Chapter 9

Immediate Treatment of the Anticoagulated Patient with Traumatic Intracranial Hemorrhage

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Additional information is available at the end of the chapter

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1. Introduction

Traumatic brain injury with associated intracranial bleeding is an emergency requiring diagnostic and supportive measures directed at limiting subsequent morbidity and mortality. If this intracranial bleeding is discovered in a patient that is anticoagulated, further aggressive steps are indicated to reverse the effects of the anticoagulant and limit further bleeding. Hematoma or bleeding volume & growth does correlate with various outcome measures [1-3]. Following spontaneous ICH, hematoma expansion on follow-up neuroimaging is noted in as much as 26% of cases [1]. Particularly in anticoagulated patients, such hematoma expansion is associated with poor outcomes [4]. Hemostatic therapy with agents directed at trying to reverse the effects of the anticoagulant have been shown to potentially be effective in reducing hematoma expansion in such patients [5,6]. Failing to correct a high INR, for example, may be associated with higher mortality [7]. Therefore, prompt recognition of this condition and taking immediate action is important in treating traumatic intracranial hemorrhage. There are more options than ever for providing systemic anticoagulation to patients. These different agents work in different ways and have different pharmacokinetics and pharmacodyanmics. Published data supporting specific strategies for reversing the effects of these agents is limited, particularly for novel anticoagulants. However, the pharmacology and mechanism of action of some anticoagulant therapies (outlined in Figure 1 & Table 1) have led to at least initial studies that can provide some guidance.

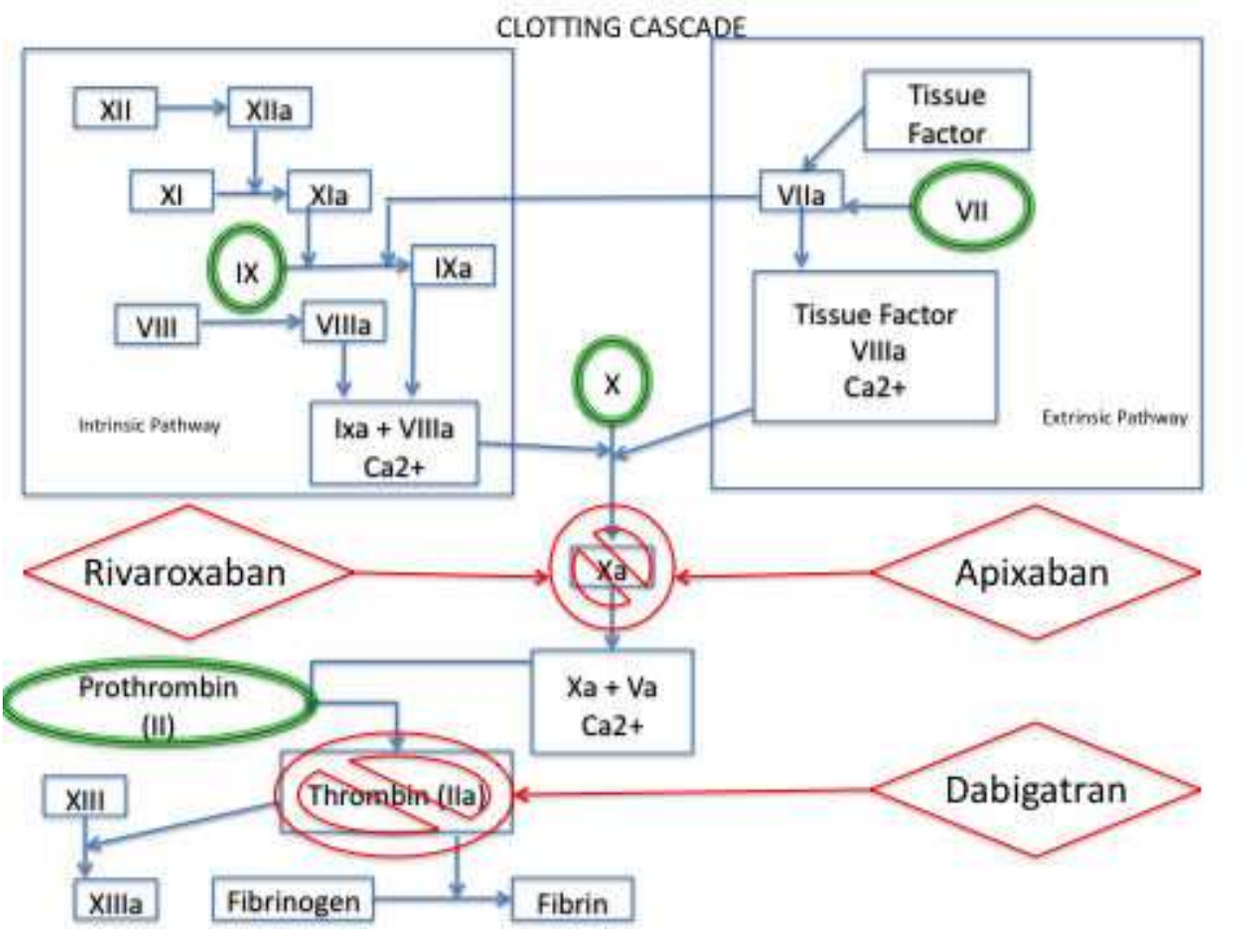

Figure 1. The clotting cascade. The vitamin K dependant factors (green circled factors) are inhibited by warfarin. Factor Xa is inhibited by rivaroxaban and apixaban. Dabigatran direrctly inhibits thrombin.

Medication	Mechanism of Action	T 1/2 (hrs)	Dose	Renal dosing	Excretion	Protein Bound
Warfarin	Vitamin K antagonist	20-60	2-10mg daily	None	92% urine bile	99%
Rivaroxaban	Direct factor Xa Inhibitor	5-13	10-30mg daily	Yes	66% urine 28% feces	92-95%
Apixaban	Direct factor Xa Inhibitor	8-12	2.5-5mg BID	Yes	27% urine feces	87%
Dabigatran	Direct thrombin inhibitor	12-17	110-150mg BID	Yes	80% urine	35%

Table 1. Pharmacology of warfarin and the novel anticoagulants.

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2. Warfarin & strategies for warfarin-associated ICH

Studies suggest that hematoma expansion in patients anticoagulated with warfarin who suffer an intracranial hemorrhage may be limited by quickly normalizing INR [8]. Mortality rates for these patients may be as high as 66% for those with an INR > 3 [9]. Historically, clinicians have used vitamin K and fresh frozen plasma (FFP) to treat warfarin-associated bleeding, including ICH. Vitamin K is given to patients that have received warfarin so as to counteract the effects of warfarin inhibiting the vitamin-K dependant gamma-carboxylation of coagulation factors II, VII, IX and X and the anticoagulant factors protein C and S. Its time to maximum effectiveness can be measured in hours, so its use alone is not recommended [10]. FFP can be transfused to replenish the lower levels of vitamin K dependant clotting factors in patients that have been taking vitamin K antagonists. Recent data have led to a change in the American College of Chest Physicians guidelines to recommend the use of four-factor prothrombin complex concentrate to reverse the effects of warfarin in the treatment of major bleeding (Level 2C evidence) [11]. FFP has fallen out of favor for multiple reasons. Firstly, it must be thawed and this process can take anywhere from 20-60 minutes, causing the clinician to lose valuable time in trying to reverse the patient's coagulopathy. Additionally, FFP is given in a large weight-based volume (as much as two to four L total) that may be unadvisable in certain patients [12]. Lastly, FFP is a blood product and it is widely recognized that blood product administration in general and FFP specifically should be minimized as much as possible in the critically ill patient. This is because of the associated risks of acute lung injury, transfusion-associated circulatory overload, infection, etc [10, 68]. Additionally, it is quite common for FFP to be transfused inappropriately, or at least outside the recommendations of published guidelines [69].

Prothrombin complex concentrates (PCC) have been shown to normalize an elevated INR within 10-30 minutes of administration [13]. Prothrombin complex concentrates (PCC) are a group of products containing virus-reduced, concentrated, pooled plasma products made of a combination of three or four vitamin K-dependant clotting factors [10]. There are two versions commercially available, so-called three-factor and four-factor PCC. These agents have varying concentrations of coagulation factors II (prothrombin), VII, IX and X. Factor VIII Inhibitor Bypassing Activity, nonfiltered – or FEIBA NF – is an FDA approved four-factor PCC that is a nanofiltered, vapor-heated freeze-dried sterile human plasma fraction [14]. Until recently, it was the only four-factor complex available in the United States. As an activated product, it may hold more thrombogenic potential, limiting its use. Introduced in the summer of 2013, *Kcentra* (known as Beriplex P/N in Europe) is the only FDA-approved four-factor PCC available in the United States [15].

The preference for four-factor PCC over the three factor formulations is because of the increased concentration of factor VII in the four factor PCCs [11]. This may account for their possible superior effectiveness at reversing warfarin-associated anticoagulation [16]. Nonactivated four-factor PCC has only recently been available in the United States [15]. Prior to this, only FEIBA, an activated form of PCC was commercially available in the US. FEIBA has been suggested as an option for reversing the effects of VKA, but there have been concerns that this

agent may increase thrombogenesis.[11]. Another option was to use one of the available three-factor PCCs, Profiline SD or Bebulin VH plus rVIIA, but this also comes with a similar thrombogenic risk, particularly arterial thromboses [18,19]. Four-factor PCC is the recommended agent for warfarin reversal in acute, severe bleeding [11]. While there are no randomized, controlled studies, there are multiple observational trials summarized by a systematic review of 18 studies in 654 patients. This review suggested that 4-factor prothrombin complex concentrates are more reliable for correcting the international normalized ratio (INR) compared with three factor formulations. This effect appears intact at least up until very elevated INRs (>4) where the effectiveness may be less reliable for both the three and four factor PCC [17]. While these agents are effective in reversing a high INR, it must be remembered that they may infer a risk of thromboembolism [18]. However, recent studies comparing four-factor PCC with FFP for urgent warfarin reversal seem to suggest that this adverse event rate - including thromboembolism - is at least the same, if not better than with FFP [71, 72].

3. Non-warfarin anticoagulants and strategies for treating ICH

An important point to remember when treating a patient that is anticoagulated with dabigatran, rivaroxaban or apixaban is that the physiologic effect of these drugs is much shorter in duration than that of warfarin. Warfarin can remain effective for up to 4 or 5 days as its half-life may be as long as 38-42 hours or longer. The direct-thrombin inhibitor, dabigatran, has a half-life of 12-17 hours. The factor Xa inhibitors, rivaroxaban (7-11hr) and apixaban (9-14hr) have similar, considerably shorter half-lives than warfarin and therefore are eliminated from the body more quickly. This elimination is somewhat dependant on renal function and therefore adjustments must be made in awaiting clearance of the drug's effect in patients with renal dysfunction. [19-22]

3.1. Dabigatran

Dabigatran is an oral direct thrombin inhibitor approved for the reduction of stroke risk in patients with nonvalvular atrial fibrillation. Maximum concentration is reached within about one hour of ingestion and the drug is cleared renally [23]. Dabigatran was shown in the RE-LY trial to be effective in the prevention of systemic embolism in non-valvular atrial fibrillation. The United States Food and Drug Administration therefore approved it in 2010 for this indication. The RE-LY study also demonstrated that dabigatran conferred a similar yearly rate of major bleeding with warfarin of about 3% and life-threatening bleeding of about 1.5%. [24]. Renal clearance of dabigatran suggests a potential role for hemodialysis in reversing the effects of this agent. [22].

FFP, however, will not reverse this agent, but rFVIIa may have a role [25]. In a murine model of ICH, FFP was shown to decrease ICH volume in animals that had received high dose, but not low dose, dabigatran. However, mortality remained higher in the mice that received high dose dabigatran and FFP did not reduce mortality. Beriplex, a four-factor PCC, decreased ICH hematoma size in both the high and low dose groups [26]. Other animal data in rabbits has

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suggested that PCC may be effective in reversing the anticoagulation effect of dabigatran [27]. There is a case report of FFP & PCC being used in combination to successfully treat dabigatran-induced gastrointestinal bleeding; however, full confirmation of this association was difficult because of patient comorbidities [28]. Similarly, FEIBA has been suggested in a case report as a potential therapy for dabigatran-associated bleeding [29].

However, a four factor PCC had no positive effect on the anticoagulant activity of dabigatran in a randomized, double-blind placebo controlled trial conducted by Eerenberg, et al. [30]. FEIBA at a lower than typical dose could have a role in reversing the anticoagulant effects of dabigatran, while the non-activated PCCs are likely less effective [31]. This same study also failed to show benefit of rVIIa for preventing hematoma expansion [31]. Conversely, a rat tail incision bleeding model suggested that rVIIa did reduce bleeding time [32]. However, there was no demonstrable positive effect on thrombin time, aPTT, or ecarin clotting time [33]. Similar results were found with both three and four factor PCC [19].

In summary, medical therapy for treatment of dabigatran associated traumatic ICH is somewhat limited by both a paucity of data and lack of consistent effectiveness demonstrated in what data does exist. Therefore, supportive therapies such as activated charcoal and dialysis may be the most prudent approach. Activated charcoal can be effective in reducing therapeutic levels of dabigatran if the ingestion was relatively recent [34] and dialysis is both pharmacologically plausible and has been shown to reduce dabigatran levels [22, 35].

3.2. Rivaroxaban

Rivaroxaban is an oral direct factor Xa inhibitor approved for the prophylaxis of deep vein thrombosis (DVT) post total knee or hip replacement [36], the treatment of DVT or pulmonary embolus (PE) [37, 38] as well as to reduce the risk of stroke in patients with nonvalvular atrial fibrillation [39]. The drug reaches maximum concentration within 2 to 4 hours of intake and has a 5 to 9 hour half-life [40]. Unlike dabigatran, rivaroxaban is highly protein-bound making it unlikely to be dialyzable [41].

Animal data suggest at most a moderate effect of rVIIa on reversing the anticoagulant effect of rivaroxaban. In a rat mesenteric bleeding model, this drug decreased the bleeding time, but had no effect on the inhibited factor Xa activity [42]. A primate model demonstrated a much less robust effect [43]. In another animal study, a four-factor PCC reversed the effect of rivaroxaban [44]. The same study by Eerenberg quoted above in regard to dabigatran suggested that the four factor PCC Cofact may have a positive effect on normalizing the inhibition of endogenous thrombin potential and the elevated PT induced by rivaroxaban [30]. In a randomized crossover *ex vivo* study in healthy volunteers, Marlu et al were able to demonstrate that the anticoagulant effect of rivaroxaban could be corrected with PCC or FEIBA and that rVIIa was much less effective [31]. This suggests that PCC may be effective for treating rivaroxaban-associated traumatic intracranial hemorrhage.

3.3. Apixaban

Apixaban is an oral factor Xa inhibitor indicated for the prevention of systemic embolism and stroke in patients with nonvalvular atrial fibrillation. It is the newest agent to be approved for use. In studies, the major bleeding event rate was approximately 2% compared with warfarin's 3% rate [49, 73]. The drug requires a dosage adjustment in renal impairment. It is also highly protein-bound and therefore not dialyzable. Activated charcoal is felt to be a potential intervention that could be employed early after ingestion, if possible [45]. There are no studies or case reports in the literature regarding treatment of apixaban-associated bleeding. Therefore, a similar approach to that used in treating rivaroxaban-associated bleeding is probably reasonable. However, in a rabbit model, bleeding induced by apixaban was not improved with either rFVIIa, PCC or fibrinogen [46]. Hopefully, with time and experience, we will learn more about treating life-threatening bleeding associated with this and the other novel anticoagulants.

4. Other agents to be considered for the treatment of traumatic ICH in the anticoagulated patient

4.1. rVIIa

Recombinant activated factor VII (rFVIIa) is indicated for hemophilia with inhibitors [47]. But it has also been used off-label for hemostasis in acute bleeding, surgical bleeding, trauma and ICH [48, 49, 50]. It has also been used as a medication to assist in hemostatic control of hemorrhage in trauma [51-56]. While this intervention has been shown to not impact mortality, it was shown to decrease overall blood product use [57].

rFVIIa works in the presence of tissue factor from injured or ischemic vascular subendothelium to promulgate clot formation as well as binding directly to platelets and enhancing thrombin burst to improve clot stability [58].

There is some concern that this agent may increase thromboembolic events [59, 60], particularly arterial thromboses [61] which tempers enthusiasm for using this agent. Its widespread use without compelling clinical evidence to do so as well as its substantial cost is concerning as well [62]. Combining these facts with the modest data available to suggest benefit in treating ICH in anticoagulated patients, there are likely better treatments except in unusual circumstances.

4.2. Summary

There is limited guidance in the literature to organize a clinical strategy for addressing the difficult problem of traumatic ICH in anticoagulated patients. However, what is available can be used to generate a reasonable strategy for treating this patient population, as some institutions have done (See Appendix 1). For warfarin-associated bleeding, the data and experience is much more robust. Unfortunately, clinical data is severely lacking on how to treat the patient population that has been taking one of the novel anticoagulants: dabigatran, rivaroxaban or apixaban. All of these patients should receive standard neurocritical care supportive measures

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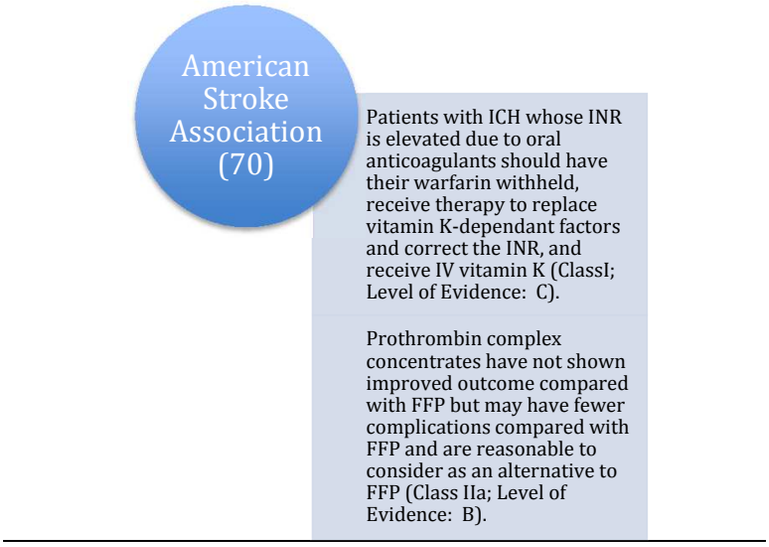
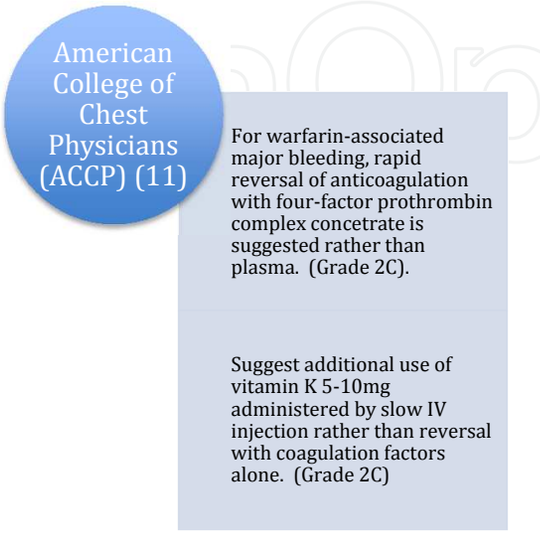
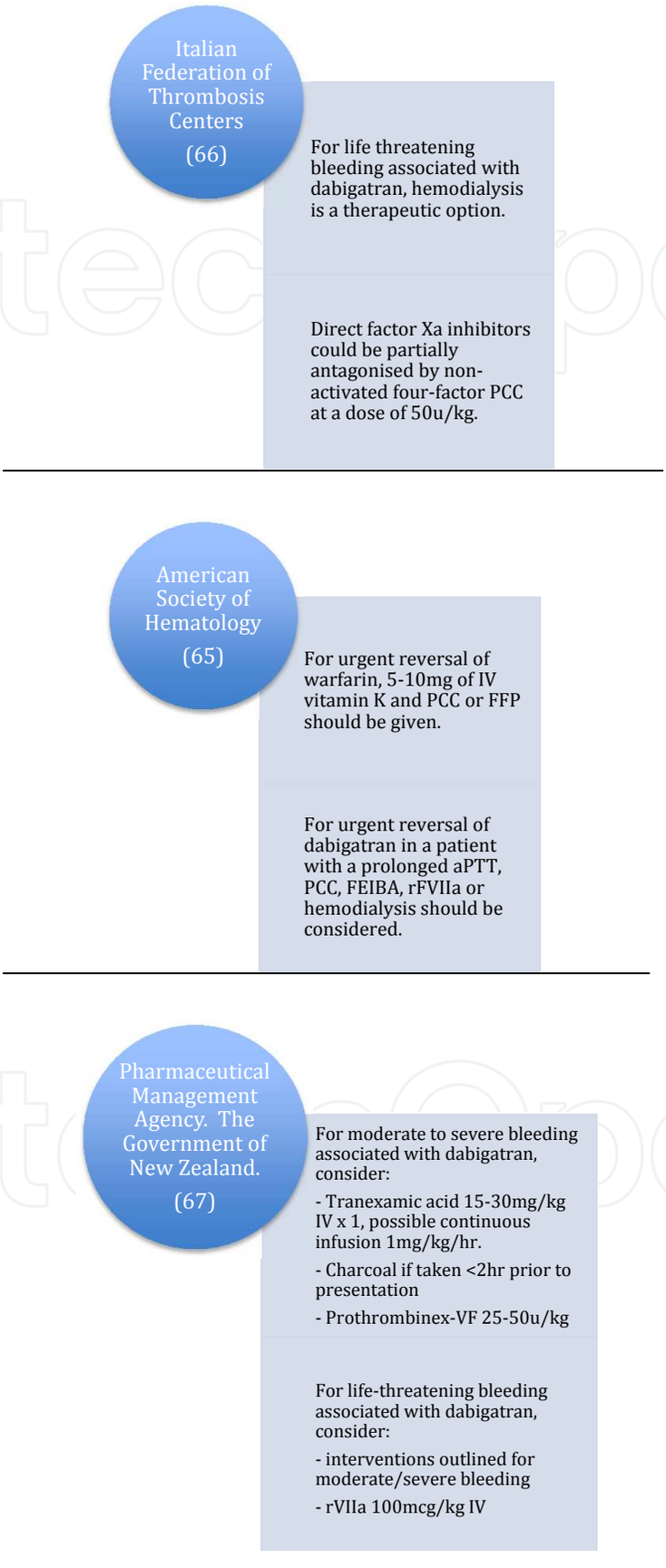
– airway protection, hemodynamic support with IVF and vasopressors, neurosurgical evaluation as well as discontinuing the patient's anticoagulant. Depending on the agent responsible for the patient's coagulopathy, some of the following may be indicated: activated charcoal, four-factor protein complex concentrate with or without vitamin K and hemodialysis/hemoperfusion (dabigatran only). FFP and rVIIa could be options, but these agents may potentially introduce unnecessary risk, namely transfusion-associated risks with FFP and thrombosis risk in the case of rVIIa [19]. It is possible that in the future, other agents such as aminocaproic acid [63, 64] may be discovered to have a role. For now, clinicians are left to rely on published guidelines from many professional organizations *(outlined below)* [11, 65-67, 70] to help the clinician sort through the multiple issues that need to be taken into consideration when attempting to reverse the effects of systemic anticoagulation in an attempt to limit the potentially substantial morbidity and mortality of traumatic brain injury in the anticoagulated patient.






Italian Federation of Thrombosis Centers (66)
For life threatening bleeding associated with dabigatran, hemodialysis is a therapeutic option.
Direct factor Xa inhibitors could be partially antagonised by non-activated four-factor PCC at a dose of 50u/kg.
American Society of Hematology (65)
For urgent reversal of warfarin, 5-10mg of IV vitamin K and PCC or FFP should be given.
For urgent reversal of dabigatran in a patient with a prolonged aPTT, PCC, FEIBA, rFVIIa or hemodialysis should be considered.
Pharmaceutical Management Agency. The Government of New Zealand. (67)
For moderate to severe bleeding associated with dabigatran, consider:
- Tranexamic acid 15-30mg/kg IV x 1, possible continuous infusion 1mg/kg/hr.
- Charcoal if taken <2hr prior to presentation
- Prothrombinex-VF 25-50u/kg
For life-threatening bleeding associated with dabigatran, consider:
- interventions outlined for moderate/severe bleeding
- rVIIa 100mcg/kg IV

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Appendix 1

Mercy Hospital St. Louis Trauma/Neuro ICU

Anticoagulant reversal protocol

This is the reversal protocol for a patient who has an intracranial hemorrhage and is taking one of the agents listed below. If the patient has had a cardiac ischemic event or other thromboembolic event within the last 30 days, the risks and benefits of PCCs, which have a higher rate of thrombotic events, over an FFP-based protocol should be weighed and clinical judgement should be applied.

If INR is 1.5-2.0 only FFP protocol should be utilized as Kcentra is not approved for reversal of warfarin in this INR range.

1. WARFARIN- Related ICH- using PCCs (Kcentra):

Warfarin with: INR < 1.2Recheck PT/INR in 12 hours

INR 1.2 – 1.4 Give Vitamin K 5 mg IV over 30 minutes if not already given and recheck PT/INR in 12 hours.

INR 1.5-1.9Use FFP protocol. Please dose based on weight and INR (See dosing Table 2]

INR ≥ 2.0 **Give Vitamin K 10 mg IV over 30 minutes** if not already given. Give Kcentra based on the table (see below). Recheck PT/INR 20 minutes after infusion complete. Treat again based on INR level.

Pre-treatment INR	2- <4	4-6	>6
Dose of Kcentra (Units of Factor IX)/kg body weight	25	35	50
Maxiumum dose (Units of Factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

Table 2.

2. WARFARIN- Related ICH- using FFP:

If the patient has had a recent MI or other thromboembolic event and the decision is to not use PCCs, then consider using FFP according to the following calculations:

Warfarin with: INR < 1.2Recheck PT/INR in 12 hours

INR 1.2 – 1.4 Give Vitamin K 5 mg IV over 30 minutes if not already given and recheck PT/INR in 12 hours.

INR > 1.5Give Vitamin K 10 mg IV over 30 minutes if not already given. Give FFPs based on the table (see below). Recheck PT/INR 20 minutes after infusion complete. Treat again based on INR level.

INR	Fresh Frozen Plasma Dose by Weight (kg)		
	Less Than 75 kg	75-100 kg	Greater than 100 kg
1.5-2.5	2 units	4 units	6 units
2.6-3.5	3 units	5 units	7 units
3.6-5	4 units	6 units	8 units*
Greater than 5	6 units	8 units*	10 units*

Table 3.

This document is intended as a guide to the correct adult dose of FFP, it is not a directive, and should not be used in place of clinical assessment.

*Caution should be exercised if using this chart for calculating FFP volumes for overweight patients as the volume suggested may be an over estimation and may risk fluid overload.

HEPARIN- Related ICH:

Reversal of Intravenous Heparin-Related Intracerebral Hemorrhage	
Immediately stop heparin source	
Protamine dosing for reversal of intravenous heparin	
Time Elapsed	Protamine dose
Immediate	1 mg per 100 units of heparin
30-60 minutes	0.5 mg per 100 units of heparin
Greater than 2 hours but less than 4 hours	0.25 mg per 100 units of heparin
Protamine _____ mg (maximum dose 50 mg) intravenous over 10 minutes.	

Table 4.

3. ENOXAPARIN- Related ICH:

If taken within 24 hours (full dose only, no treatment is indicated for prophylactic doses of LMWH), give 1 mg protamine for every 1 mg of enoxaparin which was given up to a maximum dose of 50 mg. If another LMWH compound was given, please contact the pharmacy to discuss the protamine dosing.

4. tPA- Related ICH:

Immediately stop the thrombolytic infusion.

Send PT/PTT, platelet count, fibrinogen level, and type and cross.

Transfusions should begin while waiting for lab results.

Transfuse 6 pack of platelets.

Transfuse _____ units of cryoprecipitate (recommend 0.1-0.2 units/kg).

Consider giving aminocaproic acid (Amicar) 5 grams/250 cc NS IV over 60 minutes.

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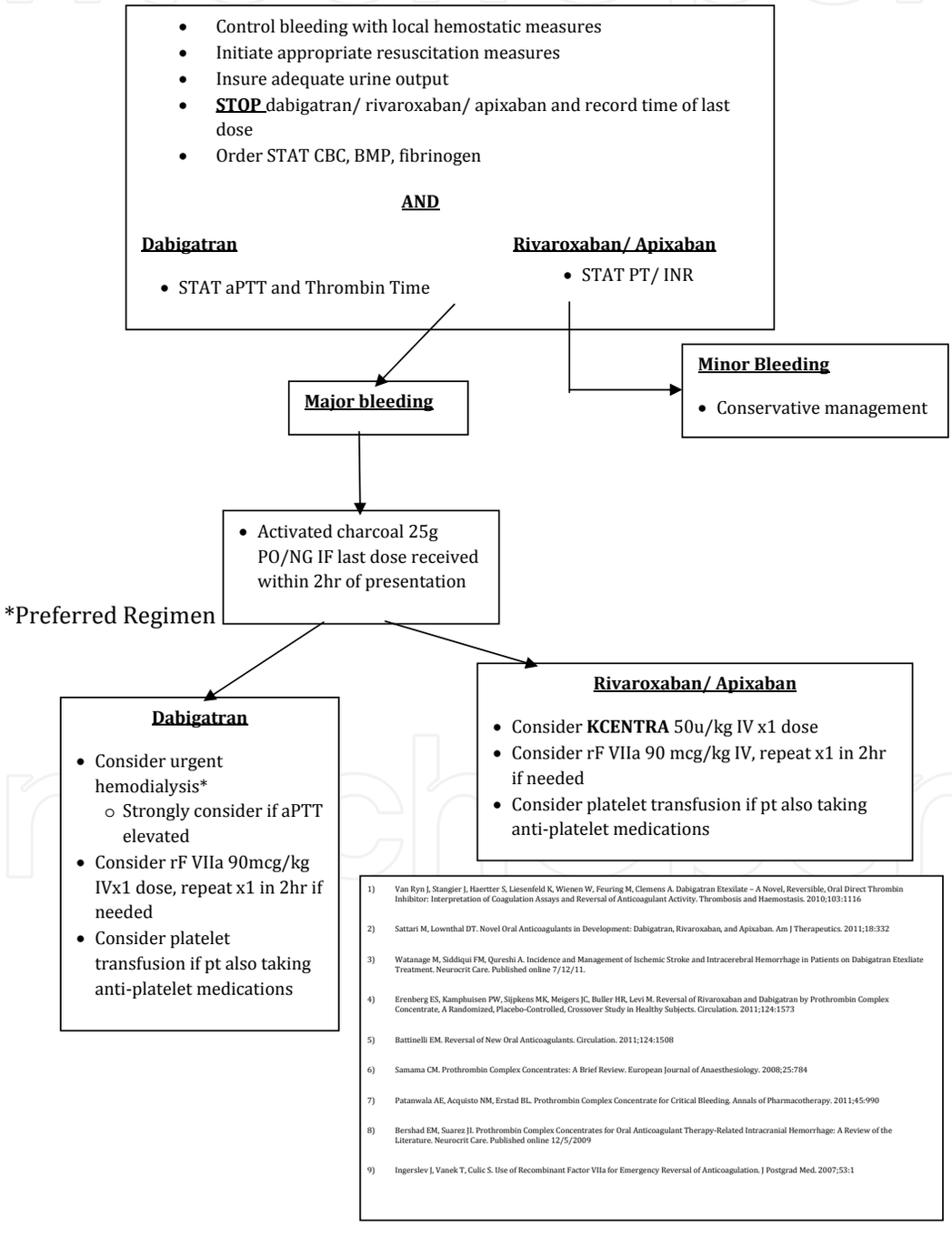
Once initial lab results return, calculate the amount of fibrinogen needed to achieve a level of > 150 mg/dl (one unit of cryoprecipitate increases fibrinogen by 7-10 mg/dl). This second dose should equal the total amount needed minus the initial dose.

Recheck CBC, PT/PTT, and fibrinogen one hour after transfusion therapy is completed.

Management of Bleeding in Patients

Taking Dabigatran/ Rivaroxaban/ Apixaban



1) Van Ryn J, Stangier J, Haertter S, Liesenfeld K, Wienen W, Feuring M, Clemens A. Dabigatran Etexilate – A Novel, Reversible, Oral Direct Thrombin Inhibitor: Interpretation of Coagulation Assays and Reversal of Anticoagulant Activity. Thrombosis and Haemostasis. 2010;103:1116

2) Sattari M, Lownthal DT. Novel Oral Anticoagulants in Development: Dabigatran, Rivaroxaban, and Apixaban. Am J Therapeutics. 2011;18:332

3) Watanage M, Siddiqui FM, Qureshi A. Incidence and Management of Ischemic Stroke and Intracerebral Hemorrhage in Patients on Dabigatran Etexliate Treatment. Neurocrit Care. Published online 7/12/11.

4) Erenberg ES, Kamphuisen PW, Sijpkens MK, Meigers JC, Buller HR, Levi M. Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate, A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects. Circulation. 2011;124:1573

5) Battinelli EM. Reversal of New Oral Anticoagulants. Circulation. 2011;124:1508

6) Samama CM. Prothrombin Complex Concentrates: A Brief Review. European Journal of Anaesthesiology. 2008;25:784

7) Patanwala AE, Acquisto NM, Erstad BL. Prothrombin Complex Concentrate for Critical Bleeding. Annals of Pharmacotherapy. 2011;45:990

8) Bershad EM, Suarez JI. Prothrombin Complex Concentrates for Oral Anticoagulant Therapy-Related Intracranial Hemorrhage: A Review of the Literature. Neurocrit Care. Published online 12/5/2009

9) Ingerslev J, Vanek T, Culic S. Use of Recombinant Factor VIIa for Emergency Reversal of Anticoagulation. J Postgrad Med. 2007;53:1

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References

[1] Brott T, Broderick J, Kothari R, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke. 1997 Jan;28(1):1-5.

[2] Davis SM, Broderick J, Hennerici M, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology. 2006 Apr 25;66(8):1175-81.

[3] Hemphill JC, Bonovich DC, Besmertis L, et al. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke. 2001;32:891-897.

[4] Cucchiara B, Messe S, Sansing L, et al. CHANT Investigators. Hematoma growth in oral anticoagulant related intracerebral hemorrhage. *Stroke.* Nov 2008;39(11):2993-6

[5] Mayer SA, Brun NC, Broderick J, et al; Europe/AustralAsia NovoSeven ICH Trial Investigators. Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke.* 2005;36(1):74-79

[6] Mayer SA, Brun NC, Begtrup K, et al; FAST Trial Investigators. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med.* 2008;358(20)2127-2137

[7] Menzin J, Hoesche J, Friedman M, Nichols C, et al. Failure to correct international normalzed ratio and mortality among patients with warfarin-related major bleeding: An analysis of electronic health records. *J Thromb Haemost.* April 2012;10(4):596-605

[8] Yasaka M, Minematsu K, Naritomi H, et al. Predisposing factors for enlargement of intracerebral hemorrhage in patients treated with warfarin. *Thromb Haemost.* Feb 2003;89(2):278-83

[9] Aguilar MI, Hart RG, Kase CS, et al. Treatment of warfarin-associated intracerebral hemorrhage: literature review and expert opinion. *Mayo Clinic Proc.* 2007;82:82-92

[10] Peacock WF, Gearhart MM, Mills RM. Emergency management of bleeding associated with old and new anticoagulants. *Clin Cardiol.* 2012

[11] Holbrook A, Schulman S, Witt D, et al. Evidence-based management of anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis, 9th edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141e152S-184S

[12] Makris M, van Veen JJ, Maclean R. Warfarin anticoagulation reversal: management of the asymptomatic and bleeding patient. *J Thromb Thrombolysis.* 2010;29:171-181

[13] Bershad EM, Suarez JL. Prothrombin complex concentrates for oral anticoagulant therapy-related intracranial hemorrhage: A review of the literature. *Neurocrit Care.* June 2010;12(3);403-13

[14] FEIBA NF package insert. http://www.fda.gov/downloads/biologicsbloodvaccines/bloodbloodproducts/approvedproducts/licensedproductsblas/fractionatedplasmaproducts/ucm221749.pdf

[15] Kcentra package insert. http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM350239.pdf

[16] Patanwala A, Acquisto N, Erstad B. Prothrombin complex concentrate for critical bleeding. *Ann Pharmacother.* 2011;45:990-999

[17] Voils SA, Baird B. Systematic review: 3-factor versus 4-factor prothrombin complex concentrate for warfarin reversal: Does it matter? *Thrombosis Research.* 130(2012): 833-840

[18] Dentali F, Marchesi C, Pierfranceschi M, et al. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. *Thromb Haemost.* 2011;106:429-438

[19] Kaatz S, Kouides P, Garcia D, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. *Am J Hematol.* 2012;87:S141-S145

[20] Mahan CE, Fanikos J. New antithrombotics: The impact on global health care. Thromb Res. 2011;127:518-524

[21] Kubitza D, Becka m, Mueck W, et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct factor Xa inhibitor. *Br J Clin Pharmacol.* 2010;70:703-12

[22] Stangler J, Rathgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate. An open-label, parallel-group, single-center study. *Clin Pharmacokinet.* 2010;49(4):259-268

[23] Pradaxa (dabigatran etexilate capsules) [package insert]. Ingelheim, Germany: Boehringer Ingelheim Pharma GmbH& Co

[24] Connolly S, Ezekowitz M, Yusuf S, et al. The RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12):1139-1151

[25] van Ryn J, Stangler J, Haertter S, et al. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost.* 2010;103(6):1116-1127

[26] Zhou W, Schwarting S, Illanes S, et al. Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. *Stroke.* 2011;42:3594-3599

[27] van Ryn J, Dorr B, Kaspereit F, et al. Beriplex P/N reverses bleeding in an acute renal injury model after dabigatran overdose in rabbits. *Pathophysiol Haemost Thromb.* 2010;37:A94-P486 (Abstract)

[28] Dumkow LE, Voss JR, Peters M, Jennings DL. Reversal of dabigatran-induced bleeding with a prothrombin complex concentrate and fresh frozen plasma. *Am J Health-Syst Pharm.* 2012;69:1646-50

[29] Dager WE, Gosselin CLS, Roberts AJ. *Crit Care Med.* 2013;41:e42-e46

[30] Eerenberg E, Kamphulsen P, Sijpkens M, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: A randomized, placebo-controlled, crossover study in healthy subjects. *Circulation.* 2011;124:1573-1579

[31] Marlu R, Hodaj E, Paris A, et al. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban. *Thromb Haemost.* 2012; 108:217-224

[32] van Ryn J, Ruehl D, Priepke H, et al. Reversibility of the anticoagulant effect of high doses of the direct thrombin inhibitor dagigatran, by recombinant factor VIIa or activated prothrombin complex concentrate (Abstract 0370). *Haematologica.* 2008;93(suppl 1):148

[33] van Ryn J, Kink-Eiband M, Clemens A. the successful reversal of dabigatran-induced bleeding by coagulation factor concentrates in a rat tail bleeding model do not correlate with ex vivo markers of anticoagulation. 53rd ASH Annual Meeting and Exposition, San Diego, CA; 2011

[34] van Ryn J, Sieger P, Kink-Elband M, et al. Adsorption of dabigatran etexilate in water or dabigatran in pooled human plasma by activated charcoal in vitro. 51st ASH Annual Meeting and Exposition. New Orleans, LA; 2009

[35] Warkentin T, Margetts P, Connolly S, et al. Recombinant factor VIIa (rFVIIa) and hemodialysis to manage massive dabigatran-associated postcardiac surgery bleeding. *Blood.* 2012 119;9:2172-2173

[36] Lassen MR, Ageno W, Borris LC, et al; for the RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med.* 2008;358(26):2776-2786

[37] The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thrombembolism. *N Engl J Med.* 2010; 363(26):2499-2510.

[38] The EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med.* 2012;366(14):1287-1297.

[39] Patel M, Mahaffey K, Garg J, et al. ROCKET AF Investigators Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883-891

[40] Xarelto (rivaroxaban) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, 2013

[41] U.S. Food and Druge Administration. Xarelto: Highlights of prescribing information. 2011. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202439s001lbl.pdf

[42] Tinel H, Huetter J, Perzborn E. Recombinant factor VIIa partially reversed the anticoagulant effect of high-dose rivaroxaban a novel, oral, direct factor Xa inhibitor in rats. *J Thromb Haemost.* 2007;5:Abstract P-W-652

[43] Gruber A, Marzec U, Buetehorn U, et al. Potential of activated prothrombin complex concentrate and activated factor VII to reverse the anticoagulant effects of rivaroxaban in primates. *Blood.* 2008;112:3825

[44] Pezborn E, Trabandt A, Selbach K, Tinel H. Prothrombin complex concentrate reverses the effects of high-dose rivaroxaban in rats (presented at the 21st International Congress on Thrombosis) [abstract]. *Pathophysiol Haemost Thromb.* 2010;37:A10-OC251

[45] Eliquis package insert. Bristol Meyers Squibb 2012. http://packageinserts.bms.com/pi/pi_eliquis.pdf

[46] Martin AC, Le Bonniec B, Fischer AM, et al. Evaluation of recombinant activated factor VII, prothrombin complex concentrate, and fibrinogen concentrate to reverse apixaban in a rabbit model of bleeding and thrombosis. *Int J Cardiol.* 2013 Aug 5 pii: S0167-5273(13)01363-6. doi: 10.1016/j.ijcard.2013.07.152. [Epub ahead of print]

[47] NovoSeven [package insert] Princeton, NJ 1999. http://factorviia.com/pi.pdf

[48] Marcel Levi, MD; Marjolein Peters, MD; Harry R. Bu®ller, MD. Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: A systematic review. *Crit Care Med*. 2005; 33:883–890

[49] Bauer K. Reversal of antithrombotic agents. *Am J Hematol.* 2012; 87:S119-S126

[50] Mayer SA, Brun NC, Broderick J, et al; Europe/AustralAsia NovoSeven ICH Trial Investigators. Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke.* 2005;36(1):74-79. 6

[51] Kenet G, Walden R, Eldad A, Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet.* 1999;354:1879

[52] Martinowitz U, Kenet G, Segal E, et al. *J Trauma.* 2001;51:431-439

[53] Dutton RP, McCunn M, Hyder M, et al. Factor VIIa for correction of traumatic coagulopathy. *J Trauma.* 2004;57:709-718

[54] Spinella P, Perkins J, McLaughlin D, et al. The effect of recombinant activated factor VII on mortality in combat-related casualties with severe trauma and massive transfusion. *J Trauma.* 2008;64:286-293

[55] Boffard K, Riou B, Warren B, et al. NovoSeven Trauma Study Group. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized placebo-controlled, double-blind clinical trials. *J Trauma.* 2005;59:8-15

[56] Hsia C, Chin-Yee I, McAlister V. Use of recombinant activated factor VII in patients without hemophilia: a meta-analysis of randomized controlled trials. *Ann Surg*. 2008;248:61-68

[57] Hauser C, Boffard K, Dutton R, et al. *J Trauma.* 2010;69:489-500

[58] Hedner U. Mechanism of action, deelopment and clinical experience of recombinant fVIIa. *J Biotechnol.* 2006;124:747-757

[59] O'Connell K, Wood J, Wise R, et al. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA.* 2006;295:293-298

[60] Thomas G, Dutton R, Hemlock B, et al. Thromboembolic complications associated with factor VIIa administration. *J Trauma.* 2007;62:564-569

[61] Levi M, Levy J, Andersen H, et al. Safety of recombinant activated factor VII in randomized clinical trials. *N Engl J Med.* 2010;363:1791-1800

[62] Yank V, Tuohy CV, Logan AC, et al. Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. *Ann Intern Med.* 2011;154:529-540

[63] Liu-DeRyke X, Rhoney D. Hemostatic therapy for the treatment of intracranial hemorrhage. *Pharmacotherapy.* 2008;28(4):485-495

[64] Piriyawat P, Morgenstern LB, Yawn DH, et al. Treatment of acute intracerebral hemorrhage with epsilon-aminocaproic acid: a pilot study. *Neurocrit Care*. 2004;1(1):47-51

[65] American Society of Hematology. 2011 Clinical practice guideline on the evaluation and management of immune thrombocytopenia (ITP) 2011. http://www.hematology.org/Practice/Guidelines/2934.aspx

[66] Pengo V, Crippa L, falanga A, et al. Questions and answers on the use of dabigatran and perspectives on the use of other new oral anticoagulants in patients with atrial fibrillation. A consensus document of the Italian Federation of Thrombosis Centers (FCSA). *Thromb Haemost.* 011;106:868-876

[67] Pharmaceutical Management Agency. 2011. Guidelines for management of bleeding with dabigatran – For possible inclusion into local management protocols. New Zealand Government. http://pharmac.govt.nz/2011/06/13/Dabigatran%20bleeding%20management.pdf

[68] O'Shaughnessy DF, Atterbury C, Bolton Maggs P, Murphy M, Thomas D, Yates S, Williamson LM, British Committee for Standards in Haematology, Blood Transfusion Task Force: Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol* 2004, 126:11-28

[69] Lauzier F, Cook D, Griffith L, Upton J, Crowther M: Fresh frozen plasma transfusion in critically ill patients. *Crit Care Med* 2007, 35:1655-1659.

[70] Morgenstern LB, Hemphill JC, Anderson C, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke.* 2010;41:2108-2129.

[71] Sarode R, Milling TJ Jr, Refaal MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation.* 2013 Sep 10;128(11):1234-43. doi: 10.1161/CIRCULATIONAHA.113.002283. Epub 2013 Aug 9.

[72] Hickey M, Gatien M, Taljaard M, et al. Outcomes of urgent warfarin reversal with frozen plasma versus prothrombin complex concentrate in the emergency department. *Circulation.* 2013 Jul 23; 128(4):360-4. doi: 10.1161/CIRCULATIONAHA.113.001875. Epub 2013 Jun 14.

[73] Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365:981-992.

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