National Advisory Committee on Blood and Blood Products | Comité consultatif national sur le sang et les produits sanguins

Recommendations for use of Prothrombin Complex Concentrates in Canada

RECOMMENDATIONS FOR USE OF PROTHOMBIN COMPLEX CONCENTRATES IN CANADA

NAC Chair:	Alan Tinmouth, MD, FRCPC, MSc
Subcommittee Members:	Andrew Shih MD, Chair Susan Nahirniak, MD Katerina Pavenski, MD Oksana Prokopchuk-Gauk, MD Meer-Taher Shabani-Rad, MD Kathryn Webert, MD (*See full list of subcommittee members on Appendix A & B)*
Provincial Ministry Representative:	Thomas Smith (ON)
NAC Coordinator:	Harleen Kahlon

Date of Original Release:	**September 16, 2008**
Date of Last Revision	**May 16, 2014**
Publication Date:	**April 7, 2022**

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ASH	American Society of Hematology
DIC	Disseminated Intravascular Coagulation
DTI	Direct Thrombin Inhibitor
HIT	Heparin Induced Thrombocytopenia
INR	International Normalized Ratio
ISTH	International Society on Thrombosis and Haemostasis
IU	International Units
IV	Intravenous
NAC	National Advisory Committee on Blood and Blood Products
PCC	Prothrombin Complex Concentrate
VKA	Vitamin K Antagonist

SUMMARY OF REVISIONS

February 2022	Updated to reflect use to replace coagulation factors in special populations when frozen plasma is not available or the risk/benefit ratio of frozen plasma is unfavorable
	NAC Statement on Reversal of Direct Oral Anticoagulants (last revision: October 2018) assimilated into this document with further revisions to incorporate latest evidence
	Addition of suggested dosing regimen using weight and INR based on randomized clinical trials and suggested pediatric dosing based on observational evidence
	Addition that adverse reactions to PCCs require mandatory report as per the Protecting Canadians from Unsafe Drugs Act (Vanessa's Law)
	Updated references, added links to the NAC Statement on Fibrinogen Concentrate Use in Acquired Hypofibrinogenemia where applicable, and further detailed risks associated with PCCs
May 2014	Dosing recommendations and use of PCCs in elective situations revised
	Clarity improved around various recommendations
June 2011	Addition of Beriplex as a licensed product
	Incorporation of two national audits of Octaplex, leading to revision of dosing recommendations

BACKGROUND

The National Advisory Committee on Blood and Blood Products (NAC) is an interprovincial medical and technical advisory body to the provincial and territorial health ministries and the blood supplier Canadian Blood Services. Its mandate is to provide professional leadership in assisting and identifying, designing and implementing cost-effective blood utilization management initiatives for the optimization of patient care throughout Canada.

Currently available four-factor prothrombin complex concentrates (PCCs) are human plasma derived products that have undergone solvent/detergent treatment and/or nanofiltration for viral, bacterial and parasite inactivation and/or removal. They contain the vitamin K dependent procoagulant factors – II, VII, IX and X as well as the vitamin K dependent natural anticoagulant factors Protein C and Protein S, manufactured with added heparin. The two currently available PCCs (Beriplex®, Octaplex®) are considered interchangeable in practice.

In 2008, NAC was approached by Canadian Blood Services and the Provinces to develop recommendations for appropriate use of PCCs as they became available in Canada. That led to the "NAC Statement on Recommendations for Use of PCCs", which underwent revisions in 2011 and 2014. Due to new evidence and changes in practice that have occurred since the last revision, a working group was convened in 2021 to revise and update the recommendations. The "NAC Statement on Reversal of Direct Oral Anticoagulants" published in 2018 has also been assimilated into this document.

The working group continues to advocate for the use of this product under the oversight of transfusion medicine services, directed by expertise in thrombosis/hemostasis/transfusion medicine, informed by the evolving medical literature, and in settings with access to appropriate diagnostic and treatment facilities for the identification and management of potential complications.

These recommendations consider available literature, audit data and consensus opinion of the working group formed in 2021. Conflict of interest disclosures of the working group members are available on the NAC website (www.nacblood.ca).

INDICATIONS

Recommended Indications:

A. **Rapid reversal of oral vitamin K antagonists (VKAs, e.g. warfarin) or deficiency of vitamin K dependent coagulation factors in patients with major bleeding**
   - Major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) bleeding scale includes: 1. [potentially] fatal bleeding; 2. symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome; 3. bleeding causing a fall in hemoglobin ≥ 20 g/L or leading to transfusion ≥ 2 units of red blood cells.
   - Critical bleeding following injury or surgical intervention also appropriately qualifies as major bleeding in this context.

B. **Rapid reversal of VKAs (e.g. warfarin) or deficiency of vitamin K dependent coagulation factors in patients requiring urgent (< 6 hours) surgical or invasive procedures associated with a moderate to high risk of bleeding**
   - The half-life of PCCs as measured by their effect on the International Normalized Ratio (INR) is approximately 6 hours due to the short half-life of factor VII. Intravenous (IV) vitamin K begins to have an effect on the INR at approximately 6 hours. Therefore, PCCs and vitamin K should be given concurrently. See "Vitamin K for VKA Reversal" section below.
   - Note: Due to their rapid onset of action, PCCs should be administered immediately prior to a surgery or invasive procedure to prevent wastage if procedure times are delayed.

Contraindicated in:

A. Patients with a history of heparin induced thrombocytopenia (HIT)

Indications Where PCCs Are Generally Not Recommended:

A. **Reversal of VKA oral anticoagulant therapy prior to a planned (non-urgent) surgery or invasive procedure or an urgent procedure associated with a low risk of bleeding**
   - For planned (non-urgent) procedures requiring temporary interruption of anticoagulation, anticoagulants should be discontinued within a timeframe to ensure minimal residual anticoagulation at the time of surgery. Vitamin K may be used for patients receiving VKAs to ensure adequate hemostasis before the procedure.

B. **Treatment of elevated INRs without bleeding or need for surgical intervention**
   - American Society of Hematology (ASH) 2018 Clinical Practice Guidelines for Management of Anticoagulation Therapy suggest that INR values elevated beyond the therapeutic range in non-bleeding patients should not be treated with PCC. Vitamin K may be considered (recommendations are outside of the scope of this document).

C. Reversal of dabigatran and other direct thrombin inhibitors (DTI)

- Idarucizumab (Praxbind ™) is a specific and effective reversal agent for dabigatran and should be used for dabigatran-treated patients with major bleeding in whom clinically important residual dabigatran anticoagulant effect is documented with specific levels, or is clinically suspected based on routine coagulation tests, timing of last dabigatran dose (if known) and creatinine clearance. If idarucizumab is unavailable, activated PCCs (FEIBA; typically at 50 IU/kg; max 2000 IU) or PCCs (typically at 50 IU/kg; max 3000 IU), as non-specific hemostatic therapies, can be used for the treatment of dabigatran-associated severe or life-threatening bleeding.
- PCCs are also not recommended for any other non-dabigatran DTI-associated bleeding.

Special patient populations*:

**There may be extenuating clinical circumstances necessitating use of PCCs in these clinical situations. They should be evaluated on a case-by-case basis with a physician experienced in the use of PCCs.*

A. Treatment of bleeding in patients receiving direct factor Xa inhibitor anticoagulants – PCCs should only be considered in patients presenting with severe or life-threatening bleeding.

- Specific reversal agents for direct factor Xa inhibitors (including rivaroxaban, apixaban, and edoxaban), such as andexanet alfa, should be used, if available. At the time of writing, andexanet alfa is not currently approved by Health Canada.
- There are no randomized trials published as of writing, evaluating the efficacy and safety of PCCs for treatment of direct factor Xa inhibitor associated bleeding.
- The optimal dosing strategy is uncertain with 2000 IU (fixed dose) or 25-50 IU/kg (to a max 3000 IU) being the most commonly recommended dosing strategy.

Other considerations for treatment:

- Other adjunctive strategies include: holding medications that increase the risk of bleeding (e.g. antiplatelet agents), bleeding source control, and use of tranexamic acid (though tranexamic acid has not been studied in direct factor Xa inhibitor associated bleeding).
- Inappropriate approaches to treatment of direct factor Xa inhibitor associated bleeding which are not to be used include: frozen plasma administration, vitamin K (unless concomitant vitamin K deficiency/antagonist is present), and recombinant factor VIIa.
- In patients presenting for urgent surgery and/or an invasive procedure taking direct factor Xa inhibitor anticoagulants in whom clinically significant anticoagulant effect is suspected or demonstrated, if it is clinically appropriate to delay the surgery/procedure, then anticoagulants should be discontinued within an appropriate timeframe to ensure minimal residual anticoagulation.
    - If surgery cannot be delayed in an anticoagulated patient, consultation with expertise from thrombosis/hemostasis/transfusion medicine is strongly recommended to guide pre-procedural lab testing (including an anti-factor

Xa level, if available, prior to proceeding especially if the direct factor Xa inhibitor has not been held for an appropriate time frame) and bleeding management.
    - Although an elevated INR is suggestive of direct factor Xa inhibitor presence, it cannot be used as a quantitative measure for the degree of anticoagulation, or alone provide guidance for administration of PCCs for surgical and/or invasive procedures. The INR may also be normal in patients who are fully anticoagulated.
    - At the time of writing, there is limited data regarding the efficacy and safety of PCCs for management of factor Xa inhibitor treated patients requiring urgent surgery.
- NAC recommends that institutional/regional protocols be developed and implemented, including relevant laboratory testing and hemostatic management.

B. Use in bleeding/massive hemorrhage patients, when plasma is unavailable – Some smaller/remote health service providers may have challenges providing plasma in bleeding patients, given the lack of thawing devices or lack of stocking due to rarity of use.

- Lack of group AB universal donor plasma may preclude its availability for resuscitation.
- PCCs and fibrinogen concentrates can be substitutes for plasma where plasma is not readily available, based on limited data showing similar outcomes compared to plasma in viscoelastic point-of-care testing guided trauma resuscitation.
    - Dosing strategies are inconclusive: a standard dose of 2000 IU (or 25 IU/kg rounded up for pediatric patients) is suggested.
    - Fibrinogen replacement should be given concurrently with PCCs. Recommendations for fibrinogen replacement are addressed in the NAC Statement on Fibrinogen Concentrate Use in Acquired Hypofibrinogenemia.

C. For management of coagulopathy in clinical scenarios where the risk/benefit profile of plasma transfusion is deemed to be unfavourable – this primarily includes use of PCCs if plasma transfusion would not be tolerated due to fluid overload. Consider concomitant assessment of fibrinogen. Recommendations for fibrinogen replacement are addressed in the NAC Statement on Fibrinogen Concentrate Use in Acquired Hypofibrinogenemia.

D. Coagulopathy associated with liver dysfunction – PCCs may be used instead of plasma in this setting to prevent fluid overload, but evidence regarding efficacy and safety is limited to support this practice.

- INR is a poor marker of coagulation disturbances in liver disease, and is not clearly linked to bleeding outcomes.
- Several guidelines endorse not correcting the INR prior to low risk procedures.
    - Example: The Society for Interventional Radiology Guidelines revised in 2019 suggest for patients with chronic liver disease: low bleeding risk procedures - INR testing is not routinely recommended and for high

bleeding risk procedures - INR should be corrected to < 2.5.

- Use of PCCs in this setting may be associated with both thrombosis and disseminated intravascular coagulation (DIC).

E. **Pediatric patients –** retrospective studies of PCC use in pediatric patients did not demonstrate any signals of harm. However, there is only observational published evidence available informing a recommendation for dosing and/or use of these products in this patient population**.**

F. **Pregnant women –** there is insufficient published evidence available to allow a recommendation for use or dosing of PCCs in this patient population. Caution should be exercised if PCCs are used in pregnancy, particularly in the peripartum/early postpartum period because of propensity for thrombosis**.**

G. **Congenital factor II or X deficient patients –** use and dosing of these products should be at the discretion and direction of the local hemophilia/inherited bleeding disorders clinic**.**

H. **For replacement of coagulation factors if plasma transfusion is refused for religious or other reasons and patients are accepting human plasma-derived protein products –** informed consent and preferences for blood products must be established for all patients, where Jehovah's Witnesses and others may have individualized beliefs about the acceptability of blood products. If appropriate, consider concomitant assessment of fibrinogen. Recommendations for fibrinogen replacement are addressed in the NAC Statement on Fibrinogen Concentrate Use in Acquired Hypofibrinogenemia.

I. **Treatment of Coagulation Defects/Bleeding in Cardiac Surgery –** Stronger and higher-quality evidence is needed for NAC to recommend PCC use in this setting as standard of care.
    - Based on current practice, dosing strategies are variable if PCCs are used in this setting with 25-50 IU/kg being most commonly used. The lowest possible dose that achieves hemostasis should be utilized.
    - Consider concomitant assessment of fibrinogen. Recommendations for fibrinogen replacement are addressed in the NAC Statement on Fibrinogen Concentrate Use in Acquired Hypofibrinogenemia.
    - Activated PCCs (including FEIBA) are not recommended as a hemostatic adjunct; and are only to be used for hemophilia patients with inhibitors as per the product monograph (control of spontaneous bleeding episodes, surgical interventions, and/or routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children older than 6 years of age).

ADVERSE EVENTS AND RISKS

- PCC use may be associated with an increased risk of thrombosis and should be used with caution in patients with recent thrombotic events (i.e. venous thromboembolism, myocardial infarction, ischemic stroke, systemic embolism) and DIC.
    - Risks of thrombosis reported with PCC use in VKA reversal range from 1.4% to 4.2% across studies in systematic reviews.
    - The risk of thrombosis after VKA reversal with PCC has not been shown to be higher than after VKA reversal with plasma.
    - If the decision is to use the product off-label in patients with liver dysfunction and DIC, please consult the product monograph for further recommendations (e.g. the need for antithrombin levels or replacement).
- PCCs also contain heparin, which can lead to/or exacerbate HIT.
- Other reported reactions can be found in the product monograph, and may include formation of inhibitor antibodies for one or more of the factors, and anaphylactic reactions.

- The *Protecting Canadians from Unsafe Drugs Act* (Vanessa's Law) introduces amendments to the *Food and Drugs Act* that mandates reporting of serious adverse drug reactions. This act came into effect December 16th, 2019, applies to purified plasma protein products, and includes the reporting of serious anticoagulant-related bleeds by hospitals.
    - Serious adverse reactions include those that require in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is life-threatening, or results in death.
    - Regulations for mandatory reporting of serious adverse drug reactions apply to all hospital facilities. Any patient or staff member is eligible to submit a severe adverse drug reaction report. Facility/regional policies should be consulted to ensure reporting per local protocol as reporting is not explicitly in the domain of transfusion medicine services. For more information, please consult Health Canada.

DOSING, ADMINISTRATION & MONITORING

There is significant variability in the dosing used for PCCs across Canada and in the literature.

- The working group felt that there was insufficient published evidence to indicate one dosing regimen for VKAs as superior to another and recommends following local policy with monitoring for efficacy.
    - Some of the variability in practice and literature stems from different target INRs for various clinical indications and whether or not weight-based and/or INR-based dosing was deemed important by local clinical groups.
- The expert consensus recommendation is to target a local INR of 1.5 or less for VKA reversal.
    - This is based on the fact that an INR of 1.5 or less has evolved to be the standard of practice across Canada. However, no data clearly supports a relationship between the surrogate outcome of lowering the INR and reduced bleeding in this situation.

    - Normal hemostasis does not require 100% factor levels. Although the product monographs recommend correcting factor levels to normal, an INR of 1.5 is likely equivalent to vitamin-K dependent factor levels of at least 30-50% which are adequate for hemostasis.
- Single doses should not exceed 3000 IU.
- Adjustments may be required in some clinical situations, such as extremes of weight where lean body weight dosing is recommended.
- Repeat doses of PCCs can be considered for patients with ongoing bleeding and demonstrated or suspected persistent anticoagulant effect, in addition to maximum supportive measures and procedural interventions.
    - For VKAs, this should be guided by a repeat INR and the need to treat ongoing bleeding. The INR can be drawn for testing immediately after the product is administered.
    - For treatment of bleeding in patients receiving direct factor Xa inhibitor anticoagulant, this should be guided by the clinical scenario. Additional laboratory testing including specific drug level testing and/or viscoelastic hemostatic assays may be helpful, but should be done in consultation with expertise from thrombosis/hemostasis/transfusion medicine. Our expert group also suggests that local policy should define a maximum total dose given, such as a maximum of 50 IU/kg or 4000 IU in a 24-hour period.
- The treating clinical team must ensure its timely administration in bleeding patients, where protocolized management improves VKA reversal outcomes.

SAMPLE adult dosing schedules for VKA reversal (if appropriate local policy is not already established):

- The group highlighted that there was no clear consensus approach to dosing in prior working groups established to create and revise this document.
    - Observational studies largely have found different dosing strategies produce similar outcomes, though the evidence base is limited by small sample sizes and lack of methodological rigor.
- Health Canada has approved dosing regimens in the product monograph, though these are rarely used in clinical practice. Thus, the expert group provides recommendations below based on practice observed across Canada and based on clinical trial data, where available.
- **Current best practice reflected by guidelines state that transfusing plasma to reverse VKAs is inappropriate (except in patients with a history of HIT).**

Sample Dosing Option #1: Standardized single dose**:**

- Standardized single doses of 25 to 40 IU/kg have been reported in the literature.
- A single French multicentre randomized trial comparing 25 IU/kg with 40 IU/kg found rapid infusion of either dose achieved an INR of 1.5 or less in all adult patients.

Sample Dosing Option #2: INR based dosing:

- The expert working group recommends that if the INR is unknown, oral anticoagulant use is suspected, and major bleeding is present, 2000 IU (80 mL) of PCCs may be administered.
- A sample INR-based dosing strategy is outlined in the table below:

	PCC dose if INR 1.5 to < 3	**PCC dose if INR 3 to 5**	**PCC dose if INR > 5**
Dose	1000 IU (40 mL)	2000 IU (80 mL)	3000 IU (120 mL)

Sample Dosing Option #3: Dosing using both weight and INR**:**

- Randomized clinical trials of PCCs to reverse warfarin used the dosing strategy outlined below. Single doses should not exceed 3000 IU.

	PCC dose if INR 2 to < 4	**PCC dose if INR 4 to 6**	**PCC dose if INR > 6**
Dose	25 IU/kg	35 IU/kg	50 IU/kg

SAMPLE pediatric dosing schedules for VKA reversal (if appropriate local policy is not already established):

Dose by Weight (kg)	**PCC dose if INR < 3**	**PCC dose if INR > 3**
< 10	250 IU (10 mL)	500 IU (20 mL)
10-25	500 IU (20 mL)	750 IU (30 mL)
25-50	750 IU (30 mL)	1000 IU (40 mL)

Administration:

- Must be administered intravenously, where medications shall not be added directly to the administration set that contains a blood component or another product.
- Should be administered by slow IV infusion (for example: 1000 IU over 5 minutes); or as per product monograph.
    - Health Canada has approved adult infusion rate recommendations based on the product monograph, though observational literature and experience at Canadian hospitals suggest more rapid infusion rates (such as 1000 IU over 5 minutes) are safe.
- Preferentially should be infused through peripheral IV access. Caution should be exercised when infusing centrally and it is prudent to use product monograph recommended infusion rates when administered through a central line.

Vitamin K for VKA Reversal:

- The expert working group recommends IV Vitamin K administration for VKA reversal. When Vitamin K is used as an alternative, the injectable formulation, which can be given orally or intravenously, is preferred. Oral vitamin K has a slower onset of action than IV vitamin K. Intramuscular and subcutaneous routes of Vitamin K administration are not recommended.
- Clinicians should not be hesitant to prescribe IV vitamin K as it does not produce the inability to resume oral anticoagulation ("warfarin resistance") when used at appropriate doses. Further, if warfarin resistance is encountered in a rare patient, there are alternative anticoagulants that can be used.
- For patients receiving VKAs with INRs of >4.5 but <10 without clinically significant bleeding, the ASH Guidelines for Management of Venous Thromboembolism suggests using temporary cessation of VKAs alone without the addition of vitamin K.

Post dose monitoring in VKA Reversal:

Since dose effect is not universally applicable, efficacy of dosing in VKA reversal must be determined using the surrogate marker INR post PCC administration.

- If correction to an INR <1.5 has not been achieved and there is insufficient time to wait for Vitamin K to take effect, a subsequent dose of PCC guided by the post-infusion INR may be required if the patient continues to demonstrate clinical bleeding.

2022 REVISION REFERENCES & REVIEWED PAPERS

Brekelmans, M. P. A., Ginkel, K. V., Daams, J. G., Hutten, B. A., Middeldorp, S., & Coppens, M. (2017). Benefits and harms of 4-factor prothrombin complex concentrate for reversal of vitamin K antagonist associated bleeding: a systematic review and meta-analysis. J Thromb Thrombolysis, 44(1), 118-129. doi:10.1007/s11239-017-1506-0

Callum, J. L., Yeh, C. H., Petrosoniak, A., McVey, M. J., Cope, S., Thompson, T., . . . Pavenski, K. (2019). A regional massive hemorrhage protocol developed through a modified Delphi technique. CMAJ Open, 7(3), E546-E561. doi:10.9778/cmajo.20190042

Chai-Adisaksopha, C., Hillis, C., Siegal, D. M., Movilla, R., Heddle, N., Iorio, A., & Crowther, M. (2016). Prothrombin complex concentrates versus fresh frozen plasma for warfarin reversal. A systematic review and meta-analysis. Thromb Haemost, 116(5), 879-890. doi:10.1160/TH16-04-0266

Connolly, S. J., Crowther, M., Eikelboom, J. W., Gibson, C. M., Curnutte, J. T., Lawrence, J. H., . . . Investigators, A.-. (2019). Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med, 380(14), 1326-1335. doi:10.1056/NEJMoa1814051

Denas, G., Marzot, F., Offelli, P., Stendardo, A., Cucchini, U., Russo, R., . . . Pengo, V. (2009). Effectiveness and safety of a management protocol to correct over-anticoagulation with oral vitamin K: a retrospective study of 1,043 cases. J Thromb Thrombolysis, 27(3), 340-347. doi:10.1007/s11239-008-0211-4

Dentali, F., Marchesi, C., Giorgi Pierfranceschi, M., Crowther, M., Garcia, D., Hylek, E., . . . Ageno, W. (2011). Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. Thromb Haemost, 106(3), 429-438. doi:10.1160/TH11-01-0052

Dietrich, S. K., Rowe, S., Cocchio, C. A., Harmon, A. J., Nerenberg, S. F., & Blankenship, P. S. (2021). Comparison of 3 Different Prothrombin Complex Concentrate Regimens for Emergent Warfarin Reversal: PCCWaR Study. Ann Pharmacother, 55(8), 980-987. doi:10.1177/1060028020978568

Endres, K., St Bernard, R., Chin-Yee, I., Hsia, C., & Lazo-Langner, A. (2020). Efficacy and safety of four-factor prothrombin complex concentrate fixed, weight-based dosing for reversal of warfarin anticoagulation. Hematology, 25(1), 489-493. doi:10.1080/16078454.2020.1855745

Erdoes, G., Koster, A., Ortmann, E., Meesters, M. I., Bolliger, D., Baryshnikova, E., . . . Ravn, H. B. (2021). A European consensus statement on the use of four-factor prothrombin complex concentrate for cardiac and non-cardiac surgical patients. Anaesthesia, 76(3), 381-392. doi:10.1111/anae.15181

Fitzgerald, J., Lenihan, M., Callum, J., McCluskey, S. A., Srinivas, C., van Rensburg, A., & Karkouti, K. (2018). Use of prothrombin complex concentrate for management of coagulopathy after cardiac surgery: a propensity score matched comparison to plasma. Br J Anaesth, 120(5), 928-934. doi:10.1016/j.bja.2018.02.017

Goldstein, J. N., Refaai, M. A., Milling, T. J., Jr., Lewis, B., Goldberg-Alberts, R., Hug, B. A., & Sarode, R. (2015). 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. Lancet, 385(9982), 2077-2087. doi:10.1016/S0140-6736(14)61685-8

Gulati, G., Hevelow, M., George, M., Behling, E., & Siegel, J. (2011). International normalized ratio versus plasma levels of coagulation factors in patients on vitamin K antagonist therapy. Arch Pathol Lab Med, 135(4), 490-494. doi:10.1043/2009-0474-OA.1

10.5858/2009-0474-OA.1

Innerhofer, P., Fries, D., Mittermayr, M., Innerhofer, N., von Langen, D., Hell, T., . . . Oswald, E. (2017). Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. Lancet Haematol, 4(6), e258-e271. doi:10.1016/S2352-3026(17)30077-7

Keeling, D., Baglin, T., Tait, C., Watson, H., Perry, D., Baglin, C., . . . British Committee for Standards in, H. (2011). Guidelines on oral anticoagulation with warfarin - fourth edition. Br J Haematol, 154(3), 311-324. doi:10.1111/j.1365-

2141.2011.08753.x

Khorsand, N., Kooistra, H. A., van Hest, R. M., Veeger, N. J., & Meijer, K. (2015). A systematic review of prothrombin complex concentrate dosing strategies to reverse vitamin K antagonist therapy. Thromb Res, 135(1), 9-19. doi:10.1016/j.thromres.2014.11.019

Majeed, A., Agren, A., Holmstrom, M., Bruzelius, M., Chaireti, R., Odeberg, J., . . . Schulman, S. (2017). Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. Blood, 130(15), 1706-1712. doi:10.1182/blood-2017-05-782060

Majeed, A., Meijer, K., Larrazabal, R., Arnberg, F., Luijckx, G. J., Roberts, R. S., & Schulman, S. (2014). Mortality in vitamin K antagonist-related intracerebral bleeding treated with plasma or 4-factor prothrombin complex concentrate. Thromb Haemost, 111(2), 233-239. doi:10.1160/TH13-07-0536

Noga, T., Bruce, A. A., Blain, H., & Nahirniak, S. (2016). Four-factor prothrombin complex concentrates in paediatric patients - a retrospective case series. Vox Sang, 110(3), 253-257. doi:10.1111/vox.12353

Parry-Jones, A. (2015). Cutting delays in reversing anticoagulation after intracerebral haemorrhage: three key changes at a UK comprehensive stroke centre. BMJ Qual Improv Rep, 4(1). doi:10.1136/bmjquality.u208763.w3521

Patel, I. J., Rahim, S., Davidson, J. C., Hanks, S. E., Tam, A. L., Walker, T. G., . . . Weinberg, I. (2019). Society of Interventional Radiology Consensus Guidelines for the Periprocedural Management of Thrombotic and Bleeding Risk in Patients Undergoing Percutaneous Image-Guided Interventions-Part II: Recommendations: Endorsed by the Canadian Association for Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe. J Vasc Interv Radiol, 30(8), 1168-1184 e1161. doi:10.1016/j.jvir.2019.04.017

Piran, S., Khatib, R., Schulman, S., Majeed, A., Holbrook, A., Witt, D. M., . . . Nieuwlaat, R. (2019). Management of direct factor Xa inhibitor-related major bleeding with prothrombin complex concentrate: a meta-analysis. Blood Adv, 3(2), 158-167. doi:10.1182/bloodadvances.2018024133

Roman, M., Biancari, F., Ahmed, A. B., Agarwal, S., Hadjinikolaou, L., Al-Sarraf, A., . . . Mariscalco, G. (2019). Prothrombin Complex Concentrate in Cardiac Surgery: A Systematic Review and Meta-Analysis. Ann Thorac Surg, 107(4), 1275-1283. doi:10.1016/j.athoracsur.2018.10.013

Sarode, R., Milling, T. J., Jr., Refaai, M. A., Mangione, A., Schneider, A., Durn, B. L., & Goldstein, J. N. (2013). 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, 128(11), 1234-1243. doi:10.1161/CIRCULATIONAHA.113.002283

Schochl, H., Nienaber, U., Hofer, G., Voelckel, W., Jambor, C., Scharbert, G., . . . Solomon, C. (2010). Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. Crit Care, 14(2), R55. doi:10.1186/cc8948

Schochl, H., Nienaber, U., Maegele, M., Hochleitner, G., Primavesi, F., Steitz, B., . . . Solomon, C. (2011). Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. Crit Care, 15(2), R83. doi:10.1186/cc10078

Shih, A. W., & Crowther, M. A. (2016). Reversal of direct oral anticoagulants: a practical approach. Hematology Am Soc Hematol Educ Program, 2016(1), 612-619. doi:10.1182/asheducation-2016.1.612

Sisti, D. J., Williams, G. D., Ding, V., Long, J., Maeda, K., Chen, S., & Navaratnam, M. (2020). The use of prothrombin complex concentrate as a warfarin reversal agent in pediatric patients undergoing orthotopic heart transplantation. Paediatr Anaesth, 30(5), 564-570. doi:10.1111/pan.13839

Steiner, T., Poli, S., Griebe, M., Husing, J., Hajda, J., Freiberger, A., . . . Veltkamp, R. (2016). Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. Lancet Neurol, 15(6), 566-573. doi:10.1016/S1474-4422(16)00110-1

Tai, C., Wu, H., San, C., & Chua, D. (2017). Management of Supratherapeutic International Normalized Ratio without Bleeding after Warfarin Use: An Evaluation of Vitamin K Administration (SUPRA-WAR-K Study). Can J Hosp Pharm,

70(3), 207-214. doi:10.4212/cjhp.v70i3.1660

Thrombosis Canada. (2020). NOACs/DOACs: Management of Bleeding. Retrieved from https://thrombosiscanada.ca/wp-uploads/uploads/2021/01/23.-NOACs-DOACs-Management-Bleeding_01August2020.pdf

Velik-Salchner, C., Tauber, H., Rastner, V., Pajk, W., Mittermayr, M., Wally, D., . . . Streif, W. (2021). Administration of fibrinogen concentrate combined with prothrombin complex maintains hemostasis in children undergoing congenital heart repair (a long-term propensity score-matched study). Acta Anaesthesiol Scand. doi:10.1111/aas.13945

Vitt, J. R., Do, L. V., Shah, N. H., Fong, G., Nguyen, N. Y., & Kim, A. S. (2018). Before-After Study of an Electronic Order Set for Reversal of Vitamin K Antagonist-Associated Intracerebral Hemorrhage. Neurohospitalist, 8(1), 18-23. doi:10.1177/1941874417714706

Witt, D. M., Nieuwlaat, R., Clark, N. P., Ansell, J., Holbrook, A., Skov, J., . . . Guyatt, G. (2018). American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv, 2(22), 3257-3291. doi:10.1182/bloodadvances.2018024893

ORIGINAL REFERENCES & REVIEWED PAPERS

octaplex® & Beriplex® P/N product monographs.

Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008 Jun; 133 (6 Suppl): 160S-198S.

Baglin TP, Keeling DM, Watson HG.Guidelines on oral anticoagulation (warfarin)- 3rd edition. British Committee for Standards in Hematology. *Brit Journal of Haematol* 2006; 132: 277-85

Benzon HT, Avram MJ, Benzon HA, Kirby-Nolan M, Nader A. Factor VII Levels and International Normalized Ratios in the early phase of warfarin therapy. Anesthesiology 2010; 112: 298-304.

Colomina MJ, Díez Lobo A, Garutti I, Gómez-Luque A, et al. Perioperative use of prothrombin complex concentrates. *Minerva Anestesiol* .2012; 78: 358-68.

Dentali F, Ageno W, Crowther M. Treatment of coumarin-associated coagulopathy: a systemic review and proposed treatment algorithms. *J Thromb Haemost* 2006; 4: 1853-63.

Desmettre T, Dehours E, Samama CM, Jhundoo S, Pujeau F, Guillaudin C, Hecquart C, Clerson P, Crave JC, Jaussaud R. Reversal of Vitamin K Antagonist (VKA) effect in patients with severe bleeding: a French multicenter observational study (Octiplex) assessing the use of Prothrombin complex Concentrate in current clinical practice. Crit Care 2012 Oct 4; 16(5): R185 epub (http://ccforum.com/content/16/5/R185)

Dezee Kj, Shimeall WT, Douglas KM, Shyumway NM, O'Malley PG. Treatment of excessive anticoagulation with phytonadione (vitamin K): A meta analysis. *Arch Intern Med* 2006 ; 166: 391-7.

Dowlatshahi D, Wasserman JK, Butcher KS, Bernbaum ML Cwinn AA, Giulivi A, Lang E, Poon MC, Tomchishen-Pope J,SharmaM, Coutts SB. Stroke Prenotification Is Associated with ShorterTreatment Times for Warfarin-Associated Intracerebral Hemorrhage. *Cerebrovasc Dis* 2013;36:383–387

Fuentes-García D, Hernández-Palazón J, Sansano-Sánchez T, Acosta-Villegas F. Prothrombin Complex Concentrate in the treatment of multitransfusion dilutional coagulopathy in a paediatric patient. *Br. J. Anaesth*. (2011) 106 (6):912-913.

Gatt A, Ridell A, van Veen JJ, Kitchen S, Tuddenham EG, Makris M. Optimizing warfarin reversal – an ex vivo study. . *J Thromb Haemost* 2009; 7: 1123-27.

Gulati G, Hevelow M, George M, Behling E, Siegel J. International Normalized Ratio Versus Plasma Levels of Coagulation Factors in Patients on Vitamin K Antagonist Therapy. Arch Pathol Lab Med. 2011; 135(April): 490-494.

Hickey M, Gatien M, Taljaard, Aujnarain A, Giulivi A, Perry JJ. Outcomes of Urgent Warfarin Reversal Using Fresh Frozen Plasma versus Prothrombin Concentrate in the Emergency Department. *Circ* 2013 June epub (http://circ.ahajournals.org/content/early/2013/06/14/CIRCULATIONAHA.113.001875).

Kerebel D, Joly LM, Honnart D, Schmidt J, Galanaud D, Negrier C, Kursten F, Coriat P and LEX 206 investigator group. A French multicenter randomized trial comparing two dose regimens of Prothrombin Complex Concentrates in urgent anticoagulation reversal. *Crit Care* 2013 Jan 10;17(1):R4 (epub http://ccforum.com/content/17/1/R4 .)

Khorsand N, Veeger NJ, van Hest RM, Ypma PF, Heidt J, Meijer K. An observational prospective two cohort comparison of a fixed versus variable dosing strategy of prothrombin complex concentrate to counteract vitamin K antagonists in 240 bleeding emergencies. *Haematologica* 2012 Oct 97(10):1501-6

Khorsand N, Veeger NJ, Muller M, Overdiek JW, Huisman W, van Hest RM, Meijer K. Fixed versus variable dose of prothrombin complex concentrate for counteracting vitamin K antagonist therapy. *Transfus Med* 2011 Apr; 21(2): 116-23.

Liumbruno G, Bennardello F, Lattanzio A, Piccoli P, Rossettias G. Recommendations for the use of antithrombin concentrates and prothrombin complex concentrates. *Blood Transfus* 2009; 7: 325-34.

Lubetsky A, Hoffman r, Zimlichman, R, Eldor, A, Zvi J, Kostenko V, Brenner B. Efficacy and Safety of a prothrombin complex concentrate (octaplex®) for rapid reversal of oral anticoagulation. *Thromb Res* 2004; 113: 371-8.

Pernod G, Godier A, Gozalo C, Tremey B, Sie P . French clinical practice guidelines on the management of patients on vitamin K antagonists in at-risk situations. *Thromb Res* 2010; 126: e167-74.

Pindur G, Morsdorf S. The use of prothrombin complex concentrates in the treatment of hemorrhages induced by oral anticoagulation. *Thromb Res* 1999; 95:s57-261.

Schick KS, Fertmann JM, Jauch KW, Hoffmann JN. Prothrombin complex concentrate in surgical patients: retrospective evaluation of vitamin K antagonist reversal and treatment of severe bleeding. *Crit Care* 2009; 13(6): R191.

Schulman S. Care of patients receiving long-term anticoagulant therapy. N Engl J Med 2003; 349: 675-83.

Sorensen B, Spahn DR, Innerhofer P, Spannagl M, Rossaint R. Clinical review: prothrombin complex concentrates – evaluation of safety and thrombogenecity. *Crit Care* 2011; 15: 201

Tran HA, Chunilal SD, Harper PL, Tran H, Wood EM, Gallus AS. Australasian Society of Thrombosis and Haemostasis (ASTH). An update of consensus guidelines for warfarin reversal. MJA; 2013; 198(4): 1-7. doi: 10.5694/mja12.10614

Van Aart L, Eijkhout HW, Kamphuis JS, Dam M, Schattenkerk ME, Schouten TJ, et al. Individualized dosing regimen for prothrombin complex concentrate more effective than standard treatment in the reversal of oral anticoagulant therapy: an open prospective randomized controlled trial. *Thromb Res* 2006; 118: 313-20.

van der Meer FJM, Rosendaal FR, Vandenbroucke JP, Briet E. Bleeding complications in oral anticoagulant therapy. *Arch Intern Med* 1993; 153: 1557-62

Warkentin TE, Schulman S, Crowther M. Department of Medicine, Hematology and Thromboembolism. McMaster University. Clinical Protocols (and Reversals): Prothrombin Complex Concentrates. http://fhs.mcmaster.ca/medicine/hematology/anticoag_octoplex.htm

Wozniak M. Kruit A. Padmore R. Giulivi A. Bormanis J. Prothrombin complex concentrate for the urgent reversal of warfarin. Assessment of a standard dosing protocol. *TransfAph Sci.* 2012; 46(3):309-14.

Yasaka M, Sakata T, Naritomi H, Minematsu K. Optimal dose of prothrombin complex concentrate for acute reversal of oral anticoagulation. *Thromb Res* 2005; 115: 455-9.

APPENDIX A:

NAC PCC Working Group Members for 2022 Revision	
Member	Title
NAC Members	
Susan Nahirniak	NAC Alberta Representative
Katerina Pavenski	NAC Ontario Representative
Oksana Prokopchuk-Gauk	Previous NAC Chair (2019-21), Saskatchewan Representative
Meer-Taher Shabani-Rad	NAC Alberta Representative
Andrew Shih	NAC PCC Working Group 2022 Revision Chair, NAC Vice-Chair, British Columbia Representative
Alan Tinmouth	NAC Chair, Ontario Representative
Kathryn Webert	Canadian Blood Services
Medical Society Representatives	
Andrew Beckett	Trauma Association of Canada Representative
Emilie Belley-Cote	Canadian Cardiovascular Society Representative
Dariush Dowlatshahi	Canadian Neurological Sciences Foundation Representative
Rita Selby	Thrombosis Canada Representative
Ashkan Shoamanesh	Canadian Neurological Sciences Foundation Representative
Deborah Siegal	Thrombosis Canada Representative
Summer Syed	Canadian Anesthesiologists' Society Representative
External Experts	
Mark Belletrutti	Hematologist
Jeannie Callum	Hematologist
Mark Crowther	Hematologist
Jennifer Duncan	Hematopathologist
David Evans	Trauma Surgeon
Keyvan Karkouti	Anesthesiologist
Blaine Kent	Anesthesiologist
Yulia Lin	Hematologist
Brian Muirhead	Anesthesiologist
Man-Chiu Poon	Hematologist
Matthew Yan	Canadian Blood Services
Special Thanks	
Naima Kotadia	Anesthesiologist, assisted in updated warfarin literature search
Rony Skaff	NAC Coordinator (PEI Term, 2019-21)

APPENDIX B:

Original NAC PCC Working Group Members	
Dr. Susan Nahirniak	NAC Initiative Lead / Working Group Chair
Dr. Nalin Ahluwalia	Canadian Association of Emergency Physicians
Dr. Brian Berry	Clinical Pathologist
Dr. Mark Crowther	Hematologist
Dr. Dana Devine	Canadian Blood Services
Dr. Dariush Dolwatshahi	Neurologist
Dr. Antonio Giulivi	Hematologist
Dr. Michael Hill	Canadian Neurosciences Federation
Dr. Vincent Laroche	NAC Quebéc Representative
Dr. Yulia Lin	Hematologist / Transfusion Medicine
Dr. Katerina Pavenski	NAC Ontario Representative
Dr. Man-Chiu Poon	Clinical Hematologist / Hemophilia
Dr. Lakshmi Rajappannair	NAC Chair
Dr. Bruce Ritchie	Clinical Hematologist / Hemophilia
Dr. Irene Sadek	NAC Nova Scotia representative
Ms. Rosemary Tanzini	Pharmacist
Mr. Rick Trifunov	Canadian Blood Services
Dr. Kathryn Webert	Canadian Blood Services
Dr. Lucinda Whitman	NAC Newfoundland and Labrador representative / Past NAC Chair