

Reversal of Antithrombotics in Intracranial Hemorrhage: An Evidence-Based Guideline

*From the Neurocritical Care Society and Society of
Critical Care Medicine*

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Disclosures

- These guidelines and the recommendations presented here are still in peer review and may be subject to change

Disclosures

- Dr. Aisiku serves on the National Advisory Board for the Medicines Company
- Dr. Alexandrov serves on the speakers bureau for Genentech.
- Dr. del Zoppo has received research funds from the NIH, Boehringer Ingelheim, and Novartis. He has served on advisory boards for Boehringer Ingelheim, Daiichi-Sankyo, and Novartis.
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- Dr. Stiefel serves as a consultant for Medtronic and Penumbra.
- The remaining authors have nothing to disclose.

Overview

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 5. Antiplatelets
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Methods

- Professional librarian performed search of PubMed/Medline, Library of Science, the Cochrane database, EMBASE, and CINAHL
- Humans, English
- Key search words:
 - the generic and commercial names of antithrombotic agents
 - intracranial hemorrhage
 - subarachnoid hemorrhage,
 - intracerebral hemorrhage,
 - intraparenchymal hemorrhage,
 - subdural hematoma,
 - subdural hemorrhage,
 - intraventricular hemorrhage,
 - epidural hemorrhage,
 - epidural hematoma, and
 - traumatic brain injury

Literature search

Drug class	Initial search	Abstract review	Final
Antiplatelets	1182	34	9
Coumarin derivative	1330	83	53
Anti Factor Xa agents	427	32	18 (oral Xa agents) + 9 (Pentasachharides)
Heparin	1247	42	20
LMWH & Heparinoids	799	28	16 (LMWH) 1 (Heparinoids)
Thrombin inhibitors	709	99	22
Thrombolytics	65	50	22
General anticoagulants	222	0	0
TOTALS	5981	368	170

Introduction

- Antithrombotic associated ICH is expected to become more common
 - Aging population
 - Higher prevalence of afib
- Antithrombotic associated ICH have higher risk of hematoma expansion, higher mortality and worse outcome
- Introduction of novel oral anticoagulants with non-specific reversal strategies

Methods

GRADE CRITERIA

Quality of Evidence	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very Low	Any estimate of effect is very uncertain

RECOMMENDATION LEVELS: “STRONG” or “WEAK/CONDITIONAL”

Vitamin K Antagonists (VKA)



Acenocoumarol
Phenprocoumon
Dicoumarol
Tecarfarin
Fluindione

VKA Background

- 0.3-1.1%/year of patients on warfarin have IPH (baseline risk 0.15%/year)
- 12-14% of all IPH are warfarin-associated
- 90% of warfarin associated deaths due to IPH
- Higher volume hematoma, increased rebleeding risk, hematoma expansion for longer time than non-coagulopathic patients
- Higher risk of death and worse functional outcome if IPH a/w warfarin

Vitamin K

- Vit K needed to synthesize factors II, VII, IX, X
- Several small randomized, controlled trials demonstrate that Vit K durably corrects INR (Crowther MA, J of thrombosis and thrombolysis 2003, Ageno Thromb Haemost 2002)
- May take up to 24 h to get INR<1.4 (Lubetsky Thromb Res 2004, Hung B J Haematol 2003)
- Not reasonable monotherapy given rapid time course of IPH expansion (Brott Stroke 1997)
- Vit K alone a/w 50% IPH expansion c/w 33% with FFP+ Vit K and 19% with PCC + Vit K (Huttner Stroke 2006)
- However, Vit K in addition to PCC or FFP is necessary to provide long lasting INR correction (t ½ of factor VII is 4-6 h)
- IV route provides faster and better INR correction than SQ or PO route (Watson Br J Haematol 2001, Nee Am J Cardiol 1999)
- ONE dose of vitamin K 10 IV is usually sufficient
- Anaphylaxis risk 3 per 10,000 doses

Prothrombin Complex Concentrates (PCC) v Fresh Frozen Plasma (FFP)

PCC

- **PROS**
- Low volume
- Fast reconstitution
- Rapid INR correction
- Lower risk of infections
- **CONS**
- Expensive
- Not widely available
- Some should not be redosed

FFP

- **PROS**
- Widely available
- Less expensive than PCC
- **CONS**
- Need to be thawed/matched
- INR correction can be >30 h
- Increased risk of pulm edema
- Risk of TRALI/TACO

Two RCT: no difference in thrombosis rates between PCC and FFP (3-8%)

(Sarode Circulation 2013; Goldstein Lancet 2015)

Time to INR correction

- Failure to correct INR within 2 h independently predicts death-severe disability, worse functional outcomes (Huttner Stroke 2006)
- Retrospective cohort study of 853 VKA-associated IPH patients found risk of IPH expansion **DOUBLED** if INR >1.3 within 4 h of admission (42% vs. 20%, $P < 0.001$) (Kuramatsu JAMA 2015)

Warfarin Reversal PCC v FFP

Vascular Medicine

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

Ravi Sarode, MD; Truman J. Milling Jr, MD; Majed A. Refaai, MD;
Antoinette Mangione, MD, PharmD; Astrid Schneider, PhD; Billie L. Durn, BS;
Joshua N. Goldstein, MD, PhD

Multicenter **Non-inferiority** RCT of

202 patients on warfarin with major bleeding requiring reversal

Randomized to Beriplex/Kcentra (25-50 IU/kg) or FFP (10-15 ml/kg).

Dosing varied by baseline INR

Co-Primary Outcomes: 24 hour hemostatic efficacy

(standard scale where poor/none=required transfusion) and $INR \leq 1.3$ within 30 min.

Table 6. Hemostatic Efficacy by Time of Rating (Post Hoc Analysis; Intention-to-Treat Efficacy Population)

	Treatment Group		Difference 4F-PCC Minus Plasma, % (95% CI)*
	4F-PCC (n=98)	Plasma (n=104)	
No. of bleeds assessed for hemostatic efficacy at 4 h (visible, musculoskeletal)	23	28	
No. (%) of patients with effective hemostasis	19 (82.6)	14 (50.0)	32.6 (4.5 to 60.7; $P=0.0200$)
No. of bleeds assessed for hemostatic efficacy at 24 h (gastrointestinal, intracranial, other nonvisible)	75	76	
No. (%) of patients with effective hemostasis	52 (69.3)	54 (71.1)	-1.7 (-17.6 to 14.2; $P=0.95$)

4F-PCC indicates 4-factor prothrombin complex concentrate; and CI, confidence interval.

*95% CI and P value based on a Wald test with continuity correction.

PCC is non-inferior
For hemostasis

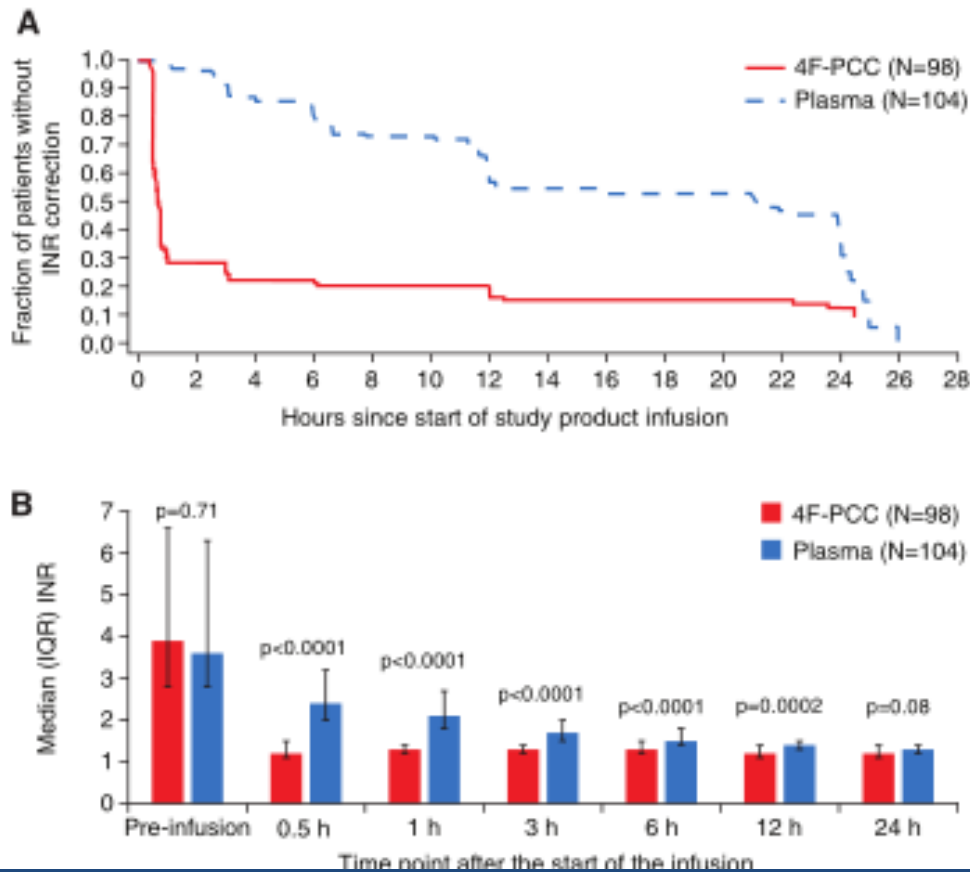


Figure 2. A, Time to international normalized ratio (INR) correction (intention-to-treat efficacy population). **B**, Median INR by time point (intention-to-treat efficacy population). 4F-PCC indicates 4-factor prothrombin complex concentrate; and IQR, interquartile range.

PCC is superior for rapid INR correction to <1.3 in 30 min (62% in PCC vs. 10% in FFP)

Safety profile- adverse events, thromboembolic events (4% PCC, 3% FFP) and deaths similar in both groups

Only 24 (12%) patients had intracranial bleeding Sarode Circulation 2013

Warfarin Reversal PCC v FFP

Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial



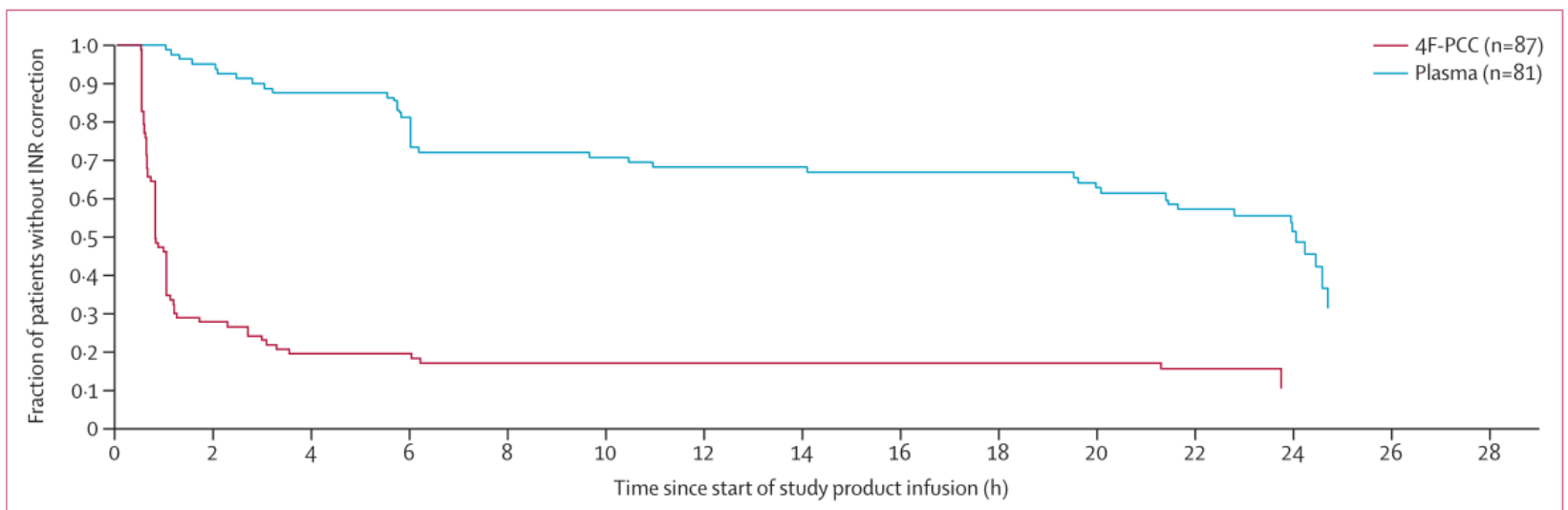
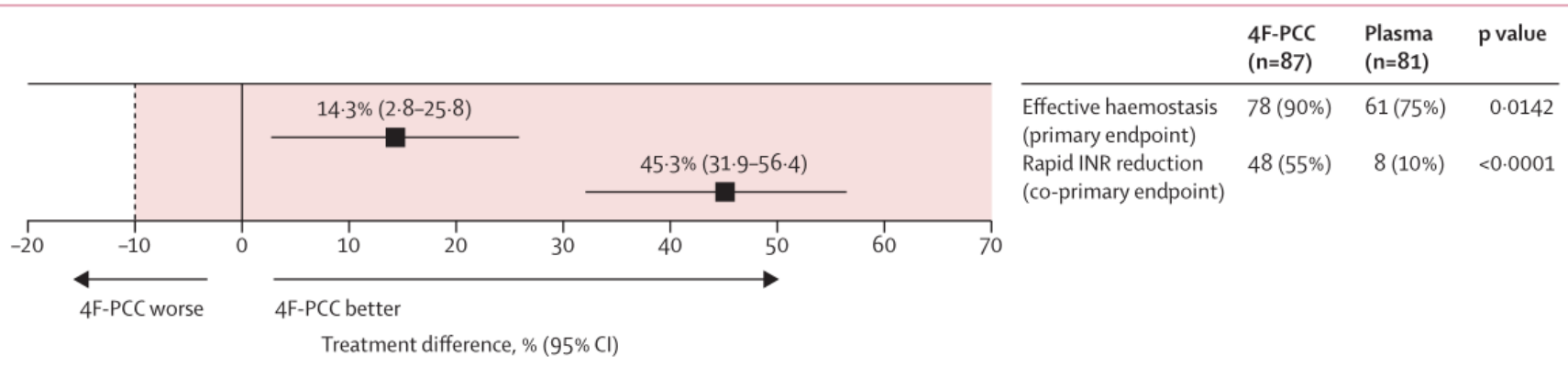
Joshua N Goldstein, Majed A Refaai, Truman J Milling Jr, Brandon Lewis, Robert Goldberg-Alberts, Bruce A Hug, Ravi Sarode

Multicenter RCT of 181 patients on warfarin requiring reversal for surgery

Randomized to Beriplex/Kcentra (25-50 IU/kg) or FFP (10-15 ml/kg).
Dosing varied by baseline INR

Co-Primary Outcomes: 24 hour hemostatic efficacy
(standard scale where poor/none=required transfusion) and $INR \leq 1.3$ within 30 min.

Study designed to assess non-inferiority, then superiority



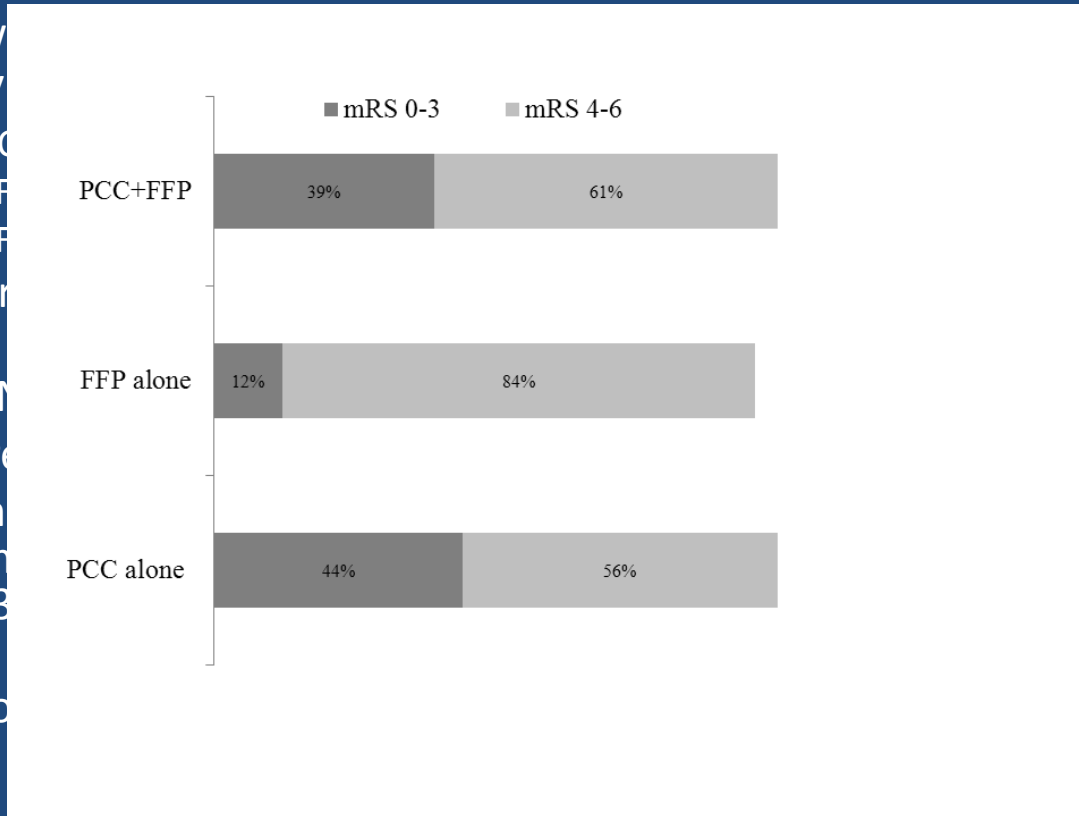
PCC was superior to FFP for both endpoints

Adverse events were similar, but more fluid overload in FFP group (13% v 3%)

Only 2 (1%) patients had cranial neurosurgery

Reversal of Coagulopathy using Prothrombin Complex Concentrates is Associated with Improved Outcome Compared to Fresh Frozen Plasma in Warfarin Associated Intracranial Hemorrhage

- 64 pts w
- All got V
- 16 PCC
- 25 FFP
- 23 FFP
- No differ
- volume,
- Higher INR
- INR corre
- FFP alone
- hemorrh
- (P=0.033)
- PCC use
- admissio



score, IPH

FFP group)

cial
in PCC groups

age,
8, P=0.039

Prothrombin Complex Concentrates

Varying amounts of Factor VII

“3-Factor”

- Bebulin
- Profilnine SD
- Preconativ
- Proplex-T
- Prothrombinex-HT

“4-Factor”

- Beriplex/Kcentra
- Cofact
- Octaplex
- Kaskadil

3 vs. 4 Factor PCC have not been directly compared

Adding FFP or rVIIa to 3-Factor does not seem to add benefit and may add risk (Frontera Neurocrit Care 2014; Switzer Stroke 2012)

Activated PCC (FEIBA) compared to FFP in small studies, but 7% adverse event rate

(Wojcik Int J Emer Med 2009, Stewart Am J Emer Med 2013)

Recombinant Factor VIIa

- Only repletes one factor
- 13-24% thrombosis rate (Aledort J Thromb Haemost 2004, O'Connell JAMA 2006)
- 5% excess arterial thrombosis rate (FAST Trial Mayer NEJM 2008)
- INR is quickly corrected but this may not correlate with hemostasis
- Expensive
- Short t_{1/2} of factor VII (4-6 h)-> potential for rebound coagulopathy

RECOMMENDATIONS for VKA Reversal

- 1) We recommend discontinuing vitamin K antagonists when intracranial hemorrhage is present or suspected.
(Strong recommendation, low quality evidence)
- 2) We recommend urgent reversal of vitamin K antagonists in patients with intracranial hemorrhage
(Strong recommendation, moderate quality evidence) with the following considerations:
 - We recommend against VKA reversal in patients where there is a high suspicion of intracranial hemorrhage due to cerebral venous thrombosis.
(Strong recommendation, very low quality evidence)
 - We recommend assessing risks and benefits when considering VKA reversal in intracranial hemorrhage patients with concurrent symptomatic or life-threatening thrombosis, ischemia, heparin-induced thrombocytopenia, or DIC.
(Strong recommendation, very low quality evidence)

RECOMMENDATIONS for VKA Reversal

- 3) We recommend administration of Vitamin K to ensure durable reversal of INR following all VKA-associated intracranial hemorrhage. Vitamin K should be dosed as soon as possible or concomitantly with other reversal agents.
(Strong recommendation, low quality evidence)
- a) We suggest one dose of Vitamin K 10 mg IV. Subsequent treatment should be guided by follow-up INR.
(Conditional recommendation, very low quality evidence)
- b) If repeat INR is still elevated ≥ 1.4 within the first 24-48 hours after reversal agent administration, we suggest re-dosing with vitamin K 10 mg IV.
(Conditional recommendation, low quality evidence)

RECOMMENDATIONS

for VKA Reversal

4) We recommend administering 3-factor or 4-factor PCC rather than FFP to patients with VKA-associated intracranial hemorrhage and INR ≥ 1.4 .

(Strong recommendation moderate quality evidence)

- a) We suggest initial reversal with PCC alone (either 3- or 4- factor) rather combined with FFP or rFVIIa.

(Conditional recommendation, low quality evidence)

- b) We suggest the use of 4-factor PCC over 3-factor PCC.

(Conditional recommendation, low quality evidence)

- c) We recommend that PCC dosing should be weight-based and vary according to admission INR and type of PCC used.

(Strong recommendation, moderate quality evidence)

d) We recommend repeating INR testing soon after PCC administration (15 – 60 min), and serially every 6-8 h for the next 24-48 hours. Subsequent treatment should be guided by follow-up INR, with consideration given to the fact that repeat PCC dosing may lead to increased thrombotic complications and risk of DIC.

(Strong recommendation, very low quality evidence)

e) If the repeat INR is still elevated ≥ 1.4 within the first 24-48 h after initial PCC dosing, we suggest further correction with FFP.

(Conditional recommendation, low quality evidence)

RECOMMENDATIONS

for VKA Reversal

5) We recommend against administration of rFVIIa for the reversal of VKA.

(Strong recommendation, low quality evidence)

6) If PCCs are not available or contraindicated, alternative treatment is recommended over no treatment. Treatment choice may be guided by available therapies and patient-specific factors.

(Strong recommendation, low quality evidence)

- a) Treatment with FFP and Vitamin K is recommended over no treatment.

(Strong recommendation, low quality evidence)

- b) We suggest dosing FFP at 10-15 ml/kg IV along with one dose of vitamin K 10 mg IV

(Conditional recommendation, low quality evidence)

**NOVEL ORAL ANTICOAGULANTS:
DIRECT THROMBIN INHIBITORS
ORAL FACTOR XA INHIBITORS**

Coagulopathy-NOAC **Summary** in Afib

	Superior for reducing all stroke or embolic events c/w Warfarin	Non-inferior for reducing all stroke or embolic events c/w Warfarin	Significantly lower major hemorrhage c/w warfarin	Significantly lower intracranial hemorrhage c/w warfarin
Apixaban	Yes*	yes	yes	yes
Rivaroxaban	no	yes	no	no
Edoxaban	no	Yes At low and high dose	Yes At low and high dose	Yes At low and high dose
Dabigatran	Yes At 150 mg dose only	Yes At 150 and 100 mg	Yes At 110 mg dose only	Yes At 150 and 100 mg

ARISTOTLE, AVEROES, ROCKET-AF, ENGAGE-AF, RE-LY

Measuring NOAC induced coagulopathy

DTI

- DTI- aPTT sensitive and useful for IV DTI
- aPTT less sensitive for dabigatran; though normal aPTT has good negative predictive value
- Dilute thrombin time, ecarin clotting time and ecarin chromogenic assay preferred

Oral Factor Xa

- Oral factor Xa prolong PT but sensitivity varies
- Prothrombinase induced clotting time and chromogenic anti-Factor Xa levels preferred

Direct Thrombin Inhibitors



Dabigatran (oral)
Bivalrudin (IV)
Desirudin (SQ)
Argatroban (IV)
Lepirudin (IV)

Approved for primary stroke prevention in patients with non-valvular afib,
treatment of DVT/PE, treatment of HIT

0.2-0.3% per year ICH rate with Dabigatran
110 mg BID/150 mg BID, respectively (RELY trial)

DTI Reversal

- Discontinue Agent
 - no reversal if after 3-5 terminal half-lives (Komori Circulation Journal 2014)
 - Caveat for dabigatran: renal failure or P450 inhibitors
- Oral Activated Charcoal for dabigatran (van Ryn Hematology 2009)
 - Within 2 h of exposure
 - Aspiration risk

PCC for Dabigatran reversal

Positive studies

- Preclinical trials of Kcentra- limits hematoma growth, improves bleeding time, hemostasis and mortality in dabigatran exposed animals (Zhou Stroke 2011, Herzog Thrombosis research 2014, Pragst JTH 2012, Hoffman Anesthesiology 2015)
- 4-factor PCC corrects dabigatran induced laboratory parameters of coagulopathy in humans and animals
 - Endogenous thrombin potential,
 - PT prolongation,
 - TEG clotting time,
 - thrombin generation,
 - clotting time(Eerenberg ES Circulation 2011, Marlu Thrombosis and haemostasis 2012, Pragst JTH 2012)

Negative Studies

- In vitro model- PCC and rVIIa had minimal effect on dabigatran induced lab abnormalities in clotting time, but aPCC normalized clotting time by 33% (Lindahl Thrombosis Research 2015)
- One human, prospective crossover study showed that 50 IU/kg 4-factor PCC (Cofact) *did not* improve ecarin clotting time, thrombin time or aPTT after dabigatran (Eerenberg Circulation 2011)

Activated PCC (FEIBA) for Dabigatran Reversal

- Several studies show aPCC corrects:
 - endogenous thrombin potential lag time,
 - thrombin generation,
 - TEG clotting time and
 - clot formation in a dose-dependent fashion (26-100 U/kg)

(Lindahl TLThrombosis research 2015; Lambourne JTH 2012; Khoo International journal of laboratory hematology 2013; Grottke Critical care 2014; Schiele Blood 2013)

- No studies directly comparing PCC and aPCC

Hemodialysis for Dabigatran Reversal

- Low protein binding (35%), high renal excretion of dabigatran
- 4 h of HD, plasma clearance of dabigatran 49% at blood flow rates of 200 ml/min, 58% at 300 ml/min and 59% at 400 ml/min. (Khadzhynov Thrombosis and Haemostasis 2013)
- Rebound increase in dabigatran 7-16% 4-8 h after HD>> need CVVHD after high flow HD
- Require blood flow rates of 200-400 ml/min and dialysate flow rates of 700 ml/min for at least 4 h followed by CVVHD (Stangier Clinical pharmacokinetics 2010)
- These rates may not be tolerated by patients with ICH (cerebral edema, hypoperfusion, abnormal autoregulation) (Osgood Neurocrit Care 2015; Lin Acta neurochirurgica Supplement 2008; Davenport International Symposium on Home Hemodialysis 2013)

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S.,
Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D.,
Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D.,
Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D.,
Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E.,
Bushu Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

Humanized antibody fragment against dabigatran- adheres to thrombin binding site of dabigatran

REVERSE-AD: Prospective cohort safety study of 5 g Idarucizumab IV
in dabigatran patients with: serious bleeding or requiring urgent reversal for a procedure

Primary endpoint: % reversal of dilute thrombin time or Ecarin Clotting time in 4 h

Interim analysis of 90 patients: 88-98% normalization of ECT or dilute thrombin time in minutes
Concentrations of unbound dabigatran < 20ng/ml at 24 h in 79%

Of those bleeding, hemostasis restored in 11.4 h

Normal hemostasis in 92% (33/36) requiring procedures

Adverse events: 18 deaths, 5 thrombotic events off AC

Pollack NEJM 2015

RECOMMENDATIONS for DTI Reversal

- 1) We recommend discontinuing direct thrombin inhibitors when intracranial hemorrhage is present or suspected.
(Strong recommendation, very low quality evidence)
- 2) We recommend assessing the time and amount of the last ingested dose, renal function, and possible medication interactions to assist in estimating the degree of anticoagulation in those exposed to direct thrombin inhibitors.
(Strong recommendation, high quality evidence)
- 3) We recommend that pharmacological reversal of direct thrombin inhibitors should be guided primarily by bleeding (major or intracranial) and not primarily by laboratory testing.
(Strong recommendation, low quality evidence)
- 4) We suggest administering activated charcoal (50 g) to intubated intracranial hemorrhage patients with enteral access and/or those at low risk of aspiration who present within 2 hours of ingestion of an oral direct thrombin inhibitor.
(Conditional recommendation, very low quality evidence)

RECOMMENDATIONS

for DTI Reversal

- 5) We suggest administering aPCC (50 units/kg) or 4-factor PCC (50 units/kg) to patients with intracranial hemorrhage associated with direct thrombin inhibitors if:
 - a) the direct thrombin inhibitor was administered within a period of 3-5 half lives and there is no evidence of renal failure
(Conditional recommendation, low quality evidence) or,
 - b) there is renal insufficiency leading to continued drug exposure beyond the normal 3-5 half-lives
(Conditional recommendation, low quality evidence) or,
 - c) the time of last ingestion is unknown and/or there is laboratory evidence of dabigatran-induced coagulopathy.
(Conditional recommendation, low quality evidence)
- 6) In patients with dabigatran associated intracranial hemorrhage and renal insufficiency or dabigatran overdose, we recommend considering hemodialysis.
(Strong recommendation, low quality data)
- 7) In patients with dabigatran-associated intracranial hemorrhage and normal renal function who have already been treated with PCC or aPCC, with ongoing clinical or laboratory evidence of bleeding or coagulopathy, we suggest considering hemodialysis.
(Conditional recommendation, low quality evidence)
- 8) We recommend against administration of rFVIIa or FFP in direct thrombin inhibitor-related intracranial hemorrhage.
(Strong recommendation, low quality evidence)

Oral Factor Xa Inhibitors



Rivaroxaban
Apixaban
Edoxaban

Prevent factor Xa dependent conversion of
prothrombin >> thrombin

Indications:

primary stroke prevention in non-valvular afib,
DVT/PE treatment,
secondary prevention of DVT/PE

Reversal of Oral Factor Xa

- Activated charcoal 50 g within 2 h of intake reduces apixaban exposure by 50% and may be helpful with rivaroxaban (Wang Am J Cardiovasc Drugs 2014; Crowther Arteriosclerosis, thrombosis, and vascular biology 2015)
- No utility of hemodialysis

PCC and aPCC for oral factor Xa reversal

- 4-factor PCC, aPCC and rFVIIa all partially correct laboratory abnormalities induced by oral factor Xa agents (Zhou Stroke 2013; Perzborn E Thrombosis and haemostasis 2013, Eerenberg ES Circulation 2011, Perzborn Thrombosis research 2014, Dinkelaar JTH 2013, Marlu Thrombosis and haemostasis 2012, Herrmann R Thrombosis and haemostasis 2014, Escolar G PloS One 2013)
- Two animal studies found no change in apixaban or rivaroxaban induced bleeding despite improved coag parameters (Godier Anesthesiology 2012, Martin Int J Cardiol 2013)
- 4-factor PCC decreases bleeding in edoxaban treated animal models of acute hemorrhage and after punch biopsies in healthy volunteers (Herzog Anesthesiology 2015, Zahir Circulation 2015)

Upcoming reversal agents for Oral Direct Factor Xa

Name	Type of Drug	What it reverses	Evidence
Andexanet (PRT064445)	Recombinant modified factor Xa molecule	Oral factor Xa (apixaban, Edoxaban, Rivaroxaban) and indirect factor Xa (LMWH, fondaparinux) (<i>Lu Nature medicine 2013</i>)	Reverses: 53% of anti-Xa rivaroxaban activity; (<i>Crowther 55th ASH annual meeting, New Orleans 2013, abstract</i>) 91% of anti-Xa apixaban activity (<i>Crowther Eur Heart J 2014</i>) 73% of anti-Xa edoxaban activity in healthy volunteers (<i>Crowther ASH 2014, Abstract</i>) Study in bleeding patients began 1/2015
Aripazine (PER977)	Synthetic small molecule	Oral factor Xa (apixaban, edoxaban, rivaroxaban) Direct thrombin inhibitors (dabigatran) Unfractionated Heparin LMWH	80 healthy volunteers on edoxaban had improved whole-blood clotting time after aripazine (<i>Ansell NEJM 2014</i>) Unclear if reverses anticoagulants or is prothrombotic

RECOMMENDATIONS

Oral Factor Xa Reversal

- We recommend discontinuing factor Xa inhibitors when intracranial hemorrhage is present or suspected.
(Strong recommendation, low quality evidence)
- We recommend obtaining information on the time elapsed since the last dose of factor Xa inhibitor
(Strong recommendation, low quality evidence).
- We suggest administering activated charcoal (50g) to intubated intracranial hemorrhage patients with enteral access and/or those at low risk of aspiration who present within 2 hours of ingestion of a direct factor Xa inhibitor.
(Conditional recommendation, very low quality evidence)

RECOMMENDATIONS

Oral Factor Xa Reversal

- We suggest administering a 4-factor PCC (50 U/kg) or activated PCC (50 U/kg) if intracranial hemorrhage occurred within 3-5 terminal half-lives of drug exposure or in the context of liver failure.
(Conditional recommendation, low quality evidence)
- We suggest administering 4-factor PCC or activated PCC over rFVIIa because of more complete reversal of laboratory parameters and lower risk of adverse thrombotic events.
(Conditional recommendation, low quality evidence)

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Protamine for UFH reversal

- Highly alkaline poly-cationic compound – binds to polyanionic heparin and neutralizes anticoagulant effect
- Several animal trials as well as healthy human trials demonstrate complete neutralization of heparin and heparin-induced blood loss
- Reduction in blood loss demonstrated in cardiac sx patient population
- 1mg neutralizes 80-120 units heparin
 - Reverse the drug “on board” (last 2-3 hrs administered)
 - Repeat dosing may be necessary – protamine $t_{1/2}$ is shorter than UFH
- Caution: anaphylaxis, hypotension, bradycardia

Unfractionated Heparin

1. We recommend discontinuing heparin infusions when intracranial hemorrhage is present or suspected. (Strong recommendation, moderate quality evidence)
2. We recommend urgently reversing anticoagulation in patients who develop intracranial hemorrhage during full dose heparin infusion. (Strong recommendation, moderate quality evidence)
3. We do not recommend routinely reversing prophylactic subcutaneous heparin. (Strong recommendation, moderate quality data)
 - a) We suggest considering reversal of prophylactic subcutaneous heparin if the aPTT is significantly prolonged. (Conditional recommendation, very low quality evidence).
4. We recommend administering intravenous protamine sulfate to reverse heparin in the context of intracranial hemorrhage. (Strong recommendation, moderate quality evidence)
 - a) We recommend dosing protamine according to the dose of heparin infused over the preceding 2-3 hours. (Strong recommendation, high quality evidence)
 - b) We recommend dosing protamine sulfate at 1 mg for every 100 units of heparin given in the previous 2-3 hours with a maximum single dose of 50 mg. (Strong recommendation, moderate quality evidence)
 - c) If the aPTT remains elevated, we suggest repeat administration of protamine at a dose of 0.5 mg protamine per 100 units of UFH. (Conditional recommendation, low quality of evidence)

Protamine for LMWH reversal

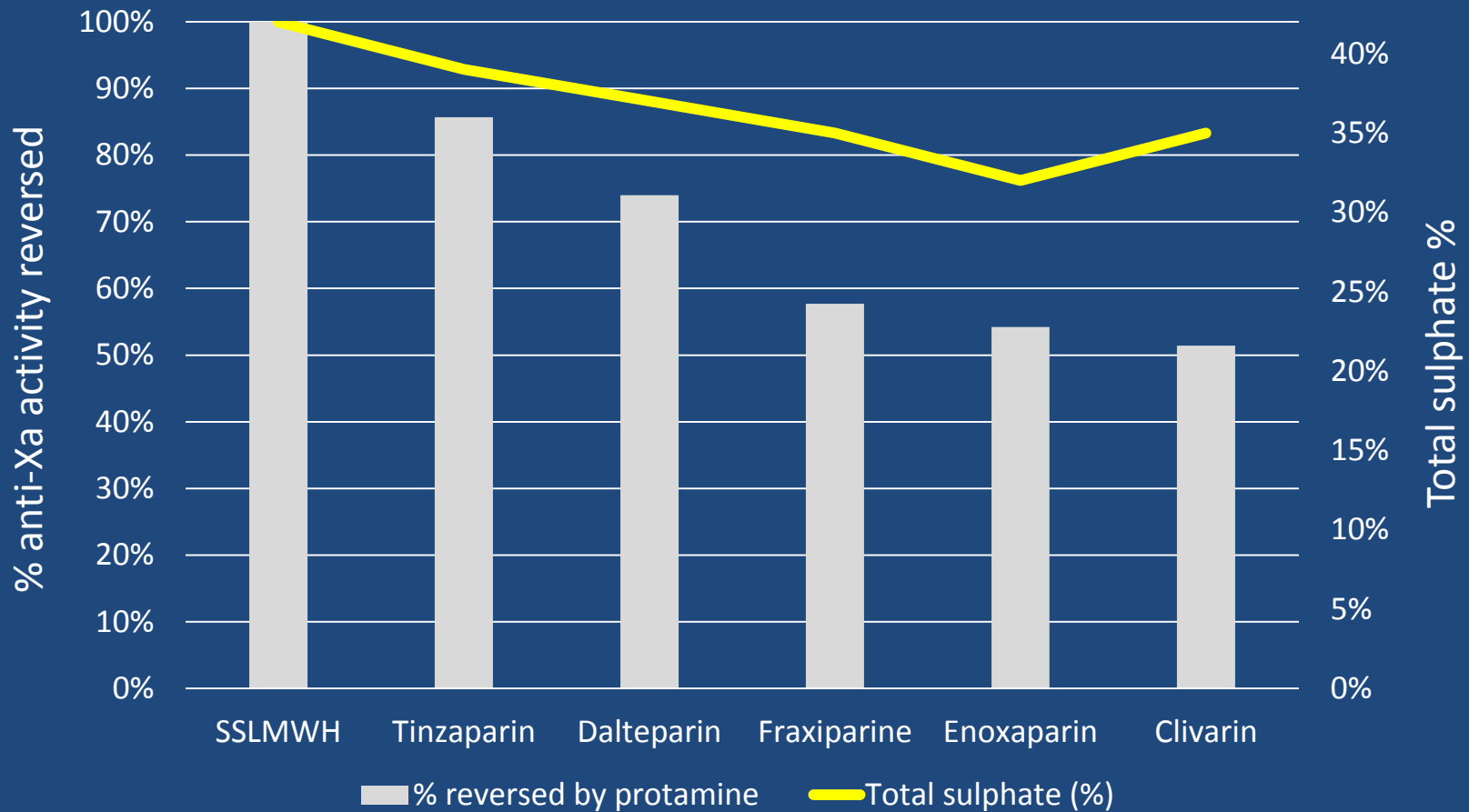
- Partially effective
 - Neutralizes anti-IIa activity (~64-99%)
 - Partially reverses anti-Xa activity (~35-40%)
- Some case series and reports suggest a reduction in bleeding despite lack of anti-Xa correction

Crowther MA, et al. British Journal of Haematology 2002; 116:178-86.

Gatt A, et al. Thromb Haemost 2008;100:350-55.

van veen JJ, et al. Blood Coagulation and Fibrinolysis 2011;22:565-70.

Protamine for LMWH reversal and sulphate content



LMWH reversal – other measures

- rFVIIa – if contraindication to protamine
 - Case reports/series, and ex vivo studies suggest it may be effective
- Hemodialysis
 - LMWHs accumulate in renal insufficiency
 - No data in the setting of bleeding/reversal
 - Removal dependent on PK/PD factors (i.e. MW)
- Andexanet alfa (investigational)
 - Partial reversal of LMWH and pentasaccharides

Young G, et al. Blood Coag & Fibrinolysis 2007;18:547-53.

Lu G, DeGuzman FR, Hollenbach SJ, et al. Nature medicine 2013;19:446-51.

Low Molecular Weight Heparin

1. We recommend discontinuing LMWH when intracranial hemorrhage is present or suspected. **(Strong recommendation, low quality evidence)**
2. We recommend reversing LMWH in patients with intracranial hemorrhage receiving therapeutic doses of LMWH. **(Strong recommendation, low quality evidence)**
 - a. We recommend protamine administration by slow intravenous injection over a period of about 10 minutes according to the following dosing:
 - i. For enoxaparin: If enoxaparin was given within 8 h, protamine sulfate should be administered at a dose of 1 mg per 1 mg of enoxaparin administered (up to a maximum single dose of 50 mg). If enoxaparin was given within 8-12 hours , a dose of 0.5 mg of protamine per 1 mg of enoxaparin should be administered. After 3-5 half-lives have expired protamine is probably not needed. **(Strong recommendation, moderate quality evidence)**
 - ii. For dalteparin, nadroparin and tinzaparin: Dose protamine at 1 mg per 100 anti-Xa units of LMWH administered in the past 3-5 half-lives of the drug, up to a maximum single dose of 50 mg 281. **(Strong recommendation, moderate quality evidence)**
 - iii. If life threatening bleeding persists, or the patient has renal insufficiency, we suggest re-dosing protamine (0.5 mg of protamine per 100 anti-Xa units or per 1 mg of enoxaparin). **(Conditional recommendation, very low quality evidence)**

Low Molecular Weight Heparin and Heparinoids

3. We suggest that laboratory monitoring guide administration of protamine sulfate in cases of renal insufficiency and extremes of age or weight. **(Conditional recommendation, low quality of evidence)**
4. We suggest considering recombinant Factor VIIa (90 mcg/kg IV) if protamine is contraindicated. **(Conditional recommendation, very low quality evidence)**
5. We recommend against the reversal of LMWH in patients with intracranial hemorrhage receiving prophylactic dosing of LMWH. **(Strong recommendation, very low quality evidence).**
6. We suggest against using FFP, PCC or aPCC to reverse LMWH. **(Conditional recommendation, moderate quality evidence)**
7. There is insufficient data to offer a recommendation on the use of hemodialysis to reverse LMWH **(no recommendation).**

Heparinoids (Danaparoid)

1. We recommend against reversing danaparoid with protamine.
(Strong recommendation, low quality evidence)
 2. We suggest reversing danaparoid with recombinant Factor VIIa (90 mcg/kg IV once) in the context of intracranial hemorrhage.
(Conditional recommendation, very low quality evidence)
- Glycosaminoglycan
 - MOA similar to LMWH, Xa:IIa ~ 25:1
 - Limited data and limited options
 - Ex vivo studies indicate PCC, FFP, and aPCC ineffective
 - rFVIIa increased ETP (~40%) and reduced anti-Xa activity (16%)
 - Potential role for andexanet alfa if approved

Pentasaccharide reversal agents

- Fondaparinux, Idraparinux
- Protamine ineffective
- In vitro study assessing rFVIIa, PCC, aPCC in healthy volunteers
 - PCC and rFVIIa – little to no effect on markers of thrombin generation
 - aPCC (20 IU/kg) normalized lab markers of coagulopathy
- Mixed results with rFVIIa

Pentasaccharides

1. We recommend discontinuing pentasaccharides when intracranial hemorrhage is present or suspected. (Strong recommendation, low quality evidence)
2. We recommend reversing pentasaccharides in patients with intracranial hemorrhage receiving full therapeutic doses. (Strong recommendation, low quality evidence)
 - a. We suggest administration of aPCC (20 IU/kg) for reversal of pentasaccharides. (Conditional recommendation, low quality evidence)
 - b. If aPCC is contraindicated or not available, we suggest administration of rFVIIa (90 mcg/kg). (Conditional recommendation, low quality evidence)
 - c. We recommend against protamine for reversal of pentasaccharides. (Strong recommendation, low quality evidence)
3. In intracranial hemorrhage patients receiving pentasaccharides for venous thromboembolism prophylaxis, we suggest against reversal unless there is evidence of bioaccumulation or impaired clearance. (Conditional recommendation, very low quality evidence)

Thrombolytics

- Mechanism
 - Alteplase, reteplase, tenecteplase - Binds to fibrin in a thrombus and converts the entrapped fibrin-bound plasminogen to plasmin initiating local fibrinolysis with limited systemic proteolysis.
 - Streptokinase/Urokinase – Binds equally to circulating and fibrin-bound plasminogen
- Thrombolytic-associated IPH occurs in 2-7% of ischemic stroke patients
 - Hematoma expansion (40%)
 - Mortality (9-61%) at 3 months

Matrat A, et al. Thrombosis Research 2013;131:e45-8. NINDS Stroke Study Group. NEJM 1995;333:1581-7.

Thrombolytics

- Retrospective analysis of prospectively collected data on 2362 stroke patients
- 21 of 311 patient receiving rt-PA had sICH (2 were IA therapy)
- 11 received treatment for coagulopathy (variety of agents employed)
- Continued bleeding (>33% increase in ICH volume) occurred in 40% of patients with follow-up scans (median time to re-scan 8.8 hrs).

Alteplase

- Pharmacokinetics

- Rapidly cleared from plasma on discontinuation

- an initial distribution phase half life ($t_{1/2\alpha}$) <5 min
- terminal elimination phase ($t_{1/2\beta}$) = 26-77 min.

- Pharmacodynamics

- 16-36% reduction in fibrinogen

- Severe reduction (<100mg/dL) in 11% of stroke patients
- Slowly corrects over 24 hours
- Associated with ↑ risk of IPH

- Antiplatelet effects ~ 12 hours

Matrat A, et al. Thrombosis Research 2013;131:e45-8. Mueller HS, et al. JACC 1987;10:479-90. Topol EJ, et al. JACC 1987;9:1205-13. Beer J, et al. J of Biol Chem 1989;264:17564-73.

Fibrinogen a marker of bleeding risk?

- 72 stroke patients treated with rt-PA
 - Lab measures at baseline, 2h, and 24h
- 6 of 72 (8.3%) had early parenchymal hematomas
 - 11 of 72 (15.3%) had early hemorrhagic infarcts
- Logistic regression adjusted for age, NIHSS, and diabetes:
 - Early fibrinogen degradation coagulopathy (Low fibrinogen, high FDP) at 2h increased odds of parenchymal hematoma
 - Reduction in fibrinogen (< 200 mg/dL) at 2 hrs multiplied the odds of early PH by 12

Agents for reversal of thrombolytics

- Cryoprecipitate
 - Fibrinogen, Factor VIII, fibronectin, Factor XIII, and von Willebrand Factor
 - Target Fibrinogen > 100mg/dL
- Antifibrinolytics
 - Bind to and inactivate plasmin and plasminogen, effectively preventing fibrinolysis
 - Aminocaproic acid, Tranexamic acid

Thrombolytics

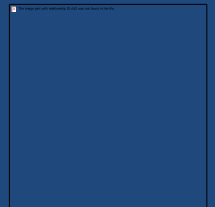
1. We recommend discontinuing thrombolytic agents when intracranial hemorrhage is present or suspected. (Strong recommendation, very low quality evidence)
2. We recommend using cryoprecipitate (10 units initial dose) in patients with thrombolytic agent-related symptomatic intracranial hemorrhage who have received a thrombolytic agent in the previous 24 hours. (Strong recommendation, very low quality evidence)
3. In cases where cryoprecipitate is contraindicated or not available in a timely manner, we suggest using an antifibrinolytic agent (tranexamic acid 10-15 mg/kg IV over 20 minutes or aminocaproic acid 4-5g IV) as an alternative to cryoprecipitate. (Conditional recommendation, very low quality evidence)
4. We suggest checking fibrinogen levels after administration of reversal agents. If fibrinogen is less than 100 mg/dL, we suggest administration of additional cryoprecipitate. (Conditional recommendation, very low quality evidence)
5. We suggest against reversing the action of plasminogen activators in small, asymptomatic hemorrhagic transformation of an ischemic stroke. (Conditional recommendation; very low quality evidence)
6. It is unclear if platelet transfusion is useful and we cannot offer a recommendation at this time.

Antiplatelet Reversal – Platelet transfusion

- Naidech et al: Single center uncontrolled study: platelet transfusion in ICH < 12 h associated with smaller follow-up ICH on CT and improved 3-month mRS
 - But 16% had adverse events related to transfusion
- Several studies failed to show impact of platelet transfusion on mortality, functional outcome or ICH growth
- Await results of PATCH (platelet transfusion in cerebral hemorrhage) trial
- Reasonable to consider in patients undergoing NSx

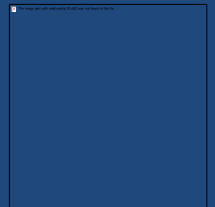
Antiplatelet reversal – Platelet transfusion

- 780 patients in China with BG hemorrhage requiring craniotomy, stratified into 5 groups:
 - a) 279 not receiving ASA
 - b) 135 ASA resistant or “semi-responsive”
 - c) 122 ASA sensitive – 2 dose of apheresis platelets
 - d) 122 ASA sensitive – 1 doses of apheresis platelets
 - e) 122 ASA sensitive – no platelets (control)



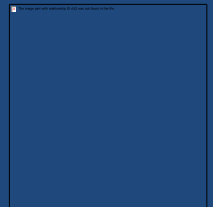
Antiplatelet reversal – Platelet transfusion

- Post-op hemorrhage, post-op ICH volume and mortality higher in ASA sensitive patients on ASA, as compared to ASA naïve (all $P < 0.005$)
- Less ICH recurrence (14% v 35%, $P = 0.02$) and smaller post-op ICH (35 v 57 ml, $P < 0.001$) in pts on ASA who got transfusion vs. no transfusion
- Reduced mortality (16% v 34%) and improved ADLs among ASA users who were transfused vs not.
- Limitation: surgery is not standard of care for BG bleeds, tells us nothing about non-surgical hemostasis, multiple comparisons without bonferonni correction



Antiplatelet Reversal - Desmopressin

- Increases endothelial display of factor VIII: vWF multimers
- Does not reverse antiplatelet effect but may improve hemostasis
- Naidech et al: 14 ICH patients with platelet inhibition received 0.4 mcg/kg DDAVP with improved platelet function and increased vWF levels
- 13 patients with intracranial hemorrhage on ASA with abnormal platelet function- DDAVP improved plt function within 30 min., but rebound effect in 3 h



Anti-platelets

1. We recommend discontinuing antiplatelet agents when intracranial hemorrhage is present or suspected. (Strong recommendation, very low quality evidence)
2. We recommend against platelet transfusion for patients with antiplatelet-associated intracranial hemorrhage who will not undergo a neurosurgical procedure, regardless of the type of platelet inhibitor, platelet function testing, hemorrhage volume, or neurological exam. (Strong recommendation, low quality evidence)
3. We suggest platelet transfusion for patients with aspirin- or ADP inhibitor- associated intracranial hemorrhage who will undergo a neurosurgical procedure. (Conditional recommendation, moderate quality of evidence)
 - a. We recommend platelet function testing prior to platelet transfusion if possible. (Strong recommendation, moderate quality evidence)
 - b. When platelet testing is not readily available, empiric platelet transfusion may be reasonable. (Conditional recommendation, low quality evidence)
 - c. We recommend against platelet transfusion for patients with laboratory documented platelet function within normal limits or documented antiplatelet resistance. (Strong recommendation, moderate quality evidence)

Anti-platelets

4. We suggest against platelet transfusion in NSAID or GP IIb/IIIa inhibitor related intracranial hemorrhage, even in the context of neurosurgical intervention. (Conditional recommendation, very low quality evidence)
5. In candidates for platelet transfusion we suggest an initial dose of one single donor apheresis unit of platelets. Platelet testing is suggested prior to repeat platelet transfusion. Repeat transfusion should be used only for those with persistently abnormal platelet function tests. (Conditional recommendation, moderate quality evidence)
6. We suggest consideration of a single dose of desmopressin (DDAVP) in antiplatelet-associated intracranial hemorrhage (0.4 mcg/kg IV). In patients deemed appropriate (e.g. those undergoing a neurosurgical procedure), DDAVP can be used in addition to platelet transfusion. (Conditional recommendation, low quality evidence)

ANTITHROMBOTIC	REVERSAL AGENT
Vitamin K Antagonists	If INR \geq 1.4: Vitamin K 10 mg IV + 4 or 3 factor PCC IV (dosing based on weight, INR and PCC type), OR FFP 10-15 ml/kg IV if PCC not available
Direct Factor Xa Inhibitors	Activated charcoal (50 g) within 2 h of ingestion, Activated PCC (FEIBA) 50 Units/kg IV OR 4 factor PCC 50 Units/kg IV
Direct Thrombin Inhibitors	Activated charcoal (50 g) within 2 h of ingestion, Activated PCC (FEIBA) 50 Units/kg IV OR 4 factor PCC 50 Units/kg IV Consider hemodialysis (dabigatran)
UFH	Protamine 1 mg IV for every 100 units of heparin administered in the previous 2-3 hours
Low Molecular Weight Heparins	Enoxaparin: Dosed within 8 hours: Protamine 1 mg IV per 1 mg enoxaparin (up to 50 mg in single dose). Dosed within 8-12 hours: Protamine 0.5 mg IV per 1 mg enoxaparin (up to 50 mg in single dose) Dalteparin, Nadroparin and Tizaparin: Dosed within 3-5 half-lives of LMWH: Protamine 1 mg IV per 100 anti-Xa units of LMWH (up to 50 mg in single dose) OR, rFVIIa 90 mcg/kg IV if protamine is contraindicated
Danaparoid	rFVIIa 90 mcg/kg IV
Pentasaccharides	Activated PCC (FEIBA) 20 Units/kg IV or rFVIIa 90 mcg/kg IV
Thrombolytic Agents	Cryoprecipitate 10 units IV OR Antifibrinolytics (tranexamic acid 10-15 mg/kg IV over 20 minutes or ϵ -aminocaproic acid 4-5g IV) if cryoprecipitate is contraindicated
Antiplatelet Agents	DDAVP 0.4 mcg/kg x 1, plus For Aspirin or ADP-receptor inhibitors: Platelet transfusion (one apheresis unit) if neurosurgical intervention

Thank you to the committee

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