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Guideline on antiplatelet and anticoagulation management in cardiac surgery

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Summary

This document presents a professional view of evidence-based recommendations around the issues of antiplatelet and anticoagulation management in cardiac surgery. It was prepared by the Audit and Guidelines Committee of the European Association for Cardio-Thoracic Surgery (EACTS). We review the following topics: evidence for aspirin, clopidogrel and warfarin cessation prior to cardiac surgery; perioperative interventions to reduce bleeding including the use of aprotinin and tranexamic acid; the use of thromboelastography to guide blood product usage; protamine reversal of heparin; the use of factor VIIa to control severe bleeding; anticoagulation after mechanical, tissue valve replacement and mitral valve repair; the use of antiplatelets and clopidogrel after cardiac surgery to improve graft patency and reduce thromboembolic complications and thromboprophylaxis in the postoperative period. This guideline is subject to continuous informal review, and when new evidence becomes available. The formal review date will be at 5 years from publication (September 2013).

Keywords: Evidence-based medicine; Guidelines; Thoracic surgery; Antiplatelet therapy; Anticoagulation therapy

1. Introduction

Antiplatelet and anticoagulant therapy is a key part of the management of patients undergoing cardiac surgery. Most heart operations depend on cardiopulmonary bypass with systemic heparinisation [1] and, postoperatively, every patient's thrombotic and haemorrhagic tendency must be carefully managed.

In recent years, the costs and availability of blood and blood products have changed dramatically. Cardiothoracic surgery uses 5% of all donated blood in the UK and 10% of blood in the USA. The cost of donor blood and blood products has increased and availability is often critically reduced. In addition to this shortage, there is concern over blood-borne infection, including new variant Creutzfeld-Jacob disease [2,3]. For these reasons it is paramount that cardiac surgeons make every effort to minimise the usage of blood and blood product usage in their patients.

This guideline will present and summarise the evidence for a range of therapeutic interventions with the aim of helping cardiac surgeons to optimise the usage of blood and blood products and to move away from current, highly variable practice [4,5] towards a unified, evidence-based approach to the perioperative use of antiplatelet and anticoagulant therapy.

The European Association for Cardio-Thoracic Surgery acknowledges the guideline development work performed by other institutions and in particular the work of the European Society for Cardiology (ESC) guidelines in the area of management of patients after valve surgery [6,7] and the Society of Thoracic Surgeons (STS) guidelines on perioperative blood transfusion and blood conservation [8].

2. Scope of the guideline

This guideline covers antiplatelet and anticoagulation management in relation to cardiac surgery, including cardiopulmonary bypass, reversal of heparinisation, assess-

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ment and treatment of postoperative coagulopathy and anticoagulation and antiplatelet treatment after discharge from hospital.

3. Methodology of the guideline

This guideline comprises several novel aspects of methodology in its derivation. Many guidelines are based on a single systematic review and multiple clinical questions are then answered on the basis of the papers found from this one review. In contrast, we felt that it was important to perform a full literature review for every single question addressed in order to maximise the robustness of the guideline. We used a structured systematic review protocol named 'Best Evidence Topics' to construct each review, where the search strategy, results of the search and a full appraisal of all papers are published in a structured format. The details of this protocol are described in the Interactive Cardiovascular and Thoracic Surgery (ICVTS) [9]. Guidelines often fall short of expectations due to a failure to consult those clinicians who are most likely to use them. For this guideline, all the literature reviews have already been published in full in the ICVTS. Topics were published online and clinicians were able to post comments on them over a 2-month period. These comments were then published together with the full paper in the ICVTS and are now available to all readers in full text online at www.icvts.org.

4. Levels of evidence and grading of recommendations

These guidelines assess individual studies according to the recommendations of the Oxford Centre for Evidence Based Medicine [9,10]. Briefly, a level 1 paper is a randomised controlled trial (RCT) or a meta-analysis of RCTs, a level 2 paper is a cohort study, a level 3 paper is a case-controlled study or a small cohort study, and a level 4 paper is an experimental study. The 'b' suffix then implies that the paper is one original article at this level and the 'a' suffix implies that the paper is a systematic review or meta-analysis of articles at that level. Once recommendations are made, they are graded according to the quality of papers used to come to our conclusion.

Grade A evidence	based on multiple level 1a or level 1b papers
Grade B evidence	based on multiple level 2a/2b papers or individual level 1a/1b papers
Grade C evidence	based on multiple level 3a/3b papers or individual level 2a/2b papers
Grade D evidence	based on individual level 3a/3b papers or level 4 papers
Grade E evidence	based on expert consensus in the absence of acceptable papers

5. Preoperative recommendations

5.1. Clopidogrel cessation before urgent cardiac surgery

Evidence was sought for whether clopidogrel should be stopped prior to urgent cardiac surgery. This search is fully documented in the ICVTS [11], together with a summary of all identified papers. We found 143 papers and all major international guidelines were also included. Of these, 14 presented the best evidence to answer the clinical question.

There are two questions to consider when deciding on the timing of surgery in a patient on clopidogrel. Does clopidogrel cause an increase in bleeding complications and their sequelae? Does withholding clopidogrel in these high-risk patients expose them to an increase in thrombotic complications prior to surgery?

In answer to the first question, a meta-analysis of 11 cohort studies in 2004 [12] combined papers providing data on patients who either did or did not receive clopidogrel. There was a mean increase in blood loss of 323 ml, a six-fold increase in the odds of re-exploration, an increase in adverse events and ventilation time, but no difference in hospital length of stay or mortality. It must be remembered that the 11 cohort studies do not take into account the fact that the clopidogrel groups are likely to be a higher risk group of patients.

Since this meta-analysis many additional studies have reported. Kapetanakis et al. [13,14] compared 281 patients having clopidogrel before off-pump surgery to 1291 patients who did not have clopidogrel. There were no differences in mean blood loss or mortality, but there was a 2—3 times increase in the odds of transfusion and a five-fold increase in the odds of re-exploration. In other studies on clopidogrel before CABG, Yende and Wunderink [15] showed an increase in re-exploration rate, Hongo et al. [16] showed an increased re-exploration rate and a 50% increase in chest drainage, Englberger et al. [17] showed an increase in re-exploration, red cell usage and a doubling in chest drain output, Leong et al. [18] showed a modest increase in chest drainage and an increase in blood transfusion but not an increase in re-exploration. Ascione [19] in a 1-year cohort study of in-patient referrals found that there was a three-fold increase in the re-exploration rate, a significantly increased mortality and more chest drainage. In contrast to these studies Karabulut et al. [20] found no increase in chest drainage, re-exploration or red cell transfusion, although the study included 1628 patients of whom only 48 were on clopidogrel. Many more similar smaller cohort studies with similar findings are not listed here. Thus in answer to the first part of our question, clopidogrel is associated with more blood product usage, a 2—5-fold increase in the risk of re-exploration and 30—100% increase in the chest drain blood loss.

The second question addresses the importance of continuing clopidogrel in these patients. The CURE [21] study in 2004 was a double-blind RCT of 12,562 patients who had suffered a non-ST elevation myocardial infarction (NSTEMI). It showed that death, myocardial infarction (MI) or stroke occurred in 9.3% of patients randomised to clopidogrel and aspirin, compared to 11.4% in the aspirin alone group. In the subgroup of 2072 patients who subsequently underwent CABG, the overall benefits of clopidogrel were maintained by the end of the study. In addition, there was a trend to fewer complications prior to surgery whilst awaiting the intervention (5.6% vs 6.7%; number needed to treat (NNT) 90). For patients continuing clopidogrel to within 5 days, preoperatively, there was a non-significant excess in re-exploration and 9.6% of clopidogrel

patients versus 6.3% of placebo patients had a major bleeding event. The CURE authors recommend that it is safe for all NSTEMI patients to be started on clopidogrel and aspirin on admission, but that clopidogrel should be stopped 5 days before surgery.

The CREDO trial [22] showed benefits for clopidogrel loading 6 h before percutaneous intervention (PCI) and continuing for up to 1 year in a RCT of 2116 patients with no significant difference in bleeding complications, although there was a high incidence of major bleeding in the subset of patients proceeding to CABG.

The CLARITY-TIMI-28 [23] trial randomised 3491 patients who had suffered MI within 12 h to clopidogrel or placebo. This showed a 7% absolute risk reduction for death, MI or stroke with clopidogrel. A small group of 136 patients who proceeded to CABG did not have an excess risk of bleeding although neither blood loss nor blood product usage were reported in detail. The ACC/AHA guidelines [24] of 2002 on the management of NSTEMI and unstable angina recommend immediate administration of clopidogrel if PCI is planned. They furthermore recommend cessation of clopidogrel for 5—7 days prior to surgery, giving this a grade B level of evidence.

The PCI-CURE study [25] provides important data when considering withholding clopidogrel for patients before CABG: 1313 patients received clopidogrel prior to PCI with 1345 placebo controls in this double-blind RCT. The mean wait for PCI was 6 days and the incidence of MI while awaiting intervention was 5.1% in the placebo group but only 3.6% in the clopidogrel group ($p = 0.04$, NNT 66 to prevent an MI pre PCI).

Thus there is a clear benefit in commencing clopidogrel for patients suffering an MI, NSTEMI or shortly to require PCI, and this therapy should not be withheld even if a possible future CABG is possible. However, once it is decided that CABG is required, the ACC/AHA guidelines [24], the STS guidelines [8], the meta-analysis and multiple cohort studies would recommend cessation of clopidogrel for 5—7 days. The CURE study and its sub-analyses show that cessation of clopidogrel in these patients for this time period is associated with a 1% increase in the risk of MI.

Recommendation:
Patients who need urgent cardiac surgery should stop clopidogrel 5—7 days before surgery if their clinical condition allows. The benefit in reducing perioperative blood loss, risk of re-exploration and blood product usage is at the expense of a 1% increase in the risk of myocardial infarction while awaiting surgery.
(Grade B recommendation based on individual level 1a and 1b studies)

5.2. Cessation of warfarin and aspirin before cardiac surgery

Several guidelines address the issue of cessation of warfarin and aspirin before non-cardiac surgery. These guidelines can also be applied to cardiac surgical patients.

The American Heart Association [26,27] recommends that in patients at a relatively low risk of thrombosis such as those with a bileaflet mechanical aortic valve with no additional risk factors, warfarin should be stopped 48—72 h prior to surgery so that the INR drops to below 1.5 and heparin is unnecessary prior to surgery. In patients at high risk of thrombosis, defined as those with a mechanical mitral valve replacement or a mechanical aortic valve replacement with additional risk factors, therapeutic doses of intravenous heparin should be started when the INR falls below 2.0 (typically 48 h before surgery), stopped 4—6 h before the procedure, restarted as early after surgery as bleeding stability allows, and continued until the INR is again therapeutic with warfarin therapy (level of evidence B).

The British Society of Haematology [28,29] recommends that warfarin be stopped at least 3 days before surgery, with higher risk patients such as those with a mechanical valve receiving intravenous heparin when the INR falls below the therapeutic range.

The American College of Chest Physicians [30] documents the results of pertinent studies but states: 'until clinical trials that specifically target the perioperative management of patients requiring vitamin K antagonist anticoagulation before surgical procedures are performed, treatment of such patients will remain controversial and we are not making a recommendation.'

With regard to aspirin cessation before cardiac surgery, the ACC/AHA guidelines [31] recommend cessation of aspirin for 7—10 days before elective CABG, due to the increased risk for transfusion, prolonged wound closure time, and a four-fold increase in early re-operation for bleeding [32]. This does not apply to patients who may have an acute coronary syndrome where the benefits may outweigh these risks. The STS also recommends cessation of aspirin in purely elective patients without acute coronary syndromes 2—3 days before surgery in the expectation that rates of blood transfusion will be reduced.

Recommendation:
Patients on warfarin before cardiac surgery should be managed in a similar manner to those undergoing major non-cardiac surgery. Warfarin should be stopped 2—4 days before surgery and patients at higher risk of thrombosis should receive intravenous heparin once the INR becomes sub-therapeutic.
(Grade B recommendation based on multiple level 2a and 2b studies)
Patients should stop aspirin 2—10 days before elective cardiac surgery in order to reduce perioperative blood loss. Patients undergoing urgent cardiac surgery with an acute coronary syndrome should continue aspirin up to the day of surgery.
(Grade B recommendation based on multiple level 2a and 2b studies)

6. Perioperative interventions to reduce bleeding and blood product usage

6.1. Aprotinin

Evidence was sought for the efficacy of aprotinin in reducing perioperative bleeding and whether there are adverse side effects that may affect renal function, graft patency or mortality after CABG. A search for the evidence surrounding the effect of graft patency is fully documented in the ICVTS [33], together with a summary of all identified papers.

In addition the STS provide a recent review in this area together with recommendations [8], and more recently a meta-analysis has been published in Circulation in 2007 [34] in the light of papers by Mangano et al. [35,36]. However on the 5th of November 2007, the FDA suspended aprotinin in the light of the BART study [37] being stopped early due to safety concerns [38] and the MRHA have since suspended the licensed use of aprotinin in the UK from the 7th of December 2007 (www.mrha.gov.uk).

The IMAGE study [39] of 870 patients in 13 centres found a higher occlusion rate of saphenous grafts after aprotinin use, with 15% of patients having an occlusion in the aprotinin group, compared to 11% in the control group. Although the study was an RCT, the authors performed a risk adjustment and concluded that after allowing for risk factors there was no difference in the occlusion rate. In another study, Laub et al. [40] also found a 30% occlusion rate in the aprotinin group and none in the control group but the study numbers were small. In the remaining studies reporting vein graft patency no significant differences were found although Lemmer et al. [41], Bidstrup et al. [42] and van der Meer et al. [43] found non-significant trends towards worse patency rates with aprotinin.

Due to the varying findings of these studies we combined their data by meta-analysis using a random effects model. We found that a significant increase in the odds of occlusion was 1.52 [1.13—2.03]. We therefore conclude that there is a small but significant increase in graft occlusion in patients undergoing CABG with aprotinin.

Of note, the amount of blood loss and blood product usage is significantly lower in the patients receiving full dose aprotinin in all the studies. The Cochrane review combined data from 61 studies and found a 30% reduction in blood transfusion, less blood drainage and a significantly lower incidence of re-operation due to bleeding [44].

The 2007 STS guidelines [8] state that high-dose aprotinin is indicated to reduce the number of patients requiring transfusion, reduce total blood loss and to limit re-exploration. They give this a grade A level of evidence recommendation but warn that high dose aprotinin may increase the incidence of renal dysfunction. They also recommend that low dose aprotinin reduces blood loss and blood transfusion with the same grading of the evidence. Of note the Food and Drug Administration also issued a safety alert suggesting that only patients for whom the benefits of aprotinin outweighed the risks in terms of renal dysfunction and hypersensitivity should receive the drug (www.fda.gov). This was based on a meta-analysis and update in 2006 of 31 studies in this area. They found that the incidence of renal dysfunction was 8.4% in patients receiving placebo and 12.9% in those receiving aprotinin. However, the incidence of renal failure was not significantly different [45,46]. The meta-analysis update [45] has now been fully published by Brown et al. in Circulation [34] after the FDA alert, comparing aprotinin, tranexamic acid and ε-aminocaproic acid. They identified 138 randomised trials from which they extracted data on eight clinical outcomes. Aprotinin significantly reduced the incidence of re-exploration (RR 0.49). High dose aprotinin reduced total blood loss by mean 184 ml (95% CI −256 to −112) compared to tranexamic acid but there was no significant difference of low dose aprotinin compared to tranexamic acid. There were no differences between these three agents in terms of mortality, stroke, myocardial infarction or renal failure but high dose aprotinin significantly increased the risk of renal dysfunction from 8.4% to 12.9% which is a number indicating harm to 22 patients. Renal dysfunction was defined as an increase of more than 0.5 mg/dl in serum creatinine. Data were not extracted on vein graft patency in this study.

Major concerns regarding aprotinin were first highlighted by Mangano et al. [35,36] who reported significantly increased adverse outcomes in 1295 patients who received aprotinin within a cohort of 4374 patients undergoing 'primary' (CABG only) or 'complex' (all other) surgery. Using logistic regression analysis and propensity scoring techniques they reported that the risk of stroke was increased by 181% and the risk of MI by 55% in 'primary' surgery, and the incidence of renal failure doubled in both 'primary' and 'complex' surgery. They also noted dose-response aprotinin effects and commented that as other antifibrinolytics such as tranexamic acid and ε-aminocaproic acid had similar blood-sparing benefits without adverse effects, continued use of aprotinin was 'not prudent'. Whilst this study has several weaknesses, including a risk of bias from systemic sampling across multiple institutions with inherently embedded practices, and higher risk factors for some adverse outcomes within the aprotinin group, it has resulted in considerable debate and may lead to some reappraisal of the role of aprotinin, particularly in uncomplicated 'primary' surgery.

An independently funded, randomised clinical trial with three study groups (aprotinin, tranexamic acid and ε-aminocaproic acid) was set up in Canada. The BART study aimed to enrol 2970 patients specifically to answer many of the safety concerns raised by Mangano et al. [36], the FDA and others [37,47]. However on the 19th of October 2007, this study was stopped early due to an increase in mortality in the aprotinin group. The Data Safety Monitoring Board reported that:

1. The 30-day mortality in the aprotinin group had nearly reached conventional statistical significance at the interim analysis, when compared to either ε-aminocaproic acid or tranexamic acid.
2. A trend toward increased mortality in the aprotinin group had been observed throughout the study.
3. The use of aprotinin was associated with less serious bleeding than either of the comparator drugs; however, more deaths due to haemorrhage had been observed among patients receiving aprotinin.

4. The DSMB concluded that continued enrolment of patients into the aprotinin group was unlikely to significantly change the study findings.

This announcement is by the FDA [38] and it is likely that further announcements will be made in the near future as the BART data is further analysed and then published.

Recommendation:
Aprotinin reduces blood loss and the need for blood transfusion in cardiac surgery; however there is a proven association with postoperative renal dysfunction and a probable association with increased mortality after a large randomised controlled trial has been stopped early due to these concerns. Routine use of aprotinin in cardiac surgery is not recommended, but use in patients at particularly high risk of bleeding may be still be justified. This is the subject of current FDA and MRHA review, and these recommendations may change in the near future.
(Grade A recommendation based on level 1a and 1b studies)

6.2. Tranexamic acid to reduce perioperative bleeding

Evidence was sought for the efficacy of tranexamic acid in reducing perioperative bleeding and whether it may adversely affect graft patency after CABG. This search is fully documented in the ICVTS [48] together with a summary of all identified papers. We found 334 papers using the presented search strategy. A subsequent meta-analysis and a guideline were added on updating. From these papers, 14 represented the best evidence on this topic.

Two recent meta-analyses, 1 cohort study and 10 RCTs documented studies comparing tranexamic acid to either aprotinin or placebo with documentation of thrombotic complications. The meta-analysis by Fremes [49] in 1994 found only two papers on tranexamic acid and concluded that either ε-aminocaproic acid or tranexamic acid reduced bleeding by 30% with no increase in perioperative myocardial infarction.

The 2001 Cochrane review by Henry et al. [44] found 61 trials of aprotinin and 18 trials of tranexamic acid and found an absolute risk reduction in red blood cell transfusion of 20% with aprotinin and 17% with tranexamic acid with no difference in transfusion rates. They conclude that the evidence is much weaker for tranexamic acid but it may well be as effective as aprotinin.

The only study that highlighted anxiety over the safety of tranexamic acid was the cohort study by Ovrum et al. [50] published in 1993. Ovrum routinely used tranexamic acid until a patient had an acute thrombosis of all her grafts and adjacent native coronaries. He stopped using it and analysed the results of his next 100 patients compared to the previous 100. There had been five MIs with tranexamic acid but only one MI without tranexamic acid, which was not statistically significant. This is a retrospective, single-surgeon study, with potential bias introduced by the change in practice.

The largest RCT was by Casati et al. [51] who compared aprotinin to tranexamic acid in 1040 primary elective CABG patients. There was no difference in survival, bleeding, re-operation for bleeding, transfusion, perioperative MI, early re-operation for ischaemia, pulmonary embolism (PE) or neurological dysfunction although the number of events in each of these categories was small. The conclusion was that tranexamic acid was clinically as effective as aprotinin at a fraction of the cost.

Five RCTs compared tranexamic acid to placebo. Four of the five showed a reduction in bleeding rates. None of the studies investigated graft patency, but other outcome measures such as MI, PE, and neurological dysfunction were reported, and no concerns were raised about the safety of tranexamic acid. It is important to note that the incidence of thrombotic complications is low and, with the largest study having fewer than 150 patients, none of these studies are sufficiently powered to exclude the possibility of increased thrombotic complications. Thus it is clear that tranexamic acid reduces the incidence of postoperative bleeding, and only one cohort study has raised any concern over its safety in terms of thrombotic complications. No study has looked directly at vein graft patency after tranexamic acid. The STS guidelines state that tranexamic acid is indicated to reduce the rate of blood transfusion but that it is slightly less potent than full dose aprotinin and its safety profile is less well studied [8].

Recommendation:
Tranexamic acid reduces blood loss, requirement for blood transfusion, and the risk of re-operation for bleeding.
(Grade A recommendation based on level 1a and 1b studies)

No study has yet looked directly at vein graft patency with tranexamic acid, but equally no randomised studies have raised concerns over its safety.
(Grade B recommendation based on individual level 1b studies)

6.3. Topical tranexamic acid to reduce perioperative bleeding

Evidence was sought for the efficacy of topical tranexamic acid in reducing perioperative bleeding. This search is fully documented in the ICVTS [52] together with a summary of all identified papers. We found 511 papers using the presented search strategy. From these papers only one represented the best evidence on this topic. One abstract has not yet been published in full and was thus excluded [53]. Two additional RCTs were published after our search had been conducted [54,55]. Several other papers deal with the use of topical tranexamic acid after bladder, dental and gynaecological surgery but are probably of doubtful relevance to cardiac

surgery. The STS guidelines on blood conservation do not consider this topic [8].

In a double-blind RCT, De Bonis et al. [56] randomised 40 consecutive patients undergoing CABG to topical tranexamic acid or placebo. One gram of tranexamic acid was added to 100 ml of normal saline and poured into the sternotomy wound prior to closure. The mediastinal drains were clamped during closure, and the clamps were only removed after the operation had been completed. Placebo patients received 100 ml of normal saline. There was a 36% reduction in bleeding at 3 h and a 25% reduction at 24 h in the tranexamic acid group. However, the absolute differences were small with a mean blood loss of 485 ml in the tranexamic acid group and 641 ml in the placebo group. In addition, no reduction in the use of blood products was demonstrated. The second more recent study was by Abdul-Azm and Abdullah in 2006 [54] who randomised 100 patients to receive 2 g of tranexamic acid in 100 ml of saline into the pericardium prior to closure, or saline alone. Bleeding was reduced from a mean of 1208 ml to 733 ml, which was highly significant, and blood transfusion usage was also reduced. The third RCT by Yasim et al. [55] which was also the smallest, randomised 10 patients to topical aprotinin, topical tranexamic acid or controls. Mean blood loss for the aprotinin group was 384 ml, for tranexamic acid 393 ml, and for controls 502 ml. This was not statistically significant due to the small sample size.

In summary, one RCT demonstrates a small reduction in blood loss, a second more recent study demonstrates a larger reduction and a third study showed a non-significant trend towards reduction. Further RCTs should be performed (and could very easily be set up and conducted) prior to any reliance on topical tranexamic acid as a strategy to reduce postoperative bleeding.

> Recommendation:
> Topical tranexamic acid may reduce postoperative bleeding after cardiac surgery. Routine use is probably safe and may be effective, but further RCTs should be performed.(Grade B recommendation based on two level 1b studies)

6.4. Hepcon® for minimisation of blood and blood product usage

Evidence was sought for whether use of the Hepcon point-of-care coagulation monitor to optimise and monitor heparin and protamine dosage for cardiopulmonary bypass could decrease bleeding and blood and blood product requirements in adult patients undergoing cardiac surgery. This search is fully documented in the ICVTS (Aziz et al. [57]) together with a summary of all identified papers.

Altogether 680 papers were identified on Medline, and 879 on Embase using the reported search strategy. Two further relevant papers were found by hand searching of reference lists. Fourteen papers represented the best evidence on the topic.

Hepcon calculates heparin doses required for cardiopulmonary bypass by establishing the heparin dose response, measures heparin concentrations during bypass and calculates protamine doses based on residual heparin. Raymond et al. [58] validated it by comparing it to a lab-based anti-Xa assay which demonstrated that heparin concentration is a better guide than activated clotting time (ACT). Murray et al. found similar correlations [59]. A number of studies report that Hepcon use results in higher total heparin doses and lower protamine doses than conventional management [60—66]. This may be due to less coagulation system activation during cardiopulmonary bypass. Several studies have confirmed decreased coagulation system and inflammatory marker activation using Hepcon-guided therapy. Ohata et al. [67] demonstrated significantly lower interleukin-8 levels after CPB and protamine, and Shigeta et al. [61] noted that lower Hepcon-guided protamine doses were associated with better platelet function. Koster et al. [68] found that anti-Xa levels were significantly higher, and thrombin-antithrombin complexes, D-dimers, and neutrophil esterase levels lower in the Hepcon-managed group. In a subgroup of a 1995 study, Despotis et al. found significantly better preservation of clotting factors V and VIII, antithrombin III, and fibrinogen in the Hepcon group prior to protamine administration [62]. Several inflammatory markers were also significantly lower in the Hepcon group. They also found that patients who bled excessively had higher D-dimer levels and plasmin—antiplasmin complexes and lower factor V, X and platelet counts before protamine administration [63]. The clinical impact of these findings remains unclear. Neither Yamanishi nor Sakurada found excessive bleeding in their Hepcon groups despite larger heparin and smaller protamine doses [60,65]. Shigeta et al. similarly observed no difference in bleeding although Hepcon management improved platelet preservation [61]. In a larger study investigating haemostatic-inflammatory activation, Koster reported no difference related to Hepcon in blood loss or blood product requirement [68]. Ohata found less blood transfusion when protamine was given according to Hepcon-measured heparin concentration [67]. Despotis found that Hepcon use was associated with significantly less bleeding in the first 4 h, more rapid chest closure, and decreased requirement for 'haemostatic intervention' [62]. Whilst red cell use just failed to reach significance, use of fresh frozen plasma (FFP), platelets and cryoprecipitate requirements was significantly less in the Hepcon group. More recently, Avidan compared Hepcon and other point-of-care tests to laboratory tests. Bleeding was similar, but blood and blood component requirements were less in point-of-care tests [69]. In contrast, Beholz et al. reported more bleeding using Hepcon leading to increased autologous transfusion requirement but no additional blood products [66], and a retrospective study by Newsome compared Hepcon and Rapidpoint® coagulation monitors and reported more bleeding and requirement for both FFP and red cells in the Hepcon group, which was attributed to the larger heparin dose [64]. Other protamine titration monitors are available. The Hemocron RxDx® device quantifies heparin and protamine doses on a patient-specific basis. Its use also leads to larger heparin and smaller protamine doses but Shore-Lesserson demonstrated no impact on bleeding or blood, FFP or platelet transfusion requirement [70]. The STS guidelines [8] consider this subject and conclude

that it is not unreasonable to use methods to lower the heparin to protamine ratio at the end of CPB, giving this a grade B level of evidence.

Recommendation:
Hepcon monitoring is associated with higher heparin and lower protamine doses and may decrease activation of the coagulation and inflammatory cascades. Some studies have shown this may decrease postoperative bleeding and blood product requirement. Its routine use is not unreasonable but larger trials are needed to investigate this further.
(Grade B recommendation based on level 1b and 2b studies)

7. Postoperative interventions to reduce bleeding and blood product usage

7.1. Thromboelastography to guide blood and blood product usage

Evidence was sought whether use of thromboelastography (TEG) could predict and decrease bleeding and blood and blood product requirements in adult patients undergoing cardiac surgery. This search is fully documented in the ICVTS [71], together with a summary of all identified papers. We found 170 papers using the reported search strategy of which 14 represented the best evidence on the topic.

Abnormal TEG data may predict patients who will bleed. Speiss et al. [72] found that TEG correlated well with ACT and coagulation profiles and whilst no coagulation test was consistently specific, the TEG was the most accurate predictor of bleeding. Ereth et al. [73] studied a 'platelet-activated clotting test' (PACT®), ACT, clotting studies and TEG. PACT sensitivity and specificity was comparable to conventional coagulation tests in predicting blood loss but TEG was superior. Essell et al. [74] found that the bleeding time and platelet count had similar sensitivity but less specificity when compared to TEG. Patients with an abnormal TEG were at increased risk of bleeding and excessive bleeding in the face of a normal TEG implied a surgical cause. Ti et al. [75] found moderate correlation between TEG parameters, total blood loss and requirements for FFP or platelets in bleeders. Other studies did not find the TEG to be a useful predictor of blood loss. Nuttall et al. [76] reported that TEG values had a low sensitivity and specificity in predicting bleeders. Dorman et al. [77] compared preoperative coagulation screens to ACT and TEG as predictors of blood loss but found no significant relationship between any TEG variable and blood losses.

A number of studies have used TEG to guide transfusion management. Avidan et al. [69] compared TEG to a laboratory-based algorithm and concluded that despite similar bloodloss, blood and blood product usage were significantly greater in the laboratory group. Speiss et al. [78] analysed 1079 patients before and after the introduction of TEG as part of an overall transfusion management strategy and found significantly less re-exploration and less use of all blood and blood components except cryoprecipitate. However, this study may have been biased by the Hawthorne effect. (The improvement in results that may be found just by monitoring a process.)

Two RCTs have been performed. Shore-Lesserson et al. [79] compared TEG-based and conventional protocols to manage postoperative bleeding. Whilst there was no significant difference in blood loss between the groups, blood and blood component therapy was significantly less in the TEG than the conventional group. However the TEG protocol did have more options than the conventional protocol and also partly depended on laboratory tests. In addition, blood products were ordered on the basis of a TEG taken at rewarming on cardiopulmonary bypass and given in the presence of continued bleeding following protamine, whereas the conventional group awaited post-protamine tests to dictate intervention. This inevitably meant earlier intervention in the TEG group. Royston and Von Kier [80] studied 60 patients who had undergone complex surgery comparing their actual blood and blood product use to a predicted usage derived from a TEG-based algorithm. 'Predicted' blood and blood product transfusion was significantly less than 'actual' transfusion. They subsequently used this algorithm comparing it to conventional management in a further 60 patients. Again they demonstrated significantly less blood and blood product usage in the TEG-based group compared to the conventional 'clinician-directed' group with no excessive mediastinal bleeding. However this study was designed to identify TEG evidence of coagulation before physical evidence of microvascular bleeding and the authors acknowledge the fact that their protocol allowed much earlier intervention in the active than the control limb.

A recent review by Samama and Ozier [81] has raised concerns that TEG remains an unvalidated technique which fails to achieve the stringent standard quality control procedures essential in lab-based tests, citing absence of a formal standard operating procedure taking into account factors such as gender and pregnancy differences, stability of blood samples, and sampling site. There is also no standardised technique and multiple modifications have been described. Several studies acknowledge that TEG facilitates earlier intervention than standard coagulation tests [69,79,80] thus making true comparisons difficult. Samama and Ozier conclude by suggesting that extended collaborative studies involving haematologists are required to evaluate and validate TEG further [81].

Recommendation:
Thromboelastography may be used to guide transfusion in the postoperative period and studies have demonstrated a reduction in blood and blood product usage if used in conjunction with a treatment algorithm. Further studies are required before thromboelastography can be recommended as the standard of care for post-operative transfusion management.
(Grade B recommendation based on level 2b studies)

7.2. Is there a protamine anticoagulant effect after cardiac surgery?

Evidence was sought as to whether large doses of protamine cause increased bleeding after cardiac surgery. This search is fully documented in the ICVTS [82] together with a summary of all identified papers. We found 268 papers using the reported search, of which five presented the best evidence to answer the clinical question.

Studies from Carr and Carr [83] and Moshizuki et al. [84] provide convincing evidence that when the ratio of protamine (in mg/l) to heparin (in unit/ml) is above 5:1, platelet aggregation and function are impaired. In addition, Moshizuki et al. demonstrated that at ratios above 2.6:1 the ACT significantly increases. Interestingly, Butterworth et al. [85] showed that protamine is eliminated in 20—30 min in physiological situations and Gundry et al. [86] provided evidence that prolonged ACT correlates poorly with the presence of free heparin. An indication of how an ACT-based protocol may affect bleeding is given by Jobes et al. [87] who showed that using protamine response tests to guide dosage reduced mediastinal blood loss by 50%. The STS guidelines [8] state that it is not unreasonable to use protamine titration or empiric low-dose regimens to reduce bleeding and blood transfusion requirements although they do not address the possibility of rebound bleeding at higher doses of protamine (level of evidence B).

> Recommendation:
> Excessive doses of protamine can impair platelet function and increase bleeding. These effects have only been demonstrated when the ratio of protamine to heparin is greater than 2.6:1.
> (Grade B recommendation based on level 1b and 2b studies)

7.3. Recombinant factor VIIa for intractable bleeding after cardiac surgery

Evidence was sought for the role of recombinant activated factor VII for intractable bleeding after cardiac surgery. This search is fully documented in the ICVTS (Tanos and Dunning [88]) together with a summary of all identified papers. Altogether 129 papers were identified using the reported search strategy of which 13 represented the best evidence on the topic. On updating, a recent review in the New England Journal of Medicine was added [47].

Roberts et al. in 2004 [89] published a review of the current use of factor VIIa across all specialties. Over 400,000 instances have been recorded, mostly in haemophiliacs, and the risk of serious adverse events was estimated as less than 1%. The risk of non-serious adverse events was estimated as 8—13%. The usual dose was 90 mcg/kg, but larger doses of 320 mcg/kg have also been recorded without major adverse effects.

In 2005, Levi et al. [90] performed a systematic review of the efficacy and safety of recombinant factor VIIa. They identified 28 clinical trials and 300 other case reports and series including 1854 patients. In haemophiliacs, efficacy over 90% has been demonstrated at a dose of 90 mcg/kg in 156 articles. If bleeding continues, an infusion of 16.5 mcg/kg h may also be started. In a further 37 patients with severe bleeding they reported a 60% efficacy in bleeding reduction. Boffard et al. [91] performed an RCT of 301 patients with severe blunt trauma showing significant reduction in RBC use, a 5% reduction in mortality (NS) and a trend to less organ dysfunction. The risk of adverse thromboembolic events in non-haemophiliacs was estimated at 1.4%. Thus factor VIIa has been well tested and its safety established in haemophiliacs and non-cardiac surgical patients.

The only RCT in high-risk cardiac surgical patients was by Diprose et al. [92] in which 20 patients were randomised to receive factor VIIa or placebo after reversal of heparin. Mean drainage was halved (630 ml down to 330 ml) and total blood product use was 13 units in the trial arm compared to 105 in the placebo arm. In a second paper, the authors reported dramatic reductions in blood loss in 17 patients when factor VIIa was used as rescue treatment in patients with massive blood loss after cardiac surgery [93].

Karkouti et al. [94] reported 51 patients with intractable bleeding after cardiac surgery who received between 35 and 70 mcg/kg of factor VIIa after blood loss exceeded 2000 ml despite platelets and FFP. They reported a significant reduction in blood loss and in the use of blood products. Four patients had a stroke, but one had loose atheroma in the aortic arch and two had a significant period of cerebral hypoperfusion.

Aggarwal et al. [95] reported the results of 24 patients who received 90 mcg/kg of factor VIIa for intractable bleeding after cardiac surgery. There was a significantly lower requirement for blood and blood products after administration compared to before administration. Only six patients survived to discharge and one patient suffered a subclavian vein thrombosis in association with central venous line. Von Heymann et al. reported 24 patients who had factor VIIa for intractable bleeding after cardiac surgery [96]. They also identified a matched paired retrospective cohort for comparison. No thrombotic complications were seen and blood loss was reduced to less than 100 ml/h in 18 of 24 patients. Interestingly, in the control group where routine treatment had been given, a similar reduction in blood loss was observed in 17 patients.

Hyllner et al. [97] reported 24 cases of factor VIIa use in intractable bleeding after cardiac surgery. There was a significant reduction in blood loss, no deaths from bleeding and no thrombotic complications. In the remaining studies Bishop et al. [98], Vanek et al. [99], Halkos et al. [100], Al Douri et al. [101] and DiDomenico et al. [102] reported between 2 and 12 cases of the use of factor VIIa for intractable bleeding after cardiac surgery. DiDomenico observed one fatal case of ECMO circuit and cardiac thrombosis and one of possible tamponade by mediastinal thrombus, but no other complications were documented in the other studies.

A review in the New England Journal of Medicine advocated factor VIIa for intractable bleeding in cardiac surgery although it voiced some reservations about the proven safety profile with regard to thrombotic complications and called for more studies to be performed [47].

The STS guidelines [8] state that it is not unreasonable to use factor VIIa for the management of non-surgical bleeding unresponsive to routine haemostatic therapy (level of evidence B).

Factor VIIa has proven efficacy and safety in over 400,000 uses worldwide outside the cardiothoracic surgical arena, mostly in haemophiliacs, with around 1% risk of serious thrombotic complications. In cardiac surgery, there have been more than 160 reports of its use for intractable bleeding and the rate of serious thrombotic complication is again around 1–2%.

> Recommendation:
> After cardiac surgery, intractable bleeding refractory to conventional haemostatic intervention may be treated successfully with factor VIIa, but there is a small risk of serious or fatal thrombotic complications.
> (Grade C recommendation based on level 2b, 3b and level 4 studies)

8. Anticoagulation after valve replacement

There are several well-conducted and up-to-date guidelines on this subject. For this reason, we elected not to perform our own literature review. Guidelines in this area include the European Society of Cardiology (ESC) valve guidelines of 2005 [6] the American College of Chest Physicians (ACCP) valve guidelines 2004 [30], The American Heart Association/American College of Cardiology (AHA/ACC) guidelines 2006 [27], the British Society of Haematology guidelines [28], the Canadian Cardiovascular Society [103] and the Scottish Intercollegiate Guidelines Network (SIGN) guidelines [104]. The findings of these guidelines are summarised in Table 1 for aortic valve replacements (AVR) and Table 2 for mitral valve replacements (MVR).

Mechanical valves require anticoagulation. Lack of anticoagulation results in an embolism or valve thrombosis rate of up to 12% per year for aortic valves and 22% per year for mitral valves [105]. With anticoagulation, this risk will be reduced to around 1–4% per year. The risk is higher for patients with a mechanical valve in the mitral position and for patients with additional risk factors such as atrial fibrillation (AF), poor left ventricular function, or a history of thromboembolism or hypercoagulability [30].

In 2005, the European Society of Cardiology (ESC) updated the 1995 guidelines and provided a comprehensive document for the management of anticoagulation for patients with mechanical valve replacements [6,106]. In this document the ESC acknowledges the increasing risk of thromboembolism due to both valve-related and patient-related factors. Thus a patient in sinus rhythm with good left ventricular function receiving a St Jude AVR would have a target INR of 2.5 but a patient in atrial fibrillation with a Bjork-Shiley valve would be given a target INR of 3.5.

Both the American Heart Association and the American College of Cardiology guidelines provide similar recommen-

Table 1
Summary of guidelines for INR for mechanical aortic valve

	Mechanical aortic valve with no risk factors	Mechanical aortic valve with risk factors
ESC guidelines [6]	Low-risk valve: INR 2.5 Medium-risk valve: INR 3.0 High-risk valve: INR 3.5	Low-risk valve: INR 3.0 Medium-risk valve: INR 3.5 High-risk valve: INR 4.0
	Low risk: Medtronic Hall, St Jude (not Silzone), Carbomedics Medium risk: bileaflet valves with insufficient data, Bjork-Shiley High risk: Lillehei-Kaster, Omniscience, Starr-Edwards	Atrial fibrillation, left atrium >50 mm, mitral valve gradient, ejection fraction <35%, spontaneous echo contrast, additional valve replacements, hypercoagulability, history of thromboembolism
AHA/ACC guidelines [27]	INR 2.0–3.0 (INR 2.5–3.5 for first 3 months)	INR 2.5–3.5 Atrial fibrillation, left ventricular dysfunction, previous thromboembolism, hypercoagulable condition, tilting disk and Starr-Edwards valves
ACCP guidelines [30]	INR 2.0–3.0 St. Jude, Carbomedics, Medtronic-Hall tilting disk	INR 2.5–3.5 AF, myocardial infarction, left atrial enlargement, endocardial damage, systemic embolism and low ejection fraction, caged ball or caged disk valve
BSH guidelines [28]	INR 2.5	INR 3.0 Tilting disc
	Bileaflet valves	INR 3.5 Caged ball or caged disk
SIGN guidelines [104]	INR 3.0 (range 2.5–3.5) Second generation valves such as St Jude, Medtronic-Hall, Monostrut	INR 3.5 (range 3.0–4.5) Starr-Edwards, Bjork-Shiley standard

Table 2
Summary of guidelines for INR for mechanical mitral valve

ESC guidelines [6]	Low-risk valves: INR 3.0 Medium-risk valves: INR 3.5 High-risk valves: INR 4.0 Low risk: Medtronic Hall, St Jude (not Silzone), Carbomedics Medium risk: bileaflet valves with insufficient data, Bjork-Shiley High risk: Lillehei-Kaster, Omniscience, Starr-Edwards
AHA/ACC guidelines [27]	INR 2.5—3.5
ACCP guidelines [30]	INR 2.5—3.5
BSH guidelines [28]	Bileaflet and tilting disc valves: INR 3.0 Caged ball or caged disc valves: INR 3.5
SIGN guidelines [104]	Second generation valves (St Jude, Medtronic, Monostrut): INR 3.0 (range 2.5—3.5) Starr-Edwards, Bjork-Shiley standard: INR 3.5 (range 3.0—4.5)

dations, although their levels of stratification according to patient-related and valve-related factors are generally less well defined.

> Recommendation:
> We recommend that European cardiothoracic surgeons follow the guidelines provided by the European Society of Cardiology. These guidelines are detailed, up to date and will continue to be updated in the future.

8.1. Warfarin after tissue valve replacement

Evidence was sought for whether warfarin should be routinely prescribed for the first 3 months after a tissue valve replacement either in the aortic or mitral position. This search is fully documented in the ICVTS [107] together with a summary of all identified papers. Altogether 620 papers were identified using the search. In addition, all major international guidelines were included and a recent high-quality review [108]. Sixteen papers presented the best evidence to answer the clinical question.

The most recent guidelines from the European Society of Cardiology in 2005 [6] recommend that, due to the absence of studies showing the safety of omitting anticoagulation for 3 months after bioprosthesis implantation, warfarin should be given at INR of 2.5 or 3.0 in higher risk patients. The ACCP guidelines from 2001 and updated in 2004 [30,109] recommend warfarin for 3 months for mitral bioprostheses, giving this a grade 1C + recommendation, and in the aortic position they also recommend warfarin but as a grade 2C recommendation, with an INR of 2.0—3.0 (grade 1C). The ACC/AHA guidelines published in 1998 [110,111] and updated in 2006 [27] stated that the greatest thromboembolic risk is in the immediate postoperative days and recommend heparin followed by warfarin for 3 months (class IIa based on grade C evidence). Thereafter, if the patient has no risk factors, warfarin may be stopped (class I).

In 1998 The Scottish Intercollegiate Guideline Network [104] recommended warfarin for 3 months for an aortic bioprosthesis (grade C) and for 3—6 months for a mitral bioprosthesis (grade A). They recommend an INR target of 2—3.

The British Society of Haematology produced guidelines in 1998 (unchanged in an update in 2005) [29] recommending that patients with mitral bioprostheses receive anticoagulation for 3—6 months. They did not recommend warfarin for aortic bioprostheses although they acknowledged that some institutions did.

Most guidelines advise 3 months of warfarin therapy, yet two large surveys have shown that this is not routine practice for aortic valves. In the 2004 survey by CTSnet (www.ctsnet.org) [5] with 726 respondents worldwide, while 80% of surgeons were aware of current guidelines, 60% did not routinely give 3 months of warfarin. In addition 60% of surgeons believed that antiplatelet therapy is an acceptable alternative to warfarin and over 60% of surgeons thought that warfarin was no longer the standard of care for tissue aortic valves. In 2005 Vaughan and Waterworth [4] surveyed UK consultant surgeons and found that 53% never use warfarin for tissue aortic valves, and 33% do not anticoagulate tissue mitral valve replacements. Only 16% of surgeons followed ACCP guidelines.

Turning to the original papers, most recently Sundt et al. [111] from the Mayo clinic published in 2005 a retrospective practice review of 1151 patients undergoing tissue AVR, half of whom were anticoagulated. In the 90 days after surgery 2.4% who were anticoagulated had a stroke compared to 1.9% of patients who were not anticoagulated. There was no difference in bleeding rates or reopening rates. They conclude that while they showed no significant benefit, they also showed no harm due to bleeding rates and acknowledged the underpowered nature of their study. Gherli et al. in 2004 [112] found no significant difference in stroke rate after tissue AVR between 108 patients who had warfarin (eight strokes) and 148 patients who had aspirin (four strokes). There was also no difference in bleeding rates. The authors advocated aspirin only after tissue AVR.

Much of the evidence quoted by the ACCP guidelines derives from a 1995 report from the Mayo Clinic by Heras et al. [113]. They quote a rate of thromboembolic events of 50 per 100 patient-year (%py) in the first 10 days after tissue AVR without warfarin but none with warfarin. In tissue MVR the event rate of 2.5% py with warfarin was significantly lower than 3.9% py without warfarin. However, the validity of the data pertaining to AVR has been called into question by authors from the same institution. Sundt et al. [111] stated that of the 424 patients who had a tissue AVR only five patients had a thromboembolic event in the first 10 days, and thereafter none of the AVR data demonstrated a significant difference.

Moinuddeen et al. [114] reported in a cohort study of 185 patients that the rate of stroke or transient ischaemic event (TIA) was 18% in both the aspirin and warfarin groups after a mean 5-year follow-up. The bleeding rate was not significantly different. They concluded that warfarin was not required for AVR although again this study is too small to exclude a benefit for warfarin in this situation.

Mistiaen et al. [115] in 2004 analysed 500 elderly patients receiving a Carpentier-Edwards pericardial valve and found on multivariate analysis that use of warfarin actually increased

the risk of thromboembolism with a risk ratio of 3.0 after 4-year follow-up. While this was a study of 500 patients, only 30 patients in sinus rhythm actually received long-term warfarin to form this high-risk group, of whom 7 had a stroke.

Yao et al. [116] in 2003 reported that the 10-year freedom from thromboembolism after tissue MVR was 100% with long-term anticoagulation but only 71% if anticoagulation was not given. However, there were only 22 patients in the anticoagulation group.

The ACCP guidelines quote the paper by Turpie et al. [117] from 1988 to demonstrate that 5% (2/40) of patients with an INR = 2.5—4.0 and 5.1% (2/39) with an INR = 2.0—2.3 had a thromboembolic event after tissue MVR, but the bleeding rate was lower in the low INR group. This paper did not have a 'no-anticoagulation' arm and was not powered to detect a significant difference. The study by Ionescu et al. from 1982 [118] is also quoted as evidence in favour of anticoagulation for tissue MVR. In this 1971—1981 series, 5.9% (4/68) who did not receive anticoagulants and none of 182 patients who received warfarin had an ischaemic event during the first 3 months.

Nowell et al. published a high-quality systematic review on antithrombotic therapy after tissue aortic valve replacement [108] in 2007, summarising 28 papers and highlighting the weaknesses of the current recommendations for warfarin. The recommendation for long-term antiplatelet therapy was also questioned as the evidence for this is also lacking, although guidelines are unanimous in their support for this therapy [119,120].

Further data may be available in the next few years from two registries that are in the early stages of data collection. The ANSWER registry (ANticoagulation Strategy With tissue valves: ostoperative Event Registry) intends to collect data on 2000 American patients who receive a Biocor™ or Biocor Supra™ valve either in the aortic or mitral position. Data on anticoagulation therapy will be collected and follow-up will be at 3 and 6 months and consists of telephone interviews (personal communication from Duke Clinical Research Institute). The second registry includes 45 centres and is called the ACTION registry (Anti Coagulation Treatment Influence On Postoperative patients). This will collect data on tissue aortic valves and has already reported initial survey results indicating a widely varying practice [121].

Recommendation:
After tissue aortic valve replacement and in the absence of other indications for anticoagulation, antiplatelet therapy alone is adequate.
Most guidelines recommend warfarin for 3 months after tissue mitral valve replacement. There is insufficient evidence to support or negate this recommendation. Patients who have an indication for anticoagulation such as atrial fibrillation should be anticoagulated. Anticoagulation for others is reasonably safe and may be beneficial. Antiplatelet therapy alone however is an acceptable alternative.
(Grade B recommendation based on level 2b and 3b studies).

8.2. Antiplatelets in addition to warfarin for patients with mechanical heart valves

Evidence was sought for whether addition of antiplatelet therapy to warfarin reduced the incidence of thromboembolic complications in patients with mechanical heart valves. This search is fully documented in the ICVTS [122] together with a summary of all identified papers. Altogether 253 papers were found using the reported search, of which only 11 papers represented the best evidence to answer the clinical question. Despite this, 12 meta-analyses or current guidelines were also found, all of which consider the evidence either from these studies or from each other.

Of the 11 trials, 6 used dipyridamole as an antiplatelet drug in doses of 225—400 mg once daily. Four trials used aspirin in doses of 500 mg once daily, 500 mg twice daily and in three recent trials, 100—200 mg once daily. The best meta-analyses were published by Massel and Little [123,124] and found that aspirin reduced the odds of all-cause mortality from 9% to 5.2%, which was significant. Breaking this down there was a significant reduction of thromboembolic events from 9% to 3.8% but with a corresponding increase in major bleeding from 5.4% to 8.5% (all significant). Massel performed many sub-analyses and sensitivity analyses to see if the dose of aspirin, the date of the study, or the quality of study had an impact and found that the risk of bleeding appears to have diminished with the lower doses of aspirin used in the more recent trials.

Of the 11 trials, only 3 investigate low-dose aspirin. Laffort et al. [125] performed a single blind RCT in 229 patients comparing aspirin 200 mg with control with warfarin at an INR of 2.5—3.5. They found a significantly reduced level of thromboembolism but an increase in major bleeding. Turpie [120] performed a double-blind RCT in 370 patients using aspirin 100 mg with warfarin at an INR of 3.0—4.5. All-cause mortality was reduced from 12% to 4.8%, with significant reductions in thromboembolism but with a non-significant rise in major bleeding. Meschengieser et al. [126] performed a RCT in 503 patients which studied aspirin (100 mg) in combination with low dose warfarin (INR of 2.5—3.5) to high dose warfarin alone (INR of 3.5—4.5). They found a trend towards more major bleeding and all major events in the warfarin only group and the rate of thromboembolism were similar.

Of the clinical guidelines, the American Heart Association recommends that aspirin 80—100 mg should be strongly considered unless contraindicated with level 2a evidence. The European Society of Cardiology 2005 guidelines [6] are more conservative due to concerns over bleeding complications. They recommend antiplatelet agents in addition to warfarin only for patients with concomitant arterial disease, previous stenting, pulmonary embolism or high-risk valve implants. The British committee for standards in haematology makes no recommendation for addition of aspirin but SIGN recommend aspirin for any patients who also suffer systemic embolism despite adequate anticoagulation. The ACCP recommend aspirin in addition to anticoagulation but acknowledge the increased risk of bleeding, giving this grade 1 status. The Massel meta-analysis finds that aspirin addition reduces the risk of all-cause mortality with a number needed to treat of 19. Most guidelines recommend addition of aspirin

to warfarin but a survey of cardiac surgeons' opinion in North America and Canada showed that cardiac surgeons very much under-prescribe additional aspirin for fear of the increased risk of bleeding despite these guidelines.

Recommendation:
Low dose aspirin (80—100 mg daily) in addition to warfarin in patients with mechanical heart valves reduces all-cause mortality (NNT = 19), with significant reductions in thromboembolism but with more bleeding complications. (Grade A recommendation based on level 1a and 1b studies)

8.3. Warfarin anticoagulation for 3 months after mitral valve repair

Evidence was sought for whether oral anticoagulants are necessary after mitral valve repair with or without an annuloplasty ring. This search is fully documented in the ICVTS [127] together with a summary of all identified papers. Altogether 127 papers were found using the reported search, of which 12 papers represented the best evidence to answer the clinical question.

The 2006 ACC/AHA guidelines [27] for the management of patients with heart valve disease do not provide recommendations for patients who have undergone a mitral valve repair and neither do the ACCP guidelines of 2004 [30]. The European Society of Cardiology provides guidelines for these patients, stating that there are no RCTs to support the safety of omitting warfarin after mitral repair. They recommend 3 months of warfarin at a target INR of 2.5 or 3.0 if there are additional risk factors. They acknowledge that this is based on expert consensus and acknowledge that many surgeons do not follow this guideline.

Mitral valve repair is now recognised as the gold standard for mitral regurgitation. Around 70% of all procedures on the mitral valve are repair with or without an annuloplasty ring. AF is a common postoperative arrhythmia and is more common after mitral valve surgery than after any other open-heart procedure. Thus while a mitral valve repair may potentially be the least pro-thrombotic treatment among valve procedures the prevalence of AF in these patients may be an indication for anticoagulation.

The thromboembolic rate is highest in the first 3 months after surgery. Around 20% of all thromboembolic complications occur during the first month, due to the hypercoagulable state, which then decreases with time. The endothelialisation process of the newly implanted valve ring takes several weeks. The sewing valve ring, suture knots, atheromatous plaques, and calcium deposits on the dissected valve apparatus are prone to platelet deposition and thrombus formation when exposed to blood. The post-operative milieu after mitral repair is suggested to be similar to that after mitral bioprosthesis implant.

Jovin et al. [128] reviewed 245 patients who underwent mitral repair for regurgitation from 1996 to 2001 and found 73 (29%) were admitted with AF, 65 (27%) left the hospital in AF and 64 (36%) had an episode of AF during the postoperative period. Of the 65 patients who were in AF at discharge, 61 (94%) were discharged on warfarin, 1 (1.5%) on warfarin and aspirin, 2 (3%) on aspirin and 1 (1.5%) received no anticoagulation at discharge. Of the 180 patients who were in sinus rhythm at discharge, 98 (54%) were discharged on warfarin, 78 (43%) were discharged on aspirin and 3 (2%) received no anticoagulation or antiplatelet therapy at discharge. Jovin anticoagulated patients undergoing mitral repair for 3 months as recommended for mitral tissue valves.

Aramendi et al. [129] studied 235 mitral surgery patients from 1990 to 1995 of whom 67 had repair and the rest tissue valves. Of the 209 survivors, 137 were assigned initially to receive ticlopidine (250 mg bd) for at least 3 months postoperatively. The remainder were treated with aspirin, warfarin or neither. Mean follow-up was 3.2 years and complete in 96% of 122 patients studied. AF was present in a greater proportion of the warfarin-treated group (50% vs 30%; $p < 0.05$). In total, six episodes of thromboembolism were reported. All occurred in the first postoperative year, four during the first 3 months, with the highest risk in the first month rapidly declining thereafter. There were four episodes of haemorrhage for the entire series, all in the first 3 months. Galloway [4] studied 148 patients after mitral repair and showed 95% 5-year freedom from thromboembolism without long-term anticoagulant therapy. All patients were started on warfarin on the third postoperative day for 3 months. Incidence of anticoagulation-related complications was 0.33% py. One episode of bleeding was reported at 50 months, six late thromboembolic complications were reported in five patients and one patient died from stroke. Freedom from late thromboembolism was 98% at 1 year and 95% for years 2—7.

Deloche et al. [130] followed up 195 patients after mitral repair. All were started on warfarin on third postoperative day for 3 months, unless otherwise indicated. At 15 years, 10 patients had a thromboembolic event, for an actuarial freedom from thromboembolism of 94% $\pm$ 2.3% at 15 years. Of the 10 events, 7 were transient, 1 permanent and 1 fatal.

Carpentier [131,132] has reported the longest follow-up of 928 patients with mitral repair up to 29 years. All had warfarin for 2 months. Only three patients had a stroke in the first 3 months. There were 37 thromboembolic events in these patients strongly associated with AF.

In a survey [4] of cardiac surgeons in Great Britain, 64% use warfarin after mitral repair with an annuloplasty ring and 54% used only aspirin in the long-term.

Recommendation:
There is insufficient evidence on the need or safety of anticoagulation after mitral repair. Patients who have an indication for anticoagulation such as atrial fibrillation should be anticoagulated. Anticoagulation for others is reasonably safe and may be beneficial. Antiplatelet therapy alone is an acceptable alternative. (Grade C recommendation based on an absence of studies demonstrating the safety of omission and level 2b and 3b studies).

9. Anticoagulation for patients with de novo AF after cardiac surgery

This issue has been addressed in our previous guideline [133] and the recommendations are documented below

Recommendation:
After cardiac surgery, patients with AF should be anticoagulated with warfarin while in AF with a target INR of 2—3, and full anticoagulation should be started within 48 h of the onset of AF due to a doubling of their risk of stroke.
(Grade A recommendation based on level 1a studies)

Immediate full anticoagulation in patients going into AF within 48 h of their operation is not supported due to the increased risk of cardiac tamponade.
(Grade C recommendation based on an individual level 2b study)

There is insufficient evidence to recommend whether patients who suffer an episode of AF after cardiac surgery but who return to sinus rhythm will benefit from a further 4—6 weeks of anticoagulation.
(Grade E recommendation based on expert consensus)

10. Heparin for thromboprophylaxis

Evidence was sought for whether the use of prophylactic postoperative unfractionated or low molecular weight heparin (LMWH) after cardiac surgery would significantly reduce morbidity by reducing the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE). This search is fully documented in the ICVTS [134] together with a summary of identified papers. Relevant major guidelines were also searched together with their reference lists. Of 390 papers, 16 represented the best evidence on the topic. After this search, the National Institute for Health and Clinical Excellence also published extensive guidance in this area in 2007 and this is summarised below [135].

Shammas, [136] in a literature review to estimate the incidence of DVT and PE after cardiac surgery, identified eight studies comprising over 18,000 patients [137—144] and found that if routine ultrasound or venography was performed the incidence of DVT was 22%, and proximal DVT 15%. The incidence of PE was 0.8% and fatal PE 0.16%. Interestingly the clinical detection of DVT was less than 2% and half were in the non-harvested leg.

Ambrosettia et al. in 2004 [145] performed serial ultrasound of 270 consecutive patients after CABG attending three rehabilitation programmes. The incidence of DVT was 17%, proximal DVT 2.6% and two patients suffered a PE. Half the DVTs were in non-harvested leg.

The data were analysed for any protective effect of heparin but the findings were inconclusive.

Ramos et al. in 1996 [146] performed a large RCT comparing subcutaneous heparin (5000 units bd) to heparin plus intermittent compression stockings. The incidence of PE decreased from 4% to 1.5% with this intervention. This study showed that even with good prophylaxis, the incidence of PE after cardiac surgery is around 3%.

Considering whether prophylaxis significantly reduces the incidence of DVT and PE, we could find no clinical trials that assessed the impact of DVT prophylaxis in patients after cardiac surgery. However the ACCP [147] in 2001 published a comprehensive systematic review and guideline on DVT prophylaxis in other specialties. In general surgery, 68 trials in nearly 20,000 patients have shown that either heparin or LMWH reduces the relative risk of DVT by 70%. In hip replacement surgery in over 40 trials with 7000 patients LMWH or heparin reduced the risk by up to 78%. Three ICU trials showed at least a halving of DVT, and three post-MI studies also showed a reduction. The general surgery trials have also demonstrated a reduction in proximal DVT, PE and fatal PE. Thus across the whole range of surgical and medical conditions the incidence of DVT is high and prophylaxis significantly reduces the incidence of DVT and its sequelae.

Gutt et al. in 2005 [148] performed a systematic review of DVT prophylaxis in general surgery and stated that LMWH at low doses reduced bleeding risk compared to heparin but the risk was higher with high doses. This risk was not quantified. In a systematic review of general surgery, Bergqvist in 2003 [149] concluded that the rate of bleeding with lower doses of LMWH was lower compared to unfractionated heparin, but this did rise as the dose increased.

Malouf et al. [150] assessed 141 patients on warfarin after cardiac surgery with serial echocardiography. The incidence of large pericardial effusion was 4% in controls and 32% on warfarin, with 12 having delayed tamponade. As a caveat, 41 patients had excessive anticoagulation at some stage and this study was in patients receiving full warfarin anticoagulation rather than prophylactic heparin.

Kulik et al. in 2006 [151] performed a systematic review of four early anticoagulation strategies after mechanical valve replacement (warfarin alone, with subcutaneous heparin, with LMWH and with intravenous heparin). The bleeding rate was highest with intravenous heparin at 8% and was lower with subcutaneous heparin or LMWH at around 4%.

The National Institute of Health and Clinical Excellence [135] recommends that all patients undergoing cardiac surgery should be offered mechanical DVT prophylaxis and any patient with an additional risk factor should also receive LMWH. These risk factors include: age over 60, active heart failure, central venous catheter in situ, BMI >30, recent MI and immobility. Mechanical DVT prophylaxis was defined as thigh-length graduated compression/anti-embolism stockings, placed from the time of admission until that time at which they have regained their normal mobility.

Recommendation:
The incidence of thromboembolism after cardiac surgery is similar to the incidence in patients undergoing high-risk general surgery. (Grade B recommendation based on level 2b studies)

The ACCP guidelines recommend heparin prophylaxis for high-risk groups and NICE recommends low molecular weight heparin and mechanical deep vein thrombosis prophylaxis for virtually all patients undergoing cardiac surgery.
After cardiac surgery, patients should receive mechanical deep vein thrombosis prophylaxis and low molecular weight heparin starting on the first postoperative day.
(Grade B recommendation based on level 1b and 2b studies)

11. Antiplatelet management for patients after cardiac surgery

11.1. Dose of aspirin after coronary artery bypass grafting

Evidence was sought for the optimal dose of aspirin for patients post-coronary artery bypass grafting. This search is fully documented in the ICVTS [152], together with a summary of all identified papers. Of 173 papers using the presented search strategy, 7 represented the best evidence on this topic. One additional paper has since been published and the ACCP and the Joint British Societies guidelines [153] have published relevant guidelines in this area.

Fremes et al.'s meta-analysis [154] demonstrated a significant benefit of low and medium dose aspirin in comparison to high dose aspirin. The benefit of medium dose aspirin was greatest but confidence intervals overlap those for low dose aspirin. Neither the antiplatelet trial investigators nor the Veterans study group were able to convincingly demonstrate an advantage of medium dose aspirin in comparison to low dose aspirin.

Mangano et al. [155] provided the first evidence for a convincing survival benefit from aspirin. However, the range of aspirin used was from 80 mg to 650 mg, so no evidence was provided for choosing a dose within this range. Of note there was no evidence of a higher rate of GI and bleeding complications in the non-aspirin group.

Lim et al. [156] performed an indirect meta-analysis in 2003, where two RCTs of medium dose aspirin (300—325 mg) [157,158] were compared to three RCTs of low dose aspirin (75—150 mg) [159—161]. The medium dose trials yielded a relative risk reduction of 45% compared with 26% for the low dose trials. This gave a relative risk ratio of 0.74 (95% confidence interval 0.52—1.06; $p = 0.10$) for graft occlusion and 0.81 (0.57—1.16; $p = 0.25$) for events in patients. Again while no statistically significant findings were reported to the $p < 0.05$ level, a trend towards benefit with medium dose aspirin was reported.

In December 2005 the Joint British Societies guidelines on prevention of cardiovascular disease in clinical practice [153] published a comprehensive document on all aspects of secondary prevention in patients with cardiovascular disease. They recommend aspirin at a dose of 75—150 mg for all patients 'at high risk' of suffering a cardiovascular event. They did not however consider CABG patients as a separate entity from general high-risk patients.

In 2001 the 6th ACCP consensus conference on antithrombotic therapy [162] recommended 325 mg/day of aspirin, starting 6 h after surgery. However in the 2004 7th ACCP consensus conference [163], this recommendation was altered to 75—325 mg at 6 h and then 75—162 mg/day indefinitely. This was graded as 1A evidence.

Recommendation:
Aspirin should be given postoperatively to all patients without contra-indications after coronary artery bypass grafting in order to improve the long-term patency of vein grafts. The dose given should be 150—325 mg. Studies show a trend towards maximal benefit with 325 mg/day in the first year.
(Grade A recommendation based on level 1a and 1b studies)

There is no evidence to promote the use of aspirin after coronary artery bypass grafting to improve the patency of arterial grafts. However aspirin may be recommended on the basis of improved survival of patients in general who have atherosclerotic disease.
(Grade E recommendation based on expert consensus)

11.2. Timing of aspirin after coronary artery bypass grafting

Evidence was sought for the optimal timing of the first dose of aspirin for patients after CABG. This search is fully documented in the ICVTS [164], together with a summary of all identified papers. We found 201 papers using the presented search strategy. From these papers, seven represented the best evidence on this topic.

Fremes et al. [154] in a meta-analysis of 12 studies found that the benefit of aspirin was optimal if started at 6 h after surgery. In the individual studies, Gavaghan [157] showed the largest risk reduction when aspirin was given at 1 h after operation, but there was a non-significant increased rate of re-operation in this group. The study by Sharma

et al. [165] showed that there was no benefit in giving aspirin if starting more than 48 h postoperatively. No significant increases in postoperative bleeding were shown in any studies.

The 7th ACCP consensus conference on antithrombotic and thrombolytic therapy recommended 75–325 mg of aspirin 6 h after surgery, giving this a grade 1A recommendation [163].

Recommendation:
Aspirin should be commenced within 24 h of coronary artery bypass grafting.
(Grade A recommendation based on level 1a and 1b studies)

There is a trend towards maximal benefit of aspirin the sooner it is given postoperatively. Giving aspirin at 6 h or when bleeding has ceased may therefore be the optimal strategy.
(Grade B recommendation based on individual level 1a and 1b studies)

11.3. Clopidogrel for the optimisation of graft patency

Evidence was sought for whether clopidogrel should be given in addition to aspirin to high-risk patients after CABG to reduce thrombotic complications. This search is fully documented in the ICVTS [166,167], together with a summary of all identified papers. We found 511 papers using the presented search strategy. From these papers, 11 represented the best evidence on this topic.

The ACCP guidelines on clopidogrel [163] recommend that it should be started in addition to aspirin and continued for 9–12 months after CABG for non-ST segment elevation acute coronary syndrome. This recommendation is based on the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study and the Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) study.

CAPRIE reported an 8.7% relative risk reduction in the primary composite endpoint (first occurrence of ischaemic stroke, myocardial infarction or vascular death) in favour of clopidogrel (75 mg/day) over aspirin (325 mg/day) in a multicentre RCT of 19,185 patients with a history of recent ischaemic stroke, recent MI or symptomatic peripheral arterial disease [168]. A sub-analysis of the CAPRIE database showed that in 1480 patients with previous cardiac surgery, clopidogrel was associated with a relative risk reduction of 39% for vascular death, 38% for myocardial infarction, 25% for all-cause re-hospitalisation, and 27% for re-hospitalisation for ischaemia or bleeding. A major drawback of this study is the lack of information about the type of cardiac surgery previously performed.

CURE randomised 12,562 patients with acute coronary syndromes to clopidogrel (300 mg then 75 mg/day) or placebo in addition to aspirin (75–325 mg/day). The antiplatelet combination resulted in a 20% risk reduction relative to aspirin alone (9.3% vs 11.4%, $p < 0.001$) in the primary endpoint of cardiovascular death, myocardial infarction or stroke over a mean 9-month treatment period [169]. The antiplatelet combination produced a 19% reduction relative to aspirin alone in the risk of cardiovascular death, myocardial infarction or stroke among those patients who underwent CABG surgery during the initial hospitalisation and an 11.0% relative risk reduction among patients who underwent CABG at any time during the treatment period. The clinical benefits of aspirin plus clopidogrel were mainly evident during the preoperative period with 18% relative risk reductions in the primary endpoint seen before CABG surgery compared to 3% relative risk reduction following CABG surgery relative to aspirin alone [21].

The Clopidogrel for the Reduction of Events During Observation (CREDO) trial evaluated the short-term benefits of combined aspirin and clopidogrel pre-treatment and the long-term benefits of sustained therapy in the setting of percutaneous coronary intervention (PCI) in an RCT of 2116 patients. After 1 year, patients receiving clopidogrel (75 mg/day) plus aspirin (81–325 mg/day) had a significant 26.9% relative risk reduction in the combined endpoint of death, myocardial infarction or stroke [22]. A subgroup analysis of patients who underwent CABG without PCI had a modest reduction of 1-year events (RRR 16.7%) with clopidogrel [170]. But this was a post-hoc analysis and the number of patients in this group was small.

The recent observational study by Gurbuz et al. [171] showed that adding clopidogrel to aspirin was independently associated with decreased symptom recurrence and adverse cardiac events following off-pump CABG. However, extending clopidogrel use beyond 30 days did not have a significant effect on defined end points.

In order to provide convincing evidence for clopidogrel and aspirin versus aspirin alone on saphenous vein graft disease after CABG, a double-blind RCT is currently underway. The CASCADE (Clopidogrel After Surgery for Coronary Artery Disease) is randomising 100 CABG patients to clopidogrel or placebo in addition to 162 mg of aspirin with 1-year angiography as the primary outcome measure [172]. This is due to report in 2008.

With regard to the other high-risk group of patients, namely patients having CABG after PCI, we found no studies that looked at the outcome of stent patency after CABG. The ACCP guidelines [173] recommend clopidogrel in addition to aspirin for all patients after PCI for 9–12 months (grade 1A). A small study by Kaluza et al. [174] demonstrated that there was an in-stent thrombosis rate of around 20% with a similar mortality in patients having surgery of any type shortly after PCI. Therefore if the stented vessel is not grafted then it would seem reasonable to follow the ACCP guideline with 9–12 months of clopidogrel. However if the stent is covered by a graft more distally, there is no evidence to support continuation of clopidogrel.

Recommendation:
Clopidogrel (75 mg) is an acceptable alternative to aspirin for the optimisation of graft patency after coronary artery bypass grafting. (Grade B recommendation based on individual level 1b studies)

The superiority of clopidogrel over aspirin for optimising graft patency after coronary artery bypass grafting has not yet been established and thus aspirin should be regarded as the drug of first choice.
(Grade B recommendation based on individual level 1b studies)

In patients having cardiac surgery for acute coronary syndrome, clopidogrel should be considered for 9—12 months in addition to aspirin.
(Grade B recommendation based on sub-analyses of level 1b studies)

Clopidogrel may further improve the patency of saphenous vein grafts when given in addition to aspirin, but this will be at the expense of an increase in bleeding complications.
(Grade B recommendation based on individual level 1a and 1b studies)

In patients having coronary bypass surgery with a coronary stent in situ, clopidogrel should be continued if the stented vessel has not been grafted.
(Grade E recommendation based on expert consensus)

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