# Critical Review Form
## Prognosis

**Immediate and delayed traumatic intracranial hemorrhage in patients with head trauma and pre-injury warfarin or clopidogrel use. *Ann Emerg Med.* 2012; 59: 460-468**

**Objectives:** **To assess "the prevalence and incidence of immediate and delayed traumatic intracranial hemorrhage in patients with blunt head trauma who were receiving either warfarin or clopidogrel." (p. 461)**

**Methods:** **Prospective, observational, multicenter study conducted at 2 trauma centers and 4 community hospitals in Northern California from April 2009 to January 2011. Included patients were adult (age ≥ 18 years) emergency department (ED) patients with blunt head injury and warfarin or clopidogrel use within the previous 7 days. Patients were included regardless of loss of consciousness or amnesia. Patients were excluded if they were transferred from outside facilities with known injuries, or if they were taking both warfarin and clopidogrel. Data was collected prospectively by the treating ED faculty physician before initial cranial CT. Imaging studies were obtained at the discretion of the treating physicians, and were interpreted by faculty radiologists. Immediate traumatic ICH was defined as the presence of any ICH or cerebral contusion on initial CT scan.**

**A stratified analysis was performed using the following strata: patients ≥ 65 years of age, GCS 13 to 15, GCS of 15, ground-level fall, evidence of trauma above the clavicles, concomitant aspirin use, community hospital setting, and degree of anticoagulation (INR ≥ 1.3 and ≥ 2.0). Sensitivity analyses were performed assuming patients without an initial CT scan had an immediate ICH, and assuming all patients lost to follow-up had a delayed ICH.**

**Data on patients not enrolled were abstracted from the medical records to assess for enrollment bias. For patients with normal initial CT scans, research coordinators and site investigators reviewed electronic medical records for INR results, CT scan results, ED disposition, and hospital course. Patients admitted for at least 14 days were evaluated for delayed intracranial hemorrhage (ICH) by review of the electronic medical record. Patients discharged from the ED or admitted for less than 14 days were assessed for delayed ICH consented, standardized telephone survey at least 14 days after the index ED visit. For patients unable to be contacted, the Social Security Death Index was reviewed to evaluate for death.**

**Delayed ICH was defined as ICH on CT scan occurring within 14 days after an initial normal CT scan, in the absence of repeated head trauma. Neurosurgical intervention was defined as:**

1) **Use of intracranial pressure monitoring or brain tissue oxygen probe.**

2) **Placement of a burr hole.**
3) **Craniotomy/craniectomy.**
4) **Intraventricular catheter or subdural drain.**
5) **Or the use of mannitol or hypertonic saline solution.**

| Guide | | Comments |
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| **I.** | **Are the results valid?** | |
| A. | **Was the sample of patients representative?**<br>*In other words, how were subjects selected and did they pass through some sort of "filtering" system which could bias your results based on a non-representative sample. Also, were objective criteria used to diagnose the patients with the disorder?* | Yes, the patients were representative, as they included patients on anticoagulant therapy with minor head injury.<br><br>This was an observational multicenter study, conducted at two trauma centers and four community hospitals. Selected patients were adults (age ≥18) with blunt head trauma and preinjury warfarin or clopidogrel use in the previous 7 days. Patients with concomitant warfarin and clopidogrel use were excluded.<br><br>There were no "objective" criteria to determine whether the patient suffered a head injury. This was at the discretion of the clinicians and investigators.<br><br>Patients were included regardless of the presence of LOC or amnesia, regardless of GCS or injury severity.<br><br>Patients with known injuries who were transferred from outside facilities were excluded to avoid falsely inflating the prevalence of traumatic ICH. |
| B. | **Were the patients sufficiently homogeneous with respect to prognostic risk?**<br>*In other words, did all patients share a similar risk during the study period or was one group expected to begin with a higher morbidity or mortality risk?* | Yes, as these patients all had relatively minor head injury with a normal initial CT scan. Certain risk factors would put some patients at higher risk of adverse outcome, including advanced age, more elevated INR, loss of consciousness associated with the traumatic event, decreased GCS, high-risk mechanism, and more severe symptoms.<br><br>Table 1 outlines patient demographic information and associated risk factors for all patients. However, there is no information related specifically to patients with normal initial CT scan (i.e. those at risk for delayed ICH). |
| C. | **Was follow-up sufficiently complete?**<br>*In other words, were the investigators able to follow-up on subjects as planned or were a significant number lost to follow-up?* | Yes, as the lost-to-follow-up rate was < 1%. Patients were assessed at 2 weeks by telephone survey or electronic medical record review (for those patients admitted to the hospital for 14 days or longer). 843 patients received telephone survey (90.6%) and 83 were assessed by medical record review (8.9%). Of the 930 patients with normal initial CT scan, 4 were lost to follow-up. None of these 4 patients was identified in the Social Security Death Index. |

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<tr><td>D.</td><td>Were objective and unbiased outcome criteria used?<br>Investigators should clearly specify and define their target outcomes before the study and whenever possible they should base their criteria on objective measures.</td><td>Yes. Assuming the criteria for initial CTs were applied to repeat CTs, ICH was defined as “the presence of any intracranial hemorrhage or contusion as interpreted by the faculty radiologist.” Delayed intracranial hemorrhage was defined as “traumatic intracranial hemorrhage on cranial CT scan, occurring within 14 days after an initial normal CT scan result and in the absence of repeated head trauma.” It is unclear if contusions were included for repeat CT scans. Repeat CT scans were performed at the discretion of treating physicians, therefore not all patients had repeat CT scans performed.<br><br>Neurosurgical intervention was defined as “the use of intracranial pressure monitor or brain tissue oxygen probe, placement of a burr hole, craniotomy/ craniectomy, intraventricular catheter or subdural drain, or the use of mannitol or hypertonic saline solution.”</td></tr>
<tr><td>II.</td><td>What are the results?</td><td></td></tr>
<tr><td>A.</td><td>How likely are the outcomes over time?<br><table><tr><th></th><th>Immediate ICH</th><th>Delayed ICH</th></tr><tr><td>All</td><td>7%</td><td>0.4%</td></tr><tr><td>Coumadin</td><td>5.1%</td><td>0.6%</td></tr><tr><td>Clopidogrel</td><td>12%</td><td>0</td></tr></table></td><td><ul><li>Between April 2009 – Jan 2011, 1101 patients were enrolled representing 83.3% of all eligible patients. The non-enrolled patients did not differ from enrolled subjects by age, gender, medication use, ED CT ordering or hospital admission rates.</li><li>The prevalence of immediate ICH in patients taking clopidogrel was 12.0% (95% CI 8.4%-16.4%); ICH rate in patients on warfarin was 5.1% (95% CI 3.6%-7.0%). The relative risk of clopidogrel compared to warfarin was 2.31 (95% CI 1.48-3.63) and was stable on stratification & sensitivity analysis.</li><li>94% of patients had a CT in the ED and 87.6% had a GCS 15 and 70.7% had evidence of trauma above the clavicles.</li><li>The frequency of outcomes are detailed to the left. Delayed traumatic intracranial hemorrhage was identified in 4/687 (0.6%; 95% CI 0.2% to 1.5%) patients receiving warfarin and 0/243 (0%; 95% CI 0% to 1.5%) patients receiving clopidogrel.</li><li>Of the four patients with delayed ICH, 2 died and 2 required no neurosurgical intervention. It is unclear if these patients required reversal of anticoagulation or had their warfarin withheld.</li><li>In patients on warfarin, ICH requiring neurosurgical intervention occurred in 2/687 (0.3%; 95% CI 0.1%-1.1%).</li><li>Most immediate ICH had GCS 15 (64%) and a few had no loss of consciousness (11% warfarin, 18% clopidogrel)</li><li>The raw agreement for individual predictor variables were good (87%-100% agreement), but no kappa</li></ul></td></tr>
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| | | values were reported. |
| B. | **How precise are the estimates of likelihood?** *In other words, what are the confidence intervals for the given outcome likelihoods?* | See 95% CI's reported above. |
| **III.** | **How can I apply the results to patient care?** | |
| A. | **Were the study patients and their management similar to those in my practice?** | Yes. These patients were sampled from 2 trauma centers and 4 community hospitals. The inclusion of patients from community hospital could potentially lead to lower risk cohort with decreased incidence of immediate and delayed ICH. Patients with normal initial CT scans were discharged home, as is our current practive. There is no demographic or risk factor data specific to those patients with a normal initial CT scan. |
| B. | **Was the follow-up sufficiently long?** | Uncertain. Two week follow-up for delayed ICH seems sufficient, and is longer than most previous studies in whom patients were observed for 24 hours. However, the optimal follow-up period has not been determined. |
| C. | **Can I use the results in the management of patients in my practice?** | Yes. The overall incidence of delayed ICH seems quite low (0.6% in patients on warfarin). Assuming a similar incidence in our level I trauma center, the results would support current practice of discharging patients on warfarin (or clopidogrel) with isolated minor head injury and a normal initial CT scan. These results could not be applied to patients on concomitant warfarin and clopidogrel. |

## Limitations

1) **Only 83.3% of eligible patients were enrolled, potentially leading to enrollment bias. However, a comparison of this included and those not included was conducted, with no significant differences in characteristics or outcomes between the two groups.**

2) **There is little demographic or risk factor data specific to those patients with normal initial CT scan (i.e. those in whom we are most interested). Would like to know INR ranges, mechanism, LOC, amnesia, and presence of concerning symptoms.**

3) **No details about unmeasured confounding predictor variables such as the fall mechanism, injury or illness severity, or geriatric syndromes such as frailty or**

**functional decline that could affect initial CT ordering and ED length-of-stay decisions.**

4) **No assessment of CT-head injury rules (New Orleans, CHIP, NEXUS-II, and Canadian) which might have been helpful to predict delayed CNS bleeding risk.**

5) **Patients with combined anticoagulant/antiplatelet therapy were excluded. Concomitant antiplatelet therapy in patients taking oral anticoagulants in the US ranges from 19.4-38.5%. (Shireman 2004) (Johnson 2007)**

**Bottom Line**

**This study found the surprising result that the rate of immediate ICH was higher in patients on clopidogrel (12%, 95% CI 8.4%-16.4%) compared to warfarin (5.1%, 95% CI 3.6%-7.0%), with a relative risk of 2.31 (95% CI 1.48-3.63). Somewhat paradoxically, the rate of delayed ICH was lower in those taking clopidogrel (0%, 95% CI 0%-1.5%) compared to warfarin (0.6, 95% CI 0.2%-1.5%). The rate of delayed ICH was low in both groups, with only 4 out of 687 patients on warfarin suffering ICH; in only two of these patients was the delayed ICH of clinical significance. Such low rates in this relatively large study would suggest that routine inpatient observation and repeat CT scanning is not warranted in such patients. One could argue that a significant portion of patients with delayed ICH was missed in this study, as patients did not routinely undergo repeat head CT. However, we are more concerned with clinically significant ICH (i.e. ICH requiring neurosurgical intervention or other change in management), which was not likely to be missed given the excellent clinical follow-up (4 patients of 930 lost to follow-up). Overall, this study reinforces the importance of obtaining CT scans in head injury patients taking warfarin or clopidogrel, as well as the safety of discharging such patients home if the initial CT scan is negative for ICH.**