**Implication of Major Adverse Postoperative Events and Myocardial Injury on Disability and Survival: A Planned Sub-analysis of the ENIGMA ll Trial**

**Authors:**

W. Scott Beattie, MD, PhD, FRCPC

R. Fraser Elliot Chair in Cardiac Anesthesia, Department of Anesthesia and Pain Management, University Health Network, Department of Anesthesia, University of Toronto, Toronto, Canada; Department of Anesthesia, Toronto General Hospital, Toronto, Canada

Duminda N. Wijeysundera, MD, PhD, FRCPC

Department of Anesthesia and Pain Management, Toronto General Hospital, Toronto, Canada; Department of Anesthesia, University of Toronto, Toronto, Canada; Li Ka Shing Knowledge Institute, St. Michael’s Hospital, Toronto, Canada

Matthew T.V. Chan, MB.BS, PhD, FANZCA, FHKCA, FHKAM

Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China

Philip J. Peyton, MB.BS, MD, PhD, FANZCA

Department of Anaesthesia, Austin Hospital, Melbourne, Australia; Department of Surgery, University of Melbourne, Melbourne, Australia

Kate Leslie, MB.BS, MD, MEpid, MHlthServMt, FANZCA, FAHMS

Department of Anaesthesia and Pain Management, Royal Melbourne Hospital, Melbourne, Australia; Anaesthesia, Perioperative and Pain Medicine Unit, Melbourne Medical School, and Department of Pharmacology and Therapeutics, University of Melbourne, Melbourne, Australia; Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia

Michael J. Paech, MBBS, DM, DRCOG, FRCA, FANZCA, FFPMANZCA, FRANZCOG (Hons)

Department of Anaesthesia and Pain Medicine, Royal Perth Hospital, Perth, Australia; School of Medicine and Pharmacology, University of Western Australia, Perth, Australia

Daniel I. Sessler, MD

Michael Cudahey Professor & Chair, Department of **O**utcomes **R**esearch, Anesthesiology Institute, Cleveland Clinic, Cleveland, United States

Sophie Wallace, MPH

Department of Anaesthesia and Perioperative Medicine, Alfred Hospital, Melbourne, Australia; Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia

Paul S. Myles, MB.BS, MD, MPH, DSc, FANZCA, FCAI, FRCA, FAHMS

Department of Anaesthesia and Perioperative Medicine, The Alfred Hospital, Melbourne Australia; Department of Anaesthesia and Perioperative Medicine, and Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia; National Health and Medical Research Council Practitioner Fellow, Melbourne, Australia

**And the ANZCA Clinical Trials Network for the ENIGMA-II investigators\***

\* listed in an appendix

From the Department of Anaesthesia and Pain Management, Royal Melbourne Hospital; Anaesthesia, Perioperative and Pain Medicine Unit, Department of Pharmacology and Therapeutics, and Department of Surgery, University of Melbourne; Department of Epidemiology and Preventive Medicine and Academic Board of Anaesthesia, Monash University**;** Department of Anaesthesia and Perioperative Medicine, The Alfred Hospital; National Health and Medical Research Council; Department of Anaesthesia, Austin Hospital, Melbourne, Australia; Department of Anaesthesia, Prince of Wales Hospital and Chinese University of Hong Kong, Hong Kong, People’s Republic of China; Department of Anaesthesia, Royal Perth Hospital, Perth, Australia; School of Medicine and Pharmacology, University of Western Australia, Perth, Australia; Department of **O**utcomes **R**esearch, Cleveland Clinic, Cleveland, United States of America; Department of Anesthesia, University of Toronto, Toronto, Canada; Department of Anaesthesia, Toronto General Hospital, Toronto, Canada; Departments of Medicine, Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada; Australian and New Zealand College of Anaesthetists Clinical Trials Network, Melbourne, Australia

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Corresponding Author:

W. Scott Beattie, MD, PhD, FRCPC

Department of Anesthesia and Pain Management, University Health Network, Department of Anesthesia, University of Toronto,

Email [scott.beattie@uhn.ca](mailto:scott.beattie@uhn.ca)

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**Abstract**

**INTRODUCTION:** Globally, more than 300 million patients have surgery annually, and up to 20% experience adverse postoperative events. We studied the impact of both cardiac and noncardiac adverse events, on 1-year disability-free survival after noncardiac surgery.

**METHODS:** We used the study cohort from the ENIGMA II Trial, an international randomized trial of 6992 non-cardiac surgical patients. All were aged 45 years or older and had moderate-to-high cardiac risk. The primary outcome was mortality within 1 postoperative year. We defined 4 separate types of postoperative adverse events. Major adverse cardiac events (MACE) included myocardial infarction, cardiac arrest, and myocardial revascularization with or without troponin elevation. Myocardial infarction (MI) was defined using the 3rd Universal Definition and was blindly adjudicated. A second cohort consisted of patients with isolated troponin increases who did not meet the definition for MI. We also considered a cohort of patients who experienced major adverse postoperative event (MAPE) including unplanned admission to intensive care, prolonged mechanical ventilation, wound infection, pulmonary embolism, and stroke. From this cohort, we identified a group without troponin elevation, and another with troponin elevation that was not judged to be an MI. Multivariable cox proportional hazard models for death at 1-year and assessments of proportionality of hazard functions were performed and expressed as an adjusted hazard ratio (aHR) and the 95% confidence intervals (CI).

**RESULTS:** MACE was observed in 469 patients**,** and another 754 patients had isolated troponin increases. MAPE were observed in 631 patients. Compared with control patients, MACE patients were at increased risk of mortality (aHR 3.36 [95% CI, 2.55 - 4.46]), similar to patients who suffered a MAPE without troponin elevation (n = 501) (aHR 2.98 [95% CI, 2.26 - 3.92]). Patients who suffered MAPE with troponin elevation but without MI had the highest risk of death (n = 116) (aHR 4.29 [95% CI, 2.89 - 6.36]). The impact of these 4 types of adverse events on 1-year disability-free survival was similarly affected.

**DISCUSSION:** MACE and MAPE occur at similar frequencies and affect survival to a similar degree. All 3 types of postoperative troponin elevation in this analysis were associated, to varying degrees, with increased risk of death and disability.

As many as 1 in 8 patients experience adverse postoperative events of the more than 300 million who have surgical procedures annually1 2 — events that are associated with increased morbidity, mortality and cost.3 The International Surgical Outcomes Study (ISOS)2 found that septic complications were the most common postoperative adverse and/or mortal events. However, due to the pragmatic nature of ISOS, biomarkers were not routinely measured and the incidence of major adverse cardiac events (MACE) was most likely underestimated.4 In other studies, myocardial injury, defined by abnormally elevated postoperative cardiac biomarkers, occurred in more than 15% of unselected older surgical patients.5-7 Myocardial injury has been reproducibly associated with increased mortality in a concentration dependent manner.4-10 In fact, seemingly minor troponin elevations have been associated with increased risk of postoperative death.5

Troponin elevation may result from a spectrum of cardiac pathologies including myocardial infarction (MI), myocardial ischemia, heart failure, arrhythmias and pulmonary embolism. Elevated postoperative troponin has also been associated with noncardiac events such as sepsis, respiratory failure, and acute and chronic renal failure.11 The effect that these diverse causes of myocardial injury have on major postoperative outcomes has not been fully investigated. The most notable etiology is an MI, which occurs in 10-35% of patients with elevated troponin.5,6 Postoperative MI is most often found to be similar to a silent non ST-elevation MI seen in the nonsurgical setting.12 It is well understood that postoperative MI increases the likelihood of mortality.13 Clinically silent non-MI troponin elevation population represents the majority of the myocardial injury episodes and includes demand ischemia secondary to common postoperative events such as tachycardia14 and severe anemia15.

The incidence and longer-term consequences of noncardiac major adverse postoperative events (MAPE) with or without troponin elevation, have not been systematically compared to major adverse cardiac events (MACE). Furthermore, since previous studies5,6 have not considered the influence of non-cardiac MAPE on outcomes, patients with troponin elevations were compared to a control group that contained some patients with MAPE, thus inflating morbidity in reference patients.

Our primary objective was to investigate and compare the independent prognostic effect of the different myocardial injury phenotypes (isolated troponin elevation and troponin elevation associated with MACE and noncardiac MAPE, on survival. The ENIGMA ll cohort16 offers a unique chance to evaluate myocardial injury since this multicenter trial, enrolled more than 7000 patients, had universal postoperative troponin measurements, independent and blinded adjudication of outcomes, along with routine postoperative surveillance for many MAPE and a 1-year follow-up.17,18 Our *a priori* hypothesis was that any postoperative troponin elevation, regardless of its association with MACE or noncardiac MAPE, is independently associated with postoperative mortality.

**METHODS**

The ENIGMA II Trial was an international, parallel-group, patient- and observer-blinded, randomized trial. A total of 7112 non-cardiac surgery patients, aged ≥ 45 years, and at risk of perioperative cardiovascular complications were enrolled. ENIGMA II was registered at ClinicalTrials.gov (NCT00430989). The protocol,17 results of the 30-day,16 and 1-year follow-up18 have been published. The approval of ethics committees was obtained and patients provided written informed consent before enrolment in the study. The consequences of isolated troponin elevation compared to the cohort with no adverse events has previously briefly presented.**19**

*Protocol*

All patients had a 12-lead electrocardiogram preoperatively, and serum troponin concentration was measured 6-12 hours postoperatively, and on the first, second, and third day after surgery while patients remained hospitalized. Thereafter, troponin analysis was undertaken as clinically indicated. We did not use a central laboratory instead each center used the troponin assay available at their institution. In this study, we expressed troponin elevation as a multiple of the site-specific upper reference limit (URL). Other investigations were ordered as clinically indicated during the 1-year follow-up period. One-year follow-up was conducted via a medical record review and telephone interview. In the event that patients were dead or incapacitated, we interviewed relatives or treating physicians.

For the purposes of this analysis we constructed composite endpoints for both cardiac and a noncardiac composite adverse surgical outcomes. Major adverse cardiac event (MACE) is composed of myocardial infarction, cardiac arrest, and myocardial revascularization, with or without troponin elevation. MI was defined using the 3rd Universal Definition and was blindly adjudicated. The troponin threshold that prompted clinical evaluation was based on the 99th percentile of a healthy reference population in the laboratory at each site.20 A major adverse postoperative event (MAPE) included unplanned admission to intensive care, prolonged mechanical ventilation, wound infection, pulmonary embolism, and stroke. These definitions result in 5 distinct cohorts: i. MACE, ii. Troponin elevation without MI, iii. MAPE, iv. MAPE with a non-MI troponin elevation, and v. and cohort without MACE, MAPE or troponin elevation who function as the reference population. All MAPE and MACE were reported through to 30 days after the index surgery. Disability at 1-year was assessed using Katz assessment of daily living (ADL) inventory.21 For the purposes of this analysis, patients with a Katz ADL of <8 were considered disabled.18

*Data analysis*:

An *a priori* analysis plan was submitted to the steering committee and was followed for these analyses. The primary outcome for this analysis was survival up to 1 year after surgery. We conducted our analyses using the following five categories of outcomes:

1. MACE
2. Troponin elevation without MI
3. MAPE
4. MAPE with troponin elevation without MI
5. Neither MAPE nor troponin elevation serving as the reference (“no adverse events”)

Our model also included patient and perioperative characteristics, including patient age (categorized as <65, 65-75 or >75 years), sex, heart failure, coronary artery disease, cerebrovascular disease (transient ischemic attack or stroke), insulin-requiring diabetes, preoperative renal function (categorized as estimated glomerular filtration rate [eGFR] <30, 30-60, and >60 ml/min), and significant preoperative anemia (hemoglobin <90 g/L). Procedure-related variables included anesthesia type, duration of surgery, dose of inhalational anesthetic agent (expressed as minimum alveolar concentration [MAC] equivalents), occurrence of intraoperative hypotension (systolic blood pressure <80 mmHg), and surgical type (emergent, general, vascular). All troponin values were expressed in multiples of each assay’s URL.

Multivariable cox proportional hazard models for death at 1-year was constructed and assessments of proportionality of hazard functions were performed and expressed as an adjusted hazard ratio (aHR) and the 95% CI. Multivariable logistic regression was used to estimate the adjusted odds ratio (aOR and 95% CI) for the association between the 4 classes of adverse events and disability free survival at 1-year.

Missing Data:

One-year follow-up data were not available in the entire ENIGMA II cohort. The major reason for missing data was discussed in our 1-year outcome study.18. We planned two sensitivity analyses to assess the effects of these missing data on the outcomes. First, a logistic regression model was fit to estimate the probability that each patient was followed up at 1-year. For each regression model, observations were weighted by the inverse of these probabilities. Patients experiencing death within the 30-day follow-up of ENIGMA II were given a weight of 1. Second, we conducted a separate analysis limited to centers where more than 90% of patients were followed. SAS version 9.3 was used for all analysis.

**RESULTS**

ENIGMA ll recruited 7112 patients with follow-up at 30 days in 6992 patients, and in 5,797 at 1 year (Supplemental Figure 1). A postoperative MI was diagnosed in 435 patients (6.2%), 99 (1.4%) patients died within 30 days of surgery, and at the 1-year 434 (7.5%) patients died. One-year disability-free survival was 87.5%.

At least one postoperative troponin assay was performed in 6957 patients (99.2%), and 1296 patients (18.5%) had a postoperative troponin elevation (Figure 1). Postoperative troponin elevation was associated with increased 30-day mortality in a concentration dependent manner (Supplemental Figure 2.)

MAPE occurred in 631 patients. 45 (0.6%) had a stroke, 40 (0.5%) had a pulmonary embolism, 122 (1.7%) required prolonged ventilation, 207 (3.0%) had an unplanned ICU admission, and 534 (7.7%) developed a wound infection. Most patients had combinations of these adverse events (Supplemental Table 1).

MACE occurred in 469 patients. of whom 57 did not have troponin elevation on postoperative days 0-3. Of those patients with MACE, 21 (4.5%) suffered a cardiac arrest, and 6 (1.3%) died before a troponin sample was obtained. Three (0.6%) patients died within 1 day of surgery, and another 32 (7.6%) patients had MI diagnosed between postoperative days 4-30. Patients with MACE had higher peak postoperative troponin levels than patients with injury. (Supplemental Table 2.)

Troponin elevation was seen in 130 (11.8%) patients with MAPE. The remaining 754 (68.5%) patients with troponin elevation had neither MACE nor non-cardiac MAPE. In 501 (45.5%) of the 1100 patients having a MAPE there were no troponin elevations on postoperative days 0-3. The remaining patients had neither a MAPE nor an elevated troponin in the first 3 postoperative days (Figure 1).

The characteristics and results of the 1-year follow-up are seen in Table 1. More patients who did not experience MAPE were missing at 1-year follow-up than patients who did experience MAPE (18.9% vs. 12.5%) (relative risk, RR: 1.49; 95% CI, 1.26 - 1.78).

The mortality at 1-year was 4.6% in patients who had neither a MAPE nor elevated troponin. In contrast, 10% of the patients with isolated elevated troponin concentration died. The mortality rates between patients suffering a non-cardiac MAPE without troponin elevation, 73 (16.7%) and the patients with a MACE, 74 (18.0%) were similar. Finally, 30 (25.9%) patients with troponin elevation who experienced a noncardiac MAPE died in the first postoperative year. The mortality difference between patients with a MAPE without troponin elevation and a MAPE with troponin elevation was not significant (aHR 1.51 [95% CI, 0.99-2.31 p=0.07). The 1-year survival curves for each of the 5 groups are shown in Figure 2.

At 1-year 206 (2.3%) patients had Katz ADL-defined disability. The logistic regression models showed that troponin elevation was associated with reduced disability-free survival across all types of adverse events (Table 2).

One-year follow-up determined the cause of death in over 80% of patients. The most frequent cause of death was cancer (36.3%), with cardiac death occurring in 67 patients (15.4%). Patients with any type of troponin elevation died of cardiac complications more often than those without troponin elevation (RR 2.3, 95%CI, 1.5- 3.5). This relationship was unchanged when we excluded patients who had experienced MACE. Patients with myocardial injury also had similar rates of deaths due to respiratory or infective causes, compared to those without troponin elevation (Table 3).

Sensitivity analyses conducted to assess the potential influence of missing data on 1-year mortality rates showed the differences between groups remained significant and minor changes in effect sizes (Supplemental Table 3).

**DISCUSSION**

This secondary analysis of the moderate to high cardiac risk ENIGMA ll cohort found that postoperative myocardial injury (as evidenced by elevated troponin) is associated with increased risk of both short and longer-term morbidity and mortality. Patients diagnosed with MI had both higher postoperative troponin concentrations and higher mortality than patients with non-MI troponin elevation. Importantly, we demonstrated that the morbidity and mortality associated with non-cardiac MAPE is similar to that experienced by patients with MACE. A cardiac etiology of death occurred relatively infrequently but was twice as frequent in patients with troponin elevation compared with patients without elevated troponins. These results demonstrate that postoperative myocardial injury, whether it is MI, non-MI/MACE-associated troponin elevation, or non-cardiac MAPE-associated troponin elevation, is prognostically important.

Routine postoperative cardiac biomarker surveillance in noncardiac surgery is not currently a widely employed standard of care. Recently both the European22 and Canadian23 guidelines have recommended measuring troponin in all patients over 65 years and those deemed to be at higher cardiac risk (Revised Cardiac Risk Index >2), whereas the American Heart Association guidelines24 and the 3rd Universal Definition of MI25 recommend surveillance in an undefined “high risk” population. Using the criteria outlined in our analysis,16% of our population was at high risk of death, and would not have been identified without routine postoperative troponin surveillance. Without knowledge of this risk, intervention and/or rescue therapy could never be initiated.

The present analysis reproduces the finding that postoperative myocardial injury is associated with increased mortality in a concentration-dependent manner. Even with the exclusion of the MI phenotype, myocardial injury is strongly associated with mortality. Unlike previous analyses,26 we did not exclude patients with pulmonary embolism, renal failure, or sepsis from our analysis of non-MI troponin elevation. Although this analysis was likely underpowered to show a statistically significant result, it does suggest that in patients with these adverse events a concomitant elevated troponin was associated with a further increase in the risk of death.

The ENIGMA ll study cohort has several limitations. More than 15% of patients had missing data at the 1-year follow-up. We found that patients with adverse events were 49% more likely to be followed than patients without adverse events. This pattern of missing data has the potential to bias and inflate the differences we have demonstrated in mortality rates of patients with and without adverse events. We investigated the effects of this detection bias on our primary outcome in two sensitivity analyses. Neither exercise appreciably altered the results. Interestingly this detection bias did not apply to patients with isolated troponin elevations who did not experience MAPE. The differential follow-up rate, where patients with myocardial injury were followed less frequently than patients with a “classic” adverse event, may also reflect a mistaken opinion that small postoperative troponin elevations are not clinically important.

Next, our study was conducted in a selected population of patients with moderate-to-high risk of a cardiac event. We believe, however, that the findings of this study are both reproducible and generalizable. Numerous studies have shown myocardial injury, as judged by troponin elevation, is associated with increased mortality at 30 days.

The lack of data on postoperative hemoglobin concentrations and blood product use limits our ability to adjust for an important factor in short and long-term outcomes.27,28

The study design did not include collection of postoperative creatinine data, and we were therefore limited in our ability to assess postoperative renal dysfunction. Postoperative renal function is common: in recent large-scale studies acute kidney injury (AKI) occurred in 6-13% of patients and was associated with short-term post-operative mortality.29,30 There is a well-recognized relationship between AKI and troponin elevation.31 Analyses of the VISION study showed that preoperative renal failure, defined as an eGFR less than 30 ml/min, decreased the effect size of elevated troponin on death at 30 days based on a threshold of ≥0.02 ng/ml.32 Thus, in this analysis we may be underestimating the incidence of MAPE since we do not know the incidence of AKI. Similarly, it is also possible that the increased morbidity in the patients with isolated troponin elevation is related to unrecognized AKI. We believe, however, that the impact of unrecognized renal dysfunction on our results is likely small. The Cox proportional hazard models included age, preoperative eGFR, anemia and intraoperative hypotension; factors that are known to be associated with postoperative AKI.

Aspects of the study design specifically related to troponin collection and assay could also be considered a limitation. Troponin is a specific marker for a variety of cardiac injuries33 and the critical signal in MI.25 While we can distinguish between MI and non-MI troponin elevation, we are limited in that the pathophysiology behind the non-MI myocardial injury could not be elucidated. We also did not measure troponin preoperatively, which has been found to be elevated in a proportion of preoperative patients and is recommended when using a high sensitivity assay.25 Furthermore, we measured troponin for 3 days only, which may underestimate the true incidence of MI.34 Finally, we did not employ a single troponin assay, relying instead on the assay at each center. The 14 different assays that were employed had a wide variety of sensitivities.

The ENIGMA II Trial has several strengths. Over 99% of the patients had cardiac biomarkers measured. We diagnosed MI using validated and objective criteria. These diagnoses were subjected to a vigorous adjudication process. ENIGMA II was also designed to evaluate postoperative infection, unplanned ICU admission, and prolonged ventilation, and we had robust data on these frequent causes of postoperative morbidity. Finally, the study had a pre-planned 1-year follow-up that included assessment of disability, survival, and the causes of death.

In conclusion this investigation suggests that if the myocardium is injured, as evidenced by troponin elevation, then it likely does not possess the reserve to cope with the short and long-term stresses of surgery. A body of evidence now exists showing that clinically silent, troponin elevation after surgery signals significantly increased risk of adverse outcomes, immediately and up to 1 year after surgery.8,10 Studies on the etiology, prevention, and treatment of myocardial injury are needed.

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**APPENDIX**

Sites participating in the one-year follow-up study:

***Australia (ANZCA Clinical Trials Network Members)***

**Alfred:** PS Myles, S Wallace, W Galagher, C Farrington, A Ditoro; **Austin:** P Peyton, S Baulch, S Sidiropoulos; **Dandenong:** R Bulach, D Bryant; **Fremantle:** E O’Loughlin. V Mitteregger; **Geelong Hospital:** S Bolsin, C Osborne; **Monash Medical Centre:** R McRae, M Backstrom; **Royal Melbourne Hospital:** K Leslie, R Cotter; **Royal Perth Hospital:** M Paech, S March; **St Vincent’s Hospital:** B Silbert, S Said; **Westmead Hospital:** R Halliwell, J Cope; **Calvary Wakefield:** D Fahlbusch, D Crump; **Peter MacCallum Cancer Centre:** G Thompson;

**Western Hospital:** A Jefferies; **North West Regional Hosptial:** M Reeves

***Canada***

**McMaster University:** N Buckley, T Tidy; **Royal Victoria Hospital:** T Schricker, R Lattermann, D Iannuzzi; **Toronto General Hospital:** S Beattie, J Carroll; **University of Alberta Hospital:** M Jacka, C Bryden; **London Health Sciences:** N Badner

***Hong Kong***

**Prince of Wales:** MTV Chan (ANZCA Clinical Trials Network member), MWY Tsang; **Tuen Mun Hospital:** BCP Cheng, ACM Fong; **Pamela Youde Nethersole Eastern Hospital:** LCY Chu, EGY Koo

***Malaysia***

**Hospital Kuala Lumpur:** N Mohd, L E Ming

***New Zealand (ANZCA Clinical Trials Network members)***

**Auckland Hospital:** D Campbell, D McAllister; **Middlemore Hospital:** S Walker, S Olliff; **Christchurch Hospital:** R Kennedy

***Saudi Arabia***

**King Saud University Hospital;** A Eldawlatly, T Alzahrani

***Singapore***

**Tan Tock Seng Hospital:** N Chua

***United Kingdom***

**Plymouth NHS Trust:** R Sneyd, H McMillan; **Royal Lancaster Infirmary:** I Parkinson; **Bradford Teaching Hospital:** A Brennan; **Hull Royal Infirmary:** P Balaji; **Portsmouth Hospital:** J Nightingale; **King’s College Hospital:** G Kunst; **Royal Surrey County Hospital:** M Dickinson

***United States of America***

**Beth Israel Deaconess Medical Center**: B Subramaniam, V Banner-Godspeed; **Cleveland Clinic:** DI Sessler, J Liu, A Kurz, B Hesler, AY Fu, C Egan, AN Fiffick, MT Hutcherson, A Turan, A Naylor; **Louisville Medical Centre:** D Obal, E Cooke