Anaesthesia 2021, 76, 381–392 doi:10.1111/anae.15181

Guidelines

A European consensus statement on the use of four-factor prothrombin complex concentrate for cardiac and non-cardiac surgical patients

G. Erdoes,[1] **A. Koster**,[2] **E. Ortmann**,[3] **M. I. Meesters**,[4] **D. Bolliger**,[5] **E. Baryshnikova**,[6] **B. Martinez Lopez De Arroyabe**,[7] **A. Ahmed**,[8,9] **M. D. Lance**,[10] **M. Ranucci**,[11] **C. von Heymann**,[12] **S. Agarwal**[13] and **H. B. Ravn**[14]

1 Professor, Department of Anaesthesiology and Pain Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland
2 Associate Lecturer, Institute for Anaesthesiology, Heart and Diabetes Centre NRW, Ruhr-University Bochum, Bad Oeynhausen, Germany
3 Consultant, Department of Anaesthesia, Kerckhoff Heart and Lung Centre, Bad Nauheim, Germany
4 Consultant, Department of Anaesthesiology, University Medical Centre Utrecht, The Netherlands
5 Professor, Department of Anaesthesia, Prehospital Emergency Medicine, and Pain Therapy, University Hospital Basel, Switzerland
6 Research Associate, 11 Professor, Department of Cardiovascular Anaesthesia and Intensive Care Unit, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy
7 Consultant, Department of Cardiac Anaesthesia and Intensive Care, Ca`Foncello Hospital of Treviso, Treviso, Italy
8 Honorary Associate Professor, Department of Anaesthesia, University Hospitals of Leicester NHS Trust, 9 Department of Cardiovascular Sciences, University of Leicester, UK
10 Professor, Hamad Medical Corporation, HMC, Anaesthesiology, ICU and Peri-operative Medicine, Doha, Qatar
12 Professor, Department of Anaesthesia, Intensive Care Medicine, Emergency Medicine and Pain Therapy, Vivantes Klinikum im Friedrichshain, Berlin, Germany
13 Honorary Senior Lecturer, Department of Anaesthesia, Manchester University Hospitals, Manchester, UK
14 Professor, Department of Cardiothoracic Anaesthesiology, Rigshospitalet, Copenhagen University, Copenhagen, Denmark

Summary

Modern four-factor prothrombin complex concentrate was designed originally for rapid targeted replacement of the coagulation factors II, VII, IX and X. Dosing strategies for the approved indication of vitamin K antagonist-related bleeding vary greatly. They include INR and bodyweight-related protocols as well as fixed dose regimens. Particularly in the massively bleeding trauma and cardiac surgery patient, four-factor prothrombin complex concentrate is used increasingly for haemostatic resuscitation. Members of the Transfusion and Haemostasis Subcommittee of the European Association of Cardiothoracic Anaesthesiology performed a systematic literature review on four-factor prothrombin complex concentrate. The available evidence has been summarised for dosing, efficacy, drug safety and monitoring strategies in different scenarios. Whereas there is evidence for the efficacy of four-factor prothrombin concentrate for a variety of bleeding scenarios, convincing safety data are clearly missing. In the massively bleeding patient with coagulopathy, our group recommends the administration of an initial bolus of 25 IU.kg^{-1}. This applies for: the acute reversal of vitamin K antagonist therapy; haemostatic resuscitation, particularly in trauma; and the reversal of direct oral anticoagulants when no specific antidote is available. In patients with a high risk for thromboembolic complications, e.g. cardiac surgery, the administration of an initial half-dose bolus (12.5 IU.kg^{-1}) should be considered. A second bolus may be indicated if coagulopathy and microvascular bleeding persists and other reasons for bleeding are largely ruled

out. Tissue-factor-activated, factor VII-dependent and heparin insensitive point-of-care tests may be used for peri-operative monitoring and guiding of prothrombin complex concentrate therapy.

Correspondence to: G. Erdoes
Email: gabor.erdoes@insel.ch
Accepted: 12 June 2020
Keywords: cardiac surgery; dosing; efficacy; monitoring; non-cardiac surgery; prothrombin complex concentrate; safety; trauma; vitamin K antagonist therapy
Twitter: @GErdoes;@SeemaMosca

Recommendations

1 In patients taking vitamin K antagonist therapy undergoing cardiac or non-cardiac surgery, the pre-operative INR should be determined.
2 For patients requiring urgent cardiac or non-cardiac surgery, and for which coagulation is affected by vitamin K antagonist therapy, reversal with four-factor prothrombin complex concentrate should be considered. In the severely bleeding patient, an initial bolus of 25 IU.kg^{-1} is recommended. In patients with a high thromboembolic risk, a stepwise approach with an initial half-dose bolus of 12.5 IU.kg^{-1} should be considered. The indication for additional doses should depend on clinical and laboratory assessment of haemostatic efficacy.
3 In patients without actual vitamin K antagonist therapy, but with coagulopathy and severe bleeding, haemostatic resuscitation with four-factor prothrombin complex concentrate may be considered. An initial bolus of 25 IU.kg^{-1}, in combination with fresh frozen plasma, appears to be effective. This applies particularly for trauma patients. In patients with an increased risk for thromboembolism, such as in cardiac surgery, a stepwise approach with an initial half-dose bolus of 12.5 IU.kg^{-1} followed by a second dose, if microvascular bleeding persists, is a rational risk-adjusted strategy.
4 In patients taking direct oral anticoagulants undergoing emergency surgery, four-factor prothrombin complex concentrate with a dose of 2000 IU (approximately 25 IU.kg^{-1}) is a rescue therapy, when a specific antidote is not available.
5 Tissue-factor-activated, coagulation factor VII-dependent and heparin-insensitive viscoelastic assays may be used to guide therapy and point-of-care monitoring of four-factor prothrombin complex concentrate effect in the peri-operative setting.

Why was this consensus developed?

There is growing use of modern four-factor prothrombin complex concentrates in a variety of clinical scenarios. However, the evidence from prospective controlled randomised studies is limited. Most studies focus on drug efficacy; however, dosing strategies vary significantly. Drug safety is a major concern when employing these highly potent haemostatic agents. Additionally, particularly in the peri-operative setting, reliable point-of-care monitoring needs to be defined.

How does this consensus statement differ from other available guidelines?

This consensus statement summarises data on the use of modern four-factor prothrombin complex concentrate in different clinical scenarios. This includes bleeding due to: vitamin K antagonist therapy; coagulopathy; trauma; and major surgery, such as cardiac surgery. The definition of risk-adjusted dosing strategies is a key aim of this statement.

What other guideline statements are available on this topic?

The European Society of Anaesthesiology published a guideline on the management of severe peri-operative bleeding in 2013, which was updated in 2016 [1, 2]. The European Society of Cardiothoracic Surgery and the European Association of Cardiothoracic Anaesthesiology published a guideline on patient blood management in cardiac surgery in 2018 [3]. Other recent statements are based on systematic reviews and meta-analyses: Cochrane

2015 [4]; Levy et al. 2019 [5]; and Roman et al. 2019 [6]. These guidelines and recommendations do not specifically address the special indications and dosing of four-factor prothrombin concentrates in cardiac and non-cardiac surgical patients. The important aspect of point-of-care monitoring in the peri-operative setting has also not been sufficiently addressed.

Introduction

Lyophilised prothrombin complex concentrates were among the first commercially available coagulation factor concentrates introduced in the early 1970s [7]. Indications were: haemophilia; factor X deficiency; bleeding due to vitamin K antagonists; severe chronic liver impairment; haemorrhagic disease in neonates; and bleeding in the context of cardiac surgery [8]. Due to the initial indication of replacement of coagulation factor IX in patients suffering from haemophilia B, the concentration of factor IX in the vial determines the $IU.ml^{-1}$ declared as activity in the different types of the prothrombin complex concentrates. The content of the other coagulation factors can vary significantly among the different preparations.

Early reports about thromboembolic events following prothrombin complex concentrate administration were attributed to remnants of activated coagulation factors. To reduce related risk, a Task Force of the International Society of Thrombosis and Haemostasis recommended the addition of heparin to prothrombin complex concentrate preparations in 1975 [9]. Accordingly, most current preparations contain heparin and antithrombin. This should be considered in patients with heparin intolerance, particularly in heparin-induced thrombocytopenia. In the early 1980s, the development of coagulation factor concentrates advanced following an increase in donor-related viral infections with allogeneic blood products, often affecting patients with haemophilia. Various methods of virus inactivation were implemented in the production process of prothrombin complex concentrate, and highly purified single factor concentrates and recombinant preparations of factors VIII, IX and VIIa became commercially available replacing prothrombin complex concentrates for the treatment of haemophilia.

Further development of modern four-factor prothrombin complex concentrates – which contain factor II, IX, X and VII (VII is not contained in three-factor prothrombin complex concentrate) – focused on urgent vitamin K antagonist reversal in the bleeding patient. In the mid-1980s, the vitamin K-dependent antithrombotic proteins C and S were added to balance the haemostatic and antithrombotic effects [10]. Interestingly, despite four decades of extensive use of prothrombin complex concentrate in Europe and the availability of considerable pharmacovigilance information, efficacy and safety data from large randomised controlled trials have not emerged [11]. In 2011, one randomised controlled trial compared two dosing regimens for prothrombin complex concentrate [12].

An early meta-analysis exclusively included non-randomised observational studies on prothrombin complex concentrate-associated thromboembolic complications for vitamin K antagonist reversal in the absence of randomised controlled trials [13]. The situation changed with the approval of four-factor prothrombin complex concentrate in the US. Two randomised controlled trials were conducted to evaluate efficacy and safety of prothrombin complex concentrates compared with FFP for urgent vitamin K antagonist reversal in adults with acute severe bleeding [14, 15]. Apart from the possibility of blood group incompatible transfusion and transfusion-related acute circulatory overload, other side effects of FFP, even when incidences are very low, should be considered. Reported random effect pooled average rates are 12 for febrile non-haemolytic transfusion reactions, 1.8 for transfusion-related lung injury and 0.8 for anaphylaxis per 100,000 units transfused [16]. Concurrently, prothrombin complex concentrate was promoted as a component of the first-line strategy to replace coagulation factors in cardiac surgery and in severe trauma [17]. The arguments were obvious: rapid reconstitution of prothrombin complex concentrate and an immediate effect due to the transfusion of small volumes. However, in cardiac surgery, the use of prothrombin complex concentrate became overshadowed by reports of catastrophic thromboembolic events [18–21].

This consensus paper aims to provide a comprehensive review of the available efficacy and safety data on four-factor prothrombin complex concentrate for cardiac and non-cardiac surgery. In addition, laboratory and point-of-care monitoring tools are discussed and dosing protocols are reviewed for different clinical scenarios.

Methods

The authors are members of the Scientific Subcommittee for Haemostasis and Transfusion in the European Association of Cardiothoracic Anaesthesiology. The scope of this consensus document had been agreed upon by all authors. All subtopics were allocated to an individual author and subsequently re-evaluated by the entire group.

A systematic literature search was performed in October 2019 in the PubMed database using the text word

'prothrombin complex concentrate'. The resulting 1051 publications were screened manually by two authors and relevant papers were categorised. The full texts were made accessible on an electronic platform for all authors. Core topics of the consensus statement were determined by discussions in the group and consensus was achieved if at least two-thirds of the authors agreed. Items that did not achieve consensus in the first round were either discussed in two additional rounds or rephrased until a consensus could be reached. All authors agreed on the core topics and literature inclusion criteria. Core topics included prothrombin complex concentrate use in: cardiac surgery with vitamin K antagonist therapy; cardiac surgery with no vitamin K antagonist therapy; non-cardiac surgery with vitamin K antagonist therapy; non-cardiac surgery without vitamin K antagonist therapy; prothrombin complex concentrate safety in cardiac surgery; prothrombin complex concentrate safety in non-cardiac surgery; and prothrombin complex concentrate for reversal of direct oral anticoagulants. Papers were eligible if studies were: published after 31 December 1999; randomised controlled or, non-randomised with more than 99 patients; with an active comparator to prothrombin complex concentrate; and without the use of factor eight inhibitor bypassing agent. Sections were written by subcommittee members, who did not have any conflicts of interest relating to the specific subtopic.

Vitamin K antagonist reversal

Traditionally, the optimal dose and dosing regimens of modern four-factor prothrombin complex concentrate are based on the manufacturers' recommendations using the INR and bodyweight, aiming for normalisation of the INR. Even before United States Food and Drugs Administration approval, no dose-finding studies had been performed and dosing recommendations in national guidelines vary largely. Authors of recent systematic reviews could not perform a meta-analysis due to heterogeneity [22, 23]. Current dose regimens based on randomised controlled trials assessing four-factor prothrombin complex concentrate efficacy are displayed in Table 1.

Data from one open prospective randomised controlled trial (n = 93), assessing the effectiveness of a 500 IU fixed dose of a four-factor prothrombin complex concentrate [24], are available. The authors compared an ultra-low fixed dose regimen with a variable-dosing strategy based on patient bodyweight, baseline INR and target INR in patients requiring vitamin K antagonist reversal due to major bleeding or for an urgent invasive procedure. A target INR either ≤ 2.1 or ≤ 1.5 was decided in each patient based on bleeding severity or type of surgical procedure. A significantly lower proportion of patients in the fixed-dose group achieved the target INR as compared with patients receiving variable dosing (43% vs. 89%, $p < 0.001$). An even lower proportion of patients achieved the target INR in the sub-group with a baseline INR ≥ 4.5 (23% vs. 81%). Consequently, 43% of patients in the fixed-dose group required a second prothrombin complex concentrate dose compared with only 6% of patients in the variable-dosing group. Another multicentre phase III open label randomised controlled trial assessed the effect of two dosages (25 IU.kg^{-1} and 40 IU.kg^{-1}) of a four-factor

Table 1 Published randomised controlled studies assessing the efficacy of four-factor prothrombin complex concentrate.

Author	Type of trial	Field	Intervention	Number of patients	Dose used.	Endpoints
Demeyere et al. [29]	Single-centre; open-label	Cardiac surgery	PCC vs. FFP	20 for PCC and 20 for FFP.	1500 IU for PCC and 2 U for FFP.	International normalised ratio ≤ 1.5
Kerebel et al. [25]	Multicentre; open-label	Non-surgery	Two different doses of four-factor PCC	29 for PCC and 30 for FFP.	25 IU.kg^{-1} for PCC and 40 ml.kg^{-1} for FFP.	INR 10 min after end of drug infusion
Sarode et al. [14]	Multicentre; open-label	Non-surgery	Four-factor PCC vs. FFP	98 for PCC and 104 for FFP.	25-50 IU.kg^{-1} for PCC and 10-15 ml.kg^{-1} for FFP.	Haemostatic efficacy and INR < 1.3 after 30 min
Goldstein et al. [15]	Multicentre; open-label	Surgery/ intervention	Four-factor PCC vs. FFP	90 for PCC and 91 for FFP.	25-35 IU.kg^{-1} for PCC and 10-12 ml.kg^{-1} for FFP.	---
Steiner et al. [39]	Multicentre; open-label	Neurology	Four-factor PCC vs. FFP	28 for PCC and 26 for FFP.	30 IU.kg^{-1} for PCC and 20 ml.kg^{-1} for FFP.	INR < 1.2 after 3 h

PCC, prothrombin complex concentrate; FFP, fresh frozen plasma; IU, international units; U, units.

prothrombin complex concentrate in 59 patients with vitamin K antagonist-related intracranial haemorrhage [25]. Both dosages reduced the INR to less than 1.5, whereas an INR of less than 1.2 was achieved in 44% of patients in the 25 IU.kg^{-1} group, and 70% of patients in the 40 IU.kg^{-1} group. No differences in clinical efficacy and safety outcomes were found.

A large prospective observational multicentre study (n = 686) assessed the use of a four-factor prothrombin complex concentrate in 33 hospitals [26]. According to French National Health Authority guidelines for vitamin K antagonist-related bleeding, dependent on availability of INR measurement, prothrombin complex concentrate was given with a dose of 25 IU.kg^{-1} or individualised according to INR and bodyweight. A mean prothrombin complex concentrate dose of 25 IU.kg^{-1} achieved an INR $\leq$ 1.5 in 78% of the patients, irrespective of the initial INR. Similar results were obtained in a retrospective review of four-factor prothrombin complex concentrate administration (n = 114) in a level-1 trauma, tertiary care facility [27] and in an observational study (n = 106) in phenprocoumon-treated patients receiving vitamin K antagonist reversal [28]. The analyses suggest that total bodyweight and initial INR do not have a significant linear relationship with prothrombin complex concentrate dose and INR after reversal. The variable success rate with prothrombin complex concentrate reversal probably reflects variation in initial INR level, dosing regimens and target INR. Not surprisingly, the lowest dosing regimen gave the lowest success rate in a study by Demeyere et al. [29], where patients received 8-18 IU.kg^{-1} and only 44% had reached the target INR < 1.5 after 15 min. However, the median (IQR) INR was 1.6 (1.2-2.2), which seems acceptable in the setting of cardiac surgery.

Only one randomised controlled trial (n = 40) has evaluated four-factor prothrombin complex concentrate vs. FFP for vitamin K antagonist reversal in the cardiac surgery setting [29]. Four-factor prothrombin complex concentrate reversed vitamin K antagonist faster and more effectively with respect to lowering the INR. Patients admitted for heart transplantation when bridged on a durable ventricular assist device, have a high risk of bleeding associated with continued vitamin K antagonist therapy and other factors (e.g. prolonged cardiopulmonary bypass or hypothermia). Also, those patients have a higher risk of massive transfusion with volume overload potentially causing right ventricular failure. Therefore, concentrated preparations for targeted replacement of coagulation factors and for 'haemostatic resuscitation' became of particular interest. After the more recent introduction of the four-factor prothrombin complex concentrate in the USA, many publications reflect its emerging use in this circumstance. However, only non-prospective and non-randomised studies, for example, comparison with historical controls or pre- and post-introduction of four-factor prothrombin complex concentrate into clinical practice, are available [30–34]. Viewing the inherent limitation of patient numbers for this special indication, no statistical tools for risk adjustment were used. Moreover, a lack of homogeneity among studies regarding timing and dosing of the prothrombin complex concentrate precludes any meta-analysis. However, data with modern four-factor prothrombin complex concentrate quite universally demonstrate a reduced need for red blood cell transfusion in comparison with FFP [30–33]. A similar trend towards an increased use of a four-factor prothrombin complex concentrate can be observed in patients undergoing implantation of a durable left ventricular assist device or major urgent surgery following implantation [35–37]. However, safety data are conflicting, as series with no thromboembolic complications [36] are contrasted to a concerning high frequency of events [38].

Outside cardiac surgery, two phase-IIIb multicentre open-label non-inferiority randomised controlled trials assessed the efficacy of four-factor prothrombin complex concentrate for vitamin K antagonist reversal vs. FFP. Dosing regimen was based on initial INR, bodyweight and a targeted INR $\leq$ 1.3. In the first trial (n = 202), haemostatic efficacy was achieved in 72% of patients in the prothrombin complex concentrate group vs. 65% in the FFP group showing non-inferiority of prothrombin complex concentrate (difference 7%, 95%CI −5.8−19.9%) [14]. Rapid reduction of INR $\leq$ 1.3 at 30 min after the end of infusion was achieved in 62% of patients in the prothrombin complex concentrate group and 9% in the FFP group, showing superiority of prothrombin complex concentrate (difference 53%, 95%CI 39.4−65.9%). In the second trial (n = 168), effective haemostasis was achieved in 90% of patients in the prothrombin complex concentrate group and 75% in the FFP group (difference 14%, 95%CI 2.8–25.8%) [15]. Rapid reduction of INR $\leq$ 1.3 at 30 min after the end of infusion was achieved in 55% in the prothrombin complex concentrate and 10% in the FFP group (difference 45%, 95%CI 31.9–56.4%). Both end-points demonstrated non-inferiority and superiority of prothrombin complex concentrate over FFP. In a multicentre, open-label randomised controlled trial (n = 50), a fixed dose of 30 IU.kg^{-1} four-factor prothrombin complex concentrate was compared with FFP in patients with intracranial haemorrhage during vitamin K antagonist therapy [39]. In the prothrombin complex concentrate group, 67% and in

the FFP group, 9% of patients reached the primary endpoint of an INR ≤ 1.2 within 3 h (adjusted OR 31, 95%CI 4.7−197, p < 0.001).

Two tertiary emergency care departments reported data of a 'before and after' retrospective cohort study (n = 314) of patients who received a four-factor prothrombin complex concentrate compared with FFP for vitamin K antagonist reversal [40]. Prothrombin complex concentrate administration was associated with a median (IQR) time-reduction to achieve the targeted INR from 12 (8.3−17.5) to 6 (3.4−11.0) h, p < 0.001, and a reduced mean (SD) transfusion rate of red blood cells from 3 (1.8) to 1 (1.7) units, p < 0.001. In an observational multicentre study (n = 135) with vitamin K antagonist-associated intracranial haemorrhage, patients received a four-factor prothrombin complex concentrate with a median dose of 22.5 IU.kg^{-1} or four units of FFP [41]. In the risk-adjusted analysis, there was no significant difference in the primary endpoint of 30-day mortality (OR 0.49, 95%CI 0.19-1.24, p = 0.130).

Haemostatic resuscitation in massively bleeding patients

The efficacy of four-factor prothrombin complex concentrate in cardiac surgery patients who are not taking vitamin K antagonist therapy has not yet been assessed in randomised controlled trials. In a systematic review and meta-analysis, four retrospective studies were identified [6]. As outlined by the authors, significant risk of bias within these studies prevented firm conclusions, in particular selection, attrition and reporting bias. All four studies could only be included for 2 of 10 pooled outcomes. In total, 861 patients received four-factor prothrombin complex concentrate (in differing doses, between 15 and 25 IU.kg^{-1}, alone or in combination with FFP) or standard therapy with FFP. Most patients underwent coronary artery bypass grafting and/or valve surgery. A single study included only patients undergoing pulmonary artery endarterectomy. In two of the studies, transfusion was performed according to an algorithm, based on measurement of INR or thromboelastometry parameters. In the remaining two studies, transfusion was based on a clinical decision made by the clinical team. Fresh frozen plasma-treated patients had an increased risk of receiving red blood cells (OR 2.22, 95%CI 1.45–3.40). However, there was no difference in re-exploration rates for bleeding (OR 1.09; 95%CI 0.66–1.82). Hospital mortality (OR 0.94; 95%CI 0.59–1.49) was comparable between the groups.

In another cohort analysis of 7118 consecutive patients operated in 15 centres, 416 patients received FFP and 119 received prothrombin complex concentrate with or without FFP [42]. Treatment algorithms varied largely between the institutions. Regression analyses with mixed effects adapted for several covariates and participating centres showed that the use of prothrombin complex concentrate was associated with a significantly lower risk of red blood cell (67% vs. 87%) and platelet (12% vs. 45%) transfusion. However, the prothrombin complex concentrate cohort received cryoprecipitate (3% vs. 1%) and fibrinogen concentrate (40% vs. 22%) more frequently. A single study compared the use of 45 mg.kg^{-1} recombinant activated factor VII (n = 73) with a four-factor prothrombin complex concentrate strategy (n = 56) using 25 IU.kg^{-1} as a haemostatic rescue therapy in severely bleeding patients [43]. There was no difference in the primary outcome of 24-h chest tube drainage.

We could not identify any prospective randomised trials assessing the use of four-factor prothrombin concentrate in non-cardiac surgery patients outside vitamin K antagonist reversal. Most available data are derived from trauma patients. In an observational study of 120 trauma patients who were not taking anticoagulants, two groups (prothrombin complex concentrate with FFP and FFP only) were propensity matched for baseline characteristics, physiological and injury parameters, and initial-INR. International normalised ratio normalisation to < 1.5 was faster (373 min vs. 955 min, p < 0.001) and fewer allogeneic blood products were required when 25 IU.kg^{-1} four-factor prothrombin complex concentrate had been administered [44]. From the American College of Surgeons-Trauma Quality Improvement Programme database, the same authors retrieved data of over 500,000 patients from 110 trauma centres and propensity matched 234 patients who received prothrombin complex concentrate and FFP with 234 patients who only received FFP [45]. Prothrombin complex concentrate patients required fewer transfusions of red blood cells and FFP and mortality was lower (17% vs. 28%, p < 0.001).

Patients undergoing orthotropic liver transplantation frequently require transfusion of blood products and/or factor concentrate to correct pre-existing and developing coagulopathy. A retrospective analysis of liver transplant patients, from a single-centre, compared 39 patients treated with four-factor prothrombin complex concentrate with 78 propensity-matched patients who had not received prothrombin complex concentrate. There was no difference in the use of other blood products, apart from fibrinogen concentrate, which was given to significantly more patients

in the prothrombin complex concentrate group (84% vs. 3%, $p < 0.001$) [46].

Safety

In the cardiac surgery setting, only one randomised controlled trial has investigated the use of four-factor prothrombin complex concentrate for vitamin K antagonist reversal. However, the number of patients included was low (n = 40), the evaluation of safety data was not defined prospectively, and follow-up was not properly characterised. This significantly impairs the conclusion reached that prothrombin complex concentrate and FFP had comparable outcomes regarding safety [29]. Data from retrospective studies are limited to patients undergoing heart transplantation during vitamin K antagonist therapy. However, safety endpoints were among secondary outcomes and in view of the limited scope, no statistical corrections have been used for risk adjustment. Four larger observational studies reported safety data for the use of four-factor prothrombin complex concentrate for the treatment of bleeding/coagulopathy [42, 47–49]. In all the studies, the incidence of acute kidney injury and/or the need for renal replacement therapy were a major safety concern. In the aforementioned pooled meta-analysis [6] of three of these studies [47–49], there was a trend towards a lower risk of acute kidney injury (OR 0.80, 95%CI 0.58–1.12, p = 0.200) and rate of renal replacement therapy (OR 0.41; 95%CI 0.16–1.02, p = 0.060) was on the verge of being significantly lower (OR 0.41, 95%CI 0.16–1.02, p = 0.060) in the FFP-treated patients. Based on these limited data, there may be a signal towards a higher risk of acute kidney injury with prothrombin complex concentrate compared with FFP.

In non-cardiac surgery, an integrated safety analysis [50] was performed for the two larger randomised controlled trials (n = 216 and n = 168), which targeted FDA approval of a four-factor prothrombin complex concentrate [14, 15]. The proportion of adverse events and serious adverse events (60% vs. 63% and 28% vs. 25%, respectively) was similar. Likewise, the incidence of thromboembolic events was similar (7%) in a further exploratory analysis [51]. A larger retrospective study (n = 336) from an academic emergency centre compared patients after administration of only four-factor prothrombin complex concentrate with only FFP for vitamin K antagonist reversal [52]. Prothrombin complex concentrate dosage followed the US Food and Drugs Administration recommendations based on patient bodyweight and INR, the mean FFP dose was 10 $ml.kg^{-1}$. Administration of prothrombin complex concentrate was associated with a significant increase in thromboembolic events (18% vs. 3%, $p < 0.001$). Since prothrombin complex concentrate was administered disproportionately in patients with intracranial haemorrhage, a sub-group analysis was performed, but with similar results (14% vs. 4%, p = 0.010). However, in a large nationwide trauma database study (n = 468), patients treated with prothrombin complex concentrate had a lower incidence of acute kidney injury (2% vs. 7%, p = 0.010) and acute respiratory distress syndrome (1% vs. 5%, p = 0.040) [45]. The incidences of deep vein thrombosis (3% vs. 5%, p = 0.100) and pulmonary embolism (1% vs. 2%, p = 0.330) were comparable.

Monitoring

In current guidelines, vitamin K antagonist therapy is monitored by the tissue-factor activated and coagulation factor VII-dependent prothrombin time and expressed as INR [53]. International normalised ratio is the most established coagulation test when monitoring the effect of prothrombin complex concentrate on vitamin K antagonist reversal, whereas the prothrombin time is a global test that is influenced by heparin, fibrinogen cleavage products and others [54]. It remains questionable whether the INR can be used as a monitor for prothrombin complex concentrate when administered peri-operatively in cardiac surgery or major trauma as global 'haemostatic resuscitation', outside the indication of targeted vitamin K antagonist reversal.

Modern viscoelastic point-of-care tests play a pivotal role in guiding peri-operative transfusion therapy. In these assays, the rotational thromboelastometry 'clotting time' (CT in ROTEM™, Instrumentation Laboratory, Bedford, MA, USA) and thromboelastography 'reaction time' (r in the TEG® (Haemonetics Corp, Boston, MA, USA)) reflect, at least partially, the thrombin generation and status of the plasmatic coagulation system [55]. In a prospective observational study of 191 patients taking vitamin K antagonist therapy and healthy controls, the correlation of INR, thrombin formation assay, clotting time and reaction time, were investigated [56]. There was a strong correlation between INR and thrombin formation. This reduced thrombin formation was reflected exactly in the tissue factor-activated EXTEM clotting time (r = 0.87), but not in the intrinsically pathway-activated assay or TEG. In this respect, data from an earlier large study were confirmed [57]. These data may lead to the hypothesis that the EXTEM clotting time is more sensitive to the loss of coagulation factors II, IX, X and particularly VII, than assays activated via the intrinsic contact pathway. This may signal that the EXTEM clotting time may also serve as a monitoring tool for replacement of these factors via four-factor prothrombin complex concentrate transfusion.

We could not find any randomised controlled trial evaluating ROTEM or TEG as monitoring tools for targeted prothrombin complex concentrate replacement in patients undergoing vitamin K antagonist therapy or haemostatic resuscitation with prothrombin complex concentrate in cardiac surgery or trauma. One observational study in trauma patients addressed the effect of four-factor prothrombin complex concentrate transfusion on the clotting time of the EXTEM and INTEM assays [58]. In the sub-group of 13 patients who only received prothrombin complex concentrate for replacement of coagulation factors, the intervention resulted in a normalisation of the EXTEM clotting time from a median (IQR) of 101 (73–172) s to 78 (65–117) s. Normal values for the EXTEM clotting time are 38–79 s. As expected, INTEM clotting time was not significantly affected by the intervention. These data, with the inherent limitations, may support the hypothesis that the tissue-factor-activated and coagulation factor VII-sensitive EXTEM clotting time may provide better monitoring of the four-factor prothrombin complex concentrate effect than assays activated via the intrinsic contact pathway. In addition, it should be noted that EXTEM is largely heparin insensitive. In this context, EXTEM does not have the limitations of conventional prothrombin time-derived INR, especially in cardiac surgery or when monitoring the effect of heparin-containing prothrombin complex concentrate.

Direct oral anticoagulants

We could not identify any prospective randomised or comparative retrospective studies dealing with the value of prothrombin complex concentrate in direct oral anticoagulant-related bleeding. In a recent meta-analysis, combined analysis of two prospective observational studies with 150 patients with bleeding in the presence of factor Xa inhibitors was performed [59]. In both studies, 2000 IU of four-factor prothrombin complex concentrate was administered. Clinical efficacy in a medical setting was evaluated against the standardised criteria for the effective treatment of major bleeding due to intake of rivaroxaban or apixaban as defined by the International Society of Thrombosis and Haemostasis. The pooled proportion of patients with effective bleeding control was 0.69 (95%CI 0.61–0.76). These results must be interpreted cautiously in view of the study design (case series without control group) and the possible selection bias (consecutive patients).

Discussion

We identified three randomised controlled trials investigating modern four-factor prothrombin complex concentrate that were adequately designed for providing evidence that modern four-factor prothrombin complex concentrate are effective in rapidly reversing vitamin K antagonist effects in bleeding patients [14, 15, 39]. Few observational studies were powered sufficiently to perform a meaningful, risk-adjusted analysis for the use of four-factor prothrombin complex concentrate for vitamin K antagonist reversal [26, 40, 60]. However, these studies confirm the findings from contemporary randomised controlled trials.

Outside the indication of urgent vitamin K antagonist reversal, data are sparse. The recent meta-analysis in cardiac surgery showed significant limitations of the available efficacy data [6]. The most informative data for the indication of 'haemostatic resuscitation' with modern four-factor prothrombin complex concentrate outside of vitamin K antagonist reversal originates from trauma patients. For this indication, four-factor prothrombin complex concentrate was administered in combination with FFP. This was especially observable in the national registry study [45], which was powered sufficiently to perform an adequate risk adjustment by slope matching with the control group.

In patients suffering severe trauma or undergoing cardiac surgery, the coagulation system seems to be affected in a similar way [61, 62]. Surgical trauma causes activation of the haemostatic and fibrinolytic systems. Additionally, significant haemodilution and hypothermia are present and contribute to a further aggravation of coagulopathy. In both conditions, therapeutic decisions are based increasingly on results from modern viscoelastic point-of-care assays [63]. Moreover, coagulation factor concentrates play an emergent role in the initial treatment of severe coagulopathy [3, 61]. In this context, findings on prothrombin complex concentrate-efficacy can be considered transferable from trauma to cardiac surgery. However, careful attention should be paid to the inherently increased rate of thromboembolic events for cardiac surgery in the multimorbid and elderly population if coagulopathies are treated, especially in view of inadequate safety data for prothrombin complex concentrate. Moreover, there are reports about massive acute intracardiac thrombosis in the context of cardiac surgery [18–21]. Thus, a more precautious approach should be favoured in these patients.

Currently available safety data on four-factor prothrombin complex concentrate from small randomised controlled trials and observational studies assessing heterogeneous treatment groups are clearly insufficient. The risk for venous thromboembolism strongly depends on the type of surgery or intervention [64]. Additionally, patients with a thrombophilia (e.g. atrial fibrillation) who

require oral anticoagulation (e.g. warfarin), are at an increased risk of up to 13% for the development of postoperative thromboembolic complications [64, 65]. Currently available safety data about the association of four-factor prothrombin complex concentrate and thromboembolic complications remain largely inconclusive. However, looking at the data of two larger randomised controlled trials, it appears that thromboembolic events in the FFP group are more clustered on the day of the intervention or early there after, whereas similar events in the prothrombin complex concentrate group are clustered between 7 and 14 days after surgery. This observation may be explained by the markedly prolonged half-life of prothrombin when compared with the contained antithrombotic components of the four-factor prothrombin complex concentrate [52].

The pre-operative INR can be considered the gold standard for assessing the effect of vitamin K antagonist therapy and guiding four-factor prothrombin complex concentrate transfusion as a targeted replacement therapy. However, in the surgical setting, it remains unclear which assays are useful to guide a therapy with factor concentrates [66, 67]. Although current evidence is weak, the clotting time of tissue-factor activated, heparin-insensitive viscoelastic tests may be preferable, even though a better validation in this indication is necessary and trigger values need to be defined.

Dosing strategies for four-factor prothrombin complex concentrate in the established indication of vitamin K antagonist reversal, provided by the manufacturer's recommendation and international and national guidelines, differ widely (Table 2) [22]. In most randomised controlled trials, a high-dose treatment targeting a normal INR was used. However, in the standard surgical setting a low to moderate dose strategy might be enough to achieve clinical haemostasis, for which a full normalisation of INR is not usually required. In patients with severe bleeding and/or signs of severe coagulopathy, an initial bolus of 25 $IU.kg^{-1}$ of a four-factor prothrombin complex concentrate appears to be an effective first-step therapy for vitamin K antagonist reversal or for 'haemostatic resuscitation' in major surgery and trauma, although this is not yet supported by meta-analysis. However, in patients with thromboembolic risk factors, as in cardiac surgery, a more tentative approach may be favoured. A stepwise strategy with an initial half dose (12.5 $IU.kg^{-1}$) bolus – followed by the second dose when microvascular bleeding persists – is considered a rational risk adjusted strategy.

Based on the current evidence, we conclude that modern four-factor prothrombin complex concentrate is an effective tool for the rapid and targeted replacement of large amounts of vitamin K-dependent coagulation factors in severely bleeding patients under vitamin K antagonist therapy. These agents also play an increasing role in off-label therapy of 'haemostatic resuscitation' in massively bleeding trauma or surgical patients with severe coagulopathy. Differentiated treatment algorithms based on the pre-operative INR and modern point-of-care monitoring tools should be established. Most importantly, convincing safety data need to be generated by sufficiently powered prospective studies and large registries and pharmacovigilance data. However, two new randomised controlled trials in the field of cardiac surgery are currently planned; the protocol of a recent Cochrane review is also available [68]. However, randomised studies are time consuming and often did not include patients groups at special risk. Performing meaningful randomised controlled trials in patients with a special risk profile or very special indications, such as heart transplantation and implantation of mechanical assist devices, is often difficult due to relatively small numbers. In these areas, large international registries [69–71] are well established and could be utilised to get further short-term insights into the efficacy and particularly the safety of these highly potent haemostatic agents.

Table 2 International dosing recommendations for prothrombin complex concentrate (IU) to reach a target INR in patients taking vitamin K antagonists [22].

Guideline	Dose for vitamin K antagonist reversal	Targeted INR
American College of Chest Physicians [72]	No recommendation	
National Advisory Committee Canada [73]	1000 2000 3000	< 3.0 3.0–5.0 > 5.0
British Committee for Standards in Haematology [74]	25–50 $IU.kg^{-1}$	not specified
Australasian Society of Thrombosis and Haemostasis [75]	25–50 $IU.kg^{-1}$	not specified
French National Authority for Health [76]	25 $IU.kg^{-1}$ (first dose) repetition based on INR/bodyweight	

Acknowledgements

EB has received consultancy fees from Werfen. AA has received consultancy fees and research funding from Masimo, Nordic Pharma, CSL Behring and Novo Nordisk.

ML received payments for consultancy work and lecture fees related to the topic of this article from CSL Behring and TEM International. MR has received consultancy fees and research funding from Roche Diagnostics, CSL Behring, TEM International and Haemonetics. CvH has received payments for consultancy work and lecture fees related to the topic of this article from CSL Behring and Haemonetics. SA is an Editor of *Anaesthesia* and has received research funding and consultancy fees from Haemonetics, Roche, Octapharma and CSL Behring. No other external funding or competing interests declared.

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