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## **Intracerebral Hemorrhage Associated With Oral Anticoagulant Therapy: Current Practices and Unresolved Questions**

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# Intracerebral Hemorrhage Associated With Oral Anticoagulant Therapy

## Current Practices and Unresolved Questions

Thorsten Steiner, MD, PhD; Jonathan Rosand, MD, MSc; Michael Diring, MD, FAHA

**Background and Purpose**—Life-threatening intracranial hemorrhage, predominantly intracerebral hemorrhage (ICH), is the most serious complication of oral anticoagulant therapy (OAT), with mortality in excess of 50%. Early intervention focuses on rapid correction of coagulopathy in order to prevent continued bleeding.

**Summary of Review**—This article reviews the epidemiology of OAT-associated ICH (OAT-ICH), and current treatment options, with the aim of providing a framework for future studies of unresolved questions. A number of acute treatments are available, but all have a significant risk of inducing thrombosis and other side effects, and vary in their rapidity of effect: vitamin K (very slow response time), fresh frozen plasma (slow response time, large volume of fluid required, transfusion-related acute lung injury), prothrombin complex concentrates, and recombinant activated factor VII. Current practice is to administer a combination of vitamin K and either fresh frozen plasma or prothrombin complex concentrates; the occasional use of recombinant activated factor VII has been reported. No prospective study has addressed the efficacy of, or outcomes from, the use of these practices.

**Conclusions**—Current management of OAT-ICH is varied and not based on evidence from randomized controlled trials. Well-designed clinical trials are essential if we are to identify the effective acute treatments for OAT-ICH that are urgently needed. (*Stroke*. 2006;37:256-262.)

**Key Words:** etiology ■ intracerebral hemorrhage ■ oral anticoagulant agents ■ therapy ■ warfarin

Spontaneous intracerebral hemorrhage (SICH) is the deadliest form of stroke, with a mortality rate between 30% and 55%,<sup>1-3</sup> increasing to as high as 67% in patients receiving oral anticoagulant therapy (OAT).<sup>3,4</sup> The incidence of OAT-related-ICH (OAT-ICH) is expected to increase in the coming years as the result of an anticipated rise in the incidence of atrial fibrillation attributable to an aging population (Figure 1).<sup>5,6</sup>

Although there has been significant progress in our understanding of the pathophysiology, rate of hematoma expansion, treatment, and the critical time window for controlling the bleeding in SICH, our current understanding of OAT-ICH remains limited. Despite ICH being the most serious and frequently fatal complication of OAT, there are currently no universally accepted guidelines for treatment.

This article reviews the epidemiology of OAT-ICH, its pathophysiology, and treatment options, based on currently available data. Pressing questions concerning optimal treatment and the time window for controlling ongoing bleeding are also discussed.

### Epidemiology

Worldwide, the incidence of SICH ranges from 10 to 20 per 100 000 population/year.<sup>7,8</sup> The reported incidence of OAT-

ICH is 7- to 10-fold higher than in patients who are not receiving OAT, and is as high as 1.8% per year in stroke-prone patients.<sup>3,4,9-12</sup> OAT-ICH comprise 70% of all OAT-related intracranial hemorrhages, with the remainder being subdural hemorrhages.<sup>10</sup> In Sweden, a prospective registry of all patients with ICH during a 1-year period found that, of 466 cases of intracranial hemorrhage, 73.2% were SICH, 22.7% were attributable to subarachnoid hemorrhage (80% aneurysmal), and the remaining 4.2% were caused by arteriovenous malformations or tumors. Whereas SICH was associated with hypertension (37%), cerebrovascular disease (41%), or OAT (12%), there was no association between OAT and subarachnoid hemorrhage.<sup>13</sup> In epidemiologic studies the incidence of all strokes range from 200 to 500 per 100 000. ICH accounts for 8% to 15% of strokes,<sup>14,15</sup> and OAT-ICH accounts for 10% to 12% of all ICH.<sup>13</sup> Thus, we estimate that OAT-ICH occurs at a rate 2 to 9 per 100 000 population/year.

The most common long-term indication for OAT is the prevention of ischemic stroke in patients with atrial fibrillation, a common condition of the elderly. Unfortunately, OAT dramatically increases the risk for ICH (placebo versus

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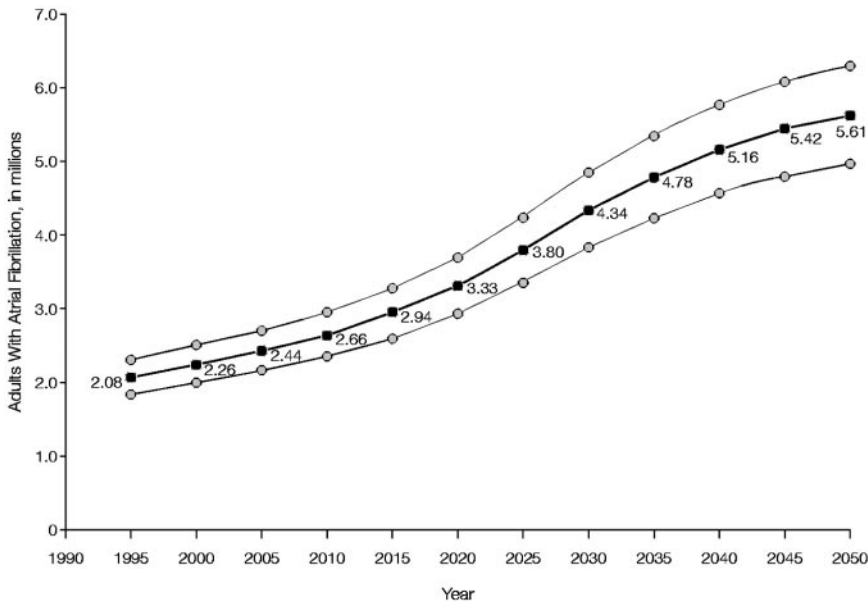
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**Figure 1.** Projected number of adults with atrial fibrillation in the United States between 1995 and 2050. (Reproduced from reference 6). Upper and lower curves represent the upper and lower scenarios based on sensitivity analyses.

warfarin, 0.1% versus 0.3% to 3.7%), worsens the severity of ICH, and significantly increases the likelihood of death when ICH occurs.<sup>5,17–19</sup> Unfortunately, with the aging of the population, the impact of OAT-ICH is likely to increase as the numbers of patients with atrial fibrillation increase.

## Pathophysiology

### Current Concepts of OAT-ICH

Hart and colleagues hypothesize that the use of OAT merely unmasks intracerebral bleeding that would otherwise remain asymptomatic, especially in patients with underlying hypertension or cerebrovascular disease.<sup>20</sup> A number of observations support this hypothesis. First, gradient-echo MRI indicates that microbleeds can be found even in neurologically normal individuals and are strongly associated with increased age and hypertension.<sup>21</sup> Second, cerebral amyloid angiopathy is most commonly found in people over 65 years of age and is a major risk factor for SICH in the elderly. Both advancing age and cerebral amyloid angiopathy are also important contributory factors to lobar ICH in patients who are receiving OAT,<sup>22,23</sup> suggesting that, in many cases, both SICH and OAT-ICH may have the same underlying cause. Third, data from the Stroke Prevention in Reversible Ischemia Trial (SPIRIT) and the European Atrial Fibrillation Trial (EAFT) indicate that patients with primary underlying cerebrovascular disease had a remarkably higher risk of OAT-ICH.<sup>24,25</sup> Moreover, studies suggest that the presence of white matter lesions, so-called “leukoaraiosis,” is an independent predictor of SICH.<sup>26</sup> The underlying causes of SICH and OAT-ICH may therefore be the same, with OAT acting as an exacerbating factor. These considerations may also explain why the distribution of locations in the brain where OAT-ICH occurs is no different from that seen in patients with SICH.<sup>4,13</sup>

Although the majority of OAT-ICH cases occur when a prothrombin time-international normalized ratio (PT-INR) is within the therapeutic range, higher intensities of anticoagulation clearly increase the risk of OAT-ICH,<sup>4,5,17,27</sup> suggesting

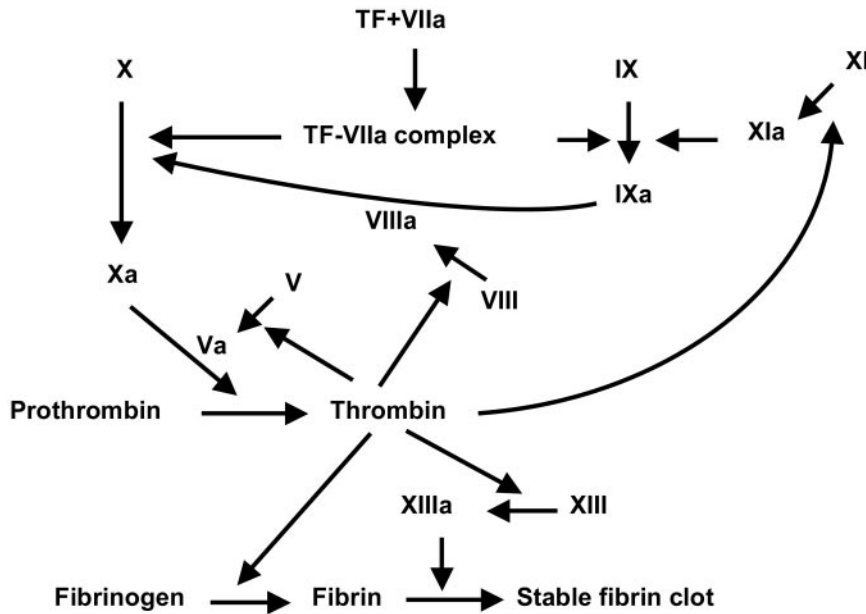
that OAT may also directly cause ICH. Oral anticoagulants interfere with the synthesis of vitamin K-dependent clotting factors, resulting in low levels of factors VII, IX, X, and prothrombin (Figures 2 and 3). It is possible that adequate levels and functional forms of these clotting factors are essential to counteract the stress placed on blood vessels as part of normal daily activities and to prevent bleeding.<sup>28,29</sup>

### Hematoma Expansion in OAT-ICH

ICH is a dynamic process. In SICH, hematoma expansion is thought to result from persistent bleeding or rebleeding from a single site of arterial rupture or secondary bleeding in the perilesional tissue.<sup>30</sup> Hematoma expansion occurs in nearly 40% of patients with SICH in the early hours following onset,<sup>1,31</sup> and extravasation of contrast media within the hematoma, a possible indicator of ongoing bleeding, has been detected in 46% of SICH cases.<sup>32</sup> Whether hematoma expansion occurs with similar frequency and time course in OAT-ICH remains unknown.

Although the incidence and dynamics of hematoma expansion in OAT-ICH remain to be established, hematoma expansion in OAT-ICH may be more common and occur over a longer time frame than in SICH, because of persistent coagulopathy. In a retrospective study of 47 patients with OAT-ICH, hematoma expansion was found in 28% of those evaluated within 24 hours of onset.<sup>33</sup> However, in this study, apart from vitamin K, some patients also received fresh frozen plasma (FFP) and prothrombin complex concentrates (PCC), and it is unclear as to which treatment(s) those patients with hematoma expansion had received. In another study, hematoma expansion up to day 7 was found in 16% (9/57) of patients who were not on OAT compared with 54% (7/13) in those on OAT.<sup>18</sup>

Presumably, a prolonged natural course of hematoma expansion in OAT-ICH would provide a longer time window for treatment with hemostatic therapy.



**Figure 2.** A simplified coagulation process. Coagulation is initiated by the binding of factor VIIa to the exposed tissue factor (TF) on subendothelium at the site of vascular injury. TF-factor VIIa complex activates factor IX and factor X. Factor IXa also activates factor X. Factor Xa, in turn, rapidly converts prothrombin to thrombin, generating small amounts of thrombin. Thrombin activates factor V and factor VIII, accelerating the activation of prothrombin and factor X, respectively. Thrombin also activates factor XI to factor XIa, which, in turn, activates factor IX. The generation of large amounts of factor Xa by factor IXa and factor VIIIa ensures that sufficient amounts of thrombin are continuously generated to convert fibrinogen to fibrin. Thrombin activates factor XIII to factor XIIIa, which then cross-links the soluble fibrin monomers to form a stable fibrin clot.

**Perihematomal Edema in OAT-ICH**

Although several studies in SICH suggest that the role of perihematomal ischemia is small at most,<sup>34,35</sup> no similar measurements have been undertaken in OAT-ICH. It is possible that acute reversal of anticoagulation might paradoxically exacerbate perihematomal edema. Factors released from activated platelets at the site of bleeding, such as vascular endothelial growth factor, may interact with thrombin to increase vascular permeability and contribute to the development of edema.<sup>36</sup> Although, in theory, a hemostatic drug that locally enhances the generation of thrombin, such as recombinant activated factor VIIa (rFVIIa), might increase brain edema, results from a recent clinical trial in SICH show that this was not the case.<sup>37</sup>

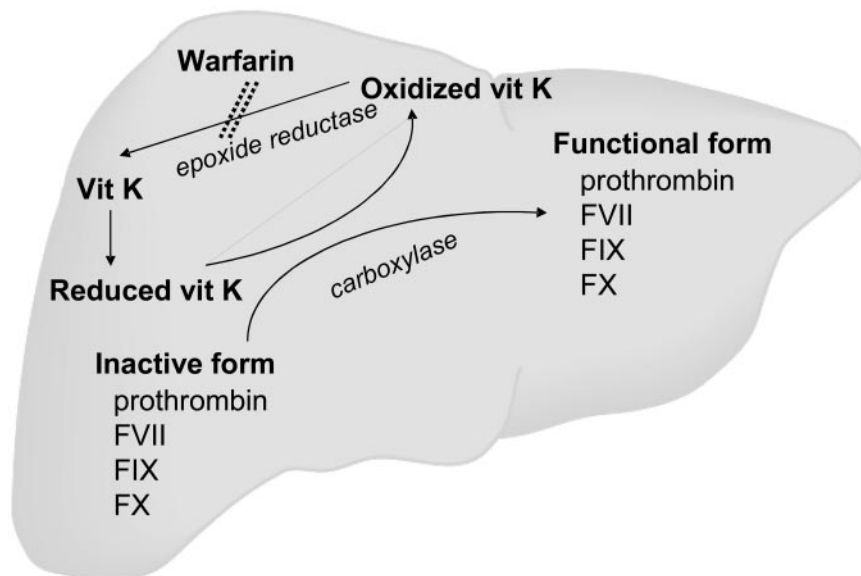
**Current Treatment Strategies**

The primary aim of OAT-ICH management is reversal of the anticoagulant effect to limit ongoing bleeding and hematoma

expansion. Treatment options include vitamin K, FFP, PCC, and rFVIIa.<sup>9,38-40</sup> Different preparations of OAT have different half-lives (HLT): for example, 36 to 42 hours for warfarin and 7 days for coumarin,<sup>41</sup> and therefore the treatment of OAT-ICH may have to be tailored to the particular type of oral anticoagulant used by the patient.

**Vitamin K**

It takes at least 2 to 6 hours, and often more than 24 hours, to achieve an effective response to vitamin K administration, although vitamin K alone is often inadequate to completely normalize the international normalized ratio in that time frame. Concomitant administration of coagulation factors is therefore required. Nevertheless, because of the short HLT of transfused coagulation factors (factor II: 48 to 60 hours; factor VII: 5 to 6 hours; factor IX: 20 to 24 hours; factor X: 24 to 48 hours), the administration of 5 to 20 mg of vitamin



**Figure 3.** Mechanism of action of vitamin K antagonists. In the liver, reduced vitamin K catalyzes the carboxylation converting an inactive form of prothrombin, factors VII, IX, and X, to an active form. In this process, reduced vitamin K is converted to oxidized vitamin K, which is converted back to vitamin K by the enzyme epoxide reductase. Vitamin K antagonists inhibit epoxide reductase; hence, oxidized vitamin K cannot be recycled back to vitamin K, resulting in a depletion of reduced vitamin K.

K is necessary to achieve a sustained reversal of anticoagulation.<sup>42–46</sup> The effect of vitamin K is more rapid when given intravenously. Although there have been concerns regarding allergic and anaphylactic reactions to intravenous vitamin K, the risk of this complication appears to be quite low,<sup>47</sup> with an incidence in one study of 3 per 10 000 doses (95% CI: 0.04 to 11 per 10 000 doses).<sup>48</sup> Subcutaneous administration may be safer but does not correct the INR as rapidly or as reliably as intravenous use.<sup>49</sup>

### Fresh Frozen Plasma

FFP contains all coagulation factors in a nonconcentrated form; hence, to achieve effective hemostasis a large volume (up to several liters) is required.<sup>9,50,51</sup> In principle, 1 mL of FFP/kg body weight increases the levels of coagulation factors by 1 to 2 International Units (IU)/dL.<sup>52</sup> The traditional dose of 10 to 15 mL of plasma/kg body weight may have to be exceeded in massive bleeding.<sup>53</sup> However, the standard of an FFP unit is based on its factor VIII content; the actual levels of vitamin K–dependent coagulation factors are not specified and vary considerably.<sup>50,54</sup> Our routine experience, and that of others, suggests that FFP volumes required to reduce the INR below 1.4 may vary considerably: for example, between 800 and 3500 mL.<sup>39,55</sup>

FFP requires compatibility testing and thawing before transfusion. Furthermore, the large volume required and a rapid transfusion rate can lead to circulatory overload. In cases of life-threatening bleeding such as ICH, or in patients with impaired cardiac function, FFP is therefore a less than ideal treatment option. In addition, FFP transfusion is associated with several potential adverse reactions, including transfusion-related acute lung injury, blood-borne infection, citrate toxicity, and allergic reactions.<sup>56,57</sup>

### PCC

PCC contain coagulation factors VII, IX, X, and prothrombin as well as proteins C, S, and Z in a concentrated form, and, unlike FFP, can be given without waiting for compatibility testing and thawing. The potency of PCC is expressed as factor IX content in IU, varying between preparations,<sup>58</sup> and a dose consists of ≈50 to 150 mL of reconstituted product. Based on data obtained from patients with hemophilia B, a dose of 1 IU of factor IX/kg body weight increases the level of plasma factor IX by 1 IU/dL.<sup>59</sup>

Studies of small numbers of patients suggest that PCC corrects a prolonged INR more rapidly than FFP.<sup>38,50,60</sup> However, a retrospective study comparing vitamin K, FFP, PCC, and no treatment in 151 patients with OAT-ICH, found no difference in 90-day mortality.<sup>61</sup> The main concerns with PCC-use focus on the potential to induce thrombosis and disseminated intravascular coagulation.<sup>62–66</sup>

### rFVIIa

rFVIIa is approved for the treatment of bleeding in patients with hemophilia. A recent clinical trial in acute SICH without coagulopathy demonstrated that rFVIIa, despite causing an increased incidence of thromboembolic events, reduced hematoma growth, reduced mortality, and improved 90-day functional outcome.<sup>37</sup> In patients with blunt trauma, rFVIIa

significantly reduced red blood cell transfusions.<sup>67</sup> Furthermore, rFVIIa has been used off-label in patients with uncontrolled bleedings attributable to hemostatic abnormalities resulting from trauma or massive blood loss, thrombocytopenia, inherited or acquired platelet dysfunction, liver dysfunction, in cardiac surgery, and for the prevention of perioperative bleedings.<sup>68,69</sup> There are limited data regarding the use of rFVIIa in OAT-ICH. A study by Erhardtson et al in healthy individuals receiving OAT demonstrated that administration of rFVIIa in doses ranging from 5 to 320  $\mu\text{g}/\text{kg}$  successfully normalized the INR, and that the effect lasted longer with higher doses.<sup>70</sup> Sørensen et al reported 6 patients who had been on OAT and were treated with rFVIIa for central nervous system bleeding.<sup>71</sup> The doses used ranged from 10 to 40  $\mu\text{g}/\text{kg}$  and the pretreatment INRs, which ranged from 1.7 to 6.6, were normalized to  $\leq 1.5$  within 10 minutes after rFVIIa administration. No adverse events, in particular thromboembolic events, were seen in the reported patients. In 2 retrospective studies including patients with OAT-ICH, rFVIIa was given alone ( $n=7$ ) or in combination with FFP ( $n=12$ ) in doses ranging from 15 to 120  $\mu\text{g}/\text{kg}$ .<sup>39,55</sup> The authors concluded that treatment with rFVIIa may have led to a faster correction of INR or decreased FFP requirements. In these studies application of rFVIIa appeared to be safe.

Several features make rFVIIa a promising candidate for OAT-ICH treatment. These include rapid action localized to the site of vascular injury, low volume required for administration, and good efficacy and safety profiles.<sup>37,40</sup> Nevertheless, patients on OAT have an increased risk for thromboembolism, and it is possible that the safety profile in patients with OAT-ICH could be different from that in SICH.

## Guidelines for Reversal of Anticoagulant Effect

There are currently no standardized guidelines for reversal of the anticoagulant effect in patients with OAT-ICH. UK guidelines issued by the British Committee for Standards in Hematology recommend 5 mg of intravenous or oral vitamin K, and 50 U/kg of PCC or 15 mL/kg of FFP.<sup>43</sup> Another UK guideline, issued by the Northern Region Hematologists' Group, reduce the recommended dose of PCC to 30 U/kg.<sup>45</sup> The American Thoracic Society recommend 10 mg of intravenous vitamin K and PCC, without specifying the dose of PCC.<sup>44</sup> The Australasian Society of Thrombosis and Hemostasis recommends 5 to 10 mg of intravenous vitamin K, 25 to 50 IU/kg of PCC, and 150 to 300 mL FFP.<sup>72</sup> The recommendation for the concomitant use of PCC and FFP is because the PCC preparation licensed in Australia and New Zealand at the time the guidelines were published in 2004 did not contain factor VII.

We recommend administering 10 mg vitamin K with every treatment to support the supply of prothrombin-dependent clotting factors. Currently, PCC appears to be a logical treatment for immediate reversal of the anticoagulant effect. However, concerns regarding thromboembolic side effects persist. Although FFP is widely available, its efficacy is difficult to predict because of the variable contents of coagulation factors in each unit. Furthermore, the large volumes required limit its use in patients with impaired

cardiac function. Treatment should be continued until the INR is normalized.

Costs of these treatments are difficult to predict for medical (interindividual variability of effect, variability of product), economic, and political reasons. Given a patient with 70 kg with an INR of 3 on admission, the costs to decrease the INR to 1.4 or lower may be €330 to 550 for FFP (2000 to 3500 mL), €400 to 900 for PCC ( $\approx$ 2000 U), and €3500 to 5000 for rFVIIa (single 80  $\mu$ g/kg dose). However, it is important to realize that the efficacy of a treatment should ultimately determine the clinical decision to use it, and, currently, no treatment has been prospectively shown to be effective.

Considerations concerning whether and when to resume therapeutic anticoagulation in patients who have experienced OAT-ICH include whether intracranial bleeding has been fully arrested, the estimated ongoing risk of thromboembolism, and the presumed pathophysiology of the ICH, which will determine the risk of hemorrhage recurrence.<sup>9,73–78</sup>

## Unresolved Issues on Treatment

### Time Window for Treatment

In SICH, evidence suggests that significant hematoma expansion tends to occur during the first 4 hours after onset, and this is likely to be the critical time window for a hemostatic treatment.<sup>30,37</sup> In OAT-ICH, the natural course of hematoma expansion is probably more prolonged, perhaps up to 24 or 48 hours,<sup>1,18,79</sup> raising the possibility that patients presenting as late as 24 hours (or even later) may benefit from effective hemostatic treatment.

### Dose Regimen

Administration of an effective hemostatic agent at an early stage of SICH appears to accelerate the formation of a fibrin clot, which stops the bleeding.<sup>37</sup> In this case, it seems that a single dose is sufficient. However, in OAT-ICH, the underlying coagulopathy may require a higher dose or repeated dosing.

### Monitoring Hemostasis During the Reversal of Anticoagulant Effect

PT-INR is routinely used for regulating OAT as well as monitoring the reversal of its anticoagulant effect. The test is sensitive to decreased levels of factor VII and factor X, and prothrombin, but not to decreased levels of factor IX.<sup>50,53,80,51,75</sup> Because FFP contains variable amounts of factor IX, the correction of the INR with FFP may not be accompanied by a correction of factor IX levels.<sup>50</sup> For example, Makris et al found that administration of 800 mL FFP decreased the mean INR from 6.73 to 2.38, whereas the mean factor IX levels were essentially unchanged (from 26.45 IU/dL to 27.36 IU/dL).<sup>50</sup> Thus, the INR may be normalized but the patient remains at risk of further bleeding.

The use of the INR for monitoring patients treated with rFVIIa is also problematic. Pharmacological doses of rFVIIa will always lower the INR regardless of the levels of other coagulation factors. Hence, when monitoring the reversal of anticoagulant effect, INR values should be interpreted with caution as they might not reflect the actual status of all vitamin K–dependent coagulation factors.<sup>53,51</sup>

Thromboelastography may provide a more meaningful measure of coagulation status. This system records a profile of clot formation in whole blood, providing an overall picture of hemostatic function.<sup>81,76</sup> Based on 7 patients with central nervous system bleeding during OAT who were treated with rFVIIa, Sørensen and colleagues showed that it may be feasible to use thromboelastography to monitor hemostatic status.<sup>71</sup> Nevertheless, more data are needed to prove the clinical utility of the measure.

## Considerations for Clinical Trials in OAT-ICH

The design of future trials will have to address choice and dose of agent, the timing of its administration, and the risk of adverse effects ranging from thromboembolism to the possibility of exacerbated neurologic injury. For ethical reasons, all patients will of necessity require some form of treatment (for example, vitamin K, FFP, PCC, rFVIIa). Dose and dosing frequency are relevant because normalization of coagulation may occur at different doses of the intervention, and the long HLT of the anticoagulation treatment may make it necessary to repeat the respective intervention. The appropriate time window for treatment is likely to be different from that of SICH,<sup>37</sup> as the time course for ongoing bleeding and hematoma expansion in OAT-ICH appears to be prolonged. Patients with OAT-ICH also differ from most patients with SICH in that they are, by definition, at elevated risk for thromboembolism, which could complicate both acute treatment and the duration selected for maintaining a normal INR following the acute event. Finally, it will be important to select an ideal test for monitoring the therapeutic response to reversal of anticoagulation, because some individuals may respond more slowly to treatment than others. Ultimately, whether such acute interventions prove cost-effective will require further study, but given the high mortality of OAT-ICH and the enormous burden of disability among survivors, the opportunity for an effective treatment to prove cost-effective, even if considered costly in the short-term, is great.

## Conclusions

Current understanding of OAT-ICH remains limited and far behind that of SICH. Although ICH is the most serious complication of OAT, standardized treatment guidelines are still lacking. Current treatments focus on normalization of the iatrogenic coagulation disorder, and are not based on evidence from randomized controlled trials. Although most patients with OAT-ICH are at high risk of thromboembolism, and may be at high risk for myocardial infarction, the risks of these events in association with the various treatment strategies available for the management of OAT-ICH are unknown.

Patients who receive chronic OAT urgently require better treatments for acute OAT-ICH, and identification of these treatments can only come from rigorous and controlled clinical trials. Furthermore, successful clinical trials could offer hope, not only to those individuals who currently receive OAT, but also for those additional millions of patients for whom OAT is deemed too risky despite a clear indication. Reducing the morbidity and mortality of OAT-ICH could alter the risk–benefit analysis of chronic anticoagulation,

with the potential for a “domino effect” reduction on the incidence of thromboembolism worldwide.

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