Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) Trial: Rationale and design

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Background Despite some concern that recent aspirin ingestion increases blood loss after coronary artery surgery, there is some evidence that this may reduce thrombotic complications. In contrast, antifibrinolytic drugs can reduce blood loss in this setting, but there is concern that they may increase thrombotic complications. Published guidelines are limited by a lack of large randomized trials addressing the risks and benefits of each of these commonly used therapies in cardiac surgery. The ATACAS Trial is a study comparing aspirin, tranexamic acid, or both, with placebo in patients undergoing on-pump or off-pump coronary artery surgery.

Methods We discuss the rationale for conducting ATACAS, a 4600-patient, multicenter randomized trial in atrisk coronary artery surgery, and the features of the ATACAS study design (objectives, end points, target population, allocation, treatments, patient follow-up, and analysis).

Conclusions The ATACAS Trial will be the largest study yet conducted to ascertain the benefits and risks of aspirin and antifibrinolytic therapy in coronary artery surgery. Results of the trial will guide the routine clinical care of patients in this setting.

Coronary artery bypass graft (CABG) surgery is one of the primary treatment options for patients with coronary artery disease, with >800,000 CABG operations done annually around the world.1 Although CABG surgery offers benefit to most patients, some die, and others experience long-term disability.1-4

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Trial registration: www.actr.org.au: no. 12605000555651.

Conflict of interest statement: Bayer HealthCare (Leverkusen, Germany) has provided aspirin and matched placebo tablets at no cost. Professor Julian Smith has received honoraria as a clinical advisor to Bayer HealthCare, Pymble, New South Wales, Australia, for advice on the use of aprotinin in cardiac surgery. None of the other authors has declared any conflict of interest.

Submitted June 9, 2007; accepted October 1, 2007.
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0002-8703/$ - see front matter
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doi:10.1016/j.ahj.2007.10.003

Antifibrinolytic therapy

In a retrospective observational study on 4374 patients undergoing CABG surgery, Mangano et al14 used propensity scores to investigate the potential adverse effects of aprotinin. They found that aprotinin was associated with an increased risk of renal impairment, MI or heart failure, stroke, and encephalopathy. A follow-up study found an association between aprotinin and poor survival.15 Another observational study published at around the same time found no association between aprotinin and poor survival.15 These observational studies have been criticized,20-22 largely because of their susceptibility to bias and confounding.23-25

Three meta-analyses of randomized trials have found that antifibrinolytic therapy reduces bleeding in cardiac
surgery. These have had a major influence on consensus guidelines. Levi et al found that aprotinin decreased mortality almost 2-fold (odds ratio 0.55, 95% CI 0.34-0.90) compared with placebo. Treatment with aprotinin and with lysine analogues decreased the frequency of reoperation (0.37 [0.25-0.55] and 0.44 [0.22-0.90], respectively). Desmopressin, but not aprotinin and TXA, increased the risk of MI.

Antifibrinolytic therapy may increase the risk of graft thrombosis. Although aprotinin is the antifibrinolytic drug most frequently implicated, there is also some concern with epsilon aminocaproic acid and desmopressin. However, there is also evidence that aprotinin inhibits various prothrombotic pathways, has antiplatelet activity, and may reduce stroke risk. In contrast, TXA increases thrombin generation.

Antifibrinolytics are recommended for reoperative and other complex cardiac surgery. However, it is not yet clear whether these drugs provide any benefit beyond limiting blood loss and may reduce stroke risk. In view of the marked cost advantages of TXA, it seems reasonable to evaluate its effectiveness in contemporary practice. It remains unclear whether the reduced bleeding outweighs an increased risk of thrombotic complications.

Aspirin and cardiac surgery
Aspirin may or may not significantly increase bleeding after cardiac surgery. Aspirin increases postoperative blood loss by <300 mL; this should not increase the need for blood transfusion. It is common practice to stop aspirin 5 to 7 days before elective cardiac surgery. Yet, aspirin-induced increased bleeding might be outweighed by a beneficial effect on reduced graft thrombosis, MI, and possibly stroke. Aspirin is routinely recommenced 8 to 36 hours after surgery, but the practice of stopping aspirin before surgery denies an opportunity to avoid thrombosis in the days before and during and crucial hours after surgery.

Society of Thoracic Surgeons practice guidelines
The Society of Thoracic Surgeons has published guidelines on the use of aspirin and antifibrinolytic therapy. They note that “there is only anecdotal information supporting the discontinuation of aspirin before elective CABG surgery.” In brief, the recommendations are to stop aspirin 3 to 5 days before elective CABG surgery in low-risk patients but in high-risk CABG surgery, to continue or commence aspirin preoperatively (both class IIa recommendations). For aspirin-treated high-risk CABG patients, they recommend antifibrinolytics to limit bleeding. These guidelines highlight the lack of published data in the literature (ie, no class I recommendations) and the need for a definitive large trial.

Study objectives
The overall study goal of ATACAS is to assess (i) whether aspirin should be continued up until the day of CABG surgery and (ii) whether should TXA be used routinely in CABG surgery. The study is funded by the Australian National Health and Medical Research Council (ID 334015).

Study design
The ATACAS Trial is a multicenter, randomized, blinded, 2 × 2 factorial trial testing whether aspirin, TXA, or both can reduce mortality and/or major morbidity after elective CABG surgery. Eligible patients are randomly allocated to 1 of the following 4 treatment groups: aspirin, TXA, aspirin with TXA, or placebo.

Primary end point
The primary end point is a composite including all-cause mortality or major ischemic morbidity (MI, stroke, pulmonary embolism, renal failure, bowel infarction) up to 30 days after surgery.

Secondary end points
The secondary end points include the following: (i) all-cause mortality; (ii) ischemic complications (MI, stroke, renal failure, pulmonary embolism, bowel infarction); and (iii) bleeding complications (major hemorrhage requiring reoperation for bleeding, cardiac tamponade) and blood transfusion ≤30 days after surgery.

Study methods
Patient population
Eligible patients consist of those undergoing elective on-pump or off-pump coronary artery surgery identified as being at an increased risk for major complications, as detailed in Table I. We are enrolling 4600 patients in 15 to 20 participating sites in Australia, New Zealand, Asia, and Europe. Institutional review board approval will be sought from each site, and all patients are asked to provide informed consent.

Eligibility criteria
After first obtaining agreement and support from cardiac surgeons and anesthesiologists at each site, all elective coronary artery surgical patients are screened for eligibility. The study allows individual surgeons to exclude any of the patient or surgical risk factors if they have a strong preference to use or avoid aspirin or
**Table I.** Specific inclusion and exclusion criteria

**Inclusion criteria**
1. Men and women, aged ≥18 y, undergoing elective coronary artery surgery (on-pump or off-pump)
2. Patient has any of the following risk factors:
   a. Age ≥70 y
   b. Left ventricular impairment (fractional area change <20%, ejection fraction <40%, or at least moderate impairment on ventriculography)
   c. Concomitant valvular or aortic surgery
   d. Chronic obstructive pulmonary disease
   e. Peripheral vascular disease

**Exclusion criteria**
1. Poor (English) language comprehension
2. Clinician preference for antifibrinolytic therapy
3. Urgent surgery for unstable coronary syndromes
4. Active peptic ulceration
5. Allergy or contraindication to aspirin or TxA
6. Aspirin therapy within 5 d of surgery
7. Warfarin or clopidogrel therapy within 7 d of surgery or glycoprotein IIb/IIIa antagonists within 24 h of surgery
8. Thrombocytopenia or any other known history of bleeding disorder
9. Severe renal impairment (serum creatinine > 2.0 mg/dL or creatinine clearance < 45 mL/min)
10. Recent hematuria
11. Thromboembolic disease: history of postoperative or spontaneous pulmonary embolism, spontaneous arterial thrombosis, or any other known history of bleeding disorder
12. Pregnancy

antifibrinolytic therapy in on-pump or off-pump cases. The number of patients eligible but not recruited into the trial are detailed in a study log. This includes the reasons for the lack of participation.

**Allocation and randomization**
After patient consent has been obtained, a central 24-hour interactive voice recognition system prompts the researcher or study coordinator to identify their study site and whether the procedure is on-pump or off-pump, and then, patients are randomly allocated to treatment group (1:1:1:1) from a computer-generated list. Randomization is stratified by site and whether the procedure is on-pump or off-pump surgery. This will equalize site-specific intergroup differences in surgical and other perioperative care. In addition, the sample size is sufficiently large to ensure comparable baseline and other perioperative characteristics.

**Study end point definitions**
Data pertaining to study end points occurring up to 30 days after surgery are sent to an adjudication committee blinded to group identity.

**Death**
This includes all deaths within 30 days of surgery from any cause.

**Myocardial infarction**
An MI is defined by the presence of either (i) a typical rise and gradual fall (troponin) or more rapid rise and fall (creatine kinase-MB [CKMB]) of biochemical markers of myocardial necrosis after surgery with at least 1 of the following: ischemic symptoms, development of pathologic Q waves on 2 adjacent leads on the electrocardiogram (ECG), or ECG changes indicative of ischemia (ST-segment elevation or depression); or (ii) pathologic findings of an acute MI. Also, in view of the difficulty of detecting ischemic chest pain in the early postoperative period, in addition, a non-Q-wave MI is defined by a cardiac enzyme elevation in isolated CABG cases, using any of the following: troponin I > 10 ng/mL at any time > 12 hours post-CABG, troponin T > 4.0 at > 12 hours post-CABG, or CKMB > 5 times the upper limit of normal at > 12 hours post-CABG surgery.

**Pulmonary embolism**
A pulmonary embolism will be diagnosed if confirmed by high-probability VQ scan or documented on pulmonary angiography.

**Stroke**
A stroke will be diagnosed if confirmed by documented cerebral infarction or hemorrhage on computed tomographic or magnetic resonance imaging scan or by new neurologic signs (paralysis, weakness, or speech difficulties) lasting > 24 hours or leading to earlier death.

**Acute renal failure**
Acute renal failure will be diagnosed if confirmed by a doubling of the serum creatinine in the postoperative period when compared with the baseline (preoperative) value or by a rise > 2.4 mg/dL from baseline.

**Bowel infarction**
Bowel infarction will be diagnosed at laparotomy if there is a need for bowel resection or if bowel infarction is diagnosed at autopsy.

**Cardiac tamponade**
Tamponade will be diagnosed by typical hemodynamic and/or echocardiographic features leading to and confirmed by surgical reexploration or pericardiocentesis.

**Major hemorrhage**
Major hemorrhage is defined by any excessive bleeding requiring reoperation. In addition, we will record the
**Table II.** Steps to be taken if there is clinical evidence of excessive bleeding, as defined by bleeding >200 mL/h for >2 h or >400 mL in any 1 h, after bypass or off-pump surgery

1. Administer further protamine, 50-100 mg, whether ACT is elevated or not
2. Consider aprotinin therapy (bolus + infusion); use the Hammersmith regimen: loading dose, 2 million U, followed by 500 000 U/h
3. Administer platelet transfusion, 5 U, if platelet count <100 000/L
4. Administer fresh frozen plasma, 5 U, if INR >1.4 or fibrinogen <150 g/L
5. Administer cryoprecipitate if fibrinogen <100 g/L
6. If bleeding remains problematic, >100 mL/h after protocol-directed therapies, consider recombinant Vila (NovoSeven), 90 μg/kg

*In some countries, this constitutes off-label use, and so, local regulations should apply.

number of units of blood products transfused within 30 days of surgery.

**Surgical and anesthetic techniques**

Preoperative demographic characteristics and details of patients’ medical and surgical history are recorded. They will also undergo a 12-lead ECG, chest x-ray, pathology testing, and other routine investigations. Clinical and laboratory data will be used to generate ≥1 risk scores.42–2

On the day of surgery, patients are allocated to 1 of the 4 treatment groups. All other perioperative clinical care is according to standard practice at each site because this is an effectiveness trial designed to represent real-world practice.45 All such relevant perioperative data are recorded on the study case report form.

Heparinization for bypass is based on a bolus dose of 300 U/kg and maintenance of an activated clotting time (ACT) >450 seconds during bypass, with additional heparin as required. Heparin reversal at the completion of cardiopulmonary bypass (CPB) is achieved with protamine 4 mg/kg, monitored with ACT (<140 seconds). Other antifibrinolytic therapy cannot be used before or during CPB but can be used if there is clinically significant bleeding after protamine administration (Table II). The study is guided by a transfusion protocol (Table III).

Blood is collected postoperatively at 12 to 24 hours for cardiac enzyme (troponin and/or CKMB) levels, and a 12-lead ECG is performed on each of the 3 days after surgery to detect MI. Additional tests are ordered if clinically indicated (eg, chest pain, dyspnea, circulatory instability). In addition, patients are contacted by phone at 30 days and their medical records reviewed to ascertain if they have experienced any adverse outcomes.

**Study medications and duration**

Two active study medications will be used: (i) oral enteric-coated aspirin, single dose of 100 mg given 1 to 2 hours preoperatively, and (ii) intravenous (IV) TxA 100 mg/kg administered postinduction but before CPB. The aspirin dose has been shown to be effective, with an onset time of <1 hour and with a suitable side effect profile54; higher doses are more likely to cause unacceptable bleeding.54 The aspirin placebo group will receive inactive placebo tablets identical in appearance to active aspirin.

Tranexamic acid will be prepared and administered by an anesthesiologist not responsible for the procedure—on some occasions this may not be possible; this information is being recorded. Tranexamic acid is to be administered within 20 minutes after induction of anesthesia as an IV bolus, over 10 to 30 minutes. This regimen has been shown to provide and maintain effective TxA concentrations throughout and after surgery.44 Placebo TxA solution will consist of normal saline.

**Study procedures, blinding, and follow-up**

The surgical team, including anesthesiologist and all other clinical staff, are blinded to aspirin allocation, with study drug coding and delivery being managed by research staff at the study coordinating center. However, for TxA, an anesthesiologist is being asked to prepare the IV study drug (TxA or placebo saline) at each site at the time of surgery. Ideally, this should not be the attending anesthesiologist responsible for the care of the patient during and after surgery. However, it is recognized that for some sites, limited staffing may make this very difficult, and so, the responsible anesthesiologist can prepare the IV study drug provided that all other staff are kept blinded to TxA/placebo group allocation. Patients, surgeons, and research staff must be blinded to treatment allocation.

**Data collection**

Data collection is done by local research staff and entered onto a paper case report form. All data are subsequently entered onto a database accessed via the study web site [www.atacas.org.au](http://www.atacas.org.au). This is managed by Monash University’s Center for Clinical Research Excellence in Therapeutics (Melbourne, Australia), and all data and processes are reviewed each day at the data management center; data fields are checked, and in conjunction with the local site research staff, missing data or inconsistencies are corrected before being automatically downloaded onto the confirmed database.

**Statistical considerations**

**Sample size and power**

Our estimate of sample size is based on a 30% reduction in the incidence of the primary end point, from
10% to 7%. The baseline incidence is a conservative estimate based on contemporary Australian data (ASCTS Victorian Cardiac Surgery Database). The effect size is less than that of the best evidence from a systematic review of randomized trials of antifibrinolytics10 and a randomized trial15 and large observational study30 of aspirin. The group distributions can be estimated, using the aspirin comparison as an example, as aspirin alone + aspirin/TxA versus TxA alone + neither: a difference of 5.95% [0.5(7% + 4.9%)] versus 8.5% [0.5(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), which accommodates for the interim analyses. Most secondary end points have a baseline incidence of about 3% to 6% in such a study cohort; our study will have 60% to 85% power for each of these. The detectable risk ratios with 80% power are 0.67 for incidence of 6% and 0.57 for incidence of 3%.

### Statistical methods

All patients who are randomly allocated 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 4 treatment groups will be tabulated using appropriate summary statistics.

Because no interaction between aspirin and TxA is expected a priori, analysis of the principal outcome of mortality/morbidity will be performed using $\chi^2$ tests for the main effects of aspirin and TxA. The groups being compared will be aspirin (n = 2300) versus no aspirin (n = 2300) and TxA (n = 2300) versus no TxA (n = 2300). Results will be expressed as risk ratios with 95% CIs. Assessment of the assumption of no interaction between aspirin and TxA will be performed using log-binomial regression. This uses a generalized 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.

Beneficial or harmful effects of aspirin and/or TxA may exist in specific subsets of CABG surgery patients, and so, we have identified subgroups for secondary analysis (Table IV).

### Data safety and monitoring committee

The DSMC consists of a cardiologist (chair), cardiac surgeon, independent statistician, cardiac anesthesiologist with an interest in medical ethics and law, and clinical pharmacologist. The DSMC will discuss the interim results and vote for continuation or stopping the trial. This will be communicated to the steering committee according to the prespecified stopping rules and consideration of other evidence relevant to the DSMC.

### Conclusions

Debate on the likely benefits and risks of aspirin and antifibrinolytics in CABG surgery will continue until we have the results from large randomized trials. The ATACAS Trial will guide clinical decision making as to whether patients should stop aspirin before elective CABG surgery and whether TxA antifibrinolytic therapy should be used more widely or far more selectively. When considering the cost and extent of CABG surgery around the world, small improvements in outcome would have major implications for health care delivery.

### References


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Appendix A. Study organization and committees

Sponsor: Alfred Hospital, Melbourne, Australia
Funding sources: Australian National Health and Medical Research Council project grant ID 334015 and the Australian and New Zealand College of Anaesthetists, Melbourne, Victoria, Australia project grant ID 07/035

Steering committee: Paul Myles (chair and principal investigator), Julian Smith, D. James Cooper, John McNeil, Henry Krum, Stephanie Poustie (project manager), and Sophia Wallace (research manager)

End point adjudication committee: James W. Tomlinson, David R. McIlroy, and D. James Cooper

Clinical pharmacologist: Henry Krum

Statistician: Andrew Forbes

Data and safety monitoring committee: Andrew Tonkin (chair), Brian Buxton, Alan Merry, Danny Liew, and Stephane Heretier (independent statistician)

Data management and quality control: Stephanie Poustie, John McNeil, and Adam Meehan

Web site design and maintenance: Adam Meehan

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