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## Review article

# Reversal of antithrombotic treatment in intracranial hemorrhage – A review of current strategies and guidelines



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## ABSTRACT

In the last few years, there has been a rapid increase in patients being treated with various anticoagulation and antiplatelet agents. In clinical neurology, these drugs are administered for primary and secondary stroke prevention or to avoid the consequences of immobilization of severe stroke patients. Additionally, thrombolytic intravenous therapy and, recently, intra-arterial therapy for stroke have been increasingly employed all over the world. These therapies are associated with an increased risk of hemorrhage, including the most dangerous, intracranial hemorrhage. The knowledge of the standards for the treatment of hemorrhagic complications in the central nervous system is crucial for doctors in neurology and stroke units as well as in emergency rooms. Therefore, we conducted a review of various guidelines and recommendations, including manufacturers' opinions contained in the summaries of product characteristics (Polish and British or European versions), in Guidelines of the Polish Neurological Society and in international and American guidelines i.e., European Stroke Organization (ESO) and American Heart Association/American Stroke Association (AHA/ASA). In addition, we compared these guidelines with expert opinions published in recent manuscripts and manuals on intensive care in neurology.

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The current usage of anticoagulant and antiplatelet therapies has rapidly increased, especially in secondary and primary prophylactics for ischemic stroke as well as for avoiding the consequences of immobilization in severe stroke patients.

In addition, in the last few years, there has been a significant increase in the number of stroke patients treated

intravenously and, more recently, intra-arterially with recombinant tissue plasminogen activator (rtPA).

The increase in the number of patients treated with these drugs is related to the growth in the risk of antiplatelet-, anticoagulation- and thrombolytic-associated intracranial hemorrhages.

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Therefore, knowledge about reversal methods in patients treated with these drugs is crucial for every-day clinical practice.

Unfortunately, the guidelines, recommendations and strategies for the reversal of drug-induced coagulopathy in cerebral hemorrhage are not consistent. Some of these guidelines, recommendations and strategies do not consider cerebral hemorrhage but merely refer to the general treatment of any hemorrhage.

Therefore, we developed a summary of the recommendations from various up-to-date sources and attempted to compare them.

The aim of this paper was to present the methods of reversing the coagulopathy in intracranial hemorrhages caused by the following:

- Anticoagulation agents: heparins, vitamin K antagonists, and non-vitamin K antagonist oral anticoagulants (formerly novel oral anticoagulants (NOACs)) (apixaban, rivaroxaban and dabigatran),
- Antiplatelet agents, including acetylsalicylic acid (aspirin), thienopyridines (as clopidogrel and prasugrel), and ticagrelor.
- Thrombolytic agents (rtPA).

Because the methods of treatment of those coagulopathies differ depending on the hemorrhage etiology, clinical center experience and evidence from clinical trials, we developed a summary of treatment recommendations from the following sources: the summary of product characteristics (SPCs) published by the manufacturer (Polish and British or European versions), current guidelines by Polish (Polish Society of Neurology – PTN) [1], European (ESO) [2], and American (AHA/ASA) [3] scientific organizations and current manuals by leading experts in the field published within the last 3 years [4–6].

The review involves primary intracranial hemorrhage (ICrH) and secondary ICrH after ischemic stroke. A generally accepted rule is that the hemorrhagic transformation of ischemic stroke with deterioration of the neurologic condition requires management that is similar to that in spontaneous ICrH. Clinically insignificant secondary hemorrhages (diagnosed with neuroimaging methods) do not require any additional measures [1].

We reviewed only pharmacological therapies, and the indications for surgical treatment of ICrH will be addressed in another review.

## 1. Vitamin K antagonists (VKA)

See Table 1.

### 1.1. Summary of product characteristics

#### 1.1.1. Acenocoumarol

Summary of product characteristics, Polish version (2013) [7], outlines therapeutic options in hemorrhage after acenocoumarol administration. In clinically insignificant hemorrhages – temporary reduction of the dose. In moderate hemorrhages – vitamin K 2–5 mg p.o. In severe hemorrhages – vitamin K 5–10 mg i.v. (not faster than 1 mg/min). This dose can be repeated every 4 h up to a daily dose of 40 mg. In the case of sudden severe hemorrhage – fresh whole blood or fresh frozen plasma (FFP) or recombinant Factor VIIa (rFVIIa) and vitamin K should be administered.

Additionally, in British version of SPC [8], manufacturer recommends management of severe hemorrhage with administering fresh whole blood or prothrombin complex concentrate (PCC) with vitamin K.

#### 1.1.2. Warfarin

Therapeutic options for warfarin (tabl. a 3 and 5 mg) described in summary of product characteristics, Polish version (2013) [9] are as below:

Warfarin's half-life is 20–55 h; therefore, overdoses require longer observation and longer vitamin K administration. In some cases, gastric lavage and activated charcoal p.o. may be useful. If severe bleeding occurs, FFP, PCC or tranexamic acid can be administered.

Manufacturers outline the management of INR increases; this management may be considered ICrH prevention. An INR increase does not automatically lead to a hemorrhage, but it is a definite ICrH risk factor; therefore, below, we present the management of such a condition.

INR > 4 without bleeding – stop warfarin, wait 1 day, adjust the dose. INR > 6 without bleeding – stop warfarin, wait 1–2 days, adjust the dose, check the INR immediately. INR > 8 without bleeding – stop warfarin, consider administering 1–2 mg of vitamin K i.v. or p.o., wait – 2 days, check the INR the following day, adjust the dose.

Small bleeding\* – stop warfarin, wait 1–2 days before using warfarin and consider administering 1–2 mg of vitamin K i.v. or p.o.

Severe bleeding\* – stop warfarin, rapidly reduce the INR to 1.5–1.6; 10 ml/kg FFP can reduce INR from 7 to 4 or from 4 to 2.2.

**Table 1 – The management of VKA-associated ICrH.**

SPC [7–10]	PNA [1]	ESO [2]	AHA/ASA [3]	Manual Wijdics [4]	NCC Wijdics [5]	Manual Frontera [6]
Withhold oral anticuagulant administration						
Vitamin K p.o. or i.v.	When INR is >1.4:	Vitamin K i.v.	Vitamin K i.v.	Vitamin K i.v.	Vitamin K i.v.	Vitamin K i.v.
PCC or FFP and vitamin K (acenocoumarol SPC only: whole blood or rFVIIa + vitamin K)	Vitamin K PCC	Add PCC or FFP	PCC, FFP	PCC, FFP or rFVIIa	PCC, FFP or rFVIIa	PCC or FFP
FFP – fresh frozen plasma, PCC – prothrombin complex concentrate, rFVIIa – recombinant factor VIIa.						

One unit of PCC is equal to 1 ml of FFP. The effect is immediate but is reduced after 6 h.

If the treatment with warfarin can be stopped, vitamin K 5–10 mg i.v. should be used together with PCC/FFP or vitamin K 2–5 mg i.v. if warfarin will be continued.

An effect of vitamin K is often observed within 6–12 h, with the maximal effect after 24 h.

Intoxication – in the case of bleeding see above.

Therapeutic options: vitamin K at a dose 10 mg i.v. should be administered 3–4 times per day until the time of the expected elimination of the warfarin effect.

Treatment should be up to a few days.

In British version of SPC [10] manufacturer specifies slightly different management of warfarin intoxication as well as of INR increases.

For patients on long-term anticoagulants:

INR > 8.0, no bleeding or minor bleeding – stop warfarin, give vitamin K 0.5–1 mg i.v.; repeat dose of vitamin K if INR still too high after 24 h.

INR 6.0–8.0, no bleeding or minor bleeding – stop warfarin, restart when INR < 5.0.

INR < 6.0 but more than 0.5 U above target value – reduce dose or stop warfarin, restart when INR < 5.0.

For patients not on long-term anticoagulants without major hemorrhage: measure the INR at presentation and sequentially every 24–48 h after ingestion depending on the initial dose and initial INR.

If the INR remains normal for 24–48 h and there is no evidence of bleeding, there should be no further monitoring necessary.

Give vitamin K if the patient has ingested more than 0.25 mg/kg or the prothrombin time is already significantly prolonged (INR > 4.0). The adult dose of vitamin K is 10–20 mg orally. Delay oral vitamin K at least 4 h after any activated charcoal has been given. Repeat INR at 24 h and consider further vitamin K.

\*SPC does not provide definitions for “small”, “moderate”, “severe” and “life-threatening” bleeding.

## 1.2. Polish Neurological Association

According to the guidelines of the Polish Neurological Association [1] there are following options of management of oral anticoagulant-associated intracerebral hemorrhage (ICeH) in patients being administered oral anticoagulants whose INR is greater than 1.4.

Withhold anticoagulants.

The INR should normalize as a result of using PCC. In addition, intravenous vitamin K should be administered.

Additional information: It is recommended to administer PCC with vitamin K due to much longer half-life of warfarin and acenocoumarol than PCC's half-life [1].

## 1.3. European Stroke Organisation

European Stroke Organization guidelines for the management of spontaneous intracerebral hemorrhage [2] state that in anticoagulant-associated intracerebral hemorrhage in the absence of randomized controlled trials (RCTs), strong recommendations cannot be made about how, when, and for whom to normalize

coagulation for patients with acute spontaneous ICeH who are being administered anticoagulant drugs. Additional information: clinical, observational and pharmacological data have led to standard clinical practice in acute ICeH being the administration of 5–10 mg of intravenous vitamin K to patients who are on vitamin K antagonists or the administration of intravenous protamine sulfate to patients on heparin. For patients who are on vitamin K antagonists at the time of an ICeH and have an elevated INR, anticoagulant medication should be discontinued, intravenous vitamin K should be administered, and either FFP (e.g., 20 ml/kg) or PCC (e.g., 25–40 IU/kg) should be added to prevent hematoma expansion. The risk of a thrombotic event occurring due to the normalization of coagulation for periods of time shorter than a week is considered to be low for most indications compared with the possible benefit of stopping hematoma expansion or re-bleeding [2].

## 1.4. AHA/ASA

The Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association Guidelines for the Management of Spontaneous Intracerebral Hemorrhage [3] outlines therapeutic options for patients with ICeH whose INR is elevated due to oral anticoagulants. The patients should have their warfarin withheld. The patients should receive therapy to replace vitamin K-dependent factors and correct the INR and should receive intravenous vitamin K. PCCs have not shown improved outcomes compared with FFP but may have fewer complications compared with FFP and are reasonable to consider as an alternative to FFP.

Recombinant FVIIa does not replace all clotting factors, and although the INR may be reduced, clotting may not be restored in vivo; therefore, rFVIIa is not routinely recommended as a sole agent for reversal of the effect of oral anticoagulants in ICeH.

Although rFVIIa can limit the extent of hematoma expansion in noncoagulopathic ICeH patients, there is an increase in thromboembolic risk with rFVIIa and no clear clinical benefit in unselected patients. Thus rFVIIa is not recommended in unselected patients [3].

## 1.5. Manual by Wijdicks

Manual by Wijdicks (2014) suggests following therapeutic options for warfarin anticoagulation effect reversal:

Vitamin K 5–10 mg i.v., FFP 10–30 ml/kg i.v. (optimal dose is unknown), PCC 8–30 IU/kg i.v., rFVIIa–20–30 µg/kg i.v. [4].

## 1.6. Neurocritical care

In Neurocritical Care E.F.M. Wijdicks and A.A. Rabinstein [5] suggest treatment options to reverse the effects of warfarin:

Vitamin K 5–10 mg i.v.,

FFP 10–40 ml/kg i.v. (optimal dose is unknown),

PCC 25–50 U/kg i.v.,

rFVIIa–20–40 µg/kg i.v. #

# – the authors added that much lower doses (5–10 µg/kg) may be sufficient based on their experience.

Additional remarks: Emergency Management of Warfarin Associated Cerebral Hemorrhage by E.F.M. Wijdicks and A.A. Rabinstein:

- Aggressively lower INR to normal (INR < 1.5).
- Aggressively control blood pressure (SBP < 160 mmHg).
- Consider ventriculostomy when INR < 1.5 and hemoven-tricle with hydrocephalus.
- Monitor EKG/troponin if rFVIIa has been administered.
- Monitor X-ray of the chest for pulmonary infiltrates if FFP has been used and consider diuretics [5].

Comments by E.F.M. Wijdicks and A.A. Rabinstein:

PCC or rFVIIa may be a more effective way to reverse warfarin.

Vitamin K and FFP may be the only available option, but the INR is corrected in only 1/3 of the patients within 12 h.

Neurosurgical evacuation of a hematoma should remain an option, but only when the INR is less than 1.5 [5].

### 1.7. Manual by Frontera

Therapeutic options for warfarin coagulopathy are also described in the chapter *Antiplatelet- and anticoagulation-associated intracranial hemorrhage* by Rincon F., et al. in *Decision Making in Neurocritical Care* by Frontera J.A. [6].

Vitamin K 10 mg i.v. over 10 min (monitor for hypotension/anaphylaxis)\*

PCC \*\* 50 U/kg i.v.

If PCC is unavailable, 15 cc/kg of FFP i.v. should be administered.

\*\*PCC, which is also known as factor IX concentrates, bebulin or proflinone, contains factors II, VII, IX and X in varying amounts. The half-life of PCC is 6–12 h [6].

Warfarin and emergency neurosurgical intervention. The guidelines are as above, moreover consider rFVIIa \*\*\* 20–80 µg/kg i.v.

- \*Vitamin K requires 6–24 h for full reversal. The half-life of recombinant factor VIIa is 2.6 h.
- \*\* The half-life of PCC is 6–12 h.
- \*\*\* The half-life of rFVIIa is 2.6 h, and many cases require repeated doses [6].

## 2. Non-vitamin K antagonist oral anticoagulants (NOACs), (also known as novel oral anticoagulants or direct oral anticoagulants (DOACs))

See Table 2.

### 2.1. Summary of product characteristics

#### 2.1.1. Rivaroxaban (Xarelto)

In Polish [11] as well as in European [12] SPCs the manufacturer states that rivaroxaban overdoses may lead to hemorrhagic complications, including ICrH, and that there is no specific antidote that able to reverse the rivaroxaban effect.

There are no specific recommendations concerning the ICrH. There are some general recommendations in the case of loss of large blood volume. In the case of rivaroxaban overdose, one may consider the administration of activated charcoal to

**Table 2 – The management of NOACs-associated ICrH.**

SPC [11–16]	PNA [1]	ESO [2]	AHA/ASA [3]	Manual Wijdicks [4]	Manual Frontera [6]
<b>Rivaroxaban</b>	No guidelines	Activated charcoal	No guidelines	<b>Rivaroxaban</b>	Hemodialysis or modified ultrafiltration
Activated charcoal		PCC, aPCC or rFVIIa		Activated charcoal	rFVIIa, PCC or FFP
Symptomatic treatment				Hemoperfusion with activated charcoal	
PCC, aPCC <sup>a</sup> or rFVIIa				4 factor PCC	
<b>Dabigatran</b>				<b>Dabigatran</b>	
Adequate diuresis, dialysis				Activated charcoal	
PCC, aPCC or rFVIIa				Hemoperfusion with activated charcoal	
				Hemodialysis	
				4 factor PCC	
<b>Apixaban</b>				<b>Apixaban</b>	
Activated charcoal				Activated charcoal	
FFP				Hemoperfusion with activated charcoal	
rFVIIa				4-factor PCC	
				FFP is contraindicated	
				rFVIIa – unclear	
				3 factor PCC – unclear	

<sup>a</sup> aPCC – activated PCC.

diminish the drug absorption. In the case of bleeding due to the control of the hemorrhage, it is possible to take the following measures:

- Consideration should be given to the implementation of appropriate symptomatic treatment, such as mechanical compression, surgical intervention, fluid administration, hemodynamic support, and the transfusion of blood or its components\*.

\*A comment by the review's authors is as follows: those actions are aimed at counteracting the effects of the loss of large blood volume, which is usually not the goal in ICrH.

- If the above measures fail to stop the life-threatening bleeding, one may consider the administration of PCC, activated prothrombin complex concentrate (aPCC) or rFVIIa. Currently, there is no clinical experience in administration of these agents in patients on rivaroxaban. This advice is based on limited nonclinical data. Depending on the intensity of bleeding, one should consider repeating administration of rFVIIa and increasing its dose.
- Protamine sulfate and vitamin K should not affect the anticoagulant activity of rivaroxaban. There is no scientific basis nor clinical experience that confirms the benefits of anti-hemorrhagic drugs (desmopresin, aprotinin, tranexamic acid, aminocaproic acid) in patients taking rivaroxaban.
- Due to the high degree of binding to plasma protein, rivaroxaban is not dialyzable [11,12].

### 2.1.2. Dabigatran (Pradaxa)

Polish [13] and European [14] SPCs state alike that:

In the case of clinically significant bleeding, dabigatran should be withdrawn. Strict clinical monitoring (including monitoring for signs and symptoms of bleeding or anemia) is advised during the entire period of treatment with dabigatran, particularly if there are other bleeding risk factors. In the case of severe bleeding (including intracranial), treatment with dabigatran should be discontinued, and the source of bleeding should be determined.

There is no specific antidote for dabigatran. Due to renal excretion of dabigatran, adequate diuresis should be maintained. Appropriate supportive treatment should be considered, e.g., surgical hemostasis, and plasma or blood volume transfusion, depending on the physician decision. Comment: this statement is due to extracranial hemorrhage. According to low protein binding, dabigatran can be removed by dialysis.

There are limited clinical data to justify the clinical utility of this method under clinical conditions.

Additionally European SPC states that (aPCC) (e.g., FEIBA) or rFVIIa or concentrates of coagulation factors II, IX and X, may be considered [14].

### 2.1.3. Apixaban (Eliquis)

Both European [15] and Polish [16] SPCs describes management of apixaban overdose as below.

- As with the use of other anticoagulants, patients taking this medicine should be carefully monitored for signs of bleeding.

- In the case of severe bleeding, drug administration should be withdrawn.
- There is no antidote for apixaban. Overdoses of apixaban may increase the risk of bleeding. In the case of hemorrhagic complications, apixaban administration should be discontinued, and the source of the bleeding should be determined.
- Appropriate treatment should be considered, i.e., surgical homeostasis or transfusion of FFP.
- In controlled clinical trials, apixaban administered orally to healthy people at doses of 50 mg per day during 3–7 days (25 mg twice a day for 7 days or 50 mg once a day per 3 days) (doses 10-times higher than maximal recommended dose) did not have any clinically significant adverse effects.
- The manufacturer states that in preclinical trials performed in dogs, the administration of activated charcoal up to 3 h after apixaban intake diminished apixaban effects. The manufacturer recommends the consideration of activated charcoal for overdose treatment.
- If life-threatening bleeding persists despite the above measures, the administration of rFVIIa should be considered. Currently, there is no clinical experience on the administration of rFVIIa in patients taking apixaban. Administering another dose of rFVIIa and modifying the dose based on the degree of reduction in bleeding should be considered [15,16].

## 2.2. Polish Neurological Association

The guidelines of the Polish Neurological Association Vascular Diseases Section Expert Group 2012 [1] outline that there are no guidelines that refer to intracerebral hemorrhage after either primary intracranial bleeding or secondary transformation of ischemic stroke due to novel oral anticoagulants usage. However, the authors indicate a lack of data, specifying when to start treatment with novel oral anticoagulants after ICrH, and they outline the lack of a specific antidote for NOACs [1].

## 2.3. European Stroke Organisation

European Stroke Organization guidelines for the management of spontaneous intracerebral hemorrhage [2] state that there is no specific antidote available for any of the NOACs, and clinical experience with haemostatic agents in NOAC-associated bleeding is limited. An expert opinion on management of bleeding emergencies associated with DOACs (NOACs) therapy has been published in consensus paper [17].

The relevant expert opinion according to above mentioned consensus paper [17] is presented below.

Recommendations: In case of intracranial hemorrhage associated with NOACs, the following measures are recommended, similar to the approach in vitamin K antagonists-associated bleedings: (1) Discontinue NOACs. (2) Within the first 2 h after the last intake of dabigatran, inhibition of the drug uptake with activated carbon is recommended. For rivaroxaban, the use of active carbon should also be taken into account. For apixaban, the use of active carbon is recommended within 3 h after last intake. (3) Single administration of 30–50 U/kg PCC i.v. If no clinical effect, further administration of aPCC or rFVIIa can be considered. (4) Lowering blood pressure to below 140 mmHg. (5) In case of

subarachnoidal hemorrhage, coiling or clipping of aneurysm according to the guidelines may be considered after hemostatic parameters have normalized: dabigatran: TT\* < fourfold URN, ECT < twofold URN, or hemoclot < 50 ng; rivaroxaban, and apixaban: anti-Xa activity test < twofold URN in plasma or rivaroxaban plasma level < 100 ng/ml or apixaban plasma level < 10 ng/ml on calibrated test systems and normal levels for aPTT and PTZ [17].

\*(TT – thrombin time; URN – upper range of normal; ECT – ecarin clotting time; hemoclot – drug-specific test systems; aPTT – partial prothrombin time; PTZ PT – prothrombin time).

#### 2.4. AHA/ASA

A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association *Guidelines for the Management of Spontaneous Intracerebral Hemorrhage* [3] states that there are no specific therapeutic guidelines for ICeH after novel oral anticoagulants usage.

#### 2.5. Manual by Wijdicks

Wijdicks (2014) #	Apixaban	Dabigatran	Rivaroxaban
Oral activated Charcoal	Yes	Yes	Yes
Hemodialysis	No	Yes	No
Hemoperfusion with activated charcoal	Possible	Yes	Yes
FFP	No	No	No
Factor VIIa	Unclear	Unclear	Unclear
3-factor PCC	Unclear	Unclear	Unclear
4-factor PCC	Possible	Possible	Possible

#Adapted from Kaatz S, Kouides PA, Garcia DA et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. *Am J Hematol* 2012; 87 (Suppl. 1): S141–S145 after Wijdicks (2014) [4].

Comment: Wijdicks EFM (2014), in his manual (p.107) “*Providing Acute Care*”, stated the following:

“Reversal of thrombin inhibitors (dabigatran) has not been clearly established. Recent guidance suggests discontinuation of the drug and possible PCC or hemodialysis”.

“Activated charcoal could be administered, if the drug was taken within hours of presentation”

“Hemodialysis and hemoperfusion can be considered in patients with impaired renal function (dabigatran); however, it is not effective with apixaban or rivaroxaban because they are highly protein bound. Recombinant Factor VIIa does not reverse the anticoagulant effect, but PCC has been shown to

normalize the prothrombin time (PT) in normal volunteers. It is unclear whether it is effective to stop bleeding, but it has been used in emergency situations” [4].

After the drug is discontinued, the anticoagulant effect is absent after 2 days.

#### 2.6. Manual Frontera

*Manual by Frontera* (2009) [6] gives treatment options in coagulopathy due to direct thrombin inhibitor (dabigatran).

There is no direct reversal agent.

- Reduce plasma concentration with hemodialysis or modified ultrafiltration.
- Increase other factors with rFVIIa or PCC/FFP [6].

### 3. Heparins

See Table 3.

#### 3.1. Summary of product characteristics

##### 3.1.1. Enoxaparin

The Polish SPC states that in low-molecular-weight heparin (LMHW) associated hemorrhage protamine sulfate or hydrochloride should be administered slowly – 1 mg of protamine per 1 mg of enoxaparin (if LMWH was administered within the last 8 h) or infusion of 0.5 mg protamine per 1 mg of enoxaparin (if it was administered more than 8 h ago or if a second dose of protamine was necessary). The administration of protamine 12 h after enoxaparin injection might not be necessary [18].

The British SPC for enoxaparin is similar to the Polish version and additionally states that the maximum dose of protamine is 50 mg. Decisions regarding the necessity and dose of subsequent protamine injections should be based on clinical response rather than measurement of anti Xa or anti XIIa results [19].

##### 3.1.2. Nadroparin

For nadroparin (Fraxiparin) the Polish SPC suggest 0.6 ml of protamine sulfate per 950 U of nadroparin taking the drug administration time into consideration [20].

##### 3.1.3. Dalteparin

For dalteparin (Fragmin) the Polish [21] and British [22] SPCs suggest the following treatment: 1 mg protamine per 100 U of anti-Xa dalteparin, the SPC do not mention the time of LMWH

**Table 3 – The management of heparins-associated ICrH.**

SPC [18–24]	PNA [1]	ESO [2]	AHA/ASA [3]	Manual Wijdicks [4]	NCC Wijdicks [5]	Manual Frontera [6]
LMWH	Stop heparin	Stop heparin	No specific guidelines	No specific guidelines	No specific guidelines	LMWH
PS	PS	PS				Protamine
UFH						UFH
Heparin withdrawal						Stop heparin
PS, FB, FFP						Protamine

UFH – unfractionated heparin, LMWH – low-molecular-weight heparin, PS – protamine sulfate, FB – fresh blood.

administration. Since protamine itself has an inhibiting effect on primary haemostasis it should be used only in an emergency [21,22]. Protamine should be given by intravenous injection over approximately 10 min [22].

Unfractionated heparin (UFH).

The Polish SPC [23] outlines that in insignificant bleeding cases, heparin withdrawal is sufficient. If more intensive bleeding occurs, one should control coagulation time as well as platelets and slowly (not faster than in 5–10 min) administer 1% protamine sulfate solution (not more than 50 mg). Each mg of protamine sulphate neutralizes approximately 115 U of heparin. In life-threatening cases one should consider transfusing fresh blood or FFP. As there are no specific recommendation for ICrH, above mentioned could be implemented also to ICrH.

British version [24] is similar to the Polish one. Decreasing amounts of protamine (1% w/v solution) are required as time from the last heparin injection increases. Thirty minutes after a dose of heparin, approximately 0.5 mg of protamine is sufficient to neutralize each 100 U of heparin. Initiation of corrective therapy should not depend on laboratory confirmation of the diagnosis.

### 3.2. Polish Neurological Association

The guidelines of the Polish Neurological Association Vascular Diseases Section Expert Group 2012 [1] state that the treatment with heparin has to be discontinued and there is a need to use protamine sulfate at a dose that depends on the dose of heparin and on the time from the end of the heparin treatment.

Additional information:

Standard dose is 1 mg protamine i.v. per 100 U of heparin.

If more than 30 min have elapsed since the injection of heparin, lower doses of protamine will be necessary.

After 30–60 min; 0.5–0.75 mg protamine i.v. per 100 U of heparin,

>60–120 min; 0.375–0.5 mg of protamine per 100 U of heparin,

>2 h; 0.25–0.375 mg of protamine per 100 U of heparin [1].

### 3.3. European Stroke Organisation

According to *The European Stroke Organization (ESO) guidelines* [2], in the absence of RCTs, ESO cannot make strong recommendations about how, when, and for whom to normalize coagulation for patients with acute spontaneous ICeH who had been on anticoagulant drugs.

Additional information: Treatment with anticoagulant drug has to be discontinued, additionally ESO stated that: clinical observational and pharmacological data have led to standard clinical practice in acute ICeH being the administration of intravenous protamine sulfate to patients on heparin [2].

### 3.4. AHA/ASA

Guidelines for Healthcare Professionals from the *American Heart Association/American Stroke Association* [3] do not suggest any specific therapeutic guidelines.

### 3.5. Manual by Frontera

The manual by Frontera outlines the following therapeutic options:

#### 3.5.1. UFH

Stop infusion, no further action for minor bleeding. For severe or intracranial bleeding, use protamine. Dosage of protamine is based on the time from the last heparin dose.

Protamine maximum dose 50 mg, maximal infusion rate 5 mg/min.

Timing: (the half life of heparin is 2 h).

0–30 min; 1.0 mg protamine i.v. per 100 U of heparin;

31–60 min; 0.75 mg protamine i.v. per 100 U of heparin;

61–120 min; 0.5 mg of protamine per 100 U of heparin;

>2 h; 0.4 mg of protamine per 100 U of heparin.

#### 3.5.2. LMWH

One milligram of protamine i.v. per 1 mg of LMWH administered in the last 8 h; if bleeding persists, administer an additional 0.5 mg of protamine i.v. per 1 mg of LMWH in the last 8 h.

(No protamine if >8 h from dose).

Important Remarks: Protamine reverses only 60–75% of the effect of enoxaparin. Protamine has minimal efficacy against danaparoid or fondaparinux [6].

## 4. Recombinant tissue plasminogen activator (rtPA)

See Table 4.

### 4.1. Summary of product characteristics

Polish and British [25,26] SPCs state that if life-threatening bleeding occurs, particularly ICeH, thrombolytic treatment should be withdrawn. However, based on the short half-life of alteplase and its small influence on the coagulation system, there is no need for coagulation factor repletion. In the majority of patients with bleeding, management is based on thrombolytic and anticoagulation treatment withdrawal, fluid restoration and closure of the bleeding vessels (if possible).

If heparin was administered, protamine administration may be considered up to 4 h after heparin usage. In patients who do not respond to conventional methods, it is advisable to transfuse blood products. Cryoprecipitate, fresh frozen plasma, and blood platelets should be transfused, and following each transfusion, the clinical and laboratory parameters should be controlled. After cryoprecipitate transfusion, a fibrinogen concentration of 1 g/l should be achieved. Anti-fibrinolytic agents should be considered as the last resort. If severe bleeding occurs, the infusion of FFP or fresh blood is recommended [25,26].

### 4.2. Polish Neurological Association

The guidelines of the Polish Neurological Association (*Vascular Diseases Section Expert Group* 2012) [1] state that asymptomatic ICrH does not require additional treatment.

**Table 4 – The management of rtPA-associated ICrH.**

SPC [25,26]	PNA [1]	ESO [2]	AHA/ASA [27]	Manual by Wijdicks [4]	NCC Wijdicks [5]	Frontera [6]
Alteplase with drawal, cryoprecipitate, FFP, PT, FB, and anti-fibrinolytics as the last resort <sup>a</sup>	Discontinuation of thrombolytic, anticoagulation and antiplatelet treatment, BPC, cryoprecipitate with factor VIII or FFP; consider surgical treatment	No specific suggestions, consider surgical treatment (GCS 9–12)	Consider administration of cryoprecipitate and/or tranexamic acid	No guidelines	No guidelines	Stop medication, – cryoprecipitate, platelets
FB – fresh blood, BPC – blood platelet concentrate, PT – platelet transfusion, GCS – glasgow coma scale. <sup>a</sup> The treatment is usually based on alteplase withdrawal, fluid restoration and closure of the bleeding vessels (if possible).						

Symptomatic secondary intracranial hemorrhage with the deterioration of neurologic condition requires management that is identical to that in spontaneous intracranial hemorrhage.

In the case of hemorrhagic transformation of ischemic stroke, thrombolytic, antithrombotic and antiplatelet treatment should be discontinued.

To minimize the risk of hemorrhagic transformation, the maintenance of good control of blood pressure is advised.

When hemorrhagic transformation is due to thrombolytic therapy in the case of life threatening complications, thrombolysis should be withdrawn.

In the case of persisting hemorrhage, measures designed to restore hemostasis should be implemented, i.e., the administration of 6–8 U of blood platelet concentrate, 12 U of cryoprecipitate with factor VIII or FFP.

Neurosurgical treatment indications are similar to those in other types of ICeH [1].

#### 4.3. European Stroke Organisation

The ESO guidelines for the management of spontaneous intracerebral hemorrhage [2] give no recommendations about pharmacological treatment of intracerebral hemorrhage after rtPA. There is also no evidence to support surgical intervention on a routine basis for improving outcome after supratentorial ICeH compared with conservative management, but early surgery may be of value for patients with a Glasgow Coma Scale score of 9–12 [2].

#### 4.4. AHA/ASA

The AHA/ASA [27] states that although no study has been conducted to determine the best way to manage post-intravenous rtPA hemorrhage, many rtPA-associated hemorrhage protocols recommend the use of cryoprecipitate to restore decreased fibrinogen levels.

A recent case report described the use of tranexamic acid for the treatment of an intravenous rtPA-associated hemorrhage in a Jehovah's Witness stroke patient. After administration, no further hematoma expansion was noted [28]. Further studies are clearly warranted to define the optimal approach to the management of fibrinolytic-associated hemorrhages.

Standardized guidelines for managing fibrinolytic-associated hemorrhages do not exist. Given insights from clinical trials, protocols recommend performing an emergent unenhanced computed tomography scan and taking blood samples for measuring complete blood count, coagulation parameters (PT, PTT, INR) and fibrinogen levels. Concurrently, other causes of neurological decline, such as hemodynamic instability, should be pursued [27].

#### 4.5. Manual by Frontera

If thrombolytic induced coagulopathy occurs, the manual suggests stopping medication, administration of 12 U of cryoprecipitate (to replace fibrinogen and factor VIII) as well as 6–8 U of platelets [6].



## 5. Aspirin and other platelet aggregation inhibitors (antiplatelet drugs)

See Table 5.

### 5.1. Summary of product characteristics

#### 5.1.1. Aspirin

For ICrH – measures were not specified [29].

The manufacturers specify only the therapeutic measures in overdose and intoxication cases.

The Polish SPC states that the intoxication might occur if aspirin dose is higher than 100 mg/kg/24 h for more than 2 days. In overdose cases – despite the specific treatment of ICrH, the treatment of associated acidosis is advised: gastric lavage, repeated administration of activated charcoal, forced alkaline diuresis. Tachypnea, hyperventilation, respiratory alkalosis: fluid and electrolyte management, hemodialysis in severe cases. Respiratory alkalosis with compensatory metabolic acidosis, fluid and electrolyte loss, dehydration, oliguria to renal failure as well as hyperpyrexia: fluid and electrolyte management [29].

The British SPC [30] states that salicylate poisoning is usually associated with plasma concentrations >350 mg/L. Single doses less than 100 mg/kg are unlikely to cause serious poisoning. Give activated charcoal if an adult presents within 1 h of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinization, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary edema.

Haemodialysis or haemoperfusion are effective methods of removing salicylate from plasma, however, haemodialysis is the treatment of choice for severe poisoning and should be

considered in patients with plasma-salicylate concentrations >700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features. Patients under 10 years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage [30].

#### 5.1.2. Clopidogrel

The Polish [31] and European [32] SPCs state that appropriate therapy should be considered if bleeding is observed. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

#### 5.1.3. Prasugrel

According to Polish [33] and European [34] SPCs, no data are available on the reversal of the pharmacological effect of prasugrel; however, if prompt correction of prolonged bleeding time is required, platelet transfusion and/or other blood products may be considered.

#### 5.1.4. Ticagrelor

The European SPC [35] states that there is currently no known antidote to reverse the effects of ticagrelor, and ticagrelor is not expected to be dialysable. Treatment of overdose should follow local standard medical practice.

It is worth noting that prasugrel and ticagrelor have been increasingly employed in patients with acute coronary syndromes, therefore management of these drugs – associated ICrH would be very important for every-day clinical practice.

### 5.2. Polish Neurological Association

According to the guidelines of the Polish Neurological Association Vascular Diseases Section Expert Group 2012 [1], the antiplatelet drug has to be temporarily withheld.

### 5.3. European Stroke Organisation

European Stroke Organization guidelines for the management of spontaneous intracerebral hemorrhage [2] state that in the absence of RCTs, the ESO cannot make strong recommendations about how, when, and for whom to normalize clotting in

**Table 5 – The management of antiplatelet drugs-associated ICrH.**

SPC <sup>c</sup> [29–35]	PNA [1]	ESO [2]	AHA/ASA [3]	Manual by Wijdicks [4]	Wijdicks NCC [5]	Frontera [6]
<b>Aspirin:</b> GL, AC, forced alkaline diuresis <sup>a</sup> , hemodialysis and hemoperfusion (severe cases), control the plasma salicylate concentration, urine pH monitoring, metabolic acidosis correction <b>Clopidogrel:</b> PT <b>Prasugrel:</b> Platelet and/or other blood products transfusion <b>Ticagrelor:</b> local standard medical practice	Temporal drug withdrawal	No specific guidelines	No specific guidelines	PT	No specific guidelines	DDAVP, PT

GL – gastric lavage, AC – activated charcoal, PT – platelet transfusion, DDAVP – desmopresin acetate.

<sup>a</sup> Forced alkaline diuresis is recommended by the Polish SPC [29]. According to British version, forced diuresis should not be used, however it recommends urine alkalinization [30].

<sup>c</sup> SPCs specify only the therapeutic measures in overdose and intoxication.

patients with acute spontaneous ICeH who had been on antiplatelet drugs.

Additional information by ESO: The concept of platelet transfusion in patients with spontaneous ICeH in association with antiplatelet drug use is to replace nonfunctional thrombocytes with functional thrombocytes and thus to increase the chance of hemostasis. ESO found one RCT ( $n = 22$ ) on the use of thrombocytes in traumatic ICeH. In this RCT, platelet transfusion had no effect on platelet function or ICeH progression. However, the small size of this RCT or the use of only 1 U of platelets may explain these findings. Two RCTs of platelet transfusion in ICeH are ongoing (NCT00699621 and The Netherlands National Trial Register NTR1303).

#### 5.4. AHA/ASA

According to AHA/ASA [3] the usefulness of platelet transfusions in ICeH patients with a history of antiplatelet use is unclear and is considered investigational. There are no specific therapeutic guidelines.

#### 5.5. Manual by Frontera

Coagulopathy by aspirin (acetylsalicylic acid) and, nonsteroidal anti-inflammatory drugs (NSAID) or platelet aggregation inhibitors (clopidogrel, ticlopidine).

Therapeutic options: Desmopresin acetate (DDAVP) 0.3  $\mu\text{g}/\text{kg}$  i.v.  $\times 1$  (20  $\mu\text{g}$  in 50 ml normal saline over 15–30 min) and transfuse 5–6 U of platelets.

Comments: Aspirin and NSAID irreversibly block platelet cyclooxygenase, inhibiting the production of thromboxane A<sub>2</sub>, resulting in the inhibition of platelet aggregation for up to 7–10 days.

Clopidogrel and ticlopidine alter platelet aggregability by irreversibly inhibiting the surface ADP binding site and by reducing ADP release from activated platelets [6].

#### 5.6. Manual by Wijdicks

Wijdicks (2014) states the following: “Whether platelet transfusions are needed in patients with ICrH and in whom prior antiplatelet use is unresolved, but one study suggested the improvement of platelet assays with two packs (containing 6 U) of apheresis platelets. Transfusion of 6 U of platelets should raise the platelet count by 60,000/ $\mu\text{L}$ –1 U increase by 10,000  $\mu\text{L}$ ” [4].

“A considerable number of donor units may be needed to reverse the combined antiaggregant effect of aspirin and clopidogrel. One study in volunteers found 10 donor units for 300 mg, but only 15 U for 600 mg of clopidogrel were needed to completely reverse antiplatelet effect, thus suggesting a nonlinear therapeutic effect” [36].

#### 5.7. Comments

The treatment options for the reversal of anticoagulation after intracranial hemorrhage differs considerably between sources.

Some of them, mainly SPCs do not refer directly to intracerebral or intracranial hemorrhage, providing only general recommendations about hemorrhage during antiplatelet

drug usage (especially acetylsalicylic acid, Aspirin) [29,30]. Therefore, such SPCs may be insufficiently valuable in neurological or neurosurgical practice for managing ICrH or ICeH patients. Additionally, Polish SPC differ in detail from the British or European versions. The differences are not crucial, but a lack of cohesion in SPCs is unfavorable, especially nowadays when we are facing increasing movement of patients among European countries. Therefore, it would be safer for health professionals and patients if all SPCs in European Union countries were harmonized.

In the case of platelet aggregation inhibitors (acetylsalicylic acid and clopidogrel) associated with cerebral hemorrhage, therapeutic suggestions by Wijdicks and ESO state that treatment with transfused higher doses of platelet units after clopidogrel would most likely be sufficient to reverse the antiplatelet effect [2,4,31,32].

The SPCs concerning other conditions in this paper were disappointingly inconclusive on many points; however, the review of the literature showed some progress.

The largest divergence in the above presented opinions was observed in the remarks about NOAC-associated hemorrhages: Wijdicks stated that rFVIIa as well as FFP does not reverse the anticoagulant effect of those drugs, whereas the manual edited by Frontera advised an increase in other coagulation factors with rFVIIa or PCC/FFP; in fact, both agreed that PCC could be worth considering and may be potentially effective [4,6].

It is also worth noting that for adults with acute spontaneous ICeH that is not associated with antithrombotic drug the ESO does not recommend the use of rFVIIa outside of ongoing trials [2].

Generally, our overview allowed us to determine that both European and American guidelines based on EBM are intelligible; however, they are often less useful in every-day clinical practice where practitioners are obliged to save patient lives and improve their conditions using any available and reasonable measures. The experts' opinions are more far-sighted in terms of emergency clinical practice. However, we still should bear in mind that such opinions mirror those of one (although usually very prominent) center's experience. Those expert opinions, although based on insufficient RTC data, could be valuable for acute emergency physicians who encounter this clinical situation.

Currently, there are no generally accepted opinions concerning most of the reviewed agents in this field, mainly due to a shortage of well-designed, methodologically satisfactory studies. On the one hand, they are extremely difficult to conduct; therefore, we most likely should rely on the longest available case series, which may be informative in terms of emergency treatment strategies.

There is a strong need for the continuation of large multicenter and international trials in this field as well as for pursuing multicenter databases. This should be helpful for the present lack of clinical trials with sufficient statistical power.

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### Important note

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### Conflict of interest

The authors report no Conflict of interest relevant to the manuscript.

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### Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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