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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 either phytonadione (Vitamin K), fresh frozen plasma (FFP) or both. The American College of Chest Physicians (ACCP), American Heart Association (AHA), and the American College of Cardiology (ACC) have developed evidence-based medicine guidelines for the reversal of warfarin with FFP and/or Vitamin K.

RECOMMENDATIONS

- **Level 1**
 - **Fresh Frozen Plasma (FFP) should be used for emergent reversal of elevated INRs.**

- **Level 2**
 - **Dosing of phytonadione (Vitamin K) should be based on the patient's current INR, risk of bleeding, and future need for anticoagulation (Tables 1 & 2).**
 - **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.**
 - **Prothrombin Complex Concentrate (PCC) should be administered to patients on warfarin with an INR >2 AND evidence of intracranial hemorrhage on CT scan (Table 3).**
 - **FEIBA NF 1000 units (one vial) IV push over 5 minutes**
 - **Check INR 30 minutes after administration**
 - **Vitamin K should not be administered to patients with prosthetic heart valves, only low doses (1mg) should be used if absolutely necessary.**

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 (1-5). However, use of this agent is associated with increased bleeding and poor outcomes in traumatically injured patients. The ACCP, AHA, and the ACC all collaborated on the development of recommendations for warfarin reversal for supratherapeutic INRs (1-5). These recommendations include the use of either fresh frozen plasma (FFP) and/or vitamin K

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.

(phytonadione) and are summarized in the tables below (1-7). While the dose of vitamin K for specific clinical situations and/or INR levels is clearly defined in the guidelines, the dosing of FFP remains practitioner-dependent. The goal of this guideline is to provide guidance for the dosing of both 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.

(Class II) Makris M, 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 1-5mg 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 (8).

(Class III) 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 (9)

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

(Class I-II) Multiple articles as well as the practice guidelines set forth by the ACCP, AHA, and the ACC provide recommendations for dosing of vitamin K (1-7). The lowest possible dose should be used, especially in patients for whom re-anticoagulation will be necessary at a later date (5-7). 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 (5). Intravenous vitamin K should be administered slowly (over at least 30 minutes) to avoid potential anaphylactic reactions (5). 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).

Factor VII

The use of recombinant Factor VIIa (rFVIIa) for rapid reversal of supra-therapeutic INRs remains controversial. There are questions related to assessment of efficacy through changes in the INR. There are also safety concerns due to the risk of thromboembolic events following treatment with rFVIIa (10). To date, there are currently no prospective, randomized controlled trials on the use of rFVIIa for traumatically injured patients on warfarin. The data is limited to one prospective, observational study, a retrospective study and a few case reports (11-14). There are also a few retrospective studies on the use of rFVIIa for warfarin reversal in patients with spontaneous intracranial hemorrhage (15).

(Class III) The use of rFVIIa is not without potential thromboembolic complications. O'Connell et.al. found 431 reports of adverse drug events related to rFVIIa over a five year period. Of these events, 185 events (in 168 patients) described thromboembolic complications including cerebrovascular events, myocardial infarctions, arterial thromboses, pulmonary embolism, other venous thromboembolism, and clotted

devices. The mortality rate in these patients was 30% (50/168). Thirty-six of the 50 deaths (72%) were attributed to the thromboembolic event (10)

(Class II) Dager et.al. conducted a prospective, observational study of 16 patients on pre-admission warfarin who were treated with rFVIIa. Each patient received rFVIIa 1.2mg IV (range 11-25 mcg/kg). Eleven of the 16 patients were either trauma (9 patients) or general surgery patients (2 patients). The mean initial INR = 2.8 ± 1.6 which was significantly reduced to a mean INR = 1.07 ± 0.27 post-rFVIIa ($p < 0.001$). Six of the 16 patients died (38%) primarily from multi-organ system failure. All patients received FFP (range 600-2400mL) either before, during, or after administration of rFVIIa. Ten of the 16 patients also received vitamin K (either 5 or 10mg doses given SQ, IM, or IV) (11)

(Class III) Ilyas et.al. conducted a retrospective review of patients receiving warfarin who sustained traumatic brain injuries. They evaluated 24 patients who received rFVIIa compared to 30 historical controls. Patients were treated with a range of rFVIIa doses (10-100 mcg/kg) in addition to a mean of 4 ± 3.2 units of FFP and 5-10mg of intravenous (IV) vitamin K. The control group patients received a mean of 7.7 ± 4.4 units of FFP plus IV vitamin K. There was a shorter time to INR correction in the rFVIIa group (2.4 ± 1.5 hours compared to 13.7 ± 15.6 hours). In this small sample, they detected a relationship between dose and duration of INR correction – larger doses provided longer duration. There was one instance of myocardial infarction related to the administration of rFVIIa (12)

(Class III) Yusim et.al. published a case series of three patients treated with rFVIIa following traumatic brain injury. One of these patients was a 79 year-old male on warfarin for atrial fibrillation. This patient received rFVIIa 34 mcg/kg IV pre-operatively instead of FFP or vitamin K. His admission INR = 6.8 and his post-administration INR = 1 (13).

(Class III) Stein et.al. conducted a retrospective study of 179 patients with relatively isolated traumatic brain injury (TBI) who were coagulopathic (INR ≥ 1.4) on admission – 111 in the No rFVIIa group and 69 in the rFVIIa group. Of these patients, 99 were on warfarin prior to admission (54 in the No rFVIIa group and 45 in the rFVIIa group, $p = 0.028$). Patients on warfarin were more likely to be admitted to the ICU ($p = 0.007$). For the 68 patients who received rFVIIa, 45 were on warfarin prior to admission (70%). There was no difference in mortality or thromboembolic complications between the two groups. Stein et.al. also demonstrated no significant difference in overall hospital charges between the two groups. This study is limited by its retrospective nature and the clear selection bias to administer to rFVIIa to more critically injured or higher risk patients (14).

(Class III) Brody et.al. retrospectively evaluated the use of rFVIIa for reversal of warfarin in patients with intracranial hemorrhages. Twenty-eight patients were enrolled in the study – thirteen in the FVIIa group (Group 1) and fifteen in the non-FVIIa group (Group 2). All patients were treated with vitamin K 10mg IV/SQ x 1 then 10mg SQ x 2 days as well as fresh frozen plasma (FFP). Group 1 had a shorter time to normalization of INR (INR ≤ 1.3) than Group 2 ($p = 0.016$) and a lower total volume of FFP administered (Group 1: 1272 ± 782 mL vs Group 2: 2044 ± 773 mL, $p = 0.022$). Although not statistically significant, Group 1 had higher mortality and lower Glasgow Coma Scale (GCS) score at discharge as compared to Group 2. This study was limited by its retrospective design, unequal groups (Group 1 had lower GCS on arrival as compared to Group 2), and the concomitant administration of vitamin K and FFP in both groups. There was two patients in Group 1 who developed thrombotic events and one patient in the Group 2 who developed respiratory distress during FFP administration (15).

In summary, the information available on the use of rFVIIa for the reversal of warfarin remains controversial. Based on the information available, low doses (such as 1 mg or 10-20 mcg/kg) provide the same amount of reversal of INR as larger doses. There may be a dose-duration relationship, with larger doses associated with a longer duration of correction. All patients received simultaneous treatment with FFP and vitamin K which confounds the results. None of the studies have demonstrated an improvement in morbidity or mortality and the issues related to thromboembolic events remain unresolved.

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 American College of Chest Physicians, now recommend PCC for warfarin reversal in patients with serious bleeds (1,16-18). Although many countries have successfully utilized these products for years, the use of PCC in the United States (US) is still not widespread, especially in the trauma population. The non-activated PCC products available in the US contain negligible amounts of Factor VII, which is the key clotting factor in trauma. These two products, Bebulin® and Profilnine®, are referred to as 3-factor products. In addition to the non-activated 3-factor PCC products there is also an activated PCC preparation, factor VIII inhibitor bypassing activity (FEIBA NF). Literature with the available US products consist of retrospective chart reviews without any prospective randomized controlled trials performed to date.

(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 (19).

(Class III) In 2011, Chapman et al published a retrospective chart review that included 31 trauma patients on warfarin with INR>1.5 on admission and received vitamin K, FFP, and/or PCC (Profilnine®). Of these 31 patients, 13 received PCC. The administration of reversal agents were prescribed at the discretion of the physician. The patients that received PCC had significantly higher ISS mean scores (17.8 vs 9.1; p<0.001) but no significant difference in initial INR (3.03 vs. 2.77; p=0.78). The PCC group had significantly shorter time to first INR<1.5 with a mean time of ~17 hours compared to ~30 hours in the patients that did not receive PCC (p=.048). No difference was seen in the percent of patients that received FFP (20).

(Class III) Safaoui et al retrospectively evaluated 28 patients with TBI and were treated with PCC (Profilnine®) for reversal of warfarin. The patients were divided into two groups based on the time to PCC administration (Group 1 < 1 hour; Group 2 > 1 hour). The median INR on admission for group 1 and group 2 were 3.1 and 3.8 with median INR after PCC administration of 1.6 and 1.2, respectively. For all patients the mean time to documented INR correction was 116 minutes (21).

(Class II) In 2011, a prospective multi-center cohort study was published which included 46 patients with intracranial hemorrhage (46% post-traumatic) and an INR >2. All patients received a dose of 3-factor PCC at 35-50 IU/kg within six hours of diagnosis along with 10mg of intravenous vitamin K. The median INR at admission was 3.5. The median INR 30 minutes post-PCC was 1.3 with 75% of patients achieving an INR <1.5. Although no patients were reported to have thromboembolic complications during the hospital stay, two patients suffered from thromboembolic events after discharge (22).

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.

(Class III) Ageno W, 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 (23).

TABLE 1: Vitamin K Dosing for Elevated INRs OR BLEEDING in Patients on Warfarin (1-7)

Condition	Intervention
INR > goal but < 5 No significant bleeding or risk of bleeding	<ul style="list-style-type: none"> • Lower dose or omit next dose
INR ≥ 5 or < 9 AND No significant bleeding or risk of bleeding	<ul style="list-style-type: none"> • Preferred: Omit next 1-2 doses • Alternatively, omit 1-2 doses and give Vitamin K (1-2.5 mg po) • Alternatively for patients at high risk of thrombosis (i.e. valves), omit 1-2 doses and use FFP 2 units IV – DO NOT use Vitamin K
INR ≥ 9 No significant bleeding AND/OR Low-moderate risk of bleeding	<ul style="list-style-type: none"> • Hold warfarin therapy • Give FFP 2 units IV • Give Vitamin K (2.5-5 mg po) • In patients with prosthetic heart valves, give FFP 2 units IV and lower dose of Vitamin K (1-2.5mg po)
Serious bleeding at any elevation of INR AND/OR High risk of bleeding	<ul style="list-style-type: none"> • Hold warfarin therapy. • Give FFP 4 units IV • Vitamin K 10mg by slow IV infusion • May repeat FFP and Vitamin K as needed • In patients with prosthetic heart valves, FFP is <i>preferred</i> over Vitamin K; use only very low doses of Vitamin K (1mg by slow IV infusion).
Life-threatening bleeding	<ul style="list-style-type: none"> • Hold warfarin therapy. • Give FFP 4 units IV • Vitamin K 10mg by slow IV infusion • Consider recombinant Factor VIIa for unresolved coagulopathy • Repeat FFP and Vitamin K as needed

INR = international normalized ratio

FFP = fresh frozen plasma

TABLE 2: Preoperative Management of Elevated (≥ 1.5 INRs) in Patients on Warfarin (1-7)

INR Value	Intervention	
	Urgent Surgery or Procedure	Surgery or Procedure Scheduled in 24-48 hours
INR ≥ 1.5 but ≤ 1.9	Treatment with FFP	Vitamin K 1mg PO
INR > 1.9 but ≤ 5 who require reversal for a procedure No significant bleeding	For rapid (< 12 hours) reversal: FFP + Vitamin K 1-3mg slow IV	Vitamin K 1-2.5mg PO If INR still elevated in 24h, repeat
INR > but < 9 who require surgery No significant bleeding	For rapid (< 12 hours) reversal: FFP + Vitamin K 2-5mg slow IV	Vitamin K 2.5-5mg PO If INR still elevated in 24h, give Vitamin K 1-2mg PO

***NOTE: High-dose Vitamin K should not 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)

The patient must meet BOTH of the following criteria:

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

- Discontinue warfarin
- Anti-inhibitor coagulant complex (FEIBA NF) 1000 units (or nearest single vial size) IV-push over 5 minutes x 1 STAT
- Fresh Frozen Plasma (FFP) Request STAT Banked 2 units Emergency Release
- Instructions: FFP Transfusion Give 2 units IV STAT x 1
- Phytonadione (Vitamin K) 10mg IVPB in 50 mL of NS x 1 over 30 minutes STAT
- PT/INR STAT 30 minutes after FEIBA NF administered

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