Transfusion Camp Rwanda
June 4th 2022
Seminar 1: Triggers for RBC and platelet transfusions

Case 1

A 70 year old male is admitted to the ICU with respiratory failure due to pneumococcal pneumonia. His past medical history is significant for coronary artery disease but he has been asymptomatic since undergoing bypass operation approximately 5 years ago. He is on antibiotics and is hemodynamically stable. He is intubated and ventilated (PS10, PEEP 8, FiO2 0.5, oxygen saturation 94%). There is no evidence of bleeding or hemolysis. However, over the last few days his hemoglobin concentration has drifted down to 7.9 g/dL.

1) Which of the following represents the most appropriate RBC transfusion strategy for this patient?
   A) Transfuse RBCs if Hgb <10 g/dL
   B) Transfuse RBCs if Hgb <9 g/dL
   C) Transfuse RBCs if Hgb <8 g/dL
   D) Transfuse RBCs if Hgb <7 g/dL

2) Which of the following strategies may minimize the patient's need for future RBC transfusion?
   A) Minimize unnecessary diagnostic phlebotomy
   B) Start an erythropoiesis stimulating agent
   C) Start B12 supplementation
   D) Start iron supplementation

3) You review the patient's laboratory results and notice that his troponin is significantly elevated. Troponin was ordered to further investigate an episode of rapid atrial fibrillation and ST changes earlier in the morning. Which one of the following represents the best transfusion strategy for this patient?

   A) No transfusion is needed at this time
   B) Transfuse 1 unit RBC rapidly
   C) Transfuse 1 unit RBC over 3 hours
   D) Transfuse 2 units RBC rapidly

Case 2

25 year old female with no significant past medical history, is seen in the emergency room with "a critically abnormal laboratory result", a hemoglobin of 6 g/dL. She has a long-standing history of menorrhagia and was sent to the ER by her family MD. On questioning, she endorses fatigue and reduced stamina but remains active and continues working full time. Her CBC reveals Hgb 6 g/dL, MCV 65 fL, platelets 487 x 10^9/L, coagulation studies are normal.

4) Which of the following represents the least appropriate intervention?
   A) Intravenous iron
   B) Oral iron
   C) Referral to gynecology
   D) Transfusion of RBC

Case 3

A 2 year-old female is seen because of pallor and her mother feels that she is less active than the other toddlers. Nutritional history indicates that the child is no longer breast feeding and her diet consists primarily of maize porridge. There is no history of fever and no splenomegaly on examination. CBC shows hemoglobin 7.9 g/dL, MCV 72 fL, WBC 7.9 x 10^9/L, platelets 475 x 10^9/L.

5) Which of the following is the most appropriate management of this child's anemia?
   A) Empiric treatment of malaria, followed by IV iron weekly for 6 weeks
   B) Resume breastfeeding
   C) Provide nutritional consultation and oral iron supplementation
   D) Transfuse a weight-based dose of RBCs

Case 4

A 27 year-old man with acute myeloid leukemia is admitted for induction chemotherapy. He is afebrile. He denies bleeding but examination reveals numerous petechiae on his lower extremities and a few large ecchymoses on his extremities and trunk. Morning CBC reveals Hgb 7.3 g/dL and platelets 5 x 10^9/L. Review of his recent CBC results indicates that his platelet count has not been above 10 for the past two weeks, despite being transfused platelets two to three times per week.

6) In addition to investigating the cause of the patient's high platelet transfusion requirements, which one of the following is the most appropriate transfusion strategy for this patient?
   A) Only transfuse platelets in the presence of active bleeding
   B) Start the patient on tranexamic acid
   C) Transfuse 1 adult dose of platelets today
   D) Transfuse 2 adult doses of platelets today

7) You suspect that he has developed platelet transfusion refractoriness due to antiplatelet antibodies. Which one of the following investigations is least likely to help you determine the cause of the refractoriness?
   A) Bone marrow aspirate and biopsy
   B) HLA antibody screen
   C) Panculture to look for occult infection
   D) Platelet count measured one hour post platelet transfusion

8) The patient is transitioned to ABO-identical, fresh platelets and on two occasions the 1-hour increment in platelet count was < 10 10^9/L. A sample of patient plasma is sent to a referral laboratory to assess for anti-HLA antibodies, and the blood supplier is notified that HLA-matched platelets may be required, if available. Which one of the following is the least appropriate management strategy while awaiting arrival of HLA-selected platelets?
   A) Give IVIg 1g/kg daily
   B) Give oral tranexamic acid to treat minor bleeding
   C) Transfuse pooled, ABO compatible and freshest available platelets
   D) Transfuse platelets only to treat clinically significant bleeding

Case 5a

A 69 year old male is admitted via ER with acute subdural hematoma following a fall. He is known to have liver cirrhosis due to alcohol. His CBC revealed Hgb 12.5 g/dL and platelets 75 x 10^9/L. His INR was 1.3. He is scheduled for a burr hole surgery later this evening.

9) Which one of the following represents the most appropriate transfusion strategy?
   A) No need for platelet transfusion
   B) Transfuse 1 adult dose of platelets and repeat CBC
   C) Transfuse 1 adult dose of platelets only if significant intra-operative bleeding
   D) Transfuse 2 adult doses of platelets

Case 5b

An 80 year-old male on aspirin and clopidogrel presents with spontaneous ICH. His GCS is 15 and no surgical intervention is planned. His platelet count is 249 x 10^9/L and INR and aPTT are normal.

10) Which one of the following is the most appropriate therapy?
   A. 1 adult dose of platelets
   B. 2 adult doses of platelets
   C. PCC 50IU/kg IV and Vitamin K 10 mg IV
   D. None of the above

Transfusion Camp Rwanda
June 4th 2022
Seminar 2: Plasma, fibrinogen and prothrombin complex concentrates

***Note: This seminar is to cover transfusions for less severe bleeding or before an invasive procedure and does not cover massive hemorrhage.**

Case 1

A 56-year-old man (78 kg) with atrial fibrillation presents to the emergency department with acute onset of severe shortness of breath and pre-syncope with any exertion. He is on warfarin – dose has been stable for 6 months without dose adjustment. He had some chest congestion last week and went to a walk-in clinic where they prescribed clarithromycin. Heart rate is 130 bpm and blood pressure is 80/30 mmHg. Heart sounds are faint. JVP is grossly distended. Chest-x-ray reveals marked cardiomegaly. Cardiology has been paged for STAT echo for pericardial tamponade from hemorrhage. INR is 10.5. Patient is to undergo the life-saving procedure immediately.

1. Which one of the following is the optimal management strategy at this time?
    A) 1 unit of plasma, vitamin K 10 mg po
    B) 4 units of plasma, vitamin K 10 mg IV
    C) 3000 IU of prothrombin complex concentrate, vitamin K 10 mg IV
    D) 3000 IU of prothrombin complex concentrate, vitamin K 2 mg po

2. How fast should prothrombin complex concentrate (PCC) be infused into the patient?
    A) As fast as you can push in by syringe
    B) Each 1000 units is infused over 1 minute
    C) Each 1000 units is infused over 5 minutes
    D) Each 1000 units is infused over 30 minutes

3. The intensivist wants to know when to expect that the INR will be normalized so that she can perform the pericardiocentesis. Which one of the following is true about warfarin reversal in this case?
    A) After infusion, the procedure should be initiated before the result is known; the INR should be rechecked after the PCC is administered to determine if additional doses are required
    B) After infusion, wait for the INR to be rechecked after the PCC is administered to determine if additional doses are required before starting the procedure
    C) The effect of PCCs will be seen immediately after administration in all patients and there is no need to recheck the INR
    D) The effect of the treatment (PCCs and vitamin K) takes 6 hours to normalize the INR, so delay the procedure for 6 hours

4. Which of the following is an appropriate indication for PCC administration?
    A) Elective reversal of oral anticoagulant therapy before a scheduled invasive procedure.
    B) Rapid reversal of warfarin therapy or vitamin K deficiency in patients exhibiting major bleeding.
    C) Reversal of warfarin therapy or vitamin K deficiency in patients requiring a surgical procedure within 12-24 hours.
    D) Treatment of INRs over 8-10 without bleeding or need for surgical intervention.

Case 2

A 15-year-old girl (45 kg) presents to the emergency department feeling unwell for 2 weeks with fever, myalgias, malaise and anorexia. She is noted on physical exam to have mild abdominal distention (query ascites) and splenomegaly. She has no bruising except at intravenous puncture sites. On laboratory testing she has markedly elevated liver enzymes (ALT 234 IU/L), a bilirubin of 76 µmol/L (4.4 mg/dL), hypoalbuminemia (24 g/L), a slightly increased INR (1.6) and decreased fibrinogen of (1.2 g/L). Her platelet count is also marked decreased at 65 x 10^9/L. A plan is made to perform an ultrasound-guided liver biopsy.

5. Which one of the following is the most appropriate transfusion strategy in this patient in lead up to the biopsy?
    A) No need for transfusion at this time
    B) Transfuse 1000 IU of PCC and 4 grams of fibrinogen concentrate (or 10 units of cryoprecipitate if fibrinogen unavailable)
    C) Transfuse 1 adult dose of platelets
    D) Transfuse 15 ml/kg of plasma

6. The radiologist refuses to perform the procedure until the INR is 1.2 or less. You should:
    A) Administer 10 mg of IV vitamin K
    B) Delay the procedure for 1 day and see if the next radiologist will do it without plasma
    C) Refer the radiologist to current guidelines on periprocedural hemostasis
    D) Transfuse 15 ml/kg of plasma to ensure the liver biopsy is done

7. The patient subsequently develops a variceal bleed with hypotensive shock. Her INR is now 3.4 and fibrinogen is 1.6 g/L. You should:
    A. Transfuse 15 ml/kg of plasma and repeat INR
    B. Transfuse 5-10 mL/kg of plasma
    C. Transfuse 15 ml/kg of plasma
    D. Transfuse 4 grams of fibrinogen concentrate (or 10 units of cryoprecipitate if fibrinogen unavailable)

Case 3a

A 35-year-old woman (65 kg) is admitted to the ICU from the ER with endocarditis within 4 hours of presenting to the hospital. She is not bleeding. She is intubated for airway protection and hemodynamically unstable on two inotropes. Her temperature is 39°C. Her blood work is as follows: Hemoglobin 10.8 g/dL, platelet count 18 x 10^9/L, INR 1.6, aPTT 42 s, and fibrinogen 1.3 g/L. Her peripheral blood smear shows occasional fragments (schistocytes). Blood cultures are positive for gram-positive organism in 2/2 bottles; final culture results are pending. You make the correct diagnosis of sepsis-related DIC. She is not bleeding and no procedures are planned in the next 6 hours.

8. Which one of the following is the most appropriate transfusion strategy for this patient?
    A) No transfusion indicated at this time
    B) Transfuse 1 adult dose of platelets
    C) Transfuse 1 adult dose of platelets and 4 units of plasma
    D) Transfuse 1 adult dose of platelets and 4 grams of fibrinogen concentrate (or 10 units of cryoprecipitate if fibrinogen unavailable)

Case 3b

A 17 year old female is seen in the ER with profuse vaginal bleeding and hemorrhagic shock 6 hours after a pregnancy termination. Her BP is 90/50 mmHg, HR 112 bpm, temperature is 38.1° C. Her blood work is as follows: Hemoglobin 6.5 g/dL, platelet count 28 x 10^9/L, INR 1.4, aPTT 40 s, and fibrinogen 1.1 g/L. Ultrasound shows retained products of conception. She is hemodynamically unstable and you have ordered 2 units of uncrossmatched (you decide it would imprudent to wait 60 minutes for crossmatched blood) group O D-negative and K-negative red cells.

9. Which one of the following is the most appropriate transfusion strategy for this patient in addition to RBCs?
    A) No transfusion indicated at this time
    B) Transfuse 1 adult dose of platelets
    C) Transfuse 1 adult dose of platelets and 4 units of plasma
    D) Transfuse 1 adult dose of platelets and 4 grams of fibrinogen concentrate (or 10 units of cryoprecipitate if fibrinogen unavailable)

Case 3c

A 35-year-old woman is admitted to the hematology service following a diagnosis of acute promyelocytic leukemia (APL). APL is associated with a high rate of early hemorrhagic deaths from intracranial hemorrhage. She is afebrile with stable vital signs and her only complaints are fatigue and a petechial rash on her legs. Her blood work is as follows: Hemoglobin 7.4 g/dL, platelet count 18 x 10^9/L, WBC 63 x 10^9/L, INR 1.4, aPTT 39 s, and fibrinogen 0.9 g/L. She is to start emergency induction chemotherapy tonight, and is not bleeding.

10. Which one of the following is the most appropriate transfusion strategy for this patient?
    A) No transfusion indicated at this time
    B) Transfuse 1 unit RBC and 1 adult dose of platelets
    C) Transfuse 1 unit RBC and 4 grams of fibrinogen (or 10 units of cryoprecipitate if fibrinogen concentrate not available)
    D) Transfuse 1 adult dose of platelets and 4 grams of fibrinogen (or 10 units of cryoprecipitate if fibrinogen concentrate not available)

Case 4

You are providing the anesthetic for an 11-year-old girl undergoing scoliosis surgery with a pre-op weight of 39 kg. Pre-op blood work: hemoglobin 11.8 g/dL, MCV 78 fL, platelet count 288 x 10^9/L. No INR was done pre-op as her bleeding questionnaire was negative for a bleeding history. At the 2 hour mark of the surgery, she has lost approximately 2500 mL and you have transfused 3 units of RBC. STAT blood work reveals: hemoglobin 7.8 g/dL, platelet count 134 x 10^9/L, INR 2.1, PTT 45s and fibrinogen 1.3 g/L. The surgeon expects to lose another 1000 mL of blood over the next hour. You have not administered any plasma, platelets or fibrinogen yet.

11. Which one of the following is the most appropriate component strategy for this patient?
    A) Transfuse 1 adult dose platelets
    B) Transfuse 2000 IU of PCC
    C) Transfuse 15 mL/kg of plasma and either 2 grams of fibrinogen (50 mg/kg) or 5 units of cryoprecipitate
    D) Transfuse either 2 grams of fibrinogen or 5 units of cryoprecipitate

JAMA | Special Communication

Clinical Practice Guidelines From the AABB
Red Blood Cell Transfusion Thresholds and Storage

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IMPORTANCE More than 100 million units of blood are collected worldwide each year, yet the indication for red blood cell (RBC) transfusion and the optimal length of RBC storage prior to transfusion are uncertain.

OBJECTIVE To provide recommendations for the target hemoglobin level for RBC transfusion among hospitalized adult patients who are hemodynamically stable and the length of time RBCs should be stored prior to transfusion.

EVIDENCE REVIEW Reference librarians conducted a literature search for randomized clinical trials (RCTs) evaluating hemoglobin thresholds for RBC transfusion (1950-May 2016) and RBC storage duration (1948-May 2016) without language restrictions. The results were summarized using the Grading of Recommendations Assessment, Development and Evaluation method. For RBC transfusion thresholds, 31 RCTs included 12 587 participants and compared restrictive thresholds (transfusion not indicated until the hemoglobin level is 7-8 g/dL) with liberal thresholds (transfusion not indicated until the hemoglobin level is 9-10 g/dL). The summary estimates across trials demonstrated that restrictive RBC transfusion thresholds were not associated with higher rates of adverse clinical outcomes, including 30-day mortality, myocardial infarction, cerebrovascular accident, rebleeding, pneumonia, or thromboembolism. For RBC storage duration, 13 RCTs included 5515 participants randomly allocated to receive fresher blood or standard-issue blood. These RCTs demonstrated that fresher blood did not improve clinical outcomes.

FINDINGS It is good practice to consider the hemoglobin level, the overall clinical context, patient preferences, and alternative therapies when making transfusion decisions regarding an individual patient. Recommendation 1: a restrictive RBC transfusion threshold in which the transfusion is not indicated until the hemoglobin level is 7 g/dL is recommended for hospitalized adult patients who are hemodynamically stable, including critically ill patients, rather than when the hemoglobin level is 10 g/dL (strong recommendation, moderate quality evidence). A restrictive RBC transfusion threshold of 8 g/dL is recommended for patients undergoing orthopedic surgery, cardiac surgery, and those with preexisting cardiovascular disease (strong recommendation, moderate quality evidence). The restrictive transfusion threshold of 7 g/dL is likely comparable with 8 g/dL, but RCT evidence is not available for all patient categories. These recommendations do not apply to patients with acute coronary syndrome, severe thrombocytopenia (patients treated for hematological or oncological reasons who are at risk of bleeding), and chronic transfusion–dependent anemia (not recommended due to insufficient evidence). Recommendation 2: patients, including neonates, should receive RBC units selected at any point within their licensed dating period (standard issue) rather than limiting patients to transfusion of only fresh (storage length: <10 days) RBC units (strong recommendation, moderate quality evidence).

CONCLUSIONS AND RELEVANCE Research in RBC transfusion medicine has significantly advanced the science in recent years and provides high-quality evidence to inform guidelines. A restrictive transfusion threshold is safe in most clinical settings and the current blood banking practices of using standard-issue blood should be continued.

JAMA. 2016;316(19):2025-2035. doi:10.1001/jama.2016.9185
Published online October 12, 2016.

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More than 100 million units of blood are collected worldwide each year,[1] and approximately 13 million red blood cell (RBC) units are collected in the United States.[2] Despite previously published guidelines,[3-7] there remains substantial variation in the practice of transfusing patients. Physicians often use hemoglobin level to decide when to transfuse,[8] although some guidelines[9,10] maintain that transfusion should be given for symptoms of anemia and not solely based on hemoglobin level.

Transfusion practices for RBCs should be designed to optimize clinical outcomes and to avoid transfusions that are not clinically indicated. Despite the risk of transfusion-transmitted infections and noninfectious adverse events, such as transfusion-related acute lung injury and transfusion-associated circulatory overload, RBC transfusion is relatively safe (**Table 1**). However, transfusing RBCs unnecessarily exposes patients to increased risk and costs without benefit. Consequently, transfusing RBCs at higher hemoglobin thresholds (ie, a liberal transfusion strategy) should be used only if a liberal strategy will improve the outcomes that are important to patients.

In addition to transfusion reactions and infectious risks associated with RBC transfusions, it has been suggested that an RBC storage lesion may result in adverse outcomes. Units of RBCs can be stored up to 42 days. The RBCs stored for longer periods have decreased ability to deliver oxygen due to decreased levels of 2,3-diphsophoglycerate, decreased nitric oxide metabolism, alterations of the RBC membrane leading to increased rigidity, and increased RBC endothelial adherence.[19,20] In addition, the storage medium may contain increased levels of free hemoglobin, iron, potassium, and inflammatory mediators that may lead to deleterious consequences.[19,21] Furthermore, observational studies[22-24] suggested that RBCs stored longer than 2 weeks may be associated with increased morbidity and mortality; however, the data were conflicting.[25-27] These considerations raise the possibility that transfusion medicine services should preferentially provide fresher RBCs for transfusion compared with standard issue RBCs.

In 2012, the AABB (formerly known as the American Association of Blood Banks) published RBC transfusion guidelines based on 19 randomized clinical trials (RCTs) that included 6264 patients.[28] Many of those RCTs were small (median, 120 patients; range, 22 to 2016 patients) and had high risk of bias. During the past 4 years, the number of patients enrolled in RBC transfusion RCTs has more than doubled, and many studies have incorporated methods to minimize the risk of bias and enrolled populations of patients receiving frequent blood transfusions. Therefore, it is timely to reexamine the evidence and provide updated guidance to the medical community.

Thirteen RCTs have evaluated the effect of RBC storage duration of transfused RBCs on patient outcomes (7 since 2012).[29-41] However, there is currently no formal guidance on the optimal length of RBC storage prior to transfusion.

Methods

These guidelines provide recommendations for (1) the clinicians caring for hospitalized adult patients who are hemodynamically stable and candidates for RBC transfusions, and (2) the transfusion medicine services responsible for storing and providing RBCs. The AABB commissioned and funded the development of these guidelines through the AABB clinical transfusion medicine committee. In addition, the board of directors charged the committee to recruit experts with an interest in RBC transfusion from other professional organizations.

Guideline Development Process

A committee of experts was assembled. Most of the experts were current or former members of the AABB clinical transfusion medicine committee (J.L.C., N.M.H., B.J.G., C.S.C., M.K.F., T.G., L.M.K., G.R., J.D.R., and A.A.R.T.). There also were experts appointed by professional organizations as subject matter experts (American Association for the Surgery of Trauma: J.B.H.; Society of Critical Care Medicine: L.J.K.; American College of Cardiology: S.V.R.; American Society of Anesthesiologists: A.S.; and American Society of Hematology: T.G.). The committee also included a patient representative (N.P.). Eight of the physicians were pathologists or hematologists (most with subspecialty expertise in transfusion medicine). The other physicians included an anesthesiologist, cardiologist, internist, critical care medicine physician, trauma or acute care surgeon, and a Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologist (G.G.).

The committee members had no substantial conflicts of interest (as defined by the AABB conflict of interest policy[42]). Pursuant to the conflict of interest policy, individual members were required to disclose actual and apparent financial, professional, or personal conflicts. Two members were authors on trials included in the systematic review on transfusion thresholds (J.L.C. and S.V.R.), 1 authored a systematic review of transfusion thresholds (J.L.C.), 2 were authors on trials of RBC storage duration (J.L.C. and N.M.H.), and 2 were authors on systematic reviews of RBC storage duration (G.G. and N.M.H.). One member (J.L.C.) was excused when voting on transfusion thresholds for patients with acute myocardial infarction due to his role as principal investigator on a pending grant proposal.

Evidence Review and Grading

Systematic Review

The guidelines were developed based on separately published updated systematic reviews of the literature on transfusion thresholds[43] and RBC storage duration.[44] We performed literature searches of RCTs evaluating transfusion thresholds from 1950 through May 2016 and the storage duration of transfused RBCs from 1948 through May 2016.[43] The systematic review included RCTs in which the transfusion groups were assigned on the basis of a clear transfusion trigger or threshold, which was described as hemoglobin or hematocrit level that had to be reached before a RBC transfusion was administered. Trials of patients treated surgically, medically, or both were included as well as those involving adults or children (but not neonates). For the RBC storage systematic review, the included RCTs enrolled patients admitted to the hospital requiring a RBC transfusion and compared fresher vs standard issue RBC transfusions.[44] The term *standard issue* used in these guidelines is defined as units selected at any point within their licensed dating period, but only a small proportion of RBC units transfused were stored for 36 days to 42 days.

The primary outcome in both systematic reviews was mortality (30-day mortality for transfusion thresholds and a composite of the longest follow-up provided in each trial, including 30 days, 90 days, and in-hospital mortality for RBC storage duration). Secondary outcomes for transfusion thresholds included morbidity (eg, nonfatal myocardial infarction, pulmonary edema or congestive heart failure, stroke, thromboembolism, renal failure, infection, rebleeding, or mental confusion); the proportion of patients transfused with allogeneic RBCs, autologous

Table 1. Approximate Risk Per-Unit Transfusion of Red Blood Cells (RBCs)

Adverse Event	Approximate Risk Per-Unit Transfusion of RBCs
Febrile reaction[11]	1:60[a]
Transfusion-associated circulatory overload[12,13]	1:100[b]
Allergic reaction[14]	1:250
Transfusion-related acute lung injury[15]	1:12 000
Hepatitis C virus infection[16]	1:1 149 000
Hepatitis B virus infection[17]	1:1 208 000 to 1:843 000[c]
Human immunodeficiency virus infection[16]	1:1 467 000
Fatal hemolysis[18]	1:1 972 000

[a] Estimated to be 1:91 with prestorage leukoreduction and 1:46 with poststorage leukoreduction.

[b] Indicates the estimated risk per recipient rather than unit.

[c] The estimate is variable depending on the length of the infectious period.

RBCs, or both; hemoglobin levels (the timing of measurement varied among trials); and the number of RBC units transfused. For RBC storage, the secondary outcomes included adverse events and nosocomial infection. The systematic reviews only included RCTs because observational studies evaluating the effect of transfusion are especially prone to confounding by indication and are likely to yield biased results.[45,46]

Each RCT was assessed for the risk of bias for sequence generation, allocation concealment, blinding, and incomplete outcome data using the methods recommended by Cochrane (for transfusion threshold review)[47] and a modified risk of bias assessment tool (for storage duration).[48] Statistical heterogeneity was assessed using both I^2 and χ^2 tests.[47] Existing criteria provided guidance for making inferences regarding subgroup effects.[49] All analyses were performed using Review Manager (RevMan) version 5.2 (Cochrane Collaboration). The relative risks (RRs) and the corresponding 95% CIs were calculated for each trial using random-effects models.[50]

Rating Quality of Evidence

The GRADE method[51,52] was used to develop these guidelines (eAppendix in the Supplement). Evidence profiles were prepared that displayed data in terms of benefits and harms for the most important outcomes. The profiles also were the basis for decisions regarding the rating down of quality for risk of bias, lack of consistency, lack of directness, lack of precision, and possible publication bias. The overall quality of evidence for each outcome was assessed for the systematic review on transfusion thresholds (J.L.C. and Simon Stanworth, MD, DPhil) and for the systematic review on RBC storage (Paul Alexander, PhD, G.G., and N.M.H.). The committee reviewed these ratings and made its final quality ratings and determined the strength of the recommendations during an in-person meeting.

Committee Values and Preferences

With respect to transfusion thresholds, the committee made its recommendations based on the assumption that patients would highly value avoiding the rare but potentially serious adverse effects associated with RBC transfusion. Moreover, the committee placed value on resource conservation related to RBC transfusion. Therefore, when the evidence suggested no harms from withholding transfusion, the committee was prepared to make a strong recommendation for a restrictive threshold. When evidence regarding harms was uncertain, the committee elected not to make a recommendation.

With respect to RBC storage duration, the committee placed a high value on feasibility and resource use considerations for RBC transfusion. Therefore, if evidence suggested no harms in using standard-issue blood, the committee was prepared to make a strong recommendation for continuing with standard practice. The recommendations were voted and then the first (J.L.C.) and last (A.A.R.T.) authors prepared the draft guideline document, which was modified and approved by all committee members and the AABB clinical transfusion medicine committee. Subsequently, the AABB board of directors reviewed and approved the guidelines.

Good Clinical Practice Statement

When deciding to transfuse an individual patient, it is good practice to consider not only the hemoglobin level, but the overall clinical context and alternative therapies to transfusion. Variables to take into consideration include the rate of decline in hemoglobin level, intravascular volume status, shortness of breath, exercise tolerance, lightheadedness, chest pain thought to be cardiac in origin, hypotension or tachycardia unresponsive to fluid challenge, and patient preferences. This practice guideline is not intended as an absolute standard and will not apply to all individual transfusion decisions.

Recommendations

First Recommendation

The AABB recommends a restrictive RBC transfusion threshold in which the transfusion is not indicated until the hemoglobin level is 7 g/dL for hospitalized adult patients who are hemodynamically stable, including critically ill patients, rather than a liberal threshold when the hemoglobin level is 10 g/dL (strong recommendation, moderate quality evidence). For patients undergoing orthopedic surgery or cardiac surgery and those with preexisting cardiovascular disease, the AABB recommends a restrictive RBC transfusion threshold (hemoglobin level of 8 g/dL; strong recommendation, moderate quality evidence). The restrictive hemoglobin transfusion threshold of 7 g/dL is likely comparable with 8 g/dL, but RCT evidence is not available for all patient categories. These recommendations apply to all but the following conditions for which the evidence is insufficient for any recommendation: acute coronary syndrome, severe thrombocytopenia (patients treated for hematological or oncological disorders who at risk of bleeding), and chronic transfusion-dependent anemia.

Evidence Summary

A total of 12 587 patients were enrolled in 31 eligible trials.[53-86] Ten trials were conducted in patients undergoing orthopedic surgery, 6 trials included patients treated in critical care units, 5 trials

were conducted in patients undergoing cardiac surgery, 5 trials were conducted in patients with gastrointestinal bleeding, 2 trials included patients with acute coronary syndrome, 2 trials included patients with leukemia or hematological malignancies, and 1 trial was conducted in patients undergoing vascular surgery. The restrictive RBC transfusion protocols commonly used a hemoglobin transfusion threshold of 7 g/dL or 8 g/dL, and liberal protocols used a hemoglobin transfusion threshold of 9 g/dL to 10 g/dL.

The association of restrictive transfusion protocols on 7 outcomes reported in the trials appears in **Table 2**. The primary outcome of 30-day mortality was reported in 23 of 30 RCTs.[53-56,58,60,61,63,64,68-72,74-76,78,79,84-87] In the restrictive transfusion group, the absolute difference in 30-day mortality was 3 fewer deaths per 1000 patients (95% CI, 15 fewer deaths to 18 more deaths per 1000). The quality assessment found no serious risk of bias, inconsistency, indirectness, or publication bias. The overall quality of evidence was moderate for 30-day mortality because the imprecision was judged as serious in that there could be up to 18 more deaths per 1000 in the restrictive transfusion group.

For all other outcomes evaluated, there was no evidence to suggest that patients were harmed by restrictive transfusion protocols, although the quality of the evidence was low for the outcomes of congestive heart failure and rebleeding. In addition, liberal transfusion was not found to be associated with an increased risk of infection as had been previously found in a prior meta-analysis.[88] There was also no difference in the other assessed outcomes (ability to walk, multiple measures of function, fatigue, and length of hospital stay) in the systematic review.[43]

The 30-day mortality for the trials that used a restrictive hemoglobin transfusion threshold of less than 8 g/dL to 9 g/dL (n = 4772) was compared with those using a restrictive hemoglobin transfusion threshold of less than 7 g/dL (n = 5765). The RRs were similar, and there is no evidence that these 2 threshold groups are statistically different (χ^2_1 = 0.34, P = .56, I^2 = 0%; **Figure 1**). However, the clinical settings were different. Most of the trials with the restrictive hemoglobin transfusion threshold of less than 7 g/dL were performed in critical care settings, whereas the clinical settings were more varied with the hemoglobin transfusion threshold of less than 8 g/dL to 9 g/dL.

The subgroup analyses for 30-day mortality by clinical setting[43] did not demonstrate statistically significant evidence to support differences in the subgroups; however, 30-day mortality was significantly lower with the restrictive transfusion threshold than the liberal transfusion threshold in patients with gastrointestinal bleeding (RR, 0.65; 95% CI, 0.43-0.97). Two small trials included 154 patients with acute coronary syndrome. There were 9 deaths with the restrictive transfusion threshold and 2 deaths with the liberal transfusion threshold (RR, 3.88 [95% CI, 0.83-18.13]; P = .08, I^2 = 67.6% for the comparison of these 2 small trials). The results for myocardial infarctions from these 2 trials (n = 154 patients) were then compared with the other 29 trials in all other clinical settings (P = .08, I^2 = 67.6%).

Rationale for Recommendation

The AABB recommendation to use a hemoglobin transfusion threshold of 7 g/dL to 8 g/dL for most hospitalized adult patients who are hemodynamically stable rather than a hemoglobin transfusion threshold of 9 g/dL to 10 g/dL is based on consistent evidence from multiple large RCTs performed in various clinical settings in more than 12 000 patients. With the possible exception of patients with acute myocardial infarction, no data suggest that a restrictive transfusion threshold is harmful compared with a liberal transfusion threshold. A restrictive transfusion threshold approach is associated with reductions in blood use, associated expense, and uncommon but potentially serious adverse events.

The AABB recommends using a restrictive hemoglobin transfusion threshold of 7 g/dL for hospitalized adult patients who are hemodynamically stable, including critically ill patients, but a hemoglobin transfusion threshold of 8 g/dL for patients undergoing orthopedic or cardiac surgery and for those with underlying cardiovascular disease. The reason for the different thresholds is that the RCTs performed in the later groups of patients used a hemoglobin transfusion threshold of 8 g/dL and not a threshold of 7 g/dL. The committee suspects that those patients might tolerate a hemoglobin transfusion threshold of 7 g/dL because the trials using a restrictive threshold of 7 g/dL were performed in critically ill patients compared with other trials with a threshold of 8 g/dL and less critically ill patients. However, this has not been assessed in RCTs and it is possible that functional recovery (in patients undergoing orthopedic surgery) or myocardial infarction rates (in patients undergoing cardiac surgery or with chronic cardiovascular disease) could be adversely affected by a hemoglobin transfusion threshold of 7 g/dL or higher even if mortality is not. An ongoing large trial among patients undergoing cardiac surgery is using a restrictive hemoglobin transfusion threshold of 7.5 g/dL and may provide a definitive answer.[89]

As in the AABB's previous guideline,[28] the committee chose not to recommend for or against a liberal or restrictive transfusion threshold in patients with acute coronary syndrome. There are 2 trials with a total of 154 patients that showed a trend toward a lower risk of death when the liberal transfusion threshold was used.[56,61] This finding is consistent with experimental studies in canines,[90-92] in an observational study of patients undergoing surgery with underlying cardiovascular disease,[93] and in the prespecified a priori hypothesis and direction in the 2 small trials.[56,61] However, small RCTs are known to be unreliable; in fact, the size of the effect observed was larger than anticipated, but the results were not statistically significant.

The AABB also did not make a recommendation for a transfusion threshold in patients treated for hematological or oncological disorders and for those with severe thrombocytopenia who are at risk of bleeding or for those with chronic transfusion–dependent anemia. Red blood cells have been shown to increase platelet responsiveness,[94] especially at lower platelet counts.[95] Data from animal experiments[96] and normal volunteers suggest that anemia increases the bleeding time, even with as little as a 15% decrease in hemoglobin level.[97] For this reason, some clinicians advocate for higher hemoglobin thresholds in patients with severe thrombocytopenia who are at increased risk of bleeding. Except for 2 pilot studies,[86,98] RCTs comparing RBC transfusion thresholds with bleeding as an end point have yet to be performed. Similarly, there have not been RCTs performed in patients with chronic transfusion–dependent anemia. The risks and benefits (ie, improved function, less fatigue) are different for patients receiving chronic transfusions outside the hospital than hospitalized patients in acute care settings.

Second Recommendation

The AABB recommends that patients, including neonates, should receive RBC units selected at any point within their licensed dating

Table 2. Evidence for the Association Between Hemoglobin Transfusion Thresholds and Clinical Outcomes in Hospitalized Adult Patients Who Are Hemodynamically Stable and in Need of a Red Blood Cell Transfusion[a]

	Quality Assessment[b]					No./Total (%) of Patients by Hemoglobin Transfusion Threshold		Effect		
No. of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Restrictive (7-8 g/dL)	Liberal (9-10 g/dL)	Relative Risk (95% CI)	Absolute Risk (95% CI)	Quality of RCTs
Primary Outcome: 30-d Mortality										
23	Not serious	Not serious	Not serious	Serious[c]	None detected	470/5221 (9.0)	497/5316 (9.3)	0.97 (0.81-1.16)	3 fewer deaths per 1000 (15 fewer deaths to 18 more per 1000)	Moderate
Secondary Outcomes										
Myocardial Infarction (MI)										
16	Not serious	Not serious	Not serious	Not serious	None detected	78/4156 (1.9)	69/4147 (1.7)	1.08 (0.74-1.60)	1 more MI per 1000 (4 fewer MIs to 10 more per 1000)	High
Pulmonary Edema (PE) or Congestive Heart Failure (CHF)										
12	Serious[d]	Not serious	Not serious	Serious[e]	None detected	87/3132 (2.8)	114/3125 (3.6)	0.78 (0.45-1.35)	8 fewer PEs or CHFs per 1000 (13 more PEs or CHFs to 20 fewer per 1000)	Low
Stroke or Cerebrovascular Accident (CA)										
13	Not serious	Not serious	Not serious	Not serious	None detected	49/3675 (1.3)	62/3668 (1.7)	0.78 (0.53-1.14)	4 fewer strokes or CAs per 1000 (2 more strokes or CAs to 8 fewer per 1000)	High
Rebleeding										
6	Not serious	Serious[f]	Not serious	Serious[g]	None detected	215/1489 (14.4)	264/1619 (16.3)	0.75 (0.51-1.10)	41 fewer events per 1000 (16 more events to 80 fewer per 1000)	Low
Pneumonia										
14	Not serious	Not serious	Not serious	Not serious	None detected	239/3140 (7.6)	256/3137 (8.2)	0.94 (0.80-1.11)	5 fewer cases of pneumonia per 1000 (9 more cases to 16 fewer per 1000)	High
Thromboembolism										
10	Not serious	Not serious	Not serious	Not serious	None detected	16/2010 (0.8)	21/2009 (1.0)	0.77 (0.41-1.45)	2 fewer thromboembolisms per 1000 (5 more thromboembolisms to 6 fewer per 1000)	High

Abbreviation: RCT, randomized clinical trial.

[a] This Table addresses the question of whether hospitalized adult patients who are hemodynamically stable should receive a restrictive transfusion approach with a hemoglobin threshold of 7 g/dL to 8 g/dL rather than a liberal transfusion approach with a hemoglobin threshold of 9 g/dL to 10 g/dL.

[b] Evaluates the risk of bias, inconsistency based on the heterogeneity among trials, indirectness based on the generalizability of the results, imprecision based on the width of the 95% CIs, and publication bias based on some trials not being published. The Grading of Recommendations Assessment, Development and Evaluation method (eAppendix in the Supplement) was used.

[c] Could be 1 more death to up to 18 more deaths per 1000 in the restrictive transfusion group.

[d] The blinding of participants and personnel was impossible. The blinding of outcome assessment was inconsistent between trials.

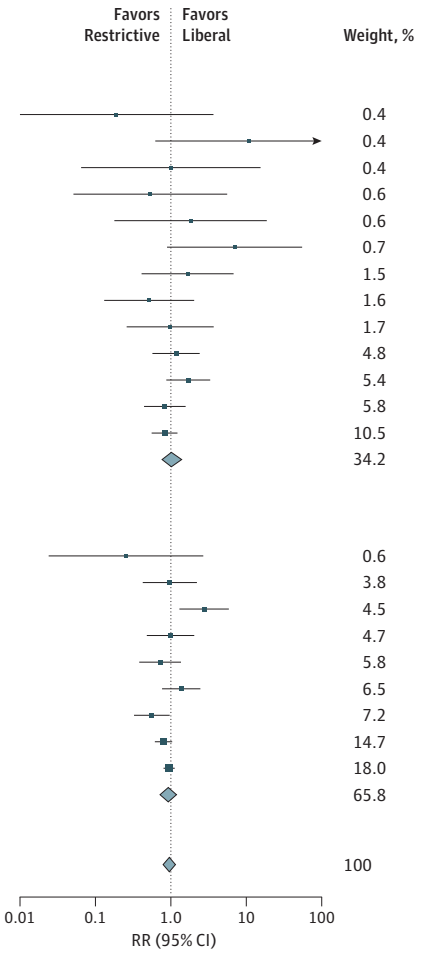
[e] Studies had moderately wide 95% CIs.

[f] I^2 = 58% and P = .04.

[g] Could be 1 more event to up to 16 more events per 1000 in patients in the restrictive transfusion group.

Figure 1. Comparison of 30-Day Mortality Using Restrictive vs Liberal Hemoglobin Transfusion Thresholds in Randomized Clinical Trials

Source	Restrictive Transfusion Threshold No. of Deaths	Restrictive Transfusion Threshold Total No.	Liberal Transfusion Threshold No. of Deaths	Liberal Transfusion Threshold Total No.	RR (95% CI)	Weight, %
Restrictive threshold, hemoglobin <8 to 9 g/dL						
Lotke et al,[75] 1999	0	62	0	65	Not estimable	
Blair et al,[53] 1986	0	26	2	24	0.19 (0.01-3.67)	0.4
Foss et al,[63] 2009	5	60	0	60	11.00 (0.62-194.63)	0.4
Carson et al,[58] 1998	1	42	1	42	1.00 (0.06-15.47)	0.4
Webert et al,[86] 2008	1	29	2	31	0.53 (0.05-5.58)	0.6
Cooper et al,[61] 2011	2	23	1	21	1.83 (0.18-18.70)	0.6
Carson et al,[56] 2013	7	55	1	55	7.00 (0.89-55.01)	0.7
Parker,[78] 2013	5	100	3	100	1.67 (0.41-6.79)	1.5
Bracey et al,[54] 1999	3	215	6	222	0.52 (0.13-2.04)	1.6
Bush et al,[55] 1997	4	50	4	49	0.98 (0.26-3.70)	1.7
Hajjar et al,[68] 2010	15	249	13	253	1.17 (0.57-2.41)	4.8
Gregersen et al,[64] 2015	21	144	12	140	1.70 (0.87-3.32)	5.4
Jairath et al,[72] 2015	14	257	25	382	0.83 (0.44-1.57)	5.8
Carson et al,[60] 2011	43	1009	52	1007	0.83 (0.56-1.22)	10.5
Subtotal	121	2321	122	2451	1.05 (0.78-1.40)	34.2
Heterogeneity: $\tau^2 = 0.02$; $\chi^2_{12} = 13.14$; $P = .36$; $I^2 = 9\%$						
Tests for overall effect: z score = 0.31; $P = .76$						
Restrictive threshold, hemoglobin <7 g/dL						
DeZern et al,[87] 2016	1	59	2	30	0.25 (0.02-2.69)	0.6
Hébert et al,[70] 1995	8	33	9	36	0.97 (0.42-2.22)	3.8
de Almeida et al,[79] 2015	23	101	8	97	2.76 (1.30-5.87)	4.5
Lacroix et al,[74] 2007	14	320	14	317	0.99 (0.48-2.04)	4.7
Walsh et al,[85] 2013	12	51	16	49	0.72 (0.38-1.36)	5.8
Murphy et al,[76] 2015	26	1000	19	1003	1.37 (0.76-2.46)	6.5
Villanueva et al,[84] 2013	19	416	34	417	0.56 (0.32-0.97)	7.2
Hébert et al,[69] 1999	78	418	98	420	0.80 (0.61-1.04)	14.7
Holst et al,[71] 2014	168	502	175	496	0.95 (0.80-1.13)	18.0
Subtotal	349	2900	375	2865	0.94 (0.74-1.19)	65.8
Heterogeneity: $\tau^2 = 0.05$; $\chi^2_8 = 16.09$; $P = .04$; $I^2 = 50\%$						
Tests for overall effect: z score = 0.53; $P = .59$						
Overall	470	5221	497	5316	0.97 (0.81-1.16)	100
Heterogeneity: $\tau^2 = 0.04$; $\chi^2_{21} = 29.75$; $P = .10$; $I^2 = 29\%$						
Tests for overall effect: z score = 0.29; $P = .77$						
Tests for subgroup differences: $\chi^2_1 = 0.34$; $P = .56$; $I^2 = 0\%$						



The size of the data markers indicates the weight of the trial; RR, relative risk. Trials published after 2012 have been published since the prior AABB transfusion guidelines.

period (standard issue) rather than limiting patients to transfusion of only fresh (storage length: <10 days) RBC units (strong recommendation, moderate quality evidence).

Evidence Summary

There were 13 trials meeting the inclusion criteria.[29-41] The trials included neonates and infants with very low birth weights and children and adults; most patients had an acute critical illness or surgical hemorrhage. The trials that were conducted in North America, South America, Europe, Australia, and Africa compared fresher blood with standard-issue blood; however, the storage duration of the standard-issue blood varied between the trials. In the 2 primary trials involving neonates, the mean storage durations at the time of transfusion were 1.6 days and 5.1 days for fresher RBCs compared with 9.0 days and 14.1 days for standard issue RBCs.[31,35] The storage duration of the transfused RBCs in the trials of adults ranged from a median of 4 days (mean, 12.1 days) for fresher RBCs compared with a median of 19 days (mean, 28 days) for standard issue RBCs.

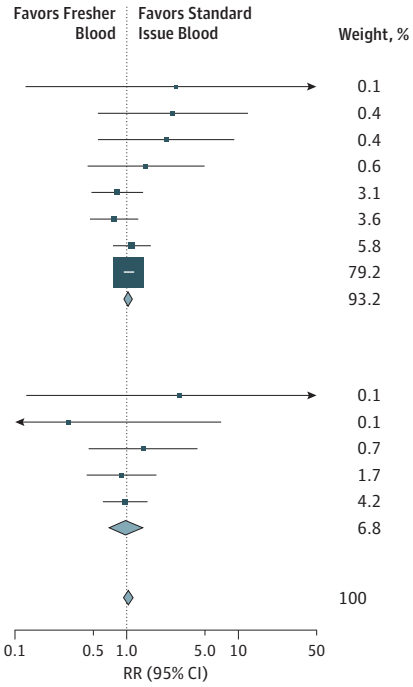
A forest plot shows no evidence that transfusion of fresher RBCs is superior to standard issue RBCs for the outcome of mortality (RR, 1.04; 95% CI, 0.95-1.14) with similar estimates in both adults and infants (**Figure 2**). The association of RBC storage duration on 3 clinical outcomes reported in the trials appears in **Table 3**. The absolute difference in 30-day mortality was 4 more deaths per 1000 with fresher blood (95% CI, 5 fewer deaths to 14 more deaths per 1000).

The RCT quality assessment found no serious risk of bias, inconsistency, indirectness, or publication bias. The overall quality of RCT evidence was moderate for 30-day mortality because the 95% CI included an important decrease in deaths with fresher blood.

There was no evidence to suggest that patients had more adverse events by receiving standard issue RBCs; however, the quality of the evidence was low. For nosocomial infections, there was a higher risk of infection among patients receiving fresher RBCs with an absolute difference of 43 more nosocomial infections per 1000 patients transfused (95% CI, 1 more nosocomial infection to 86 more nosocomial infections per 1000); however, the quality of evidence was low (Table 3).

Figure 2. Association Between Fresher vs Standard-Issue Blood and Mortality in Adults, Neonates, Infants, and Children in Randomized Clinical Trials

Source	Fresher Blood No. of Deaths	Fresher Blood Total No.	Standard Issue Blood No. of Deaths	Standard Issue Blood Total No.	RR (95% CI)	Weight, %
Adults						
Bennett-Guerrero et al,[33] 2009	1	12	0	11	2.77 (0.12-61.65)	0.1
Aubron et al,[34] 2012	5	25	2	26	2.60 (0.55-12.19)	0.4
Schulman et al,[30] 2002	4	8	2	9	2.25 (0.55-9.17)	0.4
Hébert et al,[32] 2005	5	26	4	31	1.49 (0.45-4.98)	0.6
Steiner et al,[41] 2015	23	538	29	560	0.83 (0.48-1.41)	3.1
Kor et al,[37] 2012	17	50	22	50	0.77 (0.47-1.27)	3.6
Heddle et al,[36] 2012	35	309	61	601	1.12 (0.75-1.65)	5.8
Lacroix et al,[40] 2015	448	1211	430	1219	1.05 (0.94-1.17)	79.2
Subtotal	538	2179	550	2507	1.04 (0.95-1.15)	93.2
Heterogeneity: $\tau^2=0$; $\chi^2_7=5.47$; $P=.60$; $I^2=0\%$						
Tests for overall effect: z score = 0.85; $P=.40$						
Neonates, Infants, and Children						
Dhabangi et al,[38] 2013	1	37	0	37	3.00 (0.13-71.34)	0.1
Strauss et al,[29] 1996	0	21	1	19	0.30 (0.01-7.02)	0.1
Dhabangi et al,[39] 2015	7	143	5	143	1.40 (0.45-4.31)	0.7
Fernandes da Cunha et al,[31] 2005	9	26	10	26	0.90 (0.44-1.85)	1.7
Fergusson et al,[35] 2012	30	188	31	189	0.97 (0.61-1.54)	4.2
Subtotal	47	415	47	414	0.99 (0.69-1.42)	6.8
Heterogeneity: $\tau^2=0$; $\chi^2_4=1.46$; $P=.83$; $I^2=0\%$						
Tests for overall effect: z score = 0.06; $P=.96$						
Overall	585	2594	597	2921	1.04 (0.95-1.14)	100
Heterogeneity: $\tau^2=0$; $\chi^2_{12}=7.00$; $P=.86$; $I^2=0\%$						
Tests for overall effect: z score = 0.81; $P=.42$						
Tests for subgroup differences: $\chi^2_1=0.08$; $P=.78$; $I^2=0\%$						



Mortality is based on a composite of the longest follow-up period provided in each trial including 30 days, 90 days, and in-hospital mortality. The size of the data markers indicates the weight of the trial; RR, relative risk.

Rationale for Recommendation

There was consistent evidence in multiple large RCTs performed in a variety of clinical settings among more than 5000 patients. We found no evidence that the transfusion of fresher blood decreased mortality compared with standard-issue blood. However, the RBC storage duration trials did not evaluate patients undergoing a massive or exchange transfusion; neonates and children with underlying renal disease at higher risk of hyperkalemia; patients undergoing intrauterine transfusions; or patients with hemoglobinopathies requiring chronic transfusion support.

Discussion

Transfusion is a common therapeutic intervention for which there is considerable variation in clinical practice.[3-7] If clinicians continue to adopt a restrictive transfusion strategy of 7 g/dL to 8 g/dL, the number of RBC transfusions would continue to decrease.[43] In addition, standard practice should be to initiate a transfusion with 1 unit of blood rather than 2 units. This would have potentially important implications for the use of blood transfusions and minimize the risks of infectious and noninfectious complications.

The average duration of RBC storage in the United States is 17.9 days, although storage duration differs among hospitals and patient populations.[99] Only a small proportion of patients in the RCTs would have been exposed to RBCs near the storage expiration (35-42 days), which could be the products most affected by storage lesions. The standard issue RBC storage duration for neonates is often less than for adult patients; this was true in the 2 primary trials involving neonates.[31,35] However, there was no overall signal that standard issue RBCs were harmful and the overall RR estimate trended toward a lower mortality when standard issue RBCs were used for transfusions.

Limitations

These guidelines are based on the best, but nevertheless incomplete, evidence available today. The hemoglobin transfusion thresholds that have been assessed may not be optimal. The use of hemoglobin transfusion thresholds may be an imperfect surrogate for oxygen delivery. The trials evaluating RBC storage duration have not assessed the effect of long-term storage (near the 42-day expiration for RBC units stored with additive solution); hence, the application of the AABB's recommendation to centers with predominately RBCs stored for longer than 35 days is unknown.

Comparison With Other Guidelines

Red blood cell transfusion guidelines[100-107] from 8 societies during the past 5 years addressed hemoglobin transfusion thresholds. Each of the guidelines recommended a restrictive transfusion strategy with most advising a hemoglobin threshold of 7 g/dL in asymptomatic patients.[101,103,104,106] The updated American Society of Anesthesiology task force guidelines recommended a restrictive hemoglobin transfusion strategy between 6 g/dL and 10 g/dL that was determined by the potential for ongoing bleeding and other clinical variables.[107] In symptomatic patients, these guidelines suggest that

Table 3. Evidence for the Association Between Red Blood Cell (RBC) Storage Duration and Adverse Patient Outcomes[a]

No. of RCTs	Quality Assessment[b]					Storage Duration of RBCs, No./Total (%)		Effect		Quality of RCTs
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Fresher[c]	Standard Issue[d]	Relative Risk (95% CI)	Absolute Risk (95% CI)	
Primary Outcome: 30-d Mortality[e]										
13	Not serious	Not serious	Not serious	Serious	None detected	585/2594 (22.6)	597/2921 (20.4)	1.04 (0.95-1.14)	4 more deaths per 1000 (5 fewer deaths to 14 more per 1000)	Moderate
Secondary Outcomes										
Adverse Events										
3	Not serious	Not serious	Serious	Serious	None detected	288/1781 (16.2)	295/1804 (16.4)	1.02 (0.91-1.14)	1 more adverse event per 1000 (2 fewer events to 4 more per 1000)	Low
Nosocomial Infections										
4	Not serious	Not serious	Serious	Serious	None detected	605/1958 (30.9)	568/1982 (28.7)	1.09 (1.00-1.18)	43 more infections per 1000 (1 more infection to 86 more per 1000)	Low

Abbreviation: RCT, randomized clinical trial.

[a] This Table was modified from the meta-analysis published by Alexander et al[44] with the addition of 1 trial.[39] This Table addresses the question of whether fresher blood compared with standard-issue blood should be used for patients of any age treated for a medical emergency or surgery at hospitals, intensive care units, and emergency departments.

[b] Evaluates the risk of bias, inconsistency based on the heterogeneity among trials, indirectness based on the generalizability of the results, imprecision based on the width of the 95% CIs, and publication bias based on some trials not being published. The Grading of Recommendations Assessment, Development and Evaluation method (eAppendix in the Supplement) was used.

[c] Ten studies defined fresher storage duration as 3 days to 10 days; 2 studies defined it as the freshest blood in inventory; and 1 study defined it as less than 20 days.

[d] Nine studies just used the term *standard issue* and storage duration was not provided, 3 studies defined it as greater than or equal to 20 days, and 1 study defined it as 25 days to 35 days.

[e] Based on a composite of the longest follow-up period provided in each trial including 30 days, 90 days, and in-hospital mortality.

transfusion should be administered to prevent symptoms.[102,103,106] The guidelines from the National Blood Authority of Australia emphasized that the hemoglobin level alone should not dictate transfusion but that it should also be based on clinical status.[103] The guidelines from the National Comprehensive Cancer Network for patients with anemia induced by cancer and chemotherapy did not address whether thrombocytopenia should influence transfusion thresholds but suggested transfusion for symptoms.[106]

In contrast to the AABB recommendations, several guidelines provided specific guidance for patients with acute coronary syndrome that differ from guideline to guideline. The British Committee for Standards in Haematology recommended hemoglobin level be maintained at 8 g/dL to 9 g/dL.[104] The National Comprehensive Cancer Network recommended a hemoglobin transfusion goal of greater than 10 g/dL.[106] The National Blood Authority of Australia recommended that a hemoglobin level greater than 8 g/dL be maintained to possibly reduce mortality but that higher levels are uncertain.[103] The European Society of Cardiology recommended transfusion for patients with a hemoglobin level of less than 7 g/dL unless the patient is not hemodynamically stable.[100] The American College of Physicians recommended a hemoglobin transfusion threshold of 7 g/dL to 8 g/dL in hospitalized patients who have either coronary heart disease or acute coronary syndrome.[105]

The AABB recommendation for RBC storage is more specific than those from other groups, which were promulgated prior to publication of most of the RCTs that provided evidence for the AABB recommendation. For example, the British Committee for Standards in Haematology and the American College of Critical Care Medicine noted a lack of evidence to recommend fresher compared with standard issue RBCs.[10,104] The Australian and New Zealand Society of Blood Transfusion suggested that fresher RBCs (<5 days old) may be indicated in special situations for children and neonates.[108] The guidelines from the Kidney Disease Improving Global Outcomes Work Group suggests use of fresher RBCs for patients with end-stage renal disease may maximize posttransfusion survival.[102]

Research Recommendations

Areas of uncertainty for which RCTs are needed include trials in patient populations outside the intensive care unit that include but are not limited to patients with anemia and thrombocytopenia, patients requiring chronic transfusions and those with coagulopathy, hemorrhagic shock, or both. Furthermore, trials that examine lower hemoglobin transfusion thresholds are needed in patients with acute coronary syndrome and those with cardiovascular disease. A recent meta-analysis of selected trials found a higher risk of acute coronary syndrome but not 30-day morality among patients with cardiovascular disease who received a restrictive transfusion strategy compared with a liberal transfusion strategy.[109] Although ongoing trials[110-112] evaluating RBC storage duration should be completed, additional trials do not appear warranted at this time.

Conclusions

Research in RBC transfusion medicine has significantly advanced the science in recent years and provides high-quality evidence to inform guidelines. A restrictive transfusion threshold is safe in most clinical settings and the current blood banking practices of using standard-issue blood should be continued.

JAMA | Original Investigation

Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients With Acute Myocardial Infarction and Anemia
The REALITY Randomized Clinical Trial

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IMPORTANCE The optimal transfusion strategy in patients with acute myocardial infarction and anemia is unclear.

OBJECTIVE To determine whether a restrictive transfusion strategy would be clinically noninferior to a liberal strategy.

DESIGN, SETTING, AND PARTICIPANTS Open-label, noninferiority, randomized trial conducted in 35 hospitals in France and Spain including 668 patients with myocardial infarction and hemoglobin level between 7 and 10 g/dL. Enrollment could be considered at any time during the index admission for myocardial infarction. The first participant was enrolled in March 2016 and the last was enrolled in September 2019. The final 30-day follow-up was accrued in November 2019.

INTERVENTIONS Patients were randomly assigned to undergo a restrictive (transfusion triggered by hemoglobin ≤8; n = 342) or a liberal (transfusion triggered by hemoglobin ≤10 g/dL; n = 324) transfusion strategy.

MAIN OUTCOMES AND MEASURES The primary clinical outcome was major adverse cardiovascular events (MACE; composite of all-cause death, stroke, recurrent myocardial infarction, or emergency revascularization prompted by ischemia) at 30 days. Noninferiority required that the upper bound of the 1-sided 97.5% CI for the relative risk of the primary outcome be less than 1.25. The secondary outcomes included the individual components of the primary outcome.

RESULTS Among 668 patients who were randomized, 666 patients (median [interquartile range] age, 77 [69-84] years; 281 [42.2%] women) completed the 30-day follow-up, including 342 in the restrictive transfusion group (122 [35.7%] received transfusion; 342 total units of packed red blood cells transfused) and 324 in the liberal transfusion group (323 [99.7%] received transfusion; 758 total units transfused). At 30 days, MACE occurred in 36 patients (11.0% [95% CI, 7.5%-14.6%]) in the restrictive group and in 45 patients (14.0% [95% CI, 10.0%-17.9%]) in the liberal group (difference, −3.0% [95% CI, −8.4% to 2.4%]). The relative risk of the primary outcome was 0.79 (1-sided 97.5% CI, 0.00-1.19), meeting the prespecified noninferiority criterion. In the restrictive vs liberal group, all-cause death occurred in 5.6% vs 7.7% of patients, recurrent myocardial infarction occurred in 2.1% vs 3.1%, emergency revascularization prompted by ischemia occurred in 1.5% vs 1.9%, and nonfatal ischemic stroke occurred in 0.6% of patients in both groups.

CONCLUSIONS AND RELEVANCE Among patients with acute myocardial infarction and anemia, a restrictive compared with a liberal transfusion strategy resulted in a noninferior rate of MACE after 30 days. However, the CI included what may be a clinically important harm.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02648113

Visual Abstract

Supplemental content

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JAMA. 2021;325(6):552-560. doi:10.1001/jama.2021.0135

Anemia, with or without overt bleeding, is common in patients with acute myocardial infarction (AMI) and affects prognosis. Even moderate levels of anemia (hemoglobin level of 10-12 g/dL) are associated with increased cardiovascular mortality compared with normal hemoglobin values in the context of acute coronary syndromes.[1] Transfusion is often considered to be indicated when the hemoglobin level falls below 10 g/dL, with large variations in clinical practice due to lack of robust data. Observational studies have yielded conflicting results[2-4] and only 2 small randomized trials (including 45 and 110 patients) have compared restrictive with liberal transfusion strategies in this setting.[5,6] Large randomized trials have compared transfusion strategies in patients with gastrointestinal bleeding[7] and those undergoing surgical procedures[8-10] and generally found benefit from a restrictive strategy, but these trials excluded patients with AMI.[11]

In addition to uncertain benefit in patients with AMI, transfusion has potential adverse effects, logistical implications (particularly for blood supply), and cost. The objective of this study, the Restrictive and Liberal Transfusion Strategies in Patients With Acute Myocardial Infarction (REALITY) randomized trial, was to determine whether a restrictive transfusion strategy was clinically noninferior to a liberal transfusion strategy.

Key Points

Question Is a restrictive strategy of blood transfusion noninferior to a liberal strategy among patients with acute myocardial infarction and anemia?

Findings In this randomized clinical trial that included 668 patients with acute myocardial infarction and hemoglobin level between 7 and 10 g/dL who were treated with a restrictive transfusion strategy (triggered by hemoglobin ≤8 g/dL) vs a liberal strategy (triggered by hemoglobin ≤10 g/dL), the composite outcome (all-cause death, stroke, recurrent myocardial infarction, or emergency revascularization) at 30 days occurred in 11% vs 14% of patients, a difference that met the noninferiority criterion of relative risk less than 1.25.

Meaning A restrictive transfusion strategy compared with a liberal strategy resulted in a noninferior rate of major cardiovascular events among patients with acute myocardial infarction and anemia, but the CI included what may be a clinically important harm.

Methods

The protocol and statistical analysis plan are presented in Supplement 1. The trial was approved by the Comité de Protection des Personnes, Ile de France-I, France, and the ethics committee at the Hospital Clinic, Barcelona, Spain. Patients provided written informed consent.

Trial Population

To be eligible for inclusion, patients had to be aged at least 18 years and have AMI (with or without ST-segment elevation with a combination of ischemic symptoms occurring in the 48 hours before admission and elevation of biomarkers of myocardial injury) and a hemoglobin level between 7 and 10 g/dL. Enrollment could be considered at any time during the index admission for myocardial infarction. Exclusion criteria were shock at the time of randomization (systolic blood pressure <90 mm Hg with clinical signs of low output or requiring inotropic drugs), myocardial infarction occurring after percutaneous coronary intervention or coronary artery bypass graft, life-threatening or massive ongoing bleeding (judged by the investigator), blood transfusion in the past 30 days, and malignant hematologic disease. Given the higher prevalence of chronic anemia in certain ethnic groups, race/ethnicity was recorded (self-reported using fixed categories).

Randomization and Interventions

Patients were randomly assigned in a 1:1 ratio to undergo a restrictive or a liberal transfusion strategy. A web-based randomization system was used, with a centralized block randomization list with blocks of varying size (range, 2-6), stratified by center. In the restrictive strategy group, no transfusion was to be performed unless hemoglobin level decreased to less than or equal to 8 g/dL, with a target range for posttransfusion hemoglobin of 8 to 10 g/dL (the initial protocol used a threshold of 7 g/dL but this was changed to 8 g/dL to maximize investigator adherence to the protocol before inclusion of the first patient). In the liberal strategy group, transfusion was to be performed after randomization on all patients with a hemoglobin level less than or equal to 10 g/dL, with a target posttransfusion hemoglobin level of at least 11 g/dL. Homologous leukoreduced packed red blood cells were used for transfusion.

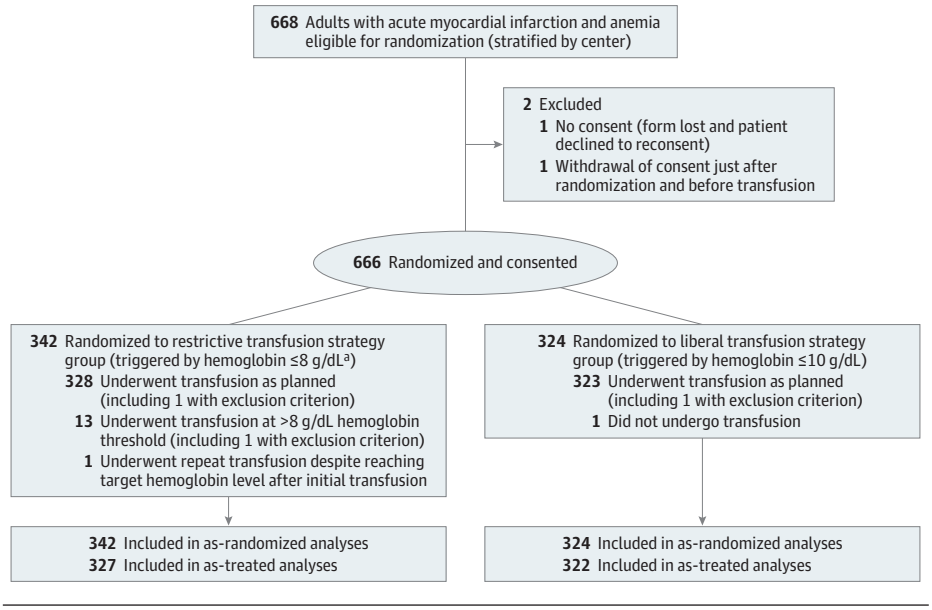
Both strategies were to be maintained until patient discharge or 30 days after randomization, whichever occurred first. The protocol allowed transfusion to be administered at any time in the following documented instances: massive overt active bleeding, presumed important decrease in hemoglobin level and no time to wait for hemoglobin measurement (indicating suspected massive bleeding), and shock presumably due to blood loss occurring after randomization.

After discharge, patient follow-up was scheduled at day 30 (±5 days) and follow-up data were collected by the investigator, either by direct contact (if the patient was still hospitalized) or by a visit, phone call, or mail. Group assignment was not blinded for data collection.

Outcome Measures and Definitions

The primary clinical efficacy outcome was a composite of major adverse cardiovascular events (MACE) at 30 days, defined as all-cause death, nonfatal stroke, nonfatal recurrent myocardial infarction, or emergency revascularization prompted by ischemia. Secondary outcomes included the individual components of the composite MACE outcome at 30 days and 1 year. Descriptive end points included the baseline characteristics of patients, use of transfusion, hemoglobin values, and bleeding episodes in each group. The current analysis reports 30-day clinical outcomes. The 1-year outcomes and the cost-effectiveness analyses will be reported separately. Adverse events were monitored during hospital stay and included the following potential adverse effects of transfusion: hemolysis, documented bacteremia acquired after transfusion, multiorgan system dysfunction, acute respiratory distress syndrome, acute heart failure, acute kidney

Figure 1. Flow of Patients in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients With Acute Myocardial Infarction and Anemia



[a] The initial protocol specified a threshold of 7 g/dL. This was changed to 8 g/dL to maximize investigator adherence to the protocol before inclusion of the first patient. Enrollment took place at any time during hospitalization. No screening log was maintained.

failure, and severe allergic reactions. All components of the primary efficacy clinical outcome as well as acute heart failure were adjudicated by a critical event committee blinded to treatment assignment and hemoglobin levels. The third universal definition of myocardial infarction was used.[12] All other safety outcomes were investigator-reported. Outcome definitions are detailed in eAppendix 1 in Supplement 2.

Statistical Analysis

Based on unpublished observations from the French nationwide FAST-MI registry of AMI,[13,14] we assumed the percentages of patients with MACE at 30 days of approximately 11% in the restrictive transfusion group and 15% in the liberal transfusion group. Noninferiority was assessed using a CI method with a 1-sided 97.5% CI and without any other statistical tests, as recommended by the International Conference on Harmonization.[15] The noninferiority margin was set using a relative, rather than absolute, risk margin to minimize the risk of overestimating event rates when planning the trial, because this can make it easy to achieve noninferiority if the overall event rate is lower than expected.[16,17] With these assumptions, a sample size of 300 patients per group would provide 80% power to demonstrate noninferiority of the restrictive group, with a margin corresponding to a relative risk equal to 1.25. With a conservative hypothesis of 5% of patients with major protocol violations, 630 patients (315 per group) were required for the trial to be adequately powered for the noninferiority analysis. Because there was no established clinical superiority of either transfusion strategy and no randomized trial of transfusion vs no transfusion, the choice of a noninferiority margin was based on clinical judgment based on what clinicians would be prepared to accept as potential loss of efficacy of a restrictive transfusion strategy compared with a liberal strategy given the expected theoretical benefits of the former of sparing scarce blood resources,[18] reducing transfusion adverse effects, and reducing logistical burden and costs. A relative margin of 1.25 appeared an acceptable compromise, given that observational studies relating hemoglobin levels and outcomes after myocardial infarction have shown that the likelihood of MACE increased, with an adjusted odds ratio of 1.45 for each 1-g/dL decrement in hemoglobin below 11 g/dL,[1] and the expected difference in hemoglobin values between treatment groups would be expected to exceed 1 g/dL.

The analysis of the primary efficacy outcome used relative risk, defined as p_1/p_2, with $p_1 = n_{11}/n_1$ and $p_1 = n_{21}/n_2$, where n_{11} is the event number and n_1 is the total number of patients in the restrictive group and n_{21} is the event number and n_2 is the total number of patients in the liberal group. Ninety-five percent CIs were estimated using the Wald method. The analysis was performed among both the as-treated population, which included all patients without a major protocol violation (including eligibility criteria not fulfilled), and the as-randomized population, which included all randomized patients with the exception of 2 patients (1 without a consent form and 1 who withdrew consent immediately after randomization). Concordance in the noninferiority analysis between the as-randomized and the as-treated populations was required to establish noninferiority. The use of multiple imputation methods was planned in the statistical analysis plan in the case of missing data for the primary clinical outcome. Given the absence of missing data at day 30, imputation was not needed. Because the trial was conducted at multiple sites, site effect was accounted for in a post hoc sensitivity analysis using a generalized linear regression mixed model with binary distribution and a log link function with strategy as a fixed effect and center as a random effect. If clinical noninferiority of the restrictive strategy was established, a test of superiority of the restrictive strategy was planned.

Table 1. Baseline Characteristics of the As-Randomized Population in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Patients With Acute Myocardial Infarction and Anemia

Characteristic	No. (%)[a] Restrictive (n = 342)	Liberal (n = 324)
Age, median (IQR), y	78 (69-85)	76 (69-84)
Sex		
Men	201 (58.8)	184 (56.8)
Women	141 (41.2)	140 (43.2)
Race (self-reported)	n = 336	n = 322
White	298 (88.7)	266 (82.6)
North African	29 (8.6)	36 (11.2)
African/Caribbean	7 (2.1)	9 (2.8)
Indian	2 (0.6)	5 (1.6)
Other Asian	0	6 (1.9)
BMI, mean (SD)	26.9 (5.3) [n = 334]	26.4 (5.0) [n = 317]
Risk factor[b]		
Hypertension	272 (79.5)	256 (79.0)
Dyslipidemia	189 (55.3)	201 (62.0)
Diabetes	176 (51.5)	158 (48.8)
Tobacco smoking status	n = 316	n = 293
Never	149 (47.2)	141 (48.1)
Former	116 (36.7)	111 (37.9)
Current	51 (16.1)	41 (14.0)
Family history of premature coronary artery disease	46 (13.6) [n = 337]	43 (13.4) [n = 321]
Cardiac history before index event[b]		
Acute coronary syndrome	121 (35.4)	119 (36.7)
Percutaneous coronary intervention	114 (33.3)	111 (34.3)
Angina	55 (16.1)	44 (13.6)
Atrial fibrillation	54 (15.8)	65 (20.1)
CABG	44 (12.9)	42 (13.0)
Congestive heart failure	44 (12.9)	38 (11.7)
Internal cardiac defibrillator	14 (4.1)	8 (2.5)
Noncardiac medical history[b]		
Chronic anemia[c]	61 (17.8)	62 (19.1)
Cancer		
Previously treated	42 (12.3)	44 (13.6)
Receiving treatment	25 (7.3)	18 (5.6)
COPD	34 (9.9)	40 (12.3)
Dialysis	25 (7.3)	30 (9.3)
History of bleeding requiring hospitalization and transfusion	23 (6.7)	20 (6.2)
Index hospitalization		
Myocardial infarction type		
Non-ST-segment elevation	234 (68.4)	231 (71.3)
ST-segment elevation	108 (31.6)	93 (28.7)
Killip class at admission[d]	n = 336	n = 321
I	189 (56.3)	183 (57.0)
II	87 (25.9)	88 (27.4)
III	54 (16.1)	39 (12.1)
IV	6 (1.8)	11 (3.4)
Delay between admission and randomization, median (IQR), d	1.6 (0.8-3.6)	1.9 (0.8-3.6)
Active bleeding[e]	36 (10.5)	49 (15.1)
1 active bleed	29 (80.6)	42 (85.7)
2 active bleeds	6 (16.7)	6 (12.2)
3 active bleeds	1 (2.8)	1 (2.0)
Creatinine clearance at randomization,[f] median (IQR), mL/min/1.73 m^2	45.1 (27.2-73.2) [n = 338]	46.6 (24.9-73.2) [n = 321]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

[a] Percentages may not add to 100 due to rounding.

[b] Collected through chart review.

[c] Preexisting anemia not caused by acute bleeding.

[d] Killip class was determined by the investigator according to clinical examination. Class I indicates no sign of congestion; class II, basal rales on auscultation; class III, acute pulmonary edema; and class IV, cardiogenic shock.

[e] Active bleeding identified and documented during the index admission prior to randomization.

[f] According to the Chronic Kidney Disease Epidemiology Collaboration formula.

Table 2. Hemoglobin Levels and Transfusions Among the As-Randomized Population in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Patients With Acute Myocardial Infarction and Anemia

Variable	No. (%)	
	Restrictive (n = 342)	Liberal (n = 324)
Hemoglobin level, mean (SD), g/dL		
At admission	10.0 (1.7)	10.1 (1.6) [n = 322]
Most recent prior to randomization	9.0 (0.8)	9.1 (0.8) [n = 323]
Lowest value during hospital stay	8.3 (0.9)	8.8 (0.9) [n = 323]
At discharge	9.7 (1.0) [n = 337]	11.1 (1.4) [n = 320]
Red blood cell transfusion		
Patients who received ≥1 unit of packed red blood cells	122 (35.7)	323 (99.7)[a]
Units transfused, No.	342	758
Per patient transfused, mean (SD)	2.9 (3.7)	2.8 (2.7)
Per patient transfused, median (IQR)	2.0 (2.0-3.0)	2.0 (2.0-3.0)
Units transfused		
0	220 (64.3)	1 (0.3)
1	25 (7.3)	43 (13.3)
2	62 (18.1)	128 (39.5)
3	12 (3.5)	47 (14.5)
≥4	19 (5.6)	54 (16.7)
≥1 (exact No. not available)	4 (1.2)	51 (15.7)
Duration of red blood cell storage, median (IQR), d	20.0 (17.0-25.0)	21.0 (15.0-30.0)
No. of units for which data were available	90	299
Transfusion		
Fresh frozen plasma	3 (0.9)	7 (2.2)
Platelet	4 (1.2)	6 (1.9)

Abbreviation: IQR, interquartile range.

[a] One patient had been transferred to a non-study site where local physicians declined to implement transfusion.

All secondary analyses were performed on the as-randomized population with available data. In a secondary analysis of the main outcome, survival was estimated using the Kaplan-Meier method and groups were compared using a log-rank test. A stratified Cox proportional hazards model was used to estimate the hazard ratios and 95% CIs for the effect of transfusion strategy on MACE-free survival and each component of the MACE outcome. Data for patients with no evidence of MACE were censored at 30 days. The risk proportionality hypothesis was verified by testing the interaction between interest variable and time.

Differences and 95% CIs between strategies were estimated using the Wald method, with continuity correction for binary variables. No adjustment was planned for multiplicity and there was no prespecified hierarchy for secondary efficacy outcomes. Because of the potential for type I error due to multiple comparisons, analyses of secondary end points should be interpreted as exploratory. The effect of transfusion strategy on the primary composite outcome was explored in subgroups of clinical interest (age, sex, body weight, presence or absence of diabetes, smoking status, presence or absence of hypertension, presence or absence of dyslipidemia, Killip class, kidney function [creatinine clearance], presence or absence of active bleeding, hemoglobin levels at the time of randomization, ST- vs non–ST-segment elevation myocardial infarction, and revascularization by percutaneous coronary intervention for the index event before or after randomization); the interaction between subgroup and transfusion strategy was tested using logistic regression. For safety adverse events, only point estimates of treatment effects with 2-sided 95% CIs are provided. All superiority tests and 95% CI were 2-sided, and *P* values <.05 were considered significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 3.6.3 (R Foundation for Statistical Computing).

Results

Descriptive Findings

From March 2016 to September 2019, a total of 668 patients with AMI and anemia were consecutively enrolled in the trial (in 26 centers in France and 9 centers in Spain; **Figure 1**). Baseline characteristics of the as-randomized population were similar between the groups (**Table 1**). The median age of patients was 77 years, 385 (57.8%) were men, and 334 (50.2%) had diabetes. In most patients, the cause of anemia was unknown; 43 patients (6.5%) had a history of bleeding requiring hospitalization and transfusion. The qualifying myocardial infarction was non–ST-elevation myocardial infarction in approximately two-thirds of the patients. A minority of patients had an identified active bleeding site (Table 1; eTable 1 in Supplement 2).

In-hospital management is detailed in eTable 2 in Supplement 2. Most patients underwent coronary angiography (81.9% in the restrictive group and 79.3% in the liberal group) and approximately two-thirds underwent myocardial revascularization. Treatments before hospitalization and during the first 24 hours of admission are shown in eTable 3 in Supplement 2. Most patients received dual antiplatelet therapy for the qualifying myocardial infarction. Baseline characteristics and treatment of the as-treated population are shown in eTable 4 in Supplement 2 and were consistent with the as-randomized population.

Hemoglobin levels were similar in both groups at admission and at randomization (**Table 2**). A total of 122 patients (35.7%) in the restrictive group and 323 (99.7%) in the liberal group received at least 1 transfusion. The distribution of the number of red blood cell units transfused per patient is shown in Table 2. In the liberal group, the majority of patients received 2 or more units. The restrictive group used 342 red blood cell units and the liberal group used 758. Few patients received concomitant fresh frozen plasma or platelet transfusion. The in-hospital hemoglobin nadir was lower in the restrictive group than the liberal group.

The median (interquartile range) length of hospitalization was 7.0 (3.0-13.0) days in both groups; 56 patients in both the restrictive strategy (16.4%) and liberal strategy (17.3%) groups were hospitalized in an intensive care unit. At discharge, mean (SD) hemoglobin was 9.7 (1.0) g/dL in the restrictive group compared with 11.1 (1.4) g/dL in the liberal group (difference, −1.4 [95% CI, −1.6 to −1.2]; Table 2). Data for the as-treated population are provided in eTable 5 in Supplement 2.

Table 3. Primary and Secondary Outcomes at 30 Days Among the As-Randomized Population in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Patients With Acute Myocardial Infarction and Anemia

Outcome	No. (%)		Difference (95% CI), %	Relative risk (1-sided 97.5% CI)
	Restrictive	Liberal		
Primary (major adverse cardiovascular events), No./total No. (%) [95% CI][a]				
As-treated population	36/327 (11.0) [7.5 to 14.6]	45/322 (14.0) [10.0 to 17.9]	−3.0 (−8.4 to 2.4)	0.79 (0.00 to 1.19)
As-randomized population	38/342 (11.1) [7.6 to 14.6]	46/324 (14.2) [10.2 to 18.2]	−3.1 (−8.4 to 2.3)	0.78 (0.00 to 1.17)
Secondary (individual outcomes in the as-randomized population)[b]	**n = 342**	**n = 324**		
All-cause death	19 (5.6)	25 (7.7)		
Cardiovascular	13 (68.4)	21 (84.0)		
Noncardiovascular	3 (15.8)	2 (8.0)		
Unknown	3 (15.8)	2 (8.0)		
Nonfatal recurrent myocardial infarction[c]	7 (2.1)	10 (3.1)		
ST-segment elevation recurrent myocardial infarction	0	3 (30.0)		
Non-ST-segment elevation recurrent myocardial infarction	7 (100.0)	7 (70.0)		
Type 1: spontaneous recurrent myocardial infarction	4 (57.1)	4 (40.0)		
Type 2: recurrent myocardial infarction secondary to an ischemic imbalance	2 (28.6)	5 (50.0)		
Type 4b: recurrent myocardial infarction related to stent thrombosis	1 (14.3)	1 (10.0)		
Emergency revascularization	5 (1.5)	6 (1.9)		
Nonfatal ischemic stroke	2 (0.6)	2 (0.6)		

[a] Composite of all-cause death, stroke, recurrent myocardial infarction, or emergency revascularization prompted by ischemia at 30 days.

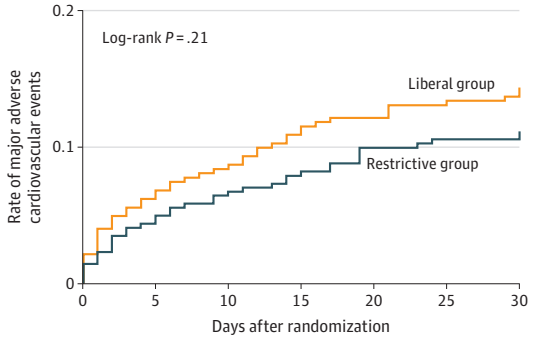
[b] Given the potential for type I error due to multiple comparisons, no formal statistical comparisons were made for secondary outcomes.

[c] Type of myocardial infarction was adjudicated by a blinded event committee, according to the third universal definition of myocardial infarction.[12]

Primary Efficacy Outcome

Follow-up data for 30-day MACE were complete for all 666 patients who consented and were randomized. In the as-treated population, 30-day MACE occurred in 36 patients (11.0% [95% CI, 7.5%-14.6%]) in the restrictive group and in 45 patients (14.0% [95% CI, 10.0%-17.9%]) in the liberal group (relative risk, 0.79 [1-sided 97.5% CI, 0.00-1.19]), fulfilling the criterion for noninferiority (**Table 3**). Noninferiority of the restrictive strategy was also achieved in the as-randomized population (relative risk, 0.78 [1-sided 97.5% CI, 0.00-1.17]). Similar results were found in post hoc sensitivity analyses accounting for site effects (as-treated population: relative risk, 0.79 [1-sided 97.5% CI, 0.00-1.18]; as-randomized population: relative risk, 0.78 [1-sided 97.5% CI, 0.00-1.17]). In the planned sequential superiority analysis performed among the as-randomized population (**Figure 2**), the restrictive strategy did not meet criteria for superiority compared with the liberal strategy (upper bound of 1-sided 97.5% CI >1.00).[19] Subgroup analyses based on age; sex; body weight; smoking status; Killip class; kidney function (creatinine clearance); type of myocardial infarction (ST- vs non-ST-segment elevation myocardial infarction); presence or absence of diabetes, hypertension, dyslipidemia, and active bleeding; and hemoglobin levels at the time of randomization yielded results consistent with the main analysis, and results of the tests for interaction were not statistically significant (eFigure in Supplement 2).

Figure 2. Rate of Major Adverse Cardiovascular Events in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy Among Patients With Acute Myocardial Infarction and Anemia



No. of patients at risk

Liberal group	324	301	293	285	281	278	275
Restrictive group	342	326	319	314	307	305	305

Results shown are of analyses including the as-randomized population. All patients were followed up to the first event or 30 days. Major adverse cardiovascular events are a composite of all-cause death, stroke, recurrent myocardial infarction, or emergency revascularization prompted by ischemia.

Secondary Efficacy Outcomes

Components of 30-day MACE are detailed in Table 3. In the restrictive group vs the liberal group, all-cause death occurred in 5.6% vs 7.7% of patients, recurrent myocardial infarction occurred in 2.1% vs 3.1% of patients, emergency revascularization prompted by ischemia occurred in 1.5% vs 1.9% of patients, and nonfatal ischemic stroke occurred in 0.6% of patients in both groups. Secondary outcomes in the as-treated population are provided in eTable 6 in Supplement 2.

Table 4. Adverse Events Among the As-Randomized Population in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Patients With Acute Myocardial Infarction and Anemia

Adverse event	No. (%)	
	Restrictive (n = 342)	Liberal (n = 324)
At least 1 adverse event	40 (11.7)	36 (11.1)
Acute kidney injury[a]	33 (9.7)	23 (7.1)
Acute heart failure[b]	11 (3.2)	12 (3.7)
Severe allergic reaction[a]	3 (0.9)	0
Acute lung injury/ARDS[a]	1 (0.3)	7 (2.2)
Multiorgan system dysfunction[a]	1 (0.3)	3 (0.9)
Infection[a,c]	0	5 (1.5)

Abbreviation: ARDS, acute respiratory distress syndrome.

[a] According to investigator judgment.

[b] Adjudicated according to the following criteria: new or worsening symptoms due to congestive heart failure, objective evidence of new congestive heart failure (physical examination, laboratory, imaging or hemodynamic evidence), and initiation or intensification of chronic heart failure treatment.

[c] Documented bacterial infection/bacteremia acquired at any time after the first transfusion.

Adverse Events

Adverse events are presented in **Table 4** for the as-randomized population and in eTable 6 in Supplement 2 for the as-treated population.

Discussion

Among patients with AMI and anemia, a restrictive compared with a liberal transfusion strategy resulted in a noninferior rate of MACE after 30 days. However, the CI included what may be a clinically important harm.

Anemia is common in patients with AMI and is associated with worse clinical outcomes.[1] In theory, transfusion should increase oxygen delivery, which would argue for a liberal transfusion strategy in patients with acute myocardial ischemia. However, data suggest that oxygen delivery is not necessarily increased in patients receiving transfusions, due to red blood cell depletion in nitric oxide and 2,3-diphosphoglyceric acid during storage, and that, conversely, transfusion may increase platelet activation and aggregation and produce vasoconstriction.[20,21] Observational studies have yielded uncertain results and are susceptible to unmeasured confounding,[22] highlighting the need for randomized trials.[23] To our knowledge, only 2 small randomized trials that examine transfusion in individuals with myocardial infarction are available, and they reported opposite conclusions. The first trial, which included 45 patients, found apparent benefit of a restrictive over a liberal transfusion strategy and the second pilot trial, which included 110 patients, found numerically fewer cardiac events and deaths with a liberal strategy, but no statistically significant difference, and led the authors to support the need for a definitive trial.[6,22] There is wide variation in clinical practice regarding the use of transfusion for patients with AMI.[24] Given the persistent equipoise in the clinical community regarding what transfusion strategy is optimal in the specific setting of AMI, there have been multiple calls for generating more evidence from randomized trials.[4,11,22,25]

Uncertainty exists on the optimal transfusion strategy and on what hemoglobin level should trigger transfusion in this population. In patients with AMI and anemia, the current trial showed statistical noninferiority of the restrictive strategy compared with the liberal strategy in both the as-randomized and as-treated populations, providing some confidence in the results.[26] However, determination of the margin used to declare noninferiority is critical to the interpretation of the result. This determination can be based on computation of preservation of at least a fraction of the benefit of an established treatment (often in the range of 50% preservation of the benefit). In the case of AMI, no trial to our knowledge has compared transfusion with no transfusion. However, a large observational analysis of the relationship between anemia and mortality after AMI showed that the risk of MACE increased, with an adjusted odds ratio of 1.45 (95% CI, 1.33-1.58) for each 1-g/dL decrement in hemoglobin below 11 g/dL.[1] A 25% relative noninferiority margin would preserve a substantial fraction of the expected benefit of transfusion, because the anticipated difference in hemoglobin value was expected to exceed 1 g/dL (as was actually observed). The noninferiority margin should also be justifiable on clinical grounds based on the estimate of what clinicians would find clinically acceptable as a potential loss of efficacy with an "experimental" strategy compared with an established strategy, given the benefits of the former. In the present setting, the theoretical advantages of the restrictive strategy would be reduced consumption of increasingly scarce blood resources,[18] reduced adverse effects from transfusion, potential cost savings, and logistical benefits related to the implementation of transfusion. The choice of a 25% relative increase as the margin for noninferiority was more conservative than the margin used in many recent large trials,[27-31] but did not eliminate inferiority. In any case, it is recommended that clinicians use their own judgment in interpreting noninferiority thresholds.[32] Although the 30-day primary clinical outcome was numerically lower with the restrictive strategy, this difference did not achieve statistical significance for superiority. Although the decision to initiate transfusion should not be based on hemoglobin level alone, the observed result suggests there may be merit to a restrictive strategy, which had no apparent downside in terms of logistics. Heart rate was not factored in the decision to initiate transfusion, particularly because most patients with AMI receive β-blockers.

Limitations

This study has several limitations. First, it was of moderate size and thus was not powered for evaluating the superiority of either strategy. A noninferiority margin of 1.25 includes potentially clinically important harm and may be considered too large. Even the observed confidence limit ranges up to an 18% increase in cardiac events, which would be clinically meaningful. A larger trial with a similar clinical design is ongoing in individuals with AMI (MINT trial; NCT02981407) and is powered for clinical superiority using the composite outcome of all-cause mortality and nonfatal recurrent AMI. Second, the

trial was open-label due to the logistical challenges of blinding transfusion in the setting of AMI. However, assessment of clinical efficacy relied on objective outcomes, which were blindly adjudicated. Third, because qualifying hemoglobin levels could be collected at any time during hospitalization, some patients may have qualified for enrollment due to shifts after catheterization, repeated blood draws during a long stay, or active bleeding from medications or procedures. Therefore, a mixture of individuals with anemia, bleeding, and dilution were included in the eligible population.[33] However, subgroup analyses based on the presence or absence of preexisting anemia or of active bleeding yielded results consistent with the main analysis. Fourth, this report was limited to analysis of 30-day outcomes. Longer follow-up to 1 year is being accrued and will allow evaluation of the potential long-term effects of the 2 transfusion strategies as well as assessment of potential quality of life and incremental cost-utility ratio differences between the groups.[34]

Conclusions

Among patients with AMI and anemia, a restrictive compared with liberal transfusion strategy resulted in a noninferior rate of major cardiovascular events after 30 days. However, the CI included what may be a clinically important harm.

ARTICLE INFORMATION

Accepted for Publication: January 7, 2021.

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Author Contributions: Dr Steg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors vouch for the integrity and the accuracy of the analysis and for the fidelity of the study to the protocol.
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Critical revision of the manuscript for important intellectual content: Ducrocq, González Juanatey, Puymirat, Lemesle, Durand-Zaleski, Arnaiz, Martínez-Sellés, Silvain, Ariza Solé, Ferrari, Calvo, Danchin, Avendaño-Solá, Frenkiel, Rousseau, Vicaut, Simon, Steg.
Statistical analysis: Cachanado, Durand-Zaleski, Frenkiel, Rousseau, Vicaut.
Obtained funding: Ducrocq, Durand-Zaleski, Silvain, Calvo, Danchin, Avendaño-Solá, Simon, Steg.
Administrative, technical, or material support: Ducrocq, González Juanatey, Arnaiz, Silvain, Ferrari, Calvo, Danchin, Avendaño-Solá, Simon, Steg.
Supervision: Ducrocq, González Juanatey, Arnaiz, Silvain, Ariza Solé, Calvo, Danchin, Avendaño-Solá, Simon, Steg.

Conflict of Interest Disclosures: Dr Danchin reported receiving personal fees from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Intercept, MSD, Novo Nordisk, Pfizer, Sanofi, Servier, UCB, and Vifor outside the submitted work. Dr Ducrocq reported receiving personal fees from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Janssen, Sanofi, and Terumo outside the submitted work. 4Dr Durand-Zaleski reported receiving grants from the Ministry of Health during the conduct of the study and personal fees from Vifor outside the submitted work and being the chair of the scientific committee of the French Blood Establishment. Dr Lemesle reported receiving personal fees from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, MSD, Mylan, Novartis, Novo Nordisk, Pfizer, Sanofi Aventis, and Servier outside the submitted work. Dr Puymirat reported receiving fees for lectures and/or consulting from Amgen, AstraZeneca, Bristol Myers Squibb, Bayer, Biotronick, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, MSD, Novartis, Pfizer, The Medicines Company, Sanofi, St Jude Medical, and Servier. Dr Silvain reported receiving grants and personal fees from AstraZeneca; personal fees from Bayer HealthCare, Boehringer Ingelheim France, BPI France, CSL Behring, Gilead Science, Sanofi-Aventis France, and Zoll; and nonfinancial support from Abbott Medical France and Terumo France and being a stockholder in Pharmaseeds outside the submitted work. Dr Simon reported receiving grants from the Programme de Recherche Medico Economique and the Instituto de Salud Carlos III (PI15/01543) for Spanish centers in the trial during the conduct of the study and personal fees from AstraZeneca, Novartis, Sanofi, Astellas, and MSD and grants from AstraZeneca, Bayer, Boehringer, Daiichi-Sankyo, Eli Lilly, GlaxoSmithKline, Novartis, and Sanofi outside the submitted work. Dr Steg reported receiving grants from the French Ministry of Health and the Spanish Ministry of Industry during the conduct of the study and grants from Amarin, Bayer, Sanofi (Odyssey Outcomes co-chair), and Servier (CLARIFY registry chair) and personal fees from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Idorsia, Novartis, Novo Nordisk, Pfizer, Sanofi, Myokardia, Phase Bio, and Janssen outside the submitted work. Dr Vicaut reported receiving personal fees from Abbott for consulting outside the submitted work. No other disclosures were reported.

Funding/Support: The trial was designed by the French Alliance for Cardiovascular Trials and was funded via a grant from the Programme de Recherche Médico-Economique (PRME) 2015 from the French Ministry of Health and a grant from the Instituto de Salud Carlos III (Spanish Ministry of Economy and Competitiveness; grant PI15/01543). There was no industry support. The sponsor of the trial was Délégation à la Recherche Clinique et au Développement, Assistance Publique-Hôpitaux de Paris, Paris, France.

Role of the Funder/Sponsor: The funders and sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: A list of the REALITY Investigators is available in eAppendix 2 in Supplement 2.

Data Sharing Statement: See Supplement 3.

Additional Contributions: Editorial support was provided by Sophie K. Rushton-Smith, PhD (MedLink Healthcare Communications, London), who was compensated via a grant from the Programme de Recherche Médico-Economique from the French Ministry of Health for her contribution.

Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial

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Summary

Background Platelet transfusion after acute spontaneous primary intracerebral haemorrhage in people taking antiplatelet therapy might reduce death or dependence by reducing the extent of the haemorrhage. We aimed to investigate whether platelet transfusion with standard care, compared with standard care alone, reduced death or dependence after intracerebral haemorrhage associated with antiplatelet therapy use.

Methods We did this multicentre, open-label, masked-endpoint, randomised trial at 60 hospitals in the Netherlands, UK, and France. We enrolled adults within 6 h of supratentorial intracerebral haemorrhage symptom onset if they had used antiplatelet therapy for at least 7 days beforehand and had a Glasgow Coma Scale score of at least 8. With use of a secure web-based system that concealed allocation and used biased coin randomisation, study collaborators randomly assigned participants (1:1; stratified by hospital and type of antiplatelet therapy) to receive either standard care or standard care with platelet transfusion within 90 min of diagnostic brain imaging. Participants and local investigators giving interventions were not masked to treatment allocation, but allocation was concealed from outcome assessors and investigators analysing data. The primary outcome was shift towards death or dependence rated on the modified Rankin Scale (mRS) at 3 months, and analysed by ordinal logistic regression, adjusted for stratification variables and the Intracerebral Haemorrhage Score. The primary analysis was done in the intention-to-treat population and safety analyses were done in the intention-to-treat and as-treated populations. This trial is registered with the Netherlands Trial Register, number NTR1303, and is now closed.

Findings Between Feb 4, 2009, and Oct 8, 2015, 41 sites enrolled 190 participants. 97 participants were randomly assigned to platelet transfusion and 93 to standard care. The odds of death or dependence at 3 months were higher in the platelet transfusion group than in the standard care group (adjusted common odds ratio 2·05, 95% CI 1·18–3·56; p=0·0114). 40 (42%) participants who received platelet transfusion had a serious adverse event during their hospital stay, as did 28 (29%) who received standard care. 23 (24%) participants assigned to platelet transfusion and 16 (17%) assigned to standard care died during hospital stay.

Interpretation Platelet transfusion seems inferior to standard care for people taking antiplatelet therapy before intracerebral haemorrhage. Platelet transfusion cannot be recommended for this indication in clinical practice.

Funding The Netherlands Organisation for Health Research and Development, Sanquin Blood Supply, Chest Heart and Stroke Scotland, French Ministry of Health.

Lancet 2016; 387: 2605–13

Published Online
May 10, 2016
http://dx.doi.org/10.1016/S0140-6736(16)30392-0

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See Online for appendix

Introduction

Haemorrhagic stroke accounts for 11–22% of incident strokes,[1] half of all stroke deaths, and around 42% of the disability-adjusted life-years lost due to stroke (47 million life-years).[2] Spontaneous (non-traumatic) intracerebral haemorrhage caused by cerebral small vessel diseases accounts for two-thirds of haemorrhagic strokes,[3] amounting to more than 2 million incident intracerebral haemorrhages worldwide each year.

Antiplatelet therapy might slightly increase the incidence of intracerebral haemorrhage.[4] In high-income countries, more than a quarter of people who have incident intracerebral haemorrhages were taking antiplatelet therapy.[5] 1 month case fatality after intracerebral haemorrhage is 40%, and people taking antiplatelet therapy beforehand have a 27% (95% CI 10–47) increased odds of death compared with those not taking antithrombotic drugs.[6] Observational analyses suggest that antiplatelet therapy use before intracerebral haemorrhage and reduced platelet activity might worsen the outcome by increasing the risk of early intracerebral haemorrhage volume growth,[7] which is an important determinant of outcome.[8]

Platelet transfusion is used prophylactically and therapeutically in many clinical settings; however, few randomised trials have investigated its effectiveness for

Research in context

Systematic review

Before we initiated the PATCH trial in 2009, a search of ClinicalTrials.gov and the Cochrane Central Register of Controlled Trials (CENTRAL) did not reveal published, ongoing, or planned randomised trials of platelet transfusion for acute intracerebral haemorrhage in people taking antiplatelet therapy. On April 1, 2016, we searched MEDLINE (PubMed) from Jan 1, 1950, Embase from Jan 1, 1947; ClinicalTrials.gov, and CENTRAL from Jan 1, 1993, using textwords for platelet transfusion ("platelet" OR "blood platelet" OR "thrombocyte") and the textword "transfusion" and terms for intracerebral haemorrhage and randomised trials, as well as bibliographies of relevant publications, for trials of platelet transfusion for acute intracerebral haemorrhage in people taking antiplatelet therapy, irrespective of language of publication. We found one ongoing randomised trial (NCT00699621) and one published randomised trial dissimilar to PATCH of platelet transfusion versus aspirin resumption for aspirin-sensitive people with acute basal ganglia intracerebral haemorrhage undergoing craniotomy.

Added value of this study

This is the only completed randomised trial of people taking antiplatelet therapy who have acute intracerebral haemorrhage to compare the effects of platelet transfusion with standard care on functional outcome. Platelet transfusion seemed inferior to standard care for reducing death or dependence after acute intracerebral haemorrhage in people taking antiplatelet therapy.

Interpretation of all the available evidence

Platelet transfusion seems inferior to standard care after acute intracerebral haemorrhage in people taking antiplatelet therapy. We cannot recommend platelet transfusion for this indication, pending the results of another similar randomised trial.

active bleeding disorders.[9–11] Observational studies have reported variable associations with outcome after platelet transfusion for acute intracerebral haemorrhage in people taking antiplatelet therapy[12–17] and the absence of randomised trials has prevented guidelines from recommending its use.[10,11] However, platelet transfusion is commonly used in emergency departments, stroke units, and neurosurgical settings in people with acute intracerebral haemorrhage associated with antiplatelet therapy use.[18] We did a randomised controlled trial of platelet transfusion in acute intracerebral haemorrhage associated with antiplatelet therapy use, aiming to assess whether platelet transfusion would reduce death or dependence compared to standard care by reducing intracerebral haemorrhage growth.

Methods

Study design and participants

We did a multicentre, randomised, open-label, parallel-group trial at 36 hospitals in the Netherlands, 13 hospitals in the UK, and 11 hospitals in France. The trial was designed and coordinated by the Department of Neurology of the Academic Medical Centre (University of Amsterdam, Netherlands). The trial protocol has been published previously[19] and case report forms are available on the trial website.

For the **PATCH trial website** see http://www.strokeamc.nl/patch

We included patients aged 18 years or older with non-traumatic supratentorial intracerebral haemorrhage confirmed by brain imaging and a Glasgow Coma Scale score of 8–15; in whom platelet transfusion could be initiated within 6 h of symptom onset (or last seen well) and within 90 min of brain imaging; who had been on antiplatelet therapy with a cyclooxygenase (COX) inhibitor (aspirin or carbasalate calcium), adenosine diphosphate (ADP) receptor inhibitor (clopidogrel), or an adenosine-reuptake inhibitor (dipyridamole) for at least 7 days preceding intracerebral haemorrhage; and who had a pre-intracerebral haemorrhage modified Rankin Scale (mRS) score of 0 (no symptoms) or 1 (no significant disability despite symptoms; able to carry out all usual duties and activities). Exclusion criteria were blood on brain imaging suggestive to the treating physician of epidural or subdural haematoma, or an underlying aneurysm or arteriovenous malformation; planned surgical evacuation of intracerebral haemorrhage within 24 h of admission; intraventricular blood more than sedimentation in the posterior horns of the lateral ventricles; previous adverse reaction to platelet transfusion; known use of vitamin K antagonist (unless international normalised ratio ≤1·3) or history of coagulopathy; known thrombocytopenia (lower than 100 cells × 10^9/L); lacking mental capacity by national legal standards before intracerebral haemorrhage; or if death appeared imminent. We did not include participants with infratentorial or large intraventricular haematomas because they are more likely to undergo surgical procedures that might confound the effects of platelet transfusion on outcome. Collaborating clinicians on the delegation log at each hospital site recruited participants, and obtained written informed consent from participants or their legal representatives.

We obtained research ethics committee approval from the Academic Medical Centre ethics committee (MEC08/006) and each participating hospital in the Netherlands; the Scotland A Research Ethics Committee (10/MRE00/36) in the UK; and the Comité de protection des personnes (CPP 12/43, 2012-A00209–34) in France. The trial was monitored by the Clinical Research Unit of the Academic Medical Centre in the Netherlands, the Clinical Research Unit of the Lille University Hospital in France, and the UK trial manager on behalf of The Academic and Clinical Central Office for Research and Development in the UK.

Randomisation and masking

Participants were randomly assigned in a 1:1 ratio to receive either standard care or platelet transfusion plus standard care. Randomisation was done by investigators via a secure, web-based, computerised randomisation system (TENALEA, Clinical Trial Data Management system; NKIAVL, Amsterdam, The Netherlands) that concealed allocation, and stratified assignment by study hospital and type of pre-intracerebral haemorrhage antiplatelet therapy (COX inhibitor alone, ADP receptor inhibitor alone, COX inhibitor with an adenosine-reuptake inhibitor, or COX inhibitor with an ADP receptor inhibitor). A biased coin randomisation was used, with coin bias factor of three and coin bias threshold of two. Participants and local investigators giving interventions were not masked to treatment allocation, but allocation was concealed to outcome assessors and investigators analysing data.

Procedures

The web-based randomisation system asked investigators to check eligibility criteria and required investigators to record participant age and type of pre-intracerebral haemorrhage antiplatelet therapy. Investigators recorded all other characteristics at the time of enrolment. Stroke severity was scored on the National Institutes of Health Stroke Scale (NIHSS, ranging 0–42, with higher scores indicating more severe stroke). Brain imaging was done at admission with either CT or MRI according to routine clinical practice.

All participants received standard care, which was not defined in the protocol but was assumed to be given according to contemporary European[20] and national guidelines. Leucocyte-depleted platelet transfusions, either buffycoat-derived or collected by apheresis, were supplied by national or regional blood supply organisations, issued by the hospital transfusion laboratory, and administered to participants in the transfusion group according to local hospital protocols for transfusion. The protocol required platelet transfusion to be initiated within 6 h of intracerebral haemorrhage symptom onset and within 90 min of diagnostic brain imaging. Participants taking a COX inhibitor, with or without adenosine-reuptake inhibitor, received one platelet concentrate (equivalent to five donor units), whereas participants taking an ADP receptor inhibitor, with or without another antiplatelet drug, received two platelet concentrates. We chose the different dosages of platelet concentrates based on in-vitro experiments.[21] Investigators recorded whether platelet transfusion started within 3 h or 3–6 h after symptom onset.

Functional outcome scored with the mRS at 3 months (ranging from 0 [no symptoms] to 6 [death]) was rated by a neurologist or research nurse who was not involved in participants' medical treatment. Each country's trial coordinating centre organised collection of the primary outcome so that it could be obtained in participants' first language by either structured telephone interview or face-to-face consultation.

Brain imaging was done at 24 h (plus or minus 3 h) after randomisation with the same technique used for diagnosis. Diagnostic and 24 h brain imaging studies were obtained in Digital Imaging and Communications in Medicine (DICOM) format from trial sites, anonymised, and analysed centrally in Amsterdam. The images were assessed for intracerebral haemorrhage location (deep or lobar) and intraventricular extension. We used an automated planimetric method to segment intracerebral haemorrhage on unenhanced baseline imaging[22] to calculate intracerebral haemorrhage volume in mL; these measurements were manually checked by MIB who was masked to treatment allocation and supervised by one of two independent neuroradiologists (CBM or LFB; not involved in the conduct of the trial and masked to allocation); values were adjusted where necessary.

Investigators recorded the occurrence of any serious adverse events and other safety outcomes that occurred during hospital admission, and also recorded the date and destination of discharge. Safety outcomes were independently verified by research nurses, or the safety committee in France, with use of discharge letters.

Data on paper case report forms were collected at the trial coordinating centre in each country (Amsterdam, Netherlands; Edinburgh, UK; and Lille, France). Good Clinical Practice-compliant internet-based remote data capture was used for entering, managing, and validating data from hospital sites (Oracle Clinical, ORACLE, Redwood Shores, CA, USA.

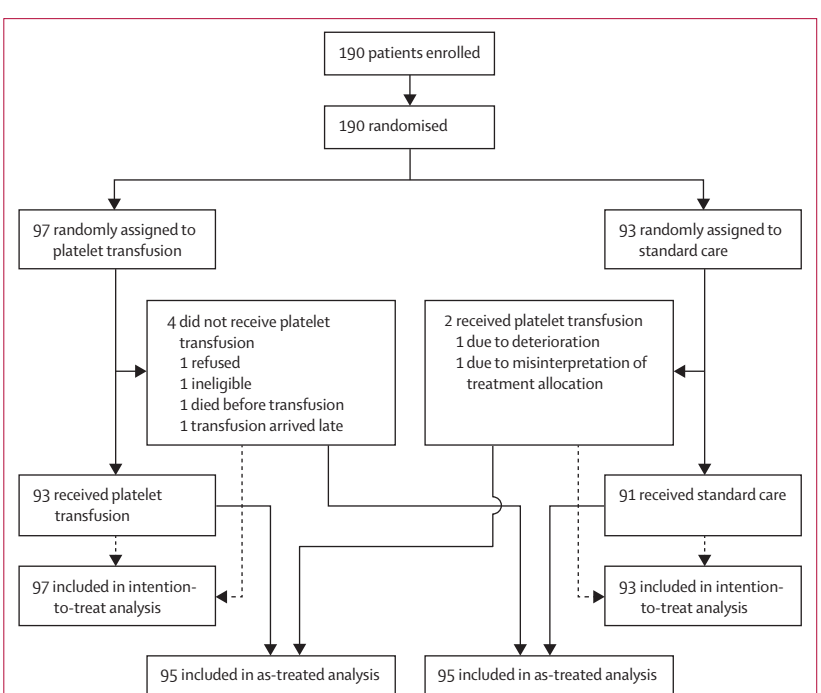

Figure 1: **Trial profile**

Outcomes

The primary endpoint was difference in functional outcome at 3 months after randomisation scored with the mRS. Secondary clinical outcomes at 3 months were survival (mRS score of 1–5), poor outcome defined as an mRS score of 4–6, and poor outcome defined as an mRS score of 3–6. The secondary explanatory outcome was median absolute intracerebral haemorrhage growth in mL after 24 h on brain imaging. Safety outcomes were defined as complications of platelet transfusion (transfusion reactions, thrombotic complications) and for other serious adverse events the treating physician was asked to specify the presumed cause as one of the following: due to complications of intracerebral haemorrhage (enlargement, intraventricular extension, hydrocephalus, oedema, or brain herniation), epileptic seizures, infection (urinary tract or pneumonia), or others that investigators wished to record. We planned a substudy of the spot sign on CT angiography and platelet function testing. We also planned to investigate determinants of poor outcome, functional outcome using the Academic Medical Center (AMC) Linear Disability score, and health economics.

	Platelet transfusion group (n=97)	Standard care group (n=93)
Mean age (years)	74·2 (49–94)	73·5 (40–92)
Men	55 (57%)	57 (61%)
Women	42 (43%)	36 (39%)
Vascular comorbidities		
Ischaemic stroke or TIA	38/94 (40%)	40 (43%)
ICH	4 (4%)	5/92 (5%)
Hypertension	68/94 (72%)	67/92 (73%)
Diabetes mellitus	15 (15%)	17/90 (19%)
Hypercholesterolaemia	46/94 (49%)	40/84 (48%)
Ischaemic heart disease	23/96 (24%)	22/90 (24%)
Peripheral arterial disease	16 (16%)	4/91 (4%)
Coagulation disorder	1/96 (1%)	2/91 (2%)
Antiplatelet therapy pre-ICH*		
COX inhibitor alone	71 (73%)	78 (84%)
COX inhibitor and dipyridamole	18 (19%)	13 (14%)
ADP inhibitor alone	4 (4%)	1 (1%)
COX inhibitor and ADP inhibitor	3 (3%)	1 (1%)
None	1 (1%)	0
Statin therapy pre-ICH	54/96 (56%)	48/92 (52%)
Median GCS score	14 (13–15)	15 (13–15)
Median NIHSS score	12 (7–19)	13 (7–17)
Mean platelet count (×10^9/L)	229 (120–622)	241 (91–461)
Country of inclusion*		
Netherlands (27 centres)	63 (65%)	57 (61%)
France (9 centres)	19 (20%)	20 (22%)
UK (5 centres)	15 (15%)	16 (17%)
ICH location		
Supratentorial deep	62/96 (65%)	70/92 (76%)
Supratentorial lobar	32/96 (33%)	22/92 (24%)
Infratentorial	2/96 (2%)	0
Median ICH volume (mL)	13·1 (5·4–42·4)	8·0 (4·4–25·8)
Intraventricular extension	12/95 (13%)	20/92 (22%)
Median total ICH Score†	1 (0–2)	1 (0–1)
Age >80 years	28 (29%)	34 (37%)
GCS score		
5–12	19 (20%)	11 (12%)
3–4	1 (1%)	0
ICH volume >30 mL	32 (34%)	19 (21%)
Intraventricular extension	12 (13%)	20 (22%)
Infratentorial ICH location	2 (2%)	0

Data are mean (range), n (%), or median (IQR), unless noted otherwise. TIA=transient ischaemic attack. ICH=intracerebral haemorrhage. COX=cyclooxygenase. ADP=adenosine diphosphate. GCS=Glasgow Coma Scale. NIHSS=National Institutes of Health Stroke Scale. *Stratification variable. †3 participants missing in the platelet transfusion group and 2 missing in the standard care group.

Table 1: **Baseline characteristics of the intention-to-treat population**

Statistical analysis

The executive committee agreed on a statistical analysis plan with the trial statistician (RJdH) without knowledge of outcome data and before closing and unmasking the trial database; this statistical analysis plan was submitted in concise format to the Netherlands Trial Register on March 14, 2016, was submitted in full to *Trials* on March 21, 2016, and the trial database was locked and unmasked on March 31, 2016. The statistical analysis plan describes the differences between the protocol and this final report; the principal change was from a fixed dichotomous analysis of the primary outcome (mRS score 4–6 at 3 months) to an ordinal logistic regression analysis of the shift of all categories of the mRS at 3 months, in view of the greater statistical efficiency of this analysis[23] and the hypothesised effect of platelet transfusion to result in a shift on a functional outcome scale by reduction of intracerebral haemorrhage growth. We originally based the target sample size of two groups of 95 participants (total 190) on an estimate of 70% frequency of the primary outcome of death or dependence (defined as mRS 4–6) with standard care,[24] a clinically important 20% absolute reduction of this risk to 50% with platelet transfusion (odds ratio [OR] 0·43), 80% power and a two-sided level of significance of 0·05. However, after the change (and with the same target sample size), power increases to 91% to detect a common OR of 0·43 in an ordinal logistic regression analysis of all pairs of mRS categories, assuming a distribution of the mRS with standard care that is similar to the control group of a recent intracerebral haemorrhage trial.[25]

The primary outcome was the shift of each category in the entire range of the mRS, assuming a common OR analysed by ordinal logistic regression (with adjustment for both the stratification variable of type of pre-intracerebral haemorrhage antiplatelet therapy as well as the Intracerebral Haemorrhage Score as a

For the **statistical analysis plan** see http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1303

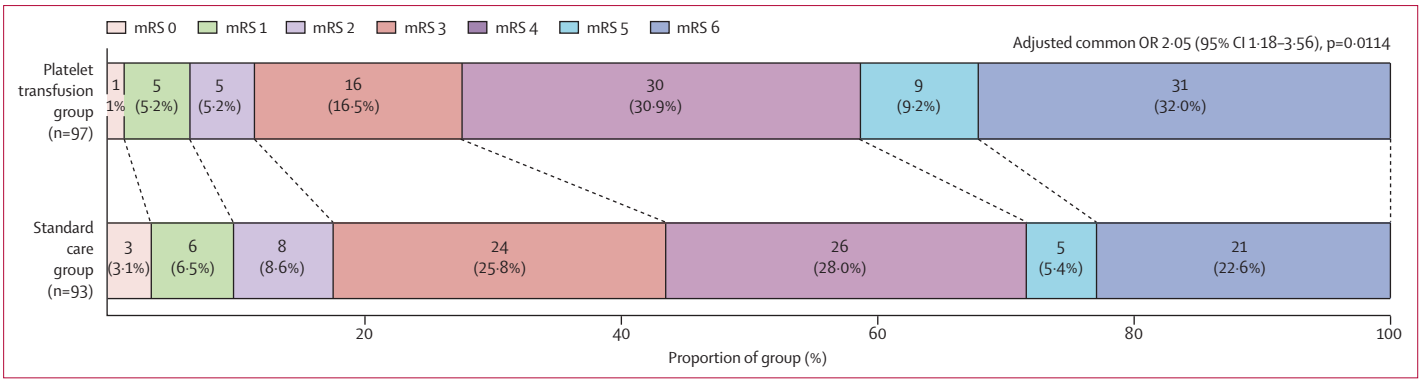

Figure 2: **Distribution of mRS score at 3 months**
mRS=modified Rankin Scale. OR=odds ratio.

predictor of outcome after intracerebral haemorrhage[26]) in the intention-to-treat population. Effect sizes are expressed as ORs with 95% CIs. Baseline characteristics and secondary endpoints were assessed in the intention-to-treat population with no imputation for missing data. Secondary outcomes were compared with the χ^2 test, except for the median difference in intracerebral haemorrhage growth, which was compared with the Mann-Whitney *U* test. Safety outcomes were compared in both the intention-to-treat and the as-treated populations. We used parametric statistics when variables had a normal distribution, and non-parametric statistics when they did not. If zero instances were reported, we added 0·5 to each cell to calculate an OR.

We did three prespecified subgroup analyses of the shift of all categories of the mRS using ordinal regression analyses to test the interaction variable, adjusted for both component variables, for type of antiplatelet therapy regimen pre-intracerebral haemorrhage (single *vs* dual); country of randomisation (Netherlands *vs* France *vs* UK); and trichotomised intracerebral haemorrhage volume at baseline (≤7 mL *vs* >7 to 30 mL *vs* >30 mL) to search for effects in small, medium, and large intracerebral haemorrhages. We did a sensitivity analysis of the effect of platelet transfusion on the primary outcome at hospitals that included at least five participants in which we also adjusted for including centre.

Analyses were done using IBM SPSS statistics version 22 (Cleveland, OH, USA). An independent data monitoring committee (appendix) oversaw the trial and agreed with the termination of the trial when it reached its prespecified sample size in Oct 8, 2015. A separate committee monitored the safety of participants enrolled in France (appendix). The trial is registered with the Netherlands Trial Register, number NTR1303.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data from the trial and had final responsibility for the results and submission for publication.

Results

Between Feb 4, 2009, and Oct 8, 2015, 41 sites enrolled 190 participants (figure 1). 97 participants were randomly assigned to receive standard care with platelet transfusion (platelet transfusion group) and 93 were assigned to standard care without transfusion (standard care group). No participants were lost to follow-up at 3 months and all were included in the final analyses after the last follow-up was completed on Jan 6, 2016.

Baseline characteristics were balanced between groups (table 1), apart from peripheral arterial disease, which was not considered of major prognostic relevance to the primary outcome. 36 (19%) participants had at least one exclusion criterion, 15 (15%) in the platelet transfusion group (12 had intraventricular haemorrhage, two had infratentorial localisation of haematoma, and one was not using antiplatelet therapy) and 21 (23%) in the standard care group (20 had intraventricular haemorrhage and one had thrombocytopenia). Baseline imaging was missing for centralised reading for two participants and intracerebral haemorrhage volume or intraventricular extension could not be measured for five participants because images were degraded by movement artifact.

Four participants assigned to platelet transfusion did not receive it, and two participants assigned to standard

	Platelet transfusion group (n=97)	Standard care group (n=93)	Odds ratio (95%CI)	p value
Alive at 3 months (survival)	66 (68%)	72 (77%)	0·62 (0·33–1·19)	0·15
mRS score 4–6 at 3 months	70 (72%)	52 (56%)	2·04 (1·12–3·74)	0·0195
mRS score 3–6 at 3 months	86 (89%)	76 (82%)	1·75 (0·77–3·97)	0·18
Median ICH growth at 24 h (mL)*	2·01 (0·32–9·34)	1·16 (0·03–4·42)	..	0·81

Data are n (%) or median (IQR). mRS=modified Rankin Scale. ICH=intracerebral haemorrhage. *n=80 in platelet transfusion group and 73 in standard care group.

Table 2: **Secondary outcomes in the intention-to-treat population**

care received a platelet transfusion (figure 1). Four protocol violations occurred in the platelet transfusion group (two participants did not receive the correct number of platelet concentrates and two received platelet transfusion out of the prespecified time window). Follow-up imaging at 24 h was missing for 17 participants in the platelet transfusion group (three omitted, five died, four imaged >27 h, and five poor quality) and for 20 participants in the control group (nine omitted, four died, two imaged >27 h, and five poor quality).

For the primary outcome, odds of a shift towards death or dependence at 3 months were higher in the platelet transfusion group than in standard care group without adjustment (crude common OR 1·84, 95% CI 1·10–3·08; p=0·0200) and with adjustment (adjusted common OR 2·05, 95% CI 1·18–3·56; p=0·0114; figure 2). In secondary analysis, more participants in the platelet transfusion group had poor outcome with an mRS score of 4–6 at 3 months than did those in the standard care group (table 2). Survival and the proportion of participants with an mRS score of 3–6 at 3 months did not significantly differ between groups; nor did intracerebral haemorrhage growth at 24 h (table 2). The distribution of the mRS was similar in participants who received platelet transfusion within 3 h of symptom onset versus those who received transfusion at 3–6 h (appendix).

40 (42%) participants who received platelet transfusion had a serious adverse event, as did 28 (29%) who received standard care (as-treated population; table 3). Most serious adverse events were intracerebral haemorrhage enlargement or urinary or pulmonary infections. One participant had a minor transfusion reaction. 24 (25%) participants assigned to platelet transfusion and 15 (16%) assigned to standard care died while in hospital. In an analysis of the as-treated population, most adverse events did not differ by group assignment. Serious adverse events due to intracerebral haemorrhage were higher in participants who received platelet transfusion than in those who received standard care (table 3). There was not a significant difference between groups in serious adverse events due to thromboembolism, but four people in the transfusion group had an event versus one in the standard therapy group. Safety outcomes in the intention-to-treat population did not differ between groups.

In the prespecified subgroup analyses, type of antiplatelet therapy, country, and haematoma volume

	Intention-to-treat population			As-treated population		
	Platelet transfusion group (n=97)	Standard care group (n=93)	Odds ratio (95% CI)	Platelet transfusion group (n=95)	Standard care group (n=95)	Odds ratio (95% CI)
Any SAE	41 (42%)	27 (29%)	1·79 (0·98–3·27)	40 (42%)	28 (29%)	1·74 (0·96–3·17)
Any fatal SAE	24 (25%)	15 (16%)	1·71 (0·83–3·51)	23 (24%)	16 (17%)	1·58 (0·77–3·22)
SAE due to ICH	24 (25%)	13 (14%)	2·02 (0·96–4·27)	24 (25%)	13 (14%)	2·13 (1·01–4·50)
ICH enlargement	15 (15%)	13 (14%)	1·13 (0·50–2·52)	15 (16%)	13 (14%)	1·18 (0·53–2·64)
Brain oedema	5 (5%)	0	11·12 (0·61–204·97)	5 (5%)	0	11·61 (0·63–212·94)
Brain herniation	2 (2%)	0	4·90 (0·23–103·33)	2 (2%)	0	5·11 (0·24–107·83)
Intraventricular extension	6 (6%)	0	13·28 (0·74–239·24)	6 (6%)	0	13·87 (0·77–249·82)
Hydrocephalus	3 (3%)	2 (2%)	1·45 (0·24–8·89)	4 (4%)	1 (1%)	4·13 (0·45–37·67)
SAE due to thromboembolism	4 (4%)	1 (1%)	3·96 (0·43–36·08)	4 (4%)	1 (1%)	4·13 (0·45–37·67)
Ischaemic stroke	1 (1%)	0	2·91 (0·12–72·26)	1 (1%)	0	3·03 (0·12–75·37)
Myocardial infarction	1 (1%)	1 (1%)	0·96 (0·06–15·55)	1 (1%)	1 (1%)	1·00 (0·06–16·23)
Extremity embolism	2 (2%)	0	4·90 (0·23–103·34)	2 (2%)	0	5·11 (0·24–107·81)
Pulmonary embolism	1 (1%)	0	2·91 (0·12–72·26)	1 (1%)	0	3·03 (0·12–75·37)
SAE due to transfusion						
Non-haemolytic	1 (1%)	0	2·91 (0·12–72·26)	1 (1%)	0	3·03 (0·12–75·37)
Anaphylactic	0	0	..	0	0	..
Acute lung injury	0	0	..	0	0	..
Post-transfusion purpura	0	0	..	0	0	..
Graft-versus-host disease	0	0	..	0	0	..
Transmitted bacterial infection	0	0	..	0	0	..
SAE due to other causes						
Infection (urinary or pulmonary)	14 (14%)	12 (13%)	1·14 (0·50–2·61)	14 (15%)	12 (13%)	1·20 (0·52–2·74)
Epileptic seizures	0	0	..	0	0	..
Other	6 (6%)	5 (5%)	1·16 (0·34–3·94)	7 (7%)	4 (4%)	1·81 (0·51–6·40)

Outcome data are n (%). Participants could have more than one SAE. Some SAEs were deemed to be due to several causes. SAE=serious adverse event. ICH=intracerebral haemorrhage.

Table 3: Safety outcomes occurring during hospital admission in the intention-to-treat and as-treated populations

had no significant interaction with the effect of platelet transfusion versus standard care (figure 3). Platelet transfusion remained inferior to standard care in our sensitivity analysis restricted to hospitals that included at least five participants (n=125; 66%) when the primary outcome was also adjusted for the hospital that included participants (adjusted OR 2·55, 95% CI 1·24–5·24, p=0·0107). In post-hoc analyses, the primary outcome remained unchanged when adjusted for intracerebral haemorrhage volume at baseline (adjusted common OR 1·90, 95% CI 1·08–3·36, p=0·0268) and after excluding the 36 participants who met at least one exclusion criterion (adjusted OR 2·22, 95% CI 1·20–4·09, p=0·0108). Due to insufficient uptake in standard clinical practice we did not perform the planned sub-studies of the spot sign on CT angiography and platelet function testing. We did not investigate causes of poor outcome, functional outcome using the AMC Linear Disability score, or health economics due to insufficient funding.

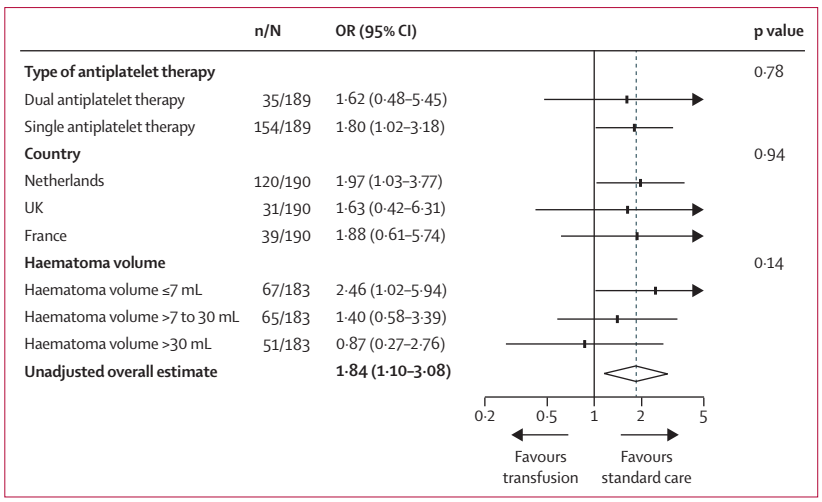

***Figure* 3: Subgroup analyses at 3 months in prespecified subgroups**
mRS=modified Rankin Scale. OR=odds ratio.

Discussion

Our randomised trial of nearly 200 participants shows that platelet transfusion seems to increase the risk of death or dependence in participants who have an acute intracerebral haemorrhage while taking antiplatelet therapy. This effect was consistent in predefined subgroups and remained after adjustment for pre-intracerebral haemorrhage antiplatelet therapy and known prognostic factors. These surprising findings are contrary to our hypothesis that platelet transfusion would reduce intracerebral haemorrhage growth and improve functional outcome, and are not consistent with small observational studies that have found better outcomes associated with the use of platelet transfusion.[12–14]

PATCH is the first randomised trial to investigate the effects of platelet transfusion on acute intracerebral haemorrhage after the use of antiplatelet therapy, and is one of few randomised trials to investigate the effect of platelet transfusion on active bleeding disorders.[9–11,16,17] In this multicentre trial, the effect of platelet transfusion on the primary outcome was consistent in three European countries, supporting the external validity of the trial (although its generalisability to low-income and middle-income countries is unknown). The baseline characteristics and outcomes of the included participants were similar to previous randomised trials for acute intracerebral haemorrhage.[25] Adherence to the assigned treatment was good and clinical follow-up for the primary outcome was complete (figure 1). The trial also achieved its target sample size.

However, the trial has some limitations. The sample size was smaller than in other acute stroke trials, reflecting the lower incidence of acute stroke due to intracerebral haemorrhage, its clinical severity,[5] and the demanding eligibility criteria we used.[27] This small sample size resulted in some chance imbalances in baseline prognostic variables, although their direction of effect was not consistent—ie, some of these imbalances might have biased the platelet transfusion group to a worse outcome and others might have biased it to a better outcome (table 1). Our findings could not be easily explained by chance imbalances in baseline characteristics, although residual confounding due to randomisation imbalances is possible, especially in light of the small sample size. Most of the participants had taken aspirin and relatively few had taken ADP inhibitors, so it is unknown whether the findings are generalisable to the increasing numbers of people who take ADP inhibitors. PATCH investigators were not required to keep screening logs, so the level of bias through selective inclusion is unknown. Furthermore, adherence to antiplatelet therapy for participants was not measured and we relied on information supplied by the participants, caregivers, or medical charts. Too few hospitals were able to test for platelet function to investigate whether function had modified treatment effect, as had been suggested by one observational study.[14] As is often the case in pragmatic trials in emergency settings, a fifth of participants (36 [19%]) met at least one exclusion criterion.[27] In particular, participants with intraventricular extension greater than sedimentation in the posterior horns of the lateral ventricles were included, possibly reflecting difficulty in interpretation of this criterion by clinicians. Because this protocol deviation was not equally distributed between treatment groups, we did a post-hoc sensitivity analysis excluding these participants, in which the findings for the primary outcome remained consistent.

Our findings contrast with the hypothesised mechanism of action of platelet transfusion. We did not find a clear mechanism to explain our findings among the reported safety outcomes (table 3), although there was a non-significant difference in serious adverse events due to thromboembolism and complications of intracerebral

haemorrhage were more common in the platelet transfusion group. Although conjecture, it remains possible that some participants actually had haemorrhagic transformation of infarction rather than intracerebral haemorrhage, or it is possible collateral perfusion around the intracerebral haemorrhage was impaired, resulting in cerebral ischaemia. Platelet transfusion could then increase the risk of thrombosis and result in lesion expansion. In a large observational study, people with thrombotic and prothrombotic disorders such as thrombotic thrombocytopenic purpura and heparin-induced thrombocytopenia who received platelet transfusions had increased mortality and myocardial infarction compared with those people who were not transfused.[28] Furthermore, platelets have proinflammatory effects and transfusions might enhance vascular permeability associated with inflammation and platelet consumption. Platelets can also be activated when stored, resulting in increased prothrombotic and inflammatory properties.[29] It is also possible that platelet transfusion might not be beneficial because the absolute increase in intracerebral haemorrhage growth associated with antiplatelet therapy is not large enough to be meaningfully modified by platelet transfusion, or that platelet transfusion is insufficient to reverse the effects of antiplatelet therapy on intracerebral haemorrhage growth. Most effective platelet transfusions are given for prophylaxis of bleeding, often in severe hypoproliferative thrombocytopenia in haematology-oncology participants.[30] The effect of platelet transfusions to stop or reverse ongoing bleeding might be beneficial or deleterious depending on the nature and location of the haemorrhage. These potential effects, combined with some baseline imbalances, could explain the detrimental effect of platelet transfusion in our trial. However, even if platelet transfusion was not harmful, our findings suggest that it is unlikely to be beneficial.

After the findings of the PATCH trial, platelet transfusion cannot be recommended for the treatment of acute intracerebral haemorrhage in people taking antiplatelet therapy because platelet transfusion seemed to worsen their outcome. A similar randomised trial is nearing completion (NCT00699621), and its results are needed to confirm our findings in acute intracerebral haemorrhage. Given the widespread use of platelet transfusion for other acute bleeding disorder despite a shortage of randomised evidence, our findings should lead to further trials so that this potentially hazardous and costly intervention is only used for prophylactic or therapeutic indications when supported by evidence from randomised controlled trials.

Contributors

MIB, CC, and RA-SS coordinated the trial and drafted the manuscript. MIB performed all analyses, supervised by YBR and RJdH. CC and RA-SS obtained funding for the trial and recruited centres and supervised the trial in the UK and France, respectively. KdG was involved in the design of the trial, recruitment of participating centres, and coordinated the trial in the Netherlands. MMK was involved in the design of the trial and coordinated availability of platelet transfusion for Dutch centres. CBM and LFB were involved in the design of the study and supervised the performance of all radiological measurements and interpretation. HAM designed the radiological endpoints and was consulted for all technical aspects of analysing the radiological parameters. He supervised and performed importing of all imaging and automated measurements with interpretation. AB and MV were involved in the original design of the trial and critically reviewed the manuscript. PJN and RJdH were involved in the design of the trial, the statistical analyses involved, and critically reviewed the manuscript. YBR designed the trial, obtained funding, recruited centres, and supervised the entire trial.

Declaration of interests

PJN reports fees for advisory work for Medtronic for atrial fibrillation registration in stroke used for the Academic Medical Center stroke research group. HAM is the cofounder and shareholder of Nico-lab. All other authors declare no competing interests.

Acknowledgments

PATCH was funded by The Netherlands Organisation for Health Research and Development (ZonMw, 170881002) and Sanquin Blood Bank in the Netherlands; French Ministry of Health (PHRC-N, 2011, 19-15; to CC); and a Chest Heart and Stroke Scotland project grant (Reference Res10; to RA-SS)) and MRC clinician scientist (G108/613 to RA-SS) and senior clinical fellowships (G1002605 to RA-SS) in Scotland. PATCH was sponsored by Academic Medical Centre, University of Amsterdam, in the Netherlands; Inserm U1171, CHU Lille, Lille, in France; and The University of Edinburgh, NHS Lothian Academic and Clinical Central Office for Research and Development (ACCORD) in Scotland. PATCH received non-financial support from Strokavenir network and Etablissement Français du Sang in France; and the UK National Institute for Health Research (NIHR) stroke research network, the Scottish Stroke Research Network, and the Scottish National Blood Transfusion Service clinical governance and safety committee in the UK. CC is a member of the Institut Universitaire de France. We are very grateful for the tireless dedication of the PATCH trial managers and research staff: Nadine Fleitour (Netherlands); Fanny Ben Oune, Thavarak Ouk, and Dominique Deplanque (France); and Bridget Colam, Robin Flaig, Katrina McCormick, Neshika Samarasekera, Aidan Hutchison, and Christine Lerpiniere (Scotland). We are grateful to all principal investigators and delegated physicians who included participants in all participating centres. We are indebted to the participants and their carers and families who consented to participate in PATCH.

References

1 Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol* 2009; **8:** 355–69.

2 Feigin VL, Krishnamurthi RV, Parmar P, et al. Update on the global burden of ischemic and hemorrhagic stroke in 1990–2013: the GBD 2013 Study. *Neuroepidemiology* 2015; **45:** 161–76.

3 Al-Shahi Salman R, Labovitz DL, Stapf C. Spontaneous intracerebral haemorrhage. *BMJ* 2009; **339:** b2586.

4 Antithrombotic Trialists Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; **373:** 1849–60.

5 Lovelock CE, Molyneux AJ, Rothwell PM; Oxford Vascular Study. Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study. *Lancet Neurol* 2007; **6:** 487–93.

6 Thompson BB, Bejot Y, Caso V, et al. Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review. *Neurology* 2010; **75:** 1333–42.

7 Naidech AM, Jovanovic B, Liebling S, et al. Reduced platelet activity is associated with early clot growth and worse 3-month outcome after intracerebral hemorrhage. *Stroke* 2009; **40:** 2398–401.

8 Davis SM, Broderick J, Hennerici M, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology* 2006; **66:** 1175–81.

9 Kumar A, Mhaskar R, Grossman BJ, et al. Platelet transfusion: a systematic review of the clinical evidence. *Transfusion* 2015; **55:** 1116–27.

bjh guideline

British Society of Haematology Guidelines on the spectrum of fresh frozen plasma and cryoprecipitate products: their handling and use in various patient groups in the absence of major bleeding

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Keywords: fresh frozen plasma, cryoprecipitate, guidelines, non-bleeding patients, plasma.

Methodology

This guideline was compiled according to the BSH process at (http://www.bcshguidances.com/BCSH_PROCESS/42_EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION.html). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

Literature review details

Recommendations are based on the systematic review of English language literature published since the previous guideline publication, from January 2004 to July 2016 (see Appendix S1 for further details). A literature search was undertaken in Medline and Embase from 2004 to 2016, using the following key search terms: blood component transfusion, FFP, fresh frozen plasma, plasma, transfusion, prophylaxis, thaw, prethaw, SDFFP, MBFFP, uniplas, octaplas, FP24, pathogen inactivated or pathogen reduced, cryoprecipitate, supernatant or cryosupernatant.

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[Correction added on 4 April 2019, after online publication: The acknowledgements section has been updated in this version].

First published online 12 March 2018
doi: 10.1111/bjh.15167

Review of the manuscript. Review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Committee Transfusion Task Force, the BSH Guidelines Committee and the Transfusion sounding board of the BSH. It was also placed on the members section of the BSH website for comment.

Introduction

Fresh frozen plasma (FFP) is given primarily for three indications: to prevent bleeding (prophylaxis), stop bleeding (therapeutic) or for plasma exchange. Prophylactic transfusions are mainly used prior to surgery or invasive procedures. Many possible indications in patients without major bleeding are not substantiated by robust trial data.

Historical and current use of plasma

Fresh frozen plasma

Between 2008 and 2012 there was a steady increase in the use of FFP in the UK, possibly influenced by the publications of observational studies in trauma demonstrating that early transfusion of FFP in bleeding patients improves outcomes (Holcomb *et al*, 2007). From 2012 onward there has been a reduction in the total number of units of FFP issued in the UK, while during the same period the number of units of solvent detergent-treated FFP (SDFFP) issued has increased (Fig 1B).

In 2009 a UK-wide audit demonstrated that in adult patients 43% of FFP transfusions were administered to patients with no documented bleeding, as prophylaxis before interventions because of abnormal coagulation tests

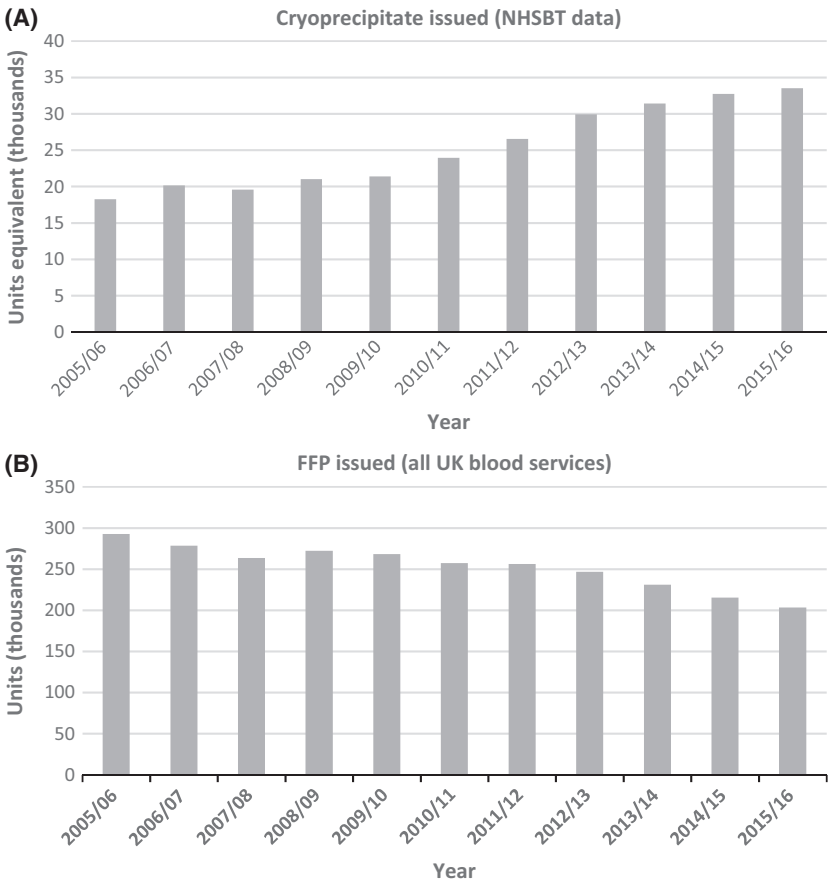

Fig 1. Total number of frozen components issued from 2003 onward. (A) Cryoprecipitate [NHS Blood and Transplant (NHSBT) data]. (B) Fresh Frozen Plasma (FFP) (all UK blood services). Data (unpublished) provided from NHSBT and Serious Hazard of Transfusion.

(Stanworth *et al*, 2011a). There is no evidence validating FFP use in these settings; this practice potentially exposes patients to unnecessary transfusion.

Cryoprecipitate

Since 2004 use of cryoprecipitate has steadily increased; in 2015/16 the number of cryoprecipitate units issued by NHS Blood and Transplant (NHSBT) had more than doubled compared with 2003 (Fig 1A). The reasons for this increase remain unclear; an audit in 39 hospitals (2009/2010) in England showed that, of 423 cryoprecipitate transfusions, 25% were transfused prophylactically and 75% were administered for bleeding, the commonest cause for all age groups being cardiac surgery, followed by trauma (Tinegate *et al*, 2012).

Specification, preparation, storage and handling of fresh frozen plasma and cryoprecipitate

Plasma specifications

Fresh frozen plasma. In the UK, FFP is produced from whole blood donations which undergo centrifugation, or by apheresis. FFP is leucocyte depleted by filtration during whole blood processing or integral to the apheresis process. Plasma is rapidly frozen to ≤−25°C to maintain the activity of labile coagulation factors. Factor VIII (FVIII) is used for quality monitoring because it is one of the most labile coagulation factors and is therefore a sensitive marker of changes to FFP induced by inappropriate processing/handling. Immediately after being thawed, standard FFP must have at least 0.7 iu/ml of FVIII in at least 75% of units. Other details of the quality monitoring required, such as residual levels of red cells, platelets and leucocytes are available elsewhere (http://www.transfusionguidelines.org.uk/red-book). Once frozen, FFP may be stored for up to 36 months at ≤25°C. Typical values for plasma are given in Table I.

Cryoprecipitate

Cryoprecipitate is manufactured by slowly thawing FFP overnight at 4°C. This precipitates out cryoproteins: FVIII, von Willebrand factor (VWF), FXIII, fibronectin and fibrinogen. After centrifugation, the cryoproteins are resuspended in a reduced volume of plasma (20–60 ml). The cryoprecipitate specification requires that 75% of packs contain at least 140 mg of fibrinogen and 70 iu of FVIII. UK Blood Transfusion Services (UKBTS) also produce pooled cryoprecipitate prepared from five single donations; the specification is five times that of a single cryoprecipitate unit (i.e. 700 mg fibrinogen and 350 iu FVIII) in a typical volume of 200–

Table I. Typical values for fresh frozen plasma and cryoprecipitate in the UK.

	FFP	MB FFP	Octaplas LG‡	Single cryoprecipitate	Pooled cryoprecipitate	Single MB cryoprecipitate	Pooled MB cryoprecipitate
Volume (ml)	267 ± 17	229 ± 12	200	49 ± 5	237 ± 28	46 ± 5	291 ± 29
FVIII	0·96 ± 0·27 iu/ml (average 256 iu/unit)	0·68 ± 0·23 iu/ml (average 156 iu/unit)	Group O: 0·53 (0·52–0·53 iu/ml) Non-O: 0·71 (63–84) 106 (iu/unit)	108 ± 33 (iu/unit)	524 ± 130 (iu/unit)	65 ± 21 (iu/unit)	385 ± 112 (iu/unit)
Fibrinogen (Clauss)	2·57 ± 0·48 g/l (on average 0·69 g/unit)*	1·70 ± 0·15 g/l (on average 0·39 g/unit)†	2·31 (2·21-2·41) g/l (on average 0·46 g/unit)	0·43 ± 0·14 (g/unit)	1·67 ± 0·27 (g/unit)	0·25 ± 0·09 (g/unit)	1·18 ± 0·31 (g/unit)
UK specification for FVIII / fibrinogen	>75% units ≥0·70 iu/ml FVIII	>75% of units >0·50 iu/ml FVIII	European Pharmacopoeia requires FV, FVIII and FXI >0·50 iu/ml	>75% of units >140 mg/unit fibrinogen >70 iu/unit FVIII	>75% of units >700 mg/unit fibrinogen >350 iu/unit FVIII	>75% of units >140 mg/unit fibrinogen >50 iu/unit FVIII	75% of units >700 mg/unit fibrinogen >250 iu/unit FVIII

FFP, fresh frozen plasma; FV, factor V; FVIII, factor VIII; FXI, factor XI; MB, methylene blue.
Data taken from routine quality monitoring data from NHSBT for April-June 2016.
Data given as mean with standard deviation.
*not monitored routinely, data taken from Lawrie *et al* (2008).
†Data taken from Backholer *et al* (2016)
‡Data taken from Lawrie *et al* (2010); average with range.

280 ml. Cryoprecipitate should be stored at a core temperature of ≤−25°C for a maximum of 36 months. Typical values for cryoprecipitate are given in Table I. Due to natural variation in coagulation factors levels between donors, there is wide variation in FVIII and fibrinogen levels between units.

There is no current clinical indication for cryoprecipitate-depleted plasma (the supernatant left after cryoprecipitate has been removed from plasma) in the UK; this product is no longer produced by the UKBTS.

Pathogen-inactivated plasma and cryoprecipitate

Pathogen inactivated (PI) plasma is indicated for all individuals born after 1 January 1996. The residual risk of a unit of plasma being infectious for known viruses that are tested for is very low (Table II). There are now three systems that are licensed in Europe for the pathogen inactivation of units of plasma within Blood centres: methylene blue (Theraflex), amotosalen (Intercept) and riboflavin (Mirasol). Of these, currently methylene blue is available in the UK. These systems are based on the addition of a photosensitiser to plasma followed by exposure to visible or ultraviolet (UV) light, and then removal of the photosensitiser (except for Mirasol). A pooled solvent-detergent treated plasma (SDFFP), Octaplas LG, which also includes a prion reduction step, is available in the UK from Octapharma AG (Lachen, Switzerland). Key features of these components are given in Table II.

All pathogen inactivation systems reduce the level of coagulation factors and inhibitors in plasma, the extent of which varies by factor and by system (Rock, 2011). In general, the worst affected factors are FVIII, fibrinogen and FXI, where losses are approximately 30–40%, although the SD process also significantly reduces protein S and antiplasmin. The FVIII specification is lower for pathogen-reduced plasma and cryoprecipitate due to the effect of pathogen-reduction on clotting factor levels (Table II). For pooled methylene blue-treated cryoprecipitate, in order to meet the specification in Table I, 6 rather than 5 units are pooled together.

All systems have good (generally >4 log) reduction of enveloped viruses, but activity against non-enveloped viruses (hepatitis A virus, parvovirus B19 and hepatitis E virus) are more variable. For this reason, plasma used as a source of SDFFP supplied in the UK is tested for the latter viruses.

Thawing of FFP

When frozen, FFP packs become relatively brittle and must be handled with care. Vulnerable parts of the pack include the stumps of the entry lines, which can break off if knocked. All UKBTS provide frozen plasma in a vacuum-packed outer container so that the plasma pack itself does not come into direct contact with thawing devices. Because of the potential for pinholes and cracks in the plastic that may not be visible, it is imperative that procedures for thawing FFP are designed

Table II. Specifications of different fresh frozen plasma.

	Standard FFP	Solvent-Detergent (Octaplas LG)	Methylene Blue (Theraplex)	Amotosalen Intercept	Vitamin B2 Mirasol
Available in UK?	YES	YES	YES	NO	NO
PLASMA					
Volume	200–300 ml	200 ml	200–260 ml (50 ml neonatal size available)	200–300 ml (input plasma 385–650 ml)	170–360 ml
Source of plasma (donations)	UK	Germany, USA	Austria	N/A	N/A
Virological testing (genomic unless stated)	HIV, HBV, HCV, HEV all donations. HTLV new donors.	All donations HIV, HBsAg and HCV by ELISA as well as HIV, HCV, HEV, HAV, HBV and parvovirus B19 by PCR	HIV, HBV, HCV, HEV all donations.	N/A	N/A
Residual viral risk	HIV 1 in 15·5 million* HBV 1 in 2·1 million* HCV 1 in 95·8 million*	No proven transmission of HIV, HBV, HCV, HEV	No proven transmission of HBV, HEV (one possible HCV and HIV in Europe)	No proven transmission of HIV, HBV, HCV. One transmission of HEV reported.	No reported transmission of HIV, HBV, HCV, HEV
Treatment step	None	1% TNBP 1% Triton X-100	1 μmol/l MB+ visible light 30 min	150 μmol/l amotosalen + UVA light 4 min	50 μmol/l riboflavin+ UV 4–10 min
Removal step for residual chemicals?	N/A	YES <2 μg/ml TNBP <5 μg/ml Triton-X	YES <0·3 μmol/l MB	YES	NO
Shelf-life –frozen/at 4°C once thawed	3 years/24 h (120 h for unexpected major haemorrhage)	4 years/24 h at 2–8°C, 8 h at −20 to 25°C	3 years/24 h	2 years/24 h	2 years/6 h
Coagulation factor losses (compared to standard FFP)		Batches tested for FV, FVIII, FXI (all >0·50 iu/ml), protein C (>0·70 iu/ml), protein S (>0·30 iu/ml), antiplasmin (>0·20 iu/ml)	20–30% loss of FVIII, FXI and fibrinogen, others less affected	20–30% loss of FVIII and fibrinogen, others less affected	20–30% loss of FVIII, FXI and fibrinogen, others less affected
Clinical studies of plasma efficacy performed	Systematic review of studies identified only small RCT's. No consistent evidence of significant benefit for prophylactic and therapeutic use across a range of indications evaluated. See text.	Observational studies: Congenital coagulation deficiency. RCTs: liver disease/transplantation and cardiac surgery, TTP	Observational studies: Congenital coagulation deficiency and cardiac surgery No large RCTs	Observational studies: Congenital coagulation deficiency, plasma exchange for TTP and liver transplantation. RCTs: liver disease, coagulopathy, warfarin reversal, plasma exchange for TTP	Observational study plasma exchange for TTP
Indications	See text	As for FFP	As for FFP Not TTP	As for FFP	As for FFP

Table II. (*Continued*)

	Standard FFP	Solvent-Detergent (Octaplas LG)	Methylene Blue (Theraplex)	Amotosalen Intercept	Vitamin B2 Mirasol
TRALI risk	Very low, selected from male donors. No cases in UK from FFP since 2009.	Very low. No cases reported in UK according to SHOT definition.	Very low. Selected from male or females tested for HLA/HNA antibodies. No reported cases in UK.	Low if selected from male or nulliparous females	Low if selected from male or nulliparous females
Allergic reactions	7·49/100 000 units issued	4·33/100 000 units issued	None reported in 2016	N/A	N/A
Total usage in Europe		>9 million	>6 million	>1·5 million	<500 000

ELISA, enzyme-linked immunosorbent assay; FFP, fresh frozen plasma; FV, factor V; FVIII, factor VIII; FXI, factor XI;HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; HLA, human leucocyte antigen; HNA, human neutrophil antigen; HTLV, Human T-cell lymphotropic virus; MB, methylene blue; N/A, not applicable; PCR, polymerase chain reaction; RCT, randomized control trial; SHOT, Serious Hazard Of Transfusion; TRALI, transfusion-related acute lung injury; TTP thrombotic thrombocytopenic purpura; UV(A) , ultra-violet (A).
*NHSBT data calculated from 2013 – 2016 (available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/645328/Safe_supplies_2016_supplementary_data.pdf)

to minimise the risk of bacterial contamination. Once thawed, the primary pack should be removed from the over-wrap bag and examined for leaks or damage. Damaged packs should not be used. If there is any unexpected appearance such as flocculation or discolouration, or apparent leaks, packs should be discarded, or referred for further opinion. There are several methods available to thaw plasma. Those that do not directly expose units to water are recommended to reduce the risk of bacterial contamination. Whatever method is used to thaw plasma, the procedure to follow, cleaning and maintenance schedules should be described by a specific standard operating procedure relevant to the method employed.

Dry heat methods. Methods that thaw plasma using dry heat with agitation are available and in use in the UK. Dry ovens (temperature-controlled fan-assisted incubators) may have a lower potential for contaminating FFP packs with microbes, although they are usually of limited capacity.

Microwave ovens. Although these can defrost FFP in 2–3 min, they have the disadvantage of limited capacity. There are also concerns over the creation of 'hot spots' in the packs and the potential for parts of the pack to act as an aerial causing arcing. Previous studies have suggested that the quality of plasma once thawed is similar to that when using water bath methods (von Heymann *et al*, 2006; Kuta *et al*, 2016).

Water bath-based methods. The majority of water baths now used in the UK do not expose plasma to water directly, but rather the unit is placed in a pocket around which a water-based solution circulates. When using a water bath, it is essential to place the FFP pack in a vacuum-sealed over-wrap to protect it from bacterial contamination. Water baths used for thawing FFP must only be used for this purpose. All maintenance should be documented and logged. The average time for thawing FFP or cryoprecipitate in water baths is 20 min.

Temperature of thawing. Scant data exist in relation to the ideal temperature for thawing of plasma. Data that do exist suggest that temperatures close to 37°C may be optimal, because cryoprecipitate will form when thawed closer to 4°C, and thawing at higher temperatures might affect the viability of plasma proteins. The current recommendation is that plasma be thawed at 33–37°C (http://www.transfusionguidelines.org.uk/document-library/supporting-papers). However, methods of thawing plasma at higher temperatures, e.g. 45°C, are available, which might improve the speed of thawing. Data on the effect of thawing plasma at 45°C or higher are lacking. It is important that alternative thawing temperatures be validated for all components, and for their maximal post-thaw shelf-life. For SDFFP, the manufacturer's instruction on thawing should be followed.

Recommendations

- **Protocols must be in place to ensure that thawing equipment is cleaned and maintained according to standard operating procedures (2A).**
- **After thawing, and at the time of administration, the component should be inspected to ensure that no precipitate is visible and that the component packaging is intact (2A).**
- **Thawing methods that do not directly expose the primary plasma pack to water must be used to minimise bacterial contamination (2A).**

Storage after thawing

Fresh Frozen Plasma. Once thawed, standard FFP may be stored at +4 ± 2°C in an approved temperature-controlled blood storage refrigerator before administration to a patient as long as the infusion is completed within 24 h of thawing. Pre-thawed plasma can also be stored at +4 ± 2°C for up to 120 h for use only in patients who develop unexpected major bleeding (e.g. following trauma). This extended storage of pre-thawed FFP for patients with unexpected major haemorrhage was recommended to enable rapid provision of FFP for these patients where delay would be detrimental while also limiting FFP wastage. Data from NHSBT show that with the exception of protein C, all clotting factors decrease between 24 and 120 h after thawing. Most FVIII loss occurs within the first 24 h following thawing, after which the rate of loss decreases. For other clotting factors, the loss of activity is more linear once thawed. However, with the exception of FVIII, mean levels remain above 70% at 120 h (http://www.transfusionguidelines.org.uk/document-library/supporting-papers).

To minimise the risk of bacterial growth during extended storage of thawed plasma (>24 h), thawing methods that do not directly expose primary plasma packs to water must be used, and time out of controlled storage must be kept to a minimum. Pre-thawed FFP that is out of a controlled temperature environment (+4 ± 2°C), can be accepted back into temperature-controlled storage if this occurs on one occasion only of less than 30 min. Transfusion of FFP should be completed within 4 h of issue out of a controlled temperature environment. *At present, there is a lack of evidence relating to how long thawed plasma can safely remain out of controlled temperature storage. This recommendation is based on current practice in other countries and expert opinion, extrapolated from evidence on red cell storage with the aim of minimising FFP wastage, while also ensuring safety of the component for recipients. The recommendation may change in the future as a result of research carried out on FFP storage and bacterial growth.*

Table III. Principles of blood group selection for plasma.

Recipients	O	A	B	AB
a)High titre (HT) positive, or HT untested units*				
1st choice	O	A	B	AB
2nd choice	A	AB	AB	A†
3rd choice	B	B†	A†	B†
4th choice	AB	–	–	–
b)HT negative*				
1st choice	O	A	B	AB
2nd choice	A	B	A	A
3rd choice	B	AB	AB	B
4th choice	AB	–	–	–

*Group O must only be given to group O recipients
†Only suitable for emergency use in adults

Methylene Blue-treated FFP (MBFFP). Once thawed, MBFFP may be stored at +4 ± 2°C in an approved temperature-controlled blood refrigerator before administration to the patient, as long as the infusion is completed within 24 h of thawing. The post-thaw shelf-life of this component was reviewed in 2016 and was not extended further (http://www.transfusionguidelines.org.uk/document-library/supporting-papers), as the coagulation factor content of PI plasma is reduced compared to standard FFP, and some studies have shown an increase in coagulation activation with extended storage of thawed MBFFP (Thiele *et al*, 2016). There are no trials that have assessed the efficacy of MBFFP *versus* standard FFP.

Solvent detergent-treated FFP (SDFFP). SDFFP is a licensed medicinal product and therefore its shelf-life following thawing should be governed by the manufacturer (Octapharma).

Cryoprecipitate. Once thawed, cryoprecipitate must not be refrozen and should be used immediately. If delay is unavoidable, the component should be stored at ambient temperature and used within 4 h. NHSBT have assessed the haemostatic properties of thawed cryoprecipitate beyond 4 h (up to 72 h), and have demonstrated that these are stable [i.e. fibrinogen, FXIII, rotational thromboelastometry (ROTEM®) and thrombin generation] (Green *et al*, 2016). However, the potential risk of bacterial contamination arising from storing cryoprecipitate at ambient temperature will need to be assessed before the shelf life of thawed cryoprecipitate can be extended beyond 4 h.

Recommendations

- **Once thawed, standard fresh frozen plasma (FFP) or methylene blue treated FFP (MBFFP) may be stored at +4 ± 2°C in an approved temperature-controlled blood storage refrigerator before administration to the patient, as long as the infusion is completed within 24 h of thawing (2A).**

Table IV. Plasma selection for patients who have undergone ABO-mismatched haematopoietic stem cell (HSC) transplantation

Recipient ABO blood group	Donor ABO blood group	Category of ABO mismatch	Phase II (when HSC are infused)		Phase III*
			First choice	Second choice	
O	A	Major	A	AB	Donor
	B	Major	B	AB	Donor
	AB	Major	AB		Donor
A	O	Minor	A	AB	Donor
	B	Major and minor	AB		Donor
	AB	Major	AB		Donor
B	O	Minor	B	AB	Donor
	A	Major and minor	AB		Donor
	AB	Major	AB		Donor
AB	O	Minor	AB		Donor
	A	Minor	AB		Donor
	B	Minor	AB		Donor

Reproduced from (O'Donghaile *et al*, 2012), and published with permission.
*Phase III starts when both forward and reverse grouping in the recipient are consistent with the donor ABO type.

- **Transfusion of FFP should be completed within 4 h of issue out of a controlled temperature environment (2A).**
- **The shelf life of pre-thawed standard FFP can be extended to 120 h, to enable its rapid provision in unexpected major haemorrhage only (2A).**
- **Pre-thawed FFP that is out of a controlled temperature environment (+4 ± 2°C) can be accepted back into temperature-controlled storage if this occurs on one occasion only of less than 30 min (2A).**

Selection of plasma components

Patients who are likely to receive multiple units of FFP should be considered for vaccination against hepatitis A and B (HAV, HBV), and patients who are likely to receive large or repeated doses of FFP should receive pathogen-reduced plasma. Such patients include those with congenital factor deficiencies for whom no pathogen-reduced concentrate is available, and patients undergoing intensive plasma exchange, e.g. for thrombotic thrombocytopenic purpura (TTP).

ABO blood group compatibility

In order to avoid the risk of ABO-associated haemolysis in recipients, plasma of donors with identical ABO blood group to the recipient should be used as the first choice. In an emergency, if the patient's blood group is unknown, ABO non-identical plasma is acceptable if it has 'low-titre' anti-A or anti-B activity. Group O FFP should only be given to group O patients (Table III). For more details on plasma group selection for MBFFP, please refer to the paediatric guideline (New *et al*, 2016).

RhD blood group compatibility

The risk of alloimmunisation following RhD mismatch FFP transfusion was reviewed in 2004 by UKBTS (https://www.transfusionguidelines.org/document-library/documents/rhd-grouping-of-ffp); FFP and cryoprecipitate contain only a small amount of red cell stroma (red cells after FFP thawing would be expected to be <0·001 ml in 300 ml FFP). This means that sensitisation following administration of RhD-positive plasma to an RhD-negative individual is very unlikely to occur (http://www.transfusionguidelines.org.uk/document-library/supporting-papers).

Recommendations

- **Plasma of donors with identical ABO blood group to the recipient should be used as the first choice. If this is not possible, ABO non-identical plasma is acceptable if it has 'low-titre' anti-A or anti-B activity (1B).**
- **Group O plasma should only be given to group O patients (1B).**
- **Fresh frozen plasma and cryoprecipitate of any RhD group may be transfused. If RhD positive plasma is given to an RhD negative individual, no anti-D prophylaxis is required (1B).**

Haematopoietic stem cell transplantation

There are three types of ABO-incompatible haematopoietic stem cell transplants (HSCT): (i) major; (ii) minor; and (iii) bi-directional (Table IV). Currently, there is no evidence-based guidance on plasma blood group selection following ABO-mismatched HSCT, and most clinical practice relies on current

understanding of basic principles of ABO incompatibility. The knowledge of both donor and recipient blood groups are important when selecting the right plasma group for patients, as well as performing both ABO forward and reverse typing. Selection of plasma for patients undergoing ABO-mismatch HSCT is given in Table IV. For patients who relapse, selection of plasma should be guided by the ABO-blood group detected at the time.

Solid organ transplantation

As for HSCT, there is no evidence-based guidance on plasma blood group selection following ABO-mismatched solid organ transplants, and most of the clinical guidance relies on the understanding of the basic principles of ABO incompatibility, and the timing of when successful engraftment (or accommodation) of the organ is expected (Koch *et al*, 2004).

Recommendations

- **Following ABO minor mismatched solid organ transplant, plasma components should be of recipient's ABO group (1C).**
- **Following ABO major mismatched solid organ transplant, plasma should be of donor's ABO group until organ accommodation (usually 4 weeks after transplant) (1C).**
- **Following ABO bidirectional mismatched solid organ transplant, group AB plasma should be given until organ accommodation (usually 4 weeks after transplant) (1C).**

Abnormal clotting tests prior to intervention in a non-bleeding patient, and role of FFP transfusion

This section will only cover the use of FFP prior to interventions in non-bleeding patients who have abnormal clotting tests. For the use of FFP in bleeding patients, or for the role of coagulation testing in unselected patients prior to surgery or invasive procedures please refer to the relevant British Society for Haematology (BSH) guidelines (Chee *et al*, 2008; Hunt *et al*, 2015).

The UK national FFP audit in 2009 showed that ~50% of patients received FFP in the absence of clinical bleeding (Stanworth *et al*, 2011a); many of these patients received it prior to invasive procedures for mild or moderate abnormalities of prothrombin time (i.e. PT <16 s) or international normalised ratio (i.e. INR < 1·5 × mean normal). More importantly, transfusion of FFP only resulted in minimal, or no correction of PT or INR (Stanworth *et al*, 2011a).

The use of prophylactic FFP prior to procedure in non-bleeding patients with abnormal clotting tests is not supported by good quality evidence, and several systematic reviews (mainly observational studies) have concluded that an abnormal PT or INR does not predict peri-procedural bleeding (Segal & Dzik, 2005; Chee *et al*, 2008). A detailed personal and family history of bleeding, drug history and knowledge of the bleeding risks associated with each surgical or other invasive procedure (Patel *et al*, 2012), are more important than clotting tests results when assessing whether a procedure is likely to be associated with clinically significant bleeding. For patients with a personal/family history of bleeding, referral to a haematologist for further work-up is needed, as standard coagulation tests may be normal. Further, there is very little evidence to support the effectiveness of prophylactic use of FFP (in any clinical settings) in correcting abnormal clotting tests or reducing bleeding events (Stanworth *et al*, 2004). All these indicate that there is a need for clinical studies to evaluate the efficacy and safety of prophylactic FFP in non-bleeding patients with abnormal clotting tests, who are undergoing a procedure, to better understand whether benefits of FFP outweigh risks.

Other global clotting tests, such as thromboelastography (TEG) or ROTEM®, have been shown to be cost-effective in reducing blood transfusion and mortality during cardiac surgery for bleeding patients (Whiting *et al*, 2015; Wikkelso, *et al* 2017). However, their role in predicting bleeding risks in non-bleeding patients with abnormal PT or activated thromboplastin time (APTT), or monitoring the effectiveness of prophylactic FFP prior to invasive procedure or surgery, remains unknown.

Key practice point

- **Abnormal standard coagulation tests (prothrombin time [PT]/activated partial thromboplastin time [APTT]) are poor predictors of bleeding risks in non-bleeding patients prior to an invasive procedure (2C).**
- **A detailed personal and family bleeding history, drug history and the bleeding risk associated with the planned procedure must be assessed as a matter of routine for all patients undergoing a planned procedure (1B).**
- **Standard coagulation tests should be considered in patients undergoing procedures with a moderate or high bleeding risk, any patients on anticoagulants, or those who have a personal/family bleeding history (1B).**
- **Patients with a positive personal/family bleeding history should be discussed with haematology as standard clotting test results may be normal in the presence of a significant bleeding tendency (1B).**
- **The impact of commonly used doses of FFP to correct clotting results, or to reduce the bleeding risk, is very limited particularly when the PT ratio or International Normalised Ratio (INR) are between 1·5–1·9 (2C).**

Dosage of FFP and cryoprecipitate in non-bleeding patients

Fresh frozen plasma

The Intensive Care Study of Coagulopathy reported wide variation in the dose of FFP administered (median 10·8 ml/

kg, first to third quartile 7·2 to 14·4 ml/kg) (Stanworth *et al*, 2011b). A recent non-inferiority randomised control trial (stopped early for futility) recruited non-bleeding critically ill patients with an INR of 1·5–3·0 who were about to undergo an invasive procedure, and randomised patients to receive either FFP 12 ml/kg or no FFP (Muller & Juffermans, 2015). The authors reported a *post hoc* analysis where coagulation factors, anticoagulant levels, thrombin generation and thromboelastometry assays (ROTEM®) were measured before and after FFP transfusion at the protocol-defined doses. FFP transfusion had only a marginally beneficial effect on improving coagulation profiles, as although levels of FII, FV and FVII were elevated, thrombin generation was unaffected and anticoagulant factors levels were elevated (Muller *et al*, 2015). Earlier work by Chowdary *et al* (2004) compared standard doses of FFP (12·2 ml/kg) versus higher doses (33·5 ml/kg) in 22 critically ill patients and reported a dose-dependent relationship, such that samples from patients in the higher dose group had significantly higher increments in FI, FV, FVII, FIX, FX and FXII levels compared to the standard dose group. Although larger doses of FFP might improve standard tests of coagulation (Yang *et al*, 2012), higher doses of blood components will be associated with further adverse risks, including fluid overload. Many published studies evaluating the use of plasma are small and unable to link improvements in laboratory tests with clinical outcomes (Yang *et al*, 2012). In summary, much of the practice of plasma transfusion as prophylaxis in non-bleeding patients before invasive procedures seems unlikely to have clinical benefit; there is currently insufficient evidence to allow an evidence based recommendation on the optimal dose for prophylactic use of FFP prior to invasive procedures in patients with abnormal clotting tests. For management of major bleeding the recommended dose for FFP is 15 to 20 ml/kg (Hunt *et al*, 2015).

Key Practice Points

- **There is insufficient evidence on which to base a recommendation about the optimal dose of FFP in patients with abnormal clotting tests undergoing procedures.**
- **For patients who have abnormal clotting tests and other factors (i.e. personal/family bleeding history, drug history, bleeding risk associated with planned procedure or thrombocytopenia) that indicate a significant bleeding risk during a procedure, then a starting dose of 15 ml/kg of FFP can be considered, although this is not evidence-based.**

Cryoprecipitate

There are few data on use of cryoprecipitate in non-bleeding patients. Audits in the UK and Canada have reported that cryoprecipitate is being administered for prophylactic use (Alport *et al*, 2008; Tinegate *et al*, 2012). Cryoprecipitate can be considered in non-bleeding patients because of low fibrinogen (for example < 1 g/l) for interventions at risk of significant bleeding, or in critical sites. If cryoprecipitate is administered in such a situation, a dose of two five-donor pools will increase fibrinogen in an average-sized adult by approximately 1 g/l (Hunt *et al*, 2015). However, there is insufficient evidence to recommend the threshold of fibrinogen at which cryoprecipitate transfusion is indicated, or the optimal dose of cryoprecipitate needed for prophylaxis in non-bleeding patients before invasive procedures.

Key Practice Points

- **There is insufficient evidence on which to base a recommendation about the threshold of fibrinogen level to transfuse cryoprecipitate, or the optimal dose, in patients with hypofibrinogenaemia undergoing procedures.**
- **If fibrinogen is <1·0 g/l, and other factors (i.e. personal/family bleeding history, drug history, bleeding risk associated with planned procedure) indicate a significant bleeding risk prior to a procedure, then a starting dose of two five-donor pools of cryoprecipitate can be considered, although this is not evidence-based.**

When to consider, and not consider the use of plasma

Hypovolaemia

While administration of FFP during the resuscitation of patients with major blood loss may contribute to supporting circulating volume, FFP and cryoprecipitate should not be used for volume replacement in patients who are not bleeding.

Recommendation

- **Plasma should not be used for volume replacement (2C).**

Abnormal clotting tests in the absence of bleeding

Intensive care units (ICU). Abnormal coagulation tests in critically ill patients are most frequently a result of the disease process, such as severe sepsis, organ failure, hypothermia, hypocalcaemia or acidosis. Coagulopathy in critical care may therefore range from profound derangement of haemostasis associated with major blood loss, to prolongation of PT and/or APTT in the absence of bleeding (Stanworth *et al*, 2011b; Hunt, 2014). Prolongation of PT and/or APTT do not always reflect bleeding risk in a critically ill patient and abnormalities are frequently due to vitamin K deficiency, or the presence of coagulation factor inhibitors, acquired through a critical illness.

In a small randomised controlled trial (RCT) (n = 81 patients) comparing FFP with no FFP in critically ill patients with an INR of 1·5–3, there was no significant difference in the incidence of bleeding between the two groups (Muller *et al*, 2015). A prospective study of 119 intensive care patients undergoing tracheostomy demonstrated no difference in bleeding between patients with INR of ≤ 1·2 or 1·3–1·84. These patients also had thromboelastometry profiles carried out with results being within the normal range in all cases except one (Durila *et al*, 2015).

Patients with traumatic brain injuries often have abnormal coagulation studies and may require insertion of an intracranial pressure monitor. Published studies where coagulation results are described quote haemorrhagic complications in 2–15% (Martinez-Manas *et al*, 2000). No high-quality data exist to guide practice in patients with a modest derangement in INR or APTT. A retrospective study examined 157 patients with traumatic brain injury, stratified according to INR [0·8–1·2 (n = 103), 1·3–1·6 (n = 42), ≥ 1·7 (n = 12)]. Twenty-two patients had component therapy prior to bolt insertion, of which 10 were in the INR 1·3–1·6 group and 12 were in the INR>1·7 group. The study described infrequent bleeding complications with one case of petechial haemorrhage in each group and found that FFP transfusion was not consistently effective in correcting the INR (Davis *et al*, 2004).

Acquired vitamin K deficiency. Many patients in ICU who are seriously ill have inadequate vitamin K intake, resulting in prolongation of the PT. This should be corrected with oral or intravenous vitamin K administration. FFP is not recommended for correction of vitamin K deficiency in such patients in the absence of significant bleeding.

Recommendations:

- **There is no evidence to support prophylactic use of FFP in non-bleeding patients with abnormal standard coagulation tests pre-procedures (2C).**
- **The impact of commonly used doses of FFP to correct clotting results, or to reduce the bleeding risk, is very limited, particularly when the PT ratio or INR are between 1·5–1·9 (2C).**
- **Vitamin K should be administered in patients with prolonged PT that is likely to be due to acquired vitamin K deficiency (1B).**

Liver disease. Synthesis of coagulation factors (except FVIII) decreases as liver dysfunction worsens in both decompensated cirrhosis and acute liver failure. Prolongation of coagulation tests (PT and APTT) is common, together with a perception among clinicians that this signifies increased bleeding risk. Observational studies have demonstrated that the prolongation in clotting times is not necessarily indicative of bleeding risk in these individuals, particularly in the setting of common liver-related complications, such as variceal haemorrhage (Tripodi & Mannucci, 2007; Hshieh *et al*, 2015). Indeed, while some liver patients have some bleeding tendency, others have a prothrombotic tendency with the same PT prolongation. This is primarily because of rebalanced haemostasis, wherein the levels of endogenous anticoagulants are decreased in the same manner as the clotting factor levels. PT bore no relevance to bleeding risk in a study of acutely ill cirrhotic patients on intensive care. A fibrinogen level <0·6 g/l and a platelet count of $<30 \times 10^9$/l were the most important predictors of bleeding (Drolz *et al*, 2016).

The rates of spontaneous bleeding and bleeding secondary to minimally invasive procedures in patients with liver disease are both low (DeAngelis *et al*, 2016). However, there is variable clinical practice in the use of FFP and cryoprecipitate for prophylaxis in patients with liver disease (Desborough *et al*, 2016). Transfusion of FFP in advanced liver disease may not correct abnormalities in coagulation results, and evidence that transfusion can mitigate the risk of bleeding is lacking (Abdel-Wahab *et al*, 2006). Transfusion of blood components has a potential for harm due to associated increases in portal pressure in patients with decompensated cirrhosis (Giannini *et al*, 2014). The risk factors for variceal haemorrhage in chronic liver disease are increased portal pressure, renal impairment and sepsis, rather than imbalances in haemostasis. Despite non-haemostatic factors contributing to the bleeding risk, FFP is often transfused in patients bleeding from varices leading to volume expansion, which may increase the re-bleeding rate through further increase in portal hypertension. There is no good evidence that transfusion of FFP or cryoprecipitate reduces re-bleeding rates or is of any clinical benefit in patients with acute variceal haemorrhage, and there is variable opinion in published guidance on its utility (National Institute for Health and Care Excellence, 2012;Tripathi *et al*, 2015). The most recent guidance on variceal haemorrhage from the American Association for the study of liver diseases recommends against the use of FFP and the measurement of INR in this context (Garcia-Tsao *et al*, 2017).

FFP is also often administered prior to liver biopsy. However, liver patients at true increased risk of bleeding are likely to be better served by modification of the procedure itself – e.g. liver biopsy via the transjugular, not percutaneous, route – rather than by prior administration of blood products (Segal & Dzik, 2005; Rockey *et al*, 2009). American and European liver association guidelines do not endorse the routine use of FFP or cryoprecipitate for low risk procedures, such as abdominal paracentesis (Runyon, 2013, European Association for the Study of the Liver 2017).

Recommendations

- **PT and APTT do not reflect the true haemostatic status of patients with advanced liver disease. Abnormalities of**

PT and APTT need to be interpreted with caution in these patients (1C).
- **There is no good evidence to endorse the use of prophylactic FFP for correction of abnormal clotting tests in non-bleeding patients prior to interventions such as elective variceal banding (1C).**
- **We endorse the liver society recommendations that prophylactic transfusion of FFP and cryoprecipitate is not given in low bleeding risk procedures, such as paracentesis (1C).**
- **There is no good evidence to support a role for prophylactic FFP to reduce the risk of bleeding from percutaneous liver biopsy. An alternative procedure with a lower bleeding risk, (e.g. transjugular liver biopsy), should be considered instead (2C).**

Inherited single clotting factor deficiency

FFP is the only currently available replacement therapy for FV deficiency and combined deficiency of FV and FVIII. It may also be effective in other rare coagulation disorders in the case of emergencies where a more specific replacement therapy is unavailable, or if the diagnosis is uncertain (Mumford *et al*, 2014).

Recommendation

- **If virally-inactivated specific clotting factors are not available, pathogen-reduced plasma may be used for factor replacement in congenital coagulation factor deficiency (1C).**

Other indications

For further details on diagnosis and management of disseminated intravascular coagulation, reversal of anticoagulant effects, management of major bleeding, TTP, and the use of plasma in children and neonates, please refer to the relevant BSH guidelines (Levi *et al*, 2009; Keeling *et al*, 2011, 2016; Scully *et al*, 2012; Makris *et al*, 2013; Wada *et al*, 2013; Hunt *et al*, 2015; New *et al*, 2016).

Safety and adverse effects of plasmas

Pathogen-reduced plasmas

Methylene blue-treated FFP (MBFFP). In France, MBFFP was withdrawn in 2012 due to concern about an increased frequency of allergic reactions compared to other plasma components (Agence Française de Sécurité Sanitaire des Produits de Santé [AFSSAPS] 2011). Analysis of reactions to MBFFP from Serious Hazard Of Transfusion (SHOT) data (2007-2013) has not demonstrated a statistically significant increase in overall acute transfusion reactions, and non-severe or severe allergic reactions when compared to standard FFP (Joint United Kingdom Blood Transfusion Services and Health Protection Agency Professional Advisory Committee, 2012). Therefore, MBFFP continues to be used in the UK and other countries, with no concerns about safety (Politis *et al*, 2014).

SDFFP. Analysis of SHOT plasma reaction rates showed a significant reduction in all acute reactions and in non-severe reactions when comparing SDFFP with standard FFP but there was no significant difference in the rates of severe allergic or severe hypotensive reactions (Bolton-Maggs *et al*, 2016).

Cryoprecipitate

Cryoprecipitate has similar risks to FFP for allergic and febrile reactions. It has also been implicated in cases of transfusion-related acute lung injury (TRALI) (Bolton-Maggs *et al*, 2016) from the devolved countries in the UK at a time when they had yet to institute a policy of excluding female plasma (all the UK countries have now moved to male-only plasma for cryoprecipitate).

Allergy

Acute transfusion reactions (allergic, hypotensive or severe febrile). Allergic, febrile and anaphylactic reactions are defined as those occurring within 24 h of transfusion and are the most common reactions following FFP transfusion. Reports of anaphylaxis in the UK remain stable at about 30–40 cases per year. It occurs early, usually within the first 15 mins and the treatment of choice is adrenaline. The widespread use of antihistamines and steroids in this setting is not based on evidence.

Other reactions may occur later during transfusion or after completion. Review by component type demonstrates that febrile reactions are very uncommon with FFP but moderate and severe allergic and anaphylactic reactions are more likely with FFP than any other blood component.

Causes of acute transfusion reactions to plasma. Immunoglobulin A (IgA) deficiency, although comparatively common in the population, is rarely diagnosed in this setting (Sandler *et al*, 2015). From 2010 to 2014 only two patients who developed anaphylaxis after FFP were shown to have IgA deficiency with anti-IgA antibodies. An atopic tendency in the recipient is thought to be a major contributory factor to reactions (Savage *et al*, 2011).

Pulmonary Complications

Reports of suspected TRALI have decreased, while there has been increasing recognition of transfusion associated circulatory overload (TACO): 30–40 cases reported in 2009–2010 to over 80 each year in 2012–2016 (Bolton-Maggs *et al*, 2017).

Cases of acute respiratory distress occurring within 24 h of transfusion that do not fit the definition for either TRALI or TACO are grouped as transfusion-associated dyspnoea. There is some evidence that patients with underlying inflammatory conditions are more susceptible to transfusion-associated dyspnoea (Garraud, 2016).

Transfusion-related acute lung injury. Risk reduction for TRALI began in 2003 with a gradual transition to male plasma donors. Now, 100% of FFP in the UK comes from male donors. Reported suspected TRALI cases have reduced from a peak of 36 in 2003 (Chapman & Williamson, 2008) to none in 2016. Deaths related to TRALI have also reduced to between none and four each year, with 12 deaths in the 12-year period 2004-2015 (Bolton-Maggs *et al*, 2016). However, many suspected TRALI cases are complex and the diagnosis is often not clear cut. The implicated components in TRALI are now red cells or platelets with no cases associated with FFP since 2009. In 2014 and 2015 patients developed TRALI after receiving cryoprecipitate pools containing plasma from female donors, all with concordant antibodies. SHOT recommended that cryoprecipitate should also be sourced from male donors only, as is the case for FFP (Bolton-Maggs *et al*, 2016), and this has now been put into practice in the UK.

Transfusion-associated circulatory overload. TACO is now the most frequent cause of death and major morbidity reported to SHOT since 2008, but other pulmonary conditions may present with similar symptoms and signs. SHOT analyses demonstrate that although elderly patients are particularly vulnerable, TACO may occur at any age and with small volumes of components (Bolton-Maggs *et al*, 2017). Patients should be fully assessed for risk factors prior to transfusion; these include concomitant intravenous fluids, pre-existing cardiac dysfunction, evidence of pre-existing circulatory overload, pre-existing pulmonary oedema and low body weight. SHOT recommends use of a checklist prior to blood transfusion of non-bleeding patients to assess the risk of TACO (Bolton-Maggs *et al*, 2017).

Infection

Transmission of infection by blood components is rare. In the 20 years of SHOT reporting there have been few reports associated with plasma components: six with FFP (four hepatitis E virus [HEV], one HBV, and one HIV in 1996) and one from cryoprecipitate (HEV in 2015) (Bolton-Maggs *et al*, 2016). Bacterial transmissions from plasma components have not been reported.

Graft-versus-host disease

There have been no case reports of FFP-associated graft-versus-host disease.

Disclaimer

While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the BSH nor the publishers accept any legal responsibility for the content of this guidance.

All members of the writing group agreed with all recommendations, with the exception of plasma dose where there was no unanimous consensus.

Acknowledgements

The authors wish to thank Dr Jacky Wilson for help in undertaking the initial literature review, Mrs June MacLeod for helping with sourcing all relevant papers, Ms Alison Watt for reviewing the ABO mismatched transplant section, Dr Patricia Hewitt for reviewing the variant CJD section. Cerus, Macopharma, Octapharma and Terumo for their input with information provided in Table II. The BSH Transfusion task force members at the time of writing this guideline were Dr Sharon Zahra, Ms Andrea Harris, Dr Dora Foukaneli, Dr Edwin Massey, Dr Gavin Cho, Ms Jenny White, Ms Joan Jones, Mr Malcolm Needs, Dr Paul Kerr, Dr Paula Bolton-Maggs, Dr Richard Soutar, Dr Susan Robinson and Ms Wendy McSporran. The authors would like to thank them, the BSH sounding board, and the BSH guidelines committee for their support in preparing this guideline. The research was supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC).

Declaration of Interests

The BSH paid the expenses incurred during the writing of this guidance. All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request. The following authors have undertaken: JT has received speaker fees from Octapharma; RC has received corporate sponsorship from Terumo, and Macopharma for research and development projects in relation to pathogen inactivation, and has collaborative research projects with Cerus. The following members of the writing group have no conflicts of interest to declare LG, SZ, CB, PBM, YK and SS.

Review Process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (http://www.b-s-h.org.uk/guidelines/).

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

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Summary

Background Rapid reversal of vitamin K antagonist (VKA)-induced anticoagulation is often necessary for patients needing urgent surgical or invasive procedures. The optimum means of VKA reversal has not been established in comparative clinical trials. We compared the efficacy and safety of four-factor prothrombin complex concentrate (4F-PCC) with that of plasma in VKA-treated patients needing urgent surgical or invasive procedures.

Methods In a multicentre, open-label, phase 3b randomised trial we enrolled patients aged 18 years or older needing rapid VKA reversal before an urgent surgical or invasive procedure. We randomly assigned patients in a 1:1 ratio to receive vitamin K concomitant with a single dose of either 4F-PCC (Beriplex/Kcentra/Confidex; CSL Behring, Marburg, Germany) or plasma, with dosing based on international normalised ratio (INR) and weight. The primary endpoint was effective haemostasis, and the co-primary endpoint was rapid INR reduction (≤1·3 at 0·5 h after infusion end). The analyses were intended to evaluate, in a hierarchical fashion, first non-inferiority (lower limit 95% CI greater than –10% for group difference) for both endpoints, then superiority (lower limit 95% CI >0%) if non-inferiority was achieved. Adverse events and serious adverse events were reported to days 10 and 45, respectively. This trial is registered at ClinicalTrials.gov, number NCT00803101.

Findings 181 patients were randomised (4F-PCC n=90; plasma n=91). The intention-to-treat efficacy population comprised 168 patients (4F-PCC, n=87; plasma, n=81). Effective haemostasis was achieved in 78 (90%) patients in the 4F-PCC group compared with 61 (75%) patients in the plasma group, demonstrating both non-inferiority and superiority of 4F-PCC over plasma (difference 14·3%, 95% CI 2·8–25·8). Rapid INR reduction was achieved in 48 (55%) patients in the 4F-PCC group compared with eight (10%) patients in the plasma group, demonstrating both non-inferiority and superiority of 4F-PCC over plasma (difference 45·3%, 95% CI 31·9–56·4). The safety profile of 4F-PCC was generally similar to that of plasma; 49 (56%) patients receiving 4F-PCC had adverse events compared with 53 (60%) patients receiving plasma. Adverse events of interest were thromboembolic adverse events (six [7%] patients receiving 4F-PCC *vs* seven [8%] patients receiving plasma), fluid overload or similar cardiac events (three [3%] patients *vs* 11 [13%] patients), and late bleeding events (three [3%] patients *vs* four [5%] patients).

Interpretation 4F-PCC is non-inferior and superior to plasma for rapid INR reversal and effective haemostasis in patients needing VKA reversal for urgent surgical or invasive procedures.

Funding CSL Behring.

Lancet 2015; 385: 2077–87

Published Online
February 27, 2015
http://dx.doi.org/10.1016/S0140-6736(14)61685-8

See Comment page 2024

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Introduction

Patients receiving therapy with a vitamin K antagonist (VKA) have an increased risk of bleeding during surgical and procedural interventions.[1] Therefore, guidelines recommend temporary interruption of VKA therapy 5 days before elective surgery to minimise perioperative bleeding.[1] However, when patients need an urgent procedure, VKA reversal is often performed in the acute setting. Findings from a 2012 clinical trial underlined the risks involved, showing that the frequency of periprocedural bleeding in patients receiving VKA therapy was 3·3% for elective procedures, but 21·6% for emergency procedures.[2] Although vitamin K alone can be effective, reversal can take several hours.[3] Therefore, emergency reversal additionally necessitates the rapid replacement of vitamin K-dependent coagulation factors (ie, factors II, VII, IX, and X).

In some countries, including the USA, plasma is the most commonly used agent for rapid VKA reversal. Although plasma contains the vitamin K-dependent coagulation factors, it needs ABO typing and thawing before use, and is associated with long infusion times.[4–6] More importantly, it can be associated with severe adverse outcomes including transfusion-related acute lung injury and transfusion-associated circulatory overload.[7] Non-activated prothrombin complex concentrates contain vitamin K-dependent coagulation factors and are categorised as three-factor (3F-PCC) or four-factor (4F-PCC) prothrombin complex concentrates (depending

on whether they contain clinically relevant amounts of factor VII).[8] Prothrombin complex concentrates are stored at room temperature as a lyophilised powder, do not need ABO typing, can be prepared within minutes, and can be delivered in smaller volumes with shorter infusion times than can plasma.[4]

Adequately powered comparative trials investigating the optimum means of VKA reversal have not been done in patients needing urgent interventions, and the best method to promptly reverse VKAs remains unclear. The only plasma-controlled randomised clinical trial was a single-centre study of 40 patients (20 per group) undergoing semiurgent cardiac surgery, which was underpowered to detect significant differences in haemostatic efficacy.[9] We therefore did a randomised clinical trial to compare 4F-PCC with plasma for urgent VKA reversal in patients needing urgent surgical or invasive procedures.

Methods

Study design and participants

In a randomised, open-label, active-controlled, non-inferiority, multicentre, phase 3b clinical trial, we enrolled patients in 33 hospitals (18 in the USA, two in Belarus, four in Bulgaria, two in Lebanon, one in Romania, and six in Russia).

Patients with an international normalised ratio (INR) of 2·0 or higher receiving VKA therapy and needing an urgent surgical or invasive procedure within 24 h were eligible for the study. The decision about the need for surgical treatment and rapid VKA reversal was made by the clinical care teams. Exclusion criteria included requirement for a procedure for which an accurate estimate of blood loss was not possible (eg, ruptured aneurysm or trauma) or coagulopathy that could be corrected solely through administration of vitamin K and withdrawal of VKA therapy. Full inclusion and exclusion criteria are provided in the appendix.

See Online for appendix

As part of ongoing review of the investigational new drug application, the United States Food and Drug Administration (FDA) reviewed the study protocol after the trial had been initiated. On July 20, 2011, after 157 patients had been enrolled, the FDA requested that enrolment of patients needing non-surgical invasive procedures be halted because of concern that no differences in haemostatic efficacy would be detected. No interim safety or efficacy analysis was done at this time. Sites were notified via letter on July 26, 2011, to immediately cease enrolment of this population, and a final protocol amendment was made on Sept 7, 2011. Patients needing urgent surgical procedures continued to be enrolled as planned.

The study was approved by the independent ethics committees and institutional review boards of the participating centres, in accordance with local legal requirements; written informed consent was obtained from all patients.

Randomisation and masking

Investigators called a 24 h randomisation centre and transmitted deidentified data for the randomisation procedure. We randomly assigned patients in a 1:1 ratio using a computerised system to receive either 4F-PCC (Beriplex/Kcentra/Confidex; CSL Behring, Marburg, Germany) or plasma. Treatment assignment was done by a centrally managed, biased-coin minimisation method,[10] which is an adaptive randomisation scheme (appendix). This method also controlled for balance, both overall and within centres, between treatment groups within urgent surgical or invasive procedures with use of two levels of stratification: one based on the type of procedure, and one on the vitamin K dose given.

The first level of strata was: all cranial neurosurgical procedures; all cardiothoracic surgical procedures; all major orthopaedic surgical procedures (eg, open reduction internal fixation of hip); all other surgical procedures (such as general surgery, ear-nose-throat, noncranial neurological [eg, spine procedures], urological, gynaecological, cardiovascular [eg, femoropopliteal bypass procedures], and minor orthopaedic interventions [eg, open reduction of ulna fracture]); and all invasive procedures (recruitment to this category was halted after protocol amendment). The second level of strata was oral vitamin K dose less than or equal to 2 mg; oral vitamin K dose more than 2 mg; and any intravenous vitamin K dose.

Surgery type was classified by the treating physician according to the first level of strata. The trial was open label; clinicians, study staff, and trial participants could not be blinded to treatment allocation because of the inherent characteristics of the study agents. The safety adjudication board (described below) was masked to treatment allocation.

Procedures

On day 1, patients received an intravenous infusion of study treatment based on baseline INR (assessed ≤3 h before start of infusion) and bodyweight, as described by Sarode and colleagues.[11] Patients with baseline INR of 2 or higher but lower than 4 were given 4F-PCC at a dose of 25 IU factor IX per kg bodyweight or plasma 10 mL/kg bodyweight; those with baseline INR of 4 to 6 (inclusive) were given 4F-PCC at a dose of 35 IU factor IX per kg or plasma 12 mL/kg; and those with baseline INR higher than 6 were given 4F-PCC at a dose of 50 IU factor IX per kg or plasma 15 mL/kg. Patients weighing more than 100 kg were given doses based on a bodyweight of 100 kg.

4F-PCC was given at an infusion rate of 3 IU/kg per min or less; plasma was infused as rapidly as possible and at the discretion of the treating clinical team. Thus, the plasma infusion rate represented standard care and maximised patient safety (because of concern that some patients might not be able to tolerate rapid volume load). Additionally, vitamin K was to be given to all patients according to American College of Chest Physicians[12] guidelines (≤5 mg orally, followed by 1–2 mg orally if

required, in patients needing urgent surgery; 10 mg by slow intravenous infusion in patients with major bleeding) or local practice if different (ie, 2–10 mg). Vitamin K administration was not standardised in the protocol because of variations in local practice and guidelines.

We recorded the total volume and total infusion time of each study product. Additional blood products and haemostatic agents given were documented from randomisation to 24 h after start of study product infusion or end of the surgery, whichever came later. Blood samples were drawn for determination of INR and levels of vitamin K-dependent coagulation factors and proteins C and S before study product infusion and at 0·5 h, 1 h, 3 h, 6 h, and 24 h after start of infusion, in addition to INR at 0·5 h after end of infusion. We assessed baseline INR 3 h or less before start of infusion.

Adverse events and serious adverse events were recorded by the investigators and assessed by an independent data and safety monitoring board, unblinded to study treatment. After study launch, the data and safety monitoring board requested that a blinded safety adjudication board be established to review possible thromboembolic serious adverse events, late bleeding events, and deaths. Serious adverse events possibly consistent with thrombotic events or late bleeds, as well as death cases, were referred to the safety adjudication board. Adjudication results were provided to the data and safety monitoring board on an ongoing basis. Adverse events were assessed up to day 10 (visit window days 7–11) and serious adverse events up to day 45 (visit window days 43–51). Fluid overload events were identified according to the Medical Dictionary for Regulatory Activities version 12.0 terms: fluid overload, pulmonary oedema, cardiac failure congestive, cardiac failure chronic, and cardiac failure.

Outcomes

The primary endpoint was haemostasis during urgent surgical or invasive procedures in the intention-to-treat efficacy (ITT-E) population. We categorised haemostasis as a binary endpoint (effective or non-effective) and this endpoint was assessed from the start of infusion to the end of the procedure. We defined effective haemostasis as: intraoperative (or intra-procedural) blood loss not exceeding predicted blood loss by 30% or 50 mL; and normal or mildly abnormal haemostasis (surgeon assessed); and no administration of non-study coagulation products. Predicted blood loss was determined by the local surgeon before the start of surgery, using all clinical information available, based on the assumption of a similar non-coagulopathic patient undergoing the same intervention. We based actual blood loss (ABL) on the anaesthesiologist's record of estimated blood loss during the procedure. If an anaesthesiologist was not present during the procedure, ABL was estimated by the surgeon or physician performing the procedure. Missing haemostatic efficacy assessments resulted in a rating of non-effective haemostasis.

The coprimary endpoint was rapid INR reduction (INR ≤1·3 at 0·5 h after the end of infusion) in the ITT-E population. A missing INR value at this timepoint, or administration of additional coagulation factor-containing products (non-study plasma, whole blood, or other non-study products containing coagulation factors, excluding packed red blood cells or platelets) from the start of treatment infusion to the start of the procedure resulted in a rating of no rapid decrease in INR.

There were four prespecified secondary endpoints: time to INR reduction (INR ≤1·3) from start of infusion; units of red blood cells (defined as packed red blood cells and whole blood) given from start of surgery to 24 h after start

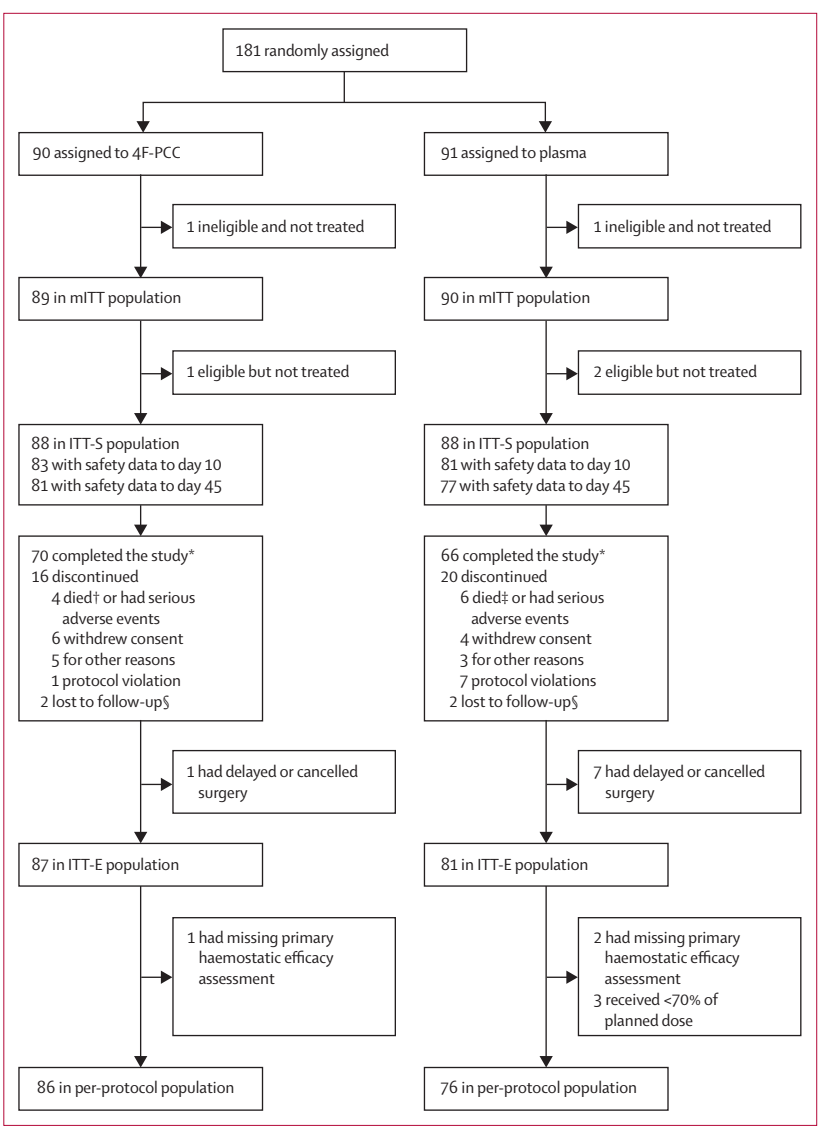


Figure 1: **Patient flow**
4F-PCC=four-factor prothrombin complex concentrate. mITT=modified intention-to-treat. ITT-E=intention-to-treat efficacy. ITT-S=intention-to-treat safety. *Study included viral follow-up to day 90. †One death occurred after study day 45 (day 48; worsening of cardiopulmonary disease). ‡Eight deaths in total in plasma group; one plasma death occurred in a completed patient and one plasma death occurred in a patient with a protocol violation. §Patient not able to be reached for follow-up.

	4F-PCC (n=87)	Plasma (n=81)
Sex		
Female	37 (43%)	31 (38%)
Male	50 (57%)	50 (62%)
Age, years	69·4 (13·5)	66·0 (13·2)
Region		
USA	44 (51%)	37 (46%)
Europe/Lebanon	43 (49%)	44 (54%)
Body-mass index, kg/m²	27·9 (6·4)	28·5 (7·9)
Baseline INR	2·90 (2·0–17·0)	2·90 (2·0–26·7)
Type of surgery or procedure		
Cranial neurosurgical	1 (1%)	1 (1%)
Cardiothoracic surgical	3 (3%)	3 (4%)
Major orthopaedic surgical	20 (23%)	15 (19%)
Other surgical	50 (57%)	47 (58%)
Invasive	13 (15%)	15 (19%)
Vitamin K dose		
Oral vitamin K dose ≤2 mg	6 (7%)	2 (2%)
Oral vitamin K dose >2 mg	9 (10%)	10 (12%)
Any IV vitamin K	70 (80%)	69 (85%)
No vitamin K	1 (1%)	0
Not available	1 (1%)	0
Reason for oral VKA therapy		
Arrhythmia	42 (48%)	31 (38%)
Vascular disease	17 (20%)	18 (22%)
Artificial heart valve or joint	13 (15%)	14 (17%)
Thromboembolic event	12 (14%)	16 (20%)
Other	3 (3%)	2 (2%)

Data are n (%), mean (SD), or median (IQR). 4F-PCC=four-factor prothrombin complex concentrate. INR=international normalised ratio. ITT-E=intention-to-treat efficacy. IV=intravenous. VKA=vitamin K antagonist.

Table 1: **Demographic and baseline characteristics (ITT-E population)**

of surgery; proportion of patients receiving red blood cells from start of surgery to 24 h after start of surgery; and plasma levels of vitamin K-dependent coagulation factors and proteins C and S. Planned exploratory endpoints (intended for future analyses) are listed in the appendix.

Statistical analysis

There were four analysis populations (figure 1). The modified intention-to-treat (mITT) population comprised all randomly assigned patients who were either eligible for the study but did not receive any portion of study product, or received any portion of study product. The intention-to-treat safety (ITT-S) population comprised all eligible patients from the mITT population who had received any portion of study product. The ITT-E population comprised all patients from the ITT-S population who had an INR higher than 1·3 before study product infusion and underwent the intended procedure; both the primary and coprimary endpoints were assessed in this population. Finally, the per-protocol population comprised all ITT-E patients who did not have any major protocol deviations.

The study was designed to test the hypothesis that 4F-PCC was non-inferior to plasma with regard to the primary and coprimary endpoints. We performed non-inferiority analyses in the ITT-E population via calculations (using the Newcombe-Wilson score method)[13] of the two-sided 95% CI, equivalent to a one-sided type I error rate of 0·025, for the difference in the proportions of patients achieving effective haemostasis, and separately for rapid INR reduction. For both haemostasis and INR reduction, non-inferiority was demonstrated if the lower limit of the 95% CI for the between-group difference (4F-PCC minus plasma) was greater than –10%. Because there is little evidence available about the haemostatic efficacy of plasma versus placebo in patients on VKA therapy requiring urgent interventions,[14] there was no independent way of determining a non-inferiority margin in terms of preserving some portion of the effect of plasma versus placebo. Therefore, the non-inferiority margin of –10% was chosen based on clinical judgment. 4F-PCC could be successfully claimed to be non-inferior to plasma if non-inferiority was shown for both the primary and co-primary endpoints. If non-inferiority was shown, 4F-PCC was also to be tested for superiority compared with plasma for each of these endpoints. Superiority for an endpoint could be declared if the lower limit of the 95% CI exceeded zero. Because testing for superiority after demonstration of non-inferiority[15] does not increase type I error, a test for superiority could be done on the nominal one-sided α-level of 0·025 after demonstration of non-inferiority.

We did sample size calculations on the haemostatic efficacy endpoint and assumed that effective haemostasis would be achieved by 85% of patients in the plasma group and 90% of patients in the 4F-PCC group. Based on the Newcombe-Wilson score method for CI calculations,[13] a non-inferiority margin of –10% and a dropout rate of 10%, the power to show non-inferiority would exceed 80% for two treatment groups of 88 patients (total target sample size of 176 patients). No sample size calculation was done on the INR endpoint because of the assumption of similar values for the percentages in the two study groups.

We adjusted four p values, one from each of the four secondary analyses, using the method of Holm.[16] This adjustment controlled the overall type I error and preserved the 0·05 significance level. We described time to INR correction by Kaplan-Meier estimation, and assessed significance of treatment differences using the log-rank test. Between-group differences for number of units of red blood cells transfused were assessed by Wilcoxon-rank-sum test. We compared the proportions of patients receiving one or more transfusions of red blood cells using Newcombe-Wilson score test. Plasma levels of vitamin K-dependent coagulation factors and proteins C and S were summarised by descriptive statistics and, in post-hoc analyses, group differences were compared by two-sided Wilcoxon test.

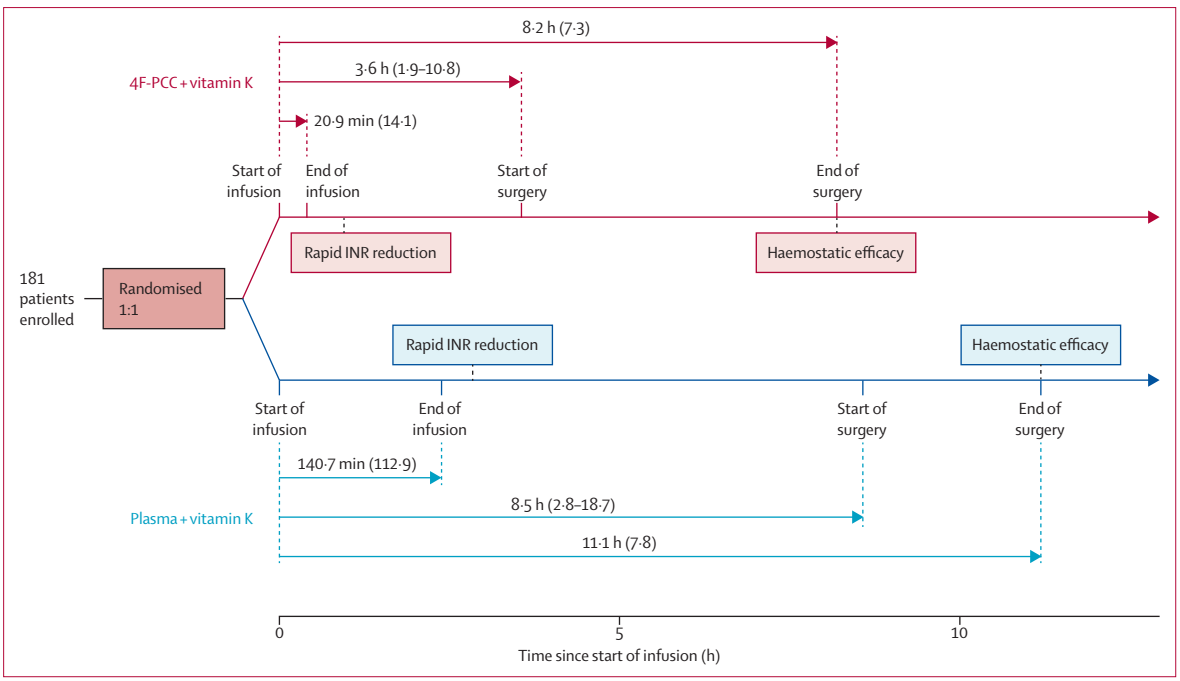
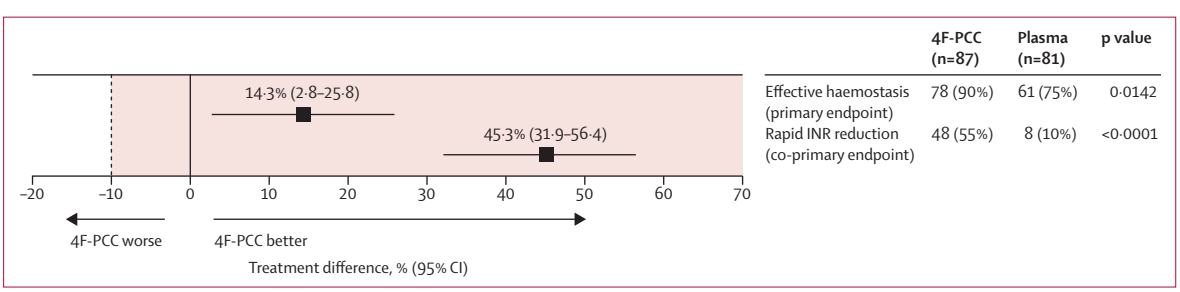


Figure 2: **Study overview (ITT-E population)**
Data are mean (SD) or median (IQR). ITT-E=intention-to-treat efficacy. 4F-PCC=four-factor prothrombin complex concentrate. INR=international normalised ratio.



	4F-PCC (n=87)	Plasma (n=81)	p value
Effective haemostasis (primary endpoint)	78 (90%)	61 (75%)	0·0142
Rapid INR reduction (co-primary endpoint)	48 (55%)	8 (10%)	<0·0001

Figure 3: **Primary and co-primary endpoints**
Figure shows effective haemostasis (haemostatic efficacy rating of excellent or good) and rapid INR reduction (INR ≤1·3 at 0·5 h after end of infusion) by non-inferiority analysis in the ITT-E population. Treatment difference refers to between-group difference of 4F-PCC minus plasma. Tinted area shows zone of non-inferiority, bounded by non-inferiority margin (dotted line) set at –10%. Superiority margin was set at 0% (solid line), meaning that 4F-PCC is superior to plasma if the lower limit of the 95% CI is to the right of the solid line. 4F-PCC=four-factor prothrombin complex concentrate. INR=international normalised ratio. ITT-E=intention-to-treat efficacy.

We applied an ANCOVA model with predicted blood loss as a dependent variable, treatment, sex, surgical type, and study site as factors, and preinfusion haemoglobin as a covariate to establish whether predicted blood loss differed by treatment, which would suggest bias in the estimation of predicted blood loss.

We compared incidences of thromboembolic events, fluid overload events, and deaths between treatment groups using Newcombe-Wilson CIs with continuity correction; other safety outcomes were analysed descriptively. We computed p values using the χ^2 test for homogeneity or Fisher's exact test when any of the cell sizes were small (less than five).

As a result of the protocol amendment to halt enrolment of patients undergoing non-surgical invasive procedures, we also planned to do non-inferiority and superiority analyses of the haemostatic efficacy and rapid INR reduction endpoints with the exclusion of patients needing non-surgical invasive procedures.

We analysed data with SAS version 9.3. This trial is registered at ClinicalTrials.gov, number NCT00803101.

Role of the funding source

This research was funded by CSL Behring. A steering committee of academic medical experts and representatives of the funder oversaw the design and conduct of the study. The funder participated in the selection of the board members. The funder was responsible for data collection, management, and analysis of the data according to a predefined statistical

	4F-PCC (n=87)		Plasma (n=81)		Treatment difference (95% CI)*	p value*
	Endpoint achieved	Endpoint not achieved	Endpoint achieved	Endpoint not achieved		
Haemostatic efficacy endpoint						
Cranial neurosurgical	0	1 (100%)	1 (100%)	0	NA†	..
Cardiothoracic surgical	3 (100%)	0	3 (100%)	0	0%	1·00
Major orthopaedic surgical	16 (80%)	4 (20%)	9 (60%)	6 (40%)	20·0% (−9·6 to 47·0)	0·27
Other surgical	46 (92%)	4 (8%)	35 (74%)	12 (26%)	17·5% (2·6 to 32·3)	0·0279
Invasive procedure	13 (100%)	0	13 (87%)	2 (13%)	13·3% (−11·4 to 37·9)	0·48
Rapid INR reduction endpoint (INR ≤1·3 at 0·5 h after end of infusion)						
Cranial neurosurgical	0	1 (100%)	0	1 (100%)	NA†	..
Cardiothoracic surgical	2 (67%)	1 (33%)	0	3 (100%)	66·7% (−5·9 to 93·9)	0·4
Major orthopaedic surgical	11 (55%)	9 (45%)	2 (13%)	13 (87%)	41·7% (9·5 to 63·1)	0·0158
Other surgical	27 (54%)	23 (46%)	2 (4%)	45 (96%)	49·7% (32·9 to 63·1)	<0·0001
Invasive procedure	8 (62%)	5 (38%)	4 (27%)	11 (73%)	34·9% (−1·4 to 60·9)	0·12

Treatment difference refers to between-group difference of 4F-PCC minus plasma. Endpoint achieved refers to effective haemostasis or rapid reduction in INR; endpoint not achieved refers to non-effective haemostasis or no rapid reduction in INR. 4F-PCC=four-factor prothrombin complex concentrate. ITT-E=intention-to-treat efficacy. NA=not available. *95% CIs and p values generated post hoc using a basic χ^2 test for homogeneity (Fisher's exact test used for small cell sizes). †Analysis not done because fewer than five patients were in this subgroup.

Table 2: **Haemostatic efficacy and rapid INR reduction by type of procedure (ITT-E population)**

analysis plan. Preparation and review of the Article and the decision to submit for publication was done by a publication steering committee that included academic medical experts and representatives of the funder. Medical writing assistance was paid for by the funder. JNG and RS had full access to all the data in the study and took responsibility for the integrity and accuracy of the data analysis.

Results

181 patients were enrolled in the trial between Feb 3, 2009, and Nov 28, 2012 (figure 1); the study completed on Feb 21, 2013. We randomly assigned 90 patients to receive 4F-PCC and 91 patients to receive plasma. The mITT population included 179 patients (89 in the 4F-PCC group and 90 in the plasma group) who were randomly assigned and were either eligible or received treatment (two patients who were randomly assigned but not eligible and not treated were excluded). The ITT-S population included 176 patients (88 in the 4F-PCC group and 88 in the plasma group); reasons for loss and exclusion are shown in figure 1. The ITT-E population included 168 patients (87 in the 4F-PCC group and 81 in the plasma group). 28 patients (13 receiving 4F-PCC and 15 receiving plasma) who needed non-surgical invasive procedures were enrolled in the study. Table 1 shows patients' baseline data and characteristics. A detailed list of surgeries and procedures is shown in the appendix.

The timing of the study treatment and interventions is shown in figure 2. Delivery of plasma (mean volume 818·7 mL [SD 230·8]) was as fast as could be done by the clinical team within the confines of local practice (including type-specific matching, thawing, delivery, and infusion). 4F-PCC was reconstituted from a lyophilised powder and infused (mean volume 89·7 mL [SD 31·9]). Vitamin K was given a median of 13 min before 4F-PCC (IQR 40 min before, 26 min after), and a median of 15 min before plasma (IQR 55 min before, 55 min after; post-hoc analysis). Two patients in the 4F-PCC group and no patients in the plasma group received no vitamin K during the study. 15 patients in the 4F-PCC group and 12 in the plasma group received vitamin K by a non-intravenous route. The median time from start of infusion to start of urgent surgical procedure was longer in the plasma group (8·5 h [IQR 2·8–18·7]) than in the 4F-PCC group (3·6 h [1·9–10·8]; p=0·0098; post-hoc analysis).

The primary endpoint, effective haemostasis in the ITT-E population, was achieved by 78 (90%) patients in the 4F-PCC group and 61 (75%) patients in the plasma group (figure 3). The treatment difference was 14·3% (95% CI 2·8 to 25·8, p=0·0142). Because the lower limit of the confidence interval for the treatment difference (2·8%) exceeded the non-inferiority margin of −10%, non-inferiority was shown for haemostatic efficacy. Analysis of superiority (lower limit of the 95% CI >0) showed that 4F-PCC was superior to plasma for this endpoint. Furthermore, we noted superiority for haemostatic efficacy for 4F-PCC compared with plasma when the per-protocol population was used (78 [91%] patients in the 4F-PCC group *vs* 58 [76%] patients in the plasma group; difference 14·4%, 95% CI 3·0 to 26·0, p=0·0128; appendix).

Intraoperative blood loss was used as part of the assessment of haemostatic efficacy. To address the possibility that enrolling investigators estimated predicted blood loss differently depending on treatment group in this open-label study, we assessed

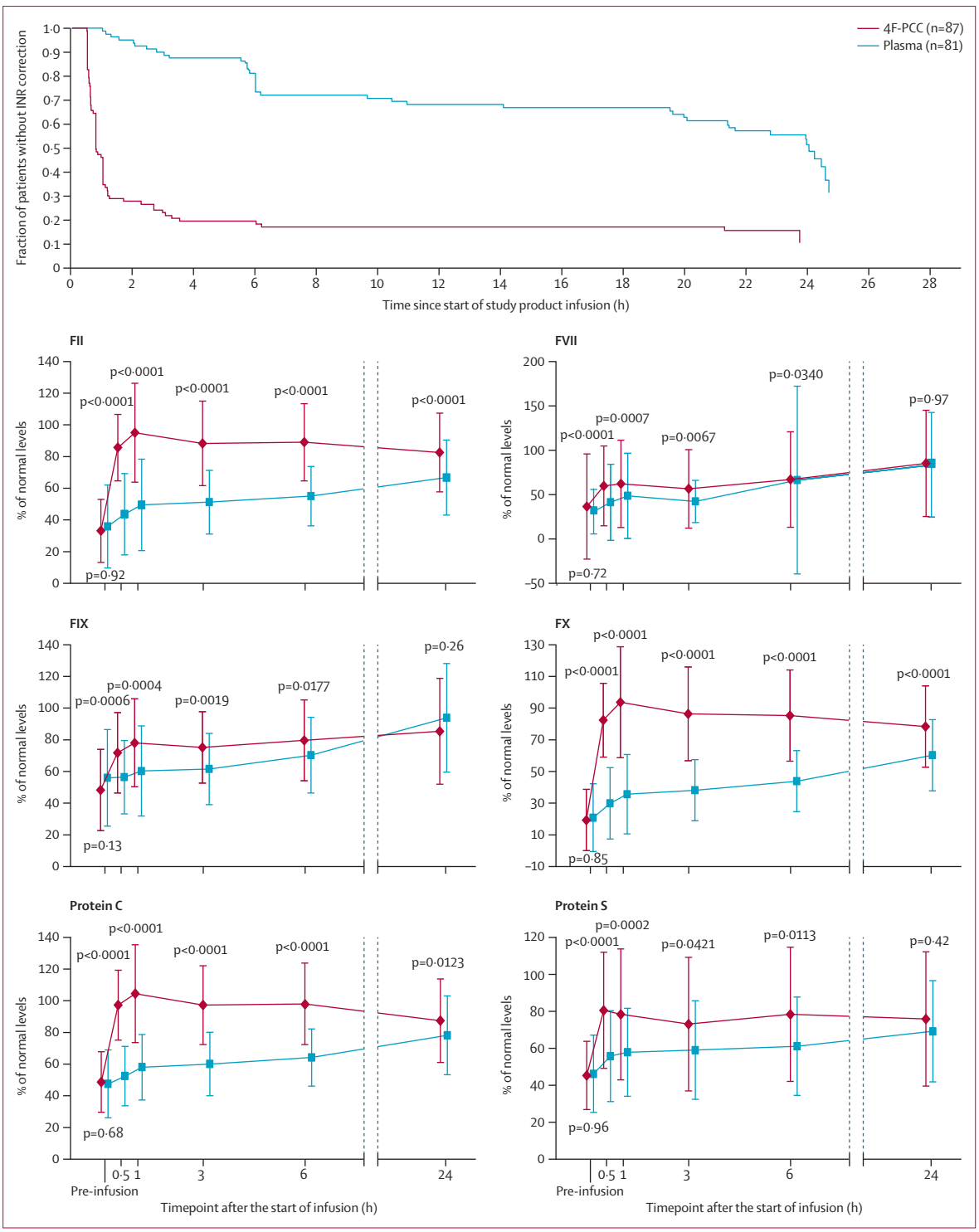


Figure 4: **Secondary endpoints**
Figure shows INR correction and factor-level repletion in the ITT-E population. Data are proportion of patients or mean percentage of normal levels (SD). 4F-PCC=four-factor prothrombin complex concentrate. INR=international normalised ratio. ITT-E=intention-to-treat efficacy.

for such bias using an ANCOVA model. We found no statistically significant difference between treatment groups in terms of predicted blood loss (mean predicted blood loss 173·7 mL [SD 188·2] for 4F-PCC *vs* 173·3 mL [188·7] for plasma), supporting the finding of no bias on the part of the investigators, and the

	4F-PCC (n=88)	Plasma (n=88)
Any adverse event	49 (56%)	53 (60%)
Related adverse event*	8 (9%)	15 (17%)
Adverse event leading to treatment discontinuation	0	0
Serious adverse event	22 (25%)	23 (26%)
Related serious adverse event*	3 (3%)	3 (3%)
Adverse events of interest		
Deaths to day 45†	3 (3%)	8 (9%)
Thromboembolic adverse event‡	6 (7%)	7 (8%)
Fluid overload or similar cardiac event	3 (3%)	11 (13%)
Bleeding after primary outcome assessment	3 (3%)	4 (5%)

Adverse events with missing treatment associations were classified as related to treatment. *Defined as events that were related to study treatment according to the investigator. †One additional death in the 4F-PCC group occurred after study day 45 (day 48; worsening of cardiopulmonary disease). ‡Thromboembolic adverse events included: six patients (seven events§) in the 4F-PCC group (deep-vein thrombosis [two events], thrombosis, ischaemic stroke [two events], vena cava filter insertion, and catheter-related complication) and seven patients (seven events) in the plasma group (acute myocardial infarction [two events], deep-vein thrombosis, ischaemic stroke [two events], pulmonary embolism, and transient ischaemic attack). §One deep-vein thrombosis and one stroke occurred in the same patient. 4F-PCC=four-factor prothrombin complex concentrate. ITT-S=intention-to-treat safety.

Table 3: **Summary of adverse events (ITT-S population)**

least-squares means of the predicted blood loss were similar for both treatments (175·6 [95% CI 86·1–265·1] for 4F-PCC *vs* 187·9 [104·1–271·6] for plasma; difference –12·3% [95% CI –64·6 to 40·1]; p=0·64).

For patients undergoing any surgical procedure (ie, excluding patients who underwent non-surgical invasive procedures), the treatment difference for effective haemostasis was 15·1% (95% CI 1·9 to 28·2, p=0·0237; 65 [88%] patients in the 4F-PCC group *vs* 48 [73%] patients in the plasma group), demonstrating superiority of 4F-PCC compared with plasma. Although the numbers in each group were small, limiting any conclusions, the treatment difference was 13·3% (95% CI –11·4 to 37·9, p=0·48; 13 [100%] patients in the 4F-PCC group *vs* 13 [87%] patients in the plasma group) for patients needing non-surgical invasive procedures. Table 2 shows the treatment differences for various prespecified subgroups.

The coprimary endpoint, rapid INR reduction in the ITT-E population, was achieved by 48 (55%) patients in the 4F-PCC group compared with eight (10%) patients in the plasma group. The treatment difference was 45·3% (95% CI 31·9 to 56·4, p<0·0001), demonstrating both non-inferiority and superiority for rapid INR reduction. Furthermore, superiority was shown for 4F-PCC compared with plasma for the per-protocol population (difference 45·3%, 95% CI 31·5 to 56·5, p<0·0001; 48 [56%] patients in the 4F-PCC group *vs* eight [11%] patients in the plasma group; appendix).

The treatment difference was 48·0% (95% CI 33·9 to 59·5, p<0·0001; 40 [54%] patients in the 4F-PCC group *vs* four [6%] patients in the plasma group) for patients undergoing any surgical procedure, demonstrating superiority of 4F-PCC over plasma. The treatment difference was 34·9% (95% CI –1·4 to 60·9, p=0·12; eight [62%] patients in the 4F-PCC group vs four [27%] patients in the plasma group) for patients undergoing a non-surgical invasive procedure. Additionally, in pre-specified subgroup analyses, we also noted treatment differences in favour of 4F-PCC for the major orthopaedic and other surgical enrolment strata (table 2).

Patients in the 4F-PCC group achieved INR of 1·3 or lower more rapidly than did those in the plasma group (figure 4). 1 h after the start of infusion, 47 patients (54%) in the 4F-PCC group had an INR of 1·3 or lower compared with no patients in the plasma group (p<0·0001).

Plasma levels of vitamin K-dependent coagulation factors and proteins C and S were significantly higher in the 4F-PCC group than in the plasma group at 0·5 h, 1 h, 3 h, and 6 h after start of infusion (all p values <0·05; figure 4).

Few patients in either group received red blood cells (14 [16%] in the 4F-PCC group and 12 [15%] in the plasma group); we noted no significant difference between groups (p=0·83). Additionally, the mean number of red blood cell units transfused per patient was similar between groups (0·3 units [SD 0·9] for 4F-PCC *vs* 0·4 units [1·0] for plasma, p=0·91).

We assessed safety outcomes in the ITT-S population. 49 patients in the 4F-PCC group and 53 patients in the plasma group had at least one adverse event (p=0·54; table 3). The frequency of adverse events and serious adverse events, including those related to treatment, was generally similar between groups. In particular, the proportion of patients with adverse events related to study treatment was eight (9%) in the 4F-PCC group and 15 (17%) in the plasma group (difference 8·0%, 95% CI –18·9 to 3·0, p=0·18; post-hoc analysis). Adverse events that occurred in at least 5% of patients in any treatment group after study product infusion are reported in the appendix.

Thromboembolic adverse events were reported during the study for six (7%) patients in the 4F-PCC group and seven (8%) in the plasma group (difference –1·1%, 95% CI –10·3 to 8·0, p=0·77). Three (3%) patients in the 4F-PCC group developed fluid overload or similar cardiac events compared with 11 (13%) in the plasma group (difference –9·1%, 95% CI –18·6 to –0·1, p=0·0478). A total of seven patients (three [3%] for 4F-PCC and four [5%] for plasma) experienced possible late bleeding events that were reviewed by the safety adjudication board (appendix).

By the day 45 visit, there were three deaths in the 4F-PCC group and eight in the plasma group, of which one (acute myocardial infarction; plasma group) was considered by the safety adjudication board to be treatment related. The difference in rates was –5·7% (95% CI –14·6 to 2·7, p=0·21), and was not considered significant. Individual mortality data are detailed in the appendix.

Discussion

Because non-inferiority was achieved for both the primary and the coprimary endpoints, non-inferiority was achieved for 4F-PCC compared with plasma overall in this open-label phase 3b study. To our knowledge, this trial is the first adequately powered comparison of 4F-PCC and plasma for rapid VKA reversal in patients needing urgent surgical or invasive interventions. Not only was 4F-PCC non-inferior to plasma for haemostatic efficacy (the comparison we were primarily powered to test), but it was additionally superior for this endpoint (an effect we had less than 70% power to detect). 4F-PCC was also both non-inferior and superior to plasma for the coprimary endpoint of rapid INR reduction.

Only one other randomised trial has addressed this question, a cardiac surgery study with only 20 patients per group that assessed INR reduction but not haemostatic efficacy.[9] Our results are consistent with findings from this trial and those from previous retrospective cohort studies (including for trauma and spontaneous haemorrhage), which have shown that 4F-PCCs used for VKA reversal can more rapidly replace vitamin K-dependent coagulation factors and lower INR than plasma.[17–20]

The time between start of infusion and start of surgery was significantly shorter in the 4F-PCC group than in the plasma group. The shorter administration time and rapid INR reduction due to higher levels of vitamin K-dependent coagulation factors in 4F-PCC probably contributed to the decreased time to start of surgery that we noted in the 4F-PCC group compared with the plasma group. We do not believe plasma may have been systematically infused more quickly; because it requires ABO typing and thawing, there is local variation in how quickly it can be obtained, and both patient-level and provider-level variation in how quickly the clinical team can infuse it. Because of ethical and logistic considerations, we could not mandate an infusion rate faster than local practice and clinicians could provide. Findings from observational studies have in fact shown substantially slower plasma infusion for VKA reversal in standard clinical practice than we noted in this trial, suggesting that patients in this trial truly did receive plasma as rapidly as was logistically feasible.[21–24] Whether variations in plasma infusion rates affect haemostatic efficacy is not clear.

Additionally, vitamin K dose and administration route were not rigidly defined by the protocol. During trial planning, there were ethical concerns that local teams would need leeway in such dosing, depending on the clinical situation. This factor seems unlikely to be a substantial confounder because we noted no evidence that vitamin K dosing was different between study groups.

Although thromboembolic complications are often listed as a concern in VKA reversal, there was no evidence of an increased risk of such for 4F-PCC compared with plasma. However, the study was not powered to detect between-group differences in the incidence of these events. Thus far, no randomised trial has shown a difference in thromboembolic event rates between prothrombin complex concentrate and plasma, probably because they were not adequately powered to do so.[9,11] A recent observational study examining the effect of introducing a 4F-PCC to the emergency department found similar results.[17] Two recent comprehensive reviews, based on single-group studies of prothrombin complex concentrates, also concluded that there is a low risk of thromboembolic events in patients treated with prothrombin complex concentrates for VKA reversal, and that underlying disease and dosing may be important factors in increasing risk.[25,26] Thromboembolism might occur with the same frequency in this patient population irrespective of the means used to reverse VKA.[27,28]

Fluid overload events, however, occurred more frequently in the plasma group than in the 4F-PCC group. Therefore, our data suggest that patients at higher risk of volume overload who need VKA reversal might specifically benefit from 4F-PCC rather than plasma.

We note that most patients in the ITT-E population completed the study to the primary endpoint (86 [99%] of 87 patients in the 4F-PCC group and 79 [98%] of 81 in the plasma group), and safety data to day 10 (including mortality) were available for 164 (93%) of 176 patients. Ten patients withdrew consent and eight withdrew from the study for other reasons; no safety data are available after withdrawal. 40 patients did not complete the study to the 90-day viral safety endpoint, which affected only the viral assessment and not our ability to analyse the primary, secondary, or other safety outcomes. Trial discontinuations did not seem to occur disproportionately in one study group compared with the other.

Eight patients had their procedure cancelled or delayed beyond 24 h, suggesting that some enrolled patients did not ultimately need an emergent or urgent procedure. This finding highlights the clinical reality of emergency care, in which decisions need to be made rapidly based on information available at the time. The clinical situation can then evolve, and for some patients their clinical status changed in a way that could not be predicted. To maximise generalisability, the criteria for entry included a judgment on the part of the participant's clinical care team that an urgent or emergency procedure was indicated and that pre-procedural urgent VKA reversal was necessary.

Overall study enrolment was fairly slow. We noted that there were several exclusion criteria, and with enrolment occurring in the acute setting, many eligible patients were probably treated by the clinical care teams before the research teams had time to approach participants and go through the informed consent process. Additionally, the scientific literature regarding which patients might benefit from VKA reversal continues to evolve,[1] and many potential participants could have been judged by the clinical teams to not need urgent reversal.

This study had several limitations. First, the study team members, clinicians, and participants could not be

Panel: Research in context

Systematic review

We used previously published systematic reviews[6,18,19,25,26] to assess the existing evidence for the use of plasma or 4F-PCCs for vitamin K antagonist (VKA) reversal. We also searched PubMed for comparative studies of VKA reversal with four-factor prothrombin complex concentrate (4F-PCC) or plasma reported since the publication of these systematic reviews (July, 2011, to March, 2014) with the terms ("prothrombin complex concentrates"[Supplementary Concept] OR "Factor IX"[MeSH]) AND "anticoagulants" [Pharmacological Action]. No language restrictions were used and the search was done on March 10, 2014. The results of these systematic reviews and the more recent references[11,17,24] suggested that international normalised ratio (INR) reduction (in patients with spontaneous bleeding, trauma, or before a surgical procedure) is more effectively and rapidly achieved with 4F-PCC than with plasma or 3F-PCC. However, there was little comparative evidence about clinical outcomes or safety.

Interpretation

For the endpoint of rapid INR reduction, the results from our trial are consistent with previously published (mainly observational) data and demonstrate that 4F-PCC is non-inferior and superior to plasma for rapid INR reduction in patients on VKA therapy. Furthermore, we noted that 4F-PCC could be given more rapidly than plasma, which is in agreement with previously published (retrospectively collected) data.[24] For the endpoint of clinical efficacy, we found no other adequately powered trial examining reversal of VKA therapy in patients needing urgent surgical procedures, and this trial therefore offers new insights into their treatment. We noted that 4F-PCC was superior to plasma for haemostatic efficacy. Although our study was not powered to assess safety, we did not detect any between-treatment differences for the occurrence of thromboembolic events or deaths, a finding in agreement with the existing scientific literature.[11,17,25,26] Additionally, although these data guide clinicians on how best to achieve urgent VKA reversal, the scientific literature concerning which patients should be urgently reversed before surgical or invasive interventions continues to evolve; for example, findings from a recent trial showed the safety of pacemaker placement without interruption of anticoagulation.[29]

blinded to treatment allocation. Such blinding could not logistically or ethically be done because of the underlying differences in delivery (PCC is reconstituted and infused quickly in a small volume, whereas type-specific plasma must be prepared and dispensed from the local blood bank in multiple bags that must be thawed and infused separately). We attempted to control for this factor by assessing whether the prediction of expected blood loss was different between treatment groups, and found no effect. Second, there was variability in timing of plasma infusion. We did note that infusion times were more rapid and consistent than those documented in routine clinical practice,[21–23] emphasising that plasma infusion was probably done as efficiently as could be achieved in view of the logistics of delivering it. Third, this study was powered to detect differences in efficacy but not differences between groups for safety outcomes; therefore, we cannot rule out differences in rare adverse events between treatment groups. Fourth, the haemostatic efficacy endpoint, although often used in haemostasis trials, includes a potentially subjective component, because clinicians must estimate predicted blood loss and might need to estimate ABL. We optimised this endpoint as much as possible; to our knowledge, it is the best currently available endpoint that can be applied across a range of surgical and invasive interventions.

This study focused on urgent reversal of VKAs rather than direct factor inhibitors. We note that direct factor IIa and Xa inhibitors are now available and are becoming more frequently used as an alternative to VKAs. Because we did not enrol patients taking these newer drugs, we cannot provide much-needed data on how best to reverse them.

In conclusion, these data show that 4F-PCC is an effective and superior alternative to plasma in terms of haemostatic efficacy and rapid INR reduction for the rapid reversal of VKA therapy before urgent procedures (panel).

Contributors

All authors contributed to the analysis and interpretation of data and drafting of the Article. The authors vouch for the accuracy and completeness of the reported data and analyses, as well as the fidelity of this report to the protocol. All authors had complete access to the data, revised the Article critically for important intellectual content, read and approved the final version submitted for publication, and shared responsibility for the decision to submit for publication. JNG and RS contributed to the study concept and design. JNG, MAR, TJM Jr, and BL were responsible for data acquisition. JNG, BAH, and RS were responsible for study supervision. RG-A had overall responsibility for the statistical analysis.

Declaration of interests

JNG has received consulting fees and a research grant from CSL Behring. MAR is a member of a CSL Behring speakers bureau. TJM Jr has received consulting fees from CSL Behring and has been a member of a CSL Behring speakers bureau. RG-A is an employee of CSL Behring LLC. BAH was an employee of CSL Behring LLC at the time the study was conducted. RS has received consulting fees and honoraria from CSL Behring and has served as a member of advisory boards for Octapharma, Instrument Laboratories, Alexion, and Kedrion. BL declares no competing interests.

Acknowledgments

Medical writing assistance was provided by Rianne Stacey (Fishawack Communications, Abingdon, UK) and was funded by CSL Behring. Joerg Pawlitschko (Aptiv Solutions, Cologne, Germany) created all table shells and performed the data analyses reported in the Article. Martin L Lee (UCLA School of Public Health, Los Angeles, CA, USA) provided additional statistical assistance. Antoinette Mangione, Astrid Schneider, and Billie Durn (CSL Behring, King of Prussia, PA, USA) contributed to the data review and quality check of the Article. BAH is currently employed by GlaxoSmithKline.

References

1 Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th edn: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141:** e326S–50S.

2 Healey JS, Eikelboom J, Douketis J, et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. *Circulation* 2012; **126:** 343–48.

3 Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th edn: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141:** e152S–84S.

4 Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th edn: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141:** e44S–88S.