Spontaneous ICH in Patients Taking Warfarin

By James R. Roberts, MD

**Author Credentials and Financial Disclosure:** James R. Roberts, MD, is the Chairman of the Department of Emergency Medicine and the Director of the Division of Toxicology at Mercy Health Systems, and a Professor of Emergency Medicine and Toxicology at the Drexel University College of Medicine, both in Philadelphia. Dr. Roberts has disclosed that he has no significant relationships with or financial interests in any commercial companies that pertain to this educational activity.

**Learning Objectives:** After reading this article, the physician should be able to:
1. Identify the incidence of spontaneous intracranial hemorrhage in patients anticoagulated with warfarin.
2. Describe the risk factors for spontaneous intracranial hemorrhage in patients anticoagulated with warfarin.
3. Summarize the symptoms of spontaneous intracranial hemorrhage in patients anticoagulated with warfarin.

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**InFocus**

It would be an unusual shift when an emergency physician did not encounter a patient taking warfarin. The drug is omnipresent — a life saver and a killer. The clinical indications are many, but the complications are gargantuan. Warfarin has been implicated as the one medication associated with the highest incidence of outpatient morbidity; and up to 10 percent of patients will experience a bleeding episode on this drug. Most emergency physicians have a limited knowledge of warfarin, and primarily understand bleeding complications. The literature on warfarin drug interactions, initiation and reversal of coagulopathy, and a plethora of related issues comprise vast literature that no physician can possibly read or totally remember.

Although we rarely start the drug, we frequently must deal with its therapeutic and untoward sequelae. I recently discussed the issue of head trauma in patients anticoagulated with warfarin, and concluded that banging your head and taking warfarin is a bad combination. Seemingly minor head trauma, especially in the elderly anticoagulated patient, is a minefield over which one must tread quite carefully.

Following patients on warfarin is a huge hassle and chasing the wandering INR consumes a lot of the internist’s and cardiologist’s time. I noted that the FDA recently mandated that coagulated patients receive specific written instructions from the pharmacy about the clinical issues and dangers of warfarin therapy. Transparency in medicine has now arrived, not only for physicians but also for our prescriptions. This information is well known to any individual with a computer. The sagacious clinician realizes that his patient and his family can quickly check on the doctor’s proper or improper use of this drug, so let the clinician beware.

This month’s discussion reviews the clinical approach to the asymptomatic patient who has an elevated INR discovered during an ED encounter.

Last month I discussed the approach to the asymptomatic patient who is serendipitously found to have an elevated INR. A very conservative approach has been promulgated, using either watchful waiting or small doses of oral vitamin K for those not bleeding and an INR less than 9.0. Simply withholding warfarin for three to five days is considered a reasonable clinical approach in the vast majority of such asymptomatic patients. This month, I discuss a more dramatic and often fatal warfarin-related issue — intracranial hemorrhage, either spontaneous or associated with other risk factors. Watchful waiting is clearly not the norm for these individuals.

**Caveats of Intracranial Hemorrhage in Patients Treated with Warfarin**

- Warfarin anticoagulation increases the risk of ICH seven- to 10-fold.
- Bleeding can be spontaneous, with no identifiable underlying cause.
- The most common type of warfarin-related ICH is intracerebral (about 70%); least common is subdural bleeding (about 30%).
- The intensity of the anticoagulation generally parallels the increased risk.
- Intracerebral hemorrhage evolves slowly over 12 to 24 hours in about half of the cases.
- Anti-platelet therapy with aspirin increases ICH risk by about 40 percent, even when low-dose aspirin is used.
- The risk of spontaneous ICH in 75-year-old patients with an INR of 2.3 is close to one percent per year.
- About half of patients with warfarin-induced ICH die within 90 days, approximately twice the mortality rate of those not taking warfarin at the time of the ICH.
- Warfarin may facilitate bleeding in otherwise benign small limited minor age-related micro-hemorrhage, the possible pathogenesis for spontaneous ICH.
- Most spontaneous ICH occurs at anticoagulation intensities that are within the accepted therapeutic range (INR=2-3).
- The major predictors of ICH with warfarin therapy include age over 70, hypertension, prior CVA, and INR greater than 3.

**Oral Anticoagulants and Intracranial Hemorrhage: Facts and Hypotheses**

Hart R, et al

Stroke

1995;26(8):1471

This article discusses the nuances and clinical significance of intracranial hemorrhage in patients anticoagulated with warfarin. The authors begin by observing that ICH is the most feared and most lethal complication of all types of outpatient anticoagulation. The report reviews the frequency, predictors, and prognosis of this complication, termed a "common" event. Anyone will concede that an anticoagulated patient with head trauma will more likely bleed, but the most scary caveat with warfarin is that such bleeding can be spontaneous.

The frequency of ICH in the general population is likely on the increase, probably because of increasing use of warfarin in the elderly. Although the benefits of anticoagulation are well accepted for patients at risk for ischemic stroke, the risk of bleeding from warfarin in some patients may be so great that it negates that benefit. ICH can be divided into three general categories: intraparenchymal (intracerebral), subdural/epidural, and subarachnoid hemorrhage. Of these, intracerebral hemorrhage is the most common, comprising about 70 percent of anticoagulant-related bleeds. Subdural hematoma is the least common category of ICH from warfarin, comprising about 30 percent of cases.

Unfortunately, although ICH is the most common neurological complication of anticoagulation, especially in the...
ICH and Warfarin

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elderly, it is the least treatable. The overall risk of ICH in patients with an INR of 2.5 to 4.5 is an impressive two-to-five fold over that of the general population. (Some quote a seven- to 10-fold increase.) The mortality rate associated with warfarin-related ICH is about 60 percent, also increased over non-anticoagulated individuals. Cerebellar hemorrhage is one particularly common type of ICH. Fortunately, ICH is readily visible on a non-enhanced CT scan when it is relatively fresh. Within minutes of a CNS bleed, the CT scan will be diagnostic.

Symptoms of ICH in anticoagulated patients are not remarkably different from those who experience this catastrophe from other causes, such as arteriovenous malformation, aneurysm, trauma, or tumor, but there is one major caveat. In about half of those affected, the bleeding is slow, evolving over 12 to 24 hours. The symptoms may be atypical when compared with other forms of ICH, such as subarachnoid hemorrhage secondary to an aneurysm. Because the ICH associated with warfarin evolves slowly, the initial symptoms can be subtle, ameliorated by the thunderclap headache of aneurysm rupture.

Although warfarin-induced hemorrhage is not always related to the intensity of the anticoagulation. There appears to be no absolutely safe level of anticoagulation or safe INR elevation in some patients. Unfortunately, many patients experience ICH with their INR well within the conventional therapeutic range. Patient factors and anticoagulant intensity appear to be a double insult that determines the absolute risk of ICH. It is generally considered that aspirin administered concomitantly with warfarin probably increases the risk of ICH if that is the only parameter that has changed.

Although warfarin-induced subdural hematoma is less frequent than ICH, this is no less life-threatening or critical to the recipient. Warfarin increases the risk of subdural hematoma four- to 15-fold, and it is likewise related to the intensity of the anticoagulation, advanced age, and probably cerebral atrophy. Hypertension does not seem to be a risk factor for warfarin-associated subdural hematoma to the extent it is with intraparenchymal bleeding. The precipitator of bleeding by minor head trauma, especially in the anticoagulated elderly, is well known. The mortality rate of warfarin-associated subdural hematoma is up to 20 percent, although rapid reversal of anticoagulation and surgical drainage can ameliorate mortality rates.

Risk Factors for Intracranial Hemorrhage in Patients Anticoagulated with Warfarin

- Over age 70.
- Uncontrolled intracranial hypertension.
- Unruptured intracranial aneurysm.
- Prior ICH.
- Prior CVA.
- Primary or metastatic brain tumor.
- Concomitant antiplatelet therapy, such as aspirin.
- Increased intensity of anticoagulation as measured by INR.
- Cerebral amyloid angiopathy.
- Head trauma.
- Possible heavy alcohol consumption.
- Cerebral atrophy.

1. Therapeutic INR is often associated with ICH.
2. There is currently no way to identify this risk factor.

There is a tenuous balance between the benefit of anticoagulation and the risk of ICH in patients who have had or are at risk to have an ischemic stroke. Whether the risks and benefits are positive is up for debate. In some patients, the risk is simply too great.

The Risk of Hemorrhage among Patients with Warfarin-Associated Coagulopathy

Garcia D, et al
J Am Coll Cardiol
2006;47:1380

Although they do not directly address spontaneous ICH in patients with a warfarin-induced coagulopathy, these authors aimed to determine the risk of major bleeding within 30 days of starting warfarin in about 1,000 patients who presented with an INR greater than 5.0. Most had an INR between 5.0 and 9.0, but 80 percent of these were less than 7.0. Thirteen (1.3%) patients experienced major hemorrhage during a 30-day follow-up period. The highest INR was 16.1, but if the INR was between 5.0 and 9.0, only 34 patients (0.96%) experienced major bleeding. None of the events were fatal, and treatment of the elevated INR generally consisted only of withholding warfarin. Of the 13 individuals with hemorrhage, the site was gastrointestinal in 11, 100 patients (0.96%) experienced major bleeding. Interestingly, there were no cases of spontaneous intracranial hemorrhage even though about half of the patients were over 75.

These authors concluded that the risk of major hemorrhage in asymptomatic patients with an INR greater than 5.0 and less than 9.0 was quite low during the following month when warfarin was simply stopped, rather than actively reversing the coagulopathy. More than 80 percent of the patients in the cohort were managed without vitamin K reversal. These data seem to suggest that spontaneous ICH is not simply related to the degree of warfarin-induced anticoagulation.

Comment:
In addition to the usual suspects, other well-known contraindications to warfarin therapy are the potential for head trauma, frequent falls, inability to take the medicine correctly, or inability to obtain serial INR testing. The elderly frequently fit many parameters of this profile. Even if they don’t fall, the elderly patient is at risk for spontaneous ICH merely because he is old and taking warfarin. The first article present a fascinating figure demonstrating multiple small areas of extravascular hemosiderin deposits adjacent to small vessels in elderly hypertensive patients. This is apparently a common occurrence in the elderly, especially if they are hypertensive. These small hemorrhages were theorized to have been totally subclinical in nature, but could be one explanation why patients on anticoagulants who may have otherwise benign silent hemorrhages will spontaneously bleed into the brain. Thinking back on patients I have seen with ICH, they rarely have a readily identified AVM, tumor, or antecedent trauma.

As part of the natural aging process, small arterioles in the brain weaken and can exhibit spontaneous microbleeds, usually self-limited and subclinical. (Neurology 2004;63:1518) The bad news for us old guys. When warfarin is added to the mix, the hypertensive elderly may continue to bleed. This pheno-
Spontaneous ICH is exquisitely sensitive to blood pressure. It has been estimated that patients with prior CVA will decrease their rate of subsequent ICH by half with a mere 9/4 mm Hg decrease in blood pressure. (Lancet 2001;358:1033.)

To make matters worse, spontaneous warfarin-induced bleeding is often slow and progressive, and if patients are seen in the ED in the first few hours, the symptoms may be quite subtle. It’s not uncommon for elderly patients to express vague symptoms that I am unable to explain. If they are on warfarin and have even vague CNS-like symptoms, the prescient and sagacious clinician always thinks ICH. Unlike those with SAH, aneurysms, or AVM who often present comatose with a sudden onset of severe headache, nausea, and vomiting, those with slow spontaneous bleeding define a different clinical scenario, and a frustratingly subtle scenario at that.

It is my bias to think long and hard before avoiding an INR in any ED patient with almost any complaint who is taking warfarin. INRs are difficult to estimate, vary greatly secondary to all sorts of medications and food, and can be astronomically different from what they were one or two weeks earlier during a routine check. Most of the time in my practice, an ED visit plus warfarin equals an INR check. In the past, I have been quite satisfied and often dismissed ICH if the INR was therapeutic, but this article makes me think twice about that cavalier approach. Both articles indicate that it is not solely the degree of elevation of the INR that correlates most with ICH; rather, it’s the mere presence of warfarin in the body of an elderly patient that defines this risk. As an example, the Garcia article was unable to identify a single patient out of 1,000 with ICH who had an INR that would get anyone’s attention, so there’s more to this than just the intensity of the anticoagulation.

In a previous column discussing in a manner that improves your patient care? If yes, please explain.

Most EDs will do a CT scan at the drop of a hat, at the inking of a headache, or for a modicum of dizziness or blurred vision, so I think it’s worth the time and effort to CT scan anticoagulated patients with minor head trauma. My approach is not standard of care and no agreed-upon approach exists, but it pays to have a healthy level of paranoia. Many clinicians will rely on a pristine exam and close follow-up for minor head bumps in the anticoagulated elderly, and this approach has its supporters in the literature. The operative terms here are “pristine exam” and “close follow-up.”

Even in the absence of any bona fide trauma in the anticoagulated individual who is under constant observation by a bevy of concerned family members, nurses, or fellow octogenarians, the problem of spontaneous ICH still looms.

Finally, a word about the ability of the CT scan to identify ICH: Even I can usually see that white stuff (fresh blood) on the CT scan. When the blood has been present for a few weeks, it’s a different story. Distant and isodense hemorrhage can be quite subtle and escape the radiologist resident at 2 a.m. Note to self: If there is a strong suspicion for a CNS bleed and the CT is read as normal, ask for another look. Better yet, ask for another radiologist to supply another set of eyes.

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Questions:

1. ICH is the most lethal complication of warfarin therapy
   - True
   - False

2. Age over 70 and hypertension are the two most common associates with ICH in patients on warfarin.
   - True
   - False

3. ICH is only seen in anticoagulated patients who have an INR greater than 5.0 and who also have other risk factors for ICH, such as trauma, aneurysm, AV malformation, or CNS tumor.
   - True
   - False

4. Aspirin increases the rate of ICH in patients anticoagulated with warfarin.
   - True
   - False

5. Slowly enlarging and initially subtle clinical findings are common with spontaneous ICH in patients taking warfarin.
   - True
   - False

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