SPECIAL ARTICLE

Treatment of Warfarin-Associated Intracerebral Hemorrhage: Literature Review and Expert Opinion

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Wider use of oral anticoagulants has led to an increasing frequency of warfarin-related intracerebral hemorrhage (ICH). The high early mortality of approximately 50% has remained stable in recent decades. In contrast to spontaneous ICH, the duration of bleeding is 12 to 24 hours in many patients, offering a longer opportunity for intervention. Treatment varies widely, and optimal therapy has yet to be defined. An OVID search was conducted from January 1996 to January 2006, combining the terms *warfarin* or *anticoagulation* with *intracranial hemorrhage* or *intracerebral hemorrhage*. Seven experts on clinical stroke, neurologic intensive care, and hematology were provided with the available information and were asked to independently address 3 clinical scenarios about acute reversal and resumption of anticoagulation in the setting of warfarin-associated ICH. No randomized trials assessing clinical outcomes were found on management of warfarin-associated ICH. All experts agreed that anticoagulation should be urgently reversed, but how to achieve it varied from use of prothrombin complex concentrates only (3 experts) to recombinant factor VIIa only (2 experts) to recombinant factor VIIa along with fresh frozen plasma (1 expert) and prothrombin complex concentrates or fresh frozen plasma (1 expert). All experts favored resumption of warfarin therapy within 3 to 10 days of ICH in stable patients in whom subsequent anticoagulation is mandatory. No general agreement occurred regarding subsequent anticoagulation of patients with atrial fibrillation who survived warfarin-associated ICH. For warfarin-associated ICH, discontinuing warfarin therapy with administration of vitamin K does not reverse the hemostatic defect for many hours and is inadequate. Reasonable management based on expert opinion includes a wide range of additional measures to reverse anticoagulation in the absence of solid evidence.

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FFP = fresh frozen plasma; ICH = intracerebral hemorrhage; INR = international normalized ratio; PCC = prothrombin complex concentrate; rFVIIa = recombinant factor VIIa

The frequent use of long-term oral anticoagulation in elderly patients, particularly to prevent stroke in individuals with atrial fibrillation, has resulted in an increase in warfarin-associated intracerebral hemorrhage (ICH).[1,2] Half of the patients with warfarin-associated ICH die within 30 days, and this uniformly high early mortality rate has remained stable over time[3-12] (Table 1). Adequate treatment remains to be defined.[3,4,6,8] No consensus exists about the optimal short-term treatment of this lethal, iatrogenic form of stroke. Randomized trials meaningfully addressing treatment are not available, and current management is based largely on small clinical case series.[9]

In the absence of well-designed clinical trials, treatment based on the opinions of experts in clinical stroke, neurologic intensive care, and hematology and coagulation is likely the best available evidence. In this article, current treatment options for warfarin-associated ICH and management recommendations solicited independently from 7 international experts are reviewed.

METHODS

A computerized search of the OVID database from January 1996 to January 2006 combining the terms *warfarin* or *anticoagulation* with *intracranial hemorrhage* or *intracerebral hemorrhage* was undertaken. The reference lists from recent review articles were also examined. From the elicited sources, 4 of the coauthors (R.G.H., C.S.K., M.I.A., and W.D.F.) drafted the narrative review of the recent literature. Because information about the practical clinical pharmacology of prothrombin complex concentrates (PCCs) is not readily accessible, 2 coauthors (B.J.H. and R.C.G.) prepared a structured pharmacological summary of these drugs (Appendix 1[13-15]).

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TABLE 1. **Early Mortality in Anticoagulant-Associated Intracranial Hemorrhage**

Reference	Method	No. of central nervous bleeds	% (No.) of 30-day mortality
Hart et al,[3] 1995	Literature review, 15 studies, 1982-1994	454	60 (272)
Neau et al,[4] 2001	Case series	79	44 (35)
Sjoblom et al,[6] 2001	Medical record review	151	54 (82)
Rosand et al,[7] 2004	Prospective case series	102	52* (53)
Berwaerts et al,[8] 2000	Case series	42	44 (35)
SPIRIT trial,[10] 1997	Randomized trial	27	43 (18)
Sjalander et al,[11] 2003	Case series	48	44 (21)
Gage et al,[12] 2001	Medicare cohort	~200	52 (104)
Pooled data		1103	53† (602)

*Three-month mortality.
†SD ± 7.

Seven experts in clinical stroke (B.N., T.S., and T.Y. or M.Y.), neurological intensive care (J.R., S.A.M., and E.F.M.W.), and hematology and coagulation (J.E.A.) were asked to independently address the following 3 questions:

1. How should anticoagulation be reversed in a patient with acute (within 6 hours of symptom onset) warfarin-associated ICH with an international normalized ratio (INR) of 2.5? What are the roles of recombinant factor VIIa (rFVIIa) and PCCs?

2. When should anticoagulation (warfarin) be restarted in survivors of warfarin-associated ICH with mechanical prosthetic heart valves?

3. Under what circumstances (if any) should anticoagulation be resumed in a patient with chronic nonvalvular atrial fibrillation who experienced an ICH during warfarin therapy? Does it matter whether the INR was 1.8 or 3.5 at the time of the hemorrhage?

An expert was defined as someone with involvement with one or more publications on the specific topic or who had personal experience treating warfarin-associated ICH. The selection of experts was also based on geographic location to reflect an international perspective (United States, Japan, Germany, and Sweden). No pharmaceutical company participated in the development of this article or in the selection of the experts.

The experts were provided with the literature review, Appendix 1, and access to all sources cited in the reference list. Rather than attempting to reach a consensus, individual responses were collated and summarized (Table 2). Full answers provided by the experts are available online at www.mayoclinicproceedings.com linked to this article. Experts did not have access to each other's responses.

LITERATURE REVIEW

FREQUENCY OF WARFARIN-ASSOCIATED ICH

Warfarin-associated ICH is not rare at hospitals that serve large numbers of patients undergoing anticoagulation and appears to be increasing.[2] A survey of consecutive patients with supratentorial ICH admitted to the Massachusetts General Hospital between 1994 and 2001 found that 24% were taking warfarin, an average of 1 patient per month with warfarin-associated ICH admitted to this tertiary care hospital.[16] Other studies of ICH in the middle to late 1990s reported that approximately 12% (range, 6%-16%) of patients with primary ICH were receiving oral vitamin K

TABLE 2. **Expert Recommendations for the Management of Warfarin-Associated ICH: Responses to 3 Specific Questions***

Question	Expert 1	Expert 2	Expert 3†	Expert 4†	Expert 5†	Expert 6	Expert 7
1. How can anticoagulation best be reversed (INR=2.5)?	rFVIIa and vitamin K	rFVIIa if deteriorating; FFP and vitamin K otherwise	rFVIIa, FFP, and vitamin K	FFP or PCCs and vitamin K	PCCs and vitamin K	PCCs and vitamin K	PCCs and vitamin K
2. When should anticoagulation with prosthetic cardiac valve be restarted?	>7 d in most patients‡	>7 d if computed tomogram stable	5-10 d	Low-dose heparin as early as 48 h	10-14 d§	1-3 d	7 d
3. Should warfarin therapy be restarted for atrial fibrillation?	With reluctance	If prior ischemic stroke	Probably never	If ICH is deep (ie, nonlobar)	If ICH is deep (ie, nonlobar)	If ICH is deep (ie, nonlobar)	In secondary prevention‡

*See text for complete statement of the questions. Complete responses available online at www.mayoclinicproceedings.com linked to this article. FFP = fresh frozen plasma; ICH = intracerebral hemorrhage; INR = international normalized ratio; PCCs = prothrombin complex concentrates; rFVIIa = recombinant activated factor VIIa.
†Expert has served as consultant for NovoNordisk.
‡If patient was older than 80 years and if moderate to severe leukoaraiosis was absent.
§Low-dose heparin as early as 24 hours after normalization of INR (<1.5).

TABLE 3. **Reversing Anticoagulation in Warfarin-Associated Intracerebral Hemorrhage**[*]

Management option	Time to anticoagulation reversal	Comments and cautions
Discontinuing warfarin therapy	5-14 d	
Vitamin K[†]	6-24 h to correct the INR	Replacement of factors IX and X takes longer than 24 hours, risk of anaphylaxis with intravenous injection, warfarin resistance in higher doses up to 1 wk
Fresh frozen plasma	3-6 h for infusion, typically 12-32 h for reversal	Volume (2-4 L to normalize INR) can be prohibitive
Prothrombin complex concentrate	15 min after 10-min to 1-h infusion	Limited availability, cost, variable cofactor content based on manufacturer, potentially prothrombotic
Factor VIIa concentrate	15 min after bolus infusion	Short half-life, cost, potentially prothrombotic, uncertain safety

[*]INR = international normalized ratio.
[†]A total of 10 mg intravenously by slow infusion throughout 10 minutes.

antagonists.[5,8,17,18] In a large population-based survey conducted in 2002 to 2003, 18% of all ICHs occurred during anticoagulation.[2] Based on these figures, approximately 8000 to 10,000 cases of warfarin-associated ICH are estimated to occur annually in the United States.

CORRELATIONS WITH ANTICOAGULATION INTENSITY

Anticoagulation with warfarin increases the risk of ICH 2 to 5 times, directly related to the intensity of anticoagulation[3,19]; nevertheless, most warfarin-associated ICHs occur during anticoagulation intensities that are within the conventional therapeutic range (ie, INRs of 2.0-3.5).[4-6,16,20] The degree of INR prolongation at the time of ICH seems to predict progressive hematoma enlargement after admission, functional outcome, and mortality,[8,16,21] although some have reported no correlation.[22] The outcome is fatal in two thirds of ICH patients with INRs greater than 3.0 at presentation.[16]

CLINICAL PRESENTATION AND DIAGNOSIS

The mean age of patients with warfarin-associated ICH is in the 70s, reflecting the age distribution of patients undergoing anticoagulation combined with the special propensity for ICH to affect elderly patients. Focal neurologic signs in a patient undergoing anticoagulation, particularly if associated with headache, nausea and vomiting, obtundation, and elevated blood pressure, warrant emergent evaluation for ICH. Symptom onset is usually sudden (ie, stroke-like). In nearly half of patients, the hematoma enlarges slowly during the initial 12 to 24 hours with attendant progression of neurologic deficits.[6,8,21-23] Hematoma enlargement after 6 to 12 hours from onset is common in warfarin-related ICH, but this is rare in spontaneous ICH.[22]

Involvement of the cerebellum in warfarin-associated ICH has been reported in several but not all studies.[2-4,6,24] The relative distribution of lobar vs deep white matter or basal ganglia locations appears to be similar in spontaneous vs warfarin-associated ICH.

Intracerebral hemorrhage is visible immediately as a hyperdense area on computed tomograms; occasionally a dark rim, presumably representing unclotted blood, can be present in actively bleeding patients with excessively prolonged INRs.[3,25] Magnetic resonance imaging with special gradient-echo techniques is highly sensitive.[26] Large hematoma volume (>50 mL), intraventricular extension, and shift of midline structures are associated with poorer outcome.[4,6,8]

REVERSING THE COAGULATION DEFECT

Warfarin-associated ICH should prompt emergent correction of anticoagulation. Even small hematomas in patients who have undergone anticoagulation therapy can expand during the initial 24 to 48 hours, particularly if the INR is greater than 3.0, and anticoagulation should be reversed without delay. Several options exist for achieving this goal (Table 3). No randomized trials assessing clinical outcomes were found on treatment of warfarin-associated ICH. The existing literature consists mainly of small case series, often retrospective and potentially biased by selection. In the absence of meaningful evidence, the management of these patients varies widely.

Vitamin K and fresh frozen plasma (FFP) are standard therapies to reverse warfarin anticoagulation, but neither agent is ideal for emergency anticoagulation reversal. Both vitamin K and FFP take several hours to reduce the INR and have a potential for adverse reactions.[27] Administration of vitamin K (10 mg intravenously) does not normalize the INR for 6 to 24 hours. A dose of 5 to 10 mg may be repeated every 12 hours, up to a total dose of 25 mg.[28-31] The infusion rate is 1 mg/min, and it can be diluted in dextrose 5% in water or dextrose 5% in normal saline.[31] Subcutaneous administration may be safer, but the effect is even slower and less reliable.[32,33]

TABLE 4. Conversion of the International Normalized Ratio (INR) to Prothrombin Complex Concentrates (PCCs) (Expressed as Percentage of Normal Plasma)*[35,37]

INR	PCCs (%)
>5	5
4.0-4.9	10
2.6-3.2	15
2.2-2.5	20
1.9-2.1	25
1.7-1.8	30
1.4-1.6	40
1.0-1.3	100

*Calculate needed milliliters of fresh frozen plasma using the following formula[35]: (target level % × present level %) × body weight[37] in kilograms.

FRESH FROZEN PLASMA

The volume of FFP required to reverse fully the coagulation defect (often 2-4 L if the INR is greatly prolonged) is an important limiting factor in this critically ill population. A rapid infusion is also required to increase the plasma protein levels significantly, increasing the risk of circulatory overload.[34] Calculation of the amount of FFP (in milliliters) required to reverse the effects of warfarin is based on the INR, body weight, and target INR after correction[35-37] (Table 4).

Time to treatment has been suggested as a main prognostic factor of anticoagulation reversal in this particular patient population. On multivariable analysis of retrospectively reviewed emergency department records of 69 patients in the Boston, Mass, area, the shorter the time to vitamin K and FFP treatment, the higher the likelihood of INR correction, but without an evident improvement in neurologic outcome.[38]

PROTHROMBIN COMPLEX CONCENTRATES

For more than a decade, PCCs (also known as factor IX concentrate) have been used to treat warfarin-associated ICH in Europe.[28] Use of PCCs normalizes the INR more rapidly than FFP infusion,[28,39] but its effect on clinical outcomes is unproved.[6,28] A single randomized trial that included only 5 patients with anticoagulation-associated ICH was confounded by concomitant infusion of FFP.[40] The PCC preparations vary in the ratio of their coagulation factor components, making even indirect comparisons tenuous[41] (Appendix 1).

In 8 studies that included a total of 107 patients treated with PCCs for warfarin-associated ICH, thrombosis was reported in 4 (7%) of 57, and early mortality occurred in 15 (24%) of 64 (Table 5). Of 7 patients in these series identified as having subsequent enlargement of the ICH, worsening occurred in 4 patients 12 to 72 hours later in association

TABLE 5. Prothrombin Complex Concentrates (PCCs) in Warfarin-Associated Intracerebral Hemorrhage (ICH)

Reference	No. of patients	Manufacturer	Composition	Median dose	% (No.) of patients		Early mortality (%)*
					ICH enlargement	Thrombosis	
Sjoblom et al,[6] 2001	23	Prothrompex-T/Immuno	Factors II, VII, IX, and X	Not reported	Not reported	Not reported	39
Yasaka et al,[21] 2003	11	PPSB-HT Nichiyaku/Nihon	20 IU of factors II, VII, IX, and X; 380 IU/mL of protein C	12.5 IU/kg (~900 IU)	22 (2/9)†	0 (0/11)	9
Fredriksson et al,[28] 1992	10	Preconativ/Kabi	Factors II (50 IU/mL), IX (60 IU/mL), and X (50 IU/mL)	26 IU/kg (1930 IU)	Not reported	10 (1/10)	20
Yasaka et al,[36] 2005	27	PPSB-HT Nichiyaku/Nihon	500 IU of factors II, VII, IX, and X; 380 IU of protein C	10.85 IU/kg (2.6-26.8 IU/kg)	7 (2/27)	Not reported	Not reported
Cartmill et al,[39] 2000	6	IXA/BPL	Not specified	50 IU/kg	Not reported	0 (0/6)	17
Boulis et al,[40] 1999	3	Konyne/Bayer	Factors II (38 IU), VII (4 IU), IX (25 IU), and X (38 IU)	40-50 IU/kg	Not reported	0 (0/3)	33
Bertram et al,[42] 2000	11	Not specified	Not specified	Not reported	27 (3/11)‡	27 (3/11)‡	9
Makris et al,[43] 1997	16	Prothrombin-T/Immuno or IXA/BPL	Factors II, VII, IX, and X	25-50 IU/kg	Not reported	0 (0/16)	Not reported

*Early mortality ranged from 2 to 30 days.
†Nine ICHs plus 1 each of subdural and epidural hematoma: 1 hematoma enlargement was associated with an international normalized ratio of 2.7, which occurred 24 hours after initial correction by PCC without coadministration of vitamin K.
‡Enlargement of ICH occurred on days 2 and 3 associated with international normalized ratio of 1.5, 3.2, and 1.9 at the time of deterioration and receiving full-dose (n=2) or low-dose heparin. Of 7 patients with prosthetic valves given PCCs, 2 had middle cerebral artery ischemic strokes on treatment days 4 and 5.

TABLE 6. Recombinant Factor VIIa in Warfarin-Associated ICH*

Reference	No. of patients	Type of bleed	Average dose	% (No.) of patients with ICH enlargement	No. of patients with thrombosis	% (No.) of early mortality
Sorensen et al,[51] 2003	7†	3 IP, 1 SAH, 1 SDH, 1 spine trauma	25 µg/kg	Not reported	None	0 (0)
Veshchev et al,[52] 2002	1	SDH	120 µg/kg	Not reported	Not reported	100 (1/1)
Freeman et al,[53] 2004	7	3 IP, 1 IP and IV, 2 IV, 1 IP and SAH	52.5 µg/kg	12-28 (3/7)	None	28 (2/7)
Brody et al,[54] 2005‡	12	4 ICH, 4 SDH, 4 others	4.8 mg (range, 2.4-9.6 mg)	Not reported	1	42 (12/28)

*ICH = intracerebral hemorrhage; IP = intraparenchymal; IV = intraventricular; SAH = subarachnoid hemorrhage; SDH = subdural hematoma.
†Only 6 patients had bleeds; 1 patient was at high risk of bleeding because of an international normalized ratio greater than 7.0 and spinal stenosis.
‡All received vitamin K and fresh frozen plasma in addition to recombinant factor VIIa.

with incomplete correction (INRs of 1.5, 1.9, 2.7, and 3.2), combined with the use of heparin in 3.[21,30,42] Many experts suggest monitoring the patient carefully to keep the INR normal for the initial 72 hours after ICH to minimize hematoma expansion.

Thrombotic events have occasionally been reported to complicate infusion of PCC,[28,41] but the risk is difficult to quantify from available reports because of different preparations, dosages (correcting the INR to different levels), and patient populations. Thrombogenic effects may well vary with the specific PCC preparation,[41,44] and whether current PCCs are associated with thrombosis has never been substantiated.[45] Most of the available data (Table 5) suggest that use of PCC in warfarin-associated ICH is relatively safe.[46] However, Bertram et al[42] reported large ischemic strokes occurring in 3 of 11 ICH patients treated with PCCs (including 2 of 7 with prosthetic cardiac valves) on days 2, 4, and 5, despite 2 patients being treated with low-dose heparin. This study did not report the dosages and composition of the PCC to allow comparison to other studies.

Dosing of PCC

The PCC dosage is calculated according to body weight, degree of INR prolongation, and desired level of correction (Appendix 1); typical dosages are 25 to 50 IU/kg. The dose is based on the factor IX content of the preparation. After initial infusion of 500 to 1000 IU at a rate of 100 IU/min, subsequent infusion should be at 25 IU/min or less. Some have safely infused higher doses (3500 IU) during 10 minutes.[46] The dose of PCC required to reverse warfarin anticoagulation is generally less than that for other causes of comparably prolonged INRs. For patients with warfarin-associated ICH, aiming for an INR of 1.2 or less is recommended.[30,41] The INR should be checked 30 minutes after the initial infusion to be certain that it is normal; if not, infusion of additional PCC should be considered.

Alternatively, Yasaka et al[30] and Hellstern et al[41] reported successful treatment of 9 Japanese patients with warfarin-associated ICH using relatively low doses of PCC: 500 or 1000 IU was given depending on prolongation of the INR of less than 4.5 vs 4.5 or greater, respectively, with additional administration of 500 IU based on a subsequent INR obtained after the initial infusion (Table 5). Correction of INR occurred within 10 minutes of completion of the infusion. The median dosage (12.5 IU/kg) resulted in rapid correction of INR to normal, hematoma enlargement in 2 of 9 patients, and no thromboembolic episodes (including 4 patients with prosthetic cardiac valves). These same investigators prospectively treated 42 patients (median age, 70 years) with warfarin-related bleeding complications with a PCC with or without vitamin K. Of these 42 patients, 27 had ICH, 7 had epidural hematomas, and 1 had acute subdural hemorrhage. Initial infusion of 500 IU rapidly normalized the INR unless the initial INR was greater than 5.

Vitamin K, 10 mg intravenously, should be given concomitantly with a PCC.[28,30,36] Some authors recommend low-dose heparin or low-dose low-molecular-weight heparin with PCC infusion to minimize the risk of thrombotic complications.[41] If the INR is corrected to normal using a PCC, many experts suggest beginning low-dose subcutaneous heparin or low-dose low-molecular-weight heparin 48 hours after ICH onset in patients with prosthetic cardiac valves and to restart warfarin therapy 7 to 14 days after ICH onset.[47,48] For ICH survivors with a lower inherent risk of thromboembolism who will not resume anticoagulation, pneumatic compression stockings should be used for prevention of venous thromboembolism.[49]

Recombinant Factor VIIa

Recombinant factor VIIa, a procoagulant agent approved for bleeding complications in patients with hemophilia, has been used to treat warfarin-associated ICH[50-54] (Table 6). Rapid correction of the INR was demonstrated in 2 small series that included 7 patients with ICH during anticoagulation treated with rFVIIa, FFP, and vitamin K.[51,53] In a

clinical case series, Sorensen et al[51] evaluated the efficacy of rFVIIa in addition to vitamin K and FFP in 7 patients with warfarin-related central nervous system bleeding. Pretreatment INRs ranged from 1.7 to 6.6. Within minutes after a single bolus dose of rFVIIa (10-40 µg/kg), all INRs were 1.5 or less. Six patients underwent drainage of the hematoma, and all patients survived. The mean Glasgow Outcome Scale score at discharge was 2 (SD ± 1). No signs of thrombosis were reported.

Doses of 10 to 50 µg/kg have been used, a dose generally lower than that required to reverse coagulation deficits associated with factor inhibitors (100 µg/kg every 2-3 hours until bleeding stops). It should be reconstituted with sterile water for injection and used within 3 hours of reconstitution.[31]

It is unclear how accurately the INR reflects coagulation status after rFVIIa infusion.[45,55] There is concern that rFVIIa transiently corrects the warfarin-induced deficiency of factor VII, but it does not replace the other factor deficiencies associated with oral vitamin K antagonist therapy. The elimination half-life is short (2.5 hours). Repeat infusion is necessary unless standard therapies of vitamin K and FFP are used concomitantly. No studies have compared rFVIIa infusion with PCC in warfarin-associated ICH. Those who advocate rFVIIa for reversal of warfarin-induced coagulation defects note that its short half-life makes induction of a thrombogenic state less likely compared with infusion of a PCC[51] (Table 6).

Mayer et al[56] reported in 2005 a double-blind, placebo-controlled trial evaluating the efficacy of rFVIIa in acute spontaneous ICH (not associated with warfarin). In this study, 399 participants with acute spontaneous ICH verified by computed tomography were assigned to receive either placebo or 1 of 3 dosages (40, 80, or 160 µg/kg) of rFVIIa within 4 hours of symptom onset. The primary outcome was hematoma growth at 24 hours. Mortality (38%; P=.02) and the combined outcome of death or severe disability (P<.05 for all 3 dosages) were reduced in patients given rFVIIa. Arterial thrombosis (ischemic stroke and myocardial infarction) occurred in 5% of those assigned to rFVIIa vs none assigned to placebo.

RECOMMENDATIONS FOR REVERSING ANTICOAGULATION IN WARFARIN-ASSOCIATED ICH

Few guidelines or consensus recommendations have been published regarding reversal of anticoagulation in this setting. A PCC administered with vitamin K is advocated by one recent guideline for patients with life-threatening bleeding undergoing anticoagulation (with rFVIIa as an alternative) but provides no specific recommendations regarding warfarin-associated ICH.[29] A review by Steiner et al[9] in early 2006 recommended a PCC coupled with 10 mg of vitamin K.

However, PCCs are not readily available at most US hospitals. When available, their use is often restricted to hematology specialists. Despite its increasing use, rFVIIa currently does not have Food and Drug Administration label indication for spontaneous ICH or warfarin-associated ICH, its use may be complicated by thrombosis,[57] and it is expensive.

SURGICAL EVACUATION AND BLOOD PRESSURE CONTROL

The role of neurosurgical evacuation of ganglionic and lobar ICH during anticoagulation is not well defined, and most neurosurgeons are reluctant to operate in a setting of impaired hemostasis. However, given the high mortality accompanying warfarin-associated ICH, surgical treatment after reversing anticoagulation may be appropriate in select patients,[42] especially if the coagulopathy can be rapidly corrected. The International Surgical Trial in Intracerebral Haemorrhage[58] included only those with spontaneous supratentorial ICH.

Blood pressure is often elevated in patients with ICH at admission. Treatment guidelines for acute, spontaneous ICH recommend treatment of hypertension with the aim of achieving a mean arterial pressure of less than 130 mm Hg.[59] Considerable controversy remains regarding whether high blood pressure contributes to continuing bleeding after ICH onset and if lowering of blood pressure can cause perihematomal ischemia or hematoma enlargement.[60] Despite the debate, some authors recommend that the systolic blood pressure be maintained below 180 mm Hg during the acute phase.[59] However, in 151 patients with anticoagulant-related ICH, acute blood pressure was not predictive of 1-month or 6-month mortality.[6]

WHICH PATIENTS SHOULD RECEIVE LONG-TERM ANTICOAGULATION AFTER WARFARIN-ASSOCIATED ICH?

The indication for restarting oral anticoagulation should be carefully reassessed in the wake of a warfarin-associated ICH. No studies provide an accurate estimation of the risk of recurrent ICH in survivors of warfarin-associated ICH who are subsequently undergoing anticoagulation. In 5 small case series that included 14 patients with prosthetic heart valves who had warfarin-associated ICH and later underwent additional anticoagulation therapy, the aggregate risk appeared low, 3% per year (Table 7). However, the absolute risk of recurrent ICH in these younger patients with prosthetic heart valves during anticoagulation is likely lower than in older patients with atrial fibrillation. The presence of lacunar strokes,[65] the burden of white matter disease,[66,67] and the existence of clinically silent microhemorrhages (detected by magnetic resonance imaging gradient-echo techniques)[68-74] may help predict the recurrence of ICH. Currently, this information provides no method for risk

TABLE 7. **Long-term Anticoagulation in Survivors of Warfarin-Associated ICH***

Reference	No. of patients	Mean age (y)	Indication	Target INR†	Mean follow-up (mo)	Outcome
Punthakee et al,[5] 2002	6	~64	Prosthetic valves	Not reported	34	No ICH
Butler & Tait,[61] 1998	4	~57	Prosthetic valves	2-3, 2.5-3, 3-3.5, 3-4.5	22	No ICH
Nakagawa et al,[62] 1995‡	1	11	Prosthetic valve	Not reported	36	No ICH
Nagano et al,[63] 1991‡	2	39	Prosthetic valves	Not reported	5	1 ICH
Lau et al,[64] 1991	1	65	Prosthetic valve	1.8-2.5	36	No ICH
Aggregate data	14	~55	Prosthetic valves		27	1 ICH (3% per year)

*ICH = intracerebral hemorrhage; INR = international normalized ratio.
†No information is available about achieved INRs during follow-up.
‡Surgical evacuation performed for index ICH.

stratification in predicting initial or recurrent ICH in clinical situations.

For *primary prevention* of ischemic stroke in elderly patients with nonvalvular atrial fibrillation, the long-term risk of recurrent ICH during anticoagulation may outweigh its benefit.[16,75] Patient preferences are important to consider in this difficult discussion. In those with prosthetic cardiac valves or for *secondary prevention* in atrial fibrillation, the risks of thromboembolism in the absence of anticoagulation are much higher, and the risk-benefit assessment favors reinitiation of anticoagulation.

The use of aspirin or other antiplatelet agents in combination with warfarin is likely to increase the risk of recurrent ICH, and this combination should not be used routinely.[76-78] Targeting the lowest efficacious INR (eg, 1.8-2.5 for patients with atrial fibrillation) should be coupled with especially vigilant INR monitoring to minimize excessive anticoagulation. Control of blood pressure is critical; lowering systolic blood pressure by 10 mm Hg will reduce the risk of recurrent ICH by half.[79]

IF INDICATED, WHEN SHOULD ANTICOAGULATION BE RESTARTED?
No large prospective trials have addressed the issue of when to restart anticoagulation after warfarin-associated ICH. The literature ranges from withholding warfarin anticoagulation for 4 to 6 weeks[80] to withholding it for 1 to 2 weeks[5,81,82] to the use of intravenous heparin immediately after the INR is corrected to normal.[42,83] Overall, the data (8 studies involving 132 patients, Table 8) suggest a low risk of thromboembolic complications between 7 and 14 days after anticoagulation reversal in patients with warfarin-associated ICH and prosthetic valves.

In a study of 141 patients with warfarin-associated ICH, Phan et al[81] reported anticoagulation interruption for a mean of 10 days. Only 3 patients (2%) experienced thromboembolic events (1 patient with a prosthetic cardiac valve); all 3 events occurred within 5 days from discontinuation of anticoagulation therapy. The authors concluded

that the risk of thromboembolism is low if warfarin therapy is discontinued for 1 to 2 weeks. No information was reported about reversal of anticoagulation and whether INRs were corrected to normal in most patients (a previous report describing part of this patient cohort reported routine use of FFP and vitamin K).[82] In contrast, Bertram et al[42] reported 2 large ischemic strokes in 7 ICH patients with prosthetic cardiac valves treated with PCCs despite concomitant treatment with low-dose heparin. The authors advocated the use of full-dose intravenous heparin on the day after treatment with PCCs. A possible explanation for the apparent difference in observed rates of thromboembolism after reversal of anticoagulation in these 2 studies is a prothrombotic state caused by infusion of high-dose PCCs in the series by Bertram et al,[42] although play of chance and/or publication bias could be operative.

If the INR is corrected to normal using PCCs, it may be sensible to begin treatment with low-dose subcutaneous heparin or low-dose low-molecular-weight heparin 48 hours after ICH onset. For patients who will resume anticoagulation, it appears that warfarin therapy can be safely restarted 7 to 14 days after ICH.

DISCUSSION

Warfarin-associated ICH is a devastating iatrogenic problem whose frequency is increasing because more elderly people are receiving anticoagulation. It is a tragic irony that anticoagulation given to prevent ischemic stroke can be complicated by severe, usually lethal, hemorrhagic stroke as its most dreaded complication. In the absence of randomized trials, management is based on a combination of anecdotal experience, pathophysiologic constructs, and expert opinion. Not surprisingly, the management recommendations by 7 experts from 3 continents vary widely.

All agree that anticoagulation should be urgently reversed, but how to achieve this varies from traditional

TABLE 8. **Timing of Additional Anticoagulation in Patients With Warfarin-Associated ICH***

Reference	No. of patients	Initiation of anticoagulation and outcomes
Punthakee et al,[5] 2002	7	Warfarin therapy started a mean of 14 d (9-15 d in 4 patients); no ICH enlargement or thrombotic events
Bertram et al,[42] 2000	13	Full-dose intravenous heparin on days 1 and 2 in 7 patients, with hematoma enlargement in 2; of 6 patients given low-dose heparin, 3 had ischemic strokes on days 2, 4, and 5 (all previously treated with prothrombin complex concentrates)
Butler & Tait,[61] 1998	4	Heparin on day 3 (range, 1-6) and warfarin on day 7 (range, 3-19) in 10 patients with ICHs (n=4) or subdural hematomas (n=6); no ICH enlargement or thrombotic events
Phan et al,[81] 2000	87	Anticoagulation withheld for mean of 10 d, acute treatment to reverse anticoagulation not reported, and 1 ischemic stroke; the 30-d thromboembolism rate estimated as 3% for those with prosthetic cardiac valves
Leker & Abramsky,[83] 1998	4	Four patients given intravenous heparin 24-36 h as soon as INR was <1.5 after vitamin K and plasma infusion; no worsening
Kawamata et al,[84] 1995	13	Six patients underwent surgery; of 20 patients with intracranial hemorrhages and prosthetic valves, 1 thromboembolism in a setting of early postoperative heparin
Babikian et al,[85] 1988	3	Of 6 patients with prosthetic cardiac valves (3 with ICHs and 3 with subdurals), warfarin therapy interrupted for a mean of 19 d without thromboembolism
Gomez et al,[86] 1988	1	Heparin on day 10 without hemorrhagic worsening in 1 patient

*Reports and/or cases with surgical evacuation are excluded.[30,31] ICH = intracerebral hemorrhage; INR = international normalized ratio.

infusion of FFP to use of PCCs and rFVIIa (all with vitamin K administration). The delay to reversal and volume overload with FFP has been acknowledged. Proponents of rFVIIa point to its rapid reversal of the INR and lack of volume overload, but other experts express concern that its safety among patients taking warfarin to prevent thrombosis is not established.

All experts favored resumption of warfarin therapy within 5 to 10 days of ICH in stable patients (Table 2). No general consensus occurred regarding additional anticoagulation for patients with atrial fibrillation who experience ICH during warfarin therapy: the risk of thromboembolism (ie, prior ischemic stroke) and the risk of recurrent ICH (ie, lobar vs deep location of the initial ICH) were the key factors considered. We do not make specific treatment recommendations but rather define the range of management used by experts in the absence of solid clinical evidence.

Is a randomized trial of short-term treatment of warfarin-associated ICH feasible? Some estimate that there are 10,000 cases annually in the United States alone.[2] The time window for effective intervention is probably longer than for spontaneous ICH and for ischemic stroke. In addition to direct benefits to those with warfarin-associated ICH, an efficacious intervention proven by randomized trials might well allay fears that cause anticoagulation to be withheld from many who would benefit. On the other hand, such a trial would be difficult to organize and expensive, require large numbers of participants (depending on the selected treatment arms), and be challenging to design, given the lack of a generally accepted standard treatment. Furthermore, some speculate that warfarin will be replaced by other oral anticoagulants in the future, but this remains speculative.

CONCLUSION

Reasonable management of warfarin-associated ICH includes a range of treatments in the absence of adequate data, as defined by the expert opinions delineated herein. Time to reversal of anticoagulation is crucial, and whatever treatment strategy is endorsed should be planned in advance in collaboration with local emergency medicine physicians and be used expeditiously. Randomized trials that address the management of warfarin-associated ICH are needed.

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APPENDIX 1. **Prothrombin Complex Concentrates (PCCs) (Also Known as Factor IX Complex [Human]) for Reversal of Warfarin-Induced Bleeding**

Factor IX Complex (Human) Drug Information[13]

US BRAND NAMES: Bebulin; Profilnine HT; Proplex T; Konyne 80

Prothrombin Complex Concentrate (PCC) Content of Factors II, VII, IX, and X*[14]

Product	Manufacturer†	Factor II	Factor VII	Factor IX	Factor X	Cost per unit of factor VII‡[15] ($)
Profilnine HT (500 U/vial)	Grifols	148	11	100	64	0.75
Konyne 80 (500 U/vial)	Bayer	100	20	100	140	0.50
Proplex T (30 mL)	Baxter	50	400	100	50	0.42
Bebulin (size not available)	Baxter	120	13	100	139	0.75

*Factors measured in units per 100 U of factor IX (ratios).

†Grifols Biologicals Inc, Los Angeles, Calif; Bayer Corp, West Haven, Conn; Baxter Biopharmaceuticals, Deerfield, Ill.

‡Example cost calculation: Proplex T vial containing 600 U total (ratios as above), cost = $0.42 × 400 = $168.

PHARMACOLOGICAL CATEGORY: Antihemophilic agent, blood product derivative.

MECHANISM OF ACTION: Replaces deficient clotting factor, including factor X. Factor IX is a vitamin K–dependent coagulation factor that is synthesized in the liver. Factor IX is activated by factor XIa in the intrinsic coagulation pathway. Activated factor IX (IXa), in combination with factor VII:C, activates factor X to Xa, resulting ultimately in the conversion of prothrombin to thrombin and the formation of a fibrin clot. The infusion of exogenous factor IX to replace the deficiency present in hemophilia B temporarily restores hemostasis.

CONTRAINDICATIONS: Liver disease with signs of intravascular coagulation or fibrinolysis, not for use in factor VII deficiencies (except Proplex T), patients undergoing elective surgery.

WARNINGS/PRECAUTIONS: Use with caution in patients with liver dysfunction; prepared from pooled human plasma—the risk of viral transmission is not totally eradicated; monitor patients who receive repeated doses twice daily with partial thromboplastin time (PTT) and prothrombin time (PT) and level of factor being replaced (eg, usually VII or IX); if PT is less than 10 seconds, this may indicate risk of hypercoagulable complication.

MONITORING PARAMETERS: Levels of factors being replaced (eg, VII or IX), PT, PTT.

PHARMACODYNAMICS/KINETICS: Half-life elimination:
- VII component: initial, 4-6 hours; terminal, 22.5 hours
- IX component: 24 hours

DOSING: ADULTS = Emergency correction of warfarin-induced coagulopathy; bleeding in factor IX deficiency: intravenous (only):
- Note: dosage is expressed in units of factor IX activity and must be individualized.
- Formula for units required to raise blood level percentage:
    Total blood volume (milliliters of blood per kilogram) = 70 mL/kg
    Plasma volume = total blood volume (milliliters) × [1 – hematocrit (in decimals)]
- For example, for a 70-kg adult with a hematocrit of 40%: plasma volume = [70 kg × 70 mL/kg] × [1 – 0.4] = 2940 mL
- To calculate number of units needed to increase level to desired range (highly individualized and dependent on patient's condition):
    Number of units = desired level increase [desired level – actual level] × plasma volume (in milliliters)
- For example, for a 100% level in the above patient who has an actual level of 20%:
    Number of units needed = [1 (for a 100% level) – 0.2] × 2940 mL = 2352 U
- As a general rule, the level of factor IX required for treatment of anticoagulant overdosage = 15 U/kg intravenously
    Sample calculation:

$$70\text{-kg patient} \times 15\ \text{U/kg of factor IX} = 1050\ \text{U of factor IX needed}$$

$$\text{Proplex T (rounded to next 100 U): } 1100\ \text{U of factor IX needed}$$

$$\text{Ratio} = \frac{400\ \text{U of factor VII}}{100\ \text{U of factor IX}} \times \frac{?}{1100\ \text{U of factor IX}} = 4400\ \text{U of factor VII needed}$$

$$\text{Cost} = 4400\ \text{U of factor VII} \times \$0.42/\text{U} = \$1848$$

DOSAGE FORMS: Injection, powder for reconstitution (single-dose vials).

ADMINISTRATION: Solution should be infused at room temperature. Intravenous administration only; should be infused slowly. Start infusion at a rate of 2 to 3 mL/min. If headache, flushing, or changes in pulse rate or blood pressure appear, the infusion rate should be decreased. Initially, stop the infusion until the symptoms disappear, then resume the infusion at a slower rate. Infuse at a rate not exceeding 3 mL/min.

SIGNIFICANT ADVERSE REACTIONS
- 1% to 10%:
    Central nervous system: fever, headache, chills
    Neuromuscular and skeletal: tingling
    Miscellaneous: following rapid administration, transient fever
- <1% (limited to important or life-threatening): disseminated intravascular coagulation, flushing, nausea, somnolence, thrombosis following high dosages because of presence of activated clotting factors, tightness in chest, tightness in neck, urticaria, vomiting

DRUG INTERACTIONS: Increased toxicity; do not coadminister with aminocaproic acid because it may increase risk of thrombosis.

PRODUCT RESTRICTIONS/ORDERING INFORMATION: Per telephone communication with a representative from Baxter Bioscience (Jennifer Randolph, 1-800-423-2090 ext 5983), because of limited product availability, distribution of these products is restricted to prevent or control bleeding in patients with factor IX deficiency, especially hemophilia B and Christmas disease, factor VII deficiency (Proplex T only), and hemophilia. Average shelf-life of ordered vials is typically 6 to 12 months.