National Institute for Health and Care Excellence

Final

Abdominal aortic aneurysm: diagnosis and management

Evidence review R: Use of tranexamic acid during transfer of people with ruptured or symptomatic abdominal aortic aneurysm

NICE guideline NG156

Methods, evidence and recommendations

March 2020

Final

This evidence review was developed by the NICE Guideline Updates Team

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Use of tranexamic acid during transfer of people with ruptured or symptomatic abdominal aortic aneurysm

Review question

Does tranexamic acid improve a person's chance of survival or improve the stability of their condition in the transfer of people with ruptured or symptomatic abdominal aortic aneurysms to a regional vascular service?

Introduction

This review question aims to determine if tranexamic acid improves a person's chance of survival or improve the stability of their condition in the transfer of people with ruptured or symptomatic abdominal aortic aneurysms to a regional vascular service.

PICO table

Table 1: Inclusion criteria

Parameter	Inclusion criteria
Population	People with a suspected or confirmed ruptured or symptomatic unruptured abdominal aortic aneurysm who need to be transferred to a regional vascular service
Intervention	Tranexamic acid
Comparator	Placebo or no intervention
Outcome	• Survival /mortality • Bleeding/need for transfusion • Myocardial infarction • Renal failure • Adverse effects of intervention – stroke, acute limb ischaemia, venous thromboembolism • Quality of life • Resource use, including of intensive care unit stay, and cost

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

A 'bulk' search was performed covering 2 review questions related to patient transfer. The database was sifted to identify all studies that met the criteria detailed in Table 1. The relevant review protocol can be found in Appendix A.

Studies were considered for inclusion if they were randomised controlled trials, quasi-randomised controlled trials or systematic reviews (of the aforementioned study types) exploring the efficacy of tranexamic acid for improving survival of people with ruptured or symptomatic AAA who were being transferred to regional vascular services.

Studies were excluded if they:

- were not in English
- were not full reports of the study (for example, published only as an abstract)
- were not peer-reviewed.

Clinical evidence

Included studies

Initial literature searches identified 572 abstracts. Of these, no full texts were retrieved as potentially relevant. Thus, no studies were included as clinical evidence. An update search was conducted in December 2017, to identify any relevant studies published during guideline development. The search yielded 10 abstracts; all of which were not considered relevant to this review question. As a result no additional studies were included.

Excluded studies

No studies were retrieved for full-text review.

Economic evidence

Included studies

An initial literature search was conducted jointly for all review questions by applying standard health economic filters to a clinical search for AAA. This search returned a total of 5,173 citations. Following review of all titles and abstracts, no studies were identified as being potentially relevant to the review question. No full texts were retrieved, and no studies were included as economic evidence.

An update search was conducted in December 2017, to identify any relevant health economic analyses published during guideline development. The search yielded 814 abstracts; all of which were not considered relevant to this review question. As a result no additional studies were identified.

Excluded studies

No studies were retrieved for full-text review.

Economic model

This review question does not lend itself to economic evaluation, and was not prioritised by the committee for economic modelling. As such, no economic model was developed for this review question.

Evidence statements

No evidence was identified for this review question.

Research recommendations

RR9. Does tranexamic acid improve survival in people who are having repair (EVAR or open surgical repair) of a ruptured AAA?

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee considered that the outcomes that matter most are perioperative morbidity and mortality. The committee considered that perioperative outcomes were more important than long-term outcomes because any benefits of tranexamic acid are likely to become apparent in the acute period.

The quality of the evidence

The committee were unable to make a clear judgement on the clinical utility of tranexamic acid as no evidence was identified from the literature searches. Furthermore, they were not aware of tranexamic acid routinely being used in people with ruptured AAA. In light of this, the committee agreed that research, in the form of well-conducted randomised controlled trials, was needed to determine whether tranexamic acid improves the chances of survival following aneurysm rupture.

Benefits and harms

The committee recognised that tranexamic acid is becoming increasingly used in people who are bleeding profusely after major trauma, and noted that clinical trials show some benefits of using tranexamic acid in this population. The committee agreed that it would not be appropriate to extrapolate the reported benefits in trauma patients to people with ruptured AAA because the 2 populations were inherently different:

- The committee noted that it is easier to determine when people with major trauma have major bleeding events because their bleeding is likely to be visible. They agreed that it would be difficult to ascertain the presence of a ruptured AAA without imaging, and the administration of tranexamic acid based on a false-positive diagnosis could potentially cause harm.
- The committee noted that NICE's trauma guideline (NICE NG39) recommends that tranexamic acid should not be administered more than 3 hours after injury in people with major trauma. The committee agreed that such a recommendation would not suit the context of AAA because of the inability to accurately determine the time of rupture.
- Finally, the committee noted that people with ruptured AAA are at risk of thrombotic complications (such as venous thromboembolism and myocardial infarction), and the prothrombotic effects of tranexamic acid may increase their risk of these events.

Cost effectiveness and resource use

The committee noted that tranexamic acid is already used in practice to treat conditions other than AAA. Since the committee agreed that a lack of recommendations would have no impact in practice, they concluded that there would also be no impact on NHS costs and resources.

Other factors the committee took into account

No other factors were discussed by the committee.

Appendices

Appendix A – Review protocol

Review protocol for use of tranexamic acid during transfer of people with ruptured or symptomatic abdominal aortic aneurysm

Review question 20	Does tranexamic acid improve a person's chance of survival or improve the stability of their condition in the transfer of people with ruptured or symptomatic abdominal aortic aneurysms to a regional vascular service?
Objectives	To determine if tranexamic acid improves a person's chance of survival or improve the stability of their condition in the transfer of people with ruptured or symptomatic abdominal aortic aneurysms to a regional vascular service
Type of review	Intervention
Language	English only
Study design	Systematic reviews of study designs listed below Randomised controlled trials Quasi-randomised controlled trials
Status	Published papers only (full text) No date restrictions
Population	People with a suspected or confirmed ruptured or symptomatic unruptured abdominal aortic aneurysm who need to be transferred to a regional vascular service
Intervention	Tranexamic acid
Comparator	Placebo or no intervention
Outcomes	Survival /mortality Bleeding/need for transfusion Myocardial infarction Renal failure Adverse effects of intervention – stroke, acute limb ischaemia, venous thromboembolism Quality of life Resource use, including of intensive care unit stay, and cost
Other criteria for inclusion / exclusion of studies	Exclusion: Non-English language Abstract/non-published (i only)
Baseline characteristics to be extracted in evidence tables	Age Sex Size of aneurysm Comorbidities
Search strategies	See Appendix B
Review strategies	Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect. All key findings from evidence will be presented in GRADE profiles and further summarised in evidence statements.
Key papers	None identified

Appendix B – Literature search strategies

Clinical search literature search strategy

Main searches

Bibliographic databases searched for the guideline

- Cumulative Index to Nursing and Allied Health Literature - CINAHL (EBSCO)
- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE Epub Ahead of Print (Ovid)
- MEDLINE In-Process (Ovid)

Identification of evidence for review questions

The searches were conducted between November 2015 and October 2017 for 31 review questions (RQ). In collaboration with Cochrane, the evidence for several review questions was identified by an update of an existing Cochrane review. Review questions in this category are indicated below. Where review questions had a broader scope, supplement searches were undertaken by NICE.

Searches were re-run in December 2017.

Where appropriate, study design filters (either designed in-house or by McMaster) were used to limit the retrieval to, for example, randomised controlled trials. Details of the study design filters used can be found in section 4.

Search strategy review question 20

Medline Strategy, searched 4th October 2017 **Database: Ovid MEDLINE(R) <1946 to September Week 3 2017>** **Search Strategy:**
1 Aortic Rupture/
2 RAAA.tw.
3 1 or 2
4 Aortic Aneurysm, Abdominal/
5 (Aneurysm* adj4 (abdom* or thoracoabdom* or thoraco-abdom* or aort* or spontan*)).tw.
6 ((juxtarenal* or juxta-renal* or juxta renal* or paraerenal* or para-renal* or para renal* or suprarenal* or supra renal* or supra-renal* or short neck* or short-neck* or shortneck* or visceral aortic segment*) adj4 aneur?sm*).tw.
7 AAA.tw.
8 or/4-7

Medline Strategy, searched 4th October 2017
Database: Ovid MEDLINE(R) <1946 to September Week 3 2017>
Search Strategy:

9 (aort* adj4 (balloon* or dilat* or bulg* or expan*)).tw.

10 (ruptur* or tear* or bleed* or trauma* or burst* or large* or big*).tw.

11 symptom*.tw.

12 or/9-11

13 8 and 12

14 3 or 13

15 Patient transfer/

16 "Transportation of Patients"/

17 "continuity of patient care"/ or patient handoff/

18 ((clinical or patient* or intershift* or nurs* or physician* or shift or staff*) adj4 (handover* or hand-off or handoff or hand off)).tw.

19 (transition* adj4 care).tw.

20 og.fs.

21 Ambulances/

22 ambulance*.tw.

23 (emergency adj4 (unit* or vehicle* or paramedic* or transport* or transfer*)).tw.

24 ((transfer* or transport* or travel* or move* or moving or continuity or transition* or hando* or journey* or arriv*) adj4 (hospital* or intrahospital* or emergenc* or paramedic* or facilit* or "cardiothoracic unit*" or "vascular unit*" or "vascular centre*" or "vascular center*" or "vascular service*" or "endovascular unit*" or "specialist unit*" or "specialist centre*" or "specialist center*" or "specialist service*" or "endovascular centre*" or "endovascular center*" or "endovascular service*" or "primary care" or "secondary care" or "tertiary care" or "tertiary centre*" or "tertiary center*" or "referral centre*" or "referral center*" or centrali* or regionali*)).tw.

25 (patient* adj4 (transfer* or transport* or travel* or move* or moving or continuity or transition* or hando* or journey* or arriv*)).tw.

26 ((transfer* or transport* or travel* or transition* or hando* or journey* or arriv*) adj4 (quick* or delay* or slow* or fast* or speed* or time* or length* or duration or mode)).tw.

27 ((interfacilit* or inter facilit* or intrafacilit* or intra facilit* or inter hospital* or interhospital* or intrahospital* or intra hospital*) adj4 (transfer* or travel* or move* or moving)).tw.

28 Time-to-treatment/

29 "time to treatment".tw.

30 "door to treatment".tw.

31 antifibrinolytic agents/

32 (antifibrinoly* or antiplasmin*).tw.

33 ((plasmin or fibrinoly*) adj4 inhibitor*).tw.

34 Tranexamic Acid/

35 ((tranexam* or tranex-am* or tranex am* or tranexan* or tranex-an* or tranex an*) adj4 acid*).tw.

36 TXA.tw.

37 or/15-36

38 14 and 37

39 animals/ not humans/

40 38 not 39

41 limit 40 to english language

Health Economics literature search strategy

Sources searched to identify economic evaluations

- NHS Economic Evaluation Database – NHS EED (Wiley) last updated Dec 2014
- Health Technology Assessment Database – HTA (Wiley) last updated Oct 2016
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

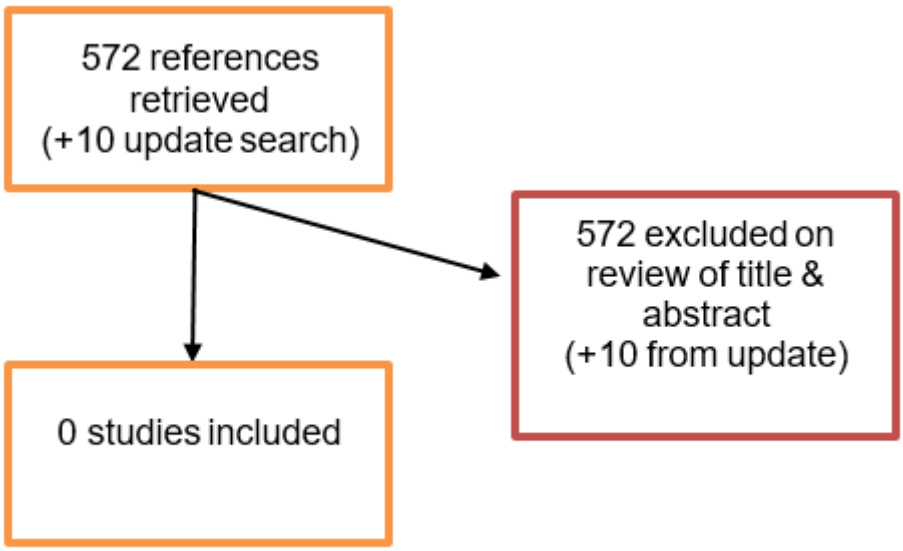
Search filters to retrieve economic evaluations and quality of life papers were appended to the population and intervention terms to identify relevant evidence. Searches were not undertaken for qualitative RQs. For social care topic questions additional terms were added. Searches were re-run in September 2017 where the filters were added to the population terms.

Health economics search strategy

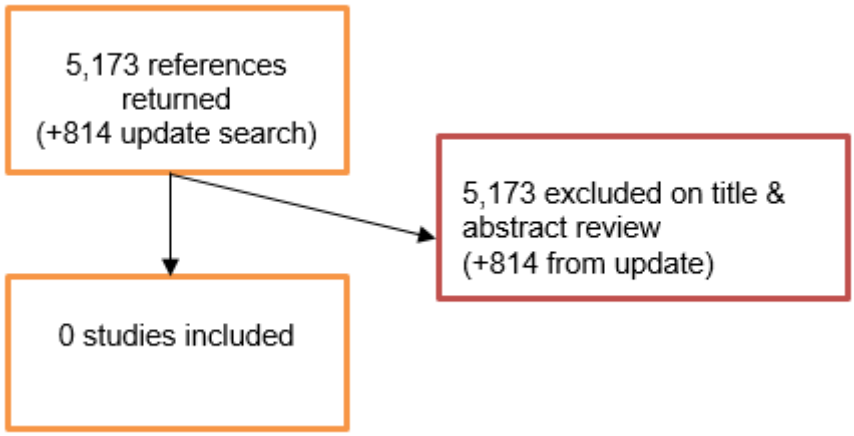
Medline Strategy
Economic evaluations 1 Economics/ 2 exp "Costs and Cost Analysis"/ 3 Economics, Dental/ 4 exp Economics, Hospital/ 5 exp Economics, Medical/ 6 Economics, Nursing/ 7 Economics, Pharmaceutical/ 8 Budgets/ 9 exp Models, Economic/ 10 Markov Chains/ 11 Monte Carlo Method/ 12 Decision Trees/ 13 econom*.tw. 14 cba.tw. 15 cea.tw. 16 cua.tw. 17 markov*.tw. 18 (monte adj carlo).tw. 19 (decision adj3 (tree* or analys*)).tw. 20 (cost or costs or costing* or costly or costed).tw. 21 (price* or pricing*).tw. 22 budget*.tw. 23 expenditure*.tw. 24 (value adj3 (money or monetary)).tw. 25 (pharmacoeconomic* or (pharmaco adj economic*)).tw. 26 or/1-25 Quality of life 1 "Quality of Life"/ 2 quality of life.tw. 3 "Value of Life"/

Medline Strategy
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly* or qald* or qale* or qtime*).tw.
7 disability adjusted life.tw.
8 daly*.tw.
9 Health Status Indicators/
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health* year* equivalent*.tw.
19 utilit*.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili*.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble*.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

Appendix C – Clinical evidence study selection



Appendix D – Economic evidence study selection



Appendix E – Excluded studies

Clinical studies

No full text papers were retrieved. All studies were excluded at review of titles and abstracts.

Economic studies

No full text papers were retrieved. All studies were excluded at review of titles and abstracts.

Appendix F – Research recommendations

Research recommendation	Does tranexamic acid improve survival in people who are having repair (EVAR or open surgical repair) of a ruptured AAA?
Population	People with a confirmed ruptured abdominal aortic aneurysm who are expected to undergo emergency aneurysm repair
Intervention(s)	Tranexamic acid (administered during transfer or upon arrival at a regional vascular service)
Comparator(s)	Placebo, or no intervention
Outcomes	• Perioperative morbidity and mortality • Bleeding/need for transfusion • Myocardial infarction • Renal failure • Adverse effects of intervention – stroke, acute limb ischaemia, venous thromboembolism • Quality of life • Resource use, including of intensive care unit stay, and cost
Study design	Randomised controlled trial

Potential criterion	Explanation
Importance to patients, service users or the population	Tranexamic acid is used to reduce blood loss in major trauma, postpartum bleeding and surgery. As a result, it could benefit people with a ruptured AAA. By slowing down blood loss from a ruptured aneurysm, the use of tranexamic acid could give emergency services more time to transfer a patient to regional vascular services, and regional vascular services more time to repair the ruptured aneurysm.
Relevance to NICE guidance	Medium priority: no recommendations were made in this guideline due to a lack of evidence, and further research would allow for recommendations to be possible in future guideline updates.
Current evidence base	No evidence was found that assessed the efficacy of tranexamic acid for increasing survival of people with ruptured AAA.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	There is a sufficiently large and well defined population available that multicentre randomised controlled trials in this area should be feasible.

Appendix G – Glossary

Abdominal Aortic Aneurysm (AAA)

A localised bulge in the abdominal aorta (the major blood vessel that supplies blood to the lower half of the body including the abdomen, pelvis and lower limbs) caused by weakening of the aortic wall. It is defined as an aortic diameter greater than 3 cm or a diameter more than 50% larger than the normal width of a healthy aorta. The clinical relevance of AAA is that the condition may lead to a life threatening rupture of the affected artery. Abdominal aortic aneurysms are generally characterised by their shape, size and cause:

- Infrarenal AAA: an aneurysm located in the lower segment of the abdominal aorta below the kidneys.
- Juxtarenal AAA: a type of infrarenal aneurysm that extends to, and sometimes, includes the lower margin of renal artery origins.
- Suprarenal AAA: an aneurysm involving the aorta below the diaphragm and above the renal arteries involving some or all of the visceral aortic segment and hence the origins of the renal, superior mesenteric, and celiac arteries, it may extend down to the aortic bifurcation.

Abdominal compartment syndrome

Abdominal compartment syndrome occurs when the pressure within the abdominal cavity increases above 20 mm Hg (intra-abdominal hypertension). In the context of a ruptured AAA this is due to the mass effect of a volume of blood within or behind the abdominal cavity. The increased abdominal pressure reduces blood flow to abdominal organs and impairs pulmonary, cardiovascular, renal, and gastro-intestinal function. This can cause multiple organ dysfunction and eventually lead to death.

Cardiopulmonary exercise testing

Cardiopulmonary Exercise Testing (CPET, sometimes also called CPX testing) is a non-invasive approach used to assess how the body performs before and during exercise. During CPET, the patient performs exercise on a stationary bicycle while breathing through a mouthpiece. Each breath is measured to assess the performance of the lungs and cardiovascular system. A heart tracing device (Electrocardiogram) will also record the hearts electrical activity before, during and after exercise.

Device migration

Migration can occur after device implantation when there is any movement or displacement of a stent-graft from its original position relative to the aorta or renal arteries. The risk of migration increases with time and can result in the loss of device fixation. Device migration may not need further treatment but should be monitored as it can lead to complications such as aneurysm rupture or endoleak.

Endoleak

An endoleak is the persistence of blood flow outside an endovascular stent - graft but within the aneurysm sac in which the graft is placed.

- Type I – Perigraft (at the proximal or distal seal zones): This form of endoleak is caused by blood flowing into the aneurysm because of an incomplete or ineffective seal at either end of an endograft. The blood flow creates pressure within the sac and significantly increases the risk of sac enlargement and rupture. As a result, Type I endoleaks typically require urgent attention.

- Type II – Retrograde or collateral (mesenteric, lumbar, renal accessory): These endoleaks are the most common type of endoleak. They occur when blood bleeds into the sac from small side branches of the aorta. They are generally considered benign because they are usually at low pressure and tend to resolve spontaneously over time without any need for intervention. Treatment of the endoleak is indicated if the aneurysm sac continues to expand.

- Type III – Midgraft (fabric tear, graft dislocation, graft disintegration): These endoleaks occur when blood flows into the aneurysm sac through defects in the endograft (such as graft fractures, misaligned graft joints and holes in the graft fabric). Similarly to Type I endoleak, a Type III endoleak results in systemic blood pressure within the aneurysm sac that increases the risk of rupture. Therefore, Type III endoleaks typically require urgent attention.

- Type IV– Graft porosity: These endoleaks often occur soon after AAA repair and are associated with the porosity of certain graft materials. They are caused by blood flowing through the graft fabric into the aneurysm sac. They do not usually require treatment and tend to resolve within a few days of graft placement.

- Type V – Endotension: A Type V endoleak is a phenomenon in which there is continued sac expansion without radiographic evidence of a leak site. It is a poorly understood abnormality. One theory that it is caused by pulsation of the graft wall, with transmission of the pulse wave through the aneurysm sac to the native aneurysm wall. Alternatively it may be due to intermittent leaks which are not apparent at imaging. It can be difficult to identify and treat any cause.

Endovascular aneurysm repair

Endovascular aneurysm repair (EVAR) is a technique that involves placing a stent –graft prosthesis within an aneurysm. The stent-graft is inserted through a small incision in the femoral artery in the groin, then delivered to the site of the aneurysm using catheters and guidewires and placed in position under X-ray guidance.

- Conventional EVAR refers to placement of an endovascular stent graft in an AAA where the anatomy of the aneurysm is such that the ‘instructions for use’ of that particular device are adhered to. Instructions for use define tolerances for AAA anatomy that the device manufacturer considers appropriate for that device. Common limitations on AAA anatomy are infrarenal neck length (usually >10mm), diameter (usually ≤30mm) and neck angle relative to the main body of the AAA

- Complex EVAR refers to a number of endovascular strategies that have been developed to address the challenges of aortic proximal neck fixation associated with complicated aneurysm anatomies like those seen in juxtarenal and suprarenal AAAs. These strategies include using conventional infrarenal aortic stent grafts outside their

'instructions for use', using physician-modified endografts, utilisation of customised fenestrated endografts, and employing snorkel or chimney approaches with parallel covered stents.

Goal directed therapy

Goal directed therapy refers to a method of fluid administration that relies on minimally invasive cardiac output monitoring to tailor fluid administration to a maximal cardiac output or other reliable markers of cardiac function such as stroke volume variation or pulse pressure variation.

Post processing technique

For the purpose of this review, a post-processing technique refers to a software package that is used to augment imaging obtained from CT scans, (which are conventionally presented as axial images), to provide additional 2- or 3-dimensional imaging and data relating to an aneurysm's, size, position and anatomy.

Permissive hypotension

Permissive hypotension (also known as hypotensive resuscitation and restrictive volume resuscitation) is a method of fluid administration commonly used in people with haemorrhage after trauma. The basic principle of the technique is to maintain haemostasis (the stopping of blood flow) by keeping a person's blood pressure within a lower than normal range. In theory, a lower blood pressure means that blood loss will be slower, and more easily controlled by the pressure of internal self-tamponade and clot formation.

Remote ischemic preconditioning

Remote ischemic preconditioning is a procedure that aims to reduce damage (ischaemic injury) that may occur from a restriction in the blood supply to tissues during surgery. The technique aims to trigger the body's natural protective functions. It is sometimes performed before surgery and involves repeated, temporary cessation of blood flow to a limb to create ischemia (lack of oxygen and glucose) in the tissue. In theory, this "conditioning" activates physiological pathways that render the heart muscle resistant to subsequent prolonged periods of ischaemia.

Tranexamic acid

Tranexamic acid is an antifibrinolytic agent (medication that promotes blood clotting) that can be used to prevent, stop or reduce unwanted bleeding. It is often used to reduce the need for blood transfusion in adults having surgery, in trauma and in massive obstetric haemorrhage.