WARFARIN REVERSAL GUIDELINE

SUMMARY

Warfarin (Coumadin®) is used to treat a number of hypercoagulable disease states. Since each patient responds differently to the same dose, this medication carries a high risk of bleeding. Some patients may ultimately require reversal with prothrombin complex concentrate (PCC), phytonadione (Vitamin K), fresh frozen plasma (FFP) or a combination of these agents. The Society of Critical Care Medicine (SCCM), the Neurocritical Care Society (NCS), the American College of Chest Physicians (ACCP), the American Heart Association (AHA), and the American College of Cardiology (ACC) have collaborated to produce several evidence-based medicine guidelines for the reversal of warfarin with PCC, FFP and/or Vitamin K.

RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **Four-factor PCC (4FPCC) should be administered to patients on warfarin with an INR ≥ 1.5 AND evidence of serious or life-threatening hemorrhage (Tables 1-3).**
    - **FEIBA NF 1000 units (one vial) IV over 15 minutes**
    - **Check INR 30 minutes after administration of FEIBA**
  - **Fresh Frozen Plasma (FFP) may be used for emergent reversal of elevated INRs if prothrombin complex concentrate (PCC) is not available.**
  - **Dosing of phytonadione (Vitamin K) should be based on the patient's current INR, risk of bleeding, and future need for anticoagulation (Tables 1-3).**
  - **Reversal of warfarin with Vitamin K should be reserved only for the most serious bleeding events or patients who will not be restarted on warfarin.**
  - **Vitamin K should be administered either orally or intravenously (IV) only.**
    - **Oral Vitamin K is the safest and most reliable route.**
    - **IV Vitamin K should be reserved for rapid reversal in serious bleeding events only.**
  - **Subcutaneous and intramuscular administration of Vitamin K should be avoided.**
- **Level 3**
  - **Initial dose of FFP based on risk of bleeding:**
    - **Low to moderate risk – FFP 2 units**
    - **High risk or active bleeding – FFP 4 units**
  - **INR should be rechecked 1 hour after administration of FFP.**
  - **Vitamin K should not be routinely administered to patients with prosthetic heart valves, only low doses (1mg) should be used if absolutely necessary.**

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

Approved 10/17/2006
Revised 08/31/2009, 01/03/2012, 11/29/17

INTRODUCTION

The use of vitamin K antagonists (e.g. warfarin) has been well described in the literature for the treatment of a number of different hypercoagulable states (1-6). However, use of this agent is associated with increased bleeding and poor outcomes in traumatically injured patients. In 2016, NCS and SCCM jointly released a guideline for anticoagulation reversal in intracranial hemorrhage (1). This guideline, combined with guidelines from AHA, ACCP, ACC and the *Institute for Safe Medicine Practices* (ISMP) provide the basis for the development of the recommendations for warfarin reversal for acute hemorrhage included in this guideline (1-6). These recommendations include the use of 4-factor prothrombin complex concentrate (4FPCC) (rather than fresh frozen plasma (FFP)) and vitamin K (phytonadione) and are summarized in the tables below (1-8). While the dose of vitamin K for specific clinical situations and/or INR levels is clearly defined in the guidelines, if FFP is chosen over 4FPCC, the dosing of FFP remains practitioner-dependent. The goal of this guideline is to provide guidance for the dosing of 4FPCC, vitamin K and FFP for the emergent reversal of elevated INRs.

Fresh Frozen Plasma (FFP)

The use of FFP for emergent reversal of elevated INRs in the presence of bleeding or high risk of bleeding has been well described in the literature. The appropriate dose of FFP to achieve the desired reversal of the INR has not, however, been clearly delineated.

Makris et al. conducted a prospective, observational study of 41 patients who required emergent reversal of their supratherapeutic INR. The patients were reversed with either FFP or clotting factor concentrates. Twelve patients received FFP. These patients had a mean pre-treatment INR of 10.2 and a post-treatment INR of 2.3. They received approximately 800 mL FFP (approximately 3 units). All patients were also given vitamin K 1-5 mg intravenously. The authors concluded that FFP was effective in lowering the INR through the replacement of Factors II, VII and X, but did not significantly change Factor IX. For this reason, they concluded that the use of clotting factor concentrates provides a greater overall reversal (9) (Class II).

Goldstein et al. conducted a retrospective chart review to evaluate the influence of time to FFP administration on the ability to correct elevated INR levels in patients admitted with warfarin-related intracranial hemorrhage. Sixty-nine patients were included in the analysis, 40% of which were on warfarin for atrial fibrillation. The patients baseline INR was > 2 in 88% of the patients. The patients received a mean of 4 units (range 2-6 units) of FFP to achieve reversal within the first 24 hours compared to a mean of 2 units (range 1-5 units) for patients requiring > 24 hours to achieve an INR < 1.5. Patients who achieved reversal of INR within the first 24 hours of hospitalization had a shorter time to administration of FFP (median 90 minutes versus 210 minutes, $p = 0.02$). However, there was no overall difference in mortality or Glasgow Outcome Scale score (10) (Class III).

Based on the information available, both time to administration (limited by thawing time) and dose of FFP play a role in rapid reversal of elevated INR levels. From the studies presented above, 3-4 units of FFP are needed to decrease an INR.

Vitamin K

Multiple articles as well as the practice guidelines set forth by the ACCP, AHA, ACC, NCS, and SCCM provide recommendations for dosing of vitamin K (1-4, 6) (Class I-II). The lowest possible dose should be used, especially in patients for whom re-anticoagulation will be necessary at a later date (5,6). Dosing of vitamin K is provided in Tables 1 and 2 below. Oral administration of vitamin K is preferred and provides the most predictable response to therapy (6,7-9). Intravenous vitamin K should be administered slowly (over at least 30 minutes) to avoid potential anaphylactic reactions (6-8). Subcutaneous and intramuscular administration of vitamin K should be avoided due to erratic absorption. Reversal of elevated INRs with vitamin K takes approximately 24 hours for maximum effect, regardless of the route of administration (5-9).

Approved 10/17/2006
Revised 08/31/2009, 01/03/2012, 11/29/17

Prosthetic-Valve Patients
The reversal of anticoagulation in patients with prosthetic heart valves remains an area of both controversy and clinical concern. No clear recommendations regarding dosing or administration of vitamin K are presently available.

Ageno et al. randomized 59 patients with mechanical heart valves and INR values between 6-12 to either vitamin K 1mg orally or no treatment. They found a quicker return to therapeutic INR levels (2.5-3.5, within 24 hours), but there was no difference in major bleeding events between the two groups (11) (Class III).

Prothrombin Complex Concentrates
Prothrombin complex concentrates (PCC) are derived from human plasma and contain the vitamin K-dependent coagulation factors II, VII, IX, and X at varying concentrations. Several guidelines, including NCS, SCCM, and ACCP now recommend 4FPCC for warfarin reversal in patients with serious bleeds (1,2,12-14). Although many countries have successfully utilized these products for years, the use of 4FPCC in the United States (US) has only recently become widespread, especially in the trauma and neurosurgical populations. In the US, there is one non-activated 4-Factor PCC product (n-4FPCC) which also includes Proteins C & S, (Kcentra®), specifically approved for warfarin reversal, A single prospective clinical trial demonstrated non-inferiority of n-4FPCC to FFP and shorter time to INR ≤ 1.3 compared to FFP (15). In addition to the n-4FPCC product, there is also an activated 4FPCC (a-4FPCC) product, factor VIII inhibitor bypassing activity (FEIBA NF). The majority of studies in the US utilizing 4FPCC are either prospective observational or retrospective studies.

Sarode et al. conducted a Phase IIIb prospective, randomized, open-label, plasma-controlled non-inferiority trial of n-4FPCC (PCC, Protein C, and Protein S) vs. FFP for warfarin reversal (INR ≥ 2) in patients with acute major bleeding. Exclusion criteria included expected survival of <3 days or surgery in < 1 day, acute trauma for which reversal of warfarin alone would not be expected to reverse or control the acute bleeding event and patients with intracranial hemorrhage (ICH). Patients received n-4FPCC 25-50 units/kg or FFP (10-15 units/kg) based on initial INR. Effective hemostasis was achieved in 72% of 4FPCC patients and 65.4% FFP patients (non-inferior). 62% of 4FPCC patients had INR ≤1.3 at the end of the infusion compared to 10% of FFP patients. There were similar numbers of adverse events in each group. 2 patients in each group developed thromboembolic events (TE); additional 1 FFP patient developed respiratory failure and 1 developed fluid overload (15) (Class II),.

Rivosecchi et al. conducted a retrospective study of 131 patients presenting with spontaneous or traumatic ICH requiring warfarin reversal with n-4FPCC. Patients received 24-26 units/kg n-4FPCC. Time between n-4FPCC and repeat INR was no different between groups. Patients with initial INR 1.4-1.9 were more likely to have repeat INR ≤ 1.3 (p=0.03). 87-93% of all patients had repeat INR ≤1.5. Three patients experience serious TE (VTE & MI, PEA arrest likely due to PE, and ischemic stroke) (16) (Class III).

Yanamadala et al. conducted a single-center prospective, observational study of all patients requiring coagulopathy reversal secondary to acute ICH. Patients were treated with either n-4FPCC or FFP per physician discretion. Five patients were treated with n-4FPCC; 3/5 achieved INR < 1.6 in ~30 minutes; 3/5 also received Vitamin K and 4/5 received FFP. Only one patient was treated with n-4FPCC only. The authors concluded that reversal was more rapid with n-4FPCC (17) (Class III).

Wojcik et al. performed a retrospective chart review on 141 patients with life-threatening bleeding in need of emergent warfarin reversal. 72 patients received FEIBA (500 units if INR<5 or 1000 units if INR>5) while 69 patients receiving FFP without FEIBA were used as controls. INR normalization was significantly better in the FEIBA group with 50.7% of the patients achieving an INR<1.4 compared with 33.7% in the FFP group (p=0.017). In addition, median time to INR normalization was significantly shorter in the FEIBA group at 2 hours versus 25.2 hours in the control group (p=.006). No difference was seen in survival between groups and FEIBA was well tolerated (18) (Class III).

Rowe et al. conducted a retrospective cohort analysis of warfarin reversal in patients with acute warfarin-associated hemorrhage treated with a-4FPCC (FEIBA) or FFP. Treatment selection was at the prescriber

discretion – patients received 500units of FEIBA if the initial INR < 5 and 1000units if the initial INR was ≥ 5. A total of 276 patients (128 FEIBA, 148 FFP) were evaluated. Patients in the FEIBA group had a higher initial INR (2.7±1.8 vs 2.3 ± 2.1, p=0.025) and were more likely to receive concurrent vitamin K (90% vs 75%, p=0.001). Patients in the FEIBA group achieved a lower post-treatment INR (1.2 ± 0.27 vs 1.5 ± 0.5, p<0.005). After controlling for multiple variables, administration of FEIBA remained an independent predictor for patients to achieve INR < 1.4 post-reversal. No new VTE events were noted in either group. Mortality was similar between groups (39% vs 35%, p=0.202) (19) (Class III).

Carothers et al. conducted a single-center retrospective chart review of all patients with traumatic intracranial hemorrhage requiring reversal of warfarin anticoagulation. They compared the percent of patients reversed with a-4FPCC vs FFP on time to reversal and efficacy of reversal to INR ≤ 1.4. The INR was reversed more effectively in the a-4FPCC group vs FFP, 90% vs 70% (p=0.029); median time to reversal was also significantly shorter at 3.75 hours vs 6.75 hours (p=0.003). There was no difference in mortality or incidence of thrombosis between groups (20) (Class III).

Administration of either 4FPCC product results in rapid INR reversal with greater consistency than FFP. Currently, there are no head-to-head studies comparing non-activated vs activated 4FPCC. With the limited data presently available, there does not appear to be a difference between the agents with respect to time to INR reversal and incidence of post-reversal VTE, Therefore, considering the cost of a-4FPCC is significantly less than n-4FPCC at ORMC, the Medical Executive Committee has chosen to utilize a-4FPCC at this time.

TABLE 1: Vitamin K Dosing for Elevated INRs OR BLEEDING in Patients on Warfarin (1-8)

Condition	Intervention
INR > goal but < 5 **No significant bleeding or risk of bleeding**	• Lower dose or omit next dose

INR ≥ 5 or < 9
AND
No significant bleeding or risk of bleeding
	• **Preferred:** Omit next 1-2 doses
	• Alternatively, omit 1-2 doses and give Vitamin K (1-2.5 mg po)
	• In patients with prosthetic heart valves/high-risk of thrombosis:
	  ○ Omit 1-2 doses
	  ○ FFP 2 units IV OR FEIBA 1000units IVPB x1 for fluid restricted patients
	  ○ DO NOT use Vitamin K

INR ≥ 9
No significant bleeding
AND/OR
Low-moderate risk of bleeding
	• Hold warfarin therapy
	• Give FFP 2 units IV
	• Give Vitamin K (2.5-5 mg po)
	• In patients with prosthetic heart valves/high-risk of thrombosis:
	  ○ FFP 2 units IV OR FEIBA 1000units IVPB x1 for fluid restricted patients
	  ○ Vitamin K 1-2.5 mg PO x 1

INR ≥ 1.5 AND
Serious OR
Life-threating bleeding
AND/OR
High risk of bleeding
	• Hold warfarin therapy.
	• Give FEIBA 1000units IVPB x 1 – repeat INR 30 minutes after dose
	• Vitamin K 10 mg IVPB x1 over 30 minutes
	• May repeat FEIBA and Vitamin K as needed
	• In patients with prosthetic heart valves/high-risk of thrombosis:
	  ○ FEIBA 1000 units IVPB x1
	  ○ Vitamin K **1 mg** IVPB x1 over 30minutes

INR = international normalized ratio FFP = fresh frozen plasma
FEIBA = anti-inhibitor coagulant complex (4-factor prothrombin complex concentrate)

Approved 10/17/2006
Revised 08/31/2009, 01/03/2012, 11/29/17

TABLE 2: Preoperative Management of Elevated (≥ 1.5 INRs) in Patients on Warfarin (1-8)

INR Value	Intervention		Repeat PT/INR
	Emergent Surgery or Procedure <u>OR</u> High-Risk for Clinical Deterioration	**Surgery or Procedure Scheduled in 24-48 hours**	
INR < 1.5	No intervention	No intervention	N/A
INR ≥ 1.5	*<u>No Prosthetic Heart Valve:</u>* FEIBA 1000 units IVPB x 1 over 15 min Vitamin K 10 mg IVPB x 1 over 30 min ***<u>Prosthetic</u>** <u>Heart Valve*:</u>* FEIBA 1000 units IVPB x 1 over 15 min Vitamin K **1 mg** IVPB x 1 over 30 min	*<u>No Prosthetic Heart Valve:</u>* INR ≥1.5-5: Vitamin K 2.5 mg PO INR >5: Vitamin K 10 mg PO ***<u>Prosthetic</u>** <u>Heart Valve*:</u>* INR ≥1.5-5: Vitamin K 1.25 mg PO INR >5: Vitamin K 5 mg PO	<u>INR 30min after FEIBA</u> <u>INR 12-24h after Vitamin K</u>

NOTE: High-dose Vitamin K <u>should not</u> routinely be given to patients with prosthetic heart valves
INR = international normalized ratio FFP = fresh frozen plasma

TABLE 3: Sample physician orders for administering Prothrombin Complex Concentrates (PCC)

<u>The patient must meet BOTH of the following criteria:</u>

- Documented traumatic brain injury (TBI) on CT scan with ICH (intracranial hemorrhage)
- INR ≥ 2 on warfarin therapy

☐ Discontinue warfarin
☐ Anti-inhibitor coagulant complex (FEIBA NF) 1000 units (or nearest single vial size) IV over 15 minutes x 1 STAT
☐ Fresh Frozen Plasma (FFP) Request STAT Banked 2 units *<u>Emergency Release</u>*
☐ Instructions: FFP Transfusion Give 2 units IV STAT x 1
☐ Phytonadione (Vitamin K) 10 mg IVPB in 50 mL of NS x 1 over 30 minutes STAT
☐ PT/INR STAT 30 minutes after FEIBA NF administered

Surgical Critical Care Evidence-Based Medicine Guidelines Committee

Primary Author: Kara Birrer, PharmD
Co-Authors: Brandon Hobbs, PharmD, Amanda Giancarelli, PharmD
Editor: Michael L. Cheatham, MD, Chadwick Smith, MD
Last revision date: November 29, 2017

Please direct any questions or concerns to: webmaster@surgicalcriticalcare.net

Approved 10/17/2006
Revised 08/31/2009, 01/03/2012, 11/29/17

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