

Aspirin and Tranexamic Acid for Coronary Artery Surgery Trial

Protocol Number: Anaesthesia Research 024

www.atacas.org.au

A collaborative project conducted by the Australian and New Zealand College of Anaesthetists Trials Group (ANZCA TG), and the NHMRC Centre for Clinical Research Excellence in Therapeutics

Australian Clinical Trials Registry Number: ACTRN012605000555651

Protocol Version 8.1: 18th July, 2011

Study title: The ATACAS Trial: Aspirin and Tranexamic Acid for Coronary Artery Surgery Trial

Protocol Number: Anaesthesia Research 024

Sponsor: Alfred Hospital, Melbourne

AGREEMENT

This document is confidential. The Investigators declare that they have read the final study protocol and any amendments. The Investigators will conduct the study according to the procedures specified in the study protocol, and in accordance with ICH GCP notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Annotated with TGA comments and NH&MRC National Statement on Ethical Conduct in Research Involving Humans.

.....
Investigator

.....
Date

The ATACAS Trial: Aspirin and Tranexamic Acid for Coronary Artery Surgery Trial

Principal Investigator

Prof. Paul Myles MB.BS, MPH, MD, FCARCSI, FANZCA, FRCA
 Director, Department of Anaesthesia and Perioperative Medicine, Alfred Hospital and Monash University

Chief Investigators

Prof. Julian Smith MB.BS, MS, FRACS
 Head, Department of Cardiothoracic Surgery, Monash Medical Centre;
 Professor, Department of Surgery, Monash University;
 Steering Committee, ASCTS Victorian Cardiac Surgery Database

A/Prof. John Knight MB.BS, FRACS
 Head, Cardiac Services, Flinders Medical Centre;
 Associate Professor, Department of Surgery, Flinders University

Prof. D. James Cooper BM.BS, MD, JFICM
 Intensive Care Department, Alfred Hospital;
 Depts. of Surgery, and Medicine, Monash University

A/Prof. Brendan Silbert MB.BS, FANZCA
 Department of Anaesthesia, StVincent's Hospital, Melbourne

Prof. John McNeil MB.BS, PhD, FRACP
 Professor & Chairman, Department of Epidemiology & Preventive Medicine,
 Monash University

Associate Investigators

Prof. Donald S. Esmore MB.BS, FRACS
 Head of Cardiothoracic Surgery, Alfred Hospital;
 Associate Professor, Department of Surgery, Monash University.

Prof. Brian Buxton MB.BS, MD, FRACS
 Professor, Department of Surgery, University of Melbourne

Clinical Pharmacologist

Prof. Henry Krum MB.BS, PhD, FRACP
 Head, Clinical Pharmacology Unit, Department of Epidemiology & Preventive Medicine, Monash University

Statistician

Prof. Andrew Forbes MSc, PhD
 Head, Biostatistics Unit, Department of Epidemiology & Preventive Medicine, Monash University

Chairman, Data and Safety Monitoring Committee

Prof. Andrew Tonkin MB.BS, MD, MRACP, FRACP
 Head, Cardiovascular Research Unit, Department of Epidemiology & Preventive Medicine,
 Monash University

TABLE OF CONTENTS

	<u>Page no.</u>
TITLE PAGE	1
AGREEMENT	2
INVESTIGATORS	3
TABLE OF CONTENTS	4
ABBREVIATIONS	7
SUMMARY/SYNOPSIS	7
Drugs under study	7
Objectives of the study	7
Study design	7
1. STUDY BACKGROUND AND SIGNIFICANCE	8
2. OBJECTIVES	18
2.1 Primary Endpoint	18
2.2 Secondary Endpoint	18
3. STUDY DESIGN	19
3.1 Experimental Design	19
3.2 Subject Selection	19
3.2.1 Definition of Disease State	19
3.2.2 Source and Number	19
3.2.3 Entrance Criteria	19
3.3 Study Medication	20
3.3.1 Form	20
3.3.2 Dosing Schedule	20
3.4 Study Procedure	21
3.4.1 General Description	21
3.4.2 Guideline for managing Excessive Bleeding after CPB or OPCAB	22
3.4.3 Red Cell Transfusion Guideline	22
3.4.4 Clinical Observations	23

4.	EXPERIMENTAL CONTROL	24
4.1	Randomisation	24
4.2	Blinding Procedure	25
4.3	Case Report Forms	25
4.4	Compliance Checks	25
4.5	Patient Completion/Withdrawal	25
4.6	Continuation of Therapy	26
4.7	Repeat and Special Laboratory Tests	26
4.8	Concomitant Medications and other Treatments	26
4.9	Adverse Experiences	26
4.10	Overdosage/Antidote	28
4.11	Emergency Unblinding of Study Drug	28
5.	DATA MANAGEMENT PROCEDURES	28
5.1	Review and Confirmation of Case Report Forms	28
5.2	Data Base Production and Verification	28
6.	STATISTICAL CONSIDERATIONS	28
6.1	Patient Categories	28
6.2	Sample Size and Power	29
6.3	Statistical Methods	29
6.4	Interim Analysis	30
6.5	Planned Subgroup Analyses	30
6.6	Planned Substudies	30
7.	PERSONNEL RESPONSIBILITIES	30
7.1	Investigators	31
7.2	Pharmacist	31
7.3	Monitor	31
7.4	Sponsor	31
7.5	Steering Committee and Adjunct Committees	31
8.	ADMINISTRATIVE PROCEDURES	33
8.1	Amendments to the Protocol	33
8.2	Early Termination or Extension of the Study	33
8.3	Drug Accountability	33
8.4	Drug Packaging and Labelling	33
8.5	Storage of Study Drugs	33
8.6	Confidentiality/Publication of Study Results	34
8.7	Retention of Records	34

8.8	Audits	34
9.	ETHICAL PROCEDURES	34
9.1	<i>Guidelines for Good Clinical Research Practice</i>	34
9.2	<i>Precautionary Advice</i>	34
9.3	<i>Participant Information and Consent Form</i>	34
9.4	<i>Ethics Committee</i>	34
10.	REFERENCES	35
11.	AUTHORSHIP PLAN	38

ABBREVIATIONS

ACT	Activated Clotting Time
ANZCA	Australian and New Zealand College of Anaesthetists
ASCTS	Australasian Society of Cardiac and Thoracic Surgeons
CABG	Coronary Artery Bypass Graft
CPB	Cardiopulmonary Bypass
CRF	Case Report Form
CTN	Clinical Trial Notification Scheme
CCRE	Centre for Clinical Research Excellence
DDAVP	1-deamino-8-D-arginine vasopressin (desmopressin)
DEPM	Department of Epidemiology and Preventive Medicine
DSMC	Data Safety Monitoring Committee
EAC	Endpoint Adjudication Committee
FFP	Fresh Frozen Plasma
ICU	Intensive Care Unit
IV	Intravenous
MI	Myocardial Infarction
OPCAB	Off-Pump Coronary Artery Bypass grafts
PI&CF	Participant Information and Consent Form
rFVIIa	Recombinant Factor VIIa (Novoseven™)
RA	Research Assistant
RACS	Royal Australasian College of Surgeons
TA	Tranexamic Acid
TGA	Therapeutic Goods Administration

SUMMARY/SYNOPSIS

Drugs under study:

Aspirin and tranexamic acid (TxA)

Objectives of the study:

- i. Should low-dose aspirin be continued up until the day of CABG or OPCAB surgery?
- ii. Should TxA be used for all at-risk CABG or OPCAB surgery?

Study design:

Multicentre, double-blind, randomised, 2x2 factorial trial

Type and number of subjects/patients:

An at-risk group of CABG and OPCAB patients will be identified in order to increase the number of outcome events. 4600 patients will be recruited into this study (i.e. 1150 into each of the 4 groups)

Principal clinical endpoint:

30-day mortality or major ischaemic morbidity (composite endpoint)

1. STUDY BACKGROUND and SIGNIFICANCE

Coronary artery disease is probably the most common single major health problem in developed countries, and coronary artery bypass graft (CABG) surgery has become one of the primary treatment options. There are approximately 200,000 CABG operations performed in the US each year, and more than 800,000 worldwide (1). The use of CABG surgery in an aging population has doubled every 5 years since 1985. Whilst CABG surgery offers benefit to the majority of patients, some die and others suffer long-term disability (1-6).

Cardiac surgery is among the most expensive surgical procedures (7,8), with a cost exceeding \$15 billion per year in the US alone. With the increasing number of patients requiring CABG surgery, efficient use of available resources is vital for the most cost-effective delivery of healthcare.

Postoperative complications have a substantial effect on the costs of cardiac surgery (7,8). The baseline cost of isolated CABG cases with no complications in the US is about \$26,000 (8). Additive costs include stroke (\$34,000), prolonged ventilation (\$40,000), renal failure (\$49,000), mediastinitis (\$63,000), and mortality (\$49,000).

The subsequent long-term care of survivors of post-CABG MI, heart failure and stroke is extremely costly to patients, their families and the community. Another common complication is cognitive impairment, which may be related to subclinical stroke (9) and dementia, and which can have a marked effect on quality of life. Perioperative aspirin may protect against post-CABG MI and stroke (10).

In the US (6,8), and Australia (11), overall case mortality is around 2%. Approximately 5-15% of cardiac surgical patients have at least one major complication within 30 days of surgery. These complications include cardiac failure, MI, respiratory failure, arrhythmias, stroke, renal failure, wound infection, thromboembolism, and a need for surgical re-exploration (1-6). Each has an incidence of 0.5-5%. A common underlying mechanism is poor myocardial function secondary to myocardial ischemia or infarction, leading to a low cardiac output state. This may be worsened by poor coronary artery (and bypass graft) flow and thrombosis. Treatments include inotropic therapy and mechanical ventilation, and prolonged (expensive) intensive care. A cascade of complications may follow.

One of the key determinants of good myocardial function in the postoperative and post-discharge periods is patency of the coronary grafts. Large follow-up angiography studies suggest complete occlusion occurs in about 14% of saphenous-vein grafts and 8% of radial-artery grafts at 12 months after surgery (12).

Cardiac Surgery, Bleeding Risk and Blood Transfusion

Cardiac surgery with cardiopulmonary bypass (CPB) is associated with haemodilution of red cells, platelets and coagulation factors, as well as platelet dysfunction and activation of the coagulation and fibrinolytic pathways (13). Excessive bleeding post-bypass is arguably the most common problem with CABG surgery, and certainly one that delays completion of surgery and/or tracheal extubation in ICU. About half of all cardiac surgical patients receive allogeneic blood transfusion (14-16); 10% of all blood transfusions are used in CABG patients (17).

Blood transfusion may be associated with immunosuppression: in a meta-analysis of 20 surgical studies (n=13,152), blood transfusion was associated with postoperative bacterial infection (OR 3.45; P<0.05) (18). This is also a common finding in observational studies of cardiac surgery (15-19).

Minimizing the risk for perioperative bleeding in patients undergoing CABG surgery is important because there is a strong association between surgical risks and blood transfusion. In one study involving 11,963 patients who underwent CABG surgery (15), of whom 49% received transfusion of red cells, transfusion was associated with significant increases in mortality (OR, 1.77; CI: 1.67-1.87), renal failure (OR, 2.06; CI: 1.87-2.27), and neurologic events (OR, 1.37; CI: 1.30 -1.44).

The risk of infection increased in proportion to the number of units of RBC transfused (20): 5% for no transfusion, 15% with 1-2 units, 22% with 3-5 units, and 29% with ≥ 6 units, P<0.001. Diabetes was the only other factor significantly associated with infection.

Despite advances in blood conservation, bleeding and a need for blood transfusion remain significant problems in cardiac surgery. A restrictive transfusion practice is safe (22) and effective (23), but antifibrinolytic therapy has become the mainstay of reducing bleeding and transfusion requirements in cardiac surgery (24,88).

Excessive bleeding may require surgical re-exploration and lead to increased morbidity and mortality (13,15). Factors associated with excessive bleeding, transfusion requirements and re-operation include older age, body size, extent of surgery, emergency surgery, CPB time and low platelet count (25-27).

Aspirin and Cardiac Surgery

Aspirin impairs platelet function (10). Many (28), but not all (26,27,29) studies have found that recent aspirin exposure increases surgical bleeding after cardiac surgery. Therefore, it is routine practice in most cardiac surgical centres to cease aspirin 5-7 days before elective surgery. Yet the increased risk of surgical bleeding could be outweighed because aspirin decreases platelet aggregation and this may have a beneficial effect on coronary graft flow and reduction in graft thrombosis (30-33), and possibly stroke (10,29,30). Aspirin is routinely recommenced 8-36 hours after surgery, but this practice denies an opportunity to avoid early thrombosis during the crucial post-bypass and early postoperative phase (30).

Also, cessation of aspirin 5-7 days before surgery poses a thrombotic risk to patients at this time, all because of the irreversible platelet inhibition requiring such a duration beforehand in order to avoid bleeding risks on the day of surgery. Sometimes the operation is cancelled or delayed and so the patient may be exposed for several weeks. In any case, this is a substantial risk period. If aspirin is found to be safe and effective on the day of CABG surgery, then there will be no need to discontinue aspirin for CABG surgery in the future.

The best aspirin dose to test in a large trial is 100 mg, which has the strongest evidence of efficacy (at least in other settings) balanced against a low risk of bleeding complications (30,34).

Potential Benefits and Risks of Aspirin in CABG Surgery

In 2002, Mangano reported on the effect of early aspirin after CABG surgery in the *New England Journal of Medicine* (29). In this observational study of 5065 patients, those who received aspirin within 48 hrs of surgery had a lower mortality (1.3% vs. 4%, $P < 0.001$). Aspirin use was associated with a 48% reduction in MI (2.8% vs. 5.4%, $P < 0.001$), and significant reductions in stroke, renal failure and bowel infarction (all $P < 0.01$). In addition, the risk of haemorrhage, gastritis, infection, or impaired wound healing was decreased (OR 0.63; 95% CI: 0.54-0.74). These differences persisted after statistical adjustment for known confounding factors. Thus, it appears that aspirin is safe and could be associated with a reduced risk of death and major complications after CABG surgery. Other observational studies have reported similar results (35,36).

However these observational studies have obvious sources of bias, in that patients who do well early after surgery have greater opportunity of receiving early aspirin therapy, are likely to have a better outcome than patients with a complicated postoperative course. Statistical adjustment for this major confounding, using multivariate techniques, cannot exclude many important but unmeasured factors (37).

There have been some small studies that found aspirin reduces graft thrombosis in CABG surgery (31-33,38), including when given preoperatively (31,39), but there is some increase in bleeding (31,32,34). Goldman et al (31) demonstrated lower graft occlusion rates (16% vs. 23%, $P < 0.05$) with preoperative aspirin. A meta-analysis of 11 trials has shown a significant reduction in vascular graft occlusion (39). Goldman et al (32) did a follow-up trial to compare preoperative aspirin therapy, 325 mg, with postoperative aspirin, 325 mg (started 6 hours after surgery) on early graft patency. In patients given preoperative aspirin, the vein graft occlusion rate was 7.4(1.3)% compared with 7.8(1.5)% in those who received placebo ($P = 0.87$). In the subgroup of patients receiving Y grafts, no grafts were occluded in the preoperative aspirin group compared with 7.0(3.6)% in the placebo group ($P = 0.07$). Patients in the aspirin group received more transfusions than those in the placebo group (median, 900 vs 725 ml, $P = 0.006$). The re-operation rate for bleeding was higher in the aspirin group (6.3% vs. 2.4%, $P = 0.036$). Median blood loss within the first 6 hrs was minimally higher, 500 ml vs. 448 ml, $P = 0.01$. Thus, although preoperative aspirin therapy had a small effect on bleeding, there appeared to be beneficial effect on early patency for Y grafts and internal mammary artery grafts. A net positive effect in CABG, if verified in a large randomized trial, would result in a major change in clinical practice around the world. The improvement in outcome, reduction in chronic disease, and cost savings, would be dramatic.

Preoperative aspirin may have additional benefits in surgical patients. The pulmonary embolism prevention (PEP) trial, testing aspirin 160 mg, found a significant reduction in major pulmonary embolism in patients undergoing hip surgery (40). Also, a meta-analysis of small trials (10) and the above observational study (23) suggest that aspirin may reduce the risk of stroke, a serious complication after CABG surgery that is believed to be associated with emboli from aortic manipulations during surgery. Thus although there is some evidence that recent aspirin therapy increases blood loss after CABG surgery, there does not appear to be an increased need for blood transfusion or re-operation. On the other hand, there may be a beneficial effect on graft patency and avoidance of MI. Other major complications and mortality could also be reduced.

Several observational studies have not found an increased bleeding risk with aspirin in CABG surgery (27,28,41). However, a retrospective analysis of 2,606 CABG surgical patients evaluated the relationship between recent aspirin therapy (incidence 63%) and transfusion requirements (42). The rate of postoperative blood transfusion was slightly increased with aspirin use, 23% vs. 19%. The use of FFP, platelets and cryoprecipitate was higher in aspirin users, 4.5% vs. 2.1% ($P < 0.05$). Re-operation rates were higher, 3.7% vs 2%, $P < 0.05$.

In an overview, Bélisle and Hardy (25) reviewed more than 50 studies including more than 10,000 patients, as well as data from 5,426 patients operated on at their institution (Montreal Heart Institute). They concluded that although aspirin therapy increases postoperative blood loss, it was < 300 mL (about 30% increase); this should not increase use of blood products if a strict transfusion protocol were followed. Ferraris et al (42) analyzed a database of 2,606 CABG patients to identify the relationship between recent aspirin therapy (incidence 63%) and transfusion requirements. The rate of postoperative blood transfusion was slightly increased with aspirin use (23% vs. 19%). Re-operation rates were higher (3.7% vs 2%, $P < 0.05$). However, use of propensity scores illustrated differing risk between groups, indicating probable sources of bias in this observational study. The authors concluded that a large randomized trial was required.

Randomized trials in non-surgical populations have identified excess bleeding complications with aspirin therapy (10), which might outweigh reductions in thrombotic events: aspirin-patients had significantly fewer recurrent ischemic strokes within 14 days (2.8% vs 3.9%, $P < 0.001$). There was a significant excess of 5 (SD 1) transfused or fatal extracranial bleeds per 1000 patients allocated aspirin (1.1% vs 0.6%, $P = 0.0004$). Fewer pulmonary emboli were recorded within 14 days with aspirin (0.6% vs 0.8%), but this difference was not significant ($P = 0.08$).

Almaghadi et al (43) did a meta-analysis of randomized and non-randomized studies involving 1748 patients showing aspirin increased blood loss and transfusion requirements. Most troubling was that aspirin seemed to increase the need for re-exploration surgery because of excessive bleeding (Figure 1), and we know this is associated with further morbidity (43).

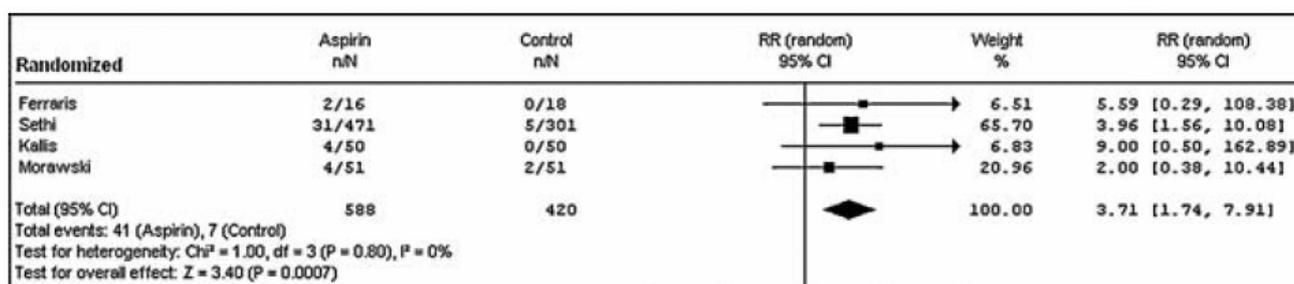


Figure 1. Meta-analysis of studies comparing rates of re-exploration between aspirin and control groups.

A later meta-analysis that included non-randomized studies, suggests aspirin doses < 325 mg/day may be safe (44). Both meta-analyses conclude that large randomized trials are necessary to determine the safety and efficacy of pre-operative aspirin in contemporary cardiac surgical practice.

In 2008 a systematic review (45) evaluated the efficacy and safety of preoperative antiplatelet therapy to maintain graft patency and reduce ischemic complications in patients undergoing CABG surgery. The summarized up-to-date data confirm that aspirin is typically withheld for 7-10 days preoperatively, but in the current era of routine antifibrinolytic therapy and the high prevalence of patients with extensive atherosclerotic disease, this practice was questioned by the authors. They concluded that questions remain regarding perioperative aspirin therapy in CABG surgery, and call for more randomized trials.

Thus there is conflicting evidence for an adverse effect of recent aspirin therapy on blood loss after cardiac surgery. There may or may not be an increased risk of blood transfusion or re-operation. There may be a beneficial effect on graft patency and avoidance of MI. Other major complications and mortality may also be reduced. But the evidence for this is equivocal if not conflicting.

This uncertain state of affairs is elucidated by the most recent expert guidelines from the US Society of Thoracic Surgeons, updated in 2005 (46). They note that "there is only anecdotal information supporting the discontinuation of aspirin before elective CABG surgery". An expert committee reviewed the published literature and recommend the following:

1. Stop aspirin 3-5 days before elective CABG surgery in low-risk patients (class IIa recommendation).
2. Continue, or commence in those not receiving aspirin, before CABG surgery in urgent/emergency CABG surgery (class IIa recommendation)
3. Aprotinin limits bleeding in aspirin-treated high-risk CABG patients (class IIa recommendation)
4. Lysine analogues (including TxA) can be used to limit bleeding in aspirin-treated high-risk CABG patients (class IIb recommendation)

The most recent transfusion guidelines jointly produced by the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists in 2011 (88) maintain their recommendation to stop aspirin only in elective patients without acute coronary syndromes before operation, with the expectation that blood transfusion will be reduced (class IIa).

In part contrast, the American Society of Chest Physicians (47) recommends continuing aspirin up to and beyond the time of CABG surgery (Grade 1C). Conflicting guidelines from such expert professional organisations highlight the lack of large trial data (i.e. no class I recommendations), and offer strong support for our study hypothesis and procedures.

Antifibrinolytic Therapy

Several systematic reviews have found that antifibrinolytic therapy with epsilon aminocaproic acid, TxA or aprotinin reduces blood loss and the need for blood transfusion, and for aprotinin, re-operation for bleeding, in cardiac surgery (24,48,49). It is likely that such drug treatment could reverse a major bleeding effect of aspirin, but studies to date have been equivocal (49).

TxA, like epsilon aminocaproic acid, is a synthetic antifibrinolytic that competitively inhibits the lysine binding sites on plasminogen and fibrinogen, preventing conversion of fibrinogen to FDPs and platelet dysfunction (50). TxA reduces post-bypass blood loss and red cell transfusion (24,50). Aprotinin is a serine protease inhibitor that reduces excessive fibrinolysis and pro-inflammatory cytokine production. But concerns have been raised about aprotinin with respect to severe hypersensitivity reactions (0.5%), and an increased risk of graft occlusion, MI and renal dysfunction (52). The recent BART study (see below) suggests that aprotinin may be associated with excess mortality compared with the lysine analogues (51). TxA appears to have sufficiently similar efficacy to aprotinin (24,50,52), at much lower cost - about \$50 per procedure - and no evidence of anaphylaxis on re-exposure. The only other antifibrinolytic drug, epsilon aminocaproic acid has not undergone such extensive evaluation and has been withdrawn from the Australian market.

Antifibrinolytic therapy may increase the risk of graft thrombosis, particularly in small patients or those with poor distal perfusion. The IMAGE trial (52), a multicentre randomised trial in 796 CABG patients compared aprotinin (n = 436) with placebo (n = 434). Among 703 patients with assessable saphenous vein grafts, occlusions occurred in 15% of aprotinin-treated patients and 11% of patients receiving placebo (P = 0.03), although this increased risk was reduced after multivariate adjustment. This trial raises the prospect that aprotinin could increase early vein graft occlusion. The lysine analogues may also have pro-thrombotic effects (53). Although aprotinin is the most frequent antifibrinolytic drug implicated, there is also some concern with epsilon aminocaproic acid (54,55) and desmopressin (48).

Levi et al (48) did a systematic review and meta-analysis of 72 trials (8409 patients) of antifibrinolytic drug therapies. They found that there was a significant decrease in perioperative blood loss and blood transfusion, but also a beneficial effect on the need for re-operation and overall mortality. When the analysis was limited to studies in complicated cardiac surgery, defined as repeat surgery or surgery in patients who were taking aspirin preoperatively, a similar effect was seen. Specifically, treatment with aprotinin decreased mortality almost two-fold (OR 0.55, 95% CI: 0.34-0.90) compared with placebo. Treatment with aprotinin and with lysine analogues decreased the frequency of re-operation (0.37 [0.25-0.55], and 0.44 [0.22-0.90], respectively). Aprotinin and lysine analogues did not increase the risk of perioperative MI; however, desmopressin was associated with a 2.4-fold increase in the risk of MI.

Levi et al (48) concluded: "*This meta-analysis further supports the use of aprotinin or lysine analogues in clinical practice. However, only a large prospective controlled trial with mortality as the primary outcome will provide definitive evidence.*" All other major reviews have come to similar conclusions (24,48,56).

The BART trial

This Canadian randomised trial of 2331 high-risk cardiac surgical patients compared aprotinin with TxA and aminocaproic acid (51). The primary outcome was massive postoperative bleeding. Aprotinin had a moderate reduction in bleeding risk when compared with the lysine analogues, RR 0.79 (95% CI: 0.59-1.05), but mortality was higher in the aprotinin group, RR

1.53 (95% CI: 1.06-2.22). This study has had a major impact on cardiac surgical practice around the world, where aprotinin use has virtually been abandoned.

We have argued (57) that the safety of *all* the antifibrinolytic drugs should be questioned: if the BART trial found that aprotinin is a more potent antifibrinolytic compared with the lysine analogues yet is associated with excess mortality, could not the lysine analogues, which are more efficacious than placebo, be associated with excess mortality when compared with placebo (i.e. no antifibrinolytic?). A large, adequately powered placebo controlled trial is urgently needed to investigate the effectiveness and safety of the lysine analogues in CABG surgery.

Henry et al (24) has done an updated meta-analysis that included the BART data. They identified 49 trials involving 7,439 participants. The summary RR for death with aprotinin versus placebo was 0.93 (95% CI: 0.69-1.25). In the 19 trials that included TxA, the RR was 0.55 (95% CI 0.24-1.25). That is, neither were statistically significant - so why has aprotinin been abandoned? They found no difference in the risk of MI with use of aprotinin compared with the lysine analogues in either direct or indirect analyses. For MI, the RR for TxA vs. placebo (1,732 participants) was 0.86 (95% CI 0.43-1.75). There was no difference in the risk of MI with the use of aprotinin or TxA (summary RR 1.0, 95% CI 0.71-1.43). The authors emphasize that this meta-analysis should not be interpreted as providing definitive evidence that aprotinin increases the risk of death.

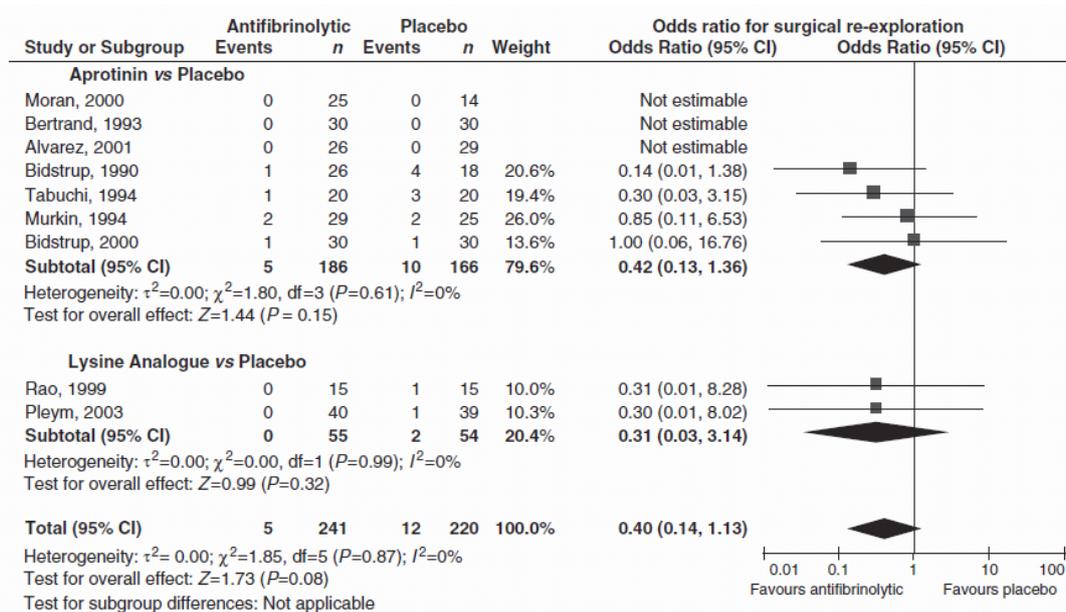
Ngaage and Bland have done a systematic review of trials and other controlled studies of TxA in comparison to aprotinin (86). There were over 11,000 patients included from 25 randomised trials and four matched studies. Compared with placebo, TxA was associated with reduced blood loss of 300 ml (95% CI: 230-370), and a decrease in rates of re-operation for bleeding by 48%, transfusion of packed red cell by 47% and use of haemostatic blood products by 67%. BUT they also found a non-significant tendency for postoperative neurological events in the TxA group. They concluded that given the potential to increase neurological complications, the current trend towards indiscriminate use of TxA for all cardiac patients needs to be re-evaluated.

Use of TxA is associated with increased risk of seizures after surgery (87), presumably related to the anti-GABA effect of TxA, but the clinical significance of this remains unclear.

Combination of Aspirin and Antifibrinolytic Therapy

Antifibrinolytics reduce blood loss and red cell transfusion in CABG surgery (24,48, but there is insufficient evidence of their effect in patients on aspirin (48,49). In a small randomized trial comparing aspirin + aprotinin (AA), aprotinin alone, and placebo in 119 CABG patients (58), there was significantly reduced blood loss with aprotinin. Interestingly, pre-treatment with aspirin led to a further *reduction* in bleeding of 18%, AA vs. placebo: $P < 0.001$. When comparing the aspirin group to the non-aspirin groups, a trend towards a reduction in MI was observed, from 15% to 5%, $P = 0.08$. Hence, not only was the antifibrinolytic associated with a reduction in postoperative blood loss, but the combination of aspirin and antifibrinolytic also reduced bleeding and may have a protective effect on perioperative MI.

We did an updated systematic review and meta-analysis of all relevant trials of antifibrinolytic therapy in CABG patients on aspirin (49). Data from 17 trials (n=1620) confirmed the efficacy of antifibrinolytic therapy to reduce both chest-tube drainage (weighted mean difference 374 ml, 95% CI 275-473 ml; $P < 0.00001$) and blood transfusion requirements (odds ratio 0.37, 95% CI 0.27-0.49; $P < 0.00001$). Nine studies ($n=461$) reported the need for surgical re-exploration, seven comparing aprotinin with placebo and two comparing lysine analogues with placebo. Only 17 events were reported in six studies. Despite a trend towards a reduced rate of re-exploration in both subgroups as well as the overall summary estimate, there was no significant difference in the rate for re-exploration between patients receiving antifibrinolytic and placebo (odds ratio 0.40, 95% CI 0.14-1.13; $P=0.08$):



Seven studies ($n=646$) reported mortality, six comparing aprotinin with placebo and two comparing lysine analogues with placebo. There were only five deaths reported across all studies. There was no difference in mortality between patients receiving antifibrinolytic and patients receiving placebo (odds ratio 1.80, 95% CI 0.29-11.31; $P=0.53$). We found no difference in the rates of adverse events between groups but observed a trend towards a reduced risk for the composite outcome of thrombotic complications (odds ratio 0.49, 95% CI 0.21-1.13; $P=0.09$). However published trial data are sparse: only five studies (total of 241 patients) reported stroke as an adverse event; only six events occurred in two studies.

Thus, there is some evidence that antifibrinolytic therapy reduces bleeding and a need for blood transfusion, and may reduce the need for re-operation in patients on aspirin. There is insufficient safety data for MI, stroke, pulmonary embolism, tamponade and mortality.

Recombinant Factor VIIa (Novoseven™)

Recombinant FVIIa (rFVIIa) is a novel haemostatic agent originally developed to treat patients with haemophilia. Several case reports and preliminary evidence from sponsored

trials suggest that rFVIIa may be effective in treating cardiac surgical patients who have uncontrolled bleeding (61-66). The main mechanism by which rFVIIa is thought to act is via an interaction with tissue factor with subsequent activation of factor IX and X, and generation of thrombin. There may also be a direct beneficial effect on platelet function. This combined effect of activated platelets and activated clotting factors is essential for the formation of a stable haemostatic fibrin plug (66). Excessive bleeding post-bypass not controlled by conventional measures may be an indication for use of rFVIIa.

In 2009 a phase II dose-escalation study of rFVIIa in patients who had undergone cardiac surgery and were bleeding found that, despite rFVIIa reducing serious bleeding, there was an increased number of critical serious adverse events, including stroke, in those patients randomized to receive rFVIIa (84). A recent meta-analysis (85) has confirmed this finding of a markedly higher risk of stroke, OR 3.69 (95% CI 1.1-12.4), $P=0.03$; and possibly overall perioperative thromboembolic events, OR 1.84 (95% CI 0.82-4.1), $P=0.14$. This raises serious safety concerns for any of the haemostatic agents, including antifibrinolytics, in that they may well reduce bleeding but at a cost of thrombotic complications such as stroke and MI. This is of course the underlying rationale for the ATACAS trial.

Why Do a Large Multicentre Trial?

Tunis et al (59), from the US Medicare and Medicaid Services, published a key paper in the September 2003 issue of *JAMA*, arguing that the quality of available scientific evidence is often inadequate to guide clinical and health policy choices. They urged an increase in the conduct of "practical clinical trials", a phrase used to describe effectiveness trials. These: (1) select clinically relevant alternative interventions to compare, (2) include a diverse population of study participants, (3) recruit participants from heterogeneous practice settings, and (4) collect data on a broad range of health outcomes. This need, recognized by us (60,61) and others, is best addressed with large multicenter trials in routine clinical settings.

Summary of Rationale and Significance

- Low-dose enteric aspirin has been shown to reduce thrombotic complications in medical and noncardiac surgical patients, but cardiac surgery has a high bleeding risk and so the risks and benefits for patients undergoing CABG surgery are unclear.
- Aspirin is used near-universally for acute coronary syndromes, and many such patients undergo urgent CABG surgery. It is unclear whether such therapy should be stopped before surgery
- The lysine analogue antifibrinolytic drugs are near-universally used and are inexpensive, yet we do not know whether or not there is an increased risk of thrombotic complications in CABG surgery. The price for a small reduction in bleeding risks and possibly blood transfusion may be outweighed by a higher rate of MI, stroke and death.
- When considering the cost and extent of CABG surgery in the US and around the world, small differences in outcome would have major implications for healthcare delivery.

- Expert professional organizations have produced guidelines that are, at least in part, contradictory and are limited by lower level evidence ratings. That is, because of insufficient clinical trials.
- The authors of all the systematic reviews and meta-analyses on these topics have emphasized the lack of high quality data, and call for definitive large randomized trials to be done.
- A large trial in coronary artery surgery needs to be done in order to demonstrate unequivocally that the benefits of aspirin, and tranexamic acid, outweigh their risks.

Preliminary Studies and Feasibility

Some of us have conducted a preliminary survey of cardiac surgical practice in Australia, illustrating the wide variations in practice regarding stopping aspirin before surgery and use of antifibrinolytic therapy (62). The feasibility for the conduct of the ATACAS trial is supported by our experience in conducting other large scale perioperative clinical trials in the US, Australia and many other countries (62-67).

Our experience of ATACAS to date is extremely positive and there have not been any unexpected adverse events.

Safety Data from the ATACAS Trial

Under the guidance of our DSMC we undertook a blinded pooled analysis of the first 744 participants in the ATACAS trial in order to confirm safety of future participants because of the reports of seizures with TxA and a concern for excessive bleeding risk. The results were reassuring. Despite ATACAS being an at-risk study cohort, there is no evidence of an increase in serious bleeding complications, peptic ulceration, or seizures in patients recruited to ATACAS.

	N=744
Intraoperative	
Red cell transfusion	103 (14%)
Platelet transfusion	57 (7.6%)
Postoperative (day 1)	
Red cell transfusion	222 (30%)
Platelet transfusion	87 (12%)
Fresh frozen plasma	106 (14%)
Aprotinin administered	7 (0.9%)
Novoseven administered	4 (0.5%)
Any adverse event reported	24 (3.3%)
Tamponade	5 (0.7%)
Serious haemorrhage, requiring re-exploration	19 (2.6%)
Peptic Ulceration	10 (1.4%)
Seizure	3 (0.4%)

Mediastinal drainage at 4 hrs, ml	270 (175-400)
Mediastinal drainage at 24 hrs, ml	750 (540-1063)
Total mediastinal drainage, ml	1010 (670-1460)

Conclusion

There are some compelling reasons to question the routine stopping of aspirin before elective CABG surgery. Although aspirin may increase bleeding, it may also reduce MI, other serious complications and death. Both aprotinin and TxA can counteract possible bleeding complications of aspirin in CABG patients, and are likely to have additional benefits. There is no evidence that the effects of TxA are significantly different from that of aprotinin. On the basis of cost and safety, the best agent to evaluate is TxA. Large outcome trial data are lacking.

When considering the cost and extent of CABG surgery in Australia (n>18,000) and around the world, small differences in outcome would have major implications for healthcare delivery.

We propose a large randomised trial to answer two clinically important questions:

- i. Should low-dose aspirin be continued up until the day of CABG surgery?
- ii. Should TxA be used for all at-risk CABG surgery?

2. OBJECTIVES

This prospective, randomised, double-blind, factorial trial will test whether aspirin, tranexamic acid, or both, can reduce mortality and/or major morbidity after elective coronary artery surgery.

We propose a large randomised controlled trial to answer two clinically important questions:

- i. Should low-dose aspirin be continued up until the day of CABG surgery?
- ii. Should TxA be used for all at-risk CABG surgery?

Nb: the factorial design has the added strengths of determining whether any beneficial effects of aspirin and TxA are additive, and whether any bleeding risk of aspirin can be avoided with TxA.

2.1 Primary Endpoint

A composite endpoint including 30-day mortality or major ischaemic morbidity (myocardial infarction, stroke, pulmonary embolism, renal failure, bowel infarction)

2.2 Secondary Endpoints

- (i) 30-day mortality
- (ii) Ischaemic complications
 - Myocardial infarction

- Stroke
 - Renal failure
 - Pulmonary embolism
 - Bowel infarction
- (iii) Bleeding complications
- Major haemorrhage (re-operation for bleeding)
 - Cardiac tamponade
 - Number of transfused blood product units

3. STUDY DESIGN

3.1 Experimental Design

Multicentre, double-blind, randomised, 2x2 factorial trial. Patients will be randomised to one of the following 4 treatment groups: aspirin, tranexamic acid, aspirin plus tranexamic acid, placebo.

A factorial trial is premised on no interaction between each of the active treatments. Aspirin is an antiplatelet drug known to reduce thrombosis, but may increase bleeding because of platelet inhibition. TxA is an antifibrinolytic drug that reduces surgical bleeding because it inhibits fibrinolysis, but this may increase thrombosis because fibrinolysis is an intrinsic defence against intravascular clot formation. Aspirin and TxA act independently, and each of their effects are preserved in the presence of the other.

3.2 Subject Selection

3.2.1 Definition of Disease State

Patient undergoing elective CABG or OPCAB surgery for any reason, who are at an increased risk of major complications due to their age, cardiac function, comorbidity, or previous cardiac surgery.

3.2.2 Source and Number

Subjects will be recruited from the elective cardiac surgery waiting lists. This will usually occur prior to the day of surgery, in the preadmission clinic or on the ward. 4600 patients in total will be required for this study (1150 in each of the 4 groups).

3.2.3 Entrance Criteria¹

Inclusion criteria will include the following:

1. Males and females, age 18 years and over

¹ Each institution or individual surgeon is at liberty to restrict the trial entry criteria further, according to local preferences or specific patient risk analysis (for example, not to include all re-do operations)

2. Written, informed consent
3. Elective coronary artery surgery (on-pump or off-pump)
4. Patient is at increased risk of major complications, defined by any of:
 - Age ≥ 70 years
 - Left ventricular impairment (fractional area change $< 20\%$, ejection fraction $< 40\%$, or at least moderate impairment on ventriculography)
 - Concomitant valvular or aortic surgery
 - Aneurysmectomy
 - Repeat cardiac surgery ("re-do")
 - Chronic obstructive pulmonary disease
 - Renal impairment (ser. creatinine $> 150 \mu\text{mol/l}$ or creatinine clearance $< 45 \text{ ml/min}$)
 - Obesity (body mass index $> 25 \text{ kg/m}^2$)
 - Pulmonary hypertension (mPAP $> 25 \text{ mmHg}$)
 - Peripheral vascular disease.

Exclusion Criteria

1. Poor (English) language comprehension
2. Clinician preference for antifibrinolytic therapy
3. Urgent surgery for unstable coronary syndromes where for clinical reasons antiplatelet medication cannot be discontinued
4. Active peptic ulceration
5. Allergy or contraindication to aspirin or tranexamic acid
6. Aspirin therapy within 4 days of surgery
7. Warfarin or clopidogrel therapy within 7 days of surgery, or GIIb/IIIa antagonists within 24 h of surgery
8. Thrombocytopenia or any other known history of bleeding disorder
9. Severe renal impairment (serum creatinine $> 250 \mu\text{mol/l}$, or estimated creatinine clearance $< 25 \text{ ml/min}$)
10. Recent haematuria
11. Thromboembolic disease relating to: history of postoperative or spontaneous pulmonary embolism, spontaneous arterial thrombosis or familial hypercoagulability (eg. Lupus anticoagulant, protein C deficiency)
12. Pregnancy.

3.3 Study Medication

3.3.1 Form

Bayer (pharmaceutical company) has provided active aspirin and matched-placebo study medication at no cost. The active medication (aspirin 100 mg) is oral enteric-coated. Details of delivery, packaging, and local handling will be provided in the Procedures Manual; these are expected to vary at some sites according to their local and national guidelines.

TxA will be provided locally, in view of this being a near-routine drug in cardiac surgery. If not used as such, or not available locally, we will provide this study drug from the trial management centre. Active drug or matched placebo (using Normal Saline as a visually indistinguishable solution) will be prepared by the anaesthetist/perfusionist or accredited professional at the time of surgery. TxA or aminocaproic acid is used near-universally in all CABG surgery (88).

3.3.2 Dosing Schedule

Oral enteric-coated Aspirin (or matched placebo) will be commenced on the day of elective surgery, using 100 mg po, ideally at about 1-2 hours before surgery. This dose has been shown to be effective, with an onset time of <1 hr, and with a suitable side effect profile (7,33); higher doses are more likely to cause unacceptable bleeding (7,21,33).

TxA (or matched placebo) will be administered by the anaesthetist/perfusionist or accredited professional responsible for the procedure. It is to be administered within 20 mins following induction of anaesthesia as an IV bolus-infusion, 100 mg/kg (1 ml/kg) over 30 mins. This regimen has been shown to provide and maintain effective TxA concentrations throughout and after surgery (36).

3.4 Study Procedure

3.4.1 General Description

Study Flow Chart

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Preadmission clinic	Day of surgery	Postop day 1	Postop day 2	Postop day 3	Hospital discharge	30 day follow up	12 mth follow up
Informed consent completed	X or	X						
Entry criteria	X							
Demographics	X							
Medical and surgical history	X							
ECG	X		X	X	X	X		
Euroscore	X							
Adverse events		X	X	X	X	X	X	
Randomisation		X						
Study drug administration		X						
Troponin (or CK-MB) levels			X*		X*			
Study endpoints		X	X	X	X	X	Telephone and MR review	Telephone and MR review

* Ideally we require 12-24 and 48-72 hour troponins.

Potentially eligible patients on the waiting list for elective CABG surgery will be screened by a research assistant ([RA] nurse or medical officer), to check that the patient meets the entry criteria for the study. Eligible patients will be approached at least the day before surgery either in preadmission clinic or on the ward. The study will be explained to them, they will be given a copy of the PI&CF and given an opportunity to ask questions and/or discuss the study with family members etc. If the patient agrees to participate they will be asked to sign the PI&CF. Preoperative demographic characteristics and details of patients' medical and surgical

history will be recorded. They will also undergo a 12-lead ECG, CXR, pathology testing, and other routine investigations. All key anaesthetic and operative characteristics, drug treatments, blood product use and relevant postoperative outcomes and interventions will be recorded in the CRF. The Euroscore (2) will be used to grade surgical risk.

On the day of surgery, or in institutions that have reliable theatre booking/availability for CABG surgery on the day before surgery, patients will be randomised to one of the 4 treatment groups. All other perioperative clinical care will be according to standard practice as this is an effectiveness trial and some elements of the trial are deliberately left to the clinicians' discretion in order to reflect usual practice and maximise generalisability. Anaesthesia and surgery will be according to local practices. This will include choice of anaesthetic drugs, use of intraoperative transoesophageal echocardiography, vein and artery harvesting, extent of grafting according to coronary angiography, myocardial protection techniques, CPB, surgical haemostasis and inotrope therapy. These will vary and are allowable in the trial. Early postoperative care in the ICU will be jointly determined by the cardiac surgical and ICU staff, as per local practices. All such relevant perioperative data will be recorded on the CRF.

Aspirin should be stopped at least 4 days before surgery (current standard practice). Other antiplatelet therapies (eg. clopidogrel, ticlodipine, etc) should be stopped at least 7 days before surgery, as is routine practice. Heparinisation for CPB will be based on a bolus dose of 3 mg/kg and maintenance of an ACT >450 sec during CPB, with additional heparin as required. Reversal with protamine 4 mg/kg will occur at the completion of CPB. The effect will be monitored with ACT (<140 sec). Other antifibrinolytic therapy cannot be used before or during CPB, but can be used if there is clinically significant bleeding following protamine administration:

3.4.2 Guideline for Managing Excessive Bleeding after CPB or OPCAB²

1. Administer further protamine, 50-100 mg, whether the ACT is elevated or not
2. Administer a platelet transfusion, 5U, if the platelet count <100,000/L
3. Administer FFP, 5U, if INR >1.4 or fibrinogen <150 g/L
4. Administer cryoprecipitate if fibrinogen <100 g/L
5. If bleeding remains problematic,³ consider rVIIa (Novoseven™), 90 µg/kg; aprotinin (bolus + infusion), loading dose 2 million U, followed by 500,000 U/h; or desmopressin.

It is recognised that in surgical units with access to near-patient testing of coagulation, local practices may dictate alternative guidelines for the management of excessive bleeding.

3.4.3 Red Cell Transfusion Guideline

² Excessive bleeding is defined as >200 ml/h for >2 h, or >400 ml in any 1 h.

³ Bleeding >100 ml/h after protocol-directed therapies.

A marked variability in transfusion practices in otherwise uncomplicated CABG surgery exists (18). We will have a transfusion guideline in this trial, in order to reduce autologous transfusion (12):

1. Before CPB - transfuse packed red cells if haematocrit <28% or haemoglobin <90 g/L
2. During CPB - transfuse packed red cells if haematocrit <20% or haemoglobin <70 g/L
3. After CPB or OPCAB - transfuse packed red cells if haematocrit <25% or haemoglobin <80 g/L.

1. Preoperative period

All patients will receive their usual preoperative care. After providing informed consent, they will be ordered premedication (if required) as per their anaesthetist's usual practice.

2. Intraoperative period

Appropriate patient and equipment monitoring will be established before induction of anaesthesia (usual practice). Choice of anaesthetic agents, muscle relaxants and perioperative analgesia will be left to the discretion of the anaesthetist. Operative characteristics will be recorded: adverse intraoperative events, duration of anaesthesia, additional surgery.

Surgery will be according to local practices.

3. Postoperative period.

Early postoperative care in the ICU will be jointly determined by the cardiac surgical and ICU staff, as per usual local practice. In general, the intensive care physician is primarily responsible for decisions regarding management in the ICU and the cardiac surgical staff are primarily responsible for most aspects of later postoperative care. Local hospital practices will vary and are allowable in this trial.

Blood will be collected postoperatively at 12-24 and 48-72 hours for two troponin levels, and a 12-lead ECG will be performed on the 3 days following surgery to detect MI.

Additional tests will be ordered if clinically indicated (eg, chest pain, dyspnoea, circulatory instability).

Additionally, patients will be contacted by phone at 30 days, and again at 12 months after surgery, and their medical record reviewed to ascertain if they have experienced any adverse outcomes.

3.4.4 Clinical Observations

The primary outcome is a composite endpoint: major ischaemic cardiovascular morbidity (MI, stroke, PE, ARF, bowel infarction), and death. Data concerning these endpoints will be coded (for group identity) and sent to a separate Endpoint Adjudication Committee (see Section 7.3).

- I. All-cause mortality within 30 days of surgery
- II. Major postoperative complications
 - 1) Myocardial infarction (MI): the presence of either (75):

- a) typical rise and gradual fall (troponin) or more rapid rise and fall (CKMB)⁴ of biochemical markers of myocardial necrosis with at least one of the following:
 - ischaemic symptoms;
 - development of pathological Q waves on two adjacent leads on the ECG;
 - ECG changes indicative of ischaemia (ST segment elevation or depression).
- b) pathological findings (autopsy) of an acute myocardial infarction
- c) in view of the difficulty of detecting ischaemic chest pain in the early postoperative period, in addition to the above a non-Q wave MI will be defined by a cardiac enzyme elevation in isolated CABG cases, using any of:
 - i. Troponin I >10 ng/ml at any time >12 hours post-CABG (76-79)
 - ii. Troponin T >4.0 at >12 hours post-CABG (78,80)
 - iii. CKMB >3 times upper limit of normal at >12 hours post-CABG (79)
- 2) Pulmonary embolism (PE): high probability VQ scan or documented on pulmonary angiogram
- 3) Stroke: cerebral infarction or haemorrhage on CT scan, or new neurological signs (paralysis, weakness or speech difficulties) lasting more than 24 hours or leading to earlier death
- 4) Acute renal failure: a doubling of preoperative serum creatinine, or a rise >100 mmol/L from baseline
- 5) Bowel infarction: a need for bowel resection or bowel infarction diagnosed at autopsy
- 6) Cardiac tamponade: typical haemodynamic and/or echocardiographic features and requiring surgical re-exploration
- 7) Major haemorrhage: any excessive bleeding requiring surgical re-exploration
- 8) Mortality - death within 30 days of surgery

Other than 12-lead ECG and cardiac enzyme measurements (which should be routine for all patients), additional laboratory investigations or imaging will be determined by the patient's clinical condition throughout the trial period.

4. EXPERIMENTAL CONTROL

4.1 Randomisation

This will be a prospective, double-blind, randomised trial. After stratification by centre, patients will be randomly allocated from a computer-generated list (1:1:1:1). Group allocation will be obtained by telephone contact to the Trial Coordinating Centre (Australia Freecall 1800 678 432; International +0800 2273 4377) after informed consent is obtained. A 24-hr interactive voice recognition system (IVRS) will be available. An alternative web-based randomisation service is expected to become available during the conduct of the trial.

This is an intention to treat trial. Any participant who is randomised to study administration will be followed for the duration of the trial (unless they withdraw consent) even if they are

⁴ Occurring after CABG surgery (ie. not a residual effect of acute coronary syndrome in the preoperative period); periprocedural cardiac enzyme elevations in the absence of Q waves will not be considered an event.

withdrawn from the active phase of the trial. Patients who do not complete the active phase of the study will not be replaced.

4.2 Blinding Procedure

The anaesthetist and all other staff will be blinded to aspirin allocation, with study drug coding and delivery being managed by research staff at the Alfred Hospital (Melbourne, Australia) or the pharmacy department of Derriford Hospital (Plymouth, UK). However, for TxA, an anaesthetist or accredited practitioner is required to prepare the IV study drug at each study site (according to group allocation, and instructions in the coded envelope provided by the study coordinating centre). Ideally, the anaesthetist or accredited practitioner preparing the IV study drug (TxA or placebo saline) should not be the anaesthetist responsible for the care of the patient during and after surgery. However, it is recognised that for some sites, limited staffing may make this very difficult and so the responsible anaesthetist can prepare IV study drug provided that all other research staff are kept blinded to TxA/placebo (saline) administration. Patients, surgeons and research staff interviewing patients postoperatively must be blind to treatment allocation. Patient demographic and perioperative characteristics will be compared.

4.3 Case Report Forms

For each form on which information is entered, the patient's initials, allocation number and the date of the visit must be entered in the appropriate space. The CRFs must be neatly handwritten with a black-ink ballpoint pen.

Errors must be corrected by drawing a single line through the incorrect entry and writing in the new value positioned as close to the original as possible. The correction must then be initialled and dated by the authorised individual making the change. Do not obliterate, write over, or erase the original entry when making a correction.

Case report forms should be opened as soon as possible following the start of screening and kept up to date as the patient continues the study.

As soon as possible after the end of each patient's participation in the study the CRF must be completed. This also applies to forms for potential study participants who were not randomised to a treatment group

4.4 Compliance Checks

Random audits of centres may be undertaken. Statistical monitoring of data completions, data variance, and risk-appropriate endpoint rates will be done for all patient data.

4.5 Patient Completion/Withdrawal

All participants who are randomised to study drug will be followed for the duration of the study (unless they withdraw consent) even if they are withdrawn from the active phase of the trial.

4.6 Continuation of Therapy

Aspirin (or matched placebo) will be given as a single oral dose before surgery. TxA will be administered as a single IV infusion after induction of anaesthesia (this will maintain an effective TxA concentration for about 6-8 hours).

4.7 Repeat and Special Laboratory Tests

To be ordered if clinically indicated.

4.8 Concomitant Medications and other Treatments

Heparinisation for CPB will be based on a bolus dose of 3 mg/kg and maintenance of an ACT >450 sec. Reversal with protamine 4 mg/kg will occur at the completion of CPB. The effect will be monitored with ACT (<140 sec).

Other antiplatelet therapies (eg. clopidogrel, ticlodipine, etc) should be stopped at least 7 days before surgery, as is routine practice. Surgical haemostasis will be achieved according to local practices. Other anti-fibrinolytic therapy cannot be used before or during CPB, but can be used if there is clinically significant bleeding following reversal of heparinisation (see 3.4.1).

4.9 Adverse Experiences

At visits 2 to 6 (from the day of surgery after study drug administration until hospital discharge), all adverse experiences either observed by the investigator or one of the clinical staff, or reported by the patient spontaneously or in response to a direct question will be evaluated by the investigator. It is expected that nearly all participants will have adverse experiences given their comorbidity and extent of surgery, and so we ask investigators to limit adverse event reporting to those not anticipated with these factors in mind. However, if there is uncertainty that cannot be resolved with the local site investigator then such events should be noted in the adverse experience section of the patient's CRF. The nature of each experience, time of onset after drug administration, duration, severity and relationship to treatment should be established. Details of changes to the dosage schedule or any corrective treatment should be recorded on the appropriate pages of the CRF. In order to assist site investigators and maintain consistency of reporting between different sites the trial chief investigator will formulate a list of common and anticipated complications that do not have to be reported as adverse events. This list of adverse events will be provided within the procedures manual and be regularly updated

Maximum intensity should be assigned to one of the following categories:

1. Mild- an adverse events which is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
2. Moderate- an adverse events which is sufficiently discomforting to interfere with normal everyday activities.
3. Severe- an adverse events which is incapacitating and prevents normal everyday activities and/or requires therapeutic intervention (i.e. use of a prescription drug or hospitalisation).

A serious adverse event (SAE) is defined as any event which is fatal, life-threatening, permanently disabling or incapacitating or results in hospitalisation, prolongs a hospital stay or is associated with congenital abnormality, carcinoma or overdose. A suspected unexpected serious adverse reaction (SUSAR) is an SAE that is unexpected; that is, not consistent with current information.

SAEs and SUSARs should be reported within 24 hours of identification by telephone and/or email to the local site investigator and the Sponsor (trial coordination centre, Australia). Note that study endpoints, including death, stroke, MI and GI bleeding, do not need to be recorded or reported as adverse events, SAEs or SUSARs. Other reporting requirements mandated by the relevant national authority should also be followed.

For SAEs and SUSARs, a preliminary telephone or e-mail report should be followed by a full report which includes copies of relevant hospital case records and other documents where applicable.

Life threatening means that the patient was at immediate risk of death from the event as it occurred; that is, it does not include a reaction that, had it occurred in a more serious form, might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though drug induced hepatitis can be fatal.

Permanent disability means a permanent and substantial disruption of a patient's ability to carry out normal life functions.

Causality

Every effort will be made by study investigators to explain each adverse experience and assess its relationship, if any, to drug treatment. Causality should be assessed using the following categories:- unassessable, unrelated, probably unrelated, probably related, related.

Possible relationship of any adverse experience to the current disease, for which the patients are being treated, any other diseases present and any concomitant drug treatment which is permitted during the study should be considered. If such a relationship could exist, it should be documented in the patient's Case Report Form.

The degree of certainty with which the relationship of an adverse experience is linked to drug treatment will be determined by how well the experience can be understood in terms of:

- a) known pharmacology of the drug.
- b) reaction of similar nature being seen previously with this drug or class of drug.
- c) the experience having often been reported in the literature for similar drugs as drug related e.g. skin rashes, blood dyscrasia.
- d) the experience being related by time to drug ingestion or reproduced on rechallenge.

4.10 Overdosage/Antidote

Treat excessive bleeding or thrombosis according to local practices, and being guided by Section 3.4.2

4.11 Emergency Unblinding of Study Drug

If an adverse clinical scenario arises that could be attributed to study medication, and cannot be dealt with by standard clinical procedures (e.g. excessive bleeding not controlled by steps outlined in Section 3.4.2), then, if in the opinion of the treating physicians, and after consultation with the site investigator, the Trial Coordinating Centre can be contacted via email or telephone at any time.

5. DATA MANAGEMENT PROCEDURES

5.1 Review and Confirmation of Case Report Forms

Data collection will be via a paper CRF and web-based data entry. This will be coordinated by the trial management centre and all data and processes will be reviewed by the trial data quality committee.

5.2 Data Base Production and Verification

Study data will be collected via the internet, monitored by the trial data management centre (CCRE and ANZCA TG) where all data fields are checked and automatically downloaded onto a database. At the end of the trial site-specific data will be sent to each site investigator on a CDROM, for long-term storage.

We will maximise data quality and protocol standardization by arranging a start-up meeting at the ANZCA, ASCTS and RACS annual scientific meetings (to save costs), and will provide regular feedback to each centre via phone and the trial web-site, along with a monthly newsletter. A complete procedures manual will be produced. All study personnel will have email and 24-hr phone access to the study coordinator to resolve any questions that arise. Regular database reports will be produced and scrutinised by the chief investigators.

6. STATISTICAL CONSIDERATIONS

All statistical analyses will be performed under the direction of Andrew Forbes (biostatistician).

6.1 Patient Categories

Following stratification by centre and bypass status (CPB or OPCAB), patients will be randomised (1:1:1:1) to one of the following 4 groups:

Group 1 = Aspirin

Group 2 = Tranexamic acid

Group 3 = Aspirin plus tranexamic acid

Group 4 = Placebo

6.2 Sample Size and Power

Our estimate of sample size is based on a 30% or greater reduction in the incidence of the primary endpoint, from 10% to 7%. We assume there is no interaction between the two study treatments. The baseline incidence is a conservative estimate based on contemporary Australian data (8, ASCTS Victorian Cardiac Surgery Database). For example, the recent Australasian cardiac surgery survey identified a primary endpoint frequency of 12.8 % in a comparable patient population (62). The effect size is less than that of the best evidence from a systematic review of RCTs of antifibrinolytics (35) and an RCT (42) and major observational study (23) of aspirin. The group distributions can be estimated, using the aspirin comparison as an example, as aspirin alone + aspirin/TxA vs. TxA alone + neither: a difference of 5.95% ($0.5 \times [7\% + 4.9\%]$) vs. 8.5% ($0.5 \times [7\% + 10\%]$). With a type I error of 0.05 and a type II error of 0.1 (power 90%), the required number was calculated at 2242 patients per group. We will recruit 4600 patients in this study (ie. 1150 patients in each subgroup, with combinations of 2300 per group for the main comparisons above), which accommodates for the interim analyses. ATACAS blinded sample size recalculation procedure document has been formalised in the event of a sample size recalculation being requested by the ATACAS steering committee. Most secondary endpoints have a baseline incidence of about 3-6% in such a study cohort; our study will have 60-85% power for each of these.

Study power for the secondary endpoints: 77% (if incidence 6%), 45% (if incidence 3%). The detectable risk ratios with 80% power are: 0.67 for 6%, and 0.57 for 3%.

6.2 Statistical Methods

All patients that are randomised to study drug administration will be considered as comprising the Intention-to-Treat population for all primary, secondary and safety analyses. Baseline characteristics of the four randomised groups will be tabulated using appropriate summary statistics.

As no interaction between Aspirin and TxA is expected *a priori*, analysis of the principal outcome of mortality/morbidity will be performed using chi-square tests for the main effects of Aspirin and TxA. The groups being compared will be aspirin (n=2300) vs. no aspirin (n=2300), and TxA (n=2300) vs. no TxA (n=2300). Results will be expressed as risk ratios with 95% confidence intervals. Assessment of the assumption of no interaction between Aspirin and TxA will be performed using log-binomial regression. This uses a generalised linear model with binary outcome and logarithmic link function, and preserves the natural association metric as the relative risk rather than as the odds ratio as would be yielded with logistic regression. Should baseline imbalances between arms in important prognostic factors occur, sensitivity analyses will adjust the main effects of Aspirin and TxA for these factors using log-binomial regression.

A secondary analysis of 1-year survival will be done for the main effects of Aspirin and TxA using Kaplan-Meier survival curves, summarised by median times to event with 95% CI, and

assessed by the log-rank test and the Cox proportional hazards model for possible covariate adjustment, with assessment of the requisite proportionality assumptions.

6.3 Interim Analysis

Interim analysis will be performed after enrolment of 2300 and 3450 patients, that is, at 50% and 75% of the target recruitment number of 4600. Results will be made available to a Data & Safety Monitoring Committee (chairman: Prof. Andrew Tonkin). The interim analyses will be adjusted according to an O'Brien and Fleming Type I error spending function, separately for the Aspirin and TxA main effects using an overall 5% significance level for each main effect. Should the result for a particular main effect (eg. aspirin versus no aspirin) cross the designated boundary at an interim analysis, consideration will be given by the DSMC to termination of study of that intervention (eg. cease recruitment to the aspirin arms, and randomise new patients to TxA or placebo only).

Planned Sub-Group Analysis

There is a large amount of pre-existing data . Defined subgroups are:

- i. Gender
- ii. Patient age greater than 65 years
- iii. LV function (LV grades 1-4)
- iv. High bleeding risk, defined by any of the following: patient age >70 years, weight <55 kg, poor LV function (grade 4), renal impairment, emergency surgery, coagulopathy, or reoperation
- v. Surgical sub-types - isolated CABG, combined (CABG + other), or OPCAB

Planned Substudies

- i. Aspirin responsiveness in the ATACAS study population (now completed).
- ii. Perioperative genomics - In conjunction with Duke University, using salivary DNA sampling to identify genetic markers of postoperative complications, and possible indicators of variations in aspirin responsiveness. A separate Protocol will be developed.
- iii. Cost-Effectiveness Analysis - A cost-effectiveness analysis will be done in the fifth year of the project, using data generated from the Alfred Hospital and Monash Medical Centre, which have patient cost databases in place. We will enlist the assistance of an experienced health economist. A separate Protocol will be developed.

7. PERSONNEL RESPONSIBILITIES

7.1 Investigators

It is the principal investigator's responsibility to design the study protocol. The Steering Committee will be chaired by the principal investigator (PSM), and include each of the chief investigators, the clinical pharmacologist and statistician.

Each study centre ("site") will have a nominated cardiac surgeon and/or anaesthetist (both "site investigators"). Each site investigator must ensure that all staff conducting the study are qualified to do so.

Each site investigator must submit the study protocol to the Ethics Committee and obtain approval prior to commencing the study.

Each site investigator must ensure that all staff involved with the study are fully instructed on the study procedures and are given access to the study protocol and other information relating to the study.

Each site investigator must ensure that the study is conducted in accordance with this protocol, relevant national regulation, ICH GCP notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and the Belmont Report on the Ethical Principles and Guidelines for the Protection of Human Subjects of Research (<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>).

It is each site investigator's responsibility to ensure that written, informed consent is obtained from each patient prior to entering the study.

Each site investigator must ensure that the web-based CRFs are complete and accurate on completion of the study. Each site investigator will ensure that the quality control procedures are performed on both the CRFs and the data base.

It is the principal investigator's responsibility, in conjunction with the chief investigators, to write the Study Report at the completion of the study. Authorship guidelines are described in Section 11.

7.2 Pharmacist

It is expected that each hospital Pharmacy Department will store and dispense the study medication. This may be shared or done in conjunction with the local hospital anaesthetic department. In either case, there is a requirement to maintain records of drug accountability.

7.3 Steering Committee and Adjunct Committees

Steering Committee

Paul S. Myles MB.BS, MPH, MD, FCARCSI, FANZCA, FRCA (chair)

Julian Smith MB.BS, MS, FRACS

Henry Krum MB.BS, PhD, FRACP

D. James Cooper BM.BS, MD, FJFICMANZCA

Brendan Silbert MB.BS, FANZCA

John McNeil MB.BS, MSc, PhD, FRACP

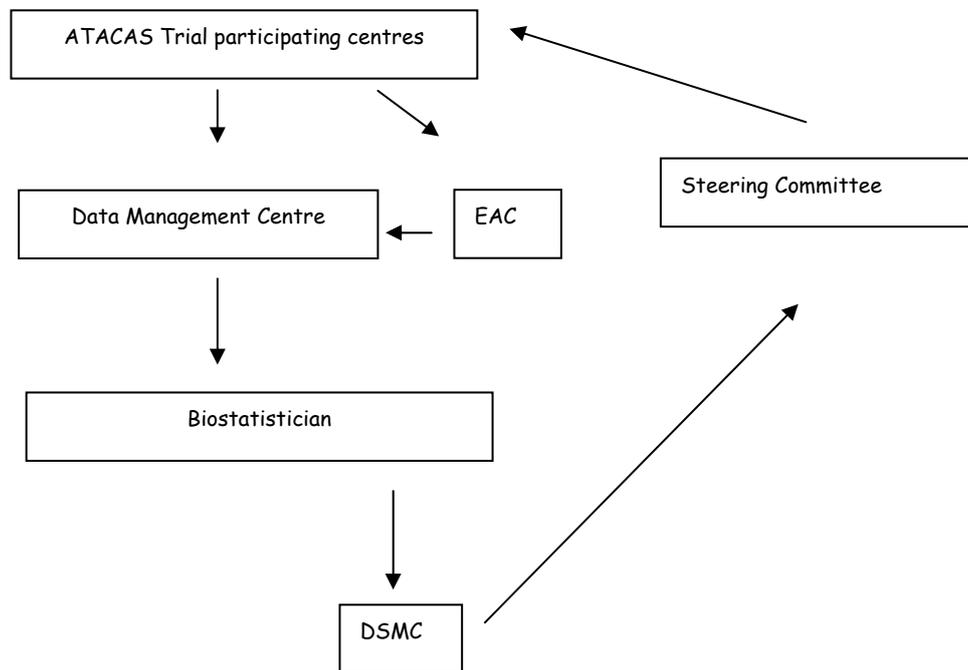
Endpoint Adjudication Committee (EAC)

The committee consists of Prof. Jamie Cooper (Chair, intensivist), Dr James Tomlinson (anaesthetist, physician), and Dr David McIlroy (anaesthetist), and their role is to resolve any uncertainty as to any of the above outcomes. In addition, they will assess a random sample (10%) of outcome events. If the rate of disagreements between the site CRF and adjudicator exceeds 10%, then the Steering Committee may consider an independent adjudication process for all trial events. A separate document provides further details outlining the procedures of the EAC.

Data Safety & Monitoring Committee (DSMC)

The committee consists of: Prof. Andrew Tonkin (Chair, cardiologist), A/Prof. Stephane Heretier (statistician; non-voting member), Ms Silvana Marasco (cardiac surgeon), Prof. Alan Merry (anaesthetist), and Dr. Danny Liew (clinical pharmacologist). The committee will be notified of any unanticipated adverse events and be given the results of the interim analyses by the statistician.

The Data & Safety Monitoring Committee (DSMC) will discuss the interim results and vote for continuation or stopping the trial. Their conduct is to be guided by the paper by DeMets et al. (67). A separate document provides further details outlining the procedures of the DSMC.



8. ADMINISTRATIVE PROCEDURES

8.1 Amendments to the Protocol

All modifications of the study will be written and filed as amendments to this protocol, maintaining original section identification. Such modification(s) will be made by the principal investigator with the approval of the Ethics Committee (where applicable).

Any modifications to the study will be applied for all subsequent patients

8.2 Early Termination or Extension of the Study

The investigator (with Ethics Committee approval) may discontinue or extend the study at any time.

8.3 Drug Accountability

The pharmacist should maintain adequate dispensing records.

8.4 Drug Packaging and Labelling

This will be coordinated by the trial management centre or designated party.

8.5 Storage of Study Drugs

The study drugs will be stored by the Pharmacy Department or Department of Anaesthesia (according to local requirements) at each hospital.

8.6 Confidentiality/Publication of Study Results

The investigators plan to publish the results in a peer-reviewed journal.

8.7 Retention of Records

In Australia, all CRFs and all other documents associated with this study must be archived for at least 15 years following the completion of the trial, in accordance with Australian TGA requirements. Relevant national guidelines or policies will dictate local archiving.

8.8 Audits

It may be necessary for a drug regulatory agency to conduct a site audit. Relevant national guidelines or policies will dictate additional auditing by responsible agencies.

9. ETHICAL PROCEDURES

9.1 Guidelines for Good Clinical Practice

This study is to be performed in accordance with ICH GCP notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and Ethical Principles and Guidelines for the Protection of Human Subjects of Research as defined in the Belmont Report.

9.2 Precautionary Advice

None specifically required.

9.3 Participant Information Sheet and Consent Form

The investigator or delegate will explain the study verbally to the patient. The patient will then be given a copy of the PI&CF and given an opportunity to read it and ask any questions of the investigator. The patient will be urged to obtain additional information about the study from an independent source.

Once the patient is satisfied with the information they have received, has had an opportunity to ask questions and obtain additional information and the investigator is satisfied that the patient truly understands the nature of the study, the patient will be asked to sign the consent form.

If local or national guidelines require a witness to the consent process, that witness must be satisfied that the patient has a good understanding of the study before co-signing the consent form. Each patient's signed consent form will be retained by the investigator.

Patients will be advised that they are free to refuse to participate in, or to withdraw from the study at any time. The medical care provided will not be affected by agreement or refusal to participate in this study. The original Consent Form for each subject will be stored in the Investigators file and a copy of the consent form will be placed in the patient's history.

9.4 Ethics Committee

This protocol will be submitted to the Ethics Committee at each site and their approval obtained.

10. REFERENCES

1. Nalysnyk L, et al. Adverse events in coronary artery bypass graft (CABG) trials: a systematic review and analysis. *Heart* 2003;89:767.
2. Nashef SA, Roques F, Hammill BG, Peterson ED, Michel P, Grover FL, Wyse RK, Ferguson TB; EurSCORE Project Group. Validation of European System for Cardiac Operative Risk Evaluation (EuroSCORE) in North American cardiac surgery. *Eur J Cardiothorac Surg* 2002;22:101-5.
3. Higgins T, et al. Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. A Clinical Severity Score. *JAMA* 1992;267:2344.
4. Shroyer A, et al. The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models. *Ann Thorac Surg* 2003;75:1856.
5. Shahian DM, O'Brien SM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1-coronary artery bypass grafting surgery. *Ann Thorac Surg* 2009;88:S2-22.
6. Aldea GS, Mokadam NA, Melford R Jr, et al. Changing volumes, risk profiles, and outcomes of coronary artery bypass grafting and percutaneous coronary interventions. *Ann Thorac Surg* 2009; 87:1828-38.
7. Taylor G, et al. Determinants of hospital charges for coronary artery bypass surgery. The economic consequences of postoperative complications. *Am J Cardiol* 1990;65:309.
8. Speir AM, Kasirajan V, Barnett SD, Fonner E Jr. Additive costs of postoperative complications for isolated coronary artery bypass grafting patients in Virginia. *Ann Thorac Surg* 2009; 88:40-5.
9. Selnes OA, et al. Neurobehavioural sequelae of cardiopulmonary bypass. *Lancet* 1999;353:1601.
10. Desai ND, Cohen EA, Naylor CD, et al. A randomized comparison of radial-artery and saphenous-vein coronary bypass grafts. *N Engl J Med* 2004;351:2302-9.
11. Antiplatelet Trialists Group. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71.
12. Dinh DT, Billah B, Shardey G, et al. Australasian Society of Cardiac and Thoracic Surgeons. Victorian Cardiac Surgery Database Project. Annual report 2005-2006. http://www.ascts.org/documents/PDF/VIC_Surgeons_report_05-06_Fina.pdf (accessed Jun 2007).
13. Khuri S, et al. Hematologic changes during and after cardiopulmonary bypass and their relationship to the bleeding time and nonsurgical blood loss. *J Thorac Cardiovasc Surg* 1992;104:94.
14. Grayson A, et al. Monitoring blood transfusion in patients undergoing coronary artery bypass grafting: an audit methodology. *Vox Sanguinis* 2003;85:96.
15. Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* 2006; 114:774-82.
16. Koch CG, Li L, Duncan AI, et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. *Crit Care Med* 2006; 34:1608-16.
17. Stanworth S, et al. Which groups of patients are transfused? A study of red cell usage in London and southeast England. *Vox Sanguinis* 2002;83:352.
18. Hill G, et al. Allogeneic blood transfusion increases the risk of postoperative bacterial infection: a meta-analysis. *J Trauma* 2003;54:908.
19. Loop F, et al. Sternal wound complications after isolated coronary artery bypass grafting: early and late mortality, morbidity, and cost of care. *Ann Thorac Surg* 1990;49:179.
20. Chelemer S, et al. Association of bacterial infection and red blood cell transfusion after coronary artery bypass surgery. *Ann Thorac Surg* 2002;73:138.
21. Goodnough LT, Johnston MF, Toy PT. The variability of transfusion practice in coronary artery bypass surgery. Transfusion Medicine Academic Award Group. *JAMA* 1991; 265:86-90.
22. Hebert PC, Wells G, Blajchman MA, et al. The Transfusion Requirements in Critical Care Investigators: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999, 340:409-17.
23. Helm RE, Rosengart TK, Gomez M, et al. Comprehensive multimodality blood conservation: 100 consecutive CABG operations without transfusion. *Ann Thorac Surg* 1998; 65:125-36.
24. Henry D, Carless P, Ferguson D, Laupacis A. The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. *CMAJ* 2009;
25. Bélisle S, Hardy JF. Hemorrhage and the use of blood products after adult cardiac operations: myths and realities. *Ann Thorac Surg* 1996;62:1908.
26. Tuman K, et al. Aspirin does not increase allogeneic blood transfusion in reoperative coronary artery surgery. *Anesth Analg* 1996;83:1178.
27. Parr K, et al. Multivariate predictors of blood product use in cardiac surgery. *J Cardiothorac Vasc Anesth* 2003;17:176.
28. Hardy JF, et al. The stratification of cardiac surgical procedures according to use of blood products: A retrospective analysis of 1480 cases. *Can J Anaesth* 1991;38:511.
29. Mangano D. Aspirin and mortality from coronary bypass surgery. *N Engl J Med*. 2002;347:1309.
30. Topol E. Aspirin with bypass surgery: from taboo to new standard of care. *N Engl J Med* 2002; 347:1359-60.
31. Goldman S, et al. Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study. *Circulation* 1988;77:1324.
32. Goldman S, et al. Starting aspirin therapy after operation: effects on early graft patency. *Circulation* 1991;84:520.

33. Gavaghan T, et al. Immediate postoperative aspirin improves vein graft patency early and late after coronary artery bypass graft surgery. *Circulation* 1991;83:1526.
34. Serebruanu VL, Steinhubl SR, Berger PB, et al. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. *Am J Cardiol* 2005;95:1218-22.
35. Dacey L, et al. Effect of preoperative aspirin use on mortality in coronary artery bypass grafting patients. *Ann Thorac Surg* 2000;70:1986.
36. Bybee KA, Powell BD, Valeti U, et al. Preoperative aspirin therapy is associated with improved postoperative outcomes in patients undergoing coronary artery bypass grafting. *Circulation* 2005; 112:1286-92.
37. Datta M. You cannot exclude the explanation you have not considered. *Lancet* 1993; 342:345-7.
38. Collaborative overview of randomised trials of antiplatelet therapy-II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. Antiplatelet Trialists' Collaboration. *BMJ* 1994;308:159.
39. Hockings BE, Ireland MA, Gotch-Martin KF, Taylor RR. Placebo-controlled trial of enteric coated aspirin in coronary bypass graft patients. Effect on graft patency. *Med J Aust* 1993; 159:376-8.
40. The PEP Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000;355:1295.
41. Srinivasan AK, Grayson AD, Pullan DM, Fabri BM, Dihmis WC. Effect of preoperative aspirin use in off-pump coronary artery bypass operations. *Ann Thorac Surg* 2003; 76: 41-5.
42. Ferraris V, et al. Aspirin and postoperative bleeding after coronary artery bypass grafting. *Ann Surg* 2002;235:820-827.
43. Ranucci M, Bozzetti G, Ditta A, Cotza M, Carboni G, Ballotta A. Surgical reexploration after cardiac operations: why a worse outcome? *Ann Thorac Surg* 2008;86:1557- 62.
44. Alghamdi AA, Moussa F, Fremes SE. Does the use of preoperative aspirin increase the risk of bleeding in patients undergoing coronary artery bypass grafting surgery? Systematic review and meta-analysis. *J Card Surg* 2007;22:247-256.
45. Sun JC, Whitlock R, Cheng J, et al. The effect of pre-operative aspirin on bleeding, transfusion, myocardial infarction, and mortality in coronary artery bypass surgery: a systematic review of randomized and observational studies. *Eur Heart J* 2008;29:1057-71.
46. Ferraris VA, Ferraris SP, Moliterno DJ, et al. The Society of Thoracic Surgeons practice guideline series: aspirin and other antiplatelet agents during operative coronary revascularization (executive summary). *Ann Thorac Surg* 2005; 79:1454-61.
47. Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2008;133:299S-339S.
48. Levi M, et al. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet* 1999;354:1940.
49. McIlroy DR, **Myles PS**, Phillips LE, **Smith JA**. Antifibrinolytics in cardiac surgical patients receiving aspirin: a systematic review and meta-analysis. *Br J Anaesth* 2009; 102:168-78.
50. Dowd N, et al. Pharmacokinetics of tranexamic acid during cardiopulmonary bypass. *Anesthesiology* 2002;97:390.
51. Fergusson DA, Hebert PC, Mazer CD, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008; 358:2319-31.
52. Alderman E, et al. Analyses of coronary graft patency after aprotinin use: results from the International Multicenter Aprotinin Graft Patency Experience (IMAGE) trial. *J Thor Cardiovasc Surg* 1998;116:716.
53. Risch A, Dorscheid E, Stein G, et al. The effect of aprotinin and tranexamic acid on fibrinolysis and thrombin generation during cardiopulmonary bypass. *Anaesthetist* 2000; 49:279-85.
54. Dentz ME, Slaughter TF, Mark JB. Early thrombus formation on heparin-bonded pulmonary artery catheters in patients receiving epsilon aminocaproic acid. *Anesthesiology* 1995;82: 583-6.
55. Kluger R, Olive DJ, Stewart AB. Epsilon-aminocaproic acid in coronary artery bypass graft surgery: preincision or postheparin? *Anesthesiology* 2003;99:1263-9.
56. Rosen M. The aprotinin saga and the risks of conducting meta-analyses on small randomised controlled trials - a critique of a Cochrane review. *BMC Health Serv Res* 2009; 9:34-41.
57. **Myles PS**. Aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008; 359:1181.
58. Klein M, et al. Aprotinin counterbalances an increased risk of perioperative hemorrhage in CABG patients pre-treated with aspirin. *Eur J Cardiothorac Surg* 1998;14: 360.
59. Tunis S, et al. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA* 2003;290:1624.
60. **Myles PS**. Why we need large randomised studies in anaesthesia. *Br J Anaesth* 1999; 83:833-4 [editorial].
61. **McNeil JJ**, Nelson MR, Tonkin AM. Public funding of large-scale clinical trials in Australia. *Med J Aust* 2003; 179:519-20. [editorial].
62. Daly DJ, **Myles PS**, **Smith JA**, Knight JL, Clavisi O, Bain DL, Glew R, Gibbs NM, Merry AF, ANZCA Trials Group. Anticoagulation, bleeding and blood transfusion practices in Australasian cardiac surgical practice. *Anaesth Intensive Care* 2007; 35: 760-8.

63. Rigg JRA, Jamrozik K, **Myles PS**, Silbert BS, Peyton PJ, Parsons RW, Collins KS, and the MASTER Anaesthesia Trial Study Group. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. *Lancet* 2002;359:1276-82.
64. **Myles PS**, Leslie K, Forbes A, **McNeil J**, Chan M, for the B-Aware Trial Group. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. *Lancet* 2004; 363:1757-63.
65. **Cooper DJ**, **Myles PS**, McDermott F, Murray LJ, Laidlaw J, Cooper G, Tremayne AB, Bernard SS, Ponsford J, for the HTS Study Investigators. Pre-hospital hypertonic saline resuscitation of patients with severe traumatic brain injury - a randomized controlled trial. *JAMA* 2004;291:1350-7.
66. **Myles PS**, Leslie K, Chan MTV, Forbes A, Paech MJ, Peyton P, Silbert BS, Pascoe E, and the ENIGMA Trial Group. Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. *Anesthesiology* 2007;107: 221-31.
67. **Myles PS**, Leslie K, Peyton P, Paech M, Forbes A, Chan MTV, Sessler D, Devereaux PJ, Silbert BS, Jamrozik K, Beattie S, Badner N, Tomlinson J, Wallace S, and the ANZCA Trials Group. Nitrous oxide and perioperative cardiac morbidity (ENIGMA-II) trial: rationale and design. *Am Heart J* 2009;157:488-94.
68. Hannan EL, van Ryn M, Burke Jet al. Access to coronary artery bypass surgery by race/ethnicity and gender among patients who are appropriate for surgery. *Med Care*. 1999;37:68-77.
69. Kim DH, Daskalakis C, Lee AN, et al. Racial disparity in the relationship between hospital volume and mortality among patients undergoing coronary artery bypass grafting. *Ann Surg* 2008;248:886-92.
70. Feng ZZ, Shi J, Zhao XW, Xu ZF. Meta-analysis of on-pump and off-pump coronary arterial revascularization. *Ann Thorac Surg* 2009;87:757-65.
71. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. *J Am Coll Cardiol* 2000; 36:959-69.
72. Sadony V, Korber M, Albes G, Podtschaske V, Etgen T, Trosten T, Ravens U, Scheulen ME. Cardiac troponin I plasma levels for diagnosis and quantitation of perioperative myocardial damage in patients undergoing coronary artery bypass surgery. *Eur J Cardiothorac Surg* 1998; 13:57-65.
73. Thielmann M, Massoudy P, Schermund A, et al. Diagnostic discrimination between graft-related and non-graft-related perioperative myocardial infarction with cardiac troponin I after coronary artery bypass surgery. *Eur Heart J* 2005; 26:2440-7.
74. Mohammed AA, Agnihotri AK, van Kimmenade RR, et al. Prospective, comprehensive assessment of cardiac troponin T testing after coronary artery bypass graft surgery. *Circulation* 2009;120:843-50.
75. Fransen EJ, Diris JH, Maessen JG, Hermens WT, van Dieijen-Visser MP. Evaluation of "new" cardiac markers for ruling out myocardial infarction after coronary artery bypass grafting. *Chest* 2002; 122:1316-21.
76. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. *JAMA* 1963; 185:914-9.
77. Williams MR, Wellner RB, Hartnett EA, Thornton B, Kavarana MN, Mahapatra R, Oz MC, Sladen R. Long-term survival and quality of life in cardiac surgical patients with prolonged intensive care unit length of stay. *Ann Thorac Surg* 2002; 73:1472-8.
78. WHO., Stroke--1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. *Stroke*, 1989. 20(10):1407-31.
79. <http://www.strokefoundation.com.au/images/stories/healthprofessionals/national%20stroke%20audit%20clinical%20report%20acute%20services.pdf>
80. Adams HP, et al., Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*, 1993. 24(1):35-41.
81. Taylor DM, **McNeil JJ**. A Guide to Good Research Practice, Monash University; 2003.
82. Awtry EH, Loscalzo J. Aspirin. *Circulation* 2000; 101:1206-18.
83. Peters RJ, Mehta SR, Fox KA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation* 2003; 108:1682-7.
84. Gill R, Herbertson M, Vuylsteke A, Olsen PS, von Heymann C, Mythen M, Sellke F, Booth F, Schmidt TA. Safety and efficacy of recombinant activated factor VII: a randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. *Circulation* 2009; 120:21-7.
85. Ponschab M, Landoni G, Biondi-Zoccai G, Bignami E, Frati E, Nicolotti D, Monaco F, Pappalardo F, Zangrillo A. Recombinant activated factor VII increases stroke in cardiac surgery: a meta-analysis. *J Cardiothorac Vasc Anesth* 2011 May 17. [Epub ahead of print]
86. Ngaage DL, Bland JM. Lessons from aprotinin: is the routine use and inconsistent dosing of tranexamic acid prudent? Meta-analysis of randomised and large matched observational studies. *Eur J Cardiothorac Surg* 2010; 37:1375-83.
87. Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M. High-dose tranexamic Acid is associated with nonischemic clinical seizures in cardiac surgical patients. *Anesth Analg* 2010; 110:350-3.
88. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Society of Cardiovascular Anesthesiologists Special Task Force on Blood Transfusion. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg* 2011; 91:944-82.

**ATACAS Trial Group
Plan for Authorship of Manuscripts**

It is planned for there to be a principal publication with the main results of the trial in a high-profile medical journal such as *The Lancet* or *New England Journal of Medicine*. The authorship of this paper will be:

Myles PS, Smith J, Knight J, Cooper DJ, Forbes A, Silbert B, Krum H, McNeil J, and the ATACAS Trial Group

It is expected that there will be several other publications, describing additional information derived from the conduct of the trial, as well as several sub-studies. These studies (and subsequent publications) must be approved by the ATACAS Trial Steering Committee, and authorship will include those investigators who have participated.

It is expected that each of the chief and associate investigators will author at least one of these additional papers.

Contributors on study subcommittees, such as Endpoint Adjudication, Data and Safety Monitoring, Statistical and Writing Committees will be listed in accordance with the respective journal's policy.

Appendix (to be published with final manuscript): The ATACAS Trial Group will be identified by naming participating centres, site coordinators, and a representative anaesthetist and surgeon from each centre. The order of centres will be ranked according to number of patients recruited to the study.