

Impact case study (REF3b)

<p>Institution: University of Sheffield</p>
<p>Unit of Assessment: A1: Clinical Medicine</p>
<p>Title of case study: A new gold standard treatment for the emergency correction of warfarin-induced coagulopathy</p>
<p>1. Summary of the impact</p> <p>As a result of University of Sheffield research in 1995-2002, a new gold standard treatment for major bleeding on warfarin has been established, ensuring the more effective treatment of tens of thousands of patients requiring emergency anticoagulation reversal each year in the UK alone. The treatment, using prothrombin complex concentrate (PCC) was demonstrated to be superior to fresh frozen plasma (FFP), the standard alternative at the time, and two PCCs have now been licensed for this indication in the UK.</p> <p>UK and international guidelines now recommend PCC over FFP.</p>
<p>2. Underpinning research</p> <p>Patients who experience venous thrombosis such as deep vein thrombosis and pulmonary embolism, those with atrial fibrillation or who have metal heart valves are anticoagulated with vitamin K antagonists, which in the UK is primarily with warfarin. Approximately 1-2% of the population are on warfarin at any time. Whilst warfarin is highly effective in preventing thrombosis, its main adverse effect is bleeding. The annual risk of bleeding is 1% for major bleeding requiring hospital admission and 0.3% for fatal bleeding. Projected for the UK population over 10,000 individuals experience life threatening bleeding annually and in 3,000 cases this is fatal.</p> <p>Up to the late 1990s the emergency management of anticoagulation reversal was using fresh frozen plasma (FFP) which was widely available in all UK hospitals. Researchers in the Department of Cardiovascular Science at the University of Sheffield, led by Prof Michael Makris (1991 to present) and Prof Eric Preston (NHS Consultant, Honorary Professor University of Sheffield, now retired) became concerned that the standard treatment with FFP was ineffective or poorly effective and set out to investigate whether an alternative treatment with concentrates (used to treat patients with haemophilia B) was superior. The research confirmed the poor efficacy of FFP and demonstrated the superiority of prothrombin complex concentrate (PCC) leading to a change in clinical practice in the management of life-threatening bleeding in patients on warfarin. It was also demonstrated that the vitamin K that was co-administered had to be given intravenously for maximum efficacy.</p> <p>In the first study (R1), the effect of FFP and PCC in patients with major bleeding on warfarin who required emergency reversal was assessed. All 41 patients were treated in Sheffield at the Royal Hallamshire Hospital by University of Sheffield staff. Patients with major bleeding were treated with either FFP or PCC and the research showed that the correction of the coagulopathy achieved by FFP was minor and insufficient for complete reversal, whilst patients treated with PCC achieved very rapid complete reversal of the coagulopathy. The paper concluded that “Clotting factor concentrates are the only effective option where complete and immediate correction of the coagulation defect is indicated in orally anticoagulated patients with life or limb threatening haemorrhage”.</p> <p>In 2001 the University of Sheffield team collaborated with groups in Aberdeen and Cambridge to show that vitamin K given with the PCC for emergency warfarin reversal was more effective if given intravenously than orally (R2). Approximately a third of the 64 patients studied in this work were from Sheffield.</p>

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In 2002 a further study from Sheffield, of 42 patients with life threatening bleeding on warfarin and who required immediate reversal, showed that one of concentrates licensed at the time to treat patients with haemophilia B, called Beriplex, was highly efficient and safe in producing immediate reversal of the coagulopathy (R3).

3. References to the research

Authors working in Sheffield at the time are indicated in bold

R1) **Makris M, Greaves M, Phillips WS, Kitchen S**, Rosendaal FR, **Preston FE**. (1997). Emergency oral anticoagulant reversal: the relative efficacy of infusions of fresh frozen plasma and clotting factor concentrate on correction of the coagulopathy. *Thrombosis and Haemostasis*. 77:477-480

The key paper that changed the management of reversal of warfarin anticoagulation was carried out in Sheffield and published in 1997. PubMed ID: 9065997 [Scopus 275 citations]

R2) Watson HG, Baglin T, **Laidlaw SL, Makris M, Preston FE**. (2001). A comparison of the efficacy of response to oral and intravenous vitamin K in reversal of over-anticoagulation with warfarin. *British Journal of Haematology*. 115: 145-149

Another publication from Sheffield, Aberdeen and Cambridge demonstrated that intravenous vitamin K was superior to oral vitamin K for the emergency reversal of warfarin. [Scopus 82 citations]

R3) **Preston FE, Laidlaw SL, Sampson B, Kitchen S**. (2002). Rapid reversal of oral anticoagulation with warfarin by a prothrombin complex concentrate (Beriplex): efficacy and safety in 42 patients. *British Journal of Haematology*. 116:619-624

A third publication demonstrated that a PCC called Beriplex used in haemophilia was highly effective for the emergency reversal of warfarin. [Scopus 125 citations].

4. Details of the impact

Patients with venous or arterial thrombosis or with prosthetic metal heart valves are treated with warfarin anticoagulation. Approximately 600,000–1,200,000 patients are on warfarin in the UK at any time and 6,000-12,000 each year are likely to require emergency reversal of their anticoagulation due to life-threatening bleeding. At the time of our original research most patients with major bleeding on warfarin were treated with fresh frozen plasma (FFP), whilst now the vast majority are treated with prothrombin complex concentrate (PCC), based on our research findings.

Impact on national and international clinical guidelines

National and international guidelines now recommend the use of PCC for the management of life-threatening bleeding on warfarin.

A. The current UK guideline on the use of FFP published by the British Committee for Standards in Haematology (BCSH) states that for reversal of warfarin “FFP has only a partial effect, is not the optimal treatment, and should never be used for the reversal of Warfarin in the absence of severe bleeding”. The evidence supporting this statement in the guideline is our publication of 1997 (R1). (S1)

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B. The current UK guideline on the management of patients on warfarin published by the BCSH recommends “All hospitals managing patients on warfarin should stock a licensed four factor prothrombin complex concentrate. Emergency anticoagulation reversal in patients with major bleeding should be with 25-50µ/kg for factor prothrombin complex concentrate..... Fresh frozen plasma produces suboptimal anticoagulation reversal and should only be used if prothrombin complex concentrate is not available.” This guideline lists our 1997 reference (R1) as showing “Complete and rapid correction of the coagulopathy is more rapidly achieved with PCC than FFP Makris et al 1997” (S2)

C. The use of PCC rather than FFP in patients on warfarin is also recommended by a 2013 guideline on the management of bleeding in patients on antithrombotic agents (S3). This is the BCSH guideline on anticoagulation reversal for all the different anticoagulant drugs.

D. In the UK, at the Dudley Group of Hospitals, the policy for reversal of warfarin in patients with intracranial or major bleeding recommends use of PCC and quotes our study R1 to support this recommendation (S4)

E. The French national guidelines on the management of major bleeding in patients on vitamin K antagonists, such as warfarin, recommend the use of PCC rather than FFP and quote our study R1 as demonstrating the superiority of PCC over FFP (S5)

F. The Italian national guidelines produced by the Italian Society for Transfusion Medicine and Immunohaematology working party also recommend the use of PCC over FFP for treatment of major bleeding on vitamin K antagonists and use all 3 of our studies R1, R2 and R3 to support this recommendation (S6).

Impacts on the economy and commerce

PCCs were introduced 40 years ago to treat haemophilia B. Initially we used them off-label in our research to treat warfarin related bleeding. PCCs are no longer used to treat haemophilia B.

In the last 7 years, however, two international pharmaceutical companies, Octapharma and CSL Behring, have brought concentrates to the market for use in emergency reversal of warfarin (Octaplex and Beriplex respectively). Beriplex, the product licensed in the UK in 2007, was the product first shown by us in 2002 (R3) to be safe and effective. CSL Behring referenced our publications (R1, R3) in the clinical section of their license dossier submitted to the European Medicines Agency (S7).

In the Australian Public Assessment Report for Human Prothrombin Complex Concentrate it is stated that our publication R3 was included in the Beriplex license application as supportive evidence (S8).

Octapharma and CSL Behring have sold more than 20 million units of Octaplex/Beriplex in the UK in 2012 (S9).

In 2012 CSL Behring has sold in excess of 300 million units of Beriplex internationally (S7). In April 2013, the US Food and Drug Administration approved KCentra™, the first US FDA-approved 4-Factor prothrombin complex concentrate for urgent warfarin reversal in patients with acute bleeding, This is the US name for Beriplex and has enabled CSL Behring to access a new and very large market with the concentrate (S10).

5. Sources to corroborate the impact (indicative maximum of 10 references)

(S1) O'Shaughnessy DF, Atterbury C, Bolton Maggs P, et al. Guidelines for the use of fresh frozen plasma, cryoprecipitate and cryosupernatant. British Journal in Haematology 2004; 126: 11-28.

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(S2) Keeling D, Baglin T, Tait C et al. Guidelines on oral anticoagulation with warfarin – fourth edition. British Journal of Haematology 2011; 154:311-324

(S3) Makris M, van Veen JJ, Tait CR, Mumford AD, Laffan M. Guideline on the management of bleeding in patients on antithrombotic agents. British Journal of Haematology 2013; 160:35-46

(S4) <http://www.dwmh.nhs.uk/sections/publications/documents/FOI28824268083.pdf>

(S5) Pernod G, Godier A, Gozalo C et al. French clinical practise guidelines on the management of patients on vitamin K antagonists in at risk situations (overdose, risk of bleeding, and active bleeding). Thrombosis Research 2010; 126:e167-e174

(S6) Liumbruno G, Bennordello F, Lattanzio A, et al. Recommendations for the use of antithrombin concentrates and prothrombin complex concentrates. Blood Transfusion 2009; 7:325-334

(S7) Email from Head of Commercial Operations CSL Behring, on 11th June 2013 confirms use of Sheffield research findings in EMA application.

(S8) <http://www.tga.gov.au/pdf/auspar/auspar-beriplex.pdf>

(S9) Email from Director of Serious Hazards of Transfusion (SHOT) on 11th June 2013 confirms sales data.

(S10) http://www.csl.com.au/docs/600/594/CSL_FINS_2013,1.pdf Page 43 of the CSL financial report corroborates availability of Beriplex in the US, under the name KCentra.