials suggesting safety of early CP, larger controlled studies may be needed to develop more robust guidelines.

Disclosure

The Get With The Guidelines-Stroke (GWTG-Stroke) program is provided by the American Heart Association/American Stroke Association. The GWTG-Stroke program is currently supported in part by a charitable contribution from Janssen Pharmaceutical Companies of Johnson & Johnson. GWTG-Stroke has been funded in the past through support from Boeringher-Ingelheim, Merck, Bristol-Myers Squib/Sanoﬁ Pharmaceutical Partnership, and the AHA Pharmaceutical Roundtable. Dr Fonarow reports research support from PCORI.

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REFERENCES


**COMMENT**

The authors present an observational cohort study of nearly 75,000 patients using data from the Get With The Guidelines-Stroke registry. The purpose of the study is to determine characteristics associated with early chemoprophylaxis (CP) after ICH. They found that while a large proportion of patients received early (<48 hrs) mechanical prophylaxis (~90%) a small proportion of patients (~8%) were receiving early CP. The factors associated with early CP were female sex, atrial fibrillation, diabetes, coronary, carotid, and peripheral artery disease, prior ischemic stroke or TIA, hospital size >500 beds, and geographic region; these were independently associated with early versus no early CP use. There was no change in early use of CP over time (2009 to 2013). The adjusted OR for venous thromboembolism occurrence comparing early CP vs all other categories was 1.2 and early CP was associated with lower mortality. This study is limited by the unavailable data in a large database such as this. It would be informative to know how ICH location, size, ICH score, and management (surgical vs non-surgical) influenced DVT prophylaxis.

This is an important study because it is large, it is based on “real-world” data that is guideline driven, and the results are somewhat surprising. Certainly the guidelines only recommend CP in high-risk patients once there is documentation that bleeding has subsided. There is evidence, however, as the authors have demonstrated in the Discussion and as many of us believe from experience, that early CP is both safe with respect to worsening ICH and effective with respect to preventing VTE. The majority of patients with ICH at Mount Sinai Hospital receive CP by post-bleed day 2 unless there is a significant contraindication. In general, we have not noticed worsening ICH secondary to the use of CP. Given that such a low percentage of patients are actually receiving CP within the first 48 hours in this nationwide sample, a randomized controlled trial is likely justified. Perhaps there should be a stronger recommendation for early CP in the next round of AHA guidelines.

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