

Critical Issues in the Management of ICH

APPLYING THE NEW 2007 AHA/ASA GUIDELINES



iTEAM™
ICH Training, Education, Awareness
and Management

CME e-Newsletter

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Interactive Web Teleconferences Continue the Educational Process to Improve Patient Care

The latest iTEAM™ Web teleconference series, which was conducted in May and June 2007, focused on critical issues in the management of patients with intracerebral hemorrhage (ICH) and related updated, practical information to help improve the care of patients with this often deadly type of stroke. In the first Web teleconference, Edward C. Jauch, MD, MS, Assistant Professor, Department of Emergency Medicine, University of Cincinnati College of Medicine, reviewed the incidence, characteristics, and outcomes of ICH associated with oral anticoagulant and thrombolytic therapy, as well as the available treatment options for lowering the international normalized ratio (INR) and the latest efficacy data for these agents. He summarized the latest findings from the literature and updates presented at the 2007 International Stroke Conference, and explored their potential application in the management of coagulopathic patients with ICH. Scheduled to correlate with the release of the new 2007 American Heart Association (AHA)/American Stroke Association (ASA) guidelines for diagnosing and managing ICH, the second Web teleconference was moderated by J. Claude Hemphill III, MD, MAS, Associate Professor of Clinical Neurology and Neurological Surgery, University of California, San Francisco School of Medicine, who reviewed the long-awaited, updated AHA/ASA recommendations for the diagnosis of ICH, the management of increased arterial blood pressure and intracranial pressure (ICP), the treatment of medical complications of ICH, and recommendations for various surgical approaches. As in the previous Web teleconferences, the presentations were followed by an exchange of comments and questions among the participants.

This activity is a CME program of the ICH Training, Education, Awareness and Management (iTEAM™) initiative, developed by the Network for Continuing Medical Education (NCME) and supported by an educational grant from Novo Nordisk Inc.

A Dramatic Increase in Clinical Trials and Their Initial Findings Provides Great Hope for New and Effective Treatments for Patients With ICH

In 1999, when the first AHA guidelines for the management of spontaneous ICH were published, only 5 small randomized medical trials and 4 small randomized surgical trials of acute ICH existed. Since that time, 16 pilot and larger randomized medical and surgical trials for ICH/intraventricular hemorrhage have been completed or are ongoing.¹

During the iTEAM™ Web teleconference, Dr. Hemphill reviewed issues in the general management of ICH in the emergency department and intensive care unit settings, as well as specific treatments to address hematoma expansion, elevated ICP, and secondary brain injury. During his timely presentation, Dr. Hemphill highlighted the updated recommendations from the AHA/ASA 2007 guidelines for the management of ICH. Several of those updates are summarized below.

Should Blood Pressure Be Lowered?

The potential benefits of blood pressure reduction include limiting hematoma growth and decreasing perihematomal edema. Excessive hypertension can challenge the brain's capacity to autoregulate cerebral blood flow and can aggravate increased ICP and cerebral edema. The potential downside includes creating or exacerbating perihematomal ischemia. However, new evidence has largely dispelled the concept of major ischemia in the edematous tissue surrounding the hemorrhage.¹

TABLE 1

AHA/ASA ICH Guidelines — 2007 Update Suggested Recommended Guidelines for Treating Elevated Blood Pressure in ICH¹

- If systolic blood pressure (SBP) is >200 mm Hg or mean arterial pressure (MAP) is >150 mm Hg, then consider aggressive reduction of blood pressure with continuous intravenous infusion, with frequent blood pressure monitoring every 5 minutes
- If SBP is >180 mm Hg or MAP is >130 mm Hg and there is evidence or suspicion of elevated ICP, then consider monitoring ICP and reducing blood pressure using intermittent or continuous intravenous medications to keep cerebral perfusion pressure >60 to 80 mm Hg
- If SBP is >180 mm Hg or MAP is >130 mm Hg and there is no evidence of or suspicion of elevated ICP, then consider a modest reduction of blood pressure (eg, MAP of 110 or target blood pressure of 160/90 mm Hg) using intermittent or continuous intravenous medications to control blood pressure, and clinically reexamine the patient every 15 minutes

TABLE 2
AHA/ASA ICH Guidelines – 2007 Update
Potential Options for Reversing Warfarin¹

Agents	Advantages/Disadvantages
Vitamin K	<ul style="list-style-type: none"> Should not be used alone—takes at least 6 hours to normalize the INR
FFP	<ul style="list-style-type: none"> Replenishes the vitamin K–dependent coagulation factors inhibited by warfarin Acts more quickly than vitamin K <p><i>However, FFP may be impractical because:</i></p> <ul style="list-style-type: none"> Normalization of the INR may take hours to days There is potential for volume overload Concentration of clotting factors varies
PCC Factor IX complex concentrate rFVIIa	<ul style="list-style-type: none"> Normalizes INR rapidly Uses smaller fluid volumes and more rapid administration than FFP May induce thromboembolic complications

Nonetheless, for primary ICH, little prospective evidence exists to support a specific blood pressure threshold. Thus, whether more aggressive control of blood pressure during the first hours after onset of ICH can decrease bleeding without compromising the perfusion of brain surrounding the ICH remains unknown. Two ongoing studies—the Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) pilot study and the international phase III Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT) study—are investigating the control of blood pressure in patients with ICH and whether lowering high blood pressure levels after the onset of ICH will reduce the chances of a person dying or surviving with a long-term disability.¹

The 2007 AHA/ASA guidelines, like the 1999 AHA guidelines, outline the important concept of selecting a target blood pressure on the basis of individual patient factors, such as baseline blood pressure, presumed cause of hemorrhage, age, and elevated ICP. Until ongoing clinical trials of blood pressure intervention for ICH are completed, physicians must manage blood pressure on the basis of the present incomplete evidence. Current suggested recommendations for target blood pressures in various situations are listed in [Table 1](#).¹

Reversing Oral Anticoagulation — A Search for Better Options

Dr. Hemphill went on to talk about the importance of reversing oral anticoagulation in patients presenting with ICH. Life-threatening intracranial hemorrhage, predominantly ICH, is the most serious complication of oral anticoagulant therapy, with mortality in excess of 50%. ICH in any patient on warfarin (with an INR ≥ 5) should be considered life-

threatening.²⁻⁴ Warfarin not only increases the risk of ICH but worsens the severity of hemorrhage when it occurs, approximately doubling the rate of mortality. Failure to rapidly normalize the INR to <1.4 increases these risks.^{5,6} Accordingly, the goal of therapy to reverse anticoagulation should be to normalize the INR to <1.4 as soon as possible.⁷

Based on the 2007 AHA/ASA guidelines, the measures available to counteract the warfarin effect include the use of vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), factor IX complex concentrate, and recombinant activated factor VII (rFVIIa). Although the guidelines recommend that patients with warfarin-associated ICH should be treated with intravenous vitamin K to reverse the effects of warfarin, vitamin K is not recommended as the sole agent due to its slow action in normalizing the INR. Physicians have the above-mentioned options; however, these agents are not without disadvantages and/or risks ([Table 2](#)).¹

Whether and When to Restart Anticoagulants

A question that is always raised is whether and when anticoagulation can be restarted after ICH. The clinical dilemma of whether and when to restart anticoagulants in patients with ICH who have cardioembolic risk will not be solved until prospectively generated data on rates of ICH recurrence after warfarin reinstatement become available.

Dr. Hemphill summarized the current guideline recommendations. The decision to restart antithrombotic therapy after warfarin-related ICH depends on the risk of subsequent arterial or venous thromboembolism, the risk of recurrent ICH, and the overall state of the patient. For patients with a comparatively lower risk of cerebral infarction (eg, atrial fibrillation [AF] without prior ischemic stroke) and a higher risk of amyloid angiopathy (eg, elderly patients with lobar ICH) or with very poor overall neurological function, an antiplatelet agent may be an overall better choice for prevention of ischemic stroke than warfarin. In patients, with a very high risk of thromboembolism in whom restarting warfarin is considered, warfarin therapy may be restarted 7 to 10 days after onset of the original ICH.¹

The Evidence on rFVIIa Thus Far

Next, Dr. Hemphill reviewed the latest data for rFVIIa as a therapy for ICH to limit early hematoma growth. rFVIIa is currently approved for use in hemophilia and is an important natural initiator of hemostasis. It exerts its primary effects locally in regions of endothelial disruption and vascular injury.⁸ Results from 2 small, dose-ranging, pilot safety studies and a larger dose-finding phase II study focusing on decreasing the growth of ICHs have been published.⁹⁻¹¹ In the 2 small safety studies, the overall thromboembolic and serious adverse event rate was low enough to encourage further testing. In the larger, randomized, phase II trial, treatment with rFVIIa within

4 hours after the onset of ICH limited the growth of the hematoma, reduced the mortality rate, and improved functional outcome at 90 days despite a small increase in the frequency of thromboembolic adverse events. A larger phase III randomized trial (FAST) has been completed, and the results were recently presented at the American Academy of Neurology 59th Annual Meeting. Although rFVIIa had a dramatic effect on reducing hematoma expansion, it did not result in a clinical benefit at 90 days. In addition, the use of rFVIIa resulted in an increase in arterial thrombotic events compared with placebo.¹²

The 2007 AHA/ASA guidelines state that although treatment with rFVIIa within the first 3 to 4 hours after onset to slow progression of bleeding has shown promise in one moderate-sized phase II trial, the efficacy and safety of this treatment must be confirmed in phase III trials (upon release of these guidelines, the FAST trial results had not yet been presented) before its use in patients with ICH can be recommended outside of a clinical trial.¹

Say No to Nihilism!

Dr. Hemphill concluded his presentation by remarking that over the last 8 years, since the previous guidelines were published, the number of trials in the area of ICH has increased dramatically, and progress has been made, especially in terms of prognostication and risk stratification. Unfortunately, a definitive treatment of proven benefit for ICH is still lacking, but Dr. Hemphill remains optimistic that with the increase in new trials and new data that continue to emerge, the outcomes for patients with ICH will continue to improve. The first scientifically proven treatments for acute ICH are likely to become a reality during the next 5 years, and possibly sooner for some. New trials of antihypertensive therapy, surgical removal of ICH, and other adjunctive therapies are ongoing, but sustained efforts are needed to decrease the high morbidity and mortality rates associated with this deadly type of stroke.

Reversing and Restarting Anticoagulation — Highlights From the International Stroke Conference 2007

With the incidence of warfarin-associated ICH projected to increase, and with the emerging use of new therapies, there is a need to better understand the patient characteristics and real-world outcomes of warfarin-associated ICH, and the potential eligibility for these emerging treatments. Dr. Jauch gave an informative presentation that focused on the latest evidence-based approaches for managing coagulopathic patients with ICH. He presented highlights from the International Stroke Conference 2007, held in San Francisco, California, from February 7-9. Two of those presentations are summarized below—the first is a study by Rodan et al that attempted to define the characteristics and outcomes of warfarin-associated ICH, and the second is a study by Toratani et al that looked at whether anticoagulant therapy is beneficial for ICH patients with AF.

Rodan et al conducted an analysis of prospectively collected data from the Registry of the Canadian Stroke Network to investigate the characteristics and outcomes linked with warfarin-associated ICH and non-warfarin-associated ICH. They reviewed data from 1506 patients—1308 with non-warfarin-associated ICH and 198 with warfarin-associated ICH. Results showed that, compared with the non-warfarin-associated ICH cohort, warfarin-associated ICH patients were older and had more atherosclerotic risk factors and comorbidities. Patients with warfarin-associated ICH were a third more likely to have infratentorial ICH (23% vs 15%; $P<.01$) and less likely to have lobar ICH (36% vs 48%; $P<.01$). The differences between warfarin-associated and non-warfarin-associated ICH patients in

regard to infratentorial and lobar locations were significant. Both cohorts were equally likely to have basal ganglia/thalamic ICH (35% vs 35%) (Figure 1).¹³

The analysis also found that patients with warfarin-associated ICH were significantly more likely to present in coma (Glasgow Coma Scale score 3-5) (21% vs 13%; $P<.01$) and deteriorate neurologically (45% vs 35%; $P<.01$). In addition, in-hospital mortality was significantly higher in warfarin-associated ICH versus non-warfarin-associated ICH (52% vs 33%, $P<.01$). Three quarters of survivors were dependent upon discharge. In a multivariate analysis, warfarin was an independent predictor of infratentorial ICH location (OR: 1.8; 95% CI, 1.2-2.6) and in-hospital death (OR: 2.2; 95% CI, 1.5-3.4). Compared with patients with non-warfarin-associated ICH, those with warfarin-associated ICH had a higher rate of poststroke myocardial infarction (4% vs 1%, respectively; $P<.01$) but did not have

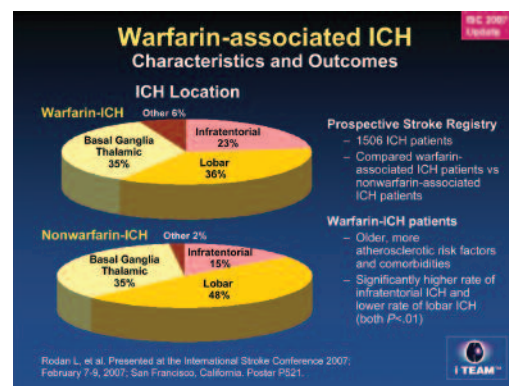


Figure 1

a higher rate of deep venous thrombosis (4%), pulmonary embolism (0.6%), or new stroke (3%). Overall, this study confirmed that oral anticoagulant therapy is an independent predictor of early death from spontaneous ICH (in-hospital mortality 52%) and that an association between warfarin and infratentorial ICH location exists (Figure 2).¹³

ICH in patients with atrial fibrillation (AF) poses a difficult management problem because anticoagulation may increase the recurrence rate of ICH in such patients. To examine whether anticoagulant therapy is beneficial for ICH patients with AF, Toratani et al performed a retrospective study in 44 ICH patients with AF (mean age, 72 years). Patients were classified into 2 groups: Group A (n=24) received oral anticoagulant therapy (OAT; warfarin) after ICH, whereas Group B (n=20) did not receive OAT after ICH. The follow-up period (approximately 3 years) was similar in both groups, and the frequencies of hypertension and other risk factors were also the same. Although the study found a somewhat higher recurrence rate in Group A (21%) than in Group B (15%), the difference was not significant (Figure 3).¹⁴

During the follow-up period, no patient had cerebral infarction in Group A, whereas 5 patients developed cerebral infarction in Group B (24%). The incidence of infarction was significantly higher in Group B than in Group A ($P=.014$). The mortality rate was the same in Group A (25%) and Group B (25%). These findings suggest that anticoagulation is likely to reduce the occurrence of cerebral infarction rather safely without a significant increase of recurrent ICH or death in ICH patients with AF. Thus, anticoagulation may be beneficial for prevention of stroke, even in ICH patients with AF (Figure 4).¹⁴

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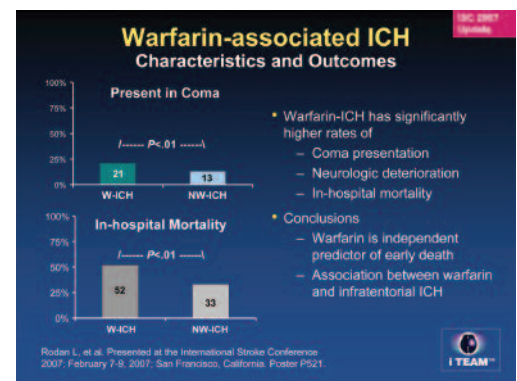


Figure 2

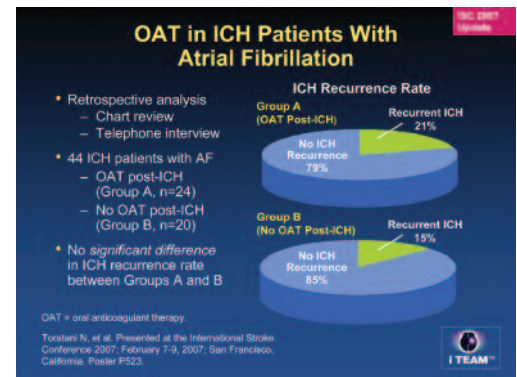


Figure 3

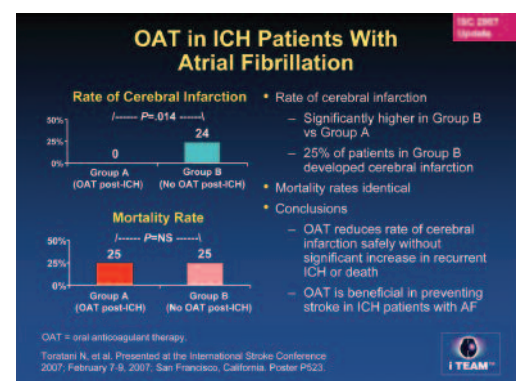


Figure 4