General

Guideline Title

Guideline on the management of bleeding in patients on antithrombotic agents.

Bibliographic Source(s)


Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (A-C) and strength of recommendation (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Specific Measures

Parenteral Anticoagulants

Unfractionated Heparin (UFH)

Stopping an UFH infusion and general haemostatic measures are often sufficient to stop or prevent bleeding (2C).

Protamine sulphate (1 mg per 80–100 units UFH) will fully reverse UFH, but should be given slower than 5 mg/min to minimize the risk of adverse reactions.

The maximum recommended dose of 50 mg protamine is sufficient to reverse UFH in most settings.

Low Molecular Weight Heparin (LMWH)

LMWH administration within 8 hours of the time of requirement for correction of anticoagulation: give protamine sulphate (1 mg per 100 anti-Xa units of LMWH). If ineffective, consider further protamine sulphate 0.5 mg per 100 anti-Xa units (2C). Protamine sulphate should be given slower than 5 mg/min to minimize the risk of adverse reactions.

LMWH administration greater than 8 hours from the time of requirement for correction of anticoagulation: consider smaller doses of protamine (2C).
Consider recombinant activated factor VII (rFVIIa) if there is continued life-threatening bleeding despite protamine sulphate and the time frame suggests there is residual effect from the LMWH contributing to bleeding. (2C).

**Danaparoid Sodium**

There is no specific antidote for danaparoid. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C). Plasmapheresis may be considered for critical bleeding.

**Fondaparinux**

There is no specific antidote for fondaparinux. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C). Recombinant FVIIa should be considered for critical bleeding (2C).

**Bivalirudin**

There is no specific antidote for bivalirudin. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C). Exceptionally, haemodialysis, haemofiltration or plasmapheresis may be considered for critical bleeding (2C).

**Argatroban**

There is no specific antidote for argatroban. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C).

**Oral Anticoagulants**

**Warfarin**

All hospitals managing patients on warfarin should stock a licensed four-factor prothrombin complex concentrate (PCC) (1C).

Emergency anticoagulation reversal in major bleeding should be with 25–50 U/kg four-factor PCC and 5 mg intravenous vitamin K (1B).

Recombinant factor VIIa is not recommended for emergency anticoagulation reversal (1B).

Fresh frozen plasma produces suboptimal anticoagulation reversal and should only be used if PCC is not available (1C).

Anticoagulation reversal for non-major bleeding should be with 1–3 mg intravenous vitamin K (1B). Patients with an international normalized ratio (INR) >5.0 but who are not bleeding should have 1–2 doses of warfarin withheld and their maintenance dose should be reduced (1B). The cause of the elevated INR should be investigated (1C).

Asymptomatic patients with an INR of ≥8.0 should receive 1–5 mg of oral vitamin K (1B). The INR should be rechecked the following day in case an additional dose of vitamin K is required.

For surgery that requires reversal of warfarin and that can be delayed 6–12 hours, the INR can be corrected by giving intravenous vitamin K. For surgery that requires reversal of warfarin and which cannot be delayed for vitamin K to have time to take effect, the INR can be corrected by giving PCC and intravenous vitamin K. PCC should not be used to enable elective or non-urgent surgery (2C).

**Other Vitamin K Antagonists**

Emergency reversal of the effect of phenprocoumon, acenocoumarol and phenindione should be with 5 mg intravenous vitamin K and 25–50 units/kg four-factor PCC.

For less severe bleeding or for correction of over anticoagulation, 1–5 mg of oral vitamin K is sufficient.

**Direct Oral Thrombin Inhibitors – Dabigatran**
There is no specific antidote for dabigatran. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C).
In bleeding patients who have taken a dose of dabigatran in the last 2 hours, consider oral activated charcoal to prevent further absorption (2C).
If rapidly deployable, haemodialysis, haemofiltration and charcoal haemoperfusion offer the possibility of enhanced clearance of the active drug (2C).
In situations with ongoing life-threatening bleeding PCC, activated prothrombin complex concentrate (APCC), and rFVIIa should be considered (2C).

Direct Oral Xa Inhibitors – Rivaroxaban and Apixaban

There is no specific antidote for rivaroxaban. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C).
In situations with ongoing life-threatening bleeding, PCC, APCC and rFVIIa should be considered (2C).

Anti-platelet Drugs

Decisions to withhold anti-platelet drugs or to administer pro-haemostatic agents should be made after a careful multi-disciplinary assessment of the risks and benefits of intervention. (1C).
Bleeding in patients during treatment with aspirin, P2Y\textsubscript{12} antagonists or glycoprotein (GP) IIa/IIIb inhibitors should be managed in the first instance with general haemostatic measures. If necessary, drug cessation and reversal of the effect of coprescribed anticoagulants should also be considered (2C).
Platelet transfusion (2–3 adult doses) should be considered as an additional measure for critical bleeding or prevention of bleeding before emergency surgery (2C).
Platelet transfusion should be considered to prevent bleeding in severe thrombocytopenia (<10 x 10\textsuperscript{9}/l) caused by abciximab (2C).

Fibrinolytic Drugs

For major bleeding (e.g., intracerebral) within 48 hours of administration, the task force recommends:

Stop infusion of fibrinolytic drugs and other antithrombotic drugs (1C).
Administer fresh frozen plasma 12 ml/kg (2C).
Administer intravenous tranexamic acid 1 g tds (2C).
If there is depletion of fibrinogen, administer cryoprecipitate or fibrinogen concentrate (2C).
Further therapy should be guided by results of coagulation tests (2C).

Definitions:

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect.
and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Bleeding during antithrombotic therapy

Guideline Category

Management
Treatment

Clinical Specialty

Anesthesiology
Cardiology
Critical Care
Emergency Medicine
Hematology
Internal Medicine
Pharmacology
Surgery

Intended Users

Advanced Practice Nurses
Clinical Laboratory Personnel
Hospitals
Guideline Objective(s)
To guide healthcare professionals in the United Kingdom on the management of patients receiving antithrombotic drugs who experience significant bleeding or who require emergency surgery or an invasive procedure

Target Population
All patients receiving antithrombotic agents who are bleeding or are at risk for bleeding

Interventions and Practices Considered

1. Management of bleeding associated with parenteral anticoagulants
   - Cessation of anticoagulant treatment
   - General haemostatic measures
   - Protamine sulphate (for reversing unfractionated heparin and low molecular weight heparin)
   - Recombinant activated factor VII (rFVIIa)
   - Haemodialysis, haemofiltration, or plasmapheresis for critical bleeding

2. Management of bleeding associated with oral anticoagulants
   - Reversal with four-factor prothrombin complex concentrate (PCC)
   - Oral or intravenous vitamin K
   - Fresh frozen plasma (if PCC is not available)
   - Withholding doses of warfarin in patients with international normalized ratio (INR) >5 but no bleeding
   - Cessation of treatment and general haemostatic measures
   - Oral activated charcoal to prevent further anticoagulant absorption
   - Haemodialysis, haemofiltration, and charcoal haemoperfusion
   - In situations with ongoing life-threatening bleeding: PCC, activated prothrombin complex concentrate (APCC), and rFVIIa

3. Management of bleeding associated with oral antiplatelets
   - Withholding antiplatelet drugs or administering pro-haemostatic agents after a careful multi-disciplinary assessment of the risks and benefits of intervention
   - General haemostatic measures
   - Drug cessation and reversal of the effect of coprescribed anticoagulants
   - Platelet transfusion for critical bleeding, prevention of bleeding before emergency surgery, or prevention of bleeding in severe thrombocytopenia caused by abciximab

4. Management of major bleeding associated with fibrinolytics
   - Stopping infusion of fibrinolytic drugs and other antithrombotic drugs
   - Fresh frozen plasma
   - Intravenous tranexamic acid
   - Cryoprecipitate or fibrinogen concentrate
   - Further therapy guided by results of coagulation tests

Major Outcomes Considered
- Morbidity
Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The MEDLINE and EMBASE databases were searched systematically for publications in English from 1966 to June 2011 and 1980 to June 2011, respectively, using the following strategy: Approved and proprietary names of the antithrombotic agents described in the guideline were combined with terms relating to antidote, reversal, haemorrhage, (activated) prothrombin complex concentrate, factor VIII inhibitor bypass activity, Beriplex, Octaplex, recombinant activated factor VII, Novoseven, fresh frozen plasma, tranexamic acid, antifibrinolytic, platelet transfusion, and desmopressin. Identified papers were also searched for additional references.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect
and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses
Systematic Review

Description of the Methods Used to Analyze the Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to quote levels and grades of evidence (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The guideline group was selected to be representative of United Kingdom-based medical experts.

The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review
Internal Peer Review

Description of Method of Guideline Validation

The guideline was reviewed by a sounding board of approximately 50 United Kingdom haematologists, the
Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for most recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of bleeding in patients receiving antithrombotic agents

Potential Harms

- Recombinant activated factor VII is often considered as a last resort when all other measures have failed and the risks and benefits are carefully documented.
- Prothrombin complex concentrate (PCC) and activated prothrombin complex concentrate (APCC) agents may increase thrombosis risk although this has not been evaluated in large-scale meta-analyses.
- Protamine can cause severe allergic reactions, including anaphylaxis, hypotension, bronchospasm and skin reactions in up to 10% of patients. Risk factors are previous exposure to protamine sulphate (including protamine-containing insulin preparations), rate of administration, vasectomy, and fish allergy.
- Many patients who are prescribed anti-platelet drugs are at high risk of arterial thrombosis. Therefore, the safety of anti-thrombotic drug withdrawal and pro-haemostatic interventions should be considered carefully through a multi-disciplinary risk assessment.
- Platelet transfusion may be considered for emergency reversal of the anti-platelet effect but may confer a risk of arterial thrombosis.

Contraindications

Desmopressin is relatively contraindicated in patients with cardiovascular disease, and there is no evidence to support efficacy in this patient group.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.
Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need
Getting Better
Staying Healthy

IOM Domain
Effectiveness
Safety
Timeliness

Identifying Information and Availability

Bibliographic Source(s)


Adaptation
Not applicable: The guideline was not adapted from another source.

Date Released
2013 Jan

Guideline Developer(s)
British Society for Haematology Guidelines - Professional Association

Source(s) of Funding
British Committee for Standards in Haematology

Guideline Committee
Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology

Composition of Group That Authored the Guideline

Writing Group Members: Mike Makris, Department of Cardiovascular Science, University of Sheffield and
Financial Disclosures/Conflicts of Interest
Not stated

Guideline Status
This is the current release of the guideline.

Guideline Availability
Electronic copies: Available from the British Committee for Standards in Haematology Web site.
Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk

Availability of Companion Documents
None available

Patient Resources
None available

NGC Status
This NGC summary was completed by ECRI Institute on January 15, 2013. This summary was updated by ECRI Institute on March 10, 2014 following the U.S. Food and Drug Administration advisory on Low Molecular Weight Heparins.

Copyright Statement
This NGC summary is based on the original guideline, which is copyrighted by the British Committee for Standards in Haematology. For more information, contact the BCSH Secretary, 100 White Lion Street, London, UK, N1 9PF; Email: bcsh@b-s-h.org.uk.

Disclaimer

NGC Disclaimer
The National Guideline Clearinghouseâ"¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.
All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.