Predicting Risk and Improving Outcomes in High Risk Patients Undergoing Major Non-Cardiac Surgery in the UK

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Declaration

I confirm that:

a) That I have composed the thesis.
b) The research outlined in chapter 2 is part of the OPTIMISE study group and my role in this is clearly described. The remainder of the research is my own work and the contribution of others is clearly outlined in the thesis.
c) This work has not been submitted for any other degree or professional qualification.

Dr Michael Gillies

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Abstract of Thesis

Introduction:

The research undertaken in this thesis was to inform OPTIMISE, a randomised controlled trial of goal directed haemodynamic therapy (GDHT) versus usual care in high-risk patients undergoing gastrointestinal surgery. The trial involved a complex intervention of cardiac output monitored administration of fluids and inotropic drugs during the perioperative period. Uncertainty exists regarding:

1. Whether the choice of fluid therapy could have influenced the outcome of the trial. 6% hydroxyl-ethyl starch (HES) has been associated with risk of death and acute kidney injury (AKI) in critically ill patients.

2. Whether he availability or provision of critical care beds is associated with improved surgical outcome and thus could have influenced the outcome of the trial. The trial intervention has traditionally been administered in a critical care setting, and this may have a bearing on outcome.

3. The trial intervention itself could have been associated with increased cardiac complications. Concerns remain regarding the administration of inotropic agents outwith traditional indications.

Methods:

1. A meta-analysis was undertaken comparing perioperative use of 6% HES solutions to any comparator.

2. Surgical activity, population demographics and critical care provision in the UK were examined using large administrative databases. 3. A UK-wide cohort of non-cardiac high-risk surgical patients admitted to intensive care was generated by combining data held by the Scottish Intensive Care Audit Group (SICSAG) and the Intensive Care National Research and Audit Centre (ICNARC) for the calendar year 2009. 4. Using this data, advanced statistical modelling techniques were used to test the association between critical care bed provision and outcome after high-risk surgery. 5. Measurement of postoperative 5th generation highly sensitive troponin (HST) release was undertaken in a subgroup of trial participants, in order to determine if the intervention was associated with increased myocardial necrosis. Logistic regression was undertaken to test if preoperative measurement of HST was associated with risk of death or major adverse cardiac events (MACE).

Results: The principal findings of this thesis were:

1. In a meta-analysis of 1567 patients from 19 clinical trials comparing perioperative administration of 6% HES solutions versus any comparator no difference was observed in 30-day mortality arms (p=0.91, I2=0%; FEM: RD 0.00, 95% CI -0.02, 0.02) or AKI (p=0.62, I2=0%; FEM: RD -0.01, 95% CI -0.04, 0.02) was observed. 2. Significant variation exists in ICU bed provision within the UK. 3. In an epidemiological study of 16 147 patients admitted to ICU following surgery in the UK, significant variation in acute hospital mortality was observed (OR 1.42; 95% CI: 1.29, 1.62). This did not appear to be accounted for by severity of illness, other patient-level factors or ICU bed provision. 4. Using HST we were unable to detect any difference in myocardial injury or infarction between GDHT and usual care groups. Preoperative HST measurement did not predict those at risk of perioperative death or MACE.

Conclusion:

Use of 6% HES in the trial intervention was unlikely to have affected trial outcome. Significant regional variation exists in outcome after surgery in the UK, which cannot be account for by patient level-factors or ICU bed provision. The trial intervention in OPTIMISE was unlikely to have caused increased incidence of myocardial infarction or necrosis. In this study preoperative measurement of 5th generation HST did not appear to predict those at risk of death at 30 or 180 days or MACE.

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List of Figures and Tables

List of Abbreviations

AKI – Acute Kidney Injury

AKIN – Acute Kidney Injury Network

APACHE – Acute Physiology and Chronic Health Evaluation

APS – Acute Physiology Score

ASA-PS – Association of Anaesthetists – Physical Status

AUC – Area under the curve

BUPA – British United Provident Association

CCI – Charleston Comorbidity Index

CI – Confidence Interval

CMP - Case-Mix Programme

CPET/CPEX – Cardiopulmonary Exercise Testing

CPR – Cardiopulmonary Resuscitation

CRP – C-Reactive Protein

CT – Computed Tomography

DBP – Diastolic Blood Pressure

DoH – Department of Health

ECG - Electrocardiogram

EQ-5D – European Quality of Life – 5 Dimensions

GDHT – Goal Directed Haemodynamic Therapy

GRO – General Register's Office

HDU – High Dependency Unit

HES – Hydroxyethyl Starch OR Hospital Episode Statistics

HRG – Healthcare Resource Group

ICER – Incremental Cost Effectiveness Ratio

ICNARC - Intensive Care National Audit and Research Centre

ICD – International Classification of Disease

ICS – Intensive Care Society

ICU – Intensive Care Unit

LCRI – Lee Cardiac Risk Index

LOS – Length of Stay

MOR – Median Odds Ratio

MPM – Mortality Prediction Model

NCEPOD – National Confidential Enquiry into Postoperative Deaths

N-GAL – Neutrophil Gelatinase Associated Lipocalin

NHS – National Health Service

NISRA - Northern Ireland Statistics and Research Agency

NSQIP - National Surgical Quality Improvement Program

OR – Odds Ratio

P-POSSUM - Portsmouth Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity

PQOL – Perceived Quality of Life

QALY – Quality Adjusted Life Year

RIFLE – Risk, Injury, Failure, Loss, End-stage: A system for classifying Acute Kidney Injury

ROC - receiver operating characteristic

RR – relative risk

RRT – Renal Replacement Therapy

SAPS – Simplified Acute Physiology Score

SIP – Sickness Impact Profile

SF30 – Short Form 30 (A quality of life scoring system)

SHA – Strategic Health Authority

SBP – Systolic Blood Pressure

SD – Standard Deviation

SICSAG – Scottish Intensive Care Audit Group

SMR - Standardised Mortality Ratio

SOFA – Sequential Organ Failure Assessment

SSI – Surgical Site Infection

TnI (TnT, TnC) – Troponin subtypes I, T, C

Chapter 1. Introduction - High Risk Surgery

1.1 Introduction

Surgery remains an effective treatment for a wide range of pathologies and is an essential component of healthcare systems worldwide. In the developed world surgical science is expanding and becoming increasingly complex. Moreover, complex surgery is being offered to an increasingly aged and co-morbid population. In the developing world it may be the only treatment option for a range of diseases and injuries. It has been estimated that as many as 40 million surgical procedures are performed in the USA and Europe every year [1] and as many as 236 million procedures worldwide. [2]

As with many medical therapies, surgery has risks as well as benefits and there is often a failure to balance these. [3] Delivery of adequate perioperative care is a major challenge for modern healthcare at every stage of the process, from patient selection and preoperative assessment, through delivery of anaesthesia and surgery to postoperative care.

The largest dataset on postoperative care available anywhere in the world is the National Surgical Quality Improvement Program (NSQIP). NSQIP is a large database of over a million patients, administered by The Department of Veterans Affairs in the USA. A recent study by Khuri et al [4] utilised the NSQIP database and the authors followed up over 100 000 patients undergoing eight surgical procedures up to 8 years. Specifically, they looked for incidence of any of 22 pre-defined types of complication within 30 days of surgery. Approximately 15% of these patients went on to develop complications within 30 days of surgery (Table 1).

A key finding of this study was that the development of short term morbidity ("complications") within the first 30 days after surgery was associated with a substantially increased long-term mortality rate compared with those patients who did not develop a complication within a similar time period (28.1% vs. 6.9%, $p<0.001$), even following adjustment for co-morbidities (Table 2).

Undergoing even relatively minor surgery may cause physiological disturbance and a pro-inflammatory state, which can have consequences extending beyond the immediate postoperative period. For example, Sweetland et al prospectively examined the incidence of thromboembolic events using the "Million Women" database in the UK. This database collected demographic data on 1.3 million women who took part in a breast cancer-screening programme between 1996 and 2001. [5] Using data linkage techniques, he looked for an association between day case or inpatient surgery (the exposure of interest) and the first diagnosis of thromboembolic disease as a day case or hospital admission or as a cause of death. He found that women were 70 times more likely to be admitted with venous thromboembolism in

the first six weeks after inpatient surgery and that frequency of a thromboembolic event peaked at 3 weeks. The risks were lower but still substantially increased 7-12 weeks after surgery. A persistent inflammatory response, proportionate to the severity and duration of the surgery and continuing beyond the operative period has been suggested as a cause of thromboembolic and other complications. [4]

Comparison can be made with cardiac surgical patients, who in some senses epitomise "high risk surgery": undergoing major thoracic procedures, often with co-existing cardiac disease, poor functional reserve and in many cases the additional insult of cardiopulmonary bypass. Moreover, as interventional cardiology advances, surgery is being increasingly offered to patients of advanced age and who are undergoing complicated surgery or reoperation. Here routine admission to an intensive care unit and protocolised management are the norm. European Association of Cardiothoracic Surgery data reports a mortality of 2.2% (0.8% excluding reoperation) for isolated coronary artery bypass grafting (CABG) and 3.4% for an isolated valve procedure. [6] This is a much lower mortality quoted for say, an emergency laparotomy, for which a mortality of 15-30% has been quoted in some studies. [7,8] Examples of some of the higher risk non-cardiac procedures carried out in the UK i.e. with a mortality of greater than 5% are outlined in Table 3.

This thesis will consider in detail means of identifying the high risk, non-cardiac surgical group using clinical and epidemiological means and also other novel methods e.g. biomarkers. In addition it will investigate whether other interventions for example critical care utilisation, choice of fluid therapy or goal directed haemodynamic therapy could improve outcomes in this group.

Table 1 Postoperative complications recognised by NSQIP.

Wound Occurrences	**CNS Occurrences**
Superficial Incisional	CVA/Stroke
Deep Incisional	Coma > 24h
Organ Space	Peripheral Nerve Injury
Wound Disruption	
Respiratory Occurrences	**Cardiac Occurrences**
Unplanned Intubation	Cardiac Arrest Requiring CPR
Pneumonia	Myocardial Infarction
Pulmonary Embolism	**Other Occurrences**
Ventilation > 48h	Bleeding > 4 units Blood
Urinary Tract Occurences	Graft/Prosthesis/Flap Failure
Progressive Renal Insufficiency	DVT/Thrombophelbitis
Acute Renal Failure	Systemic Sepsis
Urine Tract Infection	SIRS/Sepsis/Septic Shock
	Death

(adapted from "Complications in Surgery," MW Mulholland and GR Docherty)

Table 2 List of NSQIP complications in order of prognostic significance.

Complication	
1. Cardiac Arrest	9.Pulmonary Embolism
2. Failure to Wean	10. Urinary Tract Infection
3. Systemic Sepsis	11. Pneumonia
4. Cerebrovascular Accident	12. Superficial Infection
5. Renal Failure	13. Deep Wound Infection
6. Myocardial Infarction	14. Graft failure
7. Renal Insufficiency	15. Peripheral Nerve Injury
8. Coma	16. Ileus

Table 3 Selected hospital resource groups with mortality greater than 5% (from Pearse et al, 2006).

Hospital Resource Group Procedure Code	n	Urgency	Deaths (n)	Mortality (%)
Q01: Emergency aortic surgery	6,598	Emergency	2,721	41.24
F33: Large intestine; major procedures with complicating condition(s)	5,765	Emergency	1,290	22.38
F41: General abdominal; very major or major procedures aged over 69	11,648	Emergency	1,843	15.82
H05: Complex hip or knee revisions	1,667	Elective	186	11.16
H33: Neck of femur fracture; aged over 69 years or with complicating condition(s)	170,804	Emergency	15,780	9.24
F11: Stomach or duodenum; complex procedures	3,714	Elective	312	8.4

1.2 High Risk Non-Cardiac Surgery as a Global Health Issue

Little is known about the volume of surgery undertaken globally. Weiser and co-workers gathered health, demographic and economic data from 192 member states of the WHO in an attempt to estimate the global volume of major surgery. [2] The authors considered major surgery to be "any intervention occurring in a hospital operating theatre involving the incision, excision, manipulation, or suturing of tissue", however the authors acknowledge that using administrative databases to estimate this can be problematic.

For the purposes of this study, countries were pre-divided into four groups based on their annual per capita healthcare spend: high-expenditure countries spending in excess of $1000 per day; middle-expenditure countries spending $401-$1000; low-expenditure countries spending $101-400 and poor-expenditure countries spending less than $100. The investigators used data from countries where surgical volume was known and extrapolated this to countries where data did not exist, based on annual per capita healthcare spend. The investigators estimated the total global volume of surgery to be 234.2 million (95% CI 187.2-281.2million) which equated to a surgical rate of 4016 per 100 000 population or one operation per 25 people per year. A summary of surgical activity from this study divided according to healthcare expenditure is found in Table 4. [2]

Average surgical rates for selected developed nations are summarised in Table 5.
The UK had an average surgical rate of 13,365 per 100 000 population in 2004. This is higher than the average for "High Expenditure" nations (11,110 per 100 000).

Death and complication rates are even more difficult to estimate, although many commentators use studies by Gawande *et al* [9] to quote an overall 30-day mortality rate of 0.4-0.8% and studies by Kable *et al* [10] and Khuri *et al* [4] quote a major morbidity rate of 3-16%. Caution must be exercised in interpreting these figures and using them to extrapolate to other populations, as definitions of operative morbidity and mortality are arbitrary and hugely variable. This issue is considered later in the chapter. However even by conservative estimates, 7 million patients may suffer a major complication and 1 million may die every year in the perioperative period worldwide, which constitutes a major global healthcare issue. Thus predicting which patients are at risk of death and complications (the so-called "high-risk "surgical group) may allow better utilisation of resources and potentially therapeutic interventions to improve outcomes for many patients.

Table 4 Surgical activity by healthcare expenditure (Weiser et al).

Expenditure	Mean Estimated Surgical rate per 100,000 (SE*)	Estimated Volume of Surgery in millions (95% CI)	Share of Global Population (%)
Poor (n=47)	295 (53)	8.1 (3.4-12.8)	34.8
Low (n=60)	2,255 (342)	53.8 (9.8-97.4)	35.0
Middle (n=47)	4,248 (524)	34.3 (23.6-43.3)	14.6
High (n=38)	11,110 (1,300)	138 (132.5-143.9)	15.6

*standard error

Table 5. Surgical activity for selected nations (Weiser et al).

Country	Population (2004)	Annual Number of Procedures	Surgical Rate (per 100,000)
Australia	20,155,129	1,823,123	9,049
Belgium	10,419,049	1,085,065	10,414
France	60,495,537	8,268,114	13,667
Germany	82,689,210	7,715,478	9,331
Hungary	10,097,731	2,359,746	23,369
Spain	43,064,189	3,026,060	7,027
United Kingdom	59,667,844	8,135,609	13,365
United States	298,212,895	63,808,613	21,397

1.3 Geographical Variations in Surgical Outcome in the USA and Western Europe

Evidence exists that the UK performs poorly compared to other developed nations. Bennett-Guerrero *et al* prospectively followed two large cohorts undergoing high risk non -cardiac surgery from the UK (n=1056) and from the US (n=1539) to determine the applicability of the Portsmouth Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (P-POSSUM) scoring system. [1]

Patients were stratified according to risk level and in this study, for any given risk level, mortality rates were over four-fold higher in the UK cohort than in the US cohort (OR 4·50; CI 2.81-7.49; $p < 0{\cdot}001$). In the patients at the highest risk of death in hospital, i.e. a predicted mortality of greater than 20%, the observed mortality in the US cohort was 9.7% compared with 35.9% in the UK cohort. Differences in provision of and access to critical care facilities between the UK and USA were postulated as a potential cause of these findings and this issue is considered in more detail in this thesis.

A more recent study of surgical outcome was the "EuSOS" Study, a 7 day-cohort study conducted across Europe in April 2011. Data from 46,539 patients from 498 hospitals across 28 nations was included in this study and patients were followed up to a maximum of 60 days. [11] Wide differences in crude mortality were observed; the

lowest mortality was in Iceland (1.2%) and the highest in Latvia (21.5%). Nations were compared against the UK, which had the largest dataset. A logistic regression model using patient and surgical factors associated with hospital mortality (e.g. age, co-morbid disorder, emergency surgery) was constructed and used to adjust for possible confounding between countries. After correction for confounding variables, significant differences in surgical outcome remained. Ireland (OR 2.61 (1.3-5.27)), Latvia (OR 4.98(1.22-20.29)) and Poland (OR 6.92 (2.37-20.27)) were among countries where significantly worse outcomes after surgery were observed when compared with the UK. Finland (OR 0.44 (0.19-1.05)), Sweden (OR 0.58 (0.23-1.49)), Germany (OR 0.85 (0.5-1.43)) and Iceland (OR 0.47 (0.07-3.41)) were among countries with a trend towards improved survival, but this failed to reach statistical significance.

A recent study of outcomes after surgery for ruptured Abdominal Aortic Aneurysm (AAA) repair suggests that marked differences in outcome between the USA and UK remain. [12]

1.4 High Risk Non-Cardiac Surgery in the UK

Exact figures regarding volume of surgery in the UK and associated outcomes are difficult to find. In the year 2000 the NHS Executive estimated the number of surgical procedures carried out in the NHS as approximately 2.3 million [13] with an estimated mortality of 1.4%.

The Whitehall II study, a large prospective cohort study of 6478 British civil servants aged 35-55 years and published in 2008 found that certified sickness associated with a surgical procedure was associated with a greater than two fold increase in mortality. [14]

Pearse *et al* used 2 large UK databases to attempt to identify and characterise the high-risk surgical population in the UK. [15] The first was Hospital Episodes Statistics (HES), the English national statistical data warehouse for care provided by NHS hospitals. The second was the case mix programme (CMP) maintained by the Intensive Care National Audit and Research Centre (ICNARC), which collect admission and outcome data on patients admitted to ICU in England, Wales and Northern Ireland. At the time this paper was published the ICNARC collected data on ICU admissions for 94 NHS trusts. Data was extracted on all adult surgical admissions to both hospital and ICU in these 94 NHS trusts. Surgical procedures were categorised into hospital resource groups (HRGs). HRGs are groups of procedures classified together by hospital coders (for activity, funding or audit purposes) based on clinical similarity and resource requirement. HRGs with a mortality of 5% or more were classified as "high risk" in this study. Examples were: emergency aortic surgery; large bowel surgery; major general abdominal surgery with complicating condition; surgery for neck of femur fracture. All the remaining

procedures were classified as "standard risk". Of the 4 117 727 procedures studied in a 70 month period approximately 2.9 million were elective and 1.2 million were emergencies with a mortality rate of 0.44% and 5.4% respectively. This high-risk group (i.e. patients having a procedure with a greater than 5% mortality) made up only 12.5% of total procedures but approximately 80% of perioperative deaths were in this group. However fewer than 15% of these "high risk" patients were admitted directly to critical care following surgery and in this study patients admitted to ICU after initial care on a standard ward had a mortality of 37%.

Two reports published in the UK in 2011 highlighted the growing disparity in postoperative care between the UK and other developed countries (e.g. the USA) and the high rate of complications and mortality suffered by high risk patients undergoing major surgery.

The first, a report entitled "Knowing the Risk - A Review of the Perioperative Care of Surgical Patients" published by the National Enquiry into Perioperative Deaths (NCEPOD) highlighted failure to adequately assess high-risk patients before surgery and lack postoperative care in an intensive care unit for a significant number of these patients. A key recommendation of this report was to introduce a UK-wide system allowing rapid and easy identification of patients who are at high risk of postoperative mortality and morbidity. The report also recommended "to aid planning for provision of facilities for high risk patients, each Trust should analyse the volume of work considered to be high risk and quantify the critical care requirements of this cohort". [3]

The second report by the Department of Health and Royal College of Surgeons in England entitled "The Higher Risk General Surgical Patient: Towards Improved Care for a Forgotten Group" found that the mortality for higher-risk general surgery (which includes most major abdominal and vascular procedures), exceeded that for cardiac surgery by three-fold and that complication rates of over 50% are common. Poorly designed hospital services (including intensive care provision) and lack of appreciation of risk were blamed for the alarmingly high death rates of which "15 to 20 per cent are typical, and can be as high as 40 per cent in the most elderly patients". [16] Thus estimating the scale of the problem in the UK, predicting the patients at risk of dying or developing complications in the postoperative period, and finding strategies to reduce this is a major challenge.

Recent studies suggest that this problem continues to be a major issue in the UK. The UK Emergency Laparotomy Network studied 1853 patients undergoing emergency laparotomy in 35 NHS trusts in England and found an overall mortality of 14.9% rising to 24.4% in patients aged 80 or over. In addition this study described huge variability in standards of perioperative care including monitoring, consultant presence in the operating theatre and use of critical care resources. [8] In a more recent

study published in 2013, Symonds *et al* used the "Hospital Episodes Statistics" (HES) database to examine 367,796 high-risk (defined as a 30 day mortality of greater than 5%) emergency admissions in 145 NHS Hospital Trusts in England. He found an overall mortality of 15.6% in this group but found evidence of significant variability between hospitals. The authors speculated that access to emergency hospital services such as specialist radiological imaging (e.g. CT scanning of abdomen), surgical and critical care services may explain this finding. [17]

In conclusion, mortality rates after emergency and high-risk non-cardiac surgery are high and standards of care in the UK remain highly variable. This problem is not unique to the UK and has been described in other healthcare systems, for example in the USA. [18]

1.5 Outcome Measures in the Surgical Patient

Surgical patients represent a large and heterogeneous group with varied disease. Overall mortality after surgery is actually very low, 30-day mortality has recently been quoted at 1.4% in the UK [11] and those at the highest risk often have extensive co-morbidities, which pose a threat to life and may have a requirement for on-going medical management and hospitalisation. Perioperative management may have a limited impact on longer-term outcomes and considerations such as stage of malignancy, surgical procedure itself (e.g. curative or palliative) or need for other treatments (for example radiotherapy or chemotherapy) become increasingly important as time passes from the operative procedure itself. Morbidity arising from surgery may lengthen hospital stay and decrease quality of life even if survival is extended.

For these reasons, selecting appropriate outcome measures for research and comparative audit in this population can be extremely challenging. Surgery itself fulfils many of the aspects of a complex intervention as outlined by Medical Research Council (MRC) guidance [19] and so can have very varied outcomes within similar patient groups. Therefore selecting the right outcome measures (or even range of outcomes) is important to ensure adequate assessment of complex interventions given the intervention may have multiple effects. Not choosing right outcomes could mean potential benefits are missed because the outcomes used were inappropriate or lacked discrimination or responsiveness.

Outcomes often used in this group of patients include: mortality, morbidity, quality of life, hospital length of stay and societal outcomes (e.g. costs and resource utilisation). However increasingly, "composite" outcomes being are used such as "death or complications" as the overall incidence of death itself is low and complications are more prevalent (as described above). Hence it may be easier to demonstrate the overall effect for a chosen intervention.

Some of the common endpoints used in the study of surgical patients are now considered:

1.5.1 Mortality

Mortality is attractive as an outcome measure; it has a binary outcome with minimal observer bias and hospital mortality is usually reliably measured in large administrative databases.

As discussed previously, it is postulated that the pro-inflammatory and other deleterious physiological effects of surgery may last well beyond the immediate postoperative period, so the time period over which mortality is measured is important. Typically "acute hospital mortality" or 30-day mortality is used to categorise operative or short-term mortality. In his analysis of long term determinants of survival from the NSQIP database Khuri *et al* (considered by many to be a seminal publication in this field) [20] used 30-day mortality as "perioperative" mortality and 1-year and 5-year mortality as medium-term and long-term survival. [4]

More recently however, commentators have suggested that this should be extended, as 30 day mortality is too short to reflect true operative mortality and is subject to influence by external factors (e.g. healthcare targets). The recent EuSOS study measured mortality at both 30 days and 60 days and in the case of the UK 60-day mortality was more than twice as high (1.6% vs. 3.6%). [11]

Some commentators have even suggested that 90-day mortality more accurately reflects the operative mortality, for instance in major colorectal surgery. [21] However the further one moves from the intervention of interest (in this case surgery) the greater the influence of other external factors, for instance the underlying and pre-morbid disease, which for example in the case of malignancy, may be considerable.

1.5.2 Morbidity

Morbidity is increasingly recognised as an important predictor of long-term mortality. Khuri et al used the NSQIP database to examine the effect of postoperative morbidity on operative (30-day) and long-term (1-year and 5-year) mortality in 105 951 patients undergoing 8 types of operation between 1991 and 1999. The NSQIP database was developed in 1991 to allow comparative audit between multiple surgical facilities. It collects data on patient demographics, preoperative laboratory measurements, comorbidity and surgical factors. It also collects postoperative outcome data; mortality and 22 pre-defined postoperative complications occurring during the first 30 days following surgery (Table 1). Khuri concluded "the occurrence of a 30-day postoperative complication was more important than preoperative risk and intraoperative factors in determining survival after major surgery". [4] Development of any complication in the postoperative period was a better predictor of operative mortality than age, ASA class or emergency surgery. In the Khuri et al cohort, approximately 15% of patients developed complications.

Table 6 illustrates the relative importance of pre-, intra- and postoperative variables on 30-day and long-term mortality. Chafer et al prospectively examined the rate of postoperative complications and their effect on mortality using the same NSQIP dataset on patients undergoing surgery between 2005 and 2007. [22] He found complication rates were very similar - approximately 25% - in both high and low mortality hospitals and that complications alone may not predict mortality following surgery; mortality in patients with major complications was almost twice as high in hospitals with very high overall mortality as in those with very low overall mortality (21.4% vs. 12.5%, P<0.001).

Bennet Guerro et al sought to characterise postoperative morbidity in a cohort of 438 patients undergoing major non-cardiac surgery. [23] They found that although the overall mortality following major surgery was low (1.6% in this cohort), postoperative complications were common and often not related to the site of the surgery. They found that gastrointestinal complications were most common (51%) followed by pulmonary (25%) then renal (21%) and infectious (13%).

The authors developed the "Postoperative Morbidity Survey" (POMS), a 9-domain survey that assesses complications in the major organ systems and is outlined in Table 7. Its aim is to identify patients with significant postoperative complications and is designed to minimise observer bias in comparative audit, clinical trials and for healthcare providers and funders. It has been validated in a variety of surgical populations and has been recently shown to be a valid and reliable measure of short-term morbidity. [24,25]

Table 6. Relative importance of pre-, intra- and postoperative variables on 30-day and long term mortality (Top 10). [4]

Step	30-Day Mortality	OR (95%CI)	Long Term Mortality	OR (95%CI)
1	Cardiac Arrest	125.0 (106.3-147.3)	Cardiac Arrest	7.3 (6.9-7.8)
2	Failure to Wean	1.5 (1.3-1.8)	ASA Class	1.4 (1.3-1.4)
3	Serum Albumin	0.7 (0.6-0.7)	Age	1.035 (1.034-1.036)
4	ASA Class	1.7 (1.6-1.9)	Serum Albumin	0.8 (0.8-0.9)
5	Systemic Sepsis	3.6 (3.0-4.3)	Disseminated Cancer	2.4 (2.3-2.5)
6	CVA	6.7 (5.1-8.7)	Failure to Wean	1.3 (1.2-1.4)
7	Emergent Surgery	1.7 (1.5-2.0)	History of COPD	1.29 (1.26-1.33)
8	Disseminated Cancer	2.9 (2.4-3.5)	BUN >40mg/dl	1.4 (1.3-1.4)
9	Renal Failure	4.8 (3.7-6.1)	Functional Status	1.1 (1.1-1.2)
10	Myocardial Infarct	4.7 (3.7-5.9)	Smoking	1.3 (1.3-1.4)

Table 7. Postoperative morbidity survey (POMS) criteria. [23]

Pulmonary	*De novo* requirement for supplemental oxygen or other respiratory support (e.g., mechanical ventilation or CPAP)
Infectious	Currently on antibiotics or temperature >38 °C in the last 24 h
Renal	Presence of oliguria (<500 mL/d), increased serum creatinine (>30% from preoperatively), or urinary catheter in place for a nonsurgical reason
Gastrointestinal	Unable to tolerate an enteral diet (either by mouth or via a feeding tube) for any reason, including nausea, vomiting, and abdominal distension
Cardiovascular	Diagnostic tests or therapy within the last 24 h for any of the following: *de novo* myocardial infarction or ischemia, hypotension (requiring pharmacological therapy or fluid therapy >200 mL/h), atrial or ventricular arrhythmias, or cardiogenic pulmonary oedema
Neurological	Presence of a *de novo* focal deficit, coma, or confusion/delirium
Wound complication	Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organisms
Haematological	Requirement for any of the following within the last 24 h: packed erythrocytes, platelets, fresh-frozen plasma, or cryoprecipitate
Pain	Surgical wound pain significant enough to require parenteral

1.5.3 Length of Stay

Acute hospital length of stay or ICU length of stay has been used as an outcome measure in clinical trials, however there are several issues with its use as an endpoint. Firstly it makes no distinction for patient status at discharge (e.g. "alive" or "dead") and so interventions that increase mortality may give a false impression of benefit by reducing length of stay. While it is possible to report length of stay data in survivors and non-survivors, it has become increasingly common to report "ICU-free days" as a means of overcoming this problem, with patients who die in ICU being assigned a score of zero. Several noteworthy ICU trials have used this approach, [26,27] however in this author's opinion its utility is limited in surgical patients as many are only admitted to ICU for short periods of time, are discharged rapidly and the availability of downstream beds may have more bearing on length of stay.

1.5.4 Quality of Life

Health related quality of life has been measured after a variety of surgical interventions e.g. colorectal surgery, [28] upper gastro-intestinal surgery, [29] and major joint surgery. [30] Examples of such "Patient Reported Outcome Measures" are the EQ-5D system developed by the Euro-Qol group. This system asks patients to score mobility, pain, anxiety, self-care and usual activities on a visual analogue scale of 0-100. It has been used in surgical settings, often in orthopaedic surgery where control of painful symptoms may be the overriding issue around the decision to operate. [31] Other health-related quality of life measures used in survivors of critical illness but not specifically validated in the postoperative population include: Sickness Impact Profile (SIP), Perceived Quality of Life (PQOL) and Short Form 36 (SF-36). [32]

Many of these were developed for health economic evaluation (e.g. EQ-5D), whereas some are more focused on truly reflecting quality of life (e.g. SF-36). Thus all have potential limitations, depending on the reason and the population for which they were developed. Quality of life scoring systems are also usually self reported and are exposed to a high degree of subjectivity and bias. This can be patient related (affected by patient beliefs, attitudes etc.) or a feature of the questionnaire itself (e.g. closed or open questioning). Moreover, other disease processes and co morbidity may affect the outcome.

The "quality adjusted life year" or QALY is used to assess both the duration and quality of additional longevity attributed to a particular treatment and is used by the National Institute for Clinical Excellence (NICE) in the UK to assess new therapies. [33] The QALY is calculated by multiplying the number of additional years the patient might live as a result of the treatment, by a measure of "quality of life" with "0" being the worst possible health and "1" being the best possible health. "Cost utility analysis" can make comparisons between therapies for example in health technology assessment; this might typically involve using incremental cost-effectiveness ratio (ICER) to measure differences in cost and patient benefit (assessed using QALYs). There are issues around this approach, including ethical, applicability and economic criticisms and these are discussed more fully elsewhere. [34,35]

1.5.5 Economic Outcomes

Hospital or intensive care length of stay is often used as a crude or surrogate of healthcare costs and resource utilisation, despite the fact that it is affected by a range of geographical and patient factors e.g. local policy, discharge to step down units, community nursing arrangements, patient preference and home arrangements. Due to ease of measurement and ready availability it remains a popular outcome measure and it is usually reliably documented in large administrative databases.

Full healthcare economic analysis involves calculation of QALYs (e.g. by use of EQ-5D questionnaire at specific time points) and calculation of hospital resource use

from hospital admission data. An example of this in the surgical setting is the "FOCCUS" trial of fluid loading in high-risk surgery. [36]

1.6 Identification of the High Risk Surgical Population

Identifying the high-risk surgical population prior to operative intervention remains a major challenge and several methods of stratification of the surgical population according to risk exist. These include: scoring Systems, tests of functional capacity (e.g. Cardiopulmonary Exercise Testing) and biomarkers.

1.6.1 Risk Stratification and Scoring Systems

Scoring systems, which stratify patient risk on the basis of patient characteristics, are generally low cost, easy to perform and may estimate population risk (e.g. used to adjust for case mix or patient level factors in comparative audit), individual risk (used to make predictions of risk for individual cases) or both.

When scoring systems are introduced it is necessary to validate them. Usually an appropriate population is used to develop the model i.e. determine which variables are important and assign weights. The model is then validated on another cohort. "Calibration" determines the correlation between predicted and observed mortality and uses goodness of fit tests (e.g. the Homer-Lemeshow C-Statistic). Calibration is thought to be "good" if the Standardised Mortality Ratios (SMR) i.e. the ratio between predicted and observed rates of death is close to 1. Model discrimination is also tested using receiver operating characteristic (ROC) curves. The area under the curve (AUC) should be greater than 0.70.

Age is often used as a measure of physical status and although a poor indicator of co morbidity, it is often accurately documented in databases. Scoring systems serve two functions: firstly to permit co-morbidity adjustment across different populations and reduce confounding effects of physical status in epidemiological studies. Secondly they may assist with prediction of individualised risk for patients undergoing surgery. The most widely used preoperative scoring system is the American Society of Anaesthetist Physical Status (also known as the "ASA-PS" or simply "ASA score"). Other scoring systems, which have been utilised in this setting, include the Charlson Co-morbidity Index (CCI), the Surgical Risk Score (SRS) and the Physiological and Operative Severity Score for enumeration of Morbidity and Mortality (POSSUM). The APACHE II score has also been used to stratify risk in surgical patients. Also considered are predictors of cardiovascular risk: the Goldman Cardiac Risk Score and the Lee Revised Cardiac Risk Index (LRCI). Each of these will be considered in turn.

American Society of Anaesthesiologists – Physical Status

The ASA-PS score is a somewhat subjective assessment of a patient's overall health and physical status and was developed by Saklad *et al* and first used in 1941. [37] It initially had seven categories and this was rationalised to five in 1963. [38] The ASA score is set out in Table 8.

The ASA-PS score is not strictly speaking a preoperative scoring system and was developed as a categorisation system for statistical study. [39] It does not take into account the scope and nature of the surgery and therefore its predictive use in individual patients is limited. Its simplicity makes it a common and useful descriptive tool of a patient's physical status prior to surgery although inconsistencies in both its application and interpretation are well documented. [40-42]

Several studies have shown ASA-PS to correlate well with postoperative outcome. Wolters *et al* undertook a retrospective study of 6301 patients undergoing surgery in a German university teaching hospital and found ASA-PS correlated well with length of ICU stay, postoperative complications and death (Table 9). [43]

Davenport et al used the NS-QIP database to validate ASA-PS in almost 6000 patients and again found it to be a strong predictor of outcome. The investigators found the predictive power of ASA-PS was increased by the addition of 20 "co-morbidities" identified in previous work (Table 10). [44]

In conclusion ASA-PS correlates well with outcome; however, subjectivity, poor inter-observer consistency and lack consideration of nature of surgery limit its usefulness as a predictive tool.

Table 8. The ASA scoring system. [38]

Category	Description
ASA 1	A fit and healthy patient with no co morbidities
ASA 2	The patient has mild systemic disease
ASA 3	The patient has severe systemic disease which is not a constant threat to life
ASA 4	The patient has severe disease which is a constant threat to life
ASA 5	The patient is moribund and unlikely to survive 24h with or without surgery

*The suffix E is often applied to denote emergency surgery.

Table 9. Association of ASA-PS class with morbidity and mortality from Wolters *et al.* [43]

	ASA I	ASA II	ASA III	ASA IV	p
N	1133	2685	2181	290	
% age	18	42.6	34.6	4.6	
ICU LOS (days)	0.2	0.8	1.9	5.4	<0.05
Hospital LOS (days)	9.3	16.4	20.8	17.6	<0.05
Pneumonia	0.5	2.2	5.2	12.1	<0.05
Cardiac Complication	0.1	1.5	5.5	18	<0.05
Wound Infection	1.8	3.8	6.3	10.6	<0.05
Hospital Mortality	0.1	0.7	3.5	18.3	<0.05

LOS = Length of stay

Table 10. The 20 most influential risk factors in predicting ASA-PS with incidence rates and odds ratios for a higher ASA-PS Level (Davenport *et al*). [44]

Preoperative Risk Variable	Incidence (%)	Odds Ratio
Preoperative coma	0.2	18.01
Dyspnoea at rest	1.8	5.34
Preoperative impaired sensorium	2.1	5.04
On ventilator	1.2	4.36
Morbid obesity (BMI $\geq$ 39)	7.1	4.22
Totally dependent functional status	2.5	3.29
Previous PTCA	2.7	3.12
Previous cardiac operation	4.2	3.11
Current smoker	31.6	2.94
History of CVA Without Neurologic Deficit	1.3	2.54
Dyspnoea with moderate exertion	9.2	2.50
History of hypertension	32.2	2.48
Insulin-dependent diabetes	3.8	2.38
COPD	7.1	2.30
Orally treated diabetes	4.8	2.01
Age (10-yr increment)	47 yr*	1.57
High WBC	13.8	1.53
Albumin <3.5	9.7	1.47
Obesity (25 <BMI< 39)	46.7	1.22

* mean age

Charlson Age-Co morbidity Index and Associated Scores

The Charlson Age-comorbidity index or Charlson Comorbidity Index (CCI) is a list of 19 medical conditions each of which is an assigned a "weight" of 1-6. The CCI was developed as a prospective method of adjusting for co-morbid conditions, which might alter the risk of mortality and was designed for use in longitudinal studies. In the original paper Charlson *et al* developed the index in a cohort of 559 medical patients then subsequently tested its ability to predict risk of death from co-morbid disease in the second cohort of 685 patients with breast cancer during a ten-year follow-up. [45] CCI was predictive of increased risk (OR 2.3; 95% CI: 1.9-2.8) of death per increment in co-morbidity and this index was further validated in postoperative patients suffering from hypertension or diabetes. [46] A list of co-morbidities and their respective weights is outlined in Table11.

Deyo *et al* mapped out the original 19 conditions described by Charlson to ICD-9 diagnoses and performed a further validation in 27 000 patients undergoing spinal surgery. The investigators found strong associations between CCI and length of stay, costs and perioperative morbidity and mortality. [47]

Further modification to the CCI was made by Ghali *et al* [48] who reduced the number of co-morbidities and altered their weights to select those which best predicted mortality in 257 333 patients who had undergone cardiac surgical procedures in Massachusetts. The five co morbidities and their altered weights are shown in Table 12.

Although the CCI has been shown to strongly predict adverse outcomes in large administrative databases it fails to take account of surgical factors in prediction of outcome and has not been validated to predict risk on an individual basis. Therefore it cannot be used for this purpose.

Table 11. Weighted indices of co-morbidity.

Condition	Charlson Weights	Ghali Weights
Myocardial Infarct	1	1
Congestive Heart Failure	1	4
Peripheral Vascular Disease	1	2
Cerebrovascular Disease	1	1
Dementia	1	-
Chronic Pulmonary Disease	1	-
Connective Tissue Disease	1	-
Ulcer Disease	1	-
Mild Liver Disease	1	-
Diabetes	1	-
Hemiplegia	2	-
Moderate or severe renal disease	2	3
Diabetes with end organ damage	2	-
Any tumour	2	-
Leukaemia	2	-
Lymphoma	2	-
Moderate or severe liver disease	3	-
Metastatic solid tumour	6	-
AIDS	6	-

Table 12. Outcomes of lumbar spine surgery and resource use according to adapted Charlson co-morbidity index scores. [47]

Charlson Score	0	1	2	>3	p
N	19,167	5478	1626	840	<0.0005
Mean age (yr.)	71.7	71.8	72.2	72.7	<0.005
In-hospital complications (%)	7.9	8.4	9.1	10.5	<0.01
LOS (d)	12.9	14.0	15.0	16.1	<0.0005
6 Week Mortality	0.5	1.0	1.8	2.7	<0.0005

Physiological and Operative Severity Score for the Enumeration of Mortality and morbidity (POSSUM) score

The POSSUM score was originally described by Copeland *et al* [49] as a tool to compare surgical morbidity and mortality across a range of procedures and allow comparative audit of different surgical units. The investigators examined 62 physiological variables and used multi-variate analysis to select the 12 most predictive variables (Table 13). Physiological and operative severity scores are then generated and used to give a predicted morbidity and mortality using the equation:

Ln R/1-R = -7.04 + (0.13 x PSS) + (0.16 x OSS)

PSS = Physiological Severity Score; OSS = Operative Severity Score; R= risk of mortality

Because of concerns regarding the over prediction of death (by 2-fold in low risk patients) the "Portsmouth" POSSUM or "P-POSSUM" score was developed. P-POSSUM uses the same dataset but a different equation to calculate predicted mortality. [50]

Ln R/1-R = -9.065 + (0.1692 x PSS) + (0.1550 x OSS)

Drawbacks with the POSSUM system are: There remains a degree of subjectivity when assessing variables. Some variables are unknown until after the surgery has taken place (e.g. blood loss). The scoring system is complex and difficult to use at the bedside. The lowest possible mortality risk is 1.08% and this may over-estimate mortality in low risk patients. Still POSSUM has been validated across a large

number of patients, through a range of surgical specialties [51-53] in different healthcare systems [1] and the P-POSSUM equation produces very close fit with observed hospital mortality. Subspecialty specific POSSUM scoring systems exist, e.g. Cr-POSSUM and V-POSSUM for colorectal and vascular surgery respectively.

Table 13. Variables used in the POSSUM score

Physiological Variable	Operative Variable
Age	Operative Severity
Presence of Cardiac Signs	Multiple Procedure
Respiratory History	Total Blood Loss
Blood Pressure	Peritoneal Soiling
Pulse	Presence of Malignancy
Glasgow Coma Score	Mode of surgery (Urgency)
Haemoglobin	
White Cell Count	
Serum Urea	
Serum Sodium	
Serum Potassium	
Electrocardiogram	

Surgical Risk Scale

The surgical risk scale was proposed by Sutton and co-workers in 2002 and incorporates the ASA-PS Score, the Confidential Enquiry into Perioperative Deaths (CEPOD) classification for surgical urgency (elective, scheduled, urgent, emergency) and the British United Provident Association (BUPA) classification of surgical complexity (minor, intermediate, major, major plus, complex major) to create a weighted score of between 3-14. [54] This composite score was strongly predictive of death ($p<0.0001$) and a subsequent study in a larger cohort of patients from a single centre found it compared favourably to POSSUM. [55]

Critical Illness Scoring Systems

Severity scoring systems for the critically ill are used to estimate severity of disease and can be used to predict acute hospital mortality. In the UK severity of illness scores are generally used to adjust for patient level factors (sometimes referred to as "case mix") in clinical and comparative audit and to compare critically ill populations for research purposes. ICU severity of illness scoring systems attempt to consider three factors: physiological disturbance, physiological reserve (from the chronic health evaluation) and the pathological process. To enable this, detailed physiological and demographic data is collected for each ICU patient. A weighting is applied to each variable and this in turn is used to generate a score related to severity of illness.

Critical illness scoring systems have been in use for over three decades, commonly used systems include: Acute Physiology and Chronic Health Evaluation (APACHE); Simplified Acute Physiology Score (SAPS); Multiple Organ Dysfunction Score (MODS); Mortality Prediction Model (MPM); Sequential Organ Failure Assessment (SOFA).

APACHE II Scoring System

The APACHE system is the most widely used scoring system in critical care. It is commonly used to permit control for case mix in clinical audit, in comparison of ICU outcomes and in clinical trials. The original APACHE system was devised by Knaus in 1981 [56] and has undergone 2 major revisions since then; APACHE III superseded APACHE II in 1991 [57]and APACHE IV was developed in 2006. [58] However APACHE II remains the most familiar and widely used system within the UK; it forms the basis of the Intensive Care National Audit and Research Centre (ICNARC) Model used in the Case-Mix Programme (CMP) and has been recalibrated twice for this purpose. [59]

APACHE II was originally validated on 5030 non-cardiac surgery general ICU patients in the USA. It is the sum of 3 components:

1. Acute Physiology Score (APS)
2. Chronic Health Score (based on certain premorbid conditions)
3. A score based on age

The APACHE II is measured during the first 24 hours of ICU admission. The maximum possible score is 71. A score of 25 represents a predicted mortality of 50% and a score of over 35 of 80%.

APACHE II is less useful in diagnostic groups which were not reflected in the original validation cohort e.g. patients who have undergone cardiac surgery or patients with burns. APACHE II has been shown to correlate well with outcome in

emergency gastrointestinal [60] and vascular surgery [61] however it should be remembered that the APACHE II scoring system was validated in a cohort of ICU patients and also that 24 hours of patient data are required. Commentators have argued that it is too complex for routine surgical use [62].

Cardiac Risk Scoring

The link between co-existing cardiovascular disease and adverse surgical outcomes has been the focus of various scoring systems for a number of years. Several scoring systems have been developed with the aim of identifying patients at risk of adverse cardiac events in the perioperative period.

Goldman *et al* first devised a risk index based in 1977 [63]. The Goldman Cardiac Risk Index attributed points to 9 risk factors identified by retrospective analysis of 1001 patients and provided an estimated risk of death or major cardiovascular complication. In the decade that followed Detsky et al and Eagle et al proposed other cardiac risk indices. [64,65] Gilbert *et al* prospectively evaluated these scoring systems in 2035 patients in 2000 and found no system to be superior, although all performed "better than chance". [66]

Lee *et al* revised the Goldman Index, reducing the number of predictors from nine to six: high-risk type of surgery, history of ischaemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine greater than 2.0 mg/dL. These factors were prospectively validated in a cohort of 4135 patients. Rates of major cardiac complication with 0, 1, 2, or 3 of these factors were 0.5%, 1.3%, 4%, and 9%, respectively. [67] Boersma further refined and validated the Lee Revised Cardiac Risk Index (LRCRI) prospectively in 108 593 patients from a Dutch administrative database and found substantial improvement in predictive value if the type of procedure was added. [68] Current guidance from the American College of Cardiology/American Heart Association stratifies patients into High, Intermediate and Low Risk based on functional capacity, clinical factors and nature of surgery. It is recommended that patients at increased risk undergo non-invasive stress testing or angiography prior to surgery. [69]

1.6.2 Cardiopulmonary Exercise Testing (CPET)

In recent years the formal assessment of functional capacity has been used increasingly to stratify perioperative risk. Assessment of functional status has been part of routine pre-operative history taking for many years and self reported poor exercise tolerance has been shown to correlate with increased perioperative risk. [70,71] Cardiopulmonary exercise testing, often abbreviated to CPET, involves measurement of physiological variables - usually electrocardiogram (ECG) and respiratory function - during incremental exercise for example on a treadmill or an exercise bike. Although CPET has been used as a tool for functional assessment in a variety of

medical disorders it has enjoyed increasing popularity following a landmark paper published by Older *et al* in 1993 in which 187 patients aged 60 or more were evaluated using CPET testing and found that low anaerobic threshold (AT) and preoperative myocardial ischaemia were predictive of increased perioperative mortality. [72,73]

Conduct of CPET Test

The conduct of CPET testing varies but typically involves incremental exercise testing on a cycle ergometer. The patients ECG is monitored and he or she wears a nose clip and exhaled gases are collected via the mouth and analysed. This allows calculation of oxygen consumption and carbon dioxide production. Following an initial period of familiarisation the ramping stage begins which involves increasing the intensity of the exercise in 2-3 minute intervals with the aim of completing the test in 10 minutes. In a submaximal test, the test continues until the anaerobic threshold is reached. In a maximal test the test continues until the subject is unable to maintain the desired intensity of exercise. Symptoms of chest pain or pre-syncope or ST segment depression on ECG would trigger early termination of the test. Detailed protocols and guidelines on CPET testing have been published by the American Heart Association/American College of Chest Physicians [73] and is described by Older *et al.* [72]

Data Obtained During CPET Testing

Several physiological variables are measured during CPET testing and these include:

Work (Watts)

Work is the power generated by the subject in Joules (j) per second.

Oxygen Uptake (VO_2)

The amount of oxygen extracted by the subject per unit time, usually expressed in ml/min.

Anaerobic Threshold (AT)

This is the exercise level at which anaerobic Adenosine Triphosphate (ATP) is required to supplement aerobic production. The method described by Beaver *et al* uses computerised regression analysis of the CO2 uptake (VCO2) vs. O2 uptake (VO2) plot. Additional CO2 production occurs at the transition to aerobic metabolism due to buffering of increased lactate in blood. This is detected and used to determine the AT. [74]

Maximum Oxygen Uptake (VO_2max)

This is the VO_2 that cannot be exceeded by the subject and is determined when VO2 reaches a plateau during CPET.

Heart Rate Reserve

This is the difference between the observed maximum heart rate and that observed at peak exercise.

O_2 Pulse

Oxygen uptake divided by heart rate. The amount of oxygen extracted by the tissue in each stroke volume.

Ventilatory Equivalents for CO_2 and O_2 (Ve/VCO2 and Ve/VO_2)

These are the ventilatory requirements for each metabolic rate.

Clinical Use of Data from CPET

VO_2 Max, AT and Ve/VCO2 have been shown to identify high-risk surgical patients, hence they are used most commonly for risk stratification purposes. [72,75,76] CPET has now become a widely used tool for stratification of high-risk patients prior to abdominal surgery. [72,75,76] It has also been investigated prior to vascular [77] thoracic [78] and upper gastrointestinal surgery. [79] It is available in 40% of NHS Hospitals and not widely used outwith the UK.

Most of the data regarding the use of CPET as a stratification tool are from single centres and larger multicentre studies involving different patient subgroups are warranted.

1.6.3 Biomarkers

The use of biologically plausible markers to predict perioperative mortality, morbidity or risk of specific postoperative complications is an attractive proposition. They are generally easy to measure and can easily be validated in large patient cohorts.

Several biomarkers have been evaluated in the high-risk surgical population.

Biomarkers Predicting Postoperative Cardiac Injury - Troponin

Troponins are protein complexes found in skeletal and cardiac muscle. Three subtypes of cardiac troponin exist: Troponin C (TnC), Troponin I (TnI) and Troponin T (TnT). Cardiac troponins are highly specific and sensitive and specific markers of myocardial necrosis and accurately predict mortality in patients with acute coronary syndromes. [80,81]Troponins have been used to accurately predict both preoperative

myocardial infarction and short and long term outcomes in patients with stable coronary artery disease [82] and those who have undergone major vascular surgery. [83,84]A systematic review by Levy *et al* examined fourteen studies (n=3318). In this study, increased troponin measurement after surgery was an independent predictor of mortality (OR 3.4, CI 2.2-5.2). [85]

Increasingly sensitive 4th and 5th generation Troponin assays have been developed which can improve the early detection of myocardial necrosis. [86,87]Whether the benefits of earlier detection of myocardial necrosis using so-called "highly sensitive Troponins" (HST) result in patient benefit is controversial. [88]Lopez-Jimenez evaluated the incidence and prognostic significance of cardiac TnT in 772 patients who had undergone major non-cardiac surgery. 12% of patients had elevated TnT and elevated TnT was associated with increased relative risk for cardiac events of 5.4 (95% confidence interval: 2.2 to 13, p = 0.001). [89]

The more recent "Vascular Events in Non Cardiac Surgery Patients Cohort Evaluation" (VISION) Study evaluated major cardiac complications in 15,133 patients over the age of 45 undergoing major non-cardiac surgery. In this study, there was a high prevalence of cardiac risk factors in the study cohort. After adjustment for cardiovascular and respiratory risk factors and also for various operative factors logistic regression analysis suggested that elevated 4th generation Troponin I assay was associated with mortality. [90]

VISION used a 4th generation TnI assay, however as part of a sub-study in this cohort, Kavsak and co-workers investigated the incidence of elevated 5th generation troponin in these patients. Elevated 5th generation TnI above the 99th centile was demonstrated to be 45% in a cohort of 325 of these patients. Whether this was associated with worse outcomes was not reported. [91]

Biomarkers Predicting Postoperative Cardiac Injury - Brain Natiurietic Peptides

Brain Natiurietic Peptide (BNP) is a neurohormone released by the ventricular wall in response to increased ventricular wall tension associated with volume overload. It is analogous to Atrial Natiurietic Peptide (ANP) however it has a tenth of the affinity for the ANP receptor. It has vascular and renal effects causing vasodilation and promotion of sodium and water loss respectively. Wall stress of the cardiac muscle can be measured by monitoring BNP or its non-biologically active N-terminal fragment (NT pro-BNP) as both have significantly longer half-lives than ANP. BNP and NT pro-BNP have been used both as prognostic and diagnostic tools. [92]

Two recently published meta-analyses demonstrated that measuring either BNP or NT proBNP perioperatively (including pre-operatively) could independently predict cardiovascular events in the first 30 days after vascular surgery and significantly improve the predictive performance of the revised cardiac risk index. [93,94]

Markers of Postoperative Renal Dysfunction - Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a protein released by neutrophils and epithelial cells. It is released into the urine by the proximal convoluted tubule epithelium following Acute Kidney Injury (AKI). NGAL is measurable in both serum and urine and has been shown to peak at 6 hours of cardiopulmonary bypass. [95] NGAL has been shown to be correlated with and an independent predictor of duration and severity of AKI and duration of intensive care stay after adult cardiac surgery. [95,96] A systematic review and meta-analysis found that NGAL accurately predicted AKI in cardiac surgery, critically ill and post contrast patients and that both serum and urinary NGAL were equally effective. [97] NGAL appears to have a better predictive ability in children than in adults. A further study by Ronco *et al* found plasma NGAL a useful marker of AKI in a heterogeneous ICU population, even when the timing of insult was unknown. In addition it accurately predicted severity of AKI and the need for renal replacement therapy (RRT). [98] The role of NGAL in the non-cardiac surgical population is less clear. A small study (n=74) undertaken by Shavit *et al* found that serum NGAL did not correlate with postoperative AKI but did correlate with postoperative infection and death. [99]

Markers of Inflammation - C-Reactive Protein (CRP)

CRP is an acute phase protein, i.e. plasma levels rise in response to inflammation. Its role is to bind to injured or dying cells or bacteria and activate the complement cascade, hence the name. CRP rises in acute inflammation and is routinely measured to assess the inflammatory response. CRP has been shown in several prospective studies to predict both cardiovascular events and cardiac death. [100] CRP has also been used with varying success to predict major postoperative complications: elevated serum CRP concentration has been shown to correlate negatively with VO_2max in asymptomatic men. [101] CRP has been used to successfully predict anastamotic leak [102] and infectious and other complications in the colorectal population. [103,104] Preoperative levels of "Highly Sensitive" CRP (hsCRP) are associated with increased length of stay in elective orthopaedic patients. [105]

Markers of Inflammation -Inflammatory Cytokines

Cytokines are a diverse group of small immunomodulatory peptides, which are released by a variety of tissues in response to injury. They have been linked to numerous diseases and clinical syndromes including the systemic inflammatory response syndrome. Several groups of cytokines exist and act both locally and systemically to generate a variety of pro-and anti-inflammatory responses. After major surgery levels of interleukin- 1 (IL- 1), tumour necrosis factor- α (TNF- α) and IL- 6 are known to be elevated. [106] A recent study undertaken by Kvarnstrom *et*

al examined levels of complement (C3a and SC5b-9) and the release of pro- and anti-inflammatory interleukins (tumour necrosis factor-α (TNF-α)), interleukin-1β (IL-1β), IL-6, IL-8, IL-4 and IL-10) following major abdominal surgery in 50 patients. Levels of complement, pro-inflammatory interleukins IL-6 and IL-8 and anti-inflammatory interleukins IL-10 were elevated during and following major colorectal surgery. Type of anaesthesia (intravenous versus inhalational) had no effect on cytokine levels. [107] Whether cytokine levels can be used to prognosticate following major surgery is unknown.

1.7 Strategies to Improve Outcomes the High Risk Surgical Population

1.7.1 Volume of Surgery Effect

Several studies in the last decade have suggested that there was an inverse relationship between volume of surgery and adverse outcomes for selected surgical procedures in both the UK and North America. [108-110] This has led to the concentration of selected high risk surgical procedures in so called "high volume centres". A recent study undertaken by the "Leapfrog Group" examined data for more than 3.2 million Medicare patients undergoing one of eight cancer operations or cardiovascular procedures at hospitals in the United States between 1999 and 2008. [111] The authors found reduced mortality for all eight procedures over the study period in centres performing higher surgical volumes; in abdominal aortic aneurysm repair this was by 36% (4.4% to 2.8%). Higher hospital volumes were also thought to explain a large portion of the decline in mortality for pancreatectomy (67% of the decline), cystectomy (37%), and oesophagectomy (32%). Similar data have been reported in the UK echoing data using the Health Episode Statistics (HES) database. [108] More recently, Chowdhury et al undertook a systematic review and meta-analysis examining 163 papers of 42 different surgical procedures, over 13 surgical specialities. He found that high volume and centre specialisation were associated with improved outcomes and that this varied between surgical procedure and subspecialty with vascular surgery, cardio-thoracic surgery and surgical oncology among those benefitting most. [112] The recent paper published by Holt et al in 2014 comparing outcomes in the UK with the USA also found reduced mortality associated with increased hospital volumes. [12]

1.7.2 Critical Care Provision

Bennett-Guerrero *et al* compared a large prospective cohort of patients undergoing high-risk non -cardiac surgery from the US (n=1539) with a similar cohort from the UK (n=1056) to determine the applicability of the P-POSSUM score. [1] In this study, for any given risk level, mortality rates were significantly higher in the UK cohort than in the US cohort (OR 4·50; $p < 0·001$). Routine use of Critical Care beds (both ICU and HDU) for high-risk surgical patients was been postulated as a potential reason for the disparity seen between the UK and the USA. In the study undertaken by Pearse *et al* only 36% of the high risk group were admitted to the Intensive Care

Unit (ICU) following surgery and the highest mortality rate was found in those patients who were admitted to ICU after initial care on a standard ward. [15]

The UK is known to have fewer ICU beds than other developed nations. Wunsch *et al* examined the effect of resource use and hospital and ICU bed numbers per head of population on mortality in the USA, Canada and six European countries, including the UK. [113] The numbers of critical care beds and volume of admissions varied widely between countries and the UK lay at the lower end, both in terms of per capita healthcare spend and number of ICU beds. This was found to correlate negatively with hospital mortality.

Jhanji *et al* investigated utilisation of critical care beds by high-risk surgical patients in a large NHS Trust in England. He found only one-third of patients considered "high risk" were admitted to ICU at any stage of their inpatient episode. Moreover, only approximately half of those who died were admitted to critical care and only 25% of the deaths occurred within a critical care area. The authors concluded, "The outcome of high-risk general surgical patients could be improved by adequate provision and more effective utilisation of critical care resources". [114]

Wunsch et al undertook a further study examining medical ICU admissions in the United States and United Kingdom. [113,115] United Kingdom ICU admissions were less likely to be admitted directly from the emergency department, were younger, had longer hospital stays before ICU admission, and were sicker. Patients also had a higher APACHE score and were more frequently mechanically ventilated within 24 hours after ICU admission. Although there was considerably higher overall hospital mortality in the UK there was no difference in outcome for patients admitted for mechanical ventilation in ICU directly from the Emergency Department. The authors concluded that interpretation of between-country hospital outcomes is confounded by differences in case mix, processes of care, and discharge practices.

In summary, there is evidence of wide international variation in ICU bed provision in the developed world. The UK lies at the lower end of ICU bed provision compared with many other western nations. ICU outcomes are significantly worse in the UK than in the USA, however this could be confounded by process of care issues, as the healthcare systems in each nation are very different. There is widespread speculation that this may account for observed differences in surgical outcome but little objective evidence to support this assertion.

1.7.3 Goal Directed Haemodynamic Therapy

In 1973 Shoemaker *et al* observed that patients suffering from "surgical shock" were more likely to survive if they were able to achieve higher levels of cardiac output (CO) and tissue oxygen delivery (DO2). [116] He postulated that patients who were unable to maintain adequate tissue oxygen delivery were at risk of complications and death and that increasing oxygen delivery to supranormal levels may improve

outcome. In a study conducted 15 years later he randomised 398 high-risk surgical patients to have CVP guided haemodynamic management or "pulmonary artery catheter (PAC) protocol" guided management. PAC protocol management involved increasing CO to greater than 4.5L/min and DO2 to greater than 600 ml/min using fluids and inotropes (principally dobutamine). The targets used were the median peak values achieved in the survivor group in the previous observational study. In this study he demonstrated reduced length of hospital and ICU stay, reduced duration of mechanical ventilation, reduced complications and reduced costs in patients assigned to "PA protocol" management. [117] There is significant evidence that covert tissue hypoxia may be implicated in the development of postoperative complications. This generated interest in using so-called "goal-directed haemodynamic therapy (GDHT)" in the high-risk surgical group. This approach involves using cardiac output monitoring and giving fluid and inotropes to maximise cardiac output and hence oxygen delivery. There is significant evidence that overt or covert failure of oxygen delivery may be implicated in the development of postoperative complications and hence or morbidity and mortality following major surgery. For example, a study of 118 patients conducted by Pearse *et al* suggested that significant fluctuations in central venous oxygen saturation ($ScvO_2$) (a surrogate for mixed venous oxygen saturation) occur in the immediate post-operative period. Reductions in $ScvO_2$ were independently associated with post-operative complications although these fluctuations were not always associated with changes in oxygen delivery, suggesting that oxygen consumption was also relevant. [118] However alterative hypotheses do exist: GDHT may improve microvascular flow [119] or modulate the inflammatory response after surgery. [120]

There are more than 30 randomised controlled trials investigating goal directed haemodynamic therapy involving at least 5000 patients. A summary of selected trials of goal directed haemodynamic therapy in surgical patients is given in Table 14. [117,121-135]Although many of these trials have shown benefit, the largest study, a multicentre trial of almost 2000 patients conducted by Sandham *et al* did not. [129]

Use of GDHT routinely for all high-risk surgical patients remains controversial. The clear beneficial effects in studies utilising PAC or investigating GDHT in patients undergoing vascular or trauma surgery appear to be less obvious [122,124,129] than in studies of patients undergoing gastrointestinal surgery utilising non invasive cardiac output monitoring e.g. Oesophageal Doppler Monitoring (ODM) or Lithium Indicator Dilution (LiDCO).

Meta-analyses of randomised controlled trials (RCTs) investigating the effect of GDHT on gastrointestinal complications [136], renal dysfunction [137], and postoperative infection [138]after major surgery indicate these complications are significantly reduced if GDHT is used. More recently Grocott *et al* published large meta-analyses examining the use of therapy to increase perioperative blood flow using fluids with

or without inotropic agents. This study examined data from 31 clinical trials and 5292 patients. The main findings of this study were that there was no improvement in survival associated with this therapy RR 0.89 (95% CI 0.76-1.05; p=0.18). However studies with differing interventions, patient groups and measured outcomes were included. The use of this therapy did appear to reduce complications (especially renal, respiratory and wound infections) and reduce hospital length of stay. [139]

Another controversy surrounding GDHT centres on the use of pre-emptive inotropic agents and their potential contribution to myocardial ischaemia. Pearse *et al* conducted a post hoc analysis of troponin levels in blood samples taken at 24 and 48 hours following surgery in patients who had participated in a GDHT trial using dopexamine [140] and found no significant increase in troponin levels in the GDHT group. Controversy however remains regarding pre-emptive use of inotropic agents, in particular dopexamine.

A multicentre study of 412 patients undergoing major abdominal surgery conducted by Takala *et al* compared the use of placebo with dopexamine at 0.5 $mcg^{-1}kg^{-1}min^{-1}$ and 2.0 $mcg^{-1}kg^{-1}min^{-1}$. Although there was no difference in 28-day mortality (the primary outcome measure) between groups, *post-hoc* subgroup analysis suggested survival benefit in the high-risk group. [141] There was a higher incidence of arrhythmias in the group receiving dopexamine.

Two recent meta-analyses of dopexamine have been published. Both suggested no overall survival benefit associated with dopexamine however in the analysis Pearse *et al* suggested a survival benefit (OR 0.50 [0.28-0.88]; p = 0.016) and reduced length of stay associated with low-dose dopexamine. [142] The meta-analysis conducted by Gopal *et al* did not report the effect of dopexamine at lower doses. [143] Commentators have pointed out that although the two studies included largely the same papers, different endpoints were used and also different analytic techniques; the study by Gopal et al used meta-analysis with Cochrane's "Revman" software and that of Pearse et al used meta-regression. [144]

Since then a single centre randomised, double blind, placebo-controlled trial of low-dose dopexamine vs. placebo in 124 high risk colorectal or urology patients, conducted by Davies et al and published in 2011, again failed to demonstrate any difference in survival or complications between groups. There was no difference in incidence of myocardial infarction between groups. [145] Recent animal studies have suggested that dopexamine may have significant anti-inflammatory effects, which may attenuate the organ damage associated with surgery. [120]

These data show that it has not yet been fully elucidated whether goal directed fluid management alone or in combination with inotropic therapy can improve outcomes in this group and the current evidence does not support widespread implementation of this approach.

Table 14. Selected studies of goal directed therapy in surgical patients.

Study	Year	n	Surgery	Intervention	CO Modality	Inotrope	Outcome
Boyd	1993	107	General	Fluids and Inotropes	PAC	Dopexamine	Reduced mortality and complications
Bishop	1995	77	Emergent Trauma	Fluids and Inotropes	PAC	Not specified	Reduced mortality and LOS
Bender	1997	104	Vascular	Fluids and Inotropes	PAC	Dopamine	No change
Shoemaker	1998	398	General Surgery	Fluids and Inotropes	PAC	Dobutamine	Reduced Complications and LOS
Wilson	1999	138	Mixed	Fluids and Inotropes	PAC	Adrenaline and Dopexamine	Reduced Mortality and LOS
Velmahos	2000	75	Trauma	Fluids and Inotropes	Bioimpedance/PAC	Not specified	No change in outcome
Lobo	2000	37	General	Fluids/Inotropes	PAC	Dobutamine	Reduced mortality and complications
Gan	2002	100	General/Urology	Fluids	ODM	N/A	Reduced Complications and LOS
Conway	2002	57	Major Bowel Resection	Fluids	ODM	N/A	Reduced critical care admission
Sandham	2003	1994	Vascular, Thoracic, Orthopaedic	Fluids, Inotropes	PAC	Not specified	No difference
Chytra	2007	80	Trauma	Fluids	ODM	N/A	Reduced complications, LoS and Mortality
Pearse	2005	122	General	Fluids and Inotropes	LiDCO	Dopexamine	Reduced Complications and LOS
Wakeling	2005	128	Colorectal	Fluid	ODM	N/A	Reduced LoS and GI complications
Noblett	2006	108	Colorectal	Fluid	ODM		Reduced LoS and morbidity
Lopes	2007	33	General/Urology	Fluids	PPV	N/A	Reduced hospital and ICU LoS, Reduced Complication
Challand	2012	179	Colorectal	Fluids	ODM	N/A	No difference

1.7.4 Beta Blockade

For decades there has been interest in giving patients at risk of perioperative myocardial infarction beta-blocking drugs, in particular patients with known atherosclerotic disease undergoing vascular surgery. Beta-blockers may reduce myocardial oxygen demand or stabilise coronary atherosclerotic plaques. Several studies and meta-analyses have been published on this subject, often with conflicting results.

Early randomised controlled trials in the 1990s suggested that use of perioperative beta-blockade could reduce the incidence of myocardial infarction and cardiac deaths. [146,147] Subsequent studies, however have not demonstrated evidence to support widespread implementation of this strategy. The "Perioperative Beta Blockade for Patients Undergoing Infra-renal Vascular Surgery" (POBBLE) study was a multicentre trial of 103 patients undergoing infra-renal vascular procedures published in 2005. Patients were randomised to receive the oral beta-blocker Metoprolol or placebo until 7 days after surgery. A high proportion (one third) of trial participants suffered a postoperative myocardial infarction in this study and this was not attenuated by the perioperative use of beta-blockers. [148] The larger "Perioerative Ischaemic Evaluation" (POISE) study, published in 2008, investigated the effects of perioperative beta-blockade in 8351 patients from 190 hospitals in 23 countries. Participants in this trial were either known to have, or were at risk of having atherosclerotic disease and were undergoing non-cardiac surgery. The primary endpoint of this trial was a composite of cardiac death, non-fatal myocardial infarction and cardiac arrest. The group randomised to receive beta-blockers (Metoprolol) had a reduced incidence of the primary endpoint (5.8% vs. 6.9%; p=0.0399), myocardial infarction (4.2% v 5.7%; p=0.0017), coronary revascularisation or new-onset atrial fibrillation. However there was an excess mortality demonstrated in the intervention group (3.1% v 2.3%; p=0.032) attributed to an increased incidence of ischaemic stroke (1% v 0.5%; p=0.0053). Commentators have attributed this to an increase in hypotension and bradycardia associated with beta-blocker administration. It has also been pointed out that although the use of beta-blocking drugs in the perioperative period has attractions, for every 15 myocardial infarctions prevented by beta-blockade per 100 patients there would be 8 excess deaths. [149] Unsurprisingly a subsequent meta-analysis echoes these results, however the vast majority of subjects included come from this trial. [150] At present, routine use of beta blockade in the perioperative period cannot be recommended.

1.7.5 Neuraxial Blockade

Neuraxial blockade, for example epidural or spinal anaesthesia and analgesia, has theoretical cardiorespiratory benefits in the perioperative period and for at least two decades there has been great interest in investigating its routine use to reduce complications after major thoraco-abdominal surgery. [151]

In the last 15 years at least 6 meta-analyses examining perioperative neuraxial blockade have been conducted. [152-157] Benefits demonstrated include: superior analgesia when compared to patient controlled opioid analgesia, reduced perioperative myocardial infarction, acute kidney injury, venous thromboembolism and mortality. The meta-analysis published by Rodgers et al in the British Medical Journal in 2000 included 9559 patients from 141 trials and demonstrated a significant reduction in perioperative mortality (OR 0.7 95%CI 0.54-0.9;p=0.0006). [153] Despite meta-analytic data demonstrating a consistent signal that exposure to perioperative neuraxial blockade confers benefit; large RCTs have failed to demonstrate this. The large RCT of more than 1000 patients undergoing vascular and gastro-intestinal surgery conducted by Park *et al* suggested that epidural analgesia provided significantly better analgesia and reduced intensive care admission but did not significantly alter mortality, except in the vascular surgery subgroup. [158] Similarly, the "Multicentre Australian Study of Epidural Analgesia" (MASTER study) of 915 patients did not demonstrate reduction in major morbidity or mortality after major abdominal surgery. [159] It is likely that these trials have all been underpowered and investigators in Canada attempted a multicentre pilot study to assess the feasibility of conducting a very large multicentre RCT of epidural analgesia in patients undergoing non-cardiac surgery. Participants in this trial experienced high crossover rates (26.5% of the epidural group and 9.8% of the intravenous analgesia group) and low recruitment rate. The authors concluded that for this reason a large multicentre RCT might not be a feasible study design to assess this intervention. [160]

1.7.6 Other Considerations

Other factors may influence outcome after surgery:

Ventilatory Management

Futier *et al* recently published a study in the NEJM where 400 patients undergoing abdominal surgery who were at high risk of pulmonary complications were assigned to receive either lung protective or non-protective ventilation. The primary endpoint was a composite of major respiratory and non-respiratory complications within 7 days of surgery. The primary endpoint was met by 10.5% of patients in the lung protective group v 27.5% of patients in the non-protective ventilation group (RR 0.4 CI 0.24-0.68; P=0.001). Requirement for mechanical ventilation and length of hospital admission was also reduced in the lung protective group. [161]

Timing and Contextual Phenomena

Other contextual phenomena may have a bearing on outcomes after high-risk surgery. Aylin *et al* recently examined 4.1 million inpatient surgical procedures over a 3 year period and demonstrated a "weekday" effect on 30 day mortality in patients undergoing surgery i.e. mortality was higher if patients were operated on a Friday

(odds ratio 1.44, 95% CI 1.39- 1.50) or a weekend (1.82, 95% CI 1.71-1.94) compared with Monday. [162] The authors speculated that organizational effects for example: increased use of locum and agency staff at weekends; reduced staffing levels and reduced access to senior clinician input at the weekend might explain these findings.

1.8 Conclusion

This chapter has considered the epidemiology of high-risk surgery in the UK and worldwide, methods of predicting patients at the highest risk of perioperative death and complications and strategies to improve outcomes in this group. Surgical science is increasing in complexity and being offered to an increasingly elderly and co-morbid population. This presents challenges to those involved in delivering perioperative care.

Regional and international differences in outcomes suggest that improvements in quality care can be made. Organisational factors, improved utilisation of critical care resources, perioperative haemodynamic therapy and choice of anaesthetic technique may have some influence on outcome.

Improved and more consistent definitions of perioperative outcomes may help to assess these interventions. Use of functional testing, biomarkers and scoring systems may help to stratify risk in such patients and identify those most likely to benefit from these interventions.

Chapter 2: Thesis Aims

2.1 Key Questions Arising from the OPTIMISE Trial Addressed by this Thesis

The research undertaken in this thesis was to inform aspects of the OPTIMISE trial, a large multicentre trial of a goal directed haemodynamic therapy in patients undergoing high-risk surgery.

Goal directed haemodynamic therapy is a complex intervention typically comprised of fluid therapy, inotropic therapy and invasive monitoring. It is usually, although not exclusively delivered in a critical care environment. This thesis will explore meta-analysis, epidemiological investigations and the use of biomarkers of cardiac injury to further investigate whether these components could have individually affected the outcome of the OPTIMISE trial. These research questions are developed further in the next chapter.

The research outlined in this thesis was in the context of the OPTIMISE trial and intended to inform interpretation its results and future studies. The OPTIMISE study itself is included to give context to this thesis, however should not be considered as the main body of the work.

The questions addressed by this thesis were as follows:

Could the choice of colloid used in the perioperative period or trial intervention be associated with harm or benefit?

The OPTIMISE trial intervention required administration of intravenous colloid solution; however, the trial protocol did not specify a particular solution or product. During the trial period evidence appeared which suggested that use of Hydroxyethyl Starch (HES) solutions in critically ill patients was associated with increased mortality and acute kidney Injury [169,172] although it was not known if these harmful effects extend to its use in the perioperative period. A meta-analysis was therefore warranted to determine if there was increased risk of death or kidney injury associated with the perioperative use of HES solutions.

A high proportion of patients recruited to the OPTIMISE trial were admitted to Critical Care following surgery. Is the use of Critical Care in itself associated with improved outcomes after surgery?

Critical care beds have typically been necessary to deliver GDHT in surgical patients. Therefore a "snapshot" of critical care beds per capita and per surgical procedure in the UK was created. Several commentators have suggested that lack of access to critical care beds is a reason for variation in outcome after surgery. As discussed above, cardiac output guided treatment algorithms are now widely used to

optimise the dose and timing of intra-venous fluid and vasoactive drug therapies. However the systematic review by Grocott et al [139] has suggested that the treatment benefit may be more marginal than previously believed. Postoperative use of this technology is variable and there is evidence that patients undergoing high-risk surgery may not routinely be admitted to critical care for monitoring postoperatively in many institutions and whether this confers any benefit. In the light of the OPTIMISE trial, this was particularly relevant given intervention patients received individualised therapy during the post-operative period, which appeared to alter the patterns of fluid use between the groups.

The enhanced monitoring and ability to deliver timely interventions available in critical care may explain the improved outcomes seen with GDHT rather than the intervention itself. Is Critical Care essential for optimal outcomes after high-risk surgery or can protocolised delivery of postoperative care achieve comparable or better outcomes outwith the Critical Care setting?

To answer this question in the UK it was necessary to create a cohort of surgical patients admitted to ICU following surgery and use this to examine casemix, activity and outcome. Data on population, volume of surgery and critical care bed provision was then used to explore whether differences in outcome could be explained by ICU bed provision.

Is GDHT associated with increased myocardial injury as measured by 5th Generation Troponins?

Concerns remain regarding the safety of GDHT in patients with or at risk of ischaemic heart disease [173] and its incidence in this group is high. [174] Five patients in the intervention group experienced serious adverse cardiac events within 24 hours of the end of the intervention period (two cases of tachycardia, two of myocardial infarction and one of arrhythmia) compared with none in the usual care group (p=0.062). At 30 days, the incidence of cardiovascular events was similar between the groups. Evidence of increase in myocardial injury associated with GDHT in the OPTIMISE trial was sought using 5th generation serum troponin measurement on samples taken at 0, 24 and 72 hours following the intervention.

The remainder of this thesis sets out to address these questions in some detail.

Chapter 3: Optimisation of Peri-operative Cardiovascular Management to Improve Surgical Outcome: The OPTIMISE Trial

3.1 Introduction

As discussed in Chapter 1, improvements in the peri-operative care pathway may have a significant impact on patient outcomes. In particular perioperative GDHT and utilisation of Critical Care may reduce complications, hospital length of stay and improve outcomes. Clinical trials have suggested that these interventions may be most effective in the group undergoing gastrointestinal surgery. [117,121,126-128,131-134]

Over time, GDHT protocols have been refined with an aim of addressing key issues of safety and practicality, whilst remaining as effective as those used in earlier trials. [131] However subsequent meta-analyses have demonstrated the converse of this i.e. reduced effectiveness over time. [163] The aim is to deliver perioperative GDHT in a fashion that maximises patient benefit and safety and minimises the requirement for additional resources, in particular the need to routinely admit patients to a critical care unit. If effective, this intervention could therefore be rapidly introduced into all NHS hospitals after a short period of training. Refinements to cardiac output guided treatment algorithms have improved the feasibility, safety and cost of this treatment through less invasive forms of monitoring and lower doses of inotropic therapy for shorter periods. Nonetheless, controversies regarding potential harm associated with fluid excess and myocardial injury and the need or otherwise to conduct this intervention in a critical care setting remain unresolved. The clinical effectiveness of this treatment approach remains unconfirmed and as a result, there is widespread partial implementation into clinical practice. OPTIMISE was a large, multi-centre randomised controlled trial to evaluate the clinical effectiveness of a cardiac output guided haemodynamic therapy algorithm for the administration of intra-venous fluid and a low dose inotrope (dopexamine) in comparison with usual care in patients undergoing major gastrointestinal surgery.

My Role in the OPTIMISE Trial

The OPTIMISE trial was developed and designed by Professor Rupert Pearse at Queen Mary's University London and this included the intervention and analysis plan although local Principal Investigators (PI) were given the opportunity to contribute to this. I was principal investigator for OPTIMISE at the Royal Infirmary of Edinburgh site and as such was responsible for all aspects of the safety and delivery of the trial on this site. I obtained Research and Development approval for the trial in Edinburgh, was responsible for training of relevant staff to use the LIDCOrapid technology and for the safe storage and administration of the investigational medical product (IMP, Dopexamine) to trial patients. I was responsible for maintaining the trial documentation including Standard Operating

Procedures and Trial Amendments. I ensured accurate data collection for the trial intervention and that assessors were suitably blinded. I supervised a Clinical Research Facility nurse who assisted me in the running of this trial. By the conclusion of the OPTIMISE trial I recruited 108 patients to the trial and personally obtained consent and delivered the trial intervention to these patients. In addition I led the OPTIMISE biomarker sub-study, developed analysis plans and protocols and ensured that the samples were collected, processed and stored correctly. I organised transportation to Edinburgh of samples collected at other sites and developed the study protocol and analysis plan for the biomarker sub-studies. I was involved in the interpretation of the trial results, drafting of the manuscript and presenting trial results at international meetings. In this chapter I describe the trial design, conduct and results as the main work of the thesis is informed by the OPTIMISE trial.

3.2 Methods

Trial Design

The OPTIMISE trial was a multi-centre, open label, randomised controlled trial to establish whether the use of minimally invasive cardiac output monitoring to guide protocolised administration of intra-venous fluid, combined with low dose dopexamine infusion would reduce the number of patients who experienced complications within 30 days following major surgery involving the gastro-intestinal tract.

Inclusion Criteria

Adult patients undergoing major abdominal surgery involving the gastrointestinal tract expected to take longer than 90 minutes were eligible for recruitment provided they satisfied one of the following criteria: age 65 years and over OR Age 50-64 plus, one or more of: non-elective surgery; acute or chronic renal impairment (serum creatinine >130 μmol/l); diabetes mellitus; presence of a risk factor for cardiac or respiratory disease.

Exclusion criteria

The exclusion criteria were:

- Refusal of consent
- Patients receiving palliative treatment only (likely to die within 30 days)
- Acute myocardial ischaemia (within 30 days prior to randomisation)
- Acute pulmonary oedema (within 7 days prior to randomisation)
- Septic shock
- Thrombocytopenia (platelet count <50 x 109/l)
- Patients receiving Monoamine Oxidase Inhibitors (MAOIs)

- Phaeochromocytoma
- Severe left ventricular outlet obstruction e.g. due to hypertrophic obstructive cardiomyopathy or aortic stenosis
- Known hypersensitivity to dopexamine hydrochloride or disodium edetate
- Participating in another randomised trial
- Pregnancy at time of enrolment
- Failure to meet the inclusion criteria.
- Trial interventions

The trial intervention period commenced at the start of general anaesthesia and continued for six hours after surgery was completed (maximum total duration: 24 hours).

Peri-operative management (for all patients)

Care was defined for all patients in order to avoid extremes of clinical practice or practice misalignment. All patients received standard measures to maintain oxygenation (SpO2 94% or greater), haemoglobin (8 g/dl or greater), core temperature (aim 37 °C) and heart rate (less than 100 bpm). 5% dextrose was administered at 1 ml kg^{-1} h^{-1} as maintenance fluid but an alternative maintenance fluid could be administered using the same rate at the discretion of the treating clinician. Additional fluid could also be administered at the discretion of the clinician guided by pulse rate, arterial pressure, urine output, core-peripheral temperature gradient, serum lactate and base excess. Mean arterial pressure was maintained between 60 and 100 mmHg using an alpha adrenoceptor agonist or vasodilators as required. The trial interventions commenced with induction of anaesthesia and continued until six hours after surgery ended. Post-operative analgesia could be provided by epidural infusion (bupivacaine and fentanyl) or intra-venous opioid infusion (morphine or fentanyl). Regular monitoring of plasma potassium and glucose levels was recommended. The intervention period could last a maximum of 24 hours.

Additional peri-operative management for the intervention group

The trial intervention began at induction of general anaesthesia and continued for six hours following surgery. Cardiac output and stroke volume were measured using the LiDCOrapid system. This system uses uncalibrated arterial pulse waveform analysis. It was stipulated in the trial protocol that no more than 500ml of intra-venous fluid was to be administered prior to commencing cardiac output monitoring. In addition to the maintenance fluid and blood products described previously, patients received 250ml fluid challenges with a colloid solution as required in order to achieve a maximal value of stroke volume. The type of colloid used in the trial intervention

was not stipulated in the trial protocol. The absence of fluid responsiveness was defined as the absence of a sustained rise in stroke volume of at least 10% for 20 minutes or more (Figure 1).

Patients in the intervention group also received dopexamine at a fixed rate of 0.5 μg/kg/min, which was commenced after fluid replacement has been initiated. The protocol recommended that the dose of dopexamine was reduced to 0.25 μg/kg/min if the heart rate increased to either greater than 120% of the baseline value or 100bpm (whichever was the greater) for more than 30 minutes despite adequate anaesthesia and analgesia. If, despite dose reduction, the heart rate did not decrease below this level, the dopexamine infusion was discontinued completely. All other management decisions were taken at the discretion of clinical staff.

Additional Peri-operative Management for the Control Group

Patients in the control group were managed by clinical staff according to usual practice. This could include 250ml fluid challenges with a colloid solution administered at the discretion of the clinician guided by pulse rate, arterial pressure, urine output, core-peripheral temperature gradient, serum lactate and base excess. If a specific haemodynamic end-point for fluid challenges was to be used, it was suggested that the most appropriate would usually be a sustained rise in central venous pressure of at least 2 mmHg for 20 minutes or more. Cardiac output monitoring was not to be routinely used in the control group unless specifically requested by clinical staff.

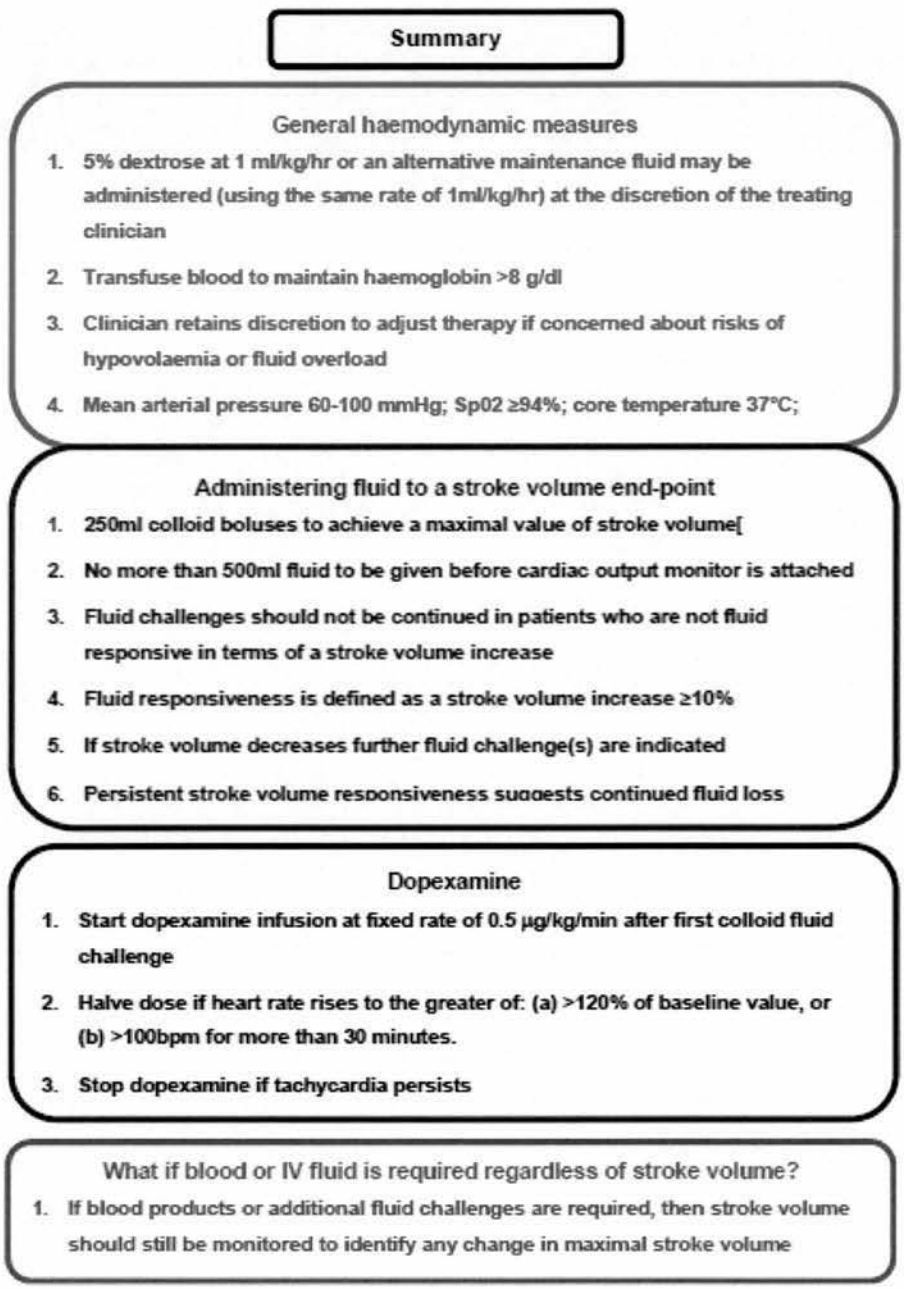
Randomisation and Procedures to Minimise Bias

Randomisation was performed through a secure internet based data entry system. Participants were centrally allocated to treatment groups using a computer generated dynamic procedure (minimisation) with a random component. Participants were allocated with an 80% probability to the group that minimised between group differences in trial site, urgency of surgery and surgical procedure category among all participants recruited to the study. OPTIMISE was a pragmatic effectiveness trial of a treatment algorithm and it was not possible to conceal treatment allocation from research staff involved in delivery of the intervention.

The possibility of bias was minimised by the following procedures: Patients were followed up for complications by a member of research staff who was unaware of trial group allocation; complications were then verified by the PI or designee at each site who was also unaware of trial group allocation; the principal investigator could nominate a senior clinician to assist with this task if he/she became aware of the trial group allocation; the decision to admit a trial participant to a critical care unit was

made by clinical staff and this decision was not to be affected by trial group allocation.

Figure 1 Haemodynamic Management Protocol for Trial Intervention Group



Trial endpoints

The primary effect estimate was the relative risk of pre-defined moderate or major post-operative complications (or death) at 30 days.

Full definitions of post-operative complications were as follows:

Myocardial ischaemia or infarction: Acute ECG changes with appropriate clinical findings and changes in cardiac troponins.

Arrhythmia: ECG evidence of rhythm disturbance resulting in a fall in mean arterial pressure of greater than 20% and considered by clinical staff to be severe enough to require treatment (anti-arrhythmic agents, vasoactive agents, intra venous fluid, etc.).

Cardiac or respiratory arrest: As per UK Resuscitation Council Guidelines.

Limb or digital ischaemia: Sustained loss of arterial pulse (as determined by palpation or Doppler) or obvious gangrene.

Cardiogenic pulmonary oedema: Appropriate clinical history and examination with consistent chest radiograph.

Pulmonary embolism: Computed tomography (CT) pulmonary angiogram with appropriate clinical history.

Acute respiratory distress syndrome: According to consensus criteria:

i) Suitable precipitating condition

ii) Acute onset of diffuse bilateral pulmonary infiltrates on chest radiograph;

iii) No evidence of cardiac failure or fluid overload (PAOP < 18 mmHg);

iv) Either:

PaO2:FiO2 < 40 kPa (Acute Lung Injury)

PaO2:FiO2 < 27 kPa (Acute Respiratory Distress Syndrome).

Gastro-intestinal bleed: Unambiguous clinical evidence or endoscopy showing blood in gastro-intestinal tract.

Bowel infarction: Demonstrated at laparotomy.

Anastomotic breakdown: Demonstrated at laparotomy or by contrast enhanced radiograph or CT scan.

Paralytic ileus: Persistent clinical evidence of intestinal ileus and failure to tolerate enteral fluid or feed associated with valid cause.

Acute kidney injury: A two-fold increase in serum creatinine or sustained oliguria of < 0.5 ml kg^{-1} $hour^{-1}$ for twelve hours.

Infection, source uncertain: Two more of the following associated with strong clinical suspicion of infection (sufficient to require intra-venous antibiotic therapy, etc.):

(i) Core temperature <36C or >38C (ii) white cell count >12 x 10^9 L^{-1} or <4 x 10^9 L^{-1} (iii) respiratory rate >20 breaths per minute or $PaCO^2$ < 4.5 kPa (iv) pulse rate >90 bpm

Multi-organ dysfunction syndrome: A life threatening but potentially reversible physiologic derangement involving failure of two or more organ systems not involved in the primary underlying disease process.

Acute psychosis: Acute episode of severe confusion or personality change which may result in hallucinations or delusional beliefs in the absence of a pre-existing diagnosis, which may account for the clinical symptoms and signs.

Urinary tract infection: A symptomatic urinary tract infection must meet at least one of the following criteria:

(i) Patient has at least one of the following signs or symptoms with no other recognized cause: fever (>38C), urgency, frequency, dysuria, or supra-pubic tenderness *and* patient has a positive urine culture, that is, $>10^5$ microorganisms per cm3 of urine with no more than two species of microorganisms.

(ii) Patient has at least two of the following signs or symptoms with no other recognized cause: fever (>38C), urgency, frequency, dysuria, or supra-pubic tenderness and at least one of the following:

a. Positive dipstick for leucocyte esterase and/or nitrate;

b. Pyuria (urine specimen with >10 WBC mm^{-3});

c. Organisms seen on Gram stain of unspun urine;

d. At least two urine cultures with repeated isolation of the same uro-pathogen with $>10^2$ colonies/ mL in non-voided specimens;

e. $>10^5$ colonies/mL of a single uro-pathogen in a patient being treated with an effective antimicrobial agent for a urinary tract infection;

f. physician diagnosis of a urinary tract infection;

g. physician institutes appropriate therapy for a urinary tract infection.

Other infections of the urinary tract (kidney, ureter, bladder, urethra, etc.): Other infections of the urinary tract must meet at least one of the following criteria:

(i) Patient has organisms isolated from culture of fluid (other than urine) or tissue from affected site.

(ii) Patient has an abscess or other evidence of infection seen on direct examination, during a surgical operation, or during a histopathology examination.

(iii) Patient has at least two of the following signs or symptoms with no other recognized cause: fever (>38C), localized pain, or localized tenderness at the involved site and at least one of the following:

a. Purulent drainage from affected site;

b. Organisms cultured from blood that are compatible with suspected site of infection;

c. Radiographic evidence of infection, for example, abnormal ultrasound, computed tomography or magnetic resonance imaging;

d. Physician diagnosis of infection of the kidney, ureter, bladder, urethra, or tissues surrounding the retroperitoneal or perinephric space;

e. Physician institutes appropriate therapy for an infection of the kidney, ureter, bladder, urethra, or tissues surrounding the retroperitoneal or perinephric space.

Surgical site infection (SSI) (superficial incisional): A superficial SSI must meet the following criteria:

(i) Infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and patient has at least one of the following:

a. Purulent drainage from the superficial incision;

b. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision;

c. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon, unless incision is culture-negative;

d. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

Surgical Site Infection (deep incisional):

A deep incisional SSI must meet the following criteria:

i) Infection occurs within 30 days after the operative procedure if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operative procedure and involves deep soft tissues (e.g., fascial and muscle layers) of the incision and patient has at least one of the following:

a. Purulent drainage from the deep incision but not from the organ/space component of the surgical site;

b. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38C) or localized pain or tenderness, unless incision is culture-negative;

c. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathology or radiologic examination;

d. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

An infection that involves both superficial and deep incision sites should be classified as a deep incisional SSI.

Surgical Site Infection (organ/space)

An organ/space SSI involves any part of the body, excluding the skin incision, fascia, or muscle layers, which is opened or manipulated during the operative procedure. Specific sites are assigned to organ/space SSI to further identify the location of the infection. An example is appendectomy with subsequent sub-diaphragmatic abscess, which would be reported as an organ/space SSI at the intra-abdominal specific site. An organ/space SSI must meet the following criteria:

i) Infection occurs within 30 days after the operative procedure if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operative procedure and infection involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure and patient has at least one of the following:

a. Purulent drainage from a drain that is placed through a stab wound into the organ/space;

b. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/ space;

c. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathology or radiologic examination;

d. Diagnosis of an organ/space SSI by a surgeon or attending physician.

Laboratory Confirmed Bloodstream Infection: Laboratory confirmed bloodstream infection must meet at least one of the following criteria:

i) Patient has a recognized pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site.

ii) Patient has at least one of the following signs or symptoms: fever (>38°C), chills, or hypotension and at least one of the following:

a. Common skin contaminant is cultured from two or more blood cultures drawn on separate occasions.

b. Common skin contaminant is cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy.

c. Positive antigen test on blood.

Signs and symptoms and positive laboratory results are not to be related to an infection at another site.

Nosocomial pneumonia Ventilator-associated pneumonia (i.e. pneumonia in persons who had a device to assist or control respiration continuously through a tracheostomy or by endotracheal intubation within the 48-hour period before the onset of infection) will be classified separately. Care will be taken to distinguish between tracheal colonization, upper respiratory tract infections and early onset pneumonia. Nosocomial pneumonia will be characterized as early or late onset i.e. before or after first 4 days of hospitalisation. Where repeated episodes of nosocomial pneumonia are suspected, a combination of new signs and symptoms and radiographic evidence or other diagnostic testing will be required to distinguish a new episode from a previous one. This category includes ventilator-associated pneumonia (i.e. pneumonia in persons who had a device to assist or control respiration continuously through a tracheostomy or endotracheal tube), however care will be taken to distinguish between tracheal colonization, upper respiratory tract infections and early onset pneumonia.

Nosocomial pneumonia must meet the following criteria:

i) Two or more serial chest radiographs with at least one of the following:

a. New or progressive and persistent infiltrate;

b. Consolidation;

c. Cavitation.

And at least one of the following:

a. Fever (>38°C) with no other recognized cause;

b. Leukopenia (WCC<4 x 10^9 L^{-1}) or leucocytosis (WCC>12 x 10^9 L^{-1})

c. For adults >70 years old, altered mental status with no other recognised cause.

And at least two of the following:

a. New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements

b. New onset or worsening cough, or dyspnoea, or tachypnoea;

c. Rales or bronchial breath sounds;

d. Worsening gas exchange

Post-operative haemorrhage: Overt blood loss requiring transfusion of two or more units of blood in two hours.

Stroke: Clinical diagnosis, with confirmation by CT scan.

Secondary outcomes were Post-Operative Morbidity Survey (POMS) defined morbidity on day seven; all cause mortality, infectious complications, critical care free days (number of days alive and not in critical care) at 30 days and all cause mortality at 180 days. The level of post-operative critical care was defined according to ICS "Levels of Care" definitions. [164] Patients were followed for 30 days by visit and using local computerised records whilst in hospital. All patients were contacted at 30 days, either by telephone for those who had left hospital or by visit for those who had not. Where necessary, investigators contacted community physicians or other hospitals by telephone and in writing for outstanding information describing the primary outcome. Mortality at 180 days was assessed through Office for National Statistics records. Data entry was performed through a secure internet site. Automated validation checks included plausibility ranges and cross checks between

data fields. Further manual data checks were performed both centrally and through source data verification during site visits.

Statistical analysis

A previous GDHT trial of 122 patients undertaken in 2005 and using similar trial endpoints showed a reduction of the primary endpoint from 68% in the usual care group to 41% in the intervention group. [131] A more conservative estimate in incidence of primary endpoint and absolute risk reduction were used for this trial. Assuming a type I error rate of 5%, 345 patients per group (690 total) were required to detect with 90% power a reduction in 30-day complications from 50% in the control group to 37.5% in the intervention group (absolute risk reduction 12.5%; relative risk reduction 25%). Allowing for a 3% one way crossover rate due to use of cardiac output monitoring in the usual care group, this was increased to 367 per group (734 total). A planned interim analysis was performed after the recruitment of 376 patients. Predefined stopping guidelines permitted early termination of the trial for harm but not effectiveness.

Analyses were performed according to an a priori statistical analysis plan including all patients on an intention to treat basis, regardless of protocol compliance. Categorical data were compared using Fisher's exact test. Differences in length of stay and critical care-free days were tested using the Wilcoxon rank-sum test. Kaplan-Meier curves were plotted for mortality up to 180 days following surgery. Adjustment for baseline data was made using a logistic regression model including age, gender, urgency of surgery, surgical procedure category, ASA grade, planned location following surgery, renal impairment, diabetes mellitus, risk factors for cardiac or respiratory disease and random effect of site. Baseline variables were selected for inclusion in the adjusted analysis according to anticipated relationship with outcome including all variables used in the minimisation algorithm. Results of primary and secondary outcomes were reported as relative risks (RR) with 95% confidence intervals (CI); results of the primary analysis were additionally reported as absolute risk reduction (ARR) with 95% CI. Results of the logistic regression model were reported as adjusted odds ratios (OR) with 95% CI with unadjusted OR for comparison. Pre-specified secondary analyses were a modified intention to treat analysis excluding patients who did not undergo surgery, a compliance-adjusted analysis in which patients who experienced protocol deviations were assumed to have the same outcome as if they had been assigned to the alternative treatment group, and scenario-based sensitivity analyses for missing primary outcomes (a best cases analysis assuming all missing outcomes in the intervention group were favourable and all missing outcomes in the usual care group were unfavourable, and a worst case analysis assuming the reverse). Pre-specified sub-group analyses were performed by surgical procedure category, urgency of surgery and the first ten

patients recruited at each site compared with subsequent patients (sites recruiting fewer than ten patients were excluded from this analysis). Continuous variables are presented as mean (SD) where normally distributed or median (quartiles) where not. Categorical variables are presented as n (%). Analyses were performed using Stata SE version 10.1. Significance was set at $p<0.05$ (two-tailed).

3.3 Results

734 patients were enrolled between June 2010 and November 2012; 368 patients were allocated to the haemodynamic intervention and 366 to usual care (Figure 2). Baseline characteristics were similar between the groups (Table 15). Most sub-groups were well represented with the exception of emergency surgery (25 patients) and urological or gynaecological surgery involving the gut (nine patients). Patient care outside the trial intervention was also similar (Table 16), including admissions to critical care. Overall volumes of intra-venous fluid (colloid and crystalloid combined) administered during the intervention period were similar (intervention group 4190 ml vs. usual care 4024 ml) (Table 16). For usual care patients most of this fluid was administered during surgery whilst intervention group patients received similar volumes during and after surgery. Intervention group patients received more colloid and less crystalloid solution than usual care patients. Use of other vasopressor and inotropic agents (other than dopexamine) was similar between the groups. Protocol compliance was good with fewer than 10% of patients in each group experiencing a deviation from the allocated intervention (Table 17). This was achieved through the presence of trained investigators where necessary, to observe, advise or deliver the intervention. Investigator self-assessment of blinding also suggested a high rate of compliance with trial procedures (Table 18).

36.6% (134 of 366) of patients in the intervention group and 43.4% (158 of 364) of usual care patients met the primary outcome. This difference was not statistically significant (RR 0.84 [0.71-1.01], ARR 6.8% [−0.3% to 13.9%]; p=0.07) (Table 19). Adjustment for baseline risk factors had little impact on the observed treatment effect (adjusted OR 0.73 [0.53-1.00]; p=0.05, unadjusted OR 0.75 [0.56-1.01]; p=0.07). This was also the case for the modified intention to treat analysis in which three patients (all usual care) who did not undergo surgery were excluded (RR 0.84 [0.70-1.00]; p=0.059). In the pre-specified compliance-adjusted analysis conducted using established methodology, [165] the observed treatment effect was strengthened by assuming that 65 patients who experienced protocol deviations would have experienced the same outcome if they had been allocated to the alternative group (RR 0.80 [0.61-0.99]; p=0.037). Scenario based sensitivity analyses demonstrated that the very small number of patients with missing primary outcomes would have had a minimal influence on treatment effect (RR 0.84 [0.70-1.00] to 0.85 [0.71-1.02]). There were no significant differences in POMS defined morbidity on day 7 or

in duration of hospital stay, critical care-free days, infectious complications or mortality at 30 days (Table 20). There was a non-significant reduction in mortality in the haemodynamic intervention group at 180 days (intervention group 28 deaths (7.7%) vs. usual care 42 deaths (11.6%), RR 0.66 [0.42-1.05]; p=0.08) (Table 19, Figure 3).

Pre-specified subgroup analyses included a comparison between the first ten recruits at each site (160 patients) with all other patients, the findings of which were consistent with an improvement in the primary outcome in the intervention group (RR 0.59 [0.41-0.84]; p=0.019) (Table 21). Following elective surgery, fewer patients in the intervention group met the primary outcome (RR 0.72 [0.52-0.99]) but outcomes were similar for patients following emergency surgery (RR 1.24 [0.23-6.74]). The intervention was also associated with a reduction in the primary outcome measure in patients undergoing small bowel +/- pancreas surgery (RR 0.53 [0.28-0.99]) but not in the other procedure subgroups. Five patients in the intervention group experienced serious adverse cardiac events within 24 hours of the end of the intervention period (two cases of tachycardia, two of myocardial infarction and one of arrhythmia) compared with none in the usual care group (p=0.062). At 30 days, the incidence of cardiovascular events was similar between the groups (Table 19).

Figure 2 CONSORT flow diagram

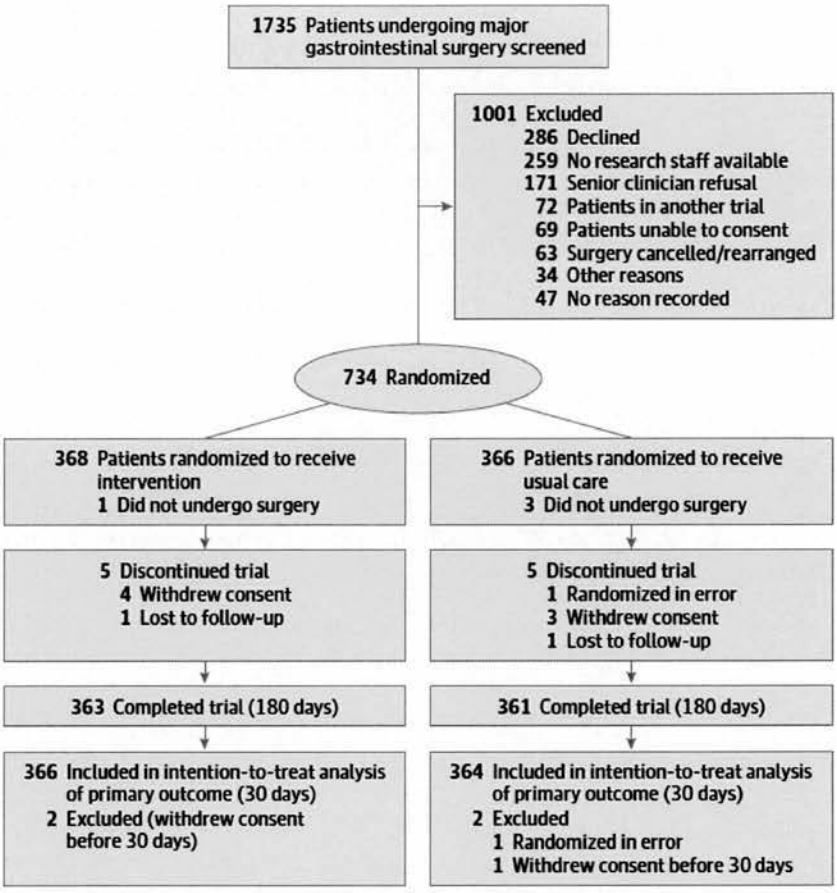


Table 15 Baseline patient characteristics.

	Haemodynamic intervention (n=368)	**Usual care (n=365)**
Age (years)	71·0 (8·4)	72·0 (8·6)
Age*		
50-64 year	70 (19·0)	59 (16·2)
≥ 65 years	298 (81·0)	306 (83·8)
Sex		
Male	237 (64·4)	229 (62·7)
Female	131 (35·6)	136 (37·3)
Urgency of surgery*†		
Elective	356 (96·7)	352 (96·4)
Non-elective	12 (3·3)	13 (3·6)
Baseline risk factors*‡		
Renal impairment	26 (7·1)	12 (3·3)
Diabetes mellitus	57 (15·5)	65 (17·8)
Risk factors for cardiac or respiratory disease	117 (31·8)	118 (32·3)
Planned surgical procedure†		
Upper gastrointestinal	110 (29·9)	114 (31·2)
Lower gastrointestinal	167 (45·4)	163 (44·7)
Small bowel +/- pancreas	86 (23·4)	84 (23·0)
Urological or gynaecological surgery involving gut	5 (1·4)	4 (1·1)
ASA grade§		
1	21 (5·7)	24 (6·6)
2	200 (54·5)	174 (48·1)
3	143 (39·0)	155 (42·8)
4	3 (0·8)	9 (2·5)
Planned location following surgery		
Critical care unit (level 3)	275 (74·7)	276 (75·6)
Critical care unit (level 2)	33 (9·0)	33 (9·0)
Post-surgical recovery unit	4 (1·1)	7 (1·9)
Ward	56 (15·2)	49 (13·4)

Table 16. Clinical management of patients during intervention period.

Data presented as mean (SD), median (IQR) or n (%).

Four patients (one goal-directed haemodynamic therapy, three usual care) who did not undergo surgery excluded.

*Two patients (one in each group) missing data for anaesthetic technique

†Two patients (both usual care) missing data for fluids during and after surgery; one patient (haemodynamic intervention) missing data for fluids post-surgery; one patient (haemodynamic intervention) missing data for intra-venous fluid during surgery; one patient (usual care) missing data for intra-venous crystalloid after surgery; one patient (haemodynamic intervention) missing data for blood products following surgery

§Two patients (one haemodynamic intervention, one usual care) missing all data for vasopressor or inotrope agents; one patient (usual care) missing data for vasopressor or inotrope infusion

	Haemodynamic intervention (n=367)	**Usual care (n=362)**
Duration of surgery (minutes)	270 (200-350)	260 (195-360)
Anaesthetic technique*		
General anaesthetic only	107 (29·2)	105 (29·1)
General anaesthetic plus epidural	259 (70·8)	256 (70·9)
Intravenous crystalloid (ml)†		
During surgery	1518 (1410)	2420 (1382)
During six hours following surgery	565 (254)	670 (367)
Intravenous colloid (ml)†		
During surgery	1465 (913)	708 (695)
During six hours following surgery	642 (498)	226 (361)
Blood products (ml)†		
During surgery	141 (723)	95 (542)
During six hours following surgery	80 (555)	10 (66)
Bolus vasopressor or inotrope agent used during intervention period§	301 (82·2)	270 (74·8)
Vasopressor or inotrope infusion (other than dopexamine) used during intervention period§	103 (28·1)	108 (30·0)
Actual location following surgery		
Critical care unit (level 3)	258 (70·3)	246 (68·0)
Critical care unit (level 2)	42 (11·4)	40 (11·0)
Post-surgical recovery unit	10 (2·7)	9 (2·5)
Ward	57 (15·5)	67 (18·5)

Table 17. Deviations from intervention guidance as pre-specified in protocol.

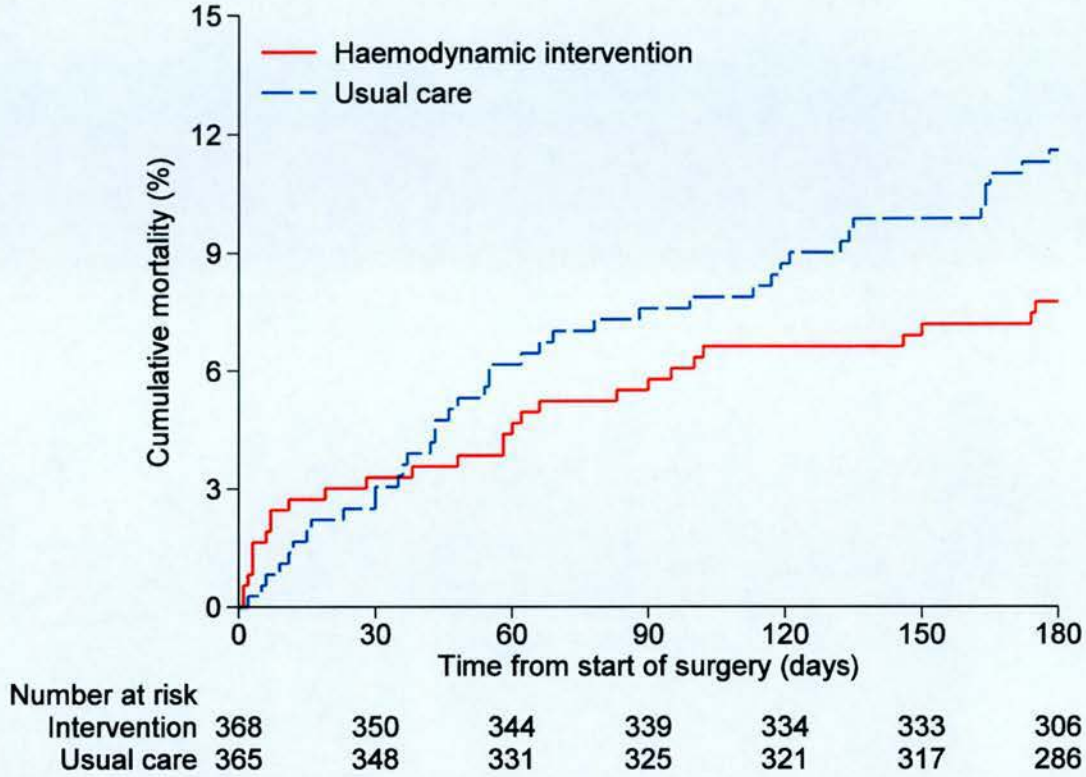
	Haemodynamic intervention (n=367)	**Usual care (n=362)**
Failure to administer dopexamine to a haemodynamic intervention group patient	7 (1.9)	N/A
Administration of incorrect dose of dopexamine to intervention group patient without reason consistent with protocol:	26 (7.1)	N/A
Lowest rate of dopexamine less than 0.5 µg/kg/min	8 (2.2)	N/A
Highest rate of dopexamine greater than 0.5 µg/kg/min	1 (0.3)	N/A
Dopexamine administered for <6 hours following surgery	20 (5.4)	N/A
Failure to monitor cardiac output in intervention group patient	3 (0.8)	N/A
Administration of dopexamine to a usual care group patient	N/A	1 (0.3)
Use of cardiac output monitoring in a usual care group patient	N/A	31 (8.6)
Overall compliance (none of above deviations)	**334 (91.0)**	**330 (91.2)**

*Data presented as n (%). One patient (usual care) randomized in error and four patients (one haemodynamic intervention, three usual care) who did not undergo surgery excluded. One patient (haemodynamic intervention) missing data for additional staff present.

Table 18 Additional staff present from investigating team during intervention period.

	Haemodynamic intervention (n=366)		Usual care (n=362)	
	During surgery	After surgery	During surgery	After surgery
Additional staff present				
Additional nurse	212 (57·9)	228 (62·3)	79 (21·8)	33 (9·1)
Additional doctor	77 (21·0)	83 (22·7)	83 (22·9)	7 (1·9)
Additional nurse & doctor	60 (16·4)	33 (9·0)	7 (1·9)	0 (0)
Role of additional staff				
Observation	6 (1·6)	7 (1·9)	98 (27·1)	5 (1·4)
Data collection	10 (2·7)	9 (2·5)	20 (5·5)	22 (6·1)
Advised on intervention	94 (25·7)	54 (14·8)	36 (9·9)	8 (2·2)
Delivered intervention	239 (65·3)	274 (74·9)	15 (4·1)	5 (1·4)

Figure 3 Kaplan-Meier survival curves by treatment allocation for 180 days following start of surgery.



*Log rank test p-value: 0.093.

Table 19 Data describing primary outcome of moderate or severe complications or death within 30 days of surgery.

	Haemodynamic intervention (n=366)	Usual care (n=364)	Relative risk (95% CI)	p-value
Complications / death within 30 days	134 (36.6)	158 (43.4)	0.84 (0.71-1.01)	0.07
Death	12 (3.3)	11 (3.0)		
Pulmonary embolism	4 (1.1)	1 (0.3)		
Myocardial ischaemia or infarction	10 (2.7)	8 (2.2)		
Arrhythmia	39 (10.7)	40 (11.0)		
Cardiac or respiratory arrest	16 (4.4)	14 (3.8)		
Limb or digital ischaemia	2 (0.5)	1 (0.3)		
Cardiogenic pulmonary oedema	1 (0.3)	2 (0.5)		
Acute respiratory distress syndrome	3 (0.8)	4 (1.1)		
Gastrointestinal bleed	13 (3.6)	8 (2.2)		
Bowel infarction	2 (0.5)	5 (1.4)		
Anastomotic breakdown	12 (3.3)	16 (4.4)		
Paralytic ileus	20 (5.5)	27 (7.4)		
Acute psychosis	3 (0.8)	8 (2.2)		
Stroke	1 (0.3)	0 (0)		
Acute kidney injury	17 (4.6)	17 (4.7)		
Infection, source uncertain	11 (3.0)	9 (2.5)		
Urinary tract infection	9 (2.5)	9 (2.5)		
Surgical site infection (superficial/deep incisional)	22 (6.0)	39 (10.7)		
Surgical site infection (organ/space)	20 (5.5)	36 (9.9)		
Laboratory-confirmed bloodstream infection	6 (1.6)	15 (4.1)		
Nosocomial pneumonia	36 (9.8)	39 (10.7)		
Post-operative haemorrhage	6 (1.6)	4 (1.1)		
Blinding of outcome assessment*				
Assessor was suitably blinded	342 (94.2)	349 (96.7)		
Assessor may have known allocation	9 (2.5)	6 (1.7)		
Assessor definitely knew allocation†	12 (3.3)	6 (1.7)		

Data presented as n (%).

***Six patients (three haemodynamic intervention, three usual care) missing data for blinding of outcome assessment**

†Includes three patients (two haemodynamic intervention, one usual care) who died within 30 days following surgery

Table 20. Data describing secondary outcomes.

	Haemodynamic intervention	Usual care	Relative risk (95% CI)	p-value
Death within 30 days following surgery	12 (3.3) (n=366)	11 (3.0) (n=364)	1.08 (0.48-2.43)	1.00
Post-Operative Morbidity Survey*	(n=275) 182 (66.2)	(n=287) 195 (67.9)	0.97 (0.87-1.09)	0.72
Infectious complications within 30 days following surgery	87 (23.8) (n=366)	108 (29.7) (n=364)	0.80 (0.63-1.02)	0.08
Duration of post-operative hospital stay Survivors Non-survivors	10 (7-14) (n=359) 10 (7-14) (n=343) 7 (3-33) (n=16)	11 (7-17) (n=356) 11 (7-17) (n=343) 16 (9-36) (n=13)	--	0.05
Critical care free days within 30 days following surgery	27 (26-29) (n=366)	28 (25-29) (n=364)	--	0.98
Death within 180 days following surgery	28 (7.7) (n=363)	42 (11.6) (n=361)	0.66 (0.42-1.05)	0.08

Unadjusted odds ratio for 30-day mortality: 1.09 (0.48-2.45). Adjusted odds ratio for 30-day mortality: 1.20 (0.51-2.82); p=0.68.
Unadjusted odds ratio for 180-day mortality: 0.63 (0.39-1.04). Adjusted odds ratio for 180-day mortality: 0.61 (0.36-1.04); p=0.071.
Data presented as mean (SD), median (quartiles) or n (%).
***For patients alive and in hospital on day 7 following start of surgery**

Table 21. Pre-specified sub-group analyses for primary outcome of complications or death within 30 days of surgery.

	Haemodynamic intervention	Usual care	Adjusted odds ratio (95% CI)	p-value
Urgency of surgery				0.53
Elective	127 (35.9) (n=354)	152 (43.3) (n=351)	0.72 (0.52-0.99)	
Emergency	7 (58.3) (n=12)	6 (46.2) (n=13)	1.24 (0.23-6.74)	
Planned surgical procedure				0.70
Upper gastrointestinal	39 (36.1) (n=108)	47 (41.2) (n=114)	0.83 (0.47-1.47)	
Lower gastrointestinal	56 (33.5) (n=167)	62 (38.0) (n=163)	0.82 (0.51-1.31)	
Small bowel +/- pancreas	37 (43.0) (n=86)	47 (56.6) (n=83)	0.53 (0.28-0.99)	
Urological or gynaecological surgery involving gut	2 (40.0) (n=5)	2 (50.0) (n=4)	0.62 (0.04-10.20)	
Timing of recruitment*				0.019
Early (first 10 patients per site)	33 (42.3) (n=78)	28 (34.1) (n=82)	1.51 (0.75-3.01)	
Late (all subsequent patients)	100 (35.0) (n=286)	129 (46.7) (n=276)	0.59 (0.41-0.84)	

Data presented as n (%). p-values represent tests for interaction.

***Eight patients (two haemodynamic intervention, six usual care) excluded from two sites, which recruited fewer than 10 patients**

3.4 Discussion

The findings of this large multi-centre effectiveness trial suggest that widespread implementation of a peri-operative haemodynamic therapy algorithm into routine clinical practice is feasible, although in 60-70% of cases the intervention was delivered by the research staff. The intervention was not associated with a significant reduction in 30-day complication rates when compared with usual clinical care. There were no differences in the secondary outcomes of POMS defined morbidity at day 7, hospital stay or mortality at 30 days. However, a pre-specified compliance adjusted analysis and a comparison of the first ten patients recruited at each site with those recruited subsequently, suggest a stronger treatment effect and consequently that the haemodynamic algorithm was associated with a reduction in complications. There was a decrease in complications amongst the large sub-group of patients undergoing elective surgery but not in the smaller emergency surgery sub-group. There was a non-significant reduction in mortality at 180 days for intervention group patients.

The trial was designed to address important methodological limitations associated with smaller trials of this complex intervention and the measures taken to minimise bias are more robust than any previous studies. [166-168] The large patient sample allowed us to compare the intervention to usual clinical care, avoiding problems associated with an alternative 'control' treatment algorithm, which might not reflect standard practice. [168] The primary outcome measure was a composite of post-operative complications and mortality at 30 days. Bias was controlled by assessing and grading this outcome according to predefined criteria. There is a plausible biological mechanism for a reduction in the incidence of some of the complications included in the primary outcome measure, for example infection. Concerns however remain that the intervention itself may have caused harm to some groups, especially as 3.9% of patients in the intervention group suffered a cardiovascular serious adverse event (SAE). Harm related to myocardial injury is the most important adverse effect of haemodynamic therapy algorithms and this might explain the smaller than predicted reduction in the primary outcome, although the incidence of cardiovascular events was similar between the groups at 30 days. The event rate in the usual care arm was slightly lower than expected and group crossover in terms of cardiac output monitoring in the usual care group was more frequent than predicted. It seems likely that these factors reduced the power of the trial, perhaps resulting in a failure to achieve statistical significance. The trial was powered for large absolute and relative risk reductions and smaller differences would still be clinically important but need a larger trial to demonstrate. 95% CI suggest a high probability of benefit and there is a chance of type 2 error in this trial.

Although it is not possible to blind staff administering complex interventions, our data suggest excellent compliance with blinding procedures for patient follow-up.

In keeping with the pragmatic nature of the trial, no attempt was made to standardise the choice of colloid in either group. As the trial was nearing completion, new evidence was published suggesting an increased incidence of acute kidney injury in critically ill patients receiving starch based colloid solutions. [169,170] Whilst individual patient data describing the use of starches was not collected a post hoc survey of investigators suggests few patients received this fluid with no differences in use between the treatment groups.

A number of haemodynamic therapy algorithms have been published representing options in terms of haemodynamic end-points, inotropic agents and cardiac output monitoring. [139] An algorithm was used that was suited to the care of patients during and after major gastrointestinal surgery, that was supported by solid clinical and mechanistic evidence with a good cardiovascular safety profile. [121,125,131,139] The algorithm was developed to maximise clinical effectiveness whilst being readily implemented into clinical practice. It specifically aimed to be deliverable in the operating room and post-anaesthetic care unit by both medical and nursing staff ensuring that critical care admission was not necessary for compliance, although in the trial itself a high proportion of patients were in fact admitted to a critical care unit. A cardiac output monitoring technology, which can be used both during and after surgery (in awake, extubated patients) was used, which is accurate and has been in widespread clinical use for more than ten years. The algorithm was readily implemented in clinical practice with high levels of protocol compliance and few safety concerns. Additional staff from the investigating team were often present and although this would not necessarily be required in clinical practice, in the setting of a clinical trial the effect of this on outcome is unknown. The CONSORT guideline extension published in 2008 acknowledges this as an issue in non-pharmacologic trials. [171] An observed learning effect is not uncommon for complex interventions and the analysis with the first 10 patients excluded from each site suggests that this effect might have been present. The high levels of compliance observed with this trial intervention contrast with the findings of a previous large trial where patients were randomised to receive a pulmonary artery catheter. [129] In this previous trial, no attempts were made either to standardise patient care or to monitor compliance with recommended treatment goals. The additional haemodynamic monitoring was not linked to any apparent changes in treatment and consequently clinical outcomes were unaffected. It should also be noted that a high proportion of patients (approximately 75%) were treated in an ICU (level 3) setting in both arms of the study.

Figure 4. Type of fluid administered.

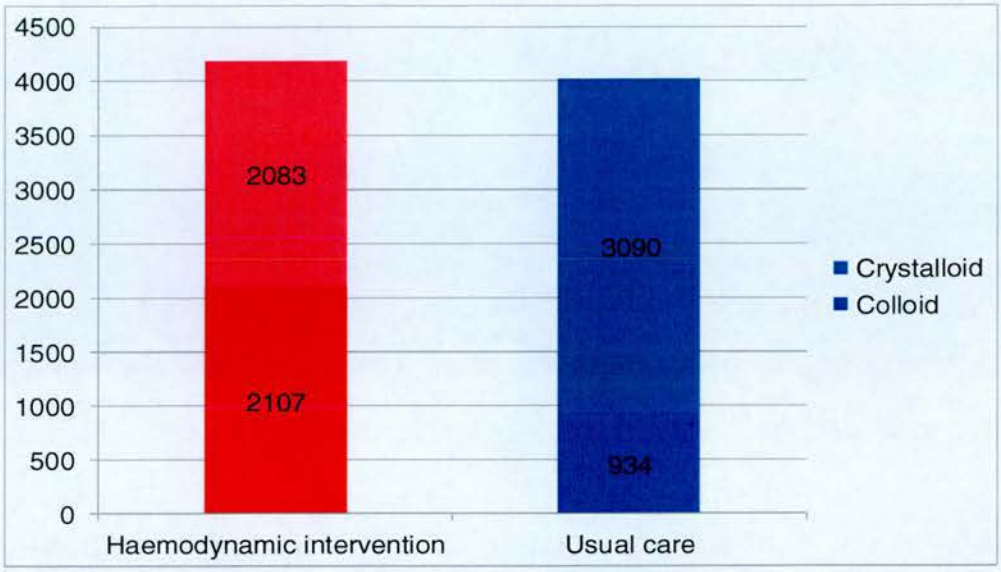
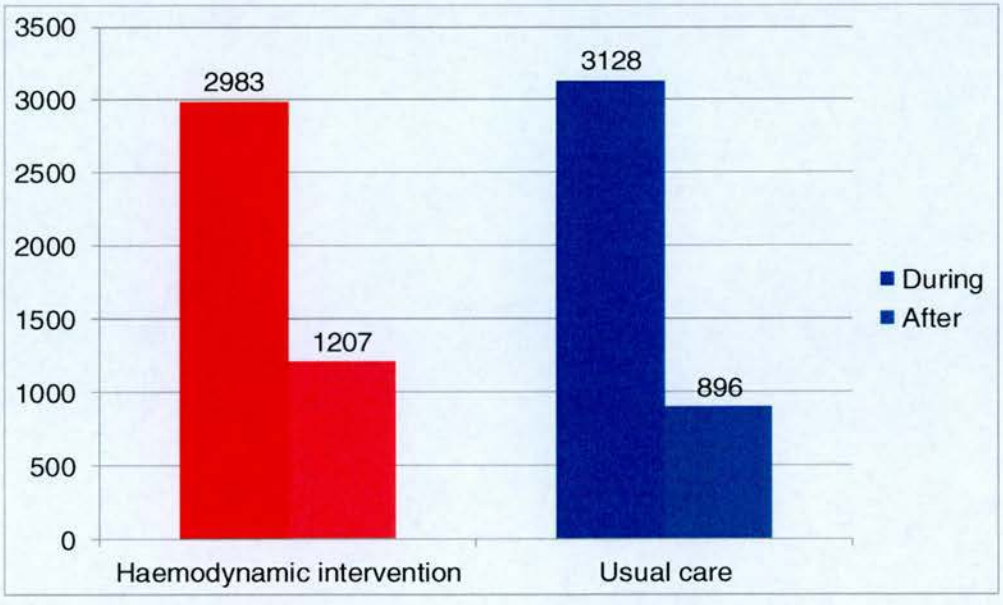


Figure 5. Timing of fluid administered



Interestingly the overall volumes of intra-venous fluid administered were similar between the groups despite a clear difference in the approach to fluid dosing. Patterns of fluid administration are described in more detail in figures 2a. and 2b. During surgery the intervention group received less fluid whereas after surgery, continued active haemodynamic management resulted in administration of greater volumes. This finding is interesting and suggests that timing of fluid may be important as well as type and volume.

3.5 Conclusions

The trial findings require careful interpretation but appear consistent with those of a recent Cochrane review of published randomised trials. This analysis suggested that fewer patients receiving cardiac output guided haemodynamic therapy develop complications after surgery (Intervention 275/960 [28.6%] vs. Controls 350/881 [39.7%]; RR 0.68 [0.58-0.80]) with a similar effect size to that identified in the current trial. [139]In keeping with the OPTIMISE findings, these results were sensitive to analytical technique suggesting some uncertainty regarding the benefits of this treatment approach. Whilst there is evidence of international differences in the peri-operative use of cardiac output monitoring,[7] treatment algorithms informed by such technology are in widespread use and are strongly promoted in at least the UK. All patients undergoing major gastro-intestinal surgery require some form of fluid therapy and the majority also require vasoactive drug therapy. Whilst there was no significant reduction in 30-day complication rates, findings of pre-specified secondary and subgroup analyses and the non-significant reduction in mortality at 180 days were all consistent with a beneficial effect of the intervention. A larger clinical trial would be required to resolve this.

Chapter 4. Is Perioperative Use of i.v. 6% Hydroxyethel Starch Solution Associated with Increased Postoperative Death or Acute Kidney Injury: A Systematic Review and Meta-analysis

4.1 Introduction

There is great interest in the optimal approach to intra-venous fluid therapy in the peri-operative period, which may have important effects on patient outcome. [175] The choice of intra-venous fluid solution is a central aspect of fluid therapy but the evidence base informing this decision is limited with wide international variations in practice. [176] Hydroxyethyl starch (HES) solutions which are derived from maize or potato starch are commonly used for intravenous fluid therapy. Modern starches are typically presented in a concentration of 6%, molecular weights (MW) of 130-200 kDa and a molecular substitution ratio of 0.4 or 0.42 (tetrastaches). Older starch solutions have higher substitution ratios e.g. 0.5 (pentastarch) or 0.7 (hetastarch); some of these solutions are still commercially available. [177] The findings of two recent large randomised trials have suggested a small but important increase in the incidence of acute kidney injury and mortality associated with the use of HES solutions in critically ill patients. [169,170] Potential mechanisms for starch mediated kidney injury are unclear but may be associated with more concentrated solutions (e.g. 10% HES) as well as molecules with high MW and greater degree of substitution. [177-179] Concerns have also been raised regarding the effects of HES on coagulation profile. These solutions have since been withdrawn from use in the critically ill. [180]

However, the generalisability of these findings to other patients groups is uncertain and use of HES for intra-venous volume replacement continues in cardiac and non-cardiac surgical patients. There is a paucity of quality data regarding the safety of starch solutions in the surgical population. To compound matters several studies investigating the use of HES in surgical patients conducted by Joachim Boldt have been retracted following allegations of scientific misconduct. [181] At least five meta-analyses on the safety of starch have been published in the last three years. [182-186] The majority of these reviews have focused on the use of starch in critically ill, septic or acutely unwell adults. [182-184] Three of these studies have considered the safety of starch in other groups. The extensive systematic review and meta-analysis conducted by Dart *et al* included a non-sepsis subgroup largely (but not exclusively) composed of surgical trials. [182] Two further reviews and meta-analyses focus on the use of starch primarily in surgical patients, [185,186] but these are limited because they only evaluate the effects of tetrastarch, in some cases in comparison to other starch solutions. These reviews also include a heterogeneous group of studies including those undertaken in trauma, burns, paediatric and transplant surgery. A systematic review and meta-analysis on the effect of all 6% HES solutions compared with non-starch solutions in clinical use on mortality and acute kidney injury exclusively in the

adult surgical population was undertaken. This work was undertaken with collaborators, and is now published. [187]

4.2 Methods

Search Strategy

Ovid Medline (1946-present), Embase, Cinhal and Cochrane Database of Systematic Reviews were searched for suitable studies using the following search strategy:

Starch.mp or starch/ OR Hetastarch.mp or hetastarch/ OR Voluven.mp OR Volulyte.mp OR Haes-steril.mp OR Hespan.mp OR Tetraspan.mp AND Surgery.mp or General Surgery/.

Search results were limited to randomised controlled trials of adult subjects. Non-English language papers were included. The bibliographies of evaluable studies and other selected papers were hand searched. Experts were contacted to ascertain if they were aware of any other studies not identified by our search strategy, namely Prof. M. Mythen (MM), Prof. Michael Sander (MS) and Dr. M. Hamilton (MH). Search strategy and analysis were carried out according to the "Preferred Reporting Items for Systematic Review and Meta-analysis" (PRISMA) statement 2009. [188]

The literature search was conducted independently by two collaborators. The results were reviewed and RP assisted with resolution of disparities in the literature search. The final list of papers was further reviewed and evaluated independently by two collaborators and disagreements adjudicated by me. The data was then extracted from the selected studies and analysed as described below.

Study Selection Criteria

Randomised controlled trials (RCT) in surgical patients were included where hospital mortality, requirement for post-operative renal replacement therapy (RRT) or author defined post-operative acute kidney injury (AKI) were reported. Trials comparing peri-operative administration of 6% HES of any MW or substitution ratio with any non-starch fluid were included, with the exception of trials where comparator fluids were experimental haemoglobin based fluids (MPOX4 and HBOC21) and hypertonic saline which are not in routine use in surgical patients. Trials in subjects undergoing all types of surgery were considered with the exception of neurosurgery, transplantation, burns or obstetric surgery. Studies where Joachim Boldt was a named author were also excluded. Studies were screened for methodological quality using the Jadad Score, an established method of assessing methodological quality of studies to be included in meta-analysis. [189] Assessment was made of the appropriateness of randomisation, blinding and whether patient withdrawal

information was provided. The maximum score attributable was five. Only studies with a Jadad score of 3 or greater were included. Disagreements on studies to be included in the final analysis were resolved by consensus between MG, RP and the expert collaborators (MM, MH, MS),

Data Extraction

Data extracted for each eligible study included: author; year of publication; surgical group studied; number of subjects; starch used; comparator fluid used; primary and other study outcomes; commercial support; hospital mortality; incidence of post-operative RRT; incidence of author defined AKI (where reported).

Outcomes

Primary outcomes studied were hospital mortality and post-operative requirement for RRT. Secondary outcome was the incidence of author-defined post-operative AKI. If data on mortality was not reported, data on AKI or RRT was used; conversely if data on mortality only was available then this was used. It was decided *a priori* that a subgroup analysis would be performed on patients undergoing cardiac surgery and patients receiving 6% HES.

Statistical Analysis

Statistical analysis was carried out using Review Manager (RevMan) v5.2. RevMan is the software used for preparing and maintaining Cochrane Reviews and forms part of the Cochrane Information Management System. Between-study statistical heterogeneity was assessed by χ^2 test and I^2 test; values of the index of 25, 50, and 75% indicated the presence of low, moderate, and high between-trial heterogeneity, respectively. A p-value of 0.1 was considered to denote statistical significance of heterogeneity. Estimation of potential publication bias used the funnel plot method for any of the outcomes, either primary or secondary. Dichotomous outcomes were expressed as a difference of proportions (risk difference, RD). For all analyses performed, if no significant heterogeneity was noted, fixed effect model (FEM) analysis using the Mantel-Haenszel (M-H) method was used; otherwise, results of the random-effects model (REM) analysis using the DerSimonian-Laird method were presented.

4.3 Results

Study Selection

The process for literature searching and study selection is outlined in Figure 6. 456 non-duplicate citations were screened of which 34 studies underwent full scoring and data extraction. However only 19 trials were suitable for inclusion in the meta-analysis, including a total of 1567 subjects. [179,190-206]

Study Quality

A funnel plot for selected studies did not reveal evidence of publication bias (**Figure 7**). Funnel plots are scatterplots of study size plotted against treatment effect and are a useful means of detecting publication bias in studies selected for meta-analysis. It assumes that larger studies will be near the mean and smaller studies will exhibit more variation. A "normal" funnel plot looks like a symmetrical inverted funnel. [207] Study heterogeneity can be estimated using the Chi-squared test to produce the I^2 statistic. In brief, this tests the consistency of confidence intervals between study results; if this is poor then there is a high chance of heterogeneity between studies. I^2 statistic was 0% for the primary outcome and therefore did not suggest evidence of between study heterogeneity. Event rates of death, requirement for RRT and new author defined AKI in selected studies were low.

Characteristics of Included Studies

The characteristics of included studies are summarised in **Table 22**. Two trials were multicentre, the remainder single centre trials. In ten studies the subjects were undergoing cardiac surgery; two studies were of patients undergoing major vascular surgery and one a mixture of cardiac and major vascular surgery. The study undertaken by Gondos was in a mixed group of surgical patients including those undergoing cardiac surgery. [194] Two trials used HES 450/0.7 and one HES 400/0.7; the remainder used molecular sizes of 200kDa or less. Comparators included crystalloid solutions, gelatin solutions and albumin. In seven studies there was a commercial sponsor. Funnel plot of studies used in the hospital mortality analysis showed no evidence of publication bias **(Figure 7)**. Studies excluded after full scoring and data extraction were conducted are summarised in **(Table 23)** in six of these studies hospital mortality, incidence of RRT or AKI was not reported. [208-213] The remainder were excluded because the comparator fluid was not valid, [208,214-220] or because the study population underwent transplant surgery. [221]

Figure 6 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram detailing search strategy and identification of studies used in data synthesis.

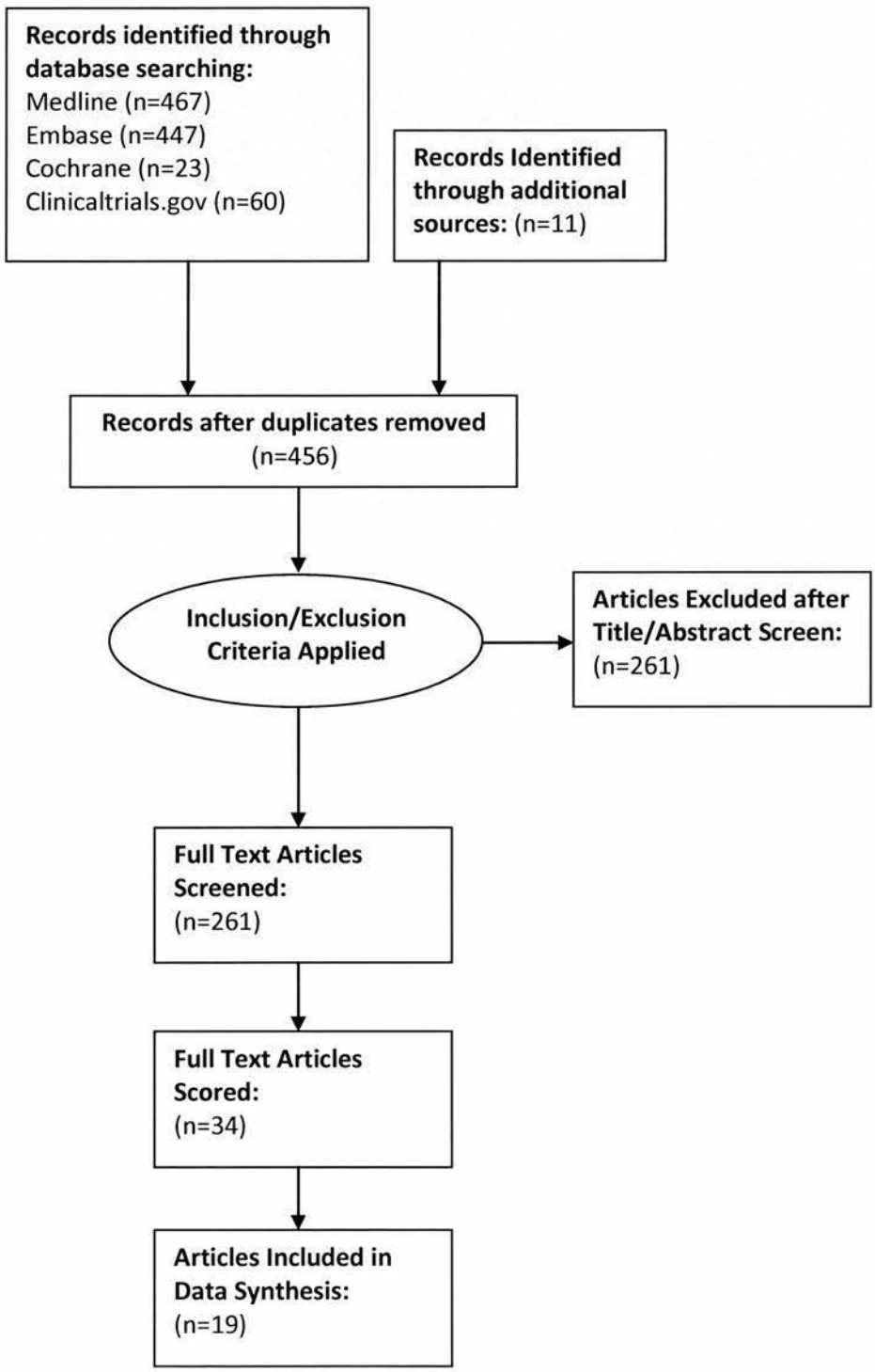


Table 22 Characteristics of included studies.

Study	Design	Type of Surgery	n	Starch	Comparator	Jadad Score	Reports Mortality	Reports RRT	Reports AKI	Author Defined AKI	Commercial Support
Alavi 2012	RCT	Cardiac	92	6% HES 130/0.4	4% gelatin, RL	3	Yes	No	No	-	Not stated
Dehne 2001	RCT	ENT	60	6% HES-200/0.5 6% HES-200/0.62 6% HES-450/0.7	RL	4	Yes	No	No	-	Fresenius
Diehl 1982	RCT	Cardiac	60	6% HES-450/0.7	5% Albumin	3	Yes	No	Yes	SCr >1.5mg dl^{-1}	Not stated
Feldheiser 2013	RCT	Gynaecological	50	6% HES 130/0.4	Balanced Crystalloid	4	Yes	No	No	-	Fresenius-Kabi
Godet 2008	Multicentre RCT	Vascular	65	6% HES 130/0.4	3% Gelatin	4	Yes	Yes	Yes	Rise in SCr from baseline of >0.5mg dl^{-1}	Fresenius-Kabi
Gondos 2010	Multicentre RCT	Mixed	200	6% HES 130/0.4	RL, 4% Gelatin, 5% Albumin	3	Yes	No	No	-	Fresenius-Kabi
Guo 2003	RCT	Gynaecological	42	6% HES-200/0.5	RL	3	Yes	Yes	No	-	Not stated
Hecht-Dolnik 2009	RCT	Cardiac	156	6% Hetastarch	5% Albumin	4	Yes	No	No	-	None
Hung 2012	RCT	Vascular	84	6% HES 130/0.4	RL	4	Yes	Yes	Yes	Not specified	Edwards
Kuitunen 2004	RCT	Cardiac	45	6% HES 120/0.7 6% HES 400/0.7	4% Albumin	4	Yes	No	No	-	Not stated
Lee 2011	RCT	Cardiac	106	6% HES 130/0.4	RL	3	No	Yes	Yes	AKIN Criteria	None
Mahmood 2009	RCT	Vascular	62	6% HES 200/0.6 6% HES 130/0.4	4% Gelatin	4	Yes	Yes	No	-	Fresenius-Kabi
Marik 1997	RCT	Vascular	30	6% Hetastarch	RL	4	Yes	No	No	-	Not stated
Munsch 1988	RCT	Cardiac	40	6% HES-450/0.7	Plasma protein fraction (PPF)	3	Yes	No	No	-	Not stated
Ooi 2009	RCT	Cardiac	90	6% HES 130/0.4	4% Gelatin	4	Yes	Yes	Yes	Not specified	Not stated
Sirvinskas 2007	RCT	Cardiac	80	NaCl 0.72%/6% HES	RL	3	Yes	No	No	-	Not stated
Van der Linden 2004	RCT	Cardiac		6% HES-200/0.5	3.5% Gelatin	3	Yes	No	No	-	Not stated
Van der Linden 2005	RCT	Cardiac	132	6% HES 130/0.4 (Voluven)	3% Gelatin	3	Yes	No	No	-	Not stated
Verheij 2006	RCT	Cardiac or Major Vascular	67	6% HES 200/0.5	4% Gelatin, NaCl 0.9%	4	Yes	No	No	-	Braun

Figure 7 Funnel plot of hospital mortality

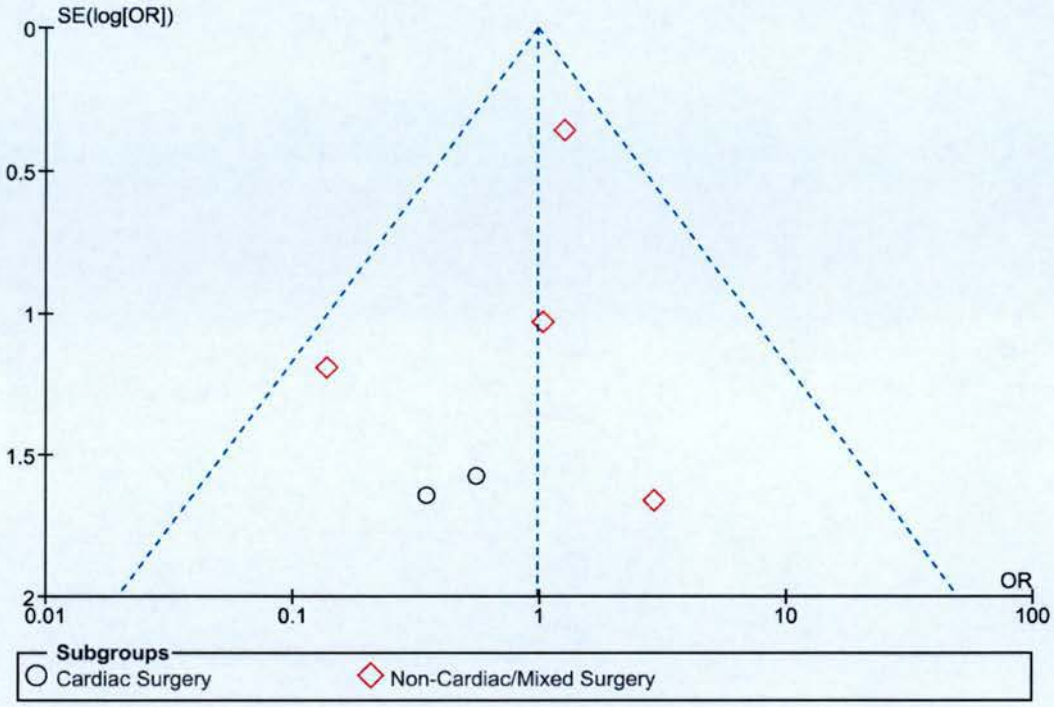


Table 23 Articles scored but not included in data synthesis.

*HES: hydroxyl-ethyl starch; AKI: acute kidney injury; RRT: renal replacement therapy; HBOC-21 and MP4-OX are artificial haemoglobin solutions

Paper	**n**	**Reason Excluded**
Ando 2008	21	Jadad Score <3; Incidence of hospital mortality, RRT and AKI not reported.
Belcher 1984	73	Jadad Score <3; Incidence of hospital mortality, RRT and AKI not reported.
Challand 2012	179	Control group received HES solution
Harten 2008	29	Incidence of hospital mortality, RRT and AKI not reported.
Honkonen 2009	49	Comparator hypertonic saline.
Kaspar 1996	13	Comparator HBOC-21
Magder 2010	237	Control group given HES solution
Mukhtar 2009	40	Population studied liver transplant surgery
Olofsson 2011	189	Comparator MP4-OX
Senagore 2009	64	Incidence of hospital mortality, RRT and AKI not reported.
Shahbazi 2011	70	Incidence of hospital mortality, RRT and AKI not reported.
Sirieix 1999	64	Control group given HES solution
Standl 1998	12	Comparator HBOC-21
Tiryakioglu 2008	140	Jadad Score <3; Incidence of hospital mortality, RRT and AKI not reported.
Van Der Linden 2011	274	Comparator MP4-OX

Primary Outcomes

Hospital Mortality

Hospital mortality was available in eighteen of the nineteen included RCTs, a total of 1461 patients. Of the 685 patients receiving HES, 19 (2.8%) died and of 776 patients receiving comparator fluid, 46 (5.9%) died. There were no deaths in twelve of the eighteen included studies. There was no difference in mortality between compared arms (p=0.91, I^2=0%; FEM: RD 0.00, 95% CI -0.02, 0.02). Subgroup analysis of studies of 872 cardiac surgery patients from 10 studies also did not demonstrate any difference (p=1.0, I^2=0%; FEM: RD 0.00, 95% CI -0.02-0.01) (Figure8).

Secondary Outcomes

Incidence of Author Defined AKI

Data on post-operative incidence of author defined AKI was available in five of the nineteen trials included, a total of 401 patients. Of 204 patients receiving HES, 11 (5.4%) developed author-defined AKI and in 197 patients receiving comparator fluid, 7 (3.6%) developed author-defined AKI. In two studies no patient developed author-defined AKI. No difference in incidence of author-defined AKI was observed between compared arms (p=0.34, I^2=0%; FEM: RD 0.02, 95% CI -0.02, 0.06). Two of these studies (n=196) were undertaken in cardiac surgery patients. No difference was observed in author defined AKI between arms (p=0.56, I^2=0%; FEM: RD 0.01, 95% CI -0.02, 0.04) (**Figure 9**).

Requirement for Post-operative Renal Replacement Therapy (RRT)

Data on new requirement for postoperative RRT was available in six of the nineteen included RCTs, a total of 445 patients. Of 233 patients receiving HES, 4 developed a new requirement for postoperative RRT (1.7%) and of the 212 patients receiving comparator fluid, 4 (1.9%) developed new requirement for postoperative RRT. There were no instances of new requirement for postoperative RRT in two of these studies. No difference in incidence of new requirement for postoperative RRT was observed between compared arms (p=0.62, I2=0%; FEM: RD -0.01, 95% CI -0.04, 0.02) (Figure 10)

Studies Involving Tetrastach Only

Nine studies (n=856) compared tetrastarch (substitution ratio of 0.4 or 0.42) with other non-starch fluids. Analysis of these studies did not detect any difference in either mortality (n=750, p=0.83, I2=0%; FEM: RD 0.00, 95% CI -0.04-0.04) or new requirement for RRT (n=382, p=0.73, I2=0%; FEM: RD -0.01, 95% CI -0.04-0.03) (Figure 11).

Figure 8 Forest plot of hospital mortality

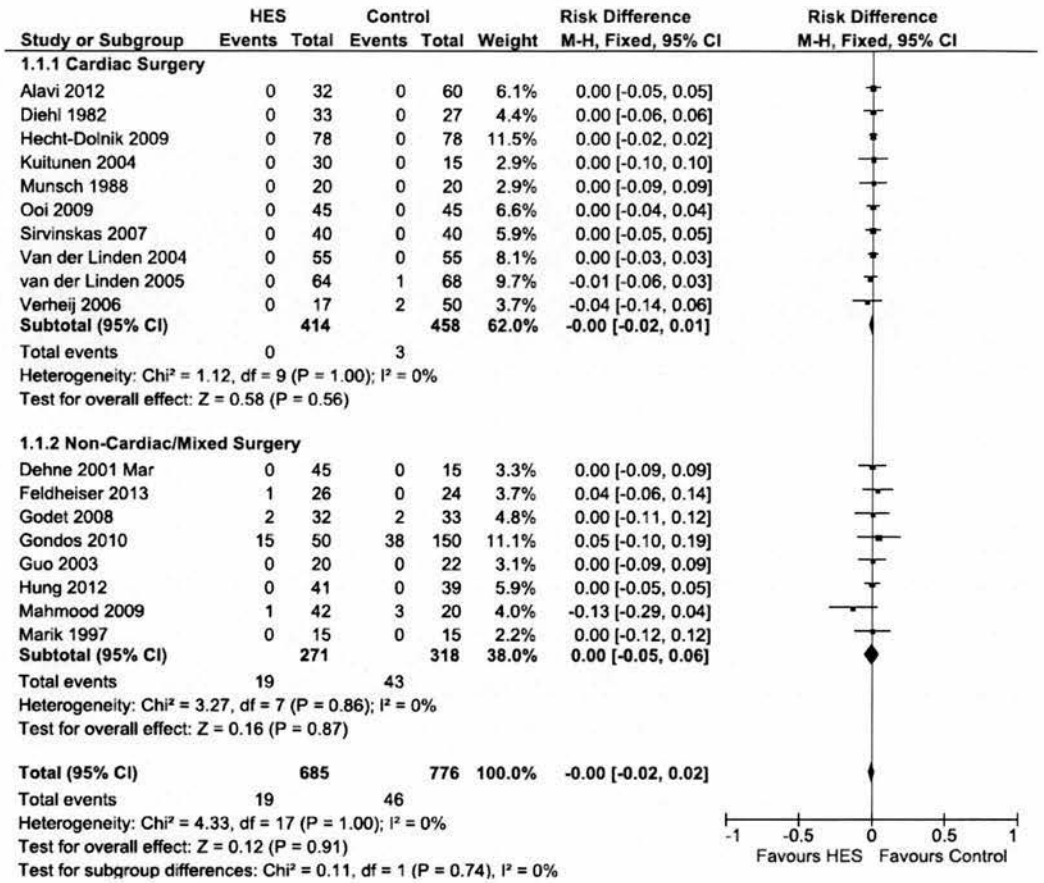


Figure 9 Forest plot of acute kidney injury.

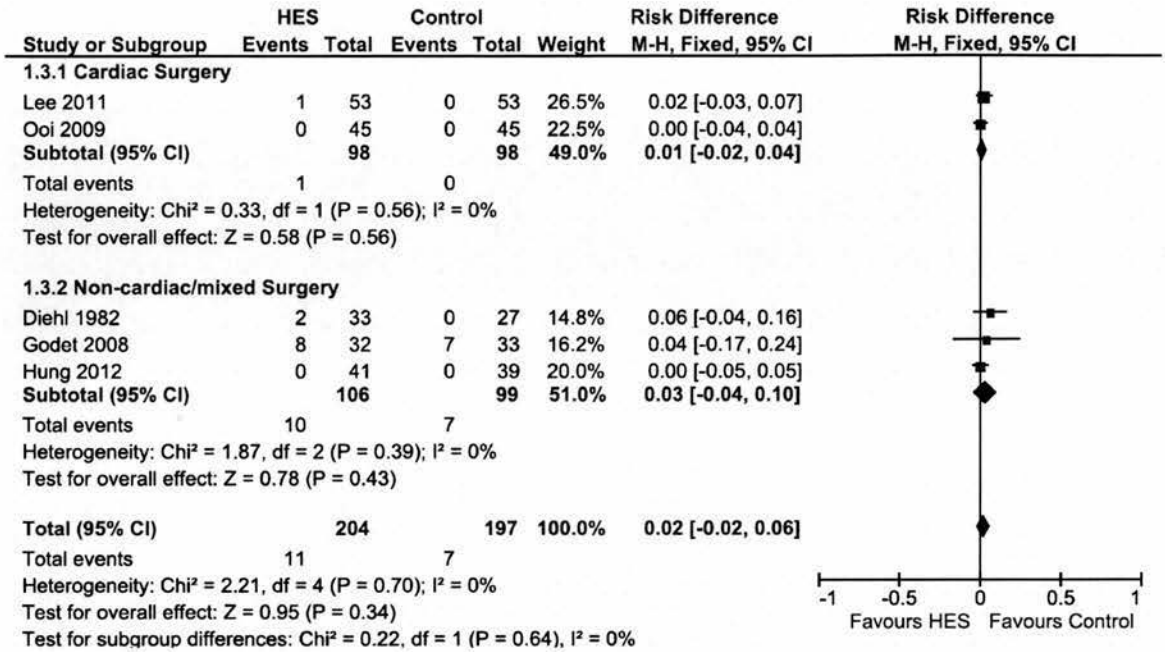


Figure 10 Forest plot of renal replacement therapy.

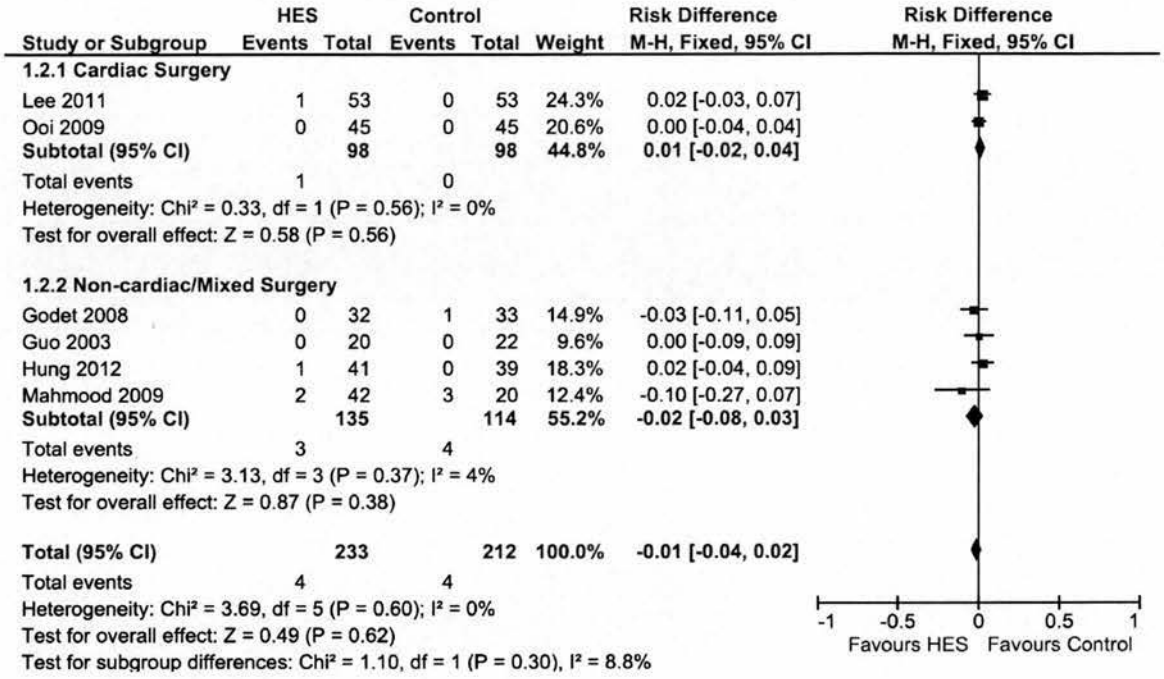
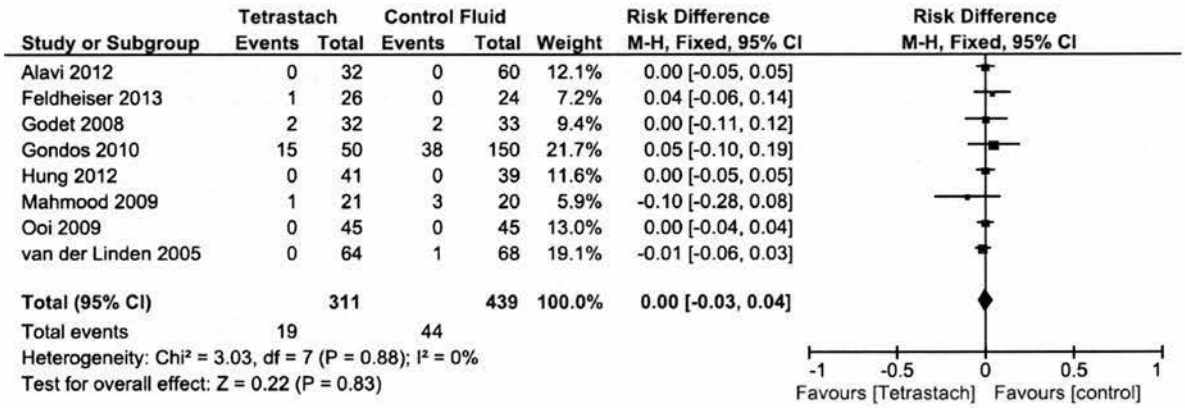


Figure 11 Forest plot of mortality of trials involving tetrastarch only.



4.4 Discussion

The principal finding of this systematic review and meta-analysis was that there was no difference in hospital mortality associated with the use of 6% HES solution in the treatment of patients undergoing surgery. Similarly, there were no differences in the secondary outcomes of acute kidney injury and the use of renal replacement therapy. These findings were consistent in sub-group analyses of patients undergoing cardiac and non-cardiac surgery and in patients receiving tetrastarch only.

In total 19 studies with less than 1600 participants were suitable for inclusion in this meta-analysis. Seven of the included studies were commercially sponsored, raising the possibility of publication bias although we found no evidence of this. Despite widespread use for more than three decades, studies comparing peri-operative use of HES with other intra-venous fluids are small, largely single centre and vulnerable to bias. The most likely cause of HES-associated harm (and hence increased mortality) in the critically ill is causation or exacerbation of kidney injury. However, data describing kidney-associated harm are not well reported in surgical studies. Few studies consistently report the requirement for renal replacement therapy or acute kidney injury using internationally defined criteria (e.g. Acute Kidney Injury Network (AKIN) or RIFLE Classification [222]) and in those that did, patients may not have been systematically followed up for these outcomes. All studies reporting post-operative RRT describe either no difference or increased use of RRT in the HES group; however this tendency towards increased use of RRT in the HES group was not statistically significant. The incidence of death, use of RRT and AKI is higher in the critically ill than in the surgical population and it is therefore possible that the low event rates for both death and acute kidney injury in included studies resulted in insufficient statistical power to detect a difference in these outcomes. It remains possible that HES solutions are associated with either undetected harm or benefit in the surgical population. We believe this approach offers significant advantages over previously published work investigating the effects of starch solutions in surgical patients. The non-sepsis subgroup of the meta-analysis undertaken by Dart *et al* included studies by Boldt, and those enrolling trauma, paediatric and renal transplant patients. They also include four studies of 10% HES which is no longer in common use. [182] The study by Van der Linden *et al* also included studies of paediatric patients, trauma and burns. [186] These heterogeneous groups were excluded from our analysis. The reviews conducted by Van der Linden *et al* and Martin *et al* only investigated tetrastarch and compared it with other solutions, including alternative HES solutions. Moreover Martin *et al's* study, which appears to be industry initiated, investigated only a single product (6% HES 130/0.4, Voluven, Fresenius, Germany). The authors of this study made no assessment of methodological quality of included studies, were supported by Fresenius-Kabi, manufacturers of the HES solution, Voluven and utilised their "study tracking system" for the literature search. [185] Several studies

included in other meta-analyses were excluded in this analysis. This included the studies by Harten, [210] (excluded because outcomes and care in the control arm were unclear), Challand (excluded because 6% HES may have been used in the control group), [220] and Tirakioglu (excluded because Jadad score was 2 and the incidence of outcomes of interest was not reported). [213]

Strengths of our review include a rigorous assessment of methodological quality of identified trials and selection of a homogeneous group of trials of direct relevance to perioperative medicine. The I^2 statistic confirms a low risk of between-study heterogeneity and this combined with narrow confidence intervals suggests our findings are valid. There are also potential limitations of this analysis. We included trials of 6% HES solutions of any MW or substitution and did not restrict inclusion to one particular HES product. It has been suggested that HES solutions with higher MW and greater substitution may be associated with an increased incidence of acute kidney injury and use of these solutions has declined in recent years. Included trials were mostly small single centre trials with a greater possibility of bias.

Synthetic colloidal solutions were introduced in the 1960s, [223] without large phase III trials. Despite little published evidence suggesting advantages over other intra-venous fluids, and emerging evidence of harm in septic and critically ill patients, they remain a popular choice for peri-operative fluid therapy. Although our systematic review did not demonstrate any harm associated with the use of 6% HES solutions these findings cannot be considered definitive. The Crystalloid versus Hydroxyethyl Starch Trial (CHEST) and 6S trials have provided robust evidence to the critical care community that resuscitation of the critically ill with 6% HES was associated with an increased incidence of acute kidney injury.[6 7] Many surgical patients receiving HES are considered at high risk of both acute kidney injury and death and may require periods of critical care following their surgery. The findings of this analysis suggest that although there should be equipoise to conduct such a trial in surgical patients, the low event rates of both death and new requirement for RRT in the surgical population indicate that a very large clinical trial would be required to confirm the safety of starch solutions in the surgical patient population. The implications of this for the OPTIMISE trial are thus: In keeping with the pragmatic nature of the trial, we made no attempt to standardise the choice of colloid in either group. Whilst individual patient data describing the use of starches was not collected, a post hoc survey of investigators suggested few patients received this fluid with no differences in use between the treatment groups. This systematic review identified no evidence of acute kidney injury associated with the use of starch solutions in surgical patients and provides reassurance that use of starch was unlikely to affect the findings of the trial.

4.5 Conclusion

The principal finding of this chapter was that there was no difference in hospital mortality, requirement for RRT or author defined AKI associated with peri-operative use of intra-venous 6%HES solutions. Although most studies were small with low event rates there was little between-study heterogeneity and narrow confidence intervals. A very large randomised trial of 6% HES solutions would be required to demonstrate either significant benefit or harm associated with use of these solutions in surgical patients. Given the absence of demonstrable benefit, the clear risks in critically ill patients and the additional cost over more widely used fluids; these data do not enable a recommendation for routine clinical use of 6% HES solution in surgical patients. However, it seems unlikely to have had an important effect on the findings of the OPTIMISE trial.

Chapter 5: Volume of Surgery and Provision of Acute and Critical Care Beds in the UK.

5.1 Introduction

Evidence of variation in surgical outcomes is known to exist between healthcare systems. As discussed in Chapter 1, a study suggested greater than 3-fold higher mortality among the highest risk surgical patients in the UK compared with the USA [1] and the more recent EuSOS study, a Europe-wide multinational prospective cohort study of 46,539 patients, demonstrated significant variation in outcome following surgery among European nations. [11] The causes of this phenomenon are uncertain but availability of Intensive Care Unit (ICU) beds, institutional differences in care pathways, [224] volume of surgery effects [111] and other factors have been suggested as contributing to outcome variation. Where there is evidence of variation in outcome, there may also be opportunities to improve it, so identifying causes is important.

In the particular case of the UK, poor outcomes are often attributed to reduced numbers and poor utilisation of critical care beds. [1] Wunsch and co-workers have demonstrated that the UK has less Critical Care beds than many other developed nations, [113] however little objective evidence exists to support the assertion that this is the cause for observed outcomes in the surgical group.

The United Kingdom is comprised of England and 3 devolved nations: Scotland, Wales and Northern Ireland with devolved governments responsible for delivery of healthcare. All regions within the UK have similar population demographics, a publicly funded healthcare system which is free at point of use, and similar medical training and practices. The largest of these, England, has historically been divided into NHS Strategic Health Authorities (SHAs) responsible for provision of healthcare and delivery of UK Department of Health (DH) Policy at regional level in England. SHAs typically had population sizes similar to a devolved nation. On the 31st of March 2013, SHAs in England and Wales were abolished by the Health and Social Care Act (2012) and their responsibilities taken over by NHS England.

Little is known about regional variation in volume of surgery, provision of acute and critical care beds, outcomes after high-risk surgery and patterns of critical care utilisation within the UK. This information was required to test the hypothesis that regional variations in surgical outcomes could be explained by variation in ICU bed provision.

As previously discussed Weiser *et al* estimated that 230 million surgical procedures are carried out each year worldwide. [2] This paper was published in 2008, but was based on data from different years in different countries; in the case of the UK it was based on data from 2004. He estimated the number of major surgical procedures (i.e. "any intervention occurring in a hospital operating theatre involving the incision,

excision, manipulation, or suturing of tissue") carried out in the UK in 2004 as 13,635 per 100 000.

In order to undertake an analysis comparing outcomes after high-risk surgery in the UK and to evaluate the possible effect of ICU bed provision on this, it would be necessary to have:

1. Detailed outcome data on a cohort of patients undergoing high risk surgery taken from the whole of the UK
2. Accurate denominator data on regional population
3. Accurate denominator data on regional volume of surgery
4. Accurate data on critical care bed provision.

Exact figures regarding volume of surgery for the UK as a whole or by region, along with associated outcomes are difficult to extract from existing sources. In the year 2000 the NHS Executive estimated the annual number of surgical procedures carried out in the NHS as approximately 2.3 million with an estimated mortality of 1.4%. [13] Subsequent work by Pearse and co-workers (discussed earlier) examined 4.1 million non-cardiac surgical procedures carried out at 94 NHS Trusts in England over a 70-month period between 1999 and 2004.

5.2 Hospital and Intensive Care Data Collection in the UK

5.2.1 England

Hospital Episodes Statistics

In England data on all surgical admissions is collected by the Hospital Episode Statistics (HES) database. HES is the English national statistical data warehouse for care provided by NHS hospitals. HES provides data for a number of organisations including national regulators, commissioners, researchers, as well as patients, carers and other individuals who are undertaking healthcare analyses. Data on all hospital admissions, outpatient appointments and emergency department attendances is supplied to HES by individual NHS trusts and also independent healthcare providers. The data is collected at local level; hospital administratve staff collect administrative and clinical data for patient care and to inform the commissioning process in England. Data is submitted to the Secondary Users Service (SUS), a data warehouse managed by British Telecom (BT) on behalf of the NHS. At prearranged dates during the year, an extract of this data is uploaded to HES. [225] The Health and Social Care Information System (HSCIS) then validates, cleans and analyses the data before it is used for published reports. The cleaning and validation process includes the removal of duplicate data and detailed provider mapping. Regular quality checks are carried out and monthly data quality check reports are published on the HES website. [226] HES data is used for commissioning and Payment by Results (PbR) in England;

however, in the most recent report "The Quality of Health and Social Care Data, England, Annual Report 2013", data inaccuracies were estimated to be 6.5% and the need to improve the quality assurance process was highlighted. [227]

Intensive Care National Audit and Research Centre

The Intensive Care National Audit and Research Centre (ICNARC) is a charitable company etablished in 1994 and sister organisation of the Intensive Care Society (ICS). ICNARC co-ordinates the Casemix Programme (CMP). The CMP is a national comparative audit of adult critical care units in England, Wales and Northern Ireland. Currently (2013) 94% of adult intensive care units participate (https://www.icnarc.org). Critical care units volunteer to join and collect case mix, patient outcome and activity data, according to a standardised dataset, on all the patients they admitted to ICU. Participation in the CMP is voluntary although the Department of Health and the NHS Executive have recommended that all units take part. Data collected on each patient are: patient identifiers, demographics, reason for admission, detailed physiological and clinical information, outcome and activity. ICNARC Model, APACHE II, APACHE III, Simplified Acute Physiology Score (SAPS) II and Mortality Probability Model (MPM) II are calculated from the data obtained. Admissions are excluded from the calculation of severity of illness scoring if: age at admission to ICU is less than 16 years or length of stay in ICU is less than 8 hours. Additionally, admissions are excluded from the calculation of APACHE II predicted hospital mortality if: the admission is for primary burns; the admission is following coronary artery bypass graft (CABG) surgery; the admission is transferred in from another critical care unit; all twelve physiological variables are missing.

5.2.2 Scotland

In Scotland, data on all hospital admissions is collected by Information Services Division (ISD) a division of National Services Scotland, part of NHS Scotland. ISD provides health information and statistical services for the NHS in Scotland. The Scottish Morbidity Record (SMR01) collects episode-level data on hospital inpatient and day-case admissions and attendances in all hospitals in Scotland. Data is collected at hospital or general practice level through Patient Administration System software (PAS). Validation rules are applied both locally (prior to data submission) then centrally at ISD. The data is also subject to regular validation checks, and the most recent quality assurance report indicated good levels of accuracy (>90%) for the fields used in this study. Up to four surgical procedure codes can be recorded on each SMR01 episode along with the date of procedure. These fields have an accuracy of more than 95% and it is recognised that health services data collected by ISD is amongst the best in the world. [228]

In Scotland the Scottish Intensive Care Society Audit Group (SICSAG) fulfils a similar role to ICNARC in England and collects data on patient demographics,

reason for admission, detailed physiological and clinical information, outcome and activity on those admitted to ICUs in Scotland. Severity of illness scoring uses the APACHE II model. Data is collected by clinical staff via a bespoke program called WardWatcher and again is extensively validated at local and central level. The database provided by ISD/SICSAG offers some advantages over that collected in England, Wales and Northern Ireland. All ICUs and HDUs in Scotland contribute data. Through patient linkage, data can be linked through multiple hospital admissions, to the SICSAG dataset and also to the General Register Office (GRO) in Scotland, which gives information on long-term outcomes.

5.2.3 Wales

The Welsh Government Statistics Directorate produces health and social care data including data on hospital admissions and outpatient/emergency department attendances in a similar manner to HES. Data on Critical Care admissions and outcomes is collected by ICNARC as described above.

5.2.4 Northern Ireland

Northern Ireland Statistics and Research Agency (NISRA) is the principal source of healthcare statistics in Northern Ireland and collects data on hospital admissions and outpatient/emergency department attendances. Data on Critical Care admissions and outcomes is collected by ICNARC as described above

5.2.5 SICSAG and CMP Data

Data for both SICSAG and CMP is collected locally according to strict definitions and validated extensively. Broadly, both systems collect data on patient demographics, source of admission, history and admission diagnosis, physiological derangement, nature and duration of organ support received on ICU, duration of ICU and hospital admission and ICU and hospital outcome.

In order to create as complete a cohort as possible of high risk surgical patients admitted to ICUs across the UK it would be necessary to combine the datasets held by ICNARC and SICSAG. To date this has not been done. Extensive advice was sought from the Chair of SICSAG, the Director of ICNARC and analysists at both ICNARC and ISD on the practicalities of doing this. The year 2009 was chosen as the most suitable year to undertake the planned analysis. This is because in 2007 and 2008 SICSAG and ICNARC made changes in their data collection manuals, and this would have made merging of datasets more problematic.

As an initial step it was of vital importance to have good quaility denominator data on regional volume of surgical procedures and acute and critical care bed provision in the UK. We set out to undertake this for the year 2009, as this was the year for which patient data could be most easily studied.

5.3 Methods

Ethical Considerations

The data accessed was in the public domain and so formal ethics approval was not required.

My Role in Work Undertaken

All data was sourced, extracted, reported and analysed by me.

Statistical Analysis

Analysis was performed using Excel (Microsoft, Seattle, WA) and STATA 11(Statacorp,TX)

To undertake the proposed analysis, the most accurate data available at national and SHA level was required on the following for the calender year 2009:

5.3.1 UK and Regional Population and Geography

Total population, adult population (for the purposes of this analysis defined as age greater than 16 years) and adult population over the age of 65 years for each devolved nation and SHA.

Population estimates were made using the following documents:

"Mid-2009 Population Estimates for Scotland" published by The General Register Office for Scotland (http://www.gro-scotland.gov.uk/files2/stats/population-estimates/mid-2009/mid-2009-pop-est-scotland.pdf accessed on 26/02/2012)

"Population Estimates for UK, England and Wales, Scotland and Northern Ireland, mid 2009" Published by the Office for National Staistics (http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-213645 accessed on 26/02/2012)

Total population, population over 16 and population over 65 were extracted for each devolved nation and region. Population density was calculated by dividing total number of inhabitants by geographical area of the region (km^2) (source ONS data).

5.3.2 Volume of Inpatient Surgery

Number of inpatient sugical procedures, excluding as far as possible, daycase procedures, cardiac procedures, imaging, radiological and injection procedures. To do this standard Office of Population Censuses and Surveys – 4 (OPCS4) codes were used. OPCS-4 is a standard coding system of surgical and other procedures used in the NHS. It is used as standard throughout the UK (i.e. Scotland, England, Wales and Northern Ireland). It is an alphanumeric four character system with 26 chapters realting to a specific organ system. It is similar to International Classification of

Diseases-10 (ICD10) or the American Medical Associations "Current Procedural Terminology".[229] Diagnostic codes OPCS Codes "Heart" (K01-078) and "Diagnostic testing & rehabilitation" (U01-U54) were excluded for this analysis and only surgical procedures requiring inpatient admission were considered.

Volume of surgery was estimated by using data from the following resources:

Scotland

"Inpatient and Day case Surgical procedures and operations - All Ages 2009" Published by Information Services Division, Scotland; (http://www.isdscotland.org/Health-Topics/Hospital-Care/Operations-and-Procedures/ accessed on 26/02/2013)

From the report described above the number of "TOTAL MAIN PROCEDURES" excluding imaging, injections, infusions, x-ray and cardiac procedure codes (as outlined above).

England

"Provider Level Analysis for HES Admitted Patient Care 2009-10)", Published by Health Episodes Statistics; (http://www.hesonline.nhs.uk/Ease/ContentServer?siteID=1937&categoryID=1453 accessed on 26/02/2013)

From "Admitted Patient Care", "Finished Consultant Episodes (FCE) with a main procedure or intervention" excluding imaging, injections, infusions, x-ray and cardiac procedure codes (as outlined above).

Wales

"NHS Wales Informatics Service, PEDW Statistics – 2009/10 (http://www.infoandstats.wales.nhs.uk/page.cfm?orgid=869&pid=41010&subjectlist=Total+Procedures&patientcoverlist=Welsh+Residents&period=2009&keyword=&action=Search accessed 15/03/2013)

"All Operations" excluding "Day Case "procedures, imaging, injections, infusions, x-ray and cardiac procedure codes (as outlined above).

Northern Ireland

"Acute Programme of Care Total Operations Summary" (http://www.dhsspsni.gov.uk/index/stats_research/hospital-stats/episode_based_activity/operations.htm accessed 15/03/2013)

From the report described above: "All Operations" excluding "Day Case "procedures, imaging, injections, infusions, x-ray and cardiac procedure codes (as outlined above).

For each dataset, only admitted patient care episodes were considered. The same procedure codes were excluded in all the datasets. The HES data was further stratified by SHA. It should also be noted that HES collect data from start to end of fiscal year (1st April), so 2009-10 was used. ISD uses calendar year (commencing 1st January) and so the year 2009 was used.

5.3.3 Acute and Critical Care Bed Data

There is no agreed definition of an acute hospital bed. In England, Wales and Northern Ireland KH03a is a quarterly bed census, which reports to the Department of Health and provides a count of available and occupied beds by healthcare provider. This includes a count of "General and Acute Beds". In Scotland, ISD defines acute beds as "acute specialty beds (excluding obstetrics and long term geriatrics)". For Critical Care beds, the definitions from the Intensive Care Society document "Levels of Critical Care for Adult Patients" were used. [164] In this document Critical Care Beds are defined as follows:

Level 0 – Normal ward care

Level 1 – Ward care with enhanced level of monitoring

Level 2 – Patients requiring more detailed observation or intervention, support for a single failing organ system or stepping down from higher levels of care.

Level 3 – Patients requiring mechanical ventilation alone, basic respiratory support plus support of two or more failing organ systems, patients in multiple organ failure.

Data was collected as outlined above. Population, surgical activity and critical care bed provision were reported by devolved nation and strategic health authority. Details of Acute and ICU bed provision were gathered from the Department of Heath (DH) Adult Critical Care Beds census (KH03a), reporting the number of available staffed beds in England on 15 July 2009; equivalent figures for the devolved nations were obtained from data held by the Intensive Care National Audit & Research Centre (ICNARC).

Scottish Intensive Care bed data was derived from The Scottish Intensive Care Society Audit Group Report "Audit of Critical Care in Scotland 2010 Reporting on 2009". ICU beds were defined as beds in adult, general ICUs or mixed intensive care/high dependency units (ICU/HDUs), excluding beds in specialist critical care units (e.g. cardiothoracic, neurosciences) and standalone HDUs.

Acute bed data for Scotland was gathered from Information Services Scotland, "Annual Trends in Available Beds" (http://www.isdscotland.org/Health-Topics/Hospital-Care/Beds/) Accessed 15/03/2013

5.4 Results

Population

Population, volume of surgery and provision of acute and critical care beds by region is summarised in Table 24. Total population ranged from 1,7888,900 (Northern Ireland) to 7,753,555 (London SHA) and the mean regional population size was 4,756,270. London also had the highest population density (by almost a factor of 10) and one of the lowest percentages of poulation over 65 (13%; mean 15.8%) although North East England was the lowest, at 10%. Scotland on the other hand had a very low population density (66.3/km^2; median 302/km^2) compared with other regions of the UK and the highest proportion of population over 65 (23%). Northern Ireland had the highest population under the age of 16, at 21%.

Volume of Surgery

Volume of surgery varied from 12,536 per 100 000 population (South Central SHA) to 19,779 per 100 000 population (North East SHA) with a mean value of 16,123 per 100 000 (Table 24).

Bed Provision

Acute hospital beds similarly varied across region from 193 per 100,000 (South Central SHA) to 328 per 100,000 (Scotland) with a mean of 245 per 100 000. Northern Ireland had the lowest number of critical care units and beds (9 and 78 respectively). Scotland had the highest number of ICUs at 23, while London SHA had the highest number of ICU beds at 448. Scotland also had the lowest number of ICU beds per ICU and London the highest (Range 7.52-26.34; mean 10.4). There was evidence of a greater than 2-fold variation in provision of ICU beds; mean number of ICU beds per 100 000 adults was 4.9 (range 3.4-7.2) and mean number of ICU beds per 100,000 surgical procedures was 24.9 (range 17.7-39.6) (Table 24, Figure 12).

Figure 12 Critical care beds per 100 000 population and per million surgical procedures.

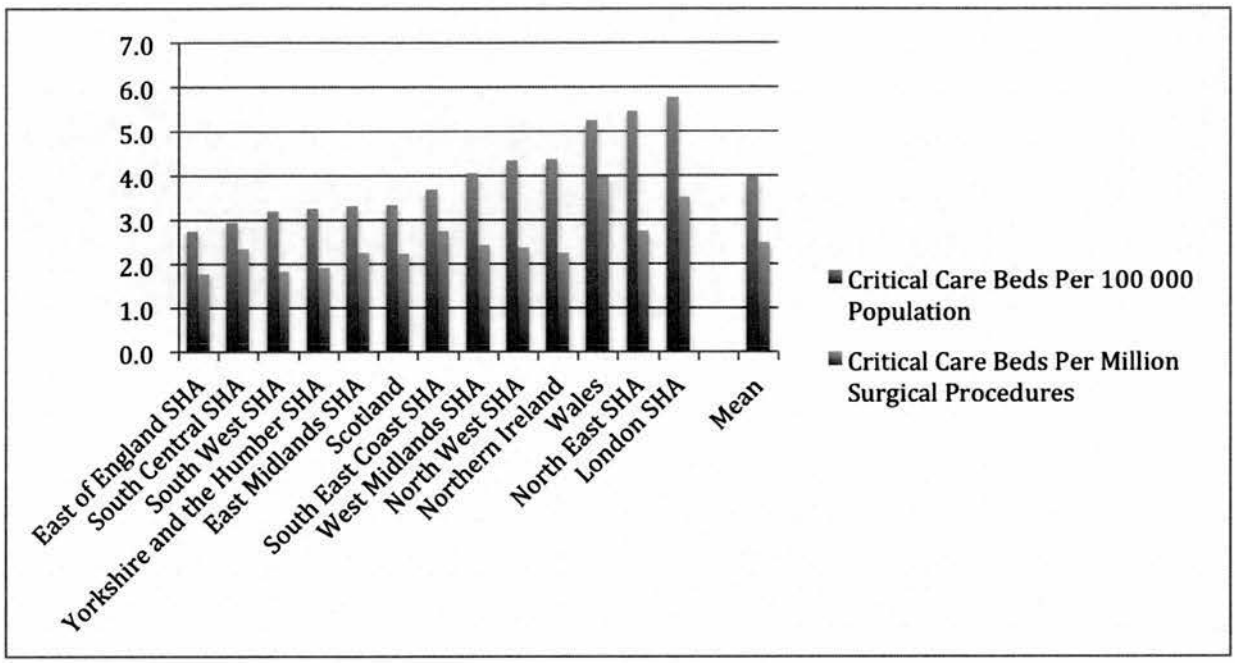


Table 24 Population, volume of surgery and bed provision by region.

Region	Total Population	Adult Population N(%)	Population >65 years N (%)	Population Density (per km^2)	Surgical Procedures	Surgical Procedures per 100,000 Population	General and Acute Hospital Beds	Acute Beds Per 100,000	Number of adult ICUs or ICU/HDUs	Beds in adult ICUs or ICU/HDUs	Average beds/ICU	Adult Intensive Care Beds per 100,000 adults	Adult Intensive Care Beds per 100 00 Surgical Procedures
East Midlands SHA	4,451,240	3,635,489 (82)	911,080 (20)	285	652,014	14,648	9,267	208.20	13	148	11.38	4.1	22.70
East of England SHA	5,766,625	4,675,061(81)	887,485 (15)	302	890,500	15,442	11,771	204.12	16	158	9.88	3.4	17.74
London SHA	7,753,555	6,254,866(81)	912,792 (12)	4941	1,277,092	16,471	17,926	231.20	17	448	26.35	7.2	35.08
North East SHA	2,584,262	2,125,717(82)	250,936 (10)	301	511,132	19,779	7,690	297.57	14	141	10.07	6.6	27.59
North West SHA	6,897,905	5,600,795(81)	644,337 (9)	487	1,267,002	18,368	18,622	269.97	24	299	12.46	5.3	23.60
Northern Ireland	1,788,900	1,406,800(79)	254,400 (14)	129	343,235	19,187	4,255	237.86	9	78	8.67	5.5	22.72
Scotland	5,194,000	4,281,000(82)	1,196,333 (23)	66.3	779524	15,008	17075	328.74	23	173	7.52	4.0	22.19
South Central SHA	4,095,376	3,314,366(81)	743,385 (18)	445	513,412	12,536	7,911	193.17	11	121	11.00	3.7	23.57
South East Coast SHA	4,340,342	3,525,056(81)	890,080 (21)	466	582,796	13,427	8,794	202.60	11	160	14.55	4.5	27.45
South West SHA	5,231,243	4,308,873(82)	907,496 (17)	220	922,509	17,635	12,993	248.37	17	168	9.88	3.9	18.21
Wales	3,038,872	2,449,888(81)	513,237 (17)	146	403,913	13,292	8,449	278.03	16	160	10.00	6.5	39.61
West Midlands SHA	5,431,079	4,378,188(81)	886,170 (16)	418	906,333	16,688	13,112	241.43	19	221	11.63	5.0	24.38
Yorkshire and the Humber SHA	5,258,114	4,286,898(82)	671,837 (13)	341	900,679	17,129	13,126	249.62	20	172	8.60	4.0	19.10
Mean	4,756,270	3,864,846 (81)	743,813(15.8)	302*	765,395.5	16,123.9	11614.7	245.5	18.1	188.2	10.40	4.9	24.9

*denotes median value

5.5 Discussion

To date, volume of surgery and critical care bed provision in the UK are not well reported. This data demonstrates regional variation in ICU bed provision across the UK when indexed either to population or to volume of surgical procedures. There was a 2.5 fold difference in Critical Care bed provision between worst and best provided regions. Differences in volume of surgery were less marked but still apparent; there was a 50% increase in volume of surgery between lowest and highest regions. The geograpaphy and population distribution of the UK may play a role in this. Densely populated urban areas (for example London) are more suited to fewer ICUs with a greater number of beds. In Scotland, where the population density is much lower, there are more ICUs with fewer beds. This may be necessary due to issues of distance and may have an impact on patient outcomes if, for example an increased number of inter-hosptal transfers are necessary. Another consideration is whether larger ICUs are able to provide better care with access to more specialist services and therapies.

The "London Effect" itself is likely to be important. Regions with major urban centres are likely to host regional and supra-regional centres, perform more surgery, treat patients with complex disease or greater co-morbidities and hence require more ICU beds and other resources. This is reflected in these findings.

Data on volume of surgery presented in this chapter are consistent with that reported by Weiser et al, [2] which estimated the number of surgical procedures carried out in the UK in 2004 as 13,635 per 100 000 population. Our figure was slightly higher at 16,123 per 100 000 population. This may be due to an increase in surgical procedures in the intervening 5 years or inclusion of more minor or endoscopic procedures in this estimate of volume of surgery. Weiser does not specify how he calculated this figure for the UK in his paper, however he defines surgery as "any intervention occurring in a hospital operating theatre involving the incision, excision, manipulation, or suturing of tissue, and that usually requires regional or general anaesthesia or profound sedation to control pain".

Wunsch *et al* compared critical care services across North America and Western Europe using large administrative databases in 2005. [224] She estimated UK acute hospital beds at 298 per 100,000 in 2005 and Critical Care beds at 3.5 per 100 000 population. The figures presented here of 245 per 100 000 Acute Beds and 4.9 Critical Care Beds per 100 000 are slightly different although Wunsch used identical data sources to this study so one would expect these figures to be close. UK and devolved government policy in the intervening 5 years to increase critical care capacity and reduce inpatient hospital beds may explain this finding. However even this current estimate of 4.9 per 100 000 adult population falls well short of provision

in Canada, USA, Belgium, Germany or other developed nations and may explain the observed disparity in surgical outcomes between the nations. England and Wales spend less on healthcare per capital than Scotland and Northern Ireland [230] and this could be reflected in acute bed provision per 100 000 although it does not seem to extend to critical care beds.

The strengths of this data is that they are derived from several well-maintained databases and audit projects which undergo regular quality assurance (as described above) and provide detailed activity and benchmarking data to the NHS and other organisations.

Possible limitations of the data are as follows:

Population data was taken from the ONS and GRO, which are the two most definitive sources available. However the accuracy of census data and population estimates have been questioned before and a recent example of inaccuracy is the 2001 census, where 900 000 men were reportedly missed. [231] A further source of bias may have been introduced into our data because we are examining population of SHA areas rather than nations. These boundaries are less distinct and SHA data is gathered from local council and GP lists. Moreover, patients who reside in the borders between SHAs may use some healthcare services in a different SHA or even country to the one in which they reside.

Volume of surgery data may be inaccurate and hence biased for a number of reasons. Firstly data from HES is collected by fiscal year and by calendar year in ISD. Secondly, some surgical services are regional or supra-regional and so patients from one SHA or devolved nation may actually receive surgical care in a different region. These procedures are, by the nature of their complexity, more likely to require critical care admission. Regions with high volume of surgery and critical care bed provision (e.g. London) may actually reflect a high concentration of tertiary and quaternary services. Thirdly, residents at the borders of SHAs and nations may not receive treatment in their region of residence as outlined above. Fourthly, due to coding practices, volume of surgery is likely to contain procedures such as endoscopy or other less invasive procedures which may result in this being an overestimate. Finally, inaccuracies in HES data in particular are known to be an issue [227] and these have been acknowledged in other studies. [2,15,114] Similar problems exist in all large administrative databases [4] and for the purposes of a study such as this, these are the most accurate data available. Also, because definitions and data collection methods have been applied consistently across databases, it would be reasonable to expect that the variation and trends observed are real.

The reliability of the acute hospital bed data also suffers from potential sources of bias. There are no consistent or nationally agreed definitions for acute hospital beds

which may make an exact estimation difficult. DH bed census definitions are different from those applied in Scotland and so this makes comparison between regions unreliable, and introduces the possibility of a systematic bias between regions. Unfortunately, it is not possible to exclude this possibility in the present study, or explore the directions of bias that might be present between different regions. However, these limitations are offset by the strength of a national study and large numbers of data from many different healthcare institutions.

Critical Care beds on the other hand are defined according to nationally agreed standards [164] which makes these numbers far more reliable across regions and nations. In addition, because critical care outcomes are subject to detailed annual audits, these numbers are reviewed regularly for accuracy. For the purposes of this study number of beds in either ICUs or mixed ICU/HDUs are used, however local practices and bed pressures could result in Level 2 beds being frequently used as Level 3 and vice-versa and this effect would be difficult to quantify from a study such as this. Areas where "Level 3" care might be offered outside an ICU setting, for example in a theatre recovery area (so called "post anaesthesia care units" (PACU) or "overnight intensive recovery"(OIR)), might also not be included in these numbers.

This data demonstrates regional differences in surgical activity and critical care bed provision within the UK, which are broadly consistent with the results of other investigators. These differences are likely to be real but may reflect the geography, demographics and spread of population in the UK. The validity of a study such as this is dependant on the quality of the available data. Accurate and high quality data is necessary, not just to inform research and epidemiological studies such as ours, but also to inform commissioners, funders, healthcare providers, clinicians and patient groups. The current arrangements make a study such as this prone to bias at several levels and this could affect the findings of subsequent studies and reports made using this data.

Whether this variation could be of any significance to the population undergoing surgery is not immediately apparent. Examining patient level data and outcomes for each region may allow a more detailed examination of the effects of this variation on patient care.

5.6 Conclusion

There is evidence of marked regional differences in volume of surgery and critical care bed provision across the UK. Pooling of patient-level data and comparing clinical outcomes of surgical patients admitted to Critical Care in different regions may allow us to determine if this variation is important.

Chapter 6: Creation of a UK Critical Care Dataset

6.1 Introduction

Having described regional variation in volume of surgery and critical care provision within the UK it was necessary to summarise activity and outcome of surgical patients admitted to ICU by UK region and to investigate whether any regional differences in outcome persist after correction for case-mix and ICU bed provision.

In order to undertake such an analysis it was necessary to create a cohort of high-risk surgical patients, drawn from the whole of the UK, with detailed demographic, physiological and outcome data. This would allow comparison of outcomes within the UK. Such data is collected by both ICNARC and SICSAG (held by ISD) on patients admitted postoperatively to intensive care units. However, as highlighted in the previous chapter, combining these two datasets to create a "UK wide" cohort of critically ill surgical patients has not previously been done and posed significant challenges.

ICNARC co-ordinates the "Casemix Programme" (CMP), a national audit of adult critical care units in England, Wales and Northern Ireland. In Scotland there is a similar but separate audit, overseen by SICSAG and data is held by ISD. All ICUs in Scotland are required to submit data to SICSAG. In England, Wales and Northern Ireland, unit participation in ICNARC is not compulsory but recommended: currently 92% of adult intensive care units in England, Wales and Northern Ireland participate.

Both SICSAG and ICNARC collect detailed patient level data including outcome and activity data in order to undertake comparative audit and benchmarking. Data are collected according to a standardised dataset on all the patients admitted to ICU and this includes: patient identifiers, demographics, reason for admission, physiological and chronic health data, ICU and acute hospital mortality, length of stay and discharge destination. In order to make comparisons between ICUs it is necessary to adjust for severity of illness and other patient factors such as admission diagnosis and chronic health conditions. This is often referred to as "casemix".

In England, Wales and Northern Ireland data are collected by trained abstractors then submitted to ICNARC for analysis. ICNARC uses the "ICNARC Model", a risk prediction model similar to APACHE II, to adjust for casemix. ICNARC Model was developed in 2007 using a cohort of 200 000 UK critical care admissions and then prospectively validated in a separate cohort of 30 000 patients. [232,233] ICNARC Model underwent recalibration in 2011. Data required for APACHE II, APACHE III, Simplified Acute Physiology Score (SAPS) II and Mortality Probability Model (MPM) II are also collected by ICNARC and these scores are also calculated.

In Scotland, the Scottish Intensive Care Society Audit Group (SICSAG) conducts a similar audit to the CMP England and all Critical Care Units in Scotland participate. Data is collected via "Wardwatcher", a data collection program provided by Information Services Division (ISD) a division of National Services Scotland, part of NHS Scotland. ISD provides health information and statistical services for the NHS in Scotland. "Wardwatcher" also collects data on patient demographics, reason for admission, physiological and chronic health data, ICU and acute hospital mortality, length of stay and discharge destination on those admitted to ICUs in Scotland. The database provided by ISD/SICSAG offers some advantages over that collected in England, Wales and Northern Ireland. Through patient identifiers, data can be linked through multiple hospital admissions, to the SICSAG dataset and also to the General Register Office (GRO) in Scotland, which gives information on long-term outcomes. APACHE II is used as the risk-prediction model and to adjust outcomes for severity of illness and other patient-level factors.

Data for both SICSAG and ICNARC are collected locally according to strict definitions and validated extensively. To date SICSAG and ICNARC datasets have never been combined to allow comparative analysis of activity and outcomes for surgical or other any other groups of ICU patients.

Study objectives for this chapter were as follows:

To construct a cohort of all adult patients admitted to Intensive Care following surgery in Scotland, England, Wales and Northern Ireland.

To report age, gender, prior CPR, emergency surgery, APACHE II score, APACHE II Acute Physiology Score (APS), Admission Diagnosis, ICU Length of Stay, ICU Mortality and Acute Hospital Mortality by region with no statistical testing.

6.2 Methods

Ethical Considerations

The Chairs of South East Scotland Research Ethics Committees 01 and 02 reviewed the proposed study protocol and the need for a full ethics submission was not deemed necessary.

My Contribution to this Work

I designed the analysis plan for the analyses carried out in this chapter (Chapter 5) and the next (Chapter 6), with guidance from KR, DH, TW and BC. Matching SICSAG and ICNARC datasets was first undertaken by me and then checked by AF. KR and DH arbitrated disagreements.

Recoding of the SICSAG data to enable import of SICSAG data into the CMP database and to then extract the summary data presented in this chapter was done by me. This was done by writing STATA "do files" (these are executable programs for the statistics and analysis package STATA (Statcorp, TX))) which were written and executed on ICNARC premises where both datasets were held. Following recoding, the SICSAG data was imported into the CMP database for further analysis. SP checked and executed these "do files" to ensure no permanent alteration was made to ICNARC data.

All work on ICNARC data must be done on ICNARC premises and supervised directly or performed by ICNARC analysts to comply with ICNARC data governance arrangements.

Selection of Study Cohort

Decisions on how to define and create the surgical cohort were taken with extensive advice from the Chairman of SICSAG (BC) and the Director and Senior Statistician at ICNARC (KR and DH). It was initially decided that data on a cohort of admissions to Scottish ICUs over the period 1st January 2007 to 31st December 2009 would be exported to ICNARC for analysis. However during the period 2007-2008 both ICNARC and SICSAG updated to different versions of data collection. To avoid the requirement to effectively combine four different datasets we decided to only analyse patients admitted to ICU during the period 1st January 2009 until 31st December 2009. Advice from the advisory group was that there would be sufficient numbers of patients admitted during this period to ensure adequate power in subsequent analyses.

Because of previous unpublished work I was aware of a large group of HDU level patients within the SICSAG dataset who had not been scored for APACHE II; it is not normal practice for SICSAG to undertake severity of illness scoring on this group of patients. For this reason it was agreed that only patients admitted directly from theatre or recovery and requiring Level 3 care (i.e. ICU care) should be included in this analysis.

In order to construct our cohort of surgical patients admitted to the ICU inclusion and exclusion Criteria were therefore as follows:

Inclusion

- Patients who's source of admission to ICU was theatre or recovery
- Patients receiving Level 3 Care in the first 48 hours following admission

Exclusion

- Patients under the age of 16
- Patients who had undergone surgery with well structured perioperative care pathways which include planned admission to critical care (e.g. cardiac surgery, neurosurgery, transplant surgery, burns surgery)
- Readmissions to critical care in the same hospital admission (do not have repeat APACHE scoring)
- Missing acute hospital mortality data (primary outcome for the intended analysis)

Data Management

SICSAG data was provided from SICSAG/ISD in the form of an Excel (Microsoft, Seattle, WA) spreadsheet. This spreadsheet was imported into STATA Version 11 (StataCorp, TX) for further manipulation and analysis. Analysis took place on ICNARC premises in Holborn, London.

In order to safely combine the two datasets it was necessary to closely examine the data collection manuals for both datasets to identify exactly how the data was defined, measured and collected.

For SICSAG I used "Wardwatcher (2008 Version) Help Pages" which provides definitions for all mandatory pages and fields for the SICSAG dataset. For the ICNARC Casemix Programme I used "ICNARC Case Mix Programme Data Collection Manual Version 3.1" and "ICNARC Case Mix Programme Flows Version 3.1"

I mapped SICSAG equivalents to Case Mix Programme "Reason for Admission" plus 83 further CMP variables used for determining source and nature of admission, acute physiological derangement and length of stay or outcome. There are 126 SICSAG variables in total in Wardwatcher v203. A full list of variables and data flows in the SICSAG and CMP datasets can be found online. [234,235]

After SICSAG data fields were mapped to CMP data fields by an analyst at ICNARC (AF) corroborated the process.

SICSAG variables fell into 4 categories:

- SICSAG variable maps exactly to equivalent CMP variable
- SICSAG variable maps to equivalent CMP variable but recoding required
- SICSAG variable similar but not exactly equivalent.
- Equivalent SICSAG variable not available.

Inconsistencies in variable mapping were further reviewed by two statisticians at ICNARC (SP and DH). In the situation where the SICSAG variable was similar but not an exact match it was reviewed by all five members of the group (MG, AF, SP, DH, KR) and a decision taken as to whether it could be included.

Where SICSAG variables fell into categories 1, 2 or 3 (i.e. were suitable for merging) variable names were recoded to the CMP equivalent.

Some categorical variables only required simple recoding. Where variables involved multiple categories, it was necessary to collapse the SICSAG data into the lowest common denominator and recode to the same categories as ICNARC before importing data. For some variables this required detailed specific field mapping, for example admission or discharge location. Following this a STATA "Do-File" was created utilising a series of "replace" commands. This allowed the SICSAG data to be recoded into the same categories as the ICNARC data.

SICSAG APACHE II diagnostic categories were mapped directly to the CMP "Reason for Admission" diagnostic category.

61 SICSAG variables could be mapped exactly or with minimal recoding to an equivalent CMP variable. For 9 CMP variables there was no equivalent SICSAG variable available. These are summarised in Table 25. None of these either related to outcomes of interest or construction of the APACHE II model that we planned to use to adjust for casemix so were not considered further.

A further 6 variables required significant recoding following discussion among the collaborators and these are listed in Table 26.

Individual solutions for each data field are outlined in this table. These mostly related to the way that time of death (or brainstem death) and discharge are recorded in the SICSAG database; in brief, to calculate time of death in the SICSAG dataset, unit outcome must equal 4 (death) and then time of death is equal to time of discharge.

Finally 6 variables were not exact matches but thought to be close enough to safely include. These are outlined in Table 27. Variables used in the APACHE II model were of most concern, as being able to adjust for severity of illness and admission diagnosis was essential to compare outcomes. "Lowest pH" required transformation of $[H^+]$ to pH, which was simple to perform using a logarithmic transformation. SICSAG does not distinguish "Non-Ventilated Respiratory Rate" and "Ventilated Respiratory Rate" so in this case the highest value of the two in the CMP was mapped to "Highest Respiratory Rate" in SICSAG. Finally there was a subtle difference in the way that lowest systolic blood pressure is recorded between the two datasets. CMP uses "lowest systolic" and SICSAG uses "systolic paired with lowest diastolic". The APACHE II algorithm uses these to calculate mean arterial pressure

(MAP). 75 000 BP measurements from data collected for previous iterations of the CMP (years 2005-7 when both were collected) were used to see if this difference in calculation resulted in significant differences on the APACHE II model. Comparison of MAPs generated by each of these two processes were examined and found to be practically identical (Table 28). Hence it was felt, in the opinion of DH, to be safe to import this value directly and include in the analysis.

Figure 13 Flow diagram outlining the process for merging of SICSAG and CMP datasets once recoding had taken place.

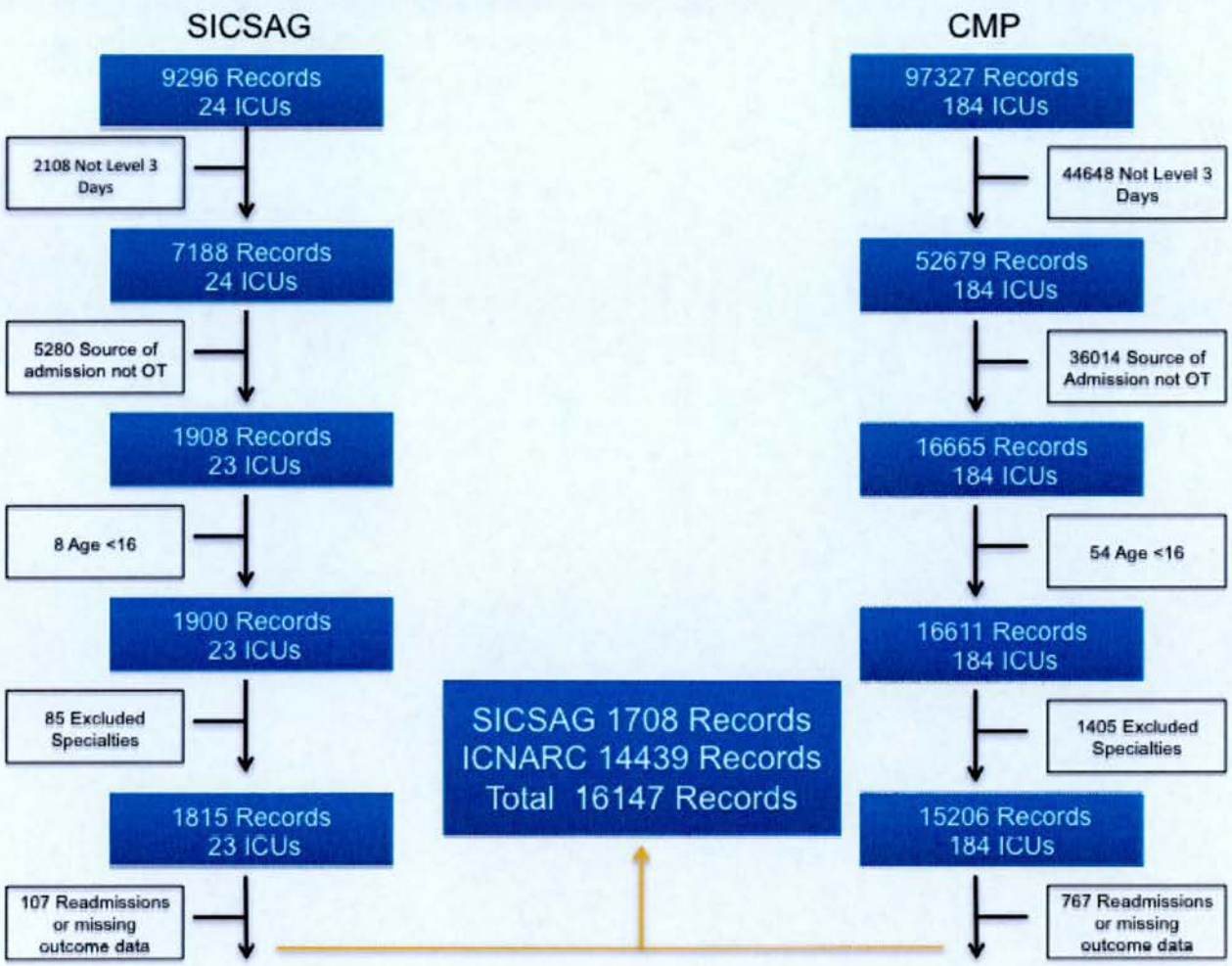


Table 25 CMP variables for which there was no equivalent SICSAG variable available.

CMP Variable	Definition	Data Type	Commentary
chemox	chemotherapy	Boolean	"ImmuSup" only covers Steroid Therapy
cicids	Congenital immunohumoral or cellular immune deficiency state	Boolean	No map –SICSAG "ImmuSup" only covers Steroid Therapy
hnctemp	Highest non-central temperature	Decimal	No longer collected and not required in APACHE 2 model
hv	Home Ventilation	Boolean	No equivalent available
lnctemp	Lowest non-central temperature	Decimal	No longer collected and not required in APACHE 2 model
radiox	radiotherapy	Boolean	No map –SICSAG "ImmuSup" only covers Steroid Therapy
rdis_v3	Reason for discharge from your unit	String	No equivalent available
Soha	Sector of other hospital (in)	String	No equivalent available
Sohd	Sector of other hospital (out)	String	No equivalent available

*CMP=Case Mix Programme SICSAG = Scottish Intensive Care Audit Group

Table 26 SICSAG Variables that required significant recoding

Variable	Data Type	CMP Definition	SICSAG v203 Variable Name	SICSAG Definition	Issue	Solution
Ddbsd	Date	Date of declaration of brainstem death	DiscDate	Discharged on (date) (in conjunction with BrainStem)	Data recorded differently	Where UnitOutcome=4 & BrainStem=1, DiscDate=DDBSD
Ddicu	Date	Date of discharge from your unit	DiscDate	Discharged on (date) (in conjunction with UnitOutcome)	Data recorded differently	Where UnitOutcome=1,2,3, DiscDate=DDICU
dod	Date	Date of death	DiscDate	Discharged on (date) (in conjunction with UnitOutcome)	Data recorded differently	Where UnitOutcome=4 and BrainStem=0, DiscDate=DOD
sedpar	String	Sedated or paralysed and sedated for whole of first 24 hours in your unit	No longer collected		Sedation not collected in SICSAG V203; only have GCS_Available field; GCS_Available=Able to assess GCS, therefore inference can be made that patient was sedated if GCS could not be assessed	Where SICSAG V0 Sedation=1,2,3, GCS_Available=0; Sedation=4,5, GCS_Available=1; Sedation=6,9, GCS_Available=NULL; CMP (both V's) where SEDPAR=S,P, GCS_Available=0; SEDPAR=N,V, GCS_Available=1
tdbsd	Time	Time of declaration of brainstem death	DiscTime	Discharged on (time) (in conjunction with BrainStem)	Data recorded differently	Where UnitOutcome=4 & BrainStem=1, DiscTime=TDBSD
tdicu	Time	Time of discharge from your unit		Discharged at (time) (in conjunction with UnitOutcome)	Data recorded differently	Where UnitOutcome=1,2,3, DiscTime=TDICU

Table 27 SICSAG variables, which were similar but not exactly equivalent.

CMP Variable Name	Data Type	CMP Definition	SICSAG v203 Variable Name	SICSAG Definition	Issue	Solution
Hnvrr	Integer	Highest non-ventilated respiratory rate	HighRR	High respiratory rate	Same Units but SICSAG don't distinguish between vent & non-vent RR	For CMP High respiratory rate value, take highest value from LNVRR, HNVRR, LVRR and HVRR and map to SICSAG HighRR field
Hvrr	Integer	Highest ventilated respiratory rate	HighRR	High respiratory rate	Same Units (but SICSAG don't distinguish between vent & non-vent RR)	For CMP High respiratory rate value, take highest value from LNVRR, HNVRR, LVRR and HVRR and map to SICSAG HighRR field
lph_v3	Decimal	pH/H+ from arterial blood gas with lowest pH (or highest H+)	HighO2pH or LowpO2pH	(Highest O2%) H+/pH or (Lowest pO2) H+/pH	Requires transformation of pH to [H+].SICSAG also records the pH from Intubated only patients at the highest FiO2 setting (this is not the same);	Always in [H+]: (highest value (in H+) out of the LowpO2pH & HighO2pH)=LPH_V3 (in H+) Have to take lowest pH (or highest H+) value from those ABG results which are available
lsys	Integer	Lowest systolic BP	pairedsys	Systolic BP paired with lowest diastolic BP	Not an exact match.	Discussed by collaborators. Close enough to include (see text)
pclph_v3	Decimal	Associated PaCO2 from arterial blood gas with lowest pH (or highest H+)	HighO2CO2 or LowpO2CO2	(Highest O2%) pCO2 or (Lowest pO2) pCO2	SICSAG also records the pCO2 from Intubated only patients at the highest FiO2 setting (this is not the same)	First take highest value (in H+) out of the LowpO2pH & HighO2pH, then the PaCO2 associated with this value, either LowpO2CO2 or HighO2CO2=PCLPH_V3 (in H+)
pdial	Integer	Paired diastolic BP for lowest systolic BP	lowdias	Lowest diastolic BP	Not an exact match.	Discussed by collaborators. Close enough to include (see text).

Table 28 Three years of mean arterial pressure measurements calculated from two different sets of measurement (data taken from CMP 2005-7).

	MAP Calculated from Highest Systolic BP	MAP calculated from Paired Systolic of Highest Diastolic BP	MAP Calculated from Lowest systolic BP	MAP Calculated from Systolic BP associated with Lowest Diastolic BP
Number of measurements	78561	76713	78884	77309
Mean	100.6	101.1	66.2	65.7
SD	17.2	17.1	14.8	14.5
P25	89	90	57	57
P50	99	100	65	65
P75	110	111	75	74

Following mapping and recoding of the SICSAG dataset to match the CMP dataset as outlined above, exclusion criteria were then applied:

- Patients who did not receive level 3 care in the first 48 hours; defined as "Highest Level of Care Received" = Level 3 (ICS Levels of Care were used).[164]
- Patients whose source of admission was not the operating theatre (OT) or recovery; defined from "Admission Source".
- Patients aged under 16 years of age.
- Patients who had undergone neurosurgery, cardiac surgery, burns or transplantation surgery; this was done as follows: if "Admission Specialty" (adspec) was "Burns surgery", "Cardiac Surgery", "Cardiology", "Neurology", "Neurosurgery", "Obstetrics", "Thoracic Surgery"; if APACHE II common descriptor (ap2desc_common), was: "ICH/SDH/SAH", "Craniotomy for Neoplasm", "Head Trauma", "Renal Transplant"; if "Operation Performed" (operperf) was "Liver transplant", "Other transplant surgery." This was excluded using APACHE II diagnostic code.
- Patients who were readmissions to ICU during the same hospital stay (readmit="yes")
- Patients where "Acute Hospital Mortality" (ahsurv) was missing.

The final datasets for SICSAG and CMP were then merged to create a cohort of all critical care admissions in the SICSAG and CMP datasets for the year 2009. A flowchart of this process is shown in Figure 13.

For subsequent analyses, APACHE II definitions were used to categorise patients as this was felt to be more consistent between groups. 29 diagnostic APACHE II groups remained in total following exclusion of unwanted groups and for ease of presentation of data; these codes were then broadly grouped by either type of surgery or disease process. MG and RP undertook this independently and then any disparity between groups was resolved by consensus by the other collaborators (TW, BC, KR, DH and SP). Descriptive statistics were applied to the dataset with no statistical testing. It should be noted that the modelling described in subsequent chapters uses the original APACHE II diagnostic groups and not these groups, which are described only for ease of presentation of data in this chapter. The original APACHE II reason for admission (prior to grouping) and numbers from CMP and SICSAG datasets are presented in Table 29. Some of these admission codes are medical in the CMP dataset. This is because CMP allows two APACHE II common descriptors and we decided *a priori* to use the first as the primary reason for admission and to construct the model in chapter 6 accordingly. This may have led to a source of measurement bias (see below).

6.3 Results

Study Cohort Characteristics

Prior to application of inclusion and exclusion criteria, the whole dataset contained 106,623 patients from 208 ICUs. A flow diagram outlining patient selection for the study cohort is presented in Figure 13. Data from 16,147 surgical ICU admissions (1,708 SICSAG, 14,439 ICNARC) from 207 ICUs (23 Scotland, 184 England, Wales and Northern Ireland) was analysed. There was a slightly higher preponderance of surgical ICU admissions in the SICSAG cohort compared with the CMP cohort (19.5% vs. 15.6%). Patients were grouped according to country or SHA and numbers of admissions by region and this, along with demographics and casemix, is outlined in Table 30. The mean number of admissions per region was 1265 per year with a range from 695 (Northern Ireland) to 1754 (London SHA) per year.

Study Cohort Demographics and Casemix

Table 30 indicates that age and gender were broadly similar across the regions. The percentage of admissions having undergone cardiopulmonary resuscitation (CPR) prior to ICU admission ranged from 1.6% (West Midlands SHA) to 3.5% (North West SHA) while admissions following emergency surgery ranged from 52.4% (London SHA) to 79.6% (Yorkshire and the Humber SHA). APACHE II Score was

broadly similar between regions (Figure 14). South East Coast SHA had the lowest mean APACHE II APS and full score at 9.9 and 14.4 respectively; however the region with the highest mean values in these variables (Northern Ireland) was not greatly different at 12.1 and 16.5 respectively.

Figure 14 Mean APACHE II score by region (error bars denote 95% CIs)

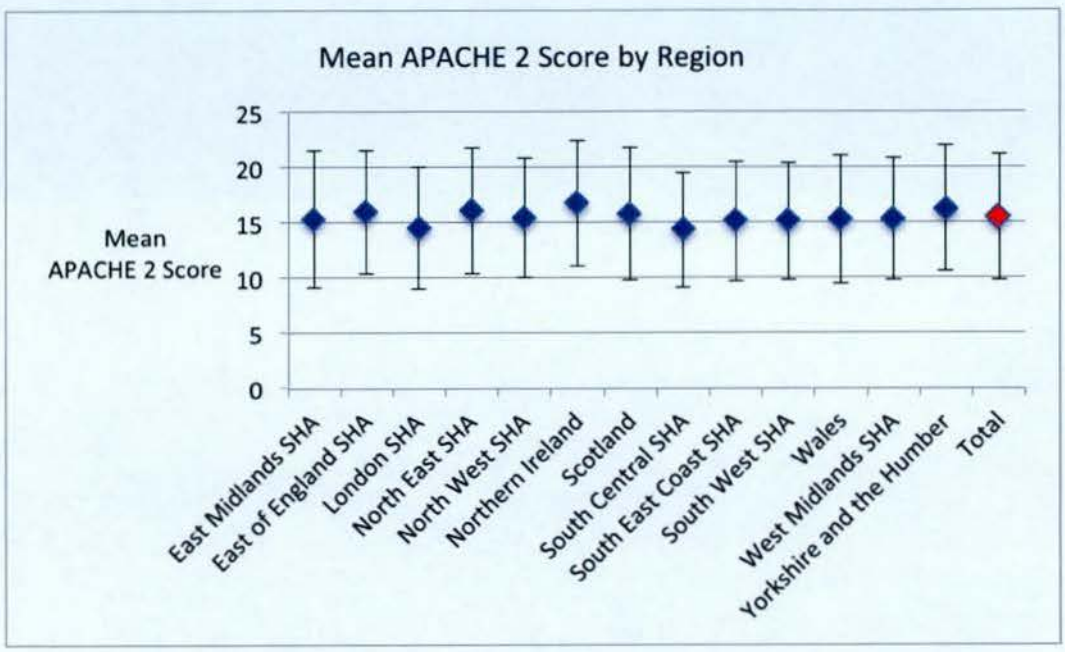


Table 29 APACHE II common descriptors for both CMP and SICSAG datasets prior to merging.

Group No	Descriptor - Reason For Admission	Frequency Rank	COMMON APACHE 2 Descriptor	CMP	SICSAG	Total
1	**GI Surgery for Bleeding Perforation or Neoplasm**					**6901**
		1	GI Perforation/Obstruction	3322	349	3671
		2	Gastrointestinal	2016	310	2326
		5	GI Bleeding	785	119	904
2	**Surgery for Neoplasm (inc GI Neoplasm)**					**2716**
		4	GI Surgery for Neoplasm	2080	124	2204
		12	Renal Surgery for Neoplasm	345	18	363
		18	Neoplasm	86	63	149
3	**Major Vascular Surgery**					**2302**
		3	Dissecting Thoracic/Abdominal Aneurysm	2144	158	2302
4	**Cardiovascular Disease**					**235**
		30	Pulmonary Embolus	22		22
		31	Coronary Artery Disease	14		14
		32	Hypertension	12		12
		20	Rhythm Disturbance	80		80
		22	Congestive Heart Failure	59		59
		24	Cardiogenic Shock	37	11	48
5	**Respiratory Disease**					**663**
		11	Respiratory	403	45	448
		19	Respiratory Infection	110		110
		23	Asthma/Allergy	50		50
		27	COPD	29		29
		29	Pulmonary Edema (Noncardiogenic)	26		26
6	**Pre-Existing Renal Disease**					**643**
		6	Renal vasculitis	643		643

Table 29 (Cont.)

Group No	Descriptor - Reason For Admission	Frequency Rank	COMMON APACHE 2 Descriptor	CMP	SICSAG	Total
7	**Trauma**					**598**
		7	Multiple Trauma	522	76	598
9	**Sepsis**					**321**
		14	Sepsis	232	89	321
10	**Other**					**414**
		16	Metabolic	220	46	266
		21	Aspiration/Poisoning/Toxic	61		61
		25	Haematologic	45		45
		33	Not documented		4	4
		34	Drug Overdose	2		2
		35	Not mapped		1	1
		26	Seizure Disorder	34		34
		36	Postrespiratory Arrest		1	1
11	**Missing**					**294**
		15	Missing	294		294

Reason for Admission

Patterns of reason for admission differed between regions. Table 31 outlines these differences. Possible reasons for this are: regions with large rural areas e.g. Scotland have a more ICUs with fewer admissions. Large urban areas e.g. London have proportionally more beds but offer tertiary and quaternary services, hence may either admit more elective surgery or cases with increased complexity. Emergency admission showed marked variation between regions; mean percentage of emergency admissions was 68.3%, however this varied from 52.6% (London SHA) to 80.8% (Yorkshire and the Humber). Admission following GI bleeding, obstruction and perforation formed the largest group across all regions (mean 41.3%) however there was evidence of variation across regions (range 32.9-48.8%). Admission following elective surgery for neoplasm and major vascular surgery also formed sizeable groups within the cohort.

ICU Resource Use and Outcome

Resource use and outcome is summarised in Table 32. Overall median ICU length of stay was 2.5 days however IQR was wide (0.8,7.5) (Table 5.8). Acute hospital length of stay varied across regions both in survivors and non-survivors. Median acute hospital length of stay ranged from 17 to 24 days for survivors; and from 9 to 13 days for non-survivors. Crude acute hospital morality for the full cohort varied by over 10% across regions (Table 32) with a mean of 23.2% and a range of 18.8% (London SHA) to 29.1% (North West SHA).

Figure 15 Percentage of admissions following emergency surgery by region.

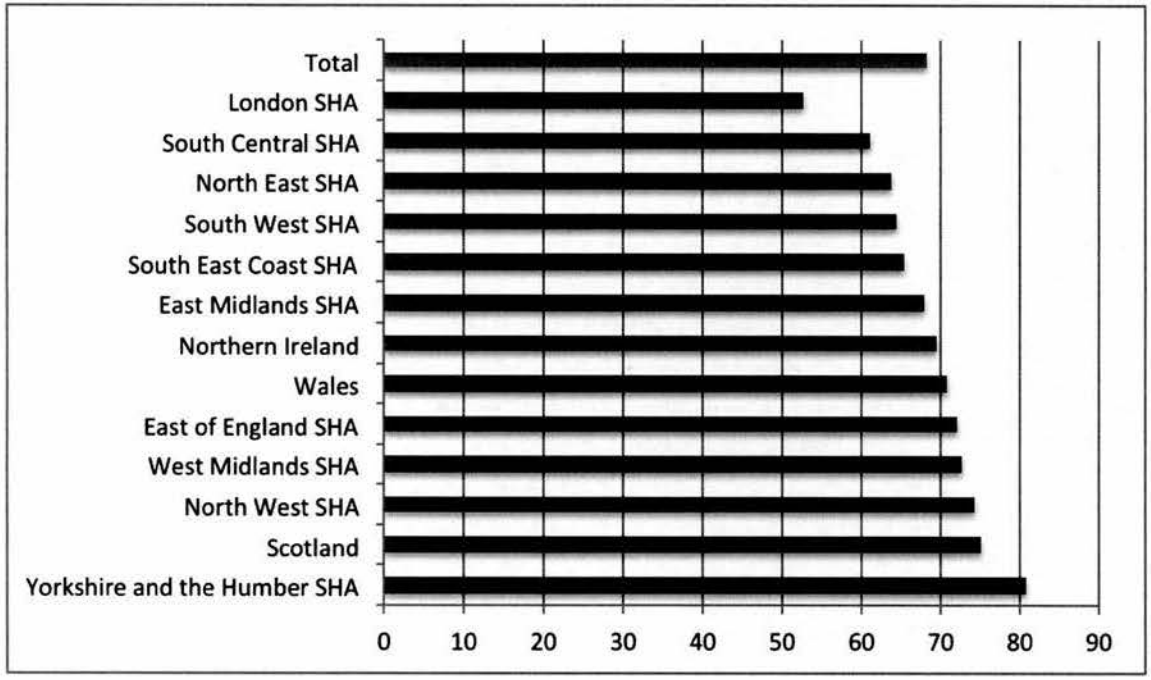


Table 30 Demographics and casemix.

	Number of admissions	Age, mean (sd)	Gender, (%) male	Prior CPR, (%) [N]	Emergency surgery, (%) [N]	APACHE II APS, mean (sd) [N]	APACHE II, mean (sd) [N]
East Midlands SHA	1,474	61.0 (17.2)	867 (58.8)	38 (2.6) [1,474]	989 (67.1) [1,474]	11.5 (5.5) [1,443]	15.4 (6.2) [1,443]
East of England SHA	1,108	66.1 (16.4)	581 (52.4)	41 (3.7) [1,107]	784 (70.8) [1,108]	11.3 (4.7) [1,070]	15.9 (5.6) [1,070]
London SHA	1,757	61.9 (17.4)	997 (56.7)	51 (2.9) [1,757]	920 (52.4) [1,757	10.6 (4.8) [1,722]	14.6 (5.6) [1,722]
North East SHA	1,024	63.5 (16.0)	585 (57.1)	33 (3.2) [1,024]	663 (64.7) [1,024]	11.4 (4.8) [1,004]	15.9 (5.8) [1,004]
North West SHA	1,357	62.9 (16.6)	764 (56.3)	48 (3.5) [1,357]	1,004 (74.0) [1,356]	11.2 (4.6) [1,321]	15.5 (5.5) [1,321]
Northern Ireland	695	63.9 (17.3)	405 (58.3)	13 (1.9) [695]	486 (69.9) [695]	12.1 (4.9) [679]	16.5 (5.7) [679]
Scotland	1,754	62.0 (16.5)	994 (56.7)	36 (2.1) [1,754]	1,280 (73.8) [1,735]	11.3 (5.3) [1,672]	15.8 (6.1) [1,672]
South Central SHA	1,048	65.5 (16.5)	598 (57.1)	24 (2.3) [1,048]	628 (59.9) [1,048]	11.4 (5.3) [1019]	15.7 (6.0) [1019]
South East Coast SHA	947	65.6 (15.8)	552 (58.3)	18 (1.9) [947]	605 (63.9) [947]	9.9 (4.2) [938]	14.4 (5.2) [938]
South West SHA	1,770	64.7 (16.6)	1,076 (60.8)	46 (2.6) [1,769]	1,123 (63.4) [1,770]	10.5 (4.6) [1,718]	14.9 (5.4) [1,718]
Wales	797	65.8 (15.4)	452 (56.7)	14 (1.8) [797]	557 (69.9) [797]	10.8 (5.0) [779]	15.2 (5.8) [779]
West Midlands SHA	1,401	63.2 (16.8)	767 (54.7)	22 (1.6) [1,401]	1,001 (71.4) [1,401]	11.0 (4.6)[1,370]	15.2 (5.5) [1,370]
Yorkshire and the Humber SHA	1,316	63.4 (17.5)	716 (54.4)	60 (4.6) [1,316]	1,047 (79.6) [1,315]	11.9 (4.9) [1,267]	16.1 (5.8) [1,267]
Total	16,448	63.5 (16.8)	9,354 (56.9)	444 (2.7) [16,446]	11,087 (67.5) [16,427]	11.1 (4.9) [16,002]	15.4 (5.8) [16,002]

Table 31 Diagnostic categories by region.

	East Midlands SHA (%)[N]	East of England SHA (%)[N]	London SHA (%)[N]	North East SHA (%)[N]	North West SHA (%)[N]	Northern Ireland (%)[N]	Scotland (%)[N]	South Central SHA (%)[N]	South East Coast SHA(%)[N]	South West SHA (%)[N]	Wales (%)[N]	West Midlands SHA (%)[N]	Yorkshire and Humber SHA (%)[N]	Total (%)[N]
Surgery for GI Bleeding, Perforation or Obstruction	589 (40.0) [1,474]	472 (43.3) [1,090]	555 (32.9) [1,689]	348 (35.1) [994]	583 (43.0) [1,355]	258 (37.2) [694]	797 (46.7) [1,708]	425 (40.8) [1,043]	657 (37.1) [947]	657 (37.1) [1,770]	353 (44.4) [795]	576 (44.4) [1,296]	630 (48.8) [1,292]	6, 670 (41.3) [16,147]
Surgery for Neoplasm (inc GI Neoplasm)	284 (19.3) [1,474]	132 (12.1) [1,090]	386 (22.9) [1,689]	209 (21.0) [994]	159 (11.7) [1,355]	82 (11.8) [694]	213 (12.5) [1,708]	191 (18.3) [1,043]	344 (19.4) [947]	344 (19.4) [1,770]	148 (18.6) [795]	229 (17.7) [1,296]	128 (9.9) [1,292]	2,719 (16.8) [16,147]
Major Vascular Surgery	209 (14.2)[1,474]	189 (17.3) [1,090]	227 (13.4) [1,689]	153 (15.4) [994]	180 (13.3) [1,355]	100 (14.4) [694]	164 (9.6) [1,708]	190 (18.2) [1,043]	294 (16.6) [947]	294 (16.6) [1,770]	110 (13.8) [795]	194 (15.0) [1,296]	202 (15.6) [1,292]	2,308 (14.3) [16,147]
Cardiovascular Disease	52 (3.5) [1,474]	75 (6.9) [1,090]	103 (6.1) [1,689]	45 (4.5) [994]	86 (6.3) [1,355]	80 (11.5) [694]	151 (8.4) [1,708]	56 (5.4) [1,043]	88 (5.0) [947]	88 (5.0) [1,770]	34 (4.3) [795]	52 (4.0) [1,296]	66 (5.1) [1,292]	931 (5.7) [16,147]
Respiratory Disease	57 (3.9) [1,474]	57 (5.2) [1,090]	70 (4.1) [1,689]	33 (3.3) [994]	75 (5.5) [1,355]	50 (7.2) [694]	46 (2.7) [1,708]	32 (3.10) [1,043]	65 (3.7) [947]	65 (3.7) [1,770]	32 (4.0) [795]	39 (3.0) [1,296]	65 (5.0) [1,292]	661 (4.1) [16,147]
Pre-Existing Renal Disease	94 (6.4) [1,474]	45 (4.1) [1,090]	79 (4.7) [1,689]	45 (4.5) [994]	51 (3.8) [1,355]	30 (4.3) [694]	0 (0) [1,708]	55 (5.3) [1,043]	58 (3.3) [947]	58 (3.3) [1,770]	29 (3.6) [795]	59 (4.6) [1,296]	75 (5.8) [1,292]	664 (4.1) [16,147]
Trauma & Orthopedics	57 (3.9) [1,474]	33 (3.0) [1,090]	100 (5.9) [1,689]	37 (3.7) [994]	51 (3.8) [1,355]	20 (2.9) [694]	85 (5.0) [1,708]	27 (2.6) [1,043]	50 (2.8) [947]	50 (2.8) [1,770]	37 (4.7) [795]	34 (2.6) [1,296]	47 (3.6) [1,292]	605 (3.7) [16,147]
Neurological	85 (5.8) [1,474]	20 (1.8) [1,090]	60 (3.6) [1,689]	77 (7.8) [994]	74 (5.5) [1,355]	22 (3.2)[694]	30 (1.8) [1,708]	18 (1.7) [1,043]	115 (6.5) [947]	115 (6.5) [1,770]	22 (2.8) [795]	48 (.7) [1,296]	31 (2.4) [1,292]	620 (3.8) [16,147]
Sepsis	3 (0.2) [1,474]	39 (3.6) [1,090]	20 (1.2) [1,689]	15 (1.5) [994]	42 (3.1) [1,355]	34 (4.9) [694]	90 (5.3) [1,708]	12 (1.6) [1,043]	16 (1.7) [947]	15(0.8) [1,770]	13 (1.6) [795]	17 (1.3) [1,296]	6 (0.5) [1,292]	322 (2.0) [16,147
Other	35 (2.4) [1,474]	20 (1.8) [1,090]	63 (3.7) [1,689]	20 (2.0) [994]	36 (2.7) [1,355]	15 (2.2) [694]	49 (2.9) [1,708]	19 (2.0) [1,043]	59 (3.3) [947]	59 (3.3) [1,770]	14 (1.8) [795]	28 (2.2) [1,296]	31 (2.4) [1,292]	421 (2.6) [16,147]
Missing	9 (0.6) [1,474]	8 (0.6) [1,090]	26 (1.5) [1,689]	12 (1.2) [994]	18 (1.3) [1,355]	3 (0.4) [694]	83 (4.9) [1,708]	3 (0.3) [1,043]	3 (0.3) [947]	25 (1.4) [1,770]	3 (0.4) [795]	20 (1.5) [1,296]	11 (0.9) [1,292]	226 (1.4) [16,147]

Table 32 Outcomes and resource use.

	Critical care unit mortality, (%) [N]	Acute hospital mortality, (%) [N]	Critical care length of stay - Unit survivors, median (IQR)	Critical care length of stay - Unit non-survivors, median (IQR)	Acute hospital length of stay – Survivors, median (IQR)	Acute hospital length of stay - Non-survivors, median (IQR)
East Midlands SHA	193 (13.1) [1,474]	291 (19.7) [1,474]	2.6 (1.2, 5.2)	2.9 (1.0, 8.0)	17 (10, 35)	9 (4, 22)
East of England SHA	196 (17.7) [1,108]	310 (28.0) [1,108]	2.8 (1.52, 5.7)	1.9 (0.7, 6.2)	21 (12, 41)	10 (3, 23)
London SHA	211 (12.0) [1,757]	331 (18.8) [1,757]	2.5 (1.1, 5.4)	3.0 (0.9, 9.9)	19 (11, 35)	13 (4, 30)
North East SHA	135 (13.2) [1,024]	248 (24.2) [1,024]	2.1 (1.0, 4.9)	2.3 (0.9, 7.3)	21 (11, 41)	12 (5, 36)
North West SHA	258 (19.0) [1,357]	395 (29.1) [1,357]	3.7 (1.9, 8.0)	3.1 (0.9, 9.0)	24 (13, 45)	11 (4, 28)
Northern Ireland	105 (15.1) [695]	165 (23.7) [695]	2.9 (1.7, 5.7)	3.3 (0.9, 8.6)	20 (12, 36)	10 (4, 24)
Scotland	216 (12.3) [1,754]	385 (21.9) [1,754]	1.9 (0.9, 3.9)	2.4 (0.8, 6.4)	20 (12, 34)	12 (5, 24)
South Central SHA	143 (13.6) [1,048]	215 (20.5) [1,048]	2.2 (1.1, 4.8)	2.1 (0.7, 5.5)	17 (10, 34)	10 (4, 22)
South East Coast SHA	117 (12.4) [947]	183 (19.3) [947]	3.0 (1.8, 6.0)	2.5 (1.1, 5.3)	17 (10, 32)	10 (4, 19)
South West SHA	251 (14.2) [1,770]	398 (22.5) [1,770]	2.7 (1.4, 5.1)	2.2 (0.7, 5.9)	18 (10, 33)	9 (3, 19)
Wales	130 (16.3) [797]	218 (27.4) [797]	3.0 (1.6, 6.4)	2.2 (0.8, 7.3)	18 (11, 35)	11 (3, 31)
West Midlands SHA	218 (15.6) [1,401]	321 (22.9) [1,401]	3.1 (1.7, 6.9)	2.6 (0.8, 9.7)	19 (11, 38)	11 (4, 22)
Yorkshire and the Humber SHA	240 (18.2) [1,316]	363 (27.6) [1,316]	2.8 (1.4, 6.6)	2.5 (0.8, 7.2)	22 (11, 44)	10 (3, 22)
Total	2,413 (14.7) [16,448]	3,823 (23.2) [16,448]	2.7 (1.3, 5.7)	2.5 (0.8, 7.5)	19 (11, 37)	11 (4, 24)

6.4 Discussion

We report successful merging of SICSAG and CMP datasets in order to produce a single UK dataset of critically ill adults. The most challenging aspects of this was the recoding of categorical data and ensuring that the data used in the APACHE 2 model for severity of illness scoring was robust. This was necessary to compare acute hospital mortality across regions and allow adjustment for severity of illness, hence making the comparisons between groups meaningful. Results of summary statistics suggest that there is little regional variation in demographic data, i.e. age, sex and APACHE 2 scores. However regional variation does seem to exist in the proportion of patients admitted after emergency surgery, reason for admission and length of stay and this might suggest regional variations in how ICU beds are utilised and whether the availability of beds influences which patients to admit. Crude hospital mortality showed a wide regional variation in acute hospital mortality (more than 10%). This does not take account of differences in age, severity of illness, chronic health and admission diagnosis (i.e. casemix) or other potential sources of bias, which I shall address below.

The preliminary findings from this work are consistent with other published work, i.e. demonstrated geographic variation in outcome after surgery [1,11] however although variation has been demonstrated between nations before, these new data suggests variation within a single country. Differences in age, severity of illness, chronic health and admission diagnosis may account for this and the data presented in this chapter is unadjusted for these factors, although these are available to us.

Strengths of this analysis are that the data was drawn from two high quality audit projects, which are used for national benchmarking. Data are known to be robust and extensively checked and validated. [228] Senior analysts and clinical staff with a large amount of experience in handling and interpreting the data from both SICSAG and ICNARC were available to assist with the analyses. This is the first time merging of these to datasets has been attempted successfully.

However, there are potentially several sources of systematic error or bias in this analysis:

1. Selection Bias

This occurs when there is a systematic difference in those who are selected for a study and those who are not. Possible sources of selection bias are:

a) To ensure that postoperative patients were selected in this analysis, only patients admitted directly to ICU from theatre or recovery were included. In reality many patients are admitted to the ward, subsequently deteriorate and then are admitted to ICU [15] and in the recent EuSOS study 73% of all

those who died were not admitted to Critical Care at any point following surgery. [11]Such patients would be excluded from this analysis.

b) Patients admitted to HDU or other postoperative care facilities were not included in this analysis, as they do not routinely submit data to ICNARC or SICSAG. Moreover, in hospitals that send large numbers of patients to these facilities, patients admitted to ICU may be sicker or more complex.

c) In Scotland SICSAG has 100% coverage of ICUs but for the years studied in this analysis, ICNARC only received data 92% of UK ICUs. This means 8% of ICUs in England, Wales and Northern Ireland did not include patients in this study.

2. Measurement Bias

a) An important difference in recording the APACHE II common descriptor for "reason for admission" exists between the two datasets. SICSAG allows only one whereas CMP allows two to be entered, hence the appearance of some medical codes in the "reason for admission" in the CMP dataset. This may have a bearing on the subgroup analysis, as not all patients for example with "GI perforation" will be included in the group if another diagnosis e.g. "Aspiration" was entered as the primary reason for admission.

b) Minor differences in the collection of some physiological data between SICSAG and CMP may have led to measurement bias. However APACHE 2 scores appear consistent through regions including Scotland where this is most likely to be an issue. Table 5.3 summarises the variables where we were concerned about this issue.

c) There may be some residual "recoding bias", arising from recoding the SICSAG variables to match the CMP datafields. Variables where recoding was problematic are summarised in **Table 27**.

In addition, there are likely to be several sources of confounding i.e. factors associated with both the outcome of interest and the exposure, which are not measured and may be unequally distributed regionally. Deprivation is one obvious example of this. It was hoped at the outset of this study that quintiles of deprivation could be collected in the original analysis plan; however, these are only available for Scotland and not for the whole cohort. It is known that regional differences in deprivation occur throughout the UK, especially in Scotland. [236]

Other confounding may result from differences in complexity of surgery and skill of surgeon and other staff: this might be particularly the case in London, which hosts a high number of tertiary and quarternary services. Other unmeasured variations in practice might include quality of postoperative care, quality of ICU care, use of HDU

or post anaesthesia care units prior to ICU admission, hospital medical emergency teams or other differences in the delivery of care.

The first and most obvious explanation for the observed differences in acute hospital mortality is the effect of case mix and we could adjust for differences using the APACHE II model, which we have already calculated. A second potential reason to explain the observed variation would be differences in provision of ICU beds within the UK. Several commentators have postulated that this is a potential explanation for differences seen in international comparisons in ICU outcome [1,11,115,224] and again this hypothesis could be readily tested using data already collected and presented in Chapter 4. Adjusting for case mix and ICU bed provision would involve multilevel modelling (individual ICU nested in region) however there are validated techniques available which could assist us to make comparisons in acute hospital mortality in surgical patients admitted to ICU and these are discussed in the next chapter.

6.5 Conclusion

Combining of SICSAG and CMP datasets for ICU patients, including data for severity of illness scoring was possible and has been undertaken for the year 2009. Extraction of patients admitted directly from recovery or the operating theatre shows a similar regional profile for age, sex and APACHE II scoring. Preliminary analysis reveals differences in reason for admission, ICU length of stay and crude (unadjusted) acute hospital mortality. As with many epidemiological studies using data of this type there are several potential sources of bias and confounding. Construction of a multilevel model taking account of patient and regional level factors might allow comparisons of outcome in surgical patients admitted to ICU between regions in the UK.

Chapter 7: Geographical Variation in Outcome after High Risk Surgery in the UK

7.1 Introduction

Detailed information on surgical activity and ICU provision within geographical regions of the UK is presented in Chapter 4 and in the previous chapter I describe in some detail how a database of a large cohort of postoperative patients admitted to an intensive care following surgery was constructed.

I also report (without statistical testing) summary data on patient demographics (e.g. age, gender, prior CPR), reason for admission (e.g. nature of surgery, emergency vs. elective surgery), severity of illness scoring (constructed from detailed physiological data) and outcome (length of hospital and ICU admission, acute hospital morality).

The cohort was comprised of adult admissions following surgery to ICUs in the UK. Patients undergoing cardiac surgery, neurosurgery, transplant surgery and burns were excluded from this dataset for the reasons previously outlined. However the cohort remains composed of a large and heterogeneous group of postoperative patients including patients who had undergone surgery for a variety of indications, emergency and elective.

Preliminary descriptive statistics revealed that, although patient demographics appear reasonably consistent throughout the UK, large differences are evident in type and urgency of surgery admitted to ICU, length of stay and mortality. This finding was surprising and warrants further exploration. However there are several reasons why confounding may exist in our data.

In epidemiology, confounding occurs when another exposure exists within the study population and is unequally distributed between the groups. Examples of this are given in the previous section. In epidemiological studies confounding can be controlled for by matching, stratification or by adjustment. Residual confounding is said to exist if there is unmeasured confounding which cannot be controlled. Confounding could have a very important influence on outcome of this study. Case mix and severity of illness is an important cause of confounding in this patient group. Case mix is a term employed to encompass reason for ICU admission, age, co-morbidities, prior CPR and severity of illness. The outcomes reported in Chapter 5 are not adjusted for this, although much of the work described in this chapter is aimed at providing the data required to adjust for casemix in the cohort. In particular, calculation of the APACHE II score allows adjustment for severity of illness, an important confounder (i.e. were patients in one region sicker than in another, and hence the observed difference in outcome). Data on ICU bed provision and volume of surgery is available from Chapter 4 and this could also be used to account for observed differences in outcome.

Other unmeasured confounding could arise from: social class and deprivation (available in SICSAG data but not CMP data), ethnicity, effect of regional centres for certain types of surgery, geographical factors (e.g. large urban centres), local care pathways and local ICU admission policies.

Using the data gathered in the previous chapters I attempt to address the following research questions:

1. Does significant regional variation in acute hospital mortality exist in this cohort of patients?
2. Did variation exist within all patient groups?
3. If significant variation was demonstrated, could it be explained by case mix i.e. patient level risk factors: age, sex, surgical urgency, APACHE II Acute Physiology Score (APS), CPR within 24h prior to admission, reason for admission (APACHE II)?
4. If significant variation remained, could other associations explain it, for example: regional level provision of ICU beds or some measure of ICU bed utilisation.

To answer these questions and overcome some of the problems inherent in the data I developed the following analysis plan following detailed discussion with collaborators TW, RP, DH and SP.

7.2 Methods

Ethical Considerations

The proposed study protocol was reviewed by the Chairs of South East Scotland Research Ethics Committees 01 and 02 (as outlined earlier) and the need for a full ethics submission was not deemed necessary. In addition the SICSAG steering group formally approved the study.

Study Cohort

The methodology for constructing the study cohort including inclusion and exclusion criteria has been described previously.

Subgroup Analysis

Subgroup analysis would allow examination of variation in outcome in patients admitted with broadly similar types of surgery. Subgroups chosen for this were those which could be grouped together easily from their APACHE II reason for admission as outlined in Chapter 5: patients undergoing emergency GI surgery for perforation, obstruction or bleeding; patients undergoing elective surgery for GI neoplasm; patients undergoing surgery for trauma. Another obvious group, "patients

undergoing vascular surgery", was rejected for two reasons. Firstly, vascular surgery has become very regionalised over the last decade. Secondly increasing use of endovascular and radiological techniques has improved outcome after surgery but these techniques are still evolving and not used ubiquitously throughout the UK. [237]

A fourth subgroup was chosen: patients who were admitted to ICU for longer than 48h. This was chosen because it was postulated that it might contain a more homogenous group of ICU patients and exclude patients who were admitted for a short period to facilitate extubation postoperatively and also patients who were moribund at the time of admission.

Generation of Funnel Plots

Funnel plots have several uses in epidemiology and involve plotting event rates against number of cases or observations, with the addition of confidence limits. Funnel plots have been used in meta-analysis (see Chapter 3) to test for publication bias. They have been used for comparative audit purposes for example to compare differences in acute hospital mortality between hospitals and geographical regions. They have also been used to compare mortality rates following surgery [238] and compare standardised mortality rates (SMR) between ICUs. [239] When used in this context these plots graph an observation (in the case of this study, acute hospital mortality) and its confidence limits against the background population. As the background population becomes larger, the confidence limits narrow, making a funnel shape. Funnel plots typically have lines displaying 2 and 3 Standard Deviations (SD) i.e. 95 and 99.7% confidence intervals (CI). When 13 regions are compared there is a possibility that one might lie outside 2SD (5%; 1 in 20) by chance, so these regions could be considered as "possibly different". If regions lie outside 3 SD there is high probability that these regions "are different" (CI 99.7%). [240,241] Examining the data using funnel plots would enable one to account for statistical confidence based on size of cohort and hence determine if these differences were truly significant.

In this analysis, funnel plots were constructed by plotting acute hospital mortality against number of cases for the full cohort and for pre-defined subgroups. 95% and 99.7% confidence intervals were added. Individual regions were not identified.

Multilevel Logistic Regression Analysis

Multilevel modelling allows quantification of the effect of region on acute hospital mortality after correction patient case mix and ICU bed provision.

Logistic regression examines the effect of a single exposure variable on a binary outcome of interest and predicts the probability (P) that an individual will be

classified into the outcome of interest, in this case hospital mortality. The logit of this probability is the natural logarithm of the "odds" of this outcome.

$$\text{log it } (p) = \text{In } p/1\text{-}p$$

However because the patients in this study are clustered both at ICU and geographical region level it is necessary to account for this using a multilevel (random effects) model. [242] This type of model considers that individual probability is also dependent on the ICU and region of treatment. This is used to reduce the possibility of residual confounding at regional and ICU level.

In this analysis, the variance between geographical regions is the outcome of interest i.e. is there significant variation in hospital mortality between the regions studied. In the null (or empty) model (i), the probability of dying in hospital is the only function of geographical region of residence. In subsequent models the effect of patient level factors is introduced to reduce the observed variance between regions. In the second model (ii) the probability of dying in hospital is a function of area of residence and patient level factors i.e. case mix, sex, age, surgical urgency, APACHE II Acute Physiology Score (APS), CPR within 24h prior to admission, reason for admission (based on APACHE II). Finally in model (iii) (the full model) the probability of dying in hospital is the function of region of treatment, case mix factors and ICU bed provision. At each stage it is possible to observe if the variance between regions can be explained by casemix factors or provision factors. If significant variance remains after adjustment for potential confounders then region of treatment is likely to remain an important factor in outcome.

There are several methods, which can be used to describe variance in clustered data and the "median odds ratio" (MOR) was chosen for this analysis. MOR converts the variance to an "odds ratio" scale, which is more intuitively understood and uses the expression:

$$\text{MOR} = \exp\{\sqrt{(2 \times V_A)} \times 0.6745\} \approx \exp(0.95\sqrt{V_A})$$ [243]

Hence MOR is a function of the cluster variance and can be conceptualised as two individuals with the same covariates chosen from two random clusters. The MOR is the median odds ration between the individual in the area of the lowest risk and the area of highest risk. If the MOR is 1 there is no variation between clusters. If there is considerable between-cluster variation the MOR will be large. [244]

In this analysis, firstly a null model was fitted and adjusted for the random effects of clustering by geographical region and by ICU. The following patient-level covariates were then included: age; gender; CPR within 24 hours prior to admission; surgical urgency; and APACHE II Acute Physiology Score, APAHE II diagnostic category. Finally ICU bed provision was added to the model at the regional level.

As a sensitivity analysis, the above was then repeated using proportion of surgical patients admitted to ICU as a proportion of overall surgical activity, to give a crude estimate of ICU bed utilisation.

To ensure adequate statistical power, MOR was calculated for the full cohort and for the ICU length of stay greater than 48 hours only.

Data Analysis

The above statistical analysis plan was agreed *a priori*, including subgroup analysis. Geographical region was defined as SHA or devolved nation. Analyses were performed using STATA SE 10.1 (StataCorp, TX, USA).

The final analysis plan was approved by both ICNARC and SICSAG. For reasons outlined earlier, analyses were undertaken on the premises of ICNARC in Holborn, London, either by or under the direct supervision of ICNARC analysts. Comparison of outcome between region and devolved nation is potentially sensitive. For this reason it was agreed by ICNARC and SICSAG that regions would not be identified in this analysis. Two teleconferences were organised to allow discussion of the results with representatives from both SICSAG and ICNARC.

7.3 Results

Data from 16,147 surgical ICU admissions (1,708 SICSAG, 14,439 ICNARC) from 207 ICUs (23 Scotland, 184 England, Wales and Northern Ireland) was analysed. Patients were grouped according to country or SHA and numbers of admissions by region plotted against acute hospital mortality. This was done for the full cohort and for subgroups (Figure 16, 17). Funnel plots show evidence of significant variation in outcome in both the full cohort where 5 regions fall out of 3 standard deviations and where length of stay was more than 48 hours, where 4 regions fall out of 3 standard deviations. In the other subgroups with the exception of the "Trauma" subgroup where the sample is much smaller, the variation is less marked but still present (Figure 17). The multilevel logistic regression analysis was undertaken for the whole cohort and for admissions to ICU of duration greater than or equal to 48 hours. Results of the logistic regression model for the full cohort and for pre-defined subgroups are presented in (Tables 33-37). The confidence intervals for the effect of geographical region of treatment are very wide in all the subgroups except for patients admitted for greater than 48 hours. This is likely to be due to the reduced power of these subgroups to demonstrate an effect. Hence median odds ratio for geographical region of treatment was only calculated for the full cohort and for the subgroup of patients admitted for less than 48h.

The MOR of regional variation for the full cohort was 1.42 (95% CI 1.29-1.62). This decreased when the model was adjusted for case mix (MOR: 1.35; 95% CI: 1.22,

1.58) and slightly further decreased when ICU bed provision was also included in the model (MOR: 1.33; 95% CI: 1.20, 1.58), although the effect of ICU bed provision was not statistically significant (OR: 1.04 per 1 additional ICU bed per 100,000 adults; 95% CI: 0.97, 1.11; p=0.25). When repeated for the subgroup of patients admitted for greater than or equal to 48 hours, the MOR of regional variation for the full cohort was 1.38 (95% CI 1.25-1.60) and similarly decreased when the model was adjusted for case-mix (MOR: 1.30 95% CI 1.15-1.61) and ICU bed provision (MOR: 1.28 95% CI 1.13-1.63). (Figure 18)

The model was repeated for the full cohort using surgical ICU admissions per 100,000 surgical procedures, this explained much more of the variation seen within regions (MOR: 1.19; 95% CI 1.02, 5.99; OR: 49.91 per 50 additional surgical ICU admission per 100,000 surgical procedures; 95% CI: 49.84, 49.97; p=0.01).

Figure 16 Funnel plot of unadjusted acute hospital mortality by region: whole cohort

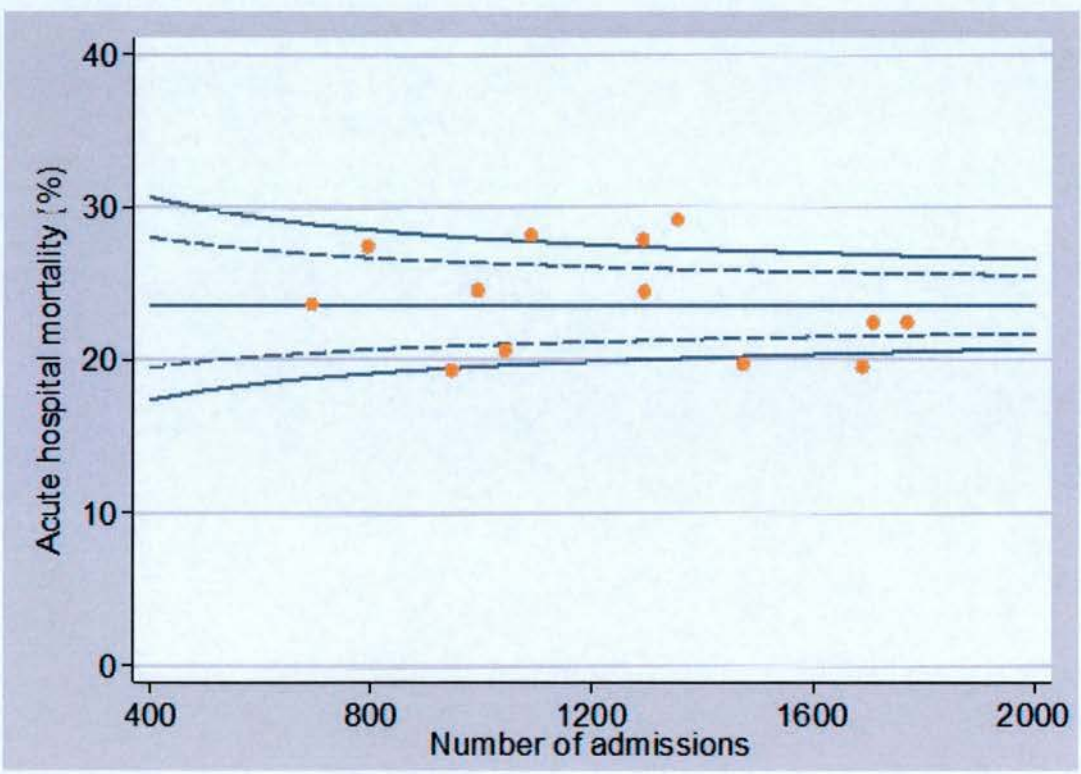
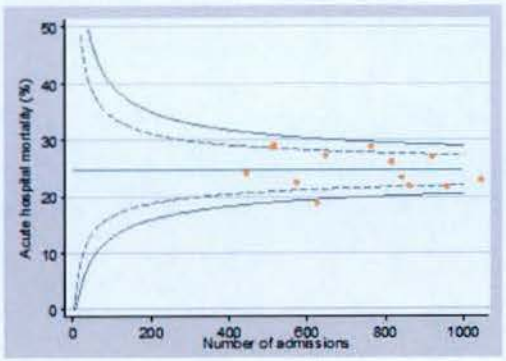
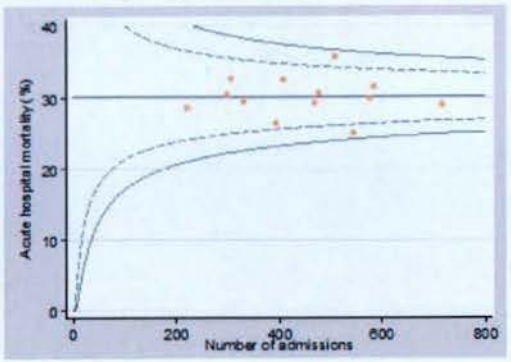


Figure 17 Funnel plot of unadjusted acute hospital mortality for subgroups

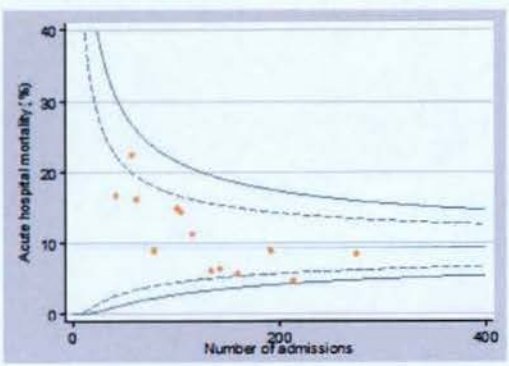
a. Admission greater than or equal to 48h.



b. Emergency GI surgery admissions.



c. Elective GI surgery admissions.



d. Admissions with trauma.

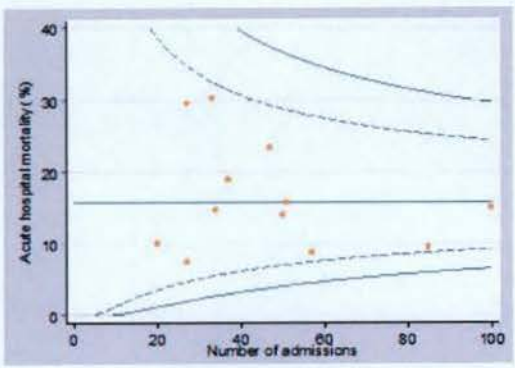


Table 33 Logistic regression model for full cohort (n=16124).

Variable	**OR (95% CI)**	**p-value**
Age	1.04 (1.04, 1.05)	<0.01
Gender	0.89 (0.82, 0.97)	<0.01
Admission type		
Elective surgical	0.42 (0.38, 0.47)	<0.01
Emergency surgical*	1.00	-
APACHE II APS	1.15 (1.14, 1.16)	<0.01
Prior CPR	2.4 (1.91, 3.01)	<0.01
Surgery for Abdominal Neoplasm	0.76 (0.66, 0.88)	<0.01
Major Vascular Surgery	0.96 (0.85, 1.08)	0.48
Cardiovascular Disease	0.92 (0.76, 1.12)	0.41
Respiratory Disease	0.52 (0.40, 0.69)	<0.01
Pre-Existing Renal Disease	0.51 (0.39, 0.67)	<0.01
Orthopaedics and Trauma	0.6 (0.46, 0.78)	<0.01
Neurological Problem	1.2 (1.01, 1.61)	<0.01
Other	0.67 (0.50, 0.91)	<0.01
Sepsis	1.57 (1.21, 2.03)	<0.01
Missing	0.78 (0.52, 1.17)	0.24
ICU Bed Provision[§]	1.03 (0.97, 1.11)	0.25
Critical Care Utilisation	0.998 (0.996, 0.999)	<0.01

OR: Odds ratio; CI: Confidence Interval APS: Acute Physiology Score * reference category.

[§] ICU beds per 100 000 population

Table 34 Logistic regression model for admissions > 48h (n=9515)

Variable	OR (95% CI)	p-value
Age	1.04 (1.03, 1.04)	<0.01
Gender	0.88 (0.79, 0.97)	0.01
Admission type		<0.01
Elective surgical	0.58 (0.51, 0.67)	-
Emergency surgical*	1.00	
APACHE II APS	1.09 (1.08, 1.10)	<0.01
Prior CPR	2.02 (1.49, 2.73)	<0.01
Surgery for Abdominal Neoplasm	0.85 (0.71, 1.02)	0.08
Major Vascular Surgery	0.94 (0.81, 1.10)	0.45
Cardiovascular Disease	0.82 (0.63, 1.05)	0.12
Respiratory Disease	0.51 (0.37, 0.71)	<0.01
Pre-Existing Renal Disease	0.79 (0.56, 1.08)	0.15
Orthopaedics and Trauma	0.6 (0.43, 0.84)	<0.01
Neurological Problem	1.7 (1.33, 2.30)	<0.01
Other	0.86 (0.59, 1.24)	0.43
Sepsis	1.49 (1.10, 2.02)	0.01
Missing	0.97 (0.57, 1.61)	0.89
ICU Bed Provision[§]	1.03 (0.98, 1.09)	0.25

OR: Odds ratio; CI: Confidence Interval APS: Acute Physiology Score

* reference category. [§] ICU beds per 100 000 population

Table 35 Logistic regression model emergency GI surgery admissions (n=5838).

Variable	OR (95% CI)	p-value
Age	1.04 (1.04,1.05)	<0.01
Gender	0.92 (0.82, 0.97)	0.21
APACHE II APS	1.16 (1.14, 1.16)	<0.01
Prior CPR	2.9 (1.91, 3.01)	<0.01
ICU Bed Provision[§]	1.04 (0.97, 1.11)	0.31

OR: Odds ratio; CI: Confidence Interval APS: Acute Physiology Score

[§] ICU beds per 100 000 population

Table 36 Logistic regression model: surgery for abdominal neoplasm admissions (n=1631).

Variable	OR (95% CI)	p-value
Age	1.04 (1.02, 1.06)	<0.01
Gender	1.06 (0.73, 1.53)	0.75
APACHE II APS	1.11 (1.07, 1.16)	<0.01
Prior CPR	3.79 (1.17, 12.2)	0.026
ICU Bed Provision[§]	0.95 (0.80, 1.13)	0.57

OR: Odds ratio; CI: Confidence Interval APS: Acute Physiology Score

[§] ICU beds per 100 000 population

Table 37 Logistic regression model: surgery for trauma admissions (n=604).

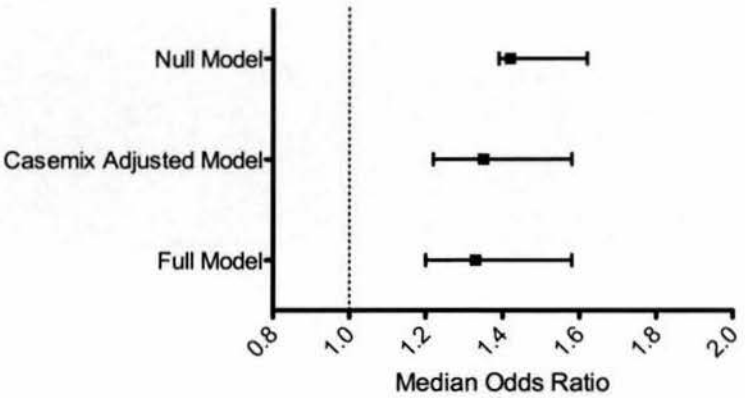
Variable	OR (95% CI)	p-value
Age	1.05 (1.03, 1.06)	<0.01
Gender	1.19 (0.68, 2.06)	0.55
APACHE II APS	1.19 (1.13-1.25)	<0.01
Prior CPR	5.9 (2,49, 14.17)	<0.01
ICU Bed Provision[§]	1.09 (0.89, 1.33)	0.41

OR: Odds ratio; CI: Confidence Interval APS: Acute Physiology Score

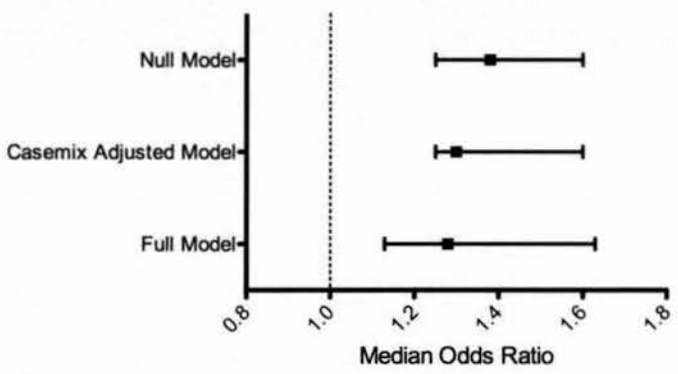
reference category. [§] ICU beds per 100 000 population

Figure 18 Median odds ratio for each model: Null Model, Casemix Adjusted Model, Model Adjusted for Critical Care Provision

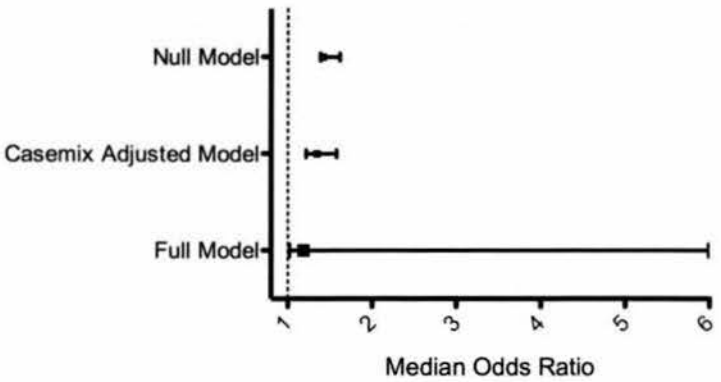
a) Full Cohort: ICU Beds per 100 000 Population



b) Admissions greater than 48 hours: ICU beds per 100 000 population



c) Full Cohort: Surgical ICU Admissions per 100 000 Surgical Procedures



7.4 Discussion

The principal finding of this analysis is that in the UK there is significant regional variation in acute hospital mortality for patients receiving level 3 care in an ICU following surgery. This variation persists after adjustment for casemix and regional intensive care bed provision. This finding was also observed in predefined subgroups. This analysis demonstrated regional variations in practice which may partly explain these findings: the proportion of elective vs. emergency surgery admitted to ICU (although this is controlled for in the casemix adjusted model); the nature of surgical procedures undertaken in patients admitted to ICU and length of stay of surgical patients in ICU. These factors may signal variations in practice which may be difficult to fully elucidate in a study such as this or may simply reflect unmeasured confounding.

Despite similar per capita healthcare spend and organisational practices, the differences in variation in volume of surgery undertaken and critical care bed provision within the UK demonstrated in our study were striking. However variation in outcome after surgery within the NHS has been demonstrated previously. Saunders *et al* examined outcome after emergency laparotomy in 35 NHS Trusts in the UK. In this study, mortality varied between 3.6 and 41.7% and in between 0 and 69% of cases postoperative care was delivered on a normal ward. [8] This variation also appears to extend to elective surgery; Aylin *et al* showed a "weekday effect" of variation in outcome following four out of five higher risk elective surgical procedures. [162] In this study, odds of death were 44% and 82% higher if the procedure was carried out on a Friday or weekend respectively. The authors suggest that organisational and staffing factors within hospitals may be implicated. Another recently published study suggested "high mortality outlier" hospitals for emergency surgery have several differences in the delivery of perioperative care when compared to "low mortality outliers". One such observed difference was significantly reduced provision of ICU beds although this finding did not appear to extend to HDU bed provision. [17]

The finding in our study that absolute provision of critical care beds did not appear to explain the observed regional variation in surgical patients admitted to ICU outcomes is at odds with the opinion of many commentators who suggest that absence of this is a major factor in the poor outcomes observed after high risk surgery in the UK. In reality the answer to this question is likely to be much more complex and be more influenced by how these resources are used. Utilisation of critical care resources may be more important, as demonstrated in this analysis by the observation that surgical ICU admissions as a proportion of overall volume of surgery (a crude measure of utilisation) seemed to better explain the variation within this model.

The EuSOS study, which also reported variation in outcome following surgery among European nations, suggested that patient co-morbidities and surgical factors have the highest effect on mortality. Several nations included in this study with higher per capita provision of critical care beds than the UK had worse surgical outcomes and vice versa. [11] Organisational factors such as "post anaesthesia care units", where interventions and monitoring traditionally delivered by critical care are provided in the recovery room for the first 24 hours following surgery or protocolised care pathways in the ward setting with enhanced monitoring and input from specialised teams may also explain this phenomenon.

Strengths of this analysis are that a large, high quality dataset with good coverage of all regions in the UK, low incidence of missing outcome data was utilised [228] and robust, well described methodology applied. [243]

Potential sources of bias and confounding remain. Many of the potential systematic causes of bias in this data have been addressed extensively in previous chapters. The most important of these remains that only surgical admissions directly to the ICU and from theatre or recovery were considered in this analysis, as it was not possible to accurately identify surgical patients admitted to the ward first and then to ICU. Several studies have shown that the worst outcome among surgical patients is from those admitted from the ward. [15,114] Moreover in the EuSOS study 73% of all deaths were never admitted to ICU at any time after surgery. [11] Patients requiring level 2 care were also not included in this analysis due to concerns about consistency and availability of severity of illness scoring in this group and hence the ability to adjust for patient level factors in the model. Increasing use of High Dependency Units, "Post Anaesthesia Care Units" or extended recovery periods, where patients are able to stay for the first postoperative night and have interventions typically delivered in an ICU setting in the recovery area may also have confounded these findings as these patients may have historically been admitted to the ICU.

Confounding may also exist in regions with higher rates of admission of patients to ICU. In these areas less unwell patients may be admitted routinely for postoperative care and this may not be completely adjusted for in the APACHE II model. Other confounding factors could include the regional effects of deprivation, ethnicity and differences in complexity of surgery and skill of surgical and other staff: this might be particularly the case in London, which hosts a high number of tertiary and quaternary services.

Evidence of geographical variation in mortality after high risk surgery within a very uniform healthcare system such as the NHS suggests some deaths may be preventable. The variation observed in this analysis does not seem to be associated with ICU bed provision per se but points towards patient selection and resource utilisation as being important factors in explaining this phenomenon. Better data

linkage and complete coverage of all healthcare providers in England and Wales would allow more sophisticated models to be developed which could examine all surgical admissions.

7.5 Conclusion

Significant regional variation in acute hospital mortality for patients admitted to ICU following surgery, not explained by casemix or intensive care bed provision is reported. Variation in admission practices, nature of surgery and length of stay were also observed. ICU resource utilisation as expressed by surgical ICU admissions per 100 00 procedures seemed to better explain this phenomenon.

Chapter 8: Does Goal Directed Haemodynamic Therapy Prevent Perioperative Cardiac Injury?

8.1 Introduction

As described in previous chapters an estimated 200 million surgical procedures are carried out worldwide each year and 1 million patients die within 30 days of surgery. [2] Historical data has estimated the incidence of myocardial infarction after general surgery as 0.7% in patients over 50 years of age, rising to 3.1% following vascular surgery. [174] However observational studies, for example those undertaken by Khuri *et al* using NSQIP data [4,44] have suggested that cardiac complications, in particular myocardial infarction although rare are more prevalent in the high risk group associated with high perioperative mortality. [4]

Definitions of myocardial infarction were recently revised [245] and are classified as follows:

Type 1: Spontaneous myocardial infarction

Type 2: Myocardial infarction secondary to an ischemic imbalance

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)

Type 4b: Myocardial infarction related to stent thrombosis

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)

Cardiac troponins have had an established role in the diagnosis of myocardial infarction and prediction of short and long-term outcomes in patients with ischaemic heart disease for many years. [80-82,88,246-248] Cardiac troponins are not expressed in skeletal muscular and are not detectable in the serum of healthy individuals. The prognostic significance is greatest if measured at least six hours after the onset of symptoms and serum troponin remains elevated for 7-10 days following a cardiac event. Conventionally a serum troponin level of greater than the 99th percentile value of the general population has been considered clinically significant and these earlier studies demonstrated that peak values of troponin correlate strongly with outcome. [246]

Increasingly sensitive 4th and 5th generation Troponin assays have been developed which can improve the early detection of myocardial necrosis. [86,87] The "Prevention of Events using Angiotensin Converting Enzyme Inhibition" (PEACE) Study

investigators measured serum troponin T using a highly sensitive, 5th Generation assay (Roche Diagnostics) in 3679 patients. 11% of asymptomatic patients with ischaemic heart disease had a serum 5th Generation Troponin T (TnT) value that exceeded the 99th percentile (≥14 ng/L) and this was strongly predictive of cardiovascular death or cardiac failure. [249] A more recent study conducted by Mills *et al* using a 5th generation assay (Abbot, IL, USA) increased the detection of myocardial infarction by 29% and predicted the patients with the greatest risk of recurrent infarction and death, although the same association with peak serum troponin concentration and adverse outcome was not observed. [88]

Serum troponin has also been used to predict outcome following surgery [83,84] and a systematic review of fourteen studies (n=3318) by Levy *et al* found increased elevated serum troponin following surgery was an independent predictor of mortality (OR 3.4, CI 2.2-5.2) although this study included various manufacturers and generations of troponin assay. [85] The more recent "Vascular Events in Non Cardiac Surgery Patients Cohort Evaluation" (VISION) Study evaluated major cardiac complications in 15 133 patients over the age of 45 undergoing major non-cardiac surgery. In this study, there was a high prevalence of cardiac risk factors in the study cohort. After adjustment for cardiovascular and respiratory risk factors and also for various operative factors logistic regression analysis suggested that elevated 4th generation Troponin I assay in the first 72 hours postoperatively was associated with mortality. [90]

"Goal Directed Haemodynamic Therapy" seeks to improve outcome by augmenting cardiac output, optimising fluid status and hence increasing oxygen delivery to the tissues. Although GDHT has been evaluated in many clinical trials, clear evidence for widespread implementation is lacking. GDHT may reduce postoperative complications, especially infectious complications, [139] however concerns remain that the pre-emptive use of inotropic therapy in the absence of traditional indications for such treatment may lead to an increased incidence of myocardial ischaemia and infarction. The incidence of ischaemic heart disease in patients undergoing major surgery is high [174] and use of pharmacological agents which increase myocardial work at a time of increased physiological stress (e.g. beta-adrenergic drugs) may result in an imbalance of myocardial oxygen supply and demand. [173] Beta adrenergic drugs, in particular dopexamine, may also provoke tachyarrhythmia and hypotension. [141] The absence of data adequately describing the myocardial effects of GDHT is an important obstacle to the wider use of this potentially beneficial treatment, and increase in Type 2 MI is the primary concern. Two small studies have examined troponin release following goal directed haemodynamic therapy (GDHT) in the perioperative setting. Pearse et al examined Troponin release over the first two postoperative days using a 3rd generation assay in 122 patients randomised to receive either GDHT (including administration of dopexamine) or usual care. In this study

he found no significant difference in Troponin release between groups. [140] Lee et al reported similar findings in 135 patients randomised to a GDHT algorithm (again involving dopexamine administration). In this study troponin was measured using three different 5th generation highly sensitive assays. [250]

The Optimisation of Peri-operative Cardiovascular Management to Improve Surgical Outcome (OPTIMISE) Trial (described in detail in chapter 2) included a biomarker sub study in participating sites. Trial participants who had agreed to take part in the biomarker sub study had samples of blood and urine taken at induction of anaesthesia and at 24 and 72 hours postoperatively.

The biomarker study was led from Edinburgh with support and advice from the Centre for Cardiovascular research at the University of Edinburgh. It included a planned analysis of troponin release in the perioperative period in both GDHT and usual care groups. The following research questions were considered:

1. Is GDHT associated with increased in myocardial injury as measured by the ARCHITECT *STAT* (Abbot, IL, USA) 5th generation highly-sensitive troponin I (HST) assay?

2. Can serum HST accurately predict death, MI or MACE at 7 or 30 days following surgery or death at 180 days following surgery?

8.2 Methods

Four Hospitals took part in the biomarker sub-study: The Royal Infirmary of Edinburgh, The Royal London Hospital, Southampton University Hospitals NHS Trust and University College London Hospital. Samples were transported to the Queen's Medical Research Institute in Edinburgh at the end of the trial. The sample analysis was carried out in the biochemistry department at the Royal Infirmary of Edinburgh using reagents provided free of charge by Abbot (Abbot, IL, USA). Clinical data for each biomarker study patient was obtained from the main OPTIMISE trial dataset.

Ethics, Sponsorship and Indemnity

The OPTIMISE trial underwent an independent Ethics Committee review in the UK and an interim analysis by a data monitoring and ethics committee in December 2011. Sample collection and analysis for the biomarker sub-studies were included as part of this application. Consent for trial participants to permit collection blood and urine samples at 0, 24 and 72 hours were taken at the time of recruitment to the main trial.

Queen Mary's University, London was the OPTIMISE Trial Sponsor. University of Edinburgh was the lead site for the OPTIMISE biomarker analysis.

Study Population

Entry criteria for the OPTIMISE trial have been described in more detail in chapter 2, but in brief were high-risk patients undergoing major abdominal surgery involving the gastrointestinal tract, expected to take longer than 90 minutes. High risk patients were defined as those aged 65 years and over or those aged 50-64 years with one or more of: non-elective surgery, acute or chronic renal impairment, diabetes mellitus or presence of a risk factor for cardiac or respiratory disease. Patients were then randomised to receive either Goal Directed Haemodynamic Therapy (GDHT) or Usual Care (UC). Patients receiving GDHT had non-invasive cardiac output monitoring and SV optimisation using the LiDCOrapid monitor and dopexamine at a dose of 0.5 mcg/kg/min for the duration of surgery and for 6 hours after. A full description of the clinical management for patients in the intervention and usual care arms can be found in Chapter 2. Participants were centrally allocated to treatment groups using a computer generated dynamic procedure (minimisation) with a random component. Participants were allocated with an 80% probability to the group that minimised between group differences in trial site, urgency of surgery and surgical procedure category among all participants recruited to the study to that date. This is applicable to patients recruited into the biomarker substudy.

Data Collection

We were permitted access to the full OPTIMISE dataset for patients enrolled in the OPTIMISE biomarker sub-study. Demographic data was extracted on: age, sex, American Association of Anaesthetists Physical Status (ASA-PS), nature and urgency of surgery, anaesthetic technique and baseline risk factors for patients in both intervention and control groups and comparison made between intervention and control groups to ensure there were no significant differences.

Outcome data was collected on: clinical diagnosis of myocardial ischaemia or infarction, major adverse cardiac events (MACE), death at 30 and 180 days.

Definitions

Myocardial Infarction: Definition was that used in Appendix 1 of the OPTIMISE Protocol i.e. ECG changes suggestive of myocardial ischemia or infarction with appropriate clinical findings and a rise or fall in cardiac troponin concentration with at least one value above the 99th percentile.

Major Adverse Cardiac Events: New diagnosis of arrhythmia, cardiogenic pulmonary oedema, myocardial infarction or cardiorespiratory arrest as defined in Appendix 1 of the OPTIMISE Protocol.

Sampling Procedure and Analysis

Participants had paired blood and urine samples collected at hour 0 (randomisation), hour 24 and hour 72. Blood samples were drawn from arterial or central venous catheter or by venepuncture. Samples were inverted five times and left for thirty minutes before centrifugation at 3000 rpm for ten minutes. The serum for each patient time point was separated into three Eppendorfs and stored at -80°C.

Prototype 5th generation Troponin I assay (Abbott Diagnostics) was carried out on the ARCHITECT STAT platform. This is a two-step assay that offers increased precision for measuring very low plasma troponin concentrations and can quantify troponin concentrations in 98% of healthy persons with a limit of detection of 1 ng/L and 10% co-efficient of variation <5.5 ng/L. Using this assay the mean population (±SD) concentration of a healthy reference population is 1.6±3.1 ng/L with the 99th percentile of 26 ng/L for the whole population, 16 ng/L for females and 34ng/l for males.

Statistical Analysis

Data was analysed using STATA v12 (Statcorp, TX, USA) and Prism v5.0 (GraphPad Software Inc, CA, USA). Data are presented as mean [SD] where normally distributed and median [IQR] where not normally distributed. Categorical variables were analysed using the Chi-Squared Test or Fishers Exact Test and continuous data using a 2-sided t-test or ANOVA where appropriate. Significance was set at $p<0.05$. To adjust for skewing and outliers, serum Troponin was transformed to natural logarithms, which resulted in a more normal distribution. Log Troponin for each time point and peak value between groups were then compared using 2-sided t-test.

8.3 Results

Of 734 patients recruited into the OPTIMISE trial, 288 were entered into the biomarker sub study; 145 in the GDHT group and 143 in the usual care group. Demographic and outcome data for each group are summarised in Table 38 and Table 39.

Patients were randomised to intervention or usual care at time of entry to the OPTIMISE trial. In the biomarker sub study cohort there was a greater percentage of patients aged over 65 years in the usual care group (87.4% vs 79.3%) although mean age was similar between groups (69.8±8.1 vs 71.6±7.5). There was also a greater

proportion of ASA 3 and 4 patients in the usual care group compared with the intervention group (52.4% vs. 34.5%)

There was no significant difference in serum troponin at baseline, 24 hours, 72 hours or peak value (Table 39, Figure 19). Troponin release following surgery was estimated by calculating the area under the curve for serum troponin for each patient at each time point and then comparison was made between groups. There was no significant difference in Troponin release in patients receiving GDHT compared with usual care as estimated by this method (Figure 20).

Logistic regression showed that, after adjustment for age and sex, the preoperative 5th generation Troponin I assay (i.e. at time point 0) did not predict MI or major adverse cardiac events within 30 days of death at 30 or 180 days. Peak serum troponin did predict MI within 30 days (OR 1.5; CI 1.14-2.11 p=0.005) but did not predict death at 30 or 180 days in this population (Table 40).

Table 38 Baseline patient characteristics.

	Biomarker Cohort		Full Cohort	
	Haemodynamic intervention (n=145)	**Usual care (n=143)**	**Haemodynamic intervention (n=368)**	**Usual care (n=365)**
Age(years) (mean, SD)	69.8 (8.1)	71.6 (7.5)	71·0 (8·4)	72·0 (8·6)
Age				
50-64 year (%)	30 (20.7)	18 (12.6)	70 (19·0)	59 (16·2)
≥ 65 years (%)	115 (79.3)	125(87.4)	298 (81·0)	306 (83·8)
Sex				
Male (n,%)	90 (62.1)	93 (65)	237 (64·4)	229 (62·7)
Female (n,%)	55 (37.9)	50 (35)	131 (35·6)	136 (37·3)
Urgency of surgery				
Elective (n,%)	138 (95.2)	137 (95.8)	356 (96·7)	352 (96·4)
Emergency (n,%)	7 (4.8)	6 (4.2)	12 (3·3)	13 (3·6)
Baseline risk factors‡				
Renal impairment (n,%)	8 (5.5)	4 (2.8)	26 (7·1)	12 (3·3)
Diabetes mellitus (n,%)	23 (15.9)	25 (17.5)	57 (15·5)	65 (17·8)
Risk factors for cardiac or respiratory disease (n,%)	45 (31)	54 (37.8)	117 (31·8)	118 (32·3)
Planned surgical procedure†				
Upper gastrointestinal (n,%)	53 (36.6)	114 (31·2)	110 (29·9)	114 (31·2)
Lower gastrointestinal (n,%)	36 (24.8)	163 (44·7)	167 (45·4)	163 (44·7)
Small bowel +/- pancreas (n,%)	53(36.6)	84 (23·0)	86 (23·4)	84 (23·0)
Urological or gynaecological surgery involving gut (n,%)	3(2.1)	4 (1·1)	5 (1·4)	4 (1·1)
ASA grade				
1 (n,%)	8 (5.5)	5 (3.5)	21 (5·7)	24 (6·6)
2 (n,%)	87 (60)	63 (44.1)	200 (54·5)	174 (48·1)
3 (n,%)	49 (33.8)	72 (50.3)	143 (39·0)	155 (42·8)
4 (n,%)	1 (0.7)	3 (2.1)	3 (0·8)	9 (2·5)

‡Patients may have had more than one risk factor.

Table 39 Data describing clinical outcomes and serum Troponin I following surgery.

	Haemodynamic intervention (n=145)	Usual care (n=143)	p
Myocardial Infarction within 30 Days (n,%)	5 (3.4)	6 (4.2)	0.74
Major Adverse Cardiac Event Within 30 Days (n,%)	24 (16.6)	32 (22.4)	0.21
Death Within 30 Days (n,%)	5 (3.4)	5 (3.5)	0.98
Death Within 180 Days (n,%)	16 (11.0)	21 (14.7)	0.36
Troponin I above 99th Centile (n,%)	67 (46.2)	68 (47.6)	0.82
Troponin Time 0 (ngL^{-1}) (median, IQR)	4.25 (2.75-7.7)	4.3 (2.9-7.4)	0.78
Troponin Time 24 Hours (ngL^{-1}) (median, IQR)	9.3 (5.1-17.0)	6.9 (4.3-17.8)	0.71
Troponin Time 72 Hours (ngL^{-1}) (median, IQR)	6.35 (4.1-15.85)	6.7 (4.0-13.1)	0.57
Maximum Troponin (ngL^{-1}) (median, IQR)	10 (5.3-21.5)	7.8 (5-21.8)	0.85
Troponin Area Under Curve (Mean, SEM)	(3.87, 0.21)	(3.67, 0.22)	0.5

Table 40 Logistic regression model of preoperative and maximum troponin within 72 hours for major clinical outcomes.

	Preoperative Troponin	Maximum Troponin
Myocardial Infarction (OR, 95% CI)	1.12 (0.53-2.4)	1.5 (1.14-2.11)*
Major Adverse Cardiac Event (OR, 95% CI)	0.73 (0.52-1.04)	1.13 (0.95-1.37)
Death Within 30 Days (OR, 95% CI)	1.4 (0.67-2.9)	1.23 (0.84-1.79)
Death Within 180 Days (OR, 95% CI)	1.01 (0.64-1.6)	1.02 (0.79-1.32)

*$p<0.05$

Figure 19 Log serum Troponin I for GDHT and UC groups at each timepoint.

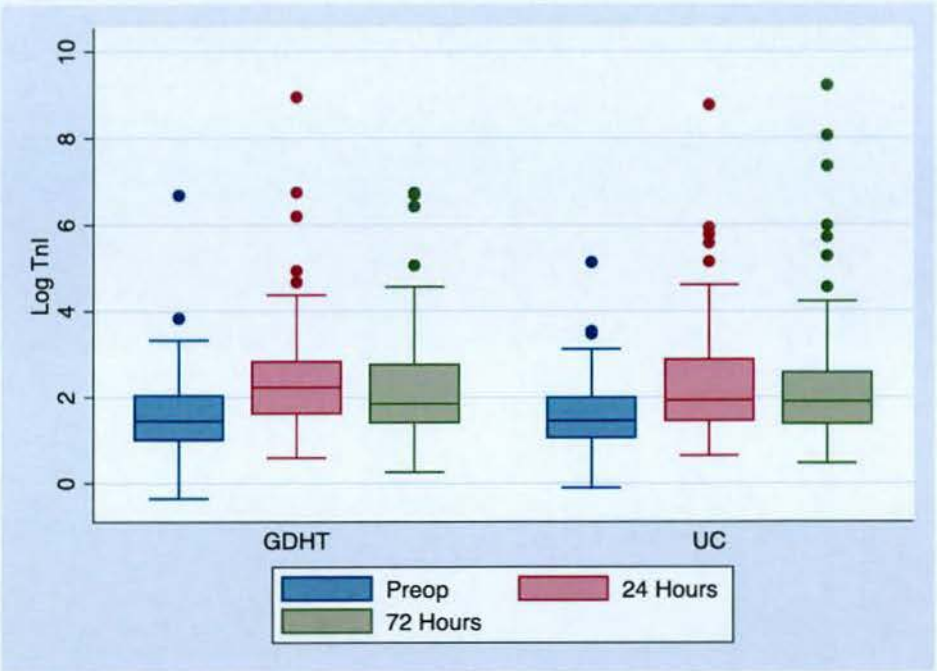
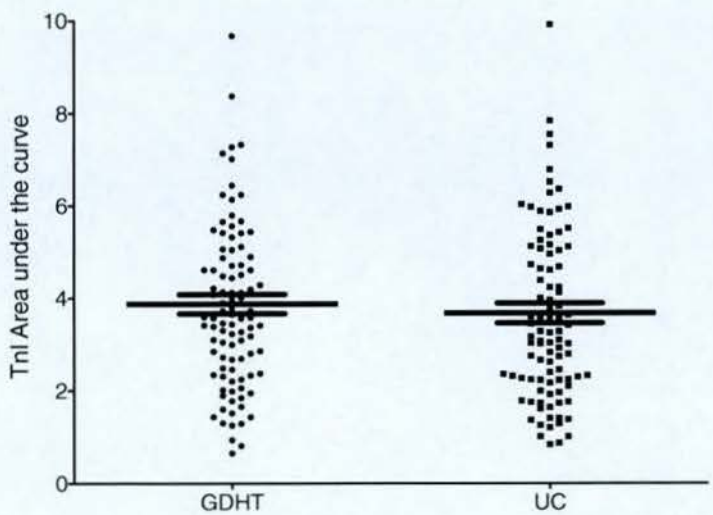


Figure 20 Troponn release expressed as area under the curve (AUC) for each group.*



*Bars represent Mean, SEM.

8.4 Discussion

The main finding from this study was that the goal directed haemodynamic therapy intervention delivered in the OPTIMISE trial was not associated with an increase in myocardial injury, as measured by 5th generation, highly sensitive Troponin I. There was no observed difference in postoperative serum troponin concentration at baseline, 24 or 72 hours, in peak serum troponin concentration or in total troponin release, as measured by area under the troponin concentration/time curve. Peak serum troponin levels were associated with increased risk of myocardial infarction but not with increased incidence of death at 30 or 180 days. Also, preoperative serum troponin levels were not predictive of myocardial infarction, major adverse cardiac event or death at 30 days, or death at 180 days.

Clinical data from the main OPTIMISE suggested that although there were increased cardiovascular serious adverse events (SAE) in the GDHT group (4, 1.6%) compared with none in the usual care group rates of cardiovascular complications at 30 days were similar. This was observed in both the main trial and the biomarker sub-study groups.

The findings from this analysis concur with the systematic review and meta-analysis conducted by Grocott and co-workers who, as part of their review, examined the association between GDHT and cardiac complications. The investigators in this study found no association between GDHT and arrhythmia (RR 0.84 (0.67-1.06); I^2 00%; p=0.14), myocardial infarction (RR 1.01 (0.71-1.45); I^2 00%; p=0.95) and congestive cardiac failure/pulmonary oedema (RR 1.00 (0.81-1.24); I^2 00%; p=0.98). Pearse and co-workers have conducted a similar analysis; they examined patterns of Troponin release in 122 patients who had participated in a single centre trial of GDHT. This study did not demonstrate increased myocardial troponin release associated with the intervention. The results of this study add weight to the assertion that GDHT in the perioperative setting is not associated with increased cardiac injury.

The other finding of interest in this study was that preoperative measurement of 5th generation highly-sensitive troponin did not predict either death or major adverse cardiac events in this cohort of patients; neither did peak serum hsTnI in the first 72 postoperative hours predict mortality at either 30 or 180 days, although was highly predictive of postoperative myocardial infarction (p=0.0005).

Whether the benefits of earlier detection of myocardial necrosis using so called "high-sensitivity troponin" assays result in patient benefit is controversial. [88] Lopez-Jimenez evaluated the incidence and prognostic significance of cardiac Troponin T (TnT) in 772 patients who had undergone major non-cardiac surgery. 12% of patients in this cohort had elevated TnT and this was associated with increased risk

for cardiac events (RR 5.4 (2.2-13.0), p=0.001). [89] More recently Kavsak and co-workers reported the incidence of elevated 5th Generation Troponin I assay (i.e. greater than 99th percentile) to be 45% in a cohort of 325 patients older than 45 years of age and undergoing elective or emergent non-cardiac surgery requiring inpatient admission. Whether this was associated with mortality was not reported. [91] The VISION study investigators measured serum Troponin T using a 4th generation assay in a cohort of 15 133 patients over the age of 45 years having inpatient non-cardiac surgery. The overall mortality in this cohort was low (1.9%), however the investigators found that peak Troponin in the first 72 hours was significantly associated with increased mortality at 30 days in this group.

Strengths of this study are that samples were collected from the largest multicentre randomised controlled trial of GDHT undertaken to date and it was reassuring to note that the intervention did not seem to be associated with increased myocardial necrosis using a highly sensitive troponin assay. Limitations of this study were that universal definitions of myocardial infarction as outlined by Thygesen et al were not employed in the OPTIMISE trial [251] and access to electrocardiograms (ECGs) for individual patients in the trial was not possible. The ability to distinguish "Type 1" Myocardial Infarction (i.e. myocardial infarction related to a coronary artery event such as plaque rupture) from "Type 2" (i.e. an ischaemic event secondary to imbalance of myocardial oxygen supply and demand or related to arrhythmia or hypotension) would have been more clinically relevant to this study. As the potential harm associated with the intervention is likely to be caused by a combination of tachycardia and tachyarrhythmia, increased myocardial oxygen demand and hypotension, the incidence of Type 2 MI in these patients would be useful. There was also evidence of imbalance between groups in age and ASA-PS score; the significance of this is uncertain. The finding that 5th generation highly sensitive troponin did not seem to predict short or long term mortality in this group of patients was also disappointing and at odds with other published work. [85,90] Possible explanations for this are: this was a small cohort, patients recruited to this trial were higher risk than studied in the VISION study and that findings may have been confounded by the trial intervention itself. Peak postoperative hsTnI was highly predictive of postoperative MI however Troponin rise was a diagnostic criterion for this in the study definitions so this finding is perhaps not surprising.

Absence of evidence of increased cardiac injury associated with this goal directed haemodynamic therapy intervention using a highly sensitive marker of cardiac injury adds reassurance that this intervention is unlikely to be associated with significant morbidity and may yet be shown to have demonstrable benefits.

8.5 Conclusion

In a sub-study of participants in the OPTIMISE trial, the GDHT intervention did not appear to be associated with troponin release in the first 72 hours postoperatively, measured as either peak troponin, serum troponin at 24 and 72 hours postoperatively or as area under the curve of troponin against time. These findings agree with other available data examining this issue.

After adjustment for age and sex preoperative hsTnI level was not predictive of death at 30 or 180 days or of postoperative cardiac events at 30 days. Peak postoperative hsTnI was predictive of postoperative myocardial infarction, but not mortality at 30 or 180 days in this cohort of patients. Large observational studies of 5th generation highly sensitive troponin are required to fully elucidate its role in predicting death or adverse outcome when measured preoperatively or in the early postoperative period.

Chapter 9 - Conclusions and Directions for Further Research

9.1 Introduction

Interventions to improve outcome after high-risk surgery could be associated with reduced mortality, morbidity and costs in the surgical population as a whole [2] and as highlighted several times in this thesis, there is a demonstrable need to improve outcomes in the highest risk groups. [1,15,114]

The OPTIMSE trial demonstrated that the delivery of a goal directed haemodynamic therapy algorithm in a group of high-risk surgical patients resulted in a trend towards reduction in a composite endpoint of death or major complications at 30 days. This effect however did not reach statistical significance (OR 0.84 (CI 0.71-1.01); p=0.07). The trial intervention was deliverable in a general NHS hospital setting and was unlikely to be associated with early cardiac injury. Despite the overall negative outcome of this trial, the results suggested benefit in important pre-specified sub-group analyses: a trend towards reduction in infectious complications (OR 0.80 (CI 0.63-1.02); p=0.08); reduction in hospital length of stay (10 v 11 days; p=0.05); a statistically significant beneficial effect on the primary outcome was observed in the elective only subgroup (OR 0.72 (CI 0.52-0.99); p=0.05), these formed the overwhelming majority of patients recruited to the trial and where the first 10 patients at each site were excluded (OR 0.59 (CI 0.41-0.84); p=0.019). Although these findings would not support widespread implementation of this goal directed haemodynamic therapy algorithm, they do suggest that the intervention may yet be associated with benefit in this group. Hence a further large, multi-centre, randomised controlled trial may be warranted to answer this question.

Investigators conducting such a trial may wish to consider factors in the OPTIMISE trial design, delivery, results as well as some of the research questions considered in this thesis to better design and deliver another such trial.

9.2 Conclusions of Research Undertaken in this Thesis

This thesis set out to inform aspects of the OPTIMISE trial with particular regard to:

1. Whether choice of fluid therapy influenced the outcome of the trial.
2. Whether availability or provision of critical care beds could have influenced the outcome of the trial.
3. Whether the trial intervention could have been associated with increased cardiac complications.

The findings of the research undertaken in this thesis are summarised as follows:

Could the choice of colloid used in the perioperative period or trial intervention associated with harm or benefit?

The OPTIMISE trial did not specify which type of colloid should be used for the trial intervention and during the study period new evidence emerged which suggested that use of Hydroxyethyl Starch (HES) solutions in critically ill patients was associated with increased mortality and acute kidney Injury. [169,172] A post-hoc survey of sites following the trial suggested that the vast majority of patients received gelofusin for the trial intervention. Nonetheless if there was an association between perioperative HES use and death or renal dysfunction then this may have had an effect on the trial outcome. There is a genuine paucity of data surrounding the use of 6% HES in the surgical population.

A detailed systematic review and meta-analysis of the perioperative use of HES was conducted. This review evaluated all types of starch against any comparator fluid, but also included a sub-analysis of 6% tetrastarch, a modern HES solution in common use in the UK. Using pooled data on 1567 patients no difference in hospital mortality, incidence of author-defined AKI or requirement for postoperative RRT between groups was demonstrated.

No evidence of harm or benefit associated with the perioperative use of HES containing solutions was demonstrated in this meta-analysis. This provided reassurance that the choice of colloid used in the trial intervention was unlikely to have a bearing on the trial outcome.

A high proportion of patients recruited to the OPTIMISE trial were admitted to Critical Care following surgery. Is the use of Critical Care in itself associated with improved outcomes after surgery?

The trial intervention in the OPTIMISE study involved cardiac output monitoring, inotrope use and fluid optimisation. These interventions are traditionally delivered in an intensive care setting, however for the purposes of the OPTIMISE trial the intervention could be delivered in a high dependency unit (HDU) the recovery room or even the ward. In the trial approximately 75% of both groups were treated postoperatively in an intensive care unit but significant numbers (more than 10% in each group) returned to a ward. The remaining patients were treated on an HDU or post-anesthesia care unit (PACU).

The bulk of this thesis explores variation in critical care provision and surgical outcome in the UK and attempts to determine if availability and utilisation of critical care beds has any demonstrable effect on outcome. A great many commentators have

attributed poor outcomes on lack of critical care bed availability despite little objective evidence of this. [11,15,23,113,114]

Marked regional differences within the UK in critical care bed provision were demonstrated and in an epidemiological study of 16 147 surgical patients admitted to ICU, regional variation in acute hospital mortality which could not be accounted for by casemix or ICU bed provision.

In summary, no evidence to support the assertion that availability of ICU beds *per se* improves surgical outcome was found. Other variations in practice, which may be difficult to fully elucidate, may be the cause of the observed variation in outcome. It is likely that postoperative care is a complex interaction of local care pathways, increasing use of HDU and PACUs and ICU bed utilisation. Alternatively these findings may simply reflect unmeasured confounding. Nonetheless, regional mortality variation within a very uniform healthcare system suggest some deaths may be preventable, as has been highlighted recently by Aylin *et al* who demonstrated differences in elective surgical outcome dependent on day of the week of operation. [162] Further research described later could be undertaken to describe patterns of critical care resource use in this population.

Is GDHT associated with increased myocardial injury as measured by 5th Generation Troponins?

Administration of beta-agonists outside traditional indications as part of a GDHT intervention continues to concern clinicians. Dopexamine is known to cause vasodilation and tachycardia [141] and this combination, in a population known to have a high prevalence of ischemic heart disease, [174] could precipitate myocardial infarction (MI). In OPTIMISE, patients receiving the trial intervention had an increased incidence of cardiovascular serious adverse events in the first 24 hours of the trial compared with the usual care arm (3.9% v 0%) although clinical cardiac events at 30 days were similar. In the biomarker study conducted as part of this thesis, myocardial injury quantified by 5th generation highly sensitive troponin I (HST) assay did not appear to be increased in the intervention group. This finding provides reassurance that the trial intervention was safe and not associated with increased risk of myocardial injury.

Using regression analysis, peak HST in the first 72 hours predicted postoperative myocardial infarction but not death at 30 or 180 days. Preoperative HST was not associated with major adverse cardiac events (MACE), MI or death at 30 or 180 days. This finding is not entirely consistent with other research, notably the recently published VISION study, which found that postoperative peak troponin, was highly predictive of 30-day mortality. [90] Possible explanations for this are: this was a small

cohort, patients recruited to this trial were higher risk than studied in the VISION study and that findings may have been confounded by the trial intervention itself.

The research questions regarding fluid therapy and myocardial injury in the context of GDHT have been addressed in this thesis. However an association between ICU bed provision and outcome using a large cohort of surgical ICU admissions was not demonstrated and the finding of significant regional variation in outcome for surgical patients admitted to ICU requires further investigation.

9.3 Directions for Future Research

The lack of positive findings of the OPTIMISE trial could be explained by lack of statistical power. There are several possible reasons for this:

1. Event rate: OPTIMISE was powered to detect a reduction in the primary endpoint of 50% to 37.5% (i.e. 25%) assuming a two sided type I error of 5% and a type II error of 10%. In the trial itself the incidence of the primary endpoint in the usual care group was 44.4%

2. Dropouts: 10 patients withdrew or were lost to follow-up in each arm, this may have resulted in the trial being underpowered. Trials in this field have historically been hampered by lack of suitable primary endpoints and hence sample size. [139]

3. Endpoints: Although complications are common after elective surgery, mortality is less so and the composite endpoint of "death or major complications within the first 30 days" has obvious attractions, because of a higher event rate. Other endpoints e.g. Infectious complications could be considered further studies. Data from the OPTIMISE trial suggests that infectious complications in particular seemed to be reduced by the trial intervention.

4. Control group care (in particular crossover) also have implications for the results of this and other similar studies. [167] In OPTIMISE 8.6% of the usual care group received cardiac output monitoring and this may also have improved outcomes in that group.

5. Harm associated with the intervention, in particular detrimental effects due to excessive or inappropriate fluid administration or myocardial injury are two questions, which remain of concern to clinicians using this therapy and which this thesis has sought to address.

6. The setting of the trial intervention is another important consideration: might admitting trial participants to a critical care in order to deliver the trial intervention confer additional benefits?

7. Biological plausibility for the intervention itself is still an area that has not yet been fully elucidated. This could be due to effects of the intervention on microcirculatory flow or inflammation. Some commentators have however suggested that a fluid restrictive approach in this group has more biological plausibility to improve outcomes.

The development of further research questions arising from the results of the work in this thesis may inform further large randomized controlled trials to improve outcomes in this group.

Does the choice, timing or other aspects of perioperative fluid therapy influence outcomes?

Choice and timing of perioperative fluid therapy remains a central component of perioperative care. [175] Specific questions which remain unanswered in this group are: whether use of colloid solutions in the perioperative period confer any benefit, whether the timing of fluid administration is important i.e. intra-operative versus post-operative and whether a fluid-restrictive strategy is preferable to a fluid-liberal one.

As outlined in Chapter 2 the publication of the CHEST and 6S studies [169,170] and several subsequent meta-analyses [182-184] have raised serious safety issues regarding the use of hydroxy-ethyl starch solutions in the critically ill, specifically with regard to acute kidney injury and mortality. This has led to withdrawal of these solutions in the European Union. [252] Whether the results of 6S and CHEST studies are applicable to the surgical population at all remain contentious. In the 6S study, patients in both arms were resuscitated with fluid (which could include HES solutions) to specific haemodynamic endpoints prior to randomisation. Patients randomized to the crystalloid arm of the CHEST study had significantly worse renal function at baseline than those randomized to receive HES. These considerations and also whether the results of these studies are applicable to adults having elective surgery at all remains an area of ongoing debate. The systemic review and meta-analysis presented in this thesis along with two others [185,186] suggest that hydroxyl-ethyl starch solutions neither confer harm or benefit in surgical patients. Many of the included trials are small, single centre, use a variety of starch solutions against a variety of comparators and have study populations drawn from diverse surgical groups. However a meta-analysis of 1567 patients found essentially no difference (RD 0.00, 95% CI -0.02, 0.02) between groups. Low study heterogeneity (I^2 =0%) with narrow confidence intervals consistent with a very tight level of precision

(±2%), suggest these findings are valid. This combined with the low event rates of acute kidney injury or death in this group suggests that any randomised controlled trial investigating the safety of starch in the perioperative period would need to very large indeed, and are likely to be futile and hence unlikely to be funded.

In the OPTIMISE trial patients in the intervention arm received approximately 50% more colloid and this was overwhelmingly in the form of gelatin solutions. Gelatins are not widely used outside the UK and have not been submitted to the same degree of scrutiny as starch solutions. Therefore their safety profile is largely unknown.[23] The results of the "Saline versus Albumin for Fluid Evaluation" (SAFE) Study and the more recent "Effects of Fluid Resuscitation With Colloids vs. Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock" (CRISTAL) Study have both suggested that the approximate ratio of crystalloid to colloid when used for resuscitation fell far short of the 2:1 or 3:1 quoted anecdotally.[253,254] With no obvious benefit associated with colloid use and similar volumes of crystalloid required for resuscitation (albeit in an intensive care setting) crystalloid solutions could feasibly be used in subsequent GDHT trials.

Timing of fluid therapy did not appear to be an issue in the OPTIMISE trial. Similar amounts of fluid were given to both groups during the operative period and an increased amount given to the GDHT group in the first 6 hours. Hence restricting the intervention period to the duration of surgery only is unlikely to have any effect.

Other investigators consider that tissue oedema is implicated in postoperative complications and that there is biological plausibility in adopting a more "fluid restrictive" strategy. The Restrictive versus Liberal Fluid Therapy in Major Abdominal Surgery (RELIEF) Study (NCT01424150) aims to recruit 2800 high-risk surgical patients and is currently underway in Australia and New Zealand. This trial may reflect a paradigm shift in the approach to perioperative fluid management. A secondary hypothesis in this trial will ascertain if the benefits of fluid restriction are seen whether or not a goal directed strategy is employed.

In conclusion, further trials evaluating either the safety or benefits of starch or any other solution in surgical patients are unlikely to be feasible or provide a definitive answer to the question of whether these solutions confer any advantage in the perioperative setting. Further studies investigating goal directed fluid therapy could conceivably use balanced crystalloid solutions such as Hartmann's Solution or Plasmalyte: other studies will investigate whether a "fluid restrictive approach" is better and the results of these are awaited with interest.

Does use of dopexamine in GDHT confer any additional benefit over fluid therapy alone?

Dopexamine was included as part of the GDHT algorithm because the results of a meta-regression suggested reduction in 28 day mortality and reduced length of hospital stay associated with it's use at low doses, [142] although another meta-analysis employing different methodology was published around the same time with conflicting results. [143] A European multi-centre trial showed a tendency towards improved survival and reduced complications in patients treated with low dose dopexamine, however at higher doses it was associated with increased rates of cardiovascular complications. [141] Possible adverse effects of dopexamine include vasodilation and tachycardia and the combination of these effects in the presence of ischaemic heart disease remain of concern to clinicians, begging the question "is dopexamine necessary as part of a GDHT trial at all"?

Although there was an increased incidence of cardiovascular SAEs in the intervention group of the OPTIMISE trial there was no difference in the incidence of cardiac complications at 30 days and in the sub-group of patients taking part in the biomarker sub-study, there was no difference in early myocardial injury as measured by 5th Generation Troponin I release. This is the largest prospective randomised trial of goal directed therapy using dopexamine to date and the absence of a demonstrable increase in myocardial injury in the intervention group is reassuring. However, what is the possible mechanism for benefit associated with its use?

Investigators have postulated that the benefits from dopexamine administration in this setting are as a result of improvements in splanchnic microvascular flow and there are experimental studies to support this. [255,256] Moreover, a more recent clinical investigation using a GDHT protocol involving dopexamine reported improved gastrointestinal function and reduced ileus in the postoperative period in the intervention group. [145]

New evidence is emerging that dopexamine may have immunomodulatory properties which could affect inflammation and immune function following surgery. In a recent study, Bangash *et al* used a rodent model of laparotomy and endotoxemia to investigate the effect of three doses of dopexamine on inflammatory markers: tumour necrosis factor (TNF) α, interleukin (IL) 1-β, IL-6 and IL-10; leukocyte cell adhesion molecule CD11b; pulmonary myeloperoxidase (a marker of pulmonary lymphocyte infiltration). He also collected data on organ dysfunction: plasma urea, creatinine, aspartate and alanine aminotransferase (AST and ALT), plasma base excess (BE) and serum lactate. Results of this study suggested a dose-dependent reduction in inflammation associated with dopexamine administration and also reduction in end organ damage. [120] Hence, the beneficial effects of dopexamine may be explained by

attenuation of the inflammatory response to surgery and endotoxemia. This may explain the particular reduction in infectious complications seen in the intervention group of the OPTIMISE trial.

Using the OPTIMISE biomarker sub-study sample bio-bank it would be possible to investigate the effects of the trial intervention and in particular the administration of dopexamine on the same markers of inflammation and this could be correlated to clinical complications and other markers of end organ damage such as serum creatinine, urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) and transaminases. A subsequent GDHT trial could include arms with or without dopexamine to investigate whether the immunomodulatory effects of dopexamine are clinically significant.

Can the use of perioperative critical care improve outcomes; how can patterns of surgical critical care utilization be further investigated and refined?

Although in Chapter 6 we attempt to use modeling techniques to ascertain if critical care provision or utilization can explain variability in outcome after high-risk surgery, a major drawback of this work is that the analysis only includes patients admitted directly to ICU following surgery. It is known that a large group of surgical patients are initially admitted to the ward before admission to ICU and in the work undertaken by Pearse *et al* this group had the worst outcomes. [15] High quality data on the numbers of high-risk patients presenting for surgery and their requirements for Intensive Care in the UK remain sparse.

In England, Wales and Northern Ireland there is no linkage between the hospital, intensive care and death databases (Health Episode Statistics, Intensive Care National Audit and Research Centre (ICNARC), Register of Deaths) and therefore it is not possible for investigators to link inpatient surgical admissions to intensive care admission or to adjust for social deprivation or preceding co-morbidities. Moreover ICNARC only capture data on 92% of Intensive Care Units in England, Wales and Northern Ireland. Therefore it has not been possible to obtain a clear picture of the epidemiology of the high-risk surgical population and their utilisation of intensive care resources.[5]

Information Services Division (ISD) Scotland holds data on all acute hospital discharges in Scotland through the Scottish Morbidity Record (SMR) databases. Through linkage, data can be extracted relating to diagnostic information, detailed physiological data from ICU admission (the Scottish Intensive Care Society Audit Group (SICSAG) database is also hosted by ISD), long-term outcomes (deaths registry), data on hospital readmissions (SMR01), and other relevant data such as social deprivation. The *SMR01 database* is subject to regular validation checks, and the most recent quality assurance report indicated good levels of accuracy (>90%)

for the fields used in this study. Up to four surgical procedure codes can be recorded on each SMR01 episode along with the date of procedure. These fields have an accuracy of more than 95%. [228] Diagnostic information fields, which could be used to derive co-morbidities, are recorded using the International Classification of Diseases version 10 (ICD-10). There are up to six fields that can be used to record diagnoses, with one allocated as the main reason for admission. Information Services Division links SMR01 routinely to the Scottish death register using patient characteristics in a probabilistic matching algorithm with a high degree of accuracy. [257]

As described earlier the Scottish Intensive Care Society Audit Group (SICSAG) holds data on to all admissions to general ICUs in Scotland and data are collected prospectively at the time of admission by clinical staff in the ICU. The database contains information relating to patient demographics, physiological measures of illness severity, number of days of organ support, diagnostic information including surgical status, and patient outcome. Quality assessment reports are produced on a regular basis, which demonstrate high levels of data quality. [228]

Using data available from ISD it would be possible to determine proportion of patients admitted to ICU directly after high-risk surgery and those admitted to the ward first. Because all hospital and ICU admissions are captured a very accurate and detailed picture of pattern of critical care utilization as well as outcomes in the short, medium and long term (i.e. 1-3 years) could be constructed. Hospital re-admission could be used to look at hospital resource use in the year following high-risk surgery and whether critical care use mitigated this. It would also be possible to construct a detailed model identifying patient, surgical, hospital and socioeconomic factors associated with morbidity and mortality following high-risk surgery.

Accurate, complete data at national level on critical care utilisation and outcomes after high-risk surgery would enable identification of the patients at highest risk of dying or developing major complications in the postoperative period. This could inform strategies to reduce morbidity and mortality. Data of this nature is highly relevant to clinicians, healthcare funders and patients, as well as those designing large clinical trials.

Can other biomarkers of organ dysfunction or inflammation predict those at risk of complications when measured either pre-operatively or in the early post-operative period?

There is a great deal of interest in the role of using novel biomarkers either pre-operatively or in the early postoperative period to predict those at risk of death or complications.

In this thesis one such biomarker, highly sensitive troponin I is used, not only to quantify myocardial injury between groups but also to ascertain if preoperative values or peak value in the first 72 hours postoperatively can predict death or major adverse cardiac events at 30 or 180 days. The urine and plasma samples collected for the OPTIMISE biomarker sub study could be used to study the predictive value of other novel and established biomarkers.

Candidates for this would be:

1. Brain Natriuretic Peptide (BNP) or N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP).

BNP can only be measured in plasma; therefore NT-proBNP measurement would need to be used on these samples. Such an analysis could answer two important questions. Firstly the ability of NT pro-BNP concentration to accurately predict patients suffering death, MI or MACE at 7 or 30 following surgery or death at 180 days following surgery in the entire cohort and each group could be assessed. Secondly, because BNP and NT-proBNP are released in response to volume overload, this could assess whether the intervention was associated with fluid overload in the early postoperative period. Excessive fluid administration has been a concern in previous GDHT studies. [220]

2. Biomarkers of Renal Dysfunction

Post-operative Acute Kidney Injury (AKI) is associated with significantly increased morbidity, mortality and cost. [258] The incidence of peri-operative AKI may be as high as 7.5% depending on the definitions used. [259] Current classifications (AKIN, RIFLE) use "fold-change" in serum creatinine (SCr) and urine output to define different stage. [260] Many authors consider SCr changes to be a poor early marker of kidney injury. [261]

Novel biomarkers have been recently described that enable the early prediction and detection of AKI prior to changes in serum creatinine. The most commonly studied of these, NGAL, is described in a previous chapter, however other renal biomarkers are emerging. Plasma Cystatin C (plasma CyC) is a produced by all nucleated cells, excreted through glomerular filtration and metabolised by the proximal tubules without any evidence of tubular secretion. Plasma CyC is therefore a good marker of GFR and discriminates small changes in GFR more accurately than SCr.

Using the OPTIMISE bio-bank, the effect of GDHT on biomarkers of renal dysfunction and the ability of these novel biomarkers to predict post operative renal dysfunction in major non-cardiac surgery could be assessed.

3. Biomarkers of Inflammation

C-reactive protein (CRP) is an acute phase protein and levels rise in response to inflammation. As described earlier it has been used to predict postoperative complications including myocardial infarction, anastomotic leak and death. Other inflammatory cytokines have been investigated in the postoperative period but whether they can be used to make prognostic decisions is largely unknown. The effect of GDHT (and in particular dopexamine) on markers of inflammation has been proposed above. Logistic regression could be used to test for association between serum levels of inflammatory biomarkers and if this was found, standard methodology using receiver-operated curves (ROC) could be used to determine optimal diagnostic points.

In summary, further research utilising the OPTIMISE trial bio-bank could be used to determine the effects of GDHT on inflammation and organ dysfunction following high-risk surgery. It could also be used to develop the role of biomarkers to predict those most at risk of developing complications.

What refinements could be made to a large trial of GDHT to successfully answer this question?

Although the OPTIMISE trial demonstrated no significant reduction in 30-day complication rates, findings of pre-specified secondary and subgroup analyses and the non-significant reduction in mortality at 180 days were all consistent with a beneficial effect of the intervention. A larger clinical trial would be required to resolve this. Were the trial to be repeated, investigators may consider several changes to trial design in order to answer the question definitely.

Firstly, detailed and accurate epidemiological data on mortality and complication rates will be vital to ensure any subsequent study is adequately powered. In OPTIMISE the estimated incidence of the primary endpoint was overestimated (50% vs. 44.4.%) and this may have resulted in the trial being underpowered once patients who withdrew consent or were lost to follow-up were considered.

Suitable endpoints should also be considered. Infectious complications seem to have been reduced most in the intervention group of OPTIMISE although overall this did not reach significance (p=0.08). A longer mortality period may also be worth considering; as noted earlier in the thesis 45, 60 and 90-day mortality have all been proposed as study endpoints for surgical patients. [11,21] The RELIEF study (described above) has similar endpoints to OPTIMISE and intends to recruit 2800 patients.

Another question for subsequent GDHT trials is the intervention itself. It would seem from considerations discussed above that dopexamine should be investigated as part of the trial intervention. However to better separate the effects of dopexamine from the goal directed fluid therapy it might be desirable to randomise patients to receive either goal directed fluid therapy or usual care and either low-dose dopexamine or placebo. This would effectively create four groups but would allow better study of the trial intervention. Finally consideration must be given to the control group care. 8.6% of patients in the usual care arm received cardiac output monitoring of some description and almost 30% received an infusion of vasoactive drugs. Like recent ARDS trials, [262,263]protocolisation of the usual care arm to reflect best current practice may also reduce the effect of the intervention.

9.4 Summary

The research undertaken in this thesis was to inform the interpretation of OPTIMISE, a randomised controlled trial of goal directed haemodynamic therapy versus usual care in high-risk patients undergoing gastrointestinal surgery. The work done in this thesis may guide future studies.

The principal findings of this thesis are:

- In a meta-analysis of 1567 patients comparing perioperative 6% hydroxyl-ethyl starch solutions versus any comparator no difference in 30-day mortality or acute kidney injury was observed.
- Significant regional variation exists in ICU bed provision within the UK.
- In an epidemiological study of 16 147 patients admitted to ICU following surgery in the UK significant variation in acute hospital mortality was observed. This did not appear to be accounted for by casemix or ICU bed provision.
- Using 5th Generation highly sensitive Troponin I no difference difference in myocardial injury or infarction between GDHT and usual care groups was detected.

Future research should concentrate on: refining the GDHT intervention and this may include further investigation of its biological mechanism; high quality epidemiological data to inform future studies and predict those patients at the highest risk; more detailed epidemiological investigation of critical care resource utilization and its effects on outcome; perioperative measurement of biomarkers to identify patients at high risk of specific complications and death.

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Appendix 1 – Publications Arising from this Thesis

To date, the following papers have been published arising from research described in this thesis (with weblinks):

1. Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blunt M, Ackland G, Grocott MP, Ahern A, Griggs K, Scott R, Hinds C, Rowan K. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. JAMA. 2014 Jun 4; 311(21):2181-90.

URL: http://jama.jamanetwork.com/article.aspx?articleid=1873985

2. Gillies, MA, Habicher M, Jhanji S, Sander M, Mythen M, Hamilton M, Pearse RM. Incidence of post-operative death and acute kidney injury associated with intravenous 6% hydroxyethyl starch use: systematic review and meta-analysis. *Br J Anaesth* 2013 112 (1) 25-34.

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