HaemSTAR
Specialty Training Audit and Research

RAPIDO

A ‘Flash-Mob’ UK national audit of the use of **R**eversal **A**gents in **P**atients ant**I**coagulated with **D**irect **O**ral anticoagulants (HaemSTAR RAPIDO)

Full study protocol

Website: https://haemstar.org/RAPIDO/

Contact: richard.buka@nhs.net

Contents

1. Study Management Group

- Richard Buka, Haematology Registrar, University Hospitals North Midlands
- Pip Nicolson, Clinical Lecturer in Haematology, University of Birmingham
- David Sutton, Consultant Haematologist, University Hospitals North Midlands
- Raza Alikhan, Consultant Haematologist, Cardiff and Vale University Health Board

Birmingham Centre for Observational and Prospective Studies (BiCOPS)

- Laura Magill, Clinical Trials Team Leader
- Rita Perry, Data Manager
- Michala Pettitt, PhD Reseearch Assistant
- Thomas Pinkney, Director

1.1. Study office / contacts

BiCOPS
BhamRed@contacts.bham.ac.uk

richard.buka@nhs.net

2. Summary

The aim of this project is to study real-world use in the UK of reversal agents in patients treated with direct oral anticoagulants (DOACs) who are bleeding.

The vast majority of patients taking DOACs in the UK take an anti-factor Xa medication which includes apixaban, rivaroxaban, and edoxaban. Until recently, treatment for major bleeding in patients taking one of these medications was supportive with the option to use prothrombin complex concentrate. However, the safety and efficacy of this intervention is uncertain.

Andexanet alfa, a decoy factor-Xa molecule is a specific reversal agent for the anti-factor Xa inhibitors. In the UK, it is formally recommended for use in Scotland for patients with acute major bleeding. In April 2021, NICE announced the intention to recommend Andexanet alfa for patients treated with rivaraoxaban or apixan who present with acute, major gastrointestinal bleeding but not intracranial haemorrhage.[1]

The data to support this is from the phase II ANNEXA-4 study[2] as well as propensity matched comparisons between patients in the ANNEXA-4 study and the ORANGE study[3]. However, data for patients treated with Andexanet alfa in the real-world are scarce.[4,5]

In this study we will prospectively study the use of reversal agents for patients bleeding on DOACs in the first three years of UK approval for Andexanet alfa. In so doing, we aim to:

- Audit the use of these agents against national and international guidelines.
- Collect data to study the factors influencing clinicians' choice of reversal agent
- Collect data on clinical outcomes and analyse these data using geographical stratification and propensity score matching
- Generate hypotheses for further prospective randomised studies

HaemSTAR is a UK-wide network of speciality trainees in clinical haematology who are interested in furthering research in non-malignant haematology. With representatives in all regions of the UK, HaemSTAR has reach into all major hospitals and many smaller hospitals in the UK, and is thus well placed to deliver this project.

3. Background

Over the past decade, the direct oral anticoagulant (DOAC) medications have begun to revolutionise the care of patients who require anticoagulation for a wide range of indications. However, a perceived major drawback to their use has been the lack of recognised agents that can be used to reverse the anticoagulant effect in situations where there is serious bleeding, or prior to urgent surgery.

Reversal of anticoagulation

For reversal of the anticoagulant effects of vitamin K antagonists, the use of prothrombin complex concentrate (PCC) is well established.[3] PCC is a plasma-derived product that contains the vitamin K dependent clotting factors, factor VII, IX, X and prothrombin, and works immediately to reverse the anticoagulant effects and normalise haemostasis. Patients who present with severe bleeding whilst taking a DOAC can also be managed with PCC in addition to supportive measures. However, PCC has been shown to have variable ability to normalise laboratory coagulation parameters in patients who are bleeding.[6] Additionally, the evidence for any clinical benefit is very limited and it is unclear as to whether PCC in addition to other supportive measures and cessation of the DOAC is more effective than cessation of the DOAC alone.[7]

Four DOACs are currently available in the UK: the direct thrombin inhibitor, dabigatran, and the three direct factor Xa inhibitors, apixaban, edoxaban, and rivaroxaban. In the last three years, two specific reversal agents for DOACs, idarucizumab for dabigatran, and andexanet alfa for apixaban, and rivaroxaban, have received regulatory approval for use in patients with acute severe bleeding. The 2018 CHEST (American College of Chest Physicians) guidelines recommended the use of specific reversal agents over general haemostatic agents such as PCC for patients with serious bleeding (expert consensus opinion).[8]

For dabigatran, the monoclonal antibody idarucizumab is available for use as a reversal agent for dabigatran. This is based on findings from the non-randomised phase II REVERSE-AD trial which enrolled 301 patients with major gastrointestinal bleeding or intracranial bleeding and 202 prior to emergency surgery.[9] Thrombotic events occurred in 4.8% patients. The primary outcome was the maximum percentage reversal of the anticoagulant effect of dabigatran within four hours. However, as there are no randomised trials, the clinical efficacy and safety compared to best supportive care including administration of PCC is not defined. Nonetheless, idarucizumab is now widely used for acute severe bleeding in patients taking dabigatran.

Andexanent alfa

More recently, a specific reversal agent for the factor Xa inhibitors has become available. Andexanet alfa is a recombinant, inactive form of factor Xa that acts as a competitive binder of the direct oral anticoagulants apixaban, edoxaban and rivaroxaban. Its efficacy has been examined in the phase II trial, ANNEXA-4 which enrolled 352 patients with acute major bleeding within 18 hours of administration of a factor Xa inhibitor.[10] The study had coprimary outcomes of: 1) percent change in anti–factor Xa activity after andexanet treatment – finding a 92% reduction and 2) the percentage of patients with excellent or good hemostatic efficacy at 12 hours after the end of the infusion – finding this outcome in 82%.

Based on these findings, andexanet alfa has received conditional FDA approval, EMA approval and a UK licence for use in acute major bleeding, pending further studies of PCC versus andexanet alfa. The availability of a highly active, specific antidote for the direct anti-Xa anticoagulants is extremely attractive, but it is clear that further data surrounding efficacy

and safety particularly with respect to thrombosis, are required to support and justify widespread adoption. Additionally, although in ANNEXA-4 treatment with Andexanet alfa demonstrates good reversal of anti-factor Xa effects, the clinical outcome of 82% patients achieving 'good or excellent haemostatic efficacy' is difficult to interpret and extrapolate to the clinic.

Prothrombin complex concentrate

PCC is widely used off-licence for the treatment of patients with major bleeding who are taking DOACs. In observational studies, it seems to be as effective in these patients as it is in patients on warfarin with comparable risk of thrombosis (2-4%). The incidence of thrombosis in ANNEXA-4 was higher than this at 10% but again, it is difficult to draw conclusions across disparate studies. It also uncertain as to whether thrombosis following the reversal of anticoagulation is a function of the increased risk in an otherwise unwell patient, the cessation of anticoagulation, the abrupt reversal, an effect of the reversal agent itself, or a combination of these factors.

As with many new therapeutics, there were strict exclusion criteria (figure 1) for the trial leading to the exclusion of patients who, in the real-world, are likely to be treated – a conclusion supported by the findings of Brown et al in their real-world analysis of 25 patients treated for major bleeding, 64% of whom would have been excluded in ANNEXA-4.[5] A larger retrospective analysis of 3030 patients suggested that andexanet alfa may be more effective than PCC, fresh frozen plasma, or both.[3] However, given the substantially higher cost of Andexanet alfa to the NHS compared with PCC, we require high-fidelity phase IV data to justify its wider adoption in a public health system which has an obligation to deliver on the ethical paradigm of social justice.

Use of reversal agents in the UK

In the UK, both PCC (off-licence) and idarucizumab are available to clinicians to manage severe bleeding or prior to emergency surgery. Until recently the use of Andexanet alfa was not recommended for use anywhere in the UK. However, in September 2020, the Scottish Medicine Consortium approved andexenet alfa for use within NHS Scotland for severe bleeding secondary to apixaban and rivaroxaban on an interim basis subject to ongoing evaluation and future reassessment.[11] In England, NICE reviewed the evidence and cost-efficacy of andexanet alfa and concluded in April 2020 that there was insufficient evidence to recommend its use.[12]

However, in April 2021, NICE announced the intention to recommend Andexanet alfa for patients treated with rivaraoxaban or apixan who present with acute, major gastrointestinal bleeding but not intracranial haemorrhage.[1]

Given the importance of anticoagulation in preventing morbidity and mortality, it is important to obtain further data on the use, efficacy and safety of Andexanet alfa as it emerges into widespread use in the UK. We will both retrospectively and prospectively gather data using the HaemSTAR network, a UK-wide network of speciality trainees in haematology, over a two to three year period. As well as auditing the use of reversal agents against national guidelines, we will perform secondary data analyses using propensity score matching to investigate the comparative efficacy of these agents.

4. Study objectives

- Audit the use of reversal agents for anticoagulation in the UK against clinical guidelines.[13]
- To determine the comparative efficacy of Andexanet alfa, Idarucizumab, and PCC by measuring clinical outcomes as described below.

5. Inclusion criteria

- Individuals ≥18 years of age
- Taking apixaban, dabigatran, edoxaban or rivaroxaban in any dose and frequency, for any indication
- Treated with andexanet alfa, idarucizumab, or prothrombin complex concentrate to mitigate bleeding or the risk of bleeding
    - For bleeding of any severity
    - Prior to surgery of any urgency or bleeding risk
- Treated from 1st October 2020

6. Outcomes

6.1. Primary outcomes

- Proportion of patients treated with a reversal agent who had severe or life-threatening bleeding as defined by the International Society for Thrombosis and Haemostasis.[14]
- Proportion of patients who received pre-operative reversal agent whose surgery was carried out within 24 hours.
- Proportion of patients treated with a reversal agent who received treatment in accordance with the dosing schedule laid out in the relevant SPC.

6.1.1. Further information on audit standards

Data from this study will allow us to audit the use of agents to reverse anticoagulation. The 2013 British Committee for Standards in Haematology guideline on the management of bleeding in patients on antithrombotic agents recommends:[13] (which we have paraphrased and summarised)

- *"Management of bleeding [in patients on rivaroxaban and dabigatran] should be through cessation of treatment and general haemostatic measures."*
- *"In situations with ongoing life-threatening bleeding, PCC, APCC and rFVIIa should be considered"*

A 2019 addendum dealt with use of idarucizumab:

- *"Idarucizumab is indicated for patients treated with dabigatran when rapid reversal of its anticoagulant effect is required [in] life-threatening or uncontrolled bleeding or [when a patient requires] emergency surgery or urgent invasive procedures"*[15]

If NICE recommend Andexanet alfa, we will also include wording from the BSH guideline addendum for this.

The 2018 CHEST guideline recommends that:

- *"Reversal agents should be used sparingly in the cases of severe and life-threatening bleeding, which includes bleeding causing hemodynamic compromise, ICH, bleeding into a critical organ or closed space, persistent bleeding despite general supportive measures and local hemostatic support, or risk of recurrent bleeding due to excess NOAC drug exposure due to delayed clearance of NOAC (eg, acute renal failure) or overdose."*[8]

The Summary Product Characteristics (SPC) for andexanet alfa, idarucizumab, and the PCC concentrates state the following indications:

Andexanet alfa[16]

- For adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

Idarucizumab[17]

- [For] adult patients treated with Pradaxa (dabigatran etexilate) when rapid reversal of its anticoagulant effects is required for emergency surgery/urgent procedures, or in life-threatening or uncontrolled bleeding.

PCC products: Beriplex[18] and Octaplex[19]

- Treatment and perioperative prophylaxis of bleedings in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required.

6.2. Secondary outcomes

- Death within 90 days
- Thrombotic events within 90 days
- Requirement for transfusion within 90 days
- Death due to bleeding within 90 days
- Death due to thrombosis within 90 days

7. Audit / study design

This is a retrospective and prospective, multi-centre, observational audit of patients treated with andexanet alfa, idarucizumab or PCC for the reversal of the anticoagulant effect of the DOACs apixaban, dabigatran edoxaban, and rivaroxaban. Any patient who received anticoagulant reversal for bleeding or prior to surgery will be included.

All clinical information will be recorded in routine clinical practice and will be extracted from existing electronic and paper patient records. Patients will be identified as eligible through interrogation of pharmacy or blood bank lists of product issue. Individual patient records will then be scrutinised to determine eligibility criteria. Records will only be accessed by NHS clinical care teams and any patient identifiable data will be anonymised. Anonymised data will be entered into a secure eCRF database (REDCap[20,21]) hosted by the Universtiy of Birmingham BiCOPS team. Patients will be assigned a study number which will be locally indexed to the patient's hospital number and stored locally in password protected documents on secure NHS trust servers. The central research team will not have access to this information.

There will be two data collection windows:

May-July 2022

To collect data from 1st October 2020 to 31st January 2022

October-December 2023

To collect data from 31st January 2022 to 30th June 2023

These windows are designed to focus the efforts of contributors and are designed to streamline the process. However, patients can be added before 90 day follow-up is complete but contributors would need to update records with follow-up data once 90 days have passed.

8. Sample size calculation

This is a prospective audit of use of reversal agents in the UK. A sample size calculation is therefore not required for the primary outcomes. For the secondary outcome measures of incidence of death and thrombosis, the following information is relevant.

The best estimate of differential effect size between PCC and Andexanet alfa is from Coleman et al's retrospective study of outcomes. This was an American study which demonstrated a 4% mortality in patients treated with andexanet alfa versus 10% in those treated with PCC. A sample size calculation with this effect size using a 2:1 ratio of patients in the PCC and andexanet/idarucizumab arms yields a required sample size of 666. An audit performed in 2017 at University Hospitals North Midlands NHS Trust, a large tertiary referral and trauma centre, found that PCC was issued 87 times in a 7-month period. 30 of these issues were for bleeding on an anti-Xa DOAC.[22] However, it is likely that initial use of Andexanet following national recommendation for its use will be much lower than PCC.

In order to maximise case identification, we aim to recruit at least 666 cases over a 2-3 year period which includes a retrospective period from September 2020. HaemSTAR is well placed to deliver this as demonstrated by two previous projects on intravenous immunoglobulin use in immune thrombocytopaenia and treatment of thrombotic thrombocytopaenic purpura respectively.[23,24]

9. Data completeness

Following data collection, only data sets with >40% data completeness will be accepted for pooled national analysis. Centres with >60% missing data points will be excluded and collaborators from those centres withdrawn from the published list of citable collaborators.

10. Statistical analysis

Descriptive analyses will be presented as raw numbers and percentages, medians IQR, and means, SD for non-parametric and parametric data respectively. The differences in outcomes will be assessed using multivariate survival analysis and multivariate logistic regression in R using treatment with andexanet alfa or PCC as covariates in the models. Differences in outcomes will be visualised using Kaplan-Meier survival analysis. For outcomes which are competing risks (e.g. incidence of thrombosis where death is a competing risk), multivariate competing risk analysis using Fine-Gray proportional hazard regression for competing events. Missing data will be treated as “missing at random”. All tests of statistical significance will be 2-sided and a p-value of <0.05 will be considered as statistically significant. Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

11. Regulatory issues

11.1. Ethical

This is an audit with no direct impact on patient care. Formal ethical approval is not required. Sites may participate once they have local clinical audit approval in place. Only routinely collected data will be collected, patients will not undergo any additional investigation or follow up, and no identifiable data will be collected in the study database as the patient’s clinical team will upload anonymised data.

11.2. Confidentiality

The study will preserve the confidentiality of participants taking part in the fulfil transparency requirements under the General Data Protection Regulation for health and care research. Patient data will be anonymised by assigning each participant a unique study number. Hospital site will not be identifiable in published data.

12. Study management

The organisation of this national audit will be carefully co-ordinated through the national HaemSTAR network. The roles of various collaborator groups are described below.

- *Birmingham Centre for Observational and Prospective Studies:* A department of the University of Birmingham that will provide support for study planning, delivery, and data management.

12.1. Collaborator groups

- *Management committee:* a core group of haematology trainees and consultants plus data management and statistician are responsible for protocol design, data handling, analysis and drafting of the paper. The management committee are responsible for use of data resulting from the project.

- *Regional leads:* a network of Haematology trainees across the UK responsible for co-ordinating teams at local hospitals. The regional leads act as a link between local teams and the management committee. They are the first point of contact for local collaborators. Each regional lead will aim to recruit 4-5 local-teams within their designated region. To qualify for authorship, regional leads must recruit at least three local-teams unless agreed in advance with the management committee.

- *Local teams:* each local centre requires a team of collaborators consisting of one supervising consultant and a team of haematology and medical trainees. Local team sizes will vary according to size of hospital but should comprise a minimum of 2 (1 trainee and 1 supervising consultant) and a maximum of 5. Local teams will contribute to identification of eligible patients and are responsible for data collection. One collaborator should be selected to act as the 'local lead'. A maximum of 5 collaborators per centre-team will be listed as 'PubMed' citable collaborators. A collaborator must have evidence of data collection via their REDCap login to be eligible for collaborator status.

In exceptional circumstances, where local teams anticipate a very high volume of patients being eligible for inclusion, they may contact the management committee for permission to add an additional collaborator to their team.

- *Local leads:* each centre will require 1 collaborator to act as the "local lead". The lead is responsible for: 1) ensuring the audit is registered locally; 2) contacting the supervising consultant; 3) sending the management committee the contact details of the collaborators from their centre; 4) making sure all deadlines are met (see front sheet); 5) ensuring all data is submitted from their centre; and 6) helping with data collection. These individuals will be listed in the final authorship as local leads, in recognition of their contribution.
- *Supervising consultant:* one consultant per centre is eligible for collaborative PubMed citable collaborator status if they meet the following criteria: 1) Supports local audit registration; 2) Circulates information about the audit and the audit protocol to consultant colleagues; 3) Facilitates presentation of local audit results at a departmental audit meeting; 4) Completes workplace-based assessments for trainees (ePortfolio), if asked. Consultants should ensure collaborators act in accordance within governance guidelines and should facilitate implementation of post-audit interventions, if required.

12.2. Local registration

It is the responsibility of the local centre-team at each site to identify a local supervising consultant haematologist and to ensure that the audit is registered appropriately. A letter addressed to trust audit officers will be available to aid the process. When registering this as a clinical audit the local team should emphasise that:

- The audit will measure current practice against established standards.
- It is a national audit.

REDCap accounts will not be issued until evidence is sent to the management committee showing the successful registration with the audit department, including the email address of the local audit officer.

Two permanent contacts at each hospital are required (supervising consultant and audit officer) to return hospital specific results.

13. Finding patients

Although every site will require a slightly different approach, we recommend the following steps to identify patients.

1) Acquire list of patient numbers from hospital pharmacy and/or blood bank depending on where each product (andexanet alfa, PCC (beriplex or octaplex), idarucizumab) is stocked.
2) Screen PCC patients to exclude patients receiving this for indications other than DOAC-reversal (e.g. warfarin reversal or DIC)

14. Dissemination of findings and publication policy

Each contributing centre will receive a summary of their own data with comparison against national data. This information will be confidential for the participating centre only. No centre's individual data will be shared with other centres and national data will be presented in an amalgamated format and no individual trust's performance will be visible. This study will be submitted for presentation at national and/or international scientific meetings and for publication in a peer reviewed journal. HaemSTAR is committed to a collaborative authorship model, and this data will be published according to this model. This means that any individual who has contributed data of at least one full patient record will be a citable collaborator which is PubMed citable and equivalent to authorship. The formal author will be "HaemSTAR Collaborators".

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Appendix 1: Data to be collected

Demographic data and medical history

- Hospital site
- Age
- Sex
- Ethnicity (Office of National Statistics categories)
- Weight
- Height

Comorbidities

- Active cancer
    - Primary site
    - Presence of cerebral metastases
- Atrial fibrillation
- Congestive cardiac failure
- Dementia
- Ischaemic heart disease
- Liver disease
- Peripheral vascular disease
- Prior major bleeding
- Prior thrombosis – arterial
- Prior thrombosis – venous
- Renal disease
- Surgery in last 6 months

Relevant concurrent medications

- Antihypertensives
- Antiplatelets
- Antidepressants

Social history

- Alcohol intake
    - None
    - ≤14 units / week
    - >14 units / week
- Smoking history
    - Current
    - Non-smoker
    - Ex-smoker

Information about DOAC treatment

- Which DOAC they are taking
- At what dose (mg)
- Hours since last taken if known

Information about bleed

- Date of bleed onset

- Time of bleed onset
- Bleeding site
    - Gastrointestinal
    - Intracranial
        - Site of haemorrhage: infratentorial or supratentorial
        - Intracranial bleed volume if known (ml)
        - Intraventricular haemorrhage Y/N
        - Worst GCS in first 6 hours from bleed onset (3-15)
    - Other – please give details
- Spontaneous, or secondary to injury or other provoking factor
- Vital signs
    - Lowest systolic blood pressure before administration of reversal agent
    - Highest heart rate before administration of reversal agent

Information will be used to categorise bleeding according to defined international criteria (ISTH). Information will also be used to retrospectively calculate Glasgow-Blatchford Bleeding Score and Rockall scores, for upper gastrointestinal haemorrhage or ICH score for intracranial haemorrhage where applicable.

Investigations at bleed onset

- Haemoglobin
- Platelets
- Creatinine
- Urea

Prior investigations

- Haemoglobin in last 12 months
- Creatinine level in last 12 months

Reversal

- Which reversal agent was used
- Dosing of reversal agent

Tranexamic acid

- Was tranexamic acid given?

Transfusions

- Were red cells transfused prior to administration of reversal agent?
    - How many units?
- Were red cells transfused after administration of reversal agent?
    - How many units?
- Was FFP transfused prior to administration of reversal agent?
    - How many units?
- Was FFP transfused after administration of reversal agent?
    - How many units?
- Were platelets transfused prior to administration of reversal agent?
    - How many units?
- Were platelets transfused after administration of reversal agent?
    - How many units?

Was there any loss of consciousness, collapse, or syncope at any time preceding or up to 4 hours following administration of the reversal agent?

Surgery / procedures

- Was surgery or a procedure planned or performed as part of the management of this bleeding episode?
    - Was this performed?
    - How many hours after administration of the reversal agent was this procedure performed?

Follow-up blood tests

- Hb at ~24h following administration of reversal agent
    - Leave blank if no Hb performed between 24 and 48 hours post-administration of reversal agent

Follow-up

Intracranial bleeding only

- Was any further neuroimaging performed 6-24 hours after administration of the reversal agent?
    - How many hours after?
    - Status of haematoma (stable, expanding)
- What was GCS 6-24 hours after administration of the reversal agent?
- Was there any functional neurological deterioration at discharge or day +30 whichever is sooner?

Resumption of anticoagulation

- Was anticoagulation planned to restart in the 90 days following administration of the reversal agent?
    - How many days was planned?
- Was anticoagulation restarted within 90 days or was there documentation of a plan to restart?
    - If so, when?

Incidence of thrombosis

- Was the patient diagnosed with a thrombotic episode at any point in the following 90 days post-treatment with the reversal agent
- If so, details:
    - Venous / arterial
    - Site: PE / DVT / Other venous / Stroke / MI / Other arterial
- Did patient die in the follow-up period?
    - If so, how many days post-reversal agent did death occur?

Further bleeding episodes

- Any further bleeding episodes requiring more treatment?
    - To be inputted in the database as a separate episode